Catalytic Dearomatisation Reactions

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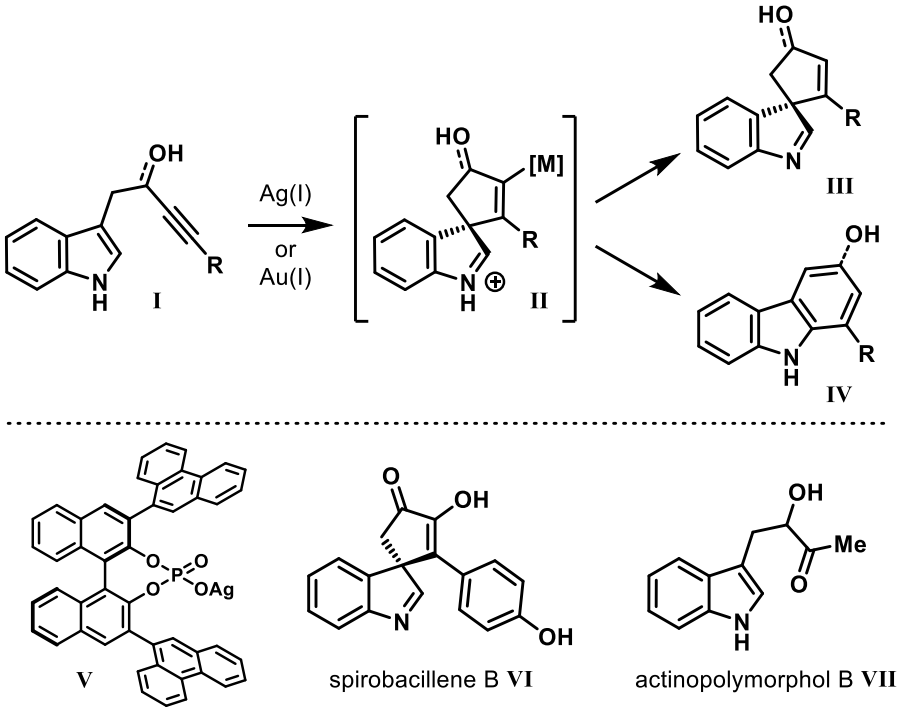
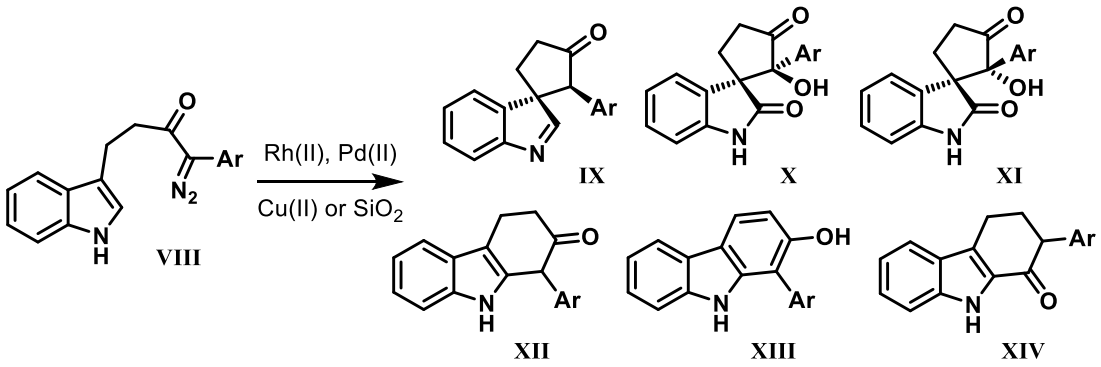
Abstract

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.

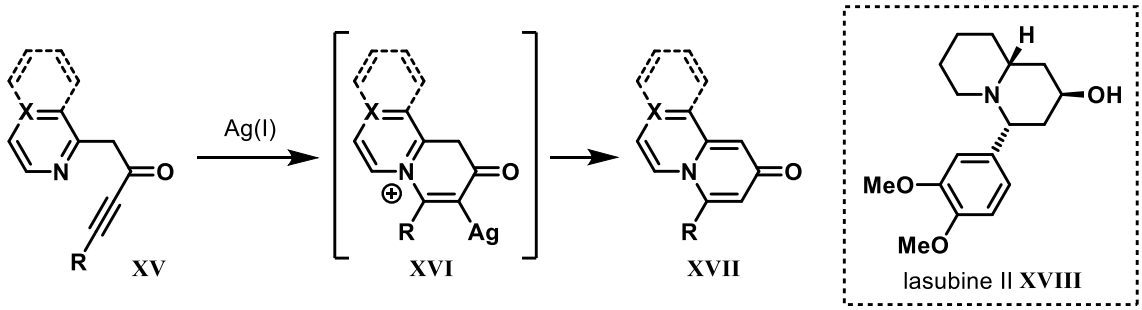
Chapter 2 describes the cyclisation of indole-alkyne systems **I**, using Ag(I) or Au(I) catalysis, to selectively form either spirocyclic indolenines **III** or carbazoles **IV** in high yield through a common vinyl metal intermediate **II**. An efficient and reusable heterogeneous catalyst system was 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 SiO_2-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**.



Contents

List of Tables

List of Figures

Acknowledgments

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I also owe a great deal of thanks to all of the amazingly talented co-workers and friends, of which there are too many to name, that I've worked alongside with and learned from. Religious coffee breaks with you all and seemingly endless, hysterical discussions of hypothetical situations or facts which always seem to resurface "Is it a fruit, a drupe or merely an aggregate of drupelets?" have been essential to my survival. Memories of golf in the sunshine and incessant laughter with you will always stay with me.

Next, I would like to thank the students that I've had the opportunity to supervise, thank you for your patience and hard work, I didn't realise how hard it would be!

Finally, I would like to thank my family, who have been an amazing source of support throughout my studies. Lastly, to Laura, my constant companion and reassuring voice in the face of self-doubt, thank you so much for your continued love and support.

Declaration

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

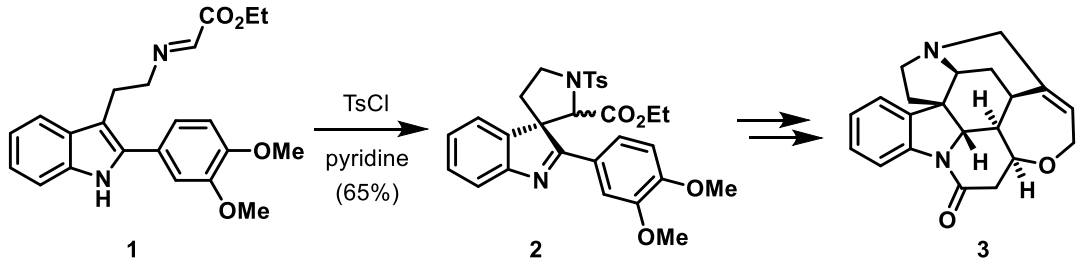
This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

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

Chapter 1. Introduction

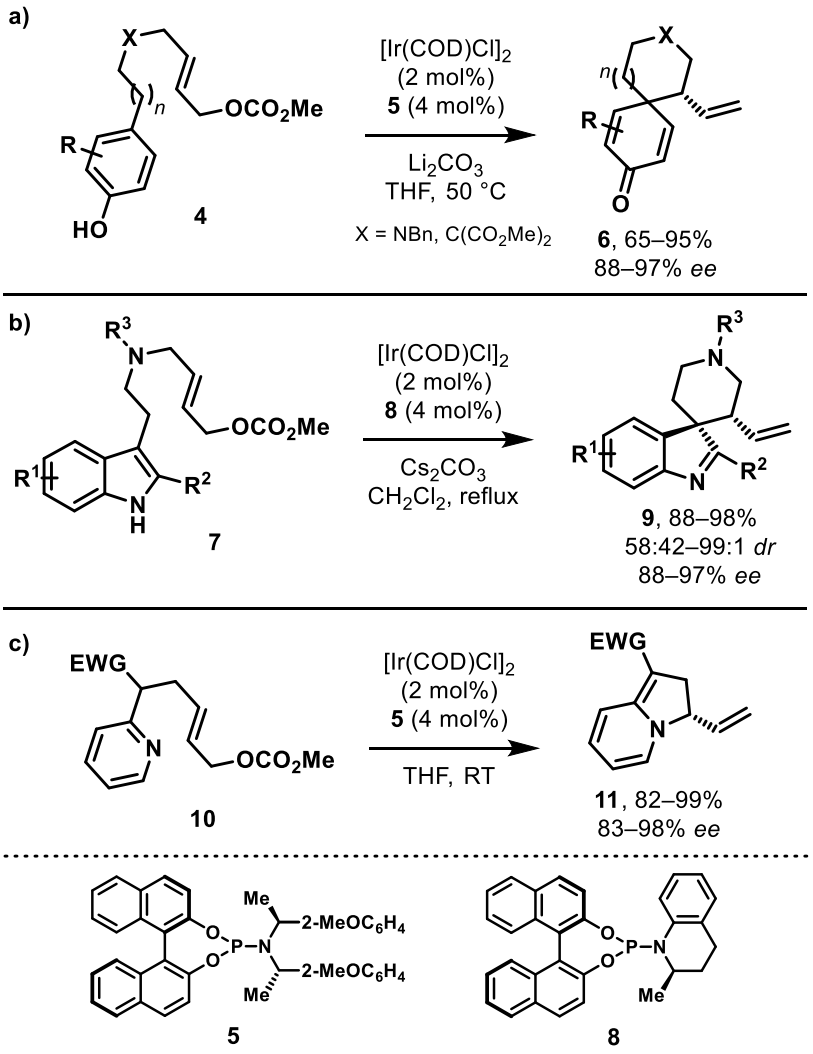
1.1 Dearomatisation reactions

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. 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 π-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]

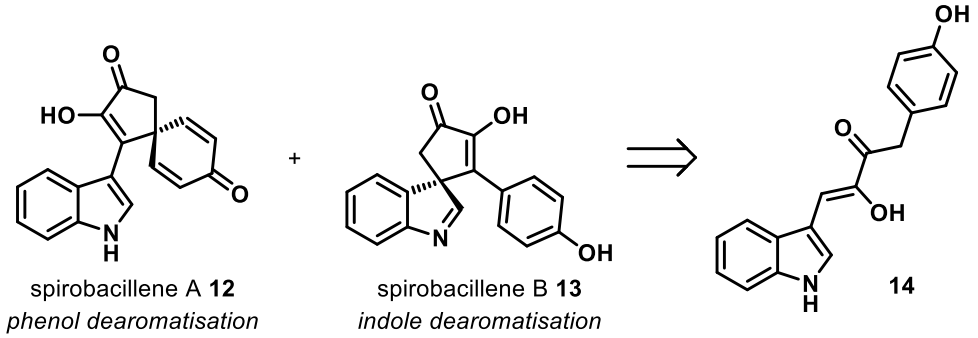


Scheme 2. CADA reactions through an intramolecular allylic alkylation approach.

1.2 Spirobacillenes A & B

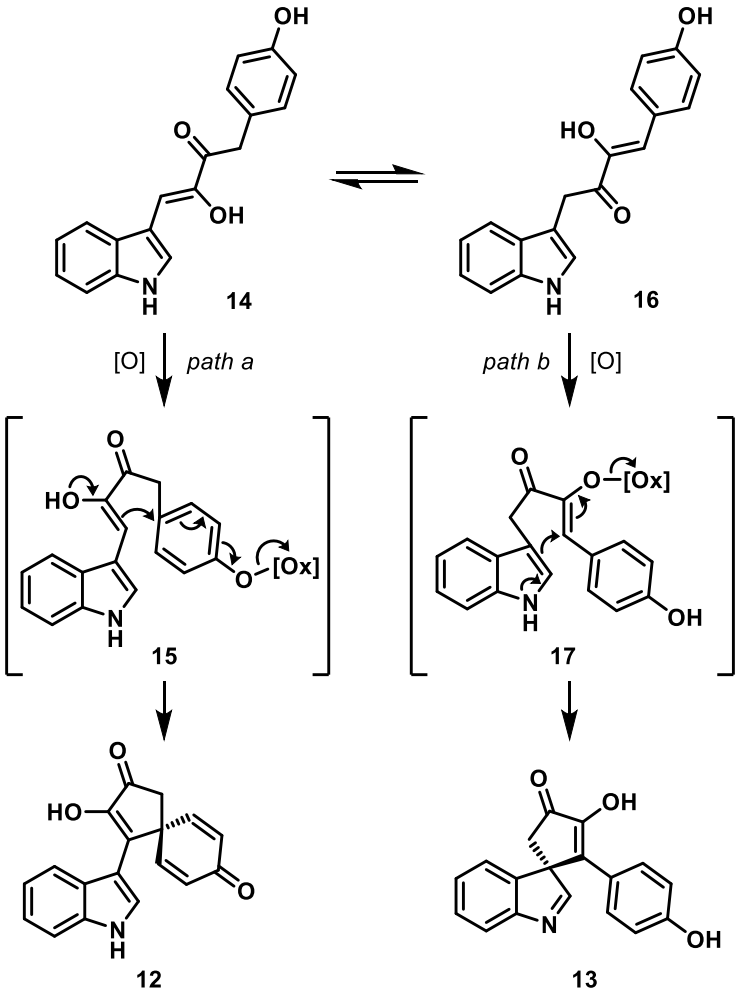
1.2.1 Isolation and previous syntheses

The Taylor group became interested in dearomatisation reactions following the reported isolation of two unusual natural products, spirobacillenes A **12** & B **13** (Scheme 4).[15] 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![15] 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.



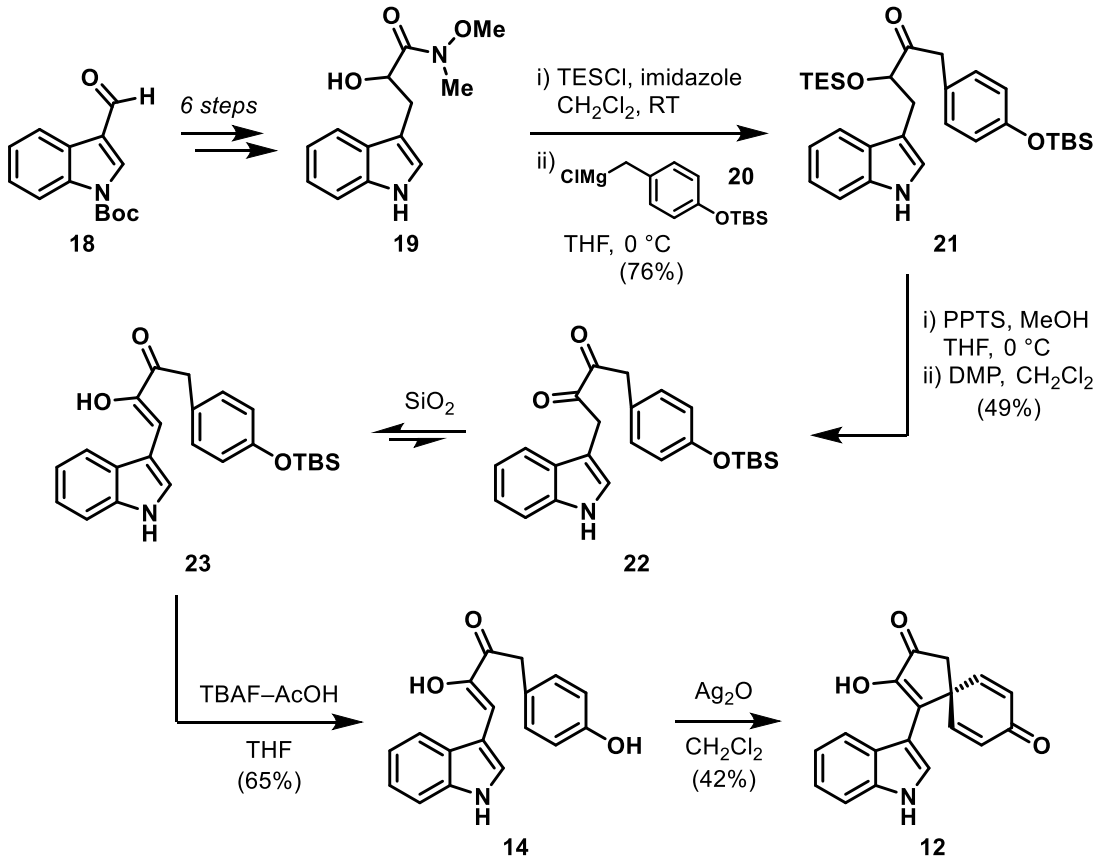
Scheme 3. Spirobacillenes A & B and their proposed biosynthetic precursor.

Mechanistically, it was proposed by Tang and co-workers that both natural products were formed by two aromatic-enol oxidative coupling processes (Scheme 4).[16] 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).



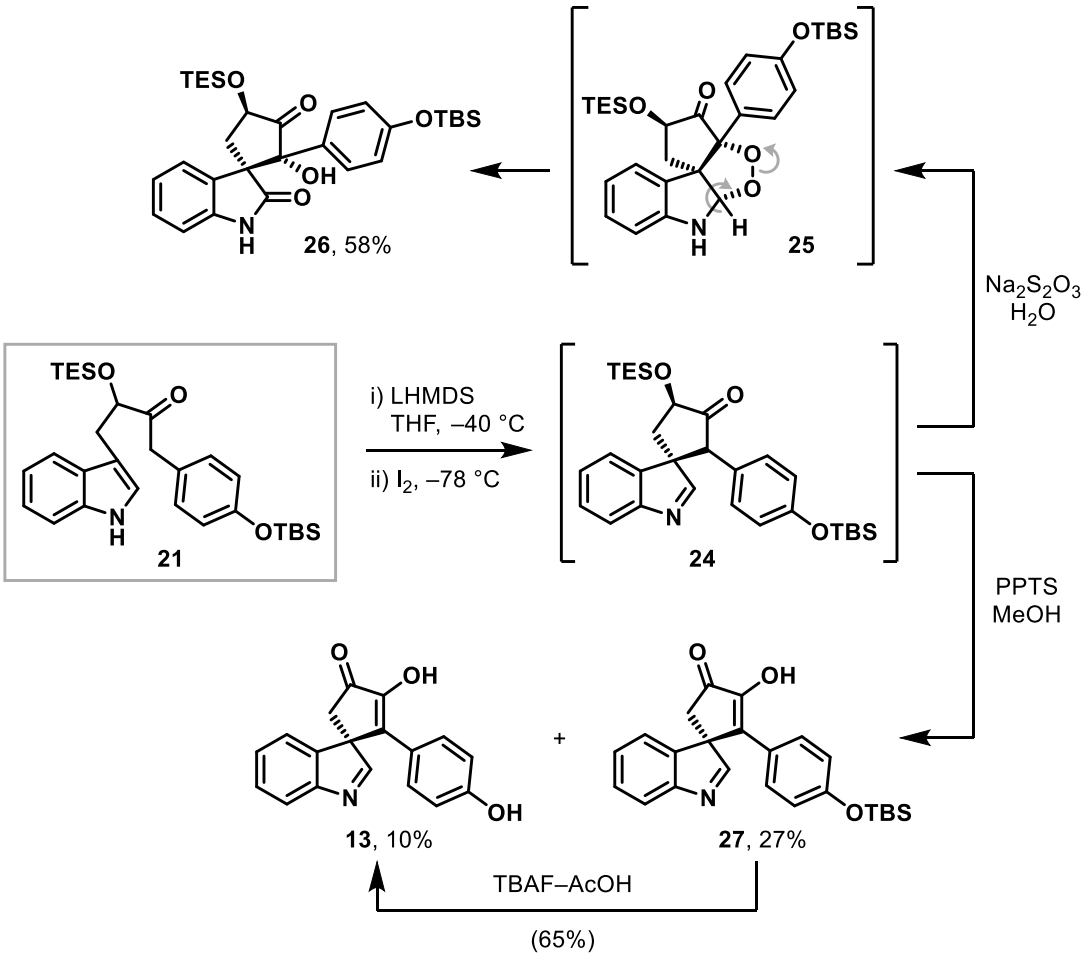
Scheme 4. Proposed biosynthetic pathways.

Tang and co-workers successfully applied a biomimetic strategy to complete the total synthesis of both spirobacillene A **12** and B **13**.[16] 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 Ag_2O to form spirobacillene A **12** in modest yield and in 12 overall steps.



Scheme 5. Tang and co-workers' synthesis of spirobacillene A **12**.

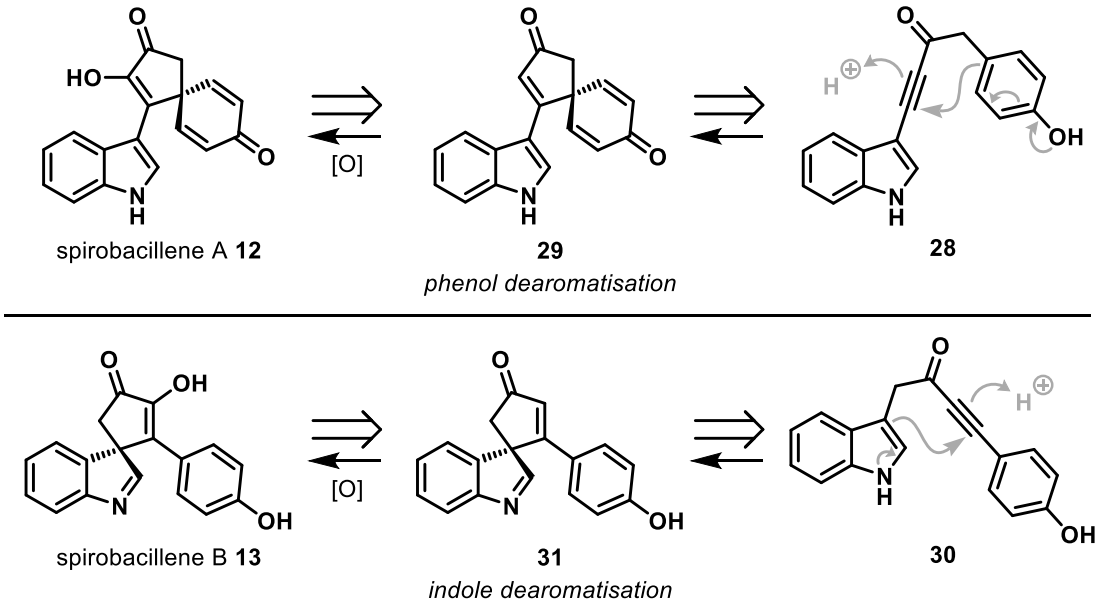
For the synthesis of spirobacillene B **13**, Tang and co-workers reacted benzyl ketone **21** with LHMDS, followed by iodine to promote the formation of spirocyclic indolenine **24** (Scheme 6). Interestingly, indolenine **24** appeared to be unstable and formed only spirocyclic oxindole **26** (with ambiguous stereochemistry) upon quenching the reaction with sat. aq. $Na_2S_2O_3$. 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 supressed 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.



Scheme 6. Tang and co-workers synthesis' of spirobacillene B **13**.

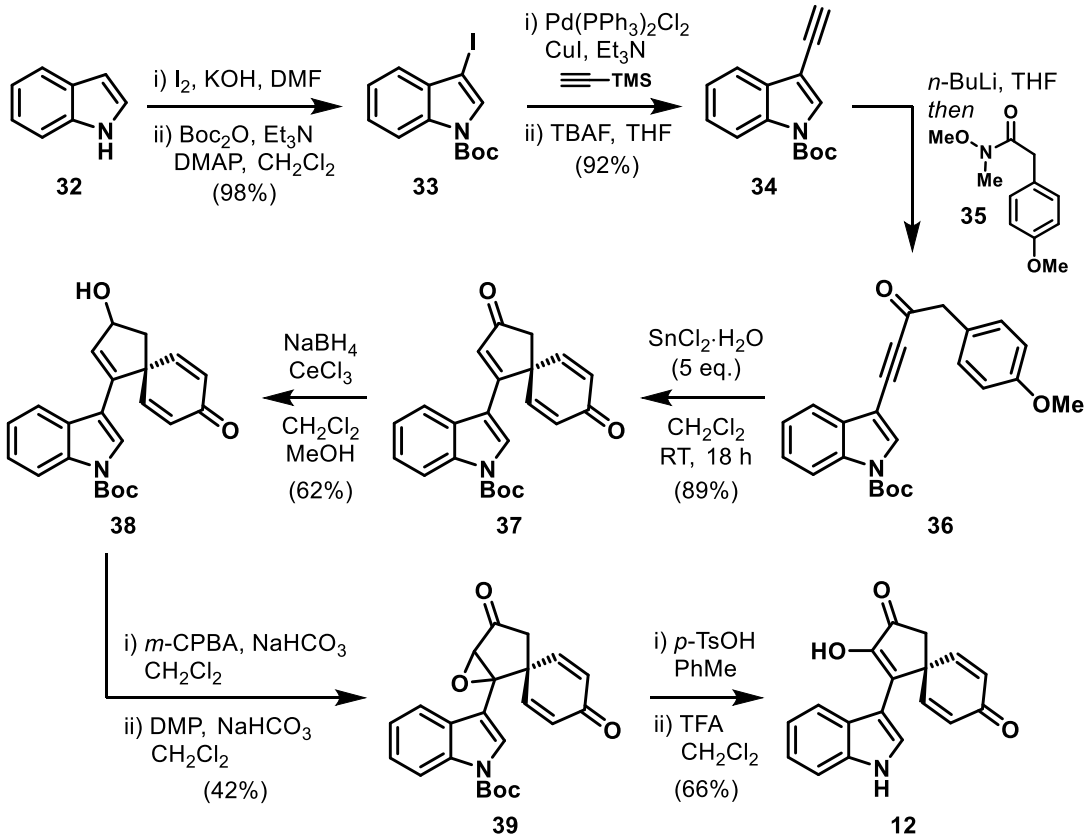
1.2.2 Taylor group synthesis and methodology

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).[17] Subsequent oxidation of the enone framework was envisaged to provide access to the desired natural products in a concise and high-yielding fashion.



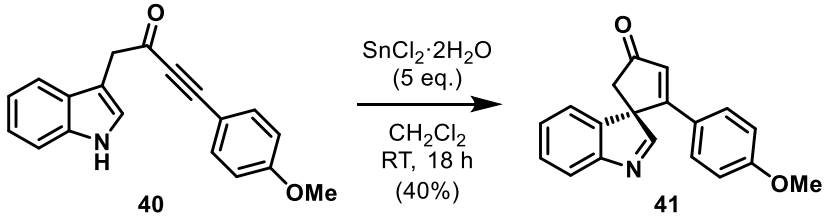
Scheme 7. Alternative retrosynthetic analysis of spirobacillene A **12** and spirobacillene B **13**.

Unsworth, Taylor and co-workers succesfully applied this strategy in the total synthesis of spirobacillene A **12** (Scheme 8).[17] 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 $SnCl_2 \cdot H_2O$, 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.



Scheme 8. Unsworth, Taylor and co-workers synthesis of spirobacillene A **12**.

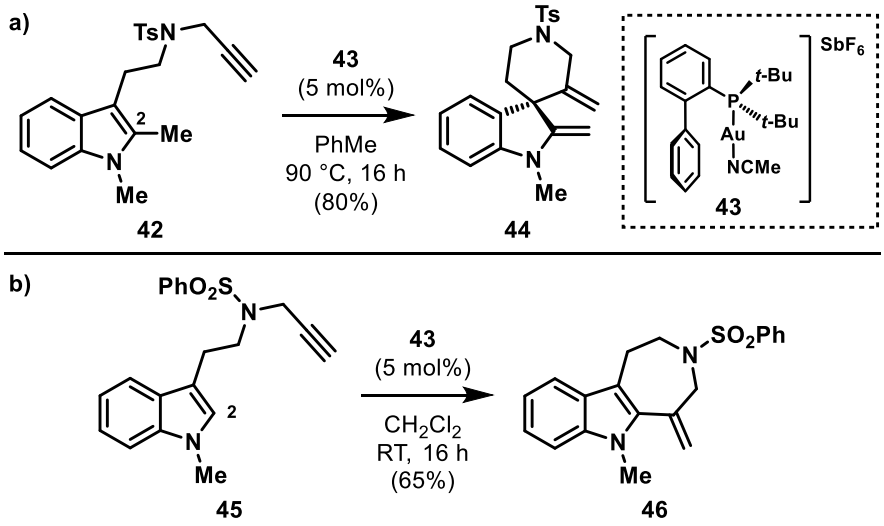
Unsworth, Taylor and co-workers also conducted preliminary studies towards spirobacillene B **13** by applying the same strategy. Unfortunately, when model ynone **40** was reacted under the same $SnCl_2 \cdot H_2O$-mediated conditions the desired spirocyclic indolenine **41** was obtained in only 40% yield, confirming the viability of this approach, but suggesting that improved spirocyclisation conditions were needed.



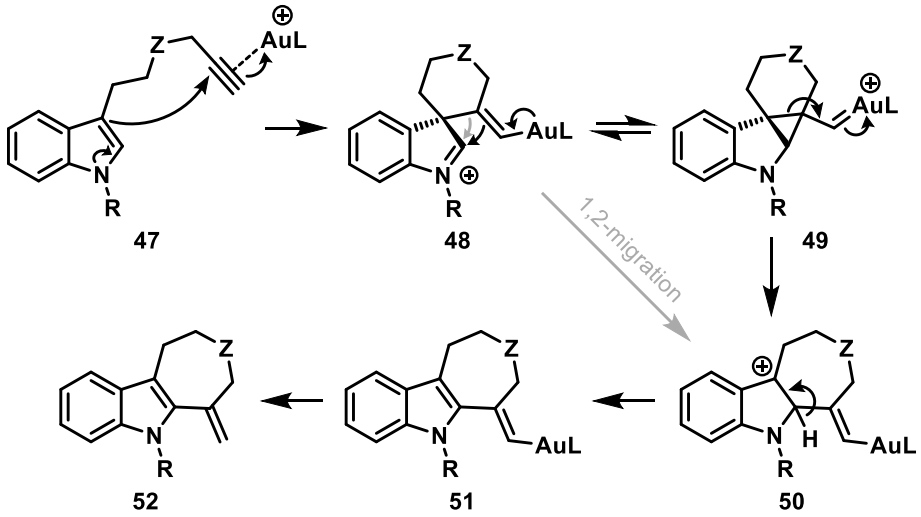
Scheme 9. Preliminary $SnCl_2 \cdot H_2O$-mediated spirocyclisation of indole-ynone **40**.

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).[18] 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**).

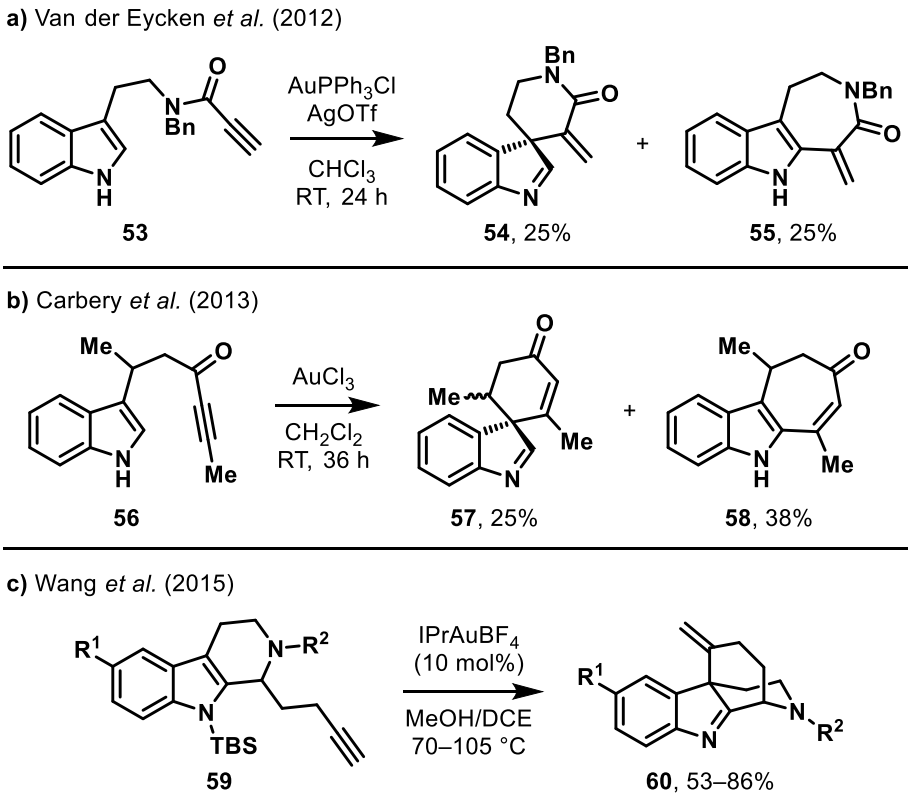


Scheme 10. The first Au(I)-catalysed cyclisations of indole-alkynes.



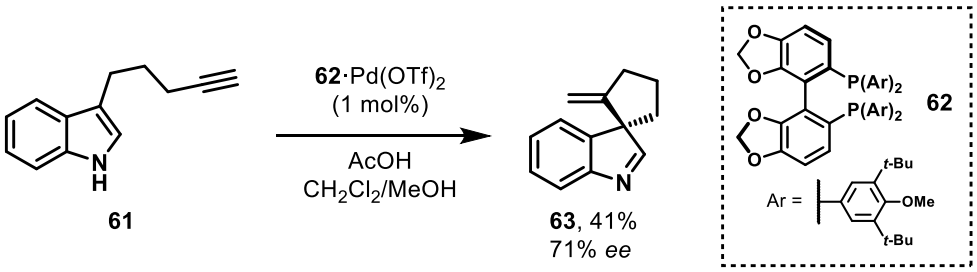
Scheme 11. Proposed mechanism for the formation of annulated indoles.

Later, in 2012, Van der Eycken and co-workers reported the first synthesis of a spirocyclic indolenine using this approach.[19] Again, a Au(I) catalyst was used with alkyne **53** to form a low yielding mixture of spirocyclic indolenine **54** and annulated indole **55** (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 **56** was reacted with $AuCl_3$ to form another low yielding mixture of spirocyclic indolenine **57** and annulated indole **58**.[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 **60**.[21] However, as the substrates **59** 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).



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).[22] 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** → **70** → **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]

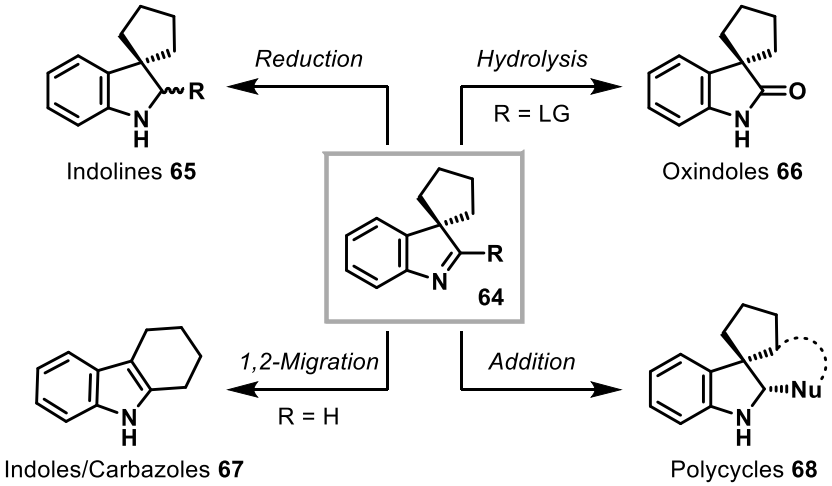


Figure 1. Synthetic utility of spirocyclic indolenines.

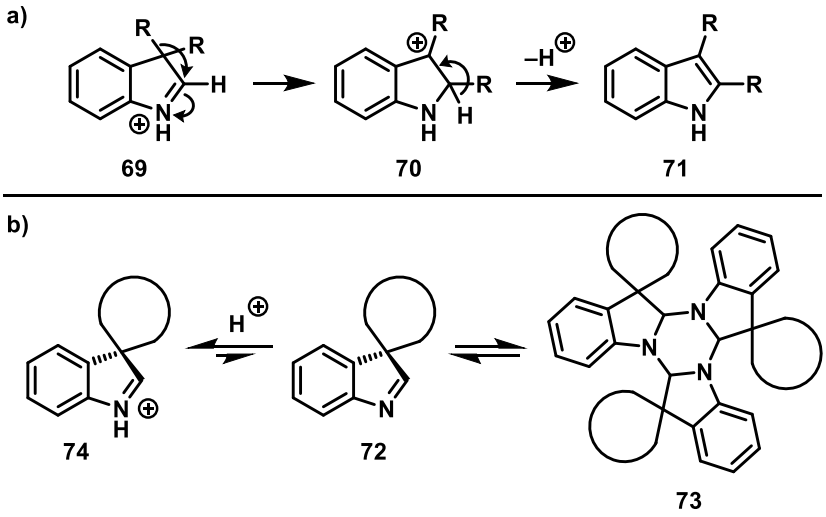
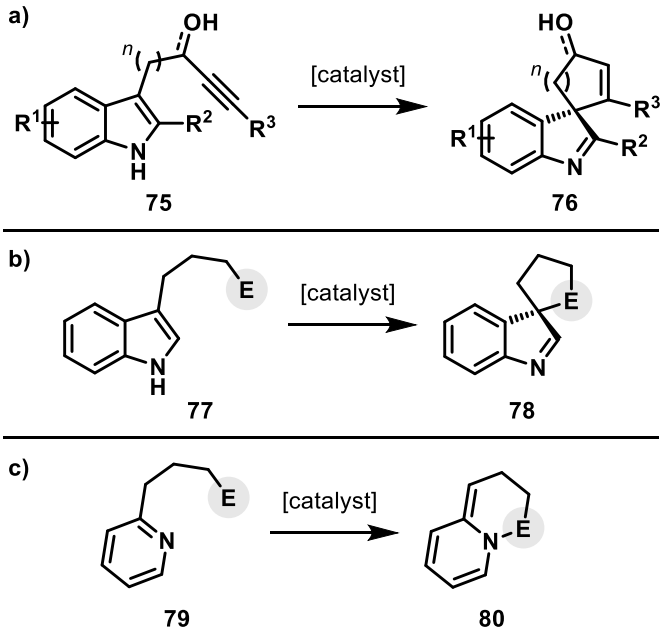


Figure 2. Reactivity of spirocyclic indolenines: a) 1,2-Migrations; b) Imine trimer formation.

1.5 Project aims

The initial goal of this project was to improve upon the preliminary $SnCl_2 \cdot 2H_2O$-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).



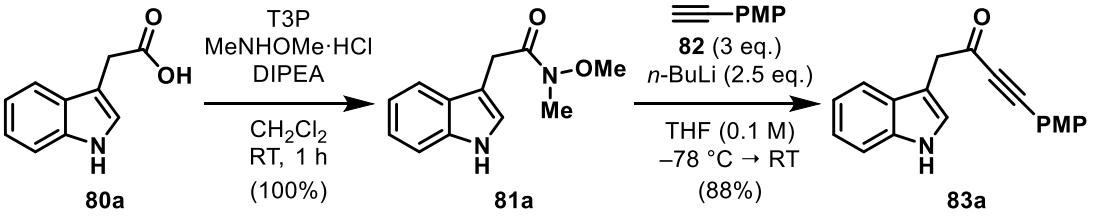
Scheme 14. Project aims overview.

Chapter 2. Indole-alkyne cyclisations

2.1 Indole-ynone cyclisations

2.1.1 Reaction discovery & optimisation studies

Studies towards the synthesis of spirobacillene B **13** 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.[47,48] 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.

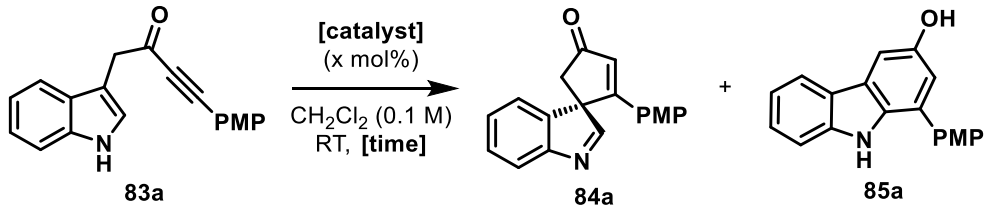


Scheme 15. Two step synthesis of model ynone **83a**.

Ynone **83a** was then reacted with a variety of potential catalysts in an attempt to improve upon the preliminary $SnCl_2 \cdot H_2O$-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 ^{1}H 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 $BF_3 \cdot OEt_2$, $SnCl_2 \cdot 2H_2O$ and in particular anhydrous $SnCl_4$ were also identified as effective catalysts (entries 4–12). Investigations into π-acid catalysts (entries 14–20) began with Ph_3PAuCl, which without an activating silver co-catalyst displayed minimal reactivity (entry 14); the combination of AgOTf and Ph_3PAuCl 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 $SnCl_4$. Finally, Ag(I) catalysts, AgOTf and $AgNO_3$ 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).



Entry	Catalyst (mol%)[a]	Time (h)	Ratio 83a:84a:85a[b]
1	aq. 12 M HCl (10)	24	82:18:0
2	TFA (10)	24	40:60:0
3	TfOH (10)	24	10:90:0
4	$AlCl_3$ (10)	24	91:9:0
5	$PdCl_2PPh_3$ (10)	24	84:16:0
6	$Sc(OTf)_3$ (10)	24	69:31:0
7	$Yb(OTf)_3$ (10)	24	54:46:0
8	$ZnCl_2$ (10)	24	45:55:0
9	$FeCl_3$ (10)	24	40:60:0
10	$BF_3{\cdot}OEt_2$ (10)	24	10:90:0
11	$SnCl_2{\cdot}2H_2O$ (10)	24	9:91:0
12	$SnCl_4$ (10)	24	0:100:0
13	Ph_3PAuCl (10)	24	88:12:0
14	**Ph_3PAuCl/AgOTf (10)**	**24**	**0:17:83**
15	CuCl (10)	24	52:48:0
16	$Cu(OAc)_2$ (10)	24	99:1:0
17	$Cu(OTf)_2$ (10)	24	0:100:0
18	AgOTf (10)	24	0:100:0
19	$AgNO_3$ (10)	24	0:100:0
20	$Cu(OTf)_2$ (1)	0.5	63:37:0
21	$AgNO_3$ (1)	0.5	7:93:0
22	**AgOTf (1)**	**0.5**	**0:100:0**
23	AgOTf (0.1)	120	15:85:0

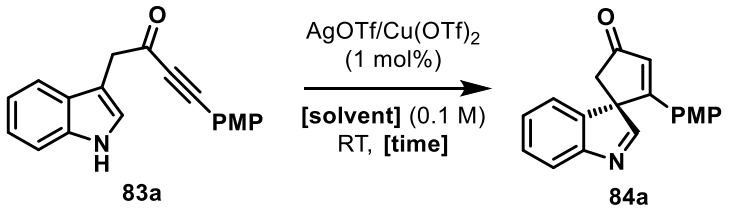
[a]All reactions performed with 0.1–0.3 mmol of ynone at RT;

[b]Calculated by ^{1}H 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_2Cl_2 was retained as the standard solvent due to its potential compatibility with a wider range of substrates.

