Synthesis and Reactions of Novel Oxindoles

A thesis submitted to the University of Sheffield in partial fulfilment of the requirements for the award of Doctor of Philosophy

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Abstract

An important issue with the assignment of $E/Z$ alkene geometry of 3-acylidene-oxindoles was addressed. A novel UV/Visible spectroscopic assay was developed in order to achieve this, taking advantage of contrasting electronic properties for different $E/Z$ isomer sets. Moreover, a novel acylidene oxindole was prepared and used to provide further supporting evidence for this spectroscopic assay. Finally, the stability of related $E/Z$ isomers was investigated, and indicated facile isomerisation to a thermodynamic minimum.

A copper promoted cyclisation of $o$-nitrophenyl iodoacetylenes to 2-iodoisatogens was discovered. These compounds were applicable as precursors to novel isatins and consequently 3-acylidene oxindoles.

The metal free aryl and alkyl cross coupling reactions of 2-iodoisatogens was developed, providing a divergent synthetic strategy to the medicinally relevant isatogen molecular group. Furthermore, an unprecedented isatogen mode of reactivity was discovered affording pseudoindoxyls, a privileged class of molecule. The mechanism for this transformation was proposed, based on control reactions and strong literature precedent.
“You can take the boy out of Wakefield but not the Wakefield out of the boy”

- J. P. A. Harrity (multiple occasions)
Acknowledgments

Initially I would like to extend my gratitude to GSK and the EPSRC for funding for this work and additionally The University of Sheffield for providing me with this opportunity.

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Rob and Rich thanks for not being completely and utterly insufferable, try to get out of West Yorkshire at some point yeah…

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetate</td>
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<tr>
<td>A</td>
<td>Ampere</td>
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<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>ATM.</td>
<td>Atmosphere</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-Butoxy carbonyl</td>
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<tr>
<td>Bn</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
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<tr>
<td>Cat.</td>
<td>Catalyst</td>
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<td>C</td>
<td>Celsius</td>
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<td>c</td>
<td>Centi</td>
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<tr>
<td>c.f.</td>
<td>conferre (compare)</td>
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<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>Cy-Pent</td>
<td>Cyclopentyl</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>Cy-Pr</td>
<td>Cyclopropyl</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical Shift</td>
</tr>
<tr>
<td>Decomp.</td>
<td>Decomposition</td>
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<tr>
<td>o</td>
<td>Degrees</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl Sulphoxide</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethyl Sulphide</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethyacetamide</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Ionisation</td>
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<tr>
<td>EPR</td>
<td>Electron Paramagnetic Resonance</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>hv</td>
<td>Energy</td>
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<td>$E$</td>
<td>Entgegen</td>
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vii
equiv. Equivalents

et al. et allia (and others)

Et Ethyl

e Extinction Coefficient

FT Fourier Transform

v Frequency

FMO Frontier Molecular Orbital

g Gram

> Greater than

IC$_{50}$ Half Maximal Inhibitory Concentration

Hex Hexyl

HPLC High Performance Liquid Chromatography

HRMS High Resolution Mass Spectroscopy

HOMO Highest Occupied Molecular Orbital

hr Hour (s)

Hz Hertz

i.e. id est (it is)

IR Infrared

IBX 2-Iodoxybenzoic acid

i iso

< Less than

L$_n$ Ligand

L Litre

LUMO Lowest Unoccupied Molecular Orbital

MHz Mega Hertz

M.p Melting Point

m meta

m-CPBA $meta$-Chloroperbenzoic acid

M Metal

m Meter

Me Methyl

µ Micro
µ w Microwave
m Mili
min Minute (s)
M Molar
mol Mole
n Nano
t normal
NMR Nuclear Magnetic Resonance
nOe Nuclear Overhauser Effect
o ortho
p para
ppm Parts-per Million
% Percent
Ph Phenyl
Pr Propyl
Phth Phthalimide
Py Pyridine
Δ Reflux
R Residue
RT Room Temperature
s Seconds
SPhos 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SAR Structure Activity Relationship
TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
t tertiary
TBAF Tetrabutylammonium Fluoride
THF Tetrahydrofuran
TLC Thin Layer Chromatography
TOF ES Time of Flight Electrospray
Ts Tosyl
TG2 Transglutaminase 2
TRPA Transient Receptor Ion Channel
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>TMM</td>
<td>Trimethylenemethane</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra Violet</td>
</tr>
<tr>
<td>Vis</td>
<td>Visible</td>
</tr>
<tr>
<td>V</td>
<td>Volt</td>
</tr>
<tr>
<td>λ</td>
<td>Wavelength</td>
</tr>
<tr>
<td>Z</td>
<td>Zusammen</td>
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1.1 – Biological and Synthetic Applications of 3-Acylidene Oxindoles

3-Acylidene-oxindoles are attractive compounds for the discovery of new medicines, and there are a vast number of such compounds that exhibit useful biological activity. Arguably, the most prominent example of a bioactive, structurally analogous, 3-alkenyl-oxindole is Sunitinib, the structure of which is shown in figure 1. Sunitinib was developed by Pfizer and Sutent), and is a tyrosine kinase inhibitor which was approved in 2006 for the treatment of renal cell carcinoma and gastrointestinal stromal tumours. \(^1\)

![Figure 1: Sunitinib](image)

Another prominent example is Nintedanib, a potent kinase inhibitor, figure 2. It has been screened in several drug assays and has shown remarkably similar efficacy to Sunitinib.\(^3\) Moreover it has very recently been approved in the European Union for the treatment of idiopathic pulmonary fibrosis. \(^4\)

![Figure 2: Nintedanib](image)

Other recent reports of biologically active acylidene oxindoles include a series of examples by Woodard and co-workers. This group identified compounds such as 1 (Figure 3) that would selectivity inhibit cyclin dependent protein kinases.
Interestingly, the authors indicated that all compounds were of a Z-configuration, however they did not report how this stereochemical assignment was made.\textsuperscript{5}

![1: CDK inhibitor](image1)

Figure 3.

Khosla and co-workers reported that acylidene oxindoles can act as reversible inhibitors of the human transglutaminase-2 enzyme. Such compounds are proposed to be useful for the treatment of several diseases such as: cancers, central nervous system disorders and celiac sprue. The authors screened several compounds in TG2 assays and highlighted compound 2 (Figure 4) as being particularly active.

![2: Reversible TG2 inhibitor](image2)

\textbf{2: Reversible TG2 inhibitor}  
\textit{IC\textsubscript{50} = 0.9 \mu m}

Figure 4.

An additional example of kinase inhibitors based on this family of heterocycles was described by Aldous and co-workers.\textsuperscript{6} Furthermore, other reported biological activities include: phosphatase inhibition,\textsuperscript{7} antifungal properties\textsuperscript{8}, and TRPA1 ion channel activation.\textsuperscript{9} Moreover, naturally occurring 3-acyldiene oxindoles have been reported; costinone A (Figure 5) was isolated from herb \textit{Isatis costata} and was found to demonstrate inhibition of butyrylcholinesterase and lipoxygenase enzymes.\textsuperscript{10}
Figure 5.

A major synthetic application of 3-alkylidene oxindoles is in their use as precursors to spirocyclic oxindoles. This has been highlighted very nicely by recent developments in the Trost group. The authors reported a catalytic [3+2] cycloaddition of 3-alkenyl-oxindoles with the trimethylenemethane (TMM) precursor 3. The Pd-catalysed reaction could be rendered asymmetric when conducted in the presence of a chiral ligand, scheme 1. In this example, the trans product was isolated as the major isomer in excellent enantiopurity. Furthermore, the minor cis product was also enantioenriched with an ee of 96%. A further 5 examples were reported, all with excellent yields (90% - 99%) and excellent ee’s (92% - 99%) for the major trans isomers, scheme 1.

Scheme 1.

Additionally, varying the naphthyl-pyrrolidine connectivity of the ligand resulted in a complete reverse of diastereoselectivity with the cis product now being afforded as the major isomer. However, the excellent enantioselectivity of the reaction was retained, affording the products in excellent yield and selectivities of up to 92% ee. Overall however, a slight reduction of enantioselectivity was observed with reported
ee’s of between 77% - 92% for the cis isomer, scheme 2. Therefore, this methodology has the opportunity to access both trans- and cis-isomers with high ee, depending on the choice of ligand.  

Scheme 2.

Trost et al. also applied this chemistry in the total synthesis of the natural product marcfortine B. The TMM precursor 4 and oxindole 5 were reacted together in the presence of catalytic palladium acetate and triisopropylphosphite to afford the key spirocyclic intermediate 6 as a racemic and diastereomeric mixture (1:1), which was converted to a single diastereoisomer at a later stage. No yield for this step was quoted as the authors carried forward the crude material. A further 16 steps were then performed to access the natural product, scheme 3.
1.2 - Synthetic Strategies Towards 3-Alkenyl-Oxindoles: Preparation from Isatin Derivatives

The first reported acylidene oxindole synthesis was by Braude and Lindwall in the early 1930’s via an aldol condensation reaction of acetone and isatin, in a single isolated example. The reaction proceeded via the addition of the enamine derived from acetone and diethylamine to isatin affording the β-hydroxy ketone in a good yield of 75%. Dehydration of the β-hydroxy ketone was carried out in a second step by heating at reflux in concentrated acid to give the desired acylidene oxindole 7 in a 42% yield and as a single isomer, representing an overall yield of 32%, scheme 4.\textsuperscript{13}

Scheme 4.

3-Acylidene oxindoles were synthesised by Khosla \textit{et al.} for biological screening, by employment of Braude and Lindwall’s original conditions.\textsuperscript{13} In doing so, they significantly expanded the scope of this reaction both with regards to the acetophenone, and the isatin derivatives, demonstrating its broad generality. However, with the main focus of this publication being the screening of compounds against two different kinase assays, only small quantities of acylidene oxindoles were prepared and as such no isolated yields were quoted. In addition, the authors also reported that the alkene geometry of all their synthesised compounds was \textit{E}, selected examples are shown in figure 6.\textsuperscript{14}
During this study, the authors highlighted an interesting method for the dehydration of the β-hydroxy ketone intermediate. Specifically, methanesulfonyl chloride dissolved in pyridine was used to form the mesylate of the alcohol, resulting in a more facile dehydration step. This protocol avoided the use of concentrated acids and as such improved compatibility towards substrates bearing basic groups such as pyridyl, scheme 5. However, this approach was limited to isatin substrates bearing a substituent at the nitrogen atom.\(^\text{14}\)

Figure 6.
With regard to alkene stereochemistry Khosla et al. assigned all compounds as E based on the relative olefinic $^1$H NMR chemical shifts. Their justification for this came from an interesting report by Righetti et al. who reported that the olefinic protons of matching acylidene $E/Z$ isomers would resonate at diagnostically different chemical shifts in the $^1$H NMR spectrum. The authors stated that $Z$ olefinic protons resonated at lower field strengths relative to their corresponding $E$ isomers, scheme 6.

The basis of these NMR studies arose from their development of a method for the isomerisation of $E$-acylidene oxindoles to the corresponding $Z$-isomers. In this protocol, the $E$-isomer was treated with one equivalent of aluminium trichloride. The $Z$-acylidene oxindoles were isolated after quenching with sodium hydrogen carbonate. An interesting observation is that exposure of the $E$-isomer to one equivalent of the Lewis acid resulted in the formation of a dark solid that proved to be the $Z$-product. In contrast, the use of two equivalents of AlCl$_3$ provided an orange solid that proved to be recovered $E$-isomer. They proposed a mechanism to explain these results. Specifically, both carbonyls are able to coordinate to one equivalent of aluminium trichloride. However, if two equivalents of Lewis acid are utilised then each carbonyl coordinates to one equivalent of Lewis acid thereby promoting formation of the more thermodynamically favoured product, scheme 7.
Another account of this type isomerisation, with structurally analogous 3-alkenyl-oxindoles, was reported by Takemoto and co-workers during their development of a rhodium promoted cyclisation of $N$-formyl anilides. Over the course of their investigations they observed that alkynes bearing aliphatic groups such as $n$-$C_4H_9$ and $n$-$C_{10}H_{21}$ underwent efficient cyclisation. The desired compounds were afforded in respective yields of 85% and 73%, and with very good stereoselectivities of $(7.4 : 1.0)$ and $(12.5 : 1.0)$ in favour of the $E$-isomer. However, when $R^1$ was aromatic then more variation in yield and stereoselectivity was observed, scheme 8.

Takemoto et al. attributed this variation to the changes in reaction times and temperatures used in these reactions. Indeed, they observed isomerisation of a pure $E$ isomer when subjecting this compound to the reaction conditions. Specifically, a pure sample of the $E$-compound, where $R^1 = "Bu$, was converted to a mixture of $E$ and $Z$ $(19.4 : 1.0)$ after heating in toluene for six hours, scheme 9.\textsuperscript{16}
Avendaño has also reported the preparation of acylidene oxindole via aldol reactions. This study was restricted to utilising N-methyl isatin that allowed them to perform the reaction under more classical conditions i.e. using an inorganic base such as potassium hydroxide, as opposed to catalytic amounts of secondary amine. Nonetheless, they also showed that piperidine was viable as a catalytic base, in contrast to previously reported conditions where diethylamine was favoured. The focus of this particular study was to condense N-methyl isatins with substituted acetophenones. Indeed, they were the first to report formation of the Z-acylidene oxindole via an elimination reaction. Specifically, treatment of 8 with hydrochloric acid in ethanol at room temperature gave the expected E-acylidene oxindole in an excellent 96% yield. Interestingly however, when dehydration occurred through employment of concentrated sulphuric acid at 0 °C the Z-acylidene oxindole was obtained in quantitative yield, scheme 10.

The use of microwave irradiation to promote acylidene oxindole synthesis via an aldol reaction has been reported recently. In this case, the acylidene oxindoles were synthesised as intermediates en route to novel bioactive spiroindole derivatives.
Nonetheless, the results reported by Pawar et al. are promising.\textsuperscript{19} In their method, isatin and the ketone were adsorbed onto basic alumina and irradiated with microwaves for 5-6 minutes at 128 °C. The authors claim that 100% conversion is achieved with the products returned in reasonable purity, as judged by TLC analysis. However, they did not go on to characterise their intermediates so no comment on product stereochemistry can be made. The authors also performed the aldol condensation reaction using the classical method reported by Braude and Lindwall\textsuperscript{13} and compared the yields and reaction times against their microwave assisted method, table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl</th>
<th>Reaction Time / min</th>
<th>Yield / %</th>
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<tr>
<td></td>
<td></td>
<td>Classical</td>
<td>Microwave</td>
</tr>
<tr>
<td>1</td>
<td>6-F(C\textsubscript{6}H\textsubscript{4})</td>
<td>300</td>
<td>5</td>
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<tr>
<td>2</td>
<td>6-CH\textsubscript{3}(C\textsubscript{6}H\textsubscript{4})</td>
<td>300</td>
<td>4</td>
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<tr>
<td>3</td>
<td>6-OMe(C\textsubscript{6}H\textsubscript{4})</td>
<td>260</td>
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Table 1.

As is evident from table 1, the microwave assisted aldol condensation reaction shows potential as the reaction time is significantly reduced and the yield is also near quantitative. In addition, microwave promoted reactions are becoming more popular in organic synthesis for reasons of reduced reaction time, and improved efficiency.\textsuperscript{20}

Another method for the synthesis of acylidene oxindoles can be achieved via olefination reactions of isatin such as the Wittig reaction. A large number of such compounds were synthesised by Shi et al. utilising stabilised phosphoranes shown in scheme 11.\textsuperscript{21}
The Wittig reactions of phosphoranes listed in scheme 11 were performed on a variety of isatin derivatives bearing substituents on the nitrogen atom such as: hydrogen, benzyl, methyl, allyl, and tert-butoxy carbonyl. Additionally, the chemistry was compatible with isatins bearing functionality such as fluoride, chloride, bromide, methyl and trifluoromethyl groups. The yields for these Wittig reactions were reported to be generally good to excellent. Moreover, the compounds were all reported to exhibit $E$-stereochemistry. Notably, the same $E$ stereochemistry was reported when these compounds were synthesised via aldol chemistry.

Wittig reactions were also performed by Barbas III and co-workers, conditions for which are outlined in scheme 12. In this particular case, no attention was paid to the alkene geometry or the yield as the crude acylidene oxindoles products were directly subjected to alkene hydrogenation. However from the reported isolated yields of their hydrogenated products, it is clear to see that the Wittig reactions were very efficient. The substrate scope generally consisted of Boc and Cbz protected isatins bearing a range of substituents, the only phosphoranes employed however were those bearing a methyl or ethyl ketone.
As such, the Wittig reaction would seem to be an excellent method for the synthesis of acylidene oxindoles. Especially for compounds such as 9, figure 6, as this would be more challenging to synthesise via aldol chemistry due to the availability of two sets of enolisable protons in the required ketone substrate. Both sets of examples above utilise very mild conditions and suggest that these reactions could be performed on a multi-gram scale. However, this method does have associated limitations such as the formation of $E$-isomers only, the fact that only simple phosphoranes are employed and the formation of phosphine oxide by-product.

In summary it has been shown that a number of conventional chemical techniques can be used to generate 3-acylidene oxindoles such as aldol reactions and Wittig reactions.11e, 13-15, 17-19, 21-22 These reactions can be performed very efficiently and in excellent yields. Furthermore, the predominant stereochemistry observed for these compounds is $E$ with only a few examples of $Z$ compounds reported.15, 17 However, all of these methodologies require isatin starting materials, greatly limiting the substrate scope to readily available isatin substrates.

1.3 - Synthetic Strategies Towards 3-Alkenyl-Oxindoles: Synthesis of the Oxindole Core

More recently, increasing interest in synthetic routes to 3-acylidene-oxindoles has led to the development of a variety of different one-pot approaches.23 The majority of these synthetic methodologies proceed via cyclisation reactions, scheme 13. The main benefit of this is that it provides the possibility of a greater substrate diversification, i.e. not limited to the starting material isatin and/or commercially available isatin analogues. Furthermore the majority of these reactions can also be performed catalytically.

![Scheme 13](image-url)
In this context there are several reports of metal catalysed cyclisations in order to generate structurally analogous 3-alkenyl oxindoles, which have then been further expanded to cover the functionally specific 3-acylidene oxindoles. An early example of this type of reaction was reported by Takashi et al. Specifically, 3-alkenyl oxindoles were prepared via rhodium catalysed carbonylative annulation of alkynyl-arylamines, scheme 14. The reaction proceeded very efficiently and required rather low catalyst loadings.

Scheme 14.

This reaction was found to proceed stereoselectively to provide the E-isomer. However the formation of additional side products was also reported. Initially, reactions were performed at higher reaction temperatures and with the addition of water and triethylamine. However, these conditions were found to favour the formation of the hydrogenated product. For example, at 175 °C the major product was 3-benzyl-1,3-dihydroindol-2-one 10 and this was isolated in a 83% yield. In addition, a small amount of the isomeric product 3-phenyl-2-quinolone 11 was also observed. Unfortunately, the authors did not comment on why these additives result in in situ hydrogenation, scheme 15. Consequently, Takashi proposed that the reaction proceeds via two steps. The first being carbonylation of the aniline followed by cyclisation onto the alkyne to give the 3-alkenyl oxindole.

Scheme 15.

The scope of this chemistry was further expanded by Chung and co-workers. However, the preferred solvent and catalyst were altered. They preferred the anhydrous solvent THF and a heterobimetallic cobalt/rhodium nanoparticulate catalyst, albeit with a higher catalyst loading of 3 mol%. Interestingly under these
slightly modified conditions, no hydrogenation of the alkene functionality was observed, scheme 16.\(^{25}\)

\[
\text{Scheme 16.}
\]

The methodology offered a broad substrate scope, and the reaction was found to proceed well when \(R^1\) was 4\(^{\prime}\)-chloro or 4\(^{\prime}\)-butyl. Secondary and primary anilines were also shown to be effective. The reaction did not discriminate between internal alkynes bearing aromatic and aliphatic groups, with both types of substrate performing well. However, it was shown that terminal alkynes did not give the desired product and instead underwent decomposition.\(^{25}\)

Regarding our specific interest in this compound class, the majority of methodologies do not accommodate the desired functionality, i.e. acylidene motif in the 3\(^{\prime}\) position. This limitation was addressed by Gabriele et al. when they reported the cyclocarbonylation of 2-ethynyl anilines via the use of a palladium catalyst under an atmosphere of carbon monoxide with methanol as the solvent, scheme 17.\(^{26}\)

\[
\text{Scheme 17.}
\]

Reactions were performed between 50 - 70 \(^{\circ}\)C with 2 - 5% \(\text{PdI}_2\) and 5 - 10 mol\% \(\text{KI}\) under 20 atmospheres pressure of CO : air (4 : 1). The reported yields were moderately good, between 48-64%. The reaction was shown to be compatible with free aniline to give the \(N\)-H acylidene oxindole and was also effective when \(R^1\) was
butyl or benzyl, thereby affording $N$-substituted analogues. The nature of $R^2$ and $R^3$ was not extensively studied, with methyl and chloride used in some cases. The authors noted that the reaction did not work when $R^2$ / $R^3$ were substituents possessing strong electron acceptor behaviour e.g. nitrile or ester groups. With regard to product stereochemistry, once again the $E$-isomer was favoured, as determined through X-ray crystallography. It was also reported that the reaction did not proceed with internal alkynes. Based on some of their earlier results, Gabriele and co-workers proposed the reaction mechanism highlighted below, scheme 18.

*Scheme 18.*

Initially, both the aniline motif and carbon monoxide coordinate to palladium forming what is referred to as a carbamoylpalladium intermediate I. Insertion of the triple bond into the carbamoylpalladium complex would result in II which rearranges to form the more stable isomer. Termination of the catalytic cycle via subsequent CO insertion and addition of methanol gives the desired product, the palladium catalyst is then re-oxidised in the presence of air. This proposed mechanism helps explain why internal alkynes do not react; a triple bond bearing a substituent is less likely to insert into the carbamoylpalladium bond. In addition this mechanism is consistent with the observation by Takahasi whereby carbonylation occurs first followed by cyclisation.
An alternative approach to \textit{in situ} carbonylation is to install a carboxy function on the aniline prior to cyclisation. Consequently, 2-ethynylanilines have been replaced by alternative alkyne substrates that bear \( N \)-carboxyl alkynyl groups, such as iodoaryl-propionamides. The very first example of this type of cyclisation was reported several decades earlier by Heaney and Jordan in 1988. In this case, the iodoaryl alkynylamides were cyclised to the form the 3-alkenyl oxindoles via a radical reaction utilising tributyltin hydride and the radical initiator 2,2'-azobis(2-methylpropionitrile) (AIBN), scheme 19.\textsuperscript{28}

Scheme 19.

Unfortunately, this reaction generally proceeded in a low yield and gave a mixture of stereoisomers with the \( Z \)-alkene predominating. Another disadvantage of this approach is in the use of tin as a reagent. The use of these reagents is discouraged due to their toxicity and difficulty in removal of organotin by-products. Subsequently, Brunton and Jones improved this chemistry by expanding the reaction scope and suggested that the \( Z \)-isomer is predominant due to the stability of the vinyl radical intermediate. They proposed that the \( E \)-isomer is less stable due to an unfavourable steric interaction between the phenyl group and the aromatic proton in the C-4 position. As vinyl radicals are known to be configurationally unstable, \( E \) and \( Z \) isomers are thought to be in equilibrium with one another with a greater population of \( Z \)-isomer thus leading to the observed ratio in the fully cyclised product, see figure 7.\textsuperscript{29}

Figure 7.
More recently, these types of cyclisations have been improved upon by removing the requirement for stoichiometric quantities of tin and focussing on the transition metal catalysed variants. One of the earliest examples of such a strategy was reported by Müller in 2005. The palladium catalysed Heck cyclisation of the tosyl protected iodoaryl alkynylamide 12 followed by the subsequent \textit{in situ} Sonogashira coupling with the alkyne 13 afforded compound 14 as a single isomer in near quantitative yield, scheme 20.\textsuperscript{30}

\begin{center}
\includegraphics[width=\textwidth]{Scheme20.png}
\end{center}

Scheme 20.

This chemistry is not exclusive to tandem Heck/Sonogashira couplings. Takemoto and co-workers have reported tandem Heck/Suzuki-Miyaura reactions. In this protocol, palladium intermediate 15 is generated and as no $\beta$-hydrides are available for elimination, this can undergo a cross coupling reaction with the boronic acid \textit{in situ} generating the 3-alkenyl oxindole, scheme 21. Caesium fluoride was found to be the optimal base giving excellent yield and exclusively the $E$ product, whereas sodium hydroxide gave a yield of 88 % $E$ and 4 % $Z$. Variation of the boronic acid employed yielded a small substrate scope; very good yields and exclusive $E$ selectivity were reported for electron rich ($p$-MeO-$C_6H_4$), electron poor ($p$-CF$_3$-$C_6H_4$) substrates, scheme 21.\textsuperscript{31}
Considering the specific interests of this thesis, i.e. the preparation of 3-acylidene oxindoles we were particularly intrigued by the report of a three step Heck/carbonylation/Suzuki-Miyaura domino procedure. The transformation is similar to the cross-coupling method highlighted earlier, but incorporates a carbon monoxide atmosphere. This procedure gave access to the 3-acylidene oxindole 16 in a very good yield of 70% with excellent stereoselectivity, and only the \( E \) isomer was observed, scheme 22.

In conclusion a diverse range of synthetic strategies to access the biologically relevant 3-acylidene-oxindoles have been developed. In particular, recent developments in transition metal catalysed cyclisation reactions have the potential to afford the desired 3-acylidene-oxindoles efficiently and from easily available starting materials.
Aims

3-Acylidene-oxindoles are an attractive template for the discovery of new medicines, and there are several compounds containing this and related moieties that exhibit useful biological activity. However, an important challenge associated with the characterisation of these compounds is the assignment of alkene stereochemistry around the acylidene moiety. In many cases, this assignment is ambiguous and there are few reports that offer any general guidance as to how stereochemistry can be assigned in a routine way. We therefore set out to address this issue by establishing a routine and consistent method for the assignment of alkene stereochemistry in this class of compounds. Furthermore, we hoped to investigate the divergent synthesis of such compounds, potentially employing catalytic conditions.
1.4 – Proposed Acyliidene Oxindole Synthesis *via* Metal Catalysed Cyclisation

Our interest in the stereochemical assignment of acyliidene oxindoles resulted from two recent reports of bioactive compound analogues. Khosla *et al.* and Woodard *et al.* demonstrated the potential use of compound 1 and 2 as kinase and transglutaminase inhibitors.\(^5,14\) However, they have assigned these compounds as *E* and *Z* isomers respectively, which we believe could be erroneous as one would suspect compound 1 to be exhibit *E* stereochemistry in order to minimise an unfavourable electrostatic interaction between the two carbonyl groups. In addition, we considered that 2 may in fact be *Z*, as to minimise a steric interaction between the 4-chloro substituent and the aryl ketone, despite the unfavourable electrostatic interaction that could arise between the two carbonyl functionalities, figure 8. Consequently, we aimed to synthesise a series of representative 3-acyliidene-oxindoles, and perform investigations into their stereochemical stability and classification.

![Figure 8](image)

Initially we attempted to develop a divergent synthesis of 3-acyliidene oxindoles *via* an intramolecular cyclisation similar to that previously reported by Larock and Babu.\(^32\) In their example, *N*-acyl-2-haloaniline 17 was converted to 3-alkyliidene oxindole 18 via the use of a palladium catalyst. Our intention was to utilise this chemistry but expand the scope in order to access 3-acyliidene oxindoles, i.e. by employing amides such as 19. Moreover, this strategy would avoid the use of toxic carbon monoxide and would require only simple starting materials, scheme 23.
To confirm the validity of the route and provide a proof of concept we initially focussed on repeating and optimising the previously reported cyclisation of amide 17 to oxindole 18. As the aryl bromide was significantly cheaper we began our studies on amide 20, which was prepared from 2-bromo aniline and cinnamoyl chloride in a good yield of 66% utilising the conditions reported by Buchwald et al. scheme 24.

Disappointingly however, when 20 was subjected to the Larock and Babu’s cyclisation conditions no desired product was isolated, and we recovered only starting material instead, scheme 25. From this we concluded that no oxidative addition of the palladium catalyst to the aryl bromide had occurred.

Scheme 23.

Scheme 24.

Scheme 25.
We were intrigued by an analogous Heck cyclisation reported by Grigg and co-workers whereby the isoindolinone 21 was prepared in a moderately good yield of 54% via employment of the catalyst system shown in scheme 26.\(^\text{34}\)

\[\text{N-Cl} \quad \underset{\text{Pd(OAc)}_2 (5 \text{ mol\%}), \text{PPh}_3 (15 \text{ mol\%})}{\text{N}} \quad \underset{\text{NaHCO}_2 (1.1 \text{ equiv.})}{\text{DMF, 120 °C, 24 h}} \quad \text{O} \quad \text{N-Bn} \quad \overset{\text{BunNCl (1.0 equiv.)}}{\text{21}} \]

Scheme 26.

Utilising these conditions on our substrate afforded the desired product 18 as solely the E stereoisomer in a low yield of 13%, scheme 27. The product stereochemistry was assigned in this case through comparison of spectroscopic literature data.\(^\text{26}\) Disappointingly however, our attempts to perform this reaction on a preparatively useful scale resulted in decomposition and no isolation of the target material. Slight variations of the reaction conditions were performed, such as varying the palladium catalyst and solvent, however yields remained low with predominantly starting material observed in most cases.

\[\text{Br} \quad \underset{\text{Pd(OAc)}_2 (5 \text{ mol\%}), \text{PPh}_3 (15 \text{ mol\%})}{\text{N}} \quad \underset{\text{NaHCO}_2 (1.1 \text{ equiv.})}{\text{DMF, 120 °C, 24 h}} \quad \text{Ph} \quad \text{18: 13\%} \]

Scheme 27.

Inspection of the proposed mechanism highlighted that, for the coupling to occur, the intermediate must adopt a conformation that places the aryl group in close proximity to the alkene. However, this presents an unfavourable steric interaction that favours the unreactive rotamer. If this effect was responsible for low conversion rates then attaching a large group such as Boc onto nitrogen should then increase the population of the reactive rotamer, figure 9.
Pleasingly, Boc protection of 20 was achieved in a near quantitative yield using di-tert-butyl dicarbonate and the nucleophilic catalyst dimethylaminopyridine, scheme 28.

With substrate 22 in hand, the cyclisation was attempted using the optimal reaction conditions observed in the cyclisation of 20. Regrettably however, no product was isolated and the reaction simply resulted in decomposition of starting material, scheme 29.
Several analogues of compounds 20 and 22 were prepared but the cyclisation yields were poor in all cases. As such, we decided that this intermolecular cyclisation approach was not a viable route to access the target 3-acylidene-oxindoles and decided to consider alternative synthetic approaches.

1.5 – Proposed Acylidene Oxindole Synthesis via a Late-Stage Intermediate

An alternative and attractive option was to generate an acylidene oxindole that could be derivatised to incorporate a range of new acylidene moieties as the final step. As previously discussed, it is possible to prepare acylidene oxindoles via Wittig reactions or aldol condensation reactions.\textsuperscript{21,13} Therefore, our strategy was to prepare a Weinreb amide such as 23 which would then allow the addition of nucleophiles in order to access a range of different 3-acylidene oxindoles, see scheme 30.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=\textwidth]{scheme30.png}};
  \node (b) at (0,-2) {	extit{Proposed divergent synthesis}};
\end{tikzpicture}
\end{center}

Scheme 30.

The ester 24 was easily prepared from the cheap and readily available reagents isatin and (carbethoxymethylene)triphenylphosphorane, in an excellent yield of 99% using the procedure reported by Shi \textit{et al.}\textsuperscript{21} Ester 24 was isolated as a single isomer which was unambiguously assigned as \textit{E} via X-ray crystallography, figure 10.
Attempting to prepare Weinreb amide 23 from N,O-dimethylhydroxylamine hydrochloride (Weinreb’s amine hydrochloride) and trimethylaluminium was unsuccessful, resulting in a complex mixture which we believe resulted from the uncontrolled addition of the amine at the various different electrophilic sites, scheme 31.

Gratifyingly however, we were able to prepare the desired Weinreb amide in excellent yield and stereoselectivity via the reaction of isatin with a phosphorane that already bears the Weinreb amide, scheme 32. Weinreb amide 23 was isolated as a single isomer which was assumed to be E based on the known stereoselectivity of the previous ester synthesis, figure 10.

With the desired substrate in hand, we next explored the potential for nucleophilic substitution reactions. Phenyl magnesium bromide and methyl magnesium bromide were initially added at -78 °C, however no reaction was observed in either case.
Attempting the reactions at an elevated temperature of -20 °C generated complex mixtures in both cases, table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organometallic</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMgBr</td>
<td>-78 °C</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>PhMgBr</td>
<td>-20 °C</td>
<td>Complex Mixture</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>-78 °C</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>MeMgBr</td>
<td>-20 °C</td>
<td>Complex Mixture</td>
</tr>
</tbody>
</table>

Table 2.

We thought it prudent to also explore nucleophilic addition reactions to protected Weinreb amides. This substrate was again prepared via the Wittig reaction of the phosphorane 25 with the N-Boc isatin. Unfortunately however, attempted reactions with either: PhMgBr, MeMgBr, or MeLi predominantly resulted in decomposition, with complex mixtures observed in the majority of cases.

Once again, we suspect that these reactions suffer from the addition of the nucleophilic reagent at various electrophilic sites on these substrates. We therefore abandoned this strategy and decided to change tack. Nonetheless, these attempted synthetic strategies provided a small series of useful 3-acyldiene-oxindoles that could be employed in stereochemical investigations (see later), scheme 33.

Scheme 33.
1.6 - 3-Acylidene Oxindoles – Preparation and Stereochemical Studies

With limited success in preparing the key acylidene oxindoles using cyclisation and Wittig routes, the focus was changed to preparing substrates via an aldol condensation reaction of isatin with different aryl methyl ketones, scheme 34.

Scheme 34.

This was considered to be the simplest method of generating a series of compounds that could be used to investigate the $E/Z$ isomeric classification and stereochemical stability of acylidene oxindoles. Furthermore, some compounds could have biological interest and as such were to be submitted for external multi assay screening.

We opted to employ the conditions first reported by Braude and Lindwall in order to generate a series of 3-acylidene oxindoles. During our preliminary attempts to condense isatin and a selection of aryl methyl ketones, we were disappointed to find that only compound 28 was produced reliably when Braude and Lindwall’s conditions were used, figure 11. Other substrates generated the corresponding products in lower yields.

Figure 11.

We identified the aldol addition reaction as the problematic step of the process, affording the $\beta$-hydroxy ketones in low yields. In contrast to this, the dehydration step generally worked well. We therefore carried out a brief solvent screen in order to optimise the aldol addition reaction. Gratifyingly, after a brief solvent screen, methanol was found to be very effective, table 3.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol Solvent</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Propanol</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>83</td>
</tr>
</tbody>
</table>

Table 3.

Consequently, the conditions outlined by Braude and Lindwall were modified for our aldol addition step with methanol being employed as the preferred solvent. Utilising these conditions we were able to prepare a small series of $\beta$-hydroxy ketones from isatin and a range of aryl methyl ketones, scheme 35.

![Scheme 35](image)

Incidentally, our attempts to employ these conditions in the preparation of the $p$-OMeC$_6$H$_4$ analogue 32 were found to be ineffective, resulting in less than 10% conversion. However, increasing the loading of the diethylamine catalyst to stoichiometric quantities successfully addressed this issue affording $\beta$-hydroxy ketone 32 in a very good 72% yield, scheme 36. The lower reactivity was attributed to reduced concentrations of reactive enamine because of the lower electrophilicity of 4-methoxyacetophenone.
These β-hydroxy ketones were then subjected to elimination using a slight modification of Braude and Lindwall’s conditions affording 3-acyldiene oxindoles 28, 33 and 34 in good to excellent yields.\textsuperscript{13} The slight modification employed here was to perform these reactions in EtOH, as incomplete solvation was observed in some cases when HCl and AcOH were used. However, substrate 35 bearing the pyridyl group was prepared in a slightly lower yield of 48%. This could have resulted from protonation of the basic pyridine which is then lost as a salt during the aqueous work up. Nonetheless, we were delighted to have optimised a synthetic route to our desired compounds in acceptable yield over two steps. Additionally, it is noted that all the 3-acyldiene oxindoles prepared were isolated as a single stereoisomer (>98:2), as judged by 400 MHz \textsuperscript{1}H NMR spectroscopy, scheme 37.
The reaction of \( p \)-methoxy acetophenone raised another interesting and unexpected observation. During the dehydration process, a small amount, <10\%, of the quinoline 36 was also observed which is formed via a Pfitzinger-type reaction. The structure of this compound was unambiguously determined via X-ray crystallography, figure 12. Consequently, in order to avoid this side reaction, all subsequent dehydrations were carried out over shorter durations and/or with greater amounts of hydrochloric acid.

![Figure 12](image)

This methodology was then extended to \( N \)-substituted analogues, simply by exchanging isatin with its \( N \)-methylated variant. \( N \)-Methyl isatin 37 was prepared in quantitative yield via deprotonation of isatin with sodium hydride followed by alkylation with iodomethane. With \( N \)-Methyl isatin 37 in hand, the aldol condensation sequence was employed to afford \( N \)-substituted 3-acyclidene oxindoles: 38, 39, and 40, scheme 38.

![Scheme 38](image)

Scheme 38.
Having prepared a series of acylidene oxindoles from the parent isatin, we opted to generate a small family of compounds bearing a 4-chlorosubstituent as these related directly to Khosla’s compounds discussed earlier (see figure 6). 3-Acylidenes oxindoles of this type were prepared by subjecting 4-chloroisatin and N-Me-4-chloroisatin to a range of aryl methyl ketones using our modified aldol condensation conditions. The addition step worked efficiently affording the β-hydroxy ketones 38 - 42 in generally high yields of 68% - 100%. Interestingly we found that the dehydration step was much more challenging, and full conversion of starting material was not observed in some cases. However gratifyingly we were able to isolate sufficient amounts of 3-acylidene-oxindoles 2 & 46 - 49 for our subsequent studies, scheme 39.

![Scheme 39](image)

Notably, the required N-Me-4-chloroisatin 50 was prepared in a moderate yields via treatment of 4-chloroisatin with iodomethane and potassium carbonate, scheme 40.

