Catalytic Dearomatisation Reactions

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Abstract

This Thesis describes the development of novel catalytic dearomatisation methodologies of indolyl and pyridyl systems for the synthesis of spirocyclic and annulated products. Chapter 1 provides an introduction to this area of research and reviews related reactions, as well as setting out the research objectives.

Chapter 2 describes the cyclisation of indole-alkyne systems I, using Ag(I) or Au(I) catalysis, to selectively form either spirocyclic indolenines III or carbazoles IV in high yield through a common vinyl metal intermediate II. An efficient and reusable heterogeneous catalyst system was also found for the synthesis of indolenines III. A high-yielding asymmetric spirocyclisation methodology was later developed by using the silver salt of a BINOL-derived chiral phosphoric acid V to furnish spirocycles in up to 89:11 er. Finally, these methodologies were applied in brief studies towards the natural product spirobacillene B VI and in an accidental synthesis of actinopolymorphol B VII.

Chapter 3 details the cyclisation of indole α-diazocarbonyls VIII, using Rh(II)-, Pd(II)-, Cu(II)- and SiO₂-based catalysts to selectively form 6 different products, namely spirocyclic indolenines IX, oxindoles X and XI, as well as annulated indole isomers XII, XIII and XIV. This work is, to the best of our knowledge, a record number products prepared through catalyst-selective synthesis. A number of diverse mechanistic pathways were proposed in this work, including a surprising reaction involving atmospheric oxygen.
Finally, Chapter 4 describes the cyclisation of pyridine-, pyrazine- and isoquinoline-ynones XV to generate annulated products XVII, which are presumed to form via a vinyl silver species such as XVI. This work ultimately led to a high-yielding 5 step dearomative synthesis of the alkaloid (±)-lasubine II XVIII.
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Declaration

The research presented in this Thesis was carried out at the University of York between October 2013 and March 2017. This work is, to the best of my knowledge, original except where due reference has been made to other workers.

This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

This work has been reproduced in a number of recent publications, which can be found in the Appendices.
Chapter 1. Introduction

1.1 Dearomatisation reactions

Dearomatisation reactions are important transformations that provide access to high value spiro-, bridged- and fused-compounds from relatively simple and inexpensive aromatic precursors.\(^1\)\(^{-4}\) The more complex three-dimensional structures typically obtained from these reactions are often found in a number of natural product systems, further extending their synthetic value.\(^5\) A prominent early example demonstrating the synthetic power of dearomatisation reactions can be found in Woodward and co-workers’ seminal total synthesis of strychnine 3 (Scheme 1).\(^6,7\) In this work, indole 1 was dearomatised in a Pictet–Spengler type spirocyclisation process to afford spirocyclic indolenine 2 in good yield, which was subsequently elaborated to produce strychnine 3.

![Scheme 1](image)

Scheme 1. The dearomatisation of indole 1 in the total synthesis of strychnine 3.

Following this pioneering work, dearomatisation reactions have been employed in a number of natural product syntheses.\(^5\) However, perhaps the greatest advancement in this area has come with the development of new catalytic asymmetric dearomatisation (CADA) reactions.\(^8\)\(^{-10}\) A number of CADA reaction strategies have been developed, with arguably the leading work in this area performed by You and co-workers, who have used an intramolecular allylic alkylation approach to great effect (Scheme 2).\(^11\) In this approach allylic carbonates are tethered to aromatic systems (such as phenols 4, indoles 7 or pyridines 10) and then reacted with a chiral catalyst (usually an iridium complex) to form a highly electrophilic \(\pi\)-allyl species, which is then nucleophilically attacked by the aromatic system to form the dearomatised product in typically high yield and with excellent enantioselectivity.\(^12\)\(^{-14}\)
Scheme 2. CADA reactions through an intramolecular allylic alkylation approach.
1.2 Spirobacillenes A & B

1.2.1 Isolation and previous syntheses

The Taylor group became interested in dearomatisation reactions following the reported isolation of two unusual natural products, spirobacillenes A 12 & B 13 (Scheme 4). Both natural products were isolated from a culture of *Lysinibacillus fusiformis* KMC003, which was obtained from acidic coal-mine drainage; a somewhat unusual source of natural products! Biosynthetically, both spirobacillene A 12 & B 13 were proposed to be derived from a common intermediate, diketone 14, which was also isolated from the same culture. Diketone 14 was presumed to form either spirobacillene A 12 or spirobacillene B 13 following oxidation and the dearomative spirocyclisation of either the phenol or indole ring, respectively.

**Scheme 3.** Spirobacillenes A & B and their proposed biosynthetic precursor.

Mechanistically, it was proposed by Tang and co-workers that both natural products were formed by two aromatic-enol oxidative coupling processes (Scheme 4). Here, spirobacillene A 12 was proposed to form via an electrophilic oxidative dearomatisation reaction, in which the enol of 14 nucleophilically attacks the activated phenol ring 15 (Scheme 4, path a). Conversely, spirobacillene B 13 was proposed to form via a nucleophilic dearomatisation reaction, in which the indole ring of 17 nucleophilically attacks the activated enol tautomer of 16 (Scheme 4, path b).
Tang and co-workers successfully applied a biomimetic strategy to complete the total synthesis of both spirobacillene A 12 and B 13. The synthesis of spirobacillene A 12 began with Weinreb amide 19, which was prepared in 6 steps from indole 18 according to literature methods (Scheme 5). The α-keto hydroxyl group of amide 19 was then protected with a TES group before reaction with benzyl Grignard 20 to form indole 21. Subsequent cleavage of the TES protecting group and oxidation with DMP afforded diketone 22, which gradually formed the enol tautomer 23 following column chromatography. The proposed biosynthetic precursor 14 was then prepared in good yield following cleavage of the TBS protecting group with TBAF. Finally, diketone 14 was reacted with an excess of Ag2O to form spirobacillene A 12 in modest yield and in 12 overall steps.
Scheme 5. Tang and co-workers’ synthesis of spirobacillene A 12.

For the synthesis of spirobacillene B 13, Tang and co-workers reacted benzyl ketone 21 with LHMDS, followed by iodine to promote the formation of spirocyclic indolenine 24 (Scheme 6). Interestingly, indolenine 24 appeared to be unstable and formed only spirocyclic oxindole 26 (with ambiguous stereochemistry) upon quenching the reaction with sat. aq. Na$_2$S$_2$O$_3$. Mechanistically, oxindole 26 was proposed to form via the Kornblum–DeLaMare rearrangement of an intermediate endoperoxide 25 formed by an autoxidation process. Fortunately, this reaction pathway could be suppressed by treating the unstable indolenine 24 with PPTS, which promoted both the deprotection and autoxidation of the TES-protected hydroxyl group to form a low-yielding mixture of spirobacillene B 13 and the TBS-protected analogue 27. Finally, the TBS-protected analogue 27 was also converted into spirobacillene B 13 by cleavage of the TBS protecting group by reaction with TBAF.
1.2.2 Taylor group synthesis and methodology

In contrast to the biomimetic approach to spirobacillenes A 12 & B 13 employed by Tang and co-workers, the Taylor group devised an alternative strategy, which focused on using ynones 28 and 30 as precursors to spirocyclic enones 29 and 31, respectively (Scheme 8). Subsequent oxidation of the enone framework was envisaged to provide access to the desired natural products in a concise and high-yielding fashion.

Unsworth, Taylor and co-workers successfully applied this strategy in the total synthesis of spirobacillene A 12 (Scheme 8). The synthesis began with the preparation of alkyne 34 from indole 32 in 4 steps according to literature methods. Alkyne 34 was then deprotonated with n-BuLi and reacted with Weinreb amide 35 to afford the anisole-based spirocyclisation precursor 36, which upon reaction with SnCl₂·H₂O, afforded the desired spirocycle 37 in excellent yield. Unfortunately, selective oxidation of this framework proved difficult and could only be achieved by first reducing the cyclopentenone moiety under Luche conditions to form allylic alcohol 38; allylic alcohol 38 was then epoxidised with m-CPBA and re-oxidised with DMP to form α-keto epoxide 39, which upon reaction with TsOH and then TFA afforded spirobacillene 12 in just 11 steps and 14% overall yield.

Unsworth, Taylor and co-workers also conducted preliminary studies towards spirobacillene B \(13\) by applying the same strategy. Unfortunately, when model ynone \(40\) was reacted under the same \(\text{SnCl}_2\cdot\text{H}_2\text{O}\)-mediated conditions the desired spirocyclic indolenine \(41\) was obtained in only 40\% yield, confirming the viability of this approach, but suggesting that improved spirocyclisation conditions were needed.

Scheme 9. Preliminary \(\text{SnCl}_2\cdot\text{H}_2\text{O}\)-mediated spirocyclisation of indole-ynone \(40\).
1.3 Spirocyclic indolenine synthesis via indole-alkyne spirocyclisation

At the time this research commenced, only a few indole-alkyne systems had ever been used to prepare spirocyclic indolenines, which were typically formed in low yield upon reaction with a gold catalyst. Inspiration for the majority of reactions of this type came from the pioneering work of Echavarren and co-workers in 2007 (Scheme 10). In this work the authors describe a single spirocyclisation reaction, in which 2-methyl substituted indole-alkyne 42 was reacted with gold catalyst 43 to form indoline 44 (Scheme 10a). Interestingly, when the analogous indole 45 (without a substituent on the indole C2-position) was reacted with the same catalyst 43 only the annulated indole 46 was formed (Scheme 10b). From these results it was hypothesised that all reactions of this type may proceed via a spirocyclic vinyl gold intermediate (48, Scheme 11) but rapidly undergo a 1,2-migration process in the absence of a steric blocking group at the indole C2-position. The 1,2-migration was proposed to proceed either directly (48 → 50) or via a cyclopropanation-ring-opening sequence (48 → 49 → 50).

Scheme 10. The first Au(I)-catalysed cyclisations of indole-alkynes.
Later, in 2012, Van der Eycken and co-workers reported the first synthesis of a spirocyclic indolenine using this approach.\(^\text{19}\) Again, a Au(I) catalyst was used with alkyne \(^5\) to form a low yielding mixture of spirocyclic indolenine \(^4\) and annulated indole \(^5\) (Scheme 12). In agreement with Echavarren and co-workers, the authors suggest that this is further evidence of a 1,2-migration process. Next, Carbery and co-workers reported a single example of spirocyclic indolenine synthesis when indole-ynone \(^6\) was reacted with AuCl\(_3\) to form another low yielding mixture of spirocyclic indolenine \(^7\) and annulated indole \(^8\).\(^\text{20}\)

However, it is important to note that both of these reactions were only performed as part of mechanistic studies in the synthesis of other annulated indoles. Finally, a recent report by Wang and co-workers described the first high yielding Au(I)-catalysed approach to form tetracyclic spirocyclic indolenines \(^9\).\(^\text{21}\) However, as the substrates \(^5\) are substituted on the 2-position the synthetic challenge is somewhat diminished as this substitution inhibits the problematic 1,2-migration pathway (as demonstrated by Echavarren and co-workers, Scheme 10).

\[ \text{Scheme 11. Proposed mechanism for the formation of annulated indoles.} \]
Scheme 12. Au(I/III)-catalysed synthesis of spirocyclic indolenines.

Finally, the only example to not use a Au-based catalyst was reported by Toste and co-workers, who instead utilised a chiral Pd(II)-catalyst in their studies towards the synthesis of the kopsifoline (Scheme 13). Here, indole-alkyne 61 was reacted with a Pd(II)-complex to afford the spirocycle 63 in only moderate yield but with promising enantioselectivity.

Scheme 13. Pd(II)-catalysed synthesis of a spirocyclic indolenine.
### 1.4 Spirocyclic indolenines

Aside from their presence in natural products, spirocyclic indolenines are also potentially valuable compounds for drug discovery when considering the dominant presence of N-heterocycles in small-molecule drugs and the rising interest in spirocyclic scaffolds.\(^{23-28}\) Interest in spirocycles stems from their ability to occupy areas of 3D chemical space, which are typically under-represented in medicinal chemistry drug discovery programs and screening libraries.\(^{29-32}\) The exploration of new chemical space in drug discovery is important to help find new lead compounds and also to ensure their commercial viability.\(^{33-35}\) Drugs containing spirocyclic heterocycles have also been shown to exhibit enhanced physicochemical and pharmaco-kinetic properties.\(^{25}\) Considering all of this, the synthesis of novel spirocyclic heterocycles is an area of interest at all levels of drug discovery.

Indolenines \(^{64}\) are also highly reactive and useful intermediates that can be converted into a range of other privileged scaffolds such as indolines \(^{65}\), oxindoles \(^{66}\), carbazoles \(^{67}\) and polycycles \(^{68}\) (Figure 1).\(^{23,36}\) However, their inherent reactivity also provides some substrate specific synthetic challenges with regards to their isolation and handling (Figure 2). Spirocyclic indolenines are known for their sensitivity to acids due to their well-documented propensity to undergo 1,2-migrations (\(69 \rightarrow 70 \rightarrow 71\)), a process driven by the reformation of the aromatic indole ring.\(^{37-39}\) Another complication lies in their tendency to exist in equilibrium between the imine \(^{72}\) and imine trimer \(^{73}\), which can hamper their characterisation and further manipulation.\(^{40-45}\) The equilibrium between imine and imine trimer can be manipulated to favour the free imine/iminium species \(^{74}\) by employing acidic conditions;\(^{43}\) however, this solution may subsequently promote the aforementioned 1,2-migrations. Overall, these properties have most likely hindered the development of new strategies for the synthesis of spirocyclic indolenines, an area of synthesis we have comprehensively reviewed (see Appendix I).\(^{46}\)
Figure 1. Synthetic utility of spirocyclic indolenines.

Figure 2. Reactivity of spirocyclic indolenines: a) 1,2-Migrations; b) Imine trimer formation.
1.5 Project aims

The initial goal of this project was to improve upon the preliminary SnCl$_2$·2H$_2$O-mediated spirocyclisation of an indole-alkyne system and to extend this work into a general methodology for the synthesis of spirocyclic indolenines (Scheme 14a). Full scoping studies of this methodology and the development of an enantioselective variant were also planned. If successful, this work was envisaged to potentially enable the total synthesis of spirobacillene B 13. Following these initial goals, the development of other novel catalytic methods for the synthesis of spirocyclic indolenines was planned by pairing indole with other electrophilic systems (Scheme 14b). Furthermore, the application of these dearomative methods to other heterocyclic systems, such as pyridine, was planned (Scheme 14c).

Scheme 14. Project aims overview.
Chapter 2. Indole-alkyne cyclisations

2.1 Indole-ynone cyclisations

2.1.1 Reaction discovery & optimisation studies

Studies towards the synthesis of spirobacillene B began with the preparation of PMP-based model substrate 83a, which was prepared in a two-step sequence from 3-indoleacetic acid 80a (Scheme 15). Acid 80a was converted into Weinreb amide 81a in quantitative yield using propyl phosphonic anhydride (T3P) as an activating agent. Amide 81a was then reacted with the lithium acetylide generated from the reaction of n-BuLi with alkyne 82 to afford ynone 83a in excellent yield.

![Scheme 15. Two step synthesis of model ynone 83a.](image)

Ynone 83a was then reacted with a variety of potential catalysts in an attempt to improve upon the preliminary SnCl₂·H₂O-catalyzed spirocyclisation conditions; dichloromethane was retained as the solvent due its compatibility with a wide range of acids and metal catalysts (Table 1). These experiments were carried out on a small scale (0.1–0.2 mmol of ynone 83a) and examined by analysis of the ¹H NMR spectra of the unpurified reaction mixtures.

First, a number of strong Brønsted acid catalysts were examined (entries 1–3), which promoted varying levels of conversion into the desired spirocycle 84a. Next, Lewis acids, such as BF₃·OEt₂, SnCl₂·2H₂O and in particular anhydrous SnCl₄ were also identified as effective catalysts (entries 4–12). Investigations into π-acid catalysts (entries 14–20) began with Ph₃PAuCl, which without an activating silver co-catalyst displayed minimal reactivity (entry 14); the combination of AgOTf and Ph₃PAuCl promoted a dramatically different reaction profile, affording primarily carbazole 85a (entry 14). Investigating common copper catalysts used in related reactions (entries 15–17) revealed Cu(OTf)₂ as a comparable catalyst to SnCl₄. Finally, Ag(I) catalysts, AgOTf and AgNO₃ were examined, which again promoted full conversion into the spirocycle. Following these results, the more easily handled Ag(I) and Cu(II) catalysts were examined further at reduced catalyst loading (1 mol%, entries 20–23). After 30 minutes, it was evident that the Ag(I) catalysts, particularly AgOTf, were most effective. The potency of AgOTf was demonstrated further when the catalyst loading was...
dropped to just 0.1 mol%, which still promoted 85% conversion into spirocycle 84a after a prolonged reaction time (entry 23).

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<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Time (h)</th>
<th>Ratio 83a:84a:85a</th>
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<td>1</td>
<td>aq. 12 M HCl (10)</td>
<td>24</td>
<td>82:18:0</td>
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<tr>
<td>2</td>
<td>TFA (10)</td>
<td>24</td>
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<tr>
<td>3</td>
<td>TfOH (10)</td>
<td>24</td>
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</tr>
<tr>
<td>4</td>
<td>AlCl₃ (10)</td>
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<td>91:9:0</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂PPh₃ (10)</td>
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<td>84:16:0</td>
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<tr>
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<td>Sc(OTf)₃ (10)</td>
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<td>Yb(OTf)₃ (10)</td>
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<td>54:46:0</td>
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<td>12</td>
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<tr>
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<td>24</td>
<td>0:100:0</td>
</tr>
<tr>
<td>20</td>
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<td>0.5</td>
<td>63:37:0</td>
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<tr>
<td>21</td>
<td>AgNO₃ (1)</td>
<td>0.5</td>
<td>7:93:0</td>
</tr>
<tr>
<td>22</td>
<td>AgOTf (1)</td>
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<td>0:100:0</td>
</tr>
<tr>
<td>23</td>
<td>AgOTf (0.1)</td>
<td>120</td>
<td>15:85:0</td>
</tr>
</tbody>
</table>

*aAll reactions performed with 0.1–0.3 mmol of ynone at RT;*  
*bCalculated by ¹H NMR spectroscopic analysis of the unpurified reaction mixture.*

Table 1. Acid catalyst optimisation results.

Solvent screening studies were also carried out with both Cu(OTf)₂ and AgOTf (Table 2), which revealed that both catalysts were compatible with a wide range of solvents. However,
CH$_2$Cl$_2$ was retained as the standard solvent due to its potential compatibility with a wider range of substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Ratio 83a:84a$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>24</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>CH$_2$Cl$_2$</td>
<td>0.5</td>
<td>0:100</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)$_2$</td>
<td>CHCl$_3$</td>
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<td>0:100</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf</td>
<td>CHCl$_3$</td>
<td>0.5</td>
<td>0:100</td>
</tr>
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<td>PhMe</td>
<td>24</td>
<td>3:97</td>
</tr>
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<td>6</td>
<td>AgOTf</td>
<td>PhMe</td>
<td>0.5</td>
<td>1:99</td>
</tr>
<tr>
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<td>Cu(OTf)$_2$</td>
<td>MeCN</td>
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<td>42:58</td>
</tr>
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<td>8</td>
<td>AgOTf</td>
<td>MeCN</td>
<td>0.5</td>
<td>37:63</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)$_2$</td>
<td>THF</td>
<td>24</td>
<td>37:63</td>
</tr>
<tr>
<td>10</td>
<td>AgOTf</td>
<td>THF</td>
<td>0.5</td>
<td>11:89</td>
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<tr>
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<td>Cu(OTf)$_2$</td>
<td>Et$_2$O</td>
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<td>41:59</td>
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<td>AgOTf</td>
<td>Et$_2$O</td>
<td>0.5</td>
<td>69:31</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OTf)$_2$</td>
<td>EtOH</td>
<td>24</td>
<td>0:100</td>
</tr>
<tr>
<td>14</td>
<td>AgOTf</td>
<td>EtOH</td>
<td>0.5</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

$^a$Calculated by $^1$H NMR spectroscopy, ratio of starting material to product.

Table 2. Solvent screening results with AgOTf and Cu(OTf)$_2$.

The variety of catalysts capable of forming the spirocycle 84a suggests that a number of mechanistic pathways are possible (Scheme 16). For example, a 5-endo-dig spirocyclisation (86/87 $\rightarrow$ 88) could be induced by either (i) co-ordination of a Lewis acid to the ynone carbonyl, increasing the electrophilicity of the β-position or (ii) co-ordination of a π-acid directly to the alkyne. Following this cyclisation, the vinyl metal intermediate 88 could either undergo protodemetalation to afford the spirocycle 84a, or react via a 1,2-migration and rearomatisiation pathway to afford the carbazole 85a formed under Au(I) catalysis (Table 1, entry 14). Alternatively, it is also possible that the electron-rich anisole, which is in direct conjugation to the ynone, could react with a Lewis acid (90 $\rightarrow$ 91) to afford an electrophilic allenyl intermediate 92, which could undergo a 5-exo-dig spirocyclisation as shown to afford spirocycle 84a.


2.1.2 Substrate Synthesis

To fully explore the scope and limitations of the reaction conditions, a wider range of substrates were prepared using the same reaction sequence demonstrated previously (Scheme 15). First, a number of Weinreb amides were prepared from commercially available carboxylic acids using the same T3P-mediated conditions (Scheme 17).

![Scheme 17. Scope of Weinreb amides synthesised using T3P.](image)

More functionalised amides were also prepared, such as amide 81g, which was prepared in 2 steps via a modified literature procedure for the alkylation of acid 80a with benzyl chloride (Scheme 18). This reaction presumably proceeds through a trianion intermediate to chemoselectively alkylate α- to the carboxylic acid. Amide 81h was synthesised via a Suzuki cross-coupling of a previously prepared bromide 93, with phenyl boronic acid.
Scheme 18. Synthesis of other functionalised Weinreb amides: a) Chemoselective α-alkylation of 80a; b) Suzuki cross-coupling of 93.

Next, the prepared Weinreb amides were reacted with a number of lithium acetylides (generated by the reaction of $n$-BuLi with the corresponding alkyne) furnishing yrones 83a–r, generally in excellent yields (Scheme 19).
Scheme 19. Scope of indole-ynones prepared.

Alternatively, the requisite alkynes were made from dibromide precursors. For example, ynone 83e was prepared using the lithium acetylide generated by a Corey-Fuchs reaction (94 → 95) and ynone 83g was prepared using the lithium acetylide generated from the reaction of 1,2-dibromopropane 96 with LDA.51
Scheme 20. Alternative ynone formations from dibromide precursors: a) Corey-Fuchs reaction of 95; b) Sequential elimination of dibromide 96.

Interestingly, the attempted formation of a methoxy ynone resulted in the unexpected formation of spirocycle 84s (Scheme 21). The reaction of amide 81a with lithium acetylide 98 (generated by a literature procedure from 2-chloro-1,1-dimethoxyethane 97)\textsuperscript{52} afforded only a modest yield of spirocycle 84s. This spontaneous spirocyclisation is suggested to proceed via allenolate intermediate 100, which following protonation would afford an electrophilic intermediate 101 that could readily spirocyclise via a 5-exo-dig cyclisation.

Scheme 21. a) Formation of spirocycle 84s; b) Proposed mechanism for the formation of spirocycle 84s.
2.1.3 Indole-ynones: scope & limitations

With a range of ynones prepared, the scope of the optimised reaction conditions using AgOTf (1 mol%) in CH$_2$Cl$_2$ (0.1 M) was investigated (Scheme 22). First, ynones with different electronic and steric properties, including different aromatics 83a–f, aliphatics 83g–h and heteroaromatics 83i were examined, which pleasingly, were all converted into the corresponding spirocycles 84a–i in typically less than 4 h and in quantitative or near-quantitative yield. The structure of spirocycle 84a was also definitively proven by X-ray crystallography (Figure 3). Next, ynones bearing a benzyl group α to the ynone carbonyl 83ej–k were converted into spirocycles 84j–k in similarly excellent yield but with no observable diastereoselectivity. Finally, ynones with substituents at the 2- and 5-positions on the indole ring 83l–n were converted into spirocycles 84l–n, again in excellent/quantitative yield. Interestingly substitution on the indole 2-position appeared to significantly increase the rate of reaction, for example 2-phenyl substituted ynone 83m underwent full conversion to the spirocycle 84m in just 6 minutes. This could be attributed to a more favourable pre-organisation of the substrate caused by the steric of the phenyl ring forcing the alkyne moiety perpendicular to the indole ring.
Scheme 22. Indole-ynone 5-endo-dig spirocyclisation substrate scope.
For a brief demonstration of complementary Cu(II)-catalysis, selected ynones were also reacted with Cu(OTf)$_2$ (1 mol%) (Scheme 22, conditions B). These Cu(II)-catalysed reactions, as observed previously, were generally slower (typically 16 h vs. <4 h) and slightly lower yielding than the Ag(I)-catalysed conditions. Aside from the differences in yield and reaction times, another interesting difference was also observed when using Cu(OTf)$_2$ in the degree of trimer formation observed in the product. Trimer formation, which is a well-documented phenomenon of indolenines,$^53$ occurred in almost every spirocycle formed when using Cu(OTf)$_2$, but was drastically reduced when using AgOTf. An illustrative example is demonstrated in the comparison of the $^1$H NMR spectra of spirocycle 84g formed using Cu(OTf)$_2$ after column chromatography (Figure 4a) and the same compound formed using AgOTf after column chromatography (Figure 4b); note the three key diagnostic singlets (highlighted in red at 4.62, 4.84 and 5.24 ppm), which are tentatively assigned to protons alpha to two aniline nitrogen atoms ($^{101}$, highlighted in red). It is somewhat surprising that there are only three major distinct chemical environments found in the imine trimer, which suggests it is formed with good diastereoccontrol. As proof that this sample was genuinely spirocycle 84g, treatment of sample (a) with catalytic TFA drastically changed the $^1$H NMR spectrum (Figure 4c), which closely aligns with the sample afforded from the AgOTf reaction (Figure 4b). Two possible rationales for this difference could be attributed to either: (i) potential leaching of the Lewis acidic AgOTf into the final products, which in a similar fashion to TFA could change the trimer equilibrium in favour of the monomer; (ii) the multivalent Cu(OTf)$_2$ catalyst could act as a nucleation centre for trimer formation by binding the indolenines and thus accelerating intermolecular reactions.

---

**Figure 3.** X-ray structure of spirocycle 84a with thermal ellipsoids shown at 50% (CCDC 1023667).
Figure 4. $^1$H NMR spectra: a) Spirocycle 84g made using Cu(OTf)$_2$; b) Spirocycle 84g made using AgOTf; c) Spirocycle 84g made with Cu(OTf)$_2$ and with the addition of TFA.

One substrate which failed to undergo any reaction with either AgOTf or Cu(OTf)$_2$ was TMS ynone 83o (Table 3). This lack of reaction was attributed to the β-silicon effect, which effectively inverts the electronics of the ynone system, inhibiting a 5-endo-dig reaction pathway. Attempts to cleave the TMS group (TBAF etc.) and isolate the terminal ynone product were unsuccessful and led only to decomposition. However, a one-pot desilylation-spirocyclisation process was identified based upon literature precedent for Ag(I)-catalysed desilylation reactions. Pleasingly, the application of these literature conditions (AgNO$_3$ in
acetone) to the TMS ynone \(83o\) readily afforded the desired unsubstituted spirocycle \(84o\) in excellent yield.

![Chemical structure](image)

**Table 3.** Optimisation of the tandem desilylation-spirocyclisation protocol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf (10 mol%)</td>
<td>CH(_2)Cl(_2)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)(_2) (10 mol%)</td>
<td>CH(_2)Cl(_2)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>AgNO(_3) (20 mol%)</td>
<td>Me(_2)CO</td>
<td>93</td>
</tr>
</tbody>
</table>

Finally, the only substrate which failed to form a 5-membered enone spirocycle under the standard reaction conditions was \(N\)-methylated ynone \(83p\), which when reacted with AgOTf in CH\(_2\)Cl\(_2\) afforded only a complex mixture (Scheme 23). This decomposition is presumed to be due to the instability of cationic intermediate 103.

![Chemical structure](image)

**Scheme 23.** Reactivity of \(N\)-methylated substrate 163.

Whilst the formation of the 5-membered enone spirocycles was relatively simple, larger ring sizes proved more problematic. For example, the extended ynone \(83q\) required elevated catalyst loading (10 mol%, AgOTf) and careful temperature control (35 °C) to effectively form the desired spirocycle \(84q\) and suppress the formation of a C2-annulated product \(85q\) (Table 4, entry 3). At room temperature, the rate of reaction was insufficient, whilst at marginally higher temperatures (40 °C) the formation of the C2-annulated by-product \(85q\) was significantly increased. The structure of the annulated indole \(85q\) was also proven by X-ray crystallography (Figure 5) and is proposed to form either via a 1,2-migration process or from direct attack from the C2-position.
In similar fashion, the further extended homologue 83r could only be induced to form another C2-annulated indole 85r in poor yield by reaction with stoichiometric AgOTf (Scheme 24). The proposed structure of 84r was also confirmed by X-ray crystallography (Figure 6).

**Figure 5.** X-ray structure of C2-annulated indole 85q with thermal ellipsoids shown at 50% (CCDC 1531214).

**Scheme 24.** Reactivity of extended ynone 83r with stoichiometric AgOTf.
2.1.4 Heterogeneous silver(I) catalysis

Heterogeneous catalysis can greatly improve the efficiency of a reaction by simplifying both catalyst recovery and product isolation, which in turn can improve reaction yields.\(^56\) Considering both this, and the high catalytic activity of Ag(I) catalysts in the spirocyclisation reaction, AgNO\(_3\) impregnated silica (AgNO\(_3\)·SiO\(_2\)), which is traditionally used in column chromatography as a method to separate \(E\)- and \(Z\)-alkene isomers, was investigated as a potential reusable heterogeneous catalyst.\(^57\)

Studies began by preparing a batch of AgNO\(_3\)·SiO\(_2\) (10 wt % AgNO\(_3\) on silica) and adding the solid supported catalyst (10 mol%) to a stirred solution of ynone \(83a\), which promoted quantitative conversion to the spirocycle \(84a\) in just 5 minutes (Scheme 25a); the catalyst was then easily recovered by filtration and reused a total of 5 times with no loss in catalyst activity. Next, the prepared AgNO\(_3\) impregnated silica was applied to a flash chromatography column to form a make-shift flow reactor (Scheme 25b). Following a typical column chromatography procedure, the ynone \(83a\) was loaded onto the column and eluted under gravity to afford the spirocycle \(84a\) in quantitative yield; this procedure was again repeated 5 times with the same column with no loss of catalyst activity observed. This flow reactor represents an attractive alternative to a typical flow chemistry set up as it forgoes the need for expensive equipment and specialist personnel to maintain it.
Scheme 25. Heterogeneous catalysis of AgNO₃·SiO₂: a) As a filtered reagent; b) For use in flow chemistry.

Further optimisation of this heterogeneous catalyst was later carried out by Aimee Clarke (PhD student), where it was found that decreasing the loading of the AgNO₃ on the silica from 10 wt % to 1 wt % dramatically increased catalyst performance (see Appendix IV). A higher proportion of silica might increase the rate of reaction by accelerating protodemetalation on the acidic silica surface, and the silica surface might also serve to stabilise potential silver nanoparticles.

The work described in this section was the subject of a recent publication.$^{58}$
2.1.5 Indole-Ynone gold(I) catalysis

During the initial catalyst screening studies the formation of carbazole 85a was observed when ynone 83a was reacted with a combination of Au(I) and Ag(I) catalysts (Ph₃PAuCl and AgOTf, see Table 1, entry 14). To investigate the role of Au(I)-catalysis in this transformation further, a commercially available cationic catalyst Ph₃PAuNTf₂ was chosen as a catalyst probe; this catalyst is preferable to other typical gold(I) chloride complexes as it does not require a Ag(I) co-catalyst, which could complicate studies with background spirocyclisation reactions and other known silver effects. As hoped, carbazole 85a was then prepared in good yield by reacting ynone 83a with Ph₃PAuNTf₂ (10 mol%) in CH₂Cl₂, confirming this transformation does not require a Ag(I) catalyst (Scheme 26). The structure of 85a was also proven by X-ray crystallography (Figure 7).

Scheme 26. Initial studies using Ph₃PAuNTf₂ to form carbazole 85a.

Interestingly, no reaction was observed when spirocycle 84a was reacted with Ph₃PAuNTf₂ under the same reaction conditions, ruling out the spirocycle 84a as a direct precursor to the carbazole 85a. This is further supported by the proven stability of spirocycle 84a under various acidic conditions (see Table 1). Considering this, it is proposed that carbazole 85a is formed either via direct attack from the indole C2-position or C3-attack followed by a 1,2-migration of a vinyl metal intermediate, which is more consistent with typical indole
reactivity. This 1,2-migration process might proceed through a three-center two-electron pathway\textsuperscript{61} (105 $\rightarrow$ 106 $\rightarrow$ 107, Scheme 27a) or via a formal cyclopropanation and fragmentation pathway (105 $\rightarrow$ 109 $\rightarrow$ 107, Scheme 27b). A vinyl gold species 105 might have a higher proclivity for 1,2-migration relative to a vinyl silver species as it can more readily stabilise positive charge through $\pi$-back bonding.\textsuperscript{62}

![Scheme 27](image)

Scheme 27. Proposed Au(I)-catalysed 1,2-migration mechanisms: a) A three-center two-electron pathway; b) A cyclopropanation and fragmentation pathway.

This work was later expanded in wider scoping studies carried out primarily by Dr John Liddon (PDRA) and are shown here only for reference (Scheme 28). The work described in this section was also the subject of a recent publication.\textsuperscript{63}
Scheme 28. Wider scoping studies using Ph$_3$PAuNTf$_2$ (conducted primarily by John T. R. Liddon).
2.1.6 Asymmetric indole-ynone spirocyclisations

2.1.6.1 Catalyst discovery & optimisation studies

Having adequately developed the racemic spirocyclication protocol, the feasibility of an asymmetric variant was next examined. A wide array of different asymmetric catalyst systems were screened, using ynone \(83a\) as the model substrate (Scheme 29), of which only the chiral phosphoric acid (CPA) silver salt \(Ag-\text{114a}\) showed any signs of asymmetric induction by chiral HPLC analysis, forming spirocycle \(84a\) in 86% yield and with 8% \(ee\). This initial hit and literature precedent for using CPA silver salts in related alkyne activations,\(^{64,65}\) prompted an in depth look into other CPA catalysts.

\[
\text{Scheme 29. Initial asymmetric catalyst screen.}
\]

A number CPA catalyst were then acquired from commercial sources or prepared by known literature procedures, using \(117\) as a common intermediate from which a telescoped reaction sequence afforded the corresponding CPAs (Table 5).
Table 5. Telescopied synthesis of BINOL-based CPA.

The electron deficient CPA 114g was synthesised via an analogous route (Scheme 30), utilising an $S_{N}$Ar reaction with hexafluorobenzene to install the C$_6$F$_5$ aromatics in the 3,3'-positions instead of employing a Suzuki cross-coupling.
A smaller number of $\text{H}_8$-BINOL based catalysts were also prepared (Scheme 31). This route did not require a directed ortho metalation strategy thanks to the ability to selectively brominate $\text{120}$ in only the 3,3'-positions.

Finally, the corresponding silver salts were prepared according to a literature procedure,\textsuperscript{66} by reacting the CPAs with $\text{Ag}_2\text{CO}_3$ in a biphasic mixture of $\text{CH}_2\text{Cl}_2$ and water, affording the silver salts in yields ranging from 35–100% (Scheme 32). These salts were used as prepared and were not fully characterised.

Scheme 30. Synthesis of $\text{C}_6\text{F}_5$ substituted catalyst $\text{187}$.

Scheme 31. Overview of $\text{H}_8$-BINOL CPA synthesis.
Before reacting ynone 83a with the full catalyst library, commercially available CPA 114h was chosen as a model catalyst to optimise the reaction conditions. Optimisation began by reacting ynone 83a with catalyst Ag-114h in CH$_2$Cl$_2$ at reduced temperature (−10 °C) to afford the spirocycle 84a in excellent yield and with 20% ee (Table 6, entry 1). Next, the same reaction was repeated in different solvents (CHCl$_3$, DCE, THF and toluene, entries 2–5), with the reaction in CHCl$_3$ proving particularly promising, affording the spirocycle 84a in quantitative yield and with 50% ee. This increase in ee was tentatively attributed to the sensitive nature of the ion pair between the Ag(I) cation and CPA anion. Reaction of ynone 83a with catalyst Ag-114h in CHCl$_3$ at lower temperatures (−40 °C) resulted in only a small increase in ee, but with a significantly reduced rate of reaction (entry 6), and thus the optimised conditions going forward were chosen as 1 mol% Ag-CPA in CHCl$_3$ at −10 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Loading</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol%</td>
<td>−10</td>
<td>CH$_2$Cl$_2$</td>
<td>0.5 h</td>
<td>98</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>1 mol%</td>
<td>−10</td>
<td>THF</td>
<td>4 h</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>5 mol%</td>
<td>−10</td>
<td>DCE</td>
<td>3 h</td>
<td>95</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>1 mol%</td>
<td>−10</td>
<td>Toluene</td>
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</tr>
<tr>
<td>5</td>
<td>1 mol%</td>
<td>−10</td>
<td>CHCl$_3$</td>
<td>1.5 h</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1 mol%</td>
<td>−40</td>
<td>CHCl$_3$</td>
<td>17 h</td>
<td>86</td>
<td>52</td>
</tr>
</tbody>
</table>

*Determined by CSP-HPLC (Chiralpak IB column, eluting with 10% IPA in hexanes, 1 mL/min).

Table 6. Optimisation of the asymmetric reaction conditions with Ag-114h.

Model ynone 83a was then reacted with the full catalyst library under the optimal reaction conditions to synthesise the spirocycle 84a.
conditions (CHCl$_3$ at $-10^\circ$C, Scheme 33), with the best catalyst, phenanthrene derivative Ag-114l, providing the spirocycle 84a with a pleasing 78% ee.

Scheme 33. Optimisation of the Ag-CPA catalyst.
From these results it was noted that generally catalysts with rigid and large bulky aromatics at the 3,3'-positions (e.g., anthracene, phenanthrene and pyrene) performed best. Next, the modification of the catalyst backbone was examined, which was prompted by the comparison of catalysts Ag-114l and Ag-123b, which showed a significant reduction in ee upon switching between a BINOL and a H₈-BINOL backbone. From this observation it was hypothesised that the larger sterics of the H₈-BINOL catalyst backbone forms a more open catalyst cavity compared to the BINOL catalyst analogue (Figure 8a, b). Following this logic it was hypothesised that a catalyst based on a SPINOL backbone would provide the narrowest, most well-defined cavity (Figure 8c). Thus, it was hoped that SPINOL based-catalyst Ag-126 would significantly improve the enantioselectivity. Therefore to conclude the asymmetric optimisation studies, the synthesis of a SPINOL based catalyst was carried out following the literature procedure to synthesise the requisite diol 136 (Scheme 34).

Figure 8. Hypothetical comparison of the different chiral phosphoric acid cavities: a) BINOL; b) H₈-BINOL; c) SPINOL.
With the enantiopure \((S)\)-SPINOL 136 in hand, attempts to perform the known selective bromination of 136 were carried out (Scheme 35). Unfortunately, repeated efforts afforded at best an inseparable mixture of the desired dibrominated product 137 and the tribrominated product 138. Submission of the brominated mixture to the Suzuki cross-coupling fortunately allowed isolation of the desired product 139, from which the routine synthesis of Ag-126 was carried out.
Chapter 2. Indole-alkyne cyclisations

Finally, the reaction of Ag-126 with ynone 83a afforded the spirocycle in a disappointing 60% ee (Scheme 36). From this result a comparison with the fable of ‘Goldilocks and the three bears’ was noted, where perhaps the BINOL-based cavity is ‘just right’.

Scheme 35. Synthesis of the SPINOL-based catalyst Ag-126.

Scheme 36. Asymmetric spirocyclisation reaction with SPINOL-based catalyst Ag-126.
2.1.6.2 Substrate Scope and absolute stereochemistry

With the catalyst development reaching its conclusion the best BINOL-based catalyst Ag-114l was used with a wider range of substrates (Scheme 37). Over the chosen substrates the asymmetric catalyst system showed good consistency, affording the spirocycles in excellent yield and typically with >70% ee. Only two main outliers were identified: (i) phenyl spirocycle 84b, which without a substituent on the 4-position suffered a surprising drop in ee; (ii) dimethylaniline spirocycle 84c, which was isolated in moderate yield and with poor ee, this reduced performance was attributed to the poor solubility of the substrate and potential inhibitory/competing ligation of the aniline moiety.

The absolute stereochemistry of the major enantiomer was determined by recrystallisation of spirocycle 84f, which initially only accrued as enantioenriched mother liquor, as the racemic crystals proved more prone to crystallisation. However, once the mother liquor was sufficiently enriched (>96% ee) further recrystallisations afforded enantiopure crystals, from which X-ray crystallography could definitively determine the stereochemistry as S (Figure 9).
To fully confirm that this stereochemistry belonged to the major enantiomer, the discrete sample used to collect the XRD data was identified by CSP-HPLC as the major enantiomer.

![Chemical Structure](image1.png)

**Figure 9.** X-ray structure of enantiopure-spirocycle 84f with thermal ellipsoids shown at 50% (CCDC 1049165).

A tentative rationale for the enantioselectivity observed is shown in Figure 10, in which favourable stercics and where possible, a potential π-stacking interaction could sufficiently lower the energy of binding mode 140 relative to 141.

![Chemical Structures](image2.png)

**Figure 10.** Proposed models for asymmetric induction.
2.2 Indole-propargyl alcohol cyclisations

2.2.1 Introduction & initial studies

All of the developed spirocyclisation reactions so far have been limited to alkynes as a part of a conjugated ynone system (83 → 84). Thus, to potentially extend the scope of these reactions further, the Ag(I)-catalysed spirocyclisation of unconjugated alkyne systems was planned (142 → 143, Scheme 38).

Scheme 38. Proposed spirocyclisation of unconjugated alkyne.

Propargyl alcohols provided an expedient route into unconjugated alkyne substrates, as they could be easily prepared by reduction of the in-hand ynone substrates. Thus, studies began with the preparation of a model propargyl alcohol substrate 144a by the NaBH₄ reduction of ynone 83a (Scheme 39). The resultant propargyl alcohol 144a was then reacted with AgOTf at elevated catalyst loading (10 mol%) in CH₂Cl₂ to afford carbazole 146a in excellent yield, with only a trace of the desired spirocycle 145a detected by ¹H NMR spectroscopy (Scheme 40).

Scheme 39. Synthesis of propargyl alcohol 144a by NaBH₄ reduction.

Scheme 40. Initial studies with propargyl alcohol 144a.
The formation of carbazole 146a represents a benzannulation reaction of indole, which was presumed to proceed via a spirocyclisation and 1,2-migration pathway (similar to that proposed in section 2.5) followed by the elimination of water.

Benzannulation reactions, whilst not within the original aims of this project, offer an attractive route into the controlled formation of valuable fused-polycyclic structures. For example, the carbazole framework is found in a number of biologically active natural products with anticancer, anti-HIV and antimalarial properties.71–74 Aside from biological activity, carbazoles have also featured in electroluminescent materials thanks to their desirable thermal, electrical and optical properties.75 Thus, the potential to access both high-value carbazoles and spirocycles from a single starting material became a challenge of significant interest.

The benzannulation of indole by the electrophilic activation of a pendant alkyne was first demonstrated by Larock and co-workers with a single example, whereby propargyl alcohol 147 was reacted with iodine monochloride to form carbazole 148 in modest yield (Scheme 41a).76 Later, Liang and co-workers demonstrated a range of similar iodocyclisations, reacting indoles 149 again with iodine monochloride to promote the formation of a range of synthetically useful carbazoles 150 in typically excellent yield (Scheme 41b).77 Interestingly, Liang and co-workers propose that carbazoles 150 also form via the 1,2-migration of a spirocyclic intermediate (151 → 152).
Other notable indole benzannulation reactions include the work of Hashmi and co-workers, who were the first to develop a transition metal-catalysed reaction of this type using Au(I)-catalysis (Scheme 42a). For example, indole 153 was transformed into carbazole 154 in near quantitative yield using (IPr)AuCl and AgNTf₂ as an activating co-catalyst. In the same year, Ma and co-workers reported a similar transformation, using Au(III)-catalysis across a wider range of substrates to afford carbazoles 156 in typically excellent yield (Scheme 42b).
Scheme 42. Gold-catalysed benzannulation reactions of alkyne-tethered indoles.
2.2.2 Reaction optimisation

To better understand the reactivity of the propargyl alcohol substrates and to potentially control the selectivity between spirocycle formation and benzannulation, a wider variety of conditions were screened across two substrates (144b and 144c, prepared as in Scheme 39), which were chosen for their differing electronic properties, allowing for a more balanced assessment of the reaction conditions. These studies were aided by four supervised BSc students, who are credited where appropriate.

Screening studies began using AgNO₃ and AgOTf as the primary catalysts and CH₂Cl₂, THF and toluene as solvents (Table 7). From these screens it was found that AgOTf in THF consistently promoted high levels of carbazole formation across both substrates (entries 2 & 8). Pleasingly, spirocycle formation was also consistently observed when using AgNO₃ in CH₂Cl₂ (entries 4 & 10, albeit with no/minimal diastereoselectivity).

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R⁻</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Ratio 144:145:146ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (144b)</td>
<td>AgOTf</td>
<td>CH₂Cl₂</td>
<td>0:10:90</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>AgOTf</td>
<td>THF</td>
<td>0:0:100</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>AgOTf</td>
<td>PhMe</td>
<td>0:0:100</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>5:95:0</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>AgNO₃</td>
<td>THF</td>
<td>10:90:0</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>AgNO₃</td>
<td>PhMe</td>
<td>90:10:0</td>
</tr>
<tr>
<td>7</td>
<td>n-Bu (144c)</td>
<td>AgOTf</td>
<td>CH₂Cl₂</td>
<td>35:65:0</td>
</tr>
<tr>
<td>8</td>
<td>n-Bu</td>
<td>AgOTf</td>
<td>THF</td>
<td>0:5:95</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>AgOTf</td>
<td>PhMe</td>
<td>95:0:5</td>
</tr>
<tr>
<td>10</td>
<td>n-Bu</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>20:80:0</td>
</tr>
<tr>
<td>11</td>
<td>n-Bu</td>
<td>AgNO₃</td>
<td>THF</td>
<td>95:3:2</td>
</tr>
<tr>
<td>12</td>
<td>n-Bu</td>
<td>AgNO₃</td>
<td>PhMe</td>
<td>0:45:55</td>
</tr>
</tbody>
</table>

ᵃAll reactions performed with 0.10–0.20 mmol of propargyl alcohol in the stated solvent (0.1 M) at RT; bCalculated by ¹H NMR spectroscopic analysis of the unpurified reaction mixture, rounded to the nearest 5%.

Table 7. Propargyl alcohol catalyst screening (experiments performed by Rosa E. Clubley, and Anthony C. Wyton).
Initial rationale for the difference in reactivity between AgOTf and AgNO₃ was tentatively attributed to acidic impurities present in the catalysts as well as subtle counterion effects. Brønsted acids are known to promote 1,2-migration reactions of indolenines and AgOTf is known to promote “hidden Brønsted acid catalysis” in related processes. Conversely, AgNO₃ does not share this feature and therefore might contain significantly less (if any) residual Brønsted acid, preventing a competing 1,2-migration process. The choice of solvent also clearly influenced the selectivity of the reaction and it is proposed that the relatively polar nature of THF favours carbazole formation by stabilising potential cationic rearrangements.

To further explore the role of Brønsted acid catalysis in these reactions a number of additives were investigated in an attempt to invoke different selectivity profiles (Table 8). As expected, the incorporation of a base (Et₃N, entry 2) with the previously carbazole-selective conditions (AgOTf, THF) resulted in only spirocycle formation, albeit with low levels of conversion. Conversely, the incorporation of an acid (p-TSA, entry 7) with the spirocycle-selective conditions (AgNO₃, CH₂Cl₂) afforded a 1:1 mixture of spirocycle to carbazole.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive</th>
<th>Ratio 144b:145b:146bᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>THF</td>
<td>-</td>
<td>0:0:100</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>THF</td>
<td>Et₃N (5 mol%)</td>
<td>55:45:0</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>THF</td>
<td>K₂CO₃ (5 mol%)</td>
<td>75:20:5</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf</td>
<td>THF</td>
<td>NaHCO₃ (5 mol%)</td>
<td>0:0:100</td>
</tr>
<tr>
<td>5</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>5:95:0</td>
</tr>
<tr>
<td>6</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>TfOH (2 mol%)</td>
<td>80:0:20</td>
</tr>
<tr>
<td>7</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>p-TSA (2 mol%)</td>
<td>20:40:40</td>
</tr>
<tr>
<td>8</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>AcOH (2 mol%)</td>
<td>15:70:15</td>
</tr>
</tbody>
</table>

ᵃAll reactions performed with 0.10–0.20 mmol of propargyl alcohol in the stated solvent (0.1 M) at RT; ᵇCalculated by ¹H NMR spectroscopic analysis, rounded to the nearest 5%.

Table 8. Propargyl alcohol additive study (experiments performed by Rosa E. Clubley, and Anthony C. Wyton).

Interestingly, when spirocycle 145b was submitted to the carbazole formation conditions (AgOTf in THF), no reaction was observed (Table 9, entry 1). However, spirocycle 145b
rapidly decomposed when reacted with TfOH (10 mol%), with traces of carbazole 146b observed by TLC analysis (entry 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf (10 mol%), THF, RT, 24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>TfOH (10 mol%), CH₂Cl₂, RT, 16 h</td>
<td>Decomposition, trace 146b detected by TLC.</td>
</tr>
</tbody>
</table>

Table 9. Attempted synthesis of carbazole 146b by 1,2-migration of spirocycle 145b.

Considering the above, it was deemed unlikely that spirocycle 145b is a direct precursor to the carbazole 146b. Thus, it is proposed that carbazole 146b is formed either via direct attack from the indole C2-position or C3-position followed by a 1,2-migration of the vinyl silver intermediate (as with the Au(I)-catalysis in section 2.5) and the elimination of water (Scheme 43). In this instance, a vinyl silver intermediate might be more prone to a three-center two-electron pathway (158 $\rightarrow$ 159 $\rightarrow$ 160) as it can stabilise positive charge more readily without the electron withdrawing effects of a conjugated carbonyl (as in the indole-ynone system). Ultimately, a 1,2-migration process requires the indolenine of vinyl silver intermediate 158 to stay protonated, and as such, selectivity is thought to be strongly affected by both Brønsted acids or bases, as demonstrated in Table 8.
Finally, to conclude optimisation studies, the developed conditions were trialled on a synthetic scale with model substrate 144c. Pleasingly, the carbazole formation proceeded as expected (Scheme 44), but the spirocyclisation protocol produced a low yielding mixture of the desired spirocycle 145c and carbazole 146c (Table 10, entry 1). Therefore, to improve the yield and selectivity of the spirocyclisation protocol further, the addition of a basic additive, which would not retard the rate of reaction (as in Table 8), was investigated. Happily, Ag(I)-based additives were found to improve both the yield and selectivity, and in particular the addition of Ag$_2$O (5 mol%) completely restored the desired selectivity and significantly improved the reaction yield (entry 3).
Chapter 2. Indole-alkyne cyclisations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Ag$_2$CO$_3$ (5 mol%)</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>Ag$_2$O (5 mol%)</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 10. Ag(I)-based additive screen with propargyl alcohol 144c.
2.2.3 Substrate Synthesis

To fully explore the scope of the two optimised reaction protocols a wider range of substrates was prepared by NaBH₄ reduction of the corresponding ynone (Scheme 45).

Attempts to prepare TMS alkyne 144h in a one-pot process (to avoid decomposition) also provided an appreciable amount of terminal alkyne 144i, presumably afforded by an adventitious sodium methoxide-mediated desilylation of 144h. Full conversion of 144h to 144i was easily achieved by reaction with K₂CO₃ in methanol.
Tertiary alcohol substrates 144j and 144k were prepared by reacting ynone 83b with an excess of the corresponding commercial organo-lithium reagent (Scheme 47a). A TBS-protected propargyl alcohol substrate 144l was also readily accessed from substrate 144b (Scheme 47b).

Scheme 47. Miscellaneous propargyl alcohol synthesis.
2.2.3 Substrate Scope

First, the propargyl alcohol library was reacted under the optimised spirocyclisation conditions (AgNO$_3$, Ag$_2$O in CH$_2$Cl$_2$), which in almost all cases, afforded the desired spirocycles in excellent or near quantitative yields regardless of steric or electronic effects, albeit with no diastereocontrol (Scheme 48).

The only substrates which failed to spirocyclise were alkynes 144h and 144l, which instead underwent a low yielding hydration reaction to form the $\alpha$-hydroxy ketone natural product, (±)-actinopolymorphol B 162 (Scheme 49). Typically $\pi$-acid catalysed alkyne hydrations are carried out at higher temperatures and so it was somewhat surprising to see hydration under these mild reaction conditions.
Chapter 2. Indole-alkyne cyclisations

Scheme 49. Unexpected hydration reaction for the synthesis of (±)-actinopolymorphol B 162.

Next, reaction of the same substrates under the carbazole-formation conditions (AgOTf in THF) afforded the desired carbazoles predominantly in excellent yield (Scheme 50). The only exceptions were: (i) tertiary alcohol 144k failed to afford any of the desired carbazole 146k, which may be due to the premature formation of unproductive carbocation intermediates; (ii) thiophenyl alkyne 144f, which afforded only a small quantity of carbazole 146f, with the major side-product being spirocycle 145f, suggesting that this heterocyclic system may be less prone to 1,2-migration. Finally, the structure of carbazole 146d was also definitively proven by X-ray crystallography (Figure 11).

Scheme 50. Substrate scope of propargyl alcohol benzannulation reactions.
Figure 11. X-ray structure of carbazole 146d with thermal ellipsoids shown at 50% (CCDC 1404713).
2.3 Towards Spirobaccillene B

To conclude studies of the indole-alkyne systems, model studies towards the synthesis of spirobacillene B analogue 164 were examined using PMP spirocycle 84a. First, a strategy based upon an acid-mediated rearrangement of an α,β-epoxyketone 163, as employed in the total synthesis of spirobacillene A, was planned (Scheme 51).17

Attempts to prepare the required α,β-epoxyketone 163 by the epoxidation of spirocycle 84a under both nucleophilic and electrophilic conditions failed (Table 11). Under most conditions only decomposition was observed, however, when using DMDO a mass consistent with N-oxide 167 was detected by HRMS (Entry 5), suggesting that the indolenine functionality is a potential source of incompatibility with this strategy.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2O2, NaHCO3, THF, H2O, RT</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>H2O2, NaHCO3, MeOH, RT</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOOH, THF, RT</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>m-CPBA, NaHCO3, CH2Cl2, 0 °C</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>DMDO, Me2CO, RT</td>
<td>Complex mixture, 167 detected</td>
</tr>
</tbody>
</table>

Table 11. Attempted synthesis of α,β-epoxyketone 163.
In an attempt to increase the reactivity of the alkene system relative to the indolenine functionality, the epoxidation of allylic alcohol spirocycle 145a was proposed. Here, it was hoped that the electron rich allylic alcohol system could be more easily epoxidized to afford 168, which following oxidation to 163 could be used to form model spirocycle 164 (Scheme 52).

Scheme 52. Retrosynthetic analysis of spirobacillene B analogue 164 by allylic alcohol epoxidation.

Unfortunately, attempts to prepare epoxide 168 by the epoxidation of spirocycle 145a with m-CPBA resulted only in rapid decomposition of the starting material (Scheme 53). This decomposition was consistent with the sensitivity of the spirocycles to Brønsted acids and oxidants previously observed. Degradation of spirocycle 145a was also observed after ~1 week of storage at ambient temperature, dissuading any further studies with the allylic alcohol spirocycles as practical starting materials.

Scheme 53. Attempted synthesis of epoxide 168.

Finally, an alternative approach based on the E1cB elimination of dihydroxylated spirocycle 169 was examined (Scheme 54).
Scheme 54. Retrosynthetic analysis of spirobacillene B analogue 164 via dihydroxylation.

The synthesis of the dihydroxylated spirocycle 169 was attempted using Os(VIII)-catalysis (Table 12). Both Upjohn and Sharpless asymmetric dihydroxylation conditions resulted primarily in the decomposition of the starting material. The only isolable product from these reactions was a small quantity of oxindole 170 under the Upjohn conditions (Entry 1), which was presumably formed by reaction with NMO. The indolenine functionality was again presumed to be incompatible with this strategy, potentially due to unproductive ligation to the OsO$_4$ catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OsO$_4$, NMO, Me$_2$CO, H$_2$O, RT</td>
<td>Complex mixture, 170 (7%)</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix α, MsNH$_2$, t-BuOH, H$_2$O, 25 ºC</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table 12. Attempted synthesis of dihydroxylated spirocycle 169.
2.4 Summary

The Ag(I)-catalysed spirocyclisation of indole-ynone and indole-propargyl alcohol systems has been developed. A wide range of spirocyclic indolenines and benzannulated indoles have been prepared in high yield through catalyst-selective synthesis. A heterogeneous catalyst in the form of AgNO₃·SiO₂ was also discovered, which could be easily reused up to five times to afford spirocyclic indolenines in quantitative yield. An asymmetric spirocyclisation protocol using the silver salt of a chiral phosphoric acid was also developed, which can be used to furnish spirocyclic indolenines in up to 89:11 er.

The developed methodologies were applied in the accidental synthesis of (±)-actinopolymorphol B and in studies towards the synthesis of spirobacillene B.

Overall, the work described in this Chapter was the subject of four publications. 58,63,85,86
Chapter 3. Indole α-diazocarbonyl cyclisations

3.1 Introduction

In Chapter 2 a number of spirocyclic indolenines were prepared by the dearomative spirocyclisation of indole tethered alkynes. This approach utilised a general strategy where a latent electrophile, such as an alkyne, is activated by a metal catalyst to promote a dearomative spirocyclisation reaction (Scheme 55). Here, the development of a new spirocyclisation methodology was planned by varying the latent electrophile from an alkyne to an α-diazocarbonyl. An indole tethered α-diazocarbonyl posed as an attractive target for catalysis as α-diazocarbonyl compounds can readily form electrophilic metal carbenoids upon reaction with a metal catalyst. 87,88

![Scheme 55. Synthesis of spirocyclic indolenines by a dearomatisation strategy.](image)

The reactivity of a diazo compound and the carbenoid it forms can be easily modulated by the electronics of the adjacent functional groups; these systems generally fall into three main categories: i) donor/acceptor, ii) acceptor and iii) acceptor/acceptor (Figure 12). 89,90 An acceptor group increases the stability of a diazo compound by decreasing its nucleophilicity through electron withdrawing effects, but these effects also destabilise the ensuing electrophilic carbenoid, promoting unselective reactivity. Conversely, a donor group increases the nucleophilicity through electron donating effects, which decreases the stability of the diazo compound. However, following decomposition, the resultant carbenoid is stabilised by the donor group, which attenuates its reactivity, allowing for greater selectivity to be observed.

![Figure 12. Diazocompound and carbenoid categories.](image)
3.2 Project background and aims

The reactivity of indole-tethered α-diazocarbonyls has been scarcely explored outside of a few known instances. Predominately Rh(II)-catalysis has been used, as first demonstrated by Jung and Slowinski, who reacted indole 173 with Rh₂(OAc)₄ to afford the C₂-annulated indole 174 in good yield with a small quantity of spirocycle 175 (Scheme 56a). Although low-yielding, the formation of 175 was a significant proof of principle for a potential spirocyclisation protocol. Next, Cuevas-Yañez and co-workers reported two similar reactions with indoles 176 and 177, again using Rh₂(OAc)₄ to promote the modest yielding formation of C₂-annulated products 178 and 179, with no other reported products (Scheme 56b). More recently, Doyle and co-workers reported a single example of a Rh₂(oct)₄-catalysed C₂-annulation reaction, affording indole 181 in excellent yield (Scheme 56c).

a) Jung & Slowinski (2001)

![Diagram of reaction](image)

b) Cuevas-Yañez et al. (2004)

![Diagram of reaction](image)

Scheme 56. Previous reactivity of indole-tethered α-diazocarbonyls with Rh(II)-based catalysts.

All of these prior examples relied solely on acceptor/acceptor carbenoid systems in combination with a Rh(II)-catalyst. Qin and co-workers were the first to differ from this approach, by using a Cu(I)-catalyst with the donor/acceptor carbenoid system of 182 to form spirocyclic cyclopropane 183 in excellent yield (Scheme 57a). Later, Qin and co-workers
Chapter 3. Indole α-diazo carbonyl cyclisations

reacted indole 184 with the same Cu(I)-catalyst to afford indoline 185, which is proposed to form via the fragmentation of a cyclopropane intermediate (186 → 187, Scheme 57b).\textsuperscript{96}

\begin{center}
\includegraphics[width=\textwidth]{scheme57.png}
\end{center}

\textbf{Scheme 57.} Previous reactivity of indole-tethered α-diazo carbonyls with a Cu(I)-based catalyst.

Thus, as briefly demonstrated by Qin and co-workers, it was envisaged that a donor/acceptor carbenoid system, as in 188, might allow for a spirocyclisation methodology to be developed, especially when exposed to a wider range of catalysts (Scheme 38a). If successful, this strategy might also be applied in the synthesis of spirobacillene B 13 (Scheme 38b).

\begin{center}
\includegraphics[width=\textwidth]{scheme58.png}
\end{center}

\textbf{Scheme 58.} a) Proposed spirocyclisation methodology; b) Potential synthesis of spirobacillene B 13.
3.3 Reaction discovery & optimisation studies

Studies began with the synthesis of model substrate 188a, which was made in two steps from the previously prepared Weinreb amide 81b (Scheme 59). Amide 81b was first reacted with benzylmagnesium chloride to form benzyl ketone 192a, which was then reacted under Regitz diazo-transfer conditions with p-ABSA and DBU to afford the desired α-diazocarbonyl 188a. However, the isolation of α-diazocarbonyl 188a proved difficult, as it was found to degrade and form another product during column chromatography. This degradation product was isolated and identified as C2-annulated indole 193a by X-ray crystallographic analysis (Figure 13). Fortunately, this reaction could be completely suppressed by the addition of 3% Et₃N to the column eluent, suggesting that the formation of indole 193a was catalysed by the Brønsted acidic silica gel. Further studies found that, if desired, indole 193a could be selectively formed in good yield by reacting 188a with an equivalent weight of silica gel in dichloromethane (Scheme 60).

Scheme 59. Synthesis of model α-diazocarbonyl substrate 188a.

Figure 13. X-ray structure of C2-annulated indole 193a with thermal ellipsoids shown at 50% (opposite enantiomer omitted for clarity, CCDC 1481930).

Scheme 60. Silica gel-catalysed synthesis of C2-annulated indole 193a.
Based on the apparent change in substitution pattern, it is proposed that indole 193a is formed by a Wolff-rearrangement process (188a → 194 → 195, Scheme 61), whereby an electrophilic ketene intermediate might cyclise by nucleophilic attack from either the indole C2- (195 → 197 → 193a) or C3-position followed by a 1,2-migration (195 → 196 → 193a).

Having successfully prepared α-diazocarbonyl 188a and controlled the formation of indole 193a, studies towards the synthesis of spirocycle 190a were resumed. The α-diazocarbonyl 188a was reacted with a range of potential catalysts (10 mol%) in dichloromethane (0.1 M) under an atmosphere of argon in an attempt to induce the formation of spirocycle 188a (Table 13). These experiments were carried out on a small scale (0.05 mmol of 188a) and the 1H NMR spectra of the unpurified reaction mixtures were examined.

Considering the literature precedent, Rh(II)-based catalysts were first examined (entries 1–4), from which Rh$_2$oct$_4$ was found to form both spirocycle 190a (~1:1 dr) as the major product and a small quantity of α,β-dicarbonyl 198a (entry 4). Interestingly, two other products were also identified during these studies, namely, another C2-annulated indole isomer 199a and a related oxidation product, carbazole 200a (entries 1–3).

Intrigued by the number of products arising from these reactions, the aims of this project were broadened to include the selective synthesis of these other products, which was pursued through further catalyst screening. The potential synthesis of five products from a single starting material became an unprecedented and exciting challenge in the field of catalyst-selective synthesis.  

Scheme 61. Proposed mechanisms for the synthesis of indole 193a.
Chapter 3. Indole α-diazocarbonyl cyclisations

![Diagram of indole α-diazocarbonyl cyclisations]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>188a</th>
<th>193a</th>
<th>190a</th>
<th>198a</th>
<th>199a</th>
<th>200a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(_{(II)})</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>50</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Rh(<em>{2})esp(</em>{2})</td>
<td>0</td>
<td>20</td>
<td>10</td>
<td>55</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Rh(<em>{2})TPA(</em>{4})</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>70</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Rh(<em>{2})oct(</em>{4})</td>
<td>0</td>
<td>0</td>
<td>95</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CuBr</td>
<td>5</td>
<td>0</td>
<td>75</td>
<td>20</td>
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<td>CuI</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(MeCN)(_{4})OTf</td>
<td>0</td>
<td>0</td>
<td>20</td>
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</tr>
<tr>
<td>8</td>
<td>Cu(MeCN)(<em>{4})PF(</em>{6})</td>
<td>15</td>
<td>0</td>
<td>65</td>
<td>20</td>
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<td>0</td>
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<tr>
<td>9</td>
<td>Cu(OAc)(_{2})</td>
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<td>0</td>
<td>85</td>
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<td>0</td>
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<td>10</td>
<td>Cu(2-ethylhexanoate)(_{2})</td>
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<td>11</td>
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<td>25</td>
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<tr>
<td>12</td>
<td>Cu(OTf)(_{2})</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>Pd(MeCN)(<em>{2})Cl(</em>{2})</td>
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<td>0</td>
<td>55</td>
<td>0</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
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<td>50</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>AgOTf</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>AgNO(_{3})</td>
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<td>35</td>
<td>35</td>
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<td>0</td>
</tr>
<tr>
<td>19</td>
<td>AgOAc</td>
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<td>65</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>Ph(_{3})PAuCl + AgOTf</td>
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<td>0</td>
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<td>0</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
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<td>0</td>
<td>35</td>
<td>0</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>Fe(ClO(<em>{4}))(</em>{2})·xH(_{2})O</td>
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<td>5</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>23</td>
<td>FeCl(<em>{2})·4H(</em>{2})O</td>
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<td>5</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>SnCl(<em>{2})·2H(</em>{2})O</td>
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<td>0</td>
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<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

\(^{a}\)Reactions performed with 0.05 mmol of 188a and 10 mol % catalyst in CH\(_{2}\)Cl\(_{2}\) (0.1 M) under argon at RT for 16 h; \(^{b}\)Calculated by \(^{1}\)H NMR spectroscopic analysis of the unpurified reaction mixture, rounded to the nearest 5%.

Table 13. Catalyst screening with α-diazocarbonyl 188a.
Investigation of Cu(I)- (entries 5–8), Cu(II)- (entries 9–12), Pd(II)- (entries 13–16), Ag(I)-
(entries 17–19), Au(I)- (entries 20–21), Fe(II)- (entries 22–23) and Sn(II)-based catalysts
(entry 24), revealed Pd(MeCN)_4(BF_4)_2 as a highly effective catalyst for the selective synthesis
of indole 199a. During these studies, the concomitant formation of carbazole 200a was also
typically observed alongside indole 199a, especially so when using Cu(OTf)_2, which is
presumed to catalyse the oxidation of indole 199a to carbazole 200a.

Having completed the initial catalyst screening studies, the three most selective catalysts,
Rh_2oct_4, Pd(MeCN)_4(BF_4)_2 and Cu(OTf)_2, were selected for further optimisation. First, the
Rh_2oct_4-catalysed formation of spirocycle 190a was examined, where it was found that
formation of the α,β-dicarbonyl 198a side-product was dependent on the presence of air in the
reaction. Thus, performing the reaction under oxygen-free conditions (with other minor
modifications, such as switching the solvent from dichloromethane to chloroform and
reducing catalyst loading) allowed spirocycle 190a to be prepared in excellent yield (Table 14,
entry 1). Furthermore, carrying out the same reaction in a flask open to air (at reduced catalys
t loading and concentration) was sufficient to completely switch the selectivity, affording the
α,β-dicarbonyl 198a in 78% yield (entry 2). The structure of 198a was also proven by X-ray
crystallography (Figure 14).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh_2oct_4 (5 mol%), CHCl_3 (0.1 M), argon, 6 h</td>
<td>190a, 92%, 54:46 dr</td>
</tr>
<tr>
<td>2</td>
<td>Rh_2oct_4 (2 mol%), CHCl_3 (0.05 M), air, 1 h</td>
<td>198a, 78%</td>
</tr>
</tbody>
</table>

Table 14. Rh_2oct_4-catalysed synthesis of spirocycle 190a and α,β-dicarbonyl 198a.
Chapter 3. Indole $\alpha$-diazocarbonyl cyclisations

Figure 14. X-ray structure of $\alpha,\beta$-dicarbonyl 198a with thermal ellipsoids shown at 50% (CCDC 1481924).

It is proposed that both of these reactions initiate by the formation of rhodium carbenoid 201, which may then form spirocycle 190a either by: (i) a cyclopropanation and fragmentation pathway ($201 \rightarrow 202 \rightarrow 190a$, Scheme 62a) or (ii) direct attack from the indole C3-position followed by protodemetallation ($201 \rightarrow 203 \rightarrow 190a$). In a flask open to air, oxygen is proposed to abstract the $\alpha$-keto H-atom of 190a to form $\alpha$-keto radical 204 and a hydroperoxyl radical, which can then immediately recombine in a radical rebound process to afford peroxide 205 (Scheme 62b).\textsuperscript{99-101} Peroxide 205 may then cyclise to form endoperoxide 206, which following fragmentation would afford $\alpha,\beta$-dicarbonyl 198a. A purified sample of spirocycle 190a in CDCl$_3$ was also observed to form $\alpha,\beta$-dicarbonyl 198a over time by $^1$H NMR analysis, confirming that spirocycle 190a was indeed a direct precursor to $\alpha,\beta$-dicarbonyl 198a.
Indirect supporting evidence for the formation of an endoperoxide intermediate was later found when endoperoxide 208 was isolated from the reaction of vinyl-substituted α-diazocarbonyl 207 under the same reaction conditions (Scheme 63a). This 7-membered ring endoperoxide is proposed to form via a similar pathway to before, except in this case, the radical rebound process may occur at the less sterically hindered alkene terminus (Scheme 63b). The structure of 208 was definitively proven by X-ray crystallography (Figure 15).
Scheme 63. Allyl α-diazocarbonyl endoperoxide formation.

Figure 15. X-ray structure of endoperoxide 208 with thermal ellipsoids shown at 50% (CCDC 1481929).

Interestingly, during purification of α,β-dicarbonyl 198a by column chromatography, the formation of small quantities of a new product was also detected. Isolation of this product and X-ray analysis revealed the structure to be spirocyclic oxindole 212a, with a syn-relationship between the oxindole carbonyl and the hydroxyl group (Figure 16). Oxindole 212a was presumed to form by an aldol reaction promoted by the acidic silica gel; this diastereoselective aldol reaction could proceed via a 6-membered transition state, such as 213, where the syn-diastereoselectivity might be dictated by hydrogen bonding between the oxindole-enol and the reactive phenone carbonyl (Scheme 64). Pleasingly, it was found that this reactivity could be harnessed in a one-pot process, where α,β-dicarbonyl 198a was formed as previously and then immediately reacted with TFA following a solvent switch to THF to afford oxindole 212a in near-quantitative yield (Scheme 65).
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Figure 16. X-ray structure of spirocyclic oxindole syn-diastereoisomer 212a with thermal ellipsoids shown at 50% (CCDC 1481927).

Scheme 64. Proposed 6-membered transition state in the diastereoselective Brønsted acid catalysed formation of oxindole 212a.

Scheme 65. One-pot Brønsted acid promoted synthesis of spirocyclic syn-oxindole 212a.

Intrigued by the reactivity of α,β-dicarbonyl 198a with Brønsted acids, Brønsted bases were next examined in hopes of accessing the opposite anti-diastereoisomer. Indeed, the anti-diastereoisomer 214a could be prepared in modest yield by another one-pot process, where the α,β-dicarbonyl 198a was formed in situ then reacted with t-BuOK in THF at −78 °C (Scheme 66). The anti-diastereoisomer is believed to be formed via a transition state such as 215 (Scheme 67), where unfavourable steric clashes are minimised and the carbonyl dipoles are opposed. The relative stereochemistry of the anti-diastereoisomer was also confirmed by X-ray crystallography (Figure 17).
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Scheme 66. One-pot Brønsted base promoted synthesis of spirocyclic *anti*-oxindole 214a.

Scheme 67. Proposed transition state for the diastereoselective Brønsted base catalysed formation of oxindole 214a.

Figure 17. X-ray structure of spirocyclic oxindole *anti*-diastereoisomer 214a with thermal ellipsoids shown at 50% (CCDC 1481928).

Next, the Pd(MeCN)$_4$(BF$_4$)$_2$-catalysed conditions for the synthesis of indole 199a were examined, which following a solvent switch to chloroform and a reduction of the catalyst loading, could be used to prepare indole 199a in excellent yield (Scheme 68). The structure of indole 199a was definitively proven by X-ray crystallography (Figure 18).
Scheme 68. The Pd(MeCN)$_4$(BF$_4$)$_2$-catalysed synthesis of indole 199a.

Figure 18. X-ray structure of indole 199a with thermal ellipsoids shown at 50% (CCDC 1481925).

Finally, the Cu(OTf)$_2$-catalysed conditions for the synthesis of carbazole 200a were optimised. To drive the oxidation of indole 199a to completion, an increased catalyst loading (20 mol%) was required, followed by the delayed introduction of an oxygen atmosphere at a higher temperature (50 °C). If the reaction was initiated under oxygen then the yield was diminished by the formation of the α,β-dicarbonyl 198a, which strongly suggests that the precursor, spirocycle 190a, is an intermediate in this reaction. The structure of carbazole 200a was definitively proven by X-ray crystallography (Figure 19).

Scheme 69. The Cu(OTf)$_2$-catalysed synthesis of carbazole 200a.
To further probe whether spirocycle 190a was indeed an intermediate in the formation of indole 199a, spirocycle 190a was reacted with both Pd(MeCN)$_4$(BF$_4$)$_2$ and Cu(OTf)$_2$ (Table 15). Interestingly, Pd(MeCN)$_4$(BF$_4$)$_2$ had no effect on spirocycle 190a (entry 1), whilst Cu(OTf)$_2$ reacted rapidly with spirocycle 190a to form indole 199a as evident by analysis of the $^1$H NMR spectrum of the reaction mixture. These results suggest that although the Pd(II)- and Cu(II)-catalysed reactions share indole 199a as a common intermediate/product, they may promote different mechanistic pathways.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(MeCN)$_4$(BF$_4$)$_2$ (5 mol%)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)$_2$ (20 mol%)</td>
<td>Rapid conversion into 199a</td>
</tr>
</tbody>
</table>

* Determined by analysis of the $^1$H NMR spectra of the unpurified reaction mixture

Table 15. Additive screening with spirocycle 190a.
Considering these results, it is proposed that Cu(OTf)$_2$ might initially promote the formation spirocycle 190a as previously proposed with Rh$_2$(oct)$_4$ (Scheme 70). However, upon formation of spirocycle 190a, Cu(OTf)$_2$ may induce a Lewis acid catalysed 1,2-migration to form indole 199a, which may then undergo a Cu(II)-catalysed oxidation (with oxygen as the terminal oxidant) to form carbazole 200a.

![Scheme 70. Proposed mechanism for the Cu(OTf)$_2$-catalysed synthesis of carbazole 200a.](image)

For the Pd(MeCN)$_4$(BF$_4$)$_2$-catalysed synthesis of indole 199a an alternative mechanism is proposed, in which the reaction is initiated by electrophilic palladation at the indole C2-position (188a $\rightarrow$ 219, Scheme 71a).$^{102-104}$ Following palladation, the diazo group could coordinate to the metal centre (219 $\rightarrow$ 220), which after the extrusion of nitrogen would afford palladium carbenoid 221; subsequent migratory insertion would generate palladium-species 222, which after protodemetallation would regenerate the Pd(II) catalyst and afford indole 199a.$^{105-108}$ Supporting evidence for a mechanism initiated by palladation at the indole 2-position was found when a control substrate 223, with a methyl group blocking the 2-position, was reacted under the standard conditions, from which no reaction was observed (Scheme 71b).
Scheme 71. a) Proposed mechanism for the Pd(MeCN)$_4$(BF$_4$)$_2$-catalysed synthesis of indole 199a; b) Supporting control reaction with 2-methyl substituted substrate 223.
Chapter 3. Indole α-diazoacarbonyl cyclisations

3.4 Substrate Synthesis

To fully explore the scope of the developed transformations, a wider range of α-diazoacarbonyl substrates were prepared. First, Weinreb amides 81\textit{i,j} were prepared in a three step sequence (Table 16). Commerically available indoles 224 were readily converted into 3-indolepropionic esters by a ZrCl$_4$-catalysed conjugate addition into ethyl acrylate,\textsuperscript{109} which following saponification and a T3P-mediated amide coupling afforded Weinreb amides 81\textit{i,j}.

![Scheme 72. Scope of benzyl ketones prepared by Grignard addition.](image)

| Table 16. Synthesis of 3-indolepropionic acid derivatives. |
|-----------------|-----------------|-----------------|
| **Entry** | **R** | **Yield over 3 steps (%)** |
| 1 | 6-Cl (81\textit{i}) | 55 |
| 2 | 5-OMe (81\textit{j}) | 65 |
The benzyl ketones 192 were then used to prepare α-diazocarbonyls 188 by Regitz diazo transfer using $p$-ABSA and DBU (Scheme 73).

Scheme 73. Scope of α-diazocarbonyls prepared by Regitz diazo transfer reactions.
3.5 Substrate Scope

With a wider range of substrates in hand, the scope of the six optimised reaction protocols were examined. First, the silica gel-promoted formation of the C2-annulated indoles 193 was investigated (Scheme 74). Pleasingly, every substrate prepared underwent the desired transformation, affording indoles 193a–d in modest to good yield, whilst indole 193e was formed in a diminished 38% yield with no other isolable products detected.

Next, the Rh$_2$oct$_4$-catalysed synthesis of spirocycles 190a–e was examined (Scheme 75). Again, every substrate successfully formed the corresponding spirocycle in modest to excellent yield. Modest diastereoselectivity was also observed, with the structure of the same major diastereoisomer assigned by nOe studies for each example (Figure 20).
Chapter 3. Indole α-diazocarbonyl cyclisations

Scheme 75. Scope of the Rh$_2$(oct)$_4$-catalysed spirocycle synthesis.