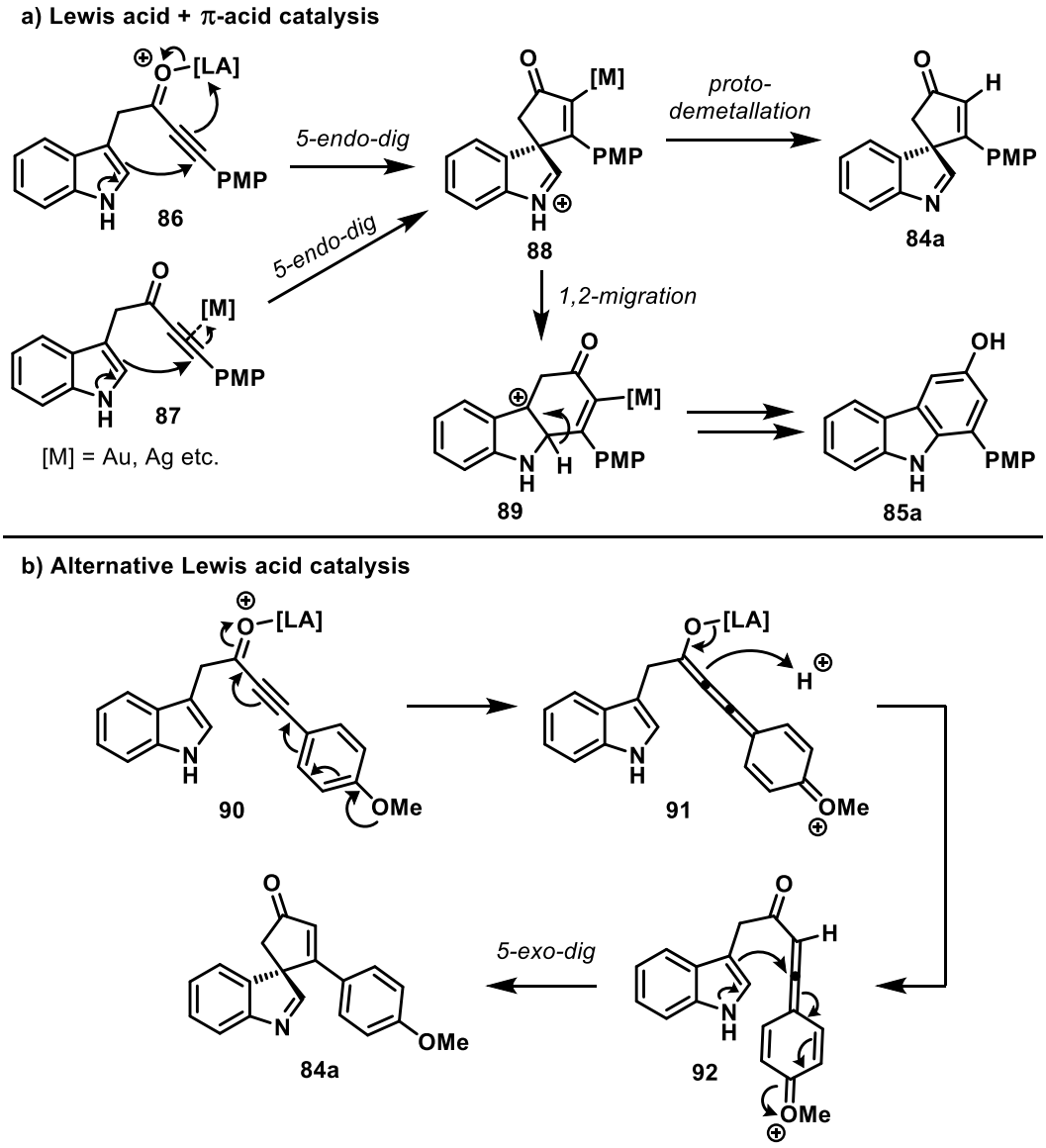


Entry	Catalyst	Solvent	Time (h)	Ratio 83a:84a[a]
1	$Cu(OTf)_2$	CH_2Cl_2	24	0:100
2	AgOTf		0.5	0:100
3	$Cu(OTf)_2$	$CHCl_3$	24	0:100
4	AgOTf		0.5	0:100
5	$Cu(OTf)_2$	PhMe	24	3:97
6	AgOTf		0.5	1:99
7	$Cu(OTf)_2$	MeCN	24	42:58
8	AgOTf		0.5	37:63
9	$Cu(OTf)_2$	THF	24	37:63
10	AgOTf		0.5	11:89
11	$Cu(OTf)_2$	Et_2O	24	41:59
12	AgOTf		0.5	69:31
13	$Cu(OTf)_2$	EtOH	24	0:100
14	AgOTf		0.5	Complex mixture

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

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

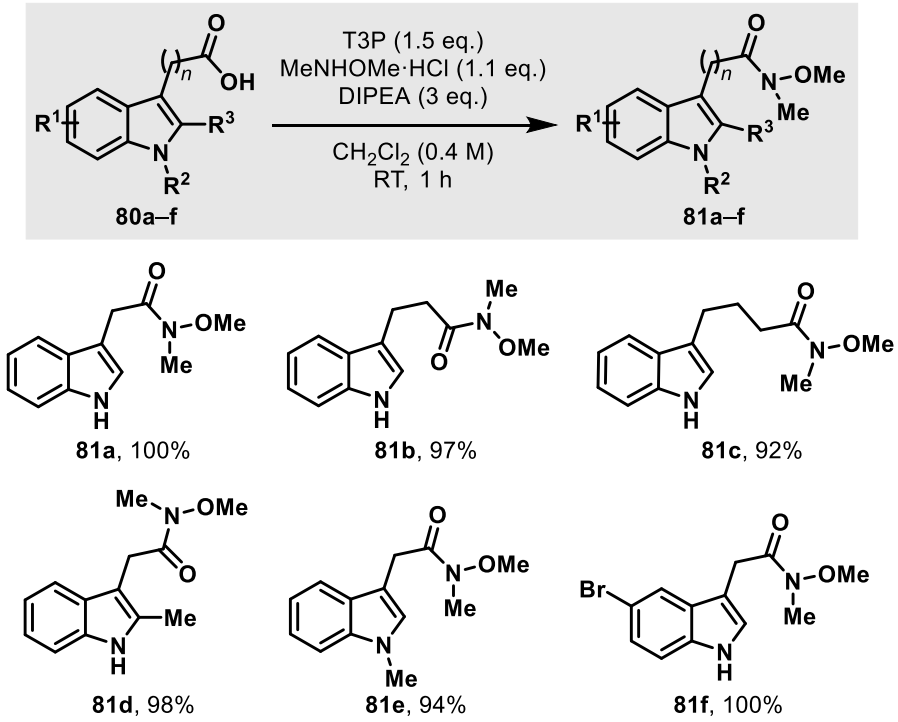
The variety of catalysts capable of forming the spirocycle **84a** suggests that a number of mechanistic pathways are possible (Scheme 16). For example, a *5-endo-dig* spirocyclisation (**86**/**87** → **88**) could be induced by either (i) co-ordination of a Lewis acid to the ynone carbonyl, increasing 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 protodemetallation 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** → **91**) to afford an electrophilic allenyl intermediate **92**, which could undergo a *5-exo-dig* spirocyclisation as shown to afford spirocycle **84a**.



Scheme 16. Potential mechanisms for the spirocyclisation of **83a**: a) Direct *5-endo-dig* cyclisation of the alkyne; b) Alternative allenolate formation and *5-exo-dig* cyclisation.

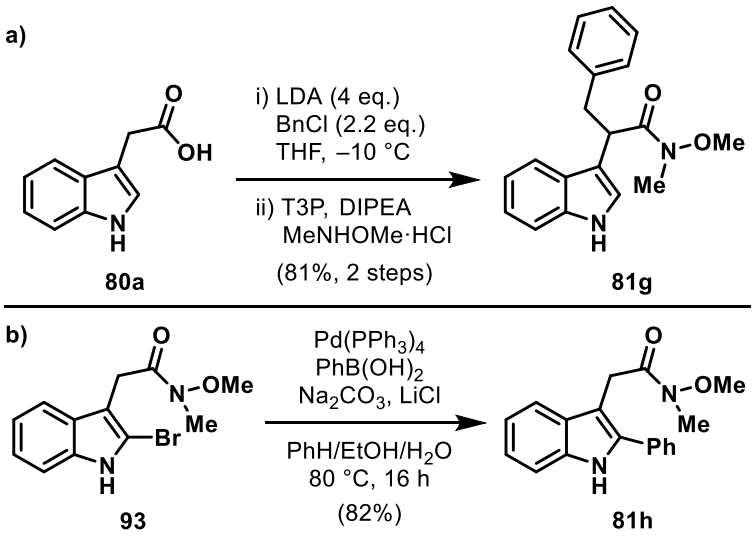
2.1.2 Substrate Synthesis

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).



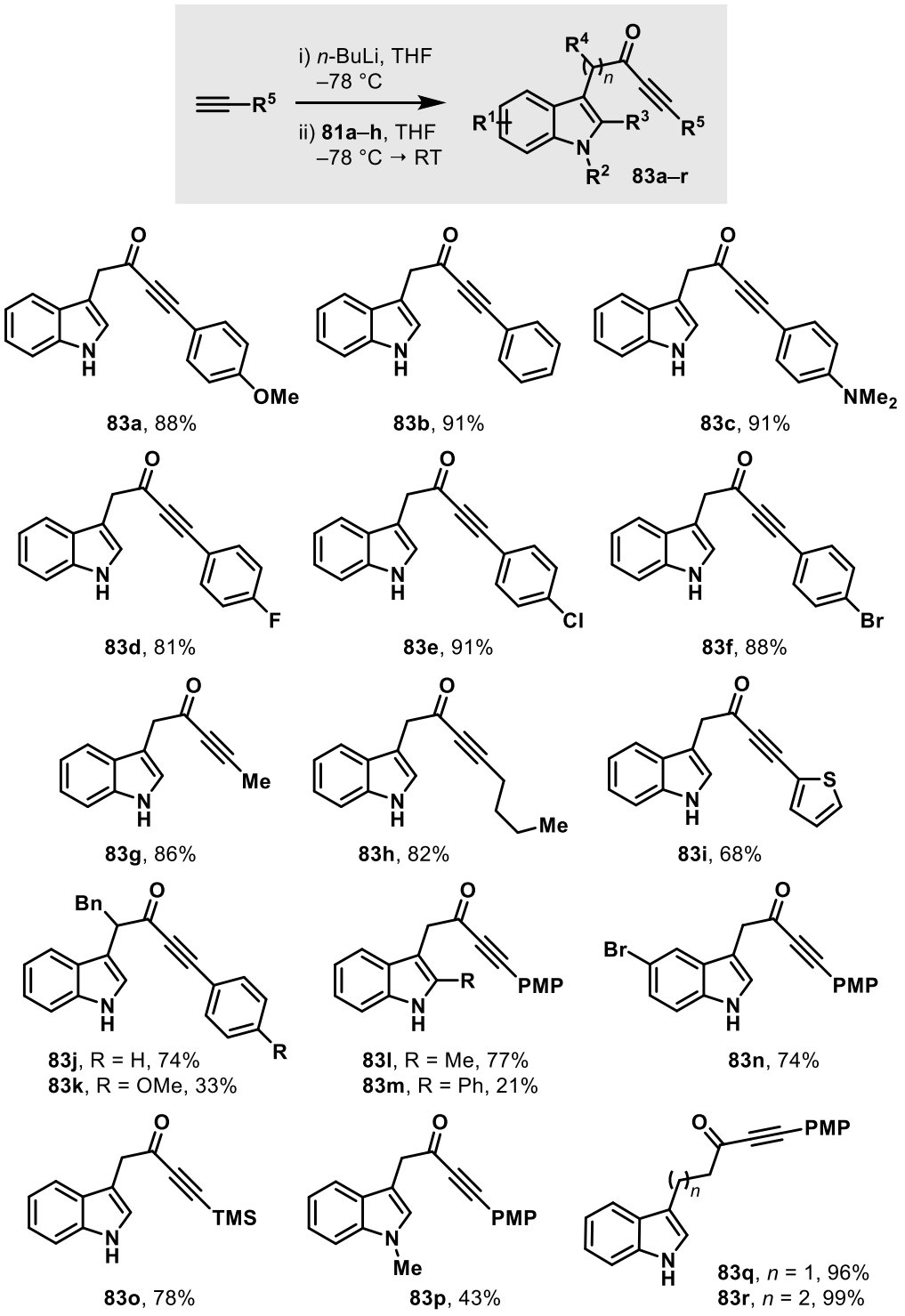
Scheme 17. Scope of Weinreb amides synthesised using T3P.

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).[49] 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**,[50] with phenyl boronic acid.



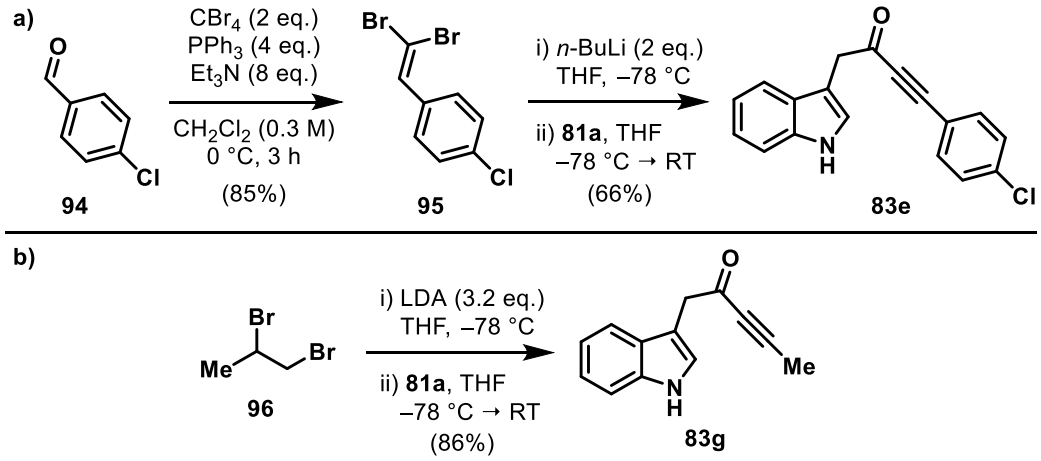
Scheme 18. Synthesis of other functionalised Weinreb amides: a) Chemoselective α-alkylation of **80a**; b) Suzuki cross-coupling of **93**.

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 ynones **83a**–**r**, generally in excellent yields (Scheme 19).



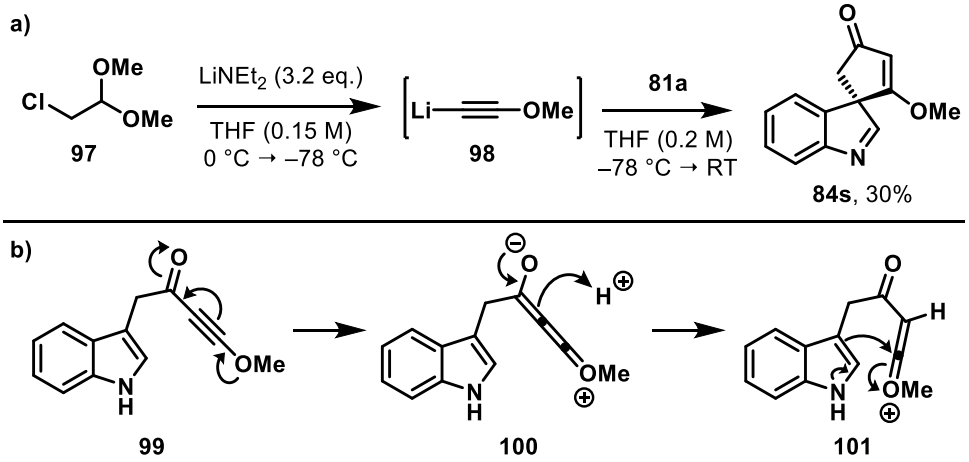
Scheme 19. Scope of indole-ynones prepared.

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**.

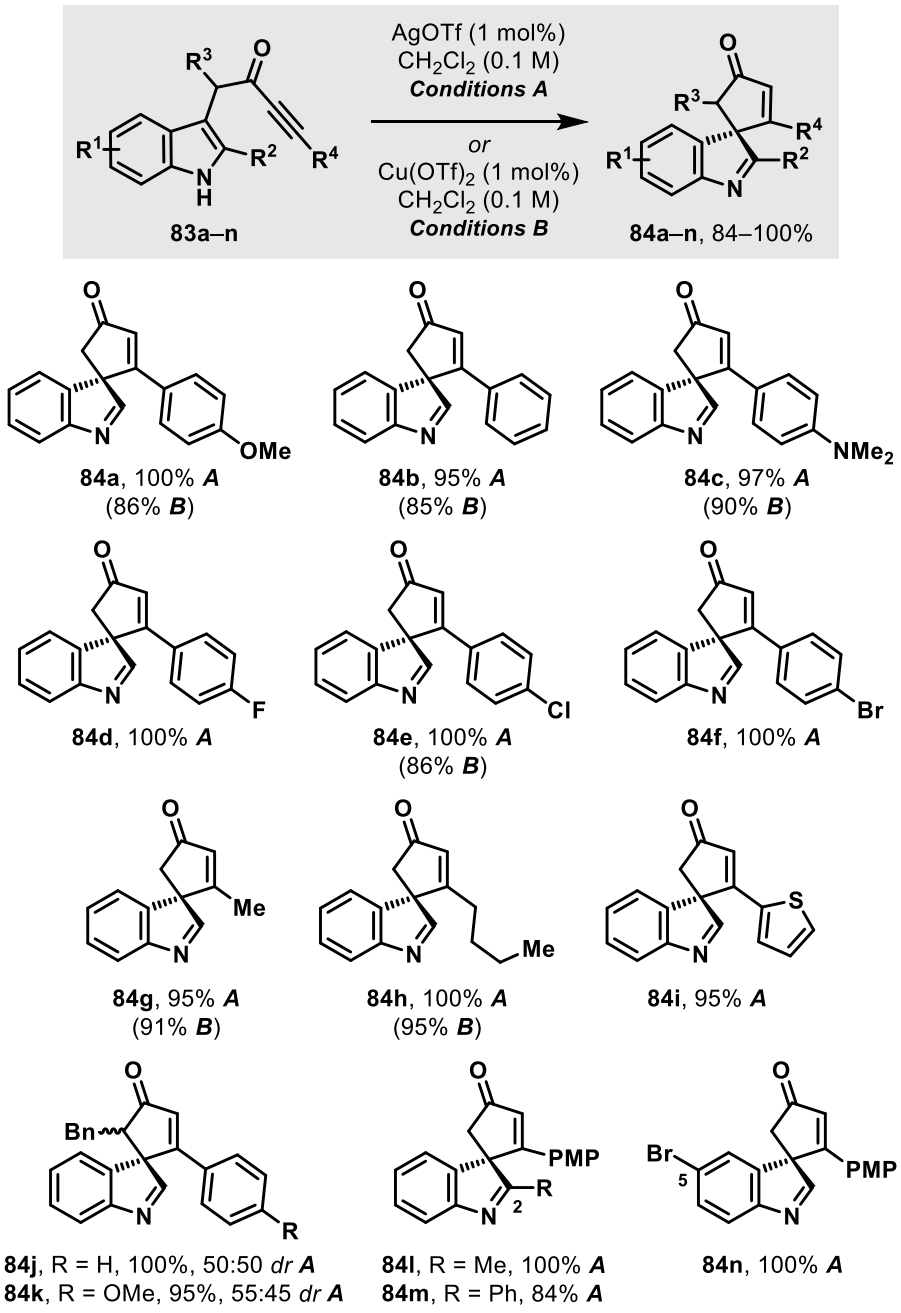
Interestingly, the attempted formation of a methoxy ynone resulted in the unexpected formation of spirocycle **84s** (Scheme 21). The reaction of amide **81a** with lithium acetylide **98** (generated by a literature procedure from 2-chloro-1,1-dimethoxyethane **97**)[52] afforded only a modest yield 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_2Cl_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 sterics of the phenyl ring forcing the alkyne moiety perpendicular to the indole ring.



Scheme 22. Indole-ynone *5-endo-dig* spirocyclisation substrate scope.

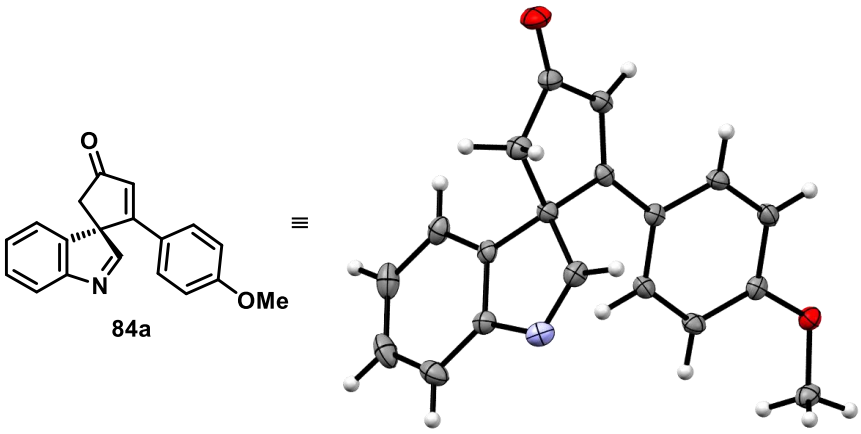


Figure 3. X-ray structure of spirocycle **84a** with thermal ellipsoids shown at 50% (CCDC 1023667).

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 diastereocontrol. 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),[41] 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.

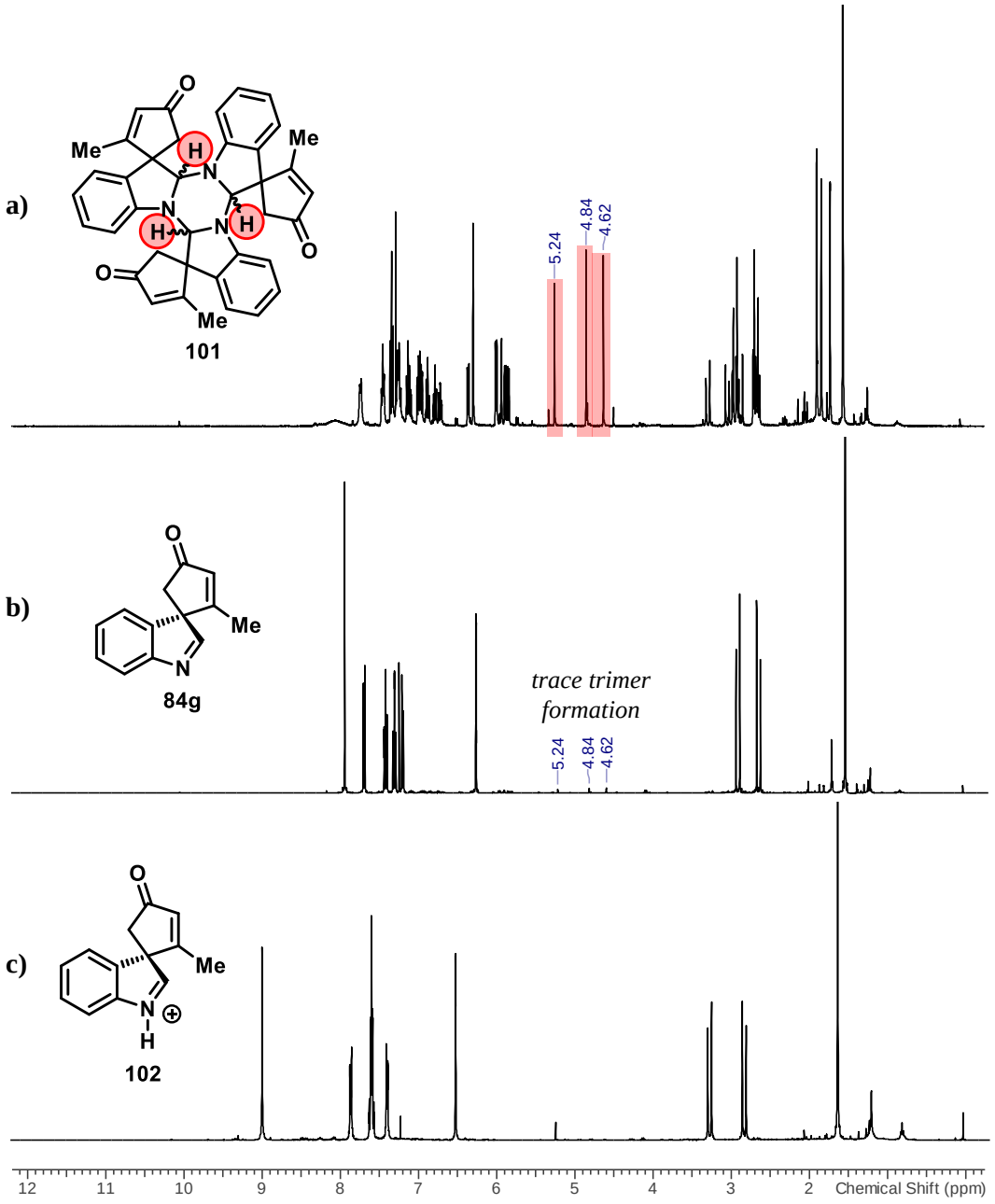
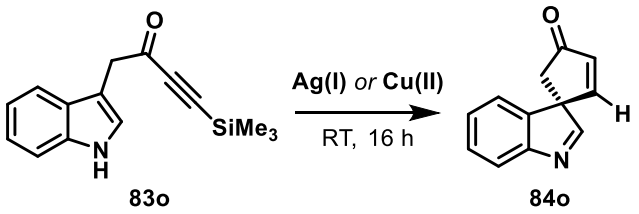


Figure 4. ^{1}H NMR spectra: a) Spirocycle **84g** made using $Cu(OTf)_2$; b) Spirocycle **84g** made using AgOTf; c) Spirocycle **84g** made with $Cu(OTf)_2$ and with the addition of TFA.

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,[54] 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.[55] 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.

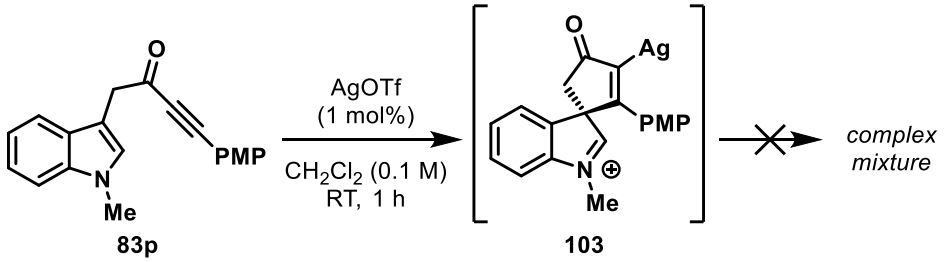


83o 84o

Entry	Catalyst	Solvent	Yield (%)
1	AgOTf (10 mol%)	CH_2Cl_2	-
2	$Cu(OTf)_2$ (10 mol%)	CH_2Cl_2	-
3	$AgNO_3$ (20 mol%)	Me_2CO	93

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

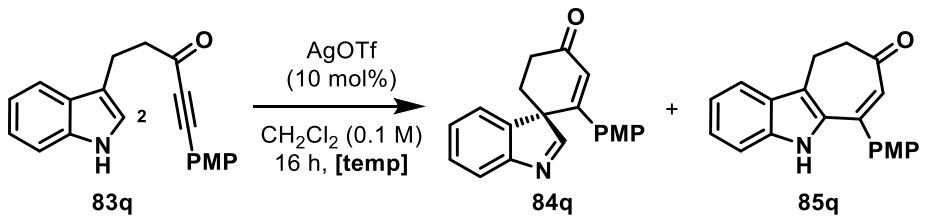
Finally, the only substrate which failed to form a 5-membered enone spirocycle under the standard reaction conditions was *N*-methylated ynone **83p**, which when reacted with AgOTf in CH_2Cl_2 afforded only a complex mixture (Scheme 23). This decomposition is presumed to be due to the instability of cationic intermediate **103**.



83p 103

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 supress 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.



		Yield (%)	
Entry	**Temperature (°C)**	**84q**	**85q**
1	RT	34	-
2	40	52	48
3	35	75	11

Table 4. Reactivity of extended ynone **83q** with AgOTf.

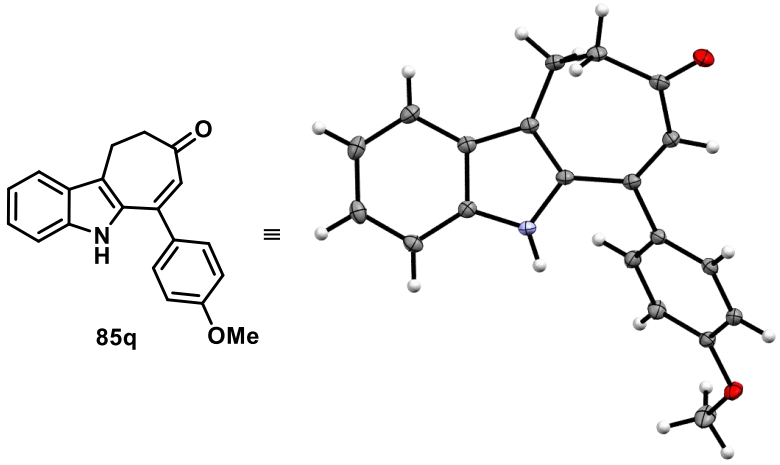
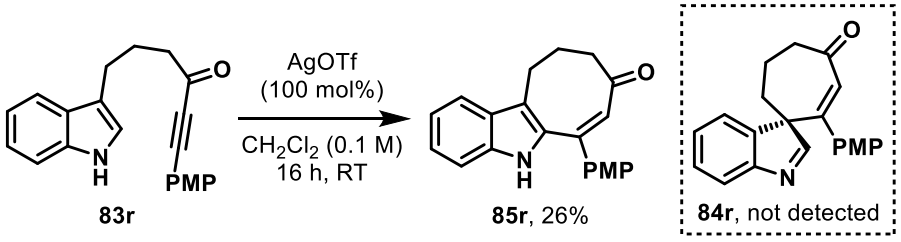


Figure 5. X-ray structure of C2-annuated indole **85q** with thermal ellipsoids shown at 50% (CCDC 1531214).

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).



Scheme 24. Reactivity of extended ynone **83r** with stoichiometric AgOTf.

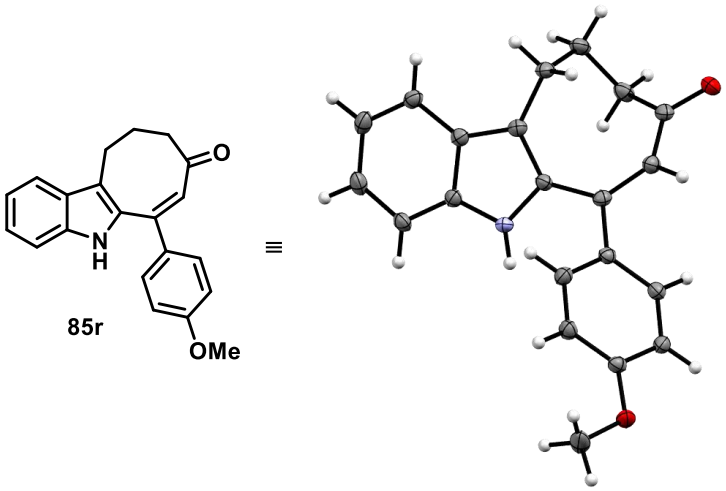
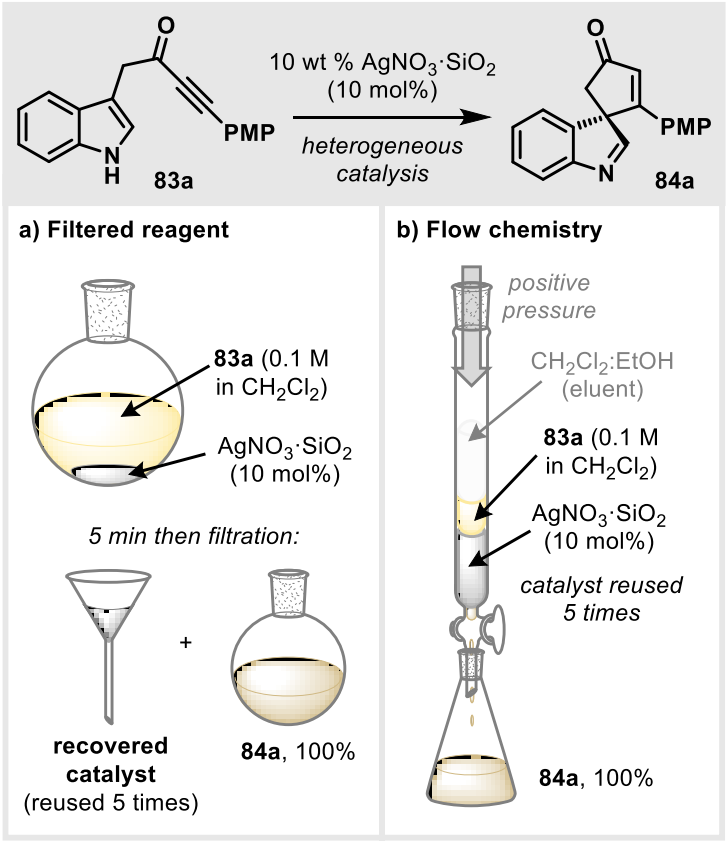


Figure 6. X-ray structure of C2-annulated indole **85r** with thermal ellipsoids shown at 50% (CCDC 1531215).

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 ($AgNO_3 \cdot SiO_2$), 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 $AgNO_3 \cdot SiO_2$ (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.



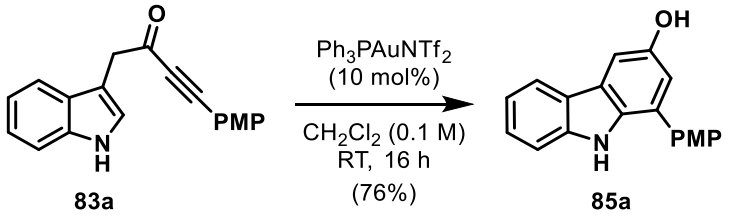
Scheme 25. Heterogeneous catalysis of $AgNO_3 \cdot SiO_2$: a) As a filtered reagent; b) For use in flow chemistry.

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 $AgNO_3$ 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 protodemetallation 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 (Ph_3PAuCl and AgOTf, see Table 1, entry 14). To investigate the role of Au(I)-catalysis in this transformation further, a commerically available cationic catalyst $Ph_3PAuNTf_2$ was chosen as a catalyst probe;[59] 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.[60] As hoped, carbazole **85a** was then prepared in good yield by reacting ynone **83a** with $Ph_3PAuNTf_2$ (10 mol%) in CH_2Cl_2, 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 $Ph_3PAuNTf_2$ to form carbazole **85a**.

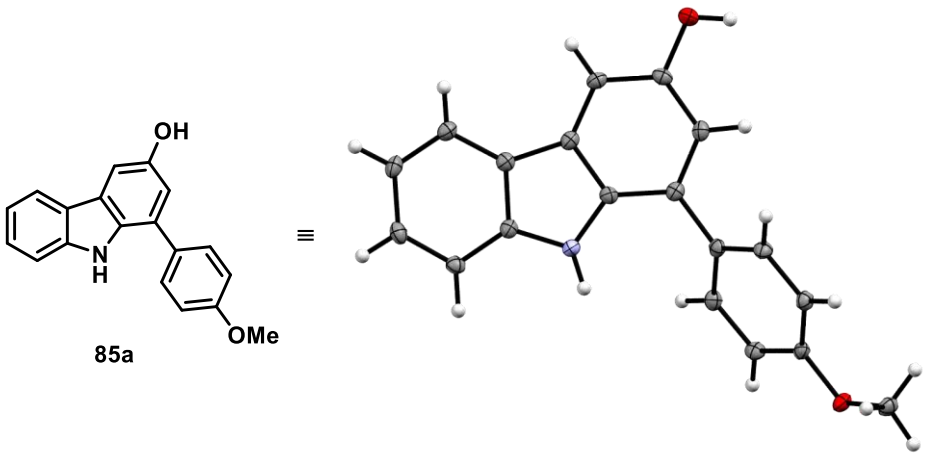
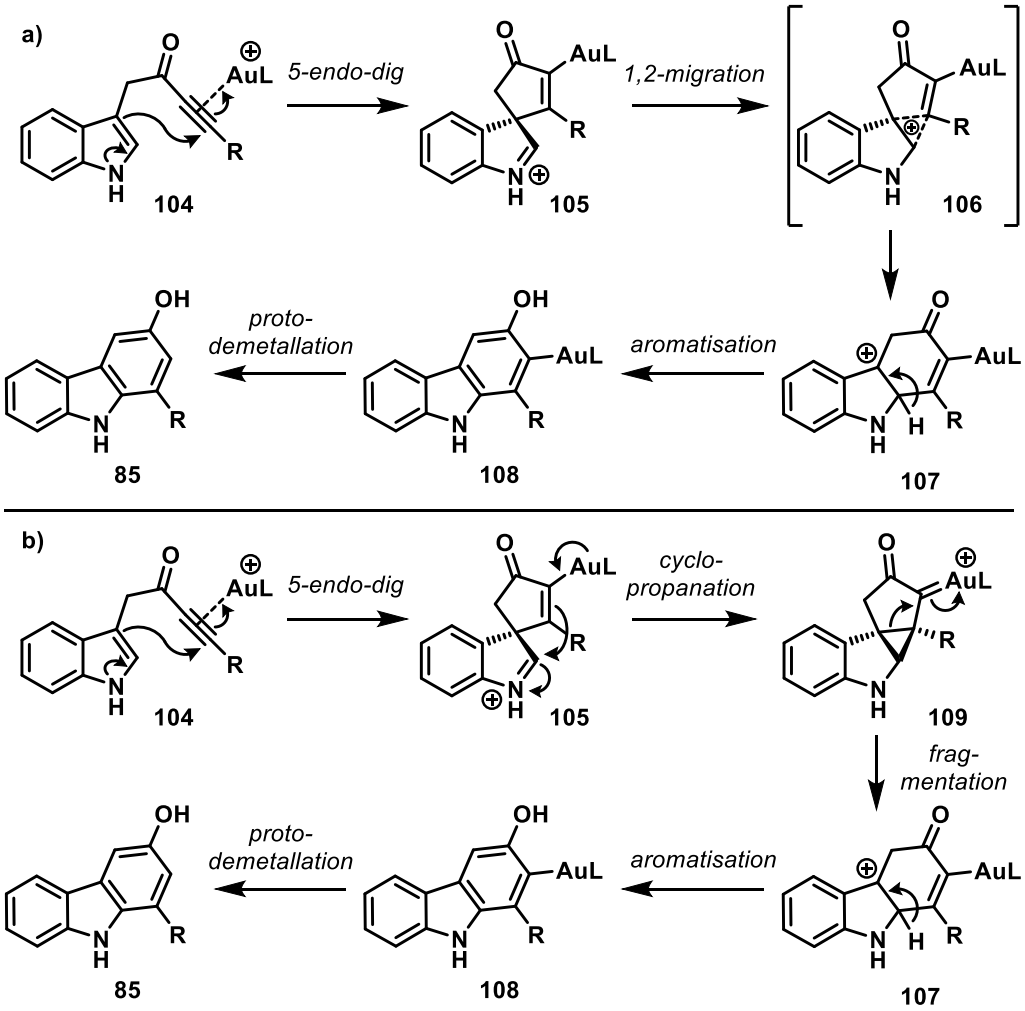


Figure 7. X-ray structure of carbazole **85a** with thermal ellipsoids shown at 50% (CCDC 1531216).