![Scheme 40](image)
With a small family of oxindoles in hand, we assessed the potential of $^1$H NMR spectroscopy to provide the most direct and simple method for alkene stereochemical assignment. We compared CH shift values in the $^1$H NMR spectrum of olefinic protons for the single isomers generated in each case. The NMR shift values follow the trend highlighted by Righetti et al. in that Z-acylidene products show a downfield shift compared to the corresponding E-isomers. However, in the event only a very narrow range was observed for these compounds. And interestingly, N-methyl derivatives 38 - 40, 48 - 49 also display a slight downfield shift relative to their N-H analogues 28, 33 - 35, 2 & 46 - 47. Overall, the relatively narrow shift range observed for these compounds ($\delta$ 7.69 - 8.03), in combination with the potential for N-substitution to affect peak position suggests that the use of $^1$H NMR spectroscopy alone for assignment of configuration could be unreliable. This would be especially problematic if only a single isomer is available as a comparative assessment of chemical shift values could not be made, table 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound$^a$</th>
<th>Alkylidene CH (ppm)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33 (E)</td>
<td>7.72</td>
</tr>
<tr>
<td>2</td>
<td>28 (E)</td>
<td>7.69</td>
</tr>
<tr>
<td>3</td>
<td>34 (E)</td>
<td>7.69</td>
</tr>
<tr>
<td>4</td>
<td>35 (E)</td>
<td>7.72</td>
</tr>
<tr>
<td>5</td>
<td>38 (E)</td>
<td>7.80</td>
</tr>
<tr>
<td>6</td>
<td>39 (E)</td>
<td>7.77</td>
</tr>
<tr>
<td>7</td>
<td>40 (E)</td>
<td>7.77</td>
</tr>
<tr>
<td>10</td>
<td>46 (Z)</td>
<td>7.94</td>
</tr>
<tr>
<td>11</td>
<td>47 (Z)</td>
<td>7.91</td>
</tr>
<tr>
<td>12</td>
<td>2 (Z)</td>
<td>7.92</td>
</tr>
<tr>
<td>13</td>
<td>48 (Z)</td>
<td>8.03</td>
</tr>
<tr>
<td>14</td>
<td>49 (Z)</td>
<td>8.01</td>
</tr>
</tbody>
</table>

$^a$Assumed compound configuration in parenthesis

$^b$NMR data for compounds dissolved in d$_6$-DMSO.

Table 4.
In order to begin the task of confirming the suspected product stereochemistry, we attempted to grow crystals of some representative 3-acylidene-oxindoles. The alkene stereochemistry of the 3-acylidene oxindoles 33, 28 and 40 was unambiguously assigned as E via X-ray crystallography, figure 13. In addition, the aforementioned compounds were found to adopt solid state conformations that minimised the interaction between the acyl-aromatic group with the proton at C-4 of the oxindole ring. With these results in hand the stereochemistry of the other 3-acylidene oxindoles was assumed to be E by comparison.

Figure 13.

In addition the crystal structures of two 4-chloro analogues were derived, and in contrast, and contrary to the reports of Khosla et al., 4-chloro derived acylidene oxindoles 46 and 49 were found to exhibit the Z-configuration, figure 14. The Z
configuration is demonstrated by the olefinic proton and the 4-chloro aromatic substituent which are clearly on the same side of the carbon-carbon double bond. Notably, all other spectroscopic data of 46 and 49 matched that of Khosla’s.

Figure 14.

With the stereochemical assignment of these compounds confirmed via X-ray crystallography, attention was briefly turned to the relative isomeric stabilities. In order to study this, we needed to isomerise the E-compounds to the corresponding Z-products. In this context, Righetti et al. reported the conversion of E-acylidene oxindoles to Z-acylidene oxindoles in the presence of 1.0 equivalent of aluminium trichloride.15 Gratifyingly, when 28 was treated with one equivalent of Lewis acid, followed by a quench with saturated sodium hydrogen carbonate we observed an inseparable mixture of the E and Z-acylidene oxindoles. Attempts to drive this isomerisation to full conversion were unsuccessful and so the mixture was employed directly. Interestingly, isomerisation of the Z-isomer back to the thermodynamically more stable E-isomer was observed under mild conditions (as a room temperature DMSO solution), scheme 41. To the best of our knowledge, this is the first time that this isomerisation has been observed under ambient conditions.
Scheme 41.

The Z-E isomerisation can be monitored over time by $^1$H NMR spectroscopy. The spectra of $E$-$28$ (red) is overlaid with the spectra of the crude reaction mixture (green), thirdly the blue spectra represents the same mixture after 4 days in d$^6$-DMSO, figure 15.

Figure 15.

The emergence of a doublet at $\delta$ 7.93 and a triplet at $\delta$ 7.31 were attributed to the aromatic protons of the $p$-Cl moiety and the indole moiety of the Z isomer respectively. Over time, these peaks are reduced in intensity relative to the peaks for the E isomer i.e. an increase in intensity of the triplet at $\delta$ 7.36 and a reduction of intensity of the triplet at $\delta$ 7.31 shows that a conversion of Z to E is occurring, figure 15. This observation implies that 3-acylidene-oxindoles can undergo facile interconversion under ambient conditions, and isomeric mixtures could in fact exist as a thermodynamic minimum. This would be an important consideration with regards to biological screening.
1.7 – 3- Acylidene Oxindoles: Novel Methodology for Stereochemical Assignment.

Although it had been shown that X-ray crystallographic techniques could be employed to unambiguously assign product stereochemistry, this type of technique can be time consuming and it is not possible to obtain a crystal structure of all compounds. Consequently we postulated whether a simpler and more general method could be devised.

Interestingly, the solid state structures of Z-acylidene oxindoles 46 and 49 deviate significantly from a planar orientation observed for the E substrates 28, 33, 40, and 24. This is demonstrated by the dihedral angle between atoms b and c, see figure 16, for the E compounds this angle is around 180° whereas for Z it is much closer to a right angle at around 90°. These conformations presumably result from dipole-dipole alignment in the case of E-isomers, or allylic strain that arises in the Z-isomer arrangement. In the case of the Z-isomers, dehydration requires that the substrate must adopt a high energy and sterically demanding planar conformation before rearranging into the bent conformation observed in the solid state structure, hence explaining why the yields of these products are generally lower.

![Figure 16.](image)

Figure 16.

Inspection of the solid state X-ray structures of compounds 28, 33, 40, 46, 49, highlight that E- and Z-acylidene oxindoles exhibit different levels of conjugation. This is visibly noticeable in that compounds 28, 33 – 35, 38 - 40 are an intense red or orange colour while compounds 2, 46 - 47 are pale yellow. Consequently we considered the use of UV-Visible spectroscopy as a convenient tool for assigning product stereochemistry. The UV-Visible spectra (over 200 – 700 nm) of these compounds were recorded as stock solutions of anhydrous MeOH (75 µM), figure 17. The spectra of compounds 28, 33 - 35, 38 - 40 (red bands) are very similar to one
another, additionally the spectra of compounds 2, 46 - 47 (green bands) show similar traces to one another as well. However, the major difference between the two data sets is their relative appearance to one another. Compounds 28, 33 - 35, 38 - 40 show three distinct peaks, whereas of 2, 46 - 47 are represented by two distinct peaks and a shoulder, figure 17.

Figure 17. Spectra recorded as 75 μM solutions in MeOH

For the purposes of this study, we were looking to identify significant differences in the respective compound spectra that would be diagnostic. It appears that the traces of 2, 46 - 47 are in fact quite similar to 28, 33 – 35, 38 - 40, showing three distinct absorption bands labelled I, II, III, figure 17. However there is significant variation for the Z-subset in regions II and III which are blue shifted and appear at higher energy (shorter wavelengths) and exhibit a reduction in intensity. Molar absorption coefficients were calculated from the maxima of regions II and III for both isomer sets. With regard to region II, the E compounds 28, 33 – 35, 38 - 40 were all found to exhibit maxima in the range of 334 - 341 nm, and with extinction coefficients in the range of 8890 - 13820 M\(^{-1}\) cm\(^{-1}\). In contrast, Z compounds 2, 46 - 47 all exhibited a shorter-wavelength maximum in the range of 292 - 302 nm, and with a smaller extinction coefficient in the range of 3980 - 6390 M\(^{-1}\) cm\(^{-1}\).
Absorption region III was then considered. The \( E \)-compound set all exhibited maxima in the range of 419 - 436 nm, and with absorption coefficients in the range of 1190 - 2890 M\(^{-1}\) cm\(^{-1}\). Whereas, for \( Z \) compounds the maxima are again blue-shifted and appear between 370 - 390 nm, similarly they have smaller extinction coefficients in the range 760 - 1190 M\(^{-1}\)cm\(^{-1}\). Given that we were able to confirm the absolute alkene stereochemistry for several compounds via X-ray crystallography, we assigned the remaining compounds on the basis of similarities shown in their UV-Vis. spectra.

To demonstrate that the observed shift in UV-Visible spectra was a result of alkene stereochemistry and not the functionality of the oxindole substrate, we decided to prepare isomeric compounds 53 and 54 from commercially available 6-chloroisatin. Both the condensation and elimination steps of the aldol reaction worked very well affording 6-chloro analogues as single isomers in yields of 77 % and 52% over the two steps, scheme 42.

![Scheme 42](image)

The UV-Visible spectra of 6-chloro substrates 53 and 54 were recorded and are shown in figure 18. Both compounds followed the established pattern for \( E \) compounds with region II showing a \( \lambda_{\text{max}} = 336 \) nm, \( \varepsilon = 11500 \) M\(^{-1}\) cm\(^{-1}\) for compound 53, and \( \lambda_{\text{max}} = 338 \) nm, \( \varepsilon = 13660 \) M\(^{-1}\) cm\(^{-1}\) for compound 54. Region III
was also in keeping with the expected trends and the \( E \) isomer showed a \( \lambda_{\text{max}} = 419 \) nm \( 2520 \ \text{M}^{-1} \ \text{cm}^{-1} \), and \( \lambda_{\text{max}} = 422 \) nm, \( \varepsilon = 2890 \ \text{M}^{-1} \ \text{cm}^{-1} \). The calculated molar extinction coefficients for region III were slightly higher than the previous \( E \)-isomers, however the value of \( \lambda_{\text{max}} \) was in accord with other analogues. Moreover, region II absorbance bands were consistent with the data for other \( E \) isomers. Therefore it was concluded that compounds 53 and 54 have the \( E \) configuration, and consequently the observed differences in the UV-Visible spectra of \( E \) and \( Z \) acylidene oxindoles is in fact a consequence of alkene geometry.

![Figure 18](image)

**Figure 18.** Spectra recorded as 75 \( \mu \)M solutions in MeOH

The complete UV-Visible absorption data for compounds 28, 33-35, 38-40, 2, 46 – 49, 53, 54 is shown in table 5. The data implies that as a general rule \( E \)-isomers exhibit absorbances between 330 - 345 nm and 415 - 440 nm with respective extinctions coefficients in the range of 8890 - 13820 \( \text{M}^{-1} \ \text{cm}^{-1} \) and 1200 - 2890 \( \text{M}^{-1} \ \text{cm}^{-1} \). In contrast, \( Z \)-isomers exhibit absorbances between 290 - 305 nm and a shoulder band at around 370 - 390 nm with respective extinction coefficients of 3980 - 6390 \( \text{M}^{-1} \ \text{cm}^{-1} \) and 890 - 1170 \( \text{M}^{-1} \ \text{cm}^{-1} \).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; / nm</th>
<th>ε / M&lt;sup&gt;1&lt;/sup&gt; cm&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; / nm</th>
<th>ε / M&lt;sup&gt;1&lt;/sup&gt; cm&lt;sup&gt;-1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33(E)</td>
<td>334</td>
<td>10200</td>
<td>422</td>
<td>1870</td>
</tr>
<tr>
<td>2</td>
<td>28(E)</td>
<td>337</td>
<td>11000</td>
<td>426</td>
<td>1800</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>341</td>
<td>11520</td>
<td>426</td>
<td>1960</td>
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<td>35</td>
<td>339</td>
<td>9080</td>
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<td>38</td>
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<td>424</td>
<td>1200</td>
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<td>6</td>
<td>39</td>
<td>337</td>
<td>11470</td>
<td>431</td>
<td>1290</td>
</tr>
<tr>
<td>7</td>
<td>40(E)</td>
<td>341</td>
<td>13820</td>
<td>426</td>
<td>1890</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
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<td>54</td>
<td>338</td>
<td>13660</td>
<td>422</td>
<td>2890</td>
</tr>
<tr>
<td>10</td>
<td>46(Z)</td>
<td>294</td>
<td>5720</td>
<td>380</td>
<td>1190</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>298</td>
<td>6390</td>
<td>380</td>
<td>940</td>
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<tr>
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<td>2</td>
<td>302</td>
<td>4080</td>
<td>380</td>
<td>760</td>
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<tr>
<td>13</td>
<td>48</td>
<td>292</td>
<td>5320</td>
<td>380</td>
<td>1080</td>
</tr>
<tr>
<td>14</td>
<td>49(Z)</td>
<td>302</td>
<td>3980</td>
<td>380</td>
<td>910</td>
</tr>
</tbody>
</table>

<sup>a</sup>Compound configuration in parenthesis assigned on the basis of X-ray crystallography.

Table 5.

We envisaged that the potential of UV-Visible spectroscopy to assist stereochemical assignment of acylidene oxindoles could be further demonstrated by performing this technique on an individual set E/Z-isomers of a specific compound. As previously described, AlCl<sub>3</sub> has been established as an effective reagent for the E-Z isomerisation of 3-acylidene-oxindoles.<sup>15</sup> Consequently, we opted to employ this methodology to generate Z-33. Accordingly, a sample of E-33 was subjected to these conditions over the course of three days, affording an inseparable mixture of the E and Z-acylidene oxindoles. Given the rate of isomerisation is relatively slow in this substrate, we were confident that we could isolate and characterise a pure sample of Z-33. Z and E isomers could be separated via preparative reverse phase high performance liquid chromatography (HPLC). Interestingly we recovered a
greater proportion of $E$ isomer after the separation relative to $Z$, implying that isomerisation could be occurring during the separation process, scheme 43.

Scheme 43. After separation the ratio of isolated isomers was $E:Z (3:1)$

The UV-Vis spectrum (75 μM solution in MeOH) of $Z$-33 was recorded and compared with the $E$-isomer, figure 19. The spectra of $Z$-33 is consistent with UV-Visible spectra of previously described Z-acylidene oxindoles, $Z$-33 shows a characteristic blue-shift and reduced absorbance intensity relative its corresponding $E$-isomer, figure 19. Furthermore, the $^1$H NMR spectrum of $Z$-33 shows a resonance at δ 7.70 for the olefinic proton, interestingly the $E$-isomer exhibits a very similar resonance at δ 7.72 ppm. This confirms that the small variations in proton chemical shift values cannot be confidently used to assign product stereochemistry. In contrast, the observed changes in the UV-Visible spectra are pronounced and consistent with the previous examples.

Figure 19. Spectra recorded as 75 μM solutions in MeOH
In an effort to further validate our methodology, 3-acyclidene oxindole 60 was prepared. Moreover, this compound was prepared via a novel isatin synthesis developed within our group, scheme 43. Details of this synthetic methodology are discussed later in this thesis. Compound 60 was isolated as a single isomer in a good yield of 52% from 4-methylisatin via a slightly modified aldol condensation reaction.

![Scheme 43](image)

The UV-Visible spectrum of 60 was recorded as a 75 µM solution in MeOH. It clearly showed two distinctive maxima and a broad shoulder at \( \lambda_{\text{max}} \): 252 nm I, 293 nm II, and 370 - 390 nm III, respectively. The molar absorption coefficients calculated for peaks II and III were 4460 M\(^{-1}\) cm\(^{-1}\) and 900 M\(^{-1}\) cm\(^{-1}\) (at 380 nm) respectively, figure 20. The pattern of peaks and intensities in the spectrum strongly indicated that this alkene has a Z-geometry. Moreover, further support for this assignment was gathered by nOe spectroscopy, see appendix.
In order to better understand the observed spectroscopic differences in the UV-Visible spectra, DFT (density functional theory) methods were used to model the UV-visible spectra of compounds $E/Z$-33. This work was carried out in collaboration with Meijer and Jiang in this department. Gratifyingly, it was clear that the calculated spectra are consistent with the observed experimental trends. Furthermore, inspection of the principle FMO (frontier molecular orbital) contributions to these bands indicated that HOMO-1, HOMO and LUMO were dominant. Electron density maps of these orbitals for $E/Z$-33 are shown in figure 21.  

![Figure 20. Spectra recorded as 75 μM solutions in MeOH](image)

![Figure 21. Calculated UV-Vis spectra of $E/Z$-33 & selected FMO’s of $E/Z$-33](image)
Calculated energies of these specific molecules indicated that the LUMO energies were significantly different whereby the LUMO of \( E-33 \) was 0.81 eV lower than the corresponding \( Z-33 \) LUMO, thus the corresponding band gap in \( E-33 \) is smaller, resulting in the observed red shift. The above electron density maps show that the two LUMO’s are fully extended, whereas the HOMO’s are predominantly localised on the oxindole fragment. Consequently, the LUMO energies are more affected by the significant structural differences between the two isomer sets.\(^{36}\)

In conclusion, we believe that the alkene stereochemistry of 3-acylidene oxindoles can be assigned through UV-Visible spectroscopy based on the following general empirical observations): \( E \)-acylidene oxindoles are expected to have two diagnostic peaks in the region of 330 - 345 nm and 415 - 440 nm, with extinction coefficients of 8890 - 13820 M\(^{-1}\) cm\(^{-1}\) and 1200 - 2890 M\(^{-1}\) cm\(^{-1}\), respectively. In contrast, \( Z \)-acylidene oxindoles have a weaker band in the range of 290 - 305 nm, with a shoulder band around 370 - 390 nm, and possess smaller extinction coefficients between 3980 - 6390 M\(^{-1}\) cm\(^{-1}\) and 890 - 1170 M\(^{-1}\) cm\(^{-1}\).\(^{36}\)

1.8 – 3-Acylidene Oxindoles: Isomeric Stability Studies

Having already demonstrated the ability of \( Z \)-acylidene oxindoles to isomerise back to their more thermodynamically stable arrangement, we decided to investigate this phenomenon further. We considered how the \( Z-E \) isomerisation rate could be affected by varying the conditions. This involved isomerising a sample of \( E \)-acylidene oxindole 28 to give a mixture of \( E:Z \) products (1.0 : 0.42), followed by storing samples of these mixtures under different conditions. Specifically, a sample was stored at 20 °C in the absence of light, and a sample was stored at 20 °C in the presence of light. In addition, a sample was stored at -20 °C in the dark (i.e. stored in the freezer), and a sample subjected to heating at 50 °C in the light. These experiments led to the conclusion that only temperature has an effect on the equilibrium position of \( E/Z \) isomers; significantly less isomerisation was observed at -20 °C. Furthermore, storing the sample in the absence of light had no discernible effect on the isomerisation rate relative to a sample stored in light at the same temperature, figure 22.
An investigation aimed at establishing whether the electronic properties of the acylidene motif could affect the rate at which equilibrium was performed. Compounds 28, 33, 34 and 38 were subjected to 1.0 equivalent of aluminium trichloride and stirred at 20 °C for a time period of 5 days. In the event, the respective E : Z percentage ratios of each compound was as follows: 33: 58% E; 28: 70% E; 34: 43% E, figure 22. The samples were stored, over several days, in DMSO and the relative isomer ratios were measured, from this initial data it could be concluded that electronic properties of the acylidene motif was not having an effect. The only variation being that 28 appeared to reach equilibrium relatively faster than 33 and 34, however, this variation was not significant enough. Finally, an interesting observation was made in relation to the N-substituted example 38; the compound was found to undergo isomerisation much slower than any of the examples bearing a free N-H. Only a very minor variation in E : Z ratios was observed, for this time scale, implying that the N-substituted analogue may in fact be kinetically stabilised, figure 23.

![Figure 22. Isomer ratios determined by 400 MHz $^1$H NMR spectroscopy](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>E : Z Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>&gt;98 : &lt;2</td>
</tr>
<tr>
<td>33</td>
<td>1 : 0.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>E : Z Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>58% E</td>
</tr>
<tr>
<td>28</td>
<td>70% E</td>
</tr>
<tr>
<td>34</td>
<td>43% E</td>
</tr>
</tbody>
</table>
Figure 23. Isomer ratios determined by 400 MHz $^1$H NMR spectroscopy

Additionally, the isomerisation was also performed on ester 24 resulting in an $E : Z$ ratio of (1.00 : 0.35). After storing in deuterated chloroform for three days, full conversion to the $E$ isomer was observed, scheme 44.

Scheme 44.

Furthermore Weinreb amide 23 was subjected to aluminium trichloride affording the isomeric ratio $E : Z$ (0.20 : 1.00). Indeed, the expected isomerisation of $Z$ to $E$ was again observed, when 23 was stored as a room temperature solution of CDCl$_3$, scheme 45.
Overall the isomerisation of ketone, amide and ester based acylidene oxindoles has been observed during this study, thus highlighting that such compounds are configurationally labile, and that they most likely exist as thermodynamic mixture. Interestingly, it was noted that $N$-substitution can dramatically reduce the rate of isomerisation under ambient conditions.

1.9 – Novel Isatin synthesis: Elaboration to 3-Acylidene Oxindole

With a synthetic methodology for preparing 3-acylidene oxindoles in hand we next turned our attention to developing a broader substrate scope. We were particularly keen to explore diversification at the oxindole motif, modifications to this region can be provided by utilising different isatins in the aldol condensation sequence. As there is a limit to the availability functionalised isatins available we sought to develop a novel isatin synthesis in the hope of applying this to prepare a range of different isatins. These functionalised isatins could then be used to prepare a more diverse array of acylidene oxindoles.

Within the literature, there are many isatin syntheses reported such as the Sandmeyer and Stolle syntheses, and more recently an example where indole is oxidised to isatin which was reported by Yadav, scheme 46. 37,38,39

Scheme 45.

Scheme 46.
However, there are very few examples of metal catalysed isatin syntheses and as such, we envisaged that this could be an interesting and practically relevant avenue of research. One such example reported by Söderberg and co-workers involves the palladium catalysed cyclisation of 1-iodoethynyl-2-nitrobenzenes. The authors demonstrated that this approach delivered 8 examples of isatins in yields of 47% - 70%, scheme 47.

Scheme 47.

In order to assess the effectiveness of this method for generating isatins, we decided to prepare 1-iodoethynyl-2-nitrobenzene 62 from 1-iodo-2-nitrobenzene. A Sonogashira cross coupling of trimethylsilylacetylene and 1-iodo-2-nitrobenzene afforded 61 excellent yield of 96%. Compound 61 was then readily iodinated affording 62 in a very good yield of 81% using N-iodosuccinimide and catalytic amounts of silver nitrate. Furthermore, the terminal alkyne 63 was also prepared in a moderate yield of 32% via the trimethylsilyl deprotection of 61 under basic methanolic conditions, scheme 48.

Scheme 48.

Unfortunately however, in our hands Söderberg's conditions proved to be unreliable providing the expected isatin 64 in a reduced yield of 46%. A solvent screen highlighted THF as a potential alternative as the desired product was isolated in a 55% yield under these conditions, scheme 49.
We aimed to try to improve upon Söderberg’s conditions through a series of empirical experiments; for example, Söderberg’s conditions were applied to the trimethylsilyl bearing alkyne 61 which resulted in no reaction, returning starting material only. In addition, when these conditions were applied to the terminal alkyne 63, decomposition of starting material was observed with the alkyne appearing to be reduced, table 6.

During our solvent screening studies, we observed compounds assigned as 65 and 66 in the crude mixture of reactions conducted in acetone ($^1$H NMR spectroscopy), figure 24. This implied the formation of acid during the cyclisation process that was subsequently promoting the aldol condensation of the acetone solvent. In addition, when the reaction was performed in THF we observed a broad peak at $\delta$ 1.8 ppm which was attributed to the ring opening polymerisation of the solvent, again presumed to be facilitated by the production of hydroiodic acid.
These observations prompted us to monitor the pH of the reaction. Initial pH at the reaction start point was a neutral pH 7. However, after several hours the pH had dropped sharply to pH ~2, scheme 50.

We considered that the formation of acid may have an adverse effect on product formation and as such we opted to repeat the reaction but in the presence of base. 2,6-Lutidine was chosen as the base as we thought it would be less likely to poison the catalyst. Unfortunately, performing the reaction in the presence of base didn’t result in any improvement of yield giving the desired compound in a comparable yield to base free conditions. Additionally, the crude reaction mixtures were still contaminated with solvent based side products, scheme 51.

Attempting to synthesise isatin directly via the metal catalysed cyclisation of 1-iodoethynyl-2-nitrobenzenes was proceeding with limited success, and as such we decided to employ a change of tactic. It was envisaged that we could potentially access the proposed intermediate 2-iodoisatogen compounds and then separately reduce and hydrolyse this to the isatin, scheme 52. The general idea of this
approach was that it would hopefully allow us to bypass some decomposition pathways, thereby generating isatins cleanly over two steps.

![Scheme 52](image)

Söderberg and co-workers provided evidence for the reaction proceeding via the proposed isatogen intermediate. Performing the cyclisation with bromo-alkynes in place of the corresponding iodides, the authors isolated 2-bromoisatogens in two separate examples. In addition, when attempting to perform the iodination of the 5-methoxy arylacetylene substrate they noted the formation varying amounts of 2-iodoisatogens, scheme 53. Furthermore, it has been reported that structurally analogous o-nitro diarylacetylenes will undergo cycloisomerisation to isatogens under the influence of transition metal catalysts.

![Scheme 53](image)

We envisaged that moving from palladium to a less electrophilic Lewis acid, such as copper, could offer access to the intermediate isatogen, and in turn prevent any decomposition as a result of the generation of HI. Initially we attempted the transformation in the presence of copper iodide, as this had shown some success
when employed in Söderberg’s conditions. However, in the event no product formation was observed with only starting material being recovered. Pleasingly when switching to a more soluble source of copper, CuBr.DMS, we observed predominantly isatogen formation, with 25 mol% of CuBr.DMS being the optimal loading level. Notably, these conditions did not preclude the formation of isatin. Evidently, it appears that CuBr.DMS will effect this transformation, complete conversion of iodoalkyne to isatin was observed with stoichiometric quantities of CuBr.DMS. Moreover, subjection of isolated isatogen 70 to additional CuBr.DMS resulted in conversion to isatin, table 7.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (loading / mol%)</th>
<th>Solvent</th>
<th>Isolated Yield / %</th>
<th>2-Iodoisatogen (70)</th>
<th>Isatin (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₂Cl₂ (5%)</td>
<td>Acetone</td>
<td>0</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₂Cl₂ (5%)</td>
<td>THF</td>
<td>0</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CuI (10%)</td>
<td>Acetone</td>
<td>0</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CuCl₂ (10%)</td>
<td>Acetone</td>
<td>0</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CuI (10%)</td>
<td>THF</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CuBr.DMS (10%)</td>
<td>THF</td>
<td>66</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><strong>CuBr.DMS (25%)</strong></td>
<td>THF</td>
<td><strong>89</strong></td>
<td><strong>8</strong></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CuBr.DMS (50%)</td>
<td>THF</td>
<td>73</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CuBr.DMS (100%)</td>
<td>THF</td>
<td>0</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.

As this was only the second reported example of a 2-iodoisatogen,⁴⁰ we sought to provide confirmation of its proposed structure. Confirmation that the compound was in fact the desired iodoisatogen 70 was evident from the solid state crystal structure, figure 25. The structure was not straightforward to solve due to the symmetrical nature of the molecule and there is some ambiguity with regards to the carbonyl and the N-oxide functionality. However, the crystal structure clearly shows the correct number of atoms and bonds and, key to our structural
assignment, the carbon-iodine bond, figure 25. Exploration of the scope of the iodoisatogen chemistry has been performed within the Harrity group and is reported elsewhere.42,43

![Figure 25](image)

With conditions for the preparation of the iodoisatogen in hand, we next turned our attention to reducing the N-oxide bond for the synthesis of novel isatins. Intriguingly, when assessing isatogen stability by monitoring its $^1$H NMR spectrum (d$_6$-DMSO), we observed complete and rapid conversion to two separate compounds in a 1.0 : 0.3 ratio after 12 hours.

The minor compound was identified as isatin whereas the major compound was determined to be the N-hydroxy isatin 71, upon isolation via fractional recrystallization. The N-hydroxy isatin was found to be a stable red solid, with only limited literature precedent. Moreover, this procedure was applicable on a preparative scale utilising reagent grade DMSO. In the event, the transformation proceeded efficiently affording a 3 : 1 mixture of N-hydroxy isatin 71 : isatin 64 in an excellent reproducible yield of 80%, scheme 54. Separation of the mixture proved to be challenging, although a small amount of analytically pure N-hydroxy isatin was afforded via fraction crystallisation.

![Scheme 54](image)

We considered alternative methods for the reduction of the nitrogen-oxygen bond. Indeed, subjecting an isatin : N-hydroxy isatin mixture to triphenylphosphine and heating at 135 °C in DMF led to formation of isatin in a very good yield, scheme 55.
Moreover, a one-pot procedure was achieved by heating isatogen 70 and triphenylphosphine in dimethylsulphoxide overnight at 135 °C, affording the desired isatin 60 in a very good yield of 70%, scheme 55.

![Scheme 55](image)

Having developed a novel synthetic route to isatins, we sought to apply this chemistry in connection with the previously discussed 3-acylidene oxindole isomer study. Consequently, we considered the preparation of the novel 4-methyl 3-acylidene oxindole from 4-methyl isatin 57, scheme 56.

![Scheme 56](image)

The relevant ethynyl iodide 56 was prepared in an excellent 84% yield via the Sonogashira cross coupling reaction of 2-iodo-3-nitrotoluene and trimethylsilyl acetylene. Iodination was achieved with stoichiometric amounts of silver nitrate and N-iodosuccinimide affording the iodoacetylene 56 in an 88% yield, scheme 57.

![Scheme 57](image)
Cycloisomerisation of iodoalkyne 56 proceeded slowly and required stoichiometric amounts of CuBr.DMS, and 24 hours to observe complete conversion. In addition, the cyclisation step afforded a 1 : 1 mixture of isatogen 58 and 4-methyl isatin 57 in practically useful quantities and a very good overall yield of 81%. Subsequent conversion of 4-methyl iodoisatogen 58 to 4-methyl isatin 57 was achieved with DMSO and triphenylphosphine mediated reduction / hydrolysis, scheme 58.

Scheme 58.

The desired novel 3-acylideneoxindole 60 was afforded via the aldol condensation of acetophenone and 4-methylisatin in a good overall yield of 52%. Moreover, it was isolated solely as the Z isomer, determined via UV-Visible spectroscopy and nOe spectroscopy (see figure 20, page 45), scheme 59.

Scheme 59.

In conclusion, we have developed a reliable catalytic system for the preparation of novel and interesting iodosatogens. It turn, the preparation of such compounds can be beneficial for the synthesis of novel acylidene oxindoles. Further studies will seek to discover new synthetic applications of iodoisatogen compounds.
2.1 – Chemistry of Isatogens

Isatogens are a class of stable 1,3-dipolar compounds, which are typically quite brightly coloured and to-date there is no report of their natural occurrence. The very first reported isatogen preparation was by Adolf Baeyer as early as the late 19th century. The compound was functionalised with a 2-carboxylic acid ethyl ester group, and generated from the corresponding o-propiolate nitrobenzene and concentrated cold sulphuric acid, scheme 60. Isatogens have been reported to possess some useful biological activities, additionally their synthetic applications have involved nucleophilic addition as well as dipolar cycloadditions. Furthermore, they have been described to be effective spin traps for radical intermediates. Unambiguous isatogen structural confirmation, via spectroscopic and crystallographic techniques, was provided by Hooper.

\[
\text{Original isatogen discovery}
\]

\[
\begin{align*}
\text{OEt} & \quad \text{H}_2\text{SO}_4 \\
\text{NO}_2 & \quad \text{OEt}
\end{align*}
\]

Scheme 60.

2.2 – Isatogen Syntheses: Classical Methodologies

The traditional methodology for isatogen synthesis is analogous to Adolf Baeyer’s initial route, the cycloisomerisations of o-nitro diarylacetylenes, under the influence of various promotors, scheme 61. Herein follows a brief description of some general methods for this transformation.

\[
\begin{align*}
\text{NO}_2 & \quad \text{Promoter} \\
\text{N} & \quad \text{O}
\end{align*}
\]

Scheme 61.
After Baeyer’s initial report, another classical and widely employed method was described independently by Pfeiffer and Kröhnke, wherein light promoted cycloisomerisation of o-nitro diarylacetylenes in the presence of pyridine at elevated temperature provided 2-arylisatogens, scheme 62. This methodology was widely employed in the early 20th century by various researchers, however only simple isatogens with limited functionalities were accessible by this technique. This was in part due to the limited availability of the corresponding pre-cyclised o-nitro diarylacetylenes.

Scheme 62.

A mechanism for this transformation was described by Rolf Huisgen. Initially, a pyridinium betaine 73 is generated via the photochemical reaction of tolane 72 with pyridine. Cyclic intermediate 74 is then generated by carbanion-nitro cyclisation, which can then re-open to provide the nitroso compound 75. The final step provides the isatogen via pseudo enolate addition to the nitroso group followed by eliminate of pyridine, scheme 63. Kröhnke et. al. have shown that treatment of betaine 73, HBr salt, with sodium carbonate would effect isatogen formation, thus implying that only the initial betaine formation requires photochemical promotion, scheme 63 inset.

Scheme 63.
However, with the development of Castro-Stephens coupling and more recently Sonogashira coupling, access to this type of o-nitro diarylacetylenes has become relatively trivial.\textsuperscript{54,55} Consequently, the first major report of diverse isatogen synthesis came from Malcolm Hooper and co-workers during the late 1960’s. They reported the preparation of 18 bespoke isatogens in generally very good yields, up to 93\%, via photo-induced catalytic pyridine promoted cycloisomerisations. A significant scope with regard to functionality was achievable both on the 3-oxindole core and pendant aryl ring, scheme 64.\textsuperscript{56,57} Hooper and co-workers also reported the nitrosobenzene promoted preparation of a small selection of 2-substituted isatogens from the cycloisomerisation of o-(alkynyl)nitrobenzenes.\textsuperscript{58}

\[
\begin{array}{c}
\text{R}^1; \text{R}^2 = \text{H}; \text{NO}_2; \text{OMe} \\
\text{Ar = Electron rich, Electron poor, Electron Neutral, and Heteroaromatic}
\end{array}
\]

Scheme 64.

An isolated example of isatogen formation was reported by Abramovitch and Cue Jr. They documented the formation of 2-cyanoisatogen 77 in a moderate 48\% yield by subjection of the corresponding o-(alkynyl)nitrobenzene 76 to ultraviolet light, scheme 65.\textsuperscript{59}

\[
\begin{array}{c}
\text{76} \\
\text{77: 48\%}
\end{array}
\]

Scheme 65.

Tour and co-workers reported a novel isatogen synthesis method, wherein a sub-stoichiometric amount tetrabutylammonium fluoride (TBAF) was used to promote the cycloisomerisation of 78 in a very good 73\% yield. This represented the first time that TBAF had been used to induce this cycloisomerisation, however, isatogen 79 was only prepared as a single isolated example. Furthermore, the generality of this technique was potentially limited, as the analogous isatogen 80 was not
accessible through this technique, and consequently was prepared via the classical pyridine promoted conditions, scheme 66. Tour’s interest in isatogens was for the application of molecular electronic devices, specifically with regards to isatogen’s potential ability to stabilise radicals. In this context, they recorded the cyclic voltammogram of isatogen 79 and identified two reductions, the first being rapidly reversible at $-0.62$ V and the latter irreversible at $-1.39$ V. The polarographic reduction of isatogens had previously been reported by Hooper and Bunney.\(^{61}\)

![Scheme 66.](image)

Within the last couple of decades, advances in isatogen formation have resulted from the employment of milder transition metal promoter systems. The first example of such was reported by Yamamoto in 2003 when employing a gold(III) catalyst. Subjection of o-(alkynyl)nitrobenzenes to AuBr$_3$ (3 mol%) in toluene afforded six isatogens in very good yields (78% - 86%, as estimated by $^1$H NMR spectroscopy), including a single alkyl example in 2-cyclohexylisatogen. Furthermore, this procedure was more practical relative to classical methods due to the use of toluene at ambient temperature as opposed to previously employed pyridine/heat. Interestingly, isomeric anthranils 81 were also observed as minor by-products, scheme 67. The relative amount of anthranils was found to vary depending on the solvent or temperature employed.\(^{41}\)
Consistent with Yamamoto’s observation, Crabtree reported the formation of anthranil in a very good yield via the cycloisomerisation of 1-nitro-2-(pent-1-yn-1-yl)benzene. Iridium complex was used to promote this cyclisation, and in the event no isatogen was observed, scheme 68.\(^{47}\)

Very recently Ramana et al. improved upon Yamamoto’s original concept, demonstrating the palladium(II) promoted highly selective isatogen forming cycloisomerisation of o-(alkynyl)nitrobenzenes. The transformation occurred efficiently under mild conditions, and with low loadings of \([\text{Pd(MeCN)}_2\text{Cl}_2]\) (5 mol%) allowing for the preparation of twenty isatogens in generally very good to excellent yields. Moreover, the reaction exhibited a remarkable functional group tolerance, representing the first general procedure to access 2-alkyl isatogens, scheme 69.\(^{62}\)

In connection with the above discovery, detailed DFT studies were performed and a plausible mechanism proposed. The initial step involves alkyne palladium complexation which promotes a 5-exo-dig cyclisation generating intermediate II. A rearrangement of II occurs and affords carbene III, the calculations indicate nitroso coordination through the nitrogen atom. Species III is then converted to IV which, after the loss of the palladium(II) species, generates the desired isatogen, scheme 70.
Scheme 69.

Selected examples

![Selected examples images]

71%  75%  87%

91%  55%  87%

Scheme 70.
Additionally, Ramana considered the anthranil formation reported by Yamamoto and Crabtree and postulated a reason for its absence under their conditions. The anthranil forming transformation is thought to initiate via a 6-endo-dig cyclisation, which after an oxygen transfer rearrangement provides carbene 84. Subsequently, a Cope type rearrangement occurs generating the vinyl iridium species, the process then terminates with a reductive elimination affording the observed anthranil, scheme 71. Calculations by Ramana indicate that for their system 6-endo-dig cyclisation is significantly disfavoured, with the relevant transition states (6-endo-dig versus 5-exo-dig) differing by 18.8 kcal mol\(^{-1}\) in energy. Therefore, it could be implied that isatogen or anthranil formation may be controlled through judicious choice of reaction conditions.