Figure 20. Assignment of spirocycle diastereoisomers based on nOe correlations.

All of the substrates were also successfully converted into the corresponding spirocyclic syn-oxindoles 212a–e in good to excellent yield (Scheme 76). Aside, from the original X-ray analysis of oxindole 212a, diagnostic signals in $^1$H NMR spectra of oxindoles 212b–e were also used to confirm their stereochemistry (Figure 21). For example, in every case noticeable shielding of the H-2 proton was observed, likely due to the positioning and magnetic anisotropic effects of the α-keto aromatic ring, which is easily visualised in the structure provided by X-ray analysis of oxindole 212a. The opposite anti-diastereoisomers 214a–c,e were also prepared in consistently modest yield (40–58%) except for oxindole 214d, which was prepared in 73% yield (Scheme 77).
Scheme 76. Scope of the acid-promoted synthesis of syn-oxindoles.

Figure 21. Diagnostic anisotropic shielding of the syn-oxindoles.
Next, the optimised Pd(MeCN)$_4$(BF$_4$)$_2$-catalysed conditions were successfully applied to every substrate, forming indoles 199a–e in modest to excellent yield (Scheme 78). Finally, the Cu(OTf)$_2$-catalysed carbazole formation conditions were examined (Scheme 79), where every carbazole 200a–d except for 200e was isolated in good yield.
Scheme 79. Scope of the Cu(OTf)$_2$-catalysed tandem annulation-oxidation reaction.
3.6 Preliminary studies towards spirobacillene B

To conclude studies with the α-diazocarbonyl system, studies towards the synthesis of spirobacillene B were resumed. Here, it was envisaged that the developed Rh(II)-catalysed spirocyclisation could be readily applied to an α-diazocarbonyl 225 derived from Tang’s intermediate 21 (Scheme 80). The resultant spirocycle 24 used by Tang and co-workers could then be deprotected and oxidised under their conditions to afford spirobacillene B (24 → 224 → 13).

![Scheme 80. Retrosynthetic analysis of spirobacillene B 13 using an α-diazocarbonyl.](image)

Attempts to prepare model substrate 227 with an oxygen substituent in the required para-position were unsuccessful (Scheme 81). The benzyl ketone 226 was prepared in good yield, but the required α-diazocarbonyl 227 could not be isolated under the Regitz diazo transfer conditions, with only decomposition of the starting material observed by TLC analysis. This result was attributed to the destabilising effects of the electron donating oxygen substituent, which is in direct conjugation to the reactive diazo centre (as shown in 228). At this point, no further studies were attempted, but future work might look to attenuate the destabilising effects of the oxygen substituent with an electron withdrawing protecting group.
3.7 Summary

The selective synthesis of six different products from a single indole α-diazocarbonyl precursor has been developed (Figure 22). This feat, which is to the best of our knowledge a record number of products formed from a single precursor, was achieved by using Brønsted acid-, Rh(II)-, Pd(II)- and Cu(II)-catalysis to exploit a variety of different mechanistic pathways. Full elucidation of the proposed mechanistic pathways, as well as the application of this chemistry to other heteroarenes, such as pyrrole, remains the focus of future work.

The work described in this Chapter was the subject of a recent publication.110

**Figure 22.** Illustrative rainbow of products from a single “pot of gold”.

**Scheme 81.** Attempted synthesis of α-diazocarbonyl 227.
Chapter 4. Dearomatisation approach to quinolizidine and indolizidine alkaloids

4.1 Introduction

In the previous chapters, all of the work was focused on the synthesis of spirocyclic indolenines through the dearomatisation of indole. Here, it was planned to tether alkynes to other heteroaromatic systems, such as pyridine 228 and pyrrole 231, in hopes of promoting cyclisation through the nitrogen atom to afford quinolizinones 229 or indolizines 232, which following a dearomative hydrogenation would provide access to quinolizidine 230 and indolizidine 233 frameworks (Scheme 82). Ideally, the two catalytic steps would be performed in a one-pot process, which could potentially be rendered asymmetric if an enantioselective hydrogenation step could be realised.

![Scheme 82. The proposed two-step cyclisation and hydrogenation of pyridine- and pyrrole-ynones.](image)

The quinolizidine and indolizidine frameworks are found in a number of bioactive natural products, such as 234–237 (Scheme 83). These natural products have typically been isolated in small quantities, which hinders their study as potential therapeutics, and so, it is hoped that the proposed sequence will provide an expedient and scalable route for their synthesis.

![Scheme 83. Quinolizidine and indolizidine alkaloids.](image)
4.2 Background

Quinolizinones have previously been prepared by the cyclisation of pyridine-alkyne systems, as first demonstrated by Katritzky and co-workers (Scheme 84a), who found that quinolizinones 240 could be prepared by heating pyridines 238 and benzotriazoles 239 in acetonitrile at 120 °C in a sealed tube. Later, Natarajan and co-workers reported a modified protocol (Scheme 84b), whereby picoline derivatives 241 were first acylated with a methyl ester 242 and then cyclised at a reduced temperature (80 °C). Both of these protocols suffered from the requirement of relatively harsh thermal cyclisation conditions as well as modest yields across a limited range of substrates. It was hoped that all of these negative aspects could be alleviated by a catalytic method.

Scheme 84. Pyridine alkyne cyclisation reactions to form quinolizinones.

Indolizines have also been prepared by the cyclisation of pyridine-alkyne systems. Notable examples include the work of Gevorgyan and co-workers, who first reported the Au(III)-catalysed cyclisation of TBS-protected propargyl alcohols 244 to afford indolizines 246 in modest to excellent yield (Scheme 85a). This reaction proceeded via the formation and cyclisation of an electrophilic vinylidene intermediate 245. Later, Gevorgyan and co-workers reported a simpler Ag(I)-catalysed protocol, where propargyl alcohols 247 were activated with AgBF₄ and cyclised to afford indolizines 249 in typically excellent yields (Scheme 85b). Finally, Sarpong and co-workers reported a Pt(II)-catalysed procedure to form indolizinones 253 from tertiary propargyl alcohols 250 by a cyclisation and 1,2-migration sequence (Scheme 85b).
The current leading methods for the catalytic synthesis of quinolizidine and indolizidine alkaloids have arguably been developed by Rovis and co-workers, who used Rh(I)-catalysis to promote [2+2+2] cycloadditions with alkenyl isocyanates and terminal alkynes to generate quinolizidine or indolizidine alkaloid precursors in good to excellent yield and with excellent enantioselectivity (Scheme 86).\textsuperscript{122,123} Rovis and co-workers first employed this methodology in the synthesis of (+)-lasubine II \textsuperscript{235} (Scheme 86a), by hydrogenating the [2+2+2] product \textsuperscript{259} to form quinolizidine \textsuperscript{260}. The hydroxyl group stereochemistry of quinolizidine \textsuperscript{260} was then inverted by a Mitsunobu and hydrolysis sequence to afford 27.0 mg of (+)-lasubine II \textsuperscript{235}.\textsuperscript{122} Later, the same group applied this methodology in the synthesis of (−)-indolizidine 209D \textsuperscript{237} (Scheme 86b), using a new phosphoramidite ligand \textsuperscript{247} to form the [2+2+2] product \textsuperscript{261} in good yield.\textsuperscript{123} The [2+2+2] product \textsuperscript{261} was then hydrogenated and deoxygenated under Barton-McCombie conditions to afford 18.2 mg of (−)-indolizidine 209D \textsuperscript{237}. Overall, whilst this [2+2+2] methodology provided access to these natural products in a concise enantioselective fashion, only small quantities were ever prepared and required an expensive catalyst system to do so. Thus, it is hoped that the proposed method could improve upon this pioneering work.
**Scheme 86.** Leading methods for the catalytic synthesis of quinolizidine and indolizidine alkaloids.
Chapter 4. Dearomatisation approach to quinolizidine and indolizidine alkaloids

4.3 Pyridine-ynone cyclisations

4.3.1 Reaction discovery & optimisation studies

Studies of the proposed pyridine-ynone system began with preparation of ynone 228a, which was made by the acylation of 2-picoline 264 with methyl phenylpropionate under modified conditions reported by Natarajan and co-workers (Scheme 87).

![Scheme 87. Synthesis of pyridine-ynone 228 by the acylation of 2-picoline 264.](image)

Ynone 228a was then reacted with a range of catalysts in dichloromethane in an attempt to promote cyclisation (Table 17). These experiments were performed on a small scale (0.2 mmol of ynone 228a) and examined by analysis of the $^1$H NMR spectra of the unpurified reaction mixtures. These studies were also aided by a York MChem student (Niall Grant).

First, a range of Cu(I/II), Au(I) and Ag(I)-based catalysts were examined (entries 1–4), of which only AgOTf was found to promote the formation of quinolinizone 229a. Further examination of other Ag(I) catalysts (at reduced catalyst loading), showed that both AgNO$_3$ and AgNTf$_2$ were the most effective catalysts (entries 9 & 10). However, only AgNO$_3$ was selected for further study as it is significantly cheaper than AgNTf$_2$. Finally, using AgNO$_3$ (1 mol%) as the optimal catalyst, the solvent system was varied (entries 11–16), which showed that the rate of reaction could be significantly improved by performing the reaction in either EtOH or to a lesser extent DCE.
The rate of reaction was believed to be highly susceptible to the degree of keto–enol
tautomerisation of ynone 228a (which exists primarily as the enol tautomer in CDCl₃, Figure
23). The geometry of the enol tautomer was assigned as the cis-alkene, based upon the high
chemical shift of the enol proton observed in the ¹H NMR spectrum (15.02 ppm in CDCl₃),
which is likely to be due to intramolecular hydrogen bonding with the nitrogen lone pair of the
pyridine ring. This cis-alkene geometry is believed to hinder reactivity by decreasing the
proximity of the nitrogen lone pair and alkyne moiety; thus, the reaction is proposed to
proceed via the electrophilic activation of the keto tautomer (which can freely rotate),
followed by a 6-endo-dig cyclisation through the nitrogen lone pair (228a → 265 → 266,
Scheme 88). Subsequent aromatisation and protodemetalation of 266 would then afford the
observed quinolizinone 229a and regenerate the Ag(I) catalyst.

*All reactions performed with 0.2 mmol of ynone 228a in the stated solvent at RT;
*Calculated by ¹H NMR spectroscopy of the unpurified reaction mixture.

Table 17. Optimisation of the pyridine-ynone cyclisation conditions.
Figure 23. $^1$H NMR spectrum of pyridone-ynone 228a in CDCl$_3$. 

Scheme 88. Proposed mechanism for Ag(I)-catalysed synthesis of quinolizinone 229a.
4.3.2 Substrate synthesis

To explore the scope of the Ag(I)-catalysed cyclisation a wider range of pyridine-ynones 228 were required. First, a number of methyl propiolate esters 269a–c, which were not commercially available, were prepared in modest, unoptimised yields from the corresponding commercially available terminal alkynes 268 by deprotonation and trapping with methyl chloroformate (Scheme 89).

Alternatively, where the requisite alkyne was not commercially available, the ester could be accessed from an aldehyde and a partial Corey-Fuchs reaction e.g. in the preparation of alkynyl ester 269d (Scheme 90).

Next, the methyl propiolate esters were used to acylate a number picoline-type systems (as demonstrated in Scheme 87) to afford pyridine-, isoquinoline- and pyrazine-ynones 228a–l in generally good yields (Scheme 91).
Scheme 91. Library of pyridine-ynone substrates prepared.
4.3.3 Substrate scope

With a number of ynones in hand, attention switched to examining the scope of the Ag(I)-catalysed cyclisation reaction. It was then realised that a number of substrates demonstrated poor solubility in EtOH, the solvent used in the originally optimised conditions, and so DCE was used as a solubilising co-solvent to alleviate this problem. The catalyst loading was also raised to 2 mol% of AgNO₃ in all examples for consistency. These new optimal conditions were then applied across the full substrate library (Scheme 92).

First, aryl and aliphatic ynones 228a–d with varying electronics were all converted into quinolizinones 229a–d in quantitative/near-quantitative yield. Thiophene and methylated ynones 228e,f were then examined, but unfortunately these substrates were unstable at room temperature and so afforded the corresponding quinolizinones 229e,f in diminished yield. Next, ynones 228g–i with different substituents on the pyridine ring were converted into quinolizinones 229g–i in excellent yield. The structure of quinolizinone 229h was proven by X-ray crystallography (Figure 24). Finally, isoquinoline- and pyrazine- ynones 228j,k were also successfully cyclised to afford the corresponding quinolizinone-type products 229j,k in excellent yield.
Scheme 92. Substrate scope of the Ag(I)-catalysed cyclisation.
The only substrate which failed to undergo the desired cyclisation under the standard conditions was TMS-ynone 228l. Interestingly, this substrate was also unreactive under the thermal conditions employed by Natarajan and co-workers. However, by changing the conditions, a one-pot desilylation-cyclisation reaction could be performed by reacting 228l with AgNO$_3$ (20 mol%) in acetone to afford quinolizinone 229l in excellent yield (Scheme 93).

**Scheme 93.** One-pot desilylation-cyclisation of ynone 228l.
4.3.4 *Synthesis of (±)-lasubine II*

Having established an operationally simple, mild and high yielding catalytic protocol for the synthesis of quinolizinones, the dearomative hydrogenation of these frameworks to access quinolizidine natural products was planned. In particular, the synthesis lasubine II 235 was envisaged, as the known intermediate 230b was expected to be readily prepared from the hydrogenation of quinolizinone 229b (Scheme 94).

Studies towards the synthesis of (±)-lasubine II began with the previously described synthesis of quinolizinone 229b, which was readily prepared on a multi-gram scale (2.09 g) in two steps from 2-picoline 264 (Scheme 95). The dearomative hydrogenation of quinolizinone 229b was then attempted by reaction with Pd/C in MeOH under an atmosphere of hydrogen, which selectively hydrogenated only one of the desired ring systems to afford pyridone 273. Fortunately, both ring systems could be fully hydrogenated to afford quinolizidine 230b by using PtO₂ as the catalyst and AcOH (3 equivalents) as an additive to prevent catalyst poisoning.¹²⁶ The unpurified quinolizidine 230b was then oxidized under Swern conditions to afford ketone 274 in good yield over two steps. Ketone 274 was then reduced under known conditions with L-Selectride to afford 0.53 g of (±)-lasubine II 235 in 36% overall yield and in just five steps from 2-picoline 264.¹²⁷–¹³⁰

![Scheme 94. Retrosynthetic analysis of lasubine II.](image-url)
Scheme 95. Synthesis of (±)-lasubine II 235.
4.4 Pyrrole- & pyrroline-alkyne cyclisations

Having proven the efficiency of this approach in the synthesis of quinolizidine alkaloids, indolizidine systems were next examined. Studies began with the preparation of pyrrole-ynone 231a, which was prepared in four steps from pyrrole 275 (Scheme 96). First, pyrrole 275 was deprotonated with MeMgCl and alkylated with ethyl bromoacetate to form ethyl ester 276 in 49% yield. Ester 276 was then saponified to afford acid 277, which was converted into Weinreb amide 278 using T3P in good yield over two steps. Amide 278 was then used to prepare ynone 231a in modest yield by reaction with a PMP-derived lithium acetylide. A small quantity of propargyl alcohol 279a was also prepared by reduction of ynone 231a with NaBH₄.

Scheme 96. Synthesis of pyrrole-ynone 231a and propargyl alcohol 279a (synthesis aided by Dr William Unsworth and Aimee Clarke).

Initial studies with the pyrrole-alkyne systems began by reacting pyrrole-ynone 231a with AgNO₃ (10 mol%) in CH₂Cl₂, which afforded spirocycle 280a in near-quantitative yield (Scheme 97a). The analogous pyrrole-based propargyl alcohol 279a was also reacted under the same conditions to afford the benzannulated product 281a in excellent yield (Scheme 97b). Whilst, none of the desired cyclisation through the nitrogen atom was observed, these reactions were considered an interesting extension of the work shown in Chapter 2 and further studies into these systems are being undertaken in the Taylor group by Aimee Clarke.

In an attempt to circumvent spirocyclisation/benzannulation reactivity and favour cyclisation through the nitrogen atom, the cyclisation of an alternative non-aromatic pyrroline-ynone system 283a was planned. The model pyrroline-ynone system 238a was readily prepared in one step by the acylation of 2-methyl-1-pyrroline 282 with methyl phenyl propiolate (Scheme 98). Pyrroline-ynone 283a was then reacted under the pyridine-ynone cyclisation conditions to afford the desired pyridone 284a in quantitative yield. The structure of pyridone 284a was also confirmed by X-ray crystallography (Figure 25).

Scheme 98. Synthesis and cyclisation of pyrroline-ynone 283a.

Figure 25. X-ray structure of pyridone 284a with thermal ellipsoids shown at 50% (CCDC 1532716).
4.4.1 Optimisation studies

The pyrroline-ynone 283a was then reacted with a range of different catalysts in an attempt to find the optimal cyclisation conditions (Table 17). These experiments were performed on a small scale (0.05-0.2 mmol of ynone 283a) and the yields were determined by analysis of the $^1$H NMR spectra of the unpurified reaction mixtures against an internal standard (1,3-bis(trifluoromethyl)-5-bromobenzene).

First, common Cu(I/II)-, Au(I)- and Ag(I)-based catalysts (10 mol%) were examined in CH$_2$Cl$_2$ at 40 °C for 18 h (entries 1–13), and both AgNO$_3$ and AgTFA were found to form pyridone 284a in quantitative yield. Further comparison between AgNO$_3$ and AgTFA at reduced catalyst loading (5 mol%), showed that AgTFA was slightly more effective in promoting the formation of pyridone 284a (entries 14–15). Solvent screening studies with AgTFA as the catalyst (entries 16–23) revealed that the rate of reaction could be significantly increased by performing the reaction in toluene. Finally, the catalyst loading of AgTFA could be further reduced to 2 mol% by raising the temperature to 110 °C, which also reduced the reaction time to 1 h (entry 24). A control experiment showed that only traces of pyridone 284a was formed under these thermal conditions without a Ag(I) catalyst (entry 25).
Chapter 4. Dearomatisation approach to quinolizidine and indolizidine alkaloids

![Chemical structure](image)

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<sup>a</sup> Reactions performed with 0.05–0.2 mmol of 283a and catalyst in the stated solvent (0.1 M) and temperature; <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (1,3-bis(trifluoromethyl)-5-bromobenzene).

Table 18. Optimisation of the pyrroline-ynone cyclisation conditions.
4.5 Future work

With initial optimisation of the pyrroline-ynone cyclisation conditions completed, future work exploring the scope of this transformation and its application in the synthesis of indolizidine alkaloids, such as 209D 237 is envisaged (Scheme 99).


The application of this chemistry in the synthesis of tricyclic alkaloid frameworks is also possible (Scheme 100). Here, it is proposed that a spirocyclic pyridine- or pyrroline-ynone 286 could be cyclised to form an iminium species 287, which following a ring-expanding 1,2-migration reaction and protodemetallation would afford tricycle 289. Hydrogenation of tricycle 289 would afford saturated tricycle 290, which could be oxidised and epimerised in a retro-Michael and Michael addition process (291 → 292 → 293) to access the relative stereochemistry found in the cyclindricine alkaloids. This process could also potentially be rendered asymmetric be using a silver salt with a chiral counterion, such as a CPA; this counterion could form a chiral ion-pair with iminium species 287 and thus promote an enantioselective 1,2-migration reaction.
Scheme 100. Proposed asymmetric synthesis of tricyclic alkaloid frameworks.
4.6 Chapter summary

The Ag(I)-catalysed cyclisation of pyridine-, isoquinoline-, pyrazine- and pyrroline-yrones has been developed. A range of quinolizinones and pyridones have been prepared in high yield under mild catalytic conditions, which is a significant improvement over previously reported thermal cyclisations. One of these products was also hydrogenated to prepare the quinolizidine alkaloid, (±)-lasubine II, in a novel dearomatisation strategy. Further studies towards indolizidine alkaloids are also planned. Finally, the development of an asymmetric hydrogenation protocol is also planned, in hopes of enabling the enantioselective synthesis of other alkaloids.

The work described in this chapter was the subject of a recent publication.\textsuperscript{132}
Chapter 5. Experimental

5.1 General experimental details

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH$_2$Cl$_2$, toluene and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. CHCl$_3$ was used as supplied without additional drying and deoxygenated CHCl$_3$ was obtained by freeze-pump-thaw degassing. $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ$_{\text{H}}$ 7.27 and δ$_{\text{C}}$ 77.0 for CDCl$_3$, δ$_{\text{H}}$ 2.50 and δ$_{\text{C}}$ 39.5 for DMSO-d$_6$, δ$_{\text{H}}$ 5.32 and δ$_{\text{C}}$ 54.0 for CD$_2$Cl$_2$, were used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.5 Hz. Signal assignment was achieved by analysis of DEPT, COSY, HSQC and HMBC experiments. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH$_2$Cl$_2$ or CDCl$_3$. Mass-spectra were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silicagel 60F$^{254}$ pre-coated aluminium foil sheets, which were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Column chromatography and silica gel mediated reactions were carried out using Fluka silica gel (SiO$_2$), 35–70 μm, 60 Å; column chromatography was carried out under a light positive pressure, eluting with the specified solvent system. Petrol refers to petroleum ether 40–60 °C. Numbering schemes for compounds refer to NMR assignments and not to compound naming. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector.
5.2 General procedures

5.2.1 Chapter 2

General procedure 2A: Weinreb amide formation

To a stirred solution of acid (1.00 mmol), MeNHOMe·HCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH₂Cl₂ (2.5 mL) was added T3P (955 mg, 1.5 mmol, 50% wt. in EtOAc). The solution was stirred for 1 h at RT. The reaction mixture was poured into water (20 mL) and acidified using 10% HCl (aq) (5 mL). The organics were collected and the aqueous was extracted with EtOAc (3 × 30 mL). The organics were combined, washed with 2 M NaOH (aq) (20 mL), brine (20 mL), dried (MgSO₄) and concentrated in vacuo to afford the crude Weinreb amide product.

General procedure 2B: Ynone formation

To a solution of alkyne (6.87 mmol) in THF (7 mL) at −78 °C under argon was added n-BuLi (3.6 mL, 5.73 mmol, 1.6 M in hexanes) dropwise. The mixture was stirred for 30 min at −78 °C and then transferred via cannula to a −78 °C solution of Weinreb amide (2.29 mmol) in THF (21 mL). Upon complete transfer the mixture was warmed to RT and stirred for 30 min after which the reaction was quenched by the careful addition of sat. NH₄Cl (aq) (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried (MgSO₄), concentrated in vacuo and purified by column chromatography to afford the ynone product.
General procedure 2C: Indole-ynone cyclisations

To a solution of ynone (0.2 mmol) in CH₂Cl₂ (2 mL) was added either AgOTf, Cu(OTf)₂ or (Ph₃P)AuNTf₂·½PhMe (1–20 mol%). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was concentrated in vacuo then purified by column chromatography to afford the cyclised product.

General procedure 2D: Asymmetric indole-ynone spirocyclisations

To a solution of ynone (0.2 mmol) in CHCl₃ (2 mL) at −10 °C was added Ag₁₁₄l (2 µmol). The mixture was stirred at −10 °C for 16 h. The reaction mixture was then directly applied to a column and purified by column chromatography to afford the spirocyclic product. Enantiomeric excess was determined by CSP-HPLC (Chiralpak IB column), eluting with 5–20% IPA in hexanes at 1 mL/min and UV detection at 280 or 254 nm.
**General procedure 2E: CPA synthesis**

(R)-3,3’-Diiodo-2,2’-bis(methoxymethoxy)-1,1’-binaphthalene (117) (100 mg, 0.160 mmol), Ba(OH)_2 (152 mg, 0.800 mmol) and the respective aryl boronic acid (0.384 mmol) were combined in 1,4-dioxane (1.2 mL) and H_2O (0.4 mL). The mixture was purged by alternating vacuum and argon three times. To the mixture was added Pd(PPh_3)_4 (28 mg, 0.024 mmol), which was again purged by alternating vacuum and argon three times. The mixture was stirred for 16 h at 80 °C under argon, then poured into 10% HCl (aq) (10 mL) and extracted with EtOAc (3 × 30 mL). The organics were collected, dried (MgSO_4), filtered through celite and concentrated *in vacuo*. The crude material was eluted through a silica plug with (1:1) MeOH:CH_2Cl_2. The material was then dissolved in 12 M HCl (aq) (0.05 mL), MeOH (1.2 mL), CH_2Cl_2 (1.2 mL) and stirred for 2 h at 50 °C. The mixture was poured into sat. NaHCO_3 (aq) (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organics were dried (MgSO_4) and concentrated *in vacuo*. The material was then dissolved in pyridine (1.5 mL), to which POCl_3 (0.03 mL, 0.32 mmol) was added dropwise. The mixture was stirred for 16 h under argon at 100 °C, then poured into 10% HCl (aq) (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were then washed with 10% HCl (aq) (5 × 30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by column chromatography (MeOH/CH_2Cl_2) then dissolved in CH_2Cl_2 (10 mL), washed with 10% HCl (aq) (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the BINOL phosphoric acid product.

**General procedure 2F: H₈-BINOL Suzuki cross-coupling**

(S)-3,3’-Dibromo-5,5’,6,6’7,7’,8,8’-octahydro-[1,1’-binaphthalene]-2,2’-diol (121) (100 mg, 0.221 mmol), Pd(OAc)_2 (2.0 mg, 0.009 mmol), di(1-adamantyl)-n-butylphosphine (3.9 mg, 0.011 mmol) and the respective aryl boronic acid (0.553 mmol) were combined in DME (2.2 mL) and 1 M K_2CO_3 (aq) (1.1 mL). The mixture was purged by alternating vacuum and argon three times. The mixture was stirred for 16 h under argon at 95 °C, then poured into sat.
Chapter 5. Experimental

NH₄Cl\textsubscript{(aq)} (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The organics were combined, washed with H₂O (10 mL), dried (MgSO₄) and concentrated \textit{in vacuo}. The crude material was then purified by column chromatography (silica gel, hexane to hexane/CH₂Cl₂) to afford the H₈-BINOL product.

**General procedure 2G: H₈-BINOL phosphorylation**

To a solution of the respective (H₈)-BINOL product (0.2 mmol) in pyridine (1 mL) was added POCl₃ (0.4 mmol) dropwise. The mixture was stirred for 16 h under argon at 70 °C, then poured into 10% HCl\textsubscript{(aq)} (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The organics were combined and concentrated \textit{in vacuo}. The crude material was combined with DMAP (0.02 mmol) in 2 M NaOH\textsubscript{(aq)} (1 mL) and THF (1 mL). The mixture was stirred for 16 h under argon at RT, then poured into 10% HCl\textsubscript{(aq)} (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The organics were then washed with 10% HCl\textsubscript{(aq)} (5 × 30 mL), dried (Na₂SO₄) and concentrated \textit{in vacuo}. The crude material was purified by column chromatography (MeOH/CH₂Cl₂) then dissolved in CH₂Cl₂ (10 mL), washed with 10% HCl\textsubscript{(aq)} (2 × 10 mL), dried (Na₂SO₄) and concentrated \textit{in vacuo} to afford the H₈-BINOL phosphoric acid product.

**General procedure 2H: Ag-CPA preparation**

To a solution the respective phosphoric acid (0.20 mmol) in CH₂Cl₂ (2 mL) in the dark was added Ag₂CO₃ (27.6 mg, 0.10 mmol), followed by H₂O (2 mL). The mixture was stirred vigorously for 1 h, then poured into H₂O (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were filtered through Celite® and concentrated \textit{in vacuo} to afford the phosphoric acid silver salt.
General procedure 2I: Ynone reduction

![Ynone reduction reaction](image)

To a solution of ynone (1.0 mmol) in MeOH (20 mL) at 0 °C was added NaBH₄ (4.0 mmol). The reaction mixture was stirred for 30 min at 0 °C before being quenched with the addition of sat. NH₄Cl (aq) (30 mL). The organics were extracted with DCM (4 × 50 mL), dried (MgSO₄) and purified by flash column chromatography to afford the desired propargyl alcohol.

General procedure 2J: Telescopied propargyl alcohol formation

![Telescopied propargyl alcohol formation reaction](image)

To a solution of terminal alkyne (3.0 mmol) in THF (3 mL) at −78 °C under argon was added n-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane). The resulting solution was stirred at −78 °C for 30 min, then transferred via cannula to a cooled (−78 °C) solution of Weinreb amide (1.0 mmol) in THF (9 mL). The mixture was stirred at −78 °C for 5 min then warmed to RT and stirred for a further 30 min. The reaction was then quenched with sat. NH₄Cl (aq) (30 mL), allowed to warm to RT, diluted with water (70 mL), extracted with ethyl acetate (3 × 100 mL). The combined organics were washed with brine, dried over MgSO₄ and concentrated in vacuo. The resulting material was then dissolved in MeOH (20 mL), cooled to 0 °C and NaBH₄ (4.0 mmol) was added. The reaction mixture was stirred for a 30 min at 0 °C before being quenched with sat. NH₄Cl (aq) (30 mL). The organics were extracted with CH₂Cl₂ (4 × 30 mL), dried (MgSO₄) and purified by flash column chromatography to afford the propargyl alcohol.
General procedure 2K: Propargyl alcohol spirocyclisation

To a solution of propargyl alcohol (0.2 mmol) in CH₂Cl₂ (2 mL) was added sequentially Ag₂O (10 µmol) and AgNO₃ (20 µmol). The mixture was stirred at RT for 24 h then concentrated in vacuo and purified by column chromatography to afford the spirocyclic indolenine product.

General procedure 2L: Propargyl alcohol benzannulation

To a solution of propargyl alcohol (0.2 mmol) in THF (2 mL) was added AgOTf (20 µmol). The mixture was stirred at RT for 24 h then concentrated in vacuo and purified by column chromatography to afford the carbazole product.
5.2.2 Chapter 3

General procedure 3A: Benzyl ketone formation

Based on a modified literature procedure.\textsuperscript{16} To a solution of Weinreb amide (1 equiv.) in THF (10 mL/mmol) at 0 °C under argon was added the benzyl Grignard (4 equiv.) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 4–5 h. The reaction was then quenched with sat. NH\textsubscript{4}Cl\textsubscript{(aq)}, diluted with water and extracted with EtOAc (3 x). The combined organics were washed with brine, dried (MgSO\textsubscript{4}), concentrated \textit{in vacuo} and purified by column chromatography to afford the desired benzyl ketone.

General procedure 3B: α-Diazocarbonyl formation

Based on a modified literature procedure.\textsuperscript{133} To a solution of benzyl ketone (1 equiv.) and p-ABSA (1.2 equiv.) in MeCN (3 mL/mmol) at RT was added DBU (1.4 equiv.) dropwise. The reaction mixture was stirred for a 30–60 min before being concentrated \textit{in vacuo}. The crude product was dissolved in CH\textsubscript{2}Cl\textsubscript{2} and purified by column chromatography (eluting with 3% Et\textsubscript{3}N as a basic additive) to afford the desired α-diazocarbonyl compound. (Note: the α-diazocarbonyl compounds were generally stable when stored at room temperature for ~1 month before significant degradation was observed).

General procedure 3C: Formation of spirocyclic indolenines

To the α-diazocarbonyl compound (1 equiv.) and Rh\textsubscript{2}oct\textsubscript{4} (5 mol%) under argon was added deoxygenated CHCl\textsubscript{3} (10 mL/mmol). The mixture was stirred at RT under argon for 6 h then
concentrated *in vacuo* and purified by column chromatography (under a positive pressure of nitrogen) to afford the spirocyclic indolenine diastereoisomers (The major diastereoisomers were identified by nOe experiments).

**General procedure 3D: Formation of spirocyclic syn-oxindoles**

To the α-diazocarbonyl compound (1 equiv.) and Rh$_2$oct$_4$ (2 mol%) in a flask open to air was added CHCl$_3$ (20 mL/mmol). The mixture was stirred at RT for 1–5 h then concentrated *in vacuo*. The crude α,β-dicarbonyl product was then dissolved in THF (10 mL/mmol) and TFA (3 equiv.) was added. The mixture was stirred at RT for 4 h then concentrated *in vacuo* and purified by column chromatography to afford the spirocyclic syn-oxindole.

**General procedure 3E: Formation of spirocyclic anti-oxindoles**

To the α-diazocarbonyl compound (1 equiv.) and Rh$_2$oct$_4$ (2 mol%) in a flask open to air was added CHCl$_3$ (20 mL/mmol). The mixture was stirred at RT for 1–5 h then concentrated *in vacuo*. The crude α,β-dicarbonyl product was then dissolved in THF (10 mL/mmol) and cooled to −78 °C, t-BuOK (3 equiv.) was added in one portion and the mixture was stirred at −78 °C for 1 h then at RT for a further 1 h. The reaction was quenched with the addition of silica gel (10 g/g) and the suspension was filtered, washing with MeOH. The obtained methanolic solution was concentrated *in vacuo* and purified by column chromatography to afford the spirocyclic anti-oxindole.
General procedure 3F: Pd(II)-catalysed indole annulation

To the α-diazocarbonyl compound (1 equiv.) and Pd(MeCN)₄(BF₄)₂ (5 mol%) under argon was added CHCl₃ (10 mL/mmol). The mixture was stirred at RT under argon for 16 h then concentrated in vacuo and purified by column chromatography to afford the C-2 annulated indole product.

General procedure 3G: Cu(II)-catalysed carbazole formation

To the α-diazocarbonyl compound (1 equiv.) and Cu(OTf)₂ (20 mol%) under argon was added CHCl₃ (20 mL/mmol). The mixture was stirred at RT under argon for 1 h then at 50 °C under oxygen for 23 h. The mixture was then concentrated in vacuo and purified by column chromatography to afford the carbazole product.

General procedure 3H: Silica-promoted indole annulation

To the α-diazocarbonyl compound (1 equiv.) and silica gel (1 g/g) was added CH₂Cl₂ (10 mL/mmol). The mixture was stirred at RT for 24 h then concentrated in vacuo and purified by column chromatography to afford the indole product.
5.2.3 Chapter 4

General procedure 4A: pyridine-ynone formation

![Chemical structure diagram]

Based on a modified literature procedure. To a solution of DIPA (2.1 mmol) in THF (15 mL) at 0 °C under argon was added n-BuLi (0.85 mL, 2.1 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C before the 2-alkylpyridine (1.0 mmol) was added dropwise. After stirring at −78 °C for 30 min the methyl propiolate ester (1.05 mmol, neat or in THF) was added and the mixture was stirred at −78 °C for a further 30 min. The reaction was then quenched at −78 °C with water (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were dried (MgSO₄), concentrated *in vacuo* and purified by column chromatography to afford the pyridine-ynone product.

General procedure 4B: pyridine-ynone cyclisations

![Chemical structure diagram]

To a solution of aryl-ynone (1 equiv.) in DCE (5 mL/mmol) and EtOH (5 mL/mmol) at RT was added AgNO₃ (2 mol%). The reaction mixture was stirred at RT until completion was observed by TLC then concentrated *in vacuo*. The crude product was dissolved in CH₂Cl₂ and purified by column chromatography (typically 5 → 10% MeOH in EtOAc) to afford the cyclised compound.
5.3 Experimental for Chapter 2

2-(1H-Indol-3-yl)-N-methoxy-N-methylacetamide (81a)

Synthesised using general procedure 2A with indole-3-acetic acid (500 mg, 2.85 mmol), T3P 50% in EtOAc (2.72 g, 4.28 mmol), DIPEA (1.49 mL, 8.55 mmol) and MeNHOMe·HCl (306 mg, 3.14 mmol) in CH₂Cl₂ (7.5 mL). Afforded the title compound 81a (623 mg, 100%) without further purification as a pale brown solid, mp 122–124 °C (lit. 134 122–124 °C); δ_H (400 MHz, CDCl₃) 3.22 (3H, s, H-12), 3.67 (3H, s, H-13), 3.92 (2H, s, H-10), 7.09–7.21 (3H, m, H-3/4/8), 7.34 (1H, d, J = 8.0 Hz, H-5), 7.65 (1H, d, J = 8.0 Hz, H-2), 8.18 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 29.1 (CH₂, C-10), 32.5 (CH₃, C-12), 61.4 (CH₃, C-13), 109.1 (C, C-9), 111.1 (CH, C-5), 118.8 (CH, C-2), 119.5 (CH, C-3), 122.0 (CH, C-4), 123.1 (CH, C-8), 127.6 (C, C-1), 136.2 (C, C-6), 173.3 (C, C-11).

Lab notebook reference: MJJ/1/12

Spectroscopic data matched those reported in the literature.¹³⁴

3-(1H-Indol-3-yl)-N-methoxy-N-methylpropanamide (81b)

Synthesised using general procedure 2A with indole-3-propionic acid (500 mg, 2.64 mmol), T3P (2.52 g, 3.96 mmol, 50% wt. in EtOAc), DIPEA (1.38 mL, 7.92 mmol) and MeNHOMe·HCl (283 mg, 2.90 mmol) in CH₂Cl₂ (7 mL). Afforded the title compound 81b (594 mg, 97%) without further purification as a yellow oil; ν_max (cm⁻¹) 3410, 3300, 2936, 1642, 1458, 743; δ_H (400 MHz, CDCl₃) 2.85 (2H, t, J = 7.5 Hz, H-11), 3.14 (2H, t, J = 7.5 Hz, H-10), 3.20 (3H, s, H-13), 3.60 (3H, s, H-14), 7.05 (1H, d, J = 2.5 Hz, H-8), 7.13 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H-3), 7.20 (1H, ddd, J = 7.5, 7.5, 1.5 Hz, H-4), 7.37 (1H, ddd, J = 7.5, 1.0, 1.0 Hz, H-5), 7.64 (1H, dd, J = 7.5, 1.5, 1.0 Hz, H-2), 8.09 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 20.2 (CH₂, C-10/11), 32.0 (CH₃, C-13), 32.6 (CH₂, C-10/11), 61.0 (CH₃, C-14), 111.1 (CH, C-5), 114.9 (C, C-9), 118.5 (CH, C-2/3/4), 118.9 (CH, C-2/3/4), 121.6 (CH, C-2/3/4), 127.6 (C, C-1), 136.2 (C, C-6), 173.3 (C, C-11).
121.7 (CH, C-8), 127.1 (C, C-1), 136.2 (C, C-6), 174.2 (C, C-12); HRMS (ESI⁺): Found: 255.1095; C₁₃H₁₀N₂O₂ (M⁺Na requiring 255.1104 (3.6 ppm error), Found: 233.1278; C₁₃H₁₂N₂O₂ (MH⁺) Requires 233.1285 (2.7 ppm error).

Lab notebook reference: MJJ1/70

4-(1H-Indol-3-yl)-N-methoxy-N-methylbutanamide (81c)

Synthesised using general procedure 2A with indole-3-butyric acid (500 mg, 2.46 mmol), T3P (2.52 g, 3.96 mmol, 50% wt. in EtOAc), DIPEA (1.38 mL, 7.92 mmol) and MeNHOMe·HCl (283 mg, 2.90 mmol) in CH₂Cl₂ (7 mL). Afforded the title compound 81c (559 mg, 92%) without further purification as a yellow oil; ν_max (cm⁻¹) 3301, 2936, 1643, 1458, 995, 743; δ_H (400 MHz, CDCl₃) 2.08 (2H, tt, J = 7.5, 7.0 Hz, H-11), 2.52 (2H, t, J = 7.0 Hz, H-12), 2.84 (2H, td, J = 7.5, 1.0 Hz, H-10), 3.19 (3H, s, H-14), 3.62 (3H, s, H-15), 7.01–7.03 (1H, m, H-8), 7.09–7.14 (1H, m, H-3), 7.16–7.22 (1H, m, H-4), 7.36 (1H, ddd, J = 8.0, 1.0, 1.0 Hz, H-5), 7.64 (1H, d, J = 8.0 Hz, H-2), 8.00 (1H, br s, H-7).

Lab notebook reference: MJJ1/60

Spectroscopic data matched those reported in the literature.¹³⁵

N-Methoxy-N-methyl-2-(2-methyl-1H-indol-3-yl)acetamide (81d)

Synthesised using general procedure 2A with 2-methyl-3-indoleacetic acid (1.00 g, 5.29 mmol), T3P (5.05 g, 7.94 mmol, 50% wt. in EtOAc), DIPEA (2.76 mL, 15.9 mmol) and MeNHOMe·HCl (567 mg, 5.82 mmol) in CH₂Cl₂ (13 mL). Afforded the title compound 81d (1.21 g, 98%) without further purification as a pale brown solid, mp 85–87 °C; ν_max (cm⁻¹) 3398, 3300, 2935, 1639, 1462, 1178, 1008, 742; δ_H (400 MHz, CDCl₃) 2.30 (3H, s, H-9), 3.21 (3H, s, H-13), 3.62 (3H, s, H-14), 3.85 (2H, s, H-11), 7.05–7.13 (2H, m, H-3,4), 7.14–7.21 (1H, m, H-5), 7.55–7.62 (1H, m, H-2), 8.17 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 11.6 (CH₃,
C-9), 28.6 (CH₂, C-11), 32.2 (CH₃, C-13), 61.1 (CH₃, C-14), 104.5 (C, C-10), 110.2 (CH, C-5), 118.1 (CH, C-2), 119.2 (CH, C-3/4), 120.8 (CH, C-3/4), 128.6 (C, C-1), 132.8 (C, C-8), 135.1 (C, C-6), 172.9 (C, C-12); HRMS (ESI⁺): Found: 255.1104; C₁₃H₁₆N₂NaO₂ (MNa⁺) Requires 255.1104 (−0.1 ppm error), Found: 233.1288; C₁₃H₁₇N₂O₂ (MH⁺) Requires 233.1285 (−1.6 ppm error).

Lab notebook reference: MJJ3/43

N-Methoxy-N-methyl-2-(1-methyl-1H-indol-3-yl)acetamide (81e)

Synthesised using general procedure 2A with 1-methyl-3-indoleacetic acid (2.00 g, 10.6 mmol), T3P (10.1 g, 15.9 mmol, 50% wt. in EtOAc), DIPEA (5.54 mL, 31.8 mmol) and MeNHOMe·HCl (1.14 g, 11.7 mmol) in CH₂Cl₂ (27 mL). Afforded the title compound 81e (2.32 g, 94%) without further purification as a brown oil; ν max (cm⁻¹) 2936, 1659, 1473, 1374, 1001, 741; δH (400 MHz, CDCl₃) 3.22 (3H, s, H-12), 3.69 (3H, s, H-13), 3.77 (3H, s, H-7), 3.91 (2H, br s, H-10), 7.08 (1H, s, H-8), 7.10–7.15 (1H, m, H-3), 7.20–7.25 (1H, m, H-4), 7.28–7.32 (1H, m, H-5), 7.63–7.67 (1H, m, H-2); δC (100 MHz, CDCl₃) 28.6 (CH₂, C-10), 32.1 (CH₃, C-12), 32.5 (CH₂, C-7), 61.2 (CH₃, C-13), 107.2 (C, C-9), 109.0 (CH, C-5), 118.7 (CH, C-3/2), 118.8 (CH, C-3/2), 121.4 (CH, C-4), 127.6 (CH, C-8), 127.7 (C, C-1), 136.6 (C, C-6), 172.7 (C, C-11); HRMS (ESI⁺): Found: 255.1107; C₁₃H₁₆N₂NaO₂ (MNa⁺) Requires 255.1104 (−1.2 ppm error), Found: 233.1288; C₁₃H₁₇N₂O₂ (MH⁺) Requires 233.1285 (−1.6 ppm error).

Lab notebook reference: MJJ1/84

2-(5-Bromo-1H-indol-3-yl)-N-methoxy-N-methylacetamide (81f)

Synthesised using general procedure 2A with 5-bromoindole-3-acetic acid (1.00 g, 3.94 mmol), T3P (3.76 g, 5.91 mmol, 50% wt. in EtOAc), DIPEA (2.06 mL, 11.82 mmol) and
MeNHOMe·HCl (422 mg, 4.33 mmol) in CH$_2$Cl$_2$ (10 mL). Afforded the title compound 81f (1.17 g, 100%) without further purification as a yellow solid, mp 98–100 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3279, 1646, 1459, 1386, 1011, 1001, 883, 793; $\delta_h$ (400 MHz, CDCl$_3$) 3.24 (3H, s, H-12), 3.71 (3H, s, H-13), 3.87 (2H, br s, H-10), 7.18 (1H, d, $J = 2.5$ Hz, H-8), 7.21 (1H, d, $J = 8.5$ Hz, H-5), 7.26 (1H, dd, $J = 8.5, 2.0$ Hz, H-4), 7.75–7.78 (1H, m, H-2), 8.24 (1H, br s, H-7); $\delta_c$ (100 MHz, CDCl$_3$) 28.6 (CH$_2$, C-10), 32.3 (CH$_3$, C-12), 61.4 (CH$_3$, C-13), 108.2 (C, C-9), 112.6 (C, C-3), 112.7 (CH, C-5), 121.2 (CH, C-2), 124.6 (CH, C-4/8), 124.7 (CH, C-4/8), 129.1 (C, C-1), 134.7 (C, C-6), 172.6 (C, C-11); HRMS (ESI$^+$): Found: 319.0048; C$_{12}$H$_{13}$BrN$_2$NaO$_2$ (MNa$^+$) Requires 319.0053 (1.3 ppm error), Found: 297.0234; C$_{12}$H$_{14}$Br$_2$N$_2$O$_2$ (MH$^+$) Requires 297.0233 (−0.1 ppm error).

Lab notebook reference: MJJ3/38

2-(1H-Indol-3-yl)-N-methoxy-N-methyl-3-phenylpropanamide (81g)

Synthesised according to a modified literature procedure.$^{136}$ To solution of DIPA (3.20 mL, 22.8 mmol) in THF (11.5 mL) at a 0 °C under argon was added n-BuLi (9.12 mL, 22.8 mmol, 2.5M in hexanes) dropwise. The solution was stirred for 15 min before being cooled to −10 °C. Indole-3-acetic acid (1.00 g, 5.71 mmol) in THF (5 mL) was added dropwise to the solution, which was stirred at −10 °C for 2 h. Benzyl chloride (1.45 mL, 12.6 mmol) was then added dropwise and the mixture was allowed to warm to RT and stirred for 18 h. The reaction mixture was cooled to −10 °C and quenched with water (50 mL). The mixture was then partially concentrated in vacuo to remove the majority of the THF. The mixture was partitioned between toluene (50 mL) and water (30 mL), the aqueous was separated and the organic phase was washed with water (30 mL). The aqueous phases were combined, acidified to pH 1 with 10% HCl$_{aq}$ and extracted with toluene (5 × 60 mL). The combined organics were washed with water until the aqueous phase was neutral and then concentrated in vacuo to afford a crude pale brown solid (1.33 g). The crude material was dissolved in CH$_2$Cl$_2$ (14 mL), to which MeNHOMe·HCl (612 mg, 6.28 mmol), DIPEA (2.98 mL, 17.1 mmol) and T3P (5.45 g, 8.57 mmol, 50% wt. in EtOAc) were added successively. The mixture was stirred for 2.5 h at RT. The reaction mixture was poured into water (30 mL) and the organics were collected.
The aqueous was extracted with EtOAc (2 × 30 mL). The organics were combined, washed with 10% HCl (aq) (2 × 20 mL), 2 M NaOH (aq) (20 mL), brine (20 mL) then dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the title compound 81g (1.32 g, 75%) as a pale brown solid, mp 139–141 °C; v max (cm⁻¹) 3422, 3288, 2936, 1637, 1455, 985, 742, 700; δH (400 MHz, CDCl₃) 3.14 (3H, s, H-12), 3.15 (1H, dd, J = 13.5, 5.5 Hz, H-14a), 3.29 (3H, br s, H-13), 3.54 (1H, dd, J = 13.5, 10.0 Hz, H-14b), 4.68–4.74 (1H, m, H-10), 7.12–7.32 (8H, m, H-3,4,8,16,17,18), 7.36–7.40 (1H, m, H-5), 7.77 (1H, d, J = 8.0, H-2), 8.35 (1H, br s, H-7); δC (100 MHz, CDCl₃) 32.1 (CH₃, C-12), 39.8 (CH₂, C-14), 40.6 (CH, C-10), 61.2 (CH₂, C-13), 111.2 (CH, C-5), 114.6 (C, C-9), 118.9 (CH, C-2/3/4/18), 119.5 (CH, C-2/3/4/18), 122.0 (CH, C-2/3/4/18), 122.6 (CH, C-2/3/4/18), 126.1 (CH, C-8), 126.5 (C, C-1), 128.2 (CH, C-16/17), 129.1 (CH, C-16/17), 136.0 (C, C-6), 140.4 (C, C-15), 174.5 (C, C-11); HRMS (ESI⁺): Found: 331.1418; C₁₉H₂₀N₂NaO₂ (MNa⁺) Requires 331.1417 (−0.2 ppm error), Found: 309.1594; C₁₉H₂₁N₂O₂ (MH⁺) Requires 309.1598 (1.2 ppm error).

Lab notebook reference: MJJ4/70

N-Methoxy-N-methyl-2-(2-phenyl-1H-indol-3-yl)acetamide (81h)

To a dry three-neck flask was charged indole 93 (490 mg, 1.65 mmol), phenylboronic acid (262 mg, 2.15 mmol), LiCl (140 mg, 3.30 mmol), Na₂CO₃ (438 mg, 4.13 mmol), toluene (3.6 mL), EtOH (3.6 mL) and water (2.5 mL). The mixture was degassed with vacuum/argon 3 times. Pd(PPh₃)₄ (95 mg, 82.5 µmol) was added to the mixture, which was then stirred for 16 h at 80 °C. The reaction mixture was cooled to RT then poured into water (20 mL), the aqueous was extracted with EtOAc (3 × 20 mL). The organics were combined, washed with water (2 × 10 mL), brine (2 × 10 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) to afford the title compound 81h (400 mg, 82%) as a pale yellow foam, mp 53–55 °C; v max (cm⁻¹) 3289, 2963, 1644, 1458, 1178, 1000, 769, 740, 700; δH (400 MHz, CDCl₃) 3.21 (3H, s, H-16), 3.55 (3H, s, H-17), 4.03 (2H, s, H-14), 7.06–7.22 (2H, m, H-3,4), 7.28–7.33 (1H, m, H-5), 7.34–7.41 (1H, m, H-12) 7.42–7.49 (2H, m, H-11), 7.57–7.63 (2H, m, H-10), 7.66–7.71 (1H, m, H-2), 8.36 (1H, br s, H-7); δC (100 MHz, CDCl₃) 28.9 (CH₂, C-14), 32.4 (CH₃, C-16), 123
61.0 (CH₃, C-17), 106.0 (C, C-13), 110.9 (CH, C-5), 119.2 (CH, C-2/3/4), 119.8 (CH, C-2/3/4), 122.3 (CH, C-2/3/4), 127.7 (CH, C-12), 128.2 (CH, C-10/11), 128.7 (CH, C-10/11), 129.1 (C, C-1/8/9), 132.8 (C, C-1/8/9), 135.8 (C, C-1/8/9), 136.1 (C, C-6), 172.9 (C, C-15);

HRMS (ESI⁺): Found: 317.1249; C₁₈H₁₈N₂NaO₂ (MNa⁺) Requires 317.1260 (3.7 ppm error), Found: 295.1434; C₁₈H₁₆N₂O₂ (MH⁺) Requires 295.1441 (2.3 ppm error).

Lab notebook reference: MJJ1/44

1-(1H-Indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one (83a)

Synthesised using general procedure 2B with 4-ethynylanisole (4.95 g, 37.4 mmol), THF (40 + 60 mL), Weinreb 81a (2.72 g, 12.5 mmol) and n-BuLi (12.5 mL, 31.3 mmol, 2.5 M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the title compound 83a (2.93 g, 81%) as a pale brown solid, mp 70–72 °C; v_max (cm⁻¹) 3411, 2196, 1658, 1602, 1509, 1172, 1082, 834, 744; δ_H (400 MHz, CDCl₃) 3.82 (3H, s, H-18), 4.08 (2H, d, J = 1.0 Hz, H-10), 6.80–6.85 (2H, m, H-16), 7.14–7.20 (1H, m, H-3), 7.21–7.27 (2H, m, H-4,8), 7.28–7.33 (2H, m, H-15), 7.38–7.42 (1H, m, H-5), 7.66–7.71 (1H, m, H-2), 8.18 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 41.8 (CH₂, C-10), 55.3 (CH₃, C-18), 87.9 (C, C-12), 93.3 (C, C-13), 107.8 (C, C-9), 111.3 (CH, C-5), 111.6 (C, C-14), 114.2 (2CH, C-16), 118.9 (CH, C-2/3/4), 119.7 (CH, C-2/3/4), 122.2 (CH, C-2/3/4), 123.7 (CH, C-8), 127.5 (C, C-1), 135.1 (2CH, C-15), 136.1 (C, C-6), 161.5 (C, C-17), 185.7 (C, C-11); HRMS (ESI⁺): Found: 312.0981; C₁₉H₁₇NNaO₂ (MNa⁺) Requires 312.0995 (4.4 ppm error), Found: 290.1168; C₁₉H₁₆NO₂ (MH⁺) Requires 290.1176 (2.6 ppm error).

Lab notebook reference: MJJ1/92
1-(1H-Indol-3-yl)-4-phenylbut-3-yn-2-one (83b)

Synthesised using general procedure 2B with phenylacetylene (0.75 mL, 6.87 mmol), THF (7 + 21 mL), Weinreb 81a (500 mg, 2.29 mmol) and n-BuLi (3.00 mL, 5.73 mmol, 1.89M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the title compound 83b (543 mg, 91%) as a brown solid, mp 90–92 °C; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3410, 2202, 1662, 1084, 743; \( \delta_H \) (400 MHz, CDCl\(_3\)) 4.08 (2H, s, H-10), 7.13–7.19 (1H, m, H-3), 7.20–7.26 (2H, m, H-4,8), 7.27–7.44 (6H, m, H-5,15,16,17) 7.67 (1H, br d, \( J = 8.0 \) Hz, H-2), 8.16 (1H, br s, H-7); \( \delta_C \) (100 MHz, CDCl\(_3\)) 42.0 (CH\(_2\), C-10), 88.0 (C, C-12), 92.1 (C, C-13), 107.8 (C, C-9), 111.3 (CH, C-5), 118.9 (CH, C-2/3/4), 119.8 (CH, C-2/3/4), 119.9 (C, C-14), 122.3 (C, C-2/3/4), 123.7 (CH, C-8), 127.7 (C, C-1), 128.5 (2CH, C-16), 130.6 (CH, C-17), 133.1 (2CH, C-15), 136.4 (C, C-6), 186.1 (C, C-11); HRMS (ESI\(^+\)): Found: 282.0881; \( \text{C}_{18}\text{H}_{13}\text{NNaO} \) (M\(^+\)) Requires 282.0889 (2.8 ppm error), Found: 260.1066; \( \text{C}_{18}\text{H}_{14}\text{NO} \) (MH\(^+\)) Requires 260.1070 (1.6 ppm error).

Lab notebook reference: MJJ/1/5

4-[4-(Dimethylamino)phenyl]-1-(1H-indol-3-yl)but-3-yn-2-one (83c)

Synthesised using general procedure 2B with 4-ethynyl-\( N,N \)-dimethylaniline (998 mg, 6.87 mmol), THF (7 + 21 mL), Weinreb 81a (500 mg, 2.29 mmol) and n-BuLi (2.29 mL, 5.73 mmol, 2.5 M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then \( \text{CH}_2\text{Cl}_2 \)) afforded the title compound 83c (624 mg, 90%) as a yellow solid, mp 157–159 °C; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2192, 2149, 1642, 1597, 1526, 1377, 1093; \( \delta_H \) (400 MHz, DMSO-d\(_6\)) 2.95 (6H, s, H-18), 4.00 (2H, s, H-10), 6.61–6.68 (2H, m, H-16), 6.99–7.05 (1H, ddd, \( J = 7.5, 7.5, 1.0 \) Hz, H-3), 7.07–7.14 (1H, ddd \( J = 7.5, 7.5, 1.0 \) Hz, H-4), 7.19–7.25 (2H, m, H-15), 7.34 (1H, d, \( J = 2.0 \) Hz, H-8), 7.39 (1H, d, \( J = 8.0 \) Hz, H-5), 7.56 (1H, d, \( J = 8.0 \) Hz, H-2) 11.05 (1H, br s, H-7); \( \delta_C \) (100 MHz, DMSO-d\(_6\)) 41.6 (CH\(_2\), C-10), 75.3 (CH\(_3\), C-18), 88.7 (C, C-12), 95.4 (C, C-
13), 103.9 (C, C-9), 106.7 (C, C-14), 111.5 (CH, C-5), 111.7 (2CH, C-16), 118.6 (CH, C-2/3), 121.1 (CH, C-2/3), 124.7 (CH, C-4), 127.4 (C, C-1), 132.2 (CH, C-8), 134.7 (2CH, C-15), 136.2 (C, C-6), 151.7 (C, C-17), 185.0 (C, C-11); HRMS (ESI⁺): Found: 325.1294; C₂₀H₁₈N₂NaO (MNa⁺) Requires 325.1311 (5.5 ppm error), Found: 303.1481; C₂₀H₁₉N₂O (MH⁺) Requires 303.1492 (3.5 ppm error).

Lab notebook reference: MJJ1/7

4-(4-Fluorophenyl)-1-(1H-indol-3-yl)but-3-yn-2-one (83d)

![Chemical Structure of 83d]

Synthesised using **general procedure 2A** with Weinreb 81a (2.00 g, 9.16 mmol), 1-ethynyl-4-fluorobenzene (3.15 mL, 27.5 mmol), n-BuLi (14.3 mL, 22.9 mmol, 1.6 M in hexanes) and THF (30 mL + 80 mL). Purification by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) afforded the **title compound 83d** (2.06 g, 81%) as an orange solid, mp 131–133 °C; \(ν_{\text{max}}\) (cm⁻¹) 3408, 2203, 1656, 1598, 1505, 1232, 1094, 837, 742; \(δ_H\) (400 MHz, CDCl₃) 4.09 (2H, s, H-10), 6.96–7.05 (2H, dd, J = 8.5, 8.5 Hz, H-16), 7.15–7.20 (1H, dd, J = 7.5, 7.5 Hz, H-3), 7.21–7.27 (2H, m, H-4,8), 7.29–7.35 (2H, m, H-15), 7.41 (1H, d, J = 7.5 Hz, H-5), 7.68 (1H, d, J = 7.5 Hz, H-2), 8.24 (1H, br s, H-7); \(δ_C\) (100 MHz, CDCl₃) 41.9 (CH₂, C-10), 87.9 (C, C-12), 91.1 (C, C-13), 107.6 (C, C-9), 111.3 (CH, C-5), 115.98 (C, d, J = 4.0 Hz, C-14), 116.0 (2CH, d, J = 22 Hz, C-16), 118.9 (CH, C-2), 119.9 (CH, C-3/4/8), 122.3 (CH, C-3/4/8), 123.7 (CH, C-3/4/8), 127.5 (C, C-1), 135.4 (2CH, d, J = 8.5 Hz, C-15), 136.1 (C, C-6), 163.9 (C, d, J = 254 Hz, C-17), 185.6 (C, C-11); \(δ_F\) (376 MHz, CDCl₃) –106.0–106.2 (1F, m); HRMS (ESI⁺): Found: 300.0795; C₁₉H₁₂FNNaO (MNa⁺) Requires 300.0795 (0.2 ppm error), Found: 278.0971; C₁₉H₁₃FNO (MH⁺) Requires 278.0976 (1.8 ppm error).

Lab notebook reference: BSC
1-Chloro-4-(2,2-dibromovinyl)benzene (95)

To a suspension of CBr₄ (4.72 g, 14.22 mmol) in CH₂Cl₂ (11 mL) at 0 °C was added PPh₃ (7.46 g, 28.4 mmol) in CH₂Cl₂ (11 mL). The mixture was stirred for 30 min at 0 °C. 4-Chlorobenzaldehyde (1.00 g, 7.11 mmol) and Et₃N (7.9 mL, 56.9 mmol) in CH₂Cl₂ (4 mL) was added to the reaction mixture, which was stirred for 3 h at RT. The reaction mixture was poured into water (30 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The organics were combined, washed with sat. NaHCO₃ (aq) (30 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (4:1 Petrol:EtOAc) to afford the title compound 95 (1.79 g, 85%) as a pale yellow oil, νₛₒₐ₅ (cm⁻¹) 1591, 1488, 1098, 1013, 872, 709, 782, 506; δₜₐₓ (400 MHz, CDCl₃) 7.35 (2H, d, J = 8.5 Hz), 7.44 (1H, s), 7.48 (2H, d, J = 8.5 Hz); δₛ (100 MHz, CDCl₃) 90.4, 128.6, 129.6, 133.6, 134.3, 135.6.
Lab notebook reference: MJJ1/13
Spectroscopic data matched those reported in the literature.¹³⁷

4-(4-Chlorophenyl)-1-(1H-indol-3-yl)but-3-yn-2-one (83e)

To a solution of 95 (1.68 g, 5.66 mmol) in THF (30 mL) at −78 °C under argon was added n-BuLi (4.16 mL, 10.4 mmol, 2.5 M in hexanes) dropwise. The mixture was warmed to 0 °C and stirred for 30 min. The mixture was cooled to −78 °C and transferred via cannula to a −78 °C solution of Weinreb 81a (413 mg, 1.89 mmol) in THF (5 mL). Upon complete transfer the reaction mixture was allowed to warm to RT and stirred for 30 min. The reaction mixture was poured into water (40 mL) and extracted with CH₂Cl₂ (3 × 40 mL). The organics were combined, washed with sat. NaHCO₃ (aq) (40 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (9:1 Petrol:EtOAc) then 7:3 Petrol:EtOAc to afford the title compound 83e (363 mg, 66%) as a brown solid, mp 127–129 °C; νₛₒ₅ (cm⁻¹) 3408, 2202, 1661, 1489, 1088, 1014, 829, 742; δₛ (400 MHz, CDCl₃) 4.09 (2H, s, H-10), 7.15–7.20 (1H, m, H-3), 7.22–7.32 (6H, m, H-4,8,15,16), 7.42 (1H, ddd, J = 8.0, 1.0, 1.0 Hz, H-5), 7.67 (1H, m, H-2), 8.20 (1H, br s, H-7); δₛ (100 MHz, CDCl₃) 41.9
(CH$_2$, C-10), 88.6 (C, C-12), 90.7 (C, C-13), 107.5 (C, C-9), 111.3 (CH, C-5), 118.3 (C, C-14), 118.9 (CH, C-2), 119.9 (CH, C-3), 122.3 (CH, C-4), 123.8 (CH, C-8), 127.4 (C, C-1), 128.9 (2CH, C-16), 134.2 (2CH, C-15), 136.1 (C, C-6/17), 137.0 (C, C-6/17), 185.5 (C, C-11); HRMS (ESI$^+$): Found: 316.0489; C$_{18}$H$_{12}$ClNNaO (MNa$^+$) Requires 316.0500 (3.5 ppm error), Found: 294.0676; C$_{18}$H$_{13}$ClNO (MH$^+$) Requires 294.0680 (1.5 ppm error).

Lab notebook reference: MJJ1/19

4-(4-Bromophenyl)-1-(1H-indol-3-yl)but-3-yn-2-one (83f)

Synthesised using general procedure 2B with 4-bromophenylacetylene (0.75 mL, 6.87 mmol), THF (6 + 18 mL), Weinreb amide 81a (421 mg, 1.93 mmol) and n-BuLi (1.93 mL, 4.83 mmol, 2.5M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) and recrystallisation from hexanes:EtOAc afforded the title compound 83f (445 mg, 68%) as a yellow solid, mp 135–136 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3409, 2202, 1660, 1485, 1068, 1011, 824, 742; $\delta$H (400 MHz, CDCl$_3$) 4.09 (2H, d, $J = 1.0$ Hz, H-10), 7.13–7.29 (5H, m, H-3,4,8,15), 7.41 (1H, br d, $J = 8.0$ Hz, H-5) 7.43–7.49 (2H, m, H-16), 6.7 (1H, br d, $J = 8.0$ Hz, H-2), 8.23 (1H, br s, H-7); $\delta$C (100 MHz, CDCl$_3$) 41.9 (CH$_2$, C-10), 88.7 (C, C-12), 90.7 (C, C-13), 107.5 (C, C-9), 111.3 (CH, C-5), 118.8 (C, C-14), 118.9 (CH, C-2), 119.9 (CH, C-3/4/8), 122.3 (CH, C-3/4/8), 123.7 (CH, C-3/4/8), 125.4 (C, C-17), 127.4 (C, C-1), 131.9 (2CH, C-16), 134.3 (2CH, C-15), 136.1 (C, C-6), 185.4 (C, C-11); HRMS (ESI$^+$): Found: 359.9993; C$_{18}$H$_{12}$BrNNaO (MNa$^+$) Requires 359.9994 (0.4 ppm error), Found: 338.0188; C$_{18}$H$_{13}$BrNO (MH$^+$) Requires 338.0175 (~3.9 ppm error).

Lab notebook reference: MJJ4/6
1-(1H-Indol-3-yl)pent-3-yn-2-one (83g)

To a −78 °C solution of DIPA (3.06 mL, 21.8 mmol) in THF (22 mL) was added dropwise n-BuLi (8.72 mL, 21.8 mmol, 2.5 M in hexanes). Upon complete addition the mixture was warmed to 0 °C and stirred for 30 min. The mixture was cooled to −78 °C before the dropwise addition of 1,2-dibromopropane (0.72 mL, 6.87 mmol). The mixture was warmed to 0 °C and stirred for 30 min. The mixture was cooled to −78 °C and transferred via cannula to a −78 °C solution of Weinreb 81a (500 mg, 2.29 mmol) in THF (23 mL). Upon complete transfer the reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. NH₄Cl (aq) (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried (MgSO₄), concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) to afford the *title compound* 83g (386 mg, 86%) as an orange oil; ν<sub>max</sub> (cm<sup>−1</sup>) 3409, 2217, 1665, 743; δ<sub>H</sub> (400 MHz, CDCl₃) 1.96 (3H, s, H-14), 3.98 (2H, d, J = 1.0 Hz, H-10), 7.12–7.18 (2H, m, H-3,8), 7.19–7.25 (1H, m, H-4), 7.38 (1H, d, J = 8.0 Hz, H-5), 7.60 (1H, dd, J = 8.0, 1.0 Hz, H-2), 8.17 (1H, br s, H-7); δ<sub>C</sub> (100 MHz, CDCl₃) 4.1 (CH₃, C-14), 42.0 (CH₂, C-10), 80.2 (C, C-12), 91.3 (C, C-13), 107.4 (C, C-9), 111.2 (CH, C-5), 118.7 (CH, C-2), 119.6 (CH, C-3), 122.1 (CH, C-4), 123.6 (CH, C-8), 127.2 (C, C-1), 136.1 (C, C-6), 185.7 (C, C-11); HRMS (ESI⁺): Found: 220.0733 (2.9 ppm error), Found: 198.0905; C₁₃H₁₂NNaO (MNa⁺) Requires 220.0726; C₁₃H₁₁NNO (MH⁺) Requires 198.0913 (4.4 ppm error).

Lab notebook reference: MJJ1/14

1-(1H-Indol-3-yl)oct-3-yn-2-one (83h)

Synthesised using *general procedure 2B* with 1-hexyne (0.79 mL, 6.87 mmol), THF (7 + 21 mL), Weinreb 81a (500 mg, 2.29 mmol) and n-BuLi (3.00 mL, 5.73 mmol, 1.89 in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded
the title compound 83h (450 mg, 82%) as a yellow solid, mp 59–61 °C; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3411, 2958, 2933, 2210, 1664, 1458, 741; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 0.86 (3H, t, \( J = 7.5 \) Hz, H-17), 1.25–1.36 (2H, m, H-16), 1.40–1.49 (2H, m, H-15), 2.28 (2H, t, \( J = 7.0 \) Hz, H-14), 3.97 (2H, d, \( J = 1.0 \) Hz, H-10), 7.12–7.17 (1H, m, H-3), 7.18–7.25 (2H, m, H-4,8), 7.39 (1H, br d, \( J = 8.0 \) Hz, H-5), 7.60 (1H, br d, \( J = 8.0 \) Hz, H-2), 8.12 (1H, br s, H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 13.4 (CH\(_3\), C-17), 18.6 (CH\(_2\), C-14), 21.8 (CH\(_2\), C-16), 29.5 (CH\(_2\), C-15), 42.0 (CH\(_2\), C-10), 80.9 (C, C-12), 95.8 (C, C-13), 107.6 (C, C-9), 111.2 (CH, C-5), 118.8 (CH, C-2), 119.6 (CH, C-3), 121.1 (CH, C-4), 123.6 (CH, C-8), 127.3 (C, C-1), 136.1 (C, C-6), 185.9 (C, C-11); HRMS (ESI\(^+\)): Found: 262.1209; C\(_{16}\)H\(_{17}\)NNaO (MNa\(^+\)) Requires 262.1202 (−2.6 ppm error), Found: 240.1386; C\(_{16}\)H\(_{18}\)NO (M\(^+\)) Requires 240.1383 (−1.5 ppm error).

Lab notebook reference: MJJ1/6

1-(1H-Indol-3-yl)-4-(thiophen-2-yl)but-3-yn-2-one (83i)

![Chemical structure of 1-(1H-Indol-3-yl)-4-(thiophen-2-yl)but-3-yn-2-one (83i)](image)

Synthesised using general procedure 2B with Weinreb 81a (306 mg, 1.40 mmol), 2-ethynylthiophene (0.40 mL, 4.21 mmol), n-BuLi (1.4 mL, 3.50 mmol, 2.5 M in hexanes) and THF (4 mL + 13 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 83i (252 mg, 68%) as a brown oil; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3405, 2178, 1651, 1215, 1091, 742, 714; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 4.07 (2H, s, H-10), 6.98 (1H, dd, \( J = 5.0, 3.5 \) Hz, H-16), 7.13–7.28 (4H, m, H-3,4,8,15), 7.37 (1H, d, \( J = 8.0 \) Hz, H-5), 7.42 (1H, dd, \( J = 5.0, 1.0 \) Hz, H-17), 7.66 (1H, d, \( J = 8.0 \) Hz, H-2), 8.23 (1H, br s, H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 41.7 (CH\(_2\), C-10), 86.2 (C, C-12), 92.6 (C, C-13), 107.4 (C, C-9), 111.3 (CH, C-5), 118.9 (CH, C-2), 119.6 (C, C-14), 119.8 (CH, C-3/4/8), 122.3 (CH, C-3/4/8), 123.7 (CH, C-3/4/8), 127.4 (C, C-1), 127.6 (CH, C-16), 131.7 (CH, C-17), 136.1 (C, C-6), 136.7 (CH, C-15), 185.2 (C, C-11); HRMS (ESI\(^+\)): Found: 288.0452; C\(_{16}\)H\(_{17}\)NNaOS (MNa\(^+\)) Requires 288.0454 (0.6 ppm error), Found: 266.0634; C\(_{16}\)H\(_{12}\)NO (M\(^+\)) Requires 266.0634 (−0.1 ppm error).

Lab notebook reference: MJJ4/84
4-(1H-Indol-3-yl)-1,5-diphenylpent-1-yn-3-one (83j)

Synthesised using general procedure 2A with Weinreb amide 81g (300 mg, 0.973 mmol), phenylacetylene (0.32 mL, 2.92 mmol), n-BuLi (0.97 mL, 2.43 mmol, 2.5 M in hexanes) and THF (3 + 9 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the title compound 83j (250 mg, 74%) as a yellow oil; ν\text{max} (cm\textsuperscript{-1}) 3413, 2195, 1653, 1489, 1456, 1099, 742, 688; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 3.29 (1H, dd, J = 14.0, 7.0 Hz, H-18a), 3.69 (1H, dd, J = 14.0, 8.0 Hz, H-18b), 4.49 (1H, dd, J = 8.0, 7.0 Hz, H-10), 7.12–7.33 (10H, m, ArH), 7.34–7.42 (4H, m, ArH), 7.75 (1H, d, J = 8.0 Hz, H-2), 8.23 (1H, br s, H-7); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 37.0 (CH\textsubscript{2}, C-18), 53.9 (CH, C-10), 87.8 (C, C-12), 92.1 (C, C-13), 111.4 (CH, C-5), 112.1 (C, C-9), 119.2 (CH, C-2/3/4/22), 119.85 (CH, C-2/3/4/22)), 119.92 (C, C-14), 122.3 (CH, C-2/3/4/22), 123.0 (CH, C-2/3/4/22), 126.3 (CH, C-8), 126.7 (C, C-1), 128.3 (2CH, C-15/16/20/21), 128.4 (2CH, C-15/16/20/21), 129.0 (2CH, C-15/16/20/21), 130.5 (CH, C-17), 132.9 (2CH, C-15/16/20/21), 136.2 (C, C-6), 139.4 (C, C-19), 187.1 (C, C-11); HRMS (ESI\textsuperscript{+}): Found: 372.1346; C\textsubscript{25}H\textsubscript{19}NNaO (MNa\textsuperscript{+}) Requires 372.1359 (3.6 ppm error), Found: 350.1538; C\textsubscript{25}H\textsubscript{20}NO (MH\textsuperscript{+}) Requires 350.1539 (0.3 ppm error).

Lab notebook reference: MJJ4/77

4-(1H-Indol-3-yl)-1-(4-methoxyphenyl)-5-phenylpent-1-yn-3-one (83k)

Synthesised using general procedure 2B with 4-ethynylanisole (0.83 mL, 6.42 mmol), THF (6.5 + 18 mL), Weinreb 81g (661 mg, 2.14 mmol) and n-BuLi (2.54 mL, 5.99 mmol, 2.36 M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 8:2
hexane:EtOAc) afforded the title compound 83k (267 mg, 33%) as a yellow solid, mp 150–152 °C; v_max (cm⁻¹) 3414, 2186, 1654, 1601, 1509, 1254, 743; δ_H (400 MHz, CDCl₃) 3.28 (1H, dd, J = 14.0, 7.0 Hz, H-19a), 3.68 (1H, dd, J = 14.0, 7.0 Hz, H-19b), 3.81 (3H, s, H-3), 4.47 (1H, t, J = 7.0 Hz, H-10), 6.79–6.84 (2H, m, H-16), 7.14–7.27 (9H, m, H-3,4,21,22,23), 7.31–7.35 (2H, m, H-15), 7.38 (1H, dt, J = 8.0, 1.0 Hz, H-5), 7.75 (1H, d, J = 8.0 Hz, H-2), 8.19 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 37.1 (CH₂, C-19), 53.8 (CH, C-10), 55.4 (CH₃, C-18), 87.7 (C, C-12), 93.2 (C, C-13), 111.3 (CH, C-5), 111.8 (C, C-9), 112.6 (C, C-14), 114.2 (2CH, C-16), 119.3 (CH, C-2/3/4/23), 119.8 (CH, C-2/3/4/23), 122.3 (CH, C-2/3/4/23), 122.9 (CH, C-2/3/4/23), 126.2 (CH, C-8), 126.8 (C, C-1), 128.3 (2CH, C-21/22), 129.0 (2CH, C-21/22), 135.0 (2CH, C-15), 136.2 (C, C-6), 139.5 (C, C-20), 161.5 (C, C-17), 187.1 (C, C-11); HRMS (ESI⁺): Found: 402.1451; C₂₆H₂₁NNaO₂ (MNa⁺) Requires 402.1465 (3.3 ppm error), Found: 380.1632; C₂₆H₂₂NO₂ (MH⁺) Requires 380.1645 (3.5 ppm error).

Lab notebook reference: MJJ1/63

4-(4-Methoxyphenyl)-1-(2-methyl-1H-indol-3-yl)but-3-yn-2-one (83l)

Synthesised using general procedure 2B with 4-ethynylanisole (0.84 mL, 6.45 mmol), THF (6.5 + 19.5 mL), Weinreb 81d (500 mg, 2.15 mmol) and n-BuLi (2.15 mL, 5.38 mmol, 2.5 M in hexanes). Purification by column chromatography (8:2 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the title compound 83l (502 mg, 77%) as a thick yellow oil; v_max (cm⁻¹) 3396, 2194, 1653, 1600, 1508, 1252, 78; δ_H (400 MHz, CDCl₃) 2.38 (3H, s, H-9), 3.77 (3H, s, H-19), 3.98 (2H, s, H-11), 6.75–6.82 (2H, m, H-17), 7.11–7.18 (2H, m, H-3,4), 7.20–7.29 (3H, m, H-5,16), 7.58–7.64 (1H, m, H-2), 8.15 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 11.6 (CH₃, C-9), 41.0 (CH₂, C-11), 55.2 (CH₃, C-19), 87.9 (C, C-13), 93.0 (C, C-14), 103.4 (C, C-10), 110.4 (CH, C-5), 111.5 (C, C-15), 114.1 (2CH, C-17), 118.0 (CH, C-2), 119.5 (CH, C-3/4), 121.1 (CH, C-3/4), 128.6 (C, C-1), 133.5 (CH, C-8), 135.0 (2CH, C-16), 135.2 (C, C-6), 161.4 (C, C-18), 185.5 (C, C-12); HRMS (ESI⁺): Found: 326.1152; C₂₀H₁₇NNaO₂ (MNa⁺) Requires 326.1151 (−0.1 ppm error), Found: 304.1332; C₂₀H₁₈NO₂ (MH⁺) Requires 304.1332 (−0.1 ppm error).

Lab notebook reference: MJJ3/44
4-(4-Methoxyphenyl)-1-(2-phenyl-1H-indol-3-yl)but-3-yn-2-one (83m)

Synthesised using general procedure 2B with 4-ethynylanisole (516 mg, 3.90 mmol), THF (4 + 12 mL), Weinreb 81h (384 mg, 1.30 mmol) and n-BuLi (1.30 mL, 3.25 mmol, 2.5 M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the title compound 83m (100 mg, 21%) as a yellow oil; \( \nu_{\text{max}} (\text{cm}^{-1}) \) 3362, 1255, 1655, 1509, 744; \( \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) \) 3.80 (3H, s, H-22), 4.16 (2H, s, H-14), 6.77–6.82 (2H, m, H-20), 7.17–7.28 (4H, m, H-3,4,19), 7.38–7.44 (2H, m, H-5,12) 7.46–7.53 (2H, m, H-11), 7.59–7.67 (2H, m, H-10), 7.70–7.74 (1H, m, H-2), 8.38 (1H, br s, H-7); \( \delta_{\text{C}} (100 \text{ MHz, CDCl}_3) \) 41.7 (CH, C-14), 55.5 (CH, C-22), 88.4 (C, C-16), 93.8 (C, C-17), 105.1 (C, C-13), 111.1 (C, C-18), 111.7 (CH, C-5), 114.3 (2CH, C-20), 119.5 (CH, C-2), 120.3 (CH, C-3/4), 122.7 (CH, C-3/4), 128.2 (3CH, C-12,10/11), 129.1 (2CH, C-10/11), 129.4 (C, C-9), 132.5 (C, C-1/8), 135.3 (2CH, C-19), 136.0 (C, C-1/8), 136.8 (C, C-6), 161.7 (C, C-21), 186.3 (C, C-15); HRMS (ESI\(^{+}\)): \( \text{Found: 388.1302} \); \( \text{C}_{25}\text{H}_{19}\text{NaO}_2 \text{(MNa}^+\text{)} \) Requires 388.1308 (1.6 ppm error), Found: 366.1491; \( \text{C}_{23}\text{H}_{20}\text{NO}_2 \text{(MH}^+\text{)} \) Requires 366.1489 (−0.5 ppm error).