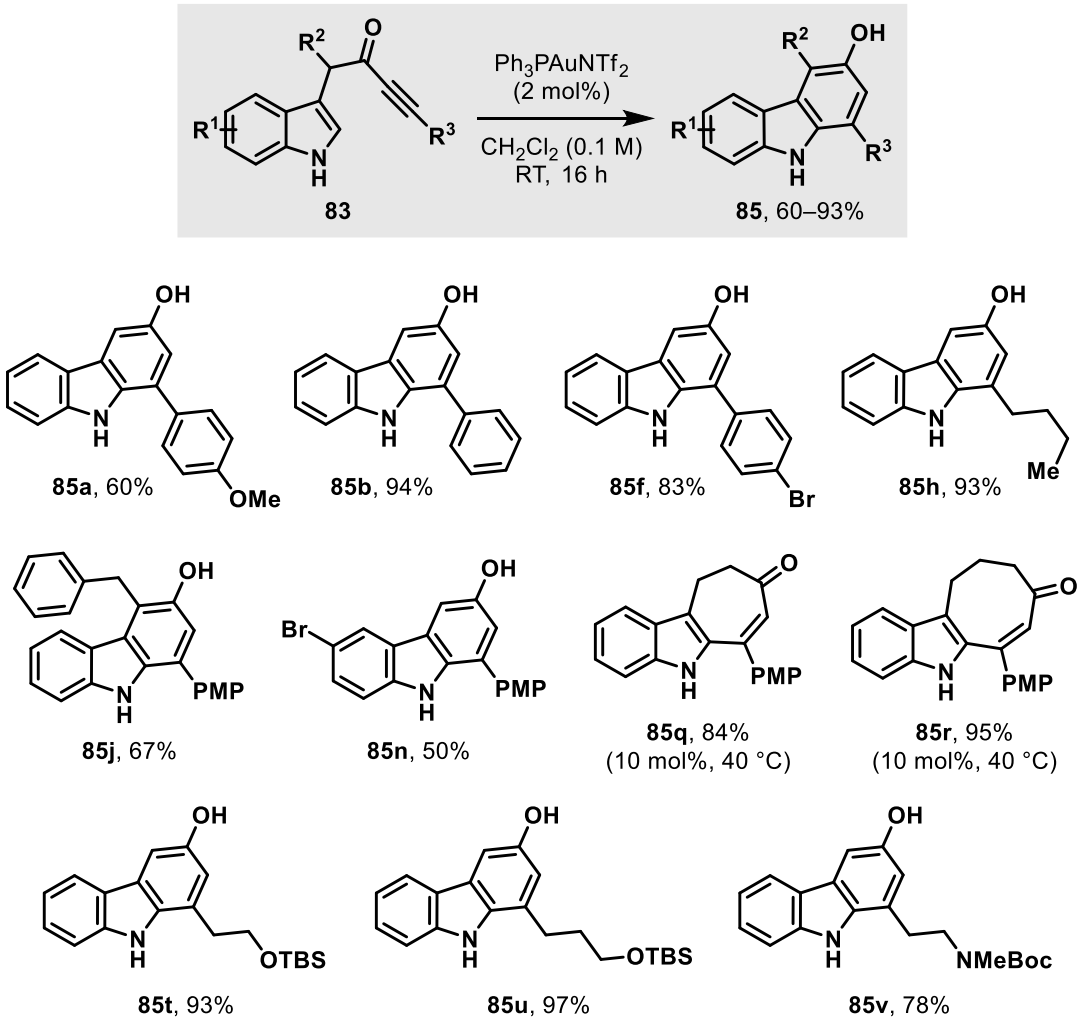
Interestingly, no reaction was observed when spirocycle **84a** was reacted with $Ph_3PAuNTf_2$ under the same reaction conditions, ruling out the spirocycle **84a** as a direct precursor to the carbazole **85a**. This is further supported by the proven stability of spirocycle **84a** under various acidic 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[61] (**105** → **106** → **107**, Scheme 27a) or via a formal cyclopropanation and fragmentation pathway (**105** → **109** → **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 π-back bonding.[62]



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.[63]

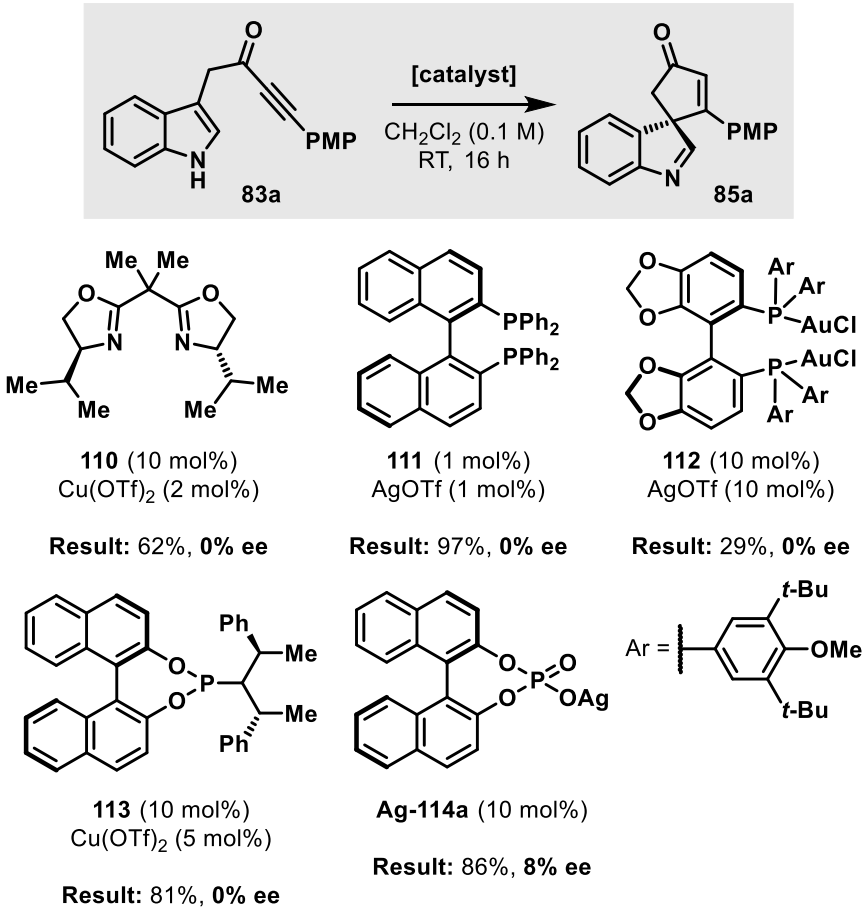


Scheme 28. Wider scoping studies using $Ph_3PAuNTf_2$ (conducted primarily by John T. R. Liddon).

2.1.6 Asymmetric indole-ynone spirocyclisations

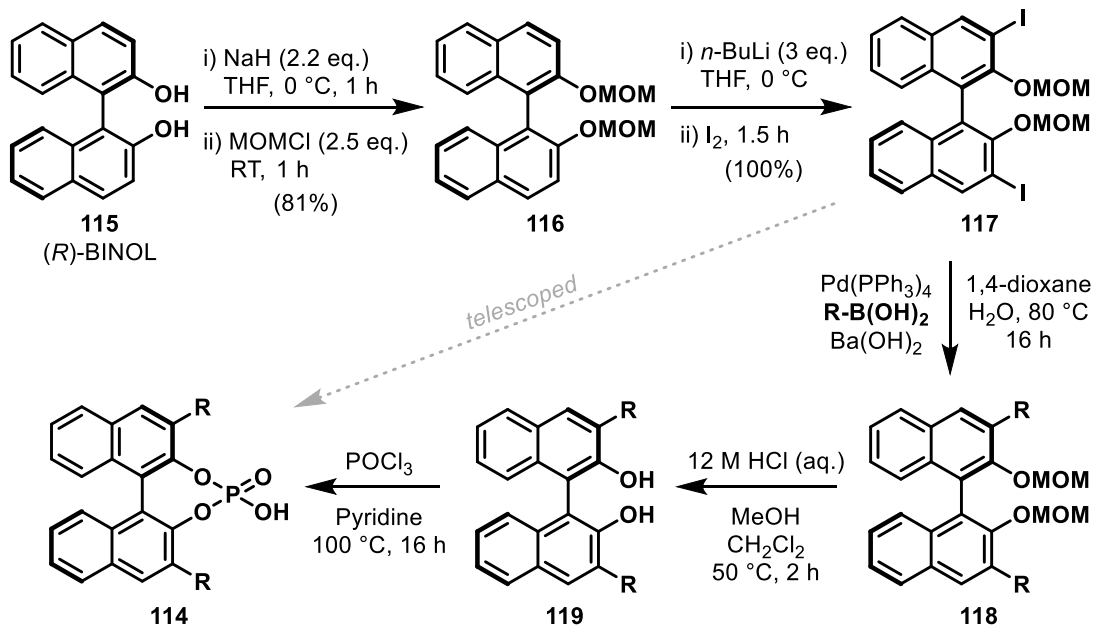
2.1.6.1 Catalyst discovery & optimisation studies

Having adequately developed the racemic spirocyclisation 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-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.



Scheme 29. Initial asymmetric catalyst screen.

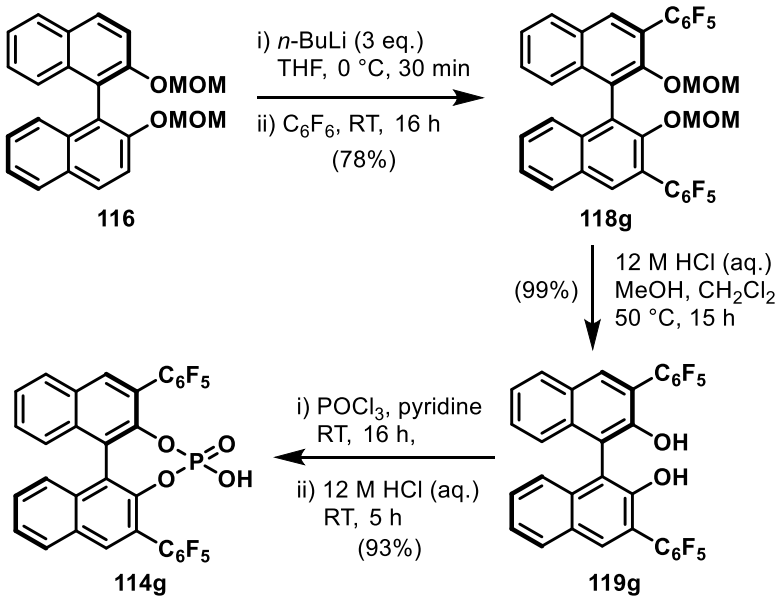
A number CPA catalyst were then acquired from commercial sources or prepared by known literature procedures, using **117** as a common intermediate from which a telescoped reaction sequence afforded the corresponding CPAs (Table 5).



Entry	R	Yield over 3 steps [%]
1	1-Naphthyl (**114b**)	59
2	2-Naphthyl (**114c**)	81
3	4-Ph-C_6H_4 (**114d**)	50
4	1-Pyrene (**114e**)	20
5	3,5-Ph_2-C_6H_4 (**114f**)	94

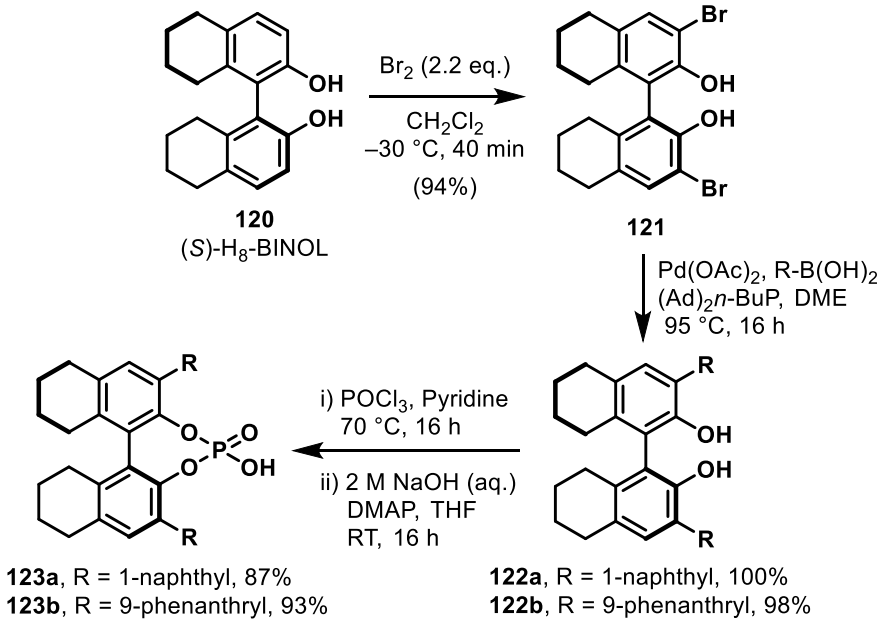
Table 5. Telescoped synthesis of BINOL-based CPA.

The electron deficient CPA **114g** was synthesised via an analogous route (Scheme 30), utilising an S_NAr reaction with hexafluorobenzene to install the C_6F_5 aromatics in the 3,3′-positions instead of employing a Suzuki cross-coupling.



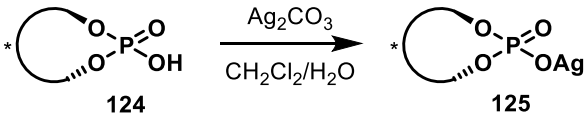
Scheme 30. Synthesis of C_6F_5 substituted catalyst **187**.

A smaller number of 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 **120** in only the 3,3′-positions.



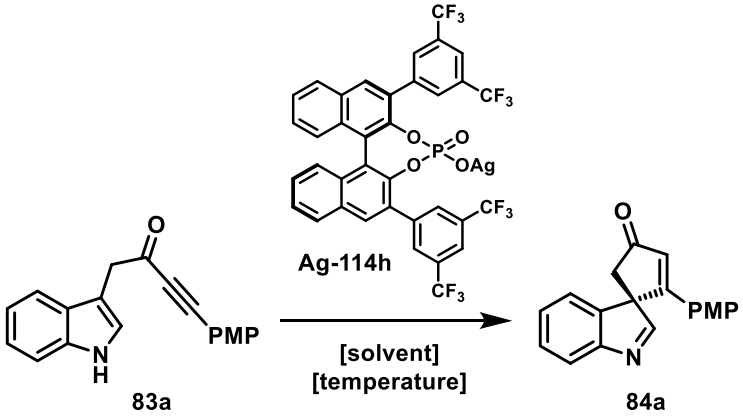
Scheme 31. Overview of H_8-BINOL CPA synthesis.

Finally, the corresponding silver salts were prepared according to a literature procedure,[66] by reacting the CPAs with Ag_2CO_3 in a biphasic mixture of CH_2Cl_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 32. Formation of Ag-CPA salts by deprotonation with Ag_2CO_3.

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_2Cl_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.



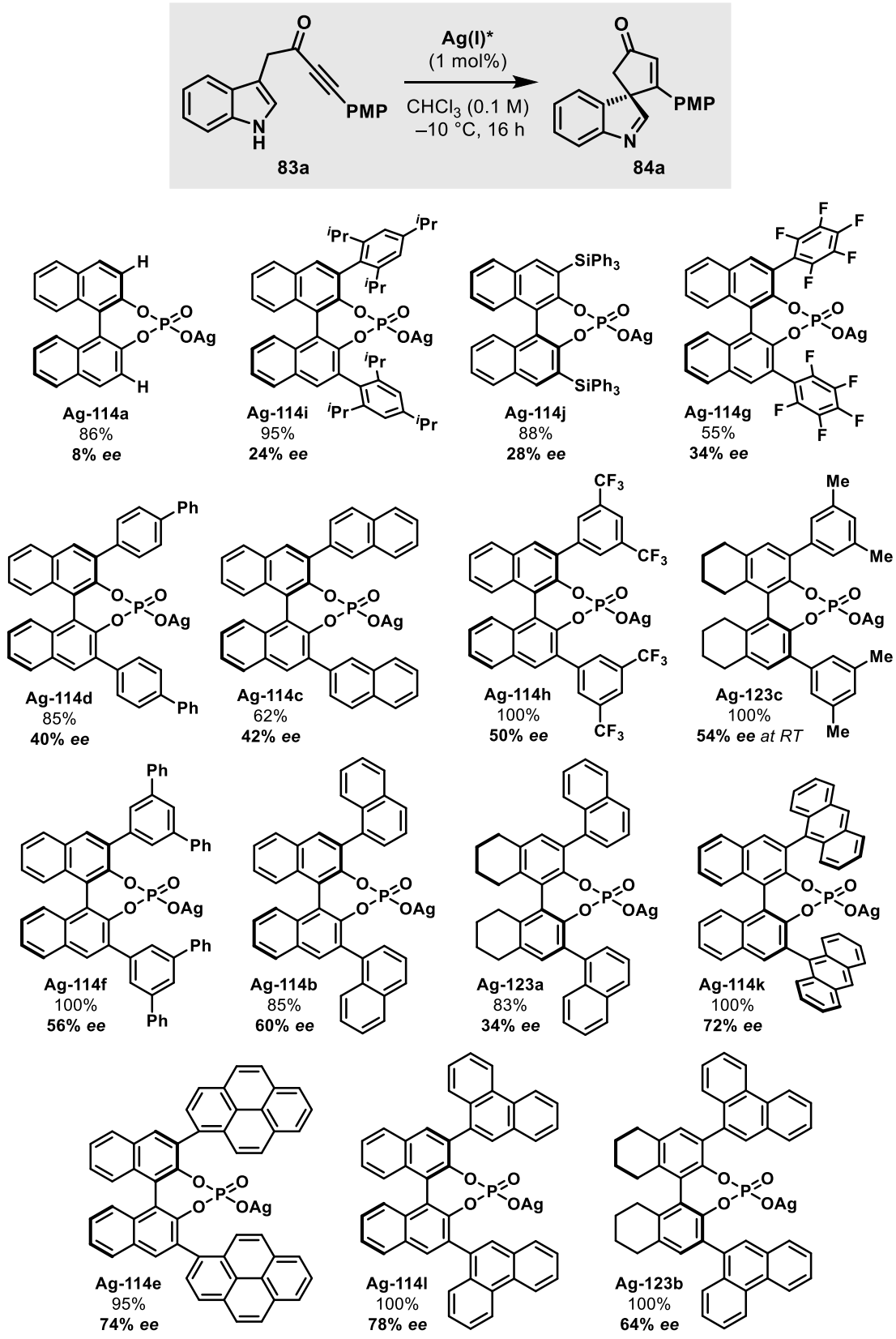
Entry	Catalyst Loading	Temp. (°C)	Solvent	Time	Yield (%)	*ee** (%)
1	5 mol%	–10	CH_2Cl_2	0.5 h	98	20
2	1 mol%	–10	THF	4 h	100	0
3	5 mol%	–10	DCE	3 h	95	8
4	1 mol%	–10	Toluene	2 h	91	26
5	1 mol%	–10	$CHCl_3$	1.5 h	100	50
6	1 mol%	–40	$CHCl_3$	17 h	86	52

**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 ($CHCl_3$ at −10 °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 H_8-BINOL backbone. From this observation it was hypothesised that the larger sterics of the H_8-BINOL catalyst backbone forms a more open catalyst cavity compared to the BINOL catalyst analogue (Figure 8a, b).[67,68] 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).[69]

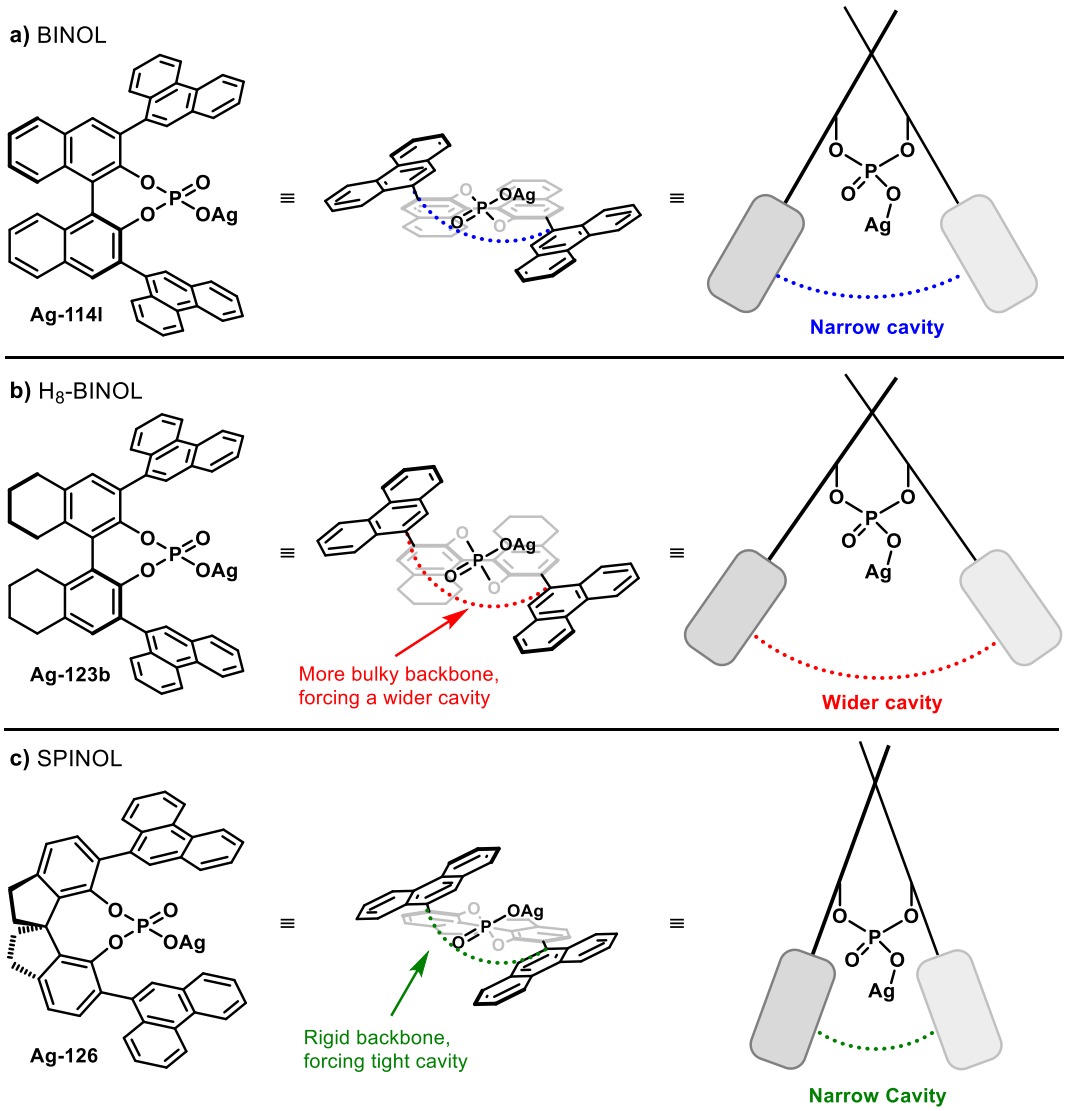
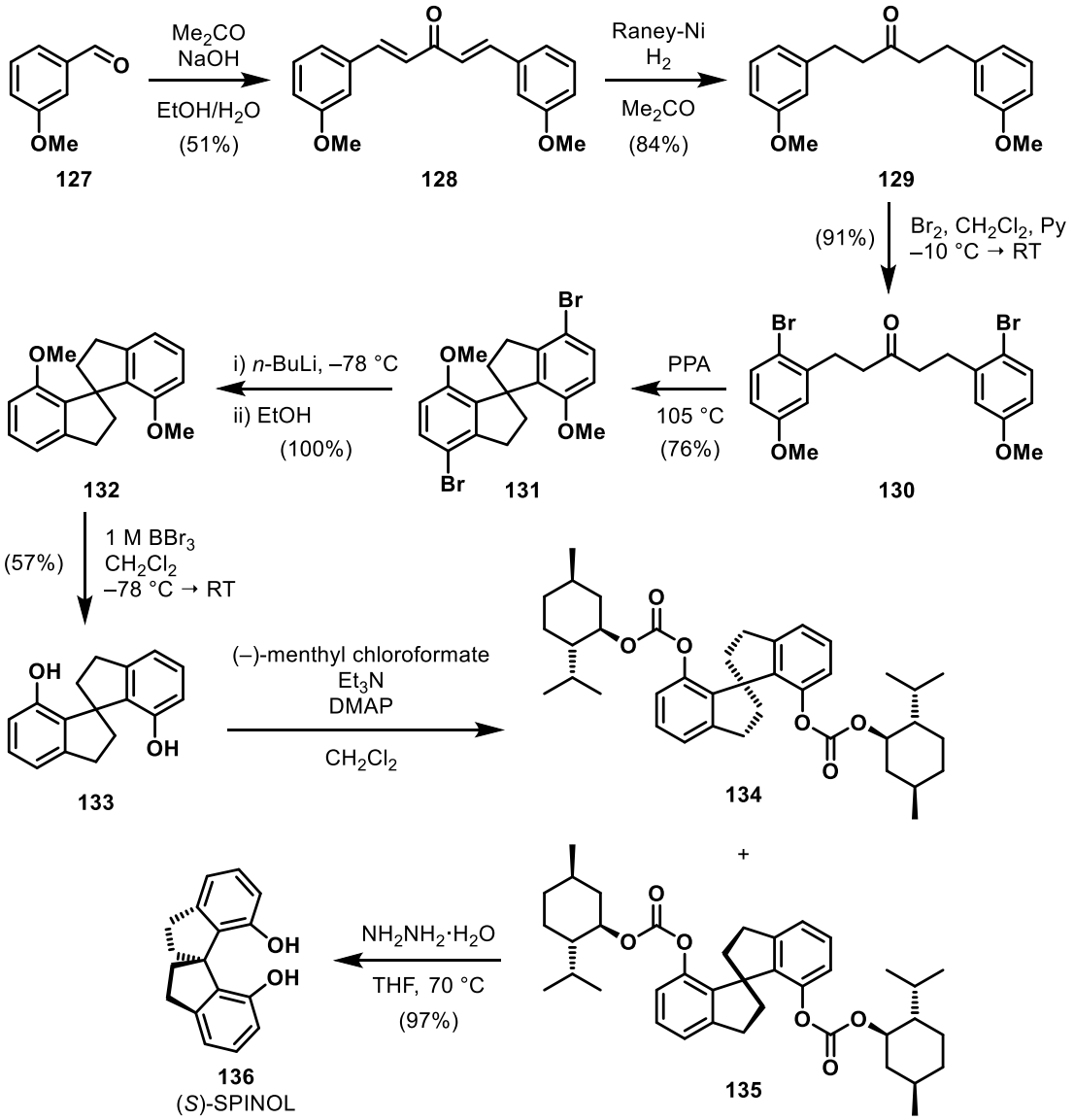
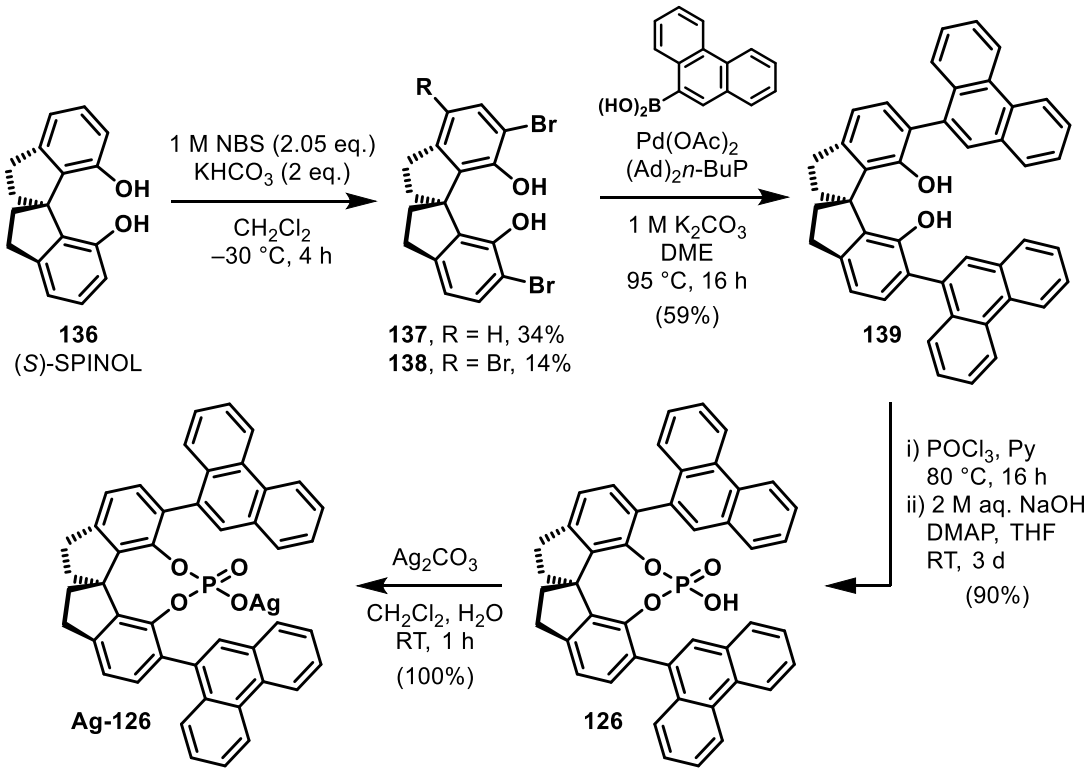


Figure 8. Hypothetical comparison of the different chiral phosphoric acid cavities: a) BINOL; b) H_8-BINOL; c) SPINOL.



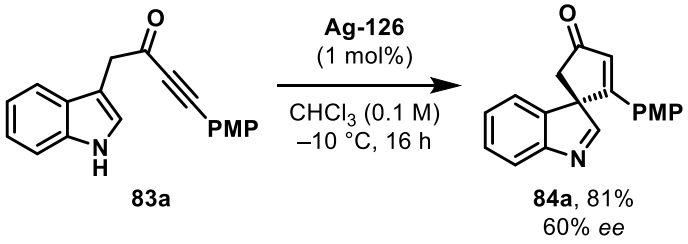
Scheme 34. Literature synthesis of (*S*)-SPINOL **136**.[69]

With the enantiopure (*S*)-SPINOL **136** in hand, attempts to perform the known selective bromination of **136** were carried out (Scheme 35).[70] 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.



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

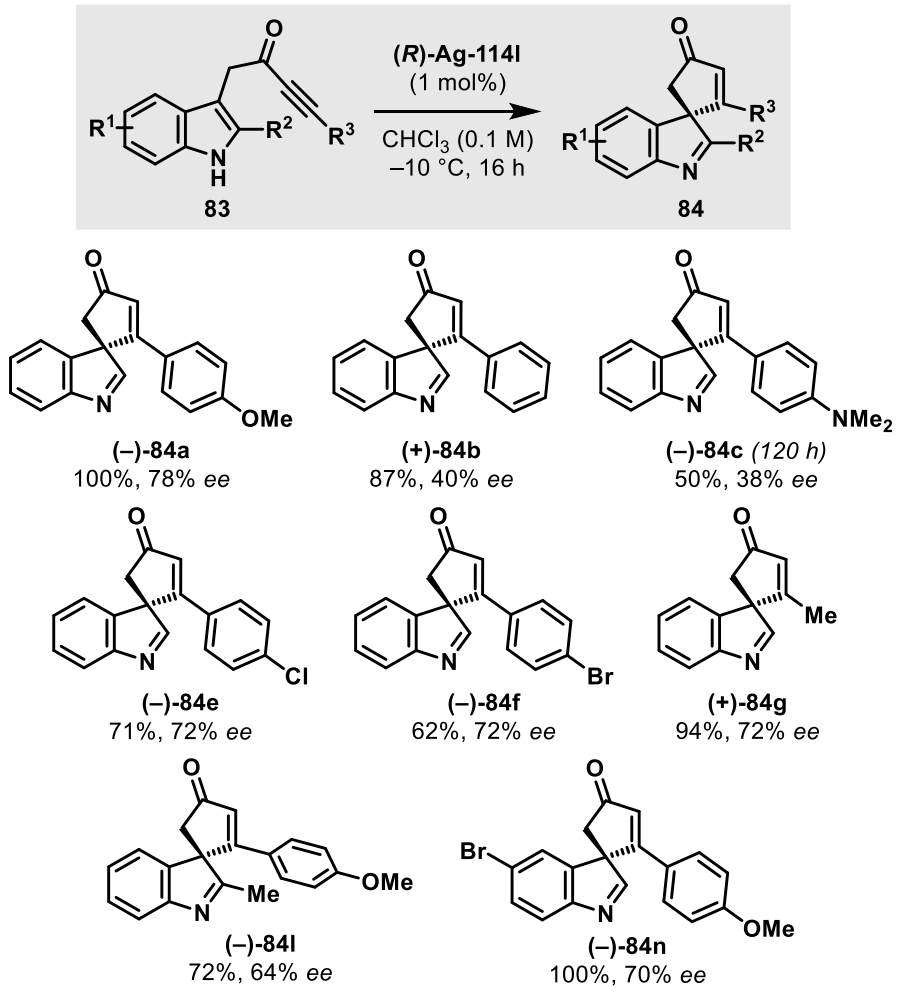
Finally, the reaction of **Ag-126** with ynone **83a** afforded the spirocycle in a disappointing 60% *ee* (Scheme 36). From this result a comparison with the fable of 'Goldilocks and the three bears' was noted, where perhaps the BINOL-based cavity is 'just right'.



Scheme 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.



Scheme 37. Overview of asymmetric substrate scope with **Ag-114l**.

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.

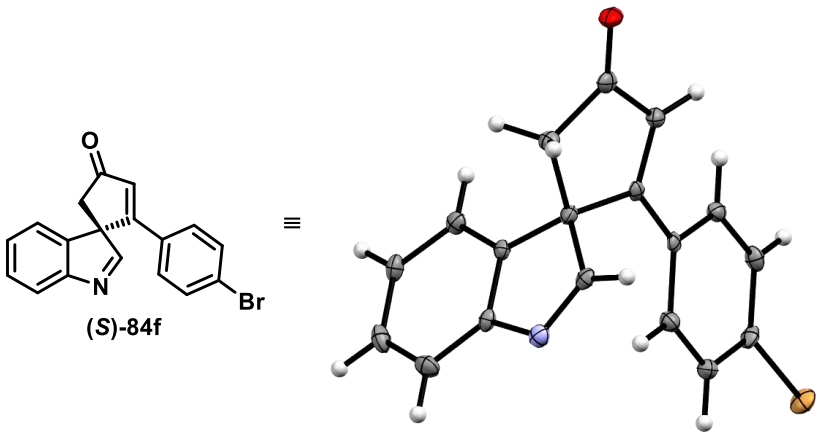


Figure 9. X-ray structure of enantiopure-spirocycle **84f** with thermal ellipsoids shown at 50% (CCDC 1049165).

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

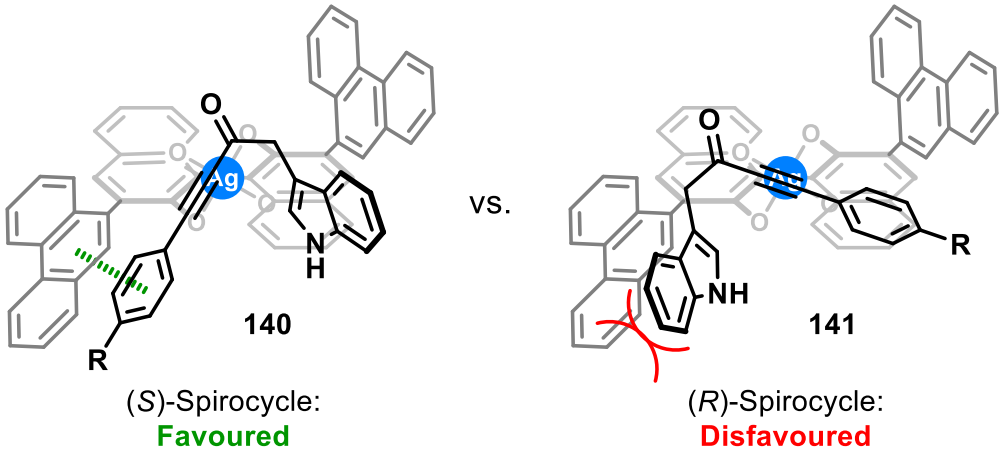
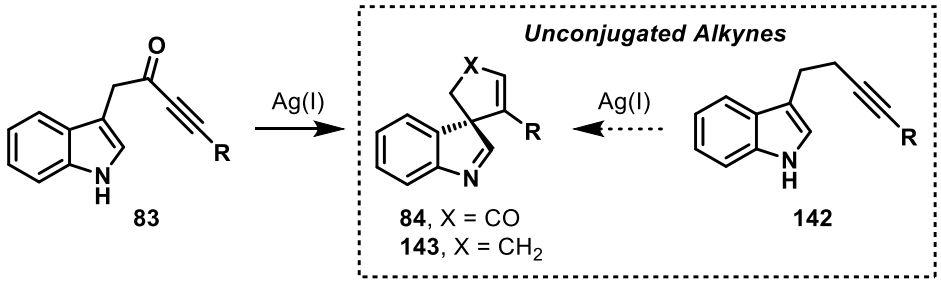


Figure 10. Proposed models for asymmetric induction.

2.2 Indole-propargyl alcohol cyclisations

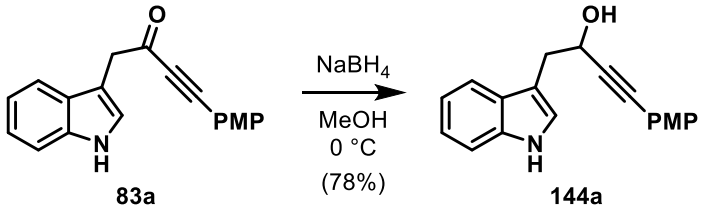
2.2.1 Introduction & initial studies

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).

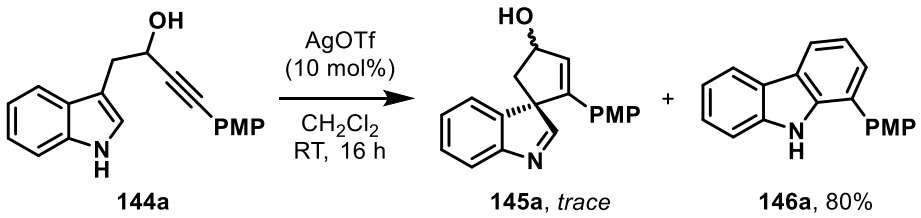


Scheme 38. Proposed spirocyclisation of unconjugated alkynes.

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 $NaBH_4$ reduction of ynone **83a** (Scheme 39). The resultant propargyl alcohol **144a** was then reacted with AgOTf at elevated catalyst loading (10 mol%) in CH_2Cl_2 to afford carbazole **146a** in excellent yield, with only a trace of the desired spirocycle **145a** detected by ^{1}H NMR spectroscopy (Scheme 40).



Scheme 39. Synthesis of propargyl alcohol **144a** by $NaBH_4$ reduction.

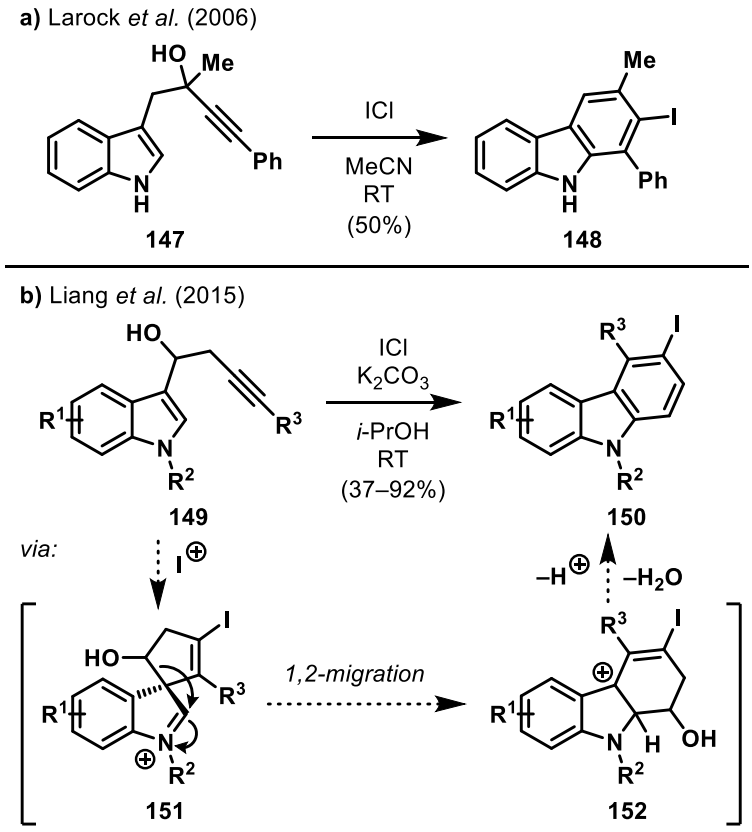


Scheme 40. Initial studies with propargyl alcohol **144a**.

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.

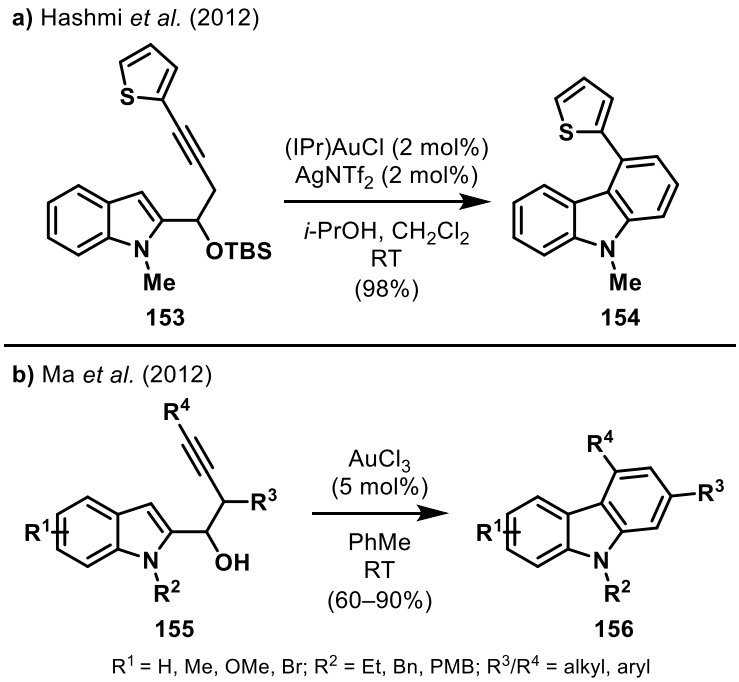
Benzannulation reactions, whilst not within the original aims of this project, offer an attractive route into the controlled formation of valuable fused-polycyclic structures. For example, the carbazole framework is found in a number of biologically active natural products with anticancer, anti-HIV and 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 to 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**).



Scheme 41. Iodocyclisation-mediated benzannulations of alkyne tethered indoles.

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).[78] For example, indole **153** was transformed into carbazole **154** in near quantitative yield using (IPr)AuCl and $AgNTf_2$ 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).[79]

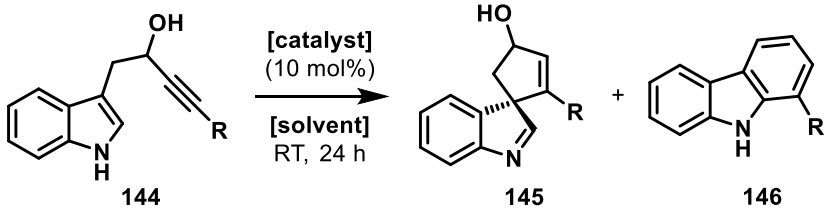


Scheme 42. Gold-catalysed benzannulation reactions of alkyne-tethered indoles.

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 $AgNO_3$ and AgOTf as the primary catalysts and CH_2Cl_2, 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 $AgNO_3$ in CH_2Cl_2 (entries 4 & 10, albeit with no/minimal diastereoselectivity).



144 145 146

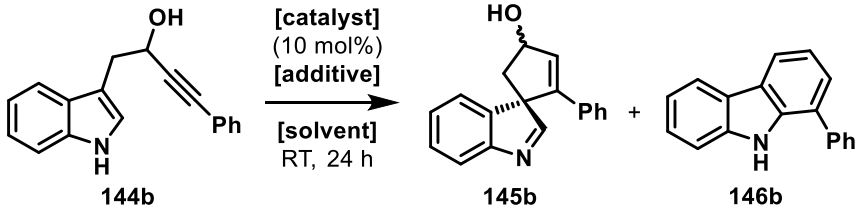
Entry	R[a]	Catalyst	Solvent	Ratio 144:145:146[b]
1	Ph (**144b**)	AgOTf	CH_2Cl_2	0:10:90
2	**Ph**	**AgOTf**	**THF**	**0:0:100**
3	Ph	AgOTf	PhMe	0:0:100
4	**Ph**	**$AgNO_3$**	**CH_2Cl_2**	**5:95:0**
5	Ph	$AgNO_3$	THF	10:90:0
6	Ph	$AgNO_3$	PhMe	90:10:0
7	*n*-Bu (**144c**)	AgOTf	CH_2Cl_2	35:65:0
8	***n*-Bu**	**AgOTf**	**THF**	**0:5:95**
9	*n*-Bu	AgOTf	PhMe	95:0:5
10	***n*-Bu**	**$AgNO_3$**	**CH_2Cl_2**	**20:80:0**
11	*n*-Bu	$AgNO_3$	THF	95:3:2
12	*n*-Bu	$AgNO_3$	PhMe	0:45:55

[a]All reactions performed with 0.10–0.20 mmol of propargyl alcohol in the stated solvent (0.1 M) at RT; [b]Calculated by ^{1}H 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 $AgNO_3$ 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.[80] Conversely, $AgNO_3$ 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 (Et_3N, 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 ($AgNO_3$, CH_2Cl_2) afforded a 1:1 mixture of spirocycle to carbazole.