Scheme 71.
2.3 – Isatogen Syntheses: Alternative methodologies

Isatogen formation is not only limited to just alkyne-nitro cycloisomerisation, scheme 72 route I. There are in fact several other reported techniques. Herein follows a brief overview of some the other alternative methodologies, which are summarised in scheme 72.

Scheme 72.

Splitter and Calvin reported the appearance of isatogens from the cycloisomerisation of ortho-nitro stilbenes, whilst performing photochemical reactions of these compounds, scheme 72, route II.\(^{63}\) In the 1970’s a similar methodology was reported by Hayward and Leznoff that involved a photo-catalysed cycloisomerisation. However, in this case only a small number of isatogens were synthesised and in poor yields, scheme 72, route II.\(^ {64}\)

Other alternative cyclisation routes were reported by Bhamare and Nepveu, scheme 72 routes III and IV.\(^ {65,66}\) Nepveu’s methodology involved the \textit{in situ} reduction of the nitro functionality to a hydroxylamine, which upon condensation to
the diketone afforded the desired isatogens, scheme 72 route IV. Four isatogens were prepared via this methodology, in yields up to 91%, scheme 73.\(^66\)

![Scheme 73](image)

Different synthetic strategies that avoid cyclisation as the key isatogen forming step, and instead involves the direct oxidation of indole derivatives have also been reported, scheme 72 route V. Hooper and co-workers demonstrated the m-CPBA (meta-chloroperoxybenzoic acid) promoted oxidation of N-hydroxy indoles to isatogens, with yields up to 60%. The method was reported to be general and also included the first example of alkyl isatogens formation.\(^67,68\) Similarly, a technique whereby (N-H)indoles were oxidised was first discovered by Sakamoto, generating 2-phenylisatogen in a good 58% yield from 2-phenylindole in the presence of MoO\(_5\).HMPA as the oxidant.\(^69\) More recently this technique was further developed by Bergman and Slätt, whereby a small series of isatogens were generated in moderate to good yields, 30% - 59%, from a two-step procedure. Initially indoles were reduced to dihydro-indoles using tin and acid, oxidation to isatogens was then readily achieved using m-CPBA, scheme 72 route VI.\(^70\)

### 2.4 – Isatogen Biological Importance

There have been a number of reports of isatogen biological activity. Various 2-substituted isatogens were reported by Wibberley, Patterson, and Hooper to show moderate antibacterial properties.\(^71,72\) Another example of bioactivity was again demonstrated by Hooper and co-workers wherein they reported the ability of 2-phenylisatogen to affect energy transfer systems in rat liver mitochondria figure 26. Specifically in this context 2-phenyl isatogen’s potency was likened to known energy
transfer inhibitors. In a later publication the authors identified that 2-phenylisatogen was actually inhibiting the mitochondrial transhydrogenase enzyme. Interestingly however, in their assays they discovered that 2-phenylisatogen’s potency was reduced due to its inability to reach its site of action.

![2-Phenylisatogen](image)

Figure 26.

The parasite associated with malaria, *P. falciparum*, is becoming increasingly resistant to conventional treatments such as chloroquine. As a consequence there is an urgent requirement to discover alternative treatments, which operate via a different mode of action. Nepveu and co-workers postulated that isatogens could potentially show antiplasmodial activity and offer novel anti-malarial compounds, their reasoning deriving from the observed electrochemical reducibility of isatogens. The activity of known antimalarial compound artemisinin is believed to be derived from the reducibility of the endoperoxide functionality, figure 27. Nepveu et al. proposed that the reducible motif on isatogens could offer a complimentary mode of action, in addition *N*-oxide derivatives have been reported to demonstrate antimalarial activity, figure 27.

![Artemisinin](image)

![3-phenylquinoxaline 1,4-di-N-oxide](image)

Figure 27.

In this context, Nepveu et al. screened sixty six isatogens against a chloroquine resistant strain of *P. falciparum* (FcB1 Strain). The authors reported some desirable biological activity and were able to derive some positive structure activity relationship (SAR) data. It was observed that the indolone moiety had to contain a
phenyl group as replacing this with either the pyridine or pyridine N-oxide resulted in a significant loss of activity. Additionally, it was noted that alkyl substituents in the 2’ position lead to a decrease in activity, and in contrast, aromatic groups bearing a mesomeric functionality improved activity. Ultimately, from their assays they identified two potential lead compounds with very high antiplasmodial activity. Moreover, the compounds demonstrated very satisfactory selectivity with low cytotoxicity against a human tumor cell line (MCF7), figure 28.

![Antiplasmodial activity against Plasmodium falciparum (FcB1 strain)](image)

Figure 28.

2.5 – Reactivity of Isatogens

Previous reports of isatogen derivatisations have been dominated by two modes of reactivity.

- Nucleophilic addition to either the carbon of the nitroxide or at the carbonyl function.
- Dipolar cycloadditions.

An early report of nucleophilic addition to isatogens came from the groups of Hooper and Robertson. The nucleophilic addition of amino acids at the C-2 position of 2-phenylisatogen was demonstrated. Around the same time, Colonna and co-workers reported that organometallics could be added to 2-phenylisatogen. In their report they stated that organolithium and Grignard reagents would add indiscriminately to either the carbonyl functionality or at the nitroxide carbon, generating a mixture of products. The authors showed that selective addition to the N-oxide carbon, generating hydroxylamine, could be achieved by protection of the carbonyl as imine, scheme 74.
Several contemporary examples of nucleophilic addition to isatogens have been demonstrated by Ramana and co-workers. An indium(III) mediated carbon-carbon bond forming reaction between isatogens and indole was reported. This process allowed the selective syntheses of indolin-3-one or N-hydroxyindolin-3-one, simply by modifying the reaction conditions. Moreover the authors employed this chemistry for the total synthesis of the natural product 13-deoxy-isatisine A in ten steps from commercial starting materials, scheme 75.²²

Scheme 74.

Scheme 75.
More recently Ramana and co-workers expanded the scope of their method to include 3-substituted indoles. Interestingly InCl₃ failed to promote any useful reactivity. Gratifyingly however, when switching to a Au(I) and Ag(I) system the reaction proceeded efficiently. The authors applied this methodology to the total synthesis of (±)-trigonoliimine C, in 4 steps from simple commercially available starting materials, scheme 76.⁸³

*Scheme 76.*

The first example of an isatogen dipolar cycloaddition was presented by Hooper and Bunney. The authors subjected various 2-substituted isatogens to ethyl cyanoacetate, and noted that reactivity occurred in cold ethanol and with catalytic pyridine, scheme 77.⁵⁶

*Scheme 77.*

Ramana and co-workers have very recently developed two different [3+2] cycloaddition reactions of isatogens with alkenes. Their first example demonstrated that 2-substituted isatogens bearing a suitably positioned alkene function would undergo spontaneous [3+2] cycloadditions, affording *spiro*-pseudoindoxyl
compounds. However, for this process to occur new substrate specific conditions had to be identified, in order to increase the efficiency of the isatogen forming cycloisomerisation. Moreover, isomeric homologues were accessible, however the authors were surprised to observe a complete reversal of exo / endo selectivity when switching from N-allyl to N-but-3-enyl moieties, scheme 78. Interestingly, exchange of the N-Boc function to a methylene resulted in no isatogen formation, with isomeric anthranils formed instead.  

Scheme 78.

The second recent example from Ramana et al. featured the [3+2] dipolar cycloaddition of isatogens with external alkenes, via a ruthenium promoter system. The reaction initially generates a tetrahydroisoxazole intermediate, which upon cleavage of the N-O bond affords β-aminoketone indoxyls. The protocol is general and tolerates functionality on the oxindole fragment as well as various alkyl or aryl groups at C-2. The scope with regard to the alkene is very good with the reaction performing efficiently with various functionalised alkenes: simple alkyls, enol ethers, and styrenes, scheme 79.  

---

```
AuCl(PPh3) (10 mol%)  
AgSbF6 (20 mol%)  
CH2Cl2, 0 °C  
```

13 examples; 13% - 79%
Finally in this context, Lu et al. very recently developed a complimentary procedure to the above methodology, whereby they described a formal [3+3] cycloaddition of isatogens and enals, affording the polycyclic heterocycles. This was achieved through the use of an N-heterocyclic carbene catalysed umpolung reaction of enals providing homoenolates as the reactive species. Furthermore, the reaction was tolerant of various functionalities and in most cases resulted in predominantly the syn-isomer, scheme 80.

Scheme 79.

Scheme 80.
2.6 – Reactivity of Novel 2-Iodoisatogens

Within this thesis the discovery of 2-iodoisatogens was reported, and their potential as synthetic intermediates was postulated. In this context, two different examples of derivatisation, in addition to isatin formation, have been demonstrated within the Harrity research group. Initially a novel enolate displacement strategy followed by carboxylation allowed accesses to a series of 2-acylidene oxindoles. This class of molecule had previously been difficult to access, and in addition are also structurally isomeric to 3-acylidene oxindoles previously discussed herein, scheme 81.43

![Scheme 81.](image)

The second piece of methodology presented was the ability of iodoisatogens to undergo cross coupling reactions via a palladium catalysed Sonogashira reaction, whereby a series of isatogens, bearing a synthetically attractive alkyne functionality, were prepared, scheme 82. Specifically in this case it was pleasantly surprising to observe successful reactivity, as it had previously been shown that 2-iodoisatogens were unstable in the presence of palladium resulting in either decomposition or conversion to isatins.43

![Scheme 82.](image)
Aims

Having a general methodology for the preparation of 2-iodoisatogen discovered we sought to investigate the potential application of this interesting class of compounds. In particular, we hoped to perform cross coupling reactions and thus develop a divergent synthesis of bespoke isatogens, a biologically and synthetically interesting class of compound.
2.7 – 2-Aryl Isatogens: Cycloisomerisation Condition Screening

Before attempting functionalisation of the carbon iodide bond, an investigation into the practicality of the copper promoted iodoisatogen forming cycloisomerisation was undertaken. The possibility of employing the optimised copper promoted reaction to 1-alkynyl-2-nitrobenzenes bearing pre-functionalised internal alkynes was considered. This class of cycloisomerisation is known, however, these processes rely on expensive gold / palladium promoters.\textsuperscript{41,62} Thus, it was hypothesised that copper salts could function as a more economical Lewis acid for the formation of other isatogens, scheme 83.\textsuperscript{42,43}

\begin{center}
\textit{Developed within Harrity Group}
\end{center}

\begin{center}
\textit{Proposed Chemistry}
\end{center}

Consequently, 1-alkynyl-2-nitrobenzene 88, prepared via the Sonogashira cross coupling of phenylacetylene and the corresponding aryl iodide, was subjected to a series of reaction conditions whereby the loading of the CuBr.DMS metal promoter was varied. Pleasingly, full conversion of phenylacetylene 88 was observed after 8 hours and afforded the cycloisomerised 5-methoxy-2-phenylisatogen 89 in an excellent 79% yield, table 8.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time / h</th>
<th>Conversion / %</th>
<th>Isolated Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>67</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>100</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 8.

Comparison of this result with the equivalent palladium promoted sequence highlighted that the palladium reaction proceeds quicker, reaching full conversion after only 1 hour in the presence of 10 mol% Pd(MeCN)$_2$Cl$_2$ and giving a 61% yield of the corresponding product.\(^{62}\) Furthermore, and with respect to substrate reactivity, the 2-iodoisatogen forming reaction proceeded much faster than the 2-phenyl analogue and was complete after only 30 minutes, scheme 84. It can be inferred from these observations that the cyclisation of iodoacetylenes is inherently more rapid than the corresponding arylacetylenes, and thus can be promoted via a less reactive Lewis acid. Moreover, a beneficial consequence of this is that the relatively mild reaction conditions also minimise decomposition of the sensitive iodoisatogen products that was evident under Söderberg’s palladium promoted conditions.\(^{40}\)

Scheme 84.\(^{62,43}\)
Cycloisomerisation to provide 5-methoxyiodoisatogen 69 was observed to be the fastest of all the iodoalkyne cyclisations studied.\(^{43}\) As such, we wanted to extend the cycloisomerisation study to a more generic, electron neutral substrate. Accordingly, 1-ethynyl-2-nitrobenzene 90 was subjected to a series of reaction conditions whereby the nature of the transition metal promoter, loading and reaction time were varied, table 9. Notably, during the preparation of the substrate 1-ethynyl-2-nitrobenzene 90, via the Pd(PPh\(_3\))\(_2\)Cl\(_2\) (10 mol%) catalysed Sonogashira cross coupling reaction, a significant amount of 2-phenylisatogen 85 was isolated, 36%, in combination with the intended alkyne product, 49%. This result confirmed the propensity of these compounds to undergo Lewis acid promoted cycloisomerisation, scheme 85.

![Scheme 85](image)

Scheme 85.

With regard to the transformation of 90 to 85, we initially screened two copper sources, CuBr.DMS and [Cu(MeCN)\(_4\)][BF\(_4\)]. Stoichiometric CuBr.DMS failed to effect cycloisomerisation, while stoichiometric [Cu(MeCN)\(_4\)][BF\(_4\)] provided only low conversion through to 2-phenylisatogen 85, entry 3. Interestingly, incomplete conversion was observed when Pd(PPh\(_3\))\(_2\)Cl\(_2\) was used, even at high loadings, entries 5 and 6. Gratifyingly however, when employing a more electrophilic source of palladium, Pd(MeCN)\(_2\)Cl\(_2\), complete conversion was achieved after only 6 hours, with the desired material isolated in a very good yield of 74%. The low reactivity observed in the case of 1-ethynyl-2-nitrobenzene 90 in the presence of a copper promoter reaffirmed the observation that these cyclisation reactions are much slower than the analogous alkynyliodide compounds, table 9.
In conclusion, it is apparent that copper salts are not efficient at promoting cycloisomerisation of 2-arylacetylene nitrobenzenes towards 2-arylisatogens. However, it is evident from their successful participation in the cycloisomerisation to the corresponding 2-iodoisatogens that these milder promoters can exploit the increased reactivity of 2-idoacetylene nitrobenzenes. Moreover, we believe that the reduced reactivity of these copper salts minimises potential decomposition pathways, thus allowing access to novel and relatively unstable 2-iodoisatogen products.

Table 9.
2.8 – 2-Iodo Isatogens: Aryl Cross Coupling Condition Screening and Scope

Research within the group had demonstrated that 2-iodoisatogens could undergo palladium catalysed sp–sp$^2$ coupling.\textsuperscript{43} In order to complement this methodology, efforts were directed to investigating the possibility of performing sp$^2$-sp$^2$ cross-couplings. Such a synthetic strategy would be of particular interest as the resulting 2-aryl isatogens have been reported to possess interesting biological activity. For example, the \textit{p}-dimethylaniline derived 2-aryl isatogen has been reported to demonstrate potent anti-malarial activity, figure 29.\textsuperscript{75}

\textit{Anti-Malarial}

\begin{center}
\begin{tikzpicture}
\node[anchor=west] (label) at (0,2) {Active against resistant strains of \textit{Plasmodium falciparum} (IC$\textsubscript{50}$ ~ 3 nM)};
\node[above] at (0,0) {\includegraphics[width=0.8\textwidth]{malarial.png}};
\end{tikzpicture}
\end{center}

Figure 29.

Conventional synthetic strategies towards 2-aryl isatogens are generally limited to pre-functionalisation of the substrate followed by isatogen formation in the final step, a process which is usually catalysed by an expensive transition metal complex. Representative examples include a gold(III) catalysed procedure developed by Yamamoto \textit{et al.}\textsuperscript{41} and the complementary palladium(II) promoted methodology developed by Ramana \textit{et al.}\textsuperscript{62} As such, a divergent synthetic approach that allows access to a varied compound library, from a single synthetic intermediate, would be beneficial with regard to compound library synthesis and screening, scheme 86.

\textit{Previous work}

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {\includegraphics[width=0.4\textwidth]{previous_work.png}};
\end{tikzpicture}
\end{center}

\textit{Proposed Strategy}

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {\includegraphics[width=0.4\textwidth]{proposed_strategy.png}};
\end{tikzpicture}
\end{center}

Scheme 86.
We began our studies by investigating the palladium-catalysed Suzuki-Miyaura cross coupling of aryl boronic acid derivatives. Unfortunately, these reactions were unsuccessful and complex mixtures were recovered. Furthermore, Kumada type cross-coupling reactions were attempted using aromatic Grignard reagents. However, once again, only intractable mixtures were isolated. These observations were not too surprising considering the previously highlighted ability of Lewis acidic transition metals such as palladium to effect decomposition of iodoisatogens, scheme 87.

Scheme 87.

Undeterred, we decided to continue the study by investigating alternative organometallic coupling partners, and explored the use of arylzinc reagents. Consequently, Negishi reactions were attempted by subjecting iodoisatogen 69 to freshly prepared PhZnCl in the presence of Pd$_2$dba$_3$ (2.5 mol%) and SPhos (5.0 mol%). Stoichiometric quantities of aromatic zinc halides were prepared via transmetallation of the corresponding Grignard reagents with anhydrous zinc chloride, conversion was assumed to be quantitative and the in situ generated organozinc halides were used immediately. Initial results were disappointing as low conversions were achieved when stoichiometric quantities of organometallic reagent were used in the presence of 5% Pd catalyst. Gratifyingly however, increasing the equivalents of PhZnCl (5 equivalents) resulted in complete conversion of starting material and the product 2-phenylisatogen 89 was successfully generated, albeit in a low yield of 30%, scheme 88.

Scheme 88.
We chose to perform these experimental studies on 5-methoxy-2-iodoisatogen, due to its ease of preparation and inherent stability *versus* other 2-iodoisatogens. 5-Methoxy-2-iodoisatogen 69 was prepared from the corresponding alkynyl iodide 68 *via* the CuBr.DMS promoted cycloisomerisation, scheme 89.

Scheme 89.

In the event, a substantial quantity of biphenyl was also observed, and although this could have originated from Wurtz coupling of the phenylmagnesium bromide, we considered other possible mechanisms for its formation. An intriguing report by Lei and co-workers highlighted that homo coupling of aryl zinc halides can take place during Negishi coupling. In their mechanistic studies they proposed two possible competing reaction pathways: *pathway a*, reductive elimination of [Ar-Pd-Ar'] complex I to afford the desired cross coupled product. Or alternatively *pathway b*, where an additional transmetallation of ArZnCl occurs generating the new [Ar-Zn-Ar] complex II. This biaryl complex II can undergo reductive elimination, thus generating homocoupled biaryl compounds and consequently converting the initial aryliodide coupling partner into the protonated analogue, scheme 90.89

Scheme 90
Pleasingly, when performing the coupling reaction in the absence of a Pd catalyst, it was discovered that the desired product was formed, and the amount of biphenyl generated was drastically reduced. Furthermore, the isolated yield for 5-methoxy 2-phenylisatogen was just over twice that of the palladium-catalysed reactions examined, scheme 91.

Scheme 91.

Having previously demonstrated the ability of a palladium catalyst to promote conversion of isatogens to isatins, the potential for side reactions in this process is the likely reason for low isolated yields. Therefore, in order to avoid decomposition of the starting isatogen it was decided to explore the scope of the process in the absence of Pd catalysts.

A small scope of 2-arylisatogens were generated via the cross coupling of 5-methoxy 2-iodoisatogen 69 with a series of aryl zinc halides. Three additional 2-arylisatogens bearing electron rich and poor groups were synthesised in good yields, scheme 92.

Scheme 92.
To conclude, the cross coupling of iodoisatogens with arylzinc halides was developed and a small scope of substrates was investigated. Further research within the Harrity group extended the scope of this reaction to include additional isatogens bearing halides in the 5- and 6-positions.\textsuperscript{90}

### 2.9 – 2-Iodo Isatogens: Alkyl Cross Coupling Condition Screening and Formation of N-Alkoxy-3-Oxindoles

Having uncovered effective conditions for aryl cross couplings of 2-iodoisatogens, it was decided to explore the possibility of generating the corresponding 2-alkylisatogens \textit{via} an analogous sp\textsuperscript{3} - sp\textsuperscript{2} cross coupling strategy. The desire to prepare such compounds derived mainly from the fact that there are very limited examples of alkylisatogens reported in the literature.\textsuperscript{62} Consequently, it was hoped that the coupling methodology would deliver a new and divergent approach to these novel heterocycles, scheme 93.

\textit{Proposed reaction conditions}

\[
\begin{array}{c}
\text{R} & \overset{\text{I}}{\text{N}} \text{-} \overset{\text{O}}{\text{O}} \\
\end{array}
\xrightarrow{\text{RZnX (excess)}}
\begin{array}{c}
\text{R} & \overset{\text{O}}{\text{O}} \\
\end{array}
\]

Scheme 93.

We opted to carry out our initial studies using ethyl zinc iodide, prepared via the insertion of Rieke zinc into iodoethane using the conditions reported by Knochel and co-workers, scheme 94.\textsuperscript{91} The concentration of alkylzinc halide solutions was determined via the iodometric titration method develop by Knochel.\textsuperscript{92}

\[
\begin{align*}
\text{I} & \text{Et} \\
\xrightarrow[1.)]{\text{BrC}_{2}\text{H}_{4}\text{Br (5 mol\%), THF, }\Delta, 10 \text{ min}} & \text{Zn (1.0 equiv.)} \\
\xrightarrow[2.)]{\text{TMSCl, Et-I (1.0 equiv.), THF, }50 \text{ C, }\text{o/n}} & \text{I} \text{Zn} \text{Et} \\
& (0.80 - 0.90 \text{ M, THF})
\end{align*}
\]

Scheme 94.
Initial studies attempted to replicate the conditions employed for the aryl cross coupling, and so a large excess of EtZnI in THF was added to 69 at room temperature. However, it was surprising to only isolate a minor amount of the expected 2-ethylisatogen together with a large quantity of an unexpected by-product. Analysis of the $^1$H NMR spectrum of the unknown compound indicated that there were two different types of ethyl group, in a 2:1 ratio. Combining this data with mass spectrometry and $^{13}$C NMR analyses led to the conclusion that the major product from the reaction was a result of double addition of ethyl groups to the isatogen at the 2-position, and a subsequent O-alkylation. The mechanism for this unusual transformation was unclear at this stage. Ultimately, the reaction afforded the interesting N-alkoxy-3-oxindole 95 as the major product in a moderate yield of 45% and the intended 2-ethyl isatogen 94 in a low 15% yield, as shown in scheme 95.

Scheme 95.

This preliminary experiment was followed by a study of the effect of organometallic stoichiometry on product distribution. The overall conclusion that was drawn from this screening study was that varying the stoichiometry of ethylzinc iodide did not result in any significant change in the proportions of the two products. Indeed, the only effect of lowering the equivalents of EtZnI was to lower conversion resulting in an increased recovery of starting material (see entries 1 and 2, table 10).
Entry | EtZn (Equiv.) | 2-Iodoisatogen (69) | 2-Ethylisatogen (94) | N-alkoxy-3-oxindole (95) |
--- | --- | --- | --- | --- |
1 | 1.0 | 44 | 31 | <10 |
2 | 2.0 | 33 | 35 | 20 |
3 | 3.0 | Trace | 22 | 37 |
4 | 4.0 | 0 | 15 | 45 |

Table 10.

In order to better understand the origin of the formation of compound 95, it was decided to subject the 2-alkylisatogen to the reaction conditions in order to determine whether this would result in formation of 95. Accordingly, 2-ethylisatogen 94 was treated with 3 equivalents of ethylzinc iodide which resulted in complete conversion of ethylisatogen, affording N-alkoxy-3-oxindole 95 in a moderate 49% yield. This result indicated that 2-alkylisatogens are potential intermediates in the production of the N-alkoxy-3-oxindoles, scheme 96.

Scheme 96.

Having demonstrated that the observed N-alkoxy-3-oxindole 95 was formed from 2-ethylisatogen, thereby consuming the desired product in the process, the possibility of optimisation towards selective formation of 2-ethylisatogen was reinvestigated. As reagent stoichiometry had little impact on by-product formation, we decided to vary the nature of the organozinc reagent and as such diethylzinc was employed. In the event, similar results were observed to those recorded during the screening of ethylzinc iodide stoichiometry, albeit with a greater degree of reproducibility. Specifically, when excess diethylzinc was employed the major product was found to
be 1-ethoxy-2,2-diethyl-5-methoxyindolin-3-one 95. Similarly, lowering the equivalents of diethylzinc afforded mixtures of products and starting materials. After some optimisation we found that the use of 1.5 – 2.0 equivalents of diethylzinc resulted in full conversion of iodoisatogen over a time period of two hours, providing N-alkoxy-3-oxindole 95 as the sole product in a good 68% yield, scheme 97. The mechanism of formation of the N-alkoxy-3-oxindole 96 will be discussed later on in this thesis.

![Scheme 97](image)

Maintaining the objective of improving selectivity for generation of the 2-alkylisatogen, the possibility of using ‘hard’ main group organometallics such as Grignards and alkyllithium reagents was investigated. However, in these cases no desired product was observed and it appeared that predominantly decomposition of 2-iodoisatogen had occurred. This was not too surprising as Grignard reagents have been shown to attack at the carbonyl position of 2-phenylisatogen. Furthermore, this procedure was reported to be somewhat capricious and low yielding, thus highlighting the observed incompatibility of iodoisatogens and Grignard reagents. Complementary to this, McWhorter, Jr. reported that exposure of the structurally analogous 2-aryl-indolones to Grignard reagents also resulted in predominant reactivity at the carbonyl position, figure 30.

![Figure 30](image)
We therefore returned to organozinc reagents, and were attracted to work reported by Knochel and Sewald whereby the reactivity of alkylzinc reagents was modulated by the use of metal salt additives.\textsuperscript{91,94,95} We were specifically interested in the \textit{in situ} transmetallation of alkylzinc halides with copper salts to generate mixed-metal higher order cuprates, analogues of Lipshutz reagents.\textsuperscript{96,97} The mixed metal higher order organocuprate, EtCu(CN)ZnI.2LiCl was prepared according to the literature procedure reported by Knochel, scheme \textbf{98}. Transmetallation of zinc to copper was assumed to be quantitative and the resulting cuprate was used immediately.\textsuperscript{91} 

\begin{equation}
\begin{array}{c}
\text{Et–ZnI} \\
\xrightarrow{\text{CuCN (1.1 equiv.), LiCl (2.2 equiv.)}} \\
\text{THF, -30 °C to 0 °C, 30 min} \\
\xrightarrow{} \\
\text{Et–Cu(CN)ZnI.2LiCl}
\end{array}
\end{equation}

Scheme \textbf{98}.

A slight excess of cuprate was added to a solution of iodoisatogen \textbf{69} and the reaction mixture left to stir overnight. We were delighted to observe the formation of the desired 2-ethylisatogen \textbf{94} as the major product, which was isolated in 57\% yield, significantly higher than the best example recorded with EtZnI. Notably, the organocopper reagent did not preclude the formation of the \textit{N}-alkoxy-3-oxindole \textbf{95}, and this was recovered in a low yield of 8\%, scheme \textbf{99}.

\begin{equation}
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\xrightarrow{\text{Et-CuCNZnI.2LiCl (1.2 equiv.)}} \\
\text{THF, 0 °C to rt, 18 h} \\
\xrightarrow{} \\
\text{MeO} \\
\text{MeO} \\
\xrightarrow{} \\
\text{MeO} \\
\text{MeO}
\end{array}
\end{equation}

Scheme \textbf{99}.

A brief stoichiometry screening was performed, however, unsurprisingly it was found that fewer equivalents (1.0) did not result in complete conversion of the starting material. A small increase in the number of equivalents of organozinc halides (1.5 equiv as opposed to 1.2 equiv) resulted in full conversion of iodoisatogen, however a greater proportion of \textit{N}-alkoxy-3-oxinolde \textbf{95} (\sim 1:3 ratio relative to 2-alkyisatogen \textbf{94}) was observed. It was therefore decided to employ our initial conditions to study alternative organozinc cuprates in order to establish the
generality of this procedure. Primary organozinc halides were prepared in the same manner as EtZnI i.e. insertion of alkyl iodides into Rieke zinc, scheme 100.

A small series of primary alkylzinc iodides were prepared, unfortunately however, this methodology was not applicable to cyclohexyl iodide as solutions of the corresponding organometallic were generated with inadequate concentrations (~0.15 M). Gratifyingly however, employment of the modified conditions developed more recently by Knochel efficiently provided a more concentrated solution of cyclohexylzinc iodide (0.44 M solution in THF), scheme 101.

The stock solutions of organozinc halides were then transmetallated to copper and reacted with 5-methoxy-2-iodoisatogen 69. The initial screening showed that the reaction was compatible with primary alkylcuprates of varying chain length, affording the desired 2-alkylisatogens in moderate to good yields. Additionally, the methodology could be successfully extended to the preparation of 2-cyclohexyl isatogen 99, albeit in a moderate 49% yield, scheme 102.
In order to further define the scope of the process, two different isatogens were reacted with ethyl zinc cuprate. Although the isolated yields were relatively low, this study confirmed that the established reaction conditions were in fact compatible with other substrates. Notably however, a significant amount of the corresponding isatins were also observed but not isolated cleanly from these reactions. This observation suggests that isatogens that do not contain a 5-MeO group are significantly less stable under the reaction conditions. Nonetheless, we were pleased to find good recovery of overall mass in each of these reactions (85% and 61%, respectively), scheme 103. 6-Methyl-2-iodoistogen 102 was prepared in a moderate 48% yield from the corresponding alkynyl iodide 101 via the CuBr.DMS (25 mol %) promoted cycloisomerisation, in THF at 65 °C for 2 hours.

Scheme 102.
Scheme 103.

With regard to applying the methodology to generating structurally interesting compounds, we were particular intrigued by a recent report from Ramana and co-workers that showed isatogens bearing a pendant alkene underwent spontaneous dipolar cycloaddition, affording the novel class of angularly fused polycycles, scheme 104.84

Scheme 104.

It was envisaged that we could employ our coupling chemistry to install a 1-pentenyl group which would undergo cycloaddition towards spiro-pseudoindoxyls, scheme 105.
We considered preparing the requisite pentenyl derived organometallic by direct insertion of zinc into the corresponding alkyl bromide, however this proved to be inefficient when employing Knochel’s conditions. Attention was turned to an alternative method developed by Shouquan Huo during the last decade. This involved the treatment of zinc dust with a sub-stoichiometric amount of molecular iodine in DMA, then addition of the required alkyl halide. Gratifyingly, this procedure was reproducible in our hands and useful concentrations of pent-4-en-1-ylzinc 0.69 M in DMF were accessible, scheme 106.

Disappointingly however, subsequent attempts to prepare the corresponding cuprate of this organometallic appeared to prove fruitless as only starting iodoisatogen was recovered from the subsequent coupling reaction. Increasing the stoichiometry of the putative organometallic reagent as well as the use of portion-wise addition failed to improve matters and recovered iodoisatogen was observed in all cases, scheme 107.
It was concluded that cuprates of this class were not compatible with the THF : DMF solvent mixture required for generation of the organozinc reagent. Pleasingly however, direct subjection of iodoisatogen 69 to pent-4-en-1-ylzinc bromide 0.69 M in DMF afforded the target tricyclic product 108 in a moderate 44% yield and as a single diastereoisomer. Additionally, the O-alkylated indoxyl 109 was isolated in a slightly lower yield of 33%, scheme 108.

Scheme 108.

The reaction shown in scheme 108 is intriguing as the product distributions reflect the relative rates of two competing processes. Specifically, if the dipolar cycloaddition was very rapid then it would not be possible to generate O-alkylated indoxyl 109. In contrast, if cycloaddition was slow it could be possible to invert product ratios by adding more organozinc reagent. Therefore, iodoisatogen 69 was subjected to a greater excess of organometallic reagent. Interestingly, a comparative yield of 37% of cycloadduct 108 was produced, indicating that cycloaddition was able to compete with indoxyl 109 formation, scheme 109.

Scheme 109.

Having explored the basic reaction scope, attention returned to the formation of the 3-oxindole by-products. The assignment of these compounds was based on NMR, MS, IR but as this compound class had not been reported before, it was
thought prudent to find additional structural evidence in order to support our proposed structure. It was hoped to elucidate this *via* X-ray crystallographic techniques. In this regard, the only solid example was the cyclohexyl derived compound 100. In order to generate sufficient material to grow appropriate quality crystals, 5-methoxy 2-iodoisatogen 69 was subjected to an excess of commercially available dicyclohexylzinc, affording the desired material 100 in a moderate 41% yield, scheme 110.

![Scheme 110](image)

A crystalline sample of 100 of sufficient quality was grown from isopropyl alcohol, and the resulting solid state structure is shown in figure 31 (hydrogen atoms are omitted for clarity). It is clear from the solid state structure that double addition of the alkyl groups has resulted at the 2 position generating the suspected germinal substitution pattern. The remaining alkyl group is clearly shown to be attached to the nitroxide, as we assumed. In addition, the carbonyl functionality is preserved which could be due to its proximity to the quaternary carbon centre.

![Figure 31](image)

Having confirmed the structural assignment of the $N$-alkoxy-3-oxindole products, the lability of the $N$-alkoxy group was investigated. It was envisaged that this compound class could potentially provide a novel synthetic strategy towards 2,2-dialkyl 3-oxindoles. This would be of interest as this structural core is present in a number of medicinally important molecules, pesticides and dyes, and also several other biologically active compounds bearing this structural fragment at their
core.\textsuperscript{100,101} Moreover, this motif is observed in a variety of natural products such as: austamide, aristotelone, and flurocarpamine, figure 32.\textsuperscript{102,103,104,105}

![Figure 32](image)

Access to these compounds is currently relatively challenging and somewhat limited. However, one very effective piece of methodology was recently developed by Gagosz and Wetzel, who reported a gold(I) catalysed conversion of 2-alkynyl arylazides to indol-3-ones. The reaction requires the presence of an external allylic alcohol nucleophile which generates an intermediate that undergoes a Claisen rearrangement to furnish the 3-oxindole, scheme 111.\textsuperscript{106}

![Scheme 111](image)

In the context of this research it was envisaged that $N$-alkoxy ethers could be cleaved via simple hydrogenolysis. Pleasingly, this was confirmed by subjecting $N$-
alkoxy-3-oxindole 95 to a catalytic amount of palladium on carbon under atmospheric hydrogen, affording 2,2-dialkyl 3-oxindole 110 in a very good 77% yield, scheme 112. Notably, use of alternative conditions such as Zn/AcOH failed to deliver the reduced product.

Scheme 112.

Overall, a novel route to 2,2-dialkyl 3-oxindoles has been uncovered. The developed route proceeds in 5 steps from commercial starting materials, and proceeds via O-alkylated indolys, a novel class of synthetic intermediates, scheme 113.

Scheme 113.

2.10 – 2-Iodo Isatogens: Alkyl Lower Order Cuprate Optimisation and Scope

With the initial reaction procedure investigated it was clear that the reaction was not proceeding as efficiently as possible with an average of 60-70% recovery of mass. It had been noted that a small amount of isatins were recovered from the reactions, around 5%, which is not too surprising as previous investigations had shown that isatins were a known decomposition product of isatogens. Additionally, over the course of reaction screening it was observed that there was a degree of irreproducibility. When employing the same reaction conditions, yields as low as 40% for 2-ethylisatogen 94 were observed together with varying amounts of
*N*-Alkoxy-3-oxindole 95 (10 – 20%). Consequently, a reinvestigation of the reaction conditions was undertaken in an attempt to increase the relative amounts of desired material and/or identify where the loss of material was occurring.

We first decided to establish the innate selectivity of lower order cuprates in order to form 2-alkylisatogens in preference to *N*-alkoxy-3-oxindoles, with the possibility of the latter originating from unreacted alkyl zinc halides. In the event, subjecting 5-methoxy 2-ethylisatogen 69 to EtCu(CN)ZnI.2LiCl resulted in complete conversion to *N*-ethoxy-3-oxindole 95, which was isolated in a very good yield of 79%, scheme 114.

This result provided further support that alkyl isatogens were intermediates towards the formation of *N*-alkoxy-3-oxindoles (c.f. alkylzinc control reaction highlighted in scheme 96).

![Scheme 114](image)

Further optimisation studies included the investigation of classical organocuprate reagents in this reaction. However, these failed to provide product, resulting in either recovered starting material or decomposition. In the context of reaction solvent, we were aware of a report by Gagné and co-workers describing the ability of organozinc reagents to react with THF resulting in ring opening and formation of butoxide.107 This behaviour was also observed by Lemaire and Knochel during some attempted Negishi cross coupling reactions.108 For this reason we also conducted a screen of ethereal solvents such as: diethyl ether, dibutyl ether, and cyclopentyl methyl ether. However, cuprate formation appeared limited to THF and in addition iodoisatogen reactivity and solubility was only observed in THF.

As variation of solvent or cuprate failed to improve the reaction, it was considered that varying the reaction atmosphere could be more effective. In order to investigate this, two side by side experiments were performed; one under argon in degassed THF and the other simply under nitrogen, i.e. essentially a repeat of the original conditions. Somewhat surprisingly, it was observed that the reaction did
not perform as well under an argon atmosphere relative to when it was conducted under a nitrogen atmosphere, and a lower isolated yield of 2-ethylisatogen was observed, table 11.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Atmosphere</th>
<th>Isolated Yield / %</th>
<th>2-Ethylisatogen (94)</th>
<th>N-Alkoxy 3-oxindole (95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N₂</td>
<td>47</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Ar</td>
<td>38</td>
<td>38</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 11.

Both sets of conditions yielded a small amount of isatin, <5%, however notably for the experiment performed under argon a significant amount of additional material, around 10%, was observed (as estimated by 1H NMR spectroscopy of the crude reaction mixture). The major impurity in this case was thought to be N-H indol-3-one 110, which could not be isolated cleanly however contributed to <10% of the overall reaction yield. One could assume that N-H indole-3-one 110 and isatin 71 are possible reduction products of N-ethoxyl indol-3-one and 2-iodoisatogen respectively, scheme 115. The appearance of such reduction products may indicate why the reaction performed better under a less anaerobic environment. Thus, it was chosen to perform the following optimisation reactions solely under a nitrogen atmosphere and not under air, as it was considered that over exposure of the reaction mixture to too much air could be detrimental in a practical sense.

**Possible reductive decomposition pathways**

Scheme 115.
It was evident from the previous reaction studies that the transformation appeared to be proceeding to full conversion of starting material over the course of 18 hours. However, we had not carried out a careful study of the actual reaction time. Therefore, experiments were performed over time frames of 2 and 5 hours. It then became apparent that the reaction had stopped at some point before 2 hours, with only a ~80% conversion of starting material. We suspected that full conversion was observed over 18 hours due to the decomposition of residual starting material under the reaction conditions, table 12.

Table 12.