Lab notebook reference: MJJ1/48

1-(5-Bromo-1H-indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one (83n)

Synthesised using general procedure 2B with 4-ethynylanisole (0.65 mL, 5.04 mmol), THF (5 + 15 mL), Weinreb 81f (500 mg, 1.68 mmol) and n-BuLi (1.70 mL, 4.20 mmol, 2.5 M in hexanes). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 83n (460 mg, 74%) as a yellow solid, mp 131–133 °C; \( \nu_{\text{max}} (\text{cm}^{-1}) \) 3414, 2195,
1655, 1601, 1509, 1255, 1170, 1095, 833; \( \delta_t (400 \text{ MHz, CDCl}_3) \) 3.82 (3H, s, H-18), 4.03 (2H, s, H-10), 6.83–6.88 (2H, m, H-16), 7.18 (1H, d, \( J = 2.5 \) Hz, H-8), 7.23 (1H, d, \( J = 8.5 \) Hz, H-5), 7.29 (1H, dd, \( J = 8.5, 2.0 \) Hz, H-4), 7.35–7.40 (2H, m, H-15), 7.83 (1H, d, \( J = 2.0 \) Hz, H-2); \( \delta_c (100 \text{ MHz, CDCl}_3) \) 41.7 (CH\(_2\), C-10), 55.4 (CH\(_3\), C-18), 87.9 (C, C-12), 93.7 (C, C-13), 107.5 (C, C-9), 111.4 (C, C-14), 112.8 (CH, C-5), 113.1 (C, C-3), 114.3 (2CH, C-16), 121.6 (CH, C-2), 124.9 (CH, C-4/8), 125.1 (CH, C-4/8), 129.2 (C, C-1), 134.8 (C, C-6), 135.2 (2CH, C-15), 161.7 (C, C-17), 185.2 (C, C-11); HRMS (ESI\(^+\)): Found: 390.0089; C\(_{19}\)H\(_{14}\)BrNNaO\(_2\) (MNa\(^+\)) Requires 390.0100 (2.8 ppm error), Found: 368.0275; C\(_{19}\)H\(_{15}\)BrNO\(_2\) (MH\(^+\)) Requires 368.0281 (1.5 ppm error).

Lab notebook reference: MJJ3/39

1-(1H-Indol-3-yl)-4-(trimethylsilyl)but-3-yn-2-one (83o)

![Diagram](image)

Synthesised using general procedure 2B with ethynyltrimethylsilane (0.95 mL, 6.87 mmol), THF (6 + 11 mL), Weinreb 81a (500 mg, 2.29 mmol) and \( n^-\text{BuLi} \) (2.29 mL, 5.73 mmol, 2.5 M in hexanes). Purification by column chromatography (15% EtOAc in hexane) afforded the title compound 83o (455 mg, 78%) as a brown oil; \( \nu_{\text{max}} (\text{cm}^{-1}) \) 3408, 1671, 1252, 1100, 847, 741; \( \delta_t (400 \text{ MHz, CDCl}_3) \) 0.18 (9H, s, H-14), 4.02 (2H, s, H-10), 7.12–7.18 (2H, m, H-3,8), 7.19–7.25 (1H, m, H-4), 7.36 (1H, d, \( J = 8.0 \) Hz, H-5), 7.62 (1H, dd, \( J = 8.0, 0.5 \) Hz, H-2), 8.25 (1H, br s, H-7); \( \delta_c (100 \text{ MHz, CDCl}_3) \) −0.9 (CH\(_3\), C-14), 41.8 (CH\(_2\), C-10), 99.3 (C, C-13), 102.0 (C, C-12), 107.1 (C, C-9), 111.2 (CH, C-5), 118.9 (CH, C-2/3), 119.7 (CH, C-2/3), 122.2 (CH, C-4), 123.7 (CH, C-8), 127.3 (C, C-1), 136.1 (C, C-6), 185.3 (C, C-11); HRMS (ESI\(^+\)): Found: 278.0974; C\(_{15}\)H\(_{17}\)BrNNaO\(_2\) (MNa\(^+\)) Requires 278.0972 (−0.7 ppm error), Found: 256.1149; C\(_{15}\)H\(_{18}\)NOSi (MH\(^+\)) Requires 256.1152 (1.3 ppm error).

Lab notebook reference: MJJ2/6
4-(4-Methoxyphenyl)-1-(1-methyl-1H-indol-3-yl)but-3-yn-2-one (83p)

Synthesised using general procedure 2B with 4-ethynylanisole (854 mg, 6.46 mmol), THF (6.5 + 19.5 mL), Weinreb 81e (499 mg, 2.15 mmol) and n-BuLi (2.28 mL, 5.38 mmol, 2.36 M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the title compound 83p (279 mg, 43%) as a yellow oil; νmax (cm⁻¹) 2197, 1660, 1602, 1509, 1254, 742; δH (400 MHz, CDCl₃) 3.80 (3H, s, H-7), 3.83 (3H, s, H-18), 4.07 (2H, d, J = 1.0 Hz, H-10), 6.81–6.86 (2H, m, H-16), 7.09 (1H, s, H-8) 7.14–7.19 (1H, m, H-3), 7.24–7.29 (1H, m, H-4), 7.30–7.36 (3H, m, H-5,15), 7.68 (1H, dt, J = 8.0, 1.0 Hz, H-2); δC (100 MHz, CDCl₃) 32.7 (CH₃, C-7), 41.7 (CH₂, C-10), 55.3 (CH₃, C-18), 88.0 (C, C-12), 93.0 (C, C-13), 106.1 (C, C-9), 109.3 (CH, C-5), 111.6 (C, C-14), 114.2 (2CH, C-16), 119.0 (CH, C-2/3), 119.2 (CH, C-2/3), 121.7 (CH, C-4), 127.9 (C, C-1), 128.2 (CH, C-8), 135.0 (2CH, C-15), 136.9 (C, C-6), 161.5 (C, C-17), 185.6 (C, C-11); HRMS (ESI⁺): Found: 326.1153; C₂₀H₁₇NNaO₂ (MNa⁺) Requires 326.1151 (−0.6 ppm error), Found: 304.1330; C₂₀H₁₈NO₂ (MH⁺) Requires 304.1332 (0.7 ppm error).

Lab notebook reference: MJJ1/86

5-(1H-Indol-3-yl)-1-(4-methoxyphenyl)pent-1-yn-3-one (83q)

Synthesised using general procedure 2B with 4-ethynylanisole (1.02 g, 7.68 mmol), THF (8 + 23 mL), Weinreb 81b (594 mg, 2.56 mmol) and n-BuLi (2.71 mL, 6.40 mmol, 2.36M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then EtOAc) afforded the title compound 83q (748 mg, 96%) as a yellow solid, mp 126–128 °C; νmax (cm⁻¹) 3406, 2190, 1658, 1601, 1509, 1254, 1172, 1094, 834, 744; δH (400 MHz, CDCl₃) 3.06–3.11 (2H, m, H-11), 3.20–3.26 (2H, m, H-10), 3.83 (3H, s, H-19), 6.87–6.92 (2H, m, H-17), 7.04–7.07 (1H, m, H-8), 7.12–7.18 (1H, m, H-3), 7.19–7.24 (1H, m, H-4), 7.38 (1H, d, J = 8.0 Hz, H-5), 7.47–7.52 (2H, m, H-16), 7.65 (1H, d, J = 8.0 Hz, H-2), 7.98 (1H, br s, H-7); δC (100 MHz,
CDCl₃) 19.8 (CH₃, C-10), 45.7 (CH₃, C-11), 55.4 (CH₃, C-19), 87.8 (C, C-13), 92.3 (C, C-14), 111.2 (CH, C-5), 111.7 (C, C-9), 114.3 (2CH, C-17), 114.7 (C, C-15), 118.6 (CH, C-2), 119.3 (CH, C-3), 121.6 (CH, C-8), 122.0 (CH, C-4), 127.1 (C, C-1), 135.1 (2CH, C-16), 136.3 (C, C-6), 161.6 (C, C-18), 187.7 (C, C-12); HRMS (ESI⁺): Found: 326.1149; C₂₀H₁₇NNaO₂ (MNa⁺) Requires 326.1151 (0.9 ppm error), Found: 304.1334; C₂₀H₁₈NO₂ (MH⁺) Requires 304.1332 (−0.6 ppm error).

Lab notebook reference: MJJ1/71

6-(1H-Indol-3-yl)-1-(4-methoxyphenyl)hex-1-yn-3-one (83r)

Synthesised using general procedure 2B with 4-ethynylanisole (0.93 mL, 7.17 mmol), THF (7 + 20 mL), Weinreb 81c (556 mg, 2.26 mmol) and n-BuLi (2.83 mL, 6.69 mmol, 2.36M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the title compound 83r (708 mg, 99%) as a pale brown solid, mp 110–112 °C; ν_max (cm⁻¹) 3411, 2943, 2191, 1656, 1601, 1509, 1253, 1095, 834, 743; δ_H (400 MHz, CDCl₃) 2.20 (2H, quin, J = 7.5 Hz, H-11), 2.75 (2H, t, J = 7.5 Hz, H-12), 2.88 (2H, J = 7.5 Hz, H-10), 3.85 (3H, s, H-20), 6.87–6.92 (2H, m, H-18), 7.01–7.03 (1H, m, H-8), 7.11–7.16 (1H, m, H-3), 7.19–7.24 (1H, m, H-4), 7.38 (1H, dt, J = 8.0, 1.0 Hz, H-5), 7.48–7.53 (2H, m, H-17), 7.65–7.68 (1H, m, H-2), 8.10 (1H, br s, H-7); δC (100 MHz, CDCl₃) 24.3 (CH₂, C-10/11), 24.6 (CH₂, C-10/11), 44.9 (CH₂, C-12), 55.3 (CH₃, C-20), 87.8 (C, C-14), 92.0 (C, C-15), 111.1 (CH, C-5), 111.6 (C, C-9), 114.3 (2CH, C-18), 115.4 (C, C-16), 118.8 (CH, C-2/3), 119.1 (CH, C2/3), 121.6 (CH, C4/8), 121.9 (CH, C4/8), 127.3 (C, C-1), 135.1 (2CH, C-17), 136.3 (C, C-6), 161.5 (C, C-19), 188.3 (C, C-13); HRMS (ESI⁺): Found: 340.1314; C₂₁H₁₉NNaO₂ (MNa⁺) Requires 340.1308 (−1.9 ppm error), Found: 318.1493; C₂₁H₁₈NNaO₂ (MH⁺) Requires 318.1489 (−1.4 ppm error).

Lab notebook reference: MJJ1/62
2-(4-Methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84a)

Synthesised using **general procedure 2C** with ynone 83a (58 mg, 0.2 mmol) and AgOTf (0.5 mg, 2 µmol) in CH₂Cl₂ (2 mL) at RT for 30 min. Purification by column chromatography (1:1 hexane:EtOAc) afforded the **title compound 84a** (58 mg, 100%) as an off-white solid, mp 48–50 °C; \( \nu_{\text{max}} \) (cm⁻¹) 2923, 1693, 1604, 1510, 1255, 1181, 1030, 832; \( \delta_H \) (400 MHz, CDCl₃) 2.64 (1H, d, \( J = 19.0 \) Hz, H-10a), 3.02 (1H, d, \( J = 19.0 \) Hz, H-10b), 3.73 (3H, s, H-18), 6.66–7.71 (2H, m, H-16), 6.77 (1H, s, H-12), 6.91–6.97 (2H, m, H-15), 7.21–7.31 (2H, m, H-2,3), 7.45 (1H, td, \( J = 7.5, 1.0 \) Hz, H-4), 7.77 (1H, d, \( J = 7.5 \) Hz, H-5), 8.21 (1H, s, H-8); \( \delta_C \) (100 MHz, CDCl₃) 42.3 (CH₂, C-10), 55.3 (CH₃, C-18), 65.8 (C, C-9), 114.3 (2CH, C-16), 121.5 (CH, C-2/5), 122.1 (CH, C-2/5), 124.8 (C, C-14), 127.7 (CH, C-3/4/12), 128.5 (CH, C-3/4/12), 128.8 (2CH, C-15), 129.0 (CH, C-3/4/12), 141.3 (C, C-1), 154.7 (C, C-6), 162.1 (C, C-17), 171.1 (C, C-13), 174.6 (CH, C-8), 204.2 (C, C-11); HRMS (ESI⁺): Found: 290.1168; \( C_{19}H_{16}NO_2 \) (MH⁺) Requires 290.1176 (2.7 ppm error).

Spirocycle 84a was also synthesised using **general procedure 2C** from ynone 83a (82 mg, 0.283 mmol) and Cu(OTf)_2 (1.0 mg, 2.8 µmol) in CH₂Cl₂ (3 mL) for 8.5 h. Purification by column chromatography afforded the **title compound 84a** (78 mg, 95%).

Spirocycle 84a was also synthesised using **general procedure 2D** from ynone 83a (58 mg, 0.2 mmol) and Ag₁₁₄l (1.6 mg, 2 µmol) in CHCl₃ (2 mL). Purification by column chromatography afforded the **title compound 84a** (58 mg, 100%) in 89:11 er (S:R). \([\alpha]_D^{20} -122.4 \) (c = 1.0, CHCl₃). CSP-HPLC conditions: 10% IPA in hexane, (R)-84a 28.1 min, (S)-84a 30.7 min, UV detection at 280 nm.

Lab notebook reference: MJJ1/32 + 2/22 + 2/66

2-Phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one (84b)

Synthesised using **general procedure 2C** with ynone 83b (52 mg, 0.2 mmol) and AgOTf (0.5 mg, 2 µmol) in CH₂Cl₂ (2 mL) at RT for 30 min. Purification by column chromatography (3:2
hexane:EtOAc) afforded the **title compound 84b** (52 mg, 100%) as a brown oil; $\nu_{\text{max}}$ (cm$^{-1}$) 1697, 1592, 754; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.69 (1H, d, $J = 18.5$ Hz, H-10a), 3.06 (1H, d, $J = 18.5$ Hz, H-10b), 6.85 (1H, s, H-12), 6.97–7.00 (2H, m, H-15), 7.17–7.23 (2H, m, H-16), 7.27–7.33 (3H, m, H-2,3,17), 7.46 (1H, ddd, $J = 7.5$, 7.5, 1.5 Hz, H-4), 7.78 (1H, d, $J = 8.0$ Hz, H-5), 8.22 (1H, s, H-8); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 42.3 (CH$_2$, C-10), 65.9 (C, C-9), 121.5 (CH, C-2), 122.1 (CH, C-5), 126.7 (2CH, C-15), 128.9 (2CH, C-16), 129.0 (CH, C-4), 130.7 (CH, C-12/17), 131.3 (CH, C-12/17), 132.4 (C, C-14), 140.8 (C, C-1), 154.8 (C, C-6), 171.9 (C, C-13), 174.0 (CH, C-8), 204.3 (C, C-11); HRMS (ESI$^+$): Found: 282.0885; C$_{18}$H$_{13}$NNaO (MNa$^+$) Requires 282.0889 (1.5 ppm error), Found: 260.1068; C$_{18}$H$_{14}$NO (MH$^+$) Requires 260.1070 (0.9 ppm error).

Spirocycle 84b was also synthesised using **general procedure 2C** from ynone 83b (133 mg, 0.513 mmol) and Cu(OTf)$_2$ (1.8 mg, 5 µmol) in CH$_2$Cl$_2$ (5 mL) for 16 h. Purification by column chromatography afforded the **title compound 84b** (114 mg, 86%).

 Spirocycle 84b was also synthesized using **general procedure 2D** from ynone 83b (52 mg, 0.2 mmol) and Ag-114l (1.6 mg, 2 µmol) in CHCl$_3$ (2 mL). Purification by column chromatography afforded the **title compound 84b** (45 mg, 87%) in 70:30 er ($S$:R). [$\alpha$]$_{D}^{20}$ +5.0 (c = 1.0, CHCl$_3$). CSP-HPLC conditions: 10% IPA in hexane, ($R$)-84b 24.3 min, ($S$)-84b 26.8 min, UV detection at 280 nm.

Lab notebook reference: MJJ1/3 + 3/16 + 3/25

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2-(4-(Dimethylamino)phenyl)spiro[cyclopent[2]ene-1,3''-indol]-4-one (84c)

Synthesised using **general procedure 2C** with ynone 83c (104 mg, 0.344 mmol), AgOTf (0.9 mg, 3.44 µmol) in CH$_2$Cl$_2$ (3.4 mL) at RT for 20 min. Purification by column chromatography (2.1 hexane:EtOAc) afforded the **title compound 84c** (101 mg, 97%) as a yellow oil; $\nu_{\text{max}}$ (cm$^{-1}$) 2923, 1685, 1570, 1202, 818; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.60 (1H, d, $J = 19.0$ Hz, H-10a), 2.93 (6H, s, H-18), 2.98 (1H, d, $J = 19.0$ Hz, H-10b), 6.39–6.45 (2H, m, H-16), 6.72 (1H, s, H-12), 6.86–6.92 (2H, m, H-15), 7.21–7.30 (2H, m, H-2,3), 7.40–7.47 (1H, m, H-4), 7.77 (1H, dt, $J = 8.0$, 1.0 Hz, H-5), 8.22 (1H, s, H-8); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 39.8 (CH$_3$, C-18), 42.3 (CH$_3$, C-10), 65.7 (C, C-9), 111.3 (2CH, C-16), 119.3 (C, C-14), 121.5 (CH, C-2), 121.9 (CH, C-5), 125.2 (CH, C-3), 127.6 (CH, C-12), 128.7 (CH, C-4), 128.9 (2CH, C-15), 142.1
(C, C-1), 152.2 (C, C-17), 154.6 (C, C-6), 171.2 (C, C-13), 175.3 (CH, C-8), 204.1 (C, C-11); HRMS (ESI⁺): Found: 325.1295; C₂₀H₁₈N₂O (MNa⁺) Requires 325.1311 (5.2 ppm error), Found: 303.1487; C₂₀H₁₉N₂O (MH⁺) Requires 303.1492 (1.7 ppm error).

Spirocycle 84c was also synthesised using general procedure 2C from ynone 83c (100 mg, 0.331 mmol) and Cu(OTf)₂ (1.1 mg, 3 µmol) in CH₂Cl₂ (5 mL) for 3 h. Purification by column chromatography afforded the title compound 84c (90 mg, 90%).

Spirocycle 84c was also synthesised using general procedure 2D from ynone 83c (60 mg, 0.198 mmol) and Ag₁₁₄l (1.6 mg, 2 µmol) in CHCl₃ (4 mL). Purification by column chromatography afforded the title compound 84c (30 mg, 50%) in 69:31 er (S:R). [α]D₂₀ −47.6 (c = 1.0, CHCl₃).

CSP-HPLC conditions: 20% IPA in hexane, (R)-84c 17.5 min, (S)-84c 19.5 min, UV detection at 280 nm.

Lab notebook reference: MJJ1/11 + 1/16 + 3/14

2-(4-Fluorophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84d)

Synthesised using general procedure 2C with ynone 83d (100 mg, 0.361 mmol) and AgOTf (0.9 mg, 3.6 µmol) in CH₃Cl (3.6 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound 84d (100 mg, 100%) as a red oil; νₚₚₚ (cm⁻¹) 1696, 1602, 1508, 1239, 1164, 835; δH (400 MHz, CDCl₃) 2.68 (1H, d, J = 19.0 Hz, H-10a), 3.05 (1H, d, J = 19.0 Hz, H-10b), 6.79 (1H, s, H-12), 6.83–6.91 (2H, m, H-16), 6.93–7.00 (2H, m, H-15), 7.24 (1H, br d, J = 8.0 Hz, H-2), 7.30 (1H, dd, J = 7.5, 7.5 Hz, H-3), 7.46 (1H, dd, J = 8.0, 7.5 Hz, H-4), 7.77 (1H, d, J = 8.0 Hz, H-5), 8.22 (1H, s, H-8); δC (100 MHz, CDCl₃) 42.3 (CH₂, C-10), 65.9 (C, C-9), 116.1 (2CH, d, J = 22 Hz, H-16), 121.5 (CH, C-2), 122.2 (CH, C-5), 127.9 (CH, C-3), 128.5 (C, d, J = 4.0 Hz, C-14), 129.0 (2CH, d, J = 8.5 Hz, C-15), 129.2 (CH, C-4), 130.6 (CH), 140.6 (C, C-1), 154.7 (C, C-6), 164.3 (C, d, J = 254 Hz, C-17), 170.5 (C, C-13), 174.1 (CH, C-8), 204.0 (C, C-11); δF (376 MHz, CDCl₃) −107.1–−107.3 (1F, m); HRMS (ESI⁺): Found: 300.0794; C₁₈H₁₂FNNaO (MNa⁺) Requires 300.0795 (0.4 ppm error).

Lab notebook reference: MJJ3/85
2-(4-Chlorophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84e)

Synthesised using **general procedure 2C** with ynone 83e (33 mg, 0.112 mmol) and AgOTf (0.3 mg, 1.1 µmol) in CH₂Cl₂ (1.1 mL) at RT for 1.5 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the **title compound 84e** (33 mg, 100%) as a pale brown oil; \( \nu_{\text{max}} (\text{cm}^{-1}) \) 1696, 1593, 1489, 1095, 828, 730; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 2.69 (1H, d, \( J = 18.5 \) Hz, H-10a), 3.05 (1H, d, \( J = 18.5 \) Hz, H-10b), 6.82 (1H, s, H-12), 6.88–6.92 (2H, m, H-15), 7.13–7.18 (2H, m, H-16), 7.24 (1H, m, H-2), 7.29 (1H, dd, \( J = 7.5, 7.5 \) Hz, H-3), 7.46 (1H, ddd, \( J = 7.5, 7.5, 1.0 \) Hz, H-4), 7.77 (1H, d, \( J = 7.5 \) Hz, H-5), 8.22 (1H, s, H-8); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 42.3 (CH₂, C-10), 65.8 (C, C-9), 121.5 (CH, C-2), 122.2 (CH, C-5), 127.8 (CH, C-3), 128.0 (2CH, C-15), 129.19 (2CH, C-16), 129.23 (CH, C-4), 130.7 (C, C-14), 131.0 (CH, C-12), 137.5 (C, C-17), 140.5 (C, C-1), 154.8 (C, C-6), 170.4 (C, C-13), 173.7 (CH, C-8), 204.0 (C, C-11); HRMS (ESI⁺): Found: 316.0494; C_{18}H_{12}ClNNaO (MNa⁺) Requires 316.0500 (1.6 ppm error), Found: 294.0673; C_{18}H_{13}ClNO (MH⁺) Requires 294.0680 (2.6 ppm error).

Spirocycle 84e was also synthesised using **general procedure 2C** from ynone 83e (87 mg, 0.296 mmol) and Cu(OTf)₂ (1.1 mg, 3 µmol) in CH₂Cl₂ (3 mL) for 16 h. Purification by column chromatography afforded the title compound 84e (75 mg, 86%).

Spirocycle 84e was also synthesised using **general procedure 2D** from ynone 83e (21 mg, 71.5 µmol) and Ag-114l (0.6 mg, 0.715 µmol) in CHCl₃ (4 mL). Purification by column chromatography afforded the title compound 84e (15 mg, 71%) in 86:14 er (S:R), \([\alpha]_D^{20}−68.9 \) (c = 1.0, CHCl₃). CSP-HPLC conditions: 10% IPA in hexane, (R)-84e 22.5 min, (S)-84e 27.2 min, UV detection at 280 nm.

2-(4-Bromophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84f)

Synthesised using general procedure 2C with ynone 83f (68 mg, 0.2 mmol) and AgOTf (0.5 mg, 2 µmol) in CH$_2$Cl$_2$ (2 mL) at RT for 1.5 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound 84f (68 mg, 100%) as an off white solid, mp 201–203 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 1694, 1589, 1075, 1008, 824, 730; $\delta_H$ (400 MHz, CDCl$_3$) 2.66 (1H, d, $J = 18.5$ Hz, H-10a), 3.02 (1H, d, $J = 18.5$ Hz, H-10b), 6.75–6.86 (3H, m, H-12,15/16), 7.17–7.35 (4H, m, H-2,3,15/16), 7.43 (1H, ddd, $J = 7.5$, 7.5, 1.0 Hz, H-4), 7.74 (1H, d, $J = 8.0$ Hz, H-5), 8.17 (1H, s, H-8); $\delta_C$ (100 MHz, CDCl$_3$) 42.2 (CH$_2$, C-10), 65.8 (C, C-9), 121.5 (CH, C-2), 122.2 (CH, C-5), 125.9 (C, C-17), 127.8 (CH, C-3), 128.2 (CH, C-15/16), 129.2 (CH, C-5), 131.1 (CH, C-12), 131.2 (C, C-14), 132.1 (2CH, C-15/16), 140.4 (C, C-1), 154.8 (C, C-6), 170.5 (C, C-13), 173.7 (CH, C-8), 203.9 (C, C-11); HRMS (ESI$^+$): Found: 360.0004; C$_{18}$H$_{12}$BrN (MNa$^+$) Requires 359.9994 (−2.6 ppm error), Found: 338.0197; C$_{18}$H$_{13}$BrNO (MH$^+$) Requires 338.0175 (−6.5 ppm error).

Spirocycle 84f was also synthesised using general procedure 2D from ynone 83f (68 mg, 0.2 mmol) and Ag-$\text{I}^{14}$l (1.6 mg, 2 µmol) in CHCl$_3$ (4 mL). Purification by column chromatography afforded the title compound 84f (42 mg, 62%) in 86:14 $er$ (S:S). $[\alpha]_D^{20}$ −148.2 (c = 1.0, CHCl$_3$); CSP-HPLC conditions: 10% IPA in hexane, (R)-84f 26.6 min, (S)-84f 32.9 min, UV detection at 280 nm.

Lab notebook reference: MJJ4/9 + 4/10

2-Methylspiro[cyclopent[2]ene-1,3'-indol]-4-one (84g)

Synthesised using general procedure 2C with ynone 83g (60 mg, 0.304 mmol) and AgOTf (0.8 mg, 3 µmol) in CH$_2$Cl$_2$ (3 mL) at RT for 2 h. Purification by column chromatography (9:1 hexane:EtOAc, then 3:2 hexane:EtOAc) afforded the title compound 84g (57 mg, 95%) as an off white solid, mp 120–122 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 1716, 1620, 1551, 773, 759; $\delta_H$ (400 MHz, CDCl$_3$) 1.57 (3H, d, $J = 1.0$ Hz, H-14), 2.68 (1H, d, $J = 19.0$ Hz, H-10a), 2.94 (1H, d, $J = 19.0$ Hz, H-8), 2.97 (1H, d, $J = 19.0$ Hz, H-10b), 6.72–6.78 (3H, m, H-12,15/16), 7.16–7.37 (4H, m, H-2,3,15/16), 7.42 (1H, ddd, $J = 7.5$, 7.5, 1.0 Hz, H-4), 7.73 (1H, d, $J = 8.0$ Hz, H-5), 8.17 (1H, s, H-8); $\delta_C$ (100 MHz, CDCl$_3$) 28.0 (CH$_2$, C-10), 65.1 (C, C-9), 121.4 (CH, C-2), 122.2 (CH, C-5), 125.9 (C, C-17), 127.8 (CH, C-3), 128.2 (CH, C-15/16), 129.1 (CH, C-5), 131.1 (CH, C-12), 131.3 (C, C-14), 132.1 (2CH, C-15/16), 140.4 (C, C-1), 154.8 (C, C-6), 170.5 (C, C-13), 173.7 (CH, C-8), 203.9 (C, C-11); HRMS (ESI$^+$): Found: 359.9994; C$_{18}$H$_{13}$BrN (MNa$^+$) Requires 359.9994 (−2.6 ppm error), Found: 338.0197; C$_{18}$H$_{13}$BrNO (MH$^+$) Requires 338.0175 (−6.5 ppm error).
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Hz, H-10b), 6.27–6.31 (1H, m, H-12), 7.22 (1H, br d, J = 7.0 Hz, H-2) 7.30–7.36 (1H, m, H-3), 7.41–7.47 (1H, m, H-5), 7.72 (1H, br d, J = 8.0 Hz, H-5), 7.96 (1H, s, H-8); δc (100 MHz, CDCl3) 14.6 (CH3, C-14), 40.4 (CH2, C-10), 67.8 (C, C-9), 121.5 (CH, C-2), 121.7 (CH, C-5), 127.4 (CH, C-3), 129.0 (CH, C-4), 132.8 (CH, C-12), 139.1 (C, C-6), 155.6 (C, C-1), 173.1 (CH, C-8), 175.7 (C, C-13); HRMS (ESI\^+): Found: 220.0726; C_{13}H_{10}NNaO (MNa^+) Requires 220.0733 (2.9 ppm error), Found: 198.0905; C_{13}H_{12}NO (MH\^+) Requires 198.0913 (4.5 ppm error).

Spirocycle 84g was also synthesised using **general procedure 2C** from ynone 83g (87 mg, 0.441 mmol) and Cu(OTf)2 (1.6 mg, 4 µmol) in CH2Cl2 (2 mL) for 5 h. Purification by column chromatography afforded the **title compound 84g** (79 mg, 91%).

Spirocycle 84g was also synthesised using **general procedure 2D** from ynone 83g (51 mg, 0.259 mmol) and insert Ag-114l (2.1 mg, 2.6 µmol) in CHCl3 (2.5 mL). Purification by column chromatography afforded the **title compound 84g** (48 mg, 94%) in 86:14 er (S:S, CSP-HPLC performed on the TFA salt). [α]D\textsuperscript{20} \textasciitilde +208.1 (c = 1.0, CHCl3). CSP-HPLC conditions: 10% IPA in hexane, (R)-84g 34.4 min, (S)-84g 40.1 min, UV detection at 254 nm.

Lab notebook reference: MJJ1/18 + 3/36 + 3/95

2-Butylspiro[cyclopent[2]ene-1,3'-indol]-4-one (84h)

Synthesised using **general procedure 2C** with ynone 83h (48 mg, 0.2 mmol), AgOTf (0.5 mg, 2 µmol) in CH2Cl2 (2 mL) at RT for 3.5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the **title compound 84h** (approximately 1:1.4 ratio of monomer:trimer, 48 mg, 100%) as a pale yellow oil; v\textsubscript{max} (cm\textsuperscript{-1}) 2957, 2929, 2871, 1715, 1694, 1610, 1475, 1458, 1267, 1174, 730; δH (400 MHz, CDCl3) 0.65 (3H, t, J = 7.5 Hz, H-17, trimer), 0.74 (3H, t, J = 7.5 Hz, H-17, trimer), 0.77 (6H, t, J = 7.5 Hz, H-17, monomer + trimer), 1.01–1.26 (8H, m, H-15,16, monomer + trimer), 1.26–1.49 (8H, m, H-15,16, monomer + trimer), 1.58–1.83 (3H, m, H-14, monomer + trimer), 1.83–2.07 (3H, m, H-14, monomer + trimer), 2.11–2.26 (1H, m, H-14, trimer), 2.28–2.44 (1H, m, H-14, trimer), 2.60
1.9 Hz, H-10, monomer, 2.64 (2H, d, J = 19.0 Hz, H-10, trimmer), 2.85 (1H, d, J = 19.0 Hz, H-10, monomer), 2.91 (1H, d, J = 19.0 Hz, H-10, trimmer), 2.93 (1H, d, J = 19.5 Hz, H-10, monomer), 3.01 (1H, d, J = 19.0 Hz, H-10, trimmer), 3.24 (1H, d, J = 19.0 Hz, H-10, trimmer), 4.59 (1H, s, H-8, trimmer), 4.81 (1H, s, H-8, trimmer), 5.21 (1H, s, H-8, trimmer), 5.78 (1H, d, J = 7.5 Hz, H-5, trimmer), 5.83 (1H, d, J = 7.5, H-5 Hz, trimmer), 5.93 (1H, t, J = 1.5 Hz, H-12, trimmer), 5.99 (1H, t, J = 1.5 Hz, H-12, trimmer), 6.00 (1H, t, J = 1.5 Hz, H-12, trimmer), 6.28 (1H, t, J = 1.5 Hz, H-12, monomer), 6.31 (1H, d, J = 8.0 Hz, H-5, trimmer), 6.68 (1H, ddd, J = 7.5, 7.5, 1.5 Hz, H3/4, trimmer), 6.75 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H-3/4, trimmer), 6.84 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H3/4, trimmer), 6.92 (1H, dd, J = 7.5, 1.0 Hz, H-2, trimmer), 6.94 (2H, dd, J = 7.0 Hz, H-3/4, trimmer), 7.04–7.12 (2H, m, H-2,3/4, trimmer), 7.20 (1H, dd, J = 7.5, 1.0 Hz, H-2, trimmer), 7.22 (1H, dd, J = 7.5, 1.0 Hz, H-2, monomer), 7.30 (1H, dd, J = 7.5, 7.5 Hz, H-3/4, monomer), 7.42 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H-3/4, monomer), 7.70 (1H, d, J = 7.5 Hz, H-5, monomer), 7.96 (1H, br s, H-8, monomer); δC (100 MHz, CDCl3) 13.5 (CH3), 13.57 (CH3), 13.63 (CH3), 13.7 (CH3), 22.07 (CH3), 22.09 (CH3), 22.11 (CH3), 22.2 (CH3), 27.9 (CH2), 28.17 (CH2), 28.21 (CH2), 28.3 (CH2), 28.8 (CH2), 29.2 (CH2), 29.3 (CH2), 29.4 (CH2), 40.3 (CH2), 44.1 (CH2), 44.2 (CH2), 45.2 (CH2), 57.8 (CH2), 60.2 (C), 62.8 (C), 78.8 (CH), 81.9 (CH), 85.0 (CH), 105.9 (CH), 107.1 (CH), 114.9 (CH), 120.2 (CH), 121.4 (CH), 121.6 (CH), 121.66 (CH), 121.67 (CH), 122.1 (CH), 123.1 (CH), 123.4 (CH), 127.3 (CH), 127.31 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 129.0 (CH), 129.6 (CH), 129.7 (CH), 130.1 (C), 131.0 (CH), 131.7 (C), 134.0 (C), 145.3 (C), 148.3 (C), 150.3 (C), 173.2 (C), 180.3 (C), 183.4 (C), 184.0 (C), 184.8 (C), 205.6 (C), 206.3 (C), 206.4 (C), 206.9 (C); HRMS (ES+) found: 240.1382; C16H15NO (MH+) requires 240.1383 (0.2 ppm error).

Spirocyle 84h was also synthesised using general procedure 2C from ynone 83h (118 mg, 0.493 mmol) and Cu(OTf)2 (1.8 mg, 5 μmol) in CH2Cl2 (5 mL) for 16 h. Purification by column chromatography afforded the title compound 84h (112 mg, 95%).

Lab notebook reference: MJ1/9 + 3/30

2-(Thiophen-2-yl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84i)

Synthesised using general procedure 2C with ynone 83i (34 mg, 0.128 mmol) and AgOTf (0.33 mg, 1.3 μmol) in CH2Cl2 (1.3 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound 84i (34 mg, 100%) as a

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brown oil; $\nu_{\text{max}}$ (cm$^{-1}$) 1719, 1689, 1584, 1572, 1198, 727, 711; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.70 (1H, d, $J = 19.0$ Hz, H-10a), 3.00 (1H, d, $J = 19.0$ Hz, H-10b), 6.53 (1H, d, $J = 3.5$ Hz, H-15), 6.68 (1H, s, H-12), 6.81 (1H, dd, $J = 5.0$, 3.5 Hz, H-16), 7.23–7.32 (2H, m, H-2,3), 7.34 (1H, d, $J = 5.0$ Hz, H-17), 7.45 (1H, ddd, $J = 8.0$, 8.0, 2.0 Hz, H-4), 7.76 (1H, d, $J = 8.0$ Hz, H-5), 8.13 (1H, s, H-8); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 41.7 (CH$_2$, C-10), 65.6 (C, C-9), 121.9 (CH, CAr), 122.0 (CH, CAr), 127.7 (CH, CAr), 128.2 (CH, CAr), 128.6 (CH, CAr), 129.3 (CH, CAr), 129.4 (CH, CAr), 130.9 (CH, CAr), 135.0 (C, C-14), 140.5 (C, C-1), 155.1 (C, C-6), 164.3 (C, C-13), 174.0 (CH, C-8), 203.7 (C, C-11); HRMS (ESI$^+$): Found: 288.0452; C$_{16}$H$_{13}$NNaOS (MNa$^+$) Requires 288.0454 (0.7 ppm error), Found: 266.0636; C$_{16}$H$_{13}$NOS (MH$^+$) Requires 266.0634 (–0.6 ppm error).

Lab notebook reference: MJJ4/91

5-Benzyl-2-phenylspiro[cyclopent[2]ene-1,3':indol]-4-one (84j)

Synthesised using general procedure 2C with ynone 83j (35 mg, 0.100 mmol), AgOTf (0.26 mg, 1 µmol) in CH$_2$Cl$_2$ (1 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound 84j (35 mg, 100%, 52:48 dr) as an off-white solid, mp 126–129 ºC; $\nu_{\text{max}}$ (cm$^{-1}$) 1699, 1591, 1445, 752, 730, 695; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.11 (1H, dd, $J = 14.0$, 10.0 Hz, H-18a, minor), 2.54 (1H, dd, $J = 15.0$, 8.5 Hz, H-18a, major), 3.17–3.31 (2H, m, H-18b, minor + major), 3.49 (1H, dd, $J = 8.5$, 6.0 Hz, H-10, major), 3.57 (1H, dd, $J = 10.0$, 4.0 Hz, H-10, minor), 6.47 (1H, s, H-12, minor), 6.49 (1H, s, H-12, major), 6.81–6.89 (4H, m, ArH), 6.89–6.96 (4H, m, ArH), 6.97–7.11 (6H, m, ArH), 7.11–7.21 (6H, m, ArH), 7.21–7.38 (6H, m, ArH), 7.48 (1H, dd, $J = 8.0$, 7.5 Hz, H-4, major), 7.56 (1H, d, $J = 8.0$ Hz, H-5, major), 7.59 (1H, d, $J = 8.0$ Hz, H-5, minor), 7.98 (1H, s, H-8, minor), 8.14 (1H, s, H-8, major); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 32.0 (CH$_2$), 32.5 (CH$_2$), 52.4 (CH), 57.9 (CH), 70.2 (C), 70.5 (C), 121.8 (CH), 122.0 (CH), 122.5 (CH), 123.2 (CH), 126.1 (CH), 126.3 (CH), 126.7 (6CH), 127.4 (CH), 127.9 (3CH), 128.2 (2CH), 128.4 (2CH), 128.7 (2CH), 128.8 (CH), 128.9 (2CH), 129.2 (CH), 129.3 (CH), 130.4 (CH), 131.1 (CH), 131.2 (CH), 132.5 (C), 132.7 (C), 137.57 (C), 137.62 (C), 137.64 (C), 140.0 (C), 155.4 (C), 156.4 (C), 170.7 (C), 171.4 (C), 173.0 (CH), 173.4 (CH), 205.1 (2C); HRMS (ESI$^+$): Found: 372.1344; C$_{25}$H$_{16}$NNaO (MNa$^+$)
Requires 372.1359 (4.0 ppm error). Found: 350.1535; C_{26}H_{34}NO_2 (MH^+) Requires 350.1539 (1.2 ppm error).

Lab notebook reference: MJJ4/88

5-Benzyl-2-(4-methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84k)

Synthesised using general procedure 2C with ynone 83k (114 mg, 0.300 mmol), AgOTf (0.8 mg, 3.00 µmol) in CH_2Cl_2 (3 mL) at RT for 30 min. Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 84k (108 mg, 95%, 55:45 dr) as a pale brown oil; v_max (cm^{-1}) 1698, 1603, 1510, 1262, 1181, 832; δ_H (400 MHz, CDCl_3) 2.10 (1H, dd, J = 14.5, 10.5 Hz, H-19a, major), 2.53 (1H, dd, J = 14.5, 9.0 Hz, H-19a, minor), 3.17–3.29 (2H, m, H-19b, minor + major), 3.46 (1H, dd, J = 9.0, 6.0 Hz, H-10, minor), 3.55 (1H, dd, J = 10.5, 4.5 Hz, H-10, major), 3.71 (3H, s, H-18, minor), 3.72 (3H, s, H-18, major), 6.44–6.49 (2H, m, H-2, minor + major), 6.62–6.70 (4H, m, H-16, minor + major), 6.78 (1H, s, H-12, major), 6.80 (1H, s, H-12, minor), 6.84–6.93 (6H, m, ArH, H-15, minor + major), 6.98–7.09 (6H, m, ArH) 7.14–7.25 (3H, m, ArH), 7.29–7.36 (2H, m, ArH), 7.47 (1H, ddd, J = 7.5, 7.5, 1.5 Hz, H-4, major), 7.56 (1H, d, J = 7.5 Hz, H-5, minor), 7.58 (1H, d, J = 7.5 Hz, H-5, major), 8.00 (1H, s, H-8, major), 8.13 (1H, s, H-8, minor); δ_C (100 MHz, CDCl_3) 32.0 (CH_2), 32.5 (CH_2), 52.1 (CH_3), 55.2 (CH_3), 55.3 (CH_3), 57.8 (CH), 70.1 (C), 70.3 (C), 114.1 (2CH), 114.23 (2CH), 121.8 (CH), 121.9 (CH), 122.4 (CH), 123.2 (CH), 124.8 (C), 125.0 (C), 126.1 (CH), 126.2 (CH), 126.7 (CH), 126.9 (CH), 127.4 (CH), 127.9 (3CH), 128.0 (CH), 128.2 (2CH), 128.4 (2CH), 128.67 (5CH), 128.70 (CH), 129.2 (CH), 137.68 (C), 137.73 (C), 138.00 (C), 140.5 (C), 155.2 (C), 156.2 (C), 161.92 (C), 161.94 (C), 169.8 (C), 170.5 (C), 173.5 (CH), 174.0 (CH), 204.95 (C), 204.97 (C); HRMS (ESI^+): Found: 402.1454; C_{26}H_{32}NNaO_2 (MN^+ \text{Na}^+) Requires 402.1465 (2.7 ppm error). Found: 380.1634; C_{26}H_{32}NO_2 (MH^+) Requires 380.1645 (3.0 ppm error).

Lab notebook reference: MJJ1/74
2-(4-Methoxyphenyl)-2'-methylspiro[cyclopent[2]ene-1,3'-indol]-4-one (84l)

Synthesised using general procedure 2C with ynone 83l (107 mg, 0.353 mmol), AgOTf (0.9 mg, 3.53 µmol) in CH₂Cl₂ (3.5 mL) at RT for 10 min. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound 84l (107 mg, 100%) as a pale yellow oil; νₘₐₓ (cm⁻¹) 1693, 1604, 1510, 1258, 1181, 1028, 829; δ_H (400 MHz, CDCl₃) 2.20 (3H, s, H-9), 2.69 (1H, d, J = 18.5 Hz, H-11a), 2.80 (1H, d, J = 18.5 Hz, H-11b), 3.72 (3H, s, H-19), 6.66–6.73 (2H, m, H-17), 6.80 (1H, s, H-13), 6.91–6.98 (2H, m, H-16), 7.14–7.24 (2H, m, H-2,3), 7.35–7.44 (1H, m, H-4), 7.66 (1H, d, J = 7.5 Hz, H-5); δ_C (100 MHz, CDCl₃) 15.7 (CH₃, C-9), 45.1 (CH₂, C-11), 55.3 (CH₃, C-19), 66.5 (C, C-10), 114.4 (2CH, C-17), 120.8 (CH, C-2), 121.6 (CH, C-5), 124.4 (C, C-15), 126.6 (CH, C-3), 128.7 (CH, C-4), 128.9 (2CH, C-16), 142.2 (C, C-1), 154.3 (C, C-6), 162.1 (C, C-18), 172.0 (C, C-14), 183.5 (C, C-8), 204.5 (C, C-12); HRMS (ESI⁺): Found: 326.1155; C₂₀H₁₇NNaO₂ (MNa⁺) Requires 326.1151 (−1.2 ppm error), Found: 304.1339; C₂₀H₁₆NO₂ (MH⁺) Requires 304.1332 (−2.3 ppm error).

Spirocycle 84l was also synthesised using general procedure 2D from ynone 83l (65 mg, 0.214 mmol) and Ag-114l (1.7 mg, 2.1 µmol) in CHCl₃ (2 mL). Purification by column chromatography afforded the title compound 84l (47 mg, 72%) in 82:64 er (S:R). [α]D²⁰⁻159.3 (c = 1.0, CHCl₃). CSP-HPLC conditions: 10% IPA in hexane, (R)-84l 33.9 min, (S)-84l 36.4 min, UV detection at 280 nm.

Lab notebook reference: MJJ3/45 + 3/70

2-(4-Methoxyphenyl)-2'-phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one (84m)

Synthesised using general procedure 2C with ynone 83m (100 mg, 0.274 mmol), AgOTf (0.7 mg, 2.74 µmol) in CH₂Cl₂ (3 mL) at RT for 6 min. Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 84m (84 mg, 84%) as a pale brown oil; νₘₐₓ (cm⁻¹) 1693, 1603, 1510, 1256, 1180, 834, 758; δ_H (400 MHz, CDCl₃) 2.66 (1H, d, J = 18.5 Hz, H-14a), 3.09 (1H, d, J = 18.5 Hz, H-14b), 3.68 (3H, s, H-22), 6.63–6.69
(2H, m, H-20), 6.91 (1H, s, H-16), 7.05–7.10 (2H, m, H-19), 7.18–7.27 (2H, m, H-2,3), 7.36–7.48 (4H, m, H-4,11,12), 7.82 (1H, d, J = 8.0 Hz, H-5), 7.96–8.01 (2H, m, H-10); δc (100 MHz, CDCl₃) 47.2 (CH₂, C-14), 55.2 (CH₃, C-22), 65.2 (C, C-13), 114.5 (2CH, C-20), 120.8 (CH, C-2), 121.7 (CH, C-5), 124.7 (C, C-18), 127.1 (CH, C-3/16), 127.3 (CH, C-3/16), 127.7 (2CH, C-10), 129.0 (2CH, C-11/19), 129.08 (2CH, C-11/19), 129.12 (CH, C-4), 131.2 (CH, C-12), 132.2 (C, C-9), 143.4 (C, C-1), 153.7 (C, C-6), 162.1 (C, C-21), 174.0 (C, C-17), 178.9 (C, C-8), 204.8 (C, C-15); HRMS (ESI⁺): Found: 388.1302; C₁₅H₁₅BrNaO₂ (MNa⁺) Requires 388.1308 (1.7 ppm error), Found: 366.1477; C₁₅H₂₅NO₂ (MH⁺) Requires 366.1489 (3.2 ppm error).

Lab notebook reference: MJJ1/56

5'-Bromo-2-(4-methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84n)

Synthesised using general procedure 2C with ynone 83n (74 mg, 0.20 mmol), AgOTf (0.5 mg, 2 µmol) in CH₂Cl₂ (2 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the title compound 84n (74 mg, 100%) as an off-white solid, mp 65–67 °C; νmax (cm⁻¹) 1692, 1603, 1509, 1255, 1180, 1030, 831, 730; δh (400 MHz, CDCl₃) 2.62 (1H, d, J = 18.5 Hz, H-10a), 3.01 (1H, d, J = 18.5 Hz, H-10b), 3.75 (3H, s, H-18), 6.68–6.74 (2H, m, H-16), 6.77 (1H, s, H-12), 6.92–6.97 (2H, m, H-15), 7.36 (1H, d, J = 2.0 Hz, H-2), 7.57 (1H, dd, J = 8.0, 2.0 Hz, H-4), 7.64 (1H, d, J = 8.0 Hz, H-5), 8.20 (1H, s, H-8); δc (100 MHz, CDCl₃) 42.1 (CH₂, C-10), 55.3 (CH₃, C-18), 66.0 (C, C-9), 114.4 (2CH, C-16), 121.6 (C, C-3), 123.4 (CH, C-5), 124.5 (C, C-14), 125.0 (CH, C-2), 128.6 (CH, C-12), 128.7 (2CH, C-15), 132.2 (CH, C-4), 143.5 (C, C-1), 153.6 (C, C-6), 162.2 (C, C-17), 170.1 (C, C-13), 174.9 (CH, C-8), 203.4 (C, C-11); HRMS (ESI⁺): Found: 390.0075; C₁₀H₁₄BrNaO₂ (MNa⁺) Requires 390.0100 (6.5 ppm error), Found: 368.0269; C₁₅H₁₅BrNO₂ (MH⁺) Requires 368.0281 (3.1 ppm error).

Spirocycle 84n was also synthesised using general procedure 2D from ynone 83n (352 mg, 0.956 mmol) and Ag·114l (7.7 mg, 9.6 µmol) in CHCl₃ (20 mL). Purification by column chromatography afforded the title compound 84n (352 mg, 100%) in 85:15 er (R:S). [α]D²⁰ −145.6 (c = 1.0, CHCl₃). CSP-HPLC conditions: 10% IPA in hexane, (R)-84n 32.4 min, (S)-84n 38.6 min, UV detection at 280 nm.
To a stirred solution of ynone 83o (51 mg, 0.200 mmol) in acetone (2 mL) was added AgNO₃ (6.8 mg, 0.040 mmol). The mixture was stirred for 16 h at RT. The reaction mixture was concentrated in vacuo then purified by column chromatography (6:4 hexane:EtOAc) to afford the title compound 84o (34 mg, 93%, ~2:1 mixture of trimer:monomer) as a pale brown oil; v_max (cm⁻¹) 1714, 1600, 1475, 753, 735; NMR data of TFA salt, δ_H (400 MHz, CDCl₃) 2.97 (1H, d, J = 19.5 Hz, H-10a), 3.46 (1H, d, J = 19.5 Hz, H-10b), 6.93 (1H, d, J = 5.5 Hz, H-12), 7.34 (1H, d, J = 5.5 Hz, H-13), 7.52–7.57 (1H, m, H-2), 7.70–7.76 (2H, m, H-3,4), 7.87–7.92 (1H, m, H-5), 9.31 (1H, s, H-8); δ_C (100 MHz, CDCl₃) 38.7 (CH₂, C-10), 63.8 (C, C-9), 118.9 (CH, C-5), 123.9 (CH, C-2), 131.5 (CH, C-3/4), 132.3 (CH, C-3/4), 136.4 (C, C-1), 138.4 (CH, C-12), 140.6 (C, C-6), 158.8 (CH, C-13), 178.4 (CH, C-8), 208.4 (C, C-11); HRMS (ESI⁺): Found: 206.0583; C₁₂H₉NNaO (MNa⁺) Requires 206.0576 (−3.1 ppm error), Found: 184.0753; C₁₂H₁₀NO (MH⁺) Requires 184.0757 (2.1 ppm error).

Lab notebook reference: MJJ3/5

To synthesize 1-(4-Methoxyphenyl)spiro[cyclohex[6]ene-2,3'-indol]-5-one (84q)

Synthesised using general procedure 2C with ynone 83q (40 mg, 0.132 mmol), AgOTf (3.4 mg, 13.2 µmol) in CH₂Cl₂ (1.3 mL) at 35 °C for 16 h. Purification by column chromatography (3:1 hexane:EtOAc) afforded the title compound 84q (30 mg, 75%) as a pale brown oil; v_max (cm⁻¹) 1664, 1603, 1510, 1240, 1179, 1030, 831, 729; δ_H (400 MHz, CDCl₃) 1.78 (1H, ddd, J = 13.5, 5.0, 5.0 Hz, H-10a), 2.55–2.64 (1H, m, H-10b), 2.70 (1H, ddd, J = 18.0, 5.0, 5.0 Hz, H-10c), 6.93 (1H, d, J = 5.5 Hz, H-12), 7.34 (1H, d, J = 5.5 Hz, H-13), 7.52–7.57 (1H, m, H-2), 7.70–7.76 (2H, m, H-3,4), 7.87–7.92 (1H, m, H-5), 9.31 (1H, s, H-8); δ_C (100 MHz, CDCl₃) 38.7 (CH₂, C-10), 63.8 (C, C-9), 118.9 (CH, C-5), 123.9 (CH, C-2), 131.5 (CH, C-3/4), 132.3 (CH, C-3/4), 136.4 (C, C-1), 138.4 (CH, C-12), 140.6 (C, C-6), 158.8 (CH, C-13), 178.4 (CH, C-8), 208.4 (C, C-11); HRMS (ESI⁺): Found: 206.0583; C₁₂H₉NNaO (MNa⁺) Requires 206.0576 (−3.1 ppm error), Found: 184.0753; C₁₂H₁₀NO (MH⁺) Requires 184.0757 (2.1 ppm error).

Lab notebook reference: MJJ3/5
Chapter 5. Experimental

H-11a), 2.81–2.92 (1H, m, H-11b), 3.71 (3H, s, H-19), 6.47 (1H, d, J=6.5 Hz, H-3), 6.63–6.68 (2H, m, H-17), 6.69–6.74 (2H, m, H-16), 7.29 (1H, ddd, J=7.5, 7.5, 0.5 Hz, H-3), 7.36 (1H, br d, J=7.5 Hz, H-2), 7.47 (1H, ddd, J=7.5, 7.5, 1.5 Hz, H-4), 7.78 (1H, br d, J=7.5 Hz, H-5), 8.19 (1H, br s, H-8); δC (100 MHz, CDCl₃) 31.9 (CH₂, C-10), 34.3 (CH₂, C-11), 55.2 (CH₃, C-19), 61.5 (C, C-9), 114.0 (2CH, C-17), 122.5 (CH, C-2/5), 122.7 (CH, C-2/5), 126.9 (CH, C-3), 127.3 (2CH, C-16), 128.3 (CH, C-13), 129.1 (CH, C-4), 129.6 (C, C-15), 140.7 (C, C-1), 154.8 (C, C-6), 157.3 (C, C-14), 160.9 (C, C-18), 176.2 (CH, C-8) 197.9 (C, C-12); HRMS (ESI⁺): Found: 326.1152; C₂₀H₁₇NNaO₂ (MNa⁺) Requires 326.1151 (-0.3 ppm error), Found: 304.1330; C₂₀H₁₈NO₂ (MH⁺) Requires 304.1332 (0.6 ppm error).

Lab notebook reference: MJJ1/81 + WPU/2134

2-Methoxyspirocyclopent[2]ene-1,3'-indol-4-one (84s)

To a 0 °C solution of Et₂NH (2.48 mL, 24.0 mmol) in THF (48 mL) under argon was added n-BuLi (8.80 mL, 22.0 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at 0 °C for 10 min and then chloroacetaldehyde dimethylacetal (0.78 mL, 6.87 mmol) was slowly added. The mixture was stirred for 2 h at 0 °C, then cooled to −78 °C before being transferred via cannula to a −78 °C solution of Weinreb 81a (500 mg, 2.29 mmol) in THF (11.5 mL). Upon complete transfer the mixture was warmed to RT and stirred for 30 min after which the reaction was quenched by the careful addition of sat. NH₄Cl (aq) (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried (MgSO₄), concentrated in vacuo and purified by column chromatography (6:4 hexane:EtOAc, then 8:2 EtOAc:hexane) to afford the title compound 84s (148 mg, 30% yield) as a pale brown oil; νmax (cm⁻¹) 1691, 1595, 1251, 749; δH (400 MHz, CDCl₃) 2.70 (1H, d, J=18.0 Hz, H-10a), 3.00 (1H, d, J=18.0 Hz, H-10b), 3.73 (3H, s, H-14), 5.63 (1H, s, H-12), 7.27–7.35 (2H, m, H-2,3), 7.44 (1H, ddd, J=7.5, 7.5, 2.0 Hz, H-4), 7.70 (1H, d, J=8.0 Hz, H-5), 8.03 (1H, s, H-8); δC (100 MHz, CDCl₃) 40.3 (CH₂, C-10), 59.4 (CH₃, C-14), 64.4 (C, C-9), 105.6 (CH, C-12), 121.2 (CH, C-2), 121.6 (CH, C-5), 127.2 (CH, C-3), 129.1 (CH, C-4), 138.4 (C, C-1), 155.4 (C, C-6), 171.5 (CH, C-8), 187.3 (C, C-13), 201.7 (C, C-11); HRMS (ESI⁺): Found: 236.0682; C₁₃H₁₃NNaO₂ (MNa⁺) Requires 236.0682 (0.1 ppm error), Found: 214.0859; C₁₃H₁₂NO₂ (MH⁺) Requires 214.0863 (1.8 ppm error).

Lab notebook reference: MJJ2/36
1-(4-Methoxyphenyl)-9H-carbazol-3-ol (85a)

Synthesised using **general procedure 2C** with ynone 83a (58 mg, 0.2 mmol) and (Ph₃P)AuNTf₂·½PhMe (15.7 mg, 0.02 mmol) in CH₂Cl₂ (2 mL) at RT for 30 min. Purification by column chromatography (3:2 hexane:EtOAc) afforded the **title compound 85a** (44 mg, 76%) as an off-white semi-solid; \(v_{\text{max}}\) (cm\(^{-1}\)) 3368, 1609, 1517, 1495, 1317, 1237, 1174, 1152, 830, 728; \(\delta_H\) (400 MHz, CDCl₃) 3.86 (3H, s, H-19), 4.58 (1H, br s, H-12), 6.96–7.05 (3H, m, H-13,17), 7.17–7.23 (1H, m, H-3), 7.35–7.43 (2H, m, H-4,5), 7.49 (1H, d, \(J = 2.5\) Hz, H-10), 7.51–7.56 (2H, m, H-16), 7.98 (1H, d, \(J = 8.0\) Hz, H-2), 8.15 (1H, br s, H-7); \(\delta_C\) (100 MHz, CDCl₃) 55.3 (CH₃, C-19), 104.5 (CH, C-10), 110.8 (CH, C-5), 114.5 (CH, C-13), 114.6 (2CH, C-17), 119.0 (CH, C-3), 120.5 (CH, C-2), 123.3 (C, CAr), 124.3 (C, CAr), 125.4 (C, CAr), 125.9 (CH, C-4), 129.3 (2CH, C-16), 130.9 (C, CAr), 132.3 (C, CAr), 140.3 (C, CAr), 149.6 (C, C-11), 159.0 (C, C-18); HRMS (ESI⁺): Found: 312.0992; C₁₉H₁₅NNaO₂ (MNa⁺) Requires 312.0995 (0.8 ppm error); Found: 290.1173; C₁₉H₁₆NO₂ (MH⁺) Requires 290.1176 (1.0 ppm error).

Lab notebook reference: MJJ6/2

6-(4-Methoxyphenyl)-9,10-dihydrocyclohepta[b]indol-8(5H)-one (85q)

Synthesised using **general procedure 2C** with ynone 83q (61 mg, 0.2 mmol) and (Ph₃P)AuNTf₂·½PhMe (31 mg, 0.04 mmol) in CH₂Cl₂ (2 mL) at 40 °C for 24 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the **title compound 85q** (51 mg, 84%) as a yellow solid, mp 209–211 °C; \(v_{\text{max}}\) (cm\(^{-1}\)) 3318, 1625, 1604, 1509, 1331, 1248, 1177, 735; \(\delta_H\) (400 MHz, CDCl₃) 2.88–2.96 (2H, m, H-11), 3.15–3.23 (2H, m, H-10), 3.89 (3H, s, H-19), 6.23 (1H, s, H-13), 6.89–7.04 (2H, m, H-17), 7.15–7.21 (1H, m, H-3), 7.23–7.32 (2H, m, H-4,5), 7.38–7.43 (2H, m, H-16), 7.66 (1H, br d, \(J = 8.0\) Hz, H-2), 7.86 (1H, br
s, H-7); δ_C (100 MHz, CDCl_3) 18.1 (CH_2, C-10), 42.8 (CH_2, C-11), 55.4 (CH_3, C-19), 111.3 (CH, C-5), 114.3 (2CH, C-17), 119.5 (CH, C-2), 120.3 (CH, C-3), 121.1 (C, C-9), 124.4 (CH, C-4), 127.0 (C, C-1), 127.7 (CH, C-13), 130.2 (2CH, C-16), 131.5 (C, C-8/15), 131.7 (C, C-8/15), 135.5 (C, C-6), 145.0 (C, C-14), 160.6 (C, C-18), 200.8 (C, C-12); HRMS (ESI\(^+\)):
Found: 326.1152; C\(_{20}\)H\(_{17}\)NNaO\(_2\) (MNa\(^+\)) Requires 326.1151 (−0.3 ppm error), Found: 304.1331; C\(_{20}\)H\(_{18}\)NO\(_2\) (MH\(^+\)) Requires 304.1332 (0.4 ppm error).

Lab notebook reference: MJJ6/3

6-(4-Methoxyphenyl)-5H,8H,9H,10H,11H-cycloocta[b]indol-8-one (85r)

Synthesised using **general procedure 2C** with ynone 83r (48 mg, 0.15 mmol) and (Ph_3P)AuNTf\(_2\)·\(\frac{1}{2}\)PhMe (24 mg, 0.03 mmol) in CH\(_2\)Cl\(_2\) (1.5 mL) at 40 °C for 24 h. Purification by column chromatography (7:3 hexane:EtOAc) afforded the **title compound 85r** (41 mg, 85%) as a yellow oil, which solidified on standing, mp 204–206 °C; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3307, 2931, 1621, 1603, 1508, 1334, 1248, 1177, 1135, 731; δ_H (400 MHz, CDCl\(_3\)) 2.25–2.35 (2H, m, H-11), 2.44–2.54 (2H, m, H-10), 2.99–3.10 (2H, m, H-12), 3.86 (3H, s, H-20), 6.90–6.95 (2H, m, H-18), 7.17–7.23 (1H, m, H-3), 7.25–7.37 (4H, m, H-4,5,17), 7.70 (1H, d, \(J = 8.0\) Hz, H-2), 8.02 (1H, br s, H-7); δ_C (100 MHz, CDCl\(_3\)) 22.4 (CH_2, C-12), 34.0 (CH_2, C-11), 38.3 (CH_2, C-10), 55.4 (CH_3, C-20), 111.3 (CH, C-5), 114.1 (2CH, C-18), 119.4 (CH, C-2), 120.0 (CH, C-3), 121.9 (C, C-9), 124.4 (CH, C-4), 127.0 (C, C-1), 127.9 (CH, C-14), 131.0 (2CH, C-17), 132.1 (C, C-8/16), 132.5 (C, C-8/16), 136.4 (C, C-6), 144.0 (C, C-15), 161.0 (C, C-19), 204.8 (C, C-13); HRMS (ESI\(^+\)):
Found: 340.1298; C\(_{21}\)H\(_{19}\)NNaO\(_2\) (MNa\(^+\)) Requires 340.1308 (3.1 ppm error), Found: 318.1478; C\(_{21}\)H\(_{20}\)NO\(_2\) (MH\(^+\)) Requires 318.1489 (3.2 ppm error).

Lab notebook reference: MJJ6/16
(R)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthalene (116)

To a suspension of NaH (307 mg, 7.68 mmol, 60% wt.) in THF (12 mL) under argon at 0 °C was added a solution of (R)-BINOL (1.00 g, 3.49 mmol) in THF (5 mL). The mixture was stirred for 1 h under argon at 0 °C, then MOMCl (0.66 mL, 8.73 mmol) was added dropwise. The mixture was stirred for a further 1 h under argon at RT, then quenched with the careful addition of sat. NH₄Cl (aq) (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (silica, 9:1 hexane:EtOAc) to afford the title compound 116 (1.06 g, 81%) as a white solid, mp 98.5–99.5 °C (lit. 98–100 °C); [α]D²⁰ = +91.7 (c 1.0, CHCl₃) [lit. 138 [α]D²⁵ = +95.0 (c 1.0, THF)]; νmax (cm⁻¹) 1592, 1506, 1238, 1147, 1031, 1012, 810, 750; δH (400 MHz, CDCl₃) 3.14 (6H, s), 4.98 (2H, d, J = 7.0 Hz), 5.09 (2H, d, J = 7.0 Hz), 7.17 (2H, d, J = 8.5 Hz), 7.20–7.26 (2H, m), 7.35 (2H, t, J = 8.0 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.88 (2H, d, J = 8.5 Hz), 7.96 (2H, d, J = 9.0 Hz); δC (100 MHz, CDCl₃) 55.8, 95.1, 117.2, 121.2, 124.0, 125.5, 126.2, 127.8, 129.3, 129.8, 134.0, 152.6.

Lab notebook reference: MJJ2/14

Spectroscopic data matched those reported in the literature.¹³⁸

(R)-3,3'-Diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (117)

To a solution of 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (116) (475 mg, 1.27 mmol) in THF (11.4 mL) under argon at 0 °C was added n-BuLi (1.52 mL, 3.81 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C and iodine (967 mg, 3.81 mmol) was added in one portion. The mixture was allowed to warm to RT and stirred for 1.5 h, then poured into sat. NH₄Cl (aq) (15 mL) and extracted with EtOAc (3 × 20 mL). The organics were combined, washed with Na₂S₂O₃ (15 mL), brine (15 mL), dried (MgSO₄) and concentrated in vacuo to afford the title compound 117 (805 mg, 100%) as a pale yellow solid, mp 81–82 °C (lit. ¹³⁹ 127–128 °C); [α]D²⁰ = −35.6 (c 1.0, CHCl₃)
[lit.\textsuperscript{139} [α]\textsubscript{D}\textsuperscript{20} = −9.3 (c 0.98, THF)]; ν\textsubscript{max} (cm\textsuperscript{-1}) 1382, 1345, 1232, 1202, 1158, 1085, 995, 955, 905, 748; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.60 (6H, s), 4.70 (2H, d, J = 6.0 Hz), 4.82 (2H, d, J = 6.0 Hz), 7.18 (2H, dd, J = 8.5, 0.5 Hz), 7.28–7.34 (2H, m), 7.41–7.46 (2H, m), 7.79 (2H, d, J = 8.0 Hz), 8.55 (2H, s); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 56.4, 92.4, 99.3, 125.8, 126.2, 126.5, 126.7, 127.1, 132.1, 133.7, 139.9, 152.1.

Lab notebook reference: MJJ2/37

Spectroscopic data matched those reported in the literature.\textsuperscript{139}

(R)-4-Hydroxy-2,6-di(naphthalen-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (114b)

![Chemical structure of 114b](image)

Synthesised using general procedure 2E with naphthalen-1-ylboronic acid (66 mg, 0.384 mmol). Purification by column chromatography (CH\textsubscript{2}Cl\textsubscript{2}, then 9:1 CH\textsubscript{2}Cl\textsubscript{2}:MeOH) afforded the title compound 114b (57 mg, 59%) as an off white solid; [α]\textsubscript{D}\textsuperscript{20} = −120.7 (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 6.83–8.03 (24H, m); δ\textsubscript{p} (162 MHz, CDCl\textsubscript{3}) 3.1 (br s). Ag-114b synthesised using general procedure 2H using CPA 114b (56 mg, 0.0932 mmol), Ag\textsubscript{2}CO\textsubscript{3} (12.9 mg, 0.0466 mmol), CH\textsubscript{2}Cl\textsubscript{2} (0.9 mL) and H\textsubscript{2}O (0.9 mL) to afford the silver salt as an off white solid (50 mg, 76%).

Lab notebook reference: MJJ2/43 + MJJ2/45

Spectroscopic data matched those reported in the literature.\textsuperscript{140}
(R)-4-Hydroxy-2,6-di(naphthalen-2-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide oxide (114c)

Synthesised using general procedure 2E with naphthalen-2-ylboronic acid (66 mg, 0.384 mmol). Purification by column chromatography (CH₂Cl₂, then 9:1 CH₂Cl₂:MeOH) afforded the title compound 114c (78 mg, 81%) as an off-white solid; [α]₂₀⁰ = −268.3 (c 1.0, CHCl₃) [lit.141 [α]₂⁰ = −265.0 (c 0.2, CHCl₃)]; v max (cm⁻¹) 1252, 1102, 857, 747; δH (400 MHz, CDCl₃) 7.00–7.19 (4H, m), 7.20–7.58 (14H, m), 7.63–7.76 (2H, m), 7.86–7.94 (2H, m), 7.97–8.07 (2H, m); δp (162 MHz, CDCl₃) 0.3 (br s).

Ag-114c synthesised using general procedure 2H using CPA 114c (78 mg, 0.130 mmol), Ag₂CO₃ (18 mg, 0.065 mmol), CH₂Cl₂ (1.3 mL) and H₂O (1.3 mL) to afford the silver salt as an off-white solid (50 mg, 54%).

Lab notebook reference: MJJ2/48 + MJJ2/49

Spectroscopic data matched those reported in the literature.141

(R)-2,6-Di([1,1'-biphenyl]-4-yl)-4-hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (114d)

Synthesised using general procedure 2E with [1,1'-biphenyl]-4-ylboronic acid (76 mg, 0.384 mmol). Purification by column chromatography (CH₂Cl₂, then 39:1 CH₂Cl₂:MeOH) afforded the title compound 114d (54 mg, 50%) as a white solid; [α]₂₀⁰ = −204.1 (c 1.0, CHCl₃) [lit.140 [α]₂⁰ = −335.6 (c 1.2, CHCl₃)]; δH (400 MHz, CDCl₃) 6.89–7.64 (24H, m) 7.74–7.89 (2H, m), 7.91–8.08 (2H, m); δp (162 MHz, CDCl₃) 1.5 (br s). Ag-114d synthesised using general
procedure 2H using CPA 114d (44 mg, 0.0674 mmol), Ag$_2$CO$_3$ (8.3 mg, 0.0337 mmol), CH$_2$Cl$_2$ (1.0 mL) and H$_2$O (1.0 mL) to afford the silver salt as an off white solid (33 mg, 64%).

Lab notebook reference: MJJ2/54 + MJJ2/58

Spectroscopic data matched those reported in the literature.$^{140}$

(R)-4-Hydroxy-2,6-di(pyren-1-yl)dinaphtho[2,1-d:1’,2’-f][1,3,2]dioxaphosphepine 4-oxide (114e)

Synthesised using general procedure 2E with pyren-1-yl boronic acid (95 mg, 0.384 mmol). Purification by column chromatography (CH$_2$Cl$_2$, then 20:1 CH$_2$Cl$_2$:MeOH) afforded the title compound 114e (24 mg, 20%) as a yellow solid; $[\alpha]_{D}^{20} = -90.0$ (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (cm$^{-1}$) 1437, 1182, 1119, 1096, 906, 842, 719, 693, 538; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.20–8.20 (28H, m); $\delta_{\text{p}}$ (162 MHz, CDCl$_3$) 29.9 (s). Ag-114e synthesised using general procedure 2H using CPA 114e (23 mg, 0.0307 mmol), Ag$_2$CO$_3$ (4.2 mg, 15.4 µmol), CH$_2$Cl$_2$ (0.5 mL) and H$_2$O (0.5 mL) to afford the silver salt as a yellow solid (23 mg, 88%)

Lab notebook reference: MJJ2/62 + MJJ2/70
(R)-2,6-Di[(1,1′:3′,1′″-terphenyl)-5′-yl]-4-hydroxydinoxaphosphine[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide (114f)

Synthesised using general procedure 2E with [1,1′:3′,1′″-terphenyl]-5′-ylboronic acid (105 mg, 0.384 mmol). Purification by column chromatography (CH₂Cl₂, then 20:1 CH₂Cl₂:MeOH) afforded the title compound 114f (121 mg, 94%) as a white solid; [α]₀ 20 = −202.3 (c 1.0, CHCl₃) [lit. 142 (S enantiomer) [α]₀ 32 = 247.1 (c 1.0, CHCl₃)]; v max (cm⁻¹) 1594, 1437, 1261, 1182, 1104, 758, 723, 696, 542; δH (400 MHz, CDCl₃) 7.03–7.14 (3H, m), 7.15–7.51 (27H, m), 7.89–8.04 (6H, m); δC (100 MHz, CDCl₃) 123.2, 124.6, 125.3, 126.2, 127.0, 127.3, 127.9, 128.1, 128.2, 128.7, 130.8, 131.0, 131.7, 131.8, 131.9, 132.5, 134.0, 138.9, 140.7, 141.3; δ3P (162 MHz, CDCl₃) 4.5 (br s).

Ag-114f synthesised using general procedure 2H using CPA 114f (121 mg, 0.150 mmol), Ag₂CO₃ (21 mg, 0.075 mmol), CH₂Cl₂ (2 mL) and H₂O (2 mL) to afford the silver salt as a pale yellow solid (113 mg, 83%).

Lab notebook reference: MJJ2/73 + MJJ2/74
Spectroscopic data matched those reported in the literature. 142

(R)-2,2′-Bis(methoxymethoxy)-3,3′-bis(perfluorophenyl)-1,1′-binaphthalene (118g)

To a solution of (R)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (117) (475 mg, 1.27 mmol) in THF (11.4 mL) under argon at 0 °C was added n-BuLi (1.52 mL, 3.81 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C and hexafluorobenzene (967 mg, 3.81 mmol) was added in one portion. The mixture was allowed to warm to RT and stirred for 16 h, then poured into sat. NH₄Cl (aq) (15 mL) and extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine (15 mL),
dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (silica, 9:1 hexane:EtOAc) to afford the title compound **118g** (745 mg, 78%) as a white solid, mp 72–74 °C; [α]₀²⁰ = −19.1 (c 1.0, CHCl₃); δₜ (400 MHz, CDCl₃) 2.63 (6H, s), 4.43 (2H, d, J = 6.0 Hz), 4.48 (2H, d, J = 6.0 Hz), 7.34 (2H, d, J = 8.5 Hz), 7.39–7.45 (2H, m), 7.48–7.54 (2H, m), 7.94 (2H, d, J = 8.0 Hz), 7.98 (2H, s); δ_F (376 MHz, CDCl₃) -162.4–-162.1 (4F, m), −154.7 (2F, t, J = 20.5 Hz), −139.7 (2F, dd, J = 23.0, 8.0 Hz), −139.1 (2F, dd, J = 23.0, 8.0 Hz).

Lab notebook reference: MJJ2/16

Spectroscopic data matched those reported in the literature.¹⁴³

**(R)-3,3’-Bis(perfluorophenyl)-[1,1’-binaphthalene]-2,2’-diol (119g)**

To a stirred solution of **(R)-2,2’-bis(methoxymethoxy)-3,3’-bis(perfluorophenyl)-1,1’-binaphthalene** (118g) (710 mg, 1.00 mmol) in MeOH (7 mL) and CH₂Cl₂ (1.5 mL) was added 12 M HCl (aq) (0.22 mL, 2.60 mmol). The mixture was stirred for 16 h at 50 °C, then poured into sat. NaHCO₃ (aq) (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The organics were dried (MgSO₄) and concentrated in vacuo to afford the title compound **119g** (613 mg, 99%) without further purification as a white solid, mp 122–124 °C; [α]₀²⁰ = +87.5 (c 1.0, CHCl₃); δₜ (400 MHz, CDCl₃) 5.25 (2H, s), 7.24–7.28 (2H, m), 7.43–7.51 (4H, m), 7.95–7.98 (2H, m), 8.04 (2H, s); δ_F (376 MHz, CDCl₃) −162.3 (4F, quind, J = 23.0, 8.0 Hz), −154.5 (2F, t, J = 20.5 Hz), −139.9 (2F, dd, J = 23.0, 8.0 Hz), −139.5 (2F, dd, J = 23.0, 8.0 Hz).

Lab notebook reference: MJJ2/17

Spectroscopic data matched those reported in the literature.¹⁴⁴
(R)-4-Hydroxy-2,6-bis(perfluorophenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (114g)

To a stirred solution of (R)-3,3'-bis(perfluorophenyl)-[1,1'-binaphthalene]-2,2'-diol (119g) (592 mg, 0.98 mmol) in pyridine (2.1 mL) was added POCl₃ (0.18 mL, 1.91 mmol) was added dropwise. The mixture was stirred for 16 h under argon at RT then cooled to 0 °C and 12 M HCl (aq) (2 mL) was added. The mixture was stirred for a further 5 h at RT then poured into 10% HCl (aq) (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The organics were then washed with 10% HCl (aq) (5 × 30 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (9:1 CH₂Cl₂:MeOH) then dissolved in CH₂Cl₂ (10 mL), washed with 10% HCl (aq) (2 × 10 mL), dried (Na₂SO₄) and concentrated in vacuo to afford the title compound 114g (612 mg, 93%) as a white powder; [α]D₂₀ = −236.0 (c 1.0, CHCl₃) [lit.¹⁴] [α]D₂⁴ = −164.5 (c 1.0, CHCl₃); δH (400 MHz, DMSO-d₆) 7.34 (2H, d, J = 8.5 Hz), 7.43–7.49 (2H, m), 7.53–7.58 (2H, m), 8.12 (2H, d, J = 8.0 Hz), 8.24 (2H, s); δF (376 MHz, DMSO-d₆) −164.4 (2F, td, J = 24.0, 7.0 Hz), −163.1–−162.9 (2F, m), −155.9 (2F, t, J = 22.0 Hz), −139.6 (2F, dd, J = 24.0, 7.0 Hz), −138.7 (2F, dd, J = 24.0, 7.0 Hz); δP (162 MHz, DMSO-d₆) 4.24.

Ag-114g synthesised using general procedure 2H using CPA 114g (50 mg, 0.0735 mmol), Ag₂CO₃ (10 mg, 0.037 mmol), CH₂Cl₂ (0.7 mL) and H₂O (0.7 mL) to afford the silver salt as a pale yellow solid (20 mg, 34%).

Lab notebook reference: MJJ/2/21 + MJJ2/23

Spectroscopic data matched those reported in the literature.¹⁴³

(S)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (121)

To a solution of (S)-(H₈)-BINOL (500 mg, 1.70 mmol) in CH₂Cl₂ (9.5 mL) under argon at −30 °C was added bromine (0.19 mL, 3.74 mmol) dropwise. The mixture was stirred for 40 min at −30 °C, then quenched with sat. Na₂S₂O₃ (aq) (10 mL) and allowed to warm to room temperature. The organics were separated, washed with sat. NaHCO₃ (aq) (10 mL), brine (10
mL), dried (MgSO$_4$) and concentrated in vacuo. The crude material was recrystallised from warm hexane to afford the title compound 121 (718 mg, 94%) as an off white solid, mp 138–140 °C; [$\alpha$]$^D_{20} = -25.7$ (c 1.0, CHCl$_3$) [lit.$^{145}$ (R enantiomer) [$\alpha$]$^D_{25} = 21.2$ (c 0.1, CHCl$_3$)]; $\nu_{\text{max}}$ (cm$^{-1}$) 3511, 1930, 1450, 1265, 1211, 1179, 1159, 909, 731; $\delta_H$ (400 MHz, CDCl$_3$) 1.60–1.79 (8H, m), 2.06–2.16 (2H, m), 2.25–2.36 (2H, m), 2.69–2.83 (2H, m), 5.11 (2H, s), 7.30 (2H, s); $\delta_C$ (100 MHz, CDCl$_3$) 22.7, 22.8, 26.9, 29.0, 107.2, 122.2, 131.5, 132.5, 136.7, 147.2.