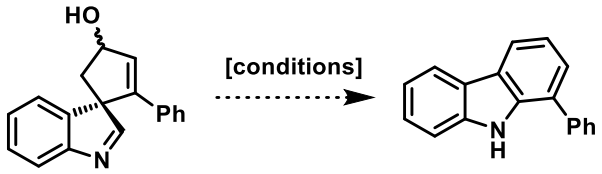
Entry	Catalyst	Solvent	Additive	Ratio 144b:145b:146b[b]
1	AgOTf	THF	-	0:0:100
2	**AgOTf**	**THF**	**Et_3N (5 mol%)**	**55:45:0**
3	AgOTf	THF	K_2CO_3 (5 mol%)	75:20:5
4	AgOTf	THF	$NaHCO_3$ (5 mol%)	0:0:100
5	$AgNO_3$	CH_2Cl_2	-	5:95:0
6	$AgNO_3$	CH_2Cl_2	TfOH (2 mol%)	80:0:20
7	**$AgNO_3$**	**CH_2Cl_2**	***p*-TSA (2 mol%)**	**20:40:40**
8	$AgNO_3$	CH_2Cl_2	AcOH (2 mol%)	15:70:15

[a]All reactions performed with 0.10–0.20 mmol of propargyl alcohol in the stated solvent (0.1 M) at RT; [b]Calculated by ^{1}H 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).

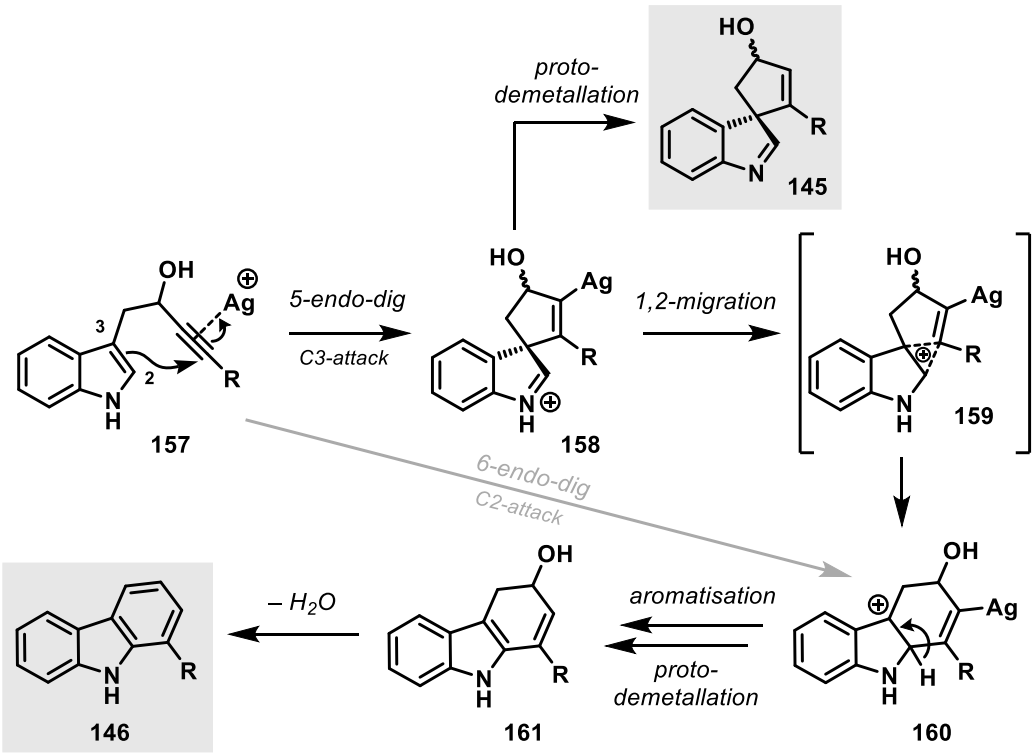


145b **146b**

Entry	Conditions	Result
1	AgOTf (10 mol%), THF, RT, 24 h	No reaction
2	TfOH (10 mol%), CH_2Cl_2, RT, 16 h	Decomposition, trace **146b** detected by TLC.

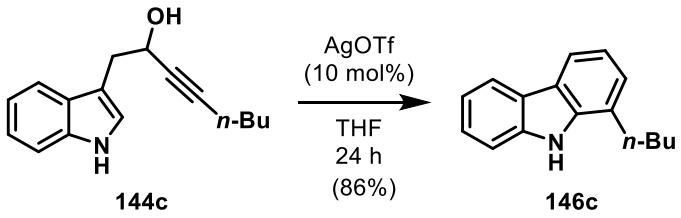
Table 9. Attempted synthesis of carbazole **146b** by 1,2-migration of spirocycle **145b**.

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** → **159** → **160**) as it can stabilise positive charge more readily without the electron withdrawing effects of a conjugated carbonyl (as in the indole-ynone system).[61] 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.

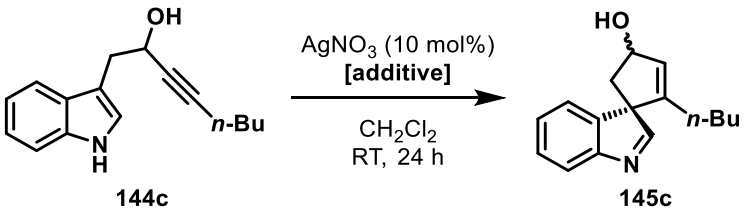


Scheme 43. Proposed mechanisms for spirocycle and carbazole formation.

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_2O (5 mol%) completely restored the desired selectivity and significantly improved the reaction yield (entry 3).



Scheme 44. Synthesis of carbazole **146c**.



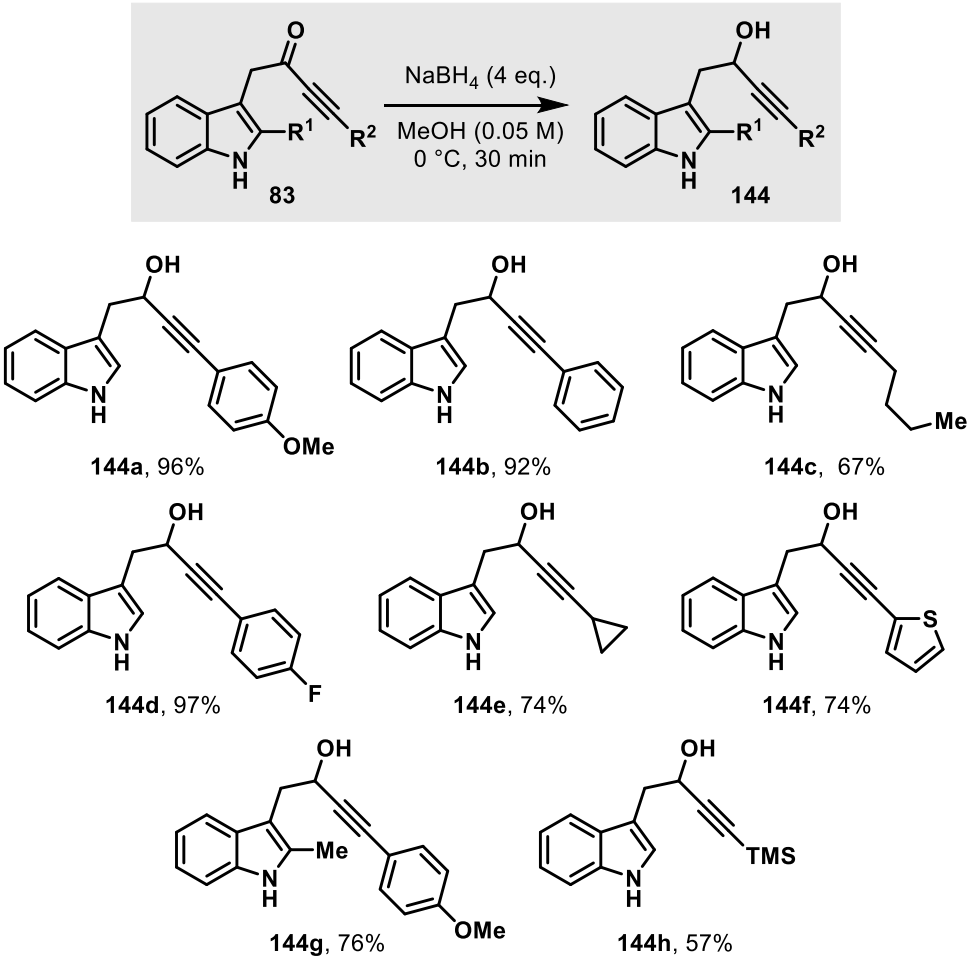
144c 145c

Entry	Additive	Yield (%)
1	-	31
2	Ag_2CO_3 (5 mol%)	40
3	Ag_2O (5 mol%)	92

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

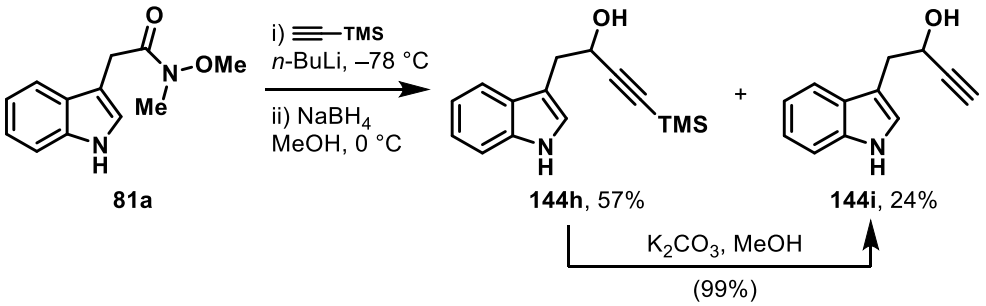
2.2.3 Substrate Synthesis

To fully explore the scope of the two optimised reaction protocols a wider range of substrates was prepared by $NaBH_4$ reduction of the corresponding ynone (Scheme 45).



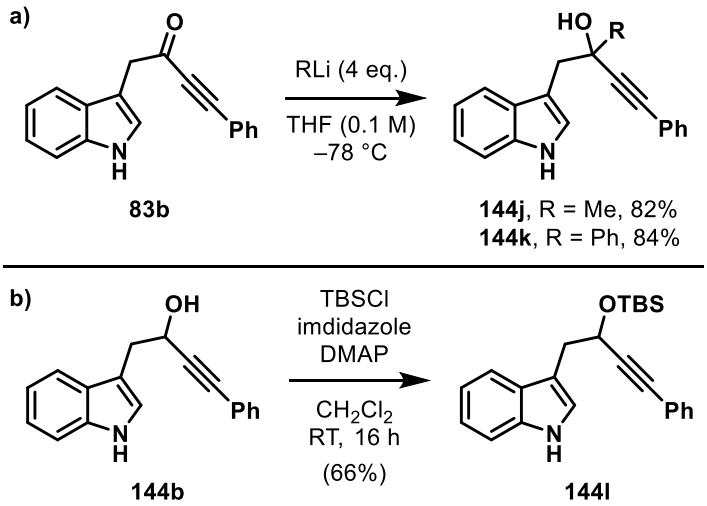
Scheme 45. Propargyl alcohols prepared by sodium borohydride reduction.

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 K_2CO_3 in methanol.



Scheme 46. Synthesis of TMS alkyne **144h** and **144i** by desilylation.

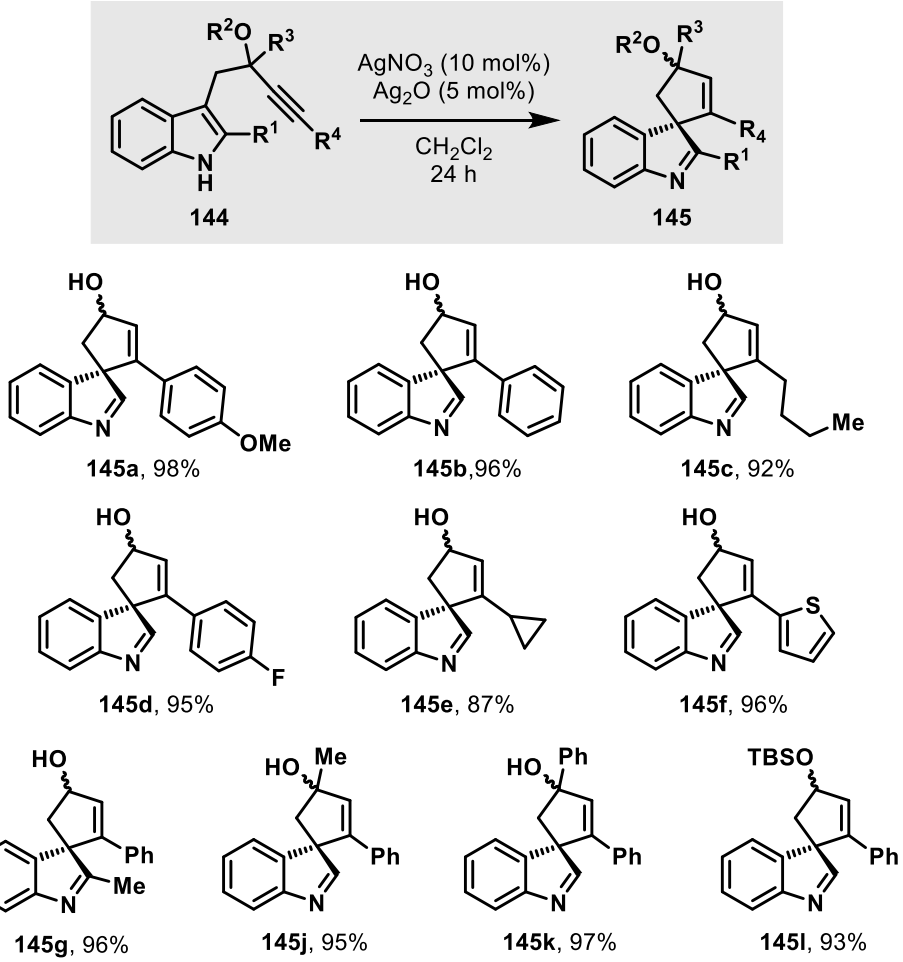
Tertiary alcohol substrates **144j** and **144k** were prepared by reacting ynone **83b** with an excess of the corresponding commercial organo-lithium reagent (Scheme 47a). A TBS-protected propargyl alcohol substrate **144l** was also readily accessed from substrate **144b** (Scheme 47b).



Scheme 47. Miscelleanous propargyl alcohol synthesis.

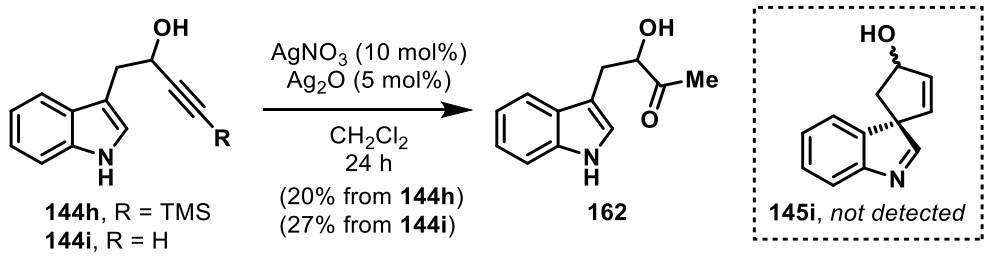
2.2.3 Substrate Scope

First, the propargyl alcohol library was reacted under the optimised spirocyclisation conditions ($AgNO_3$, Ag_2O in CH_2Cl_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).



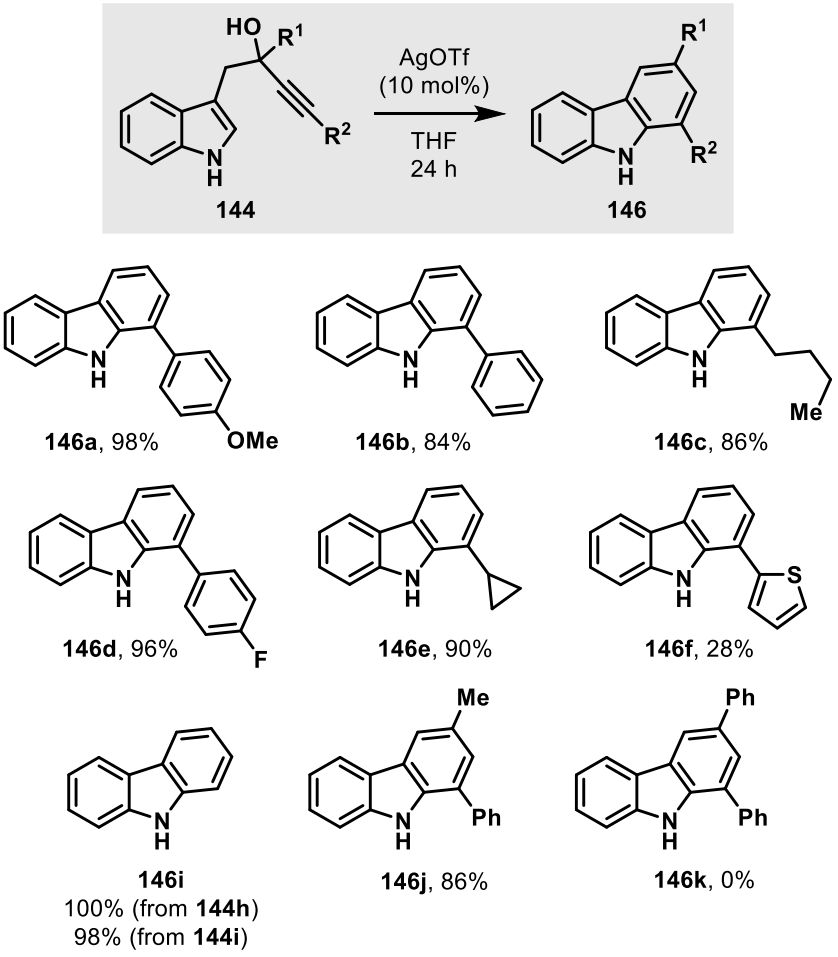
Scheme 48. Substrate scope for propargyl alcohol spirocyclisations.

The only substrates which failed to spirocyclise were alkynes **144h** and **144l**, which instead underwent a low yielding hydration reaction to form the α-hydroxy ketone natural product, (±)-actinopolymorphol B **162** (Scheme 49).[81] Typically π-acid catalysed alkyne hydrations are carried out at higher temperatures and so it was somewhat surprising to see hydration under these mild reaction conditions.[82–84]



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.

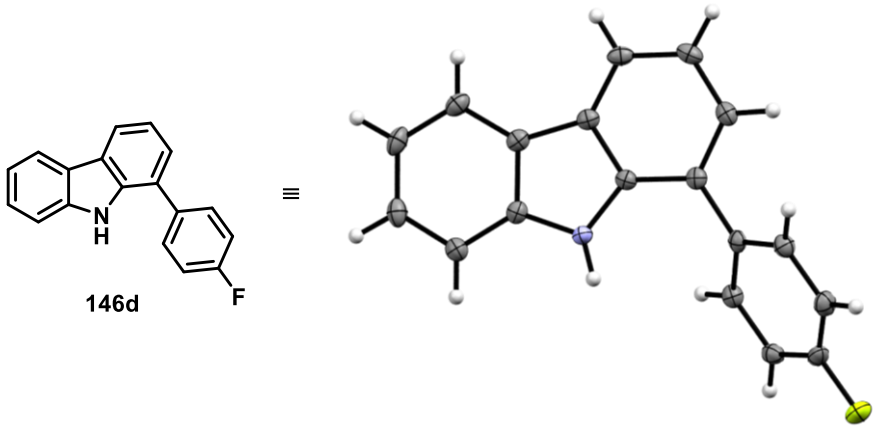
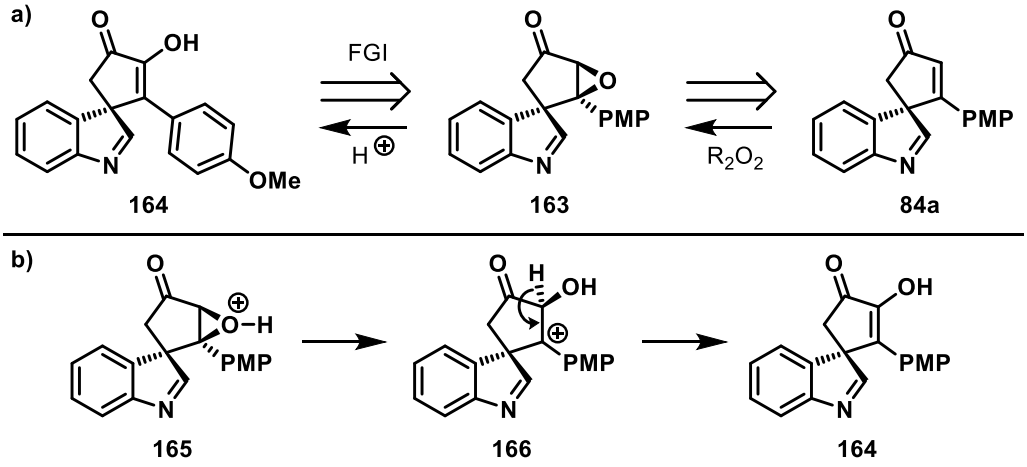


Figure 11. X-ray structure of carbazole **146d** with thermal ellipsoids shown at 50% (CCDC 1404713).

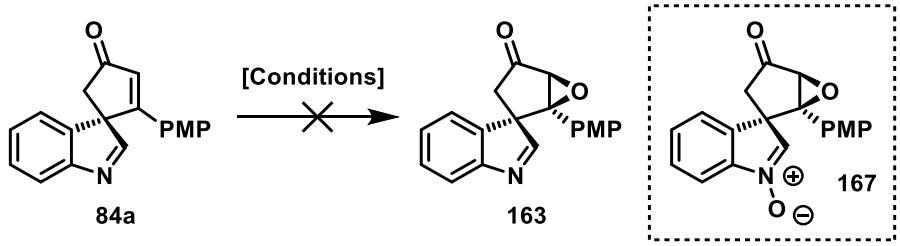
2.3 Towards Spirobacillene B

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]



Scheme 51. Retrosynthetic analysis of spirobacillene B analogue **164**: a) Epoxidation and acid-mediated rearrangement; b) Envisaged rearrangement.

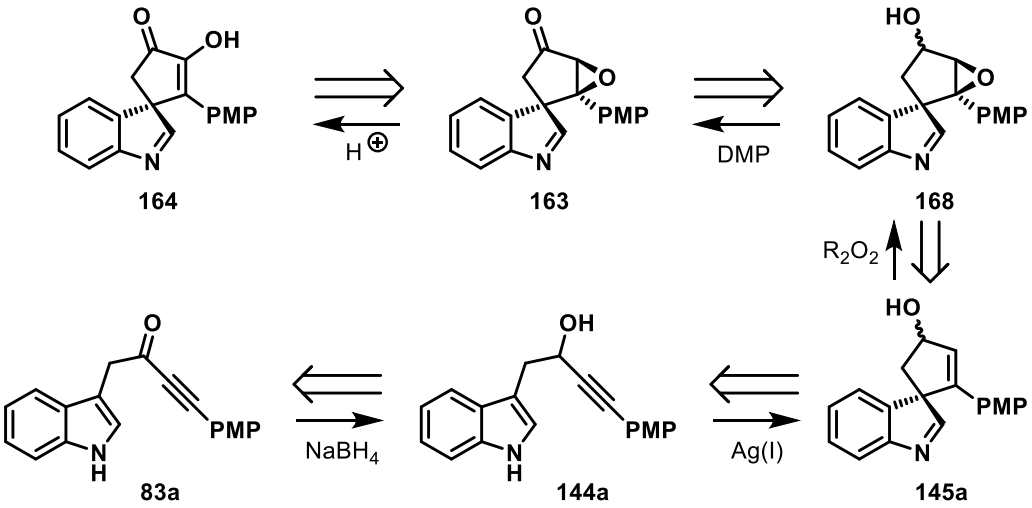
Attempts to prepare the required α,β-epoxyketone **163** by the epoxidation of spirocycle **84a** under both nucleophilic and electrophilic conditions failed (Table 11). Under most conditions only decomposition was observed, however, when using DMDO a mass consistent with *N*-oxide **167** was detected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



Entry	Conditions	Result
1	H_2O_2, $NaHCO_3$, THF, H_2O, RT	Complex mixture
2	H_2O_2, $NaHCO_3$, MeOH, RT	Complex mixture
3	*t*-BuOOH, THF, RT	No reaction
4	*m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C	Complex mixture
5	DMDO, Me_2CO, RT	Complex mixture, **167** detected

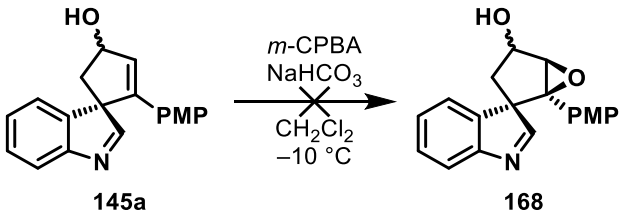
Table 11. Attempted synthesis of α,β-epoxyketone **163**.

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).



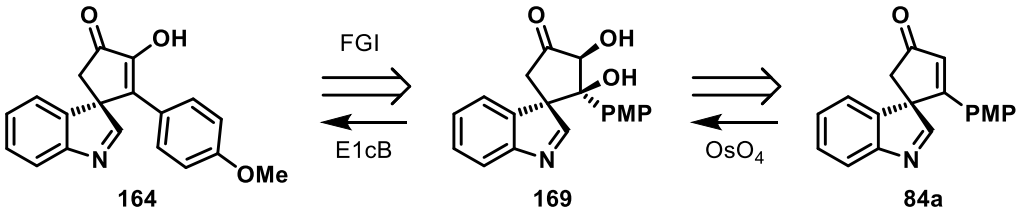
Scheme 52. Retrosynthetic analysis of spirobacillene B analogue **164** by allylic alcohol epoxidation.

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.



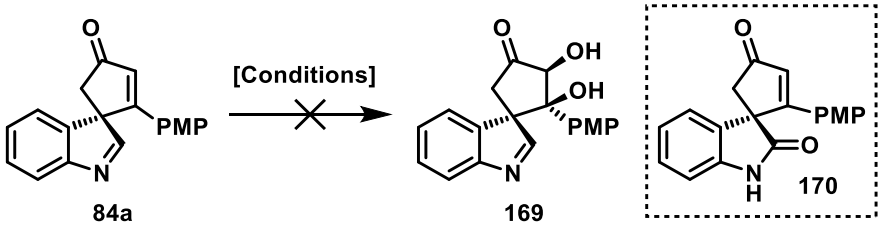
Scheme 53. Attempted synthesis of epoxide **168**.

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.



Entry	Conditions	Result
1	OsO_4, NMO, Me_2CO, H_2O, RT	Complex mixture, **170** (7%)
2	AD-mix α, $MsNH_2$, *t*-BuOH, H_2O, 25 °C	Complex mixture

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 $AgNO_3 \cdot SiO_2$ 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*.

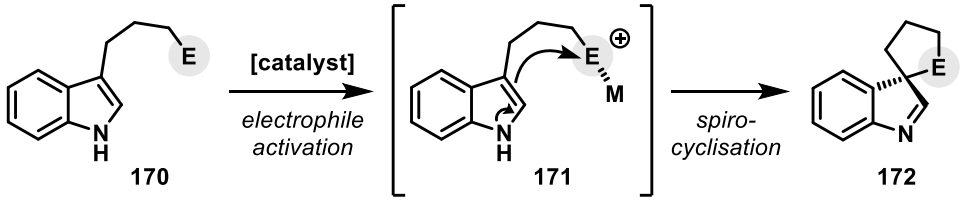
The developed methodologies were applied in the accidental synthesis of (±)-actinopolymorphol B and in studies towards the synthesis of spirobacillene B.

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.

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.

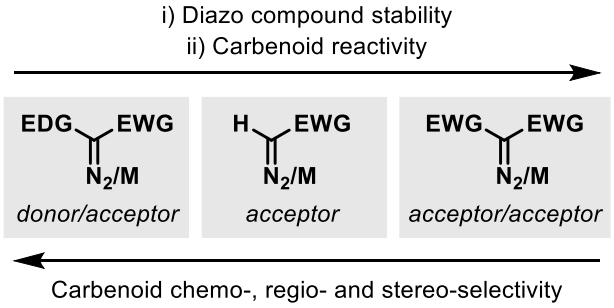
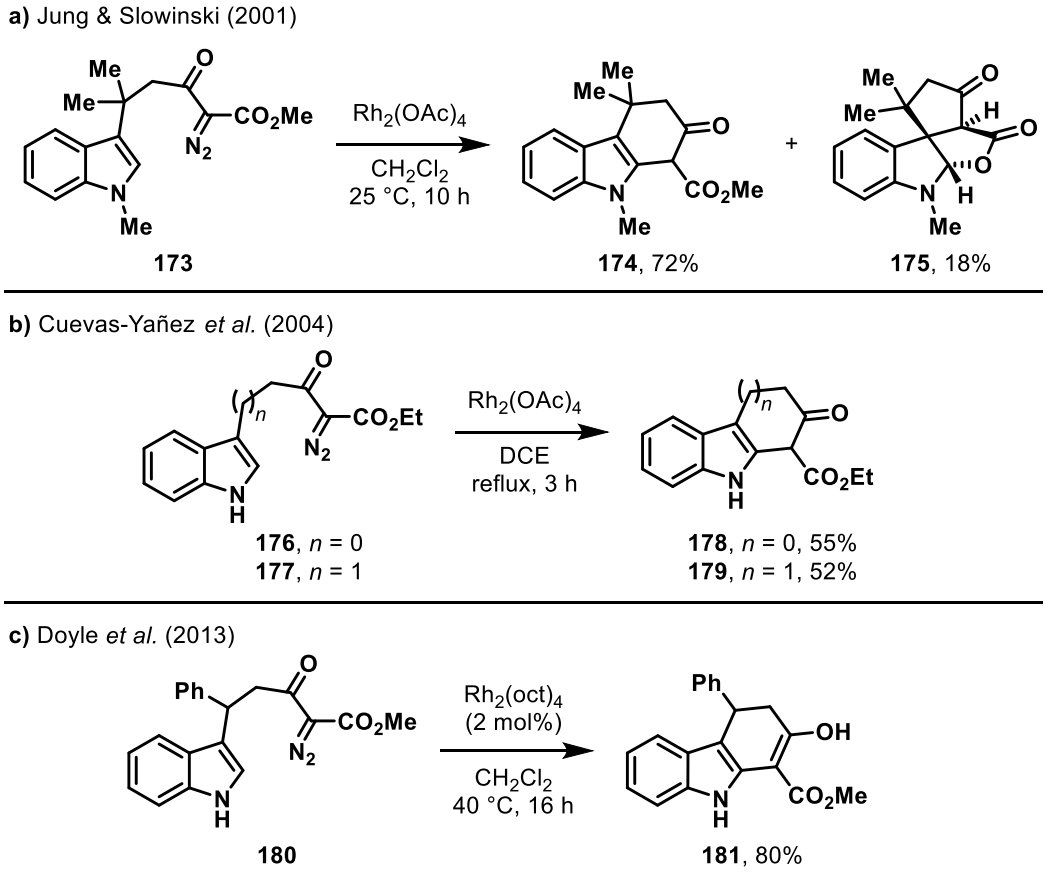


Figure 12. Diazo compound and carbenoid categories.

3.2 Project background and aims

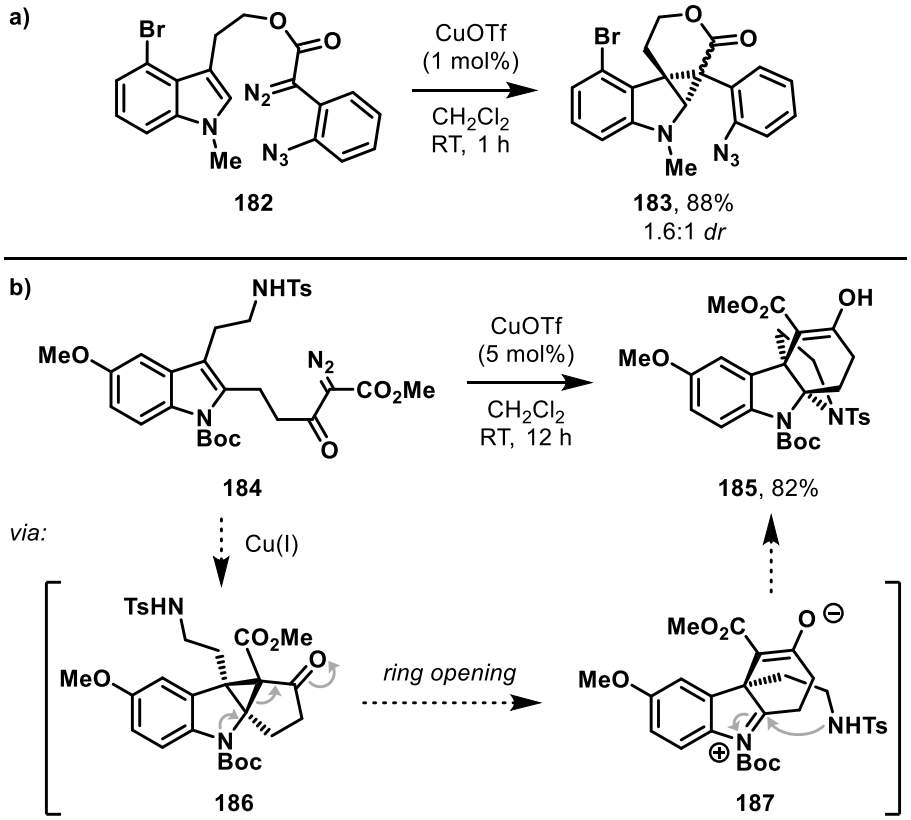
The reactivity of indole-tethered α-diazocarbonyls has been scarcely explored outside of a few known instances. Predominately Rh(II)-catalysis has been used, as first demonstrated by Jung and Slowinski, who reacted indole **173** with $Rh_2(OAc)_4$ to afford the C2-annulated indole **174** in good yield with a small quantity of spirocycle **175** (Scheme 56a).[91] 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 $Rh_2(OAc)_4$ to promote the modest yielding formation of C2-annulated products **178** and **179**, with no other reported products (Scheme 56b).[92] More recently, Doyle and co-workers reported a single example of a $Rh_2(oct)_4$-catalysed C2-annulation reaction, affording indole **181** in excellent yield (Scheme 56c).[93]



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

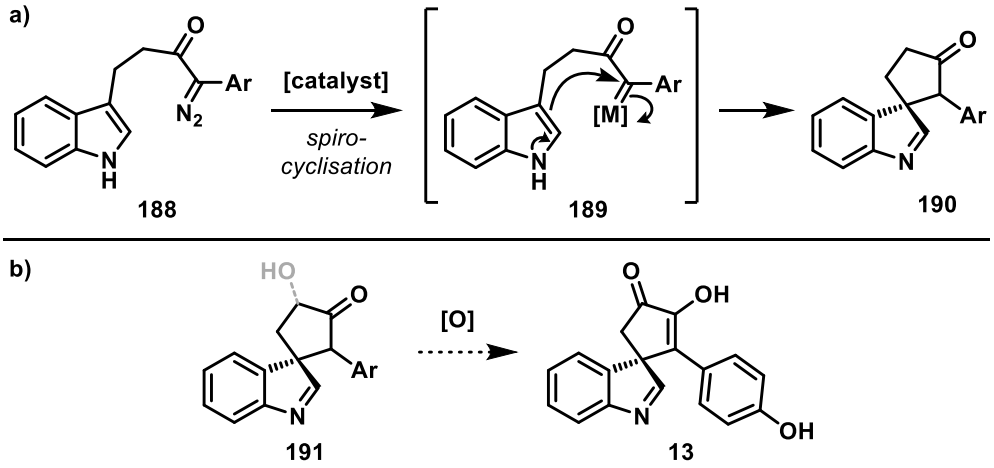
All of these prior examples relied solely on acceptor/acceptor carbenoid systems in combination with a Rh(II)-catalyst. Qin and co-workers were the first to differ from this approach, by using a Cu(I)-catalyst with the donor/acceptor carbenoid system of **182** to form spirocyclic cyclopropane **183** in excellent yield (Scheme 57a).[94,95] Later, Qin and co-workers

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).[96]



Scheme 57. Previous reactivity of indole-tethered α-diazcarbonyls with a Cu(I)-based catalyst.

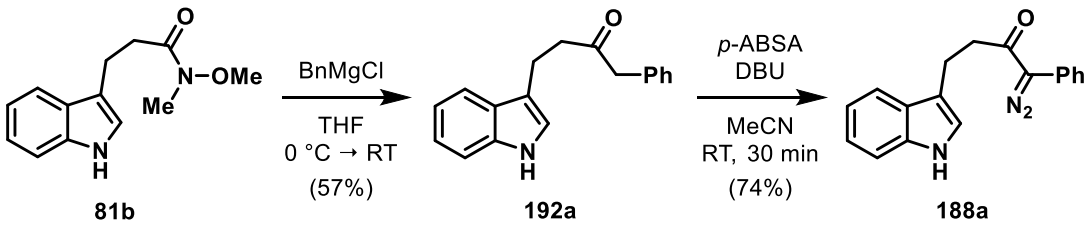
Thus, as briefly demonstrated by Qin and co-workers, it was envisaged that a donor/acceptor carbenoid system, as in **188**, might allow for a spirocyclisation methodology to be developed, especially when exposed to a wider range of catalysts (Scheme 38a). If successful, this strategy might also be applied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



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**.[88] 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% Et_3N 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**.

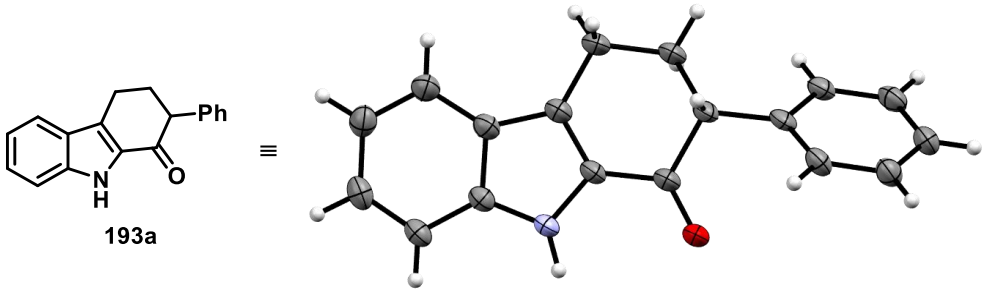
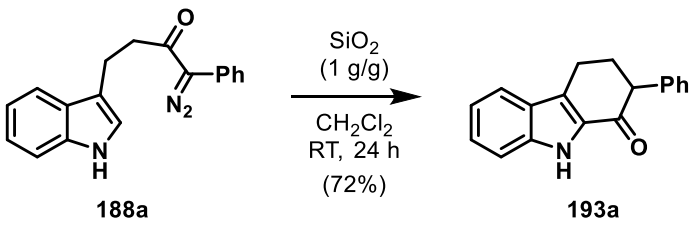
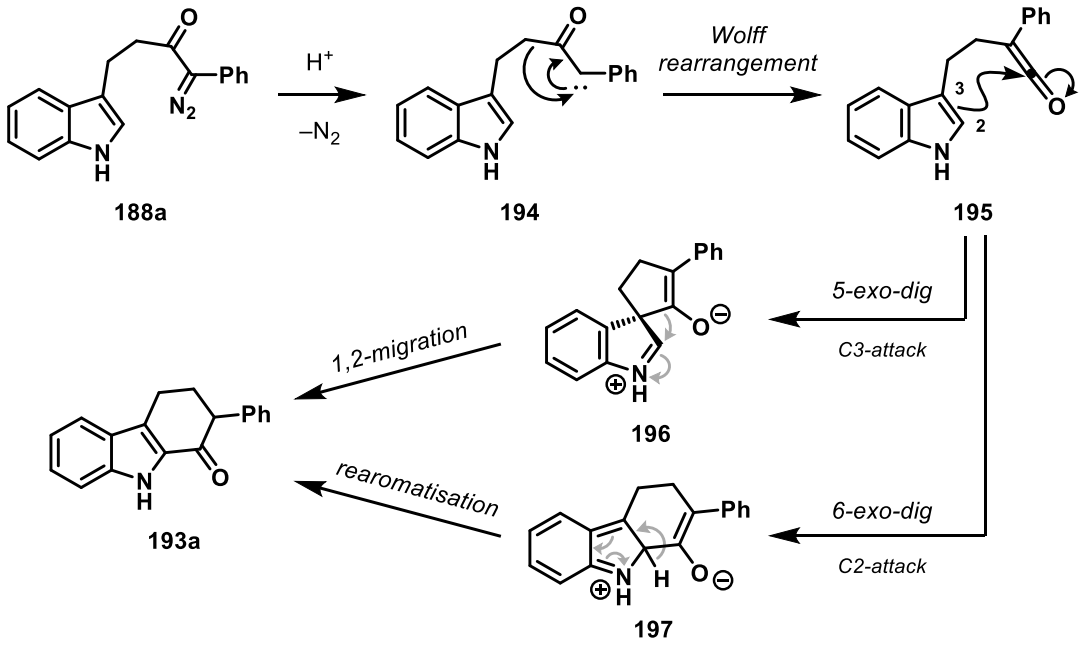


Figure 13. X-ray structure of C2-annulated indole **193a** with thermal ellipsoids shown at 50% (opposite enantiomer omitted for clarity, CCDC 1481930).



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),[97] 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**).