Taking into account the incomplete conversion of starting material under the optimal conditions, an empirical study was performed in an attempt to identify a more effective cuprate stoichiometry. Several experiments were performed whereby 2-iodoisatogen 69 was subjected to increasing amounts of ethyl cuprate, then left to react over the course of 2 hours. In the event, 1.7 equivalents were found to be optimal and resulted in the best overall yield of 86%, table 13. The conditions employing 1.7 equivalents, entry 4, were repeated and left over an extended period of 18 hours and gratifyingly, it appeared to have no adverse impact on product yield.
Optimal conditions had employed an isatogen concentration of 0.03 M, in the hope that this would limit the formation of N-alkoxy 3-oxindole by-products. As expected, performing the reaction at a relatively high concentration (0.3 M) resulted in a larger proportion of N-alkoxy 3-oxindole 95 being formed, 32% versus the 18% isolated for 2-ethylisatogen 94. In addition, more decomposition resulted when employing these conditions, with an overall yield of only 50% observed. In keeping with the previous observation, a low conversion of starting material resulted when a very low concentration of 0.003 M was employed, table 14.

Table 13.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Overall Molarity</th>
<th>Isolated Yields / %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>/ M</td>
<td>2-Ethylisatogen (94)</td>
</tr>
<tr>
<td>1</td>
<td>0.3</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>0.03</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>0.003</td>
<td>40% conversion</td>
</tr>
</tbody>
</table>

Table 14.
The optimised reaction conditions arising from the studies described in this section are summarised in scheme 116. Cuprates were prepared in situ as THF solutions from their corresponding alkylzinc halides (also generated as THF solutions). Iodoisatogens were prepared as a 0.03 M THF solutions, and the reactions were conducted under a nitrogen atmosphere and were subjected to 1.7 equivalents of cuprate at an ambient temperature before being stirred over the course of 18 hours.

![Scheme 116](image)

Scheme 116.

Before investigating the scope of the reaction, the generation of appropriate organozinc reagents was required. Primary organozinc halides were prepared from alkyl iodides utilising the procedure outlined by Knochel. These organometallics were all prepared in useful concentrations, scheme 117.

![Scheme 117](image)

Scheme 117.

Secondary organic zinc halides, specifically cyclic variants, were again accessible from Knochel’s modified conditions, scheme 118.
With these organometallics in hand, the scope of the reaction was investigated under the newly optimised conditions. The main product in each case was the desired 2-alkylisatogen. In addition, the corresponding N-alkoxy 3-oxindoles were observed in various proportions (<5 – 23%), the yields for which are quoted in parenthesis, scheme 119. It was assumed that transmetallation from zinc to copper was a quantitative process. The cyclopropyl substrate was derived from commercial cyclopropyl zinc iodide (0.14 M, THF).

Scheme 119.
The optimised conditions provided quite consistent product yields and these were generally higher than those obtained in our preliminary studies (c.f. scheme 102). With specific attention to the lower yielding compounds, 2-cyclopentylisatogen was still afforded in a good yield of 49%. However, the major additional material from the reaction with the N-alkoxy 3-oxindole 114 isolated in 23%, the highest amount observed across the compound class, thus the overall yield for the reaction was still a very good 72%. 2-Cyclopropylisatogen 113 was isolated in a moderately good yield of 45%, albeit lower than the other examples. Unfortunately, isatogens bearing a 6-chlorohexylgroup were not accessible as the reaction did not proceed to completion, scheme 119.

The optimised conditions were extended to different iodoisatogens, specifically the 6-methyliodoisatogen and the parent unsubstituted iodoisatogen. In these cases, the overall yields were considerably lower relative to 2-ethyl-5-methoxyisatogen 94, and this was consistent with observations made in our preliminary screening, (c.f. scheme 103). However, utilisation of the newly optimised conditions did pleasingly afford higher yields of the desired 2-ethylisatogens and their N-alkoxy 3-oxindole variants, than had been previously observed. Yields for 2-ethylisatogen 103 and 2-ethyl-6-methyl isatogen 105 formation were improved to ~40% as compared to ~30-35%, scheme 120.
In order to confirm the impact of using pre-prepared and stored cuprate reagents on the efficiency of the coupling reaction, a sample of the \( n \)-hexyl iodide derived cuprate was prepared. Using an aliquot of this material in the iodoisatogen substitution reaction resulted in full conversion of the starting material with isolated yields of 72\% and 18\% (alkylisatogen 97 and \( N \)-alkoxy-3-oxindole 98, respectively). The remaining sample was stored over a period of 24 h at room temperature before reacting with iodoisatogen 69. In the event, only an 80\% conversion of iodoisatogen was observed. This confirmed that cuprate reagents should be used immediately after their preparation by reported literature procedures, scheme 121.:\(^{91}\)

\*Product could not be isolated cleanly

Scheme 120.

Cuprate stored at 22 °C for 24 hours prior to use

Scheme 121.
Having established the scope of the coupling reaction using simple alkyl and cycloalkyl groups, it was decided to investigate more elaborate alkyl groups i.e. those that contain additional functionality. Accordingly, substrates bearing an ester, a boronic ester and a terminal olefin were prepared. Unfortunately, zinc insertion did not occur at all when the corresponding alkyl bromides were used, the exception being the more activated allyl bromide.

The low reactivity of zinc towards the key insertion reaction was solved simply by changing to the corresponding iodides. Therefore, performing a Finkelstein reaction of the alkyl bromides with excess sodium iodide provided the more reactive alkyl iodides in excellent yield on useful scales, scheme 122.109

\[
\text{R-Br} \xrightarrow{\text{NaI (2 equiv.)}} \text{Acetone, 60 °C, 2 h}} \xrightarrow{} \text{R-I}
\]

Scheme 122.

Gratifyingly, insertion of zinc into these alkyl iodides proceeded smoothly, affording the organozinc reagents bearing functional tags in useful concentrations. Insertion was achieved by using Knochel’s recently reported modified conditions, scheme 123.98

\[
\text{R-X} \xrightarrow{\text{i.) Zn (2.0 equiv.), LiCl (2.0 equiv.), BrC}_{6}H_{4}Br (5 \text{ mol\%), THF, } \Delta, \text{ 10 min}} \xrightarrow{} \text{R-ZnX.2LiCl}
\]

\[
\text{ii.) TMSCl, I}_2, \text{ R-I (1.0 equiv.), THF, 50 °C, o/n}
\]

Scheme 123.
With these four functionalised organometallics in hand, their reactivity towards iodoisatogens was investigated. To begin this investigation, 5-methoxy iodoisatogen 69 was subjected to 1.7 equivalents of organometallic in THF at room temperature, in accordance with the previously optimised conditions, scheme 124.

Scheme 124.

In the event, it was disappointing to only observe successful coupling in two out of the four organometallic reagents investigated. The ethyl butyrate example 120 and the terminal butene substituted example 119 provided products in isolated yields of 50% and 29%, respectively. In addition, variable amounts of the corresponding N-alkoxy-3-oxindoles were also observed. It is not clear why the remaining two examples did not promote product formation, although in both cases isatogen decomposition was observed rather than the recovery of starting material. We therefore believe that the reagents were generated in these cases, indeed, there is literature precedent for both reagent classes.\textsuperscript{110,111,112} Regardless, the successful application of the terminal alkene and terminal ester examples 119 and 120 were deemed enough evidence to demonstrate that this chemistry was compatible with some functional groups and so further examples were not pursued.
The final aspect of this chemistry to be pursued was a reinvestigation into the formation of the interesting tricyclic compound 108, as this would represent a very attractive iodoisatogen functionalisation methodology. Previously it had been shown that this could only be afforded in a moderate 44% yield when utilising pent-4-en-1-ylzinc bromide, with the intramolecular [3+2] dipolar cycloaddition running in competition with N-alkoxy-3-oxindole formation. It was hoped that using alkyl iodide substrates would allow the zinc insertion step to take place in THF, and thus consequently allowing for efficient copper transmetallation. In the event, a 0.71M THF solution of pent-4-en-1-ylzinc iodide was realised via the above mentioned strategy, scheme 125.

With a THF solution of the relevant organometallic in hand, the corresponding cuprate was prepared and reacted with iodoisatogen 69, in accordance with the optimised conditions. Pleasingly, the desired cycloadduct 108 was isolated in a good yield of 62% which was notably higher than the 44% isolated previously when directly employing the organozinc halide. In addition, a significant amount of material accounted for the structurally attractive spirocyclic amino alcohol 123, the reduced derivative of cycloadduct 108. It can therefore be inferred that the overall yield of the intermediate isatogen 124 was around 91%. Finally, the N-alkoxy-3-oxindole 109 was isolated in a 14% yield, a similar yield to that observed in the other cuprate reactions, scheme 126.
The generality of this methodology was also briefly demonstrated via subjection of the parent iodoisatogen 70 to the same conditions. Pleasingly, the product was isolated in a good 52% yield. In addition, a small amount, <9%, of \( N \)-alkoxy-3-oxindole was also observed, however this was not isolated in pure form, scheme 127.

In conclusion, the cross coupling of 2-iodoisatogens with alkyl organometallics has been developed that allows a series of 2-alkylisatogens to be prepared in good to excellent yields. Moreover, this methodology was then extended to more interesting substrates bearing additional functionalities. However, in all cases the formation of \( N \)-alkoxy-3-oxindoles was observed and this prompted us to undertake an investigation into the mechanism of their formation.
CHAPTER III

3.1 – N-Alkoxy-3-oxindole: Condition Screening

Intrigued by the observed formation and potential application of N-alkoxy-indoles 95, 106, 104, 100, 98, 112, 121, and 109 we decided to undertake studies to elucidate the mechanism of their formation, figure 33.

Figure 33.

The generation of N-alkoxy-oxindoles from a variety of isatogens took place when employing different organometallics such as: dialkylzinc reagents, alkylzinc halides and also higher order alkylzinc cuprates. Alkylzinc halides were initially chosen as the primary organometallic for the mechanistic investigations as they were easier to access and handle relative to the other reagents. Furthermore, 2-phenyl isatogen 85 was chosen as the model substrate as it was easily prepared. In addition, it was thought that the overall transformation would be simplified when starting from a 2-alkylisatogen as opposed to the 2-iodoisatogens.

As we had decided to employ a 2-arylisatogen (as opposed to the 2-alkylisatogens largely studied up until this point), we decided to revisit the effect of alkylzinc halide stoichiometry, table 15. It was immediately clear that three equivalents of
organometallic were required to achieve complete conversion of starting material, entry 3, with the desired product 126 isolated in a 60% yield. Unfortunately, a significant amount of decomposition material was also observed which proved to be difficult to remove. Interestingly however, with two equivalents of organometallic only a 50% conversion of starting material was observed. It was not clear as this stage if the additional equivalent of organometallic was required to affect O-alkylation or was consumed via some other means. In connection with these studies, the reaction was also conducted under nitrogen, air, and argon. However, no significant variations were apparent and similar amounts of N-alkoxy-3-oxindole product and decomposed material were isolated in each case.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>EtZnI /equiv.</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting Material (85)</td>
<td>N-alkoxy-oxindole (126)</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>5.00</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield contains additional unknown material (~5%)

<sup>b</sup>Variation of reaction medium (Ar, N<sub>2</sub>, air) had no significant impact

Table 15.

Additional organometallic reagents were tested in order to assess the consistency of these conditions. Hexylzinc iodide performed as expected affording the product 127 in a moderately good 61% yield, three equivalents of the organometallic were still required with fewer equivalents resulting in lower conversions. Interestingly however, attempting the reaction with methylzinc iodide did not result in any conversion, and starting isatogen 85 was recovered from this experiment. This observation is consistent with the reaction of methyl cuprate which only afforded trace amounts of the corresponding N-alkoxy-3-oxindole. We attributed this result to the lower nucleophilicity of methyl organometallics. In addition, if this process proceeds through the intermediacy of alkyl radicals, then one would suspect this.
transformation to be disfavoured as a methyl radical is less readily formed relative to other carbon based radicals. Finally, secondary alkyl zinc halides were investigated, however in the event both cyclopentylzinc iodide and cyclohexylzinc iodide produced only small amounts of desired material. Moreover, these compounds were heavily contaminated with undefined side-products, scheme 128.

\[ \begin{align*}
\text{Scheme 128.} \\
\end{align*} \]

Pleasingly, N-alkoxy ether cleavage of one of these new N-alkoxy-3-oxindoles was achievable through the previously employed hydrogenolysis conditions. In the event, 2,2-disubstituted oxindole 128 was afforded in a moderately good 62% yield, thus further justifying this chemistry as a viable route towards these biologically relevant molecules. Additionally, compound 128 featured two different groups at the 2-position, strengthening the possible practical applications of this chemistry, scheme 129.

\[ \begin{align*}
\text{Scheme 129.} \\
\end{align*} \]

*Contains impurities (~5%)
3.2 – \textit{N}-Alkoxy-3-oxindole: Mechanistic Proposal

A literature search provided some insights as to how this interesting transformation could be occurring. It was originally reported by Whitesides and Newirth, that the oxygen centred radical TEMPO (\((2,2,6,6\text{-tetramethylpiperidin-1-yl})\text{oxyl}\)) could be alkylated by \(^7\text{BuLi}.^{113}\) Moreover, Curran and Nagashima further demonstrated the generality of this transformation. The reaction was found to be quite general when employing a series of different organometallics, including alkylzinc halides and higher order zinc cuprates, scheme 130.\(^\text{114}\)

\[
\text{TEMPO} \xrightarrow{\text{\(\eta\)Hex-M}} \text{TEMPO}^* \quad \text{THF, } -78 \degree \text{C to RT} \quad \text{21\% - 78\%}
\]

\(M = \text{Li, MgBr, Ti(O\(\text{OPr})_3, Zr(\text{Cl})_2\text{Cp}_2, CuCN.Li, Znl, CuCN.Znl, Sml}_2\)

Scheme 130.

Investigations into this interesting transformation were further performed by Bertrand and co-workers. In the context of their research they were specifically focusing on the reactions of dialkylzinc reagents with oxygen, which was monitored via electron paramagnetic resonance spectroscopy (EPR) techniques. In this study, TEMPO was subjected to diethylzinc and in accordance with Curran they suggest that TEMPO is trapped by an ethyl radical. This radical can either be generated from the reaction of diethylzinc with oxygen or via the single electron reduction of TEMPO to the corresponding zinc alkoxide \(^{129}\), consequently affording an ethyl radical in the process. This latter step was found to be reversible when reintroducing oxygen into the system. Specifically, it was shown that oxygen could convert the “mute” zinc alkoxide species back into TEMPO, which could be further trapped by an ethyl radical, scheme 131.\(^\text{115}\)

\[
\text{Et}_2\text{Zn} \xrightarrow{\text{Me}^*} \text{Et}_2\text{Zn} \xrightarrow{\text{O}_2} \text{Et}^* \xrightarrow{\text{O}_2} \text{Et}_2\text{Zn} \xrightarrow{\text{O}_2} \text{Et}^* \xrightarrow{\text{Me}_2\text{Zn}} \text{Me}_2\text{Zn}
\]

Scheme 131.
The reaction of organometallic reagents with oxygen is well established, and was originally reported by Walling and Buckler. Evidence for a free radical reaction mechanism was later provided by Hock and Ernst. With the development of EPR techniques, investigations into this reaction were performed by Davies and Roberts, prompting them to propose a radical chain mechanism, which is now generally accepted, scheme 132:

$$\text{R-MX} \xrightarrow{O_2} \text{XMOO}^* \text{R}^*$$

$$\text{XMOO}^* \text{R}^* \xrightarrow{\text{R-MX}} 2 \text{ROMX}$$

Scheme 132.

On the basis of Curran’s original observations and Bertrand’s more recent results, an initial mechanism was proposed which is outlined in scheme 133. The first step involves nucleophilic addition to isatogen 130 providing zinc alkoxide 131, which undergoes oxidation to give nitroxyl radical 132. We believe that this intermediate should behave in a similar manner to TEMPO, based on their structural similarities. Accordingly, the final step involves combination of 132 with an alkyl radical, thus affording the N-alkoxy-3-oxindole product 133. With regard to reactions of iodoisatogens, a preliminary step occurs involving the displacement of iodide by an additional equivalent of organometallic, scheme 133 inset.

Scheme 133.
Although the proposed scheme is based on strong literature precedent, it requires an oxidant to promote the transformation. It was not clear how these oxidative processes were occurring and so we considered the possibility that adventitious oxygen was mediating these steps. Evidence to suggest that intermediate zinc alkoxide 131 could be prone to air oxidation is provided by Pedulli and co-workers. Over the course of their investigations into hydroxylamines as oxidation catalysts, they report that nitroxy radical 135 was readily generated from the corresponding nitroxide 134 simply from exposure to molecular oxygen, scheme 134. In our case however, the effect of changing reaction atmosphere from nitrogen and argon to air had little impact on the product distribution, which doesn’t appear to be fully consistent with this proposal (c.f. table 15). Considerations into other possibilities are discussed later on in this thesis.

![Scheme 134](image)

**Scheme 134.**

### 3.3 – N-Alkoxy-3-oxindole: Expansion of Scope

Regarding the efficiency of the transformation of isatogens to N-alkoxy-3-oxindoles, diethylzinc proved to show the highest degree of consistency versus other organometallic reagents, (c.f. scheme 97). A possible reason for this could due to diethylzinc’s propensity to generate ethyl radicals relative to other ethyl organometallics. Bertrand and co-workers described how diethylzinc could be employed in a similar manner to the known radical precursor triethylborane. Consequently, our subsequent studies into this transformation were performed with diethylzinc. Furthermore, it was decided to perform the reactions under a nitrogen atmosphere in non-degassed dry solvent, which we believed would provide a sufficiently aerobic environment without the risk of igniting pyrophoric dialkylzinc reagents. Gratifyingly, treatment of phenylisatogen 85 with a slight excess diethylzinc afforded the desired N-alkoxy-3-oxindole 126 in a good 61% yield. Moreover this procedure was found to be much more reproducible relative to
related reactions with ethylzinc iodide, and also proceeded more cleanly with smaller amounts of decomposed material observed, scheme 135.

![Scheme 135](image)

This methodology was then extended to a small variety of iodoisatogens. Pleasingly, $N$-ethoyl-3-oxindoles 104, and 106 were afforded in good yields, which were consistent with those reported for 95, scheme 136.

![Scheme 136](image)

Finally, we demonstrated that it was possible to perform this chemistry on a selection of 2-alkylisatogens, prepared using the cuprate chemistry described in the previous chapter. In the event, $N$-alkoxy-3-oxindoles 136 and 137 were generated in good overall yields, scheme 137.

![Scheme 137](image)
3.4 – N-Alkoxy-3-oxindole: Additional Mechanistic Considerations

Returning to the proposed reaction mechanism (c.f. scheme 133) it was clear that electron transfer processes on N-alkoxy 3-oxindoles are important for product formation. In other words, a formal oxidation was required for this transformation to occur. However, the identity of the oxidant was not clear. In this context, Tour and co-workers had originally reported the electrochemical reduction of a specific isatogen (c.f. scheme 66). More recently this has been further demonstrated by Nepveu et al., wherein they undertook electrochemical investigations that showed isatogen 138 was readily reversibly reduced to the radical anion 139, based on in situ EPR studies, scheme 138. Furthermore, it was shown that this is a general phenomenon for 2-arylisatogens, and the reduction potential of a series of these compounds was recorded. In addition to this, isatogens are known to be redox active and have in fact been reported to form a redox pair with the structurally analogous indolone, in a manner analogous to benzoquinone and hydroquinone.

\[
\text{Scheme 138.}
\]

Based on these observations, we postulated that starting isatogens may act as internal oxidants. However, this idea proved difficult to fully rationalise. Specifically:

- If isatogens were acting as oxidants, we would expect these to be consumed in the process. Unfortunately however, we were unable to identify any redox related by-products.
- Isatogens could not be acting as the sole oxidant to form radical species 132 (c.f. scheme 133) as this would limit the maximum potential reaction yield to 50%. Many experiments provided yields >50% suggesting that this could not be the case.

As well as the isatogens, other potential oxidants were considered. For example, we envisaged that the reaction solvent THF could undergo reduction to ring opened compounds, but with no indication of n-butanol formation this was ruled out. We
next considered the reaction products, \( N \)-alkoxy-3-oxindoles. This was in part due to an experimental observation whereby a rapid colour change from a dull brown to an intense yellow occurred during the reaction quench. It should be noted that the \( N \)-alkoxy-3-oxindoles form bright yellow solutions. We hypothesised that \( N \)-alkoxy-3-oxindoles could be acting as \textit{in situ} oxidants, thus being reduced in the process. If this reduced form of \( N \)-alkoxy-3-oxindole was stable under the reaction conditions the final product could be formed upon exposure to air during the reaction quench, hence the rapid and intense colour change.

In order to see if the reduction of \( N \)-alkoxy-3-oxindoles was possible an electrochemical study was performed. The cyclic voltammogram of \( N \)-alkoxy-3-oxindole 95 was recorded figure 34. It was clear from, from figure 34, that \( N \)-alkoxy-3-oxindole 95 could in fact undergo reduction, with two reductions at -2.00 V and -2.11 V, the first appearing to be irreversible and the latter being rapidly reversible. With this observation in mind, it was proposed that \( N \)-alkoxy-3-oxindoles could act as potential oxidising agents. However, it should be noted that this process requires a very low potential.

\[ \text{MeO} \quad \text{O} \quad \text{Et} \quad \text{Et} \quad \text{OEt} \]

Figure 34. Cyclic voltammogram of 95 (7 mmol cm\(^{-3}\)) at a glassy carbon electrode in MeCN-NBu\(_4\)PF\(_6\) (0.1 mol cm\(^{-3}\)), potential scan rate 0.1 V \text{s}^{-1}.
Additionally, we noted an oxidation at -0.33 V, which we believed could be the reverse of the reduction at -2.00 V. This was confirmed as when the cyclic voltammogram was recorded without going below a potential of –1.9 V then the proposed opposite oxidation event is not observed, figure 35. From this it can be implied that the reduced species formed at -2.00 V is in fact stable over a large range of oxidising conditions, which is consistent with our proposal that a stable reduced form of N-alkoxy-3-oxindoles is formed under the reaction conditions. The final piece of information gained from this data is that N-alkoxy-3-oxindoles can in fact be reversibly oxidised (c.f. the peak at +1.08 V). However, this is not too surprising as one could easily imagine the generation of an aryl cationic species being responsible for this.

Figure 35. Cyclic voltammogram of 95 (7 mmol cm⁻³) at a glassy carbon electrode in MeCN-NBu₄PF₆ (0.1 mol cm⁻³), potential scan rate 0.1 V s⁻¹

Further data that could help substantiate the reversible reduction of N-alkoxy oxindoles was gleaned from control experiment alkoxy-3-oxindole 126. Specifically, subjection of this compound to either diethylzinc or ethylzinc iodide resulted in recovery of starting material without any apparent decomposition of the carbonyl or N-alkoxy ether. Notably however in the case of the EtZnI reaction, a discolouration of the reaction mixture occurred which was attributed to the
apparent formation of molecular iodine, an apolar purple band (characteristic of I₂) was observed during silica gel chromatographic purification. This formally represents an oxidation of the organometallic reagent. As the above electrochemical data suggested that N-alkoxy-3-oxinoles can act as oxidants, we wondered if these compounds were responsible for the apparent oxidation of the ethylzinc iodide. A proposed mechanism that illustrates this hypothesis is presented in scheme 140. Moreover, if something akin to this process is occurring then it could explain why a super-stoichiometric amount of organometallic reagent is required (c.f. table 15), as the formed product would potentially consume an additional equivalent of organozinc reagent.

![Scheme 140](image)

In conclusion, the generality of N-alkoxy-3-oxindole formation from various isatogens has been established, with dialkylzinc reagents proving to be optimal for this transformation. Additionally, we have formulated a mechanism that appears to highlight the potential of these compounds to undergo reversible redox processes.
Chapter IV - Experimental

4.1 – General Experimental

Infrared (IR) Spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, $\nu_{\text{max}}$ in cm$^{-1}$. Samples were recorded as thin films using sodium chloride plates. Bands are characterised as broad (br), strong (s), medium (m), and weak (w). 1H NMR spectra were recorded on a Bruker AC-250 (250 MHz), Bruker AMX-400 (400 MHz) or Avance-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in ppm from tetramethylsilane with the residual protic solvent resonance as the internal standard (CHCl$_3$: $\delta$ 7.27 ppm), (DMSO: $\delta$ 2.50 ppm). Data are reported as follows: chemical shift, integration, multiplicity (app = apparent, s = singlet, d = doublet, q = quartet, quin = quintet, m = multiplet), coupling constants (Hz), and assignment. $^{13}$C NMR spectra were recorded on a AMX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl$_3$: $\delta$ 77.0 ppm), (DMSO: $\delta$ 39.52 ppm), (Acetone: 29.84 ppm & 206.26 ppm).

High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+), Electrospray mode (TOF ES-) or Electron ionisation(EI+) mode.

Melting points performed on recrystallised solids, were recorded on a Gallenkamp melting point apparatus and are uncorrected. All solvents and reagents were purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Armarego and Chai. THF was distilled from sodium metal/benzophenone ketyl (for preliminary iodoisatogen research). THF (for optimisation of the reaction of iodoisatogen 69 with organometallics, and subsequent studies including N-alkoxy-3-oxindole synthesis), DMF, Et$_2$O, and PhMe were purified in accordance to the procedure described by Grubbs.

Chemicals purchased from; Sigma-Aldrich® Company Ltd, Alfa Aesar®, VWR international®, and Fluorochem® Ltd
Flash chromatography was performed on silica gel (BDH Silica Gel 60 43-60). Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (Merck TLC silicagel 60 F254) which were developed using standard visualizing agents: Ultraviolet light or potassium permanganate.

UV-Visible spectra were recorded between 200 – 800 nm as 75 μm MeOH solutions with a 1 cm path length on a Perkin Elmer lambda 35 spectrometer.

Cyclic voltammograms were performed on a Princeston Applied Electronics VersaSTAT3 with glassy carbon and platinum electrodes and Ag/AgCl as the reference in degassed MeCN with tetrabutylammonium hexafluorophosphate (0.1 M) as the electrolyte at a scan rate of 0.1 V s⁻¹.

All reactions were performed using flame dried glassware and under an inert nitrogen atmosphere, unless otherwise stated.
2-Bromoaniline (2.5 g, 14.6 mmol) was dissolved in EtOAc (30 mL), and cinnamoyl chloride (5.3 g, 32.1 mmol) in EtOAc (5.0 mL) was added drop-wise at 20 °C resulting in the formation of a slurry. The slurry was heated to 85 °C and stirred for 90 minutes until it became homogeneous, after which the reaction mixture was cooled to 0 °C and 3N NaOH was added dropwise until the pH reached 8. Saturated NaHCO$_3$(aq) (25 mL) was added and aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over MgSO$_4$, filtered and then concentrated in vacuo affording a crude colourless solid which was purified by flash column chromatography on silica gel (1:4 ethyl acetate : petroleum ether) providing the title compound as a colourless solid (2.8 g, 66%).

$^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.51 (d, $J = 7.5$ Hz, 1H, ArH), 7.88 (s, 1H, NH), 7.80 (d, $J = 16.0$ Hz, 1H, CH, alkene), 7.62 – 7.53 (m, 3H, ArH), 7.44 – 7.39 (m, 3H, ArH), 7.34 (t, $J = 7.5$ Hz 1H, ArH), 7.00 (t, $J = 7.5$, 1H), 6.63 (d, $J = 15.5$ Hz, 1H, CH, alkene); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 163.9, 143.0, 135.9, 134.4, 132.3, 130.2, 128.9, 128.5, 128.1, 125.2, 122.0, 120.6, 113.5. M.p = 108 – 110 °C (lit = 107 – 108 °C).

(18) $E$-3-Benzylideneindolin-2-one

$N$-(2-Bromophenyl)cinnamamide (100 mg, 0.34 mmol) was dissolved in dry DMF (1 mL), to this was added sodium formate (26 mg, 0.37 mmol), tetrabutylammonium chloride (78 mg, 0.34 mmol), triphenylphosphine (9 mg, 0.03 mmol), and palladium(II) acetate (4 mg, 0.02 mmol). The resultant reaction mixture was heated at 120 °C for 24 hours, after which it was diluted with EtOAc (10.0 mL) and then
washed with water (2x 10 mL) followed by brine (5 mL). Organic layer was dried over MgSO₄, filtered and then concentrated in vacuo to give a yellow residue which was purified by flash column chromatography on silica gel (1:4 ethyl acetate : petroleum ether) providing the title compound as a yellow solid as single stereoisomer (20 mg, 13%). Stereochemistry of alkene assigned as E based on literature precedent.²⁵

¹H NMR (250 MHz, CDCl₃) δ 8.42 (s, 1H, NH), 7.86 (s, 1H, CH alkene), 7.74 – 7.63 (m, 3H), 7.55 – 7.42 (m, 3H), 7.23 (t, 1H, J = 7.5), 6.92 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 170.2, 141.6, 137.7, 135.0, 132.1, 130.0, 129.8, 129.5, 128.8, 128.5, 123.2, 122.0, 110.3; M.p = 190 – 194 °C (CH₂Cl₂) (lit = 195 – 196 °C).²²

(22) (E)-Tert-butyl (2-bromophenyl)(cinnamoyl)carbamate

N-(2-Bromophenyl)cinnamamide (0.500 g, 1.7 mmol) was dissolved in THF (20 mL), to this was added 4-dimethylaminopyridine (0.250 g, 2.21 mmol) and di-tert-butyl dicarbonate (0.480 g, 2.21 mmol). The resulting reaction mixture was stirred at 20 °C for 50 minutes and then diluted with Et₂O (50 mL). The organic layer washed with 1N HClₐq (15 mL) then saturated NaHCO₃ₐq (15 mL) and then brine (10 mL). Organic layer dried over MgSO₄, filtered and then concentrated in vacuo to afford the title compound as a colourless solid (0.670 g, 98%).

¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 15.5 Hz, 1H, CH Alkene), 7.70 (d, J = 15.5 Hz, 1H CH Alkene), 7.68 (dd, J = 8.5, 1.0 Hz, 1H, ArH), 7.65 – 7.61 (m, 2H, ArH), 7.44 – 7.38 (m, 4H, ArH), 7.27 (d, J = 7.5 Hz, 2H, ArH), 1.45 (s, 9H, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 167.5, 151.8, 144.9, 138.4, 135.0, 133.0, 130.2, 130.2, 129.5, 128.8, 128.4, 128.2, 123.3, 120.3, 83.6, 27.8; FTIR (film cm⁻¹)νmax: 2984 (m), 1736 (s), 1686 (s), 1474 (m), 1370 (m), 1336 (m), 1298 (s), 1103 (s), 843 (m); HRMS (TOF MS ES⁺) m/z calculated for [C₂₀H₂₁BrNO₃]⁺: 402.0705 [M+H]⁺, found 402.0722; M.p = 108 – 109 °C (CH₂Cl₂)
(24) *(E)*-Ethyl 2-(2-oxoindolin-3-ylidene)acetate\(^{21}\)

![Chemical structure of (E)-Ethyl 2-(2-oxoindolin-3-ylidene)acetate](image)

Isatin (1.00 g, 6.8 mmol) was dissolved in PhMe (20 mL), to this was added (carbethoxymethylene)triphenylphosphorane (2.61 g, 7.5 mmol) and the resultant reaction mixture was then stirred at 21 °C for 16 hours. After which the reaction mixture was concentrated *in vacuo* to give a crude orange solid which was purified by flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) providing the title compound as an orange solid (1.46 g, 99%).

\(^1\)H NMR (400 MHz, DMSO) \(\delta\) 10.80 (s, 1H, NH), 8.34 (d, J = 7.5 Hz, 1H, ArH), 7.35 (td, J = 7.5, 1.0 Hz, 1H, ArH), 7.00 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.87 (d, J = 7.5 Hz, 1H, ArH), 6.58 (s, 1H, CH alkene), 4.27 (q, J = 7.0 Hz, 2H, CH\(_2\)), 1.29 (t, J = 7.0 Hz, 3H, CH\(_3\)); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta\) 167.8, 165.1, 145.0, 138.2, 133.0, 128.0, 121.9, 120.7, 119.6, 110.3, 61.0, 14.0; M.p = 178 – 179 °C (EtOAc) (lit = 183 – 185 °C).\(^{21}\)

(26) *(E)*-N-methoxy-N-methyl-2-(2-oxoindolin-3-ylidene)acetamide

![Chemical structure of (E)-N-methoxy-N-methyl-2-(2-oxoindolin-3-ylidene)acetamide](image)

Isatin (1.00 g, 6.8 mmol) was dissolved in PhMe (20 mL), to this was added N-methoxy-N-methyl(triphenylphosphoranylidene)acetamide (2.70 g, 7.5 mmol), The resultant reaction mixture was then stirred at 21 °C for 18 hours. After which the reaction mixture was concentrated *in vacuo* to give a crude orange solid which was purified by flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) providing the title compound as an orange solid (1.48 g, 94%).
\( ^1\text{H NMR} \ (250 \text{ MHz, } \text{CDCl}_3) \ \delta \ 8.73 \ (s, \ 1\text{H}, \ \text{NH}), \ 8.36 \ (d, \ J = 7.5 \text{ Hz, } 1\text{H, ArH}), \ 7.35 \ (s, \ 1\text{H}, \ \text{CH \ alkene}), \ 7.26 \ (\text{td, } J = 7.5, \ 1.0 \text{ Hz, } 1\text{H, ArH}), \ 6.98 \ (\text{td, } J = 7.5, \ 1.0 \text{ Hz, } 1\text{H, ArH}), \ 6.85 \ (d, \ J = 7.5 \text{ Hz, } 1\text{H, ArH}), \ 3.76 \ (3\text{H, CH}_3), \ 3.35 \ (3\text{H, CH}_3); \ ^{13}\text{C NMR} \ (100.6 \text{ MHz, CDCl}_3) \ \delta \ 169.8, \ 165.9, \ 143.0, \ 136.4, \ 132.0, \ 128.5, \ 122.9, \ 122.5, \ 120.6, \ 110.2, \ 62.4, \ 32.5. \ \text{FTIR (film cm}^{-1}\text{)} \ \nu_{\text{max}}:\ 1718 \ (s), \ 1650 \ (s), \ 1464 \ (s), \ 1369 \ (w), \ 1343 \ (s), \ 1213 \ (m), \ 1090 \ (w), \ 785(m); \ \text{HRMS (TOF MS ES+) m/z calculated for [C}_{12}\text{H}_{13}\text{N}_{2}\text{O}_{3}]^{+}: \ 233.0926 \ [M+H]^+, \ \text{found} \ 233.0916; \ \text{M.p} = 132 – 134 \degree \text{C (CH}_2\text{Cl}_2)\)

\((26) \ \text{Tert-butyl 2,3-dioxoindoline-1-carboxylate (N-Boc Isatin)}^{129}\)

Isatin (5.00 g, 34.0 mmol) was dissolved in THF (200 mL), 4-dimethylaminopyridine (4.95 g, 44.2 mmol) and di-tert-butyl dicarbonate (9.60 g, 44.2 mmol) were added. The reaction mixture was stirred at 20 \degree \text{C for 50 minute and then diluted with Et}_2\text{O (200 mL). The organic layer washed with 1N HCl(aq) (100 mL) then saturated NaHCO}_3(aq) \ (100 mL) and then brine (50 mL). Organic layer dried over MgSO}_4, filtered and then concentrated in vacuo to afford the title compound as a yellow solid (8.77 g, 100%).

\( ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 8.07 \ (d, \ J = 8.5 \text{ Hz, } 1\text{H, ArH}), \ 7.75 – 7.66 \ (m, \ 2\text{H, ArH}), \ 7.28 \ (\text{td, } J = 7.5, \ 0.5 \text{ Hz, } 1\text{H, ArH}), \ 1.65 \ (s, \ 9\text{H, CH}_3); \ ^{13}\text{C NMR} \ (100.6 \text{ MHz, CDCl}_3) \ \delta \ 180.4, \ 155.8, \ 150.5, \ 148.4, \ 138.9, \ 125.5, \ 118.7, \ 116.9, \ 85.7, \ 28.1; \ ^1\text{M.p} = 119 – 120 \degree \text{C (CH}_2\text{Cl}_2)\)

\(^1\) Quaternary carbon not observed.
(27) (E)-Tert-butyl 3-(2-(methoxy(methyl)amino)-2-oxoethylidene)-2-oxoindoline-1-carboxylate

Tert-butyl 2,3-dioindoline-1-carboxylate (2.00 g, 6.3 mmol) was dissolved in PhMe (20 mL), and to this was added N-Methoxy-N-methyl-(triphenylphosphoranylidene)acetamide (2.53 g, 7.0 mmol). The resultant reaction mixture was then stirred at 21 °C for 16 hours. The reaction mixture was then concentrated *in vacuo* to give a crude orange solid which was purified by flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) providing the title compound as a yellow solid (2.10 g, 100%).

¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, J = 7.5 Hz, 1H, ArH), 7.81 (d, J = 8.0 Hz, 1H, ArH), 7.31 (s, 1H, CH alkene), 7.30 (app td, J = 7.5, 1.0 Hz, 1H, ArH), 7.06 (app td, J = 8.0, 1.0 Hz, 1H, ArH), 3.65 (s, 3H, CH₃), 3.26 (s, 3H, CH₃), 1.57 (s, 9H, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 166.2, 165.6, 149.0, 141.3, 134.3, 132.1, 127.5, 124.6, 123.4, 120.2, 114.9, 84.6, 62.3, 32.3 28.1; FTIR (film cm⁻¹)ν_{max}: 2980 (m), 1755 (s), 1732 (s), 1655 (s), 1423 (s), 1351 (s), 1253 (m), 1153 (s), 1093 (m), 1004 (w), 784 (w); HRMS (TOF MS ES⁺); HRMS (TOF MS ES⁺) m/z calculated for [C₂₀H₂₁N₂O₅]⁺: 333.1450 [M+H]⁺, found 333.1452; M.p = 198 – 192 °C (CH₂Cl₂)
4.2 – Representative Procedure: 1

(29) 3-Hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one$^{13}$

![Chemical structure](image)

Isatin (5.00 g, 34.0 mmol) was dissolved in MeOH (340.0 mL) and to this was added acetophenone (6.10 g, 34.0 mmol) followed by diethylamine (catalytic). The reaction mixture was stirred at 20 °C for 20 hours upon which the title compound precipitated as a colourless solid, isolated via filtration and dried in vacuo (8.85 g, 64%).