Lab notebook reference: MJJ2/68

Spectroscopic data matched those reported in the literature.$^{146}$

(S)-5′,5″,6′,6″,7′,7″,8′,8″-octahydro-[1,2′:4′,1″:3″,1‴-quaternaphthalene]-2″,3′-diol (122a)

Synthesised using general procedure 2F with (S)-3,3′-dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′-binaphthalene]-2,2′-diol 121 (100 mg, 0.221 mmol), Pd(OAc)$_2$ (2.0 mg, 0.009 mmol), di(1-adamantyl)-n-butylphosphine (3.9 mg, 0.011 mmol), naphthalen-1-ylboronic acid (95 mg, 0.553 mmol), DME (2.2 mL) and 1 M K$_2$CO$_3$ (aq) (1.1 mL). Purification by column chromatography (silica gel, hexane to 9:1 hexane:EtOAc) afforded the title compound 122a (129 mg, 100%) as a pale yellow oil, [$\alpha$]$^D_{20} = +25.0$ (c 1.0, CHCl$_3$) [lit.$^{147}$ (R enantiomer) [$\alpha$]$^D_{18} = -35.2$ (c 1.0, CHCl$_3$)]; $\nu_{\text{max}}$ (cm$^{-1}$) 3527, 2928, 1449, 1234, 802, 778, 753; $\delta_H$ (400 MHz, CDCl$_3$) 1.79–1.99 (8H, m), 2.40–2.74 (4H, m), 2.81–2.94 (4H, m), 4.77 (0.5H, s, rotamer), 4.79 (0.5H, s, rotamer), 4.83 (0.5H, s, rotamer), 4.86 (0.5H, s, rotamer), 7.14–7.19 (2H, m), 7.38–7.65 (8H, m), 7.73 (0.5H, d, $J = 8.5$ Hz, rotamer), 7.79–7.87 (1.5H, m, rotamers), 7.89–8.00 (4H, m).

Lab notebook reference: MJJ2/89

Spectroscopic data matched those reported in the literature.$^{147}$
(S)-3,3’-Di(phenanthren-9-yl)-5,5’,6,6’,7,7’,8,8’-octahydro-[1,1’-binaphthalene]-2,2’-diol (122b)

Synthesised using **general procedure 2F** with (S)-3,3’-dibromo-5,5’,6,6’,7,7’,8,8’-octahydro-[1,1’-binaphthalene]-2,2’-diol 121 (100 mg, 0.221 mmol), Pd(OAc)$_2$ (2.0 mg, 0.009 mmol), di(1-adamantyl)-n-butylphosphine (3.9 mg, 0.011 mmol), phenanthren-9-ylboronic acid (123 mg, 0.553 mmol), DME (2.2 mL) and 1 M K$_2$CO$_3$ (aq) (1.1 mL). Purification by column chromatography (silica gel, hexane to 7:3 hexane:CH$_2$Cl$_2$) afforded the **title compound 122b** (140 mg, 98%) as a white solid, mp 206–209 °C (lit. $^{148}$ 193–195 °C); $[\alpha]_D^{20} = 50.4$ (c 1.0, CHCl$_3$) [lit.$^{148}$ R enantiomer $[\alpha]_D^{23} = -45.3$ (c 0.5, CHCl$_3$)]; $\nu_{\text{max}}$ (cm$^{-1}$) 3528, 2928, 1450, 1227, 771, 747, 726; $\delta_H$ (400 MHz, CDCl$_3$) 1.83–2.04 (8H, m), 2.47–2.81 (4H, m), 2.86–2.98 (4H, m), 4.87 (0.5H, s, rotamer), 4.88 (0.5H, s, rotamer), 4.92 (0.5H s, rotamer), 4.97 (0.5H, s, rotamer), 7.21–7.28 (2H, m), 7.47–7.60 (1H, m), 7.61–7.85 (8H, m), 7.87–8.02 (5H, m), 8.73–8.87 (4H, m).

Lab notebook reference: MJJ2/79

Spectroscopic data matched those reported in the literature.$^{148}$
(S)-4-Hydroxy-2,6-di(naphthalen-1-yl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1- 
d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (123a)

Synthesised using general procedure 2G with diol 122a (129 mg, 0.236 mmol), pyridine (1 mL) and POCl$_3$ (0.04 mL, 0.429 mmol). Then DMAP (3 mg, 0.022 mmol), 2 M NaOH$_{aq}$ (1 mL) and THF (1 mL). Purification by column chromatography (19:1 CH$_2$Cl$_2$:MeOH then 9:1 CH$_2$Cl$_2$:MeOH) afforded the title compound 123a (125 mg, 87%) as an off white solid, [α]$_D$ = 65.0 (c 0.5, CHCl$_3$) [lit. $^{147}$ (R enantiomer) [α]$_D$ = −146.5 (c 1.0, CH$_2$Cl$_2$)]; $\nu_{max}$ (cm$^{-1}$) 2929, 1261, 1089, 1017, 801, 778; $\delta$H (400 MHz, DMSO-d$_6$) 1.61–1.94 (8H, m), 2.31–2.47 (2H, m), 2.73–2.95 (6H, m), 7.33–7.56 (8H, m), 7.59–7.71 (2H, m), 7.81–7.98 (4H, m); $\delta$$_p$ (162 MHz, DMSO-d$_6$) 3.2 (s); Ag-123a synthesised using general procedure 2H using CPA 123 (122 mg, 0.200 mmol) Ag$_2$CO$_3$ (27.6 mg, 0.100 mmol), CH$_2$Cl$_2$ (2 mL) and H$_2$O (2 mL) to afford the silver salt as an off white solid (117 mg, 82%).

Lab notebook reference: MJJ2/92 + MJJ2/95

Spectroscopic data matched those reported in the literature. $^{149}$
(S)-4-hydroxy-2,6-di(phenanthren-9-yl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-
d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (123b)

Synthesised using general procedure 2G with diol 122b (140 mg, 0.216 mmol), pyridine (0.5 mL) and POCl₃ (0.04 mL, 0.429 mmol). Then DMAP (3 mg, 0.022 mmol), 2 M NaOH(ₐq) (1 mL) and THF (1 mL). Purification by column chromatography (19:1 CH₂Cl₂:MeOH) afforded the title compound 123b (142 mg, 93%) as a white solid, [α]D²⁰ = +26.5 (c 1.0, CHCl₃); νmax (cm⁻¹) 2931, 1423, 1243, 1101, 1087, 749, 727; δH (400 MHz, DMSO-d₆) 1.58–1.94 (8H, m), 2.35–2.51 (2H, m), 2.71–2.94 (6H, m), 7.00–7.09 (2H, m), 7.44–7.68 (10H, m), 7.85–8.01 (4H, m), 8.76–8.88 (4H, m); δp (162 MHz, DMSO-d₆) 0.39 (br s). Ag-123b synthesised using general procedure 2H using CPA 123b (132 mg, 0.186 mmol) Ag₂CO₃ (26 mg, 0.0931 mmol), CH₂Cl₂ (2 mL) and H₂O (2 mL) to afford the silver salt as an off white solid (112 mg, 74%).

Lab notebook reference: MJJ2/84 + MJJ2/87
Spectroscopic data matched those reported in the literature.

(S)-2,6-Bis(3,5-dimethylphenyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (123c)

Synthesised using general procedure 2G with (S)-3,3'-bis(3,5-dimethylphenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-dil (102 mg, 0.203 mmol), pyridine (0.5
mL) and POCl₃ (0.04 mL, 0.429 mmol). Then DMAP (2.5 mg, 0.0203 mmol), 2 M NaOH (aq) (1 mL) and THF (1 mL). Purification by column chromatography (9:1 CH₂Cl₂:MeOH) afforded the title compound 123c (38 mg, 33%) as a pale yellow solid; [α]D²⁰ = +260.8 (c 1.0, CH₂Cl₂); v max (cm⁻¹) 2925, 1260, 1234, 1098, 1082, 845, 801, 713; δH (400 MHz, CDCl₃) 1.56–1.68 (2H, m), 1.76–1.87 (6H, m), 2.13 (12H, br s), 2.25–2.36 (2H, m), 2.62–2.93 (6H, m), 6.79 (2H, br s, ArH), 7.04 (2H, br s, ArH), 7.09 (2H, br s, ArH); δC (100 MHz, CDCl₃) 21.4 (CH₃), 23.3 (CH₂), 23.4 (CH₂), 28.3 (CH₂), 29.7 (CH₂), 30.3 (CH₂), 128.0 (CH), 128.6 (C), 128.9 (CH), 131.2 (CH), 132.0 (C), 132.1 (C), 134.4 (C), 137.2 (C), 138.0 (C), 138.6 (C), 144.8 (C), 144.9 (C); δp (162 MHz, CDCl₃) −0.24 (br s); HRMS (APCI⁺): Found: 565.2481; C₃₆H₃₈O₄P (MH⁺) Requires 565.2502 (3.8 ppm error).

Ag-123c synthesised using general procedure 2H using CPA 123c (31 mg, 0.0549 mmol), Ag₂CO₃ (7.6 mg, 0.0275 mmol), CH₂Cl₂ (0.6 mL) and H₂O (0.6 mL) to afford the silver salt as an off white solid (17 mg, 46%).

Lab notebook reference: MJJ2/15 + MJJ2/18

(1E,4E)-1,5-Bis(3-methoxyphenyl)penta-1,4-dien-3-one (128)

To a solution of NaOH (15 g, 375 mmol) in EtOH/H₂O (264 mL, 1:1 v/v) was added drop-wise a solution of m-anisaldehyde (20 g, 147 mmol) in acetone (5.4 mL, 73.4 mmol) and EtOH (20 mL). The mixture was stirred for 2 h at RT. The mixture was poured into water (300 mL) and extracted with CH₂Cl₂ (3 × 300 mL). The organics were combined, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (15–30% EtOAc in hexane) to afford the title compound 128 (10.95 g, 51%) as a yellow oil; v max (cm⁻¹) 1652, 1619, 1577, 1594, 1253, 1184, 1157, 1041, 982, 783; δH (400 MHz, CDCl₃) 3.87 (6H, s), 6.97 (2H, ddd, J = 8.0, 3.0, 1.0 Hz), 7.07 (2H, d, J = 16.0 Hz), 7.13–7.16 (2H, m), 7.23 (2H, br d, J = 7.5 Hz), 7.34 (2H, dd, J = 8.0, 7.5 Hz), 7.71 (2H, d, J = 16.0 Hz); δC (100 MHz, CDCl₃) 55.2, 113.2, 116.2, 121.0, 125.5, 129.8, 136.0, 143.1, 159.8, 188.7.

Lab notebook reference: MJJ2/69

Spectroscopic data matched those reported in the literature.⁶⁹
1,5-Bis(3-methoxyphenyl)pentan-3-one (129)

To a suspension of Raney Ni (34 mL, volume of solid in undisturbed suspension) in acetone (40 mL) was added a solution of dienone 128 (5.32 g, 18.1 mmol) in acetone (85 mL). The mixture was stirred for 16 h at RT under H₂. The reaction mixture was carefully decanted through celite, ensuring the Raney Ni remained wet. To the retained Raney Ni was added a second solution of dienone 129 (5.63 g, 19.1 mmol) in acetone (85 mL). The mixture was stirred for 16 h at RT under H₂. The mixture was carefully decanted through celite and the two filtrates were combined. The combined filtrates were poured into water (100 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The organics were dried (MgSO₄) and concentrated in vacuo to afford the title compound 129 (crude, 9.35 g, 84%) as a pale yellow oil; ν_max (cm⁻¹) 2938, 1713, 1601, 1584, 1490, 1258, 1153, 1043, 781, 696; δ_H (400 MHz, CDCl₃) 2.72 (4H, dd, J = 8.0, 7.5 Hz), 2.88 (4H, dd, J = 8.0, 7.5 Hz), 3.80 (6H, s), 6.71–6.78 (6H, m), 7.20 (2H, t, J = 8.0 Hz); δ_C (100 MHz, CDCl₃) 29.7, 44.3, 55.1, 111.4, 114.0, 120.6, 129.4, 142.6, 159.7, 209.0.

Lab notebook reference: MJ2/75

Spectroscopic data matched those reported in the literature.⁶⁹

1,5-Bis(2-bromo-5-methoxyphenyl)pentan-3-one (130)

To a solution of ketone 129 (9.35 g, 31.3 mmol) in CH₂Cl₂ (172 mL) and pyridine (9.39 mL, 116 mmol) at −10 °C was added Br₂ (4.01 mL, 78.3 mmol) dropwise. Upon complete addition the reaction mixture was allowed to warm to RT and stirred for 4 h. The mixture was poured into Na₂S₂O₃ (aq) (200 mL), the organics were collected, washed with 10% HCl (aq) (100 mL) and water (100 mL). The organics were dried (MgSO₄) and concentrated in vacuo to afford the title compound 130 (crude, 13.05 g, 91%) as a yellow oil; ν_max (cm⁻¹) 2936, 1714, 1572, 1471, 1241, 1163, 1056, 1016, 802, 601; δ_H (400 MHz, CDCl₃) 2.74 (4H, dd, J = 8.0, 7.5 Hz), 2.97 (4H, dd, J = 8.0, 7.5 Hz), 3.78 (6H, s), 6.64 (2H, dd, J = 9.0, 3.0 Hz), 6.78 (2H, d, J
= 3.0 Hz), 7.40 (2H, d, $J = 9.0$ Hz); $\delta_C$ (100 MHz, CDCl$_3$) 30.6, 42.5, 55.4, 113.6, 114.6, 116.2, 133.3, 141.2, 159.0, 208.4.

Lab notebook reference: MJJ2/81

Spectroscopic data matched those reported in the literature.$^{69}$

**4,4'-Dibromo-7,7'-dimethoxy-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (131)**

Ketone 130 (13.05 g, 28.6 mmol) was dissolved in PPA (115 g) and stirred for 6 h at 105 °C. The mixture was carefully poured into water (500 mL) and extracted with CH$_2$Cl$_2$ (5 × 500 mL). The organics were dried onto silica gel and eluted through a pad of silica gel with hexane:EtOAc (9:1). The filtrate was concentrated in vacuo to afford the title compound 131 (crude, 9.53 g, 76%) as a yellow solid; $v_{\text{max}}$ (cm$^{-1}$) 2934, 1471, 1262, 1081, 798; $\delta_H$ (400 MHz, CDCl$_3$) 2.13–2.21 (2H, m), 2.27–2.37 (2H, m), 2.90–3.01 (2H, m), 3.02–3.12 (2H, m), 3.53 (6H, s), 6.53 (2H, d, $J = 8.5$ Hz), 7.27 (2H, d, $J = 8.5$ Hz); $\delta_C$ (100 MHz, CDCl$_3$) 33.1, 37.9, 55.3, 61.8, 110.5, 110.8, 130.3, 138.0, 144.8, 155.6.

Lab notebook reference: MJJ2/82

Spectroscopic data matched those reported in the literature.$^{69}$

**7,7'-Dimethoxy-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (132)**

To a solution of 131 (9.53 g, 21.7 mmol) in THF (190 mL) at −78 °C was added n-BuLi (34.7 mL, 86.8 mmol, 2.5 M in hexanes) drop-wise. The mixture was stirred for 1 h at −78 °C then quenched with the slow addition of EtOH (8 mL). The mixture was diluted with water (150 mL) and extracted with CH$_2$Cl$_2$ (3 × 150 mL). The organics were dried (MgSO$_4$) and concentrated in vacuo to afford the title compound 132 (crude, 6.10 g, 100%) as a yellow solid; $v_{\text{max}}$ (cm$^{-1}$) 2931, 1586, 1475, 1232, 1097, 1085, 1061, 773; $\delta_H$ (400 MHz, CDCl$_3$) 2.14–
2.23 (2H, m), 2.31–2.41 (2H, m), 2.95–3.13 (4H, m), 3.55 (6H, s), 6.64 (2H, d, J = 8.0 Hz), 6.87 (2H, d, J = 7.5 Hz), 7.15 (2H, dd, J = 8.0, 7.5 Hz); δC (100 MHz, CDCl₃) 31.6, 38.8, 55.2, 59.2, 108.6, 116.8, 127.5, 136.9, 145.3, 156.5.

Lab notebook reference: MJJ2/85

Spectroscopic data matched those reported in the literature.⁶⁹

### 2,2',3,3'-Tetrahydro-1,1'-spirobi[indene]-7,7'-diol (133)

To a solution of 132 (6.10 g, 22.8 mmol) in CH₂Cl₂ (100 mL) at −78 °C was added drop-wise BBr₃ (52.4 mL, 52.5 mmol, 1M in CH₂Cl₂). Upon complete addition the mixture was allowed to warm to RT and stirred overnight. The reaction mixture was carefully poured into water (100 mL) and extracted with CH₂Cl₂ (2 × 100 mL). The organics were combined, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (5–10% EtOAc in hexane) to afford the title compound 133 (3.14 g, 57%) as a white solid, mp 112–113 °C (lit.⁶⁹ 115–116 °C); vₘₐₓ (cm⁻¹) 3516, 2936, 1586, 1463, 1278, 1231, 1181, 995, 777, 734; δH (400 MHz, CDCl₃) 2.15–2.26 (2H, m), 2.29–2.36 (2H, m), 2.97–3.13 (4H, m), 4.60 (2H, s), 6.69 (2H, d, J = 8.0 Hz), 6.91 (2H, dd, J = 7.5, 1.0 Hz), 7.19 (2H, dd, J = 8.0, 7.5 Hz); δC (100 MHz, CDCl₃) 31.2, 37.4, 57.4, 114.2, 117.6, 129.8, 130.5, 145.8, 152.8.

Lab notebook reference: MJJ2/90

Spectroscopic data matched those reported in the literature.⁶⁹
7,7'-Bis-(L-methyloxy-carbonyloxy)-1,1'-spiorbiindane (134 and 135)

To a solution of 133 (3.14 g, 12.4 mmol), Et₃N (6.47 mL, 46.4 mmol) and DMAP (152 mg, 1.24 mmol) in CH₂Cl₂ (124 mL) was added L-menthyl chloroformate (6.45 mL, 30.1 mmol). The mixture was stirred for 16 h at RT. The mixture was washed with water (100 mL), 10% HCl (aq) (100 mL) and brine (100 mL). The organics were dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (3% Et₂O in hexane) to afford the title compound 135 (1.81 g, 24%) as a white solid (134 not isolated), mp 187–188 °C (lit. 69 185.5–186 °C); v_{max} (cm⁻¹) 2951, 1753, 1267, 1258, 1236; δ_H (400 MHz, CDCl₃) 0.68 (6H, d, J = 7.0), 0.74–1.03 (18H, m), 1.17–1.28 (2H, m), 1.33–1.46 (2H, m), 1.47–1.57 (2H, m), 1.57–1.67 (4H, m), 1.86–1.94 (2H, m), 2.12–2.22 (2H, m), 2.23–2.32 (2H, m), 2.91–3.11 (4H, m), 4.36 (2H, ddd, J = 11.0, 10.5, 4.5 Hz), 6.93 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 7.5 Hz), 7.21 (2H, dd, J = 8.0, 7.5 Hz); δ_C (100 MHz, CDCl₃) 14.1, 16.0, 20.7, 21.9, 22.6, 23.0, 25.5, 31.1, 31.3, 31.6, 34.0, 38.4, 40.4, 46.7, 58.9, 78.6, 120.4, 122.2, 128.0, 139.2, 145.6, 147.5, 153.3.

Lab notebook reference: MJJ2/91

Spectroscopic data matched those reported in the literature. 69
(S)-SPINOL (136)

To a solution of 135 (731 mg, 1.19 mmol) in THF (8 mL) was added NH₂NH₂·H₂O (0.41 mL). The mixture was stirred for 2 h at 70 °C under argon. The mixture was diluted with CH₂Cl₂ (50 mL) and washed with 10% HCl (aq) (20 mL) and water (20 mL). The organics were dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (15% EtOAc in hexane) to afford the title compound (S)-SPINOL (291 mg, 97%) as a white solid, mp 153–155 °C (lit. 155–156 °C); [α]D⁰⁻²⁰ = −24.9 (c 1.0, CHCl₃) [lit. 69] [α]D²⁵ = −32.7 (c 1.0, CHCl₃); νmax (cm⁻¹) 3516, 2936, 1586, 1463, 1278, 1231, 1181, 995, 777, 734; δH (400 MHz, CDCl₃) 2.15–2.26 (2H, m), 2.29–2.36 (2H, m), 2.97–3.13 (4H, m), 4.60 (2H, s), 6.69 (2H, d, J = 8.0 Hz), 6.91 (2H, dd, J = 7.5, 1.0 Hz), 7.19 (2H, dd, J = 8.0, 7.5 Hz); δC (100 MHz, CDCl₃) 31.2, 37.4, 57.4, 114.2, 117.6, 129.8, 130.5, 145.8, 152.8.

Lab notebook reference: MJJ3/2

Spectroscopic data matched those reported in the literature. 69

(S)-6,6'-Di(phenanthren-9-yl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol (139)

To a solution of 136 (25 mg, 0.10 mmol), KHCO₃ (20 mg, 0.20 mmol) in CH₂Cl₂ (0.5 mL) at −30 °C was added a solution of NBS (36.5 mg, 0.205 mmol) in CH₂Cl₂ (2 mL) over 30 min. The mixture was stirred for 4 h at −30 °C. The mixture was poured into 10% HCl (aq) (5 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The organics were concentrated in vacuo and then eluted through a silica plug (9:1 hexane:EtOAc) to afford a crude inseparable mixture of
dibrominated (137) and tribrominated (138) material. The crude material was combined with Pd(OAc)$_2$ (0.45 mg, 2 µmol), (Ad)$_2$BuP (0.9 mg, 2.5 µmol), phenanthen-9-ylboronic acid (39 mg, 0.175 mmol) in 1 M K$_2$CO$_3$ (aq) (0.25 mL) and DME (0.5 mL). The mixture was purged by alternating vacuum and argon three times. The mixture was stirred for 16 h under argon at 95 °C, then poured into sat. NH$_4$Cl (aq) (5 mL) and extracted with CH$_2$Cl$_2$ (3 × 5 mL). The organics were combined, dried (MgSO$_4$) and concentrated in vacuo. The crude material was purified by column chromatography (5% EtOAc in hexane) to afford the title compound 139 (12 mg, 20%) as a colourless oil; [α]$_D^{20}$ = −37.9 (c 1.0, CHCl$_3$); $v_{	ext{max}}$ (cm$^{-1}$) 3524, 2929, 1440, 1226, 748, 726; δ$_H$ (400 MHz, CDCl$_3$) 2.42–2.62 (4H, m), 3.06–3.28 (4H, m), 4.79 (0.5H, s, rotamer), 4.86 (0.5H, s, rotamer), 4.88 (0.5H, s, rotamer), 4.97 (0.5H, s, rotamer), 6.68–6.74 (0.5 H, m), 6.95–7.02 (2H, m), 7.07–7.13 (0.5H, m), 7.15–7.23 (2H, m), 7.41–7.92 (13H, m), 8.68–8.83 (4H, m).


Spectroscopic data matched those reported in the literature.$^{151}$

(S)-6,6’-Bis(9-phenanthryl)-1,1’-spirobiindanyl-7,7’-diylhydrogenphosphate (126)

Synthesised using general procedure 2G with diol 126 (12 mg, 0.020 mmol), pyridine (0.2 mL) and POCl$_3$ (0.01 mL, 0.040 mmol). Then DMAP (0.24 mg, 2 µmol), 2 M NaOH (aq) (0.2 mL) and THF (0.2 mL) for 2 days. Purification by column chromatography (CH$_2$Cl$_2$ then 9:1 CH$_2$Cl$_2$:MeOH) afforded the title compound 126 (12 mg, 90%) as a colourless oil; [α]$_D^{20}$ = −297.6 (c 1.0, CHCl$_3$); $v_{	ext{max}}$ (cm$^{-1}$) 2926, 1618, 1440, 1258, 1218, 1093, 1025, 815, 748, 726; δ$_H$ (400 MHz, CDCl$_3$) 2.41–2.64 (4H, m), 2.77–3.12 (2H, m), 3.15–3.35 (2H, m), 7.14–7.23 (6H, m), 7.30–7.77 (11H, m), 7.79–7.87 (1H, m), 8.36–8.63 (4H, m); δ$_p$ (162 MHz, CDCl$_3$) −7.5 (br s), −9.2 (br s). Ag-126 synthesised using general procedure 2H using CPA 126 (12 mg, 0.186 mmol) Ag$_2$CO$_3$ (2.5 mg, 9 µmol), CH$_2$Cl$_2$ (0.2 mL) and H$_2$O (0.2 mL) to afford the silver salt as a pale yellow solid (14 mg, 100%).

Lab notebook reference: MJJ3/35 + MJJ3/37
Spectroscopic data matched those reported in the literature.\(^{151}\)

1-(1H-Indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-ol (144a)

Synthesised using **general procedure 2I** with ynone 83a (100mg, 0.346 mmol), MeOH (13 mL) and NaBH\(_4\) (52 mg, 1.38 mmol). Purified by column chromatography (3:2 hexane:EtOAc) to afford **title compound 144a** (97 mg, 96%) as a brown oil; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3412, 1605, 1509, 1248, 1029, 832, 744; \(\delta_H\) (400 MHz, CDCl\(_3\)) 2.49 (1H, br s, H-18), 3.27 (1H, ddd, \(J=14.5, 6.5, 0.5\) Hz, H-10a), 3.34 (1H, ddd, \(J=14.5, 6.0, 0.5\) Hz, H-10b), 3.80 (3H, s, H-19), 4.90 (1H, dd, \(J=6.5, 6.0\) Hz, H-11), 6.81–6.86 (2H, m, H-16), 7.12–7.20 (2H, m, H-3,8), 7.21–7.26 (1H, m, H-4), 7.31–7.38 (3H, m, H-5,15), 7.75 (1H, d, \(J=8.0\) Hz, H-2), 8.24 (1H, br s, H-7); \(\delta_C\) (100 MHz, CDCl\(_3\)) 34.0 (CH\(_2\), C-10), 55.2 (CH\(_3\), C-19), 62.9 (CH, C-11), 84.9 (C, C-12), 88.8 (C, C-13), 110.4 (C, C-9), 111.2 (CH, C-5), 113.8 (2CH, C-16), 114.6 (C, C-14), 119.0 (CH, C-2), 119.4 (CH, C-3), 122.0 (CH, C-4), 123.5 (CH, C-8), 127.6 (C, C-1), 133.1 (2CH, C-15), 136.1 (C, C-6), 159.5 (C, C-17); HRMS (ESI\(^+\)): Found: 314.1136; C\(_{19}\)H\(_{17}\)NNaO\(_2\) (MNa\(^+\)) Requires 314.1151 (4.9 ppm error), Found: 292.1330; C\(_{19}\)H\(_{18}\)NO\(_2\) (MH\(^+\)) Requires 292.1332 (0.7 ppm error).

Lab notebook reference: MJJ4/43

1-(1H-Indol-3-yl)-4-phenylbut-3-yn-2-ol (114b)

Synthesised using **general procedure 2I** with ynone 83b (250 mg, 0.96 mmol), NaBH\(_4\) (140 mg, 3.70 mmol) and MeOH (19 mL). Purified by column chromatography (7:3 petrol:EtOAc) afford the **title compound 144b** (230 mg, 92%) as a yellow oil; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3413, 1489, 1457, 1070, 1029, 743, 691; \(\delta_H\) (400 MHz, CDCl\(_3\)) 2.24 (1H, br s, H-18), 3.29 (1H, ddd, \(J=14.5, 6.5, 0.5\) Hz, H-10a), 3.35 (1H, ddd, \(J=14.5, 5.5, 0.5\) Hz, H-10b), 4.91 (1H, dd, \(J=6.5, 5.5\) Hz, H-11), 7.14–7.20 (2H, m, H-8,17), 7.21–7.27 (1H, m, H-3), 7.28–7.36 (3H, m, H-4,16),
7.37–7.43 (3H, m, H-5,15), 7.73–7.77 (1H, m, H-2), 8.15 (1H, br s, H-7); \( \delta_c \) (100 MHz, CDCl\(_3\)) 34.0 (CH\(_2\), C-10), 62.9 (CH, C-11), 85.0 (C, C-12), 90.1 (C, C-13), 110.5 (C, C-9), 111.2 (CH, C-5), 119.1 (CH, C-2), 119.6 (CH, C-3), 122.1 (CH, C-4), 122.6 (C, C-14), 123.5 (CH, C-8), 127.7 (C, C-1), 128.2 (2CH, C-16), 128.3 (CH, C-17), 131.7 (2CH, C-15), 136.2 (C, C-6); HRMS (ESI\(^+\)): Found: 284.1057; C\(_{18}\)H\(_{15}\)NNaO (MNa\(^+\)) Requires 284.1046 (−4.0 ppm error), Found: 262.1233; C\(_{18}\)H\(_{16}\)NO (MH\(^+\)) Requires 262.1226 (−2.6 ppm error).

Lab notebook reference: MJJ3/10

1-(1H-Indol-3-yl)oct-3-yn-2-ol (144c)

Synthesised using general procedure 2I with ynone 83h (500 mg, 2.09 mmol), MeOH (42 mL) and NaBH\(_4\) (316 mg, 8.36 mmol). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 144c (340 mg, 67 %) as a brown oil; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3410, 2930, 1457, 1027, 1010, 738; \( \delta_h \) (400 MHz, CDCl\(_3\)) 0.91 (3H, t, \( J = 7.5 \) Hz, H-17), 1.33–1.54 (4H, m, H-15,16), 2.21 (2H, td, \( J = 7.5, 2.0 \) Hz, H-14), 2.49 (1H, br s, H-18), 3.14 (1H, dd, \( J = 14.5, 7.5 \) Hz, H-10a), 3.23 (1H, dd, \( J = 14.5, 6.0 \) Hz, H-10b), 4.62–4.72 (1H, m, H-11), 7.12–7.18 (2H, m, H-3,8), 7.19–7.25 (1H, m, H-4), 7.38 (1H, d, \( J = 8.0 \) Hz, H-5), 7.69 (1H, d, \( J = 8.0 \) Hz, H-2), 8.14 (1H, br s, H-7); \( \delta_c \) (100 MHz, CDCl\(_3\)) 13.6 (CH\(_3\), C-17), 18.4 (CH\(_2\), C-14), 21.9 (CH\(_2\), C-15/16), 30.6 (CH\(_2\), C-15/16), 34.4 (CH\(_2\), C-10), 62.6 (CH, C-11), 81.0 (C, C-12/13), 85.7 (C, C-12/13), 110.9 (C), 111.1 (CH, C-5), 119.1 (CH, C-2), 119.5 (CH, C-3), 122.1 (CH, C-4), 123.3 (CH, C-8), 127.7 (C, C-1), 136.2 (C, C-6); HRMS (ESI\(^+\)): Found: 264.1352; C\(_{16}\)H\(_{20}\)NNaO (MNa\(^+\)) Requires 264.1359 (2.4 ppm error), Found: 242.1534; C\(_{16}\)H\(_{20}\)NO (MH\(^+\)) Requires 242.1539 (2.2 ppm error).

Lab notebook reference: BSC
4-(4-Fluorophenyl)-1-(1H-indol-3-yl)but-3-yn-2-ol (144d)

Synthesised using **general procedure 2I** with ynone 83d (2.06 g, 7.43 mmol), MeOH (150 mL) and NaBH₄ (1.12 g, 29.7 mmol). Purification by column chromatography (1:1 petrol:EtOAc) afforded the **title compound 144d** (2.02 g, 97%) as a brown oil; $v_{\text{max}}$ (cm⁻¹) 3411, 1601, 1506, 1229, 1011, 836, 743; $\delta$H (400 MHz, CDCl₃) 2.18 (1H, br s, H-18), 3.27 (1H, dd, $J = 14.0, 6.5$ Hz, H-10a), 3.34 (1H, ddd, $J = 14.0, 5.5$ Hz, H-10b), 4.88 (1H, dd, $J = 6.0, 6.0$ Hz, H-11), 6.96–7.03 (2H, m, H-16), 7.13–7.18 (1H, m, H-3), 7.20 (1H, br d, $J = 2.5$ Hz, H-8), 7.21–7.26 (1H, m, H-4), 7.32–7.38 (2H, m, H-15), 7.40 (1H, br d, $J = 8.0$ Hz, H-5), 7.74 (1H, br d, $J = 7.5$ Hz, H-2), 8.15 (1H, br s, H-7); $\delta$C (100 MHz, CDCl₃) 34.0 (CH₂, C-10), 62.9 (CH, C-11), 84.0 (C, C-12), 89.7 (C, C-13), 110.5 (C, C-9), 111.2 (CH, C-5), 115.5 (2CH, d, $J = 22$ Hz, C-16), 118.7 (C, d, $J = 3.0$ Hz, C-14), 119.1 (CH, C-2), 119.6 (CH, C-3), 122.2 (CH, C-4), 123.4 (CH, C-8), 127.7 (C, C-1), 133.6 (2CH, d, $J = 8.5$ Hz, C-15), 136.2 (C, C-6), 162.5 (C, d, $J = 250$ Hz, C-17); $\delta_F$ (376 MHz, CDCl₃) –110.6–110.8 (1F, m); HRMS (ESI⁺): Found: 302.0937; C₁₈H₁₄FNNO (MNa⁺) Requires 302.0952 (4.7 ppm error), Found: 280.1121; C₁₈H₁₄FNO (MH⁺) Requires 280.1132 (4.0 ppm error).

Lab notebook reference: BSC

4-Cyclopropyl-1-(1H-indol-3-yl)but-3-yn-2-ol (144e)

Synthesised using **general procedure 2J** with Weinreb 81a (500 mg, 2.29 mmol), ethynylcyclopropane (0.58 mL, 6.87 mmol), n-BuLi (2.29 mL, 5.73 mmol, 2.5 M in hexanes) and THF (7 mL + 21 mL). Then NaBH₄ (346 mg, 9.16 mmol) and MeOH (46 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the **title compound 144e** (384 mg, 74%) as a yellow oil; $v_{\text{max}}$ (cm⁻¹) 3408, 2236, 1456, 1027, 1010, 740; $\delta$H (400 MHz, CDCl₃) 0.61–0.83 (4H, m, H-15), 1.21–1.32 (1H, m, H-14), 2.13 (1H, br s, C-16), 3.13 (1H, dd, $J = 14.5, 7.0$ Hz, H-10a), 3.22 (1H, dd, $J = 14.5, 5.5$ Hz, H-10b), 4.59–4.69 (1H, m, H-11),
7.09 (1H, d, J = 2.5 Hz, H-8), 7.16 (1H, dd, J = 8.0, 7.5 Hz, H-3), 7.23 (1H, dd, J = 8.0, 7.5 Hz, H-4), 7.36 (1H, d, J = 8.0 Hz, H-5), 7.69 (1H, d, J = 8.0 Hz, H-2), 8.18 (1H, br s, H-7); δC (100 MHz, CDCl3) −0.6 (CH, C-14), 8.0 (2CH2, C-15), 34.3 (CH2, C-10), 62.6 (CH, C-11), 76.3 (C, C-12/13), 88.7 (C, C-12/13), 110.7 (C, C-9), 111.1 (CH, C-5), 119.0 (CH, C-2), 119.4 (CH, C-3), 122.0 (CH, C-4), 123.4 (CH, C-8), 127.6 (C, C-1), 136.1 (C, C-6); HRMS (ESI+): Found: 248.1047; C15H15NNaO (MNa+) Requires 248.1046 (−0.3 ppm error).

Lab notebook reference: MJJ5/14

1-(1H-Indol-3-yl)-4-(thiophen-2-yl)but-3-yn-2-ol (144f)

Synthesised using general procedure 21 with ynone 83i (186 mg, 0.701 mmol), NaBH4 (106 mg, 2.80 mmol) and MeOH (14 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 144f (139 mg, 74%) as a brown oil; νmax (cm⁻¹) 3411, 2221, 1456, 1033, 743, 704; δH (400 MHz, CDCl3) 2.20 (1H, d, J = 5.0 Hz, H-18), 3.25 (1H, dd, J = 14.0, 6.5 Hz, H-10a), 3.32 (1H, dd, J = 14.0, 5.5 Hz, H-10b), 4.84–4.92 (1H, m, H-11), 6.95 (1H, dd, J = 4.5, 4.0 Hz, H-16), 7.12–7.27 (5H, m, ArH), 7.37 (1H, d, J = 8.0 Hz, H-5), 7.72 (1H, d, J = 8.0 Hz, H-2), 8.12 (1H, br s, H-7); δC (100 MHz, CDCl3) 33.8 (CH2, C-10), 63.0 (CH, C-11), 78.4 (C, C-12), 93.9 (C, C-13), 110.3 (C, C-9), 111.2 (CH, C-5), 119.1 (CH, C-2), 119.6 (CH, CAr), 122.2 (CH, CAr), 122.5 (C, C-14), 123.5 (CH, CAr), 126.9 (CH, CAr), 127.2 (CH, Ar), 127.6 (C, C-1), 132.2 (CH, C-17), 136.2 (C, C-6); HRMS (ESI+): Found: 290.0611; C16H13NNaOS (MNa+) Requires 290.0610 (−0.3 ppm error), Found: 268.0782; C16H14NOS (MH+) Requires 268.0791 (3.3 ppm error).

Lab notebook reference: MJJ4/94
1-(2-Methyl-1H-indol-3-yl)-4-phenylbut-3-yn-2-ol (144g)

Synthesised using **general procedure 2J** with Weinreb **81a** (313 mg, 1.35 mmol), phenylacetylene (0.44 mL, 4.05 mmol), n-BuLi (1.35 mL, 3.38 mmol, 2.5 M in hexanes) and THF (4 mL + 12 mL). Then NaBH₄ (204 mg, 5.40 mmol) and MeOH (27 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound **144g** (282 mg, 76%) as a yellow oil; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3400, 1489, 1462, 1041, 1011, 908, 739, 691; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 2.45 (3H, s, H-9), 3.25 (1H, dd, J = 14.0, 6.5 Hz, H-11a), 3.30 (1H, dd, J = 14.0, 6.0 Hz, H-11b), 4.86–4.94 (1H, m, H-12), 7.11–7.21 (2H, m, ArH), 7.28–7.36 (4H, m, ArH), 7.38–7.43 (2H, m, ArH), 7.67 (1H, dd, J = 8.0 Hz, H-2), 7.92 (1H, br s, H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 11.9 (CH\(_3\), C-9), 32.9 (CH\(_2\), C-11), 63.3 (CH, C-12), 84.8 (C, C-13), 90.3 (C, C-14), 106.0 (C, C-10), 110.2 (CH, C-5), 118.2 (CH, C-2), 119.4 (CH, CA), 121.1 (CH, CA), 122.6 (C, C-15), 128.17 (2CH, C-17), 128.23 (CH, CA), 128.9 (C, C-1), 131.6 (2CH, C-16), 133.4 (C, C-6/8), 135.2 (C, C-6/8); HRMS (ESI\(^+\)): Found: 298.1212; C\(_{19}\)H\(_{17}\)NNaO (MNa\(^+\)) Requires 298.1202 (−3.4 ppm error), Found: 276.1390; C\(_{19}\)H\(_{18}\)NO (MH\(^+\)) Requires 276.1383 (−2.4 ppm error).

Lab notebook reference: MJJ4/51

1-(1H-Indol-3-yl)-4-(trimethylsilyl)but-3-yn-2-ol (144h) & 1-(1H-Indol-3-yl)but-3-yn-2-ol (114i)

Synthesised using **general procedure 2J** with **79** (1.00 g, 4.58 mmol), trimethylsilylacetylene (1.94 mL, 13.7 mmol), n-BuLi (4.60 mL, 11.5 mmol, 2.5 M in hexanes) and THF (14 mL + 41 mL). Then NaBH₄ (692 mg, 18.3 mmol) and MeOH (90 mL). Purification by column chromatography (7:3 then 3:2 hexane:EtOAc) afforded the title compounds **144h** (676 mg, 57%) as a brown oil and **144i** (205 mg, 24%) as a brown oil.
Chapter 5. Experimental

Data for **144h**: $v_{\text{max}}$ (cm$^{-1}$) 3412, 1457, 1249, 838, 737; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 0.19 (9H, s, H-14), 2.27 (1H, d, $J = 5.5$ Hz, H-15), 3.17 (1H, dd, $J = 14.5$, 7.0 Hz, H-10a), 3.25 (1H, dd, $J = 14.5$, 5.5 Hz, H-10b), 4.62–7.41 (1H, m, H-11), 7.06 (1H, d, $J = 2.0$ Hz, H-8), 7.16 (1H, dd, $J = 7.5$, 7.5 Hz, H-3), 7.23 (1H, dd, $J = 8.0$, 7.5 Hz, H-4), 7.34 (1H, d, $J = 8.0$ Hz, H-5), 7.71 (1H, d, $J = 7.5$ Hz, H-2), 8.17 (1H, br s, H-7); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) −0.26 (CH$_3$, C-14), 33.8 (CH$_2$, C-10), 62.7 (CH, C-11), 89.6 (C, C-13), 106.6 (C, C-12), 110.2 (C, C-9), 111.2 (CH, C-5), 119.1 (CH, C-2), 119.4 (CH, C-3), 122.0 (CH, C-4), 123.5 (CH, C-8), 127.5 (C, C-1), 136.1 (C, C-6); HRMS (ESI$^+$): Found: 280.1121; C$_{15}$H$_{19}$NNaO (MNa$^+$) Requires 280.1128 (2.7 ppm error), Found: 258.1303; C$_{15}$H$_{20}$NO (MH$^+$) Requires 258.1309 (2.2 ppm error).

Propargyl alcohol **144i** was also synthesised by adding K$_2$CO$_3$ (475 mg, 3.44 mmol) to a solution of alcohol **144h** (589 mg, 2.29 mmol) in MeOH (11.5 mL). After stirring for 5 h the reaction mixture was diluted with H$_2$O (20 mL) and extracted with DCM (4 × 30 mL). The organics were combined, washed with brine, dried (MgSO$_4$) and concentrated in vacuo. The crude material was purified by column chromatography (3:2 hexane:EtOAc) to afford the title compound **144i** (420 mg, 99%) as a brown oil.

Lab notebook reference: MJJ4/27 + 4/54

**1-(1H-Indol-3-yl)-2-methyl-4-phenylbut-3-yn-2-ol (144j)**

To a solution of ynone **83b** (200 mg, 0.771 mmol) in THF (7.7 mL) at −78 °C under argon was added drop-wise MeLi (1.93 mL, 3.08 mmol, 1.6 M in Et$_2$O) and the mixture was stirred for 4 h at −78 °C. The mixture was quenched by the careful addition of sat. NH$_4$Cl(aq) (10 mL)
and diluted with EtOAc (5 mL). The organics were separated and the aqueous extracted with EtOAc (2 × 10 mL). The organics were combined, washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (7:3 hexanes:EtOAc) to afford the title compound 114j (175 mg, 82%) as a yellow oil; \(v_{\text{max}}\) (cm⁻¹) 3411, 1489, 1104, 742, 691; \(\delta_{\text{H}}\) (400 MHz, CDCl₃) 1.71 (3H, s, H-19), 2.42 (1H, br s, H-18), 3.33 (1H, d, \(J = 14.0\) Hz, H-10a), 7.11–7.16 (1H, m, H-3), 7.18–7.23 (2H, m, H-4,8), 7.24–7.34 (5H, m, H-15,16,17), 7.37 (1H, d, \(J = 8.0\) Hz, H-5), 7.79 (1H, dd, \(J = 8.0, 1.0\) Hz, H-2), 8.17 (1H, br s, H-7); \(\delta_{\text{C}}\) (100 MHz, CDCl₃) 29.4 (CH₃, C-19), 39.6 (CH₂, C-10), 68.7 (C, C-11), 83.4 (C, C-12), 93.4 (C, C-13), 110.5 (C, C-9), 111.1 (CH, C-5), 119.6 (CH, C-2/3), 119.7 (CH, C-2/3), 122.0 (CH, C-4), 122.8 (C, C-14), 124.0 (CH, C-8), 128.1 (3CH, C-16,17), 128.3 (C, C-1), 131.6 (2CH, C-15), 136.0 (C, C-6); HRMS (ESI⁺): Found: 298.1201; \(\text{C}_{19}\text{H}_{17}\text{NNaO}^+(\text{M}^+\text{Na})\) Requires 298.1202 (0.6 ppm error).

Lab notebook reference: MJJ4/11

1-(1H-Indol-3-yl)-2,4-diphenylbut-3-yn-2-ol (144k)

To a solution of ynone 83b (159 mg, 0.613 mmol) in THF (6.1 mL) at −78 °C under argon was added drop-wise PhLi (1.29 mL, 2.45 mmol, 1.9 M in Bu₂O) and the mixture was stirred for 5 h at −78 °C. The mixture was quenched by the careful addition of sat. NH₄Cl (aq) (10 mL) and diluted with EtOAc (5 mL). The organics were separated and the aqueous extracted with EtOAc (2 × 10 mL). The organics were combined, washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (8:2 hexanes:EtOAc) to afford the title compound 144k (173 mg, 84%) as a yellow oil; \(v_{\text{max}}\) (cm⁻¹) 3416, 1490, 1456, 1070, 1010, 756, 742, 692; \(\delta_{\text{H}}\) (400 MHz, CDCl₃) 2.84 (1H, br s, H-18), 3.45 (1H, d, \(J = 14.0\) Hz, H-10a), 3.53 (1H, d, \(J = 14.0\) Hz, H-10b), 7.08–7.16 (2H, m, ArH), 7.22 (1H, dd, \(J = 7.5, 7.0\) Hz, ArH), 7.26–7.40 (7H, m, ArH), 7.43 (2H, dd, \(J = 8.0, 7.5\) Hz, ArH), 7.72 (1H, d, \(J = 8.0\) Hz, ArH), 7.81 (2H, d, \(J = 7.5\) Hz, ArH), 8.11 (1H, br s, H-7); \(\delta_{\text{C}}\) (100 MHz, CDCl₃) 42.2 (CH₂, C-10), 73.6 (C, C-11), 85.9 (C, C-12), 92.0 (C, C-13), 110.2 (C, C-9), 111.0 (CH, CAr), 119.6 (CH, CAr), 119.7 (CH, CAr), 122.0 (CH, CAr), 122.6 (C, C-14), 124.2 (CH, CAr), 125.6 (2CH, CAr), 127.7 (CH, CAr), 128.15 (2CH, CAr), 128.16 (2CH, CAr), 128.3 (CH, CAr), 128.4 (C, C-1), 131.7 (2CH, CAr), 135.9 (C, C-6), 144.4 (C,
C-19); HRMS (ESI⁺): Found: 360.1355; C₂₄H₁₉NNaO (MNa⁺) Requires 360.1359 (1.1 ppm error).

Lab notebook reference: MJJ4/93

3-(2-((tert-Butyldimethylsilyl)oxy)-4-phenylbut-3-yn-1-yl)-1H-indole (144l)

To a stirred solution of propargyl alcohol 144b (100 mg, 0.383 mmol), imidazole (37, 0.536 mmol) and DMAP (5 mg, 0.038 mmol) in CH₂Cl₂ (4 mL) was added TBSCI (115 mg, 0.766 mmol). The mixture was stirred for 16 h, then filtered through Celite, washing with CH₂Cl₂ (20 mL). The collected filtrate was washed with 10% HCl(aq) (10 mL) and water (10 mL) successively. The organics were collected, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by column chromatography (hexane then 9:1 hexane:EtOAc) to afford the title compound 144l (95 mg, 66%) as a pale red oil; v_max (cm⁻¹) 3420, 2958, 2927, 2856, 1490, 1457, 1253, 1081, 778, 756, 740; δ_H (400 MHz, CDCl₃) 0.05 (3H, s, H-19a), 0.07 (3H, s, H-19b), 0.92 (9H, s, H-21), 3.25 (1H, dd, J = 14.0, 7.0 Hz, H-10a), 3.29 (1H, dd, J = 14.0, 6.5 Hz, H-10b), 4.83 (1H, dd, J = 7.0, 6.5 Hz, H-11), 7.12–7.18 (2H, m, H-8,17), 7.19–7.24 (1H, m, H-3), 7.28-7.33 (3H, m, H-4,16), 7.35–7.41 (3H, m, H-5,15), 7.71 (1H, d, J = 8.0 Hz, H-2), 8.03 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) –5.0 (CH₃, C-19a), –4.8 (CH₃, C-19b), 18.3 (C, C-20), 25.8 (3CH₃, C-21), 34.9 (CH₃, C-10), 64.3 (CH, C-11), 84.4 (C, C-12), 91.3 (C, C-13), 111.0 (CH, C-5), 111.9 (C, C-9), 119.0 (CH, C-2), 119.3 (CH, C-3), 121.8 (CH, C-4), 123.1 (C, C-14), 123.2 (CH, C-8), 127.9 (C, C-1), 128.0 (CH, C-17), 128.2 (2CH, C-16), 131.5 (2CH, C-15), 136.0 (C, C-6); HRMS (ESI⁺): Found: 398.1892; C₂₄H₂₉NNaO(Si) (MNa⁺) Requires 398.1911 (4.8 ppm error).

Lab notebook reference: MJJ4/53
2-(4-Methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-ol (145a)

Synthesised using general procedure 2K with alcohol 144a (81 mg, 0.278 mmol), Ag$_2$O (3.2 mg, 0.0139 mmol), AgNO$_3$ (4.7 mg, 0.0278 mmol) and CH$_2$Cl$_2$ (2.8 mL). Purification by column chromatography (2%→10% MeOH in DCM) afforded the title compound 145a (77 mg, 98%, 54:46 dr) as a yellow oil; $v_{\text{max}}$ (cm$^{-1}$) 3295, 2930, 1606, 1510, 1251, 1180, 1032, 908, 828, 756, 730; $\delta$H (400 MHz, CDCl$_3$) 2.06 (1H, dd, $J = 14.0$, 4.0 Hz, H-10a, major), 2.33 (1H, dd, $J = 13.5$, 4.0 Hz, H-10b minor), 2.46 (2H, br s, H-19, major + minor), 2.47 (1H, dd, $J = 13.5$, 6.5 Hz, H-10b, minor), 2.80 (1H, dd, $J = 14.0$, 7.0 Hz, H-10b, major), 3.68 (6H, s, H-18, major + minor), 5.20–5.27 (1H, m, H-11, major), 5.28–5.35 (1H, m, H-11, minor), 6.49 (2H, br s, H-12, major + minor), 6.57–6.63 (4H, m, ArH, major + minor), 6.71–6.78 (4H, m, ArH, major + minor), 7.17–7.29 (3H, m, ArH, major + minor), 7.38 (2H, m, J = 8.0, 7.5 Hz, ArH, major + minor), 7.44 (1H, d, $J = 7.5$ Hz, H-2, major), 7.70 (1H, d, $J = 8.0$ Hz, H-5, major), 7.72 (1H, d, $J = 8.0$ Hz, H-5, minor), 8.11 (1H, s, H-8, major), 8.25 (1H, s, H-8, minor); $\delta$C (100 MHz, CDCl$_3$) 42.5 (CH$_2$), 43.6 (CH$_2$), 55.0 (2CH$_3$), 69.6 (C), 69.9 (C), 74.7 (CH), 74.8 (CH), 113.65 (2CH), 113.69 (2CH), 121.2 (CH), 121.5 (CH), 121.8 (CH), 123.0 (CH), 126.4 (2C), 126.87 (CH), 126.93 (2CH), 127.0 (3CH), 128.2 (2CH), 132.4 (CH), 142.0 (C), 142.5 (C), 144.0 (C), 144.8 (C), 154.58 (C), 154.61 (C), 159.48 (C), 159.54 (C), 177.3 (CH), 177.4 (CH); HRMS (ESI$^+$): Found: 292.1321; C$_{19}$H$_{18}$NO$_2$ (MH$^+$) Requires 292.1332 (3.8 ppm error).

Lab notebook reference: MMJ4/46

2-Phenylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (145b)

Synthesised using general procedure 2K with alcohol 144b (100 mg, 0.383 mmol), Ag$_2$O (4.4 mg, 0.0192 mmol), AgNO$_3$ (6.5 mg, 0.0383 mmol) and CH$_2$Cl$_2$ (3.8 mL). Purification by column chromatography (2%→10% MeOH in DCM) afforded the title compound 145b (96 mg, 96%, 54:46 dr) as a brown oil; $v_{\text{max}}$ (cm$^{-1}$) 3294, 1549, 1455, 1445, 1075, 1014, 907, 776,
752, 731, 692; δ_H (400 MHz, CDCl₃) 2.08 (1H, dd, J = 13.5, 4.0 Hz, H-10a, major), 2.35 (1H, dd, J = 13.5, 4.0 Hz, H-10a, minor), 2.47 (1H, dd, J = 13.5, 6.5 Hz, H-10b, major), 2.61 (2H, br s, H-18, major + minor), 2.80 (1H, dd, J = 13.5, 7.0 Hz, H-10b, major), 5.22–5.29 (1H, m, H-11, major), 5.31–5.37 (1H, m, H-11, minor), 6.58 (1H, d, J = 2.5 Hz, H-12, major), 6.59 (1H, d, J = 2.5 Hz, H-12, minor), 6.76–6.84 (4H, m, ArH, major + minor), 7.03–7.17 (6H, m, ArH, major + minor), 7.18–7.26 (3H, m, ArH, major + minor), 7.34–7.41 (2H, m, ArH, major + minor), 7.45 (1H, d, J = 7.5 Hz, H-2, major), 7.70 (1H, d, J = 8.0 Hz, H-5, major), 7.72 (1H, d, J = 8.0 Hz, H-5, minor), 8.11 (1H, s, H-8, major), 8.25 (1H, s, H-8, minor); δ_C (100 MHz, CDCl₃) 42.5 (CH₂), 43.6 (CH₂), 69.6 (C), 69.9 (C), 74.68 (CH), 74.71 (CH), 121.2 (CH), 121.5 (CH), 121.7 (CH), 123.0 (CH), 125.6 (2CH), 125.7 (2CH), 126.9 (CH), 127.1 (CH), 128.25 (3CH), 128.28 (2CH), 128.32 (3CH), 133.9 (2C), 134.2 (CH), 134.4 (CH), 141.8 (C), 142.3 (C), 144.6 (C), 145.3 (C), 154.6 (2C), 177.0 (CH), 177.1 (CH); HRMS (ESI⁺): Found: 262.1214; C₁₈H₁₆NO (MH⁺) Requires 262.1226 (−4.7 ppm error).

Lab notebook reference: MJJ4/44

2-n-Butylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (145c)

Synthesised using general procedure 2K with alcohol 144c (154 mg, 0.638 mmol), Ag₂O (7.4 mg, 0.0319 mmol), AgNO₃ (10.8 mg, 0.0638 mmol) and CH₂Cl₂ (6.4 mL). Purification by column chromatography (2%→10% MeOH in DCM) afforded the title compound 145c (141 mg, 92%, 53:47 dr) as a brown oil; v_max (cm⁻¹) 3315, 2956, 2828, 2871, 1551, 1455, 1048, 1022, 751; δ_H (400 MHz, CDCl₃) 0.74 (6H, dd, J = 7.5, 7.0 Hz, H-17, major + minor), 1.05–1.30 (8H, m, H-15,16, major + minor), 1.34–1.51 (4H, m, H-14, major + minor), 2.01 (1H, dd, J = 14.0, 4.0 Hz, H-10a, major), 2.22 (1H, dd, J = 14.0, 3.0 Hz, H-10a, minor), 2.46 (1H, dd, J = 14.0, 6.5 Hz, H-10b, minor), 2.71 (2H, br s, H-18, major + minor), 2.72 (1H, dd, J = 14.0, 7.0 Hz, H-10b, major), 5.12–5.18 (1H, m, H-11, major), 5.18–5.22 (1H, m, H-11, minor), 5.94–5.96 (1H, m, H-12, major), 5.96–5.99 (1H, m, H-12, minor), 7.17 (1H, dd, J = 7.5, 1.5 Hz, H-2, major/minor), 7.22–7.30 (2H, m, ArH, major + minor), 7.32–7.38 (2H, m, ArH, major + minor), 7.39–7.42 (1H, m, ArH, major/minor), 7.63 (1H, br d, J = 7.5 Hz, H-5, major), 7.64 (1H, br d, J = 8.0 Hz, H-5, minor), 7.88 (1H, s, H-8, major), 8.07 (1H, s, H-8, minor); δ_C (100 MHz, CDCl₃) 13.7 (2CH₃), 22.2 (2CH₃), 26.7 (CH₂), 26.9 (CH₂), 29.6 (CH₂), 29.8 (CH₂), 40.7 (CH₂), 41.6 (CH₂), 71.1 (C), 71.5 (C), 75.60 (CH), 75.63 (CH), 120.8 (CH),
121.0 (CH), 121.8 (CH), 122.8 (CH), 126.5 (CH), 126.6 (CH), 128.06 (CH), 128.09 (CH), 131.3 (CH), 131.6 (CH), 141.2 (C), 141.6 (C), 147.6 (C), 149.0 (C), 155.2 (C), 155.4 (C), 176.7 (CH), 177.0 (CH); HRMS (ESI⁺): Found: 264.1364; C₁₆H₁₉NaN (MNa⁺) Requires 264.1359 (−1.8 ppm error), Found: 242.1546; C₁₆H₂₀NO (MH⁺) Requires 242.1539 (−2.8 ppm error).

Lab notebook reference: MJJ4/55

2-(4-Fluorophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-ol (145d)

Synthesised using general procedure 2K with alcohol 144d (95 mg, 0.340 mmol), Ag₂O (3.9 mg, 0.0170 mmol) and CH₂Cl₂ (3.4 mL). Purification by column chromatography (2→10% MeOH in DCM) afforded the title compound 145d (93 mg, 98%, 52:48 dr) as a brown oil; v_max (cm⁻¹) 3330, 2928, 1673, 1600, 1507, 1259, 1233, 1160, 1023, 832, 732; δ_H (400 MHz, CDCl₃) 2.09 (1H, dd, J = 14.0, 4.0 Hz, H-10a, major), 2.35 (1H, dd, J = 13.5, 3.5 Hz, H-10a, minor), 2.41 (2H, br s, H-18, major + minor), 2.50 (1H, dd, J = 13.5, 6.5 Hz, H-10b, minor), 2.81 (1H, dd, J = 14.0, 7.0 Hz, H-10b, major), 5.21–5.29 (1H, m, H-11, major), 5.29–5.36 (1H, m, H-11, minor), 6.51 (1H, d, J = 2.5 Hz, H-12, major), 6.52 (1H, d, J = 2.0 Hz, H-12, minor), 6.72–6.81 (8H, m, ArH, major + minor), 7.17–7.30 (3H, m, ArH, major + minor), 7.39 (2H, dd, J = 8.0, 7.5 Hz, ArH, major + minor), 7.44 (1H, d, J = 7.5 Hz, H-2, major), 7.69 (1H, d, J = 8.0 Hz, H-5, major), 7.71 (1H, d, J = 7.5 Hz, H-5, minor), 8.10 (1H, s, H-8, major), 8.26 (1H, s, H-8, minor); δ_C (100 MHz, CDCl₃) 42.4 (CH₂), 43.6 (CH₂), 69.7 (C), 70.0 (C), 74.75 (CH), 74.82 (CH), 115.29 (2CH, d, J = 22 Hz), 115.32 (2CH, d, J = 22 Hz), 121.3 (CH), 121.6 (CH), 121.8 (CH), 123.0 (CH), 127.0 (CH), 127.1 (CH), 127.5 (2CH, d, J = 7.5 Hz), 127.6 (2CH, d, J = 8.5 Hz), 128.4 (2CH), 130.0 (C), 130.1 (C), 133.9 (CH), 134.1 (CH), 141.6 (C), 142.0 (C), 143.8 (C), 144.6 (C), 154.69 (C), 154.74 (C), 162.5 (C, d, J = 248 Hz), 162.6 (C, d, J = 249 Hz), 176.8 (CH), 176.9 (CH); δ_F (376 MHz, CDCl₃) −112.6—−112.7 (1F, m, minor), −112.7—−112.8 (1F, m, major); HRMS (ESI⁺): Found: 302.0948; C₁₈H₁₄FNNaO (MNa⁺) Requires 302.0952 (1.2 ppm error), Found: 280.1125; C₁₈H₁₄FNO (MH⁺) Requires 280.1132 (2.6 ppm error).

Lab notebook reference: MJJ4/31
2-Cyclopropylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (145e)

Synthesised using general procedure 2K with alcohol 144e (152 mg, 0.675 mmol), Ag₂O (7.8 mg, 0.0338 mmol), AgNO₃ (11.5 mg, 0.0675 mmol) and CH₂Cl₂ (6.8 mL). Purification by column chromatography (30%→100% EtOAc in hexane) afforded the title compound 145e (132 mg, 87%, 53:47 dr) as a brown oil; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3305, 1456, 1020, 752, 733; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 0.24–0.58 (10H, m, H-14,15, major + minor), 2.03 (1H, dd, \( J = 14.0, 4.0 \) Hz, H-10a, minor), 2.24 (1H, dd, \( J = 14.0, 3.0 \) Hz, H-10a, major), 2.38 (2H, br s, H-18, major + minor), 2.50 (1H, dd, \( J = 14.0, 6.5 \) Hz, H-10b, major), 2.75 (1H, dd, \( J = 14.0, 7.0 \) Hz, H-10b, minor), 5.08–5.14 (1H, m, H-11, minor), 5.14–5.20 (1H, m, H-11, major), 5.68 (1H, d, \( J = 2.0 \) Hz, H-12, minor), 5.70 (1H, d, \( J = 2.0 \) Hz, H-12, major), 7.20–7.32 (4H, m, ArH, major + minor), 7.33–7.40 (2H, m, ArH, major + minor), 7.45 (1H, d, \( J = 7.5 \) Hz, H-2, major), 7.64 (1H, d, \( J = 8.0 \) Hz, H-5, minor), 7.65 (1H, d, \( J = 7.5 \) Hz, H-5, major), 7.93 (1H, s, H-8, minor), 8.11 (1H, s, H-8, major); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 7.5 (CH₂), 7.7 (CH₂), 8.1 (CH), 8.2 (CH), 8.35 (CH₂), 8.37 (CH₂), 40.7 (CH₂), 41.7 (CH₂), 71.3 (C), 71.6 (C), 75.4 (2CH), 120.8 (CH), 121.0 (CH), 122.0 (CH), 123.0 (CH), 126.5 (CH), 126.6 (CH), 127.2 (CH), 127.4 (CH), 128.07 (CH), 128.10 (CH), 141.4 (C), 141.7 (C), 150.3 (C), 151.5 (C), 155.2 (C), 155.4 (C), 176.7 (CH), 177.0 (CH); HRMS (ESI⁺): Found: 248.1042; C₁₅H₁₅NNaO (MNa⁺) Requires 248.1046 (1.4 ppm error), Found: 226.1224; C₁₅H₁₆NO (MH⁺) Requires 226.1226 (1.1 ppm error).

Lab notebook reference: MJJ5/21

2-(Thiophen-2-yl)spiro[cyclopent[2]ene-1,3'-indol]-4-ol (145f)

Synthesised using general procedure 2K with alcohol 144f (68 mg, 0.254 mmol), Ag₂O (2.9 mg, 0.0127 mmol), AgNO₃ (4.3 mg, 0.0254 mmol) and CH₂Cl₂ (2.5 mL). Purification by column chromatography (2→10% MeOH in DCM) afforded the title compound 145f (65 mg, 96%, 59:41 dr) as a pale brown oil; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3307, 1455, 1046, 754, 731, 701; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 0.24–0.58 (10H, m, H-14,15, major + minor), 2.03 (1H, dd, \( J = 14.0, 4.0 \) Hz, H-10a, minor), 2.24 (1H, dd, \( J = 14.0, 3.0 \) Hz, H-10a, major), 2.38 (2H, br s, H-18, major + minor), 2.50 (1H, dd, \( J = 14.0, 6.5 \) Hz, H-10b, major), 2.75 (1H, dd, \( J = 14.0, 7.0 \) Hz, H-10b, minor), 5.08–5.14 (1H, m, H-11, minor), 5.14–5.20 (1H, m, H-11, major), 5.68 (1H, d, \( J = 2.0 \) Hz, H-12, minor), 5.70 (1H, d, \( J = 2.0 \) Hz, H-12, major), 7.20–7.32 (4H, m, ArH, major + minor), 7.33–7.40 (2H, m, ArH, major + minor), 7.45 (1H, d, \( J = 7.5 \) Hz, H-2, major), 7.64 (1H, d, \( J = 8.0 \) Hz, H-5, minor), 7.65 (1H, d, \( J = 7.5 \) Hz, H-5, major), 7.93 (1H, s, H-8, minor), 8.11 (1H, s, H-8, major); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 7.5 (CH₂), 7.7 (CH₂), 8.1 (CH), 8.2 (CH), 8.35 (CH₂), 8.37 (CH₂), 40.7 (CH₂), 41.7 (CH₂), 71.3 (C), 71.6 (C), 75.4 (2CH), 120.8 (CH), 121.0 (CH), 122.0 (CH), 123.0 (CH), 126.5 (CH), 126.6 (CH), 127.2 (CH), 127.4 (CH), 128.07 (CH), 128.10 (CH), 141.4 (C), 141.7 (C), 150.3 (C), 151.5 (C), 155.2 (C), 155.4 (C), 176.7 (CH), 177.0 (CH); HRMS (ESI⁺): Found: 248.1042; C₁₅H₁₅NNaO (MNa⁺) Requires 248.1046 (1.4 ppm error), Found: 226.1224; C₁₅H₁₆NO (MH⁺) Requires 226.1226 (1.1 ppm error).
MHz, CDCl$_3$) 2.11 (1H, dd, $J = 14.0$, 4.0 Hz, H-10a, major), 2.34 (1H, dd, $J = 13.5$, 3.0 Hz, H-10a, minor), 2.54 (1H, dd, $J = 13.5$, 6.5 Hz, H-10b, major), 2.81 (1H, dd, $J = 14.0$, 7.0 Hz, H-10b, minor), 3.02 (2H, br s, H-18, major + minor), 5.22–5.28 (1H, m, H-11, major), 5.28–5.33 (1H, m, H-11, minor), 6.12 (1H, s, H-12, major/minor), 6.13 (1H, s, H-12, major/minor), 6.50 (1H, d, $J = 2.5$ Hz, H-15, major), 6.52 (1H, d, $J = 2.5$ Hz, H-15, minor), 6.63–6.68 (2H, m, ArH, major + minor), 7.01–7.06 (2H, m, ArH, major + minor), 7.22–7.30 (3H, m, ArH, major + minor), 7.37–7.44 (2H, m, ArH, major + minor), 7.48 (1H, d, $J = 7.5$ Hz, H-2, major), 7.68–7.75 (2H, m, H-5, major + minor), 8.05 (1H, s, H-8, major), 8.22 (1H, s, H-8, minor); δ$_C$ (100 MHz, CDCl$_3$) 41.8 (CH$_3$), 43.0 (CH$_3$), 69.7 (C), 69.9 (C), 75.0 (CH), 75.1 (CH), 121.2 (CH), 121.4 (CH), 122.1 (CH), 123.1 (CH), 124.66 (CH), 124.73 (CH), 125.5 (CH), 125.6 (CH), 126.9 (CH), 127.1 (CH), 127.45 (CH), 127.47 (CH), 128.55 (CH), 128.56 (CH), 132.4 (CH), 132.9 (CH), 136.2 (C), 136.3 (C), 138.0 (C), 139.1 (C), 141.4 (C), 141.7 (C), 154.8 (C), 155.0 (C), 176.6 (CH), 176.8 (CH); HRMS (ESI$^+$): Found: 290.0612; C$_{16}$H$_{13}$NNaOS (MNa$^+$) Requires 290.0610 (−0.8 ppm error), Found: 268.0791; C$_{16}$H$_{14}$NOS (MH$^+$) Requires 268.0791 (−0.1 ppm error).

Lab notebook reference: MJJ5/4

2'-Methyl-2-phenylspiro[cyclopent[2]ene-1,3'-indol]-4'-ol (145g)

Synthesised using general procedure 2K with alcohol 144g (106 mg, 0.385 mmol), Ag$_2$O (4.5 mg, 0.0193 mmol), AgNO$_3$ (6.5 mg, 0.0385 mmol) and CH$_2$Cl$_2$ (3.9 mL). Purification by column chromatography (1→10% MeOH in DCM) afforded the title compound 145g (102 mg, 96%, 50:50 dr) as a yellow oil; $v_{max}$ (cm$^{-1}$) 3234, 1575, 1457, 1445, 1051, 909, 757, 730, 692; δ$_H$ (400 MHz, CDCl$_3$) 2.14 (1H, dd, $J = 14.0$, 4.0 Hz, H-11a), 2.18 (3H, s, H-9), 2.25 (3H, s, H-9), 2.30 (1H, dd, $J = 13.5$, 5.0 Hz, H-11a), 2.46 (1H, dd, $J = 13.5$, 7.0 Hz, H-11b), 2.66 (1H, dd, $J = 14.0$, 7.0 Hz, H-11b), 3.45 (2H, br s, H-18), 5.26–5.33 (1H, m, H-12), 5.40–5.47 (1H, m, H-12), 6.60 (2H, br s, H-13), 6.76–6.83 (4H, m, ArH), 7.02–7.20 (9H, m, ArH), 7.30–7.37 (2H, m, ArH), 7.39 (1H, d, $J = 7.5$ Hz, H-2), 7.59 (1H, d, $J = 8.0$ Hz, H-5), 7.62 (1H, d, $J = 8.0$ Hz, H-5); δ$_C$ (100 MHz, CDCl$_3$) 15.9 (CH$_3$), 16.3 (CH$_3$), 44.7 (CH$_2$), 45.5 (CH$_2$), 70.5 (C), 70.8 (C), 74.6 (CH), 74.7 (CH), 119.8 (CH), 120.2 (CH), 121.5 (CH), 123.0 (CH), 125.6 (2CH), 125.7 (2CH), 125.8 (CH), 126.1 (CH), 128.15 (CH), 128.17 (CH), 128.27 (CH), 128.30 (CH), 128.4 (2CH), 128.5 (2CH), 133.66 (C), 133.74 (C), 134.4 (CH), 134.5
4-Methyl-2-phenylspiro[cyclopent[2]ene-1,3’-indol]-4-ol (145j)

Synthesised using **general procedure 2K** with alcohol 144j (40 mg, 0.134 mmol), Ag2O (1.7 mg, 7.26 µmol), AgNO3 (2.5 mg, 0.0145 mmol) and CH2Cl2 (1.7 mL). Purification by column chromatography (2→10% MeOH in DCM) afforded the **title compound 145j** (38 mg, 95%, 50:50 *dr*) as a brown oil; ν_{max} (cm\(^{-1}\)) 3324, 2965, 1456, 1098, 908, 755, 731, 693; δ\(_H\) (400 MHz, CDCl\(_3\)) 1.69 (3H, s, H\(_{19}\)), 1.72 (3H, s, H-19), 2.27 (1H, d, _J_ = 14.0 Hz, H-10a), 2.38 (1H, d, _J_ = 14.0 Hz, H-10a), 2.45 (1H, d, _J_ = 14.0 Hz, H-10b), 2.59 (1H, d, _J_ = 14.0 Hz, H-10b), 6.48 (1H, s, H-12), 6.49 (1H, s, H-12), 6.77–6.84 (4H, m, ArH), 7.00–7.16 (6H, m, ArH), 7.19–7.26 (3H, m, ArH), 7.33–7.40 (2H, m, ArH), 7.47 (1H, d, _J_ = 7.5 Hz, H-2), 7.69 (1H, _J_ = 8.0 Hz, H-5), 7.71 (1H, d, _J_ = 7.5 Hz, H-5), 8.15 (1H, s, H-8), 8.36 (1H, s, H-8); δ\(_C\) (100 MHz, CDCl\(_3\)) 28.6 (CH\(_3\)), 28.8 (CH\(_3\)), 47.8 (CH\(_2\)), 48.8 (CH\(_2\)), 70.1 (C), 70.2 (C), 80.9 (C), 81.1 (C), 121.2 (CH), 121.4 (CH), 122.1 (CH), 122.9 (CH), 125.6 (2CH), 125.7 (2CH), 126.8 (CH), 127.0 (CH), 128.15 (CH), 128.18 (3CH), 128.25 (2CH), 128.29 (2CH), 133.88 (C), 133.89 (C), 138.0 (CH), 138.2 (CH), 142.08 (C), 142.12 (C), 142.5 (C), 143.7 (C), 154.5 (C), 154.9 (C), 176.9 (CH), 177.5 (CH); HRMS (ESI\(^+\)): Found: 298.1197; C\(_{19}\)H\(_{17}\)NNa (MNa\(^+\)) Requires 298.1202 (1.9 ppm error), Found: 276.1384; C\(_{19}\)H\(_{18}\)N (MH\(^+\)) Requires 276.1383 (−0.4 ppm error).

Traces of the imine trimer were also observed, characteristic data: δ\(_H\) (400 MHz, CDCl\(_3\)) 4.86 (s, H-8a), 5.39 (s, H-8b), 5.94 (s, H-8c)

Lab notebook reference: MJJ4/64
2,4-Diphenylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (145k)

Synthesised using **general procedure 2K** with alcohol 144k (69 mg, 0.205 mmol), Ag₂O (2.4 mg, 0.0103 mmol), AgNO₃ (3.5 mg, 0.0205 mmol) and CH₂Cl₂ (2.1 mL). Purification by column chromatography (2→10% MeOH in DCM) afforded the **title compound 145k** (67 mg, 97%, 64:36 *dr*) as a brown oil; $v_{\text{max}}$ (cm⁻¹) 3255, 3058, 1491, 1446, 906, 754, 727, 695; $\delta_H$ (400 MHz, CDCl₃) 2.45 (1H, d, J = 14.0 Hz, H-10a, minor), 2.61 (1H, d, J = 14.0 Hz, H-10a, major), 2.73 (1H, d, J = 14.0 Hz, H-10b, minor), 2.89 (2H, br s, H-18, major + minor), 6.66 (1H, s, H-12, minor), 6.68 (1H, s, H-12, major), 6.83–6.91 (4H, m, ArH, major + minor), 7.03–7.20 (9H, m, ArH, major + minor), 7.28–7.38 (4H, m, ArH, major + minor), 7.38–7.47 (4H, m, ArH, major + minor), 7.57–7.71 (7H, m, ArH, major + minor), 8.00 (1H, s, H-8, minor), 8.48 (1H, s, H-8, major); $\delta_C$ (100 MHz, CDCl₃) 49.0 (CH₂), 51.1 (CH₂), 70.2 (C), 70.3 (C), 84.3 (C), 84.9 (C), 121.3 (CH), 121.4 (CH), 122.4 (CH), 123.2 (CH), 125.28 (2CH), 125.32 (2CH), 125.8 (2CH), 125.9 (2CH), 126.9 (CH), 127.1 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 128.4 (3CH), 128.45 (3CH), 128.51 (CH), 128.6 (2CH), 128.7 (2CH), 133.88 (C), 133.91 (C), 136.3 (CH), 136.5 (CH), 141.5 (C), 141.9 (C), 145.4 (C), 146.0 (C), 146.19 (C), 146.21 (C), 154.6 (C), 155.2 (C), 176.5 (CH), 177.6 (CH); HRMS (ESI⁺): Found: 338.1528; C₂₄H₂₀NO (MH⁺) Requires 338.1539 (3.5 ppm error).

Lab notebook reference: MJJ5/8

4-((Tert-butyldimethylsilyl)oxy)-2-phenylspiro[cyclopent[2]ene-1,3'-indole] (145l)

Synthesised using **general procedure 2K** with alcohol 144l (44 mg, 0.117 mmol), Ag₂O (1.4 mg, 5.85 µmol), AgNO₃ (2.0 mg, 0.0117 mmol) and CH₂Cl₂ (1.1 mL). Purification by column
chromatography (8:2 hexane:EtOAc) afforded the title compound 145l (41 mg, 93%, 52:48 dr) as a colourless oil; $\nu_{\text{max}}$ (cm$^{-1}$) 2954, 2928, 2856, 1252, 1087, 836, 776, 751, 692; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 0.12 (3H, s, H-18a, major/minor), 0.13 (3H, s, H-18a, major/minor), 0.15 (3H, s, H-18b, major/minor), 0.16 (3H, s, H-18b, major/minor), 0.94 (18H, br s, H-20, major + minor), 2.01 (1H, dd, $J = 13.5$, 4.0 Hz, H-10a, major), 2.29 (1H, dd, $J = 13.5$, 6.5 Hz, H-10b, major), 2.14–5.19 (1H, m, H-11, major), 6.47 (1H, d, $J = 2.5$ Hz, H-12, major), 6.49 (1H, d, $J = 2.5$ Hz, H-12, minor), 6.76–6.83 (4H, m, ArH, major + minor), 7.02–7.14 (6H, m, ArH, major + minor), 7.33–7.40 (2H, m, ArH, major + minor), 7.52 (1H, d, $J = 7.5$ Hz, H-2, major), 7.68 (1H, d, $J = 7.5$ Hz, H-5, major), 7.70 (1H, d, $J = 7.5$ Hz, H-5, minor), 8.09 (1H, s, H-8m major), 8.26 (1H, s, H-8, minor); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) −4.7 (CH$_3$), −4.6 (CH$_3$), −4.5 (2CH$_3$), 18.2 (2C), 25.9 (6CH$_3$), 42.7 (CH$_2$), 44.3 (CH$_2$), 69.6 (C), 69.8 (C), 75.1 (CH), 75.3 (CH), 121.1 (CH), 121.6 (CH), 121.8 (CH), 123.5 (CH), 125.6 (2CH), 125.7 (2CH), 126.7 (CH), 126.8 (CH), 128.09 (2CH), 128.11 (CH), 128.13 (CH), 128.3 (4CH), 134.2 (C), 134.3 (C), 134.69 (CH), 134.72 (CH), 142.1 (C), 142.3 (C), 143.9 (C), 144.4 (C), 154.8 (C), 155.1 (C), 177.1 (CH), 177.5 (CH); HRMS (ESI$^+$): Found: 398.1909; C$_{24}$H$_{29}$NNaOSi (MNa$^+$) Requires 398.1911 (0.3 ppm error), Found: 376.2084; C$_{24}$H$_{30}$NOSi (MH$^+$) Requires 376.2091 (2.0 ppm error).