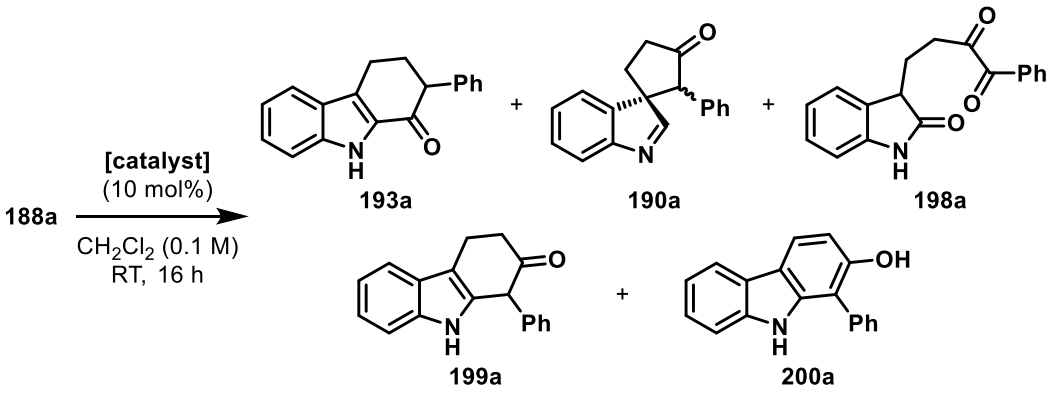


Scheme 61. Proposed mechanisms for the synthesis of indole **193a**.

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 ^{1}H 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_2oct_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.[98]



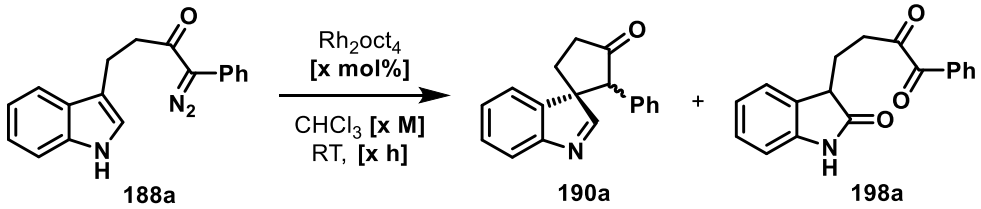
Entry		Catalyst[a]	Ratio[b]					
			188a	193a	190a	198a	199a	200a
1	Rh(II)	$Rh_2(OAc)_4$	0	15	0	50	20	15
2		Rh_2esp_2	0	20	10	55	15	0
3		Rh_2TPA_4	0	10	0	70	20	0
4		**Rh_2oct_4**	**0**	**0**	**95**	**5**	**0**	**0**
5	Cu(I)	CuBr	5	0	75	20	0	0
6		CuI	0	0	80	20	0	0
7		$Cu(MeCN)_4OTf$	0	0	20	0	60	20
8		$Cu(MeCN)_4PF_6$	15	0	65	20	0	0
9	Cu(II)	$Cu(OAc)_2$	0	0	85	15	0	0
10		Cu(2-ethylhexanoate)$_2$	10	0	90	0	0	0
11		$CuCl_2$	25	0	0	0	50	25
12		**$Cu(OTf)_2$**	**0**	**0**	**0**	**0**	**70**	**30**
13	Pd(II)	$Pd(MeCN)_2Cl_2$	0	0	55	0	45	0
14		**$Pd(MeCN)_4(BF_4)_2$**	**0**	**0**	**0**	**0**	**95**	**5**
15		$Pd(OAc)_2$	40	0	50	0	10	0
16		$PdCl_2$	30	5	50	10	5	0
17	Ag(I)	AgOTf	0	0	0	0	90	10
18		$AgNO_3$	30	0	35	35	0	0
19		AgOAc	20	0	65	15	0	0
20	Au(I)	Ph_3PAuCl + AgOTf	0	0	0	0	95	5
21		$Ph_3PAuNTf_2$	0	0	35	0	65	0
22	Fe/Sn(II)	$Fe(ClO_4)_2 \cdot xH_2O$	0	5	0	0	80	15
23		$FeCl_2 \cdot 4H_2O$	95	5	0	0	0	0
24		$SnCl_2 \cdot 2H_2O$	0	0	0	0	0	0

*[a]Reactions performed with 0.05 mmol of **188a** and 10 mol % catalyst in CH_2Cl_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 catalyst 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).



Entry	Conditions	Result
1	Rh_2oct_4 (5 mol%), $CHCl_3$ (0.1 M), argon, 6 h	**190a**, 92%, 54:46 *dr*
2	Rh_2oct_4 (2 mol%), $CHCl_3$ (0.05 M), air, 1 h	**198a**, 78%

Table 14. Rh_2oct_4-catalysed synthesis of spirocycle **190a** and α,β-dicarbonyl **198a**.

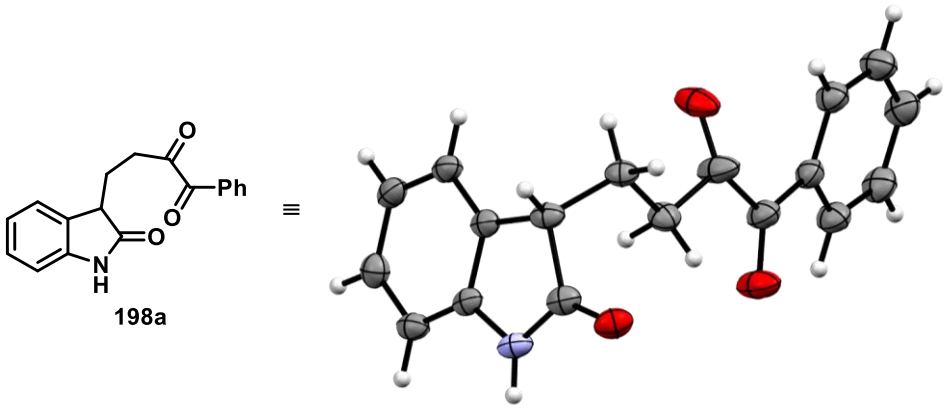
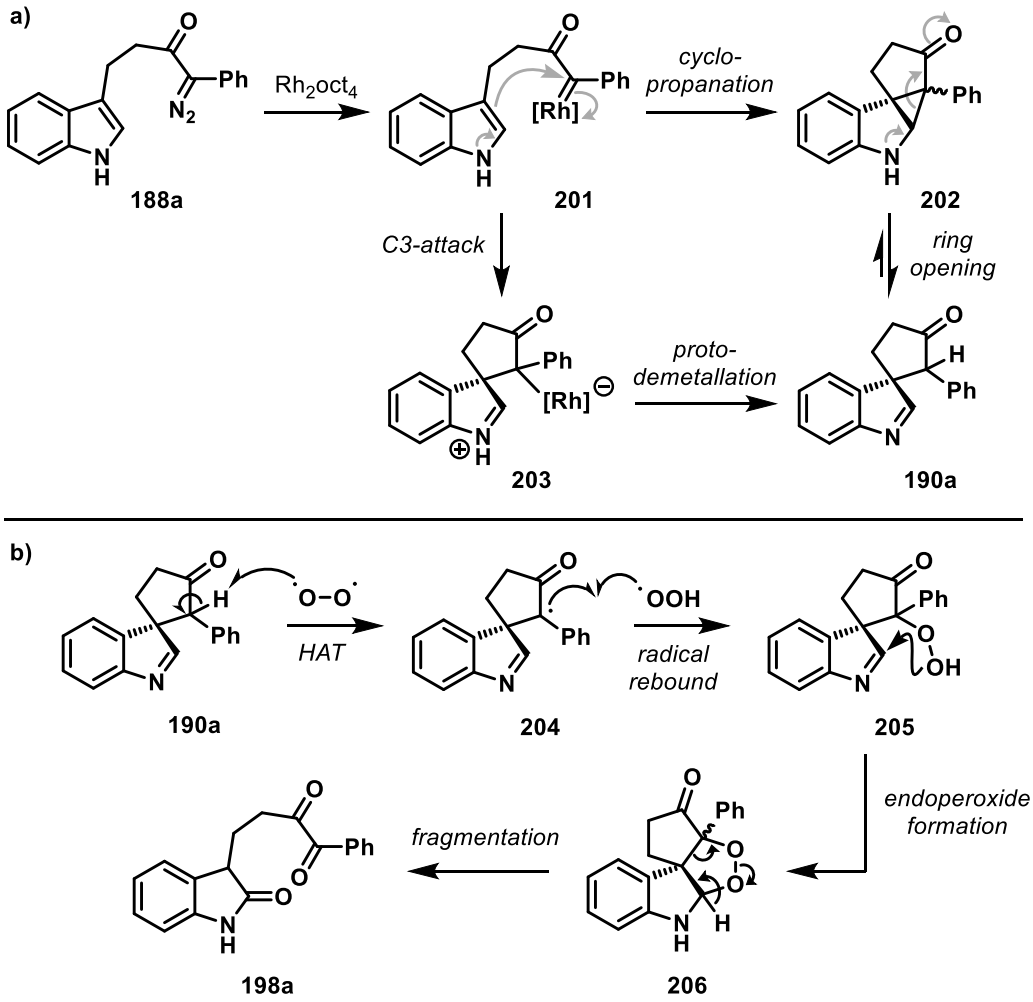


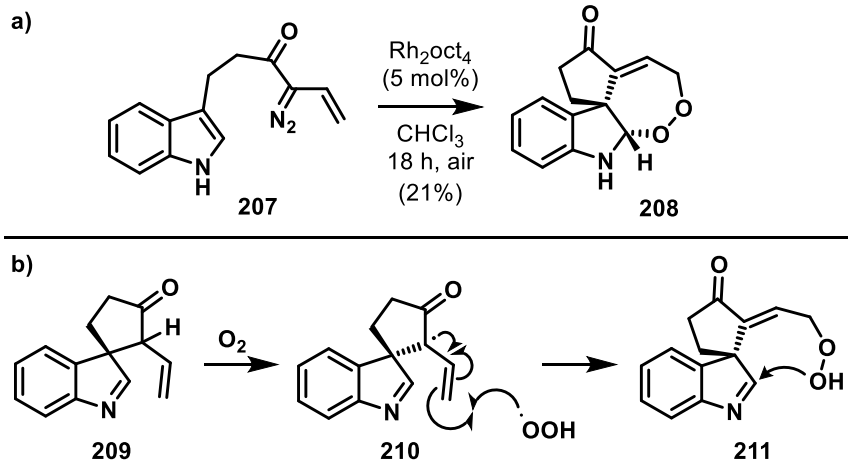
Figure 14. X-ray structure of α,β-dicarbonyl **198a** with thermal ellipsoids shown at 50% (CCDC 1481924).

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** → **202** → **190a**, Scheme 62a) or (ii) direct attack from the indole C3-position followed by protodemetallation (**201** → **203** → **190a**). In a flask open to air, oxygen is proposed to abstract the α-keto H-atom of **190a** to form α-keto radical **204** and a hydroperoxyl radical, which can then immediately recombine in a radical rebound process to afford peroxide **205** (Scheme 62b).[99–101] Peroxide **205** may then cyclise to form endoperoxide **206**, which following fragmentation would afford α,β-dicarbonyl **198a**. A purified sample of spirocycle **190a** in $CDCl_3$ was also observed to form α,β-dicarbonyl **198a** over time by ^1H NMR analysis, confirming that spirocycle **190a** was indeed a direct precursor to α,β-dicarbonyl **198a**.



Scheme 62. a) Proposed mechanism for the Rh_2oct_4 catalysed formation of spirocycle **190a**; b) Proposed mechanism for the formation of α,β-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.

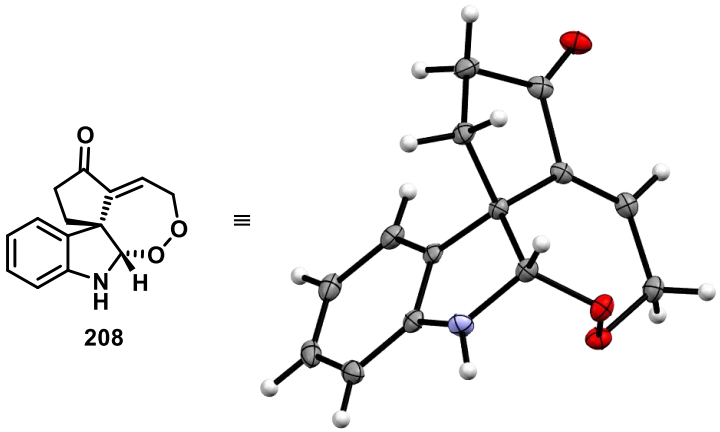


Figure 15. X-ray structure of endoperoxide **208** with thermal ellipsoids shown at 50% (CCDC 1481929).

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).

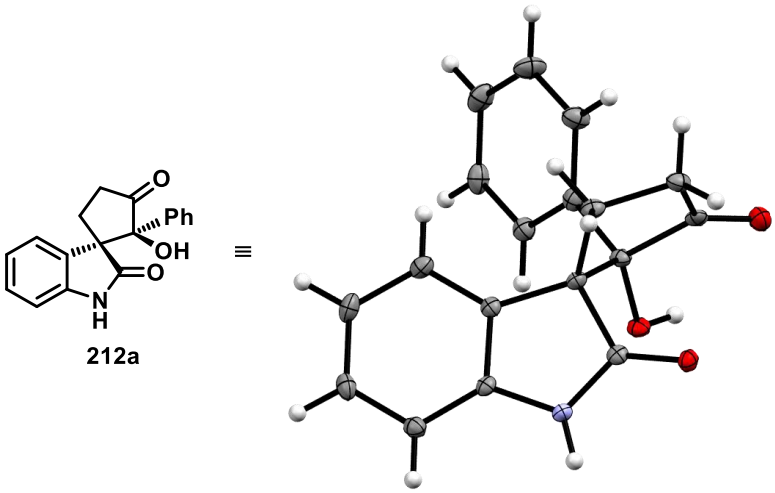
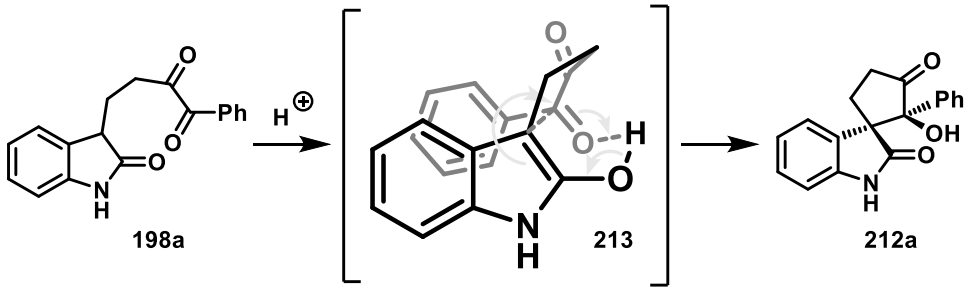
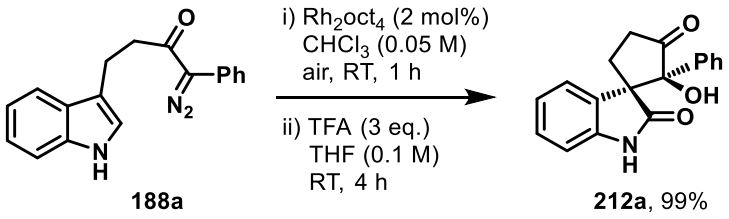


Figure 16. X-ray structure of spirocyclic oxindole *syn*-diastereoisomer **212a** with thermal ellipsoids shown at 50% (CCDC 1481927).

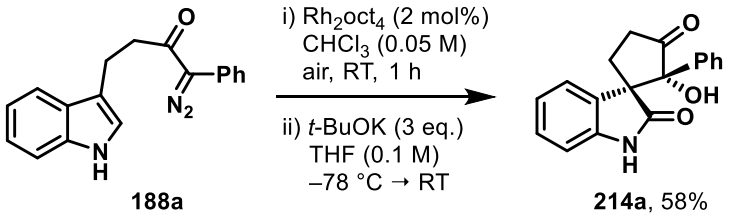


Scheme 64. Proposed 6-membered transition state in the diastereoselective Brønsted acid catalysed formation of oxindole **212a**.

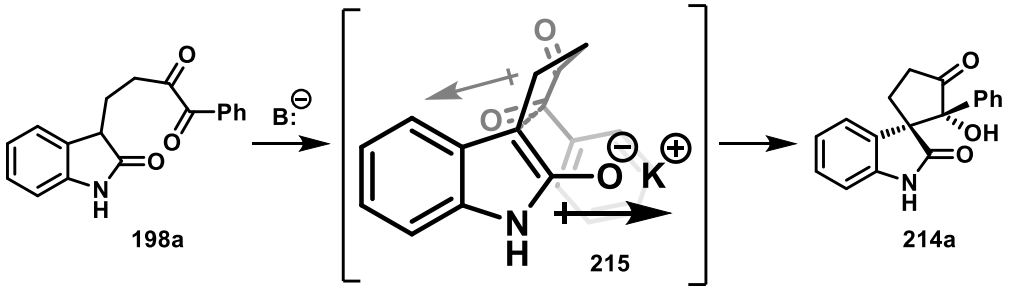


Scheme 65. One-pot Brønsted acid promoted synthesis of spirocyclic *syn*-oxindole **212a**.

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).



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**.

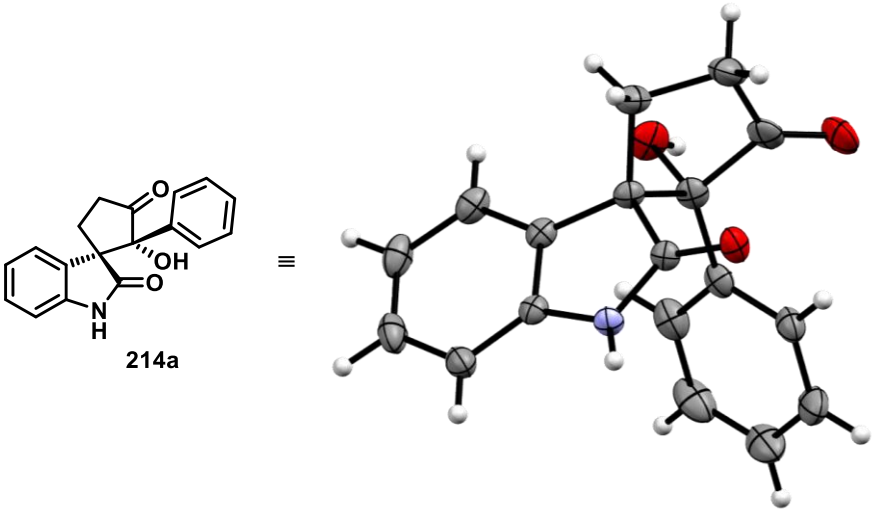
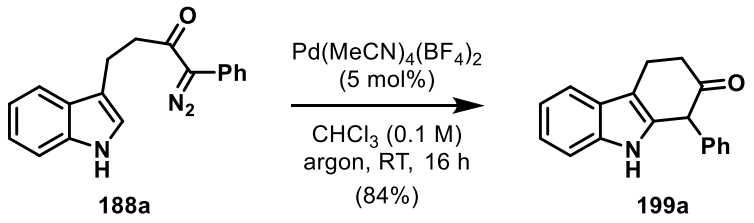


Figure 17. X-ray structure of spirocyclic oxindole *anti*-diastereoisomer **214a** with thermal ellipsoids shown at 50% (CCDC 1481928).

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**.

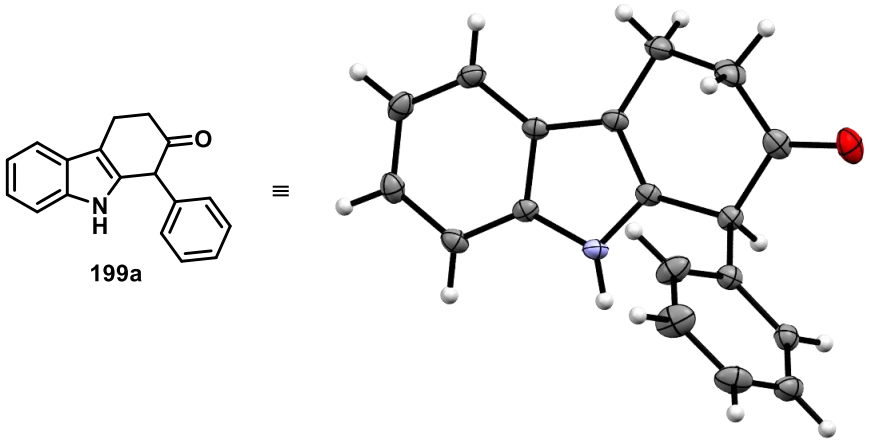
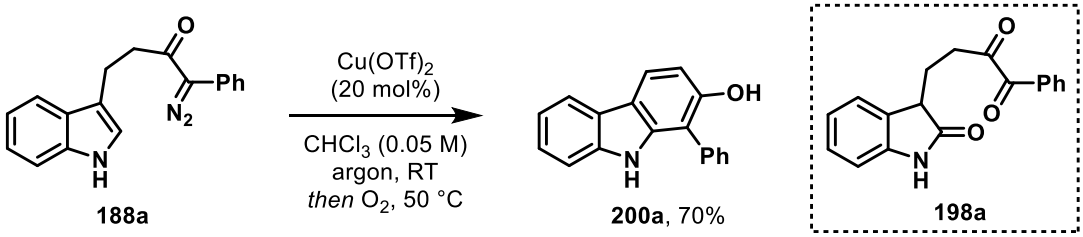


Figure 18. X-ray structure of indole **199a** with thermal ellipsoids shown at 50% (CCDC 1481925).

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**.

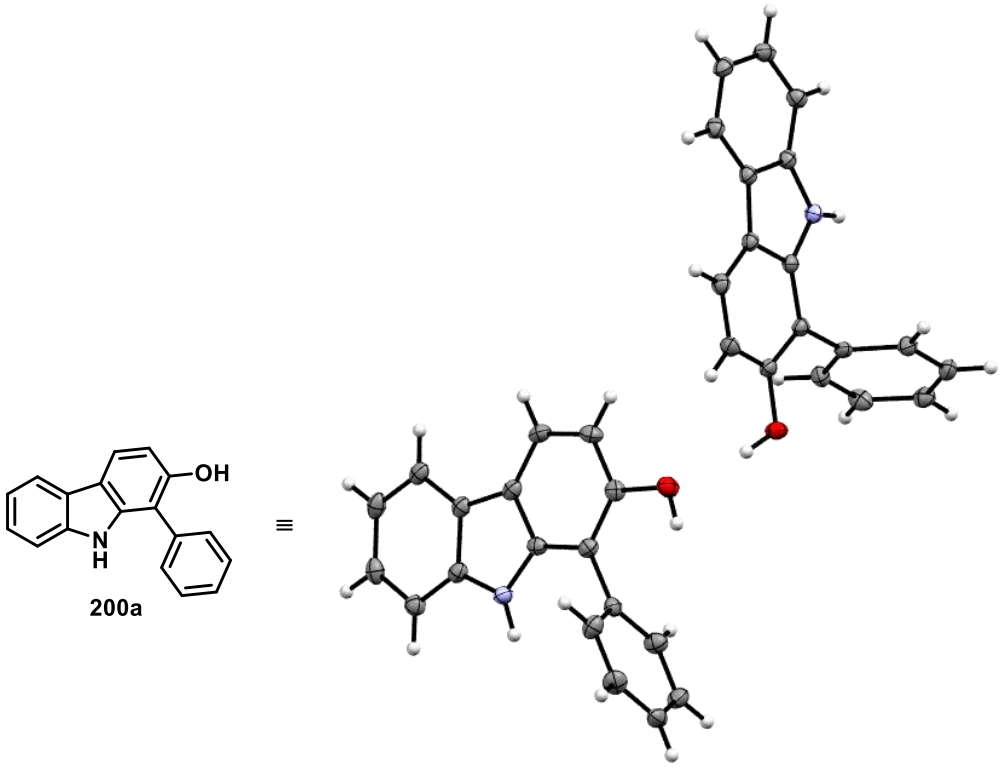
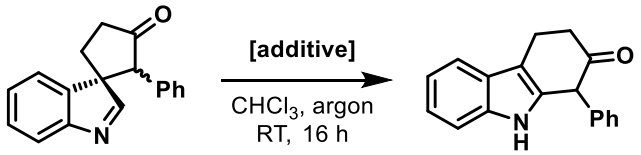


Figure 19. X-ray structure of carbazole **200a** with thermal ellipsoids shown at 50% (CCDC 1481926).

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.



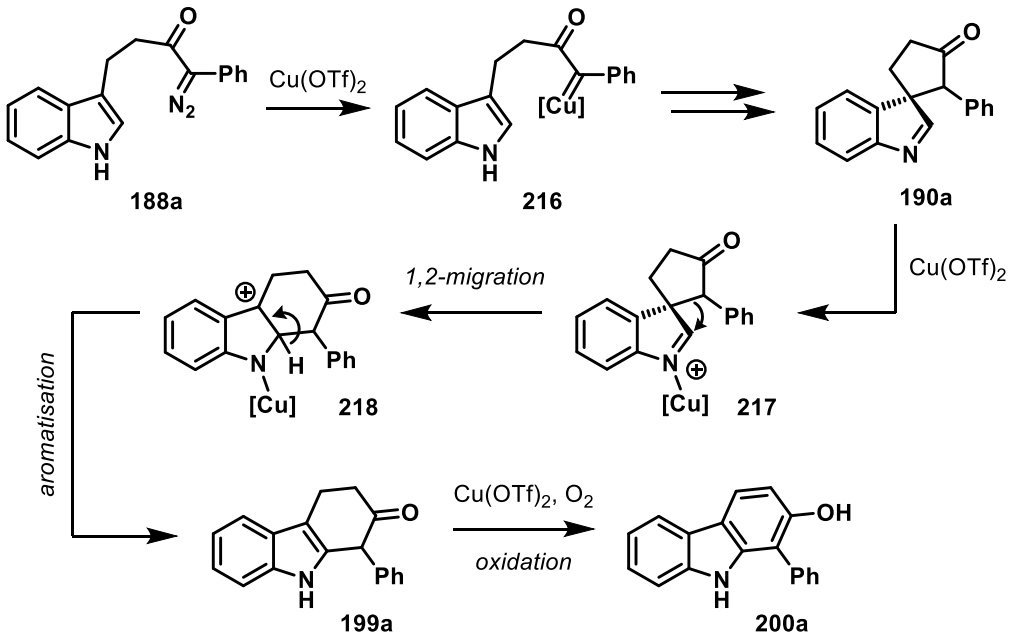
190a **199a**

Entry	Additive	Result[a]
1	$Pd(MeCN)_4(BF_4)_2$ (5 mol%)	No reaction
2	$Cu(OTf)_2$ (20 mol%)	Rapid conversion into **199a**

[a]Determined by analysis of the ^{1}H NMR spectra of the unpurifed reaction mixture

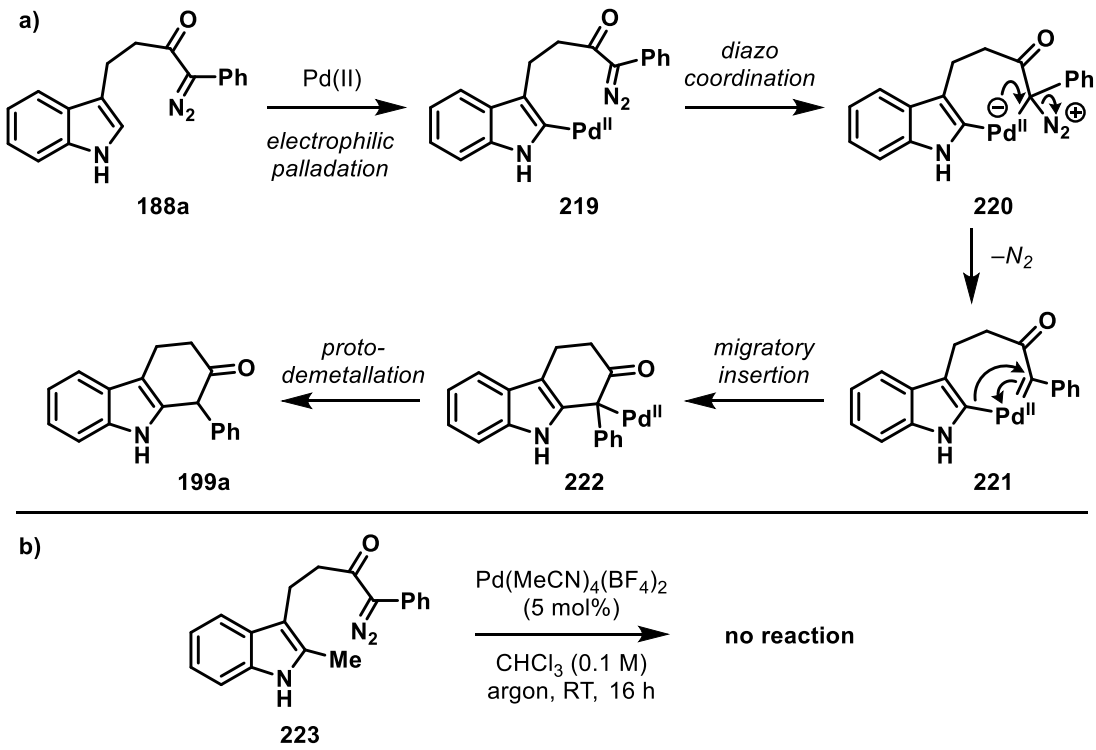
Table 15. Additive screening with spirocycle **190a**.

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**.

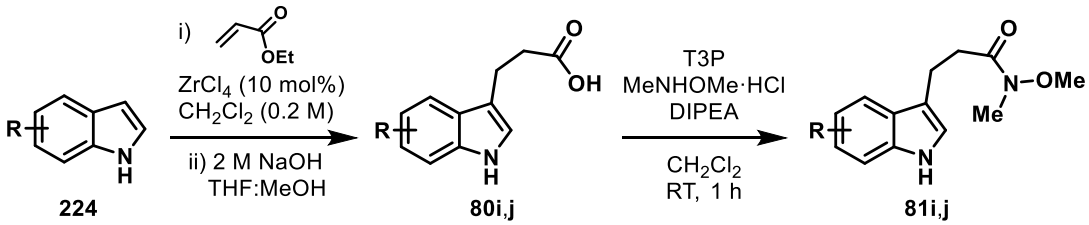
For the $Pd(MeCN)_4(BF_4)_2$-catalysed synthesis of indole **199a** an alternative mechanism is proposed, in which the reaction is initiated by electrophilic palladation at the indole C2-postion (**188a** → **219**, Scheme 71a).[102–104] Following palladation, the diazo group could coordinate to the metal centre (**219** → **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**.

3.4 Substrate Synthesis

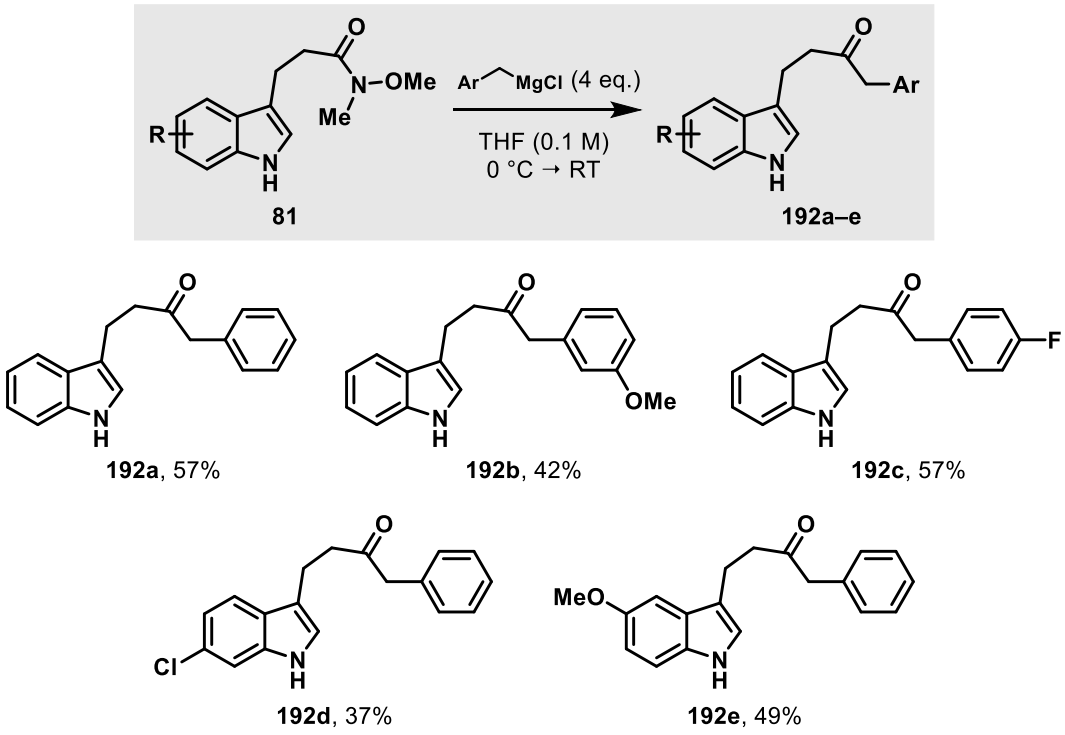
To fully explore the scope of the developed transformations, a wider range of α-diazocarbonyl substrates were prepared. First, Weinreb amides **81i**,**j** were prepared in a three step sequence (Table 16). Commerically available indoles **224** were readily converted into 3-indolepropionic esters by a $ZrCl_4$-catalysed conjugate addition into ethyl acrylate,[109] which following saponification and a T3P-mediated amide coupling afforded Weinreb amides **81i**,**j**.



Entry	R	Yield over 3 steps (%)
1	6-Cl (**81i**)	55
2	5-OMe (**81j**)	65

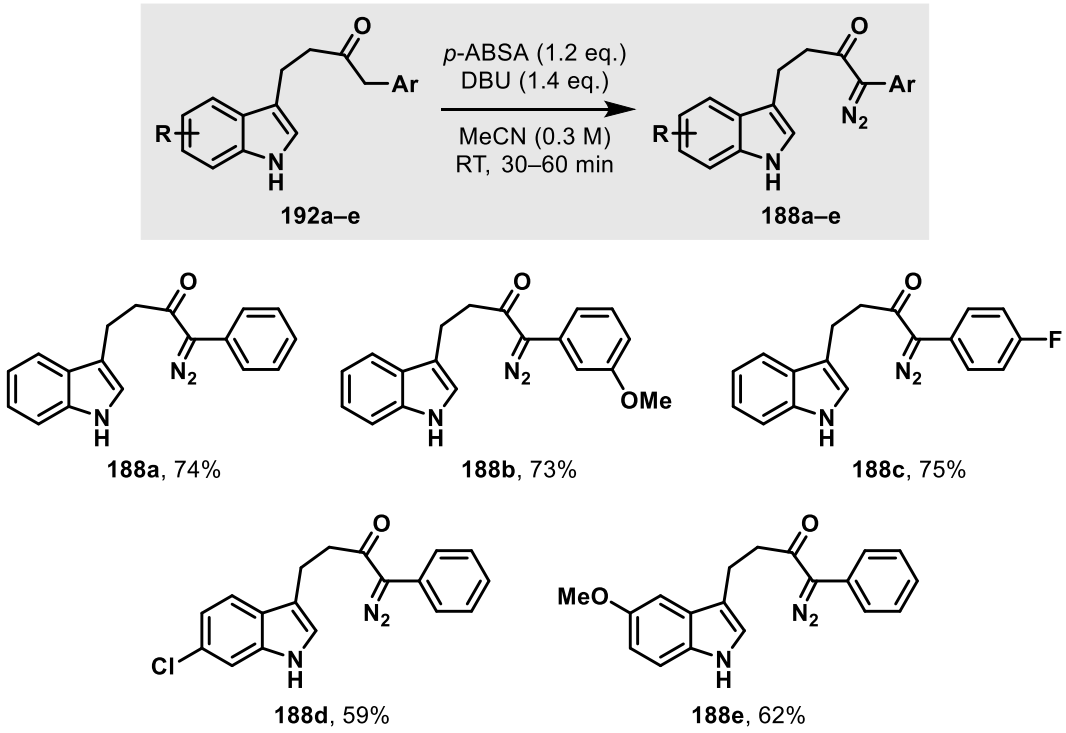
Table 16. Synthesis of 3-indolepropionic acid derivatives.

The 3-indolepropionic acid derived Weinreb amides **81** were than reacted with the appropriate benzyl Grignard reagents to form benzyl ketones **192a**–**e** (Scheme 72).



Scheme 72. Scope of benzyl ketones prepared by Grignard addition.

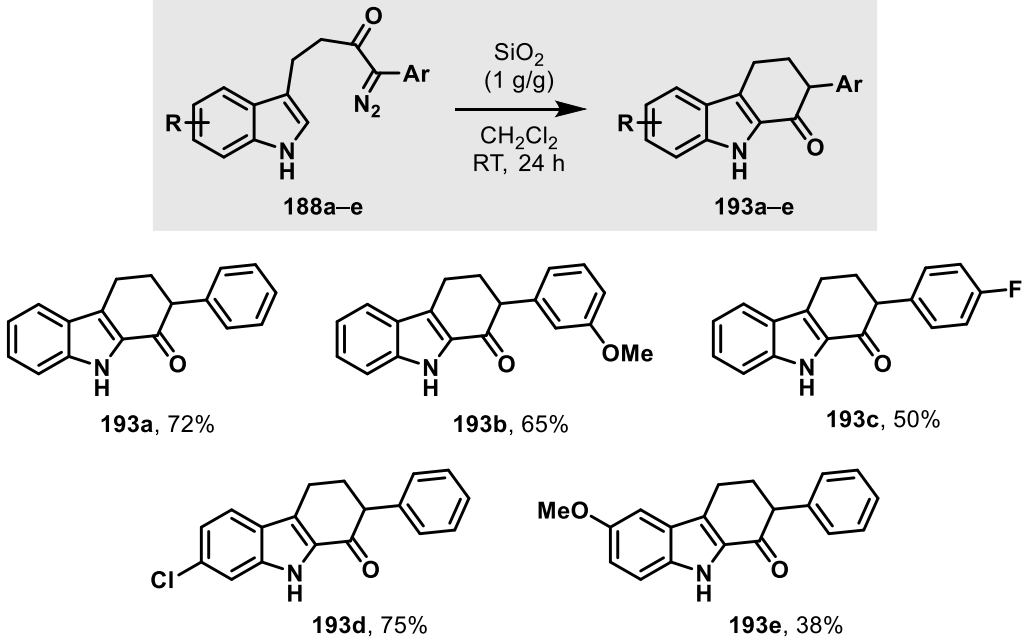
The benzyl ketones **192** were then used to prepare α-diazocarbonyls **188** by Regitz diazo transfer using *p*-ABSA and DBU (Scheme 73).



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

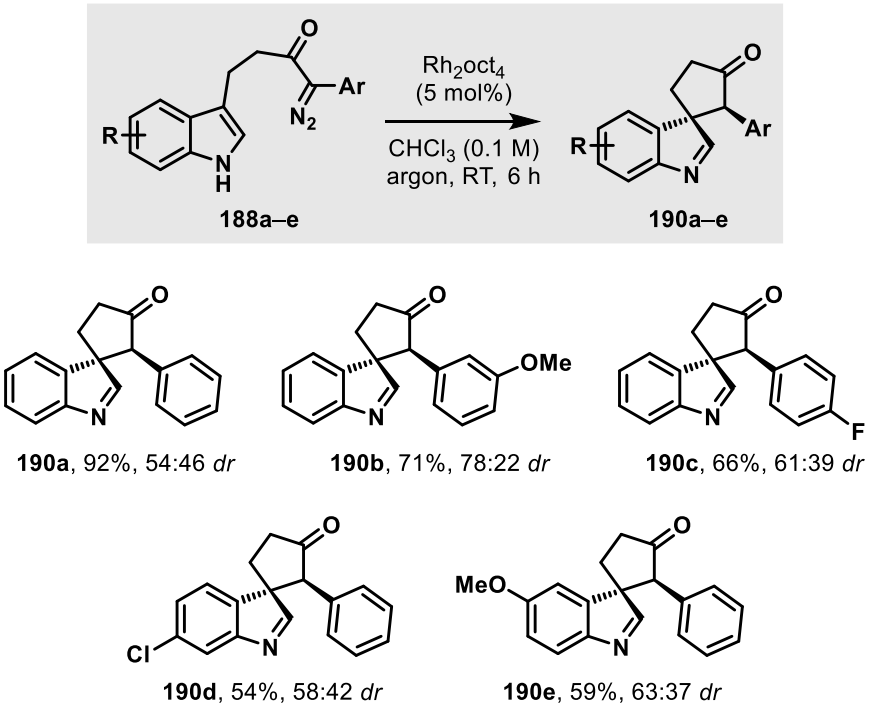
3.5 Substrate Scope

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.



Scheme 74. The silica gel-catalysed cyclisation substrate scope.

Next, the Rh_2oct_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).



Scheme 75. Scope of the $Rh_2(oct)_4$-catalysed spirocycle synthesis.

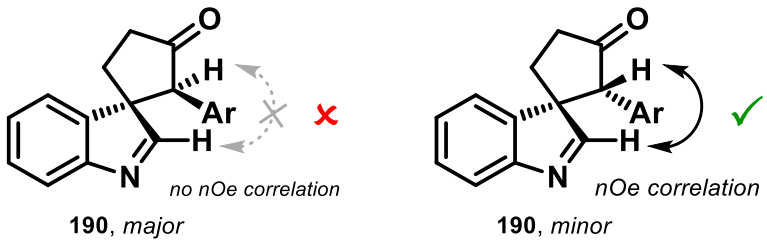
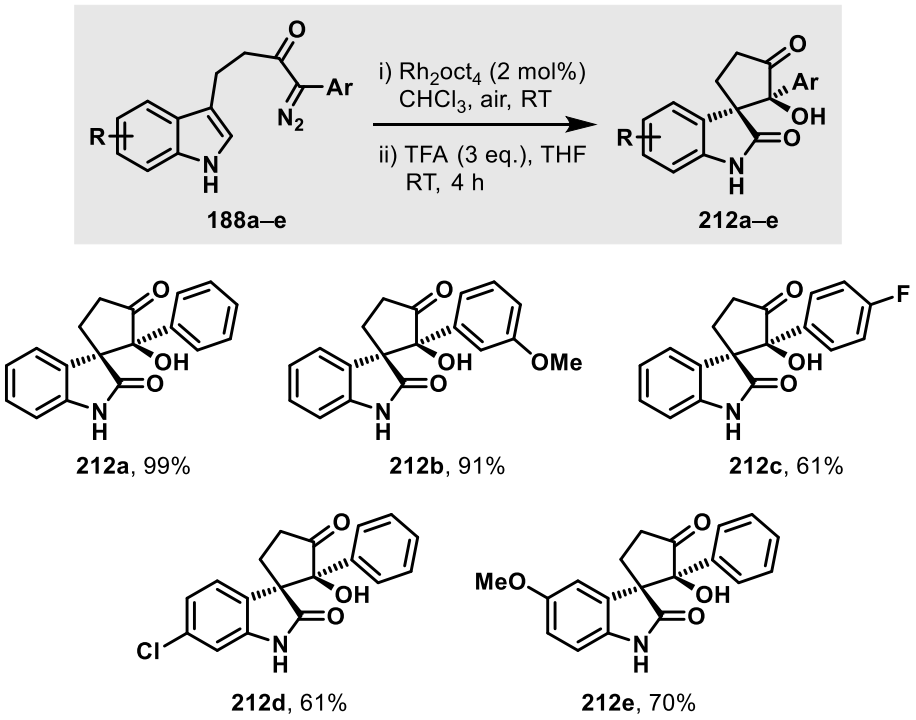


Figure 20. Assignment of spirocycle diastereoisomers based on nOe correlations.