$^1$H NMR (250 MHz, DMSO) δ 10.27 (s, 1H, NH), 7.88 (d, $J = 8.5$ Hz, 2H, ArH), 7.67 – 7.56 (m, 1H, ArH), 7.54 – 7.43 (m, 2H, ArH), 7.27 (d, $J = 7.0$ Hz, 1H, ArH), 7.16 (td, $J = 7.5$, 1.0 Hz, 1H, ArH), 6.89 – 6.74 (m, 2H, ArH), 6.07 (s, 1H, OH), 4.07 (d, $J = 17.5$ Hz, 1H, CH$_2$), 3.58 (d, $J = 17.5$ Hz, 1H CH$_2$); $^{13}$C NMR (100.6 MHz, DMSO) δ 197.0, 178.8, 143.4, 136.6, 133.9, 132.2, 129.4, 129.2, 128.4, 124.1, 121.6, 109.9, 73.5, 46.2; M.p = 200 – 201 °C (MeOH) (lit = 196.6 – 197.8 °C).$^{130}$

(30) 3-(2-(4-Chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one

![Chemical structure](image)

Using representative procedure 1, isatin (0.50 g, 3.40 mmol), 4-chloroacetophenone (0.53 g, 3.40 mmol) and diethylamine (catalytic) in EtOH (35 mL) gave 38 as a colourless solid (1.00 g, 100%).
\(^1\)H NMR (250 MHz, DMSO) \(\delta 10.28 (s, 1H, NH), 7.89 (d, J = 8.5 Hz, 2H, ArH), 7.56 (d, J = 8.5 Hz, 2H, ArH), 7.26 (d, J = 7.0 Hz, 1H, ArH), 7.16 (app td, J = 7.5, 1.0 Hz, 1H, ArH), 6.90 – 6.75 (m, 2H, ArH), 6.08 (s, 1H, OH), 4.05 (d, J = 17.5 Hz, 1H, CH\(_2\)), 3.55 (d, J = 17.5 Hz, 1H, CH\(_2\)); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta 195.6, 178.3, 142.9, 138.4, 134.9, 131.6, 129.9, 129.0, 128.8, 123.7, 121.2, 109.5, 73.04, 45.8; M.p = 189 – 192 °C (MeOH) (lit = 196.0 – 197.4 °C).\(^{31}\)

(31) 3-Hydroxy-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one

Using representative procedure 1, isatin (1.00 g, 6.80 mmol), 3-acetylpyridine (1.23 g, 3.40 mmol) and diethylamine (catalytic) in MeOH (50.0 mL) afforded the title compound as a colourless solid (1.60 g, 88%).

\(^1\)H NMR (250 MHz, DMSO) \(\delta 10.30 (s, 1H, NH), 9.05 (d, J = 1.5 Hz, 1H, ArH), 8.77 (dd, J = 5.0, 1.5 Hz, 1H, ArH), 8.25 – 8.17 (m, 1H, ArH), 7.52 (dd, J = 8.0, 5.0 Hz, 1H, ArH), 7.28 (d, J = 7.0 Hz, 1H, ArH), 7.16 (app td, J = 8.0, 1.5 Hz, 1H, ArH), 6.90 – 6.75 (m, 2H, ArH), 6.11 (s, 1H, OH), 4.10 (d, J = 17.5 Hz, 1H, CH\(_2\)), 3.59 (d, J = 17.5 Hz, 1H, CH\(_2\)); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta 196.2, 178.2, 153.6, 149.3, 142.8, 135.5, 131.5, 131.5, 129.0, 123.8, 123.8, 121.2, 109.5, 73.0, 46.0; FTIR (film cm\(^{-1}\)\(v_{max}\): 3211 (br), 1722 (s), 1693 (s), 1621 (m), 1588 (m), 1472 (m), 1356 (m), 1182 (w), 754 (m), 734 (m), 700 (m); HRMS (TOF MS ES+) m/z calculated for [C\(_{15}\)H\(_{13}\)N\(_3\)O\(_3\)]\(^+\): 269.0926 [M+H]\(^+\), found 269.0923; M.p = 73 – 75 °C (MeOH)
(32) 3-Hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one

Using representative procedure 1, isatin (2.00 g, 13.6 mmol), 4-methoxyacetophenone (3.10 g, 20.4 mmol) and diethylamine (1.50 g, 20.4 mmol) in MeOH (100.0 mL) afforded the title compound as a colourless solid (3.00 g, 72%).

$^1$H NMR (250 MHz, DMSO) δ 10.24 (s, 1H, NH), 7.85 (d, $J = 9.0$ Hz, 2H, ArH), 7.24 (d, $J = 7.0$ Hz, 1H, ArH), 7.15 (app td, $J = 7.5$, 1.0 Hz, 1H, ArH), 7.00 (d, $J = 9.0$ Hz, 2H, ArH), 6.89 – 6.75 (m, 2H, ArH), 6.02 (s, 1H, OH), 4.00 (d, $J = 17.5$ Hz, 1H, CH$_2$), 3.50 (d, $J = 17.5$ Hz, 1H, CH$_2$); $^{13}$C NMR (100.6 MHz, DMSO) δ 194.8, 178.5, 163.3, 143.0, 131.9, 130.3, 129.2, 128.9, 123.6, 121.10, 113.9, 109.4, 73.1, 55.6, 45.4; M.p = 172 – 173 °C (MeOH) (lit = 181.2 – 183.7 °C).$^{130}$

4.3 – Representative Procedure: 2

(33) (E)-3-(2-Oxo-2-phenylethylidene)indolin-2-one

3-Hydroxy-3-(2-oxo-2-phenethyl)indolin-2-one (5.00 g, 18.7 mmol) was dispersed in EtOH (100.0 mL) and treated with 37% HCl$_{(aq)}$ (2.0 mL) and glacial ethanoic acid (50.0 mL). The reaction mixture was heated to reflux upon which it became homogeneous and turned red. After heating at reflux for 24 hours, the reaction mixture was cooled to room temperature and quenched with saturated NaHCO$_3$(aq). The reaction mixture was extracted with ethyl acetate (2 x 100 mL), and the combined extracts were dried over magnesium sulphate. The solvent was removed in vacuo to afford the title compound as an orange solid, (4.10 g, 95%).
\( ^1 \text{H NMR (250 MHz, DMSO)} \delta 10.82 (s, 1H, NH), 8.07 (d, J = 7.0 Hz, 2H, ArH), 8.01 (d, J = 7.5 Hz, 1H, ArH), 7.75 – 7.67 (m, 2H, ArH, CH alkene), 7.65 – 7.55 (m, 2H, ArH), 7.35 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.95 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.88 (d, J = 7.5 Hz, 1H, ArH); \(^{13}\text{C NMR (100.6 MHz, CDCl}_3 \delta 191.1, 169.7, 143.4, 137.5, 136.9, 133.9, 132.8, 129.0, 128.8, 128.0, 126.5, 122.9, 120.6, 110.3; FTIR (thin film cm}\(^{-1}\)) \(\nu_{\text{max}}\): 1714 (s), 1660 (s), 1462 (m), 1326 (s), 1228 (s), 1016 (m), 780 (w), 749 (w); HRMS (TOF MS ES+) m/z calculated for \([\text{C}_{16}\text{H}_{12}\text{NO}_2]^+\): 250.0869 [M+H]^+, found 250.0871; M.p. = 179-180 \text{°C (PrOH)} \)

(28) (E)-3-(2-(4-Chlorophenyl)-2-oxoethylidene)indolin-2-one

![Chemical structure](image)

Using representative procedure 2, 3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (1.00 g, 3.40 mmol) in EtOH (35.0 mL), HCl \(_{\text{aq}}\) (0.4 mL), and glacial ethanoic acid (10.0 mL) provided the title compound as a dark red solid, (0.68 g, 70%).

\( ^1 \text{H NMR (250 MHz, DMSO)} \delta 10.83 (s, 1H, NH), 8.09 (d, J = 8.5 Hz, 2H, ArH), 8.05 (d, J = 7.5 Hz, 1H), 7.69 (s, 1H, CH alkene), 7.67 (d, J = 8.5 Hz, 2H, ArH), 7.36 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.96 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.89 (d, J = 7.5 Hz, 1H, ArH); \(^{13}\text{C NMR (100.6 MHz, DMSO)} \delta 190.1, 168.1, 145.1, 139.0, 136.8, 135.8, 133.2, 130.5, 129.3, 126.9, 125.3, 121.8, 119.9, 110.4; FTIR (thin film cm}\(^{-1}\)) \(\nu_{\text{max}}\): 1717 (s), 1667 (w), 1602 (m), 1403 (w), 1332 (m), 1233 (w), 1009 (w), 839 (m), 782 (m); HRMS (TOF MS ES+) m/z calculated for \([\text{C}_{16}\text{H}_{11}\text{ClNO}_2]^+\): 284.0478 [M+H]^+, found 284.0490; M.p. = 177-178 \text{°C (PrOH)} \)
(35) (E)-3-(2-Oxo-2-(pyridin-3-yl)ethylidene)indolin-2-one

Using representative procedure 2, 3-hydroxy-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one (1.00 g, 3.40 mmol) in EtOH (30.0 mL), 37% HCl \(_{(aq)}\) (0.4 mL), and glacial ethanoic acid (10.0 mL) provided the title compound as a dark red solid, (0.23 g, 48%).

\(^1\)H NMR (250 MHz, DMSO) \(\delta\) 10.84 (s, 1H, NH), 9.21 (s, 1H, ArH), 8.86 (dd, \(J = 5.0, 1.0\) Hz, 1H, ArH), 8.49 – 8.36 (m, 1H, ArH), 8.16 (d, \(J = 7.5\) Hz, 1H, ArH), 7.72 (s, 1H, CH alkene), 7.64 (dd, \(J = 7.5, 5.0\) Hz, 1H, ArH), 7.64 (dd, \(J = 7.5, 5.0\) Hz, 1H, ArH), 7.38 (t, \(J = 7.5\) Hz, 1H, ArH), 6.98 (t, \(J = 7.5\) Hz, 1H, ArH), 6.89 (d, \(J = 7.5\) Hz, 1H, ArH); \(^13\)C NMR (100.6 MHz, DMSO) \(\delta\) 191.3, 169.1, 154.8, 150.5, 146.2, 138.2, 137.0, 134.3, 133.6, 128.0, 125.7, 125.1, 122.7, 120.8, 111.4; FTIR (thin film cm\(^{-1}\))\(\nu_{\text{max}}\): 1714 (m), 1599 (s), 1462 (w), 1015 (m), 786 (m), 751 (m); HRMS (TOF MS ES\(^+\)) m/z calculated for \([C_{15}H_{11}N_2O_2]^+\): 251.0821 \([M+H]^+\), found 251.0828; M.p. = 160-161 °C (EtOH)

(34) (E)-3-(2-(4-Methoxyphenyl)-2-oxoethylidene)indolin-2-one & (36) Ethyl 2-(4-methoxyphenyl)quinoline-4-carboxylate

Following representative procedure 2, 3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one(1.00 g, 3.37 mmol) in EtOH (35.0 mL), HCl \(_{(aq)}\) (0.4 mL) and glacial ethanoic acid (10.0 mL) gave a mixture of two products which were separated by flash column chromatography on silica gel (1:1 ethyl acetate :
petroleum ether). The major product 34 was afforded as an orange solid, (0.58 g, 62%). The minor product 36 was afforded as a white crystalline solid (0.09 g, 9%)

- (34)

\(^1\)H NMR (250 MHz, DMSO) \(\delta 10.78 (s, 1H, NH)\), 8.03 (d, \(J = 9.0 \text{ Hz}, 2H, ArH\)), 7.96 (d, \(J = 8.0 \text{ Hz}, 1H, ArH\)), 7.65 (s, \(1H, ArH\)), 7.31 (td, \(J = 8.0, 1.0 \text{ Hz}, 1H, ArH\)), 7.08 (d, \(J = 9.0 \text{ Hz}, 2H, ArH\)), 6.93 (t, \(J = 8.0 \text{ Hz}, 1H, ArH\)), 6.87 (d, \(J = 8.0 \text{ Hz}, 1H, ArH\)), 3.85 (s, \(3H, CH_3\)); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta 189.6, 168.3, 163.9, 144.7, 135.7, 132.6, 131.1, 130.0, 126.6, 126.5, 121.7, 114.4, 110.3, 55.7\); FTIR (thin film cm\(^{-1}\))\(V_{\text{max}}\): 1715 (s), 1655 (m), 1614 (m), 1572 (m), 1465 (w), 1335 (w), 1241 (m), 1181 (m), 1015 (w), 842 (w), 782 (m); HRMS (TOF MS ES\(^+\)) m/z calculated for [C\(_{17}\)H\(_{14}\)NO\(_2\)]\(^+\): 280.0974 [M+H]\(^+\), found 280.0983; M.p. = 169-170°C (iPrOH).

- (36)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.72 (d, J = 8.5 \text{ Hz}, 1H), 8.35 (s, 1H), 8.22 (d, \(J = 9.0 \text{ Hz}, 2H), 8.18 (d, J = 8.5 \text{ Hz}, 1H), 7.75 (t, J = 8.5 \text{ Hz}, 1H), 7.60 (t, J = 8.5 \text{ Hz}, 1H), 7.07 (d, J = 9.0 \text{ Hz}, 2H), 4.55 (q, J = 7.0 \text{ Hz}, 2H), 3.90 (s, 3H), 1.51 (t, J = 7.0 \text{ Hz}, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta 166.7, 161.2, 156.4, 149.4, 149.4, 136.1, 131.5, 130.2, 129.9, 129.0, 127.4, 125.5, 123.8, 119.9, 114.4, 62.0, 55.5, 14.5\); FTIR (thin film cm\(^{-1}\))\(V_{\text{max}}\): 2916 (m), 2853 (w), 1594 (s), 1548 (m), 1504 (s), 1370 (m), 1346 (s), 1253 (s), 1175 (s), 1194 (s), 1033 (s), 775 (m); HRMS (TOF MS ES\(^+\)) m/z calculated for [C\(_{19}\)H\(_{18}\)NO\(_3\)]\(^+\): 308.1287 [M+H]\(^+\), found 308.1296; M.p. = 70 – 72°C (CH\(_2\)Cl\(_2\)).

(37) 1-Methylindoline-2,3-dione (N-methylisatin)

Isatin (1.00 g, 6.8 mmol) was added to a suspension to of sodium hydride (0.41 g, 10.2 mmol) in THF (50 mL) at 0 °C. Reaction stirred at 0 °C for 1 hour after which methyl iodide (1.10 g, 7.5 mmol) was added and reaction was heated at reflux for a further 16 hours. The reaction mixture was cooled to 19 °C and quenched with H\(_2\)O (50 mL) then extracted with ethyl acetate (2 x 70 mL). The organic layers were
combined and dried over MgSO₄, filtered and then concentrated \textit{in vacuo} to afford the title compound as a red solid, which was purified via recrystallisation (CH₂Cl₂ : Petroleum ether 40-60) (1.10 g, 100 %).

\(^{1}\)H NMR (400 MHz, DMSO) δ 7.67 (td, \(J = 7.5, 1.2\) Hz, 1H, ArH), 7.53 (d, \(J = 7.5\) Hz, 1H, ArH), 7.14 (d, \(J = 7.5\) Hz, 1H, ArH), 7.12 (t, \(J = 7.5\) Hz, 1H, ArH), 3.13 (s, 3H, CH₃); \(^{13}\)C NMR (100.6 MHz, CDCl₃) δ 183.4, 158.2, 151.4, 138.5, 125.2, 123.8, 117.4, 110.0, 26.2; M.p = 121-123 °C (lit = 129 -130 °C).\(^{131}\)

(38a) 3-Hydroxy-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one

Using representative procedure \(^{1}\)N-methylisatin (1.00 g, 6.2 mmol), acetophenone (1.12 g, 9.32 mmol) and diethylamine (catalytic) in MeOH (50.0 mL) afforded the title compound as a colourless solid (1.08 g, 65%).

\(^{1}\)H NMR (400 MHz, DMSO) δ 7.87 (d, \(J = 8.5\) Hz, 2H, ArH), 7.62 (t, \(J = 7.5\) Hz, 1H, ArH), 7.48 (app t, \(J = 8.0\) Hz, 2H, ArH), 7.34 (d, \(J = 7.5\) Hz, 1H, ArH), 7.27 (t, \(J = 7.5\) Hz, 1H, ArH), 6.98 (d, \(J = 7.5\) Hz, 1H, ArH), 6.94 (t, \(J = 7.5\) Hz, 1H, ArH), 6.15 (s, 1H, OH), 4.14 (d, \(J = 17.5\) Hz, 1H, CH₂), 3.65 (d, \(J = 17.5\) Hz, 1H, CH₂), 3.15 (s, 1H, CH₃); \(^{13}\)C NMR (100.6 MHz, DMSO) δ 196.5, 176.7, 144.4, 136.0, 133.5, 131.1, 129.1, 128.7, 127.9, 123.2, 121.8, 108.2, 72.7, 46.1, 26.0; M.p = 177 – 179 °C (CH₂Cl₂) (lit = 176.5 – 178.0 °C).\(^{130}\)
(38) (E)-1-Methyl-3-(2-oxo-2-phenylethylimidened)indolin-2-one

Using representative procedure 2, 3-hydroxy-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (0.90 g, 3.20 mmol) in EtOH (30.0 mL), HCl\(_{\text{aq}}\) (0.4 mL) and glacial ethanoic acid (10.0 mL) for 3 hours afforded the title compound as a red solid, (0.54 g, 94%).

\(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.08 (d, \(J = 7.5\) Hz, 2H, ArH), 7.99 (d, \(J = 7.5\) Hz, 1H, ArH), 7.80 (s, 1H, CH alkene), 7.73 (t, \(J = 7.5\) Hz, 1H, ArH), 7.61 (t, \(J = 7.5\) Hz, 2H, ArH), 7.44 (t, \(J = 7.5\) Hz, 1H, ArH), 7.07 (d, \(J = 7.5\) Hz, 1H, ArH), 7.02 (t, \(J = 7.5\) Hz, 1H, ArH), 3.21 (s, 3H, C\(_3\)H\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 188.6, 146.3, 137.3, 135.7, 134.7, 133.3, 129.7, 129.3, 129.1, 127.4, 126.6, 122.8, 119.7, 109.7, 26.7; FTIR (thin film cm\(^{-1}\))\(\nu_{\text{max}}\): 1715 (s), 1662 (s), 1601 (s), 1367 (m), 1338 (m), 1228 (s), 1100 (w), 1011 (w), 778 (w), 750 (m); HRMS (TOF MS ES\(^+\)) m/z calculated for [C\(_{17}\)H\(_{14}\)NO\(_2\)]\(^+\): 264.1025 [M+H]\(^+\), found 264.1036; M.p. = 97-98 °C. (CH\(_2\)Cl\(_2\) : Petroleum ether 40 - 60)

(39a) 3-(2-(4-Chlorophenyl)-2-oxoethyl)-3-hydroxy-1-methylindolin-2-one

Using representative procedure 1, N-methylisatin (0.50 g, 3.10 mmol), 4-chloroacetophenone (0.72 g, 4.66 mmol) and diethylamine (5 drops) in MeOH (30 mL) gave a crude colourless solid. This was purified by recrystallisation with CH\(_2\)Cl\(_2\)
and petroleum ether, affording the title compound as a colourless solid (0.81 g, 97%).

$^1$H NMR (400 MHz, DMSO) δ 7.88 (app d, J = 8.5 Hz, 2H, ArH), 7.55 (app d, J = 8.5 Hz, 2H, ArH), 7.33 (dd, J = 7.5, 1.0 Hz, 1H, ArH), 7.27 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.98 (d, J = 7.5 Hz, 1H, ArH), 6.94 (td, J = 7.5, 1.0 Hz, 1H, ArH), 6.18 (s, 1H, OH), 4.13 (d, J = 17.5 Hz, 1H, CH$_2$), 3.63 (d, J = 17.5 Hz, 1H, CH$_2$), 3.14 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, DMSO) δ 195.5, 176.6, 144.3, 138.4, 134.7, 130.9, 129.9, 129.1, 128.8, 123.2, 121.9, 108.2, 72.7, 46.0, 26.0; FTIR (film cm$^{-1}$)$\nu_{\text{max}}$: 3345 (br), 1683 (s), 1618 (m), 1590 (w), 1479 (m), 1355 (w), 1212 (w), 1694 (m), 990 (w), 754 (w); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{17}$H$_{15}$ClNO$_3$]$^+$: 316.0740 [M+H]$^+$, found 316.0725; M.p = 156 – 158°C (CH$_2$Cl$_2$).

(39) (E)-3-(2-(4-Chlorophenyl)-2-oxoethylidene)-1-methylindolin-2-one

Using representative procedure 2, 3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxy-1-methylindolin-2-one (0.81 g, 2.60 mmol) in EtOH (25.0 mL), HCl$_{(aq)}$ (0.3 mL), and glacial ethanoic acid (8.0 mL) for 3 hours provided the title compound as a red solid, (0.73 g, 94%).

$^1$H NMR (400 MHz, DMSO) δ 8.10 (app d, J = 8.5 Hz, 2H, ArH), 8.02 (d, J = 7.5 Hz, 1H, ArH), 7.77 (s, 1H, CH alkene), 7.68 (app d, J = 8.5 Hz, 2H, ArH), 7.46 (app td, J = 8.0, 1.0 Hz, 1H, ArH), 7.08 (d, J = 8.0 Hz, 1H, ArH), 7.04 (app td, J = 7.5, 1.0 Hz, 1H, ArH), 3.21 (s, 1H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 189.7, 167.9, 146.3, 140.4, 137.2, 136.1, 133.0, 129.3, 128.0, 125.3, 122.9, 120.1, 108.4, 26.4; FTIR (thin film cm$^{-1}$)$\nu_{\text{max}}$: 1705 (s), 1660 (s), 1601 (s), 1470 (m), 1402 (w), 1369 (m), 1336 (m), 1231 (s), 1093 (m), 1009 (m), 837 (m), 780 (m), 743 (s); HRMS (TOF MS ES$^+$) m/z
calculated for \([\text{C}_{17}\text{H}_{13}\text{ClNO}_2]^+\): 298.0635 [M+H]^+, found 298.0646; M.p. = 140-141°C (CH₂Cl₂: Petroleum ether 40 - 60).

(40a) 3-Hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-methylindolin-2-one

Using representative procedure 1, \(N\)-methylisatin (0.50 g, 3.10 mmol), 4-chloroacetophenone (0.70 g, 4.66 mmol) and diethylamine (5 drops) in MeOH (30 mL) gave a crude colourless solid. This was purified by recrystallisation with CH₂Cl₂ and petroleum ether, affording the title compound as a colourless solid (0.88 g, 91%).

\(^1\)H NMR (250 MHz, DMSO) \(\delta\) 7.84 (d, \(J = 9.0\) Hz, 1H, ArH), 7.36 – 7.20 (m, 2H, ArH), 7.04 – 6.87 (m, 4H, ArH), 6.10 (s, 1H, OH), 4.07 (d, \(J = 17.5\) Hz, 1H, CH₂), 3.82 (s, 3H, CH₃), 3.56 (d, \(J = 17.5\) Hz, 1H, CH₂), 3.14 (s, 3H, CH₃); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta\) 194.7, 176.8, 163.3, 144.4, 131.2, 130.3, 129.1, 129.0, 123.1, 121.8, 113.9, 108.2, 72.7, 55.5, 45.7, 25.9; M.p = 186 – 189°C (CH₂Cl₂) (lit = 192.3 -193.8°C).

(40) (\(E\))-3-(2-(4-Methoxyphenyl)-2-oxoethylidene)-1-methylindolin-2-one

Using representative procedure 2, 3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-methylindolin-2-one (0.88 g, 2.82 mmol) in EtOH (30.0 mL), HCl\(_{\text{aq}}\) (0.3 mL), and
glacial ethanoic acid (8.0 mL) for 3 hours provided the title compound as an orange solid, (0.77 g, 94%).

\(^1\)H NMR (400 MHz, DMSO) \( \delta \) 8.06 (app d, \( J = 9.0 \) Hz, 2H, ArH), 7.91 (d, \( J = 7.5 \) Hz, 1H, ArH), 7.77 (s, 1H, CH, alkene), 7.43 (t, \( J = 7.5 \) Hz, 1H, ArH), 7.13 (app d, \( J = 9.0 \) Hz, 2H, ArH), 7.07 (d, \( J = 7.5 \) Hz, 1H, ArH), 7.01 (t, \( J = 7.5 \) Hz, 1H, ArH), 3.87 (s, 3H, CH\(_3\)), 3.21 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 189.4, 167.9, 164.0, 145.7, 135.6, 132.1, 131.1, 130.6, 127.4, 126.7, 122.6, 120.0, 114.0, 108.0, 55.5, 26.1; FTIR (thin film cm\(^{-1}\)) \( \nu_{\text{max}} \): 1713 (m), 1656 (m), 1602 (s) 1469 (m), 1337 (m), 1238 (s), 1172 (m), 1100 (w), 1026 (m), 841 (w), 783 (w), 752 (w); HRMS (TOF MS ES+) m/z calculated for \([C_{18}H_{16}NO_3]^+\): 294.1130 [M+H]\(^+\), found 294.1124; M.p. = 104-105 °C (CH\(_2\)Cl\(_2\) : Petroleum ether 40 - 60).

\[\text{(41) 4-Chloro-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one}\]

Using representative procedure 1, 4-chloroisatin (1.00 g, 5.50 mmol), acetophenone (0.72 g, 6.00 mmol) and diethylamine (0.44 g, 6.00 mmol) in MeOH (50 mL) afforded the title compound as a colourless solid (1.25 g, 75%).

\(^1\)H NMR (400 MHz, DMSO) \( \delta \) 10.55 (s, 1H, NH), 7.89 (d, \( J = 8.5 \) Hz, 2H, ArH), 7.64 (t, \( J = 7.5 \) Hz, 1H, ArH), 7.50 (app t, \( J = 8.0 \) Hz, 2H, ArH), 7.19 (s, \( J = 8.0 \) Hz, 1H, ArH), 6.84 (dd, \( J = 8.0, 1.0 \) Hz, 1H, ArH), 6.79 (dd, \( J = 8.0, 1.0 \) Hz, 1H, ArH), 6.28 (s, 1H, OH), 4.37 (d, \( J = 18.0 \) Hz, 1H, CH\(_2\)), 3.66 (d, \( J = 18.0 \) Hz, 1H, CH\(_2\)), 3.33 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100.6 MHz, DMSO) \( \delta \) 197.0, 178.0, 145.7, 136.1, 134.1, 131.2, 130.2, 129.3, 128.3, 128.1, 122.5, 109.1, 74.4, 44.8; \(^{132}\)M.p = 201 – 205 °C (MeOH).
(46) (Z)-4-Chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one$^{14}$

Using representative procedure 2, 4-chloro-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (0.50 g, 1.66 mmol) in EtOH (15.0 mL), HCl$_{aq}$ (0.2 mL) and glacial ethanoic acid (5.0 mL) for 4 hours, provided the title compound as a yellow solid, (0.21 g, 45%).

$^1$H NMR (400 MHz, DMSO) δ 10.90 (s, 1H, NH), 7.95 (s, 1H, CH alkene), 7.93 (d, J = 8.0 Hz, 2H, ArH), 7.67 (app t, J = 7.5 Hz, 1H, ArH), 7.54 (t, J = 7.5 Hz, 2H, ArH), 7.34 (t, J = 8.0 Hz, 1H, ArH), 7.11 (d, J = 8.0 Hz, 1H, ArH), 6.87 (d, J = 8.0 Hz, 1H, ArH); $^{13}$C NMR (100.6 MHz, DMSO) δ 194.4, 166.2, 145.3, 138.9, 136.0, 135.0, 132.5, 131.3, 130.8, 129.8, 129.4, 123.3, 118.0, 109.6; $^{14}$ M.p. = 156-158 °C (iPrOH).

(42) 4-Chloro-3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one

Using representative procedure 1, 4-chloroisatin (1.00 g, 5.50 mmol), acetophenone 4-chloroacetophenone (0.93 g, 6.00 mmol) and diethylamine (5 drops) in MeOH (50 mL) afforded the title compound as a colourless solid (1.26 g, 68%).

$^1$H NMR (400 MHz, DMSO) δ 10.57 (s, 1H, NH), 7.92 (d, J = 8.5 Hz, 2H, ArH), 7.58 (d, J = 8.5 Hz, 2H, ArH), 7.20 (t, J = 8.0 Hz, 1H, ArH), 6.85 (d, J = 8.0 Hz, 1H, ArH), 6.80 (d, J = 8.0 Hz, 1H, ArH), 6.31 (s, 1H, OH), 4.34 (d, J = 18.0 Hz, 1H, CH$_2$), 3.67 (d, J = 18.0 Hz, 1H, CH$_2$); $^{13}$C NMR (100.6 MHz, DMSO) δ 195.6, 177.5, 145.2, 138.8, 134.4, 130.8, 129.8, 129.0, 127.6, 122.1, 108.7, 74.0, 44.3; $^2$ FTIR (film cm$^{-1}$)$v_{max}$: 3095 (br),

$^2$ Two signals at same chemical shift
1706 (m), 1673 (s), 1618 (m), 1445 (m), 1180 (m), 1092 (m), 1054 (w), 991 (m);
HRMS (TOF MS ES+) m/z calculated for \([\text{C}_{16}\text{H}_{12}\text{Cl}_{2}\text{NO}_{3}]^+\): 336.0194 \([M+H]^+\), found 336.0198; M.p = 194 – 198 °C (MeOH).

(47) (Z)-4-Chloro-3-(2-(4-chlorophenyl)-2-oxoethylidene)indolin-2-one

![Chemical structure of (Z)-4-Chloro-3-(2-(4-chlorophenyl)-2-oxoethylidene)indolin-2-one](image)

Using representative procedure 2, 4-chloro-3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (0.56 g, 1.66 mmol) in EtOH (15.0 mL), HCl(aq) (0.2 mL) and glacial ethanoic acid (5.0 mL) for 4 hours, provided the title compound as a yellow solid, (0.43 g, 81%).

\(^1\)H NMR (250 MHz, DMSO) \(\delta\) 10.91 (s, 1H, NH), 7.93 (d, \(J = 8.0\) Hz, 2H, ArH), 7.91 (s, 1H, CH alkene), 7.59 (d, \(J = 8.0\) Hz, 2H, ArH), 7.34 (t, \(J = 7.5\) Hz, 1H, ArH), 7.10 (d, \(J = 7.5\) Hz, 1H, ArH), 6.86 (d, \(J = 7.5\) Hz, 1H, ArH), \(^13\)C NMR (100.6 MHz, DMSO) \(\delta\) 194.8, 165.7, 144.8, 136.2, 135.7, 133.6, 131.9, 130.5, 129.3, 128.8, 128.5, 122.8, 117.7, 109.0; \(^{14}\)M.p = 218-219 °C (iPrOH).

(43) 4-Chloro-3-hydroxy-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one

![Chemical structure of 4-Chloro-3-hydroxy-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one](image)

Using representative procedure 1, 4-chloroisatin (0.50 g, 2.75 mmol), 3-acetyl pyridine (0.50 g, 4.13 mmol) and diethylamine (0.30 g, 4.13 mmol) in MeOH (30 mL) afforded the title compound as a colourless solid (0.83 g, 100%).
\(^1\)H NMR (400 MHz, DMSO) \(\delta\) 9.06 (s, 1H, NH), 8.78 (d, \(J = 5.0\) Hz, 1H, ArH), 8.23 (d, \(J = 8.0\) Hz, 1H, ArH), 7.52 (dd, \(J = 8.0, 5.0\) Hz, 1H, ArH), 7.30 (t, \(J = 8.0\) Hz, 1H, ArH), 7.00 (d, \(J = 8.0\) Hz, 1H, ArH), 6.94 (d, \(J = 8.0\) Hz, 1H, ArH), 6.64 (s, 1H, OH), 4.46 (d, \(J = 18.0\) Hz, 1H, CH\(_2\)), 3.84 (d, \(J = 18.0\) Hz, 1H, CH\(_2\)); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta\) 196.2, 177.5, 153.9, 149.2, 145.1, 135.6, 131.1, 130.9, 129.9, 127.6, 124.0, 122.2, 108.8, 74.0, 44.6; FTIR (film cm\(^{-1}\)) \(\nu_{\text{max}}\): 3090 (br), 1715 (s), 1693 (s), 1589 (s), 1451 (m), 1355 (m), 1227 (w), 1176 (m), 1672 (w), 992 (w), 782 (m); HRMS (TOF MS ES+) m/z calculated for \([C_{15}H_{12}^{35}ClN_2O_3]^+\): 303.0538 [M+H]\(^+\), found 303.0538; M.p = 160 – 161 °C (MeOH).

(2) (Z)-4-Chloro-3-(2-oxo-2-(pyridin-3-yl)ethylidene)indolin-2-one\(^{14}\)

Using representative procedure 2, 4-chloro-3-hydroxy-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one (0.25 g, 0.93 mmol) in EtOH (10.0 mL), HCl\(_{\text{aq}}\) (0.4 mL) and glacial ethanoic acid (1.0 mL) for 1.5 hours, provided the title compound as a yellow solid, (0.04 g, 17%).

\(^1\)H NMR (400 MHz, DMSO) \(\delta\) 10.93 (s, 1H), 9.05 (s, 1H, NH), 8.80 (d, \(J = 5.0\) Hz, 1H, ArH), 8.27 (d, \(J = 8.0\) Hz, 1H, ArH), 7.92 (s, 1H, CH alkene), 7.57 (dd, \(J = 8.0, 5.0\) Hz, 1H, ArH), 7.34 (t, \(J = 8.0\) Hz, 1H, ArH), 7.10 (d, \(J = 8.0\) Hz, 1H, ArH), 6.86 (d, \(J = 8.0\) Hz, 1H, ArH); 194.5, 165.6, 153.6, 149.5, 144.9, 135.8, 134.8, 132.0, 131.2, 131.2, 129.4, 124.0, 122.8, 117.6, 109.2;\(^{14}\) M.p. = 193-194 °C (iPrOH).
(50) 4-Chloro-1-methylindoline-2,3-dione (N-methyl-4-chloroisatin)\textsuperscript{14}

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Me} \\
\end{array}
\xrightarrow{\begin{array}{c}
\text{K}_2\text{CO}_3 \text{(3.0 equiv.)} \\
\text{MeI} \text{(1.1 equiv.)}
\end{array}}
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Me}
\end{array}
\]

DMF, 19 °C, 24 h

4-Chloroisatin (2.0 g, 11.0 mmol) was dissolved in DMF (20 mL), potassium carbonate (4.6 g, 33.0 mmol) followed by methysl iodide (1.7 g, 12.1 mmol) was added. The resultant reaction mixture stirred for 24 hours at 19 °C, then diluted with ethyl acetate (50 mL) and then washed with H\textsubscript{2}O (3 x 50 mL). The organic layer then dried over MgSO\textsubscript{4}, filtered and then concentrated \textit{in vacuo} to afford the title compound as an orange solid, which was purified via recrystallisation, (CH\textsubscript{2}Cl\textsubscript{2} : Petroleum ether 40-60) (1.00 g, 50%).

\textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \(\delta\) 7.53 (t, \(J = 8.0 \text{ Hz, ArH}\)), 7.09 (dd, \(J = 8.0, 0.5 \text{ Hz, 1H, ArH}\)), 6.82 (dd, \(J = 8.0, 0.5 \text{ Hz, 1H, ArH}\)), 3.29 (s, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (100.6 MHz, DMSO) \(\delta\) 180.2, 157.5, 152.7, 138.7, 130.8, 124.1, 114.3, 109.3, 26.2; FTIR (film cm\textsuperscript{-1}) \(\nu_{max}\): 1733 (s), 1598 (m), 1452 (w), 1351 (w), 1208 (w), 1158 (w), 1127 (w), 1045 (w), 787 (m); HRMS (TOF MS ES+) m/z calculated for [C\textsubscript{9}H\textsubscript{6}\textsubscript{35}ClNO\textsubscript{2}]\textsuperscript{+}: 196.0165 [M+H]\textsuperscript{+}, found 196.0159; M.p = 121-123 °C (EtOAc)

(44) 4-Chloro-3-hydroxy-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Me}
\end{array}
\xrightarrow{(1.5 \text{ equiv.})}
\begin{array}{c}
\text{Cl} \\
\text{HO} \\
\text{N} \\
\text{Me}
\end{array}
\]

MeOH, HNE\textsubscript{3} (1.5 equiv.)
20 °C, 20 h

Using representative procedure 1, N-methyl-4-chloroisatin (0.50 g, 2.56 mmol), acetophenone (0.46 g, 3.84 mmol) and diethylamine (0.28 g, 3.84 mmol) in MeOH (25 mL) gave a crude colourless solid which was purified by recrystallisation (CH\textsubscript{2}Cl\textsubscript{2} : petroleum ether 40 - 60) to afford the title compound as a colourless solid (0.81 g, 100%).
$^1$H NMR (250 MHz, DMSO) δ 7.89 (d, $J = 7.0$ Hz, 2H, ArH), 7.64 (t, $J = 7.0$ Hz, 1H, ArH), 7.53 (t, $J = 7.5$ Hz, 2H, ArH), 7.30 (t, $J = 8.0$ Hz, 1H, ArH), 7.01 (d, $J = 7.0$ Hz, 1H, ArH), 6.93 (dd, $J = 8.0, 1.0$ Hz, 1H, ArH), 4.44 (d, $J = 18.0$ Hz, 1H, CH$_2$), 3.72 (d, $J = 18.0$ Hz, 1H, CH$_2$), 3.16 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, DMSO) δ 196.5, 175.9, 146.5, 135.6, 133.7, 130.8, 129.4, 128.9, 127.9, 127.0, 122.8, 107.4, 73.6, 44.4, 26.3; FTIR (film cm$^{-1}$) $\nu_{\text{max}}$: 3372 (br), 1713 (s), 1685 (s), 1611 (s), 1460 (s), 1393 (w), 1350 (m), 1226 (m), 1124 (m), 992 (w), 754 (m); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{17}$H$_{15}$ClNO$_3$]$^+$: 316.0739 [M+H$^+$], found 316.0740; M.p. = 134 – 135 °C (MeOH).

(48) (Z)-4-Chloro-1-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-one

![Structural diagram]

Using representative procedure 2, 4-chloro-3-hydroxy-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (0.75 g, 2.50 mmol) in EtOH (25.0 mL), HCl$_{\text{(aq)}}$ (0.3 mL) and glacial ethanoic acid (7.0 mL) for 2 hours, provided the title compound as a yellow solid, (0.54 g, 58%).