Lab notebook reference: MJJ4/67

1-(4-Methoxyphenyl)-9H-carbazole (146a)

![Diagram of 1-(4-Methoxyphenyl)-9H-carbazole](image)

Synthesised using general procedure 2L with alcohol 144a (70 mg, 0.240 mmol), AgOTf (6.2 mg, 0.024 mmol) and THF (2.4 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the title compound 146a (64 mg, 98%) as a white solid, mp 134–136 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3418, 1924, 1611, 1515, 1456, 1246, 750; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 3.92 (3H, s, H-18), 7.09–7.14 (2H, m, H-16), 7.25–7.31 (1H, m, H-3), 7.34 (1H, dd, $J = 7.5$, 7.5 Hz, H-11), 7.41–7.46 (3H, m, H-4,5,12), 7.62–7.67 (2H, m, H-15), 8.08 (1H, d, $J = 7.5$ Hz, H-10), 8.14 (1H, d, $J = 7.5$ Hz, H-2), 8.31 (1H, br s, H-7); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 55.4 (CH$_3$, C-18), 110.6 (CH, C-5), 114.7 (2CH, C-16), 119.0 (CH, C-10), 119.5 (CH, C-3/11), 119.9 (CH, C-3/11), 120.5 (CH, C-2), 123.6 (2C, C-1/9,13), 124.8 (C, C-1/9), 125.6 (CH, C-4/12), 125.9
(CH, C-4/12), 129.5 (2CH, C-15), 131.4 (C, C-14), 137.3 (C, C-6), 139.4 (C, C-6), 159.1 (C, C-17); HRMS (APCI⁺): Found: 274.1234; C₁₉H₁₆NO (MH⁺) Requires 274.1226 (−2.7 ppm error).

Lab notebook reference: MJJ4/47

Spectroscopic data matched those reported in the literature.¹⁵²

**1-Phenyl-9H-carbazole (146b)**

![Image of 1-Phenyl-9H-carbazole (146b)]

Synthesised using **general procedure 2L** with alcohol 144b (92 mg, 0.352 mmol), AgOTf (9.0 mg, 0.0352 mmol) and THF (3.5 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the **title compound 146b** (72 mg, 84%) as a white solid, mp 124–126 °C; νₘₐₓ (cm⁻¹) 3435, 3057, 2923, 1456, 1413, 1232, 749, 734, 701; δ_H (400 MHz, CDCl₃) 7.30 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H-3), 7.38 (1H, dd, J = 7.5, 7.5 Hz, H-11), 7.40–7.52 (4H, m, H-4,5,12,17), 7.60 (2H, dd, J = 8.0, 7.5 Hz, H-16), 7.73 (2H, d, J = 7.5 Hz, H-15), 8.13 (1H, d, J = 7.5 Hz, H-10), 8.16 (1H, d, J = 7.5 Hz, H-2), 8.33 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 110.7 (CH, C-5), 119.46 (CH, C-2/3/10/11), 119.9 (CH, C-2/3/10/11), 120.5 (CH, C-2/3/10/11), 123.5 (C, C-1/9/13), 123.7 (C, C-1/9/13), 125.0 (C, C-1/9/13), 125.7 (CH, C-4/12/17), 125.9 (CH, C-4/12/17), 127.5 (CH, C-4/12/17), 128.3 (2CH, C-15), 129.2 (2CH, C-16), 137.2 (C, C-8), 139.0 (C, C-6/14), 139.4 (C, C-6.14); HRMS (APCI⁺): Found: 244.1127; C₁₈H₁₄N (MH⁺) Requires 244.1121 (−2.7 ppm error).

Carbazole 146b also synthesised using **general procedure 2A** with alcohol 144l (45 mg, 0.120 mmol), AgOTf (3.1 mg, 0.012 mmol) and THF (1.2 mL). Purification by column chromatography afforded the **title compound 146b** (27 mg, 93%) as a white solid.

Lab notebook reference: MJJ4/45 + 4/68

Spectroscopic data matched those reported in the literature.¹⁵³
1-\(n\)-Butyl-9\(H\)-carbazole (146c)

Synthesised using **general procedure 2L** with alcohol 144c (133 mg, 0.551 mmol), AgOTf (14.2 mg, 0.0551 mmol) and THF (5.5 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the **title compound** 146c (106 mg, 86%) as an off-white solid, mp 53–54 °C; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3429, 2955, 2927, 1501, 1455, 1425, 1325, 1232, 748; \(\delta\)H (400 MHz, CDCl\(_3\)) 1.02 (3H, t, \(J = 7.0\) Hz, H-17), 1.50 (2H, tq, \(J = 7.5, 7.0\) Hz, H-16), 1.81 (2H, tt, \(J = 7.5\) Hz, H-15), 2.93 (2H, t, \(J = 7.5\) Hz, H-14), 7.19–7.31 (3H, m, ArH), 7.41–7.52 (2H, m, ArH), 7.97 (1H, d, \(J = 7.5\) Hz, H-2/10), 8.01 (1H, br s, H-7), 8.11 (1H, d, \(J = 7.5\) Hz, H-2/10); \(\delta\)C (100 MHz, CDCl\(_3\)) 14.0 (CH\(_3\), C-17), 22.7 (CH\(_2\), C-16), 31.1 (CH\(_2\), C-14), 31.7 (CH\(_2\), C-15), 110.6 (CH, C-5), 117.9 (CH, CAr), 119.4 (CH, CAr), 119.5 (CH, CAr), 120.4 (CH, CAr), 123.0 (C, C-1/9/13), 123.8 (C, C-1/9/13), 124.6 (C, C-1/9/13), 125.4 (CH, CAr), 125.6 (CH, CAr), 138.3 (C, C-6/8), 139.3 (C, C-6/8); HRMS (ESI\(^{+}\)): Found: 246.1250; C\(_{16}\)H\(_{17}\)NNa (M\(^{+}\)Na) Requires 246.1253 (1.4 ppm error), Found: 224.1432; C\(_{16}\)H\(_{15}\)N (MH\(^{+}\)) Requires 224.1434 (0.8 ppm error).

Lab notebook reference: MJJ4/56

1-(4-Fluorophenyl)-9\(H\)-carbazole (146d)

Synthesised using **general procedure 2L** with alcohol 144d (96 mg, 0.344 mmol), AgOTf (8.8 mg, 0.0344 mmol) and THF (3.4 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the **title compound** 146d (86 mg, 96%) as a white solid, mp 155–157 °C; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3468, 1603, 1509, 1455, 1314, 1222, 1156, 840, 749, 738; \(\delta\)H (400 MHz, CDCl\(_3\)) 7.19–7.36 (4H, m, ArH), 7.37–7.49 (3H, m, ArH), 7.60–7.70 (2H, m, ArH), 8.09 (1H, d, \(J = 7.5\) Hz, H-2/10), 8.12 (1H, d, \(J = 8.5\) Hz, H-2/10), 8.21 (1H, br s, H-7); \(\delta\)C (100 MHz, CDCl\(_3\)) 110.7 (CH, CAr), 116.2 (2CH, d, \(J = 22.0\) Hz, C-16), 119.5 (CH, CAr), 119.6 (CH, CAr), 119.9 (CH, CAr), 120.5 (CH, CAr), 123.5 (C, C-2/9/13), 123.7 (C, C-2/9/13), 124.0 (C,
C-2/9/13), 125.7 (CH, CAr), 126.0 (CH, CAr), 129.9 (2CH, d, J = 8.5 Hz, C-15), 135.0 (C, d, J = 4.0 Hz, C-14), 137.2 (C, C-6/9), 139.4 (C, C-6/8), 162.3 (C, d, J = 246 Hz, C-17); δ_F (376 MHz, CDCl_3) −114.3—114.5 (1F, m); HRMS (ESI⁺): Found: 262.1015; C_{18}H_{13}FN (M^+) Requires 262.1027 (4.3 ppm error).

Lab notebook reference: MJJ4/32

1-Cyclopropyl-9H-carbazole (146e)

Synthesised using general procedure 2L with alcohol 144e (160 mg, 0.710 mmol), AgOTf (18.2 mg, 0.0710 mmol) and THF (7.1 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the title compound 146e (133 mg, 90%) as an off-white solid, mp 88–90 °C; ν_{max} (cm⁻¹) 3433, 1455, 1234, 749; δ_H (400 MHz, CDCl_3) 0.77–0.86 (2H, m, H-15a), 1.01–1.09 (2H, m, H-15b), 2.07–2.18 (1H, m, H-14), 7.14–7.21 (2H, m, H-11,12), 7.25 (1H, dd, J = 8.0, 7.5 Hz, H-3), 7.43 (1H, dd, J = 8.0, 7.5 Hz, H-4), 7.50 (1H, d, J = 8.0 Hz, H-5), 7.91–7.98 (1H, m, H-10), 8.08 (1H, d, J = 8.0 Hz, H-2), 8.28 (1H, br s, H-7); δ_C (100 MHz, CDCl_3) 5.6 (2CH_2, C-15), 11.1 (CH, C-14), 110.7 (CH, C-5), 118.1 (CH, C-10), 119.36 (CH, C-2/3/11), 119.39 (CH, C-2/3/11), 120.4 (CH, C-2/3/11), 122.6 (C, C-1/9/13), 123.7 (CH, C-12), 123.8 (C, C-1/9/13), 125.0 (C, C-1/9/13), 125.7 (CH, C-4), 139.3 (C, C-6/8), 139.8 (C, C-6/8); HRMS (ESI⁺): Found: 208.1124; C_{15}H_{14}NO (M^+) Requires 208.1121 (−1.5 ppm error).

Lab notebook reference: MJJ5/20

1-(Thiophen-2-yl)-9H-carbazole (146f)

Synthesised using general procedure 2L with alcohol 144f (77 mg, 0.288 mmol), AgOTf (7.4 mg, 0.0288 mmol) and THF (2.9 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 146f (20 mg, 28%) as an off white semi-solid; ν_{max} (cm⁻¹) 3430, 1493, 1455, 1420, 1317, 1231, 746, 698; δ_H (400 MHz, CDCl_3) 7.20–7.32
(3H, m, ArH), 7.40–7.49 (4H, m, ArH), 7.57 (1H, d, \( J = 8.0 \text{ Hz, H-12} \)), 8.06 (1H, d, \( J = 8.0 \text{ Hz, H-2/10} \)), 8.10 (1H, d, \( J = 8.0 \text{ Hz, H-2/10} \)), 8.54 (1H, br s, H-7); \( \delta_c \) (100 MHz, CDCl\(_3\)) 110.8 (CH, C-5), 117.9 (C, C-13), 119.8 (2CH, CAr), 119.9 (CH, CAr), 120.5 (CH, CAr), 123.5 (C, C-1/9), 124.0 (C, Cl/9), 124.8 (CH, CAr), 125.1 (CH, CAr), 125.6 (CH, CAr), 126.1 (CH, CAr), 128.0 (CH, CAr), 136.8 (C, C-6/8), 139.4 (C, C-6/8), 141.0 (C, C-14); HRMS (ESI\(^+\)): Found: 250.0685; \( \text{C}_{16}\text{H}_{12}\text{NS} \) (MH\(^+\)) Requires 250.0685 (0.1 ppm error).

Lab notebook reference: MJJS/3

9H-Carbazole (146i)

Synthesised using general procedure 2L with alcohol 144i (70 mg, 0.378 mmol), AgOTf (9.7 mg, 0.0378 mmol) and THF (3.8 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the title compound 146i (62 mg, 98%) as an off-white solid, mp 242–243 °C; \( v_{\text{max}} \) (cm\(^{-1}\)) 3416, 1450, 746, 722, 573; \( \delta_h \) (400 MHz, DMSO-d\(_6\)) 7.15 (2H, dd, \( J = 7.5, 7.5 \text{ Hz} \)), 7.38 (2H, dd, \( J = 8.0, 7.5 \text{ Hz} \)), 7.49 (2H, d, \( J = 8.0 \text{ Hz} \)), 8.11 (2H, d, \( J = 7.5 \text{ Hz} \)), 11.26 (1H, br s); \( \delta_c \) (100 MHz, DMSO-d\(_6\)) 111.0 (2CH), 118.5 (2CH), 120.2 (2CH), 122.4 (2C), 125.5 (2CH), 139.7 (2C); HRMS (ESI\(^+\)): Found: 168.0812; \( \text{C}_{12}\text{H}_{10}\text{N} \) (MH\(^+\)) Requires 168.0813 (0.6 ppm error).

Carbazole 146i also synthesised using general procedure 2L with alcohol 144h (46 mg, 0.179 mmol), AgOTf (4.6 mg, 0.0179 mmol) and THF (1.8 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the title compound 146i (30 mg, 100%) as an off-white solid.

Lab notebook reference: MJJS/36 + 4/38

Spectroscopic data matched those reported in the literature.\(^\text{154}\)
3-Methyl-1-phenyl-9H-carbazole (146j):

![Chemical Structure Image]

Synthesised using **general procedure 2L** with alcohol 144j (36 mg, 0.131 mmol), AgOTf (3.4 mg, 0.0131 mmol) and THF (1.3 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the **title compound 146j** (29 mg, 86%) as a colourless oil; $v_{\text{max}}$ (cm$^{-1}$) 3435, 3031, 2919, 1608, 1499, 1488, 1452, 1317, 1235, 776, 734, 703, 578; $\delta_H$ (400 MHz, CDCl$_3$) 2.63 (3H, s, H-18), 7.27 (1H, br dd, $J = 7.0, 7.0$ Hz, H-3), 7.32 (1H, s, H-12), 7.38–7.45 (2H, m, H-5, 17), 7.47 (1H, dd, $J = 7.5, 7.0$ Hz, H-4), 7.59 (2H, dd, $J = 7.5, 7.5$ Hz, H-16), 7.73 (2H, d, $J = 7.5$ Hz, H-15), 7.92 (1H, br s, H-10), 8.12 (1H, d, $J = 8.0$ Hz, H-2), 8.23 (1H, br s, H-7); $\delta_C$ (100 MHz, CDCl$_3$) 21.4 (CH$_3$, C-18), 110.6 (CH, C-5), 119.3 (CH, C-3/10), 119.4 (CH, C-3/10), 120.3 (CH, C-2), 123.4 (C, C-1/9/13), 123.9 (C, C-1/9/13), 124.6 (C, C-1/9/13), 125.7 (CH, C-17), 127.1 (CH, C-4/12), 127.4 (CH, C-4/12), 128.3 (2CH, C-15), 129.2 (C + 2CH, C-11,16), 135.5 (C, C-6/8/14), 139.1 (C, C-6/8/14), 139.7 (C, C-6/8/14); HRMS (ESI$^+$): Found: 280.1099; C$_{19}$H$_{15}$NNa (MNa$^+$) Requires 280.1097 (−0.8 ppm error), Found: 258.1278; C$_{19}$H$_{16}$N (MH$^+$) Requires 258.1277 (−0.3 ppm error).

Lab notebook reference: MJJ4/65

**Actinopolymorphol B (162)**

![Chemical Structure Image]

To a solution of alcohol 144i (112 mg, 0.605 mmol) in CH$_2$Cl$_2$ (6.1 mL) was added sequentially Ag$_2$O (7.0 mg, 0.0303 mmol) and AgNO$_3$ (10.3 mg, 0.0605 mmol). The reaction mixture was stirred for 24 h then concentrated in vacuo. The crude material was purified by column chromatography (3:2 hexane:EtOAc) to afford the **title compound 162** (33 mg, 27%) as a pale brown oil; $v_{\text{max}}$ (cm$^{-1}$) 3408, 1710, 1457, 1355, 1093, 744; $\delta_H$ (400 MHz, CDCl$_3$) 2.21 (3H, s), 3.15 (1H, dd, $J = 15.0, 7.0$ Hz), 3.33 (1H, dd, $J = 15.0, 4.5$ Hz), 3.47 (1H, d, $J = 5.0$ Hz), 4.50–4.57 (1H, m), 7.11–7.18 (2H, m), 7.22 (1H, dd, $J = 8.0, 7.5$ Hz), 7.37 (1H, d, $J = 8.0$ Hz), 7.65 (1H, d, $J = 8.0$ Hz), 8.09 (1H, br s); $\delta_C$ (100 MHz, CDCl$_3$) 25.8 (CH$_3$), 29.5 (CH$_2$), 77.1 (CH), 110.4 (C), 111.2 (CH), 118.7 (CH), 119.6 (CH), 122.2 (CH), 122.9 (CH), 190
127.4 (C), 136.0 (C), 209.8 (C); HRMS (ESI⁺): Found: 226.0833; C₁₂H₁₃NNaO₂ (MNa⁺) 
Requires 226.0838 (2.3 ppm error).

Compound 162 also synthesised using alcohol 144h (45 mg, 0.175 mmol), CH₂Cl₂ (1.8 mL), 
Ag₂O (2.0 mg, 8.75 µmol) and AgNO₃ (3.0 mg, 0.0175 mmol). After stirring for 24 h the 
reaction mixture was stirred was purified by column chromatography (3:2 hexane:EtOAc then 
EtOAc) to afford the title compound 162 (7 mg, 20%) as a pale brown oil.

Lab notebook reference: MJJ4/35 + 4/37

Spectroscopic data matched those reported in the literature.⁸¹
5.4 Experimental for Chapter 3

3-(6-Chloro-1H-indol-3-yl)propanoic acid (80i)

Synthesised according to a modified literature procedure.\(^{109}\) To a solution of 6-chloroindole (2.00 g, 13.2 mmol), ethyl acrylate (1.71 mL, 15.8 mmol) in anhydrous CH\(_2\)Cl\(_2\) (66 mL) under argon was added ZrCl\(_4\) (308 mg, 1.32 mmol) in one portion. The mixture was stirred at RT under argon for 48 h then concentrated \textit{in vacuo}. The crude ester was then dissolved in MeOH:THF (1:1 v/v, 264 mL) and 2 M NaOH (aq) (66 mL) was added. The mixture was stirred at RT for 18 h then concentrated \textit{in vacuo}, the crude material was dissolved in H\(_2\)O (50 mL) and washed with CH\(_2\)Cl\(_2\) (2 × 50 mL). The organics were discarded and the aqueous was acidified to pH 1 with 10% HCl (aq) and extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). The organics were dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to afford the title compound 80i (1.86 g, 63%) as an off-white solid, mp 94–96 °C; \(\nu\)\(_{\text{max}}\) (cm\(^{-1}\)) 3438, 1705, 1410, 1279, 1205, 804, 463; \(\delta\)\(_{\text{H}}\) (400 MHz, DMSO-d\(_6\)) 2.57 (2H, t, \(J = 7.5\) Hz, H-11), 2.91 (2H, t, \(J = 7.5\) Hz, H-10), 6.98 (1H, dd, \(J = 8.5, 2.0\) Hz, H-3), 7.16 (1H, d, \(J = 2.5\) Hz, H-8), 7.37 (1H, d, \(J = 2.0\) Hz, H-5), 7.52 (1H, d, \(J = 8.5\) Hz, H-2), 10.95 (1H, br s, H-7), 12.10 (1H, br s, H-13); \(\delta\)\(_{\text{C}}\) (100 MHz, DMSO-d\(_6\)) 20.1 (CH\(_2\), C-10), 34.5 (CH\(_2\), C-11), 111.0 (CH, C-5), 113.8 (C, C-9), 118.6 (CH, C-3), 119.7 (CH, C-2), 123.5 (CH, C-8), 125.7 (C, C-1/4), 125.8 (C, C-1/4), 136.6 (C, C-6), 174.2 (C, C-12); HRMS (ESI\(^+\)): Found: 246.0300; C\(_{11}\)H\(_{10}\)ClNNaO\(_2\) (MNa\(^+\)) Requires 246.0292 (−3.1 ppm error).

Lab notebook reference: MJJ7/48

3-(5-Methoxy-1H-indol-3-yl)propanoic acid (80j)

Synthesised according to a modified literature procedure.\(^{109}\) To a solution of 5-methoxyindole (2.00 g, 13.6 mmol), ethyl acrylate (1.77 mL, 16.3 mmol) in anhydrous CH\(_2\)Cl\(_2\) (68 mL) under argon was added ZrCl\(_4\) (317 mg, 1.36 mmol) in one portion. The mixture was stirred at RT
under argon for 24 h then concentrated in vacuo. The crude ester was then dissolved in MeOH:THF (1:1 v/v, 272 mL) and 2 M NaOH\textsubscript{aq} (68 mL) was added. The mixture was stirred at RT for 18 h then concentrated in vacuo, the crude material was dissolved in H\textsubscript{2}O (50 mL) and washed with CH\textsubscript{2}Cl\textsubscript{2} (2 × 50 mL). The organics were discarded and the aqueous was acidified to pH 1 with 10% HCl\textsubscript{aq} and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 50 mL). The organics were dried (MgSO\textsubscript{4}) and concentrated in vacuo to afford the title compound 80j (2.36 g, 79%) as a white solid, mp 132–134 °C; \(v\textsubscript{max} \text{ (cm}^{-1})\) 3343, 1714, 1488, 1211, 1177, 1018, 797, 640, 621, 541; \(\delta\text{H} \text{ (400 MHz, DMSO-}d\textsubscript{6})\) 2.58 (2H, t, \(J = 7.5 \text{ Hz}, H\text{-}12\)), 2.89 (2H, t, \(J = 7.5 \text{ Hz}, H\text{-}11\)), 3.76 (3H, s, \(H\text{-}4\)), 6.71 (1H, dd, \(J = 8.5, 2.5 \text{ Hz}, H\text{-}5\)), 6.99 (1H, d, \(J = 2.5 \text{ Hz}, H\text{-}2\)), 7.07 (1H, d, \(J = 2.0 \text{ Hz}, H\text{-}9\)), 7.22 (1H, d, \(J = 8.5 \text{ Hz}, H\text{-}6\)), 10.62 (1H, br s, H-8), 12.08 (1H, br s, H-14); \(\delta\text{C} \text{ (100 MHz, DMSO-}d\textsubscript{6})\) 20.4 (CH\textsubscript{2}, \(C\text{-}11\)), 34.5 (CH\textsubscript{2}, \(C\text{-}12\)), 55.3 (CH\textsubscript{3}, \(C\text{-}4\)), 100.0 (CH, \(C\text{-}2\)), 111.1 (CH, \(C\text{-}5\)), 112.0 (CH, \(C\text{-}6\)), 113.2 (C, \(C\text{-}10\)), 122.9 (CH, \(C\text{-}9\)), 127.2 (C, \(C\text{-}1\)), 131.4 (C, \(C\text{-}7\)), 153.0 (C, \(C\text{-}3\)), 174.4 (C, \(C\text{-}13\)); HRMS (ESI\textsuperscript{+}): Found: 242.0789; C\textsubscript{12}H\textsubscript{13}NNaO\textsubscript{3} (MNa\textsuperscript{+}) Requires 242.0788 (−0.7 ppm error), Found: 220.0970; C\textsubscript{12}H\textsubscript{14}NO\textsubscript{3} (MH\textsuperscript{+}) Requires 220.0968 (−0.8 ppm error).

Lab notebook reference: MJJ7/46

3-(2-Methyl-1\textsubscript{H}-indol-3-yl)propanoic acid (S1)

![Reaction Scheme]

Synthesised according to a modified literature procedure.\textsuperscript{109} To a solution of 2-methylindole (2.67 g, 20.4 mmol), ethyl acrylate (2.65 mL, 24.5 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (102 mL) under argon was added ZrCl\textsubscript{4} (475 mg, 2.04 mmol) in one portion. The mixture was stirred at RT under argon for 24 h then concentrated in vacuo. The crude ester was then dissolved in MeOH:THF (1:1 v/v, 408 mL) and 2 M NaOH\textsubscript{aq} (102 mL) was added. The mixture was stirred at RT for 18 h then concentrated in vacuo, the crude material was dissolved in H\textsubscript{2}O (50 mL) and washed with CH\textsubscript{2}Cl\textsubscript{2} (2 × 50 mL). The organics were discarded and the aqueous was acidified to pH 1 with 10% HCl\textsubscript{aq} and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 50 mL). The organics were dried (MgSO\textsubscript{4}) and concentrated in vacuo to afford the title compound S1 (2.95 g, 71%) as a grey solid, mp 128–130 °C (lit. 121–123 °C); \(v\textsubscript{max} \text{ (cm}^{-1})\) 1464, 1405, 1306, 1295, 1211; \(\delta\text{H} \text{ (400 MHz, DMSO-}d\textsubscript{6})\) 3.11 (3H, s); 2.45 (2H, t, \(J = 7.5 \text{ Hz}), 2.87 \text{ (2H, t, } J = 7.5 \text{ Hz}, H, 6.91 \text{ (1H, dd, } J = 7.5, 7.5, 1.0 \text{ Hz), 6.97 \text{ (1H, dd, } J = 7.5, 7.5, 1.0 \text{ Hz), 7.21 \text{ (1H, br d, } J = 7.5 \text{ Hz), 7.39 \text{ (1H, br d, } J = 7.5 \text{ Hz), 10.68 \text{ (1H, s), 12.01 \text{ (1H, br s); } \delta\text{C} \text{ (100 MHz, DMSO-}d\textsubscript{6})\) 20.4 (CH\textsubscript{2}, \(C\text{-}11\)), 34.5 (CH\textsubscript{2}, \(C\text{-}12\)), 55.3 (CH\textsubscript{3}, \(C\text{-}4\)), 100.0 (CH, \(C\text{-}2\)), 111.1 (CH, \(C\text{-}5\)), 112.0 (CH, \(C\text{-}6\)), 113.2 (C, \(C\text{-}10\)), 122.9 (CH, \(C\text{-}9\)), 127.2 (C, \(C\text{-}1\)), 131.4 (C, \(C\text{-}7\)), 153.0 (C, \(C\text{-}3\)), 174.4 (C, \(C\text{-}13\)); HRMS (ESI\textsuperscript{+}): Found: 242.0789; C\textsubscript{12}H\textsubscript{13}NNaO\textsubscript{3} (MNa\textsuperscript{+}) Requires 242.0788 (−0.7 ppm error), Found: 220.0970; C\textsubscript{12}H\textsubscript{14}NO\textsubscript{3} (MH\textsuperscript{+}) Requires 220.0968 (−0.8 ppm error).
11.2 (CH₃), 19.4 (CH₂), 35.1 (CH₂), 108.9 (C), 110.4 (CH), 117.3 (CH), 118.1 (CH), 119.9 (CH), 127.9 (C), 131.7 (C), 135.2 (C), 174.2 (C).

Lab notebook reference: MJJ7/92

Spectroscopic data matched those reported in the literature.¹⁵⁵

3-(6-Chloro-1H-indol-3-yl)-N-methoxy-N-methylpropanamide (81i)

Synthesised using general procedure 2A with 80i (1.86 g, 8.31 mmol), T3P 50% in EtOAc (7.96 g, 12.5 mmol), DIPEA (4.34 mL, 24.9 mmol) and MeNHOMe·HCl (891 mg, 9.14 mmol) in CH₂Cl₂ (21 mL) afforded the title compound 81i (1.92 g, 87%) as a pale brown solid, mp 104–106 °C; νmax (cm⁻¹) 3281, 1641, 1457, 803; δH (400 MHz, CDCl₃) 2.81 (2H, t, J = 7.5 Hz, H-11), 3.09 (2H, t, J = 7.5 Hz, H-10), 3.19 (3H, s, H-13), 3.59 (3H, s, H-14), 7.04 (1H, br d, J = 2.0 Hz, H-8), 7.09 (1H, dd, J = 8.5, 1.5 Hz, H-3), 7.35 (1H, d, J = 1.5 Hz, H-5), 7.53 (1H, d, J = 8.5 Hz, H-2), 8.00 (1H, br s, H-7); δC (100 MHz, CDCl₃) 20.1 (CH₂, C-10), 32.2 (CH₃, C-13), 32.5 (CH₂, C-11), 61.2 (CH₃, C-14), 111.0 (CH, C-5), 115.5 (C, C-9), 119.6 (CH, C-2), 119.9 (CH, C-3), 122.3 (CH, C-8), 125.9 (C, C-1/4), 127.8 (C, C-1/4), 136.6 (C, C-6), 174.0 (C, C-12); HRMS (ESI⁺): Found: 289.0713; C₁₃H₁₃⁵ClN₂NaO₂ (MNa⁺) Requires 289.0714 (0.5 ppm error), Found: 267.0896; C₁₃H₁₅⁵ClN₂O₂ (MH⁺) Requires 267.0895 (−0.5 ppm error).

Lab notebook reference: MJJ7/55

N-Methoxy-3-(5-methoxy-1H-indol-3-yl)-N-methylpropanamide (81j)

Synthesised using general procedure 2A with 80j (2.36 g, 8.31 mmol), T3P 50% in EtOAc (8.59 g, 13.5 mmol), DIPEA (4.70 mL, 27.0 mmol) and MeNHOMe·HCl (965 mg, 9.90 mmol) in CH₂Cl₂ (23 mL) afforded the title compound 81j (2.31 g, 82%) as a brown oil; νmax (cm⁻¹) 3301, 2967, 1639, 1485, 1440, 1214, 1062, 797; δH (400 MHz, CDCl₃) 2.84 (2H, t, J =
N-Methoxy-N-methyl-3-(2-methyl-1H-indol-3-yl)propanamide (S2)

Synthesised using general procedure 2A with S1 (2.95 g, 14.5 mmol), T3P 50% in EtOAc (13.9 g, 21.8 mmol), DIPEA (7.57 mL, 43.5 mmol) and MeNHOMe·HCl (1.56 g, 16.0 mmol) in CH\(_2\)Cl\(_2\) (36 mL) afforded the title compound S2 (3.28 g, 92%) as a brown oil; \(\nu\) \text{max} (cm\(^{-1}\)) 3300, 1640, 1463, 1439, 742; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 2.39 (3H, s, H-9), 2.76 (2H, t, \(J = 7.5\) Hz, H-12), 3.07 (2H, t, \(J = 7.5\) Hz, H-11), 3.19 (3H, s, H-14), 3.55 (3H, s, H-15), 7.06–7.15 (2H, m, H-3,4), 7.24–7.28 (1H, m, H-5), 7.51–7.55 (1H, m, H-2), 7.97 (1H, br s, H-7); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 11.5 (CH\(_3\), H-9), 19.3 (CH\(_2\), C-11), 32.1 (CH\(_2\), C-12), 32.8 (CH\(_3\), H-14), 61.1 (CH\(_3\), H-15), 110.2 (CH, C-5), 110.6 (C, C-10), 117.8 (CH, C-2), 119.0 (CH, C-3), 120.8 (CH, C-4), 128.3 (C, C-1), 131.3 (C, C-6/8), 135.2 (C, C-6/8), 174.3 (C, C-13); HRMS (ESI\(^+\)): Found: 269.1253; C\(_{14}\)H\(_{18}\)N\(_2\)NaO\(_2\) (MNa\(^+\)) Requires 269.1260 (2.7 ppm error), Found: 247.1450; C\(_{14}\)H\(_{19}\)N\(_2\)O\(_2\) (MH\(^+\)) Requires 267.1390 (1.3 ppm error).

Lab notebook reference: MJJ7/94
4-(1H-Indol-3-yl)-1-phenylbutan-2-one (192a)

Synthesised using **general procedure 3A** with Weinreb amide 81b (3.97 g, 17.1 mmol), BnMgCl (42.8 mL, 85.5 mmol, 2.0 M in THF) and THF (171 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the **title compound** 192a (2.58 g, 57%) as a white solid, mp 105–107 °C; $v_{\text{max}}$ (cm$^{-1}$) 3310, 1708, 745; $\delta$H (400 MHz, CDCl$_3$) 2.88 (2H, t, $J = 7.5$ Hz, H-11), 3.05 (2H, t, $J = 7.5$ Hz, H-10), 3.68 (2H, s, H-13), 6.92 (1H, d, $J = 2.0$ Hz, H-8), 7.09–7.41 (8H, m, ArH), 7.54 (1H, d, $J = 8.0$ Hz, H-2), 7.94 (1H, br s, H-7); $\delta$C (100 MHz, CDCl$_3$) 19.4 (CH$_2$, C-10), 42.4 (CH$_2$, C-11), 50.3 (CH$_2$, C-13), 111.1 (CH, C-5), 115.1 (C, C-9), 118.6 (CH, C-2), 119.3 (CH, C-3/4/17), 121.5 (CH, C-8), 122.0 (CH, C-3/4/17), 127.0 (CH, C-3/4/17), 127.1 (C, C-1), 128.7 (2CH, C-15/16), 129.4 (2CH, C-15/16), 134.2 (C, C-14), 136.2 (C, C-6), 208.2 (C, C-12); HRMS (ESI$^+$): Found: 286.1193; C$_{18}$H$_{17}$NNaO (MNa$^+$) Requires 286.1202 (3.2 ppm error), Found: 264.1377; C$_{18}$H$_{18}$NO (MH$^+$) Requires 264.1383 (2.3 ppm error).

Lab notebook reference: MJJ5/97

1-(1H-Indol-3-yl)hex-5-en-3-one (S3)

Synthesised using **general procedure 3A** with Weinreb amide 81b (978 mg, 4.21 mmol), AllylMgBr (16.8 mL, 16.8 mmol, 1.0 M in Et$_2$O) and THF (30 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the **title compound** S3 (840 mg, 94%) as a white solid, mp 60–62 °C; $v_{\text{max}}$ (cm$^{-1}$) 3410, 1708, 1457, 743; $\delta$H (400 MHz, CDCl$_3$) 2.87 (2H, t, $J = 7.5$ Hz, H-11), 3.07 (2H, t, $J = 7.5$ Hz, H-10), 3.17 (2H, d, $J = 7.0$ Hz, H-13), 5.11 (1H, dd, $J = 17.0$, 1.5 Hz, H-15trans), 5.17 (1H, dd, $J = 10.5$, 1.5 Hz, H-15cis), 5.92 (1H, ddt, $J = 17.0$, 10.5, 7.0 Hz, H-14), 7.00 (1H, d, $J = 2.0$ Hz, H-8), 7.13 (1H, dd, $J = 7.5$, 7.5 Hz, H-3), 7.21 (1H, dd, $J = 7.5$, 7.5 Hz, H-4), 7.37 (1H, d, $J = 7.5$ Hz, H-5), 7.60 (1H, d, $J = 7.5$ Hz, H-2), 7.95 (1H, br s, H-7); $\delta$C (100 MHz, CDCl$_3$) 19.2 (CH$_2$, C-10), 42.7 (CH$_2$, C-11), 47.9 (CH$_2$, C-13), 111.1 (CH, C-5), 115.1 (C, C-9), 118.6 (CH, C-2), 118.8 (CH, C-14/15), 119.3 (CH, C-
14/15), 121.5 (CH, C-3), 122.0 (CH, C-8), 127.1 (C, C-1), 130.5 (CH, C-4), 136.2 (C, C-6), 208.6 (C, C-12); HRMS (ESI⁺): Found: 236.1051; C_{14}H_{14}NaO (MNa⁺) Requires 236.1046 (−2.0 ppm error), Found: 214.1226; C_{14}H_{15}NO (MH⁺) Requires 214.1226 (0.3 ppm error).

Lab notebook reference: MJJ7/23

4-(2-Methyl-1H-indol-3-yl)-1-phenylbutan-2-one (S4)

Synthesised using general procedure 3A with Weinreb amide 81b (1.00 g, 4.06 mmol), BnMgCl (8.1 mL, 16.2 mmol, 2.0 M in THF) and THF (41 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound S4 (697 mg, 62%) as a pale yellow oil; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3398, 1708, 1462, 741, 700; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 2.33 (3H, s, H-9), 2.80 (2H, t, \( J = 7.5 \text{ Hz} \), H-12), 2.97 (2H, t, \( J = 7.5 \text{ Hz} \), H-11), 7.05–7.16 (4H, m, ArH), 7.22–7.34 (4H, m, ArH), 7.41 (1H, d, \( J = 8.0 \text{ Hz} \), H-2), 7.74 (1H, br s, H-7); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 11.5 (CH\(_3\), C-9), 18.6 (CH\(_2\), C-11), 42.3 (CH\(_2\), C-12) 50.6 (CH\(_2\), C-14), 110.2 (CH, C-5), 110.3 (C, C-10) 117.7 (CH, C-2), 119.1 (CH, C-3), 120.9 (CH, C-4), 126.9 (CH, C-18), 128.2 (C, C-1), 128.6 (2CH, C-16/17), 129.4 (2CH, C-16/17), 131.1 (C, C-6/8/15), 134.1 (C, C-6/8/15), 135.2 (C, C-6/8/15), 208.5 (C, C-13); HRMS (ESI⁺): Found: 300.1355; C_{19}H_{19}NaO (MNa⁺) Requires 300.1359 (1.1 ppm error), Found: 278.1531; C_{19}H_{21}NO (MH⁺) Requires 278.1539 (−3.9 ppm error).

Lab notebook reference: MJJ9/16

4-(1H-Indol-3-yl)-1-(3-methoxyphenyl)butan-2-one (192b)

Iodine (2 crystals) was sublimed over freshly crushed magnesium turnings (836 mg, 34.4 mmol) under argon by heating the solids with a heat gun (30 seconds). THF (4 mL) was then added, followed by 3-methoxybenzyl chloride (0.10 mL, 0.69 mmol), once a dark grey colour change was observed the mixture was diluted with THF (36 mL) and further 3-methoxybenzyl
chloride (2.40 mL, 16.5 mmol) was added. The mixture was stirred at RT under argon for 1 h then transferred via cannula into a cooled 0 °C solution of Weinreb amide 81b (1.18 g, 5.08 mmol) in THF (22 mL). The resulting solution was allowed to warm to room temperature and stirred for 2 h then quenched with sat. NH₄Cl(s) (30 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried (MgSO₄), concentrated in vacuo and purified by column chromatography (35% EtOAc in hexane) to afford the title compound 192b (620 mg, 42%) as a white solid, mp 72–74 °C; δmax (cm⁻¹) 3409, 2920, 1711, 1598, 1260, 744; δH (400 MHz, CDCl₃) 2.88 (2H, t, J = 7.5 Hz, H-11), 3.05 (2H, t, J = 7.5 Hz, H-10), 3.65 (2H, s, H-17), 3.78 (3H, s, H-13), 6.70–6.73 (1H, m, H-15), 6.76 (1H, d, J = 7.5 Hz, H-20), 6.81 (1H, dd, J = 8.0, 2.5 Hz, H-18), 6.92 (1H, d, J = 2.0 Hz, H-8), 7.12 (1H, dd, J = 7.5, 7.5 Hz, H-3), 7.18–7.26 (2H, m, H-4,19), 7.35 (1H, d, J = 8.0 Hz, H-5), 7.55 (1H, d, J = 7.5 Hz, H-2), 7.97 (1H, br s, H-7); δC (100 MHz, CDCl₃) 19.4 (CH₂, C-10), 42.3 (CH₂, C-11), 50.4 (CH₂, C-13), 55.1 (CH₃, C-17), 111.1 (CH, C-5), 112.5 (CH, C-18), 114.95 (CH, C-15), 115.0 (C, C-9), 118.6 (CH, C-2), 119.2 (CH, C-3), 121.5 (CH, C-8), 121.8 (CH, C-20), 122.0 (CH, C-4), 127.1 (C, C-1), 129.6 (CH, C-19), 135.6 (C, C-14), 136.2 (C, C-6), 159.7 (C, C-16), 208.1 (C, C-12); HRMS (ESI⁺): Found: 316.1305; C₁₉H₁₅N₂O (MNa⁺) Requires 316.1308 (0.8 ppm error).

Lab notebook reference: MJJ7/26

1-(4-Fluorophenyl)-4-(1H-indol-3-yl)butan-2-one (192c)

Iodine (2 crystals) was sublimed over freshly crushed magnesium turnings (1.67 g, 68.8 mmol) under argon by heating the solids with a heat gun (30 seconds). THF (5 mL) was then added, followed by 4-fluorobenzyl chloride (0.10 mL, 0.83 mmol), once a dark grey colour change was observed the mixture was diluted with THF (74 mL) and further 4-fluorobenzyl chloride (4.02 mL, 33.6 mmol) was added. The mixture was stirred at RT under argon for 1 h then transferred via cannula into a cooled 0 °C solution of Weinreb amide 81b (2.00 g, 8.60 mmol) in THF (43 mL). The resulting solution was allowed to warm to room temperature and stirred for 4 h then quenched with sat. NH₄Cl(aq) (30 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried (MgSO₄), concentrated in vacuo and purified by column chromatography (35% EtOAc in hexane).
hexane) to afford the *title compound 192c* (1.39 g, 57%) as a white solid, mp 111–113 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3379, 1714, 1509, 1221, 743; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.88 (2H, t, $J = 7.5$ Hz, H-11), 3.06 (2H, t, $J = 7.5$ Hz, H-10), 3.64 (2H, s, H-13), 6.93 (1H, d, $J = 1.5$ Hz, H-8), 6.98 (2H, dd, $J = 8.5$, 8.5 Hz, H-16), 7.06–7.17 (3H, m, H-3,15), 7.21 (1H, dd, $J = 7.5$, 7.5 Hz, H-4), 7.36 (1H, d, $J = 7.5$ Hz, H-5), 7.55 (1H, d, $J = 8.0$ Hz, H-2), 7.96 (1H, br s, H-7); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 19.4 (CH$_2$, C-10), 42.5 (CH$_2$, C-11), 49.3 (CH$_2$, C-13), 111.1 (CH, C-5), 114.9 (C, C-9), 115.4 (2CH, d, $J = 21.0$ Hz, C-16), 118.6 (CH, C-2), 119.3 (CH, C-3), 121.5 (CH, C-8), 122.0 (CH, C-4), 127.0 (C, C-1), 129.7 (C, d, $J = 4.0$ Hz, C-14), 130.9 (2CH, d, $J = 7.5$ Hz, C-15), 136.2 (C, C-6), 161.9 (C, d, $J = 245$ Hz, C-17), 207.9 (C, C-12); $\delta_{\text{F}}$ (376 MHz, CDCl$_3$) $-115.7$–$-115.8$ (1F, m); HRMS (ESI$^+$): Found: 304.1105; C$_{18}$H$_{16}$FN$_2$O (MNa$^+$) Requires 304.1108 (0.9 ppm error), Found: 282.1278; C$_{18}$H$_{17}$FNO (MH$^+$) Requires 282.1289 (3.8 ppm error).

Lab notebook reference: MJJ7/38

4-(6-Chloro-1H-indol-3-yl)-1-phenylbutan-2-one (192d)

Synthesised using *general procedure 3A* with Weinreb amide 81i (1.92 g, 7.20 mmol), BnMgCl (14.4 mL, 28.8 mmol, 2.0 M in THF) and THF (72 mL). Purification by column chromatography (3:2 hexane:EtOAc) afforded the *title compound 192d* (794 mg, 37%) as a white solid, mp 113–115 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3367, 1710, 1454, 1060, 804, 700; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.85 (2H, t, $J = 7.5$ Hz, H-11), 3.00 (2H, t, $J = 7.5$ Hz, H-10), 3.67 (2H, s, H-13), 6.89 (1H, d, $J = 1.5$ Hz, H-8), 7.07 (1H, d, $J = 8.5$, 1.5 Hz, H-3), 7.16 (2H, d, $J = 7.0$ Hz, H-15), 7.23–7.35 (4H, m, H-5,16,17), 7.41 (1H, d, $J = 8.5$ Hz, H-2), 7.96 (1H, br s, H-7); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 19.2 (CH$_2$, C-10), 42.2 (CH$_2$, C-11), 50.4 (CH$_2$, C-13), 111.0 (CH, C-5), 115.2 (C, C-9), 119.5 (CH, C-2), 120.0 (CH, C-3), 122.1 (CH, C-8), 125.7 (C, C-14), 127.0 (CH, C-17), 127.9 (C, C-14), 128.7 (2CH, C-16), 129.4 (2CH, C-15), 134.0 (C, C-14), 136.5 (C, C-6), 208.0 (C, C-12); HRMS (ESI$^+$): Found: 320.0824; C$_{16}$H$_{16}$ClINaO (MNa$^+$) Requires 320.0813 (−3.5 ppm error).

Lab notebook reference: MJJ7/56
4-(5-Methoxy-1H-indol-3-yl)-1-phenylbutan-2-one (192e)

Synthesised using **general procedure 3A** with Weinreb amide \textit{81j} (2.20 g, 8.39 mmol), BnMgCl (16.8 mL, 33.6 mmol, 2.0 M in THF) and THF (84 mL). Purification by column chromatography (3:2 hexane:EtOAc) afforded the **title compound** 192e (1.20 g, 49%) as a brown oil which solidified to a pale brown solid on standing, \(\text{mp 48–50 °C; } v_{\text{max}} (\text{cm}^{-1}) 3407, 1709, 1454, 1214, 1058, 700; \delta_H (400 MHz, CDCl}_3) 2.87 (2H, t, \(J = 7.5 \text{ Hz, H-12}), 3.01 (2H, t, \(J = 7.5 \text{ Hz, H-11}), 3.68 (2H, s, H-14), 3.86 (3H, s, H-4), 6.86 (1H, dd, \(J = 8.5, 2.5 \text{ Hz, H-5}), 6.90 (1H, d, \(J = 2.0 \text{ Hz, H-9}), 6.97 (1H, d, \(J = 2.5 \text{ Hz, H-2}), 7.17 (2H, d, \(J = 7.0 \text{ Hz, H-16}), 7.21–7.35 (4H, m, H-6,17,18), 7.85 (1H, br s, H-8); \delta_C (100 MHz, CDCl}_3) 19.4 (CH\textsubscript{2}, C-11), 42.2 (CH\textsubscript{2}, C-12), 50.4 (CH\textsubscript{2}, C-14), 55.9 (CH\textsubscript{3}, C-4), 100.5 (CH, C-2), 111.8 (CH, C-6), 112.2 (CH, C-5), 114.8 (C, C-10), 122.3 (CH, C-9), 127.0 (CH, C-18), 127.5 (C, C-1), 128.7 (2CH, C-17), 129.4 (2CH, C-16), 131.4 (C, C-7), 134.2 (C, C-15), 153.9 (C, C-3), 208.3 (C, C-13); HRMS (ESI\textsuperscript{+}): Found: 316.1301; \textit{C}_{19}\textit{H}_{19}\textit{NNaO}_2 (MNa\textsuperscript{+}) Requires 316.1308 (2.1 ppm error).

Lab notebook reference: MJJ7/59

1-Diazo-4-(1H-indol-3-yl)-1-phenylbutan-2-one (188a)

Synthesised using **general procedure 3B** with benzyl ketone \textit{192a} (527 mg, 2.00 mmol), \textit{p}-ABSA (576 mg, 2.40 mmol), DBU (0.42 mL, 2.80 mmol) and MeCN (6 mL). Purification by column chromatography (70:27:3 hexane:EtOAc:Et\textsubscript{3}N) afforded the **title compound** 188a (426 mg, 74%) as a yellow solid, \(\text{mp 105–106 °C (decomposition); } v_{\text{max}} (\text{cm}^{-1}) 3406, 2925, 2074, 1640, 744; \delta_H (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}) 2.98 (2H, t, \(J = 7.5 \text{ Hz, H-11}), 3.16 (2H, t, \(J = 7.5 \text{ Hz, H-10}), 7.05 (1H, d, \(J = 2.0 \text{ Hz, H-8}), 7.08 (1H, dd, \(J = 8.0, 7.0 \text{ Hz, H-3}), 7.17 (1H, dd, \(J = 8.0, 7.0 \text{ Hz, H-4}), 7.24 (1H, dd, \(J = 7.5, 7.5 \text{ Hz, H-17}), 7.34–7.42 (3H, m, H-5,16), 7.44–7.50 (2H, m, H-15), 7.57 (1H, d, \(J = 8.0 \text{ Hz, H-2}), 8.10 (1H, br s, H-7); \delta_C (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}) 20.7 (CH\textsubscript{2}, C-10), 40.3 (CH\textsubscript{2}, C-11), 72.7 (C, C-13), 111.7 (CH, C-5), 115.3 (C, C-9), 119.1 (CH, C-19).
Chapter 5. Experimental

C-2), 119.8 (CH, C-3), 122.35 (CH, C-4/8), 122.45 (CH, C-4/8), 126.40 (C, C-1/14), 126.44 (2CH, C-15), 127.4 (CH, C-17), 127.7 (C, C-1/14), 129.4 (2CH, C-16), 136.9 (C, C-6), 192.9 (C, C-12); HRMS (ESI'): Found: 312.1111; C_{18}H_{15}N_{3}NaO (MNa') Requires 312.1107 (−1.2 ppm error).

Lab notebook reference: MJJ6/8

4-Diazo-1-(1H-indol-3-yl)hex-5-en-3-one (207)

Synthesised using general procedure 3B with allyl ketone S3 (727 mg, 3.41 mmol), p-ABSA (982 mg, 4.09 mmol), DBU (0.71 mL, 4.77 mmol) and MeCN (10 mL). Purification by column chromatography (70:27:3 hexane:EtOAc:Et$_3$N) afforded the title compound 207 (466 mg, 57%) as a pale orange solid, mp 102–104 °C (decomposition); $\nu_{\text{max}}$ (cm$^{-1}$) 3410, 2078, 1635, 1609, 1292, 742; $\delta$H (400 MHz, CD$_2$Cl$_2$) 2.90 (2H, t, $J = 7.5$ Hz, H-11), 3.12 (2H, t, $J = 7.5$ Hz, H-10), 4.87 (1H, d, $J = 17.5$ Hz, H-15$^{\text{trans}}$), 5.17 (1H, d, $J = 11.0$ Hz, H-15$^{\text{cis}}$), 6.28 (1H, dd, $J = 17.5$, 11.0 Hz, H-14), 7.03 (1H, d, $J = 2.0$ Hz, H-8), 7.09 (1H, dd, $J = 7.5$, 7.0 Hz, H-3), 7.17 (1H, dd, $J = 8.0$, 7.0 Hz, H-4), 7.37 (1H, d, $J = 8.0$ Hz, H-5), 7.57 (1H, d, $J = 7.5$ Hz, H-2), 8.12 (1H, br s, H-7); $\delta$C (100 MHz, CD$_2$Cl$_2$) 20.5 (CH$_2$, C-10), 39.8 (CH$_2$, C-11), 108.6 (CH, C-15), 111.7 (CH, C-5), 115.2 (C, C-9), 119.0 (CH, C-2), 119.7 (CH, C-3), 120.6 (CH, C-14), 122.3 (CH, C-4/8), 122.4 (CH, C-4/8), 127.7 (C, C-1), 136.9 (C, C-6), 191.9 (C, C-12), CN$_2$ not observed.; HRMS (ESI'): Found: 262.0958; C$_{14}$H$_{13}$N$_3$NaO (MNa') Requires 262.0951 (−2.9 ppm error).

Lab notebook reference: MJJ7/25

1-Diazo-4-(2-methyl-1H-indol-3-yl)-1-phenylbutan-2-one (223)

Synthesised using general procedure 3B with benzyl ketone S4 (359 mg, 1.29 mmol), p-ABSA (372 mg, 1.55 mmol), DBU (0.27 mL, 1.81 mmol) and MeCN (4 mL). Purification by
column chromatography (70:27:3 hexane:EtOAc:Et3N) afforded the title compound 223 (136 mg, 35%) as a yellow solid, mp 77–79 °C (decomposition); \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3400, 2071, 1630, 1462, 724, 693; \( \delta_h \) (400 MHz, CD3Cl2) 2.36 (3H, s, H-9), 2.89 (2H, t, \( J = 7.5 \) Hz, H-12), 3.11 (2H, t, \( J = 7.5 \) Hz, H-11), 7.04 (1H, ddd, \( J = 7.5, 7.5, 1.5 \) Hz, H-3), 7.09 (1H, ddd, \( J = 7.5, 7.5, 1.5 \) Hz, H-4), 7.22–7.29 (2H, m, H-5,18), 7.35–7.41 (2H, m, H-17), 7.41–7.47 (3H, m, H-2,16), 7.94 (1H, br s, H-7); \( \delta_c \) (100 MHz, CD3Cl2) 11.8 (CH3, C-9), 20.0 (CH2, C-11), 40.4 (CH2, C-12), 72.7 (C, C-14), 110.5 (C, C-10), 110.7 (CH, C-5), 118.1 (CH, C-2), 119.6 (CH, C-3), 121.4 (CH, C-4), 126.4 (C + 2CH, C-1/15,16), 127.3 (CH, C-18), 128.9 (C, C-1/15), 129.4 (2CH, C-17), 132.1 (C, C-8), 135.9 (C, C-6), 193.2 (C, C-13); HRMS (ESI\(^+\)): Found: 326.1261; C19H17N3NaO (MNa\(^+\)) Requires 326.1264 (−0.8 ppm error).

Lab notebook reference: MJJ9/18

1-Diazo-4-(1H-indol-3-yl)-1-(3-methoxyphenyl)butan-2-one (188b)

Synthesised using general procedure 3B with benzyl ketone 192b (568 mg, 1.94 mmol), p-ABSA (560 mg, 2.33 mmol), DBU (0.41 mL, 2.72 mmol) and MeCN (6 mL). Purification by column chromatography (70:27:3 hexane:EtOAc:Et3N) afforded the title compound 188b (455 mg, 73%) as a yellow solid, mp 87–89 °C (decomposition); \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3408, 2075, 1632, 1601, 1231, 743; \( \delta_h \) (400 MHz, CD3Cl2) 2.98 (2H, t, \( J = 7.5 \) Hz, H-11), 3.17 (2H, t, \( J = 7.5 \) Hz, H-10), 3.80 (3H, s, H-17), 6.79 (1H, dd, \( J = 8.0, 2.5 \) Hz, H-18), 6.99 (1H, d, \( J = 8.0 \) Hz, H-20), 7.04 (1H, br s, H-8), 7.09 (1H, dd, \( J = 8.0, 7.5 \) Hz, H-3), 7.12–7.21 (2H, m, H-4/15), 7.30 (1H, dd, \( J = 8.0, 8.0 \) Hz, H-19), 7.36 (1H, d, \( J = 8.0 \) Hz, H-5), 7.57 (1H, d, \( J = 8.0 \) Hz, H-2), 8.15 (1H, br s, H-7); \( \delta_c \) (100 MHz, CD3Cl2) 20.7 (CH2, C-10), 40.4 (CH2, C-11), 55.8 (CH3, C-17), 72.8 (C, C-13), 111.7 (CH, C-5), 112.1 (CH, C-15), 112.8 (CH, C-18), 115.3 (C, C-9), 118.3 (CH, C-20), 119.1 (CH, C-2), 119.8 (CH, C-3), 122.4 (CH, C-4/8), 122.5 (CH, C-4/8), 127.7 (CH, C-19), 127.8 (C, C-1), 130.4 (C, C-14), 136.9 (C, C-6), 160.6 (C, C-16), 192.8 (C, C-12); HRMS (ESI\(^+\)): Found: 342.1209; C19H17N3NaO2 (MNa\(^+\)) Requires 342.1213 (1.1 ppm error).

Lab notebook reference: MJJ7/30
1-Diazo-1-(4-fluorophenyl)-4-(1H-indol-3-yl)butan-2-one (188c)

Synthesised using general procedure 3B with benzyl ketone 192c (1.34 g, 4.76 mmol), p-ABSA (1.37 g, 5.71 mmol), DBU (0.99 mL, 6.66 mmol) and MeCN (14 mL). Purification by column chromatography (65:32:3 hexane:EtOAc:Et3N) afforded the title compound 188c (1.09 g, 75%) as a yellow solid, mp 95–97 °C (decomposition); \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3316, 2075, 1636, 1508, 1226, 1200, 832, 739; \(\delta_H\) (400 MHz, CD\(_2\)Cl\(_2\)) 2.96 (2H, t, \(J = 7.5\) Hz, H-11), 3.16 (2H, t, \(J = 7.5\) Hz, H-10), 7.04 (1H, d, \(J = 1.5\) Hz, H-8), 7.06–7.13 (3H, m, H-3,16), 7.17 (1H, dd, \(J = 8.0, 7.5\) Hz, H-4), 7.37 (1H, d, \(J = 8.0\) Hz, H-5), 7.40–7.49 (2H, m, H-15), 7.56 (1H, d, J = 8.0 Hz, H-2), 8.13 (1H, br s, H-7); \(\delta_C\) (100 MHz, CD\(_2\)Cl\(_2\)) 20.7 (CH\(_2\), C-10), 40.2 (CH\(_2\), C-11), 72.0 (C, C-13), 111.7 (CH, C-5), 115.2 (C, C-9), 116.4 (2CH, d, \(J = 22.0\) Hz, C-16), 119.1 (CH, C-2), 119.8 (CH, C-3), 122.2 (C, d, \(J = 3\) Hz, C-14), 122.4 (CH, C-4/8), 122.5 (CH, C-4/8), 127.7 (C, C-1), 128.5 (2CH, C-15), 136.9 (C, C-6), 162.1 (C, d, \(J = 246\) Hz, C-17), 192.9 (C, C-12); \(\delta_F\) (376 MHz, CDCl\(_3\)) −114.5–−116.5 (1F, m); HRMS (ESI\(^+\)): Found: 330.1009; C\(_{18}\)H\(_{14}\)FN\(_3\)NaO (MNa\(^+\)) Requires 330.1013 (1.2 ppm error).

Lab notebook reference: MJJ7/52

4-(6-Chloro-1H-indol-3-yl)-1-diazo-1-phenylbutan-2-one (188d)

Synthesised using general procedure 3B with benzyl ketone 192d (774 mg, 2.60 mmol), p-ABSA (749 mg, 3.12 mmol), DBU (0.54 mL, 3.64 mmol) and MeCN (8 mL). Purification by column chromatography (57:40:3 hexane:EtOAc:Et3N) afforded the title compound 188d (496 mg, 59%) as a yellow solid, mp 110–112 °C (decomposition); \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3343, 2074, 1621, 1203, 803, 698; \(\delta_H\) (400 MHz, CD\(_2\)Cl\(_2\)) 2.95 (2H, t, \(J = 7.5\) Hz, H-11), 3.14 (2H, t, \(J = 7.5\) Hz, H, H-10), 7.03–7.08 (2H, m, H-5,8), 7.25 (1H, dd, \(J = 7.5, 7.5\) Hz, H-17), 7.35–7.43 (3H, m, H-3,16), 7.43–7.52 (3H, m, H-2,15), 8.13 (1H, br s, H-7); \(\delta_C\) (100 MHz, CD\(_2\)Cl\(_2\)) 20.5 (CH\(_2\), C-10), 40.1 (CH\(_2\), C-11), 66.9 (C, C-13), 111.6 (CH, C-5), 115.7 (C, C-9), 120.1 (CH, C-2), 120.4 (CH, C-3), 123.2 (CH, C-8), 126.5 (CH, C-17), 127.4 (2CH, C-15), 128.2 (C, C-1/4),
128.6 (C, C-1/4), 129.5 (2CH, C-16), 131.3 (C, C-14), 137.1 (C, C-6), 192.6 (C, C-12); HRMS (ESI?): Found: 346.0721; C_{18}H_{14}ClINaO (MNa⁺) Requires 346.0718 (−1.0 ppm error).

Lab notebook reference: MJJ7/63

1-Diazo-4-(5-methoxy-1H-indol-3-yl)-1-phenylbutan-2-one (188e)

Synthesised using general procedure 3B with benzyl ketone 192e (1.16 g, 3.95 mmol), p-ABSA (1.14 g, 4.74 mmol), DBU (0.83 mL, 5.53 mmol) and MeCN (12 mL). Purification by column chromatography (70:27:3 hexane:EtOAc:Et₃N) afforded the title compound 188e (780 mg, 62%) as a dark yellow solid, mp 85–87 °C (decomposition); ν max (cm⁻¹) 3311, 2082, 1634, 1204, 759; δ H (400 MHz, CD₂Cl₂) 2.97 (2H, dd, J = 7.5, 7.5 Hz, H-12), 3.14 (2H, dd, J = 7.5, 7.5 Hz, H-11), 3.81 (3H, s, H-4), 6.81 (1H, dd, J = 9.0, 2.5 Hz, H-5), 6.99–7.02 (2H, m, H-2,9), 7.22–7.28 (2H, m, H-16), 7.39 (2H, dd, J = 8.0, 8.0 Hz, H-17), 7.45–7.51 (2H, m, H-6,18), 8.06 (1H, br s, H-8); δ C (100 MHz, CD₂Cl₂) 20.8 (CH₂, C-11), 40.3 (CH₂, C-12), 56.2 (CH₃, C-4), 72.7 (C, C-14), 100.8 (CH, C-2), 112.4 (CH, C-5/6), 112.6 (CH, C-5/6), 115.1 (C, C-10), 123.1 (CH, C-9), 126.4 (C + CH, C-14,18), 127.4 (2CH, C-16), 128.1 (C, C-1), 129.4 (2CH, C-17), 131.9 (C, C-7), 154.5 (C, C-3), 192.9 (C, C-13); HRMS (ESI?): Found: 342.1203; C_{19}H_{17}NO NaO₂ (MNa⁺) Requires 342.1218 (4.4 ppm error).

Lab notebook reference: MJJ7/65

2-Phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (193a)

Synthesised using general procedure 3H with α-diazocarbonyl 188a (43 mg, 0.149 mmol), silica gel (34 mg) and CH₂Cl₂ (1.5 mL). Purification by column chromatography (40% Et₂O in hexane) afforded the title compound 193a (28 mg, 72%) as a white solid, mp 169–171 °C; ν max (cm⁻¹) 3275, 1642, 739; δ H (400 MHz, CDCl₃) 2.49–2.62 (2H, m, H-11), 3.03–3.20 (2H,
m, H-10), 3.91 (1H, dd, J = 9.0, 8.5 Hz, H-12), 7.16–7.22 (1H, m, H-3), 7.22–7.32 (3H, m, ArH), 7.33–7.45 (4H, m, ArH), 7.70 (1H, d, J = 8.0 Hz, H-2), 8.84 (1H, br s, H-7); δc (100 MHz, CDCl₃) 20.5 (CH₂, C-10), 33.4 (CH₂, C-11), 53.7 (CH, C-12), 112.7 (CH, C-5), 120.4 (CH, C-3), 121.3 (CH, C-2), 125.8 (C, C-1/9), 127.0 (CH, C-4), 127.1 (CH, C-17), 128.5 (2CH, C-15/16), 128.6 (2CH, C-15/16), 129.2 (C, C-1/9), 131.5 (C, C-6/8/14), 138.3 (C, C-6/8/14), 139.6 (C, C-6/8/14), 191.5 (C, C-13); HRMS (ESI⁺): Found: 284.1036; C₁₈H₁₅NNaO (MNa⁺) Requires 284.1046 (3.4 ppm error), Found: 262.1216; C₁₈H₁₆NO (MH⁺) Requires 262.1226 (3.9 ppm error).

Lab notebook reference: 6/92

2-Phenylspiro[cyclopentane-1,3'-indol]-3-one (190a)

Synthesised using general procedure 3C with α-diazocarbonyl 188a (29 mg, 0.1 mmol), Rh₂oct₄ (3.9 mg, 5.0 µmol) and deoxygenated CHCl₃ (1 mL). Purification by column chromatography (40→60% EtOAc in hexane, positive pressure of N₂) afforded the title compound 190a (24 mg, 92%, 54:45 dr) as a colourless oil; vₘₐₓ (cm⁻¹) 1745, 1453, 734, 699; δH (400 MHz, CDCl₃) 2.07–2.16 (1H, m, H-10a, minor), 2.17–2.27 (1H, m, H-10a, major), 2.43–2.55 (1H, m, H-10b, major), 2.61–2.73 (1H, m, H-10b, minor), 2.76–3.03 (4H, m, H-11, major + minor), 4.02 (1H, s, H-13, major), 4.18 (1H, s, H-13, minor), 6.74–6.86 (4H, m, H-15, major + minor), 7.05–7.19 (8H, m, ArH, major + minor), 7.24–7.30 (1H, m, ArH, major/minor), 7.35–7.41 (2H, m, ArH, major + minor), 7.48 (1H, d, J = 7.5 Hz, ArH, minor), 7.51–7.57 (2H, m, ArH, major + minor), 8.12 (1H, s, H-8, major), 8.23 (1H, s, H-8, minor); δc (100 MHz, CDCl₃) 26.7 (CH₂), 28.2 (CH₂), 36.5 (CH₂), 38.1 (CH₂), 59.8 (CH), 62.5 (CH), 66.0 (C), 66.2 (C), 121.1 (CH), 121.58 (CH), 121.63 (CH), 122.6 (CH), 126.0 (CH), 126.8 (CH), 127.5 (CH), 127.7 (CH), 128.0 (2CH), 128.4 (2CH), 128.5 (3CH), 128.7 (CH), 129.2 (2CH), 132.3 (C), 133.0 (C), 138.7 (C), 139.7 (C), 155.1 (C), 155.4 (C), 173.1 (CH), 175.1 (CH), 213.6 (C), 214.4 (C); HRMS (ESI⁺): Found: 262.1231; C₁₈H₁₆NO (MH⁺) Requires 262.1226 (~1.7 ppm error).

Lab notebook reference: MJJ6/99
4-(2-Oxindolin-3-yl)-1-phenylbutane-1,2-dione (198a)

To α-diazocarbonyl 188a (57 mg, 0.197 mmol) and Rh_{2}oct_{4} (3.1 mg, 3.94 μmol) in a flask open to air was added CHCl_{3} (20 mL/mmol). The mixture was stirred at RT for 1 h then purified by rapid (compound reacts with silica) column chromatography (1:1 hexane:EtOAc) to afford the title compound 198a (45 mg, 78%) as a yellow solid, mp 122–123 °C; \( \nu_{\text{max}} (\text{cm}^{-1}) \) 1695, 1667, 1470, 749, 691; \( \delta_{\text{H}} (400 \text{ MHz, CDCl}_{3}) \) 2.27–2.52 (2H, m, H-10), 2.95–3.15 (2H, m, H-11), 3.62 (1H, dd, \( J = 6.5, 6.5 \text{ Hz, H-9} \)), 6.88 (1H, d, \( J = 8.0 \text{ Hz, H-5} \)), 7.06 (1H, dd, \( J = 8.0, 7.5 \text{ Hz, H-3} \)), 7.20–7.30 (2H, m, H-2,4), 7.48 (2H, dd, \( J = 7.5, 7.5 \text{ Hz, H-16} \)), 7.63 (1H, dd, \( J = 7.5, 7.5 \text{ Hz, H-17} \)), 7.91–7.99 (3H, m, H-7,15); \( \delta_{\text{C}} (100 \text{ MHz, CDCl}_{3}) \) 23.3 (CH\text{2}, C-10), 34.5 (CH\text{2}, C-11), 44.4 (CH, C-9), 109.7 (CH, C-5), 122.6 (CH, C-3), 124.3 (CH, C-2), 128.3 (CH, C-4), 128.6 (C, C-1), 128.8 (2CH, C-16), 130.3 (2CH, C-15), 131.8 (C, C-14), 134.6 (CH, C-17), 141.2 (C, C-6), 179.0 (C, C-8), 191.7 (C, C-13), 201.9 (C, C-12); HRMS (ESI\(^{+}\)): Found: 316.0955; C\text{18}H\text{15}N\text{NaO}_{3} (M\text{Na}^{+}) Requires 316.0950 (−1.6 ppm error).

Lab notebook reference: MJJ6/21

4-(2-Oxindolin-3-yl)-1-phenylbutane-1,2-dione (208)

To α-diazocarbonyl 207 (53 mg, 0.221 mmol) and Rh_{2}oct_{4} (8.6 mg, 11.1 μmol) in a flask open to air was added CHCl_{3} (4.4 mL). The mixture was stirred at RT for 24 h then purified by column chromatography (35% EtOAc in hexane) to afford the title compound 208 (10 mg, 19%) as a white solid, mp 151–153 °C; \( \nu_{\text{max}} (\text{cm}^{-1}) \) 3401, 2918, 1721, 1652, 1483, 1206, 1049, 745; \( \delta_{\text{H}} (400 \text{ MHz, CDCl}_{3}) \) 2.10–2.25 (2H, m, H-10), 2.58 (1H, ddd, \( J = 18.5, 7.5, 2.5 \text{ Hz, H-11a} \)), 2.69–2.82 (1H, m, H-11b), 4.58 (1H, ddd, \( J = 20.0, 2.5, 2.0 \text{ Hz, H-15a} \)), 4.78–4.86 (1H, m, H-7), 5.02 (1H, d, \( J = 20.0, 2.0 \text{ Hz, H-15b} \)), 5.51 (1H, d, \( J = 2.5 \text{ Hz, H-8} \)), 6.68–6.76 (3H, m, H-3,5,14), 6.83 (1H, d, \( J = 7.0 \text{ Hz, H-2} \)), 7.11 (1H, dd, \( J = 7.5, 7.5 \text{ Hz, H-4} \)); \( \delta_{\text{C}} (100 \text{ MHz, CDCl}_{3}) \) 35.3 (CH\text{2}, C-10), 36.0 (CH\text{2}, C-11), 55.5 (C, C-9), 75.2 (CH\text{2}, C-15), 106.2 (CH, C-8), 107.9 (CH, C-5), 118.7 (CH, C-3), 120.8 (CH, C-2), 128.0 (CH, C-4), 133.0 (CH, C-14),
136.3 (C, C-1/6), 138.1 (C, C-1/6), 146.5 (C, C-13), 205.2 (C, C-12); HRMS (ESI\(^+\)): Found: 266.0781; \(\text{C}_{14}\text{H}_{13}\text{NaO}_3\) (MNa\(^+\)) Requires 266.0788 (2.5 ppm error).

Lab notebook reference: MJJ8/6

**syn-2-Hydroxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (212a)**

Synthesised using **general procedure 3D** with \(\alpha\)-diazocarbonyl 188a (29 mg, 0.1 mmol), Rh\(_2\)oct\(_4\) (1.6 mg, 2.0 \(\mu\)mol) and CHCl\(_3\) (2 mL) for 1 h then TFA (23 \(\mu\)L, 0.3 mmol) and THF (1 mL) for 4 h. Purification by column chromatography (40→60% EtOAc in hexane) afforded the **title compound** 212a (29 mg, 99%) as a white solid, mp 175–177 °C; \(v\)\(_{\text{max}}\) (cm\(^{-1}\)) 3257, 1746, 1703, 729, 699; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 2.29 (1H, ddd, \(J\) = 13.5, 10.0, 10.0 Hz, H-10a), 2.41–2.51 (1H, m, H-10b), 2.85 (1H, ddd, \(J\) = 20.0, 10.0, 2.5 Hz, H-11a), 3.33 (1H, ddd, \(J\) = 20.0, 10.0, 10.0 Hz, H-11b), 3.83 (1H, s, H-14), 5.82 (1H, d, \(J\) = 8.0 Hz, H-2), 6.74 (1H, dd, \(J\) = 8.0, 7.5 Hz, H-3), 6.85 (1H, d, \(J\) = 8.0 Hz, H-5), 7.11–7.21 (3H, m, H-4,16), 7.29–7.39 (3H, m, H-17,18), 7.89 (1H, br s, H-7); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 27.4 (CH\(_2\), C-10), 34.4 (CH\(_3\), C-9), 59.6 (C, C-9), 84.6 (C, C-13), 109.7 (CH, C-5), 121.9 (CH, C-3), 125.4 (CH, C-2), 126.7 (2CH, C-16), 127.9 (C, C-1), 128.1 (2CH, C-17), 128.5 (CH, C-4(18)), 128.6 (CH, C-4(18)), 137.4 (C, C-15), 141.1 (C, C-6), 180.0 (C, C-8), 215.9 (C, C-12); HRMS (ESI\(^+\)): Found: 316.0956; \(\text{C}_{18}\text{H}_{15}\text{NaO}_3\) (MNa\(^+\)) Requires 316.0944 (−3.8 ppm error).

Lab notebook reference: MJJ6/94

**anti-2-Hydroxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (214a)**

Synthesised using **general procedure 3E** with \(\alpha\)-diazocarbonyl 188a (29 mg, 0.1 mmol), Rh\(_2\)oct\(_4\) (1.6 mg, 2.0 \(\mu\)mol) and CHCl\(_3\) (2 mL) for 1 h then t-BuOK (34 mg, 0.3 mmol) and THF (1 mL) for 2 h. Purification by column chromatography (40→60% EtOAc in hexane) afforded the **title compound** 214a (17 mg, 58%) as a white solid, mp 184–186 °C; \(v\)\(_{\text{max}}\) (cm\(^{-1}\))
3276, 1742, 1697, 1471, 740; δH (400 MHz, CDCl3) 2.29 (1H, dd, J = 12.5, 9.5 Hz, H-10a), 2.71 (1H, ddd, J = 12.5, 10.0, 9.5 Hz, H-10b), 2.86 (1H, dd, J = 19.5, 9.5 Hz, H-11a), 3.00 (1H, s, H-14), 3.20 (1H, ddd, J = 19.5, 10.0, 9.5 Hz, H-11b), 6.64 (1H, d, J = 7.5 Hz, H-5), 7.02–7.21 (7H, m, ArH), 7.24 (1H, dd, J = 8.0, 8.0 Hz, H-4), 7.73 (1H, d, J = 8.0 Hz, H-2); δC (100 MHz, CDCl3) 28.3 (CH2, C-10), 34.3 (CH2, C-11), 51.0 (C, C-9), 81.4 (C, C-13), 109.1 (CH, C-5), 122.5 (CH, C-3), 126.8 (CH, C-2), 127.45 (2CH, C-16), 127.50 (2CH, C-17), 127.7 (C, C-1), 128.4 (CH, C-4/18), 128.7 (CH, C-4/18), 135.2 (C, C-15), 140.8 (C, C-6), 178.8 (C, C-8), 212.6 (C, C-12); HRMS (ESI+): Found: 316.0941; C18H15NNaO3 (M+H) Requires 316.0944 (1.0 ppm error).

Lab notebook reference: MJJ7/7

1-Phenyl-3,4-dihydro-1H-carbazol-2(9H)-one (199a)

![Compound 199a](image)

Synthesised using general procedure 3F with α-diazocarbonyl 188a (57 mg, 0.197 mmol), Pd(MeCN)4(BF4)2 (4.4 mg, 9.85 µmol) and CHCl3 (2 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the title compound 199a (43 mg, 84%) as a white solid, mp 153–155 °C; νmax (cm⁻¹) 3395, 1713, 1455, 1236, 741; δH (400 MHz, CDCl3) 2.66–2.75 (1H, m, H-11a), 2.86–2.97 (1H, m, H-11b), 3.09–3.20 (1H, m, H-10a), 3.26–3.36 (1H, m, H-10b), 4.83 (1H, s, H-13), 7.15–7.38 (9H, m, ArH), 7.60 (1H, d, J = 8.0 Hz, H-2), 7.67 (1H, br s, H-7); δC (100 MHz, CDCl3) 20.2 (CH2, C-10), 36.8 (CH2, C-11), 55.1 (CH, H-13), 111.0 (CH, C-5), 111.4 (C, C-9), 118.4 (CH, C-2), 119.8 (CH, C-3), 122.4 (CH, C-4/17), 126.4 (C, C-1), 127.8 (CH, C-4/17), 128.5 (2CH, C-15/16), 128.9 (2CH, C-15/16), 132.3 (C, C-8), 136.9 (C, C-6/14), 137.3 (C, C-6/14), 207.7 (C, C-12); HRMS (ESI+): Found: 262.1238; C18H16NO (M+H) Requires 262.1226 (~4.6 ppm error).

Lab notebook reference: MJJ6/35
1-Phenyl-9H-carbazol-2-ol (200a)

Synthesised using **general procedure 3G** with α-diazocarbonyl 188a (43 mg, 0.149 mmol), Cu(OTf)$_2$ (10.9 mg, 30 µmol) and CHCl$_3$ (3 mL). Purification by column chromatography (20→30% EtOAc in hexane) afforded the **title compound 200a** (27 mg, 70%) as a white solid, mp 211–213 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3389, 1460, 1175, 739; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 5.20 (1H, s, H-13), 6.95 (1H, d, $J$ = 8.5 Hz, H-11), 7.19–7.26 (1H, m, H-3), 7.29–7.37 (2H, m, H-4,5), 7.49–7.57 (1H, m, H-18), 7.58–7.68 (4H, m, H-16,17), 7.88 (1H, br s, H-7), 7.95 (1H, d, $J$ = 8.5 Hz, H-10), 8.01 (1H, d, $J$ = 8.0 Hz, H-2); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 108.8 (CH, C-11), 110.3 (CH, C-5), 110.4 (C, C-1/9), 117.1 (C, C-1/9), 119.5 (CH, C-2/3), 119.6 (CH, C-2/3), 120.6 (CH, C-10), 123.8 (C, C-14), 124.6 (CH, C-4), 128.6 (CH, C-18), 130.0 (2CH, C-16/17), 130.09 (2CH, C-16/17), 133.0 (C, C-6/8/15), 151.0 (C, C-12); HRMS (ESI$^+$): Found: 260.1070; C$_{18}$H$_{14}$NO (MH$^+$) Requires 260.1070 (0.0 ppm error).

Lab notebook reference: 6/93

2-(3-Methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-one (193b)

Synthesised using **general procedure 3H** with α-diazocarbonyl 188b (32 mg, 0.10 mmol), silica gel (32 mg) and CH$_2$Cl$_2$ (1 mL). Purification by column chromatography (50% Et$_2$O in hexane) afforded the **title compound 193b** (19 mg, 65%) as a white solid, mp 146–148 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3279, 1646, 1251, 739; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 2.49–2.60 (2H, m, H-11), 3.02–3.19 (2H, m, H-10), 3.80 (3H, s, H-17), 3.85–3.92 (1H, m, H-12), 6.78–6.87 (3H, m, H-5,18,20), 7.16–7.22 (1H, m, H-3), 7.24–7.30 (1H, m, H-19), 7.36–7.46 (2H, m, H-4,15), 7.69 (1H, d, $J$ = 8.0 Hz, H-2), 8.79 (1H, br s, H-7); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 20.5 (CH$_2$, C-10), 33.4 (CH$_2$, C-11), 53.7 (CH, C-12), 55.2 (CH$_3$, C-17), 112.2 (CH, C-5), 112.7 (CH, C-15), 114.5 (CH, C-18), 120.4 (CH, C-3), 120.9 (CH, C-20), 121.3 (CH, C-2), 125.8 (C, C-1/9), 127.1 (CH, C-4), 129.2 (C, C-1/9), 129.5 (CH, C-19), 131.4 (C, C-6/8/14), 138.3 (C, C-6/8/14), 141.2 (C, C-6/8/14), 159.7 (C, C-16), 191.3 (C, C-13); HRMS (ESI$^+$): Found: 314.1138; C$_{19}$H$_{17}$NNaO$_2$.
(MNa⁺) Requires 314.1151 (4.4 ppm error), Found: 292.1321; C₁₈H₁₈NO₂ (MH⁺) Requires 292.1332 (3.8 ppm error).