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.

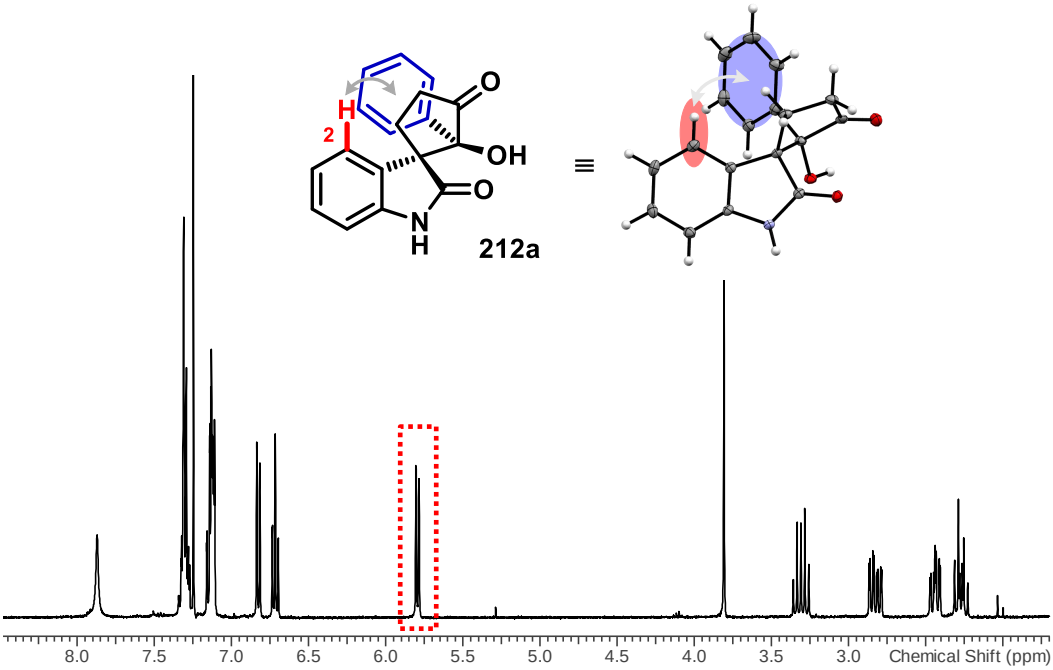
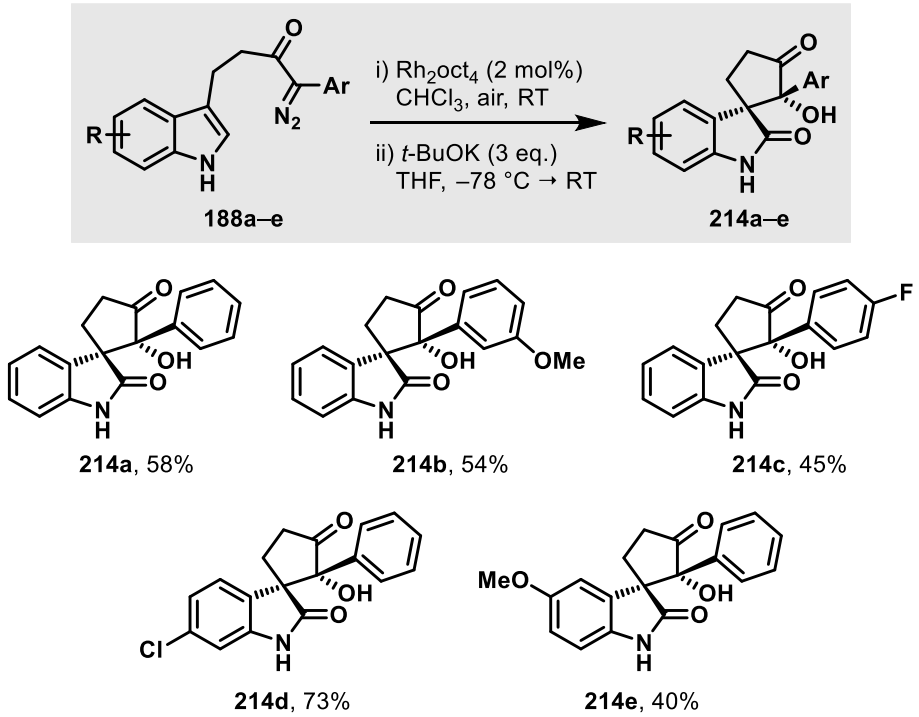
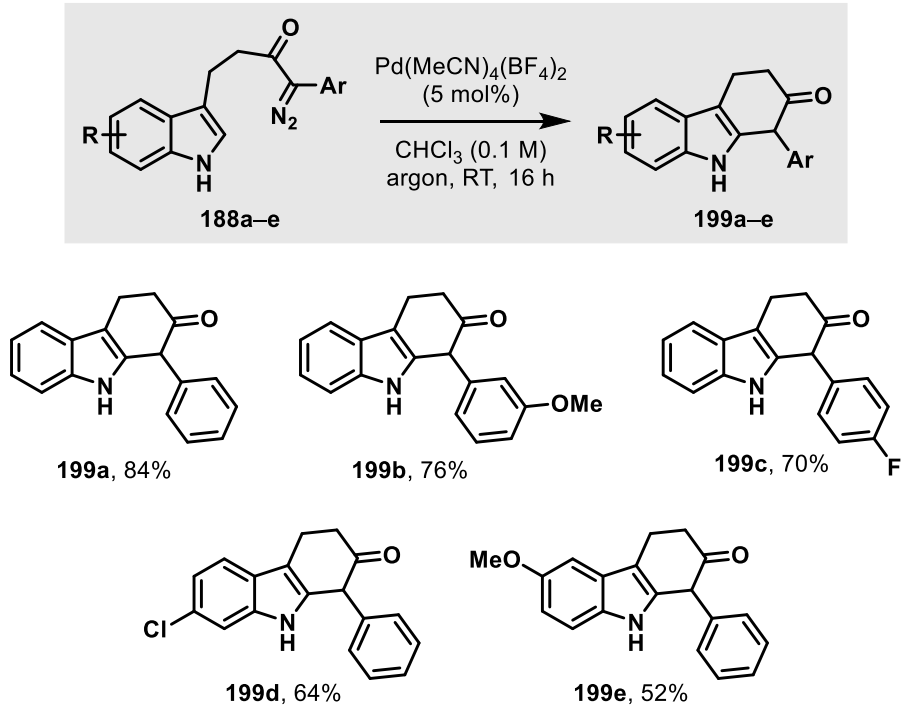


Figure 21. Diagnostic anisotropic shielding of the *syn*-oxindoles.

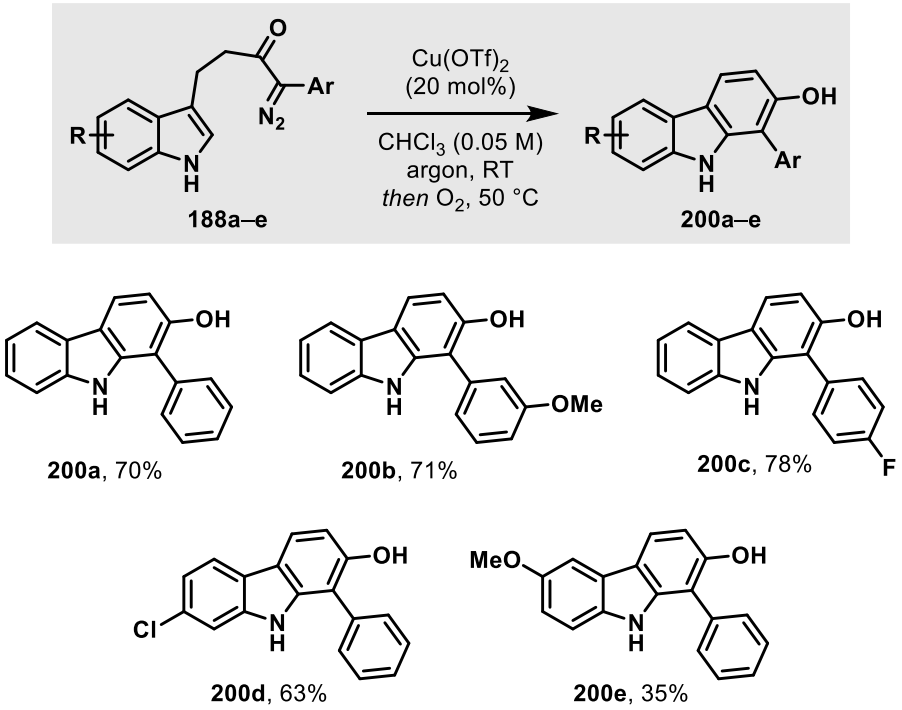


Scheme 77. Scope of the base-promoted synthesis of *anti*-oxindoles.

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.



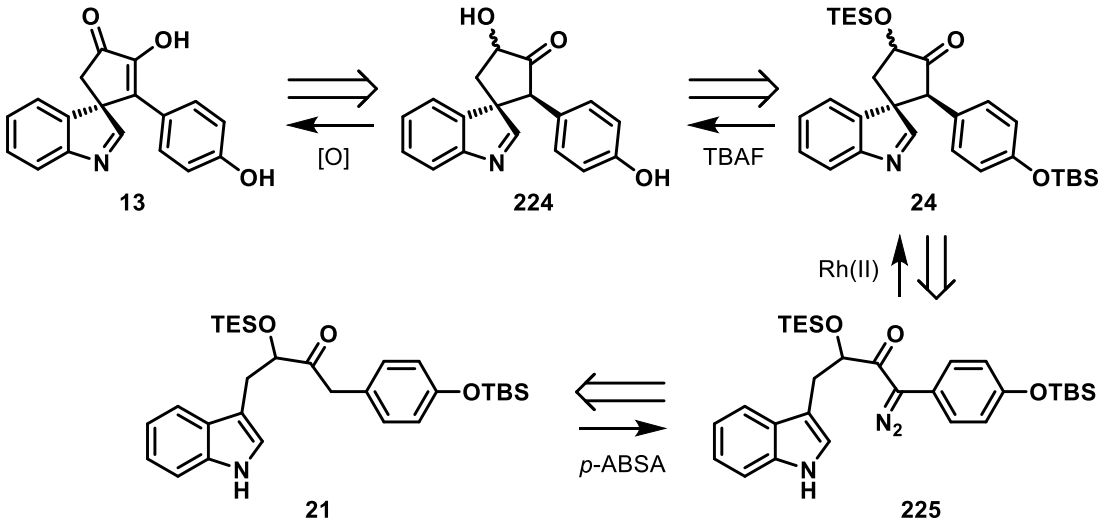
Scheme 78. Scope of the $Pd(MeCN)_4(BF_4)_2$-catalysed annulation reaction.



Scheme 79. Scope of the $Cu(OTf)_2$-catalysed tandem annulation-oxidation reaction.

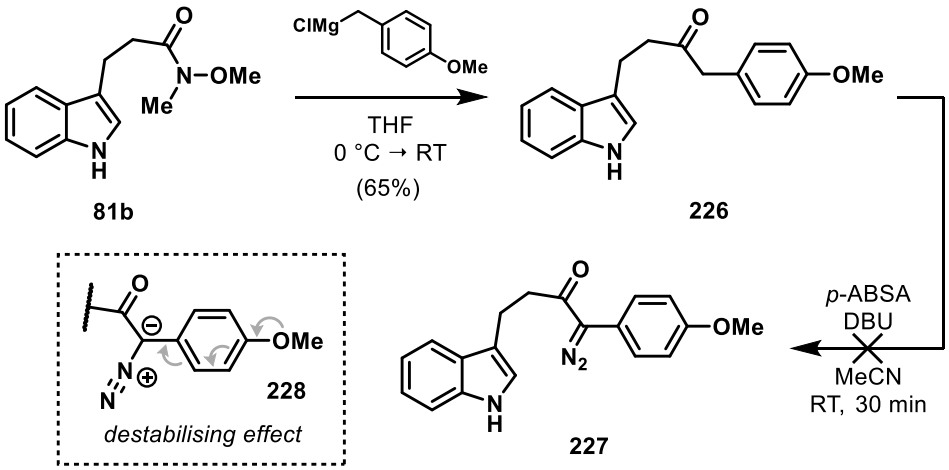
3.6 Preliminary studies towards spirobacillene B

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).[16] 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.

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.



Scheme 81. Attempted synthesis of α-diazocarbonyl **227**.

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]

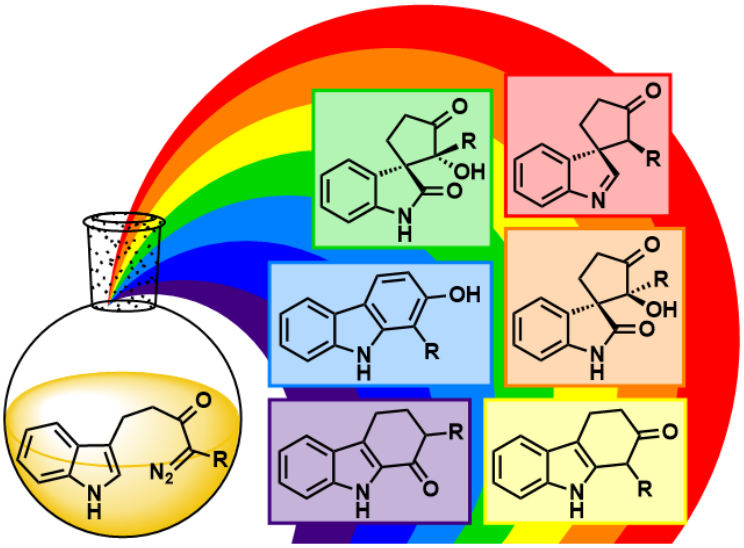
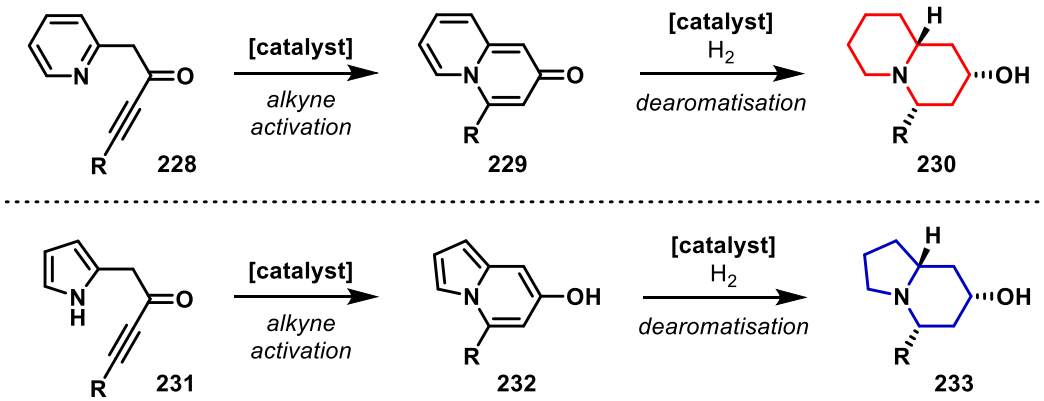


Figure 22. Illustrative rainbow of products from a single "pot of gold".

Chapter 4. Dearomatisation approach to quinolizidine and indolizidine alkaloids

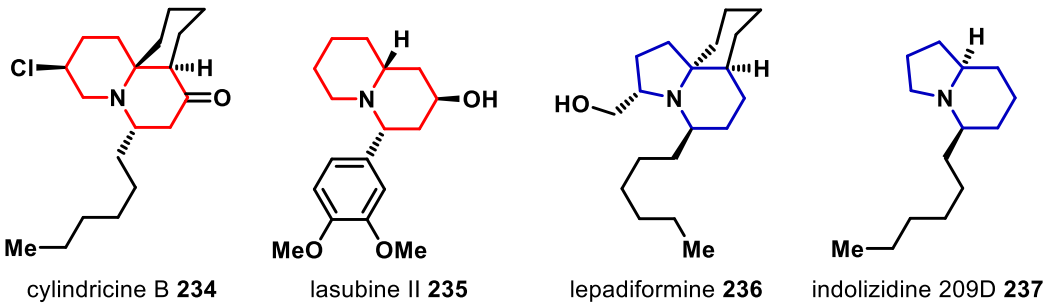
4.1 Introduction

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.

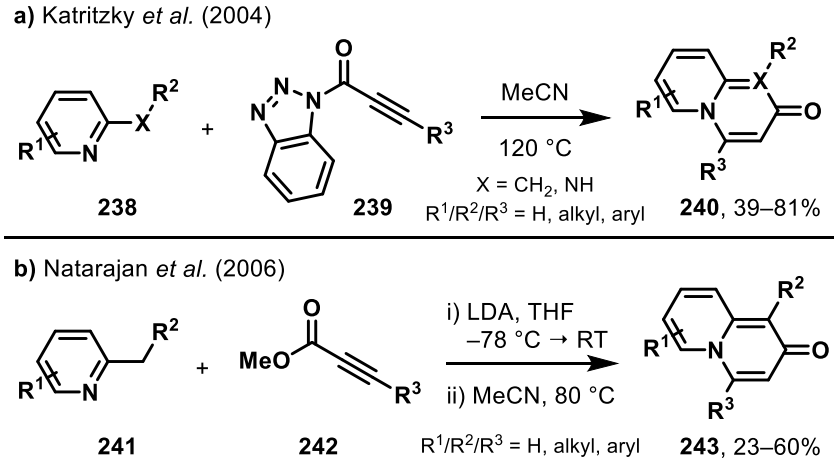
The quinolizidine and indolizidine frameworks are found in a number of bioactive natural products, such as **234**–**237** (Scheme 83).[111–115] These natural products have typically been isolated in small quantities, which hinders their study as potential therapeutics, and so, it is hoped that the proposed sequence will provide an expedient and scalable route for their synthesis.



Scheme 83. Quinolizidine and indolizidine alkaloids.

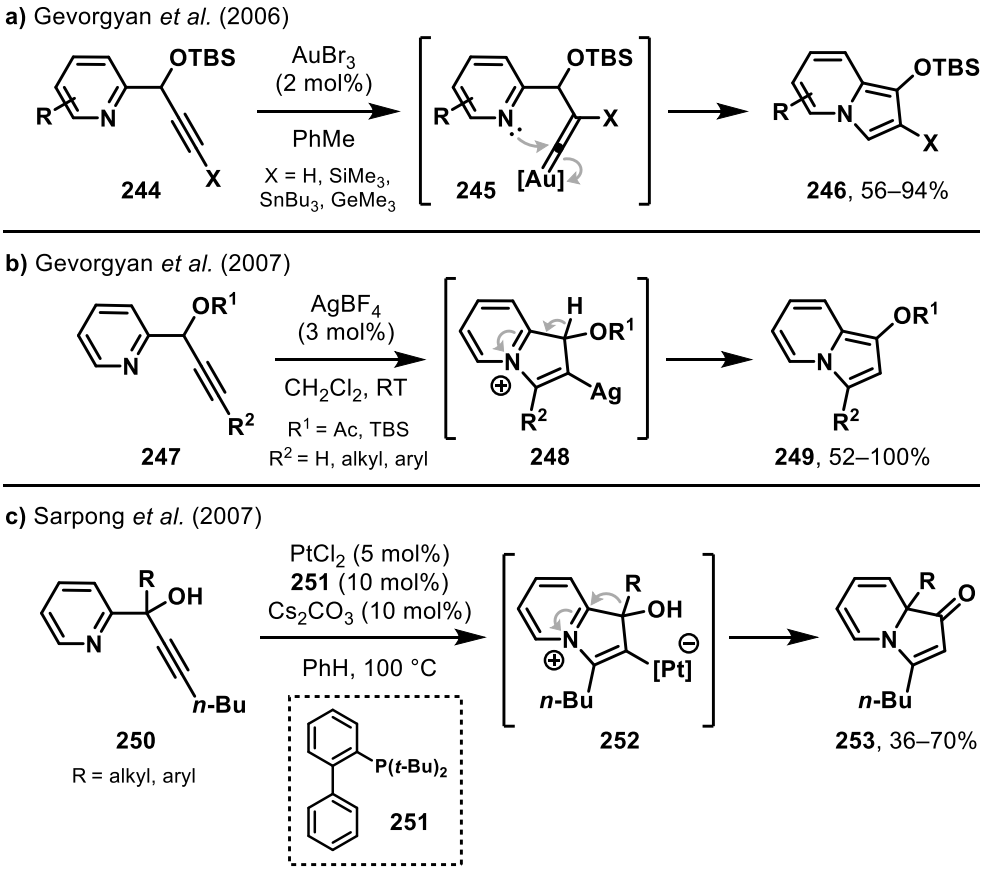
4.2 Background

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.[116] 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).[117,118] 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.



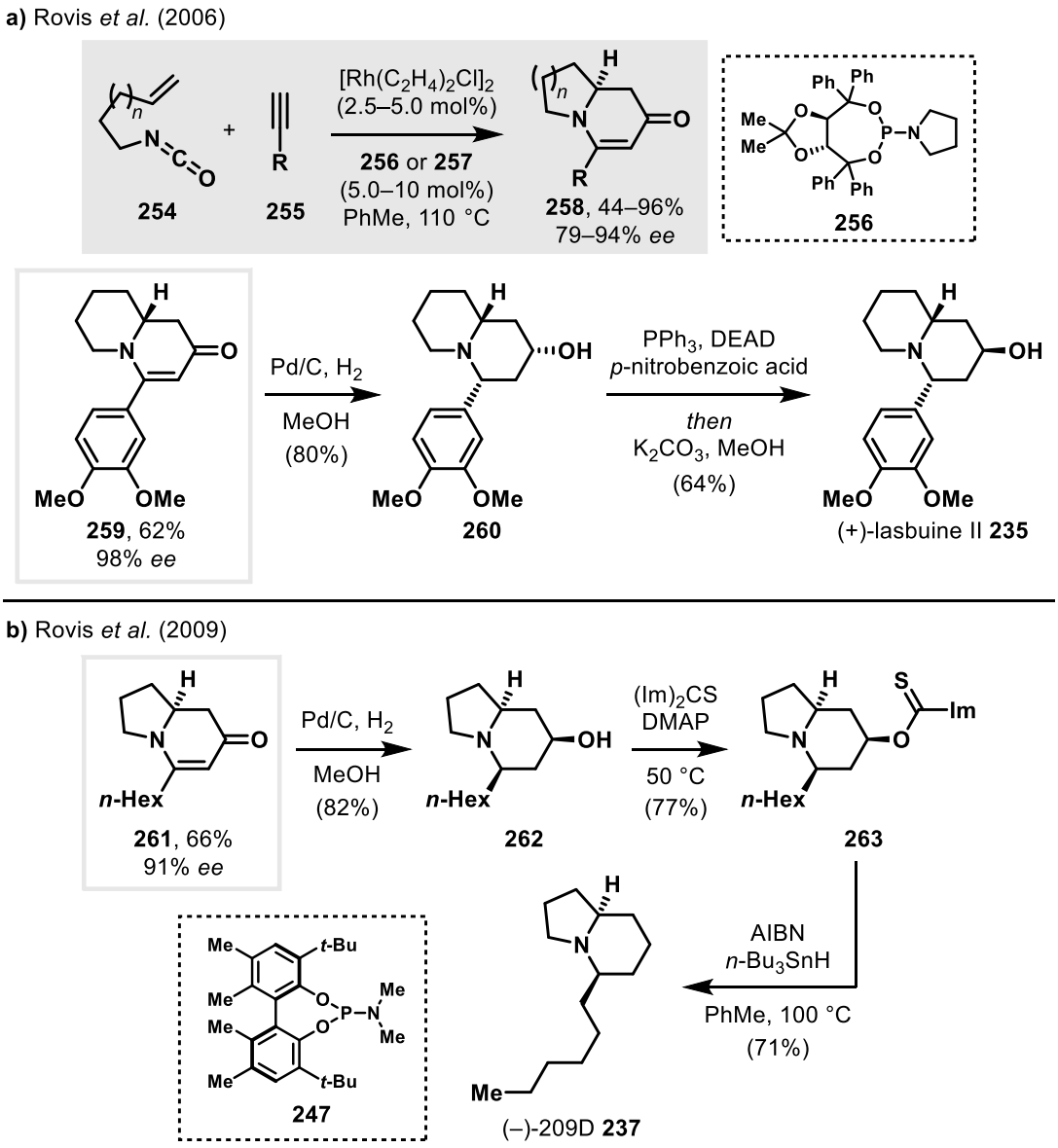
Scheme 84. Pyridine alkyne cyclisation reactions to form quinolizinones.

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).[119] 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 $AgBF_4$ and cyclised to afford indolizines **249** in typically excellent yields (Scheme 85b).[120] 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).[121]



Scheme 85. Pyridine alkyne cyclisation reactions to form indolizidines.

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 **254** and terminal alkynes **255** to generate quinolizidine or indolizidine alkaloid precursors **258** in good to excellent yield and with excellent enantioselectivity (Scheme 86).[122,123] Rovis and co-workers first employed this methodology in the synthesis of (+)-lasubine II **235** (Scheme 86a), by hydrogenating the [2+2+2] product **259** to form quinolizidine **260**. The hydroxyl group stereochemistry of quinolizidine **260** was then inverted by a Mitsunobu and hydrolysis sequence to afford 27.0 mg of (+)-lasubine II **235**.[122] Later, the same group applied this methodology in the synthesis of (−)-indolizidine 209D **237** (Scheme 86b), using a new phosphoramidite ligand **247** to form the [2+2+2] product **261** in good yield.[123] The [2+2+2] product **261** was then hydrogenated and deoxygenated under Barton-McCombie conditions to afford 18.2 mg of (−)-indolizidine 209D **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.

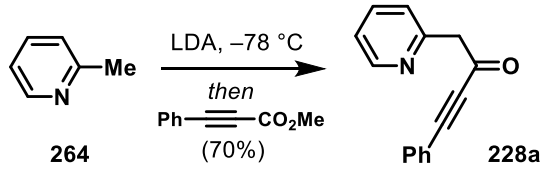


Scheme 86. Leading methods for the catalytic synthesis of quinolizidine and indolizidine alkaloids.

4.3 Pyridine-ynone cyclisations

4.3.1 Reaction discovery & optimisation studies

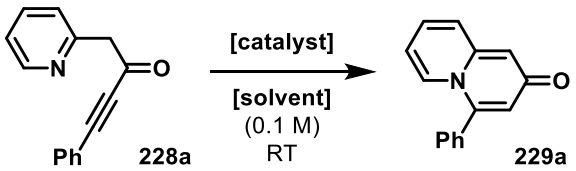
Studies of the proposed pyridine-ynone system began with preparation of ynone **228a**, which was made by the acylation of 2-picoline **264** with methyl phenylpropiolate under modified conditions reported by Natarajan and co-workers (Scheme 87).[117]



Scheme 87. Synthesis of pyridine-ynone **228** by the acylation of 2-picoline **264**.

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 quinolizinone **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.



Entry	Catalyst[a]	mol %	Solvent	Time (h)	Ratio[b] 228a:229a
1	$Cu(MeCN)_4PF_6$	10	CH_2Cl_2	16	100:0
2	$Cu(OTf)_2$	10	CH_2Cl_2	16	100:0
3	$Ph_3PAuNTf_2$	10	CH_2Cl_2	16	100:0
4	AgOTf	10	CH_2Cl_2	16	5:95
5	AgOTf	2	CH_2Cl_2	2	10:90
6	$AgSbF_6$	2	CH_2Cl_2	2	75:25
7	Ag_2O	2	CH_2Cl_2	2	68:32
8	AgOAc	2	CH_2Cl_2	2	36:64
9	$AgNTf_2$	2	CH_2Cl_2	2	5:95
10	$AgNO_3$	2	CH_2Cl_2	2	5:95
11	$AgNO_3$	1	CH_2Cl_2	0.5	50:50
12	$AgNO_3$	1	Toluene	0.5	100:0
13	$AgNO_3$	1	THF	0.5	100:0
14	$AgNO_3$	1	$CHCl_3$	0.5	10:90
15	$AgNO_3$	1	DCE	0.5	5:95
16	$AgNO_3$	1	EtOH	0.5	0:100

*[a]All reactions performed with 0.2 mmol of ynone **228a** in the stated solvent at RT;*

[b]Calculated by ^{1}H NMR spectroscopy of the unpurified reaction mixture.

Table 17. Optimisation of the pyridine-ynone cyclisation conditions.

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 $CDCl_3$, 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 ^{1}H NMR spectrum (15.02 ppm in $CDCl_3$), 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).[124] Subsequent aromatisation and protodemetallation of **266** would then afford the observed quinolizinone **229a** and regenerate the Ag(I) catalyst.

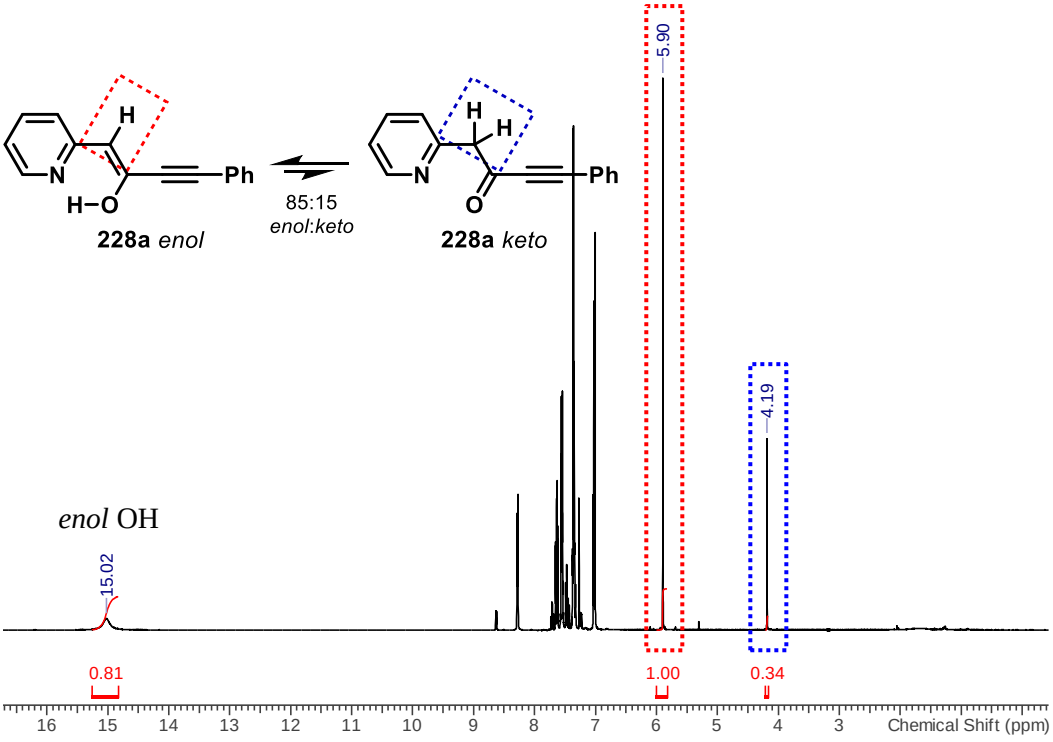
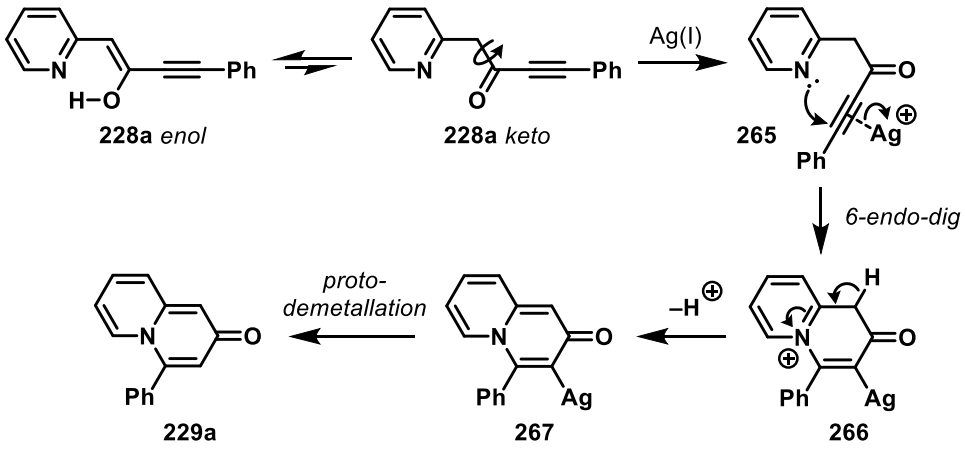


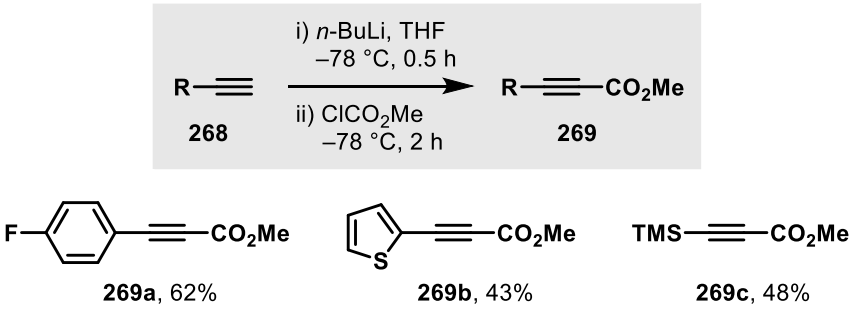
Figure 23. ^{1}H NMR spectrum of pyridone-ynone **228a** in $CDCl_3$.



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

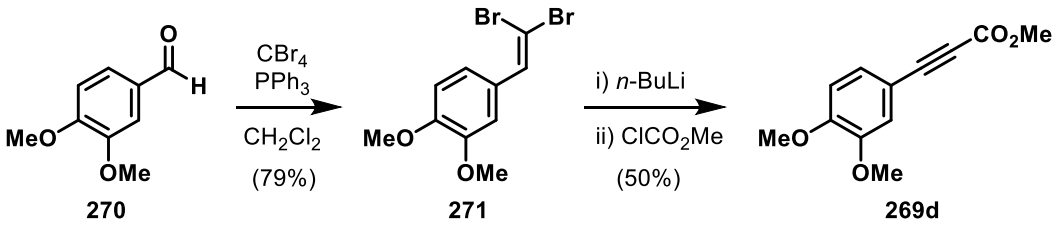
4.3.2 Substrate synthesis

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 commerically available terminal alkynes **268** by deprotonation and trapping with methyl chloroformate (Scheme 89).



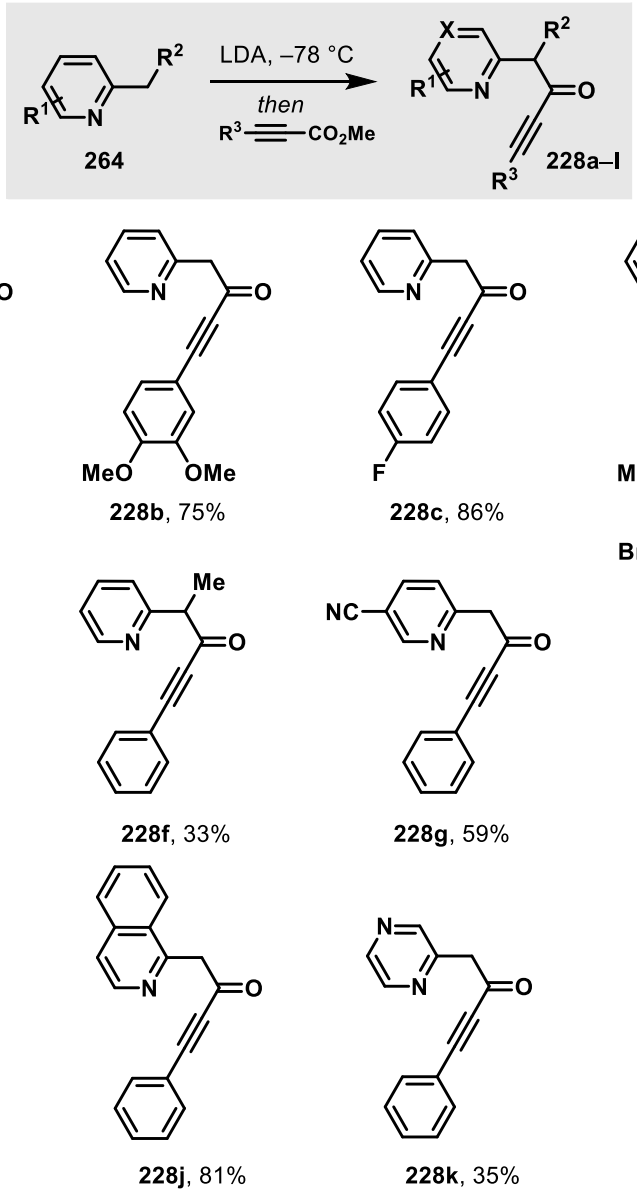
Scheme 89. Synthesis of methyl propiolate esters.

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).[125]



Scheme 90. Synthesis of ester **269d** from a partial Corey-Fuchs reacton.

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).

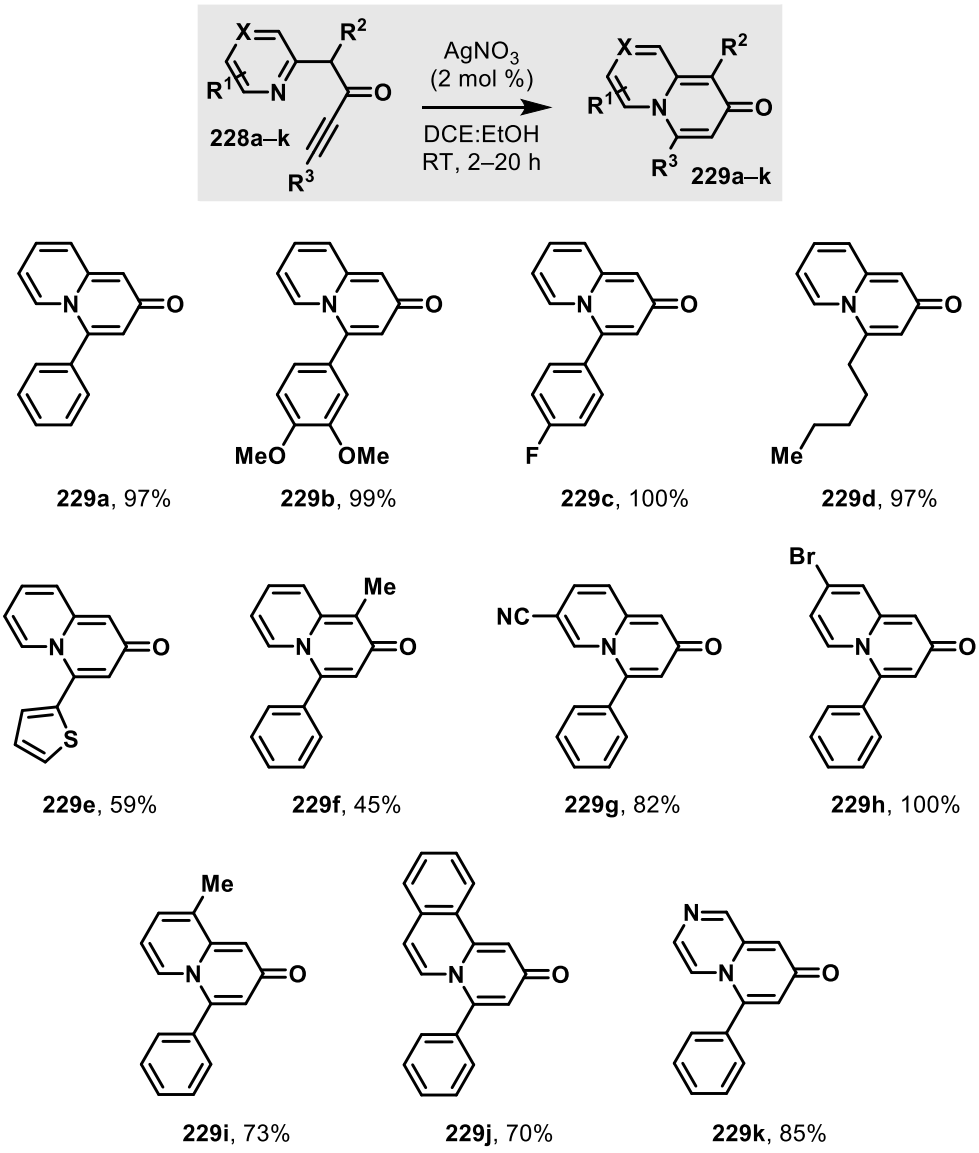


Scheme 91. Library of pyridine-ynone substrates prepared.

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 $AgNO_3$ 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.

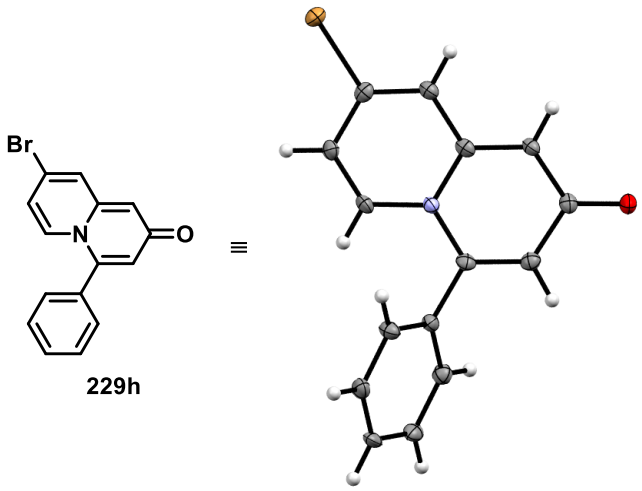
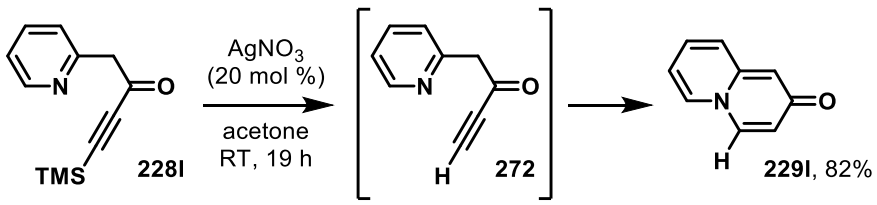


Figure 24. X-ray structure of quniolizinone **229h** with thermal ellipsoids shown at 50% (CCDC 1507022).