$^1$H NMR (250 MHz, DMSO) δ 8.03 (s, 1H, CH alkene), 7.97 – 7.87 (m, 2H, ArH), 7.67 (t, $J = 7.0$ Hz, 1H, ArH), 7.59 – 7.48 (m, 2H, ArH), 7.43 (t, $J = 8.0$ Hz, 1H, ArH), 7.17 (d, $J = 8.0$ Hz, 1H, ArH), 7.07 (d, $J = 7.0$ Hz, 1H, ArH), 7.08 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, DMSO) δ 195.1, 164.7, 146.3, 137.2, 136.2, 134.2, 132.3, 129.9, 129.6, 129.3, 129.0, 123.8, 117.4, 108.6, 26.5; FTIR (thin film cm$^{-1}$) $\nu_{\text{max}}$: 1713 (s), 1663 (s), 1609 (s), 1457 (m), 1330 (m), 1241 (w), 1123 (m), 1057 (w), 768 (m), 704 (m); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{17}$H$_{13}$ClNO$_3$]$^+$: 298.0635 [M+H$^+$], found 298.0633; M.p. = 196-198 °C (CH$_2$Cl$_2$ : Petroleum ether 40 - 60).
(45) 4-Chloro-3-hydroxy-1-methyl-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one

Using representative procedure 1, N-methyl-4-chloroisatin (1.07 g, 5.50 mmol), 3-acetyl pyridine (0.73 g, 6.00 mmol) and diethylamine (0.44 g, 6.0 mmol) in MeOH (50 mL) gave a crude colourless solid, which was purified by recrystallisation (CH$_2$Cl$_2$ : petroleum ether 40 - 60) to afford the title compound as a colourless solid (1.60 g, 92%).

$^1$H NMR (400 MHz, DMSO) δ 9.06 (s, 1H, ArH), 8.79 (dt, $J$ = 5.0, 2.0 Hz, 1H, ArH), 8.24 (dt, $J$ = 8.0, 2.0 Hz, 1H, ArH), 7.53 (dd, $J$ = 8.0, 5.0 Hz, 1H, ArH), 7.31 (t, $J$ = 8.0 Hz, 1H, ArH), 7.02 (d, $J$ = 8.0 Hz, 1H, ArH), 6.94 (d, $J$ = 8.0 Hz, 1H, ArH), 6.42 (s, 1H, OH), 4.43 (d, $J$ = 18.0 Hz, 1H, CH$_2$), 3.78 (d, $J$ = 18.0 Hz, 1H, CH$_2$), 3.16 (s, 3H, NCH$_3$), $^{13}$C NMR (100.6 MHz, DMSO) δ 196.6, 176.3, 154.3, 153.8, 150.0, 149.5, 146.8, 136.0, 131.4, 130.0, 127.2, 124.4, 124.3, 123.3, 107.9, 74.0, 45.1, 26.9 ; FTIR (film cm$^{-1}$)$V_{max}$: 3187 (br), 1717 (s), 1693 (s), 1610 (s) 1590 (m), 1460 (m), 1422 (w), 1353 (m), 1236 (w), 1125 (m), 1073 (m), 1028 (m), 993 (w), 781 (m), 735 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{16}$H$_{14}$ClN$_2$O$_3$]$^+$: 317.0693 [M+H]$^+$, found 317.0698; M.p = 120 – 121 °C (MeOH).

(49) (Z)-4-chloro-1-methyl-3-(2-oxo-2-(pyridin-3-yl)ethylidene)indolin-2-one

Using representative procedure 2, 4-chloro-3-hydroxy-1-methyl-3-(2-oxo-2-(pyridin-3-yl)ethyl)indolin-2-one (0.10 g, 0.32 mmol) in EtOH (3 mL), HCl$_{aq}$ (0.04 mL) and glacial ethanoic acid (1.0 mL) for 2 hours, provided the title compound as a yellow solid, (0.54 g, 57%).
(51) 6-Chloro-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one

Using representative procedure 1, 6-chloroisatin (0.50 g, 2.75 mmol), acetophenone (0.47 g, 4.13 mmol) and diethylamine (0.30 g, 4.13 mmol) in MeOH (30 mL) afforded the title compound as a colourless solid (0.65 78%).

\[ \begin{align*}
\text{Cl} & \quad \text{N} \\
\text{CH} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\end{align*} \]

Using represent procedure 1, 6-chloroisatin (0.50 g, 2.75 mmol), acetophenone (0.47 g, 4.13 mmol) and diethylamine (0.30 g, 4.13 mmol) in MeOH (30 mL) afforded the title compound as a colourless solid (0.65 78%).

\[ \begin{align*}
\text{Cl} & \quad \text{N} \\
\text{CH} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\end{align*} \]
(53) (E)-6-Chloro-3-(2-oxo-2-phenylethylidene)indolin-2-one

Using representative procedure 2, 6-chloro-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one (0.45 g, 1.49 mmol) in EtOH (15.0 mL), HCl\textsubscript{(aq)} (0.5 mL), and glacial ethanoic acid (1.5 mL), for 3 hours, provided the title compound as an orange solid, (0.77 g, 99%).

\(^1\)H NMR (250 MHz, DMSO) \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.00 (s, 1H, NH), 8.09 (t, \(J = 7.5\) Hz, 2H, ArH), 7.77 (s, 1H, CH alkene), 7.73 (t, \(J = 7.5\) Hz, 2H, ArH), 7.61 (t, \(J = 7.5\) Hz, 2H, ArH), 7.04 (dd, \(J = 7.5, 2.0\) Hz, 1H, ArH), 6.91 (d, \(J = 2.0\) Hz, 1H, ArH); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta\) 191.0, 168.2, 146.3, 137.0, 135.4, 134.1, 129.1, 128.8, 128.6, 128.2, 126.2, 121.6, 118.8, 110.4; FTIR (thin film cm\(^{-1}\)\(\nu_{\text{max}}\)), 1728 (s), 1663 (m), 1624 (w) 1600 (m), 1578 (w), 1334 (m), 1236 (w), 1016 (m), 842 (m), 824 (s) 722 (s); HRMS (TOF MS ES+) m/z calculated for [C\(_{16}\)H\(_{11}\)Cl\(_5\)NO\(_2\)]\(^+\): 284.0478 [M+H]\(^+\), found 284.0487; M.p. = 229-230 °C (iPrOH).

(52) 6-Chloro-3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one

Using representative procedure 1, 6-chloroisatin (0.50 g, 2.75 mmol), 4-chloroacetophenone (0.64 g, 4.13 mmol) and diethylamine (0.30 g, 4.13 mmol) in MeOH (30 mL) afforded the title compound as a colourless solid (0.67 g, 72%).
\[^1\text{H}\ \text{NMR} \ (400 \ \text{MHz, DMSO}) \ \delta \ 10.47 \ (s, \ 1\text{H}, \ ANH), \ 7.90 \ (\text{app} \ d, \ J = 8.5 \ \text{Hz}, \ 2\text{H}, \ Ar\text{H}), \ 7.57 \ (\text{app} \ d, \ J = 8.5 \ \text{Hz}, \ 2\text{H}, \ Ar\text{H}), \ 7.29 \ (d, \ J = 8.0 \ \text{Hz}, \ 1\text{H}, \ Ar\text{H}), \ 6.91 \ (dd, \ J = 8.0, \ 2.0 \ \text{Hz}, \ 1\text{H}, \ Ar\text{H}), \ 6.82 \ (d, \ J = 2.0 \ \text{Hz}, \ 1\text{H}, \ Ar\text{H}), \ 4.10 \ (d, \ J = 18.0 \ \text{Hz}, \ 1\text{H}, \ CH_2), \ 3.60 \ (d, \ J = 18.0 \ \text{Hz}, \ 1\text{H}, \ CH_2); \ ^{13}\text{C} \ \text{NMR} \ (100.6 \ \text{MHz, DMSO}) \ \delta \ 195.6, \ 178.2, \ 144.5, \ 138.5, \ 134.7, \ 133.2, \ 130.6, \ 129.9, \ 128.9, \ 125.1, \ 120.8, \ 109.5, \ 72.6, \ 45.7; \ \text{FTIR} \ (\text{film cm}^{-1})_{\text{v}}^{\text{max}}: \ 3299 \ (\text{br}), \ 1730 \ (\text{m}), \ 1683 \ (\text{s}), \ 1625 \ (\text{w}), \ 1589 \ (\text{m}), \ 1399 \ (\text{m}), \ 1220 \ (\text{m}), \ 1065 \ (\text{s}), \ 812 \ (\text{m}); \ \text{HRMS} \ (\text{TOF} \ \text{MS} \ \text{ES}^+) \ m/z \ \text{calculated for} \ [C_{16}H_{13}\text{ClNO}_3]^+: \ 336.0194 \ [M+H]^+, \ \text{found} \ 336.0190; \ M.p. = 180 – 184 \ ^\circ \text{C (MeOH)}. \n
(54) \ (E)-6-Chloro-3-(2-(4-chlorophenyl)-2-oxoethylidene)indolin-2-one

\[
\begin{align*}
\begin{array}{c}
\text{Cl} \quad \text{O} \\
\text{Cl} \quad \text{O} \\
\text{H} \quad \text{N}
\end{array} 
\quad \text{HCl (4 equiv.),} \quad \text{AcOH (10 equiv.)} 
\quad \text{EtOH, } \Delta 
\quad \begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{N}
\end{array}
\end{align*}
\]

Using representative procedure 2, 6-chloro-3-(2-(4-chlorophenyl)-2-oxoethyl)-3-hydroxyindolin-2-one (0.50 g, 1.49 mmol) in EtOH (15.0 mL) using HCl\text{aq} (0.5 mL) and glacial ethanoic acid (1.5 mL), for 3 hours, provided the title compound as a red solid, (0.34 g, 72%).

\[^1\text{H}\ \text{NMR} \ (400 \ \text{MHz, DMSO}) \ \delta \ 10.99 \ (s, \ 1\text{H}, \ NH), \ 8.12 \ (d, \ J = 8.5 \ \text{Hz}, \ 1\text{H}, \ Ar\text{H}), \ 8.07 \ (\text{app} \ d, \ J = 8.5 \ \text{Hz}, \ 2\text{H}, \ Ar\text{H}), \ 7.65 \ (\text{app} \ d, \ J = 8.5 \ \text{Hz}, \ 2\text{H}, \ Ar\text{H}), \ 7.03 \ (dd, \ J = 8.5, \ 2.0 \ \text{Hz}, \ 1\text{H}, \ Ar\text{H}), \ 6.89 \ (d, \ J = 2.0 \ \text{Hz}, \ 1\text{H}, \ Ar\text{H}); \ ^{13}\text{C} \ \text{NMR} \ (100.6 \ \text{MHz, DMSO}) \ \delta \ 189.7, \ 168.1, \ 146.4, \ 139.0, \ 137.2, \ 135.9, \ 135.7, \ 130.5, \ 129.2, \ 128.4, \ 125.5, \ 121.6, \ 118.8, \ 110.4; \ \text{FTIR} \ (\text{thin film cm}^{-1})_{\text{v}}^{\text{max}}: \ 1726 \ (\text{s}), \ 1665 \ (\text{m}), \ 1622 \ (\text{m}), \ 1603 \ (\text{m}), \ 1436 \ (\text{m}), \ 1329 \ (\text{m}), \ 1231 \ (\text{w}), \ 1010 \ (\text{w}), \ 840 \ (\text{m}), \ 824 \ (\text{m}); \ \text{HRMS} \ (\text{EI}^+) \ m/z \ \text{calculated for} \ [C_{16}H_{10}\text{Cl}_2\text{NO}_2]^+: \ 317.0010 \ [M+H]^+, \ \text{found} \ 316.9999; \ M.p. = 239-241 \ ^\circ \text{C (iPrOH)}.}
(Z-33) \( (Z)-3-(2\text{-Oxo-2-phenylethylidene})\text{indolin-2-one}\) \(^{15}\)

\[
\begin{center}
\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{image}}
\end{array}
\end{center}
\]

\((E)-3-(2\text{-oxo-2-phenylethylidene})\text{indolin-2-one}\) (0.50 g, 2.00 mmol) was dissolved in dichloromethane (25 mL). To this was added aluminium trichloride (0.27 g, 2.00 mmol) and resultant reaction mixture was stirred at 20 °C for three days under an argon atmosphere upon which a black precipitate formed. Reaction quenched \textit{via} the slow addition of saturated NaHCO\(_3\)(aq) at 0 °C and then extracted with ethyl acetate (2x 40 mL). The combined extracts were dried over MgSO\(_4\) and the solvent was removed \textit{in vacuo} to give an orange solid which was a 1.0 : 2.5 \((E : Z)\). Separation of isomers was achieved via reverse phase preparative HPLC (Waters XBridge™ Prep C18 5 \(\mu\)m OBD 19 x 25 mm; eluting with 70:30 methanol : water at 17 mL/min.) affording the title compound as a yellow solid (19 mg, 4 %).

\(^{1}\)H NMR (400 MHz, DMSO) \(\delta\) 10.59 (s, 1H, NH), 7.93 (d, \(J = 7.5\) Hz, 2H, ArH), 7.70 (s, 1H, CH alkene), 7.77 – 7.63 (m, 2H, ArH), 7.54 (t, \(J = 7.5\) Hz, 2H, ArH), 7.31 (t, \(J = 7.5\) Hz, 1H, ArH), 7.04 (t, \(J = 7.5\) Hz, 1H, ArH), 6.87 (d, \(J = 7.5\) Hz, 1H); \(^{13}\)C NMR (100.6 MHz, DMSO) \(\delta\) 195.5, 166.8, 143.4, 136.4, 132.7, 132.6, 131.4, 129.3, 129.0, 122.4, 122.1, 110.6; \(^{3}\) FTIR (CH\(_2\)Cl\(_2\) film cm\(^{-1}\))\(\nu_{\text{max}}\): 1706 (s), 1660 (m), 1619 (w), 1468 (m), 1349 (m), 1196 (w), 745 (m); HRMS (TOF MS ES+) \(m/z\) calculated for \([C_{17}H_{13}NO_2]^+\): 250.0868 [M+H]\(^+\), found 250.0865; M.p = 155-157 °C.

\(^3\) Two signals at same chemical shift
(59) 3-Hydroxy-4-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one

4-Methylindoline-2,3-dione (4-methylisatin) (0.08 g, 0.50 mmol) was dissolved in MeOH (5 ML). To this was added acetophenone (0.09 g, 0.75 mmol) followed by diethylamine (0.06 g, 0.75 mmol). The reaction mixture was stirred at 20 °C for 48 hours and then concentrated in vacuo to give a pale orange solid, which was purified via flash column chromatography (1:1 ethyl acetate : petroleum ether) affording the title compound as a colourless solid (0.08 g, 57 %)

^1^H NMR (250 MHz, DMSO) δ 10.24 (s, 1H, NH), 7.87 (d, J = 7.5 Hz, 2H, ArH), 7.62 (t, J = 7.5 Hz, 1H, ArH), 7.48 (t, J = 7.5 Hz, 2H, ArH), 7.04 (t, J = 7.5 Hz, 1H, ArH), 6.61 (d, J = 7.5 Hz, 2H, 2 x ArH), 6.03 (s, 1H, OH), 4.10 (d, J = 17.5 Hz, 1H, CH₂), 3.61 (d, J = 17.5 Hz, 1H, CH₂); ^13^C NMR (100.6 MHz, Acetone) δ 197.6, 157.7, 145.3, 137.8, 134.0, 132.1, 131.5, 129.6, 129.5, 128.8, 106.0, 104.0, 103.9, 55.6, 45.1; FTIR (thin film cm⁻¹)ν max: 3190 (br), 1713 (m), 1680 (s), 1615 (m), 1499 (w), 1468 (w), 1348 (m), 1278 (s), 1215 (m), 1060 (w), 993 (w), 783 (w); HRMS (TOF MS ES+) m/z calculated for [C₁₇H₁₆NO₃]^+: 282.1130 [M+H]^+, found 282.1126; M.p. = 158 - 159 °C (EtOH).

(60) (Z)-4-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-one

Using representative procedure 2, 43-hydroxy-4-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (0.07 g, 0.22 mmol) in EtOH (2.0 mL), HCl (aq) (0.08 mL, 0.99 mmol) and glacial ethanoic acid (0.23 mL, 3.96 mmol), for 2.5 hours, provided the title compound as a yellow solid, (0.05 g, 80%).
**1H NMR** (400 MHz, DMSO) δ 10.58 (s, 1H, NH), 7.93 (d, J = 7.5 Hz, 2H, ArH), 7.65 (t, J = 7.5 Hz, 1H, ArH), 7.52 (t, J = 7.5 Hz, 2H, ArH), 7.43 (s, 1H, CH alkene), 7.20 (t, J = 8.0 Hz, 1H, ArH), 6.86 (d, J = 8.0 Hz, 1H, ArH), 6.70 (d, J = 8.0 Hz, 1H, ArH), 3.34 (s, 3H, CH3); **13C NMR** (100.6 MHz, DMSO) δ 195.7, 167.1, 142.2, 136.3, 135.8, 134.1, 133.8, 133.4, 130.7, 129.0, 128.8, 125.2, 119.5, 108.3, 20.7; **FTIR** (CH2Cl2 film cm\(^{-1}\))\(v_{\text{max}}\): 2824 (w), 2853 (w), 1710 (s), 1662 (s), 1616 (m), 1597 (m), 1449 (w), 1336 (m), 1244 (w), 742 (m); **HRMS** (TOF MS ES+) \(m/z\) calculated for [C\(_{17}\)H\(_{13}\)NO\(_2\)]\(^{+}\): 264.1025 [M+H]\(^{+}\), found 264.1019; M.p = 182-184 °C

(61) Trimethyl((2-nitrophenyl)ethynyl)silane\(^{40}\)

\[
\begin{array}{c}
\text{I} \\
\text{NO}_2 \\
\text{HNPr}_2 \\
\text{THF, 15 h}
\end{array}
\]

1-iodo-2-nitrobenzene (5.00 g, 20.0 mmol) was dissolved in THF (100 mL), to this was added bis(triphenylphosphine)palladium(II) dichloride (0.70 g, 1.0 mmol), copper iodide (0.38 g, 2.0 mmol), diisopropylamine (6.10 g, 30.0 mmol), and ethynyltrimethylsilane (2.50 g, 25.0 mmol). The reaction mixture was stirred at 20 °C for 16 hours, after which it was diluted with ethyl acetate (200 mL) and then washed with saturated NaHCO\(_3\) (aq) at 0 °C (3x 100 mL) and then brine (50 mL). The organic layer was then dried over MgSO\(_4\) and reduced *in vacuo* to give a brown viscous oil which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as a light yellow oil (4.20 g, 96%).

\(^1\)H NMR (250 MHz, CDCl\(_3\)) δ 7.99 (dd, J = 8.0, 1.0 Hz, 1H, ArH), 7.64 (dd, J = 7.5, 1.5 Hz, 1H, ArH), 7.54 (app td, J = 7.5, 1.5 Hz, 1H, ArH), 7.43 (app td, J = 8.0, 1.0 Hz, 1H, ArH), 0.26 (s, 9H, CH\(_3\)); **13C NMR** (100.6 MHz, CDCl\(_3\)) δ 150.2, 135.1, 132.7, 128.9, 124.5, 118.3, 103.7, 99.4, 0.3.\(^{40}\)
(62) 1-(Iodoethyl)yl-2-nitrobenzene

Trimethyl(2-nitrophenyl)ethynyl)silane (3.00 g, 13.7 mmol) and AgNO₃ (0.117 g, 0.69 mmol) were dissolved in DMF (50.0 mL). To this was added N-iodosuccinimide (3.40 g, 15.1 mmol) in DMF (25.0 mL). The resulting reaction mixture was then stirred at room temperature and in the absence of light for 18 hours. The reaction mixture was then diluted with Et₂O (200 mL) and then washed with brine (5 x 100 mL), after which the organic layer was dried over MgSO₄, filtered and then reduced in vacuo to give a pale yellow solid which was purified via recrystallisation (CH₂Cl₂ : petroleum ether 40-60) affording the title compound as a pale yellow solid (3.03 g, 81%).

¹H NMR (400 MHz, CDCl₃) δ 8.05 (dd, J = 8.0, 1.0 Hz, 1H, ArH), 7.65 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 7.58 (app td, J = 7.5, 1.0 Hz, 1H, ArH), 7.47 (app td, J = 8.0, 1.5 Hz, 1H, ArH); ¹³C NMR (100.6 MHz, CDCl₃) δ 150.5, 136.0, 133.0, 129.3, 124.8, 118.7, 89.1, 16.8; M.p = 63-65°C (CH₂Cl₂ : petroleum ether 40-60) (lit 68-70°C). ⁴⁰

(63) 1-Ethynyl-2-nitrobenzene

Trimethyl(2-nitrophenyl)ethynyl)silane (1.00 g, 4.57 mmol) and K₂CO₃ (0.63 g, 4.57 mmol) were dissolved in MeOH (5 mL) and stirred at room temperature for 3 hours. After which the reaction mixture was then filtered and extracted with EtOAc (10 mL) then washed with water (2 x 10 mL). The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo to afford the title compound as a grey solid (0.21 g, 32%).
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.90 (dd, $J = 8.0$, 1.0 Hz, 1H, ArH), 7.56 (dd, $J = 7.5$, 1.5 Hz, 1H, ArH), 7.49 (app td, $J = 7.5$, 1.0 Hz, 1H, ArH), 7.40 (app td, $J = 7.5$ 1.5 Hz, 1H, ArH), 3.47 (s, 1H, CH terminal); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 150.43, 135.66, 132.98, 129.50, 124.74, 117.59, 85.27, 78.65; M.p = 55–60°C (CHCl$_3$) (lit = 52–54°C).133

(64) Indoline-2,3-dione (Isatin)

![Indoline-2,3-dione (Isatin) diagram]

1-(Iodoethynyl)-2-nitrobenzene (0.100 g, 0.37 mmol) was dissolved in THF (10 mL), and Pd(PPh$_3$)$_2$Cl$_2$ (0.013 g, 0.09 mmol) was added. The reaction mixture was then heated at reflux for 16 hours, after which it was cooled to room temperature and then filtered through Celite. The filtrate was then concentrated in vacuo to give a dark brown viscous oil, which was purified via flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) providing the title compound as a red crystalline solid (0.030 g, 55%).

$^1$H NMR (400 MHz, DMSO) δ 11.04 (s, 1H, NH), 7.57 (t, $J = 7.5$, 1H, ArH), 7.49 (d, $J = 7.5$ Hz, 1H, ArH), 7.05 (t, $J = 7.5$ Hz, 1H, ArH), 6.90 (d, $J = 7.5$ Hz, 1H, ArH); $^{13}$C NMR (100.6 MHz, DMSO) δ 184.4, 159.4, 150.7, 138.4, 124.7, 122.8, 117.8, 112.2; M.p = 192 – 194°C (lit = 195 – 197°C).134

(70) 2-Iodo-3-oxo-3H-indole 1-oxide (2-Iodoisatogen)

1-(Iodoethynyl)-2-nitrobenzene (0.100 g, 0.366 mmol) was dissolved in THF (10.0 mL), and CuBr.DMS (0.020 g, 0.090 mmol) was added. The reaction mixture was then heated at reflux for 16 hours, after which it was cooled to room temperature and then filtered through Celite. The filtrate was then concentrated in vacuo affording a red amorphous solid, which was purified via flash column chromato
chromatography on silica gel (1:4 ethyl acetate : petroleum ether) affording the title compound as a red crystalline solid (0.090 g, 90%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.67 - 7.62 (m, 3H, ArH), 7.56 - 7.50 (m, 1H, ArH); ^{13}\)C NMR (100.6 MHz, DMSO) \(\delta 183.3, 149.0, 134.8, 131.4, 124.1, 122.4, 114.2, 97.1;\) FTIR (film cm\(^{-1}\))\(\nu_{max}: 1710 (s), 1599 (m), 1491 (s), 1447 (s), 1283 (s), 1191 (m), 1127 (m), 1853 (m), 760 (s), 689 (s), 652 (s);\) HRMS (EI+) \(m/z\) calculated for \([C_8H_4NO_2]^+: 272.9287 [M+H]\(^+\), found 272.9289; M.p = 85 \(^\circ\)C decomp.

(71) 1-Hydroxyindoline-2,3-dione (N-hydroxy isatin)

2-Iodo-3-oxo-3H-indole 1-oxide (0.20 g, 0.73 mmol) was dissolved in DMSO (10 mL) and stirred at 30 \(^\circ\)C for 20 hours. The solution was then diluted with EtOAc (20 mL) and washed with water (3 x 10 mL) then dried over MgSO\(_4\), filtered and then concentrated \textit{in vacuo} to give a crude amorphous red solid. This was purified via flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) gave a 3:1 mixture of 1-hydroxyindoline-2,3-dione 71 and indoline-2,3-dione 64 (0.09 g, 80%). It was then possible to further isolate an analytic quantity of 1-hydroxyindoline-2,3-dione 71 \textit{via} fractional recrystallisation (acetone : Et\(_2\)O).

\(^1\)H NMR (400 MHz, DMSO) \(\delta 11.23 (s, 1H, OH), 7.64 (t, J = 7.5 Hz, 1H, ArH), 7.49 (d, J = 7.5 Hz, 1H, ArH), 7.11 (t, J = 7.5 Hz, 1H, ArH), 7.04 (d, J = 7.5 Hz, 1H, ArH); ^{13}\)C NMR (100.6 MHz, DMSO) \(\delta 181.4, 153.9, 149.4, 138.1, 123.8, 123.4, 116.4, 108.8;\) FTIR (film cm\(^{-1}\))\(\nu_{max}: 1750 (s), 1699 (s), 1453 (m), 1323 (m), 1092 (w), 889 (m), 758 (s), 471 (m);\) HRMS (TOF MS ES-) \(m/z\) calculated for \([C_8H_4NO_3]^+: 162.0191 [M-H]\(^-\), found 162.0185; M.p = 177 \(^\circ\)C decomp.
(64) Indoline-2,3-dione (Isatin)

A mixture (1.0 : 3.0) of 1-hydroxyindoline-2,3-dione and isatin (0.020 g, 0.20 mmol) were dissolved in DMF (1.0 mL), and to this was added triphenyl phosphine (0.288 g, 1.10 mmol). The resulting reaction mixture then heated at 135 °C for 18 hours, after which it was cooled to room temperature and diluted with EtOAc (10 mL). The organic extract was washed with brine (5 x 10 mL) then dried over MgSO₄, filtered and then concentrated in vacuo to give a red amorphous solid, which was purified via flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) providing the title compound as an orange solid (0.012 g, 68%).

For characterisation data, see page 148.

(64) Indoline-2,3-dione (Isatin)

2-Iodo-3-oxo-3H-indole 1-oxide (0.200 g, 0.73 mmol) and triphenyl phosphine (0.288 g, 1.10 mmol) were dissolved in DMSO (5.0 mL). The resulting reaction mixture then heated at 135 °C for 16 hours, after which it was cooled to room temperature and diluted with EtOAc (20 mL). The organic extract was washed with brine (5 x 10 mL) then dried over MgSO₄, filtered and then concentrated in vacuo to give a crude orange solid, which was purified via flash column chromatography on silica gel (1:1 ethyl acetate : petroleum ether) providing the title compound as an orange solid (0.075 g, 70%)

For characterisation data, see page 148.
Trimethyl[(2-methyl-6-nitrophenyl)ethynyl]silane

![Chemical structure](image)

2-Iodo-3-nitrotoluene (5.00 g, 19.0 mmol) and bis(triphenylphosphine)palladium(II) dichloride (1.33 g, 1.9 mmol) were dissolved in triethylamine (100 mL). Ethynyltrimethylsilane (3.73 g, 38.0 mmol) was added to the resultant mixture which was then heated at reflux for 24 hours. It was then cooled to room temperature and the solvent removed \textit{in vacuo} affording a crude brown oil, which was purified \textit{via} flash column chromatography on silica gel (1:19 ethyl acetate : petroleum ether) providing the title compound as an yellow oil (3.66 g, 83%)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.0$ Hz, 1H, ArH), 7.47 (d, $J = 8.0$ Hz, 1H, ArH), 7.31 (t, $J = 8.0$ Hz, 1H, ArH), 2.52 (s, 3H, CH$_3$), 0.28 (s, 9H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 151.0, 143.8, 133.7, 128.0, 121.7, 117.7, 108.5, 97.7, 21.2, -0.3. FTIR (film cm$^{-1}$)$\nu_{\max}$: 2961 (s), 2159 (m), 1532 (s), 1459 (m), 1349 (s), 1289 (m), 1251 (s), 1219 (m), 1088 (m), 867 (s), 790 (m), 742 (s); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{12}$H$_{15}$NO$_2$Si]$^+$: 234.0950 [M+H]$^+$, found 234.0942.

2-(Iodoethynyl)-1-methyl-3-nitrobenzene

Trimethyl[(2-methyl-6-nitrophenyl)ethynyl]silane (3.50 g, 15.0 mmol) and AgNO$_3$ (2.55 g, 15.0 mmol) were dissolved in DMF (50.0 mL). N-iodosuccinimide (3.71 g, 16.5 mmol) was added as a solution of DMF (100 mL). The resulting reaction mixture was then stirred at room temperature and in the absence of light for 1.5 hours. The reaction mixture was then diluted with Et$_2$O (100 mL) and washed with brine (5 x 50 mL). The organic layer was then dried over MgSO$_4$, filtered and then reduced \textit{in vacuo} to give a pale yellow solid which was purified \textit{via} recrystallisation (CH$_2$Cl$_2$ : Petroleum ether 40 - 60) affording the title compound as a pale yellow solid (3.79 g, 82%).
(57) 4-Methylindoline-2,3-dione (4-Methylisatin) & (58) 2-Iodo-4-methyl-3-oxo-3H-indole 1-oxide

2-(Iodoethyl)-1-methyl-3-nitrobenzene (0.43 g, 1.5 mmol) was dissolved in THF (20 mL), and CuBr.DMS (0.31 g, 1.5 mmol) was added. The reaction mixture was then heated at reflux for 24 hours, after which it was cooled to room temperature and filtered through Celite. The filtrate was then concentrated in vacuo to give a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether - 3:7 ethyl acetate : petroleum ether) providing 2-Iodo-4-methyl-3-oxo-3H-indole 1-oxide 58 as a yellow crystalline solid (0.28 g, 39%) and also 4-Methylindoline-2,3-dione 57 as an orange solid (0.10 g, 41%).

- (57)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.40 (s, 1H, NH), 7.40 (t, $J = 8.0$ Hz, 1H, ArH), 6.88 (d, $J = 8.0$ Hz, 1H, ArH), 6.72 (d, $J = 8.0$ Hz, 1H, ArH), 2.57 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 183.4, 159.3, 149.0, 141.7, 126.2, 116.4, 111.2, 109.6, 18.1; FTIR (film cm$^{-1}$) $\nu_{\text{max}}$: 1729 (s), 1603 (s), 1496 (w), 1459 (w), 1318 (w), 1039 (w), 933 (w), 779 (w), 727 (w); HRMS (TOF MS ES+); m/z calculated for [C$_9$H$_7$NO$_2$] 162.0555 [M+H]$^+$, found 162.0547; M.p = 170 – 174 °C (EtOAc).

- (58)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54 – 7.44 (m, 2H), 7.33 – 7.24 (m, 1H), 2.63 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$; $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 184.2, 181.6, 149.3, 148.1, 137.9, 137.8, 134.3, 134.2, 134.0, 133.8, 121.2, 120.2, 119.6, 111.9, 111.8, 17.6; FTIR (film cm$^{-1}$) $\nu_{\text{max}}$: 1712 (s), 1698 (m), 1513 (s), 1501 (s), 1350 (w), 1340 (w), 1295 (s), 1177 (m), 1041 (w), 870 (w), 778 (w), 727 (w).
1303 (m), 1252 (w), 1170 (m), 793 (m); HRMS (TOF MS ES+); m/z calculated for [C₉H₆NO₂] 287.9522 [M+H]⁺, found 287.9521; M.p = 102 °C decomp.⁴

(57) 4-Methylindoline-2,3-dione (4-Methylisatin)

2-Iodo-4-methyl-3-oxo-3H-indole 1-oxide (0.20 g, 0.79 mmol) and triphenylphosphine (0.28 g, 1.05 mmol) were dissolved in DMSO (20.0 mL). The resultant reaction mixture was then heated at 135 °C for 16 hours, after which it was cooled to room temperature and diluted with EtOAc (20 mL). The organic extracts were then washed with brine (5 x 10 mL) then dried over MgSO₄, filtered and then concentrated in vacuo to give a crude orange solid. This crude solid was then purified via flash column chromatography on silica gel (3:7 ethyl acetate : petroleum ether) providing the title compound as an orange solid (0.08 g, 80%)

For characterisation data, see page 152.

(88) 4-Methoxy-1-nitro-2-(phenylethynyl)benzene

2-iodo-4-methoxy-1-nitrobenzene (2.00 g, 7.17 mmol) was dissolved in THF (50 mL), to this was added bis(triphenylphosphine)palladium(II) dichloride (0.25 g, 0.36 mmol), copper iodide (0.14 g, 0.72 mmol), diisopropylamine (2.18 g, 21.50 mmol), and phenylacetylene (0.88 g, 8.60 mmol) at 0 °C. The resultant reaction mixture was stirred for 18 hours and allowed to warm to room temperature, after which it was

⁴Appeared to decompose in solution, thus NMR data is characterisation for 58 and unknown decomposition product
diluted with ethyl acetate (30 mL) and then washed with saturated NaHCO₃(aq) (3x 30 mL) and then brine (15 mL). The organic layer was then dried over MgSO₄, filtered and then reduced in vacuo to give a brown viscous oil which was purified via flash column chromatography on silica gel (3:7 ethyl acetate : petroleum ether) providing the title compound as a light yellow oil (4.20 g, 96%).

\[ ^1H \text{ NMR (250 MHz, CDCl}_3 \] \( \delta \) 8.15 (d, \( J = 9.0 \) Hz, 1H, ArH), 7.67 – 7.56 (m, 2H, ArH), 7.43 – 7.35 (m, 3H, ArH), 7.15 (d, \( J = 3.0 \) Hz, 1H, ArH), 6.94 (dd, \( J = 9.0, 3.0 \) Hz, 1H, ArH), 3.93 (s, 3H, OCH₃); \n
\[ ^{13}C \text{ NMR (100.6 MHz, CDCl}_3 \] \( \delta \) 163.0, 142.8, 132.2, 129.4, 128.6, 127.4, 122.6, 121.2, 118.6, 114.7, 97.1, 85.6, 56.2; M.p = 58 - 59 °C (CH₂Cl₂ : petroleum ether 40 - 60) (lit = 64.5 – 65.5 °C). 135

(89) 5-Methoxy-3-oxo-2-phenyl-3H-indole 1-oxide

4-Methoxy-1-nitro-2-(phenylethynyl)benzene (0.050 g, 0.180 mmol) was dissolved in THF (5.0 mL), and CuBr.DMS (0.090 g, 0.005 mmol) was added. The reaction mixture was then heated at reflux for 8 hours, after which it was cooled to room temperature and then filtered through celite. The filtrate was then concentrated in vacuo affording a dark purple amorphous solid, which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as a purple crystalline solid (0.037 g, 81%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \] \( \delta \) 8.61 – 8.57 (m, 2H, ArH), 7.59 (d, \( J = 8.5 \) Hz, 1H, ArH), 7.53 – 7.43 (m, 3H, ArH), 7.17 (d, \( J = 2.5 \) Hz, 1H, ArH), 7.09 (dd, \( J = 8.5, 2.5 \) Hz, 1H, ArH), 3.91 (s, 3H, OCH₃). \n
\[ ^{13}C \text{ NMR (100.6 MHz, CDCl}_3 \] \( \delta \) 186.8, 162.6, 140.9, 131.9, 130.5, 128.6, 127.6, 126.2, 124.7, 118.4, 115.6, 108.0, 56.3; M.p = 134 - 136 °C (CH₂Cl₂: petroleum ether) (lit: 135.3 - 135.7 °C). 75
1-Iodo-2-nitrobenzene (5.00 g, 20.1 mmol) was dissolved in THF (50 mL), to this was added bis(triphenylphosphine)palladium(II) dichloride (0.70 g, 1.0 mmol), copper iodide (0.38 g, 2.0 mmol), diisopropylamine (6.1 g, 60.3 mmol), and phenylacetylene (2.50 g, 24.1 mmol). The resultant reaction mixture was stirred at RT for 24 hours, after which it was diluted with ethyl acetate (100 mL) and then washed with saturated NaHCO$_3$(aq) (3x 50 mL) and then brine (30 mL). The organic layer was then dried over MgSO$_4$, filtered and then reduced in vacuo to give a brown viscous oil which was purified via flash column chromatography on silica gel (5:95 ethyl acetate: petroleum ether to 1:4 ethyl acetate: petroleum ether to) affording 90 as an orange oil (2.18 g, 49%) and the by-product 85 as a bright orange crystalline solid (1.70 g, 36%).

- **(90)**

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.09 (dd, $J = 8.0$ 1.0 Hz, 1H, ArH), 7.73 (dd, $J = 8.0$, 1.0 Hz, 1H, ArH), 7.64 – 7.58 (m, 3H, ArH), 7.50 – 7.45 (m, 1H, ArH), 7.42 – 7.37 (m, 3H, ArH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 149.8, 134.7, 132.9, 132.2, 129.4, 128.7, 128.6, 124.9, 122.6, 119.0, 97.3, 84.9.$^{136}$

- **(85)**

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.69 – 8.64 (m, 2H, ArH), 7.74 – 7.69 (m, 2H, ArH), 7.69 – 7.64 (m, 1H, ArH), 7.60 – 7.46 (m, 4H, ArH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 187.1, 148.0, 135.0, 132.3, 131.3, 130.9, 128.7, 128.0, 126.0, 123.0, 121.8, 114.4; M.p = 195 - 196 °C (CH$_2$Cl$_2$: petroleum ether) (lit: 186 - 190 °C).$^{62}$

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1-Nitro-2-(phenylethynyl)benzene (0.10 g, 0.448 mmol) was dissolved in THF (5.0 mL), and Pd(MeCN)$_2$Cl$_2$ (0.012 g, 0.01 mmol) was added. The reaction mixture was then heated at reflux for 6 hours, after which it was cooled to room temperature and then filtered through Celite. The filtrate was then concentrated in vacuo affording a dark purple amorphous solid, which was purified via flash column chromatography on silica gel (1:4 ethyl acetate : petroleum ether) providing the title compound as a bright orange crystalline solid (0.074 g, 74%).