Lab notebook reference: MJJ7/37

2-(4-Fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-one (193c)

Synthesised using general procedure 3H with α-diazocarbonyl 188c (61 mg, 0.2 mmol), silica gel (61 mg) and CH₂Cl₂ (2 mL). Purification by column chromatography (40% Et₂O in hexane) afforded the title compound 193c (28 mg, 50%) as an off-white solid, mp 185–187 °C; νmax (cm⁻¹) 3277, 1640, 1510, 1228, 742; δH (400 MHz, CDCl₃) 2.44–2.60 (2H, m, H-11), 3.03–3.21 (2H, m, H-10), 3.90 (1H, dd, J = 10.0, 5.0 Hz, H-12), 7.01–7.09 (2H, m, H-16), 7.16–7.25 (3H, m, H-3,15), 7.38–7.44 (2H, m, H-4,5) 7.69 (1H, d, J = 8.0 Hz, H-2), 8.90 (1H, br s, H-7); δC (100 MHz, CDCl₃) 20.6 (CH₂, C-10), 33.5 (CH₂, C-11), 53.0 (CH, C-12), 112.7 (CH, C-5), 115.4 (2CH, d, J = 21.0 Hz, C-16), 120.5 (CH, C-3), 121.4 (CH, C-2), 125.7 (C, C-1/9), 127.2 (CH, C-4), 129.3 (C, C-1/9), 130.0 (2CH, d, J = 7.5 Hz, C-15), 131.3 (C, C-6/8), 135.3 (C, d, J = 3.0 Hz, C-14), 138.4 (C, C-6/8), 161.9 (C, d, J = 245 Hz, C-17), 191.3 (C, C-13); δF (376 MHz, CDCl₃) −115.7−115.9 (1F, m); HRMS (ESI⁺): Found: 302.0954; C₁₈H₁₅FNNaO (MNa⁺) Requires 302.0952 (−0.9 ppm error), Found: 280.1133; C₁₈H₁₅FNO (MH⁺) Requires 280.1132 (−0.2 ppm error).

Lab notebook reference: MJJ7/57

7-Chloro-2-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (193d)

Synthesised using general procedure 3H with α-diazocarbonyl 188d (65 mg, 0.2 mmol), silica gel (65 mg) and CH₂Cl₂ (2 mL). Purification by column chromatography (0→1% MeOH in CH₂Cl₂) afforded the title compound 193d (44 mg, 75%) as a white solid, mp 230–232 °C; νmax (cm⁻¹) 3241, 1649, 1636, 936, 737, 698; δH (400 MHz, DMSO-d₆) 2.31–2.50 (2H, m, H-11), 2.96–3.10 (2H, m, H-10), 3.97 (1H, dd, J = 11.0, 4.5 Hz, H-12), 7.12 (1H, dd, J =
8.5, 2.0 Hz, H-3), 7.20–7.29 (3H, m, H-15/16,17), 7.30–7.36 (2H, m, H-15/16), 7.42 (1H, d, J = 2.0 Hz, H-5), 7.73 (1H, d, J = 8.5 Hz, H-2), 11.83 (1H, br s, H-7); δC (100 MHz, DMSO-d6) 20.2 (CH2, C-10), 33.0 (CH2, C-11), 53.2 (CH, C-12), 112.2 (CH, C-5), 120.4 (CH, C-3), 123.0 (CH, C-2), 124.0 (C, C-1/9), 126.6 (CH, C-17), 127.8 (C, C-1/9), 128.3 (2CH, C-15/16), 128.7 (2CH, C-15/16), 130.7 (C, C-4/6/8/14), 132.2 (C, C-4/6/8/14), 138.5 (C, C-4/6/8/14), 140.3 (C, C-4/6/8/14), 190.8 (C, C-13); HRMS (ESI+): Found: 318.0658; C18H1435ClNNaO (MNa+)) Requires 318.0656 (−0.6 ppm error), Found: 296.0837; C18H1535ClNO (MH+) Requires 296.0837 (0.0 ppm error).

Lab notebook reference: MJJ7/67

7-Chloro-2-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (193e)

Synthesised using general procedure 3H with α-diazocarbonyl 188e (64 mg, 0.2 mmol), silica gel (64 mg) and CH2Cl2 (2 mL). The crude reaction mixture was then filtered (washing with MeOH) and concentrated in vacuo. The crude material was then suspended in a 0 °C solution of CH2Cl2:Et2O (1:1 v/v, 0.5 mL), after filtration the obtained solution was discarded and the remaining insoluble solids (product) were collected to afford the title compound 193e (22 mg, 38%) as an off-white solid, mp 197–199 °C; νmax (cm−1) 3268, 1638, 1483, 1215; δH (400 MHz, CDCl3) 2.47–2.63 (2H, m, H-12), 2.98–3.16 (2H, m, H-11), 3.88 (3H, s, H-4), 3.88–3.95 (1H, m, H-13), 7.00–7.09 (2H, m, H-2,5), 7.22–7.41 (6H, m, H-6,16,17,18), 9.45 (1H, br s, H-8); δC (100 MHz, CDCl3) 20.5 (CH2, C-11), 33.4 (CH2, C-12), 53.7 (CH, C-13), 55.7 (CH3, C-4), 101.0 (CH, C-2), 113.7 (CH, C-6), 118.9 (CH, C-5), 125.8 (C, C-1/9), 126.9 (CH. C-18), 128.5 (2CH, C-16/17), 128.56 (2CH, C-16/17), 128.58 (C, C-1/9), 132.0 (C, C-7/9/15), 133.8 (C, C-7/9/15), 139.7 (C, C-7/9/15), 154.5 (C, C-3), 191.4 (C, C-14); HRMS (ESI+): Found: 314.1155; C19H1535ClNO2 (MNa+) Requires 314.1151 (−1.1 ppm error).

Lab notebook reference: MJJ7/80
2-(3-Methoxyphenyl)spiro[cyclopentane-1,3’-indol]-3-one (190b)

Synthesised using general procedure 3C with α-diazocarbonyl 188b (48 mg, 0.15 mmol), Rh₂oct₄ (5.8 mg, 7.5 µmol) and deoxygenated CHCl₃ (1.5 mL). Purification by column chromatography (40→70% EtOAc in hexane, positive pressure of N₂) afforded the title compound 190b (31 mg, 71%, 78:22 dr) as a colourless oil; νmax (cm⁻¹) 1740, 1600, 1455, 1248, 733; δH (400 MHz, CDCl₃) 2.06–2.14 (1H, m, H-10a, minor), 2.16–2.26 (1H, m, H-10a, major), 2.40–2.52 (1H, m, H-10b, major), 2.59–2.70 (1H, m, H-10b, minor), 2.75–3.02 (4H, m, H-11, major + minor), 3.57 (3H, s, H-17, minor), 3.59 (3H, s, H-17, major), 3.98 (1H, s, H-13, major), 4.15 (1H, s, H-13, minor), 6.27 (1H, br s, H-15, major), 6.31 (1H, br s, H-15, minor), 6.39 (1H, d, J = 8.0 Hz, H-20, major), 6.43 (1H, d, J = 7.5 Hz, H-20, minor), 6.62 (1H, dd, J = 8.0, 2.0 Hz, H-18, minor), 6.67 (1H, dd, J = 8.0, 2.0 Hz, H-18, major), 6.99 (1H, dd, J = 8.0, 8.0 Hz, H-19, minor), 7.04 (1H, dd, J = 8.0, 8.0 Hz, H-19, major), 7.14–7.20 (2H, m, ArH, minor), 7.24–7.32 (1H, m, ArH, minor), 7.35–7.41 (2H, m, ArH, major), 7.48–7.58 (3H, m, ArH, major + minor), 8.09 (1H, s, H-8, major), 8.20 (1H, s, H-8, minor); δC (100 MHz, CDCl₃) 26.8 (CH₂), 28.2 (CH₂), 36.4 (CH₂), 38.2 (CH₂), 55.0 (2CH₃), 59.7 (CH), 62.1 (CH), 65.8 (C), 66.0 (C), 113.0 (CH), 113.3 (CH), 114.3 (CH), 114.6 (CH), 120.6 (CH), 121.1 (CH), 121.6 (CH), 121.66 (CH), 121.69 (CH), 122.6 (CH), 125.9 (CH), 126.7 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.4 (CH), 133.8 (C), 134.5 (C), 138.8 (C), 139.9 (C), 155.1 (C), 155.4 (C), 159.0 (C), 159.2 (C), 173.1 (CH), 175.1 (CH), 213.3 (C), 214.1 (C); HRMS (ESI⁺): Found: 314.1152; C₁₉H₁₇NNaO₂ (MNa⁺) Requires 314.1151 (−0.0 ppm error).

Lab notebook reference: MJJ7/64

2-(4-Fluorophenyl)spiro[cyclopentane-1,3’-indol]-3-one (190c)

Synthesised using general procedure 3C with α-diazocarbonyl 188c (61 mg, 0.199 mmol), Rh₂oct₄ (7.7 mg, 9.95 µmol) and deoxygenated CHCl₃ (2 mL). Purification by column...
chromatography (40–70% EtOAc in hexane, positive pressure of N\textsubscript{2}) afforded the **title compound 190c** (37 mg, 66%, 61:39 dr) as a pale brown oil; \( \nu_{\text{max}} \) (cm\textsuperscript{-1}) 1742, 1511, 1225, 733; \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{3}) 2.06–2.13 (1H, m, H-10a, minor), 2.18 (1H, ddd, \( J = 13.5, 8.5, 1.5 \) Hz, H-10a, major), 2.45–2.57 (1H, m, H-10b, major), 2.64–2.75 (1H, m, H-10b, minor), 2.75–3.02 (4H, m, H-11, major + minor), 4.01 (1H, s, H-13, major), 4.19 (1H, s, H-14, minor), 6.70–6.84 (8H, m, H-15,16, major + minor), 7.15–7.21 (2H, m, H-2,3, minor), 7.25–7.32 (1H, m, H-4, minor), 7.35–7.43 (2H, m, H-2,3 major), 7.49 (1H, d, \( J = 8.0 \) Hz, H-5, minor), 7.51–7.58 (2H, m, H-4,5, major), 8.10 (1H, s, H-8, major), 8.21 (1H, s, H-8, minor); \( \delta_{\text{F}} \) (100 MHz, CDCl\textsubscript{3}) 2.40 (CH), 27.9 (CH\textsubscript{3}), 36.2 (C), 114.9 (2CH, d, \( J = 22 \) Hz), 115.4 (2CH, d, \( J = 21 \) Hz), 121.1 (CH), 121.6 (CH), 121.8 (CH), 122.4 (CH), 126.1 (CH), 126.9 (CH), 127.9 (C, d, \( J = 3.0 \) Hz), 128.6 (C, d, \( J = 3.0 \) Hz), 128.7 (CH), 128.8 (CH), 130.2 (2CH, d, \( J = 7.5 \) Hz), 130.8 (2CH, d, \( J = 8.5 \) Hz), 138.5 (C), 139.3 (C), 155.1 (C), 155.4 (C), 161.9 (C, d, \( J = 247 \) Hz), 162.1 (C, d, \( J = 247 \) Hz), 172.7 (CH), 174.9 (CH), 213.2 (C), 213.9 (C); \( \delta_{\text{C}} \) (376 MHz, CDCl\textsubscript{3}) –114.03–114.14 (1F, m, major), –114.3–114.4 (1F, m, minor); HRMS (ESI\textsuperscript{+}): Found: 280.1125; C\textsubscript{18}H\textsubscript{15}FNO (MH\textsuperscript{+}) Requires 280.1132 (2.4 ppm error).

Lab notebook reference: MJJ7/66

### 6'-Chloro-2-phenylspiro[cyclopentane-1,3'-indol]-3-one (190d)

Synthesised using **general procedure 3C** with \( \alpha \)-diazocarbonyl 188d (49 mg, 0.15 mmol), Rh\textsubscript{2}oct\textsubscript{4} (5.8 mg, 7.5 \( \mu \)mol) and deoxygenated CHCl\textsubscript{3} (4.5 mL). Purification by column chromatography (40–70% EtOAc in hexane, positive pressure of N\textsubscript{2}) afforded the **title compound 190d** (24 mg, 54%, 58:42 dr) as a pale brown oil; \( \nu_{\text{max}} \) (cm\textsuperscript{-1}) 1745, 1453, 735, 699; \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{3}) 2.05–2.14 (1H, m, H-10a, minor), 2.15–2.24 (1H, m, H-10a, major), 2.40–2.52 (1H, m, H-10b, major), 2.58–2.70 (1H, m, H-10b, minor), 2.75–3.02 (4H, m, H-11, major + minor), 3.98 (1H, s, H-13 major), 4.15 (1H, s, H-13 minor), 6.73–6.86 (4H, m, H-15, minor + major), 7.01 (1H, d, \( J = 8.0 \) Hz, H-2, minor), 7.07–7.19 (7H, m, H-3,16,17 major + minor), 7.36 (1H, dd, \( J = 8.0, 1.5 \) Hz, H-3, major), 7.44 (1H, d, \( J = 8.0 \) Hz, H-2, major), 7.47 (1H, br s, H-5, minor), 7.52 (1H, br s, H-5, major), 8.15 (1H, s, H-8, major), 8.26 (1H, s, H-8, minor); \( \delta_{\text{C}} \) (100 MHz, CDCl\textsubscript{3}) 26.7 (CH\textsubscript{2}), 28.1 (CH\textsubscript{2}), 36.5 (CH\textsubscript{2}), 38.0 (CH\textsubscript{2}), 59.5 (CH), 62.4 (CH), 65.9 (C), 66.1 (C), 121.8 (CH), 122.1 (CH), 122.2 (CH), 123.2 (CH), 125.9
(CH), 126.8 (CH), 127.6 (CH), 127.8 (CH), 128.1 (2CH), 128.47 (2CH), 128.51 (2CH), 129.1 (2CH), 132.2 (C), 132.7 (C), 134.1 (C), 134.2 (C), 137.2 (C), 138.2 (C), 156.2 (C), 156.6 (C), 174.7 (CH), 176.7 (CH), 213.1 (C), 213.7 (C); HRMS (ESI⁺): Found: 318.0665; \( \text{C}_{18}\text{H}_{14}^{35}\text{CINaO} \) (MNa⁺) Requires 318.0656 (−2.9 ppm error), Found: 296.0831; \( \text{C}_{18}\text{H}_{15}^{35}\text{CINO} \) (MH⁺) Requires 296.0837 (1.8 ppm error).

Lab notebook reference: MJJ7/88

5′-Methoxy-2-phenylspiro[cyclopentane-1,3′-indol]-3-one (190e)

Synthesised using general procedure 3C with α-diazocarbonyl 188e (64 mg, 0.20 mmol), \( \text{Rh}_2\text{oct}_4 \) (7.8 mg, 10.0 µmol) and deoxygenated \( \text{CHCl}_3 \) (2 mL). Purification by column chromatography (40→80% EtOAc in hexane, positive pressure of \( \text{N}_2 \)) afforded the title compound 190e (34 mg, 59%, 63:37 dr) as a colourless oil; \( \nu_{\text{max}} \) (cm⁻¹) 1744, 1470, 1284, 1027, 734, 699; \( \delta_H \) (400 MHz, CDCl₃) 2.12 (1H, ddd, \( J = 13.0, 8.0, 4.0 \) Hz, H-11a, minor), 2.19 (1H, ddd \( J = 13.5, 9.0, 2.0 \) Hz, H-11a, major), 2.38–2.49 (1H, m, H-11b, major), 2.60 (1H, ddd, \( J = 13.5, 9.0, 9.5 \) Hz, H-11b, minor), 2.73–3.01 (4H, m, H-12, major + minor), 3.74 (3H, s, H-4, minor), 3.89 (3H, s, H-4, major), 3.96 (1H, s, H-14, major), 4.12 (1H, s, H-14, minor), 6.60 (1H, d, \( J = 2.0 \) Hz, H-2, minor), 6.72–6.91 (6H, m, H-5,16, major + minor), 7.06 (1H, d, \( J = 2.0 \) Hz, H-2, major), 7.08–7.17 (6H, m, H-17,18 major + minor), 7.37 (1H, d, \( J = 8.5 \) Hz, H-6, minor), 7.43 (1H, d, \( J = 8.0 \) Hz, H-6, major), 7.99 (1H, s, H-9, major), 8.08 (1H, s, H-9, minor); \( \delta_C \) (100 MHz, CDCl₃) 26.9 (CH₂), 28.6 (CH₂), 36.5 (CH₂), 38.1 (CH₂), 55.7 (CH₃), 55.8 (CH₃), 59.6 (CH), 62.6 (CH), 65.9 (C), 66.1 (C), 107.9 (CH), 109.8 (CH), 112.7 (CH), 112.8 (CH), 121.8 (CH), 121.9 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.4 (CH), 128.6 (CH), 129.2 (CH), 132.6 (C), 133.0 (C), 140.3 (C), 141.5 (C), 148.8 (C), 149.0 (C), 158.2 (C), 159.0 (C), 170.9 (CH), 173.0 (CH), 213.8 (C), 214.3 (C); HRMS (ESI⁺): Found: 292.1339; \( \text{C}_{19}\text{H}_{18}\text{NO}_2 \) (MH⁺) Requires 292.1332 (−2.5 ppm error).

Lab notebook reference: MJJ7/89
syn-2-Hydroxy-2-(3-methoxyphenyl)spiro[cyclopentane-1,3'-indoline]-2’,3-dione (212b)

Synthesised using general procedure 3D with α-diazocarbonyl 188b (48 mg, 0.15 mmol), Rh₂oct₄ (2.3 mg, 3.0 µmol) and CHCl₃ (3 mL) for 1 h then TFA (35 µL, 0.45 mmol) and THF (1.5 mL) for 4 h. Purification by column chromatography (50% EtOAc in hexane) afforded the title compound 212b (44 mg, 91%) as an off-white solid, mp 151–153 °C; ν_max (cm⁻¹) 3286, 1753, 1702, 1471, 731; δ_H (400 MHz, CDCl₃) 2.26–2.37 (1H, m, H-10a), 2.38–2.48 (1H, m, H-10b), 2.83 (1H, ddd, J = 19.5, 10.0, 2.5 Hz, H-11a), 3.31 (1H, ddd, J = 19.5, 10.0, 10.5 Hz, H-11b), 3.68 (3H, s, H-20), 5.88 (1H, d, J = 8.0 Hz, H-2), 6.68–6.73 (2H, m, H-16,21), 6.76 (1H, dd, J = 8.0, 7.5 Hz, H-3), 6.83–6.92 (2H, m, H-5,18), 7.16 (1H, dd, J = 7.5, 7.5 Hz, H-4), 7.24 (1H, dd, J = 7.5, 7.5 Hz, H-17), 8.42 (1H, br s, H-7); δ_C (100 MHz, CDCl₃) 27.3 (CH₂, C-10), 34.4 (CH₂, C-11), 55.2 (CH₃, C-20), 59.7 (C, C-9), 84.6 (C, C-13), 109.9 (CH, C-5), 112.8 (CH, C-21), 114.4 (CH, C-18), 118.5 (CH, C-16), 121.9 (CH, C-3), 125.4 (CH, C-2), 127.8 (C, C-1), 128.7 (CH, C-4), 129.0 (CH, C-17), 138.9 (C, C-15), 141.3 (C, C-6), 159.2 (C, C-19), 180.4 (C, C-8), 215.9 (C, C-12); HRMS (ESI⁺): Found: 346.1048; C₁₉H₁₇N₂O₄ (M⁺ Na⁺) Requires 346.1050 (0.5 ppm error).

Lab notebook reference: MJJ7/43

syn-2-(4-Fluorophenyl)-2-hydroxyspiro[cyclopentane-1,3’-indoline]-2’,3-dione (212c)

Synthesised using general procedure 3D with α-diazocarbonyl 188c (61 mg, 0.20 mmol), Rh₂oct₄ (3.1 mg, 4.0 µmol) and CHCl₃ (4 mL) for 1 h then TFA (46 µL, 0.60 mmol) and THF (2 mL) for 4 h. Purification by column chromatography (50% EtOAc in hexane) afforded the title compound 212c (38 mg, 61%) as an off-white solid, mp 142–144 °C; ν_max (cm⁻¹) 3299, 1755, 1704, 1508, 1471, 1231, 1205, 734; δ_H (400 MHz, CDCl₃) 2.25 (1H, ddd, J = 13.5, 10.0, 9.5 Hz, H-10a), 2.51 (1H, ddd, J = 13.5, 10.0, 3.0 Hz, H-10b), 2.83 (1H, ddd, J = 20.0, 10.0, 3.0 Hz, H-11a), 3.32 (1H, ddd, J = 20.0, 10.0, 9.5 Hz, H-11b), 4.04 (1H, br s, H-14), 5.98 (1H, d, J = 8.0 Hz, H-2), 6.80 (1H, dd, J = 8.0, 8.0 Hz, H-3), 6.85 (1H, d, J = 8.0 Hz, H-
Chapter 5. Experimental

syn-6'-Chloro-2-hydroxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (212d)

Synthesised using general procedure 3D with α-diazocarbonyl 188d (65 mg, 0.20 mmol), Rh₂oct₄ (3.1 mg, 4.0 µmol) and CHCl₃ (6 mL) for 5 h then TFA (46 µL, 0.60 mmol) and THF (2 mL) for 4 h. Purification by column chromatography (40% EtOAc in hexane) afforded the title compound 212d (40 mg, 61%) as an off-white solid, mp 153–155 °C; νmax (cm⁻¹) 3258, 1743, 1702, 1207, 744, 696; δH (400 MHz, DMSO-d₆) 2.06–2.27 (2H, m, H-10), 2.89 (1H, ddd, J = 19.5, 9.5, 1.5 Hz, H-11a), 3.02 (1H, ddd, J = 19.5, 10.0, 9.5 Hz, H-11b), 5.40 (1H, d, J = 8.0 Hz, H-2), 6.34 (1H, br s, H-14), 6.63 (1H, dd, J = 8.0, 1.5 Hz, H-3), 6.78 (1H, d, J = 1.5 Hz, H-5), 7.09–7.16 (2H, m, H-16), 7.31–7.40 (3H, m, H-17,18), 10.51 (1H, br s, H-7); δC (100 MHz, DMSO-d₆) 26.5 (CH₂, C-10), 34.5 (CH₂, C-11), 59.0 (C, C-9), 84.8 (C, C-13), 109.0 (CH, C-5), 120.0 (CH, C-3), 126.0 (CH, C-2), 126.7 (2CH, C-16/17), 127.2 (C, C-1), 127.8 (2CH, C-16/17), 128.1 (CH, C-18), 132.6 (C, C-4/15), 139.0 (C, C-4/15), 144.6 (C, C-6), 179.3 (C, C-8), 217.3 (C, C-12); HRMS (ESI⁺): Found: 350.0568; C₁₈H₁₄ClNNaO₃ (MNa⁺) Requires 350.0554 (−3.8 ppm error).

Lab notebook reference: MJ7/71
**syn-2-Hydroxy-5'-methoxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (212e)**

Synthesised using **general procedure 3D** with α-diazocarbonyl 188e (64 mg, 0.20 mmol), Rh₂oct₄ (3.1 mg, 4.0 μmol) and CHCl₃ (4 mL) for 1 h then TFA (46 μL, 0.60 mmol) and THF (2 mL) for 4 h. Purification by column chromatography (40% EtOAc in hexane) afforded the **title compound** 212e (45 mg, 70%) as an off-white solid, mp 161–163 °C; ν\text{max} (cm⁻¹): 3262, 1739, 1690, 1489, 1205, 700, 615; δ\text{H} (400 MHz, DMSO-d₆) 2.05–2.24 (2H, m, H-11), 2.87 (1H, ddd, J = 19.5, 9.5, 1.5 Hz, H-12a), 3.03 (1H, ddd, J = 19.5, 10.0, 9.5 Hz, H-12b), 3.34 (3H, s, H-4), 5.04 (1H, d, J = 2.0 Hz, H-2), 6.22 (1H, br s, H-15), 6.61–6.70 (2H, m, H-5,6), 7.11–7.18 (2H, m, H-17/18), 7.33–7.41 (3H, m, H-17/18,19), 10.17 (1H, br s, H-8); δ\text{C} (100 MHz, DMSO-d₆) 27.0 (CH₂, C-11), 34.5 (CH₂, C-12), 54.9 (CH₃, C-4), 59.4 (C, C-10), 84.8 (C, C-14), 109.2 (CH, C-6), 111.4 (CH, C-2), 113.3 (CH, C-5), 126.8 (2CH, C-17/18), 127.8 (2CH, C-17/18), 127.9 (CH, C-19), 129.5 (C, C-1), 136.3 (C, C-7/16), 139.3 (C, C-7/16), 153.6 (C, C-3), 179.3 (C, C-9), 217.6 (C, C-13); HRMS (ESI⁺): Found: 346.1044; C₁₉H₁₇NNaO₄ (MNa⁺) Requires 346.1050 (1.6 ppm error).

Lab notebook reference: MJJ7/83

**anti-2-Hydroxy-2-(3-methoxyphenyl)spiro[cyclopentane-1,3'-indoline]-2',3-dione (214b)**

Synthesised using **general procedure 3E** with α-diazocarbonyl 188b (48 mg, 0.15 mmol), Rh₂oct₄ (2.3 mg, 3.0 μmol) and CHCl₃ (3 mL) for 1 h then t-BuOK (51 mg, 0.45 mmol) and THF (1.5 mL) for 2 h. Purification by column chromatography (40% EtOAc in hexane) afforded the **title compound** 214b (21 mg, 54%) as a white solid, mp 208–210 °C; ν\text{max} (cm⁻¹): 3348, 3240, 1745, 1685, 1211, 760, 691; δ\text{H} (400 MHz, DMSO-d₆) 2.08–2.18 (1H, m, H-10a), 2.52–2.63 (1H, m, H-10b), 2.70–2.91 (2H, m, H-11), 3.35 (3H, s, H-20), 6.51 (1H, br s, H-21), 6.58–6.65 (2H, m, H-5,16), 6.72 (1H, dd, J = 8.0, 2.5 Hz, H-18), 6.85 (1H, s), 6.99–7.06 (2H, m, H-3,17), 7.17 (1H, dd, J = 7.5, 7.5 Hz, H-4), 7.62 (1H, d, J = 7.5 Hz, H-2), 10.07 (1H, br s, H-7); δ\text{C} (100 MHz, DMSO-d₆) 27.7 (CH₂, C-10), 33.5 (CH₂, C-11), 54.6 (CH₃, C-20),
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60.7 (C, C-9), 80.5 (C, C-13), 108.9 (CH, C-5), 112.9 (CH, C-18), 113.5 (CH, C-21), 120.1 (CH, C-16), 121.3 (CH, C-3), 126.1 (CH, C-2), 127.7 (CH, C-17), 128.3 (CH, C-4), 128.5 (C, C-1), 137.9 (C, C-15), 142.3 (C, C-6), 157.7 (C, C-19), 178.9 (C, C-8), 210.9 (C, C-12); HRMS (ESI⁺): Found: 346.1047; C₁₉H₁₇NNaO₄ (MNa⁺) Requires 346.1050 (0.9 ppm error), Found: 324.1230; C₁₉H₁₈NO₄ (MH⁺) Requires 324.1230 (0.2 ppm error).

Lab notebook reference: MJJ7/44

anti-2-(4-Fluorophenyl)-2-hydroxyxyspiro[cyclopentane-1,3'-indoline]-2',3-dione (214c)

Synthesised using general procedure 3E with α-diazo carbonyl 188c (61 mg, 0.20 mmol), Rh₂oct₄ (3.1 mg, 4.0 µmol) and CHCl₃ (4 mL) for 1 h then t-BuOK (67 mg, 0.60 mmol) and THF (2 mL) for 2 h. Purification by column chromatography (35% EtOAc in hexane) afforded the title compound 214c (28 mg, 45%) as a white solid, mp 200–202 °C; v_max (cm⁻¹) 3416, 1748, 1698, 1470, 1219, 824, 759, 750, 538, 526; δ_H (400 MHz, DMSO-d₆) 2.09–2.20 (1H, m, H-10a), 2.53–2.64 (1H, m, H-10b), 2.72–2.91 (2H, m, H-11), 6.61 (1H, d, J = 7.5 Hz, H-5), 6.92 (1H, br s, H-14), 6.93–7.06 (5H, m, H-3,16,17), 7.17 (1H, ddd, J = 8.0, 8.0, 1.0 Hz, H-4), 7.61 (1H, d, J = 7.5 Hz, H-2), 10.09 (1H, br s, H-7); δ_C (100 MHz, DMSO-d₆) 28.1 (CH₂, C-10), 33.9 (CH₂, C-11), 61.2 (C, C-9), 80.8 (C, C-13), 109.4 (CH, C-5), 114.1 (2CH, d, J = 21.0 Hz, C-17), 121.9 (CH, C-3), 126.6 (CH, C-2), 128.7 (C, C-1), 129.0 (CH, C-4), 130.3 (2CH, d, J = 7.5 Hz, C-16), 133.1 (C, d, J = 3.0 Hz, C-15), 142.8 (C, C-6), 162.1 (C, d, J = 243 Hz, C-18), 179.4 (C, C-8), 211.6 (C, C-12); δ_F (376 MHz, DMSO-d₆) −114.8—−114.9 (1F, m); HRMS (ESI⁺): Found: 334.0838; C₁₉H₁₄FNNaO₃ (MNa⁺) Requires 334.0850 (3.7 ppm error).

Lab notebook reference: MJJ7/62
anti-6’-Chloro-2-hydroxy-2-phenylspiro[cyclopentane-1,3’-indoline]-2’,3-dione (214d)

Synthesised using **general procedure 3E** with α-diazocarbonyl 188d (49 mg, 0.15 mmol), Rh2oct4 (2.3 mg, 3.0 µmol) and CHCl3 (4.5 mL) for 5 h then t-BuOK (51 mg, 0.45 mmol) and THF (1.5 mL) for 2 h. Purification by column chromatography (35% EtOAc in hexane) afforded the **title compound 214d** (36 mg, 73%) as a white solid, mp 168–170 °C; νmax (cm⁻¹) 3237, 1737, 1698, 1617, 749, 694; δH (400 MHz, CDCl3) 2.29 (1H, ddd, J = 13.0, 9.5, 1.5 Hz, H-10a), 2.69 (1H, ddd, J = 13.0, 10.5, 9.5 Hz, H-10b), 2.79 (1H, s, H-14), 2.87 (1H, ddd, J = 19.5, 9.5, 1.5 Hz, H-11a), 3.20 (1H, ddd, J = 19.5, 10.5, 9.5 Hz, H-11b), 6.66 (1H, d, J = 2.0 Hz, H-5), 6.97 (1H, br s, H-7), 7.03–7.08 (2H, m, H-16), 7.12 (1H, dd, J = 8.0, 2.0 Hz, H-3), 7.13–7.19 (2H, m, H-17), 7.19–7.23 (1H, m, H-18), 7.65 (1H, d, J = 8.0 Hz, C-2); δC (100 MHz, CDCl3) 28.3 (CH2, C-10), 34.2 (CH2, C-11), 60.8 (C, C-9), 81.3 (C, C-13), 109.9 (CH, C-5), 122.6 (CH, C-3), 126.1 (C, C-1), 127.4 (2CH, C-16), 127.6 (2CH, C-17), 127.7 (CH, C-2), 128.5 (CH, C-18), 134.4 (C, C-4/15), 134.9 (C, C-4/15), 141.8 (C, C-6), 179.0 (C, C-8), 212.4 (C, C-12); HRMS (ESI⁺): Found: 350.0561; C18H14ClINaO3 (MNa⁺) Requires 350.0554 (~1.9 ppm error).

Lab notebook reference: MJJ7/79

anti-2-Hydroxy-5’-methoxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (214e)

Synthesised using **general procedure 3E** with α-diazocarbonyl 188e (64 mg, 0.20 mmol), Rh2oct4 (3.1 mg, 4.0 µmol) and CHCl3 (4 mL) for 1 h then t-BuOK (67 mg, 0.60 mmol) and THF (2 mL) for 2 h. Purification by column chromatography (50% EtOAc in hexane) afforded the **title compound 214e** (26 mg, 40%) as an off-white solid, mp 194–196 °C; νmax (cm⁻¹) 3221, 1742, 1684, 1491, 1201, 1032, 751, 696; δH (400 MHz, DMSO-d6) 2.07–2.17 (1H, m, H-11a), 2.51–2.62 (1H, m, H-11b), 2.69–2.90 (2H, m, H-12), 3.74 (3H, s, H-4), 6.50 (1H, d, J = 8.0 Hz, H-6), 6.73 (1H, dd, J = 8.0, 3.0 Hz, H-5), 6.82 (1H, s, H-15), 7.00–7.06 (2H, m, H-17), 7.09–7.18 (3H, m, H-18,19), 7.23 (1H, d, J = 3.0 Hz, H-2), 9.89 (1H, br s, H-
8); δC (100 MHz, DMSO-d$_6$) 28.0 (CH$_2$, C-11), 33.5 (CH$_2$, C-12), 55.4 (CH$_3$, C-4), 61.1 (C, C-10), 80.6 (C, C-14), 109.0 (CH, C-6), 112.7 (CH, C-5), 113.2 (CH, C-2), 126.7 (2CH, C-18), 127.4 (CH, C-19), 127.8 (2CH, C-17), 129.8 (C, C-1), 135.6 (C, C-7/16), 136.4 (C, C-7/16), 154.5 (C, C-3), 178.7 (C, C-9), 211.0 (C, C-13); HRMS (ESI$^+$): Found: 346.1046; C$_{19}$H$_{19}$NNaO$_4$ (M$^{+}$Na$^+$) Requires 346.1050 (1.0 ppm error).

Lab notebook reference: MJJ7/84

1-(3-Methoxyphenyl)-3,4-dihydro-1H-carbazol-2(9H)-one (199b)

![Chemical structure](image)

Synthesised using general procedure 3F with α-diazocarbonyl 188b (48 mg, 0.15 mmol), Pd(MeCN)$_4$(BF$_4$)$_2$ (3.3 mg, 7.5 µmol) and CHCl$_3$ (1.5 mL). Purification by column chromatography (30% EtOAc in hexane) afforded the title compound 199b (33 mg, 76%) as a white solid, mp 143–145 °C; ν$_{max}$ (cm$^{-1}$) 3389, 1709, 1462, 1260, 1236, 737; δH (400 MHz, CDCl$_3$) 2.63–2.76 (1H, m, H-11a), 2.87–3.00 (1H, m, H-11b), 3.08–3.20 (1H, m, H-10a), 3.24–3.37 (1H, m, H-10b), 3.76 (3H, s, H-17), 4.79 (1H, s, H-13), 6.74–6.88 (3H, m, H-5,15,18), 7.13–7.34 (4H, m, H-3,4,19,20), 7.59 (1H, d, $J$ = 7.5 Hz, H-2), 7.72 (1H, br s, H-7); δC (100 MHz, CDCl$_3$) 20.2 (CH$_2$, C-10), 36.7 (CH$_2$, C-11), 55.0 (CH, C-13), 55.2 (CH$_3$, C-17), 111.0 (CH, C-20), 111.3 (C, C-9), 113.0 (CH, C-5), 114.4 (CH, C-15), 118.3 (CH, C-2), 119.7 (CH, C-3), 120.8 (CH, C-18), 122.3 (CH, C-4/19), 126.3 (C, C-1), 129.9 (CH, C-4/19), 132.2 (C, C-8), 136.9 (C, C-6/14), 138.8 (C, C-6/14), 160.0 (C, C-16), 207.6 (C, C-12); HRMS (ESI$^+$): Found: 314.1144; C$_{19}$H$_{17}$NNaO$_2$ (M$^{+}$Na$^+$) Requires 314.1151 (2.4 ppm error), Found: 292.1325; C$_{19}$H$_{18}$NO$_2$ (MH$^+$) Requires 292.1332 (2.5 ppm error).

Lab notebook reference: MJJ7/39
1-(4-Fluorophenyl)-3,4-dihydro-1H-carbazol-2(9H)-one (199c)

Synthesised using **general procedure 3F** with α-diazocarbonyl 188c (61 mg, 0.20 mmol), Pd(MeCN)₄(BF₄)₂ (4.4 mg, 10 µmol) and CHCl₃ (2 mL). Purification by column chromatography (35% EtOAc in hexane) afforded the **title compound 199c** (39 mg, 70%) as a white solid, mp 172–174 °C; \( v_{\text{max}} \) (cm⁻¹) 3394, 1714, 1505, 1224, 741; \( \delta_H \) (400 MHz, CDCl₃) 2.73 (1H, ddd, \( J = 13.5, 6.0, 6.0 \) Hz, H-11a), 2.89 (1H, ddd, \( J = 13.5, 8.0, 8.0 \) Hz, H-11b), 3.11–3.22 (1H, m, H-10a), 3.24–3.35 (1H, m, H-10b), 4.83 (1H, s, H-13), 6.99–7.07 (2H, m, H-16), 7.14–7.26 (4H, m, H-3,4,15), 7.31 (1H, d, \( J = 8.0 \) Hz, H-5), 7.59 (1H, d, \( J = 8.0 \) Hz, H-2), 7.62 (1H, br s, H-7); \( \delta_C \) (100 MHz, CDCl₃) 20.2 (CH₂, C-10), 36.7 (CH₂, C-11), 54.1 (CH, C-13), 111.1 (C, C-9), 111.5 (CH, C-5), 115.8 (2CH, d, \( J = 22.0 \) Hz, C-16), 118.4 (CH, C-3), 119.9 (CH, C-2), 122.5 (CH, C-4), 126.3 (C, C-1), 130.1 (2CH, d, \( J = 7.5 \) Hz, C-15), 132.0 (C, C-8), 133.0 (C, d, \( J = 3.0 \) Hz, C-14), 136.9 (C, C-6), 162.4 (C, d, \( J = 246 \) Hz, C-17), 207.5 (C, C-12); \( \delta_F \) (376 MHz, CDCl₃) −114.2−114.3 (1F, m); HRMS (ESI⁺): Found: 280.1142; C₁₈H₁₅FNO (MH⁺) Requires 280.1132 (−3.4 ppm error).

Lab notebook reference: MJJ7/58

7-Chloro-1-phenyl-3,4-dihydro-1H-carbazol-2(9H)-one (199d)

Synthesised using **general procedure 3F** with α-diazocarbonyl 188d (65 mg, 0.20 mmol), Pd(MeCN)₄(BF₄)₂ (4.4 mg, 10 µmol) and CHCl₃ (2 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the **title compound 199d** (38 mg, 64%) as a white solid, mp 222–224 °C; \( v_{\text{max}} \) (cm⁻¹) 3353, 1712, 1465, 1453, 909, 735, 705; \( \delta_H \) (400 MHz, CDCl₃) 2.65–2.74 (1H, m, H-11a), 2.85–2.95 (1H, m, H-11b), 3.07–3.17 (1H, m, H-10a), 3.22–3.32 (1H, m, H-10b), 4.81 (1H, s, H-13), 7.14 (1H, d, \( J = 8.5, 1.5 \) Hz, H-3), 7.17–7.22 (2H, m, H-15), 7.23–7.28 (1H, m, H-5), 7.29–7.38 (3H, m, H-16,17), 7.48 (1H, d, \( J = 8.5 \) Hz, H-2), 7.66 (1H, br s, H-7); \( \delta_C \) (100 MHz, CDCl₃) 20.1 (CH₂, C-10), 36.6 (CH₂, C-11), 54.9 (CH, C-13), 111.0 (CH, C-5), 111.5 (C, C-9), 119.2 (CH, C-2), 120.5 (CH, C-3), 125.0 (C, C-
1), 128.0 (CH, C-17), 128.3 (C, C-8), 128.5 (2CH, C-15), 129.0 (2CH, C-16), 133.1 (C, C-4/6/14), 137.0 (C, C-4/6/14), 137.2 (C, C-4/6/14), 207.2 (C, C-12); HRMS (ESI\(^+\)): Found: 318.0653; C\(_{18}\)H\(_{14}\)\(^{35}\)ClNaO (MNa\(^+\)) Requires 318.0656 (0.9 ppm error), Found: 296.0843; C\(_{18}\)H\(_{15}\)\(^{35}\)CNO (MH\(^+\)) Requires 296.0837 (−2.2 ppm error).

Lab notebook reference: MJJ7/68

6-Methoxy-1-phenyl-3,4-dihydro-1\(^{H}\)-carbazol-2(9\(^{H}\))-one (199e)

Synthesised using **general procedure 3F** with \(\alpha\)-diazocarbonyl 188e (64 mg, 0.20 mmol), Pd(MeCN)\(_4\)(BF\(_4\))\(_2\) (4.4 mg, 10 µmol) and CHCl\(_3\) (2 mL). Purification by column chromatography (30% EtOAc in hexane) afforded the **title compound** 199e (30 mg, 59%) as a white solid, mp 153–155 °C; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3395, 1714, 1485, 1456, 1217; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 2.65–2.75 (1H, m, H-12a), 2.85–2.97 (1H, m, H-12b), 3.06–3.17 (1H, m, H-11a), 3.21–3.32 (1H, m, H-11b), 3.90 (3H, s, H-4), 4.82 (1H, s, H-14), 6.87 (1H, dd, \(J = 8.5, 2.5\) Hz, H-5), 7.04 (1H, d, \(J = 2.5\) Hz, H-2), 7.15–7.23 (3H, m, H-6,16), 7.29–7.36 (3H, m, H-17,18), 7.57 (1H, br s, H-8); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 20.3 (CH\(_2\), C-11), 36.8 (CH\(_2\), C-12), 55.2 (CH, C-14), 56.0 (CH\(_3\), C-4), 100.5 (CH, C-2), 111.2 (C, C-10), 111.8 (CH, C-6), 112.2 (CH, C-5), 126.8 (C, C-1), 127.8 (CH, C-18), 128.5 (2CH, C-16), 128.9 (2CH, C-17), 131.9 (C, C-7/9/15), 133.2 (C, C-7/9/15), 137.3 (C, C-7/9/15), 154.3 (C, C-3), 207.7 (C, C-13); HRMS (ESI\(^+\)): Found: 314.1147; C\(_{19}\)H\(_{17}\)NNaO\(_2\) (MNa\(^+\)) Requires 314.1151 (1.3 ppm error).

Lab notebook reference: MJJ7/81

1-(3-Methoxyphenyl)-9\(^{H}\)-carbazol-2-ol (200b)

Synthesised using **general procedure 3G** with \(\alpha\)-diazocarbonyl 188b (48 mg, 0.15 mmol), Cu(OTf)\(_2\) (10.9 mg, 30 µmol) and CHCl\(_3\) (3 mL). Purification by column chromatography (20→30% EtOAc in hexane) afforded the **title compound** 200b (31 mg, 71%) as an off-white
solid, mp 146–148 °C; \( v_{\text{max}} \) (cm\(^{-1}\)) 3409, 1604, 1460, 1413, 1219, 1178, 737; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 3.88 (3H, s, H-18), 5.29 (1H, br s, H-13), 6.95 (1H, d, \( J = 8.5 \) Hz, H-11), 7.06 (1H, dd, \( J = 8.5, 2.5 \) Hz, H-19), 7.12–7.16 (1H, m, H-16), 7.18 (1H, d, \( J = 7.5 \) Hz, H-21), 7.23 (1H, ddd, \( J = 7.5, 6.0, 2.5 \) Hz, H-3), 7.29–7.37 (2H, m, H-4,5), 7.55 (1H, dd, \( J = 8.0, 7.5 \) Hz, H-20), 7.91–7.98 (2H, m, H-7,10), 8.02 (1H, d, \( J = 8.0 \) Hz, H-2); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 55.4 (CH\(_3\), C-18), 108.7 (CH, C-11), 110.2 (C, C-1/9), 110.4 (CH, C-5), 114.2 (CH, C-19), 115.3 (CH, C-16), 117.1 (C, C-1/9), 119.5 (CH, C-2/3), 119.6 (CH, C-2/3), 120.7 (CH, C-10), 122.0 (CH, C-21), 123.8 (C, C-14), 124.6 (CH, C-4), 131.3 (CH, C-20), 134.3 (C, C-6/8/15), 138.8 (C, C-6/8/15), 139.3 (C, C-6/8/15), 151.0 (C, C-12), 160.9 (C, C-17); HRMS (ESI\(^+\)): Found: 312.0983; C\(_{19}\)H\(_{15}\)NNaO\(_2\) (M\(^{+}\)Na\(^+\)) Requires 312.0995 (3.7 ppm error), Found: 290.1164; C\(_{19}\)H\(_{16}\)NO\(_2\) (MH\(^+\)) Requires 290.1176 (3.9 ppm error).

Lab notebook reference: MJJ7/40

1-(4-Fluorophenyl)-9H-carbazol-2-ol (200c)

Synthesised using general procedure 3G with \( \alpha \)-diazocarbonyl 188c (61 mg, 0.20 mmol), Cu(OTf)\(_2\) (14.5 mg, 40 µmol) and CHCl\(_3\) (4 mL). Purification by column chromatography (30→40% EtOAc in hexane) afforded the title compound 200c (43 mg, 78%) as a brown solid, mp 122–124 °C; \( v_{\text{max}} \) (cm\(^{-1}\)) 3457, 1603, 1459, 1222, 1157, 840, 737; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 5.02 (1H, br s, H-13), 6.93 (1H, d, \( J = 8.5 \) Hz, H-11), 7.20–7.25 (1H, m, H-3), 7.30–7.37 (4H, m, H-4,5,17), 7.56–7.62 (2H, m, H-16), 7.80 (1H, br s, H-7), 7.94 (1H, d, \( J = 8.5 \) Hz, H-10), 8.01 (1H, d, \( J = 8.0 \) Hz, H-2); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 108.8 (CH, C-11), 109.5 (C, C-9), 110.4 (CH, C-5), 116.9 (2CH, d, \( J = 22.0 \) Hz, C-17), 117.2 (C, C-1), 119.5 (CH, C-3/10), 119.7 (CH, C-3/10), 120.7 (CH, C-7), 123.8 (C, C-14), 124.7 (CH, C-4), 128.9 (C, d, \( J = 4.0 \) Hz, C-15), 131.9 (2CH, d, \( J = 8.5 \) Hz, C-16), 139.1 (C, C-6/8), 139.4 (C, C-6/8), 151.1 (C, C-12), 162.6 (C, d, \( J = 248 \) Hz, C-18); \( \delta_{\text{C}} \) (376 MHz, CDCl\(_3\)) \(-112.5--112.6 \) (1F, m); HRMS (ESI\(^+\)): Found: 300.0810; C\(_{18}\)H\(_{13}\)FNNaO (M\(^{+}\)Na\(^+\)) Requires 300.0795 (−4.9 ppm error), Found: 278.0971; C\(_{18}\)H\(_{14}\)FNO (MH\(^+\)) Requires 278.0976 (1.6 ppm error).

Lab notebook reference: MJJ7/60
7-Chloro-1-phenyl-9H-carbazol-2-ol (200d)

Synthesised using general procedure 3G with α-diazocarbonyl 188d (65 mg, 0.20 mmol), Cu(OTf)₂ (14.5 mg, 40 µmol) and CHCl₃ (4 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the title compound 200d (37 mg, 63%) as a pale yellow solid, mp 157–159 °C; ν_max (cm⁻¹) 3522, 3435, 1613, 1601, 1453, 1441, 1166, 911, 798, 734; δ_H (400 MHz, CDCl₃) 5.19 (1H, br s, H-13), 6.96 (1H, d, J = 8.5 Hz, H-11), 7.19 (1H, dd, J = 8.0, 2.0 Hz, H-3), 7.29 (1H, d, J = 2.0 Hz, H-5), 7.50–7.69 (5H, m, H-16,17,18), 7.86 (1H, br s, H-7), 7.87–7.92 (2H, m, H-2,10); δ_C (100 MHz, CDCl₃) 109.3 (CH, C-11), 110.5 (CH, C-5), 110.6 (C, C-9), 116.5 (C, C-1), 120.2 (CH, C-3), 120.3 (CH, C-2/10), 120.6 (CH, C-2/10), 122.5 (C, C-14), 128.8 (CH, C-18), 130.0 (2CH, C-16), 130.15 (C, C-4/6/8/15), 130.19 (2CH, C-17), 132.6 (C, C-4/6/8/15), 139.2 (C, C-4/6/8/15), 139.8 (C, C-4/6/8/15), 151.3 (C, C-12); HRMS (ESI⁺): Found: 316.0499; C₁₈H₁₂ClNNaO (MNa⁺) Requires 316.0500 (±0.3 ppm error), Found: 294.0681; C₁₈H₁₃ClNO (MH⁺) Requires 294.0680 (~0.2 ppm error).

Lab notebook reference: MJJ7/69

6-Methoxy-1-phenyl-9H-carbazol-2-ol (200e)

Synthesised using general procedure 3G with α-diazocarbonyl 188e (64 mg, 0.20 mmol), Cu(OTf)₂ (14.5 mg, 40 µmol) and CHCl₃ (4 mL). Purification by column chromatography (30% EtOAc in hexane) afforded the title compound 200e (20 mg, 35%) as a brown oil; ν_max (cm⁻¹) 3415, 1612, 1483, 1288, 1165; δ_H (400 MHz, CDCl₃) 3.93 (3H, s, H-4), 5.20 (1H, br s, H-14), 6.92 (1H, d, J = 8.5 Hz, H-12), 6.97 (1H, dd, J = 8.5, 2.5 Hz, H-5), 7.21 (1H, d, J = 8.5 Hz, H-6), 7.48–7.55 (2H, m, H-2,19), 7.57–7.66 (4H, m, H-17,18), 7.74 (1H, br s, H-8), 7.89 (1H, d, J = 8.5 Hz, H-11); δ_C (100 MHz, CDCl₃) 56.0 (CH₃, C-4), 102.7 (CH, C-2), 108.5 (CH, C-12), 110.4 (C, C-9), 111.0 (CH, C-6), 113.4 (CH, C-5), 117.2 (C, C-1), 120.6 (CH, C-11), 124.3 (C, C-15), 128.6 (CH, C-19), 130.0 (2CH, C-17/18), 130.1 (2CH, C-17/18), 133.0
HRMS (ESI$^+$): Found: 312.0994; C$_{19}$H$_{15}$NNaO$_2$ (MNa$^+$) Requires 312.0995 (0.2 ppm error).

Lab notebook reference: MJJ7/82
5.5 Experimental for Chapter 4

Methyl 3-(4-fluorophenyl)propiolate (269a)

![Chemical structure of methyl 3-(4-fluorophenyl)propiolate]

To a solution of 1-ethynyl-4-fluorobenzene (533 mg, 4.44 mmol) in THF (44 mL) at −78 °C was added n-BuLi (1.95 mL, 4.88 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.38 mL, 4.88 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. NH₄Cl (aq) (10 mL) and diluted with Et₂O (20 mL). The organics were separated and the aqueous extracted with Et₂O (3 × 30 mL). The organics were combined, washed with brine, dried (MgSO₄), concentrated in vacuo and purified by column chromatography (0 → 5% Et₂O in hexane) to afford the title compound 269a (494 mg, 62%) as a white solid, mp 57–59 °C (lit. 156 57–59 °C); νmax (cm⁻¹) 2224, 1708, 1304, 1203, 833; δH (400 MHz, CDCl₃) 3.85 (3H, s), 7.08 (2H, dd, J = 8.5, 8.0 Hz), 7.59 (2H, dd, J = 8.5, 5.5 Hz); δC (100 MHz, CDCl₃) 52.8 (CH₃), 80.2 (C), 85.4 (C), 115.6 (C, d, J = 4.0 Hz), 116.1 (2CH, d, J = 22.0 Hz), 135.3 (2CH, d, J = 8.5 Hz), 154.4 (C), 163.9 (C, d, J = 254.0 Hz); δF (376 MHz, CDCl₃) −106.1—−106.2 (1F, m).

Lab notebook reference: MJJ8/55

Spectroscopic data matched those reported in the literature.¹⁵⁷

Methyl 3-(thiophen-2-yl)propiolate (269b)

![Chemical structure of methyl 3-(thiophen-2-yl)propiolate]

To a solution of 2-ethynylthiophene (0.5 mL, 4.99 mmol) in THF (50 mL) at −78 °C was added n-BuLi (2.20 mL, 5.49 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.42 mL, 5.49 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. NH₄Cl (aq) (10 mL) and diluted with EtOAc (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with brine, dried (MgSO₄), concentrated in vacuo and purified by column chromatography (5 → 10% EtOAc in hexane) to afford the title compound 269b (357 mg, 43%) as a yellow solid, mp 49–51 °C (lit. ¹⁵⁶ 54–55 °C); νmax (cm⁻¹) 2207, 1709, 1269, 1221, 1160; δH (400 MHz, CDCl₃) 3.85 (3H, s), 7.07 (1H, dd, J = 5.0, 3.5 Hz), 7.48 (1H, dd, J = 5.0 Hz), 7.50 (1H, dd, J = 3.5 Hz); δC (100 MHz, CDCl₃) 52.8 (CH₃), 80.5 (C), 84.6 (C), 119.3 (C), 127.5 (CH), 131.2 (CH), 136.6 (CH), 154.3 (C).
Lab notebook reference: MJJ8/57

Spectroscopic data matched those reported in the literature.156

**Methyl 3-(trimethylsilyl)propiolate (269c)**

![TMS—CO₂Me]

To a solution of ethynyltrimethylsilane (0.5 mL, 3.62 mmol) in THF (36 mL) at −78 °C was added $n$-BuLi (1.59 mL, 3.98 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.31 mL, 3.98 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. NH₄Cl(aq) (10 mL) and diluted with EtOAc (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with brine, dried (MgSO₄), concentrated *in vacuo* and purified by column chromatography (0 → 5% EtOAc in hexane) to afford the *title compound* 269c (271 mg, 48%) as a colourless oil; $\delta$H (400 MHz, CDCl₃) 0.25 (9H, s), 3.78 (3H, s); $\delta$C (100 MHz, CDCl₃) −0.9 (3CH₃), 52.7 (CH₃), 94.3 (C), 99.9 (C), 192.2 (C).

Lab notebook reference: MJJ8/58

Spectroscopic data matched those reported in the literature.158

**4-(2,2-dibromovinyl)-1,2-dimethoxybenzene (271)**

![MeO-CO-CH₂-CH₃]

To a suspension of CBr₄ (20.0 g, 60.2 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added PPh₃ (31.6 g, 120.4 mmol) portionwise and the mixture was stirred at 0 °C for 30 min. 3,4-dimethoxybenzaldehyde (10 g, 60.2 mmol) was then added and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into a 1:1 mixture of brine:water (100 mL) and the organics were separated. The aqueous was further extracted with a 1:1 mixture of CH₂Cl₂:hexane (2 × 100 mL) and the organics were combined, dried (MgSO₄) and concentrated *in vacuo*. The crude material was purified by column chromatography (hexane then 15% EtOAc in hexane) to afford the *title compound* 271 (15.3 g, 79%) as a yellow oil; $\delta$H (400 MHz, CDCl₃) 3.88 (6H, s), 6.85 (1H, d, $J = 8.0$ Hz), 7.09 (1H, d, $J = 8.0$ Hz), 7.18 (1H, s), 7.40 (1H, s); $\delta$C (100 MHz, CDCl₃) 55.9, 87.4, 110.7, 111.0, 121.9, 127.9, 136.4, 148.5.
149.3; HRMS (ESI⁺): Found: 342.8933; C_{10}H_{10}{^{79}}Br_2NNaO (MNa⁺) Requires 342.8940 (2.1 ppm error).

Lab notebook reference: MJJ5/49

Spectroscopic data matched those reported in the literature.¹²⁵

**Methyl 3-(3,4-dimethoxyphenyl)propiolate (269d)**

To a solution of dibromide 271 (15.3 g, 47.5 mmol) in THF (190 mL) at −78 °C was added n-BuLi (62 mL, 99.8 mmol, 2.5 M in hexanes) dropwise and the mixture was stirred at −78 °C for 45 min then at 0 °C for 45 min. The mixture was then recooled to −78 °C and methylchloroformate (3.67 mL, 97.5 mmol) was added dropwise. The mixture was stirred at 0 °C for 2h then quenched with sat. NH₄Cl (aq) (100 mL) and the organics were separated. The aqueous was further extracted with Et₂O (2 × 100 mL) and the organics were combined, dried (MgSO₄) and concentrated in vacuo. The crude material was purified by successive recrystallisations (EtOAc:hexane, washing with cold hexane and Et₂O) to afford the title compound 269d (5.22 g, 50% after 2 crops) as a brown solid, mp 81–83 °C (lit.¹²⁵ 76–77 °C); \( \nu_{\text{max}} \) (cm⁻¹) 2211, 1708, 1515, 1252, 1232, 1157, 1137, 1023; \( \delta_H \) (400 MHz, CDCl₃) 3.84 (3H, s), 3.89 (3H, s), 3.92 (3H, s), 6.85 (1H, d, \( J = 8.5 \) Hz), 7.08 (1H, d, \( J = 2.0 \) Hz), 7.24 (1H, dd, \( J = 8.5, 2.0 \) Hz); \( \delta_C \) (100 MHz, CDCl₃) 52.7, 56.0, 79.6, 87.5, 111.0, 111.3, 115.3, 127.3, 148.8, 151.5, 154.7

Lab notebook reference: MJJ5/50

Spectroscopic data matched those reported in the literature.¹²⁵

**4-Phenyl-1-(pyridin-2-yl)but-3-yn-2-one (228a)**

Synthesised using general procedure 4A with DIPA (0.60 mL, 4.26 mmol), n-BuLi (1.70 mL, 4.26 mmol, 2.5 M in hexanes), 2-methylpyridine (0.20 mL, 2.03 mmol), methyl phenylpropiolate (0.31 mL, 2.13 mmol) and THF (30 mL). Purification by column
chromatography (10% EtOAc in hexane) afforded the title compound 228a (316 mg, 70%, 85:15 enol:keto) as a yellow solid, mp 71–73 °C; νmax (cm⁻¹) 1741, 1694, 1491, 1388, 1366, 1160; δH (400 MHz, CDCl₃) 4.19 (2H, s, H-6, keto), 5.90 (1H, s, H-6, enol), 6.97–7.06 (2H, m, H-2, enol), 7.24 (1H, dd, J = 7.5, 5.0 Hz, H-2 keto), 7.31–7.40 (6H, m, H-4,13,14, enol + keto), 7.41–7.50 (3H, m, H-12,14, keto), 7.51–7.59 (2H, m, H-12, enol), 7.64 (1H, dd, J = 8.0, 8.0, 2.0 Hz, H-3, enol), 7.71 (1H, dd, J = 8.0, 8.0, 2.0 Hz, H-3, keto), 8.28 (1H, br d, J = 5.0 Hz, H-1, enol), 8.64 (1H, br d, J = 4.5 Hz, H-1, keto), 15.02 (1H, br s, H-8, enol); ¹³C NMR data of enol tautomer δc (100 MHz, CDCl₃) 86.4 (C, C-9), 89.6 (C, C-10), 103.7 (CH, C-6), 119.1 (CH, C-2/4), 121.4 (CH, C-2/4), 122.0 (C, C-11), 128.3 (2CH, C-13), 128.9 (CH, C-14), 131.9 (2CH, C-12), 137.4 (CH, C-3), 144.0 (CH, C-1), 149.5 (C, C-5), 157.6 (C, C-7); Characteristic ¹³C NMR data of keto tautomer δc (100 MHz, CDCl₃) 54.3 (CH₂, C-6); HRMS (ESI⁺): Found: 222.0915; C₁₃H₁₂NO (MH⁺) Requires 222.0913 (±0.7 ppm error).

Lab notebook reference: MJJ8/50

4-(3,4-Dimethoxyphenyl)-1-(pyridin-2-yl)but-3-yn-2-one (228b)

Synthesised using general procedure 4A with DIPA (2.94 mL, 21.0 mmol), n-ButLi (8.4 mL, 21.0 mmol, 2.5 M in hexanes), 2-methylpyridine (0.99 mL, 10.0 mmol) in THF (100 mL) and a solution of ester 269d (2.31 g, 10.5 mmol) in THF (50 mL). Purification by column chromatography (40% EtOAc in hexane) afforded the title compound 228b (2.11 g, 75%, 77:23 enol:keto) as a yellow solid, mp 78–80 °C; νmax (cm⁻¹) 2200, 1595, 113, 1252, 1023, 808; δH (400 MHz, CDCl₃) 3.87 (3H, s, H-14/16, keto), 3.89 (3H, s, H-14/16, enol), 3.91 (6H, s, H-14/16, enol + keto), 4.17 (2H, s, H-6, keto), 5.87 (1H, s, H-6, enol), 6.80 (1H, d, J = 8.5 Hz, H-17, keto), 6.81 (1H, d, J = 8.5 Hz, H-17, enol), 6.95 (1H, d, J = 1.5 Hz, H-12, keto), 6.97–7.04 (2H, m, H-2,4, enol), 7.06 (1H, d, J = 1.5 Hz, H-12, enol), 7.12 (1H, dd, J = 8.5, 1.5 Hz, H-18, keto), 7.16 (1H, dd, J = 8.5, 1.5 Hz, H-18, enol) 7.24 (1H, d, J = 7.0, 5.5 Hz, H-2, keto), 7.33 (1H, d, J = 8.0 Hz, H-4, keto), 7.62 (1H, dd, J = 8.0, 7.5 Hz, H-3, enol), 7.71 (1H, dd, J = 7.5, 7.5 Hz, H-3, keto), 8.24–8.30 (1H, m, H-1, enol), 8.61–8.65 (1H, m, H-1, keto), 15.03 (1H, br s, H-8, enol); ¹³C NMR data of enol tautomer δc (100 MHz, CDCl₃) 55.86 (CH₃, C-14/16), 55.89 (CH₂, C-14/16), 85.2 (C, C-9), 90.0 (C, C-10), 103.2 (CH, C-6), 110.9 (CH, C-17), 114.0 (C, C-11), 114.5 (CH, C-12), 118.9 (CH, C-2/4), 121.3 (CH, C-2/4), 125.5 (CH, C-18), 137.4 (CH, C-3), 143.9 (CH, C-1), 148.6 (C, C-5) 149.8 (C, C-13/15), 150.0 (C, C-
13/15), 157.7 (C, C-7); Characteristic $^{13}$C NMR data of keto tautomer $\delta_{C}$ (100 MHz, CDCl$_3$) 54.2 (CH$_2$, C-6); HRMS (ESI$^+$): Found: 304.0944; C$_{17}$H$_{16}$NNaO$_3$ (MNa$^+$) Requires 304.0944 (−0.1 ppm error), Found: 282.1128; C$_{17}$H$_{16}$NO$_3$ (MH$^+$) Requires 282.1125 (−1.2 ppm error).

Lab notebook reference: MJJ5/51

4-(4-Fluorophenyl)-1-(pyridin-2-yl)but-3-yn-2-one (228c)

Synthesised using general procedure 4A with DIPA (0.30 mL, 2.12 mmol), n-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (10 mL) and a solution of methyl ester 269a (189 mg, 1.06 mmol) in THF (5 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the title compound 228c (209 mg, 86%, 81:19 enol:keto) as a yellow solid, mp 74–76 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 1620, 1597, 1507, 1374, 1224, 834, 801; $\delta_{H}$ (400 MHz, CDCl$_3$) 4.17 (2H, s, H-6, keto), 5.87 (1H, s, H-6, enol), 6.96–7.12 (6H, m, H-2,4,13 enol + keto), 7.24 (1H, dd, $J = 8.0, 5.0$ Hz, H-2, keto), 7.32 (1H, d, $J = 8.0$ Hz, H-4, keto), 7.44–7.50 (2H, m, H-12, keto), 7.50–7.57 (2H, m, H-12, enol), 7.63 (1H, ddd, $J = 8.0, 8.0, 1.5$ Hz, H-3, enol), 7.71 (1H, ddd, $J = 8.0, 8.0, 1.5$ Hz, H-3, keto), 8.27 (1H, d, $J = 5.0$ Hz, H-1, enol), 8.62 (1H, d, $J = 4.5$ Hz, H-1, keto), 15.04 (1H, br s, H-8, enol); $^{13}$C NMR data of enol tautomer $\delta_{C}$ (100 MHz, CDCl$_3$) 86.1 (C, C-9), 88.5 (C, C-10), 103.6 (CH, C-6), 115.7 (2CH, d, $J = 22.0$ Hz, C-13), 118.1 (C, d, $J = 4.0$ Hz, C-11), 119.1 (CH, C-2/4), 121.4 (CH, C-2/4), 133.9 (2CH, d, $J = 7.5$ Hz, C-12), 137.5 (CH, C-3), 144.0 (CH, C-1), 149.5 (C, C-5), 157.5 (C, C-7), 162.9 (C, d, $J = 250.0$ Hz, C-14); Characteristic $^{13}$C NMR data of keto tautomer $\delta_{C}$ (100 MHz, CDCl$_3$) 54.3 (CH$_2$, C-6); $\delta_{F}$ (376 MHz, CDCl$_3$) −105.7−105.8 (1F, m, keto), −109.4−109.5 (1F, m, enol); HRMS (ESI$^+$): Found: 240.0810; C$_{13}$H$_{13}$FNO (MH$^+$) Requires 240.0819 (4.0 ppm error).

Lab notebook reference: MJJ8/56
1-(Pyridin-2-yl)non-3-yn-2-one (228d)

Synthesised using general procedure 4A with DIPA (0.30 mL, 2.12 mmol), n-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (15 mL) and methyl 2-octynoate (0.18 mL, 1.06 mmol). Purification by column chromatography (20% EtOAc in hexane) afforded the title compound 228d (154 mg, 71%, 67:33 enol:keto) as a yellow oil; $v_{\text{max}}$ (cm$^{-1}$) 2930, 2228, 1618, 1594, 1550, 1470, 1361, 1151, 805, 739; $\delta_H$ (400 MHz, CDCl$_3$) 0.89 (3H, t, $J = 7.5$ Hz, H-15, keto), 0.92 (3H, t, $J = 7.5$ Hz, H-15, enol), 1.24–1.68 (12H, m, H-12,13,14, enol + keto), 2.31 (2H, t, $J = 7.0$ Hz, H-11, keto), 2.39 (2H, t, $J = 7.0$ Hz, H-11, enol), 4.06 (2H, s, H-6, keto), 5.71 (1H, s, H-6, enol), 6.92–7.01 (2H, m, H-2,4, enol), 7.22 (1H, dd, $J = 7.5$, 5.5 Hz, H-2, keto), 7.24–7.28 (1H, m, H-4, keto), 7.60 (1H, dd, $J = 8.0$, 8.0 Hz, H-3, enol), 7.68 (1H, dd, $J = 8.0$, 1.5 Hz, H-3, keto), 8.25 (1H, br d, $J = 5.5$ Hz, H-1, enol), 8.59 (1H, br d, $J = 4.5$ Hz, H-1, keto), 14.87 (1H, br s, H-8, enol); $^{13}$C NMR data of enol tautomer $\delta_C$ (100 MHz, CDCl$_3$) 13.9 (CH$_3$, C-15), 19.2 (CH$_2$, C-11), 22.2 (CH$_2$, C-12,13,14), 27.9 (CH$_2$, C-12,13,14), 31.0 (CH$_2$, C-12,13,14), 77.9 (C, C-9), 91.8 (C, C-10), 102.6 (CH, C-6), 118.7 (CH, C-2/4), 121.1 (CH, C-2/4), 137.2 (CH, C-3), 144.0 (CH, C-1), 149.7 (C, C-5), 157.8 (C, C-7); Characteristic $^{13}$C NMR data of keto tautomer $\delta_C$ (100 MHz, CDCl$_3$) 54.4 (CH$_2$, C-6); HRMS (ESI$^+$): Found: 216.1385; C$_{14}$H$_{18}$NO (MH$^+$) Requires 216.1383 (−1.0 ppm error).

Lab notebook reference: MJI8/44

1-(Pyridin-2-yl)-4-(thiophen-2-yl)but-3-yn-2-one (228e)

Synthesised using general procedure 4A with DIPA (0.30 mL, 2.12 mmol), n-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (10 mL) and a solution of methyl ester 269b (176 mg, 1.06 mmol) in THF (5 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the title compound 228e (96 mg, 42%, 85:15 enol:keto) as a yellow oil. (Note: this compound degrades overnight when stored at room temperature.); $v_{\text{max}}$ (cm$^{-1}$) 2198, 1615, 1552, 1472, 705; $\delta_H$ (400 MHz, CDCl$_3$) 4.17 (2H, s, H-6, keto), 5.87 (1H, s, H-6, enol), 6.98–7.08 (4H, m, H-2,4,13, enol + keto), 7.21–
7.28 (2H, m, H-2,4, keto), 7.33–7.36 (2H, m, H-12,14, enol), 7.41 (1H, d, J = 3.5 Hz, H-12, keto), 7.49 (1H, d, J = 5.5 Hz, H-14, keto), 7.63 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H-3, enol), 7.71 (1H, ddd, J = 7.5, 7.5, 1.0 Hz, H-3, keto), 8.26 (1H, br d, J = 5.0 Hz, H-1, enol), 8.62 (1H, br d, J = 4.5 Hz, H-1, keto), 15.07 (1H, br s, H-8, enol); \(^{13}\)C NMR data of enol tautomer \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 83.1 (C, C-9), 90.1 (C, C-10), 103.5 (CH, C-6), 119.0 (CH, C-2/4), 121.5 (CH, C-2/4), 122.0 (C, C-11), 127.2 (CH, C-13), 128.4 (CH, C-12/14), 133.3 (CH, C-12/14), 137.5 (CH, C-3), 143.8 (CH, C-1), 149.7 (C, C-5), 157.5 (C, C-7); Characteristic \(^{13}\)C NMR data of keto tautomer \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 54.0 (CH\(_2\), C-6); HRMS (ESI\(^+\)): Found: 228.0470; \(\text{C}_{13}\text{H}_{10}\text{NO} (\text{MH}^+\) Requires 228.0478 (3.5 ppm error).

Lab notebook reference: MJJ8/60

1-Phenyl-4-(pyridin-2-yl)pent-1-yn-3-one (228f)

Synthesised using **general procedure 4A** with DIPA (0.52 mL, 3.68 mmol), \(n\)-BuLi (1.47 mL, 3.68 mmol, 2.5 M in hexanes), 2-ethylpyridine (0.20 mL, 1.75 mmol), methyl phenylpropiolate (0.27 mL, 1.84 mmol) and THF (26 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the **title compound 228f** (138 mg, 33%, 97:3 enol:keto) as a yellow/green oil. (Note: this compound degrades overnight when stored at room temperature.); \(v_{\text{max}}\) (cm\(^{-1}\)) 1589, 1551, 1488, 1461, 755, 690; \(^1\)H NMR data of enol tautomer \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 2.26 (3H, s, H-7), 7.11 (1H, d, J = 7.0, 5.5 Hz, H-2), 7.26 (1H, d, J = 8.0 Hz, H-4), 7.32–7.40 (3H, m, H-14,15), 7.54–7.61 (2H, m, H-13), 7.76 (1H, ddd, J = 8.0, 8.0, 1.0 Hz, H-3), 8.39 (1H, br d, J = 5.5 Hz, H-1), 15.73 (1H, br s, H-9); \(^{13}\)C NMR data of enol tautomer \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 15.4 (CH\(_3\)), 85.6 (C, C-10), 94.4 (C, C-11), 108.3 (C, C-6), 119.4 (CH, C-4), 119.7 (CH, C-2), 122.4 (C, C-12), 128.3 (2CH, C-14), 128.8 (CH, C-15), 131.7 (2CH, C-13), 137.6 (CH, C-3), 144.6 (CH, C-1), 145.1 (C, C-5), 159.2 (C, C-8); Characteristic \(^{13}\)C NMR data of keto tautomer \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 56.9 (CH, C-6); HRMS (ESI\(^+\)): Found: 258.0887 \(\text{C}_{16}\text{H}_{13}\text{NNaO} (\text{MNa}^+) \) Requires 258.0889 (0.7 ppm error), Found: 236.1078; \(\text{C}_{16}\text{H}_{14}\text{NO} (\text{MH}^+) \) Requires 236.1070 (−3.5 ppm error).

Lab notebook reference: MJJ8/52
6-(2-Oxo-4-phenylbut-3-yn-1-yl)nicotinonitrile (228g)

Synthesised using general procedure 4A with DIPA (0.29 mL, 2.1 mmol), n-BuLi (0.84 mL, 2.1 mmol, 2.5 M in hexanes) in THF (10 mL), a solution of 5-Cyano-2-picoline (118 mg, 1.0 mmol) in THF (5 mL) and methyl phenylpropiolate (0.16 mL, 1.1 mmol). Purification by column chromatography (10% EtOAc in hexane) afforded the title compound 228g (145 mg, 59%, 96:4 enol:keto) as a yellow solid, mp 126–128 °C; νmax (cm⁻¹) 2227, 2196, 1638, 1587, 1521, 1162, 837, 749, 688, 551; ¹H NMR of enol tautomer δH (400 MHz, CDCl₃) 5.97 (1H, s, H-7), 7.09 (1H, d, J = 9.0 Hz, H-5), 7.34–7.44 (3H, m, H-14,15), 7.53–7.60 (2H, m, H-13), 7.83 (1H, dd, J = 9.0, 2.0 Hz, H-4), 8.63 (1H, d, J = 2.0 Hz, H-1), 14.03 (1H, br s, H-9); ¹³C NMR data of enol tautomer δC (100 MHz, CDCl₃) 85.3 (C, C-10), 92.3 (C, C-11), 104.3 (CH, C-7), 104.5 (C, C-2), 116.7 (C, C-3), 121.18 (CH, C-4), 121.24 (C, C-12), 128.5 (2CH, C-14), 129.6 (CH, C-15), 132.1 (2CH, C-13), 139.4 (CH, C-4), 149.3 (CH, C-1), 151.0 (C, C-6), 160.6 (C, C-8); Characteristic ¹³C NMR data of keto tautomer δC (100 MHz, CDCl₃) 54.1 (CH₂, C-7); HRMS (ESI⁺): Found: 247.0869; C₁₆H₁₁N₂O (MH⁺) Requires 247.0866 (−1.2 ppm error).

Lab notebook reference: MJJ8/36

1-(4-Bromopyridin-2-yl)-4-phenylbut-3-yn-2-one (228h)

Synthesised using general procedure 4A with DIPA (0.25 mL, 1.76 mmol), n-BuLi (0.70 mL, 1.76 mmol, 2.5 M in hexanes), 4-bromo-2-methylpyridine (0.10 mL, 0.84 mmol), methyl phenylpropiolate (0.14 mL, 0.92 mmol) and THF (13 mL). Purification by column chromatography (10% EtOAc in hexane) afforded the title compound 228h (221 mg, 88%, 76:24 enol:keto) as a yellow solid, mp 93–95 °C; νmax (cm⁻¹) 2202, 1616, 1573, 1531, 756, 690; δH (400 MHz, CDCl₃) 4.17 (2H, s, H-6, keto), 5.84 (1H, s, H-6, enol), 7.19–7.24 (2H, m, H-2,4 enol), 7.33–7.48 (7H, m, ArH, enol + keto), 7.50–7.59 (5H, m, ArH, enol + keto), 8.16 (1H, d, J = 6.0 Hz, H-1, enol), 8.44 (1H, d, J = 5.5 Hz, H-1, keto), 14.46 (1H, br s, H-8, enol); ¹³C NMR data of enol tautomer δC (100 MHz, CDCl₃) 85.7 (C, C-9), 90.7 (C, C-10), 103.6 (CH, C-6), 121.7 (C, C-11), 122.8 (CH, C-2/4), 124.1 (CH, C-2/4), 128.4 (2CH, C-13), 129.2 233
(CH, C-14), 132.0 (2CH, C-12), 133.8 (C, C-3), 145.8 (CH, C-1), 149.1 (C, C-5), 158.8 (C, C-7); Characteristic $^{13}$C NMR data of keto tautomer $\delta_{C}$ (100 MHz, CDCl$_3$) 53.8 (CH$_3$); HRMS (ESI$^+$): Found: 300.0006; C$_{15}$H$_{11}$BrNO (MH$^+$) Requires 300.0019 (4.3 ppm error).

Lab notebook reference: MJJ8/33

1-(3-Methylpyridin-2-yl)-4-phenylbut-3-yn-2-one (228i)

![Chemical structure of 1-(3-Methylpyridin-2-yl)-4-phenylbut-3-yn-2-one (228i)](image)

Synthesised using **general procedure 4A** with DIPA (0.26 mL, 1.85 mmol), n-BuLi (0.74 mL, 1.85 mmol, 2.5 M in hexanes), 2,3-lutidine (0.10 mL, 0.88 mmol), methyl phenylpropiolate (0.14 mL, 0.92 mmol) and THF (13 mL). Purification by column chromatography (30% EtOAc in hexane) afforded the **title compound 228i** (165 mg, 80%, 92:8 enol:keto) as a yellow solid, mp 76–78 °C; $\nu_{max}$ (cm$^{-1}$) 2202, 1589, 1562, 1435, 757, 690; $\delta_{H}$ (400 MHz, CDCl$_3$) 2.28 (3H, s, H-5, enol), 2.34 (3H, s, H-5, keto), 4.22 (2H, s, H-7, keto), 5.88 (1H, s, H-7, enol), 6.87 (1H, dd, J = 7.5, 5.5 Hz, H-2, enol), 7.17 (1H, dd, J = 7.5, 5.0 Hz, H-2, keto), 7.32–7.40 (6H, m, H-14,15, enol + keto), 7.42–7.48 (3H, m, H-3,13, enol + keto), 7.52 (1H, d, J = 8.0 Hz, H-3, keto), 7.55–7.60 (2H, m, H-13, enol), 7.98 (1H, br d, J = 5.5 Hz, H-1, enol), 8.47 (1H, br d, J = 5.0 Hz, H-1, keto), 16.18 (1H, br s, H-9, enol); $^{13}$C NMR data of enol tautomer $\delta_{C}$ (100 MHz, CDCl$_3$) 18.3 (CH$_3$, C-5), 87.7 (C, C-10), 88.5 (C, C-11), 97.9 (CH, C-7), 117.4 (CH, C-2), 122.1 (C, C-12), 128.3 (2CH, C-14), 128.9 (CH, C-15), 129.0 (C, C-4), 132.0 (2CH, C-13), 138.1 (CH, C-3), 138.5 (CH, C-1), 154.6 (C, C-6/8), 155.9 (C, C-6/8); Characteristic $^{13}$C NMR data of keto tautomer $\delta_{C}$ (100 MHz, CDCl$_3$) 52.6 (CH$_3$, C-7); HRMS (ESI$^+$): Found: 236.1062; C$_{16}$H$_{12}$NO (MH$^+$) Requires 236.1070 (3.3 ppm error).