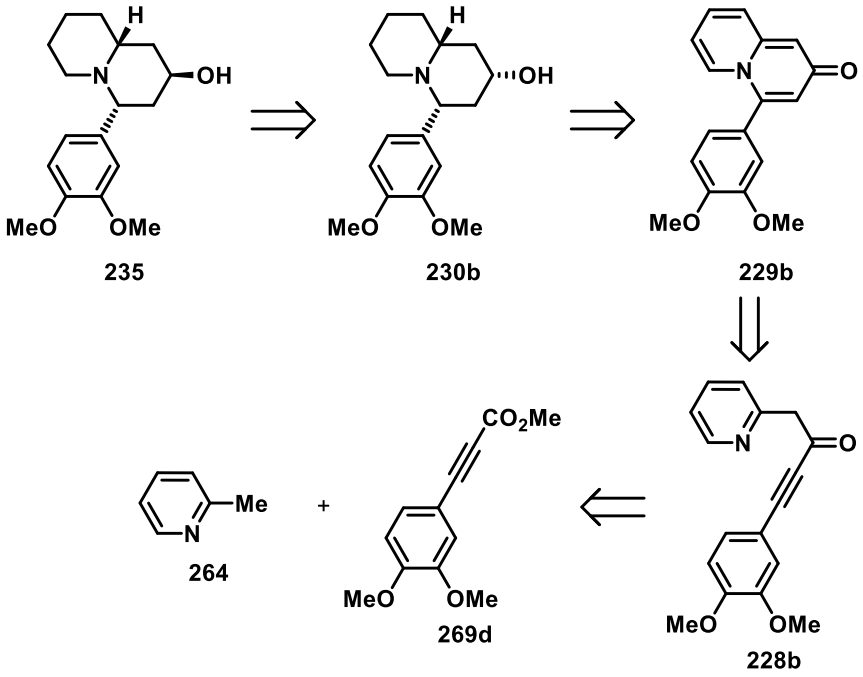
The only substrate which failed to undergo the desired cyclisation under the standard conditions was TMS-ynone **228l**. Interestingly, this substrate was also unreactive under the thermal conditions employed by Natarajan and co-workers.[117] However, by changing the conditions, a one-pot desilylation-cyclisation 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**.

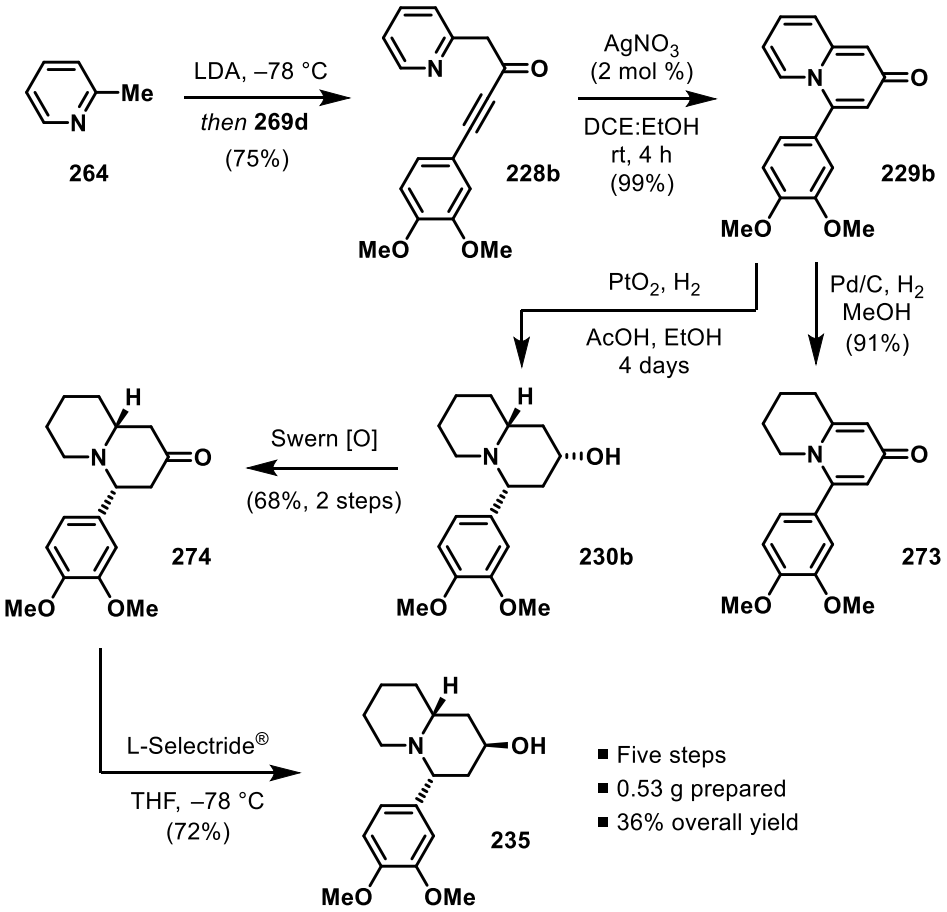
4.3.4 Synthesis of (±)-lasubine II

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).



Scheme 94. Retrosynthetic analysis of lasubine II.

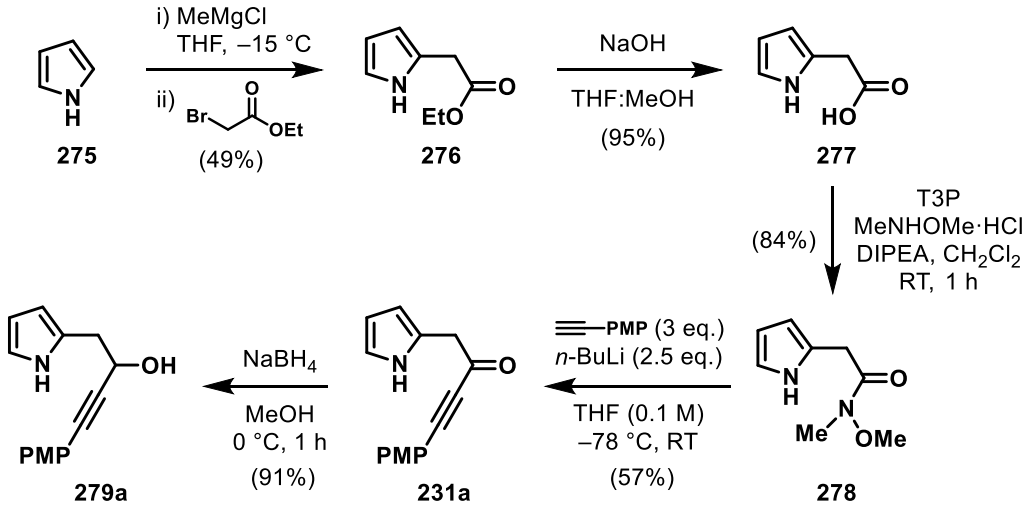
Studies towards the synthesis of (±)-lasubine II began with the previously described synthesis of quinolizinone **229b**, which was readily prepared on a multi-gram scale (2.09 g) in two steps from 2-picoline **264** (Scheme 95). The dearomative hydrogenation of quinolizinone **229b** was then attempted 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 PtO_2 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 95. Synthesis of (±)-lasubine II **235**.

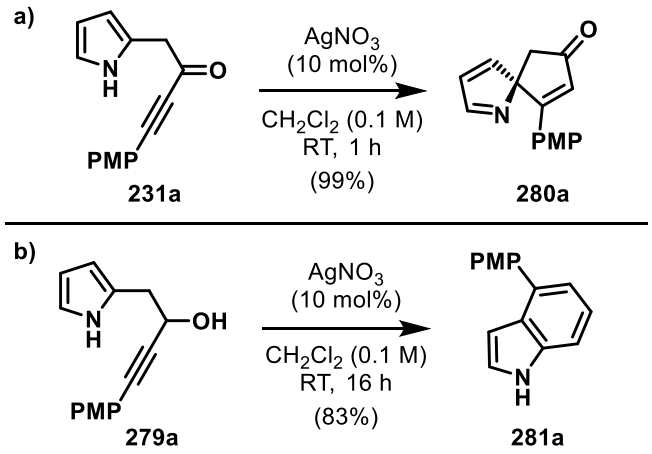
4.4 Pyrrole- & pyrroline-alkyne cyclisations

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.[131] 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 $NaBH_4$.



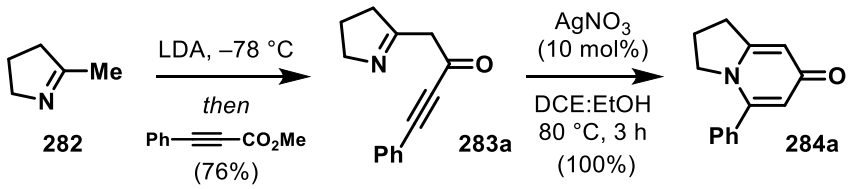
Scheme 96. Synthesis of pyrrole-ynone **231a** and propargyl alcohol **279a** (synthesis aided by Dr William Unsworth and Aimee Clarke).

Initial studies with the pyrrole-alkyne systems began by reacting pyrrole-ynone **231a** with $AgNO_3$ (10 mol%) in CH_2Cl_2, 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.



Scheme 97. Reactivity of pyrrole-alkyne systems: a) Pyrrole-ynones; b) Pyrrole-propargyl alcohols.

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**.

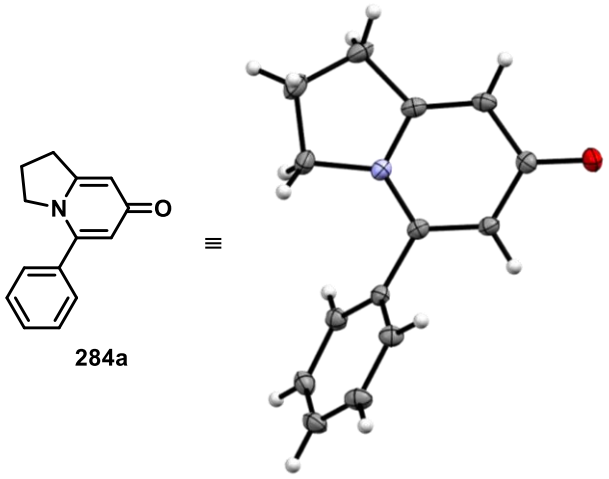
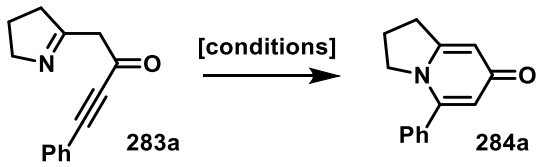


Figure 25. X-ray structure of pyridone **284a** with thermal ellipsoids shown at 50% (CCDC 1532716).

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_2Cl_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).



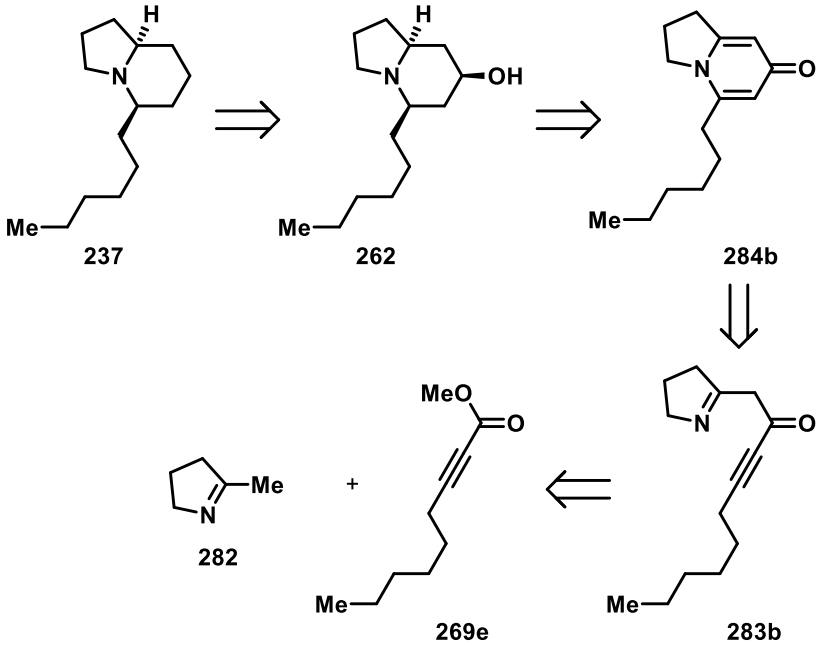
Entry	Catalyst[a]	mol %	Solvent	Temp (°C)	Time / h	Yield[b] (%)
1	$Cu(MeCN)_4PF_6$	10	CH_2Cl_2	40	18	no reaction
2	$Cu(OTf)_2$	10	CH_2Cl_2	40	18	no reaction
3	$Ph_3PAuNTf_2$	10	CH_2Cl_2	40	18	no reaction
4	$AgSbF_6$	10	CH_2Cl_2	40	18	no reaction
5	$AgBF_4$	10	CH_2Cl_2	40	18	no reaction
6	AgOAc	10	CH_2Cl_2	40	18	<5 trace
7	AgMs	10	CH_2Cl_2	40	18	34
8	AgTs	10	CH_2Cl_2	40	18	36
9	AgOTf	10	CH_2Cl_2	40	18	36
10	$AgNTf_2$	10	CH_2Cl_2	40	18	64
11	$AgNO_3 \cdot SiO_2$	10	CH_2Cl_2	40	18	no reaction
12	$AgNO_3$	10	CH_2Cl_2	40	18	100
13	AgTFA	10	CH_2Cl_2	40	18	100
14	$AgNO_3$	5	CH_2Cl_2	40	21	>95
15	AgTFA	5	CH_2Cl_2	40	21	100
16	AgTFA	5	MeCN	40	11	no reaction
17	AgTFA	5	MeOH	40	11	49
18	AgTFA	5	EtOH	40	11	55
19	AgTFA	5	CH_2Cl_2	40	11	57
20	AgTFA	5	DCE	40	11	60
21	AgTFA	5	THF	40	11	68
22	AgTFA	5	$CHCl_3$	40	11	75
23	AgTFA	5	PhMe	40	11	100
24	AgTFA	2	PhMe	110	1	100
25	no catalyst	-	PhMe	110	1	<5 trace

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

Table 18. Optimisation of the pyrroline-ynone cyclisation conditions.

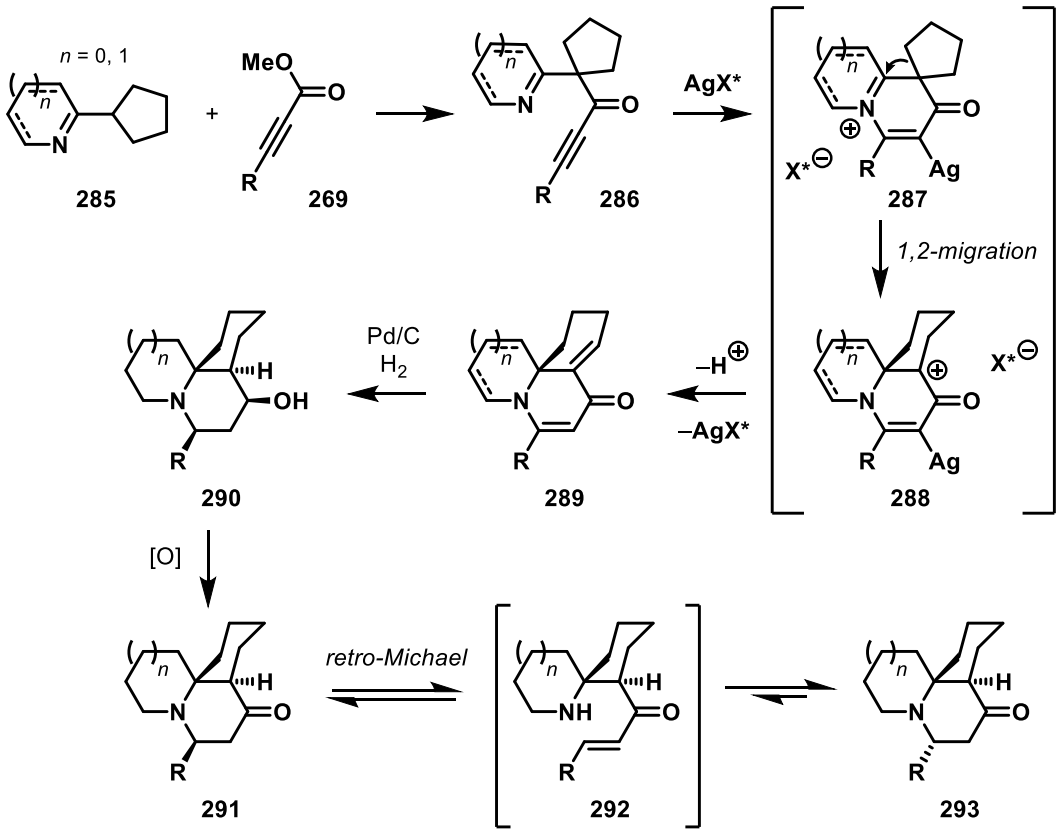
4.5 Future work

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).



Scheme 99. Retrosynthetic analysis of indolizidine 209D **237**.

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-ynones 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.[132]

Chapter 5. Experimental

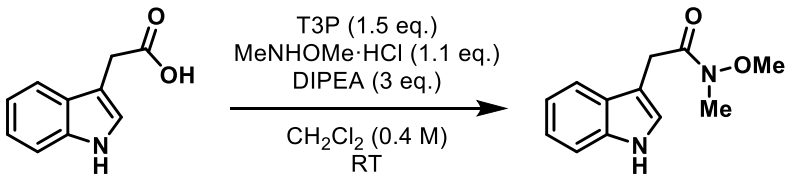
5.1 General experimental details

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_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_H 7.27 and δ_C 77.0 for $CDCl_3$, δ_H 2.50 and δ_C 39.5 for DMSO-d_6, δ_H 5.32 and δ_C 54.0 for CD_2Cl_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_2Cl_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 Mercksilica gel $60F_{254}$ 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

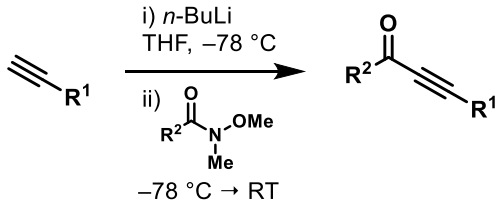
5.2.1 Chapter 2

General procedure 2A: Weinreb amide formation



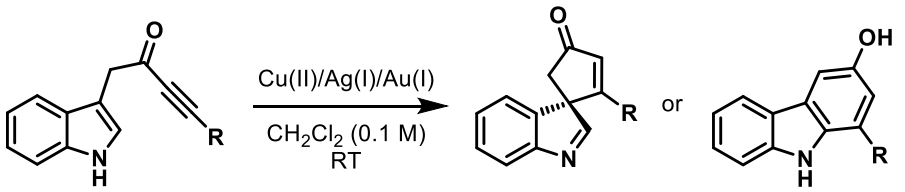
To a stirred solution of acid (1.00 mmol), MeNHOMe·HCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH_2Cl_2 (2.5 mL) was added T3P (955 mg, 1.5 mmol, 50% wt. in EtOAc). The solution was stirred for 1 h at RT. The reaction mixture was poured into water (20 mL) and acidified using 10% $HCl_{(aq)}$ (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 ($MgSO_4$) and concentrated *in vacuo* to afford the crude Weinreb amide product.

General procedure 2B: Ynone formation



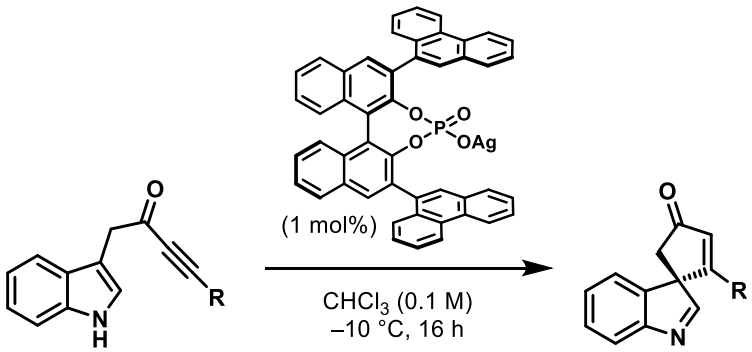
To a solution of alkyne (6.87 mmol) in THF (7 mL) at −78 °C under argon was added *n*-BuLi (3.6 mL, 5.73 mmol, 1.6 M in hexanes) dropwise. The mixture was stirred for 30 min at −78 °C and then transferred *via* cannula to a −78 °C solution of Weinreb amide (2.29 mmol) in THF (21 mL). Upon complete transfer the mixture was warmed to RT and stirred for 30 min after which the reaction was quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography to afford the ynone product.

General procedure 2C: Indole-ynone cyclisations



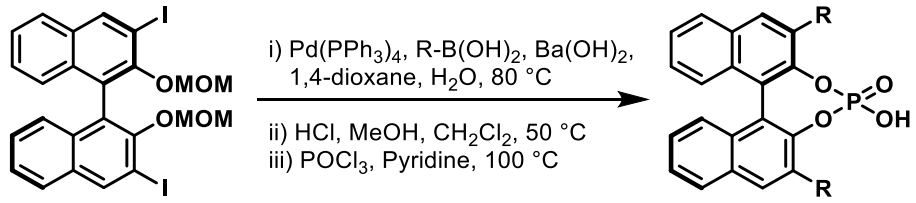
To a solution of ynone (0.2 mmol) in CH_2Cl_2 (2 mL) was added either AgOTf, $Cu(OTf)_2$ or $(Ph_3P)AuNTf_2$·½PhMe (1–20 mol%). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was concentrated *in vacuo* then purified by column chromatography to afford the cyclised product.

General procedure 2D: Asymmetric indole-ynone spirocyclisations



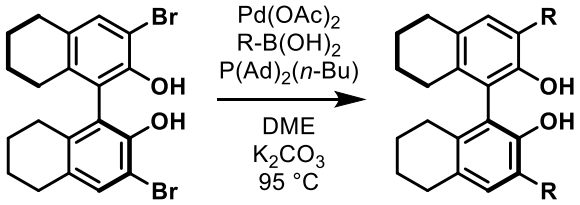
To a solution of ynone (0.2 mmol) in $CHCl_3$ (2 mL) at −10 °C was added **Ag-114l** (2 µmol). The mixture was stirred at −10 °C for 16 h. The reaction mixture was then directly applied to a column and purified by column chromatography to afford the spirocyclic product. Enantiomeric excess was determined 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 × 10 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 to afford the BINOL phosphoric acid product.

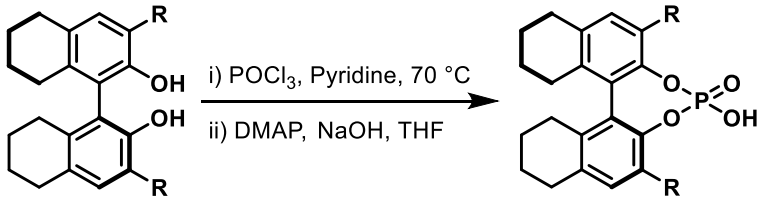
General procedure 2F: H_8-BINOL Suzuki cross-coupling



(*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.

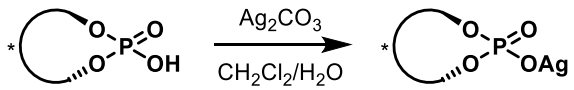
$NH_4Cl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, washed with H_2O (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was then purified by column chromatography (silica gel, hexane to hexane/CH_2Cl_2) to afford the H_8-BINOL product.

General procedure 2G: H_8-BINOL phosphorylation



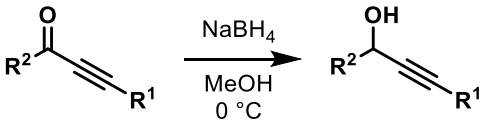
To a solution of the respective (H_8)-BINOL product (0.2 mmol) in pyridine (1 mL) was added $POCl_3$ (0.4 mmol) dropwise. The mixture was stirred for 16 h under argon at 70 °C, then poured into 10% $HCl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined and concentrated *in vacuo*. The crude material was combined with DMAP (0.02 mmol) in 2 M $NaOH_{(aq)}$ (1 mL) and THF (1 mL). The mixture was stirred for 16 h under argon at RT, 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 H_8-BINOL phosphoric acid product.

General procedure 2H: Ag-CPA preparation



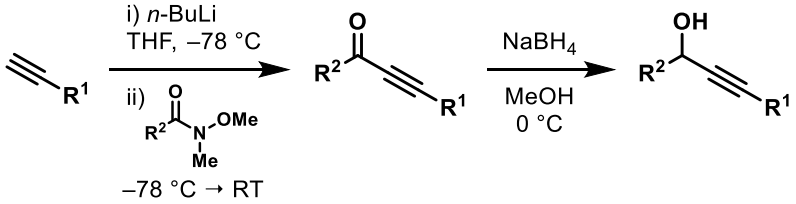
To a solution the respective phosphoric acid (0.20 mmol) in CH_2Cl_2 (2 mL) in the dark was added Ag_2CO_3 (27.6 mg, 0.10 mmol), followed by H_2O (2 mL). The mixture was stirred vigorously for 1 h, then poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were filtered through Celite® and concentrated *in vacuo* to afford the phosphoric acid silver salt.

General procedure 2I: Ynone reduction



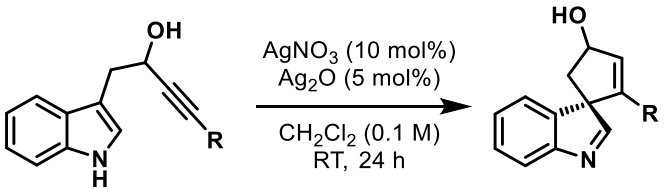
To a solution of ynone (1.0 mmol) in MeOH (20 mL) at 0 °C was added $NaBH_4$ (4.0 mmol). The reaction mixture was stirred for a 30 min at 0 °C before being quenched with the addition of sat. $NH_4Cl_{(aq)}$ (30 mL). The organics were extracted with DCM (4 × 50 mL), dried ($MgSO_4$) and purified by flash column chromatography to afford the desired propargyl alcohol.

General procedure 2J: Telescoped propargyl alcohol formation



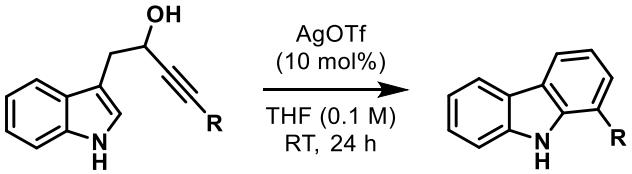
To a solution of terminal alkyne (3.0 mmol) in THF (3 mL) at −78 °C under argon was added *n*-BuLi (1.0 mL, 2.5 mmol, 2.5 M in hexane). The resulting solution was stirred at −78 °C for 30 min, then transferred via cannula to a cooled (−78 °C) solution of Weinreb amide (1.0 mmol) in THF (9 mL). The mixture 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. $NH_4Cl_{(aq)}$ (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 $MgSO_4$ and concentrated *in vacuo*. The resulting material was then dissolved in MeOH (20 mL), cooled to 0 °C and $NaBH_4$ (4.0 mmol) was added. The reaction mixture was stirred for a 30 min at 0 °C before being quenched with sat. $NH_4Cl_{(aq)}$ (30 mL). The organics were extracted with CH_2Cl_2 (4 × 30 mL), dried ($MgSO_4$) 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 CH_2Cl_2 (2 mL) was added sequentially Ag_2O (10 µmol) and $AgNO_3$ (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.

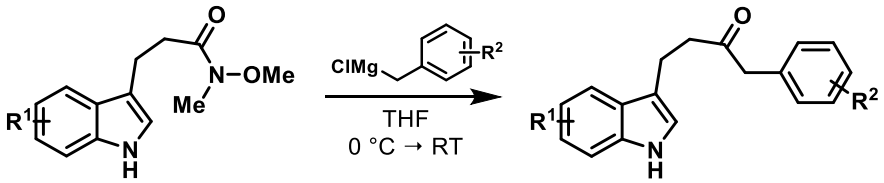
General procedure 2L: Propargyl alcohol benzannulation



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

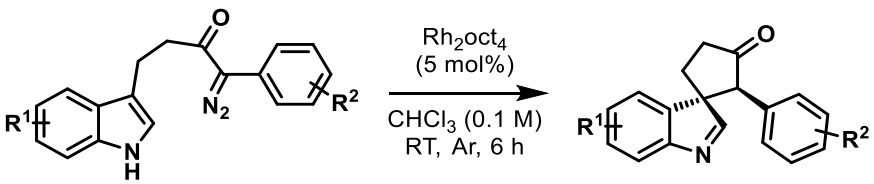


Based on a modified literature procedure.[16] To a solution of Weinreb amide (1 equiv.) in THF (10 mL/mmol) at 0 °C under argon was added the benzyl Grignard (4 equiv.) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 4–5 h. The reaction was then quenched with sat. $NH_4Cl_{(aq)}$, diluted with water and extracted with EtOAc (3 ×). The combined organics were washed with brine, dried ($MgSO_4$), concentrated *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.[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 *in vacuo*. The crude product was dissolved in CH_2Cl_2 and purified by column chromatography (eluting with 3% Et_3N as a basic additive) to afford the desired α-diazocarbonyl compound. (Note: the α-diazcarbonyl compounds were generally stable when stored at room temperature for ~1 month before significant degradation was observed).

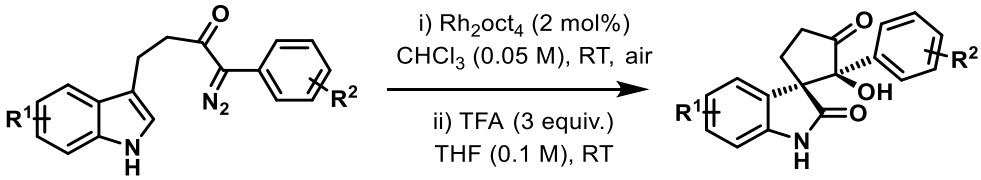
General procedure 3C: Formation of spirocyclic indolenines



To the α-diazocarbonyl compound (1 equiv.) and Rh_2oct_4 (5 mol%) under argon was added deoxygenated $CHCl_3$ (10 mL/mmol). The mixture was stirred at RT under argon for 6 h then

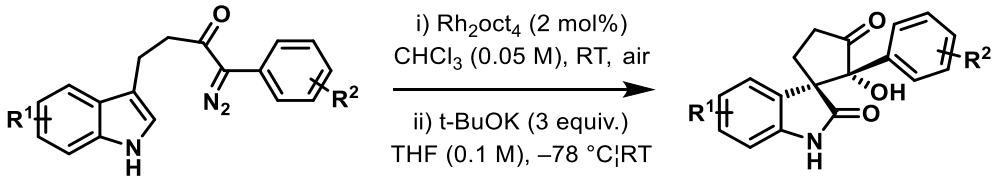
concentrated *in vacuo* and purified by column chromatography (under a positive pressure of nitrogen) to afford the spirocyclic indolenine diastereoisomers (The major diasteroisomers were identified by nOe experiments).

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



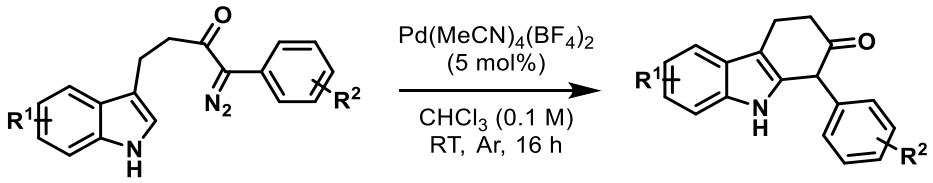
To the α-diazocarbonyl compound (1 equiv.) and Rh_2oct_4 (2 mol%) in a flask open to air was added $CHCl_3$ (20 mL/mmol). The mixture was stirred at RT for 1–5 h then concentrated *in vacuo*. The crude α,β-dicarbonyl product was then dissolved in THF (10 mL/mmol) and TFA (3 equiv.) was added. The mixture 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



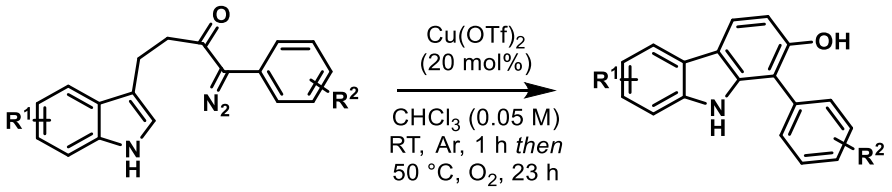
To the α-diazocarbonyl compound (1 equiv.) and Rh_2oct_4 (2 mol%) in a flask open to air was added $CHCl_3$ (20 mL/mmol). The mixture was stirred at RT for 1–5 h then concentrated *in vacuo*. The crude α,β-dicarbonyl product was then dissolved in THF (10 mL/mmol) and cooled to −78 °C, *t*-BuOK (3 equiv.) 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



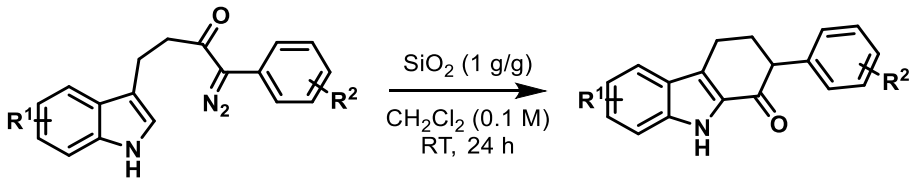
To the α-diazocarbonyl compound (1 equiv.) and $Pd(MeCN)_4(BF_4)_2$ (5 mol%) under argon was added $CHCl_3$ (10 mL/mmol). The mixture was stirred at RT under argon for 16 h then concentrated *in vacuo* and purified by column chromatography to afford the C-2 annulated indole product.

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 $CHCl_3$ (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.

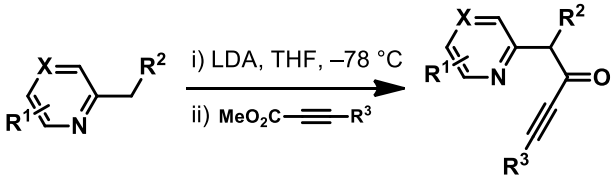
General procedure 3H: Silica-promoted indole annulation



To the α-diazocarbonyl compound (1 equiv.) and silica gel (1 g/g) was added CH_2Cl_2 (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.

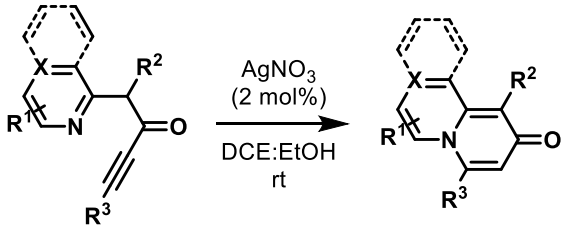
5.2.3 Chapter 4

General procedure 4A: pyridine-ynone formation



Based on a modified literature procedure.[117] 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 ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography to afford the pyridine-ynone product.

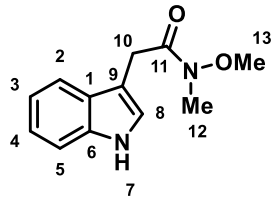
General procedure 4B: pyridine-ynone cyclisations



To a solution of aryl-ynone (1 equiv.) in DCE (5 mL/mmol) and EtOH (5 mL/mmol) at RT was added $AgNO_3$ (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 CH_2Cl_2 and purified by column chromatography (typically 5 → 10% MeOH in EtOAc) to afford the cyclised compound.

5.3 Experimental for Chapter 2

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

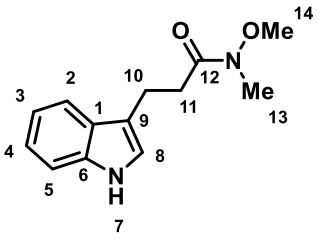


Synthesised using **general procedure 2A** with indole-3-acetic acid (500 mg, 2.85 mmol), T3P 50% in EtOAc (2.72 g, 4.28 mmol), DIPEA (1.49 mL, 8.55 mmol) and MeNHOMe·HCl (306 mg, 3.14 mmol) in CH_2Cl_2 (7.5 mL). Afforded the *title compound* **81a** (623 mg, 100%) without further purification as a pale brown solid, mp 122–124 °C (lit.[134] 122–124 °C); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 29.1 (CH_2, C-10), 32.5 (CH_3, C-12), 61.4 (CH_3, 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-(1*H*-Indol-3-yl)-*N*-methoxy-*N*-methylpropanamide (81b)

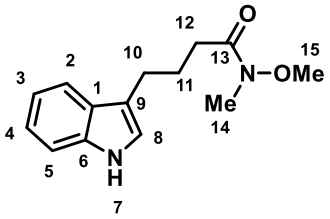


Synthesised using **general procedure 2A** with indole-3-propionic acid (500 mg, 2.64 mmol), T3P (2.52 g, 3.96 mmol, 50% wt. in EtOAc), DIPEA (1.38 mL, 7.92 mmol) and MeNHOMe·HCl (283 mg, 2.90 mmol) in CH_2Cl_2 (7 mL). Afforded the *title compound* **81b** (594 mg, 97%) without further purification as a yellow oil; ν_{max} (cm^{-1}) 3410, 3300, 2936, 1642, 1458, 743; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 20.2 (CH_2, C-10/11), 32.0 (CH_3, C-13), 32.6 (CH_2, C-10/11), 61.0 (CH_3, 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),

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; $C_{13}H_{16}N_2NaO_2$ (MNa^+) Requires 255.1104 (3.6 ppm error), Found: 233.1278; $C_{13}H_{17}N_2O_2$ (MH^+) Requires 233.1285 (2.7 ppm error).

Lab notebook reference: MJJ1/70

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

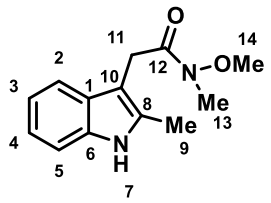


Synthesised using **general procedure 2A** with indole-3-butyric acid (500 mg, 2.46 mmol), T3P (2.52 g, 3.96 mmol, 50% wt. in EtOAc), DIPEA (1.38 mL, 7.92 mmol) and MeNHOMe·HCl (283 mg, 2.90 mmol) in CH_2Cl_2 (7 mL). Afforded the *title compound* **81c** (559 mg, 92%) without further purification as a yellow oil; ν_{max} (cm^{-1}) 3301, 2936, 1643, 1458, 995, 743; δ_H (400 MHz, $CDCl_3$) 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-1*H*-indol-3-yl)acetamide (81d)**

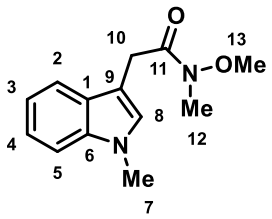


Synthesised using **general procedure 2A** with 2-methyl-3-indoleacetic acid (1.00 g, 5.29 mmol), T3P (5.05 g, 7.94 mmol, 50% wt. in EtOAc), DIPEA (2.76 mL, 15.9 mmol) and MeNHOMe·HCl (567 mg, 5.82 mmol) in CH_2Cl_2 (13 mL). Afforded the *title compound* **81d** (1.21 g, 98%) without further purification 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, $CDCl_3$) 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, $CDCl_3$) 11.6 (CH_3,

C-9), 28.6 (CH_2, C-11), 32.2 (CH_3, C-13), 61.1 (CH_3, 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; $C_{13}H_{16}N_2NaO_2$ (MNa^+) Requires 255.1104 (−0.1 ppm error), Found: 233.1288; $C_{13}H_{17}N_2O_2$ (MH^+) Requires 233.1285 (−1.6 ppm error).

Lab notebook reference: MJJ3/43

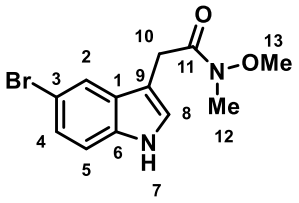
_N_-Methoxy-_N_-methyl-2-(1-methyl-1_H_-indol-3-yl)acetamide (81e)



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 CH_2Cl_2 (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; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 28.6 (CH_2, C-10), 32.1 (CH_3, C-12), 32.5 (CH_3, C-7), 61.2 (CH_3, 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; $C_{13}H_{16}N_2NaO_2$ (MNa^+) Requires 255.1104 (−1.2 ppm error), Found: 233.1288; $C_{13}H_{17}N_2O_2$ (MH^+) Requires 233.1285 (−1.6 ppm error).

Lab notebook reference: MJJ1/84

2-(5-Bromo-1_H_-indol-3-yl)-_N_-methoxy-_N_-methylacetamide (81f)

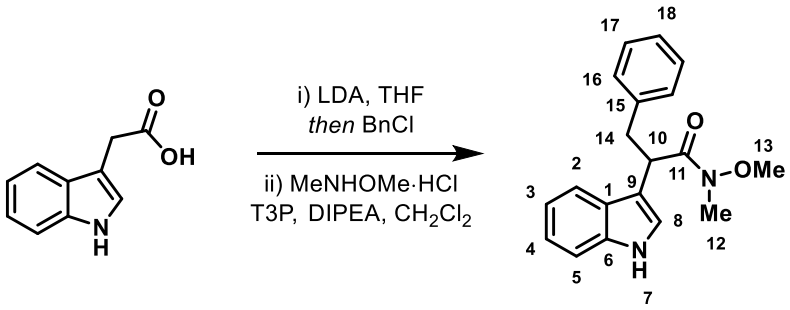


Synthesised using **general procedure 2A** with 5-bromoindole-3-acetic acid (1.00 g, 3.94 mmol), T3P (3.76 g, 5.91 mmol, 50% wt. in EtOAc), DIPEA (2.06 mL, 11.82 mmol) and

MeNHOMe·HCl (422 mg, 4.33 mmol) in CH_2Cl_2 (10 mL). Afforded the *title compound* **81f** (1.17 g, 100%) without further purification as a yellow solid, mp 98–100 °C; ν_{max} (cm^{-1}) 3279, 1646, 1459, 1386, 1101, 1001, 883, 793; δ_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); δ_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; $C_{12}H_{13}{}^{79}BrN_2NaO_2$ (MNa^+) Requires 319.0053 (1.3 ppm error), Found: 297.0234; $C_{12}H_{14}{}^{79}BrN_2O_2$ (MH^+) Requires 297.0233 (−0.1 ppm error).