_For characterisation data, see page 155._

2-Iodo-4-methoxy-1-nitrobenzene (5.00 g, 17.92 mmol) was dissolved in THF (70 mL), to this was added bis(triphenylphosphine)palladium(II) dichloride (0.63 g, 0.90 mmol), copper iodide (0.34 g, 1.79 mmol), diisopropylamine (5.43 g, 53.76 mmol), and ethynyltrimethylsilane (2.10 g, 21.50 mmol). The reaction mixture was stirred at RT for 24 hours, after which it was diluted with ethyl acetate (120 mL) and then washed with saturated NaHCO$_3$(aq) at 0°C (3x 100 mL) and then brine (75 mL). The organic layer was then dried over MgSO$_4$, filtered and then reduced in vacuo to give a brown viscous oil which was purified via flash column chromatography on silica gel (dry loaded) (1:9 ethyl acetate : petroleum ether to 1:4 ethyl acetate : petroleum ether) providing the intermediate arylalkyne as a colourless solid (4.20 g, 96%). The intermediate arylalkyne (1.50 g, 6.02 mmol) and AgNO$_3$ (0.102 g, 0.60 mmol) were dissolved in DMF (15.0 mL). _N-iodosuccinimide_ (1.49 g, 6.62 mmol) was
added as a solution of DMF (15.0 mL). The resulting reaction mixture was then stirred at 0 °C and in the absence of light for 0.5 hours. The reaction mixture was then diluted with Et₂O (30 mL) and washed with brine (5 x 30 mL). The organic layer was dried over MgSO₄, filtered and then reduced in vacuo to give a pink solid which was purified via flash column chromatography on silica gel (dry loaded) (1:9 ethyl acetate : petroleum ether to 1:4 ethyl acetate : petroleum ether) affording the title compound as a pale pink solid (1.39 g, 76% - 73% over 2 steps).

1H NMR (400 MHz, CDCl₃) δ 8.12 (d, J = 9.0 Hz, 1H, ArH), 7.09 (d, J = 3.0 Hz, 1H, ArH), 6.95 (dd, J = 9.0, 3.0 Hz, 1H, ArH), 3.92 (s, 3H, OCH₃); 13C NMR (100.6 MHz, CDCl₃) δ 162.9, 143.3, 127.1, 120.8, 119.9, 115.2, 89.6, 56.1, 16.7; M.p = 88 - 90 °C (CH₂Cl₂ : Petroleum ether 40-60) (lit = 87 - 88 °C).

(69) 2-Iodo-5-methoxy-3-oxo-3H-indole 1-oxide

![Chemical Structure](image)

2-(Iodoethynyl)-4-methoxy-1-nitrobenzene (1.390 g, 4.58 mmol) was dissolved in THF (50.0 mL), and CuBr.DMS (0.236 g, 1.15 mmol) was added. The reaction mixture was then heated at reflux for 0.5 hours, after which it was cooled to room temperature and filtered through Celite. The filtrate was then concentrated in vacuo to give a purple amorphous solid which was purified via flash column chromatography on silica gel (dry loaded) (CH₂Cl₂) providing the title compound as a purple crystalline solid (4.35 g, 95%).

1H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 8.5 Hz, 1H, ArH), 7.16 (d, J = 2.5 Hz, 1H, ArH), 7.02 (dd, J = 8.5, 2.5 Hz, 1H, ArH), 3.90 (s, 3H, OCH₃); 13C NMR (100.6 MHz, CDCl₃) δ 183.2, 162.5, 142.2, 126.0, 117.8, 115.5, 109.1, 95.0, 56.4; FTIR (film cm⁻¹) νmax: 3082 (w), 2980 (w), 2939 (w), 1709 (s), 1487 (s), 1284 (s), 1234 (m), 1008 (m), 823 (s); HRMS (TOF MS ES+); m/z calculated for [C₉H₇INO₃] 162.0555 [M+H]⁺, found 162.0547; M.p = 175 – 178 °C (CH₂Cl₂) (lit: 172 - 175 °C).
4.3 – Representative Procedure: 3

(89) 5-Methoxy-3-oxo-2-phenyl-3H-indole 1-oxide

A flame dried flask, equipped with a magnetic stirrer bar, was charged with a solution of phenylmagnesium bromide (0.83 mL, 2.500 mmol, 3.0 M Et₂O) and flushed with nitrogen. A solution of Zinc chloride (2.75 mL, 2.750 mmol, 1.0 M Et₂O) was added dropwise and the resultant mixture was stirred at 20 °C for 15 minutes resulting in the formation of a white precipitate and affording a solution of PhZnCl. A separate flame dried flask, equipped with a magnetic stirrer bar, was charged with 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.150 g, 0.500 mmol) and THF (20.00 mL). To this solution was added PhZnCl (3.50 mL) via cannula and the resultant reaction mixture was stirred at 20 °C for 5 hours. After which the reaction was quenched with saturated NH₄Cl(aq) (10.00 mL) and brine (20.0 mL) then extracted with EtOAc (2 x 30.0 mL). Organic extracts were combined and dried over MgSO₄ then concentrated in vacuo to afford a purple amorphous solid which was purified via flash column chromatography on silica gel (2:8 ethyl acetate : petroleum ether) providing the title compound as a dark red-purple crystalline solid (0.078 g, 62%).

For characterisation data, see page 154.

(91) 5-Methoxy-2-(4-methoxyphenyl)-3-oxo-3H-indole 1-oxide

Using representative procedure 3, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.150 g, 0.500 mmol) in THF (20.0 mL) with 4-methoxyphenylmagnesium bromide (5.0 mL, 2.500 mmol, 0.50 M Et₂O) and zinc chloride (2.75 mL, 2.750 mmol, 1.0 M Et₂O) was stirred at 20 °C for 15 minutes resulting in the formation of a white precipitate and affording a solution of PhZnCl. The reaction mixture was quenched with saturated NH₄Cl(aq) (10.00 mL) and brine (20.0 mL) then extracted with EtOAc (2 x 30.0 mL). Organic extracts were combined and dried over MgSO₄ then concentrated in vacuo to afford a purple amorphous solid which was purified via flash column chromatography on silica gel (2:8 ethyl acetate : petroleum ether) providing the title compound as a dark red-purple crystalline solid (0.078 g, 62%).

For characterisation data, see page 154.
Et₂O) afforded a dark purple amorphous solid which was purified via flash column chromatography on silica gel (1:19 ethyl acetate : petroleum ether) providing the title compound as a purple crystalline solid (0.094 g, 66%).

^1^H NMR (400 MHz, CDCl₃) δ 8.65 (d, J = 9.0 Hz, 2H, ArH), 7.53 (d, J = 8.5 Hz, 1H, ArH), 7.11 (d, J = 2.5 Hz, 1H, ArH), 7.04 (dd, J = 8.5, 2.5 Hz, 1H, ArH), 7.00 (d, J = 9.0 Hz 2H, ArH), 3.88 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃); ^1^3^C NMR (100.6 MHz, CDCl₃) δ 187.3, 162.2, 161.2, 153.5, 141.0, 129.6, 124.7, 119.2, 118.4, 115.3, 114.2, 108.0, 56.3, 55.5; M.p = 196 - 198 °C (CH₂Cl₂ : petroleum ether) (lit: 196 - 196.8 °C).^75

(92) 5-Methoxy-3-oxo-2-(4-(trifluoromethyl)phenyl)-3H-indole 1-oxide

Using representative procedure 3, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.150 g, 0.500 mmol) in THF (20.0 mL) with 4-(trifluoromethyl) benzylmagnesium bromide (2.5 mL, 2.500 mmol, 1.00 M Et₂O) and zinc chloride (2.75 mL, 2.750 mmol, 1.0 M, Et₂O) afforded a dark red amorphous solid which was purified via flash column chromatography on silica gel (2:8 ethyl acetate : petroleum ether) providing the title compound as a dark red crystalline solid (0.093 g, 59%).

^1^H NMR (400 MHz, CDCl₃) δ 8.73 (d, J = 8.5 Hz, 2H, ArH), 7.72 (d, J = 8.5 Hz, 2H, ArH), 7.59 (d, J = 8.5 Hz, 1H, ArH), 7.16 (d, J = 2.5 Hz, 1H, ArH), 7.09 (dd, J = 8.5, 2.5 Hz, 1H, ArH), 3.96 (s, 3H, CH₃); ^1^3^C NMR (100.6 MHz, CDCl₃) δ 186.4, 163.1, 140.7, 131.4 (q, J = 31 Hz), 130.8, 129.5, 127.6, 125.5 (q, J = 4 Hz), 124.7, 123.7 (q, J = 231 Hz), 118.7, 115.9, 108.2, 56.4; ^1^9^F NMR (376.6 MHz, CDCl₃) δ -63.10; M.p 195 - 196 °C (CH₂Cl₂ : petroleum ether) (lit: 193-198 °C).^75
Using representative procedure 3, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.150 g, 0.500 mmol) in THF (20.0 mL) with 4-chlorophenylmagnesium bromide (2.5 mL, 2.500 mmol, 1.00 M Et$_2$O) and zinc chloride (2.75 mL, 2.750 mmol, 1.0 M, Et$_2$O) afforded a purple amorphous solid which was purified via flash column chromatography on silica gel (2:8 ethyl acetate : petroleum ether) providing the title compound as a purple crystalline solid (0.093 g, 65%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.61 (d, $J = 8.5$, 2H, ArH), 7.58 (d, $J = 8.5$ Hz, 1H, ArH), 7.46 (d, $J = 8.5$, 2H, ArH), 7.16 (d, $J = 2.5$ Hz, 1H, ArH), 7.09 (dd, $J = 8.5$, 2.5 Hz, 1H, ArH), 3.91 (s, 3H, OC$_3$H$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 186.7, 162.7, 154.5, 140.8, 136.4, 129.0, 128.8, 124.7, 118.6, 116.8, 115.7, 108.2, 56.4; M.p 192 - 193 °C(CH$_2$Cl$_2$: petroleum ether) (lit: 190.5-191.1 °C).}$^{75}$

**(94) 2-Ethyl-5-methoxy-3-oxo-3H-indole 1-oxide & (95) 1-Ethoxy-2,2-diethyl-5-methoxyindolin-3-one**

A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in anhydrous THF (5.0 mL) at 20 °C. EtZnI (0.80 mL, 0.660 mmol, 0.83 M THF) was added dropwise, the resultant reaction mixture was stirred under nitrogen for 18 hours. The reaction mixture was quenched with saturated NH$_4$Cl(aq) (5.0 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried over MgSO$_4$, filtered and then concentrated in vacuo to give a viscous brown oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether to 1:85:95 ethyl acetate : petroleum ether) affording 94 (0.005 g, 15%) as a red crystalline solid and 95 as a bright yellow oil (0.020 g, 45%).
(94)  1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 8.5$ Hz, 1H, ArH), 7.08 (d, $J = 2.5$ Hz, 1H, ArH), 7.01 (dd, $J = 8.5$, 2.5 Hz, 1H, ArH), 3.87 (s, 3H, CH$_3$), 2.65 (q, $J = 7.5$ Hz, 2H, CH$_2$), 1.21 (t, $J = 7.5$ Hz, 3H, CH$_3$); 13C NMR (100.6 MHz, CDCl$_3$) $\delta$ 186.6, 162.3, 140.3, 139.6, 125.0, 117.3, 115.0, 108.2, 56.2, 15.0, 9.8; FTIR (film cm$^{-1}$) $\nu_{\text{max}}$: 2937 (w), 1704 (s), 1618 (w), 1531 (s), 1486 (s), 1435 (m), 1390 (s), 1356 (s), 1280 (m), 1230 (m), 1097 (m), 821 (m), 801 (w); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{11}$H$_{12}$NO$_3$]$^+$: 206.0817 [M+H]$^+$, found 206.0807; M.p = 51 – 55 °C (CH$_2$Cl$_2$).

(95)  1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20 (dd, $J = 9.0$, 2.5 Hz, 1H, ArH), 7.14 (d, $J = 9.0$ Hz, 1H, ArH), 7.02 (d, $J = 2.5$ Hz, 1H, ArH), 4.10 (q, $J = 7.0$ Hz, 2H, CH$_2$), 3.79 (s, 3H, CH$_3$), 1.92 (dq, $J = 14.5$, 7.5 Hz, 2H, CH$_2$), 1.77 (dq, $J = 14.5$, 7.5 Hz, 2H, CH$_2$), 1.37 (t, $J = 7.0$ Hz, 3H, CH$_3$), 0.70 (t, $J = 7.5$ Hz, 6H, CH$_3$); 13C NMR (100.6 MHz, CDCl$_3$) $\delta$ 201.4, 158.3, 155.3, 126.8, 122.6, 114.8, 103.1, 80.3, 71.7, 55.8, 29.3, 14.4, 8.8; FTIR (thin film cm$^{-1}$) $\nu_{\text{max}}$: 2969 (w), 2929 (w), 1706 (s), 1488 (s), 1439 (m), 1266 (m), 1229 (w), 1145 (w), 1030 (m), 826 (w), 804 (w); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{15}$H$_{22}$NO$_3$]$^+$: 264.1600 [M+H]$^+$, found 264.1593.

(95)  1-Ethoxy-2,2-diethyl-5-methoxyindolin-3-one

![Chemical Structure]

A flame dried flask equipped with magnetic stirrer bar was charged with 2-ethyl-5-methoxy-3-oxo-3H-indole 1-oxide (0.030 g, 0.146 mmol) in anhydrous THF (1.5 mL) at 20 °C. EtZnI (0.53 mL, 0.438 mmol, 0.83 M THF) was added dropwise, and the resultant reaction mixture was stirred under nitrogen for 18 hours. The reaction mixture was quenched with H$_2$O (1.8 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried over MgSO$_4$, filtered and then concentrated in vacuo to give a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a bright yellow oil (0.026 g, 49 %).

For characterisation data, see page 161.
(95) 1-Ethoxy-2,2-diethyl-5-methoxyindolin-3-one

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{O} & \quad \text{N} \quad \text{I} \\
\text{Et} & \quad \text{Zn (1.5 equiv.)} \\
\text{THF}, \text{RT, 2 h} \\
& \Rightarrow \\
\text{MeO} & \quad \text{O} \\
\text{Et} & \quad \text{Et} \\
\text{OEt} & \quad \text{N} \\
\end{align*}
\]

A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-3-oxo-3H-indole 1-oxide (0.030 g, 0.100 mmol) in anhydrous THF (3.0 mL) at 20 °C. Et₂Zn (0.25 mL, 0.150 mmol, 0.6 M hexanes) was added dropwise, the resultant reaction mixture was stirred under nitrogen for 2 hours. The reaction mixture was quenched with H₂O (1.8 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried over MgSO₄, filtered and then concentrated in vacuo to give a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a bright yellow oil (0.018 g, 68%).

For characterisation data, see page 161.

(100) 2,2-Dicyclohexyl-1-(cyclohexyloxy)-5-methoxyindolin-3-one

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{O} & \quad \text{N} \quad \text{I} \\
\text{Cy} & \quad \text{Zn (3.0 equiv.)} \\
\text{THF}, \text{RT, 2 h} \\
& \Rightarrow \\
\text{MeO} & \quad \text{O} \\
\text{Cy} & \quad \text{Cy} \\
\text{OCy} & \quad \text{N} \\
\end{align*}
\]

A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-3-oxo-3H-indole 1-oxide (0.100 g, 0.367 mmol) in anhydrous THF (10.0 mL) at 20 °C. Cy₂Zn (2.48 mL, 0.990 mmol, 0.40 M THF) was added dropwise, the resultant reaction mixture was stirred under nitrogen for 2 hours. The reaction mixture was quenched with H₂O (5.0 mL), extracted with ethyl acetate (25.0 mL) and washed with brine (15.0 mL). The organic layer was dried over MgSO₄, filtered and then concentrated in vacuo to give a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a bright yellow oil (0.057 mg, 41%).
\( ^1 \text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 7.15 (dd, J = 9.0, 2.5 \text{ Hz, 1H, ArH}), 7.12 (d, J = 9.0 \text{ Hz, 1H, ArH}), 6.96 (d, J = 2.5 \text{ Hz, 1H, ArH}), 3.93 (tt, J = 10.0, 3.5 \text{ Hz, 1H, CH}_3), 3.77 (s, 3H, CH), 2.20 – 2.11 (m, 2H, CH), 2.09 – 2.01 (m, 2H, CH), 1.92 – 1.81 (m, 9H, CH), 1.48 – 1.25 (m, 7H, CH), 1.32 – 1.02 (m, 9H, CH), 0.94 – 0.80 (m, 3H, CH); ^{13} \text{C NMR} (100.6 \text{ MHz, CDCl}_3) \delta 202.8, 159.6, 155.1, 126.6, 123.2, 115.3, 102.5, 84.9, 82.4, 55.8, 41.4, 32.4, 28.5, 27.1, 26.9, 25.9, 24.8; \text{FTIR (film cm}^{-1}) \nu_{\text{max}}: 2933 (s), 2853 (m), 1698 (s), 1487 (s), 1487 (s), 1448 (w), 1342 (w), 1272 (m), 1272 (m), 1030 (w), 823 (w), 785 (w), 754 (w); \text{HRMS (TOF MS ES+) m/z calculated for } [\text{C}_{27}\text{H}_{40}\text{NO}_3]^{+}: 426.3008 [M+H]^+, \text{found 426.3002}; \text{M.p} = 148 – 151 \text{oC (iPrOH)}. \\

(95) 1-\text{Ethoxy-2,2-diethyl-5-methoxyindolin-3-one}

\[
\text{MeO} \quad \text{EtCu(CN)ZnI (3.0 equiv.)} \quad \text{THF, RT, 18 h} \quad \text{O} \quad \text{Et}
\]

A flask, equipped with a magnetic stirrer bar, was charged with LiCl (0.194 g, 4.58 mmol), then thoroughly flame dried and backfilled with nitrogen. CuCN (0.205 g, 2.29 mmol) was added and the two solids were dissolved in THF (2.5 mL), over 20 minutes, providing a yellow green solution of CuCN.2LiCl. This solution was cooled to -30 °C and ethylzinc iodide (2.5 mL, 2.08 mmol, 0.83 M THF) was added dropwise. After stirring at -30 °C for 10 minutes the solution was gradually warmed to 0 °C and the resulting alkylcuprate, EtCu(CN)ZnI.2LiCl, was used immediately.\(^{91,137}\)

A flame dried flask equipped with magnetic stirrer bar was charged with 2-ethyl-5-methoxy-3-oxo-3H-indole 1-oxide (0.025 g, 0.122 mmol) in anhydrous THF (1.5 mL) at 20 °C. EtCu(CN)ZnI.2LiCl (0.89 mL, 0.366 mmol, 0.41 M THF) was added dropwise over 5 minutes. The reaction mixture was stirred at 20 °C for 18 hours then quenched with saturated NH\(_4\)Cl(aq) (1.5 mL) and brine (10.0 mL) then extracted with EtOAc (2 x 15.0 mL). The organic extracts were combined and dried over MgSO\(_4\), filtered and then concentrated \textit{in vacuo} to afford a red amorphous solid which was purified via flash column chromatography on silica gel (1:18 ethyl acetate : petroleum ether) providing the title compound as a yellow (0.025 g, 79%).

\textit{For characterisation data, see page 161.}
(101) 1-(Iodoethynyl)-4-methyl-2-nitrobenzene

1-iodo-4-methyl-2-nitrobenzene (2.50 g, 9.50 mmol) was dissolved in THF (45 mL), to this was added bis(triphenylphosphine)palladium(II) dichloride (0.33 g, 0.48 mmol), copper iodide (0.18 g, 0.95 mmol), diisopropylamine (2.88 g, 28.5 mmol), and ethynyltrimethylsilane (1.12 g, 11.40 mmol). The reaction mixture was stirred at RT for 24 hours, after which it was diluted with ethyl acetate (80 mL) and then washed with saturated NaHCO₃(aq) at 0 °C (3x 50 mL) and then brine (50 mL). The organic layer was then dried over MgSO₄, filtered and then reduced in vacuo to give a brown viscous oil which was purified via flash column chromatography on silica gel (dry loaded) (1:9 ethyl acetate : petroleum ether to 1:4 ethyl acetate : petroleum ether) providing the intermediate arylalkyne as a colourless solid (1.45 g, 65%). The intermediate arylalkyne (1.40 g, 6.00 mmol) and AgNO₃ (0.510 g, 3.00 mmol) were dissolved in DMF (15.0 mL). N-iodosuccinimide (1.19 g, 5.29 mmol) was added as a solution of DMF (15.0 mL). The resulting reaction mixture was then stirred at 0 °C and in the absence of light for 0.5 hours. The reaction mixture was then diluted with Et₂O (30 mL) and washed with brine (5 x 30 mL). The organic layer was dried over MgSO₄, filtered and then reduced in vacuo to give a orange solid which was purified via flash column chromatography on silica gel (dry loaded) (1:9 ethyl acetate : petroleum ether to 1:4 ethyl acetate : petroleum ether) affording the title compound as a light yellow solid (1.07 g, 99% - 64% over 2 steps).

¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H, ArH), 7.54 (d, J = 8.0 Hz, 1H, ArH), 7.40 (d, J = 8.0 Hz, 1H, ArH), 2.47 (s, 3H, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 150.6, 140.2, 135.6, 133.7, 125.0, 115.7, 89.1, 21.3, 15.1; M.p = 92-94 °C (lit = 94-96 °C)
1-(Iodoethynyl)-4-methyl-2-nitrobenzene (1.000 g, 3.48 mmol) was dissolved in THF (40.0 mL), and CuBr.DMS (0.179 g, 0.87 mmol) was added. The reaction mixture was then heated at reflux for 2.0 hours, after which it was cooled to room temperature and filtered through Celite. The filtrate was then concentrated in vacuo to give a purple amorphous solid which was purified via flash column chromatography on silica gel (dry loaded) (1:4 EtOAc : Petroleum ether 40 - 60) providing the title compound as a purple crystalline solid (0.823 g, 48%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, $J$ = 7.5 Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.31 (d, $J$ = 7.5 Hz, 1H, ArH), 2.53 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 183.1, 149.5, 146.9, 131.5, 122.5, 121.7, 115.0, 97.5, 22.5; FTIR (film cm$^{-1}$)$\nu_{\text{max}}$: 3062 (w), 1716 (s), 1596 (m), 1505 (s), 1467 (m), 1302 (m), 1189 (w), 811 (m); HRMS (TOF MS ES$^+$); m/z calculated for [C$_9$H$_7$INO$_2$] 287.9522 [M+H]$^+$, found 287.9528; M.p = 208 - 210 °C (CH$_2$Cl$_2$).
4.4 – Representative Procedure: 4

(94) 2-Ethyl-5-methoxy-3-oxo-3H-indole 1-oxide & (95) 1-Ethoxy-2,2-diethyl-5-methoxyindolin-3-one

A flask, equipped with a magnetic stirrer bar, was charged with LiCl (0.254 g, 6.00 mmol), then thoroughly flame dried and backfilled with nitrogen. CuCN (0.269 g, 3.00 mmol) was added and the two solids were dissolved in THF (3.0 mL), over 20 minutes, providing a yellow green solution of CuCN.2LiCl. This solution was cooled to -30 °C and ethylzinc iodide (3.0 2.mL, 2.73 mmol, 0.91 M THF) was added dropwise. After stirring at -30 °C for 10 minutes the solution was gradually warmed to 0 °C and the resulting alkylcuprate, EtCu(CN)ZnI.2LiCl, was used immediately.91,137

A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in anhydrous THF (5.0 mL) at 20 °C. EtCu(CN)ZnI.2LiCl (0.62 mL, 0.281 mmol, 0.45 M THF) was added dropwise over 5 minutes. The reaction mixture was stirred at 20 °C for 18 hours then quenched with saturated NH₄Cl(aq) (5.0 mL) and brine (10.0 mL) then extracted with EtOAc (2 x 15.0 mL). The organic extracts were combined and dried over MgSO₄ then concentrated in vacuo to afford a red amorphous solid which was purified via flash column chromatography on silica gel (1:18 ethyl acetate : petroleum ether) providing 94 as a red crystalline solid (0.023 g, 68%) and the by-product 95 as a bright yellow oil (0.008 g, 18%)

- (94)

For characterisation data, see page 161.

- (95)

For characterisation data, see page 161.
(97) 2-Hexyl-5-methoxy-3-oxo-3H-indole 1-oxide & (98) 2,2-Dihexyl-1-(hexyloxy)-5-methoxyindolin-3-one

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and n-HexCu(CN)ZnI (0.70 mL, 0.281 mmol, 0.40 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing 97 compound as a red crystalline solid (0.031 g, 72%) and the by-product 98 as bright yellow oil (0.013 g, 13%).

- (97)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, $J = 8.4$ Hz, 1H, ArH), 7.09 (d, $J = 2.5$ Hz, 1H, ArH), 7.01 (dd, $J = 8.4$, 2.5 Hz, 1H, ArH), 3.88 (s, 3H, OCH$_3$), 2.66 – 2.60 (m, 2H, CH$_2$), 1.69 – 1.59 (m, 2H, CH$_2$), 1.40 – 1.24 (m, 6H, CH$_3$), 0.92 – 0.85 (m, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 186.8, 162.4, 140.5, 139.0, 125.2, 117.4, 115.0, 108.3, 56.3, 31.6, 29.4, 25.6, 22.6, 21.6, 14.1; FTIR (film cm$^{-1}$) $\nu_{max}$: 2953 (w), 2929 (m), 1702 (s), 1619 (w), 1528 (s), 1487 (m), 1435 (s), 1388 (s), 1281 (w), 821 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{15}$H$_{20}$NO$_3$]$^+$: 262.1443 [M+H]$^+$, found 262.1436; M.p = 46 – 49 °C (CH$_2$Cl$_2$).

- (98)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.20 (dd, $J = 9.0$, 2.5 Hz, 1H, ArH), 7.12 (d, $J = 9.0$ Hz, 1H, ArH), 7.02 (d, $J = 2.5$ Hz, 1H, ArH), 4.05 (t, $J = 6.5$ Hz, 2H, OCH$_2$), 3.79 (s, 3H, OCH$_3$), 1.91 – 1.80 (m, 2H, CH$_2$), 1.80 – 1.64 (m, 4H, CH$_2$), 1.50 – 1.41 (m, 2H, CH$_2$), 1.40 – 1.31 (m, 4H, CH$_2$), 1.26 – 1.12 (m, 16H, CH$_2$), 0.92 (t, $J = 7.0$ Hz, 3H, CH$_3$), 0.82 (t, $J = 7.0$ Hz, 6H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 201.6, 158.0, 155.3, 126.8, 122.4, 114.8, 103.2, 79.6, 76.6, 55.8, 36.8, 31.7, 31.5, 29.7, 29.6, 28.9, 25.9, 24.0, 22.6, 22.6, 14.0; FTIR (film cm$^{-1}$) $\nu_{max}$: 2934 (m), 2929 (s), 2855 (m), 1708 (s), 1448 (s), 1339 (w), 1273 (w), 1029 (w), 824 (w); HRMS (TOF MS ES+) m/z calculated for [C$_{27}$H$_{45}$NaNO$_3$]$^+$: 454.3297 [M+Na]$^+$, found 454.3285.
(111) 2-Isobutyl-5-methoxy-3-oxo-3H-indole 1-oxide & (112) 1-Isobutoxy-2,2-diisobutyl-5-methoxyindolin-3-one

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and i-BuCu(CN)ZnI (0.41 mL, 0.281 mmol, 0.44 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing 111 as a red crystalline solid (0.032 g, 83%) providing the by-product 112 as a bright yellow oil (0.007 g, 12%).

- (111)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (d, $J$ = 8.5 Hz, 1H, ArH), 7.10 (d, $J$ = 2.5 Hz, 1H, ArH), 7.02 (dd, $J$ = 8.5, 2.5 Hz, 1H, ArH), 3.89 (s, 3H, OCH$_3$), 2.53 (d, $J$ = 7.5 Hz, 2H, CH$_2$), 2.25 – 2.13 (m, 1H, CH), 0.97 (d, $J$ = 7.0 Hz, 6H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 187.1, 162.4, 140.5, 138.5, 125.1, 117.5, 115.1, 108.3, 56.3, 30.3, 26.9, 22.9; FTIR (film cm$^{-1}$)$\nu_{\text{max}}$: 2951 (m), 1702 (s), 1618 (w), 1531 (m), 1487 (m), 1435 (s), 1383 (s), 1360 (s), 1275 (m), 1231 (m), 823 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{13}$H$_{16}$NO$_3$]$^+$: 234.1130 [M+H]$^+$, found 234.1129; M.p = 113 – 114 $^\circ$C (CH$_2$Cl$_2$).

- (112)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20 (d, $J$ = 9.0, 2.5 Hz, 1H, ArH), 7.14 (d, $J$ = 9.0 Hz, 1H, ArH), 7.05 (d, $J$ = 2.5 Hz, 1H, ArH), 3.88 (d, $J$ = 6.5 Hz, 2H, CH$_2$), 3.80 (s, 3H, CH$_3$), 2.03 (hept, $J$ = 6.5 Hz, 1H, CH$_3$), 1.82 – 1.69 (m, 4H, CH), 1.35 – 1.19 (m, 2H, CH), 1.05 (d, $J$ = 6.5 Hz, 6H, CH$_3$), 0.82 (d, $J$ = 6.5 Hz, 6H, CH$_3$), 0.63 (d, $J$ = 6.5 Hz, 6H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 201.6, 157.8, 155.5, 126.8, 123.0, 115.0, 103.5, 83.1, 79.2, 55.9, 46.9, 28.3, 24.7, 24.5, 23.8, 19.8; FTIR (film cm$^{-1}$)$\nu_{\text{max}}$: 2957 (s), 2934 (m), 2870 (w), 1709 (s), 1489 (s), 1338 (w), 1276 (m), 1223 (m), 1029 (m), 824 (w); HRMS (TOF MS ES+) m/z calculated for [C$_{21}$H$_{34}$NO$_3$]$^+$: 348.2533 [M+H]$^+$, found 348.2530.
(96) 2-Methyl-5-methoxy-3-oxo-3H-indole 1-oxide

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and MeCu(CN)ZnI.2LiCl (0.40 mL, 0.281 mmol, 0.70 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as a red crystalline solid (0.022 g, 70%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 (d, $J = 8.5$ Hz, 1H, ArH), 7.08 (d, $J = 2.5$ Hz, 1H, ArH), 7.00 (dd, $J = 8.8, 2.5$ Hz, 1H, ArH), 3.87 (s, 3H, OCH$_3$), 2.15 (s, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 186.7, 162.3, 140.5, 135.6, 125.2, 117.4, 115.0, 108.5, 56.3, 6.9; FTIR (film cm$^{-1}$) $\nu$ max: 2917 (w), 1700 (s), 1639 (w), 1487 (m), 1399 (s), 1344 (s), 1288 (m), 1226 (m), 1091 (m), 831 (s); HRMS (TOF MS ES+) m/z calculated for [C$_{10}$H$_{10}$NO$_3$]$^+$: 192.0655 [M+H]$^+$, found 192.0654; M.p = 125 – 128 °C (CH$_2$Cl$_2$).

(113) 2-Cyclopropyl-5-methoxy-3-oxo-3H-indole 1-oxide

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and Cy-PrCu(CN)ZnI (4.01 mL, 0.281 mmol, 0.07 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as an orange crystalline solid (0.016 g, 45%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 (d, $J = 8.5$ Hz, 1H, ArH), 7.02 (dd, $J = 8.5, 2.5$ Hz, 1H, ArH), 6.99 (dd, $J = 8.5, 2.5$ Hz, 1H, ArH), 3.86 (s, 3H, OCH$_3$), 2.20 – 2.12 (m, 1H, CH), 1.54 – 1.49 (m, 2H, CH$_2$), 1.12 – 1.06 (m, 2H, CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 186.2, 162.1, 140.2, 138.6, 124.8, 117.5, 114.6, 108.3, 56.3, 7.0, 6.8k; FTIR (film cm$^{-1}$) $\nu$ max: 3051 (w), 2980 (w), 1700 (s), 1538 (w), 1486 (m), 1437 (s), 1408 (s), 1359 (s),
1284 (m), 1229 (m), 825 (m), 723 (m); HRMS (TOF MS ES+) m/z calculated for [C_{12}H_{12}NO_{3}]^{+}: 218.0812 [M+H]^{+}, found 218.0814; M.p = 121 – 122 °C (PrOH).

**114) 2-Cyclopentyl-5-methoxy-3-oxo-3H-indole 1-oxide & (115) 2,2-Dicyclopentyl-1-(cyclopentyloxy)-5-methoxyindolin-3-one**

![Chemical structure of 114 and 115](image)

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and Cy-PentCu(CN)Znl (1.04 mL, 0.281 mmol, 0.27 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing 114 as an orange crystalline solid (0.021 g, 49%) and the by-product 115 as a bright yellow oil (0.016 g, 23%).

- **(114)**

{^1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, $J = 8.4$ Hz, 1H, ArH), 7.07 (d, $J = 2.4$ Hz, 1H, ArH), 7.01 (dd, $J = 8.4$, 2.4 Hz, 1H, ArH), 3.88 (s, 3H, OCH$_3$), 3.38 – 3.27 (m, 1H, CH), 2.03 – 1.85 (m, 6H, CH$_2$), 1.71 – 1.64 (m, 2H, CH$_2$); {^{13}}C NMR (100.6 MHz, CDCl$_3$) δ 186.7, 162.3, 140.9, 140.4, 125.2, 117.4, 115.0, 108.1, 56.3, 33.4, 29.2, 26.4; FTIR (film cm$^{-1}$) $\nu_{max}$: 2959 (w), 1698 (s), 1616 (w), 1524 (m), 1485 (w), 1396 (m), 1358 (m), 1281 (w), 1230 (w), 822 (w); HRMS (TOF MS ES+) m/z calculated for [C$_{14}$H$_{16}$NO$_3$]$^+$: 246.1138 [M+H]$^+$, found 246.1138; M.p = 114 – 115 °C (CH$_2$Cl$_2$).

- **(115)**

{^1}H NMR (400 MHz, CDCl$_3$) δ 7.19 (dd, $J = 9.0$, 2.5 Hz, 1H, ArH), 7.08 (d, $J = 9.0$ Hz, 1H, ArH), 7.00 (d, $J = 2.5$ Hz, 1H, ArH), 4.65 – 4.57 (m, 1H, CH$_3$), 3.81 (s, 3H, OCH$_3$), 2.61 – 2.47 (m, 2H, CH$_2$), 1.96 – 1.79 (m, 7H, CH$_2$), 1.78 – 1.64 (m, 5H, CH$_2$), 1.56 – 1.41 (m, 9H, CH$_2$), 1.32 – 1.17 (m, 3H, CH$_2$); {^{13}}C NMR (100.6 MHz, CDCl$_3$) δ 202.2, 158.9, 155.3, 126.7, 123.0, 115.2, 102.9, 86.5, 82.5, 55.9, 45.5, 32.0, 28.3, 26.5, 25.4, 25.2,
24.3; FTIR (film cm⁻¹)ν_max: 2954 (m), 2868 (w), 1698 (s), 1487 (s), 1437 (w), 1270 (m), 1222 (w), 1028 (w), 822 (w); HRMS (TOF MS ES+) m/z calculated for [C_{24}H_{34}NO_{3}]⁺: 384.2533 [M+H]⁺, found 384.2532.

(99) 2-Cyclohexyl-5-methoxy-3-oxo-3H-indole 1-oxide & (100) 2,2-Dicyclohexyl-1-(cyclohexyloxy)-5-methoxyindolin-3-one

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and Cy-HexCu(CN)ZnI (1.28 mL, 0.281 mmol, 0.22 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) 99 as an orange crystalline solid (0.035 g, 82%) and the by-product 100 as a bright yellow oil (0.016 g, 23%).

(99)

¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 8.5 Hz, 1H, ArH), 7.06 (d, J = 2.5 Hz, 1H, ArH), 7.00 (dd, J = 8.5, 2.5 Hz, 1H, ArH), 3.87 (s, 3H, OCH₃), 3.07 – 2.95 (m, 1H, CH), 1.94 – 1.78 (m, 4H, CH₂), 1.76 – 1.67 (m, 3H, CH₂), 1.38 – 1.27 (m, 3H, CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 186.80, 162.4, 141.1, 140.2, 125.0, 117.4, 115.1, 108.0, 56.3, 33.4, 27.8, 26.2, 25.7; FTIR (film cm⁻¹)ν_max: 3048 (w), 2934 (m), 2856 (m), 1701 (s), 1616 (m), 1522 (s), 1489 (s), 1398 (s), 1359 (s), 1284 (m), 1232 (m), 1014 (w), 822 (m), 737 (m); HRMS (TOF MS ES+) m/z calculated for [C_{15}H_{18}NO₃]⁺: 260.1281 [M+H]⁺, found 260.1280; M.p = 109 – 110 °C (CH₂Cl₂).

(100)

For characterisation data, see page 163.
(103) 2-Ethyl-3-oxo-3H-indole 1-oxide, (104) 1-ethoxy-2,2-diethylindolin-3-one & (64) isatin

Using representative procedure 4, 2-iodo-3-oxo-3H-indole 1-oxide (0.022 g, 0.082 mmol) in THF (2.5 mL) and EtCu(CN)ZnI (0.31 mL, 0.139 mmol, 0.45 M THF), afforded an orange amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether - 1 : 1 ethyl acetate : petroleum ether) providing 103 as a yellow viscous oil (0.006 g, 42%) and the byproducts: 104 as a bright yellow oil (0.002 g, 10%) and 64 as an impure orange solid (0.004 g, ~33%)

- (103)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.69 – 7.47 (m, 4H, ArH), 2.70 (q, $J = 7.5$ Hz, 2H, CH$_2$), 1.23 (t, $J = 7.5$ Hz, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 186.89, 147.59, 134.51, 131.14, 123.30, 121.53, 113.92, 15.04, 9.85; FTIR (film cm$^{-1}$) $\nu_{max}$: 2918 (m), 2852 (w), 1699 (s), 1638 (m), 1453 (w), 1390 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{10}$H$_{10}$NO$_2$]$^+$: 176.0712 [M+H]$^+$, found 176.0713.

- (104)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, $J = 8.0$ Hz, 1H, ArH), 7.56 – 7.51 (m, 1H, ArH), 7.18 (dt, $J = 8.0$, 1.0 Hz, 1H, ArH), 6.99 – 6.93 (m, 1H, ArH), 4.13 (q, $J = 7.0$ Hz, 2H, CH$_2$), 1.93 (dq, $J = 14.5$, 7.5 Hz, 2H, CH$_2$), 1.78 (dq, $J = 14.5$, 7.5 Hz, 2H, CH$_2$), 1.38 (t, $J = 7.0$ Hz, 3H, CH$_3$), 0.69 (t, $J = 7.5$ Hz, 6H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 201.4, 162.9, 136.8, 123.2, 122.1, 121.4, 112.9, 79.7, 72.0, 29.3, 14.5, 8.8; FTIR (thin film cm$^{-1}$) $\nu_{max}$: 2972 (s), 2936 (m), 1710 (s), 1608 (m), 1476 (w), 1455 (m), 1143 (w), 1047 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{14}$H$_{20}$NO$_2$]$^+$: 223.1494 [M+H]$^+$, found 234.1485.