Lab notebook reference: MJJ8/64
1-(Isoquinolin-1-yl)-4-phenylbut-3-yn-2-one (228j)

Synthesised using **general procedure 4A** with DIPA (0.22 mL, 1.58 mmol), n-BuLi (0.63 mL, 1.58 mmol, 2.5 M in hexanes), 1-methylisoquinoline (0.10 mL, 0.75 mmol), methyl phenylpropiolate (0.12 mL, 0.79 mmol) and THF (11 mL). Purification by column chromatography (40% EtOAc in hexane) afforded the **title compound 228j** (166 mg, 81%, >99:1 enamine:imine) as a yellow solid, mp 123–125 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 1588, 1550, 1493, 1250, 1207, 1143; $\delta_H$ (400 MHz, CDCl$_3$) 6.42 (1H, s, H-11), 6.90 (1H, d, $J = 6.5$ Hz, H-3), 7.33–7.45 (4H, m, H-2,17,18), 7.56 (1H, dd, $J = 8.5$, 7.5 Hz, H-7), 7.58–7.65 (3H, m, H-5,16), 7.70 (1H, dd, $J = 7.5$, 7.5 Hz, H-6), 8.14 (1H, d, $J = 8.5$ Hz, H-8), 15.67 (1H, br s, H-1); $\delta_C$ (100 MHz, CDCl$_3$) 86.6 (C, C-13), 90.2 (C, C-14), 92.6 (CH, C-11), 112.1 (CH, C-3), 121.8 (C, C-15), 123.8 (C, C-4), 124.7 (CH, C-8), 127.1 (CH, C-5), 127.7 (CH, C-2/7/18), 127.8 (CH, C-2/7/18), 128.3 (2CH, C-17), 129.2 (CH, C-2/7/18), 132.3 (CH, C-6), 132.4 (2CH, C-16), 135.6 (C, C-9), 154.0 (C, C-10), 168.8 (C, C-12); HRMS (ESI$^+$): Found: 294.0890; C$_{19}$H$_{13}$NNaO (MNa$^+$) Requires 294.0889 (−0.1 ppm error), Found: 272.1069; C$_{19}$H$_{14}$NO (MH$^+$) Requires 272.1070 (0.4 ppm error).

Lab notebook reference: MJJ8/39

4-Phenyl-1-(pyrazin-2-yl)but-3-yn-2-one (228k)

Synthesised using **general procedure 4A** with DIPA (0.30 mL, 2.12 mmol), n-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyrazine (0.09 mL, 1.01 mmol), methyl phenylpropiolate (0.16 mL, 1.06 mmol) and THF (15 mL) (**Note**: Reaction stirred at −78 °C for 1 h after the addition of the methyl ester). Purification by column chromatography (20 → 40% EtOAc in hexane) afforded the **title compound 228k** (77 mg, 35%, 95:5 enol:keto) as a pale brown solid, mp 42–44 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 1618, 1506, 1117, 755; $^1$H NMR data of enol tautomer $\delta_H$ (400 MHz, CDCl$_3$) 6.00 (1H, s, H-5), 7.34–7.44 (3H, m, H-12,13), 7.53–7.61 (2H, m, H-11), 8.30–8.34 (1H, m, H-2), 8.34–8.36 (1H, m, H-1), 8.42 (1H, d, $J = 1.5$ Hz, H-3), 13.26 (1H, br s, H-7); $^{13}$C NMR data of enol tautomer $\delta_C$ (100 MHz, CDCl$_3$) 85.1 (C, C-8),
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91.5 (C, C-9), 102.3 (CH, C-5), 121.5 (C, C-10), 128.4 (2CH, C-12), 129.4 (CH, C-13), 132.0 (2CH, C-11), 140.0 (CH, C-1/2), 140.4 (CH, C-1/2), 143.8 (CH, C-3), 148.5 (C, C-4), 153.3 (C, C-6); Characteristic $^{13}$C NMR data of keto tautomer $\delta_C$ (100 MHz, CDCl$_3$) 51.5 (CH$_2$, C-5), 102.3 (CH, C-5), 121.5 (C, C-10), 128.4 (2CH, C-12), 129.4 (CH, C-13), 132.0 (2CH, C-11), 140.0 (CH, C-1/2), 140.4 (CH, C-1/2), 143.8 (CH, C-3), 148.5 (C, C-4), 153.3 (C, C-6); HRMS (ESI$^+$): Found: 245.0692; C$_{14}$H$_{10}$N$_2$O (MNa$^+$) Requires 245.0685 (−2.6 ppm error).

Lab notebook reference: MJJ8/43

1-(Pyridin-2-yl)-4-(trimethylsilyl)but-3-yn-2-one (228l)

Synthesised using general procedure 4A with DIPA (0.49 mL, 3.47 mmol), n-BuLi (1.39 mL, 3.47 mmol, 2.5 M in hexanes), 2-methylpyridine (0.16 mL, 1.65 mmol) in THF (16.5 mL) and a solution of methyl ester 269c (270 mg, 1.73 mmol) in THF (9 mL). Purification by column chromatography (15% EtOAc in hexane) afforded the title compound 228l (240 mg, 67%, 91:9 enol:keto) as a yellow oil; $\nu_{\text{max}}$ (cm$^{-1}$) 1617, 1595, 1552, 1472, 1249, 1149, 932, 843; $\delta_H$ (400 MHz, CDCl$_3$) 0.18 (9H, s, H-11, keto), 0.25 (9H, s, H-11, enol), 4.07 (2H, s, H-6, keto), 5.82 (1H, s, H-6, enol), 6.98 (1H, d, J = 8.0 Hz, H-4, enol), 7.02 (1H, dd, J = 7.5, 5.0 Hz, H-2, enol), 7.22 (1H, dd, J = 7.5, 5.0 Hz, H-2, keto), 7.26 (1H, d, J = 8.0 Hz, H-4, keto), 7.62 (1H, ddd, J = 8.0, 7.5, 5.0 Hz, H-3, keto), 7.68 (1H, ddd, J = 8.0, 7.5, 1.5 Hz, H-3, keto), 8.28 (1H, br d, J = 5.0 Hz, H-1, enol), 8.59 (1H, br d, J = 5.0 Hz, H-1, keto), 14.78 (1H, br s, H-8, enol); $^{13}$C NMR data of enol tautomer $\delta_C$ (100 MHz, CDCl$_3$) −0.4 (3CH$_3$, C-11), 95.6 (C, C-10), 101.1 (C, C-9), 104.3 (CH, C-6), 119.3 (CH, C-2), 121.4 (CH, C-4), 137.4 (CH, C-3), 144.4 (CH, C-1), 148.3 (C, C-5), 157.6 (C, C-7); Characteristic $^{13}$C NMR data of keto tautomer $\delta_C$ (100 MHz, CDCl$_3$) 54.1 (CH$_2$, C-6); HRMS (ESI$^+$): Found: 218.0988; C$_{12}$H$_{16}$NOSi (MH$^+$) Requires 218.0996 (3.6 ppm error).

Lab notebook reference: MJJ8/62
4-Phenyl-2H-quinoliniz-2-one (229a)

Synthesised using general procedure 4B with pyridine-ynone 228a (66 mg, 0.3 mmol), AgNO₃ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 2 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the title compound 229a (64 mg, 97%) as a pale brown solid, mp 174–176 °C; νₘₐₓ (cm⁻¹) 3378, 1620, 1576, 1505, 749, 703; δ_H (400 MHz, CDCl₃) 6.42 (1H, dd, J = 7.5, 6.5 Hz, H-2), 6.63 (1H, br s, H-6/8), 6.75 (1H, br s, H-6/8), 7.06 (1H, dd, J = 8.5, 6.5 Hz, H-3), 7.19 (1H, d, J = 8.5 Hz, H-4), 7.37–7.45 (2H, m, H-11/12), 7.50–7.59 (3H, m, H-11/12,13), 7.62 (1H, d, J = 7.5 Hz, H-1); δ_C (100 MHz, CDCl₃) 111.6 (CH, C-6/8), 111.9 (CH, C-2), 124.5 (CH, C-4/6/8), 124.7 (CH, C-4/6/8), 128.4 (CH, C-3), 129.0 (2CH, C-11/12), 129.3 (CH, C-1/13), 129.5 (2CH, C-11/12), 130.1 (CH, C-1/13), 132.9 (C, C-10), 144.8 (C, C-5/9), 145.8 (C, C-5/9), 175.5 (C, C-7); HRMS (ESI⁺): Found: 244.0738; C₁₅H₁₁NNaO (MNa⁺) Requires 244.0733 (−2.1 ppm error), Found: 222.0923; C₁₅H₁₀NO (MH⁺) Requires 222.0913 (−4.5 ppm error).

Lab notebook reference: MJJ8/51

4-(3,4-Dimethoxyphenyl)-2H-quinoliniz-2-one (229b)

Synthesised using general procedure 4B with pyridine-ynone 228b (2.11 g, 7.50 mmol), AgNO₃ (25.5 mg, 0.15 mmol) in DCE (37.5 mL) and EtOH (37.5 mL) for 4 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the title compound 229b (2.09 g, 99%) as a pale brown solid, mp 211–213 °C; νₘₐₓ (cm⁻¹) 3379, 1622, 1576, 1516, 1491, 1263, 1022, 756; δ_H (400 MHz, CDCl₃) 3.88 (3H, s, H-13/15), 3.95 (3H, s, H-13/15), 6.44 (1H, ddd, J = 8.0, 6.5, 1.5 Hz, H-2), 6.62 (1H, d, J = 2.5 Hz, H-6/8), 6.77 (1H, d, J = 2.5 Hz, H-6/8), 6.89 (1H, d, J = 1.5 Hz, H-11), 6.96–7.03 (2H, m, H-16,17), 7.06 (1H, dd, J = 9.0, 6.5 Hz, H-3), 7.20 (1H, br d, J = 9.0 Hz, H-4), 7.72 (1H, d, J = 8.0 Hz, H-1); δ_C (100 MHz,
CDCl$_3$) 56.0 (CH$_3$, C-13/15), 56.1 (CH$_3$, C-13/15), 111.4 (CH, C-6/8/11/16), 111.6 (CH, C-6/8/11/16), 111.8 (CH, C-6/8/11/16), 111.9 (CH, C-2), 121.9 (CH, C-17), 124.4 (CH, C-6/8), 124.7 (CH, C-4), 125.2 (C, C-10), 128.4 (CH, C-3), 129.5 (CH, C-1), 144.8 (C, C-5/9), 145.7 (C, C-5/9), 149.6 (C, C-12/14), 150.3 (C, C-12/14), 175.4 (C, C-7); HRMS (ESI$^+$): Found: 282.1121; C$_{17}$H$_{16}$NO$_3$ (MH$^+$) Requires 282.1125 (1.3 ppm error).

Lab notebook reference: MJJ8/67

4-(4-Fluorophenyl)-2H-quinolizin-2-one (229c)

Synthesised using general procedure 4B with pyridine-ynone 228c (72 mg, 0.3 mmol), AgNO$_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 2 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229c (72 mg, 100%) as a pale brown solid, mp 244–246 °C; $\nu_{\text{max}}$ (cm$^{-1}$) 3380, 1623, 1577, 1515, 1486; $\delta_H$ (400 MHz, CDCl$_3$) 6.42 (1H, dd, $J = 7.0, 7.0$ Hz, H-2), 6.60 (1H, d, $J = 2.5$ Hz, H-6/8), 6.71 (1H, d, $J = 2.5$ Hz, H-6/8), 7.05 (1H, dd, $J = 9.0, 7.0$ Hz, H-3), 7.18 (1H, d, $J = 9.0$ Hz, H-4), 7.21–7.29 (2H, m, H-12), 7.38–7.45 (2H, m, H-11), 7.57 (1H, br d, $J = 7.0$ Hz, H-1); $\delta_C$ (100 MHz, CDCl$_3$) 111.8 (CH, C-6/8), 111.9 (CH, C-2), 116.8 (2CH, d, $J = 22.0$ Hz, C-12), 124.7 (CH, C-4), 124.9 (CH, C-6/8), 128.3 (CH, C-3), 129.0 (C, d, $J = 4.0$ Hz, C-10), 129.1 (CH, C-1), 131.2 (2CH, d, $J = 8.5$ Hz, C-11), 144.6 (C, C-5/9), 144.8 (C, C-5/9), 163.5 (C, d, $J = 251.0$ Hz, C-13), 175.5 (C, C-7); $\delta_F$ (376 MHz, CDCl$_3$) −109.4−109.5 (1F, m); HRMS (ESI$^+$): Found: 240.0825; C$_{15}$H$_{11}$FNO (MH$^+$) Requires 240.0819 (−2.2 ppm error).

Lab notebook reference: MJJ8/59
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4-Pentyl-2H-quinolizin-2-one (229d)

Synthesised using general procedure 4B with pyridine-ynone 228d (153 mg, 0.711 mmol), AgNO₃ (2.4 mg, 14.2 μmol) in DCE (3.6 mL) and EtOH (3.6 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229d (149 mg, 97%) as a pale brown solid, mp 69–71 °C; vₘₐₓ (cm⁻¹) 3369, 1622, 1574, 1489, 1177, 726; δ_H (400 MHz, CDCl₃) 0.93 (3H, t, J = 7.0 Hz, H-14), 1.33–1.50 (4H, m, H-12,13), 1.74 (2H, tt, J = 8.0, 7.0 Hz, H-11), 2.84 (2H, t, J = 8.0 Hz, H-10), 6.58 (1H, d, J = 2.5 Hz, H-6/8), 6.64 (1H, dd, J = 7.5, 7.5 Hz, H-2), 6.77 (1H, d, J = 2.5 Hz, H-6/8), 7.09 (1H, dd, J = 9.0, 7.5 Hz, H-3), 7.20 (1H, d, J = 9.0 Hz, H-4), 7.57 (1H, br d, J = 7.5 Hz, H-1); δ_C (100 MHz, CDCl₃) 13.8 (CH₃, C-14), 22.3 (CH₂, C-12/13), 26.2 (CH₂, C-11), 111.3 (CH, C-6/8), 112.4 (CH, C-2), 122.8 (CH, C-6/8), 125.2 (CH, C-4), 127.1 (CH, C-1), 127.9 (CH, C-3), 145.0 (C, C-5/9), 145.1 (C, C-5/9), 175.9 (C, C-7); HRMS (ESI⁺): Found: 216.1381; C₁₄H₁₈NO (MH⁺) Requires 216.1383 (1.1 ppm error).

Lab notebook reference: MJJ8/46

4-(Thiophen-2-yl)-2H-quinolizin-2-one (229e)

Synthesised using general procedure 4B with pyridine-ynone 228e (80 mg, 0.352 mmol), AgNO₃ (1.2 mg, 7.0 μmol) in DCE (1.8 mL) and EtOH (1.8 mL) for 9 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229e (47 mg, 59%) as a brown oil; vₘₐₓ (cm⁻¹) 3379, 1618, 1577, 1485, 754; δ_H (400 MHz, CDCl₃) 6.49 (1H, ddd, J = 7.0, 7.0, 1.5 Hz, H-2), 6.64 (1H, d, J = 2.5 Hz, H-6/8), 6.93 (1H, d, J = 2.5 Hz, H-6/8), 7.08 (1H, dd, J = 8.0, 7.0 Hz, H-3), 7.20 (1H, d, J = 8.0 Hz, H-4), 7.22 (1H, dd, J = 5.0, 3.5 Hz, H-12); 7.29 (1H, dd, J = 3.5, 1.0 Hz, H-11), 7.60 (1H, dd, J = 5.0, 1.0 Hz, H-13), 7.89 (1H, d, J = 7.0 Hz, H-1); δ_C (100 MHz, CDCl₃) 112.0 (CH, C-2/6/8), 112.2 (CH, C-2/6/8), 124.6 (CH, C-4), 126.6 (CH, C-6/8), 127.9 (CH, C-12), 128.7 (CH, C-3), 129.1 (CH,
C-1/13), 129.3 (CH, C-1/13), 130.1 (CH, C-11), 132.7 (C, C-10), 138.7 (C, C-5/9), 145.1 (C, C-11), 175.2 (C, C-7); HRMS (ESI\(^+\)): Found: 228.0474; \(\text{C}_{13}\text{H}_{10}\text{NOS} (\text{MH}^+)\) Requires 228.0478 (1.7 ppm error).

Lab notebook reference: MJJ8/61

1-Methyl-4-phenyl-2H-quinolizin-2-one (229f)

![Structure](image)

Synthesised using general procedure 4B with pyridine-ynone 228f (42 mg, 0.178 mmol), AgNO\(_3\) (0.6 mg, 3.6 μmol) in DCE (0.9 mL) and EtOH (0.9 mL) for 18 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229f (19 mg, 45%) as a brown oil; \(\nu_{\max} (\text{cm}^{-1})\) 3401, 1622, 1508, 761, 703; \(\delta_h \) (400 MHz, CDCl\(_3\)) 2.34 (3H, s, H-7), 6.41 (1H, ddd, \(J = 7.5, 7.0, 1.5 \text{ Hz}\), H-2), 6.80 (1H, s, H-9), 7.11 (1H, dd, \(J = 9.0, 7.0 \text{ Hz}\), H-3), 7.37–7.43 (2H, m, H-12/13), 7.47 (1H, d, \(J = 9.0 \text{ Hz}\), H-4), 7.51–7.57 (3H, m, H-12/13,14), 7.68 (1H, d, \(J = 7.5 \text{ Hz}\), H-1); \(\delta_c \) (100 MHz, CDCl\(_3\)) 10.3 (CH\(_3\), C-7), 111.0 (CH, C-2), 118.1 (C, C-6), 122.0 (CH, C-4), 122.5 (CH, C-9), 127.7 (CH, C-3), 129.1 (2CH, C-12/13), 129.4 (2CH, C-12/13), 129.9 (CH, C-1/14), 130.0 (CH, C-1/14), 133.5 (C, C-11), 141.6 (C, C-5/10), 144.3 (C, C-5/10), 174.4 (C, C-8); HRMS (ESI\(^+\)): Found: 236.1071; \(\text{C}_{16}\text{H}_{14}\text{NO} (\text{MH}^+)\) Requires 236.1070 (−0.3 ppm error).

Lab notebook reference: MJJ8/54

2-Oxo-4-phenyl-2H-quinolizine-7-carbonitrile (229g)

![Structure](image)

Synthesised using general procedure 4B with pyridine-ynone 228g (74 mg, 0.3 mmol), AgNO\(_3\) (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229g (61 mg, 82%) as a pale yellow solid, mp 243–245 °C; \(\nu_{\max} (\text{cm}^{-1})\) 2230, 1628, 1602, 1585, 1519,
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1306; δH (400 MHz, CDCl₃) 6.58 (1H, d, J = 2.5 Hz, H-7/9), 6.74 (1H, d, J = 2.5 Hz, H-7/9), 6.97 (1H, d, J = 9.5 Hz, H-5), 7.17 (1H, d, J = 9.5 Hz, H-4), 7.37–7.45 (2H, m, H-12/13), 7.56–7.67 (3H, m, H-12/13,14), 7.97 (1H, s, H-1); δC (100 MHz, CDCl₃) 97.4 (C, C-2), 113.4 (CH, C-7/9), 115.6 (C, C-3), 125.4 (CH, C-7/9), 125.7 (CH, C-4), 125.9 (CH, C-5), 128.9 (2CH, C-12/13), 130.0 (2CH, C-12/13), 131.0 (CH, C-14), 131.4 (C, C-11), 136.6 (CH, C-1), 143.1 (C, C-6/10), 146.2 (C, C-6/10), 176.2 (C, C-8); HRMS (ESI⁺): Found: 269.0694 C₁₆H₁₀N₂NaO (MNa⁺) Requires 269.0685 (−3.1 ppm error), Found: 247.0872; C₁₆H₁₁N₂O (MH⁺) Requires 247.0866 (−2.6 ppm error).

Lab notebook reference: MJJ8/38

8-Bromo-4-phenyl-2H-quinolizin-2-one (229h)

Synthesised using general procedure 4B with pyridine-ynone 228h (90 mg, 0.3 mmol), AgNO₃ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229g (90 mg, 82%) as a yellow solid, mp >300 °C; νmax (cm⁻¹) 1625, 1578, 1505, 752; δH (400 MHz, CDCl₃) 6.44 (1H, dd, J = 8.0, 2.0 Hz, H-2), 6.51 (1H, d, J = 2.5 Hz, H-6/8), 6.71 (1H, d, J = 2.5 Hz, H-6/8), 7.36 (1H, d, J = 2.0 Hz, H-4), 7.37–7.43 (2H, m, H-11/12), 7.46 (1H, d, J = 8.0 Hz, H-1), 7.52–7.61 (3H, m, H-11/12,13); δC (100 MHz, CDCl₃) 111.1 (CH, C-6/9), 115.4 (CH, C-2), 123.2 (C, C-3), 124.7 (CH, C-6/9), 125.7 (CH, C-4), 129.0 (2CH, C-11/12), 129.6 (2CH, C-11/12), 130.1 (CH, C-1/13), 130.4 (CH, C-1/13), 132.6 (C, C-10), 144.7 (C, C-5/9), 145.8 (C, C-5/9), 175.7 (C, C-7); HRMS (ESI⁺): Found: 300.0022; C₁₅H₁₀BrNO (MH⁺) Requires 300.0019 (−1.2 ppm error).

Lab notebook reference: MJJ8/35
9-Methyl-4-phenyl-2H-quinolizin-2-one (229i)

Synthesised using general procedure 4B with pyridine-ynone 228i (71 mg, 0.3 mmol), AgNO₃ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 5 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229i (52 mg, 73%) as a yellow oil; ν_max (cm⁻¹) 3391, 1625, 1586, 1524; δ_H (400 MHz, CDCl₃) 2.37 (3H, s, H-5), 6.37 (1H, dd, J = 7.0, 7.0 Hz, H-2), 6.72–6.78 (2H, m, H-7,9), 6.96 (1H, d, J = 7.0 Hz, H-3), 7.37–7.45 (2H, m, H-12/13), 7.50–7.60 (4H, m, H-1,12/13,14); δ_C (100 MHz, CDCl₃) 19.6 (CH₃, C-5), 109.0 (CH, C-7/9), 111.2 (CH, C-2), 124.1 (CH, C-7/9), 127.7 (CH, C-3), 128.0 (CH, C-1/14), 129.1 (2CH, C-12/13), 129.4 (2CH, C-12/13), 130.0 (CH, C-1/14), 130.9 (C, C-4), 133.6 (C, C-11), 145.2 (C, C-6/10), 146.4 (C, C-6/10), 175.8 (C, C-8); HRMS (ESI⁺): Found: 236.1065; C₁₆H₁₄NO (MH⁺) Requires 236.1070 (2.0 ppm error).

Lab notebook reference: MJJ8/65

4-Phenyl-2H-pyrido[2,1-a]isoquinolin-2-one (229j)

Synthesised using general procedure 4B with ynone 228j (81 mg, 0.3 mmol), AgNO₃ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 20 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the title compound 229j (58 mg, 70%) as a pale yellow solid, mp 139–141 °C; ν_max (cm⁻¹) 1626, 1601, 1572, 1582; δ_H (400 MHz, CDCl₃) 6.64 (1H, d, J = 8.0 Hz, H-2), 6.72 (1H, d, J = 2.5 Hz, H-10/12) 7.40–7.69 (10H, ArH), 8.27 (1H, d, J = 7.5 Hz, H-7); δ_C (100 MHz, CDCl₃) 109.9 (CH, C-10/12), 112.1 (CH, C-2), 122.5 (CH, C-10/12), 124.3 (CH, C-7), 125.3 (C, C-3/8), 125.7 (CH, ArC), 126.9 (CH, ArC), 128.9 (CH, ArC), 129.1 (2CH, C-15/16), 129.4 (2CH, C-15/16), 129.6 (C, C-3/8), 130.0
(CH, ArC), 131.1 (CH), 133.7 (C, C-14), 143.5 (C, C-9/13), 147.8 (C, C-9/13), 176.7 (C, C-11); HRMS (ESI+): Found: 272.1069; C_{19}H_{14}NO (MH+) Requires 272.1070 (0.2 ppm error).

Lab notebook reference: MJJ8/40

6-Phenyl-8H-pyrido[1,2-a]pyrazin-8-one (229k)

Synthesised using general procedure 4B with pyridine-ynone 228k (66 mg, 0.3 mmol), AgNO\(_3\) (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 5 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the title compound 229k (56 mg, 85%) as a yellow solid, mp 170–172 °C; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3400, 1619, 1600, 1567, 1505; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 6.81 (1H, d, \(J = 2.5\) Hz, H-5/7), 6.84 (1H, d, \(J = 2.5\) Hz, H-5/7), 7.32–7.38 (2H, m, H-1,2), 7.38–7.45 (2H, m, H-10/11), 114.1 (CH, C-5/7), 119.6 (CH, C-1/2), 126.3 (CH, C-5/7), 127.4 (CH, C-1/2), 129.0 (2CH, C-10/11), 130.7 (CH, C-12), 131.3 (C, C-9), 137.7 (C, C-4/8), 145.8 (C, C-4/8), 152.6 (CH, C-3), 176.5 (C, C-6); HRMS (ESI+): Found: 245.0678; C_{14}H_{10}N_{2}NaO (MNa+) Requires 245.0685 (2.9 ppm error), Found: 223.0865; C_{14}H_{4}N_{2}O (MH+) Requires 223.0866 (0.4 ppm error).

Lab notebook reference: MJJ8/45

2H-Quinolizin-2-one (229l)

To a solution of TMS-ynone 228l (98 mg, 0.451 mmol) in acetone (4.5 mL) was added AgNO\(_3\) (15.3 mg, 90.2 μmol). The reaction mixture was stirred at rt for 19 h then concentrated in vacuo. The crude product was dissolved in CH\(_2\)Cl\(_2\) and purified by column chromatography (5 → 20% MeOH in EtOAc) to afford the title compound 229l (54 mg, 82%) as a brown solid, mp 38–40 °C; \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3301, 1649, 1571, 1513, 1486, 1427, 851; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 6.53 (1H, d, \(J = 2.5\) Hz, H-6), 6.56 (1H, ddd, \(J = 7.0, 6.5, 1.0\) Hz, H-2), 6.78 (1H, dd, \(J = 7.5, 1.0\) Hz, H-1).
2.5 Hz, H-8), 7.05 (1H, d, J = 9.0, 6.5 Hz, H-3), 7.11 (1H, br d, J = 9.0 Hz, H-4), 7.61 (1H, d, J = 7.0 Hz, H-1), 7.79 (1H, d, J = 7.5 Hz, H-9); δ_C (100 MHz, CDCl_3) 111.2 (CH, C-6), 112.2 (CH, C-2), 123.0 (CH, C-8), 123.9 (CH, C-4), 128.5 (CH, C-3), 132.0 (CH, C-1), 135.1 (CH, C-9), 144.1 (C, C-5), 176.2 (C, C-7); HRMS (ESI⁺): Found: 146.0604; C_9H_8NO (MH⁺) Requires 146.0600 (−2.7 ppm error).

Lab notebook reference: MJJ8/63

6-(3,4-Dimethoxyphenyl)-3,4-dihydro-1H-quinolizin-8(2H)-one (273)

To a solution of quinolizidine 229b (28 mg, 0.1 mmol) in MeOH (1 mL) was added Pd/C (14 mg). The mixture was evacuated in vacuo and backfilled with argon three times then evacuated in vacuo and backfilled with hydrogen three times. The mixture was stirred at rt for 16 h before being filtered through Celite®, eluting with EtOAc. The filtrate was then concentrated in vacuo to afford the title compound 273 (26 mg, 91%) as a pale yellow oil; ν_max (cm⁻¹) 3359, 2935, 1623, 1509, 1262, 1248, 1024, 729; δ_H (400 MHz, CDCl_3) 1.78–1.90 (4H, m, H-2,3), 2.78 (2H, t, J = 6.5 Hz, H-1/4), 3.68 (2H, t, J = 5.5 Hz, H-1/4), 3.87 (3H, s, H-13/15), 3.91 (3H, s, H-13/15), 6.27–6.29 (2H, m, H-6/8,11), 6.79 (1H, d, J = 1.5 Hz, H-6/8), 6.86 (1H, dd, J = 8.0, 2.5 Hz, H-17), 6.92 (1H, d, J = 8.0 Hz, H-16); δ_C (100 MHz, CDCl_3) 18.3 (CH_2, C-2/3), 22.4 (CH_2, C-2/3), 28.4 (CH_2, C-1/4), 47.0 (CH_2, C-1/4), 55.9 (CH_3, C-13/15), 56.0 (CH_3, C-13/15), 111.0 (CH, C-16), 111.6 (CH, C-6/8), 116.5 (CH, C-6/8/11), 119.1 (CH, C-6/8/11), 121.2 (CH, C-17), 126.9 (C, C-10), 149.0 (C, C-5/9), 149.8 (C, C-5/9), 150.7 (C, C-12/14), 151.9 (C, C-12/14), 178.4 (C, C-7); HRMS (ESI⁺): Found: 308.1265; C_{17}H_{19}NNaO_3 (MNa⁺) Requires 308.1257 (−2.5 ppm error), Found: 286.1447; C_{17}H_{20}NO_3 (MH⁺) Requires 286.1438 (−3.4 ppm error).

Lab notebook reference: MJJ6/5
4-(3,4-Dimethoxyphenyl)hexahydro-1H-quinolizin-2(6H)-one (274)

To a solution of quinolizidine 229b (1.05 g, 3.73 mmol) in AcOH (0.64 mL, 11.2 mmol) and EtOH (37 mL) was added PtO₂ (254 mg, 1.12 mmol). The mixture was evacuated in vacuo and backfilled with nitrogen three times then evacuated in vacuo and backfilled with hydrogen three times. The mixture was stirred at rt for 4 days before being filtered through Celite®, eluting with EtOAc. The filtrate was poured into sat. NaCHO₃ (aq) (30 mL) and diluted with EtOAc (50 mL). The organics were separated and the aqueous was extracted with EtOAc (4 × 50 mL). The organics were combined, dried (MgSO₄), and concentrated in vacuo to afford the crude hydrogenation product 230b, which was used in the next step without further purification.

To a solution of dry DMSO (1.33 mL, 18.7 mmol) in CH₂Cl₂ (65 mL) at −78 °C under argon was added oxalyl chloride (0.80 mL, 9.33 mmol). The mixture was stirred at −78 °C for 1 h, then a solution of the above crude product in CH₂Cl₂ (19 mL) was added. The mixture was stirred at −78 °C for 1 h, then Et₃N (5.72 mL, 41.0 mmol) was added, the mixture was then allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was quenched by the careful addition of 2 M NaOH (aq) (30 mL) and diluted with CH₂Cl₂ (20 mL). The organics were separated and the aqueous extracted with CH₂Cl₂ (3 × 60 mL). The organics were combined, dried (MgSO₄), and concentrated in vacuo and purified by column chromatography (0 → 2% MeOH in CH₂Cl₂) to afford the title compound 274 (730 mg, 68%) as a yellow oil; vₚₓₙₓ (cm⁻¹) 2932, 1722, 1516, 1263, 1028; δ_H (400 MHz, CDCl₃) 1.19–1.35 (1H, m), 1.38–1.81 (6H, m), 2.22–2.37 (2H, m), 2.41 (1H, ddd, J = 13.5, 3.0, 3.0 Hz), 2.51 (1H, dd, J = 13.5, 13.0 Hz), 2.68 (1H, dd, J = 13.5, 12.5 Hz), 2.75–2.83 (1H m), 3.21 (1H, br s); δ_C (100 MHz, CDCl₃) 24.2 (CH₂), 25.8 (CH₂), 34.3 (CH₂), 48.7 (CH₂), 50.9 (CH₂), 52.8 (CH₂), 55.8 (CH₃), 56.0 (CH₃), 62.4 (CH), 70.0 (CH), 109.6 (CH), 110.9 (CH), 119.5 (CH), 135.1 (C), 148.3 (C), 149.3 (C), 208.0 (C); (ESI⁺): Found: 290.1752; C₁₇H₂₄NO₃ (MH⁺) Requires 290.1751 (−0.6 ppm error).

Lab notebook reference: MJJ8/68 + MJJ8/71

Spectroscopic data matched those reported in the literature.¹²⁸,¹²⁹,¹²⁷
(±)-Lasubine II (235)

To a solution of ketone 274 (724 mg, 2.50 mmol) in THF (25 mL) at −78 °C was added L-Selectride® (5.0 mL, 5.00 mmol, 1.0 M in THF) dropwise. The mixture was stirred at −78 °C for 3 h then warmed to 0 °C before being quenched by the careful addition of sat. NaHCO₃ (aq) (25 mL). The suspension was stirred at room temperature for 2 h and then diluted with EtOAc (40 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 50 mL). The organics were combined, dried (MgSO₄), concentrated in vacuo and purified by column chromatography (10 → 20 → 30% MeOH in CH₂Cl₂) to afford the title compound 235 (527 mg, 72%) as an off-white foam, mp 41–43 °C; νmax (cm⁻¹) 2930, 1516, 1261, 1230, 1136, 1028; δH (400 MHz, CDCl₃) 1.20–2.00 (12H, m), 2.33–2.47 (1H, m), 2.70 (1H, br d, J = 11.0 Hz), 3.32 (1H, br d, J = 10.5 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.12–4.19 (1H, m), 6.79 (1H, d, J = 8.0 Hz), 6.82–7.00 (2H, m); δC (100 MHz, CDCl₃) 24.8 (CH₂), 26.1 (CH₂), 33.6 (CH₂), 40.3 (CH₂), 42.7 (CH₂), 53.2 (CH₂), 55.8 (CH₃), 55.9 (CH₃), 56.4 (CH), 63.4 (CH), 65.0 (CH), 110.4 (CH), 110.8 (CH), 119.7 (CH), 137.1 (C), 147.7 (C), 148.9 (C); HRMS (ESI⁺): Found: 292.1918; C₁₇H₂₆NO₃ (MH⁺) Requires 292.1907 (−3.6 ppm error).

Lab notebook reference: MJJ8/75

Spectroscopic data matched those reported in the literature.⁶

Ethyl 2-(1H-pyrrol-2-yl)acetate (276)

To a solution of pyrrole (13.9 mL, 200 mmol) in THF (300 mL) at ~−15 °C was slowly added MeMgCl (64 mL, 192 mmol, 3.0 M in THF). The reaction mixture was allowed to warm to RT and stirred for 30 min. The reaction mixture was then recooled to ~−10 °C and ethyl bromoacetate (8.85 mL, 80 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 30 min and then quenched with NH₄Cl (aq) (200 mL). The organics were separated and the aqueous was extracted with Et₂O (2 × 200 mL). The organics were combined, dried over MgSO₄ and concentrated in vacuo. The crude material was purified by
fractional distillation in vacuo to afford the title compound 276 as a colourless oil (6.02 g, 49%); \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3388, 2983, 1727, 1370, 1243, 1157, 1028, 720; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 1.30 (3 H, t, \( J = 7.0 \) Hz), 3.68 (2 H, s), 4.19 (2 H, q, \( J = 7.0 \) Hz), 6.02–6.05 (1 H, m), 6.14–6.18 (1 H, m), 6.76–6.79 (1 H, m), 8.76 (1 H, br s); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 14.1 (CH\(_3\)), 33.2 (CH\(_2\)), 61.1 (CH\(_2\)), 107.2 (CH), 108.2 (CH), 117.7 (CH), 123.3 (C), 171.2 (C).

Lab notebook reference: MJJ7/86

Spectroscopic data matched those previously reported in the literature.\(^{159}\)

2-(1H-Pyrrol-2-yl)acetic acid (277)

To a solution of ethyl 2-(1H-pyrrol-2-yl)acetate 276 (804 mg, 5.25 mmol) in THF (37 mL) and MeOH (3.7 mL) at 0 °C was added 2 M NaOH\(_{\text{(aq)}}\) (30 mL) dropwise. The reaction mixture was warmed to RT and stirred for 1 h 20 min. Water (20 mL) was added and the aqueous layer was washed with EtOAc (20 mL). The organic extract was discarded. The aqueous layer was acidified with 10% HCl\(_{\text{(aq)}}\) (20 mL) until pH = 1 and then extracted with EtOAc (2 x 20 mL). The organics were combined, dried over MgSO\(_4\) and concentrated in vacuo to afford the title compound 277 without further purification as an off white solid (621 mg, 95%); mp 77–79 °C; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3341, 3325, 3119, 2910, 1696, 1415, 1243, 1209, 745; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 3.74 (2 H, s), 6.07–6.11 (1 H, m), 6.17–6.20 (1 H, m), 6.77–6.80 (1 H, m), 8.57 (1 H, br s), 10.67 (1 H, br s); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 33.1 (CH\(_2\)), 107.9 (CH), 108.5 (CH), 118.1 (CH), 122.2 (C), 177.3 (C).

Lab notebook reference: akc01-92

Spectroscopic data matched those previously reported in the literature.\(^{160}\)
N-Methoxy-N-methyl-2-(1H-pyrrol-2-yl)acetamide (278)

Synthesised using general procedure 2A with 2-(1H-pyrrol-2-yl)acetic acid 277 (596 mg, 4.76 mmol), T3P 50% in EtOAc (4.55 g, 7.14 mmol), DIPEA (2.49 mL, 14.3 mmol) and MeNH(OMe)-HCl (511 mg, 5.24 mmol) in CH₂Cl₂ (24 mL) at RT for 1.5 h. Afforded the title compound 278 without further purification as a pale brown solid (633 mg, 79%); mp 63–65 °C; ν max (cm⁻¹) 3322, 2938, 1646, 1432, 1386, 1175, 1002, 723; δ H (400 MHz, CDCl₃) 3.22 (3 H, s, H-8), 3.72 (3 H, s, H-9), 3.83 (2 H, s, H-6), 6.01–6.03 (1 H, m, H-4), 6.12–6.15 (1 H, m, H-2/3), 6.74–6.76 (1 H, m, H-2/3), 9.05 (1 H, br s, H-1); δ C (100 MHz, CDCl₃) 30.4 (CH₂, C-6), 32.0 (CH₃, C-8), 61.5 (CH₃, C-9), 107.0 (CH, C-4), 107.9 (CH, C-2/3), 117.5 (CH, C-2/3), 124.3 (C, C-5), 171.6 (C, C-7); HRMS (ESI⁺): Found: 191.0791; C₈H₁₂N₂NaO₂ (MNa⁺) Requires 191.0791 (0.1 ppm error), Found: 169.0977; C₈H₁₃N₂O₂ (MH⁺) Requires 169.0972 (−3.3 ppm error).

Lab notebook reference: akc01-93 + WPU

Spectroscopic data matched those previously reported in the literature.⁸⁵

4-(4-Methoxyphenyl)-1-(1H-pyrrol-2-yl)but-3-yn-2-one (231a)

Synthesised using general procedure 2B with 4-ethynylanisole (919 mg, 6.96 mmol), THF (15 + 10 mL), Weinreb amide 278 (390 mg, 2.32 mmol) and n-BuLi (2.32 mL, 5.80 mmol, 2.5M in hexanes). Purification by column chromatography (10:1 hexane:EtOAc, then 2:1 hexane:EtOAc) afforded the title compound 231a as a pale yellow solid (314 mg, 57%); mp 112–114 °C; ν max (cm⁻¹) 3337, 2938, 1655, 1597, 1508, 1253, 1089, 1023, 839, 798, 739; δ H (400 MHz, CDCl₃) 3.85 (3H, s, H-14), 4.00 (2H, s, H-6), 6.12 (1H, br s, H-3/4) 6.19–6.21 (1H, H-3/4), 6.80 (1H, H-2), 6.88–6.92 (2H, m, H-12), 7.48–7.52 (2H, m, H-11); δ C (100 MHz, CDCl₃) 43.6 (CH₂, C-6), 55.4 (CH₃, C-14), 87.7 (C, C-8), 94.2 (C, C-9), 108.1 (CH, C-
2/3/4, 108.6 (CH, C-2/3/4), 111.4 (C, C-10), 114.4 (2CH, C-11), 118.1 (CH, C-2/3/4), 123.0 (C, C-5), 135.3 (2CH, C-12), 161.9 (C, C-13), 184.7 (C, C-7); HRMS (ESI⁺): Found: 262.0835; C₁₃H₁₃NNaO₂ (MNa⁺) Requires 262.0838 (1.9 ppm error), Found: 240.1022; C₁₅H₁₄NO₂ (MH⁺) Requires 240.1019 (−1.9 ppm error).

Lab notebook reference: WPU

4-(4-Methoxyphenyl)-1-(1H-pyrrol-2-yl)but-3-yn-2-ol (279a)

Synthesised using general procedure 21 with pyrrole-ynone 231a (76 mg, 0.318 mmol), NaBH₄ (48 mg, 1.27 mmol) and MeOH (13 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the title compound 279a (70 mg, 91%) as a pale brown oil; ν_max (cm⁻¹) 3380, 1605, 1508, 1290, 1245, 1172, 1027, 831, 716; δ_H (400 MHz, CDCl₃) 2.65 (1H, br s, H-8), 3.09 (1H, dd, J = 15.5, 7.0 Hz, H-6a), 3.15 (1H, dd, J = 15.5, 5.5 Hz, H-6b), 3.83 (1H, s, H-15), 4.77 (1H, dd, J = 7.0, 5.5 Hz, H-7), 6.08–6.13 (1H, m, H-4), 6.17–6.22 (1H, m, H-3), 6.73–6.76 (1H, m, H-2), 6.83–6.89 (2H, m, H-13), 7.35–7.42 (2H, m, H-12), 8.63 (1H, br s, H-1); δ_C (100 MHz, CDCl₃) 36.1 (CH₂, C-6), 55.2 (CH₃, C-15), 62.7 (CH, C-7), 85.3 (C, C-10), 88.1 (C, C-9), 107.4 (CH, C-4), 108.1 (CH, C-3), 113.9 (2CH, C-13), 114.2 (C, C-11), 117.4 (CH, C-2), 127.3 (C, C-5), 133.1 (2CH, C-12), 159.7 (C, C-14); HRMS (ESI⁺): Found: 264.0985; C₁₃H₁₃NNaO₂ (MNa⁺) Requires 264.0995 (3.8 ppm error), Found: 242.1168; C₁₅H₁₄NO₂ (MH⁺) Requires 242.1176 (3.2 ppm error).

Lab notebook reference: MJJ3/74
9-(4-Methoxyphenyl)-1-azaspiro[4.4]nona-1,3,8-trien-7-one (280a)

To a solution of ynone 231a (23.9 mg, 0.100 mmol) in CH$_2$Cl$_2$ (1 mL) was added AgNO$_3$ (1.7 mg, 10.0 µmol), the mixture was stirred for 1 h at RT. The crude material was then purified by column chromatography (EtOAc) to afford the title compound 280a as a pale brown oil (23.8 mg, 99%); $\nu$$_{max}$ (cm$^{-1}$) 3337, 2198, 1655, 1597, 1508, 1253, 1089, 1023, 839, 798, 739; $\delta$$_H$ (400 MHz, CDCl$_3$) 2.65 (1H, d, $J$ = 18.0 Hz, H-5a), 2.72 (1H, d, $J$ = 18.0 Hz, H-5a), 3.81 (3H, s, H-13), 6.55 (1H, s, H-7), 6.77–6.81 (3H, m, H-2/3,11), 7.05–7.09 (2H, m, H-10), 7.65 (1H, d, $J$ = 5.0 Hz, H-2/3), 8.66 (1H, s, H-1); $\delta$$_C$ (100 MHz, CDCl$_3$) 40.8 (CH$_2$, C-5), 55.4 (CH$_3$, C-13), 89.0 (C, C-4), 114.5 (2CH, C-11), 124.4 (C, C-9), 128.4 (CH, C-2/3), 128.6 (2CH, C-10), 130.3 (CH, C-7), 159.4 (CH, C-2/3), 162.4 (C, C-12), 168.9 (C, C-8), 172.3 (CH, C-1), 201.1 (C, C-6); HRMS (ESI$^+$): Found: 262.0841; C$_{15}$H$_{13}$NNaO$_2$ (MNa$^+$) Requires 262.0838 (0.9 ppm error), Found: 240.1024; C$_{15}$H$_{14}$NO$_2$ (MH$^+$) Requires 240.1019 (~1.8 ppm error).

Lab notebook reference: WPU

4-(4-Methoxyphenyl)-1H-indole (281a)

Synthesised using general procedure 2L with alcohol 279a (47 mg, 0.195 mmol), AgNO$_3$ (3.3 mg, 19.5 µmol) and CH$_2$Cl$_2$ (2 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the title compound 281a (36 mg, 83%) as a colourless oil; $\nu$$_{max}$ (cm$^{-1}$) 3412, 1608, 1518, 1492, 1244, 1178, 1031, 836, 753; $\delta$$_H$ (400 MHz, CDCl$_3$) 3.91 (3H, s, H-14), 6.76 (1H, br s, H-2), 7.04–7.10 (2H, H-12), 7.21 (1H, d, $J$ = 7.5 Hz, H-6), 7.25 (1H, dd, $J$ = 3.0, 3.0 Hz, H-3), 7.30 (1H, dd, $J$ = 8.0, 7.5 Hz, H-7), 7.38 (1H, d, $J$ = 8.0 Hz, H-8), 7.66–7.73 (2H, m, H-11), 8.23 (1H, br s, H-4); $\delta$$_C$ (100 MHz, CDCl$_3$) 55.3 (CH$_3$, C-14), 102.1 (CH, C-2), 109.7 (CH, C-8), 113.9 (2CH, C-12), 119.4 (CH, C-6), 122.3 (CH, C-7), 124.3 (CH, C-
3), 126.0 (C, C-1), 129.7 (2CH, C-11), 133.8 (C, C-5/9/10), 134.1 (C, C-5/9/10), 136.2 (C, C-5/9/10), 158.7 (C, C-13); HRMS (ESI\(^*\)): Found: 246.0881; \(\text{C}_{15}\text{H}_{13}\text{NNaO (MNa\(^+\))}\) Requires 246.0889 (3.3 ppm error).

Lab notebook reference: MJJ3/80

Spectroscopic data matched those reported in the literature.\(^{161}\)

1-(3,4-Dihydro-2H-pyrrol-5-yl)-4-phenylbut-3-yn-2-one (283a)

![Diagram of 283a]

Synthesised using **general procedure 4A** with DIPA (0.31 mL, 2.23 mmol), \(n\)-BuLi (0.89 mL, 2.23 mmol, 2.5 M in hexanes), 2-methyl-1-pyrroline (0.10 mL, 1.06 mmol), methyl phenylpropionate (0.16 mL, 1.11 mmol) and THF (15 mL). Purification by column chromatography (60:40 EtOAc in hexane) afforded the **title compound 283a** (172 mg, 76%, >99:1 *enamine:imine*) as a pale yellow solid, mp 98–100 °C; \(v_{\text{max}}\) (cm\(^{-1}\)) 1593, 1532, 1507, 1295, 1270, 1134, 759, 691; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 2.03 (2H, tt, \(J = 7.5, 7.0\) Hz, H-3), 2.68 (2H, t, \(J = 7.5\) Hz, H-4), 3.65 (2H, t, \(J = 7.0\) Hz, H-2), 5.44 (1H, s, H-6), 7.30–7.39 (3H, m, H-12,13), 7.51–7.56 (2H, m, H-11), 10.03 (1H, br s, H-1); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 21.1 (CH\(_2\), C-3), 32.5 (CH\(_2\), C-4), 48.0 (CH\(_2\), C-2), 85.6 (C, C-8), 89.9 (C, C-9), 93.5 (CH, C-6), 121.7 (C, C-10), 128.3 (2CH, C-12), 129.2 (CH, C-13), 132.4 (2CH, C-11), 169.2 (C, C-5), 172.5 (C, C-7); HRMS (ESI\(^*\)): Found: 212.1067; \(\text{C}_{14}\text{H}_{12}\text{NO (MH\(^+\))}\) Requires 212.1070 (−1.4 ppm error).

Lab notebook reference: MJJ9/33

5-Phenyl-2,3-dihydroindolizin-7(1H)-one (284a)

![Diagram of 284a]

Synthesised using **general procedure 4B** with pyrroline-ynone 283a (21 mg, 0.1 mmol), AgNO\(_3\) (0.33 mg, 2.0 \(\mu\)mol) in DCE (0.5 mL) and EtOH (0.5 mL) at 80 °C for 3 h. Purification by column chromatography (20 → 30% MeOH in EtOAc) afforded the **title
compound 284a (21 mg, 100%) as a white solid, mp 97–99 °C; \( \nu_{\text{max}} \) (cm\(^{-1}\)) 1629, 1536; \( \delta_H \) (400 MHz, CDCl\(_3\)) 2.17 (2H, tt, \( J = 7.5, 7.0 \) Hz, H-3), 3.07 (2H, td, \( J = 7.5, 1.0 \) Hz, H-4), 3.89 (2H, t, \( J = 7.0 \) Hz, H-2), 6.31 (1H, d, \( J = 3.0 \) Hz, H-8), 6.34–6.36 (1H, m, H-6), 7.35–7.40 (2H, ArH), 7.44–7.48 (3H, ArH); \( \delta_C \) (100 MHz, CDCl\(_3\)) 22.2 (CH\(_2\), C-3), 31.0 (CH\(_2\), C-4), 52.7 (CH\(_2\), C-2), 112.5 (CH, C-8), 118.2 (CH, C-6), 128.1 (2CH, C-11/12), 128.8 (2CH, C-11/12), 129.6 (CH, C-13), 134.3 (C, C-10), 149.0 (C, C-5/9), 153.6 (C, C-5/9), 179.8 (C, C-7); HRMS (ESI\(^+\)): Found: 212.1074; C\(_{14}\)H\(_{14}\)NO (MH\(^+\)) Requires 212.1070 (1.8 ppm error).

Lab notebook reference: MJJ9/34
Appendices

Appendix I. Synthesis of Spirocyclic Indolenines

Organic Chemistry

Synthesis of Spirocyclic Indolenines

Michael J. James, Peter O’Brien, Richard J. K. Taylor, and William P. Unsworth
Abstract: This Review provides an in-depth account of the synthesis of spirocyclic indolines. Over the last 77 years, a wide array of diverse synthetic methods has been developed in order to generate these synthetically useful and biologically important spirocyclic scaffolds. The main synthetic strategies discussed are grouped into three main categories, namely interrupted Fischer indolisations, deaeromatization reactions of indoles and condensation reactions. The historical background, common synthetic challenges, current state-of-the-art and future perspectives of this field are examined.

1. Introduction

The importance of nitrogen heterocycles in medicinal chemistry is demonstrated by their presence in a significant proportion of FDA approved pharmaceuticals. Rigid, three-dimensional molecular scaffolds have also attracted significant attention in drug discovery research in recent years; this interest is driven by a desire to examine under-explored regions of three-dimensional chemical space, as part of the search for new lead compounds, with spirocyclic compounds occupying a prominent position in this area. Spiroacyclic indolines (sometimes referred to as spiroindolene or spirocyclic 3H-indoles), compounds which fall into both of these categories, are therefore important; the spiroacyclic indoline motif has significant therapeutic potential in its own right, exemplified by its presence in a range of biologically active natural products (1–6). Figure 1) while their versatile reactivity also enables them to act as precursors for other privileged heterocycles. Including indoles, oxindoles, carbazoles, indoles, and others (Figure 2).

Considering this, an in-depth account of the various strategies used for the direct synthesis of spirocyclic indolines is timely and is likely to be useful to both synthetic and medicinal chemists.

A wide array of synthetic procedures for the synthesis of spirocyclic indolines have been reported over the last 77 years, the majority of which can be grouped into three main categories: 1) interrupted Fischer indolisations (12–13), Scheme 1), 2) deaeromatization reactions of indoles (14–15), and 3) condensation reactions (16–17). Each of these reaction classes is described in turn, with an additional section dealing with miscellaneous reactions. This review is focused on synthetic methods for the direct synthesis of spirocyclic indolines, involving at least one C–C or C–heteroatom bond that is integral to the spirocyclic indoline framework. Less direct methods based on the manipulation of preformed frameworks (e.g., redox reactions, isomerisation reactions of pre-formed spirocyclic scaffolds) or cyclisations of 3,3'-disubstituted

Figure 1. Spiroacyclic indoline natural products.

Figure 2. Spiroacyclic indolines as precursors for other heterocyclic scaffolds.

Scheme 1. Spiroacyclic indoline synthetic strategies.

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indolenines are not covered here.\textsuperscript{81–83} Likewise, the synthesis of related spirocyclic compounds at the oxindole oxidation level, including oxindoles, imidates and thionimidates are not covered, and have been reviewed previously elsewhere.\textsuperscript{84–86}

The methods described herein span eight decades and, unsurprisingly, significant progress has been made over this time. From the earliest reported procedures (which typically involved the use of strong acidic acids at high temperatures) much milder methods evolved, including asymmetric variants, many of which rely on powerful modern organometallic methods. The aim of this review is to give a balanced account of classical methods for spirocyclic indoline synthesis and their historical context, as well as the current state-of-the-art (covering the literature until August 2015). Applications of these methods in complex natural product synthesis are also described (highlighting the effectiveness of many of the synthetic processes, as well as the interest in the products themselves) and perspectives on the future of the field are offered.

2. Synthetic Challenges

Before focusing on each synthetic strategy in detail, it is useful to consider some of the challenges peculiar to the 3,3-disubstituted indolene motif (Scheme 2). First, this framework is known for its propensity to undergo 1,2-migrations under acidic conditions;\textsuperscript{87–90} this is driven by the formation of an aromatic indole product, which is typically a thermodynamically favourable process. Second, as is common with other imines, 3,3-disubstituted indolenines are known to exist as an equilibrium between the imine and the imine trimmer form (22–23). This equilibrium may not always affect their subsequent reactivity (as the trimmer 23 can usually collapse to the imine 22 in situ), but may serve to impede both their isolation and correct identification, as their analytical data is significantly complicated (note that this phenomenon is generally not observed with indolenines bearing a substituent at the 2-position).\textsuperscript{82–83} Under acidic conditions this equilibrium can be altered to favour the (protonated) imine but this is often not an ideal solution, partly due to the tendency of acids to promote the aforementioned 1,2-migration.\textsuperscript{89} In addition to these factors, the usual stereo, stereoelectronic and stereochemical issues concerning the generation of quaternary carbon centers must also be taken into account. An appreciation of all of these factors is important when designing new synthetic procedures to generate spirocyclic indolenines.

3. Interrupted Fischer Indolinations

The interrupted Fischer indolination constitutes, to the best of our knowledge, the oldest reported synthesis of a spirocyclic indolene. One of the challenges associated with this approach is preventing the acid catalysed 1,2-migration described above (Scheme 2). The first example of this strategy, reported by Hughes and Lons in 1938, concerned the synthesis of various simple cyclohexyl spirocyclic indolenes 25, by heating hydrazones 24 in acetic acid at reflux; no yields were quoted, but this pioneering work is notable for propagating

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Peter O’Brien carried out undergraduate and postgraduate studies at the University of Cambridge under the supervision of Dr. Stuart Warren. In 1995, he moved to York as a Royal Commission for the Exhibition of 1851 Research Fellow and was appointed as a lecturer at York in 1996. He was promoted to a Personal Chair (2005) and has been an Associate Editor for Tetrahedron since 1999. His research focuses on asymmetric synthesis of nitrogen heterocycles using organocatalysts reagents and the exploration of 3D pharmaceutical space.

Richard J.K. Taylor obtained his B.Sc. and Ph.D. from the University of Sheffield. Postdoctoral periods were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to the Chair of Organic Chemistry at the University of York. His research interests centre on the synthesis of bioactive natural products and the development of new synthetic methodology. He is a past President of the International Society of Heterocyclic Chemistry and the RSC Organic Division and the current UK Editor of Tetrahedron.
Appendices

Scheme 2. General synthetic challenges associated with spirocyclic indoleamine synthesis.

Further synthetic investigations by several other research groups (Scheme 3) have also explored the synthesis of cyclopropyl spirocyclic indoleamines 27 under the same conditions. A common feature of the early work of both Hughes/Lions and Withkoop/Patricks is the incorporation of a substituent on the indole 2-position; presumably, this suppresses unwanted 1,2-migrations, serving to block the completion of the full Fischer indole reaction sequence. Next, Jones and Stevens reported one of the first examples of this strategy in the synthesis of a spirocyclic indoleamine 29 without a substituent on the indole 2-position. This was achieved using Lewis acid catalysis, as opposed to the previously used transtio acid catalysis, but the efficacy of this procedure cannot be judged as no yields were reported. Later, Rodriguez and co-workers investigated the synthesis of a range of other cyclopropyl spirocyclic indolines 31 from the corresponding hydrazone 30. Through skilful optimisation of the reaction parameters (concentration, solvent, acid, temperature, time), the competing 1,2-migration (to form fused ring system 32) could be inhibited to deliver the desired spirocyclic 31 in modest to excellent yield. More recently, Rodriguez, Garcia-Mera and co-workers expanded upon these works with welcome additions to the substrate scope.

The incorporation of heterocyclic frameworks into interruptted Fischer indolisation reactions has been well used in drug discovery research. The first reaction of this type was reported by Lyle and Skarlos, who synthesised spirocyclic pipericline 35 in excellent yield, with the reaction promoted by either acetic acid or ZnCl₂ (Scheme 4). Other early work into the synthesis of similar spirocyclic pipericlines was carried out by Wang, who synthesised benzoxepine fused 37 as a precursor towards a fused indole-azepine motif. More recently, Fan and co-workers reported a select range of heterocyclic spirocyclic indolines 39, under the typical acid-catalysed conditions. The vast majority of heterocyclic spirocyclic indolines synthesised in this manner are frequently not isolated, but are reduced in situ to afford more stable indoline derivatives 41. As a testament to the popularity of this strategy to generate medicinally interesting products, several academic and industrial groups have published or filed patents in this area.}

Another interesting example of a heterocyclic Fischer indolisation spirocyclisation was reported by Dohanec and co-workers (Scheme 5). Here, rather than using an acid to promote the reaction, hydrazone 42 was instead treated with Meerwein’s salt; this was proposed to form an imidate, which following isomerisation underwent the desired interrupted Fischer indolisation, affording the unusual spirocyclic product 43 in 13% yield.

The interrupted Fischer indolisation strategy has also featured prominently in a range of natural product or target synthesis. Controlling the regiochemical outcome is a challenge in more complex examples such as these, where two isomeric products can be produced, depending on which of the two regiosomers forms prior to the 3,3-sigmatropic rearrangement step. For such processes to proceed selectively, there should be an energetic bias for the preferential formation of one of these regiosomers, with an illustrative example of this being found in Stork and Dolfini’s total synthesis of aspidospermidine (Scheme 6). This report, which utilised standard acetic acid catalysed conditions, only one of the two possible Fischer indolisation products was isolated; presumably the selectivity is controlled by the reaction proceeding via the more stabilised tetrasubstituted amine 46 rather than 45. Stork and Dolfini did not report an isolated product.
yield for this process, but its efficacy and selectivity has been demonstrated by others since[186-188] for example, Zand and co-workers reported the formation of 48 in 62% yield using this procedure.[189]

In another synthesis of a fused ring system, Bid and co-workers (who were inspired by the earlier work of Georgi) described the formation of compounds 50 and 51 to evaluate their biological properties (Scheme 7). Similarly, Lazarine, Levy and co-workers described the synthesis of spirocycles 53 in order to explore their use as alternatives to morphine, with both reaction systems performed by heating the requisite ketone and hydrazine derivatives in refluxing acetic acid. Fu-
Finally, the interrupted Fischer indolisation method has been employed in the development of light- and ion-responsive dual-mode signal transducers by Inouye and co-workers.\textsuperscript{235} Spirocrown ether \textsuperscript{70} was synthesised in good yield from ketone \textsuperscript{69} using Zn(II) as the catalyst (Scheme 9).

4. Indole Dearomatisations

Probably the most popular method to access spirocyclic indole
olines today is through the dearomatisation of an indole precursor.\textsuperscript{236} Dearomatisation reactions offer an attractive and powerful method to create complex 3D structures from simple aromatic starting materials, furnishing synthetically challenging quaternary stereogenic centres with relative ease.\textsuperscript{236,237} The following section details many such processes, and is organised into sections based on the nature of the electrophilic component in the reaction.

4.1 Addition to iminium ions

This class of reaction may be thought of as an interrupted Pictet-Spengler reaction, given that spirocyclic indolone intermediates (e.g., \textsuperscript{73}) are known intermediates in these pro-
cesses (Scheme 10). In a traditional Pictet–Spengler reaction, the desired tetrahydro-β-carboline product 75 is formed in situ from this spirocyclic intermediate, either via a 1,2-migration-elimination sequence (73 — 74 — 75) or regeneration of the iminium intermediate 72 followed by direct C-2 attack (72 — 74 — 75). Thus, the challenge in the context of spirocyclic indolene synthesis is to design a process in which the initial spirocyclisation step (72 — 73) proceeds, but then no further reaction takes place.

This strategy was first demonstrated in the pioneering work of Woodward and co-workers in their seminal total synthesis of strychnine (Scheme 11).

![Scheme 10: Overview of Pictet–Spengler mechanistic possibilities.](image)


![Scheme 12: Activated amine induced spirocyclisation (Sandler et al.)](image)

A similar strategy was devised by Sandler and co-workers, who implemented the reaction of pentafluoropropionic anhydride (PFPA) and amine 82, presumably to form a reactive imidate or N-acylimidate ion poised to undergo an addition–decomposition sequence (Scheme 12). Precise yields for 83 were not reported, but selected examples are nominally referred to as being near quantitative. However, the authors stress the need to minimise the reaction time and to maintain low temperature, in order to avoid decomposition and suspected polyamidation.

Another method to access reactive iminium ion species for spirocyclic indolene synthesis is by an in situ amine-aldoldehyde condensation. This approach was first described by Kuehne and co-workers, who treated indole 84 and aldehyde 83 with BF₃·OEt₂ to furnish the impressive tetracyclic framework 86 in good yield, as a 1:1 mixture of two diastereoisomers. The reaction is proposed to proceed through sequential condensation to form an imine, conjugate addition (from the enol form of the malonate moiety) and spirocyclisation by nucleophilic attack of the indole C-3 position into the resultant imine. The first enantioselective variant of this intermolecular strategy was reported by Wu, Cao, Zhao and co-workers (Scheme 13). The Jørgensen–Hayashi catalyst [B] was used to promote a condensation–spirocyclisation sequence between α,β-unsaturated aldehydes 88 and β-ketoamido-indoles 87 to form spirocycles 90. In excellent yield and with high enantioselectivity.

Fukuyama and co-workers demonstrated an elegant intramolecular variant of an in situ aldehyde condensation–spirocyclisation sequence. TFA was used to catalyse both the imine formation and the Boc cleavage, with the removal of the Boc group, thus increasing the nucleophlicity of the indole C-3 position and promoting spirocyclisation. This resulted in the formation of the impressive pentacyclic framework 92 in...
excellent yield, which was subsequently used as a precursor in the total synthesis of (-)-aplysiaphyline (Scheme 14).

The strategy of converting a larger ring system into a polycyclic scaffold through transannular spirocyclisation has also been adopted by others, using alternative methods to generate the electrophilic iminium intermediate (Scheme 15). For example, Langlois and co-workers used the Jones oxidation of hydroxylamine 93,278 this process is proposed to proceed through chemoselective oxidation α- to the nitrogen to form the requisite iminium species, which promptly undergoes spirocyclisation to form the hexacyclic framework 94 in impressive yield. In another example, van Vranken and co-workers treated citrytophan 95 with TFA to form a reactive N-acyl iminium species 99 that either undergoes spirocyclisation or N-alkylation, depending on which diastereomer is used.271 This overall transformation formed the ring-fused indolene 96 in 56% yield.

Finally, the most recent example of spirocyclic indolene synthesis by iminium ion trapping was reported by Xu, Sun and co-workers, who described an intriguing intramolecular spirocyclisation reaction between a range of indoles 101 and amino-benzaldehyde derivatives 100 (Scheme 16).274 It is proposed that following an initial condensation between the indole and substituted benzaldehyde, a 1,5-hydride shift generates a reactive iminium ion, which undergoes the typical indole addition to generate the spirocyclic. These operationally simple reaction conditions afforded a broad range of spirocycles 102 in good yield and moderate diastereoselectivity. A simple diisopropyl ether trituration to enhance the diastereoselectivities to >20:1 was also described.

4.2 Allylations

Spiroyclic indolene frameworks can also be accessed by a deoxymethyl spirocyclisation involving an alkylation process (Scheme 17). One of the earliest such examples was reported by Closson and co-workers, who revealed that the treatment of tryptophyl tosylate 103 with potassium tert-butoxide afforded spirocyclic cyclopropane 106.271 This process was later reported with more detailed description by Rapport, where an analogous tryptophyl bromide underwent intramolecular alkylation in the presence of potassium carbonate in refluxing acetonitrile.270 Homologues of this reaction class to afford spirocyclic cyclopropane and cyanoethyl systems were first reported by Jackson and co-workers,274 using potassium tert-butoxide to promote the intramolecular alkylation of tosylates 107. The formation of side-products arising from competing 1,2-migration reactions (see section 2 of Scheme 2) were also described, leading to a reduction in the yield of the spirocyclic products during these processes. More recently, Zheng, You and co-workers prepared phenyl substituted spirocyclo 110 in modest yield for use in mechanistic studies, by treating benzyl bromide derivative 109 with sodium hydride.271 An intriguing example
of intramolecular $S_{N}^{2}$ alkylation followed by a $[3,3]$-sigmatropic rearrangement was demonstrated by Shta and co-workers.\textsuperscript{76} It was found that a wide variety of substrates 111 undergo this reaction to afford spirocyclic cyclopentenyl indolines 112 in good to excellent yields. However, the substituent on the 2-position is limited to aromatic groups in this procedure, as a competing $[3,3]$-sigmatropic rearrangement sequence took place preferentially in the other substrates tested. In a similar fashion, Nakazaki, Kobayashi and co-workers reported a single example of a presumed $S_{N}^{2}$ alkylation as a side product during their synthesis of spirocyclic oxindoles,\textsuperscript{77} during which the reaction of the allylic alcohol 114 with elemental iodine afforded spirocycle 115 in 30\% yield.

The robustness of the alkylation strategy is highlighted by the fact that many of the examples in this class of reaction are found in natural product studies. The majority of these reactions proceed via a base-mediated halide or pseudo-halide displacement. One of the earliest examples was reported by Huffman, Iago and Kamya in their synthesis of desethyllobogamine,\textsuperscript{78} treatment of tosylate 116 with potassium tert-butoxide furnished spirocycle 117 in low yield (Scheme 18). Sakai and co-workers also demonstrated a similar transformation in their configurational studies of loxamicine 118 via a two-step mesylation-alkylation sequence, forming the intriguing ring system 119 in good yield.\textsuperscript{79} Rubirola and co-workers demonstrated the utility of chilamine indole derivatives in the synthesis of spirodimerine; the final precursor was accessed by an in situ tosylation-alkylation of 120 to furnish the skeleton of spirodimerine 121.\textsuperscript{80} This strategy to access the Aspidosperma alkaloid framework was also used by Kim and co-workers using a pendant alkyl chloride 122 in the presence of potassium tert-butoxide to afford the spirocyclic indolenine 123 in excellent yield.\textsuperscript{81,82}

Spirocycle formation was also reported by Manzi and co-workers, as side-products 126, during a study directed towards the formation of azetidiones 125 (Scheme 19).\textsuperscript{83} Later, Smith and co-workers utilised the phosphene base BTPP to promote the mesylate displacement of 127, to furnish spirocyclic scaffold 128, an advanced precursor of (+)-scholarine A.\textsuperscript{84} Next, Fucigna and co-workers reported the impressive alkylation of bromoacetamide 129 with cesium carbonate to form the choline-C skeleton 130 in excellent yield.\textsuperscript{85} Finally, Bach and co-workers reported two procedures to convert alcohol 131 into spirocycle 132 in good isolated yields, either using tosyl or mesyl chloride, followed by treatment with potassium tert-butoxide.\textsuperscript{86}
In a similar fashion, both Martin and Andrade described an adaptation of an intriguing one-pot N-desulfonylation/O-sulfonylation protocol originally reported by Bosch, Rubinova and co-workers. Martin and co-workers first used this protocol to furnish pentacycle 134, a key intermediate towards the synthesis of (+)-pseudobemisone, and Andrade and co-workers later used the same method in their synthesis of the Apoikiosperma alkaloid precursor 136 (Scheme 20).

Another popular alkylation strategy is the use of Ag salts to promote the mild alkylation through the activation of pendant alkyl halides (Scheme 21). Heathcock and co-workers detailed this reaction type in their synthesis of apoiokiospersamide; a Finkelstein reaction of chloroacetamide 137 and subsequent treatment with AgOTf afforded the desired indolizine 138 in excellent yield. Andrade and co-workers used a similar strategy to diastereomeric bromoacetamide derivative 139, which upon treatment with AgOTf and a weak base underwent a facile spirocyclisation to afford indolizine 140 in excellent yield. This indolizine was then used in a novel intramolecular aza-Baylis-Hillman reaction to furnish the tetra cyclic natural product framework 141. Inspired by this approach, Xiao and co-workers implemented this strategy in their synthesis of (+)-biphylindine, utilising a similar telescoped spirocyclisation-aza-Baylis-Hillman reaction sequence to afford the pentacyclic skeleton 144 (a precursor to (+)-biphylindine) in excellent yield. Banwell and co-workers also used a AgOTf promoted alkylation of 145 in their total synthesis of (+)-limazospermidine...
4.3 Addition to α-allyl intermediates

Some of the most impressive routes to spirocyclic indolines proceed by nucleophilic addition reactions involving electrophilic α-allyl intermediates, which are usually derived from allylic acetates or carbonates (Scheme 23). Sakal and co-workers reported the first example of this class of reaction in their biosynthetic studies of koimine; it was proposed that the treatment of an allylic carbonate (159) with palladium(II) acetate and triphenylphosphine formed the reactive α-allyl species, which followed attack from the indole C-3 position, furnishing spirocyclic indoline 160 in modest yield. Next, You and co-workers expanded this strategy, utilising allylic carbonate 161 and [Ni(COD)Cl] with chiral phosphoramidite ligand 162 to furnish an array of spirocyclic indolines 163 in excellent yield and also with high enantioselectivity and diastereoselectivity.[209] Later, this group utilised the same iridium catalyst with phosphoramidite ligand 165 and shorter malonate derivatives 164 to afford a range of indolines 168, again in excellent yield and with high enantioselectivity and diastereoselectivity. It should be noted that while several spirocyclic indolines were generated as part of this work, only one indolene 166 was isolated as a discrete product; in general, the spirocyclic indolene intermediates 166 were immediately converted into the respective indolines 168 or tert-butyloctanes 167 (via an acid-mediated 1,2-migration) and isolated at this stage. The conversion of indolene products into more stable compounds prior to isolation in this way is relatively common, and in many cases this is likely to be connected to the stability and characterisation difficulties of the imine highlighted in section 2. The same group also described a related rhenium-catalysed approach using rhenium complex 170, again based on the activation of allylic carbonates 169, to generate a much wider range of products (171) than those formed using the previously reported iridium-based catalyst systems.[210]


Reactive α-allyl intermediates can also be generated from propargyl carbonates 172, as first demonstrated by Hermada and co-workers as an extension of their phenol deoxygenation precatalyst methodology (Scheme 24).[216] This reaction is proposed to proceed by the formation of a η2-α-allyl-palladium complex 178, which following nucleophilic attack from the indole C-3 position and a protonation-elimination.
sequence, furnishes spirocyclic indolines 173 in good to moderate yield. Similarly, Fujii, Ohno and co-workers adopted a similar strategy with propargyl chlorides 174, to synthesise the tetracyclic framework 176 by an in situ nucleophilic substitution with a primary amine. Furthermore, although they were not the desired targets in this study, they also reported the isolation of numerous spirocyclic indolines 175 as side-products, some being formed in good yield.

A similar strategy which was developed around the same time by the You and Rawal groups, is the use of propargyl carbonates in intermolecular reactions; these reactions are proposed to proceed first by the interception of a typical 2-allyl-1,3-dipolar cycloaddition species with a nucleophile tethered onto the indole, before undergoing a protonation/cycloisomerisation sequence to form the spirocyclic indoline products (Scheme 25). The contribution by You and co-workers concerns the reaction of malonates 182 with methyl propargyl carbonate, [Pd(dba)2] and an appropriate phosphine ligand, to afford spirocyclic indolines 183 in moderate to excellent yield, with preliminary results suggesting that an asymmetrical variant is possible using (R)-oxophos or related derivatives. Meanwhile, Rawal and co-workers reported the reaction of a variety of indole-tethered pro-nucleophiles, [Pd(dba)2] and xanthates, and in some cases a base, to furnish an impressive variety of spirocyclic indolines 185/186, generally in good yield. Recently, Rawal and co-workers also described an asymmetric adaptation of this reaction, where in a similar fashion to You and co-workers, chiral phosphine ligands (188) were used to furnish the indolines 189 in good to excellent yield and with high enantiomeric excess.

Finally, Liu and co-workers described an intriguing spirocyclisation methodology using a chiral palladium complex with vinyl cyclopropane 194, a reactive 1,3-dipole is formed in situ, which then undergoes a formal [3+2]-cycloaddition with the [2+2]unsaturated indolene (afforded by the extrusion of phenyl sulfonic acid from sulfone 193 to furnish the spirocycles 196. A range of substrates were well tolerated, generating spirocyclic indolines as single diastereoisomers, typically in good yield and with excellent enantioselectivity (Scheme 26).
4.4 Addition to alkenes, alkynes and allenes

To the best of our knowledge, the only examples of spirocyclic indolene synthesis by the electrophilic activation of a simple allene were reported recently by Tang, Shi and co-workers\(^{197}\) using AgOTf to activate the strained indolycyclopropane 197, promoting spirocyclisation and the formation of indolenines 198, generally in good yields (Scheme 27). A single example of allene activation for spirocyclic indolene synthesis was also reported by Bandini and co-workers; who used Au\(^{+}\) catalysis with allenamide 199 to afford the vinyl spirocycle 200 in excellent yield and with good diastereoselectivity.

In recent years, the electrophilic activation of allenes has received considerable interest in the synthetic community\(^{102,110}\) and accordingly the majority of the examples in this reaction class are based on allene activation. These cyclisations typically proceed by activation of the allene by a \(\alpha\)-acidic catalyst, followed by nucleophilic attack of the indole through its C-3 position. The first example of this reaction type was reported by Van der Eycken and co-workers, who isolated spirocyclic

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\text{Scheme 24. Intramolecular addition to \(\alpha, \beta\)-unsaturated intermediates generated from spirocyclic systems (Homada et al.\(^{110}\), Fuji, Ohno et al.\(^{115}\)).}
\]

\[
\text{Scheme 25. Intermolecular addition to \(\alpha, \beta\)-unsaturated intermediates generated from propargyl pyridine systems (Yua et al.\(^{206}\), Rawal et al.\(^{190}\)).}
\]

\[
\text{Scheme 26. Intermolecular addition to \(\alpha, \beta\)-unsaturated intermediates generated from a vinyl cyclopropane system (Liu et al.\(^{209}\)).}
\]
only a 1:1 mixture of the desired indole 203 and spirocyclic 202 (which is likely an intermediate en route to 203). Similarly, Carbery and co-workers reported an example of spirocycloisolation of indole 204 in their mechanistic studies of a Au catalyzed synthesis of the fused indole framework 206. As in the Van der Eycken study, the spirocyclic 205 was a side-product in this reaction, with the major fused indole products presumably being formed via a 1,2-migration of spirocyclic 205. Next, Toste and co-workers reported a single example of a Pd catalyzed spirocycloisolation in their studies towards the synthesis of the kopsolone. Submission of alkyne 207 to the asymmetric Pd conditions furnished the spirocyclic 208 in moderate yield and good enantioselectivity. Interestingly, the authors noted an improved reaction profile under acidic conditions. Next, Enders and co-workers reported an intermolecular variant, combining both conjugate addition and alkyne activation with 209 and 210 to form a single example of spirocyclic indolenines 212 as a mechanistic probe.

In a study that directly targeted spirocyclic products (rather than their ring-annulated analogues) our own group reported the first high yielding examples of this reaction class, using catalytic AgOTf in DCM at RT to activate yrones 213 to form spirocyclic indolenines 215. This work was well informed by the approach of Carbery and co-workers, who showed that indolepyrones 204 spirocylized under a-acidic conditions, but it was found that the use of AgOTf rather than a Au catalyst meant that 1,2-migration was completely avoided (Scheme 29). An asymmetric variant of this reaction was also described, achieving moderate to good enantioselectivity using silver chlorophosphoric acid salt Ag-214 as the catalyst, in place of AgOTf. Furthermore, in a recent report expanding upon this work, it has been demonstrated that the analogous propargyl alcohol substrates 216 also undergo spirocycloslation effectively, forming indolenines 217 in high yields. Interestingly, subtle changes to the reaction conditions allowed carbazoles 218 to also be formed efficiently from the same precursors, further highlighting the facility of 1,2-migration reactions in this product class and the often delicate balance that exists between the formation of spirocyclic indolenines and other rearrangement products. Finally, in another recent report, Wang and co-workers describe an impressive Au catalyzed approach to form tetracyclic spirocycles 220. In this process the authors noted a key difference in chemoselectivity between C-N and C-C cyclization by protecting the indole N-H with a silyl group (TBs). This method was used to form a wide range of spirocyclic indolenines 220 (with promising biological activity vs. MIRSA) in good to excellent yield.

4.5 Oxidative couplings and radical cyclisations

Another prominent strategy to generate spirocyclic indolenines is the use of oxidative couplings and related radical cyclisation processes (Scheme 30). Ma and co-workers pioneered the oxidative coupling approach for spirocyclic indoline synthesis in their total synthesis of (−)-communein F. This approach, along with other related processes (initiated by Itami and co-
complex scaffold 231 in good yield. Finally, one of the most recent examples of the oxidative coupling approach to spirocyclic indolene synthesis was reported by Tang and co-workers in their total synthesis of spirobacillene B (one of two spirocyclopentenone natural products with unique spirocyclic scaffolds isolated in 2012). Employing the typical oxidative coupling conditions and a PPTS-MeOH quench they promoted tandem oxidative coupling, cleavage of the TBS protecting group, autooxidation and partial cleavage of the TBS protecting group to afford the spirocyclic indolenines 233 and 234 in a combined 37% yield.

An interesting example of a tributyltin hydride mediated spirocyclisation was reported by Miranda and co-workers (Scheme 32). In this process, dialkyl peroxide (DLP) is proposed to act as both a radical initiator and oxidant. The overall reaction is thought to proceed by a typical bromine atom abstraction from 235 by the tributyltin radical to form 236, followed by cyclisation onto the adjacent vinyl amide; the resultant α-nitrogen radical 239 is then thought to be oxidised by dialkyl peroxide to afford an N-acyliminium ion 240, which following attack from the indole C-3 position, affords the spirocyclic indolenines 236 and 237 as single diastereoisomers in modest yield. This reaction is of particular interest as related N-acyliminium trappings of this type afford only the C-2 ring annulated products, most likely via a 1,2-migration process.

Inspired by this approach, Higuchi and co-workers applied this methodology in their synthesis of the scholarianine A framework (Scheme 31). After screening a variety of oxidants, it was found that NIS could also be used in place of iodosylbenzoic acid to form...
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One of the most recent examples of a radical spirocyclisation was reported by Stevens and co-workers, who employed a CuCl-mediated atom transfer radical cyclisation (ATRC, Scheme 33) to a small selection of indoyl dichloracetamides 241. They were treated with CuCl and either TMEDA or PMDETA (N,N,N',N'-pentamethyldiethylenetriamine) to furnish the spirocyclic indolines 242, generally in excellent yield.