- (64)

For characterisation data, see page 148.
(105) 2-Ethyl-6-methyl-3-oxo-3H-indole 1-oxide, (106) 1-Ethoxy-2,2-diethyl-6-methylindolin-3-one & (107) 6-Methylisatin

Using representative procedure 4, 2-iodo-6-methyl-3-oxo-3H-indole 1-oxide (0.024 g, 0.082 mmol) in THF (2.5 mL) and EtCu(CN)ZnI (0.31 mL, 0.139 mmol, 0.45 M THF), afforded an orange amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether - 1 : 1 ethyl acetate : petroleum ether) providing 105 as a yellow viscous oil (0.006 g, 39%) and the byproducts: 106 as a bright yellow oil (0.002 g, 10%) and 107 as an impure orange solid (0.004 g, ~30%) - (105)

\[ ^1H \text{NMR (400 MHz, CDCl}_3) \delta 7.44 (d, J = 7.5 \text{ Hz}, 1H, ArH), 7.42 (s, 1H, ArH), 7.28 (d, J = 7.5 \text{ Hz}, 1H, ArH), 2.68 (q, J = 7.5 \text{ Hz}, 2H, CH}_2), 2.49 (s, 3H, CH}_3), 1.22 (t, J = 7.5 \text{ Hz}, 3H, CH}_3); ^13C \text{NMR (100.6 MHz, CDCl}_3) \delta 186.6, 148.1, 146.3, 140.43, 131.11, 121.5, 120.8, 114.8, 29.8, 15.0, 9.8; FTIR (film cm}^{-1}\nu_{\text{max}}: 2979 (m), 2921 (m), 1710 (s), 1644 (m), 1546 (s), 1387 (m), 1364 (m), 884 (m); HRMS (TOF MS ES+) m/z calculated for [C\text{11}H\text{12}NO\text{2}]^{+}: 190.0863 [M+H]^+, found 190.0864.

- (106)

\[ ^1H \text{NMR (400 MHz, CDCl}_3) \delta 7.48 (d, J = 8.0 \text{ Hz}, 1H, ArH), 6.97 (s, 1H, ArH), 6.78 (d, J = 8.0 \text{ Hz}, 1H, ArH), 4.12 (q, J = 7.0 \text{ Hz}, 2H, CH}_2), 2.41 (s, 3H, CH}_3), 1.91 (dq, J = 14.5, 7.5 \text{ Hz}, 2H, CH}_2), 1.77 (dq, J = 14.5, 7.5 \text{ Hz}, 2H, CH}_2), 1.38 (t, J = 7.0 \text{ Hz}, 3H, CH}_3), 0.68 (t, J = 7.5 \text{ Hz}, 6H, CH}_3); ^13C \text{NMR (100.6 MHz, CDCl}_3) \delta 200.7, 163.2, 148.4, 123.1, 123.0, 120.0, 112.9, 79.9, 71.9, 29.3, 22.7, 14.5, 8.8. FTIR (thin film cm}^{-1}\nu_{\text{max}}: 2970 (m), 2936 (m), 1706 (s), 1613 (s), 1456 (w), 1286 (w), 1116 (w), 1046 (m); HRMS (TOF MS ES+) m/z calculated for [C\text{15}H\text{22}NO\text{2}]^{+}: 248.1651 [M+H]^+, found 248.1653.
(107) 

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.34 (s, 1H, NH), 7.51 (d, $J = 7.5$ Hz, 1H, ArH), 6.93 (d, $J = 7.5$ Hz, 1H, ArH), 6.75 (s, 1H, ArH), 2.42 (s, 3H, CH$_3$).

(119) 2-(But-3-en-1-yl)-5-methoxy-3-oxo-3H-indole 1-oxide

Using representative procedure 4, 2-ido-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and n-but-1-lyCu(CN)Znl (1.00 mL, 0.281 mmol, 0.54 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as an orange crystalline solid (0.011 g, 29%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, $J = 8.5$ Hz, 1H, ArH), 7.10 (d, $J = 2.5$ Hz, 1H, ArH), 7.02 (dd, $J = 8.5$, 2.5 Hz, 1H, ArH), 5.83 (ddt, $J = 17.0$, 10.0, 6.5 Hz, 1H, CH, alkene), 5.07 (dd, $J = 17.0$, 1.5 Hz, 1H, CH, alkene), 4.99 (dd, $J = 10.0$, 1.5 Hz, 1H, CH, alkene), 3.89 (s, 3H, OCH$_3$), 2.75 (t, $J = 7.5$ Hz, 2H, CH$_2$), 2.48 – 2.40 (m, 2H, CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 186.7, 162.4, 140.4, 138.1, 136.7, 125.1, 117.4, 116.1, 115.1, 108.3, 56.3, 29.5, 21.0.; FTIR (film cm$^{-1}$) $\nu_{max}$: 3080 (w), 2967 (m), 2921 (m), 1699 (s), 1641 (s), 1531 (m), 1482(s), 1384 (s), 1280 (s), 1020 (w), 827 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{13}$H$_{14}$NO$_3$]$^+$: 232.0968 [M+H]$^+$, found 232.0966; M.p = (48 - 50 °C) (CH$_2$Cl$_2$).

$^5$ Suitable $^{13}$C NMR not obtained, $^1$H NMR consistent with literature.
(120) 2-(4-Ethoxy-4-oxobutyl)-5-methoxy-3-oxo-3H-indole 1-oxide & (121) Diethyl 4,4’-(1-(4-ethoxy-4-oxobutoxy)-5-methoxy-3-oxoindoline-2,2-diyl)dibutanoate

Using representative procedure 4, 2-ido-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and C(O)OEt(CH₂)₃Cu(CN)ZnI (0.91 mL, 0.281 mmol, 0.31 M THF), afforded a red amorphous solid which was purified via flash column chromatography on silica gel (15:85 ethyl acetate : petroleum ether) providing 120 as an orange crystalline solid (0.024 g, 50%) and the by-product 121 as a bright yellow oil (0.013 g, 15%).

(120)  
$^1$H NMR (400 MHz, CDCl₃) δ 7.48 (d, $J = 8.5$ Hz, 1H, ArH), 7.09 (d, $J = 2.5$ Hz, 1H, ArH), 7.01 (dd, $J = 8.5$, 2.5 Hz, 1H, ArH), 4.10 (q, $J = 7.0$ Hz, 2H, OCH₂), 3.87 (s, 3H OCH₃), 2.68 (t, $J = 7.5$ Hz, 2H, CH₂), 2.36 (t, $J = 7.5$ Hz, 2H, CH₂), 1.99 (p, $J = 7.5$ Hz, 2H, CH₂), 1.23 (t, $J = 7.0$ Hz, 3H, CH₃); $^{13}$C NMR (100.6 MHz, CDCl₃) δ 186.6, 172.9, 162.5, 140.3, 137.9, 125.1, 117.4, 115.1, 108.4, 60.6, 56.3, 34.0, 21.1, 20.9, 14.3; FTIR (film cm⁻¹)$\nu_{max}$: 2973 (m), 2910 (m), 2857 (w), 1711 (s), 1702 (s), 1529 (w), HRMS (TOF MS ES+) m/z calculated for $[C_{15}H_{18}NO_5]^+$: 292.1179 [M+H]$^+$, found 292.1179; M.p = 79 – 80 °C (CH₂Cl₂).

(121)  
$^1$H NMR (400 MHz, CDCl₃) δ 7.22 (dd, $J = 9.0$, 2.5 Hz, 1H, ArH), 7.15 (d, $J = 9.0$ Hz, 1H, ArH), 7.02 (d, $J = 2.5$ Hz, 1H, ArH), 4.21 – 4.12 (m, 4H, CH₂), 4.11 – 4.03 (m, 4H, CH₂), 3.80 (s, 3H OCH₃), 2.52 (t, $J = 7.5$ Hz, 2H, CH₂), 2.26 – 2.16 (m, 4H, CH₂), 2.12 – 2.04 (m, 2H, CH₂), 1.96 – 1.84 (m, 2H, CH₂), 1.82 – 1.69 (m, 2H, CH₂), 1.34 – 1.15 (m, 14H,
CH₂CH₃; ¹³C NMR (100.6 MHz, CDCl₃) δ 200.5, 173.3, 157.8, 155.8, 127.2, 122.5, 115.3, 103.5, 78.9, 75.5, 60.6, 60.4, 55.9, 53.6, 35.9, 34.4, 31.1, 29.8, 24.5, 19.7, 14.3; FTIR (film cm⁻¹)νmax: 2970 (w), 2918 (m), 1732 (s), 1489 (s), 1439 (m), 1271 (m), 1182 (m), 1027 (m), 912 (m);

HRMS (TOF MS ES⁺) m/z calculated for [C₂₇H₄₀NO₉]⁺: 522.2698 [M+H]⁺, found 522.2699.

(108) ±9-Methoxy-2,3,3a,4-tetrahydrocyclopenta[3,4]isoxazolo[2,3-a]indol-11(1H)-one, (109) 5-Methoxy-2,2-di(pent-4-en-1-yl)-1-(pent-4-en-1-yloxy)indolin-3-one & (123) ± 2-(hydroxymethyl)-5′-methoxyspiro[cyclopentane-1,2′-indolin]-3′-one

Using representative procedure 4, 2-iodo-5-methoxy-3-oxo-3H-indole 1-oxide (0.050 g, 0.165 mmol) in THF (5.0 mL) and n-pent-1-lyCu(CN)ZnI (0.80 mL, 0.281 mmol, 0.35 M THF), afforded a brown oil which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) to (2:8 ethyl acetate : petroleum ether) providing the cyclo-adduct 108 as a bright yellow oil (0.025 g, 62%), the by-products: 109 as a bright yellow oil (0.009 g, 14%), and 123 as a bright yellow oil (0.008 g, 15%).

(108) ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 9.0 Hz, 1H, ArH), 7.26 (dd, J = 9.0, 2.5 Hz, 1H, ArH), 7.06 (d, J = 2.5 Hz, 1H, ArH), 3.82 (s, 3H, CH₃), 3.79 (d, J = 9.0 Hz, 1H, OCH₂), 3.66 (dd, J = 9.0, 6.0 Hz, 1H, OCH₂), 2.89 (dt, J = 9.0, 6.0 Hz, 1H, CH₃), 2.32 – 2.22 (m, 1H, CH₂), 2.15 – 1.94 (m, 3H, CH₂), 1.93 – 1.84 (m, 1H, CH₂), 1.81 – 1.72 (m, 1H, CH₂);

¹³C NMR (100.6 MHz, CDCl₃) δ 200.9, 158.4, 156.2, 126.9, 126.8, 119.7, 103.8, 87.3, 74.1, 55.9, 53.7, 35.4, 33.6, 27.8; FTIR (film cm⁻¹)νmax: 2957 (m), 2867 (w), 1713 (s), 1227 (w), 1486 (s), 1438 (m), 1341 (m), 1278 (m), 1444 (w), 1026 (m); HRMS (TOF MS ES⁺) m/z calculated for [C₁₄H₁₆NO₃]⁺: 246.1130 [M+H]⁺, found 246.1142.
- (109)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.20 (dd, $J = 9.0$, 2.5 Hz, 1H, ArH), 7.13 (d, $J = 9.0$ Hz, 1H, ArH), 7.01 (d, $J = 2.5$ Hz, 1H, ArH), 5.86 (ddt, $J = 17.0$, 10.0, 6.5 Hz, 1H, CH alkene), 5.69 (ddt, $J = 17.0$, 10.0, 6.5 Hz, 2H, CH alkene), 5.09 (dd, $J = 17.0$, 3.5 Hz, 1H, CH alkene), 5.03 (dd, $J = 10.0$, 3.5 Hz, 1H, CH alkene), 4.93 (dd, $J = 17.0$, 3.5 Hz, 2H, CH alkene), 4.90 (dd, $J = 10.0$, 3.5 Hz, 4H, CH alkene), 4.07 (t, $J = 6.5$ Hz, 2H, OCH$_2$), 3.79 (s, $J = 4.2$ Hz, 3H, OCH$_3$), 3.59 (d, $J = 4.9$ Hz, 2H, OCH$_3$), 2.62 – 2.50 (m, 1H, CH$_2$), 2.23 – 2.13 (m, 1H, CH), 2.08 – 1.96 (m, 2H, CH), 1.91 – 1.82 (m, 1H, CH), 1.81 – 1.73 (m, 1H, CH), 1.74 – 1.63 (m, 1H, CH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 201.4, 158.1, 155.6, 138.5, 137.9, 127.2, 122.5, 115.4, 114.9, 103.4, 79.4, 75.9, 55.9, 36.3, 34.3, 30.5, 28.2, 23.5; FTIR (film cm$^{-1}$) $\nu_{max}$: 3076 (w), 2938 (m), 2869 (m), 1706 (s), 1641 (w), 1488 (s), 1438 (m), 1230 (m), 1269 (m), 1144 (w), 1028 (m), 912 (m), 825 (w); HRMS (TOF MS ES+) m/z calculated for [C$_{24}$H$_{34}$NO$_3$]$^+$: 384.2533 [M+H]$^+$, found 384.2529.

- (123)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.16 (dd, $J = 9.0$, 2.5 Hz, 1H, ArH), 7.08 (d, $J = 2.5$ Hz, 1H, ArH), 6.90 (d, $J = 9.0$ Hz, 1H, ArH), 4.50 (s, 1H, NH), 3.79 (s, 3H, OCH$_3$), 3.59 (d, $J = 4.9$ Hz, 2H, OCH$_2$), 3.49 (s, 1H, OH), 2.62 – 2.50 (m, 1H, CH), 2.23 – 2.13 (m, 1H, CH), 2.08 – 1.96 (m, 2H, CH), 1.91 – 1.82 (m, 1H, CH), 1.81 – 1.73 (m, 1H, CH), 1.74 – 1.63 (m, 1H, CH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 205.1, 156.0, 154.2, 127.5, 122.5, 115.0, 104.7, 62.5, 55.9, 50.4, 39.5, 29.8, 27.4, 23.7; FTIR (film cm$^{-1}$) $\nu_{max}$: 3328 (br), 2946 (w), 1669 (m), 1497 (s), 1439 (w), 1274 (m), 1226 (m), 1028 (m), 787 (w); HRMS (TOF MS ES+) m/z calculated for [C$_{14}$H$_{18}$NO$_3$]$^+$: 248.1281 [M+H]$^+$, found 248.1283.
**Using representative procedure 4**, 2-iodo-3-oxo-3H-indole 1-oxide (0.027 g, 0.099 mmol) in THF (3.0 mL) and n-pent-1-lyCu(CN)ZnI (0.53 mL, 0.168 mmol, 0.32 M THF), afforded a brown oil which was purified via flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) to (2:8 ethyl acetate : petroleum ether) providing the cyclo-adduct compound as a light yellow oil (0.011 g, 52%).

**1H NMR** (400 MHz, CDCl₃) δ 7.69 – 7.61 (m, 2H, ArH), 7.41 (dt, J = 8.0, 1.0 Hz, 1H, ArH), 7.25 (td, J = 8.0, 1.0 Hz, 1H, ArH), 3.80 (d, J = 9.0 Hz, 1H, OCH₂), 3.67 (dd, J = 9.0, 6.0 Hz, 1H, OCH₂), 2.90 (dt, J = 9.0, 6.0 Hz, 1H, CH₃), 2.33 – 2.23 (m, 1H, CH₂), 2.15 – 1.96 (m, 3H, CH₂), 1.94 – 1.85 (m, 1H, CH₃), 1.82 – 1.71 (m, 1H, CH₂);

**13C NMR** (100.6 MHz, CDCl₃) δ 200.9, 162.0, 137.0, 126.0, 125.7, 123.6, 118.2, 86.4, 74.7, 53.6, 35.4, 33.7, 27.8;

**FTIR** (film cm⁻¹) Vmax: 2953 (m), 2866 (w), 1716 (s), 1607 (s), 1477 (m), 1456 (m), 1326 (w), 1294 (m), 1191 (w), 1150 (w);

**HRMS** (TOF MS ES+) m/z calculated for [C₁₃H₁₄NO₂]⁺: 216.1019 [M+H]⁺, found 216.1017.

**2,2-Diethyl-5-methoxyindolin-3-one**

To a solution of 1-ethoxy-2,2-diethyl-5-methoxyindolin-3-one (0.020 g, 0.076 mmol) in MeOH (2.0 mL) was added 10% palladium on carbon (0.008 g). The reaction mixture was stirred under a hydrogen atmosphere for 4 hours then filtered through Celite and washed with MeOH and concentrated in vacuo to afford a yellow oil which was purified by flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as a yellow oil (0.013 g, 77 %).
**1H** NMR (400 MHz, CDCl$_3$) δ 7.13 (dd, $J$ = 9.0, 2.5 Hz, 1H, ArH), 7.01 (d, $J$ = 2.5 Hz, 1H, ArH), 6.84 (d, $J$ = 9.0 Hz, 1H, ArH), 4.21 (s, 1H, NH), 3.77 (s, 3H, CH$_3$), 1.78 (dq, $J$ = 15.0, 7.5 Hz, 2H, CH$_2$), 1.65 (dq, $J$ = 15.0, 7.5 Hz, 3H, CH$_2$), 0.77 (t, $J$ = 7.5 Hz, 6H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 205.7, 157.1, 153.2, 127.8, 122.3, 113.8, 104.2, 72.0, 55.9, 30.2, 7.9; FTIR (thin film cm$^{-1}$) $\nu_{\text{max}}$: 3339 (w, br), 2966 (w), 2929 (w), 1672 (m), 1497 (s), 1457 (w), 1262 (w), 1142 (w), 1031 (w), 789 (m), 668 (w); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{13}$H$_{18}$NO$_2$]$^+$: 220.1338 [M+H]$^+$, found 220.1328.

**(116) 4-Iodobut-1-ene**

![Chemical structure](image)

To a solution of 4-bromobut-1-ene (3.00 g, 22.2 mmol) in acetone (50.0 mL) was added NaI (6.66 g, 44.4 mmol), and then heated at 60 °C for 2 hours. The mixture was cooled to room temperature and filtered, after which it was extracted with pentane (50.0 mL) and washed with saturated Na$_2$S$_2$O$_3$ (aq) (20.0 mL) followed by brine (30.0 mL). The organic extract was dried with MgSO$_4$, filtered and then concentrated *in vacuo* at 0 °C to afford the title compound as a clear oil (3.30 g, 81%).

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 5.82 – 5.69 (m, 1H, CH alkene), 5.15 – 5.13 (m, 1H, CH alkene), 5.13 – 5.08 (m, 1H, CH alkene), 3.18 (t, $J$ = 7.2 Hz, 2H, CH$_2$), 2.62 (app q, $J$ = 7.0 Hz, 2H, CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 137.0, 117.1, 37.8, 4.8.

**(117) Ethyl 4-iodobutanoate**

![Chemical structure](image)

To a solution of ethyl 4-bromobutanoate (3.90 g, 20.0 mmol) in acetone (50.0 mL) was added NaI (6.00 g, 40.0 mmol), and then heated at 60 °C for 2 hours. The mixture was cooled to room temperature and filtered, after which it was extracted with pentane (50.0 mL) and washed with saturated Na$_2$S$_2$O$_3$ (aq) (20.0 mL) followed by
brine (30.0 mL). The organic extract was dried with MgSO₄, filtered and then concentrated in vacuo at 0 °C to afford the title compound as a clear oil (4.76 g, 98%).

³¹H NMR (400 MHz, CDCl₃) δ 4.15 (q, J = 7.0 Hz, 2H, OCH₂), 3.25 (t, J = 7.0 Hz, 1H, CH₂), 2.45 (t, J = 7.0 Hz, 1H, CH₂), 2.20 – 2.08 (m, 2H, CH₂), 1.27 (t, J = 7.0 Hz, 2H, CH₃);
³¹C NMR (100.6 MHz, CDCl₃) δ 172.5, 60.7, 34.9, 28.6, 14.4, 5.7.

(118) 2-(3-Iodopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of 2-(3-bromopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.50 g, 10.0 mmol) in acetone (20.0 mL) was added NaI (3.01 g, 20.1 mmol), and then heated at 60 °C for 2 hours. The mixture was cooled to room temperature and filtered, after which it was extracted with pentane (25.0 mL) and washed with saturated Na₂S₂O₃(aq) (10.0 mL) followed by brine (15.0 mL). The organic extract was dried with MgSO₄, filtered and then concentrated in vacuo at 0 °C to afford the title compound as a clear oil (2.88 g, 92%).

³¹H NMR (400 MHz, CDCl₃) δ 3.19 (t, J = 7.0 Hz, 2H, CH₂), 1.91 (app quint, J = 7.0 Hz, 1H, CH₂), 1.22 (s, 12H, CH₃), 0.86 (t, J = 7.0 Hz, 2H, CH₂);
³¹C NMR (100.6 MHz, CDCl₃) δ 83.3, 34.2, 28.4, 24.9, 10.1; B NMR (128 MHz, CDCl₃) δ 33.59.

(122) 5-Iodopent-1-ene

To a solution of 5-bromopent-1-ene (2.50 g, 16.8 mmol) in acetone (30.0 mL) was added NaI (5.02 g, 33.6 mmol), and then heated at 60 °C for 2 hours. The mixture was cooled to room temperature and filtered, after which it was extracted with
pentane (50.0mL) and washed with saturated Na$_2$S$_2$O$_3$(aq)(20.0 mL) followed by brine (30.0 mL). The organic extract was dried with MgSO$_4$, filtered and then concentrated in vacuo at 0 °C to afford the title compound as a clear oil (2.75 g, 84%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.77 (ddt, $J = 17.0, 10.0, 6.5$ Hz, 1H, CH, alkene), 5.09 (dd, $J = 17.0, 2.0$ Hz, 1H, CH, alkene), 5.03 (dd, $J = 10.0, 2.0$ Hz, 1H, CH, alkene), 3.20 (t, $J = 7.0$ Hz, 2H, CH$_2$), 2.18 (app q, $J = 7.0$Hz, 2H, CH$_2$), 1.93 (app quint, $J = 7.0$ Hz, 2H, CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 136.5, 116.0, 34.3, 32.5, 6.4.

4.5 – Representative Procedure: 5

(126) 1-Ethoxy-2-ethyl-2-phenylindolin-3-one:

A flame dried flask equipped with magnetic stirrer bar was charged with 2-iodo-3-oxo-3H-indole 1-oxide (0.50 g, 0.244 mmol) in anhydrous THF (5.0 mL) at 20 °C. EtZnI (0.81 mL, 0.672 mmol, 0.81 M THF) was added dropwise, the resultant reaction mixture was stirred under nitrogen for 3 hours. The reaction mixture was quenched with H$_2$O (1.8 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried over MgSO$_4$, filtered and then concentrated in vacuo to give a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a bright yellow oil (0.038 g, 60%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.50 (m, 2H, ArH), 7.38 – 7.34 (m, 2H, ArH), 7.27 – 7.16 (m, 4H, ArH), 6.97 – 6.92 (m, 1H, ArH), 3.96 – 3.82 (m, 2H, CH$_2$), 2.49 (dq, $J = 14.5, 7.0$ Hz, 1H, CH$_2$), 2.23 (dq, $J = 14.5, 7.5$ Hz, 1H, CH$_2$), 1.17 (t, $J = 7.0$ Hz, 3H, CH$_3$), 0.72 (t, $J = 7.5$ Hz, 3H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 199.6, 162.7, 139.5, 137.2, 128.5, 127.8, 127.2, 124.0, 121.9, 120.9, 112.8, 80.1, 71.7, 27.39, 14.3, 9.4; FTIR (thin film cm$^{-1}$)$\nu_{max}$: 2974 (w), 1714 (s), 1607 (s), 1475 (m), 1457 (m), 1381 (w), 1322 (w), 1044 (m), 1756 (m); HRMS (TOF MS ES+) m/z calculated for [C$_{18}$H$_{20}$NO$_2$]$^+$: 282.1494 [M+H]$^+$, found 282.1497
Using representative procedure 5, 3-oxo-2-phenyl-3H-indole 1-oxide (0.050 g, 0.224 mmol) in THF (5.0 mL) and n-HexZnI (0.81 mL, 0.672 mmol 0.83 M THF), afforded a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 diethyl ether : petroleum ether - 1:9 ethyl acetate : petroleum ether) providing the title compound as a yellow oil, (0.054 g, 61 %).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \text{) } \delta 7.60 - 7.54 (m, 2H, ArH), 7.43 - 7.39 (m, 2H, ArH), 7.31 - 7.19 (m, 4H, ArH), 3.98 - 3.79 (m, 2H, OCH}_2 \text{), 2.51 - 2.39 (m, 2H, CH}_2 \text{), 2.26 - 2.15 (m, 1H, CH}_2 \text{), 1.63 - 1.54 (m, 1H, CH}_2 \text{), 1.32 - 1.16 (m, } \text{14H, CH}_2 \text{), 0.85 (t, } J = 7.0 \text{ Hz, 3H, CH}_3 \text{), 0.80 (t, } J = 7.0 \text{ Hz, 3H, CH}_3 \text{); } ^{13}C \text{ NMR (100.6 MHz, CDCl}_3 \text{) } \delta 199.7, 162.5, 139.6, 137.2, 128.4, 128.4, 127.8, 127.2, 124.1, 121.9, 120.8, 112.8, 79.7, 76.4, 34.5, 31.7, 31.6, 29.8, 28.8, 25.8, 24.4, 22.7, 22.7, 14.1; \text{ FTIR (thin film cm}^{-1})_{\text{Vmax:}} 2955 (m), 2929 (s), 2857 (m), 1716 (s), 1607 (m), 1474 (m), 1458 (w), 1305 (w), 1037 (w), 756 (m); \text{ HRMS (TOF MS ES+)} m/z calculated for [C}_{26}H_{36}NO_2]^+ 394.2746 [M+H]^+, found 394.2763.

(127) 2-Hexyl-1-(hexyloxy)-2-phenylindolin-3-one

(128) 2-Hexyl-2-phenylindolin-3-one

To a solution of 2-hexyl-1-(hexyloxy)-2-phenylindolin-3-one (0.060 g, 0.153 mmol) in MeOH (4.0 mL) was added 10% palladium on carbon (0.015 g). The reaction mixture was stirred under a hydrogen atmosphere for 6 hours then filtered through Celite and washed with MeOH and concentrated in vacuo to afford a yellow oil which was purified by flash column chromatography on silica gel (1:9 ethyl acetate : petroleum ether) providing the title compound as a yellow solid (0.028 g, 62 %).
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.53 (m, 3H, ArH), 7.47 (t, $J = 7.5$ Hz, 1H, ArH), 7.36 – 7.30 (m, 2H, ArH), 7.28 – 7.23 (m, 1H, ArH), 6.96 (d, $J = 8.0$ Hz, 1H, ArH), 6.81 (t, $J = 7.5$ Hz, 1H, ArH), 5.03 (s, 1H, NH), 2.19 – 2.02 (m, 2H, CH$_2$), 1.34 – 1.14 (m, 8H, CH$_2$), 0.83 (t, $J = 7.0$ Hz, 1H, CH$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 202.0, 160.5, 139.4, 137.4, 128.8, 127.6, 125.8, 125.5, 119.9, 119.1, 112.0, 72.1, 38.5, 31.7, 29.6, 24.1, 22.7, 14.2; FTIR (film cm$^{-1}$): $\nu$$_{max}$: 3351 (w br), 2957 (m), 2930 (m), 2856 (m), 1683 (s), 1621 (s), 1492 (m), 1468 (m), 1325 (m), 1294 (w), 751 (w); HRMS (TOF MS ES$^+$) m/z calculated for [C$_{20}$H$_{24}$NO]+: 294.1852 [M+H]$^+$, found 294.1851; M.p = 67 – 69 °C (CH$_2$Cl$_2$).

(95) 1-Ethoxy-2-ethyl-2-phenylindolin-3-one:

Using representative procedure 5, 3-oxo-2-phenyl-3H-indole 1-oxide (0.022 g, 0.100 mmol) in THF (3.0 mL) and Et$_2$Zn (0.25 mL, 0.150 mmol, 0.60 M THF), afforded a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 diethyl ether : petroleum ether - 1:9 ethyl acetate : petroleum ether) providing the title compound as a yellow oil, (0.017 g, 61 %).

For characterisation data, see page 181.
(104) 1-Ethoxy-2,2-diethylindolin-3-one

Using representative procedure 5, 2-iodo-3-oxo-3H-indole 1-oxide (0.045 g, 0.165 mmol) in THF (5.0 mL) and Et₂Zn (0.50 mL, 0.495 mmol, 1.00 M THF), afforded a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a yellow oil, (0.024 g, 60 %).

For characterisation data, see page 172.

(106) 1-Ethoxy-2,2-diethyl-6-methylindolin-3-one

Using representative procedure 5, 2-iodo-6-methyl-3-oxo-3H-indole 1-oxide (0.047 g, 0.165 mmol) in THF (5.0 mL) and Et₂Zn (0.50 mL, 0.495 mmol, 1.00 M THF), afforded a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a yellow oil, (0.026 g, 61 %).

For characterisation data, see page 173.

(136) 2-Cyclohexyl-1-ethoxy-2-ethyl-5-methoxyindolin-3-one

Using representative procedure 5, 2-cyclohexyl-5-methoxy-3-oxo-3H-indole 1-oxide (0.015 g, 0.059 mmol) in THF (1.75 mL) and Et₂Zn (0.30 mL, 0.178 mmol, 0.60 M THF), afforded a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a bright yellow oil, (0.016 g, 85 %).
{H NMR (400 MHz, CDCl₃) δ 7.18 (dd, J = 9.0, 2.5 Hz, 1H, ArH), 7.11 (d, J = 9.0 Hz, 1H, ArH), 7.00 (d, J = 2.5 Hz, 1H, ArH), 4.14 (q, J = 7.0 Hz, 2H, OCH₂), 3.79 (s, 3H, CH₃), 2.01 (dq, J = 14.5, 7.5 Hz, 1H, CH₂), 1.96 – 1.86 (m, 1H, CH₃), 1.79 (dq, J = 14.5, 7.5 Hz, 1H, CH₂), 1.70 – 1.65 (Hz, 3H, CH₃), 1.36 (t, J = 7.0 Hz, 3H, CH₃), 1.29 – 1.15 (m, 3H, CH₂), 0.95 – 0.78 (m, 2H, CH₂), 0.68 (t, J = 7.5 Hz, 3H, CH₃); {C NMR (100.6 MHz, CDCl₃) δ 202.1, 158.8, 155.3, 126.8, 122.9, 114.5, 103.1, 82.5, 71.7, 55.9, 43.9, 28.4, 27.0, 26.7, 26.6, 14.4, 8.9; FTIR (thin film cm⁻¹)νmax: 2930 (s), 2852 (m), 1705 (s), 1488 (s), 1439 (m), 1277 (m), 1147 (w), 1032 (m); HRMS (TOF MS ES+) m/z calculated for [C₁₉H₂₈NO₃]+: 318.2064 [M+H]+, found 318.2062.

(137) 1-Ethoxy-2-ethyl-5-methoxy-2-methylindolin-3-one

Using representative procedure 5, 5-methoxy-2-methyl-3-oxo-3H-indole 1-oxide (0.020 g, 0.105 mmol) in THF (3.0 mL) and Et₂Zn (0.26 mL, 0.158 mmol, 0.60 M THF), afforded a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing the title compound as a bright yellow oil, (0.016 g, 61 %).

{H NMR (400 MHz, CDCl₃) δ 7.21 (dd, J = 9.0, 2.5 Hz, 1H, ArH), 7.16 (d, J = 9.0 Hz, 1H, ArH), 7.04 (d, J = 2.5 Hz, 1H, ArH), 4.18 – 4.06 (m, 2H, OCH₂), 3.79 (s, 3H, CH₃), 1.96 (dq, J = 14.5, 7.5 Hz, 1H, CH₂), 1.77 (dq, J = 14.5, 7.5 Hz, 1H, CH₂), 1.36 (t, J = 7.0 Hz, 3H, CH₃), 0.76 (t, J = 7.5 Hz, 3H, CH₃); {C NMR (100.6 MHz, CDCl₃) δ 201.9, 157.6, 155.8, 126.8, 121.9, 116.0, 103.8, 77.0, 71.9, 55.9, 29.7, 21.8, 14.5, 8.9; FTIR (thin film cm⁻¹)νmax: 2976 (s), 2932 (s), 2881 (m), 2837 (w), 1711 (s), 1618 (w), 1491 (s), 1442 (m), 1341 (m), 1277 (m), 1147 (m), 1046 (m), 1031 (m); HRMS (TOF MS ES+) m/z calculated for [C₁₄H₂₀NO₃]+: 250.1438 [M+H]+, found 250.1435.
(126) 1-Ethoxy-2-ethyl-2-phenylindolin-3-one

A flame dried flask equipped with magnetic stirrer bar was charged with 1-ethoxy-2-ethyl-2-phenylindolin-3-one (0.027 g, 0.096 mmol) in anhydrous THF (3.0 mL) at 20 °C. EtZnI (0.23 mL, 0.192 mmol, 0.83 M THF) was added dropwise, and the resultant reaction mixture was stirred under nitrogen for 3 hours. The reaction mixture was quenched with H₂O (2.0 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried over MgSO₄, filtered and then concentrated in vacuo to give a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing a significant amount of apparent Iodine and also the title compound as a bright yellow oil (0.023 g, 82 %).

*For characterisation data, see page 181*

(95) 1-Ethoxy-2,2-diethyl-5-methoxyindolin-3-one

A flame dried flask equipped with magnetic stirrer bar was charged with 1-ethoxy-2,2-diethyl-5-methoxyindolin-3-one (0.017 g, 0.130 mmol) in anhydrous THF (2.0 mL) at 20 °C. EtZnI (0.16 mL, 0.130 mmol, 0.83 M THF) was added dropwise, and the resultant reaction mixture was stirred under nitrogen for 3 hours. The reaction mixture was quenched with H₂O (2.0 mL), extracted with ethyl acetate (10.0 mL) and washed with brine (5.0 mL). The organic layer was dried over MgSO₄, filtered and then concentrated in vacuo to give a viscous orange oil, which was purified by flash column chromatography on silica gel (5:95 ethyl acetate : petroleum ether) providing a significant amount of apparent Iodine and also the title compound as a bright yellow oil (0.014 g, 82 %).

*For characterisation data, see page 161*
4.6 – General procedure: 1 (Preparation of Alkylzinc Halides)\textsuperscript{91}

A flame dried flask, equipped with magnetic stirrer bar and reflux condenser, was charged with a dispersion of zinc dust (26.00 mmol) in THF (2.00 mL) and flushed with nitrogen. 1,2-dibromoethane (0.10 mL) was added and the reaction mixture was heated to reflux with a heat gun, this process was repeated a further two times. After which the reaction mixture was cooled to room temperature and TMSCl (0.10 mL) was added slowly followed by 10 minutes of vigorous stirring. Primary alkyl iodide (26.00 mmol) was then added as a solution of THF (10.0 mmol), the resultant reaction mixture was stirred vigorously and heated at 50 °C for 18 hours. The molarity of the newly afforded alkylzinc iodides was determined by iodometric titration in a 0.5 M solution of LiCl in THF.\textsuperscript{92}

\[
\begin{array}{c}
1.) \quad \text{R-I} \quad \text{Zn (1.0 equiv)} \\
\quad \quad \quad \text{BrC}_2\text{H}_4\text{Br (5 mol%), THF, } \Delta, 10 \text{ min} \\
2.) \quad \text{TMSCl, R-I (1.0 equiv), THF, } 50 ^\circ \text{C, } \text{o/n}
\end{array}
\]

\[
\begin{array}{ccc}
\text{Et-ZnI} & \text{Me-ZnI} & \text{ZnI} \\
(0.81, 0.83 & 0.91 \text{ M}) & (1.40 \text{ M}) & (0.80 & 0.83 \text{ M}) \\
\text{Cl-ZnI} & \text{ZnI} \\
(0.74 \text{ M}) & (0.88 \text{ M})
\end{array}
\]

General procedure: 2 (Preparation of Alkylzinc Halides) \textsuperscript{98}

A flame dried flask, equipped with magnetic stirrer bar and reflux condenser, was charged with a dispersion of zinc dust (20.00 mmol) and dry LiCl (20.00 mmol) in THF (9.00 mL) and flushed with nitrogen. 1,2-dibromoethane (0.10 mL) was added and the reaction mixture was heated to reflux with a heat gun, this process was repeated a further two times. After which the reaction mixture was cooled to room temperature and TMSCl (0.10 mL) was added slowly followed by 10 minutes of vigorous stirring. A solution of iodine (0.50 mmol) in THF (1.00 mL) was added and the reaction mixture was stirred until the resultant brown colour had dissipated, around 2 minutes. Alkyl iodide (10.00 mmol) was then added neat, the resultant reaction mixture was stirred vigorously and heated at 50 °C for 18 hours. The molarity of the newly afforded alkylzinc halides was determined by iodometric titration in a 0.5 M solution of LiCl in THF.\textsuperscript{92}
R-X \xrightarrow{\text{1.} Zn (2.0 equiv), LiCl (2.0 equiv), BrC\textsubscript{6}H\textsubscript{4}Br (5 mol\%), THF, \Delta, 10 \text{ min}} \text{R-ZnX.2LiCl} \\
\text{2. TMSCl, I\textsubscript{2}, R-X (1.0 equiv), THF, 50 °C, o/n}

\begin{align*}
\text{cyclohexyl-ZnI} & \quad (0.54 \text{ M}) \\
\text{hexyl-ZnI} & \quad (0.44 \text{ M}) \\
\text{propyl-ZnI} & \quad (0.70 \text{ M}) \\
\text{acetyl-ZnI} & \quad (0.62 \text{ M}) \\
\text{BrZn-} & \quad (0.56 \text{ M}) \\
\text{I-Zn-} & \quad (0.55 \text{ M}) \\
\text{I-Zn-} & \quad (0.24 \text{ M})
\end{align*}
References


Appendix.

- nOe spectra of 95.

For X-Ray crystallographic data of compounds: 24, 28, 33, 36, 40, 46, 49, 70, & 100 - see attached CD-ROM

- For raw data of figures 17 – 20, 22 – 23, 34 – 35 see attached CD-ROM