4.6 Conjugate additions

A lesser utilised strategy to access spirocyclic indolines is to harness the nucleophilicity of the indole moiety in a conjugate addition reaction. One of the earliest examples of this was demonstrated by Angle and co-workers in an attempt to account for the formation of spirocyclic indolines 247 in low yield (Scheme 34). This reaction presumably proceeds by N-acetylation followed by conjugate addition into the resultant acrylamide 248.

Later, Takeuchi and co-workers reported a curious conjugate addition of nitrobenzylamine 250 with a bis-indole species 252 formed upon the reaction of indole with TFA (Scheme 35). The overall yield for this process is modest, but it is nonetheless impressive, given the significant increase in complexity of the spirocyclic indolines 251 compared with the starting materials.

One of the first high-yielding examples of this strategy was demonstrated by Noland and Hammer (Scheme 36). Ag2O was used to oxidise electron-rich phenol 255 to the...
corresponding quinone methide, which following conjugate addition and another oxidation-rearrangement sequence (co-catalysed by silica gel) led to the formation of spirocyclic indolenine 257 in excellent yield. Later, Markó and co-workers described the silica gel catalysed intramolecular conjugate addition of indole 258 to afford the sensitive spirocyclic indolenone 259 in excellent yield. Finally, You and co-workers reported a similar transformation employing a racemic BINOL-derived phosphoric acid catalyst to promote the conjugate addition of 260 to furnish the spirocyclic indolenine 261 in modest yield.

4.7 Addition to electrophilic nitrogen

A small number of strategies to form spirocyclic indolenines by the direct reaction of indoles with electrophilic nitrogen species have also been reported. The first examples of this type were described by Narasaka and co-workers; the mesylation of oxime 261 was used to promote formal nucleophilic substitution at the oxime oxo nitrogen, affording spirocycles 262 in good to excellent yield (Scheme 37). In a similar fashion, Nishikawa, Isobe and co-workers treated O-nitrated hydroxamic acids 263 with LHMDS to afford the synthetically challenging spirocyclic β-lactam framework 264, found in the chartreline natural products. Finally, Kundu and co-workers reported an unusual SnCl2·2H2O-mediated reduction of nitro-indole 265 to afford a range of products consisting of spirocyclic indolenine 266 and side product 267 (which presumably forms from spirocycle 266 via a 1,2-migration reaction) in 10 and 35% yield, respectively, along with simple reduction product 268.

4.8 Addition to thio/oxo-carbenium ions

In a strategy pioneered by Bosch and co-workers, dibromoacetil 269 was treated with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) to generate a thionium ion, which is subsequently attacked by the nucleophilic indole to deliver the spirocyclic indolenine 270 in good yield (Scheme 38). This method was further adapted by Shibasaki and co-workers who found that by incorporating molecular sieves and increasing the reaction concentration they could access a similar framework in excellent yield. These conditions were also employed by Itano and co-workers to good effect in the synthesis of polycyclic framework 274. An alternative to the DMTSF-mediated conditions was demonstrated by Ogawara and co-workers, using a combination of AgNO3 and NCS in two stop protocol, which was originally developed by Nicolaou and co-workers for a related process. Finally, Hart and co-workers provided the sole example of an oxonium ion reacting to form a spirocyclic indolenine; the treatment of alcohol 277 with dimethoxyethane and ethylaluminium dicloride is presumed to generate a terminal oxonium ion, which is attacked by nucleophilic indole C-3 position to form indolenine 278 in good overall yield.

4.9 Harley-Mason rearrangements

Another approach to the spirocyclic indolenine framework was developed by Harley-Mason and co-workers, whereby indole
270 was heated in neat BF₃·OEt₂ to initiate a rearrangement sequence to afford the spirocyclic indolene 280 in good yield. Further work by Fujii and co-workers replicated this activity using high temperatures and either boron trifluoride etherate or triflic acid to synthesise the spirocyclic indolene 282 in modest to good yield. A more recent and elegant example of this reaction was demonstrated by Tsuchiya and co-workers who utilised a chiral acidic condition to promote a sequential one-pot Pictet–Spengler reaction and spirocyclisation to afford the spirocyclic indolene 282, which was further reduced in situ to afford (+)-spirospirodine 285 in an impressive overall yield.

Mechanistic conjecture for the rearrangement of 281 to 282 is detailed in a report by Heathcock and co-workers (Scheme 39, 286–287–288).

4.10 Addition to nitriles/isonitriles

Nucleophilic addition to nitriles has also been utilised in spirocyclic indolene synthesis, as first demonstrated by Kobayashi and co-workers. Treatment of nitriles 289 with hydrochloric acid led to the formation of spirocycles 290 in unreported yield. Sakai and co-workers further proved the efficacy of this strategy when they reported a single example of an

AgBF₄-mediated nucleophilic addition to a pendant nitrile 291, affording amidine 292 in 74% yield (Scheme 40). More recently, Feng and co-workers utilised an intriguing intermolecular Michael/Friedel–Crafts/Mannich cascade sequence between isonitrile 293 and alkylidene malonate 294. This process was catalysed by a combination of Mg(OiPr)₂ with ligand 295 to afford a variety of spirocyclic indolines 296 in excellent yield and with high diastereoselectivity and enantioselectivity.

4.11 Cross-coupling reactions

A powerful strategy first developed by You and co-workers is the Pd²⁺-catalysed deaminative arylation of indoles. This reaction is proposed to proceed by Pd²⁺ oxidative addition into an aryl bromide 297, followed by intramolecular carboligation on the indole 3-position and subsequent reductive elimination. Using this strategy, impressive...
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Hary-Mason et al.

Kobayashi et al.

Sakai et al.

Tromiska et al.

Feng et al.

You et al.

Wu, Gong et al.

Scheme 39.Spirocyclic indoline synthesis by Hary-Mason rearrangements [Hary-Mason et al. \(^{246,247}\), Fuji et al. \(^{249,250}\), Tromiska et al. \(^{258}\)].

Scheme 40. Spirocyclisation by addition to a nitro/isonitrile [Kobayashi et al. \(^{205}\), Sakai et al. \(^{244}\), Feng et al. \(^{247}\)].

4.12 Miscellaneous deaeromatisation reactions

Other deaeromatisation reactions which do not fit into a clearly defined theme are described in this section. One of the oldest examples of spirocyclic indoline synthesis was detailed in 1965 by Schumann and Schmidt, who used platinum oxide and an atmosphere of oxygen to generate (--)-subtuline 362 from indole precursors 301 in good yield (Scheme 42).\(^{164,165}\) This unusual procedure, which is presumed to proceed via the formation of an iminium ion, has since been employed by others to similar effect in related systems.\(^{168}\)

The generation of a spirocyclic indolene through an acylation reaction was first described by Szántay and co-workers (Scheme 43). The treatment of acid 303 with ethyl chloroformate is proposed to form a mixed anhydride, which following indole C3 addition furnished the spirocyclic indolene 304 in moderate yield. Later, Movassaghi and co-workers reported the near-quantitative formation of spirocyclic indolene 306 upon the treatment of carbamoyl chloride 305 with AgOTf at 70°C in acetonitrile.\textsuperscript{118}

The Curtius rearrangement has also been employed in spirocyclic indolene synthesis as demonstrated by Laronze and co-workers; the treatment of acid 307 with DPPA at 120°C affords the typical isocyanate intermediate, which is trapped in situ by the indole by attack through its 3-position, forming a small selection of indolenes 308 in modest to good yield (Scheme 44).

Cook and co-workers demonstrated spirocyclisation by addition to an aldehyde (Scheme 45). Utilising an indole C3 addition to a pendant aldehyde 309 and trapping the resultant alcohol with acetic anhydride afforded the spirocyclic indolene 310 in good yield.\textsuperscript{119}

An intriguing umpolung protocol to transform the usually nucleophilic indole into an electrophile for attack by a pendant amide was developed by Baran and co-workers (Scheme 46).\textsuperscript{120} This process was initiated by the thermal cleavage of the Boc protecting group of indole 311, followed by treatment with HIBS, which is proposed to form a highly reactive 3-bromo indolene 315, which can then react with the tethered amide under the basic reaction conditions to furnish the spirocyclic β-lactam 312 in excellent yield. This process was ultimately used to complete the total synthesis of chartreuse C skeleton.\textsuperscript{118}

In other synthetic studies geared towards the synthesis of the chartelle marine natural products, Nishikawa and co-workers reported the unexpected synthesis of spirocyclic indolene 318 (Scheme 47).\textsuperscript{121} This product was isolated during attempts to form a macrocyclic enamide, by the intramolecular condensation of the O-allylhydroxamate 317 with a tethered vinyl enol ether under acidic conditions. Further studies on this unexpected reaction suggested that this process is mediated by adventitious oxygen, suggesting that a radical mechanism operates. Evidence of a radical mechanism was further demonstrated, when the O-allylhydroxamate 317 was treated with AIBN in refluxing DMF to afford the spirocyclic 318 in improved yield.

Finally, Jiang, Zhou and co-workers recently reported that the combination of sulfone 319 and sulfur ylide 300 under basic conditions afforded a variety of spirocyclic indolenes 321 in good to excellent yield and with high diastereoselectivity (Scheme 48).\textsuperscript{122} The reaction presumably proceeds via the conjugate addition of a sulfur ylide into an unsaturated intermediate 322 (itself formed via the extrusion of tolyl sulfonic acid from sulfone 319) to access a reactive sulfonium species 324 which then quickly undergoes cyclopropanation to furnish the spirocyclic indolene 321.
Spinocyclo indoline synthesis can also be achieved by the intramolecular condensation of aniline derivatives with a suitable carbonyl species. All of the examples of this strategy demand the careful tweaking of either the nucleophilic amine or electrophilic carbonyl functionality. To achieve this, some ingenuity is needed, and typically this is accomplished by utilising a tandem process, usually involving the deprotection of an amine or a nitro reduction. However, another strategy, which was employed in pioneering work carried out by Overman and co-workers, utilises an electrophilic cationicaza-Cope rearrangement sequence to reveal the requisite ketone for condensation (Scheme 49). The first examples were performed by treating cyclopentenamides 325 with CSA to promote sequential iminium ion formation, aza-Cope rearrangement, enol addition to the resultant iminium ion and finally condensation with the pendant amine to furnish a small selection of spinocyclo indolines 326 in good to quantitative yield. The same group further demonstrated the power of this protocol by treating hemiaminal 327 under the same reaction conditions, which led to the formation of pentacycle 328 in quantitative yield. This framework was then used as a common intermediate to complete the total syntheses of (-)-deoxapodine, (-)-meloicine, (-)-epimeloaicine, and the formal synthesis of (-)-1-acetylaspidoalbulins. Finally, Overman and co-workers applied this reaction sequence in the synthesis of (±)-dehydrobifurfoline. Amide 329 was used to access the intermediate ketone 330, and subsequent hydrolysis of the amide group with KOH resulting in a condensation reaction to form the natural product (±)-dehydrobifurfoline 331 in excellent yield.

Another elegant multistep sequence was developed by Bonjoch, Bosch and co-workers in their synthesis of (±)-dehydrobifurfoline, the key tandem cross-coupling, nitro reduction and condensation sequence was realised by employing a Ni^II catalyst, furnishing the desired natural product 331 in good yield, considering the number of synthetic operations taking place (Scheme 50). Bonjoch, Bosch and co-workers also demonstrated the enone-nitro condensation reaction without the initial cross-coupling. This powerful methodology has also been used to complete the total synthesis of both (±)-kayamicine and (±)-norfluorocaine.

Finally, another multistep one-pot procedure was reported by Zhu and co-workers who utilised their KORC (integrated oxidation/reduction/cyclisation) process for the synthesis of (±)-1,2-dehydroaspidospermidine 339 (Scheme 51). This process proceeds through a sequential one-pot ozonolysis, noryl cleavage, iminium formation, and nitro reduction and condensation sequence, furnishing the natural product in good yield. Polycyclic intermediate 339 was then used as common precursor for the total syntheses of (±)-goniomitine, (±)-aspidosperridine and (±)-vincadifformine.
6. Miscellaneous Reactions

The remaining examples described in this review are those which do not fit into any of the three main reaction themes detailed in sections 3–5. In the oldest of these examples, Witskop and Patrick reported the Wagner–Meerwein rearrangement of both 343 and 345 upon reaction with methyl magnesium iodide, with the rearrangement of indolene 345 affording the spirocyclic indolene 344 in good yield (Scheme 52).170

Photolysis has also briefly featured in spirocyclic indolene synthesis (Scheme 53). First, Süss, Horner and co-workers described the photolysis of diazaisindolene 349 in cyclooctene 350 to furnish a product that was tentatively assigned as being spirocyclic cyclopropane 351, in an undisclosed yield. Johnson and co-workers later reported the photolysis of benzotriazole 352, which is presumed to form a diradical species 354 that undergoes subsequent cyclisation to form the spirocyclic indolene 353 in low yield.171

Zeeh reported an unusual two step procedure, combining aryloxycarboxylic acids 355 with cyclic ketones 356 in BF₃·OEt₂ to furnish spirocyclic indolenes 357 and 358 in modest yield. This reaction was proposed to proceed through a multistep process, as depicted below in Scheme 54.172

An interesting S₅Ar reaction was reported by Ong and co-workers in attempts to access the medicinally important spirocyclic pipéridine framework (Scheme 55).173 The treatment of nitrile 364 with phenyl magnesium bromide afforded only the unusual biphenyl spirocyclic indolene 365 in low yield. The authors propose that the reaction proceeds by nucleophilic...
attack of the Grignard reagent into the nitrile, followed by an
$\text{S}_2\text{Ar}$ reaction to displace the fluoride and then another
Grignard addition into intermediate 367 which then reaormatizes by eliminating hydride.

Snyder and co-workers reported one of the more recent
spirocyclic indolene syntheses in their impressive total
synthesis of (1,2)-schclareine. This reaction is proposed to
proceed by triethylamine radical halogen abstraction of 369, 1-O-H
transfer, cyclisation into the phenyl ring and then a radical
terminating oxidation-rearrangement sequence to form the
spirocyclic indolene 370 (Scheme 56).

Finally, Driver and co-workers recently reported an intriguing
tandem reduction and cyclisation of nitrostyrenes 374 to
afford spirocyclic indolenes 375 in good yields. The exact
role of each metal and reaction mechanism is yet to be fully
determined; but one proposed mechanism suggests the
reaction proceeds via a 1,2-shift reaction of a metallated inter-
mediate 376 (Scheme 57).

7. Summary and Outlook
In this review, a wide range of impressive methodologies for
the synthesis of spirocyclic indolenes are described. As is
evident from the number of examples included, indole
desmethylations reactions are by far the most popular method
for spirocyclic indolene synthesis. However, we believe that
there are still several under-utilised and under-developed stra-
tegies, for example the condensation strategy, which in our
opinion, contains some of most elegant examples of spirocyclic
indolene synthesis, notably those reported by Overman and
co-workers. The impressive @HIC approach of Zhou and co-workers further demonstrates the power of the condensation approach. Another area of current interest, which has only briefly appeared in spirocyclic indolinenine synthesis are photochemical methods, and we envisage that a photoredox strategy might find application in spirocyclic indolinenine synthesis in the future. At present, there are relatively few efficient catalytic asymmetric protocols for the synthesis of spirocyclic indolinenines, which is a key area in need of further developments. For inspiration in this area, the work performed in enantiomer cyclisations by the You group and others represents the current state-of-the-art. Our own contributions into this field using electrophilic activation of allynes also demonstrate the potential for the development of other asymmetric reaction modes. It is likely that over time, more powerful asymmetric methodologies will emerge; for example, the recent pioneering work of List and co-workers in catalytic asymmetric Fischer indolisations, might readily be applied in spirocyclic indolinenine synthesis. Overall, we trust that this review will serve to inform researchers wishing to synthesise spirocyclic indolinenines, draw attention to the synthetic utility of the products themselves and encourage further growth in this area.

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Keywords: 3H-indoles • dearomatization • indolinenines • spirocycles • spiroindolinenines
Appendix II. Silver(I)- or Copper(II)-Mediated Dearomatization of Aromatic Ynones:

Michael J. James, James D. Cuthbertson, Peter O’Brien, Richard J. K. Taylor,* and William P. Unsworth*

Abstract: A high-yielding silver(I)- or copper(II)-catalyzed dearomatizing Spirocyclization strategy allows the conversion of simple aromatic compounds containing ynone substituents, including indole, anilino, pyrrole, and benzofuran derivatives into functionalized Spirocyclic scaffolds. A high-yielding asymmetric variant furnishes Spirocyclic indolines in up to 89:11 e.r.

Dearomatizing Spirocyclization reactions are an effective means to generate functionalized three-dimensional scaffolds from simple aromatic precursors, which is important in research programs driven by the formation of molecular complexity and the exploration of chemical space. The dearomatization strategy described herein is based on the conversion of aromatic ynone derivatives intoSpirocycles through alkyn activation with a simple Lewis or π-acidic catalyst, illustrated by the conversion of indole derivative 1 into 3,3-substituted Spirocyclic indolene 2 (Figure 1a). A significant problem with this type of transformation is the proximity of the Spirocyclic products to undergo a facile 1,2 migration under acidic conditions, which is driven by the restoration of aromaticity. This issue is particularly prevalent with indolines. An illustrative example was recently reported by Van der Eycken (Figure 1b) who in his work 4a was formed in low yield when alkene 3 was treated with AuPPh3/CuI/AgOTf, the other major product being the reacromatized indole 4b. Indeed, while processes involving the electrophilic activation of alkynes have been well studied in recent years, Van der Eycken’s example is, to the best of our knowledge, the highest-yielding acid-catalyzed Spirocyclization of its type reported in the literature. Related processes, reacromatized products such as compound 4b are reported far more often (not only with indoles, but across a range of heteroaromatics).

The new methods described herein provide a general, high-yielding strategy for the conversion of a range of alicyclic heteroaromatics (left in Figure 2) into complex, Spirocyclic enones (right in Figure 2) using low loadings of simple silver(I) or copper(II) salts. The ynone subunit was chosen on the basis of its synthetic accessibility and the utility of the Spirocyclic products, but is also a key design feature, as the carbonyl group reduces the migratory aptitude of the adjacent alkene, thus stabilizing the Spirocyclic products with respect to 1,2 migration. Studies demonstrating that asymmetric dearomatizing Spirocyclization reactions can be achieved in high yield and good e.r. are also reported.

To begin our study, we examined the conversion of indole 5a into Spirocyclic 6a using a range of Bronsted, Lewis, and π-acidic acids to activate the alkene. Full details of this screen can be found in the Supporting Information, with the key results given in Table 1. The most effective catalysts that were screened were Cu(OOTf), AgNO3, and AgOTf (Table 1), while surprisingly, standard gold π-acidic6c were ineffective; as was triflic acid (Table 1, entry 3). The dearomatizing Spirocyclization reaction of indole 5a can be performed efficiently under a range of conditions (Table 1, entries 3–7) with the use of 0.01 equivalents of AgOTf in dichloromethane at room
temperature being optimal, furnishing spirocyclic indolene 6a in quantitative yield (entry 7, for X-ray crystallographic data see the Supporting Information).11 The importance of the ynone carbonyl group is noteworthy, as demonstrated by the contrasting reactivity of propargyl alcohol 7 (Table 1, compare entries 6 and 8); treatment of compound 7 with 0.1 equivalents of AgOTf for 1 h at room temperature resulted in its complete conversion into known carbazole 8,14 presumably through an initial spirocyclization, followed by 1,2 migration (compare 4a to 4b, Figure 1b) and dehydration.15 The relative ease of the migration in the conversion of 7 into 8 is presumably driven by the higher migratory aptitude of the more electron-rich alkene.

In addition to ynone 5a, three electronically diverse aryl substrates 5b–5d were treated with 0.01 equivalents of AgOTf in dichloromethane and furnished indolenes 6a–6d in very good yields with short reaction times at room temperature (Table 2, entries 1–4). Alkyl-substituted yrones 5e and 5f were similarly good substrates, furnishing indolenes 6e and 6f, respectively, in excellent yields under the same conditions (Table 2, entries 5 and 6).17 Additional substitution around the indole system is also well tolerated: for example, benzyl- and bromo-substituted spirocycles 4g and 4h were each formed in high yields (Table 2, entries 7 and 8). Indololones 6i and 6j were also formed rapidly in excellent yields under the standard conditions (Table 2, entries 9 and 10). These results are particularly pleasing as the proximity of the substituents on the 2-position of the indole to the reaction site could have impeded the reaction. The six-membered-ring product 6k was also formed using ynone homologue 5k. In this case, the reaction was slower and required moderate heating (35°C) in order to reach completion within 16 h, but nonetheless, the desired product was still obtained in good yield (Table 2, entry 11). Indolone 10a13 was also synthesized, through a desilylation/spirocyclization sequence, by stirring ynone 9 with 0.2 equivalents of AgNO3 in acetonitrile at room temperature for 16 h, affording spirocyclic cyclopentenone 10b, which is unsubstituted at C3 (Table 2, entry 12). This high-yielding one-pot process is important, given that the terminally unsubstituted alkyne (i.e. 9 with

| Table 2: Substrate scope of indole/ynone spirocyclization. |
|---|---|---|---|
| Entry | Starting material | Yield (%) | Isolated product |
| 1 | 5a Ar=4-MeOC6H4 | 0.5 | 6a Ar=4-MeOC6H4 |
| 2 | 5b Ar=Ph | 0.5 | 6b Ar=Ph |
| 3 | 5c Ar=4-MeOC6H4 | 0.5 | 6c Ar=4-MeOC6H4 |
| 4 | 5d Ar=4-BHCH3 | 1.5 | 6d Ar=4-BHCH3 |
| 5 | 5e R=Me | 2 | 6e R=Me |
| 6 | 5f R=nbBu | 3.5 | 6f R=nbBu |
| 7 | 5g Ar=4-MeOC6H4 | 0.5 | 6g Ar=4-MeOC6H4 |
| 8 | 5h Ar=4-MeOC6H4 | 1 | 6h Ar=4-MeOC6H4 |
| 9 | 5i Ar=4-MeOC6H4 | 0.2 | 6i Ar=4-MeOC6H4 |
| 10 | 5j Ar=4-MeOC6H4 | 0.1 | 6j Ar=4-MeOC6H4 |
| 11 | 5k Ar=4-MeOC6H4 | 16 | 6k Ar=4-MeOC6H4 |
| 12 | 9 | 16 | 10 | 93 |

[a] All reactions performed using 0.01 equiv AgOTf as catalyst in CH2Cl2 (0.1 w) at RT, unless otherwise stated. [b] Compounds 6a–d and 6e–f can also be formed using 0.01 equiv CuOTf2 (see the Supporting Information). [c] d.r. = 55:45. [d] Reaction performed using 0.1 equiv AgOTf as catalyst at 30°C. [e] Reaction performed in acetonitrile using AgNO3 (0.2 equiv) as catalyst.
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TM-Si (1) required to access spirocyclic H in the standard way is unstable and could not be isolated.

Promising preliminary studies have also been performed using Ag salts of chiral phosphoric acids (CPAs) as catalysts for the indolycyclone spirocyclization (Figure 3). Six catalysts were screened, all of which are simple Ag(I) salts of commercially available BINOL-based CPAs. First, ynone 5a was treated with 0.1 equivalents of catalyst A in dichloromethane at room temperature, which led to the rapid formation of spirocycle 6a, with a small amount of asymmetric induction (54-46% e.e.). Bulkier CPA catalysts B-F were next examined and additional modifications were also made; chloroform replaced dichloromethane as the solvent, the catalyst loading was reduced to 0.01 equivalents, the temperature was lowered to -10°C, and the reaction time was increased to 16 h. These modifications significantly improved the enantioselectivity, with the highest e.e. observed using 9-phenanthryl derivative F, which furnished spirocycle 6a in quantitative yield, in 89-11% e.e.

These conditions were then applied to other ynone substrates. Pleasingly, in all cases the spirocyclic products were isolated in high yields (6b-6e, 6h, 6l, 62-100%) and with consistently good enantioselectivity (e.e., 70:30-89:11), thus indicating that the reaction is likely to be applicable to a broad range of substrates (Figure 4). Notably, the e.e. of compounds 6a and 6d could be easily increased (98.2% e.e.) following recrystallization from ethyl acetate/hexane. The fact that good enantiomeric ratios were achieved by testing relatively small numbers of commercially available CPAs augurs well for further optimization to lead to greater improvements. The major enantiomer formed in reactions using (R)-CPA catalysts is the 3S-spirocyclic (as shown in Figures 3 and 4) based on X-ray crystallographic data of spirocycle 6d. A tentative mechanism consistent with this outcome is included in the Supporting Information.

Finally, preliminary studies demonstrate that a wider range of aromatic yrones undergo deamortating spirocyclization, expanding the potential scope of the method (Table 3). Anisole-substituted ynone 11 furnished spirocyclic diene 12 upon treatment with 0.1 equivalents of Cu(OAc)_2, while ynone 13 reacted very efficiently when treated with 0.1 equivalents of AgNO_3, affording spirocycle 14, with both reactions proceeding in excellent yields (Table 3, entries 1 and 2). Benzofuran 15 also reacted well, in this case furnishing the unusual spirocyclic enol ether 16 in good yield (Table 3, entry 3).

In summary, a range of high-yielding deamortating spirocyclization reactions are described, including an asymmetric variant, for the generation of synthetically useful spirocyclic building blocks from simple heteroaromatic precursors containing ynone side chains. The reactions are easy to perform, proceed at room temperature or -10°C, and are insensitive to both air and moisture.

Table 3: Alternative spirocyclization reaction systems.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>t [h]</th>
<th>Isolated product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Ar = 4-MeOC_6H_4</td>
<td>1</td>
<td>12 Ar = 4-Me_3NC_6H_4</td>
<td>95</td>
</tr>
<tr>
<td>20</td>
<td>Ar = 4-MeOC_6H_4</td>
<td>0.5</td>
<td>14 Ar = 4-Me_3NC_6H_4</td>
<td>99</td>
</tr>
<tr>
<td>31</td>
<td>Ar = 4-MeOC_6H_4</td>
<td>18</td>
<td>16 Ar = 4-Me_3NC_6H_4</td>
<td>68</td>
</tr>
</tbody>
</table>

[a] Reactions performed in CH_2Cl_2 (0.1 M) at RT. [b] 0.1 equiv Cu(OAc)_2 used as catalyst. [c] 0.1 equiv AgNO_3 used as catalyst. [d] R = 4-MeOC_6H_4.

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Keywords: asymmetric catalysis - deoxygenation - indolines - silver - spinycles

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[10] A complex mixture of products was formed when the mixed Ag/Pd/Cu(OTf) catalyst system was used in the work of Van der Eycken (see Figure 1 b and reference [5]) was tested.

[11] The unoptimized reaction mixture (Table 1, entry 2) contained approximately 90% unreacted 8a, along with a trace of unidentifiable impurities and only trace amounts of spirocyclic 8a. This appears to rule out the possibility that the successful reactions using AgOTf or Cu(OTf) are catalyzed by adventitious trivalent acid through "hidden bromated acid catalysis". See: T. T. Dang, F. Broek, L. Hintermann, J. Organ. Chem. 2011, 80, 9555.

[12] Dichloromethane was retained as the optimal solvent for further development, although the reaction can also be performed with comparable efficacy in chloroform, THF, toluene, or dichloroethane (see Supporting Information).

[13] CCDC 192060 (8a) and 1049165 (8b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request. (8a) and 1049165 (8b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request. (8a) and 1049165 (8b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request. (8a) and 1049165 (8b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.
Appendices

Appendix III. Silver(I)-Catalyzed Dearomatization of Alkyne-Tethered Indoles: Divergent Synthesis of Spirocyclic Indolenines and Carbazoles

Silver(I)-Catalyzed Dearomatization of Alkyne-Tethered Indoles: Divergent Synthesis of Spirocyclic Indolenines and Carbazoles

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Supporting Information

ABSTRACT: A high-yielding, divergent approach to generate either spirocyclic indolenines or carbazoles from a common indole-tethered propargyl alcohol precursor is described, with mechanistic insight provided. Either product can be obtained upon treatment with different Ag(I) catalysts at rt. An unexpected hydration reaction to afford (2,3)-aminopropyl alcohol B is also reported.

Figure 1. Carbazole and indoline natural products.

The indole subunit can be found in numerous biologically active natural products and pharmaceutical compounds. For example, benzo-fused indoles (carbazoles) have well established, broad therapeutic potential, with prominent examples exhibiting antitumor, antiviral, and antimicrobial properties (1–3, Figure 1). Spirocyclic indolenines have also attracted attention in recent years, in view of their presence in various natural products (4–6, Figure 1) and their ability to act as precursors for other privileged heterocycles such as imidazoles and thiazoles and as scaffolds to evaluate underexplored regions of chemical space in a range of bioassays. New methods that expedite the synthesis of each of these scaffolds are of significant interest.

Herein, a high yielding, divergent strategy for the selective synthesis of either spirocyclic indolenines (8) or carbazoles (9) from a common indole precursor (7) is described (Scheme 1).

During a previous study in our research group, we reported a single example of a novel carbazole-forming reaction based on the activation of an indole-derived propargyl alcohol with AgOTf. This transformation was proposed to proceed via an initial Ag(I)-catalyzed spirocyclization (cf. 7 → 8), before undergoing 1,2-migration and subsequent elimination in situ, furnishing a carbazole product (cf. 9). In this study, it was planned to identify reaction conditions that would deliver either spirocyclic indolene 8 or carbazole 9 selectively. The known propensity for related spirocyclic allenes to undergo the aforementioned 1,2-migrations makes the isolation of the spirocyclic products a challenge, but by careful choice of the Ag(I) catalyst and solvent, we have established that either product can be formed in high yield. Optimised procedures for the synthesis of either product class are reported, as well as mechanistic speculation to account for their formation.

The study began by examining the reaction of novel indole 7a with either AgOTf or AgNO3 as catalyst (Table 1). First, compound 7a was treated with 10 mol % AgOTf in CH2Cl2 at rt for 24 h (entry 1) and the major component of the unpurified reaction mixture was carbazole 9a (88%), although a small amount of spirocyclic indolene 8a (10%) was also formed. Pleasingly, full conversion into carbazole 9a could be achieved simply by changing the reaction solvent to either THF or toluene (entries 2 and 3). Interestingly, by switching the catalyst to AgNO3, the selectivity was reversed under otherwise identical conditions; in each of the three solvents tested, the only product formed was the spirocyclic indolene 8a, as a

Scheme 1. Divergent Synthesis of Spirocyclic Indolenines and Carbazoles

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Table 1. Ag(I)-Mediated Reactions of Alkyne 7a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>additive</th>
<th>%a</th>
<th>8a</th>
<th>9a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>CH₂Cl₂</td>
<td>—</td>
<td>10</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>THF</td>
<td>—</td>
<td>10</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>PMe₅</td>
<td>—</td>
<td>10</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>—</td>
<td>trace</td>
<td>&gt;95</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>AgNO₃</td>
<td>THF</td>
<td>—</td>
<td>10</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>AgNO₃</td>
<td>PMe₅</td>
<td>—</td>
<td>10</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>AgOTf</td>
<td>THF</td>
<td>β₂NO₃</td>
<td>55</td>
<td>45</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>β₂TSA</td>
<td>20</td>
<td>40</td>
<td>40</td>
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<td>9</td>
<td>AgNO₃</td>
<td>CH₂Cl₂</td>
<td>AgNO₃</td>
<td>100</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Reactions performed with 0.1–0.2 mmol of 7a and 10 mol % catalyst in the stated solvent (0.1 M) at rt. *5 mol %, 2 mol %. Calculated using the 'H NMR spectrum of the unpurified reaction mixture, rounded to the nearest %.

roughly 1:1 mixture of diastereoisomers (entries 4–6). One theory account for this complementary reactivity is the presence of adventitious Brønsted acid (either present in the AgOTf reagent or formed in situ) in the carbazole formation reactions. In order to probe this, triethylamine was included in a reaction with AgOTf in THF (entry 7); the expectation was that the basic additive would quench any Brønsted acid present and promote spirocyclic indolenedione formation rather than carbazole formation. Pleasingly, this switch was indeed observed, albeit with an accompanying decrease in overall conversion. Furthermore, when p-TSA was included in a reaction with AgNO₃ in CH₂Cl₂ (which had selectively furnished spirocycle 8a in the absence of acid), an appreciable amount of carbazole 9a was formed, further corroborating the idea that a Brønsted acid has an important influence on the reaction outcome. Having learned that basic additives facilitate the formation of spirocycle 8a over 9a, other additives were tested, this time in combination with AgNO₃, in order to establish a reliable synthetic procedure for spirocycle formation; several additives were tried, and the addition of 5 mol % of AgNO₃ was found to be the most effective (entry 9). The optimal conditions for the formation of either product (entries 2 and 9) were taken on to further exploring studies (see later).

A number of mechanistic possibilities were considered to account for the formation of the two products (Scheme 2). The formation of spirocycle 8a is the more straightforward of the two pathways: activation of the alkyne with the α-acid Ag(I) catalyst, presumably promotes spirocyclization via nucleophilic attack of the indolene 3-position (route A; 7a → 10) before protodemetalation reveals the indolenedione product (10 → 8a). The formation of carbazole 9a is more complicated. One possibility is that indolenedione 8a is an intermediate on route to 9a and that it undergoes 1,2-migration (route B; 8a → 11) followed by elimination (11 → 9a). However, this pathway is unlikely, given that subjecting a purified sample of indolenedione 8a to the optimal carbazole-forming reaction conditions (10 mol % AgOTf THF for 24 h) resulted in no reaction, while its treatment with various Brønsted acids under the same conditions resulted in the formation of complex product mixtures. A more likely pathway is therefore one in which the same vinyl silver intermediate (10) is formed and that 1,2-migration occurs at this stage (route C; 10 → 12) before subsequent protodemetalation and elimination (12 → 9a). A third possibility, in which intermediate 12 is formed directly via metathepic attack through the indole 2-position (route D; 7a → 12) cannot be ruled out, although it is less likely based on typical indole reactivity and on related precedent.No reaction occurs when compound 7a is treated with Brønsted acids in the absence of a Ag(I) catalyst, confirming the importance of Ag(I), presumably in promoting the initial spirocyclization reaction. It is less clear what species is responsible for the 1,2-migration step: but the initial screening results and additive studies clearly demonstrate the importance of a Brønsted acid in those reactions, indicating that this step may be mediated by a Brønsted acid, rather than the Ag(I) catalyst itself. Further studies are clearly needed to fully elucidate the precise mechanism, but the observation that it is likely to be vinyl silver intermediate 10, rather than spirocycle 8a, which undergoes the key 1,2-migration is intriguing and is expected to be instructive for future endeavors in the field of Ag-catalysts.

The scope of each of the two reaction modes was examined using the optimized conditions, beginning with the spirocyclization procedure (Figure 2). Good reactivity was observed for electron-neutral (8a), electron-rich (8c), and electron-poor (8d) aromatic examples, and stilyl protection on the alcohol is also well tolerated (8h). Similarly, simple ally1 (8e) and cyclopropyl (8f) spirocycles were formed in excellent yield. It was also shown that the protocol is not limited to secondary alcohols, with tertiary alcohol containing spirocycles (8g and 8h) both formed in excellent yield. The inclusion of a thioephene group in product 8h indicates that other heterocycles can be used in this method. Finally, indoles substituted on the 2-position are also suitable substrates, with indolenedione 8i being formed in quantitative yield under the standard conditions. There was no diazotetracontol in any of the reactions (all products were isolated as approximately 1:1 mixtures of diastereoisomers; see Supporting Information), but the consistently high yields are pleasing nonetheless, especially in view of the fact that related spirocyclic alkenes have been shown to be unstable with respect to 1,2-migration. Previously, it was suggested that an electron-withdrawing carbonyl group is needed to reduce the migratory aptitude of the alkenic product, but this study shows that this is not a strict requirement, provided suitably mild conditions are used; in particular, the absence of a Brønsted acid appears to be crucial. This knowledge is likely to be of importance during the development
Appendices

![Chemical structures](image)

Figure 2. Ag(I)-mediated deaminative spirocyclization to form spirocyclic indolines.

of other deaminative reactions involving electrophilic alkyne activation.

The only substrates tested which failed to deliver the desired spirocyclic indolines are shown in Scheme 3. The terminal alkyne starting material 7k and its trimethylsilyl-substituted analogue 7J were each treated under the standard conditions for indoline formation in the expectation of forming spirocycle 8k. However, none of the desired product was isolated in either example in both cases the bulk of the reaction mixture was unreacted starting material, along with a small amount of the natural product (α,β-unsaturated polyacrolein) B 13.13

Allene hydration reactions of this type have traditionally been performed under acidic conditions using a Hg(II) catalyst, although, more recently, Ag(I) and Au(I) variants have also been reported; these variants are typically performed at much higher temperatures than used in this study; hence, it was somewhat surprising to isolate natural product 13 under such mild conditions.

The scope of the carbazole formation protocol was also explored. Generally good functional group compatibility was observed, with carbazoles 9a-c-g all being formed in good to excellent yield upon treatment with AgOTf in THF (Figure 3). However, there are some differences between the scope of each protocol. Carbazole 9h was not formed under the standard reaction conditions, which instead furnished a complex mixture of products. Also, carbazole 9k was isolated in much lower yield in this series, with the majority of the material recovered being spirocycle 8k, indicating that there is a higher energy barrier to the 1,2-migration pathway in this system. However, in contrast to the indolone series, terminal alkyne starting material 7l and its trimethylsilyl-substituted analogue 7m were both very well tolerated, furnishing parent carbazole 9k in excellent or quantitative yield, respectively. Note that the carbazole product was formed as a single regiosomer in all cases, with the regiochemical outcome being consistent with the 1,2-migration of the alkynyl group (see 10  12, Scheme 2). This outcome is to be expected, based on a consideration of the relative migratory aptitudes of the two substituents in the presumed intermediate spirocycle and is supported by comparing the spectroscopic data of carbazoles 9a and 9c to those previously reported, and also by X-ray crystallographic data for carbazole 9d (See Supporting Information).22

In summary, we have identified mild and operationally simple conditions to selectively generate spirocyclic indolines and carbazoles from the same readily available starting material. Both procedures typically proceed in high yield and have been shown to work on a range of functionalized allene tethered indoles. The results accrued shed light on the mechanism of each process, indicating that the spirocyclisation step is Ag(I)-catalysed, whereas the 1,2-migration step, which appears to proceed via a vinyl silver intermediate, could be promoted by an adventitious brominated acid. Finally, the natural product (α,β-unsaturated polyacrolein) B was synthesized unexpectedly when the standard indolone-forming conditions were applied to terminal alkyne substrate 7k, or its TMS-substituted analogue 7l. Although the yields of the two hydration reactions are low at present, these preliminary results offer hope that with additional optimisation other allene-mediated hydration com-
Appendix IV. Silica-Supported Silver Nitrate as a Highly Active Dearomatizing Spirocyclization Catalyst: Synergistic Alkyne Activation by Silver Nanoparticles and Silica

Aimee K. Clarke, Michael J. James, Peter O’Brien, Richard J. K. Taylor,* and William P. Unsworth*

Abstract: Silica-supported AgNO₃ (AgNO₃–SiO₂) catalyzes the dearomatizing spirocyclization of alkyne-tethered aromatics far more effectively than the analogous unsupported reagent; in many cases, reactions which fail using unsupported AgNO₃ proceed effectively with AgNO₃–SiO₂. Mechanistic studies indicate that this is a consequence of silver nanoparticle formation on the silica surface combined with a synergistic effect caused by the silica support itself. The remarkable ease with which the reagent can be prepared and used is likely to be of much synthetic importance, in particular, by making nanoparticle catalysis more accessible to non-specialists.

Proceeded in the 1960s, silica-supported AgNO₃ (AgNO₃–SiO₂) is well-known for its use as a support in the separation of E- and Z-alkenes by column chromatography. However, the synthetic potential of AgNO₃–SiO₂ as a catalyst has been mostly overlooked, with just a handful of reports on its use as a reagent in organic synthesis. To the best of our knowledge, examples are limited to syntheses of 5-membered heterocycles from alkynes and alkenes, reported by Marshall and Knight. As part of a wider program on deaminating spirocyclization reactions, we decided to investigate the catalytic potential of AgNO₃–SiO₂ due to its limited previous use in synthesis and with the intention of exploiting the practical benefits of using a solid-supported reagent. To our surprise, we found that AgNO₃–SiO₂ offers vastly superior reactivity compared with unsupported AgNO₃ in deaminating spirocyclization reactions of alkyne-tethered heteroaromatics of the type shown in Figure 1.

Of much significance, several deaminatization reactions that previously failed with unsupported AgNO₃ can now be carried out in high yield with the AgNO₃–SiO₂ catalyst. These unexpected findings prompted a mechanistic investigation which ultimately, via the combined use of in situ infrared spectroscopy (via ReactIR) and TEM, implicated a key role for silver nanoparticles (Ag NPs) formed during the preparation of AgNO₃–SiO₂, together with a synergistic effect from the silica support itself. Pre-prepared Ag NPs have been used as catalysts previously but to the best of our knowledge, the catalytic role of Ag NPs formed while supporting silver salts on silica has not been documented. In this paper, we highlight AgNO₃–SiO₂ as an easily prepared and highly active catalyst for dearomatizing spirocyclizations (Figure 1), showcasing the methodology with the AgNO₃–SiO₂-mediated synthesis of 23,6-g of a spirocycle in a simple continuous flow set-up. Furthermore, our mechanistic finding of the synergistic alkyne activation by Ag NPs and silica provides a new alkyne activation pathway that could have much synthetic scope for alkyne functionalization.

To start, we examined the conversion of ynone 1a into spirocycle indoline 2a. Commercial AgNO₃–SiO₂ (10 wt% AgNO₃ on silica) was found to effect this transformation with reasonable efficiency and following additional optimization (see Supporting Information) it was discovered that “home-made” AgNO₃–SiO₂ with a reduced AgNO₃ loading of 1 wt% was an even more effective catalyst: stirring ynone 1a at RT in CH₂Cl₂ with catalytic (1 mol%) 1 wt% AgNO₃–SiO₂ led to the formation of spirocycle 2a in 98% isolated yield in 30 minutes (Scheme 1, conditions A). Interestingly, this is significantly faster than the same reaction with unsupported AgNO₃ (6 h, conditions B). Even more dramatic differences were seen in the reactions of yrones tethered to other aromatics; phenol 3a, pyrone 5a and benzonuran 7 were reacted with both catalyst systems, and while spirocyclic products 4a, 6a, and 8 were isolated in high yields when 1 wt% AgNO₃–SiO₂ was used, AgNO₃ alone led to no reaction in all three cases (Scheme 1).

In view of these marked differences, a mechanistic study was initiated. We first monitored the conversion of ynone 1a into spirocycle 2a with in situ infrared spectroscopy (via ReactIR), using the decrease in intensity of the C=C stretch of ynone 1a (2208 cm⁻¹) to monitor reaction progress. Using 1 mol% of the 1 wt% AgNO₃–SiO₂ catalyst, ynone 1a was converted into spirocycle 2a in 30 min (blue line, A, Figure 2),

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201608263.
fully consistent with the synthetic reaction. In contrast, as expected from the synthetic work, the unsupported AgNO₃ reaction was much slower, requiring >6 h to reach completion (purple line, B); interestingly, there was a clear induction period of around 2 h, and even after this time the reaction was slower.

To explore the role of silica, AgNO₃ and silica were both added to a solution of 1a in CH₂Cl₂ (i.e. the AgNO₃ was not supported on the silica in advance). In this experiment (pink line, C), an induction period was still observed (around 90 min), but once this period had passed, the reaction proceeded at a similar rate to the standard AgNO₃-SiO₂ reaction (blue line, A). Silica is not able to promote spirocyclization on its own (try removing 1a in silica in CH₂Cl₂ led to no reaction after several days) but clearly its presence significantly increases the rate of the Ag-mediated spirocyclization reaction. We suggest that this may be due to accelerated protodemetalation[26] silanol groups on the silica surface might be expected to facilitate this step, thus releasing the silver for further catalysis and increasing the turnover rate.

Our results also indicate a clear difference between the supported AgNO₃-SiO₂ catalyst and unsupported AgNO₃ in the presence of silica (which should have the same elemental composition). This led us to propose that AgNO₃ is a pre-catalyst in the unsupported reaction and that the induction period is connected to the time taken for Ag-NPs to form in situ. To test this, unsupported AgNO₃ was "aged" by stirring the standard reaction dose in CH₂Cl₂ for 24 h before adding ynone 1a; the expectation was that by ageing the catalyst, Ag-NPs would form in advance and after the reaction profile[10]. The initially colorless solution became yellow during the ageing process, which is indicative of Ag-NP formation[12] and the aged catalyst did indeed perform differently (gray line, D). The reaction proceeded at a similar rate to the standard AgNO₃ reaction (purple line, B), but crucially there was no induction period. A mercury drop test was also performed which led to the complete cessation of the reaction[13], adding additional support to the idea that Ag-NPs are the true catalyst. Further supporting evidence was obtained using transmission electron microscopy (TEM); AgNO₃ was stirred for 24 h at RT in CH₂Cl₂ and an aliquot of the solution (≈5 µL) was removed and dropped onto a copper TEM grid. The deposit that remained after the CH₂Cl₂ had evaporated was then analyzed using TEM, and Ag-NPs were found to be present (Figure 3).

In view of the above results, we considered it likely that Ag-NPs were also present in our supported AgNO₃-SiO₂ (1 wt%) catalyst system, as they could potentially form during the preparation of the supported reagent. This was confirmed by TEM imaging of the supported catalyst; crystalline Ag-NPs were observed (Figure 4) and the electron diffraction pattern enabled the identification of a cubic silver crystal phase (space group Fm3m) and showed that the particles had a spacing of around 0.205 nm, which is representative of cubic silver[14].

Thus, it appears that in both the supported and unsupported systems, Ag-NPs rather than AgNO₃ are predominately responsible for the conversion of 1a into 2a. Silica was also shown to be important, leading to an increased reaction rate, even when added separately to the silver. This may be due to faster protodemetalation, and hence more effective catalyst turnover and/or its role may also be to adsorb the Ag-NPs and control their growth/aggregation.
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Next, to more fully evaluate the synthetic utility of our AgNO₃-SiO₂ catalyst, the optimized spirocyclization conditions were applied to other alkylene-tethered aromatics, and compared to unsupported AgNO₃ in each case (Scheme 2).

Indolyl spirocyclic products 2a-e were all obtained in excellent yields (94–100%), with AgNO₃-SiO₂ promoting a faster transformation than with unsupported AgNO₃ in all cases. More pronounced differences in reactivity were observed for 2- and 4-phenyl derivatives 3a-f: these substrates did not react at all using unsupported AgNO₃, but using AgNO₃-SiO₂, spirocyclic dienes 4a-f were all formed in high yield, notably including compound 4f, an advanced intermediate in a published route to spirobacilene A.⁶⁻⁷ Pyrrole derivatives 5a-g are also well tolerated, with AgNO₃-SiO₂ superior to unsupported AgNO₃ in all examples. The quantitative formation of spirocycles 6a-g is especially noteworthy, given the rarity of decaaromatized products derived from 3-pyrrroles.³² Thus a wide range of substituted aromatics are compatible with this simple, mild method, and furthermore, even broader functional group tolerance was demonstrated by an extensive robustness screen, detailed in the Supporting Information.³³⁻³⁵

Finally, the use of our AgNO₃-SiO₂ catalyst in a continuous flow reactor has been demonstrated. A 0.1 M solution of ynone 1a in toluene was simply passed through a 1 cm diameter column packed with 1.93 g of our standard 1 wt% catalyst (19.3 mg of AgNO₃) at a flow rate of 0.3 mL min⁻¹, concentrated in vacuo, and analyzed using H NMR spectroscopy. This reaction proceeded very efficiently, converting a total of 23.6 g of ynone 1a into spirocycle 2a in quantitative yield over a 51 h period (Scheme 3). This corresponds to a total catalyst loading of 0.12 mol% and an NMR aliquot measured after 51 h showed that the product was still being formed cleanly, indicating that the catalyst remained active.

In summary, 1 wt% AgNO₃-SiO₂ is a very effective catalyst for the decaaromatizing spirocyclization of alkylene-tethered heteroaromatics, with its efficacy believed to stem from a synergistic relationship between the siliceous support and Ag-NPs formed during its preparation. It is much more reactive than unsupported AgNO₃, and in our hands, it is also more reactive than silica-supported Ag-NPs made by literature methods in which the Ag-NPs were prepared separately.³⁶ In contrast to existing methods to prepare supported

Figure 4. TEM images for AgNO₃-SiO₂.

Scheme 2. Supported and unsupported Ag* catalysts spirocyclization. Isolated yields (following catalyst removal) are quoted, for incomplete reactions, conversion (conv.) was calculated based on analysis of the ¹H NMR spectrum on the unpurified product mixture.


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Scheme 3. Flow spirocyclization of ynone 1a.

Acknowledgements

We thank the University of York (A.K.C., M.L.J., W.P.U.) and the Leverhulme Trust (for an Early Career Fellowship ECF-2015-013, W.P.U.) for financial support. We are also grateful for help from Dr. Charlotte Ellington (ReactIR), Robert Mitchell and Alan Reay (TEM) and Dr. Victor Chechik for helpful advice.

Keywords: dearomatization - flow chemistry - heterogeneous catalysis - silver nanoparticles - spirocycles

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[11] Ynone 1a (0.1 mmol) was stirred with 10 mol-% AgNO₃·6H₂O (0.151 g, Sigma-Aldrich, 207957) in CH₃CN for 10 min, resulting in full conversion into spirocycle 2a.

[12] 1 wt% Ag(NO₃)₂ was prepared by adding Ag(NO₃)₂ (100 mg) to a slurry of Fluor silica gel (90-100, pore size 40–60 Å, 220–440 mesh particle size) in deionized water (27 mL). The mixture was stirred for 15 min, concentrated in vacuo at 80°C to form a free-flowing powder and dried by heating to 140°C under high vacuum for 4–5 h.


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[18] The reaction of ynone 1a with unsupported AgNO₃ was allowed to proceed to ca. 90% conversion, before mercury was added (200 equivalents with respect to AgNO₃), which stopped the further reaction.

[19] Qualitatively, the supported Ag-NPs appear to be much more uniform in size than those obtained from aged AgNO₃ in CHCl₃; more detailed studies will be required in future to probe this observation and its implications more rigorously.


[23] Silica-supported Ag-NPs synthesized by literature methods (references [6a] and [6b]) were tested in the transformation of ynone 1a into spirocycle 2a, resulting in 45% and 28% conversion into 2a, respectively, with unreacted starting material accounting for the remainder of the mass balance.

[24] See Supporting Information for details. Very consistent (high) yields were achieved in these recycling studies, highlighting the reliability and reproducibility of these reactions.


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Appendix V. Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones

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Synthetic Methods

Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones

Abstract: Medicinally relevant spirocyclic indolenines, carbazoles and quinolines can each be directly synthesised selectively from common indolyl ynone starting materials by catalyst variation. The high yielding, divergent reactions all proceed by an initial deoxygenating spirocyclisation reaction to generate an intermediate vinyl-metal species, which then rearranges selectively by careful choice of catalyst and reaction conditions.

The synthesis of structurally diverse compounds is central to the discovery of pharmaceutical lead compounds. However, the formation of distinct compound sets usually requires multiple synthetic routes, which is time-consuming and labour-intensive; therefore, strategies capable of selectively forming multiple products from common starting materials are of high value. The concept underpinning our approach is the formation of a common reactive intermediate (from a simple, inexpensive starting material), which depending on the catalyst used can rearrange into different scaffolds (e.g., spirocycles, aromatics and heterocycles/carbonic acids; Figure 1). This approach has the potential to significantly streamline existing synthetic methods, and lead to a broader understanding of catalyst and reaction mechanisms. Although there have been numerous examples of catalyst variation leading to different products in recent years,[1,5] such methods have mainly focused on the formation of products with similar frameworks (e.g., redox iso- mers, regiosomers or stereoisomers). In this work, our aim was to develop a series of divergent processes capable of selectively delivering multiple products with the level of scaffold diversity outlined in Figure 1.

To demonstrate the synthetic potential of our scaffold-diversity approach, we chose to explore the formation and subsequent reaction of spirocyclic vinyl-metal intermediates of the form 2 (Scheme 1). Previous work in our research group has demonstrated that the deoxygenating spirocyclisation[6] of ynones 1 into spirocyclic indolenines 3 can be catalysed by AgOTf, with vinyl-silver species 2 (M=Ag) as likely intermediates.[10] A key design feature of our strategy was the idea that varying the catalyst would alter the nature and reactivity of the vinyl-metal intermediate 2 in a programmable way, such that alternative products could be formed by different rearrangement reactions. Herein, we report the successful realisation of this approach. Notably, by judicious choice of catalyst, simple, inexpensive ynone starting materials 1 can be converted into spirocyclic indolenines[3] 3 using Ag1, carbazoles 5 using Au1 and quinolines 7 using Ag/Au2 in high yield, each by

Figure 1. Catalyst-driven scaffold diversity.

Scheme 1. Divergent synthesis of spirocycles 3, carbazoles 5, quinolines 7 and heterocyclic scaffolds 8 from indolyl ynone 1.
a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetracyclic scaffolds 8 can be formed with complete diasteroselectivity, by a telescoped spirocyclisation/nucleophilic addition sequence, which was performed using a chiral Ag salt to furnish an enantiopure product.

The spirocyclisation of 1a using AgOTf formed indolenone 3a in quantitative yield (Scheme 2); the mild reaction condi-

Scheme 2. Formation of spiroyclic indolenone 3a.

tions are believed to play a key role in this process, stabilising the spirocycle with respect to further reactions. However, in the proposed scaffold diversity approach, in which the synthesis of carbazole 5a was an initial goal, the challenge was to deliberately promote 1,2-migration\(^1\) in a controlled manner. A Ph3P=CHTF catalyst was chosen based on the prediction that the x-pleated gold(III) catalyst would effectively promote the initial spirocyclisation reaction and that the intermediate vinyl-gold species (2a-Au) would be prone to 1,2-migration, based on known reactivity of related vinyl-gold and gold-carbeneoid species.\(^4\) This idea was validated (94%) yield of 5a) with a likely reaction mechanism depicted in Scheme 3; the ring enlargement is believed to proceed either via cyclopropane intermediate 9a, or by a direct 1,2-migration reaction (2a-Au → 10a) based on related precedent.\(^3\) The importance of vinyl-gold intermediate 2a-Au in the 1,2-migration is evidenced by the fact that no reaction takes place when spirocycle 3a is treated with Ph3P=CHTF under the same conditions.

We next examined whether we could initiate an alternative rearrangement commencing from ynone 1a, by seeking to promote cyclopropanation of an enolate from the less substituted branch of the cyclopentene; more oxophilic catalysts were chosen for this task, as it was thought that they would better promote the necessary enolate formation. We were unable to uncover a catalyst that could successfully initiate spirocyclisation and subsequent rearrangement on its own. However, first performing the spirocyclisation using 2 mol% of AgOTf as catalyst in isopropanol, followed by the addition of 5 mol% of AlCl3·6H2O and subsequent heating in a microwave gave quinoline 7a in high yield (Scheme 4). Following Ag-

Scheme 3. Formation of carbazole 5a: [Au] = Ph3P=CHTF, L = ligand.

mediated spirocyclisation, it is thought that the AF\(^1\) catalyst promotes enolate formation and subsequent cyclopropanation to form 12a, which can then fragment to form 13a and aromatise to give quinoline 7a (either by simple proton shuttling, or by a series of 1,5-sigmatropic H-transfer reactions).

Supporting evidence for this unprecedented rearrangement was obtained: treatment of spirocycle 3a with LHMDS in THF (i.e. conditions which almost certainly would result in enolate formation) also led to the formation of quinoline 7a. In 81% yield. Furthermore, the importance of the carbonyl group was shown by the fact that treatment of known cyclopentenone 14\(^1\) with AlCl3·6H2O did not result in quinoline formation. Instead, 1,2-migration of the alkynyl group took place, furnishing carbazole 15 following tautomerisation and dehydration (Scheme 5).

Scheme 4. Formation of quinoline 7a; X = O or PhO.

Scheme 5. Base-mediated formation of quinoline 7a and the contrasting reactivity of spirocyclic cyclopentenone 14.

To probe the scope of all three reaction manifolds, various functionalised indole-tethered yrones 1a–1m were prepared, substituted in several positions with electron-rich and -poor aromatics, alkyl substituents, O- and N-protected alkyl groups and PHX. First, using the AgOTf-mediated spirocyclisation
Table 1. Reaction scope for the formation of spirocyclic indolines, carbazoles and quinolines.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><img src="image1" alt="Structure A" /></td>
<td>87%</td>
</tr>
<tr>
<td>B</td>
<td><img src="image2" alt="Structure B" /></td>
<td>75%</td>
</tr>
<tr>
<td>C</td>
<td><img src="image3" alt="Structure C" /></td>
<td>90%</td>
</tr>
</tbody>
</table>

(a) AgOTf (1 mol%) in CH2Cl2 (0.1 M) at RT for 0.5 - 3 h. (b) PhPAuNTf2 (2 mol%) in CH2Cl2 (0.1 M) at RT for 1 - 3 h. (c) AgOTf (1 mol%) in CH2Cl2 (0.1 M) at RT for 1 - 3 h. (d) AICl4H2O (10 mol%) in 100°C for 1 - 2 h. (e) Reaction performed in toluene. (f) AgOTf (1 mol%) in CH2Cl2 (0.1 M) at RT for 1 - 3 h. then solvent swap for PhOH (1 h) then AICl4H2O (10 mol%) in 100°C for 1 - 2 h. PhPAuNTf2 - para-methylphenyl.

Methodology: substrates 1a-1m were cleanly converted into the corresponding spirocyclic indolines 3a-3m, all in excellent yield. (Table 1, conditions A). The PhPAuNTf2-mediated carbazole-forming reaction was similarly broad in scope (conditions B); some reactions were less efficient than the analogous spirocyclic formations, and ynone 1d did not produce any of the desired product (instead stalling at the formation 3d), but the majority of the carbazole products 5a-j were isolated in very good yields.23 Finally, the quinoline-forming reaction sequence was also found to be very general (conditions C). For ynone 1a-1e, 1j, 1k-1l, the sequential AgOTf spirocyclisation and AICl4H2O mediated rearrangement steps could both be performed in PhOH in one-pot as described, whereas for ynone with more sensitive functional groups (1f, 1h, 1i, 1j, 1m), the process benefited from a solvent swap, with the spirocyclisation first being performed in CH2Cl2 before concentration and addition of PhOH prior to the AICl4H2O step. The AICl4H2O reactions were typically performed under microwave irradiation at 100°C, but they were also shown to proceed well on a gram scale with conventional heating, albeit with a longer reaction time being required.24 The structure of quinoline 7f was confirmed by X-ray crystallography.25

Another strand of scaffold diversity starting from more functionalized ynone 1h-1j was briefly explored. Tetraycyclic scaffolds 8h-8j, equipped with additional complexity, were equally obtained following reaction of ynone 1h-1j with AgOTf and subsequent acid-mediated protecting group cleavage in one pot (Scheme 6), and see the Supporting Information for details.26

In summary, readily available indolyl yrones have been shown to be versatile starting materials for the synthesis of spirocyclic indolines 3a-m, carbazoles 5a-j, quinolines 7a-m and tetracyclic compounds 8h-8j using a catalyst-driven scaf-

Scheme 6. One-pot spirocyclization/trapping to form tetracycles 8h-8j.
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Appendix VI. Selective Synthesis of Six Products from a Single Indolyl $\alpha$-Diazocarbonyl Precursor

**Diazo Compounds**

Selective Synthesis of Six Products from a Single Indolyl $\alpha$-Diazocarbonyl Precursor

Michael J. James, Peter O’Brien, Richard J. K. Taylor,* and William P. Unsworth*

Abstract: Indolyl $\alpha$-diazocarbonyls can be selectively cyclized to give six distinct products through the careful choice of catalyst and reaction conditions. A range of catalysts were used, including complexes of Rh, Pd, and Cu, as well as SiO$_2$, to promote diazo decomposition and subsequent cyclization/rearrangement through a range of mechanistic pathways.

The ability to access structurally diverse compounds is the cornerstone of lead generation in the pharmaceutical and agrochemical industries. In most cases, such compounds are generated using organic synthesis, and over the years, a number of reliable and predictable methods have emerged. The importance of such methods cannot be overstated, but nonetheless, there is also value in the examination of reaction systems which react less predictably. Reactive precursors known to participate in a wide range of synthetic transformations can significantly streamline the synthesis of diverse compounds by allowing multiple products to be generated from a single precursor, provided their reactivity can be controlled.

With this in mind, we initiated the research described herein, focusing on the reactions of indolyl $\alpha$-diazocarbonyl compounds. The utility of diazo precursors in diversity-oriented synthesis was elegantly demonstrated by Warnrin, Nelson and co-worker in 2014, who exploited the unpredictable reactivity of diazocarbonyls to generate product mixtures for bioscreens. In our research, we have taken an alternative approach, using a different reaction system, and focused on controlling the “unpredictable” nature of diazocarbonyl reactivity by catalyst variation. The ability to access several distinct products from a common precursor is synthetically important, and such research can also lead to advances in the study of catalysis and mechanism. With this as motivation, we challenged ourselves to uncover a reaction system capable of delivering as many product scaffolds as possible from a single precursor by varying the catalyst and reaction conditions. Most reported methods of this type allow the selective synthesis of two distinct products, with protocols able to deliver three or more products being much more rare. However, herein we report the catalyst-selective synthesis of six structurally distinct cyclic scaffolds from a single $\alpha$-diazocarbonyl, of the form I, by a series of mild rhodium(II)-, palladium(II)-, copper(II)-, and SiO$_2$-catalyzed processes, as discovered through a mix of careful reaction design and serendipity (Figure 1).

![Figure 1. Catalyst-selective synthesis: six scaffolds from one precursor.](image)

Our studies began with the three-step synthesis of the $\alpha$-diazocarbonyl 1a from the commercially available acid 2a (Table 1), which was then treated with a range of potential catalysts (10 mol%) in CH$_2$Cl$_2$ at room temperature for 16 hours. Selected results are given in Table 1 (for full details, see the Supporting Information).

A number of catalysts able to promote diazo decomposition and cyclization were uncovered. Five identifiable products were observed in total, with mechanistically related products grouped to aid the subsequent discussion: the spirocycle indolenine 3a and $\beta$-diazocarbonyl 4a (group A), C2 annulated indole 5a and carboxane 6a (group B), and isomeric indole 7a (group C). As expected, many of the catalysts afforded complex mixtures of products, as exemplified by the reactions of the rhodium(II)- and copper(II)-based catalysts (Table 1, entries 1-4). However, the most promising results were found and they enabled the selective synthesis of group A products 3a and 4a [Rh(OTf)$_2$], group B redox isomers 5a and 6a [Pd(MeCN)$_2$(BF$_4$)], or Cu(OTf)$_2$, and the rearrangement product 7a (SiO$_2$), and these catalysts were therefore selected for further optimization.

To the best of our knowledge, the [Rh(OTf)$_2$]-catalyzed procedure, to form 3a represents the first reported synthesis of a spirocycle indole, similar from a diazocarbonyl precursor, although C3 functionalization of indoles using diazocarbonyl compounds has been reported,

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Supporting Information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/jate.201603337.
We propose that both reactions start with the formation of the rhodium carbenoid \( A^{[29]} \), which then reacts with the nucleophilic indole to form the spirocycle \( B \) before undergoing protodemetalation to furnish \( 3a \) (Scheme 2). Then, in the presence of oxygen, we propose that \( 3a \) forms the intermediate endoperoxide \( D^{[29]} \) possibly by a radical rebound process (\( 3a \rightarrow C \rightarrow D^{[29]} \)) before fragmenting as shown to afford the product \( 4a^{[17]} \). Additional evidence for this mechanism (including an X-ray structure for a related endoperoxide) can be found in the Supporting Information. While \( 4a \) could be isolated in good yield, it was found to be relatively short-lived as it degraded during silica gel chromatography and upon storage, but pleasingly, we were able to exploit its high reactivity to deliver two new oxindole scaffolds, \( 8a \) and \( 9a \) (Scheme 3). Thus, two highly diastereoselective intramolecular aldol-type reactions were developed using either Brønsted acidic or Brønsted basic conditions.

### Table 1: Initial catalyst screening.

<table>
<thead>
<tr>
<th>Entity</th>
<th>Catalyst( ^{[x]} )</th>
<th>Product composition ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([\text{Rh}(\text{DCA})]^{[2]})</td>
<td>1a 50 20 15 75</td>
</tr>
<tr>
<td>2</td>
<td>([\text{Rh}(\text{acac})]^{[2]})</td>
<td>2a 10 55 15 70</td>
</tr>
<tr>
<td>3</td>
<td>([\text{Cu}(\text{MeCN})\text{OTf}])</td>
<td>3a 20 60 20 20</td>
</tr>
<tr>
<td>4</td>
<td>([\text{Cu}(\text{MeCN})\text{PF}_6])</td>
<td>4a 35 65 20 35</td>
</tr>
<tr>
<td>5</td>
<td>([\text{Rh}(\text{acac})])</td>
<td>5a 95 5 20 20</td>
</tr>
<tr>
<td>6</td>
<td>([\text{Pd}(\text{MeCN})\text{BF}_4])</td>
<td>6a 95 5 20 20</td>
</tr>
<tr>
<td>7</td>
<td>([\text{Cu}(\text{DTf})_2])</td>
<td>7a 70 30 20 20</td>
</tr>
<tr>
<td>8</td>
<td>([\text{SiO}_2, (1 \text{~g})])</td>
<td>8a 10 5 20 20</td>
</tr>
</tbody>
</table>

\( ^{[x]} \) Reactions performed with 0.05 mmol of \( 2a \) and 10 mol\% catalyst in \( \text{CH}_2\text{Cl}_2 \) (0.4 \text{~mL}) under argon at 87 for 14 h. \( ^{[2]} \) Calculated using the \( ^1\text{H} \) NMR spectrum of the unpurified reaction mixture. esp...
Both reactions were performed in one pot, thus requiring only a solvent switch to THF and the addition of an excess of either TFA or Bu3OK. Under acidic conditions 4a was selectively converted into the syn-diastereomer 8a in 99% yield, and we propose this to be the result of hydrogen bonding between the oxindole and α,β-dicarbonyl moieties ([E]). Conversely, under basic conditions, the anti-diastereomer 9a was formed, and we propose that it results from a reactive conformation of the form [E], in which the destabilizing steric interactions are lower than those in [E], and the carbonyl dipole is opposed. Both product structures were confirmed by X-ray analysis.[10]

Next, the palladium(II)- and copper(II)-catalyzed reactions were optimized, thus allowing selective formation of the C2-annulated product 5a and carboxyl 6a using Pd(MeCN)₃(CF₃SO₂)₂ (5 mol%) and CuOTf₂ (20 mol%), respectively (Scheme 4).[11,12] A key difference between these reactions is that it is necessary to perform the carboxyl-promoted reaction under oxygen at 50 °C. It is difficult to unambiguously determine whether these reactions proceed by direct nucleophilic attack from the indole C2 or by initial C3 attack followed by a 1,2-migration. Based on related precedent,[13] and the observation that 3a can be converted into a mixture of 5a and 6a upon reaction with CuOTf₂, the latter appears more likely.

The silica-promoted C2-annulation reaction required minimal deviation from the initial screen. The compound 7a was prepared in good yield by reacting 1a with an equivalent weight of SiO₂ in CH₂Cl₂ (Scheme 5). The reaction likely proceeds by a Wolff rearrangement, induced by the mildly acidic silica,[14] and trapping by the nucleophile indole (either by direct C2 attack or by an initial C3 attack followed by a L2-migration). To the best of our knowledge, only one other example of a C2-annulation reaction of this type has been reported.[15]

Finally, the scope of all six procedures was tested on five diazacarbonyl substrates (1a-e), thus delivering 30 diene tetracyclic products in total (Scheme 6). The spirocycles 3a-e were each formed in good yield, with variable diastereomeric ratios, and is likely due to epimerization of the α-keto stereocenter during chromatography. The other five procedures were all well tolerated by the same precursor set. The spirocyclic oxindoles 6a-e and 9a-e, as well C2 annulation products 5a-e, 6a-e, and 7a-e were formed in generally good yields, and is pleasing given that no additional optimization was performed for any of these reactions.[16]

In summary, we report a novel catalyst-controlled approach to form six structurally diverse products from a single α-diazocarbonyl precursor. While other catalyst-selective synthesis systems are known,[17,18] we know of no other capable of delivering the level of scaffold diversity by simply varying the catalyst and reaction conditions. Given the importance and diversity of the compound classes accessible, the methods are expected to be of much synthetic interest,[19,20] while the novel reactivity and mechanistic information uncovered is likely to be useful to researchers studying catalysis. These discoveries (some of which were serendipitous) were made as a result of challenging the methodology in terms of the number of products which could be selectively formed. Much as natural product synthesis has long been used to inspire the invention of new synthetic processes,[21] we believe that the same principles apply in catalyst-selective synthesis.

Acknowledgments

We wish to thank the University of York (M.G.B. and W.P.L.) and the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-013, W.P.L.) for financial support and Dr. A. C. Whitwood for X-ray crystallography.

Keywords: cyclizations - diazo compounds - indoles - spirocycles – synthetic methods

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Scheme 6. Catalyst-selective synthesis of six products from a single indeno-1,2-dehydroxybenzene precursor (yields are those of products isolated after column chromatography).


[10] We are unable to account for the difference in product ratio of the three rhodium(II)-catalyzed reactions in Table 1 (entries 1, 2, and 5). Subtle differences in the solubility, coordination chemistry, and solvent potential of the cations/intermediates can all influence the reaction outcome. It is noteworthy that all of these reactions had a distinct dark red/orange color, which is often indicative of the corresponding formation.


[14] CCDC 1481024 (4a), 1481025 (5a), 1481026 (6a), 1481027 (8a), 1481028 (9a), and 1481029 (7a) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[17] Purified 3a slowly converts into 4a when stored in solution open to air, thus confirming that the rhodium catalyst is not essential for oxidation.
[21] No reaction took place when Et3N was included as an additive.
[23] For all entries a single product was isolated and we observed no appreciable amounts of any of the other products in these reactions. In the low-wielding examples, the main balance was largely made up of intractable, polar material, which we were unable to identify.
[25] Efforts to extend these methods to other heteroarenes are ongoing.

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Appendix VII. Catalytic Dearomatization Approach to Quinolizidine Alkaloids: Five Step Total Synthesis of (±)-Lasubine II

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Department of Chemistry, University of York, Heslington, York, YO10 5DD, U.K.

Supporting Information

ABSTRACT: A series of high-yielding silver(I)-catalyzed cyclization reactions of pyridines, isquinolines, and pyrazones were described. The operationally simple and mild reaction conditions are a significant improvement over previously reported thermal cyclizations. The quinolizine alkaloids were also used in a novel dearomatization strategy to prepare 0.53 g of the alkaloid lasubine II in five steps and 36% overall yield.

Pyridine and piperidine are the two most prevalent N-heterocycles used in medicinal chemistry, with a recent study showing their presence in 12% of all US FDA approved drugs. New methods for the synthesis of these heterocycles and their derivatives, such as quinolizines/quinolizidines, are therefore of high value. The saturated quinolizidine framework is particularly notable for its presence in a number of bioactive natural products, such as 1-3 (Figure 1A), which makes them highly attractive synthetic targets.

![Scheme 1. Pyridine-ynone Cyclizations](image)

Figure 1. (A) Natural products containing the saturated quinolizidine framework; (B) proposed dearomatization retrosynthesis.

An unexplored and expedient strategy by which to access these bicyclic frameworks is by the dearomatization of a 2H-quinolin-2-one system 4 (Figure 1B). Dearomatization reactions are important transformations as they enable high value spiro-1,4-oxazinones or bridged-compounds to be formed from inexpensive and readily available aromatic feedstocks. However, current methods for the synthesis of 2H-quinolizin-2-ones are limited, relying primarily on harsh thermal conditions, with catalytic examples being rare. Seeking to address this limitation, an opportunity to build upon our recent work on the catalytic dearomatization/cyclization of aromatic alkenes was identified. This previous work is based on the activation of alkenes with acidic catalysts to promote cyclization to generate spirocyclic/annulated products, and based on this, it was considered that pyridine-yrones would serve as useful precursors to 2H-quinolin-2-ones. The viability of a related cyclization protocol had already been briefly demonstrated by both Kazukiyo and Natarajan (Scheme 1A), however, in this work the pyridine-ynone species is formed and cyclized in situ via the acylation of 2-picoline under relatively harsh, thermal conditions and the reported yields are modest. Herein, we describe a simple and scalable alternative approach, in which pyridine-ynone is cyclized to form annulated products 6 at room temperature using mild silver(I)-catalyzed conditions (Scheme 1B).

Using this new method, a diverse array of quinolineone products have been prepared in high yield, including reactions performed on gram scale. The methodology is likely to be of high value in natural product synthesis, and to demonstrate this,
an efficient five-step synthesis of 0.53 g of the aldehyd lausbine II has also been developed, including a catalytic deprotonation of a quinolinemone product as a key step.

Our studies began with the preparation of pyridine-ynone 5a via the deprotonation and acyllistion 3-cyclohexone with methyl phenylpropiolate (Table 1). Ynone 5a was then reacted with

### Table 1. Optimization of the Pyridine-Ynone Cyclization

<table>
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<tr>
<th>Entry</th>
<th>Catalyst (eq)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<td>AgNO3 (0.01)</td>
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<td>8</td>
<td>AgNO3 (0.01)</td>
<td>CH2Cl2</td>
<td>0.5</td>
<td>90</td>
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</table>

Reaction performed with 0.2 mmol of 5a and catalyst in the stated solvent (0.1 M) at rt. Calculated by measuring the ratio of starting material to product in the 1H NMR spectrum of the unpurified reaction mixture, rounded to the nearest 3%.

four α-acidic catalysts in dichloromethane (Table 1, entries 1–4), of which only AgOTf was effective for the formation of quinolinemone 6a. This prompted further scrutiny of other silver(I) catalysts, and of those tested, AgNO3 provided the best reactivity (entries 7 and 8).

The silver(I) catalyst is proposed to catalyze this transformation as depicted in Scheme 2. The ynone starting material, which exists as an equilibrium of keto—enol tautomers (with the enol tautomer believed to be an unproductive resting state), is presumably activated by the α-acidic silver(I) catalyst (A), promoting nucleophilic attack from the pyridine lone pair to form ynone species B (which is likely a reversible process). Deprotonation of the pyridinium species B at the acidic α-keto position then forms vinyl silver intermediate C; subsequent protodemetalation of this species then affords the final quinolinemone product 6 and regenerates the silver(I) catalyst.

The scope of this transformation was then examined, with minor modifications made to the conditions shown in Table 1. The solvent system was switched to a 1:1 mixture of ethanol/1,2-dichloromethane (see ref 13 for details) and 2 mol % of AgNO3 was used as the catalyst in all of the examples for consistency (Scheme 3).

### Scheme 3. Substrate Scope for the Silver(I)-Catalyzed Cyclization

First, the electronics of the ynone substrate were varied to afford quinolinemones 6a–c in quantitative/ near-quantitative yield. Pleasingly, these reactions were equally effective on gram scales for example, 2.09 g of quinolinemone 6b were prepared in a single reaction in 99% yield. The aliphatic quinolinemone 6d was also afforded in near-quantitative yield. Thiophene-substituted and methylated quinolinemones 6e and 6f were also prepared, albeit in lower yield, which is believed to be a direct consequence of the instability of the ynone precursors (see Supporting Information for details). Substituents on the pyridine ring were also well tolerated, with quinolinemones 6g–i bearing cyano, bromo, and methyl substituents, all being furnished in excellent to quantitative yield. The structure of the bromide 6h was also confirmed by X-ray crystallography. Finally, this methodology was also demonstrated on other heterocyclic systems, to afford isoquinoline and pyrazine derived products 6j and 6k in excellent yield. The fully unsubstituted quinolinemone 6l was also synthesized in excellent yield from TMS-ynone SI by using 20 mol % AgNO3 and acetone to promote a one-pot desilylation—cyclization sequence (Scheme 4). This reaction is particularly pleasing.
as the TMS ynone SI is completely unreactive under the
previously reported thermal conditions.16

Scheme 4. Tandem Ag(I)-Catalyzed Deallylation—Cyclization

![Chemical structures](image)

The ease of formation of these quinolizidino products is likely to be of significant value in target synthesis projects,
especially given the prevalence of saturated quinolizidino
frameworks in Nature.1 This was demonstrated in the five-
step deamsonative synthesis of (±)-lauseline II (Scheme 5).

Scheme 5. Five-Step Total Synthesis of (±)-Lauseline II

![Chemical structures](image)

The synthesis began with the LDA-mediated deprotonation
and acylation of 2-picoline with methyl ester 112 to form ynone
5b in good yield. Next, the silver(I)-catalyzed cyclization
afforded the quinolizine 6b in near-quantitative yield.
Interestingly, the two ring systems of 6b could then be
selectively hydrolyzed with either Pd/C or PdO, to form
products 8 and 9 respectively.13 The unpurified quinolizidine 9
was then oxidized under Swern conditions to form ketone
10 in excellent yield over the two-step sequence.14 Finally, the known
1,3-Schmidt reduction of ketone 10 afforded 0.53 g of
(±)-lauseline II 3 in 36% overall yield.15

In summary, we have developed a mild and operationally
simple protocol for the high-yielding catalytic synthesis of
quinolizidino simple protocols. Furthermore, we demonstrated the synthetic utility of the products by preparing 0.53 g of (±)-lauseline II in just five steps and 36% overall yield from 2-picoline. The development of a protocol for the asymmetric hydrogenation of
quinolizidino remains the focus of future work,16 in hopes of
enabling the enantioselective synthesis of lauseline II and other
related alkaloids.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.org-
exlett.0c03017.

Experimental procedures and compound characterization
data (PDF)

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Notes

The authors declare no competing financial interest.

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Appendices

Organic Letters

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(10) For examples of similar mechanistic pathways, see: (a) Yang, Z.; 
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(11) CCDC 1507022 (68) contains the supplementary crystallographic 
data for this paper. These data can be obtained free of charge from 
The Cambridge Crystallographic Data Centre via www.ccdc.cam. 
ac.uk/data_request.

(12) For details of solvent screening studies see the Supporting 
Information. Note that whilst the reactions generally proceeded faster 
in pure ethanol, 1,2-dichloroethane was included as a cosolvent in 
the final optimized conditions to improve solubility across a wider range 
of substrates.

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hydrogenation of a 2H-quinolin-3-one.

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(20) For a recent review on asymmetric hydrogenation, see: Zhao, 
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<td>acac</td>
<td>acetylacetone</td>
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<td>Ad</td>
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