Lab notebook reference: MJJ3/38

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

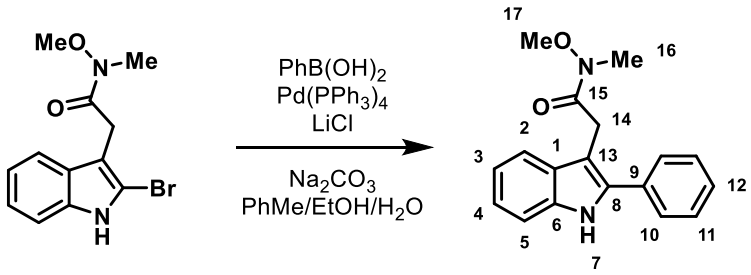


Synthesised according to a modified literature procedure.[136] To solution of DIPA (3.20 mL, 22.8 mmol) in THF (11.5 mL) at a 0 °C under argon was added *n*-BuLi (9.12 mL, 22.8 mmol, 2.5M in hexanes) dropwise. The solution was stirred for 15 min before being cooled to –10 °C. Indole-3-acetic acid (1.00 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_2Cl_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 ($MgSO_4$) 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; ν_{max} (cm^{-1}) 3422, 3288, 2936, 1637, 1455, 985, 742, 700; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 32.1 (CH_3, C-12), 39.8 (CH_2, C-14), 40.6 (CH, C-10), 61.2 (CH_3, 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; $C_{19}H_{20}N_2NaO_2$ (MNa^+) Requires 331.1417 (−0.2 ppm error), Found: 309.1594; $C_{19}H_{21}N_2O_2$ (MH^+) Requires 309.1598 (1.2 ppm error).

Lab notebook reference: MJJ4/70

_N_-Methoxy-_N_-methyl-2-(2-phenyl-1_H_-indol-3-yl)acetamide (81h)

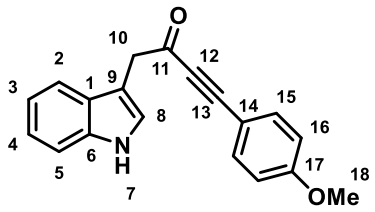


To a dry three-neck flask was charged indole **93** (490 mg, 1.65 mmol), phenylboronic acid (262 mg, 2.15 mmol), LiCl (140 mg, 3.30 mmol), Na_2CO_3 (438 mg, 4.13 mmol), toluene (3.6 mL), EtOH (3.6 mL) and water (2.5 mL). The mixture was degassed with vacuum/argon 3 times. $Pd(PPh_3)_4$ (95 mg, 82.5 µmol) 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 ($MgSO_4$) 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; ν_{max} (cm^{-1}) 3289, 2963, 1644, 1458, 1178, 1000, 769, 740, 700; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 28.9 (CH_2, C-14), 32.4 (CH_3, C-16),

61.0 (CH_3, 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; $C_{18}H_{18}N_2NaO_2$ (MNa^+) Requires 317.1260 (3.7 ppm error), Found: 295.1434; $C_{18}H_{19}N_2O_2$ (MH^+) Requires 295.1441 (2.3 ppm error).

Lab notebook reference: MJJ1/44

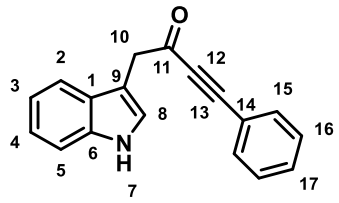
1-(1*H*-Indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one (83a)



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; ν_{max} (cm^{-1}) 3411, 2196, 1658, 1602, 1509, 1255, 1172, 1082, 834, 744; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 41.8 (CH_2, C-10), 55.3 (CH_3, 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; $C_{19}H_{15}NNaO_2$ (MNa^+) Requires 312.0995 (4.4 ppm error), Found: 290.1168; $C_{19}H_{16}NO_2$ (MH^+) Requires 290.1176 (2.6 ppm error).

Lab notebook reference: MJJ1/92

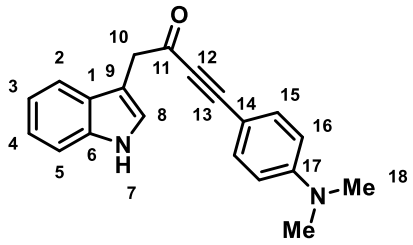
1-(1*H*-Indol-3-yl)-4-phenylbut-3-yn-2-one (83b)



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; ν_{max} (cm^{-1}) 3410, 2202, 1662, 1084, 743; δ_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); δ_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; $C_{18}H_{13}NNaO$ (MNa^+) Requires 282.0889 (2.8 ppm error), Found: 260.1066; $C_{18}H_{14}NO$ (MH^+) Requires 260.1070 (1.6 ppm error).

Lab notebook reference: MJJ/1/5

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

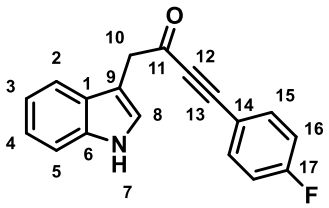


Synthesised using **general procedure 2B** with 4-ethynyl-*N*,*N*-dimethylaniline (998 mg, 6.87 mmol), THF (7 + 21 mL), Weinreb **81a** (500 mg, 2.29 mmol) and *n*-BuLi (2.29 mL, 5.73 mmol, 2.5 M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then CH_2Cl_2) afforded the *title compound* **83c** (624 mg, 90%) as a yellow solid, mp 157–159 °C; ν_{max} (cm^{-1}) 2192, 2149, 1642, 1597, 1526, 1377, 1093; δ_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); δ_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; $C_{20}H_{18}N_2NaO$ (MNa^+) Requires 325.1311 (5.5 ppm error), Found: 303.1481; $C_{20}H_{19}N_2O$ (MH^+) Requires 303.1492 (3.5 ppm error).

Lab notebook reference: MJJ1/7

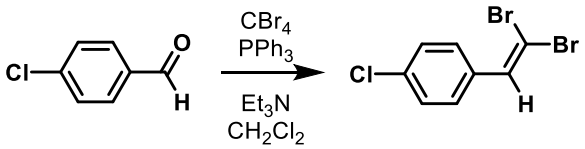
4-(4-Fluorophenyl)-1-(1*H*-indol-3-yl)but-3-yn-2-one (83d)



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_{max} (cm^{-1}) 3408, 2203, 1656, 1598, 1505, 1232, 1094, 837, 742; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 41.9 (CH_2, 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, $CDCl_3$) −106.0–−106.2 (1F, m); HRMS (ESI^+): Found: 300.0795; $C_{18}H_{12}FNNaO$ (MNa^+) Requires 300.0795 (0.2 ppm error), Found: 278.0971; $C_{18}H_{13}FNO$ (MH^+) Requires 278.0976 (1.8 ppm error).

Lab notebook reference: BSC

1-Chloro-4-(2,2-dibromovinyl)benzene (95)

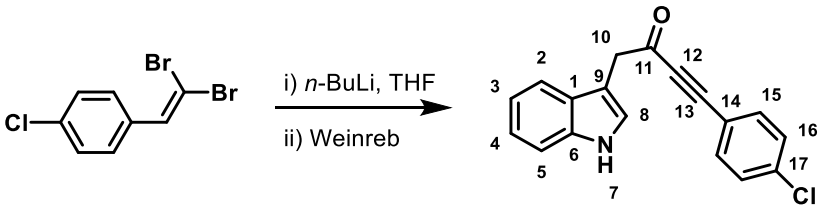


To a suspension of CBr_4 (4.72 g, 14.22 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added PPh_3 (7.46 g, 28.4 mmol) in CH_2Cl_2 (11 mL). The mixture was stirred for 30 min at 0 °C. 4-Chlorobenzaldehyde (1.00 g, 7.11 mmol) and Et_3N (7.9 mL, 56.9 mmol) in CH_2Cl_2 (4 mL) was added to the reaction mixture, which was stirred for 3 h at RT. The reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organics were combined, washed with sat. $NaHCO_{3\,(aq)}$ (30 mL), dried ($MgSO_4$) 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, ν_{max} (cm^{-1}) 1591, 1488, 1098, 1013, 872, 709, 782, 506; δ_H (400 MHz, $CDCl_3$) 7.35 (2H, d, J = 8.5 Hz), 7.44 (1H, s), 7.48 (2H, d, J = 8.5 Hz); δ_C (100 MHz, $CDCl_3$) 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-(1*H*-indol-3-yl)but-3-yn-2-one (83e)

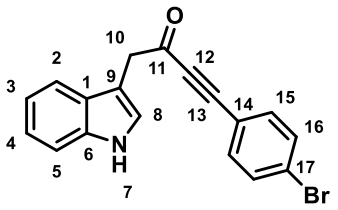


To a solution of **95** (1.68 g, 5.66 mmol) in THF (30 mL) at –78 °C under argon was added *n*-BuLi (4.16 mL, 10.4 mmol, 2.5 M in hexanes) dropwise. The mixture was warmed to 0 °C and stirred for 30 min. The mixture was cooled to –78 °C and transferred *via* cannula to a –78 °C solution of Weinreb **81a** (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 CH_2Cl_2 (3 × 40 mL). The organics were combined, washed with sat. $NaHCO_{3\,(aq)}$ (40 mL), dried ($MgSO_4$) 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; ν_{max} (cm^{-1}) 3408, 2202, 1661, 1489, 1088, 1014, 829, 742; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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; $C_{18}H_{12}{}^{35}ClNNaO$ (MNa^+) Requires 316.0500 (3.5 ppm error), Found: 294.0676; $C_{18}H_{13}{}^{35}ClNO$ (MH^+) Requires 294.0680 (1.5 ppm error).

Lab notebook reference: MJJ1/19

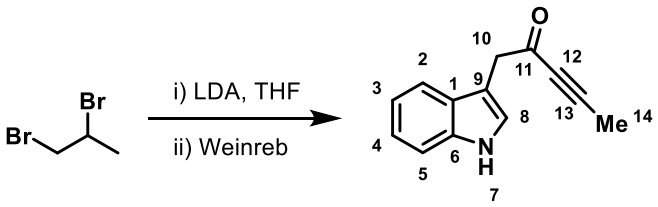
4-(4-Bromophenyl)-1-(1*H*-indol-3-yl)but-3-yn-2-one (83f)



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; ν_{max} (cm^{-1}) 3409, 2202, 1660, 1485, 1068, 1011, 824, 742; δ_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), 7.67 (1H, br d, *J* = 8.0 Hz, H-2), 8.23 (1H, br s, H-7); δ_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; $C_{18}H_{12}{}^{79}BrNNaO$ (MNa^+) Requires 359.9994 (0.4 ppm error), Found: 338.0188; $C_{18}H_{13}{}^{79}BrNO$ (MH^+) Requires 338.0175 (−3.9 ppm error).

Lab notebook reference: MJJ4/6

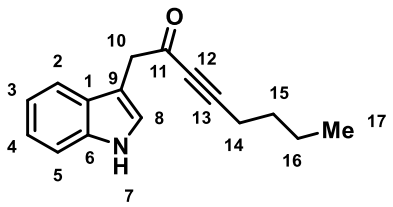
1-(1*H*-Indol-3-yl)pent-3-yn-2-one (83g)



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. $NH_4Cl_{(aq)}$ (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried ($MgSO_4$), 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_{max} (cm^{-1}) 3409, 2217, 1665, 743; δ_H (400 MHz, $CDCl_3$) 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_C (100 MHz, $CDCl_3$) 4.1 (CH_3, C-14), 42.0 (CH_2, 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: 220.0726; $C_{13}H_{11}NNaO$ (MNa^+) Requires 220.0733 (2.9 ppm error), Found: 198.0905; $C_{13}H_{12}NO$ (MH^+) Requires 198.0913 (4.4 ppm error).

Lab notebook reference: MJJ1/14

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

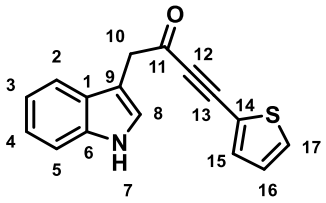


Synthesised using **general procedure 2B** with 1-hexyne (0.79 mL, 6.87 mmol), THF (7 + 21 mL), Weinreb **81a** (500 mg, 2.29 mmol) and *n*-BuLi (3.00 mL, 5.73 mmol, 1.89 in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded

the *title compound* **83h** (450 mg, 82%) as a yellow solid, mp 59–61 °C; ν_{max} (cm^{-1}) 3411, 2958, 2933, 2210, 1664, 1458, 741; δ_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); δ_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), 122.1 (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; $C_{16}H_{18}NO$ (MH^+) Requires 240.1383 (−1.5 ppm error).

Lab notebook reference: MJJ1/6

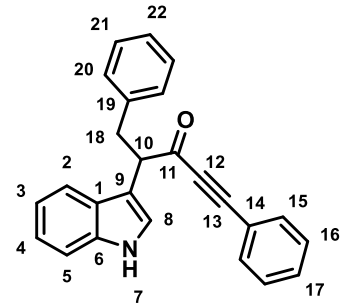
1-(1*H*-Indol-3-yl)-4-(thiophen-2-yl)but-3-yn-2-one (83i)



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; ν_{max} (cm^{-1}) 3405, 2178, 1651, 1215, 1091, 742, 714; δ_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); δ_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; $C_{16}H_{11}NNaOS$ (MNa^+) Requires 288.0454 (0.6 ppm error), Found: 266.0634; $C_{16}H_{12}NOS$ (MH^+) Requires 266.0634 (−0.1 ppm error).

Lab notebook reference: MJJ4/84

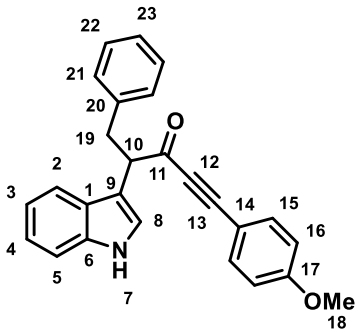
4-(1*H*-Indol-3-yl)-1,5-diphenylpent-1-yn-3-one (83j)



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_{max} (cm^{-1}) 3413, 2195, 1653, 1489, 1456, 1099, 742, 688; δ_H (400 MHz, $CDCl_3$) 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_C (100 MHz, $CDCl_3$) 37.0 (CH_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^+): Found: 372.1346; $C_{25}H_{19}NNaO$ (MNa^+) Requires 372.1359 (3.6 ppm error), Found: 350.1538; $C_{25}H_{20}NO$ (MH^+) Requires 350.1539 (0.3 ppm error).

Lab notebook reference: MJJ4/77

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

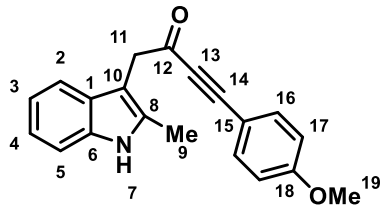


Synthesised using **general procedure 2B** with 4-ethynylanisole (0.83 mL, 6.42 mmol), THF (6.5 + 18 mL), Weinreb **81g** (661 mg, 2.14 mmol) and *n*-BuLi (2.54 mL, 5.99 mmol, 2.36M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then 8:2

hexane:EtOAc) afforded the *title compound* **83k** (267 mg, 33%) as a yellow solid, mp 150–152 °C; ν_{max} (cm^{-1}) 3414, 2186, 1654, 1601, 1509, 1254, 743; δ_H (400 MHz, $CDCl_3$) 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-18), 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, $CDCl_3$) 37.1 (CH_2, C-19), 53.8 (CH, C-10), 55.4 (CH_3, 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; $C_{26}H_{21}NNaO_2$ (MNa^+) Requires 402.1465 (3.3 ppm error), Found: 380.1632; $C_{26}H_{22}NO_2$ (MH^+) Requires 380.1645 (3.5 ppm error).

Lab notebook reference: MJJ1/63

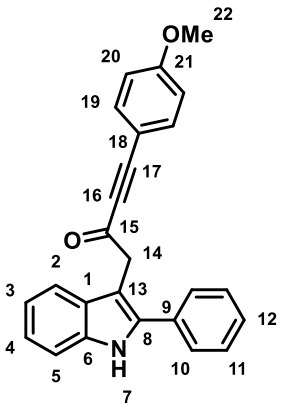
4-(4-Methoxyphenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one (83l)



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; ν_{max} (cm^{-1}) 3396, 2194, 1653, 1600, 1508, 1252, 832, 728; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 11.6 (CH_3, C-9), 41.0 (CH_2, C-11), 55.2 (CH_3, 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; $C_{20}H_{17}NNaO_2$ (MNa^+) Requires 326.1151 (−0.1 ppm error), Found: 304.1332; $C_{20}H_{18}NO_2$ (MH^+) Requires 304.1332 (−0.1 ppm error).

Lab notebook reference: MJJ3/44

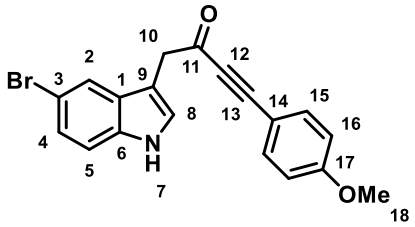
4-(4-Methoxyphenyl)-1-(2-phenyl-1*H*-indol-3-yl)but-3-yn-2-one (83m)



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; ν_{max} (cm^{-1}) 3362, 1255, 2196, 1655, 1601, 1509, 744; δ_H (400 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); δ_C (100 MHz, $CDCl_3$) 41.7 (CH_2, C-14), 55.5 (CH_3, 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^+): Found: 388.1302; $C_{25}H_{19}NNaO_2$ (MNa^+) Requires 388.1308 (1.6 ppm error), Found: 366.1491; $C_{25}H_{20}NO_2$ (MH^+) Requires 366.1489 (−0.5 ppm error).

Lab notebook reference: MJJ1/48

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

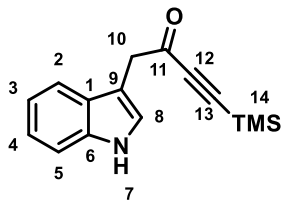


Synthesised using **general procedure 2B** with 4-ethynylanisole (0.65 mL, 5.04 mmol), THF (5 + 15 mL), Weinreb **81f** (500 mg, 1.68 mmol) and *n*-BuLi (1.70 mL, 4.20 mmol, 2.5 M in hexanes). Purification by column chromatography (7:3 hexane:EtOAc) afforded the *title compound* **83n** (460 mg, 74%) as a yellow solid, mp 131–133 °C; ν_{max} (cm^{-1}) 3414, 2195,

1655, 1601, 1509, 1255, 1170, 1095, 833; δ_H (400 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), 8.35 (1H, br s, H-7); δ_C (100 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; $C_{19}H_{14}{}^{79}BrNNaO_2$ (MNa^+) Requires 390.0100 (2.8 ppm error), Found: 368.0275; $C_{19}H_{15}{}^{79}BrNO_2$ (MH^+) Requires 368.0281 (1.5 ppm error).

Lab notebook reference: MJJ3/39

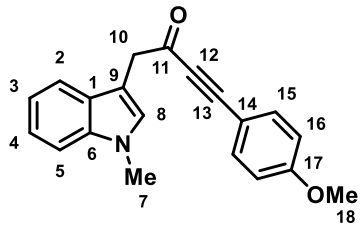
1-(1*H*-Indol-3-yl)-4-(trimethylsilyl)but-3-yn-2-one (83o)



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*-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; ν_{max} (cm^{-1}) 3408, 1671, 1252, 1100, 847, 741; δ_H (400 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); δ_C (100 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; $C_{15}H_{17}NNaOSi$ (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

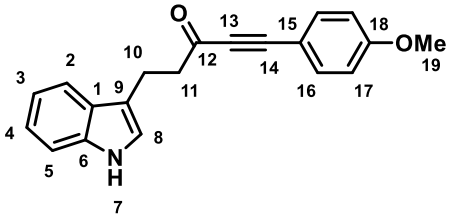
4-(4-Methoxyphenyl)-1-(1-methyl-1*H*-indol-3-yl)but-3-yn-2-one (83p)



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; ν_{max} (cm^{-1}) 2197, 1660, 1602, 1509, 1254, 742; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 32.7 (CH_3, C-7), 41.7 (CH_2, C-10), 55.3 (CH_3, 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; $C_{20}H_{17}NNaO_2$ (MNa^+) Requires 326.1151 (−0.6 ppm error), Found: 304.1330; $C_{20}H_{18}NO_2$ (MH^+) Requires 304.1332 (0.7 ppm error).

Lab notebook reference: MJJ1/86

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

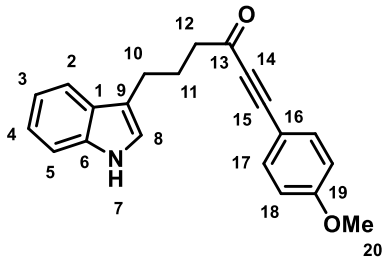


Synthesised using **general procedure 2B** with 4-ethynylanisole (1.02 g, 7.68 mmol), THF (8 + 23 mL), Weinreb **81b** (594 mg, 2.56 mmol) and *n*-BuLi (2.71 mL, 6.40 mmol, 2.36M in hexanes). Purification by column chromatography (9:1 hexane:EtOAc, then EtOAc) afforded the *title compound* **83q** (748 mg, 96%) as a yellow solid, mp 126-128 °C; ν_{max} (cm^{-1}) 3406, 2190, 1658, 1601, 1509, 1254, 1172, 1094, 834, 744; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz,

$CDCl_3$) 19.8 (CH_2, C-10), 45.7 (CH_2, C-11), 55.4 (CH_3, 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; $C_{20}H_{17}NNaO_2$ (MNa^+) Requires 326.1151 (0.9 ppm error), Found: 304.1334; $C_{20}H_{18}NO_2$ (MH^+) Requires 304.1332 (−0.6 ppm error).

Lab notebook reference: MJJ1/71

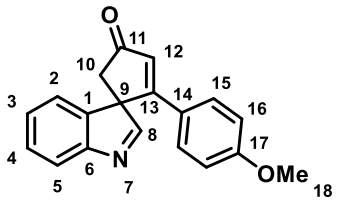
6-(1*H*-Indol-3-yl)-1-(4-methoxyphenyl)hex-1-yn-3-one (83r)



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, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 24.3 (CH_2, C-10/11), 24.6 (CH_2, C-10/11), 44.9 (CH_2, C-12), 55.3 (CH_3, 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; $C_{21}H_{19}NNaO_2$ (MNa^+) Requires 340.1308 (−1.9 ppm error), Found: 318.1493; $C_{21}H_{19}NNaO_2$ (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)



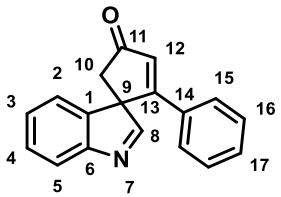
Synthesised using **general procedure 2C** with ynone **83a** (58 mg, 0.2 mmol) and AgOTf (0.5 mg, 2 μmol) in CH_2Cl_2 (2 mL) at RT for 30 min. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84a** (58 mg, 100%) as an off-white solid, mp 48–50 °C; ν_{max} (cm^{-1}) 2923, 1693, 1604, 1510, 1255, 1181, 1030, 832; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 42.3 (CH_2, C-10), 55.3 (CH_3, 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 CH_2Cl_2 (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 **Ag-114l** (1.6 mg, 2 μmol) in $CHCl_3$ (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, $CHCl_3$). 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 CH_2Cl_2 (2 mL) at RT for 30 min. Purification by column chromatography (3:2

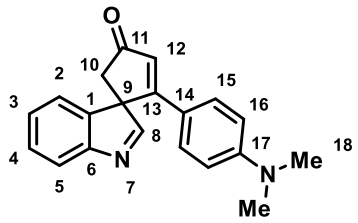
hexane:EtOAc) afforded the *title compound* **84b** (52 mg, 100%) as a brown oil; ν_{max} (cm^{-1}) 1697, 1592, 754; δ_H (400 MHz, $CDCl_3$) 2.69 (1H, d, *J* = 18.5 Hz, H-10a), 3.06 (1H, d, *J* = 18.5 Hz, H-10b), 6.85 (1H, s, H-12), 6.97–7.00 (2H, m, H-15), 7.17–7.23 (2H, m, H-16), 7.27–7.33 (3H, m, 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); δ_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), 127.7 (CH, C-3), 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_2Cl_2 (5 mL) for 16 h. Purification by column chromatography afforded the *title compound* **84b** (114 mg, 86%).

Spirocycle **84b** was also synthesised 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

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_2Cl_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; ν_{max} (cm^{-1}) 2923, 1685, 1605, 1570, 1522, 1202, 818; δ_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); δ_C (100 MHz, $CDCl_3$) 39.8 (CH_3, C-18), 42.3 (CH_2, 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

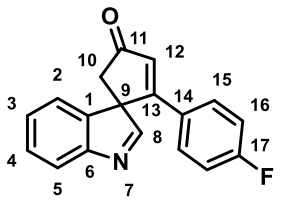
(C, C-1), 152.2 (C, C-17), 154.6 (C, C-6), 171.2 (C, C-13), 175.3 (CH, C-8), 204.1 (C, C-11); HRMS (ESI$^+$): Found: 325.1295; $C_{20}H_{18}N_2NaO$ (MNa^+) Requires 325.1311 (5.2 ppm error), Found: 303.1487; $C_{20}H_{19}N_2O$ (MH^+) Requires 303.1492 (1.7 ppm error).

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 CH_2Cl_2 (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 **Ag-114l** (1.6 mg, 2 μmol) in $CHCl_3$ (4 mL). Purification by column chromatography afforded the *title compound* **84c** (30 mg, 50%) in 69:31 *er* (*S*:*R*). $[\alpha]_D^{20}$ −47.6 (c = 1.0, $CHCl_3$). 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

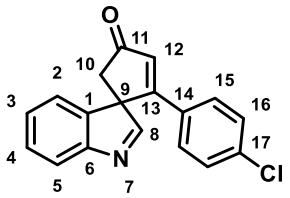
2-(4-Fluorophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84d)



Synthesised using **general procedure 2C** with ynone **83d** (100 mg, 0.361 mmol) and AgOTf (0.9 mg, 3.6 μmol) in CH_2Cl_2 (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; ν_{max} (cm^{-1}) 1696, 1602, 1508, 1239, 1164, 835; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 42.3 (CH_2, 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)*;* δ_F (376 MHz, $CDCl_3$) −107.1–−107.3 (1F, m); HRMS (ESI$^+$): Found: 300.0794; $C_{18}H_{12}FNNaO$ (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)



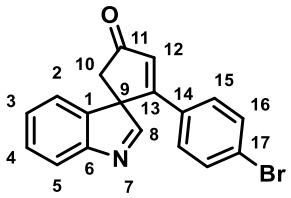
Synthesised using **general procedure 2C** with ynone **83e** (33 mg, 0.112 mmol) and AgOTf (0.3 mg, 1.1 μmol) in CH_2Cl_2 (1.1 mL) at RT for 1.5 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84e** (33 mg, 100%) as a pale brown oil; ν_{max} (cm^{-1}) 1696, 1593, 1489, 1095, 828, 730; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 42.3 (CH_2, 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; $C_{18}H_{12}{}^{35}ClNNaO$ (MNa^+) Requires 316.0500 (1.6 ppm error), Found: 294.0673; $C_{18}H_{13}{}^{35}ClNO$ (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 CH_2Cl_2 (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 $CHCl_3$ (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, $CHCl_3$). CSP-HPLC conditions: 10% IPA in hexane, **(*R*)-84e** 22.5 min, **(*S*)-84e** 27.2 min, UV detection at 280 nm.

Lab notebook reference: MJJ3/21 + 1/24 + 3/23

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

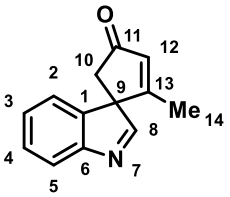


Synthesised using **general procedure 2C** with ynone **83f** (68 mg, 0.2 mmol) and AgOTf (0.5 mg, 2 μmol) in CH_2Cl_2 (2 mL) at RT for 1.5 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84f** (68 mg, 100%) as an off white solid, mp 201–203 °C; ν_{max} (cm^{-1}) 1694, 1589, 1075, 1008, 824, 730; δ_H (400 MHz, $CDCl_3$) 2.66 (1H, d, *J* = 18.5Hz, 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); δ_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; $C_{18}H_{12}{}^{79}BrNNaO$ (MNa^+) Requires 359.9994 (−2.6 ppm error), Found: 338.0197; $C_{18}H_{13}{}^{79}BrNO$ (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-114l** (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*:*R*). $[\alpha]_D^{20}$ −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_2Cl_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; ν_{max} (cm^{-1}) 1716, 1620, 1551, 773, 759; δ_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

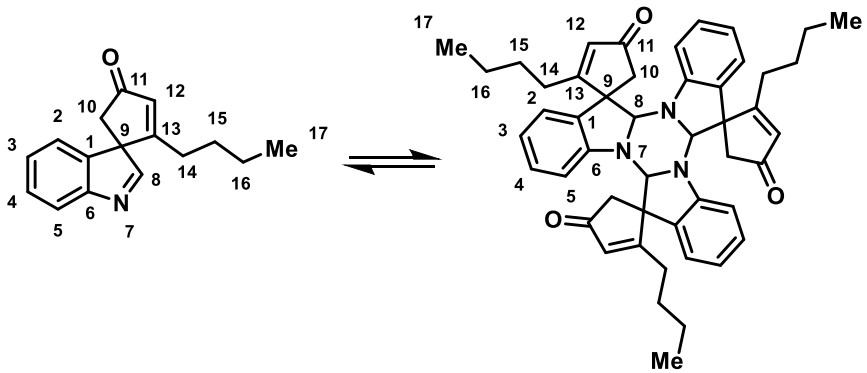
Hz, H-10b), 6.27–6.31 (1H, m, H-12), 7.22 (1H, br d, *J* = 7.0 Hz, H-2) 7.30–7.36 (1H, m, H-3), 7.41–7.47 (1H, m, H-5), 7.72 (1H, br d, *J* = 8.0 Hz, H-5), 7.96 (1H, s, H-8); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3, C-14), 40.4 (CH_2, C-10), 67.8 (C, C-9), 121.5 (CH, C-2), 121.7 (CH, C-5), 127.4 (CH, C-3), 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), 205.6 (C, C-11); HRMS (ESI^+): Found: 220.0726; $C_{13}H_{11}NNaO$ (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 CH_2Cl_2 (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 $CHCl_3$ (2.5 mL). Purification by column chromatography afforded the *title compound* **84g** (48 mg, 94%) in 86:14 *er* (*S*:*R*, CSP-HPLC performed on the TFA salt). $[\alpha]_D^{20}$ +208.1 (c = 1.0, $CHCl_3$). 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)



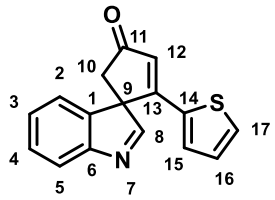
Synthesised using **general procedure 2C** with ynone **83h** (48 mg, 0.2 mmol), AgOTf (0.5 mg, 2 μmol) in CH_2Cl_2 (2 mL) at RT for 3.5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **84h** (approximately 1:1.4 ratio of *monomer*:*trimer*, 48 mg, 100%) as a pale yellow oil; ν_{max} (cm^{-1}) 2957, 2929, 2871, 1715, 1694, 1610, 1475, 1458, 1267, 1174, 730; δ_H (400 MHz, $CDCl_3$) 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

(1H, d, *J* = 19.5 Hz, H-10, *monomer*), 2.64 (2H, d, *J* = 19.0 Hz, H-10, *trimer*), 2.85 (1H, d, *J* = 19.0 Hz, H-10, *trimer*), 2.91 (1H, d, *J* = 19.0 Hz, H-10, *trimer*), 2.93 (1H, d, *J* = 19.5 Hz, H-10, *monomer*), 3.01 (1H, d, *J* = 19.0 Hz, H-10, *trimer*), 3.24 (1H, d, *J* = 19.0 Hz, H-10, *trimer*), 4.59 (1H, s, H-8, *trimer*), 4.81 (1H, s, H-8, *trimer*), 5.21 (1H, s, H-8, *trimer*), 5.78 (1H, d, *J* = 7.5 Hz, H-5, *trimer*), 5.83 (1H, d *J* = 7.5, H-5 Hz, *trimer*), 5.93 (1H, t, *J* =, 1.5 Hz, H-12, *trimer*), 5.99 (1H, t, *J* = 1.5 Hz, H-12, *trimer*), 6.00 (1H, t, *J* = 1.5 Hz, H-12, *trimer*), 6.28 (1H, t, *J* = 1.5 Hz, H-12, *monomer*), 6.31 (1H, d, *J* = 8.0 Hz, H-5, *trimer*), 6.68 (1H, ddd, *J* = 7.5, 7.5, 1.5 Hz, H3/4, *trimer*), 6.75 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz, H-3/4, *trimer*), 6.84 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz, H3/4, *trimer*), 6.92 (1H, dd, *J* = 7.5, 1.0 Hz, H-2, *trimer*), 6.94 (2H, dd, *J* = 7.0 Hz, H-3/4, *trimer*), 7.04–7.12 (2H, m, H-2,3/4, *trimer*), 7.20 (1H, dd, *J* = 7.5, 1.0 Hz, H-2, *trimer*), 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*); δ_C (100 MHz, $CDCl_3$) 13.5 (CH_3), 13.57 (CH_3), 13.63 (CH_3), 13.7 (CH_3), 22.07 (CH_2), 22.09 (CH_2), 22.11 (CH_2), 22.2 (CH_2), 27.9 (CH_2), 28.17 (CH_2), 28.21 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 40.3 (CH_2), 44.1 (CH_2), 44.2 (CH_2), 45.2 (CH_2), 57.8 (CH_2), 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), 127.30 (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 (ESI^+): Found: 240.1382; $C_{16}H_{18}NO$ (MH^+) Requires 240.1383 (0.2 ppm error).

Spirocycle **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 CH_2Cl_2 (5 mL) for 16 h. Purification by column chromatography afforded the *title compound* **84h** (112 mg, 95%).

Lab notebook reference: MJJ1/9 + 3/30

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

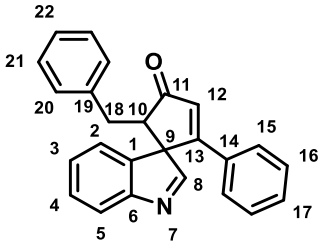


Synthesised using **general procedure 2C** with ynone **83i** (34 mg, 0.128 mmol) and AgOTf (0.33 mg, 1.3 µmol) in CH_2Cl_2 (1.3 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84i** (34 mg, 100%) as a

brown oil; ν_{max} (cm^{-1}) 1719, 1689, 1584, 1572, 1198, 727, 711; δ_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); δ_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; $C_{16}H_{11}NNaOS$ (MNa^+) Requires 288.0454 (0.7 ppm error), Found: 266.0636; $C_{16}H_{12}NOS$ (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)

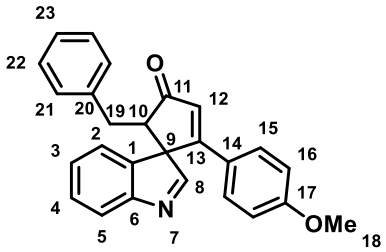


Synthesised using **general procedure 2C** with ynone **83j** (35 mg, 0.100 mmol), AgOTf (0.26 mg, 1 μmol) in CH_2Cl_2 (1 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84j** (35 mg, 100%, 52:48 *dr*) as an off-white solid, mp 126–129 °C; ν_{max} (cm^{-1}) 1699, 1591, 1445, 752, 730, 695; δ_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*); δ_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; $C_{25}H_{19}NNaO$ (MNa^+)

Requires 372.1359 (4.0 ppm error), Found: 350.1535; $C_{25}H_{20}NO_2$ (MH^+) Requires 350.1539 (1.2 ppm error).

Lab notebook reference: MJJ4/88

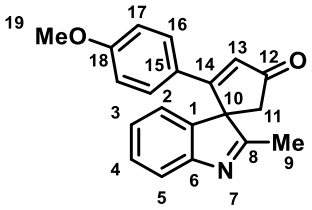
5-Benzyl-2-(4-methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one (84k)



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; ν_{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), 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; $C_{26}H_{21}NNaO_2$ (MNa^+) Requires 402.1465 (2.7 ppm error), Found: 380.1634; $C_{26}H_{22}NO_2$ (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)

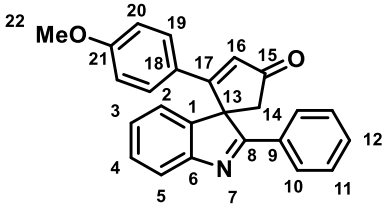


Synthesised using **general procedure 2C** with ynone **83l** (107 mg, 0.353 mmol), AgOTf (0.9 mg, 3.53 μmol) in CH_2Cl_2 (3.5 mL) at RT for 10 min. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84l** (107 mg, 100%) as a pale yellow oil; ν_{max} (cm^{-1}) 1693, 1604, 1510, 1258, 1181, 1028, 829; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 15.7 (CH_3, C-9), 45.1 (CH_2, C-11), 55.3 (CH_3, 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; $C_{20}H_{17}NNaO_2$ (MNa^+) Requires 326.1151 (−1.2 ppm error), Found: 304.1339; $C_{20}H_{18}NO_2$ (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 $CHCl_3$ (2 mL). Purification by column chromatography afforded the *title compound* **84l** (47 mg, 72%) in 82:64 *er* (*S*:*R*). $[\alpha]_D^{20}$ −159.3 (c = 1.0, $CHCl_3$). 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)

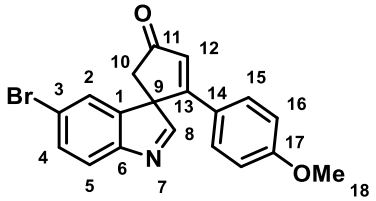


Synthesised using **general procedure 2C** with ynone **83m** (100 mg, 0.274 mmol), AgOTf (0.7 mg, 2.74 μmol) in CH_2Cl_2 (3 mL) at RT for 6 min. Purification by column chromatography (7:3 hexane:EtOAc) afforded the *title compound* **84m** (84 mg, 84%) as a pale brown oil; ν_{max} (cm^{-1}) 1693, 1603, 1510, 1256, 1180, 834, 758; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 47.2 (CH_2, C-14), 55.2 (CH_3, 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; $C_{25}H_{19}NNaO_2$ (MNa^+) Requires 388.1308 (1.7 ppm error), Found: 366.1477; $C_{25}H_{20}NO_2$ (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)

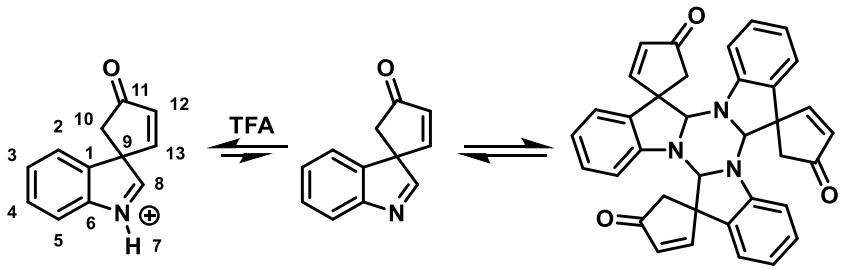


Synthesised using **general procedure 2C** with ynone **83n** (74 mg, 0.20 mmol), AgOTf (0.5 mg, 2 μmol) in CH_2Cl_2 (2 mL) at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **84n** (74 mg, 100%) as an off-white solid, mp 65–67 °C; ν_{max} (cm^{-1}) 1692, 1603, 1509, 1255, 1180, 1030, 831, 730; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 42.1 (CH_2, C-10), 55.3 (CH_3, 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; $C_{19}H_{14}{}^{79}BrNNaO_2$ (MNa^+) Requires 390.0100 (6.5 ppm error), Found: 368.0269; $C_{19}H_{15}{}^{79}BrNO_2$ (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 $CHCl_3$ (20 mL). Purification by column chromatography afforded the *title compound* **84n** (352 mg, 100%) in 85:15 *er* (*R*:*S*). $[\alpha]_D^{20}$ −145.6 (c = 1.0, $CHCl_3$). CSP-HPLC conditions: 10% IPA in hexane, **(*R*)-84n** 32.4 min, **(*S*)-84n** 38.6 min, UV detection at 280 nm.

Lab notebook reference: MJJ3/41 + 3/42

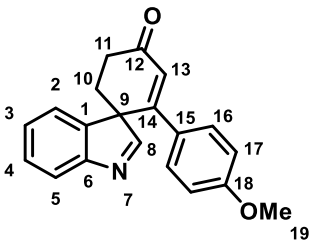
Spiro[cyclopent[2]ene-1,3'-indol]-4-one (84o)



To a stirred solution of ynone **83o** (51mg, 0.200 mmol) in acetone (2 mL) was added $AgNO_3$ (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; ν_{max} (cm^{-1}) 1714, 1600, 1475, 753, 735; NMR data of TFA salt, δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 38.7 (CH_2, 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; $C_{12}H_9NNaO$ (MNa^+) Requires 206.0576 (−3.1 ppm error), Found: 184.0753; $C_{12}H_{10}NO$ (MH^+) Requires 184.0757 (2.1 ppm error).

Lab notebook reference: MJJ3/5

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

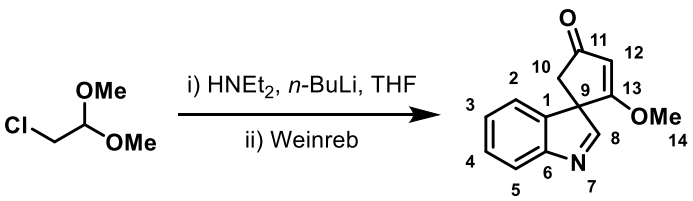


Synthesised using **general procedure 2C** with ynone **83q** (40 mg, 0.132 mmol), AgOTf (3.4 mg, 13.2 μmol) in CH_2Cl_2 (1.3 mL) at 35 °C for 16 h. Purification by column chromatography (3:1 hexane:EtOAc) afforded the *title compound* **84q** (30 mg, 75%) as a pale brown oil; ν_{max} (cm^{-1}) 1664, 1603, 1510, 1240, 1179, 1030, 831, 729; δ_H (400 MHz, $CDCl_3$) 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-11a), 2.81–2.92 (1H, m, H-11b), 3.71 (3H, s, H-19), 6.47 (1H, s, H-13), 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); δ_C (100 MHz, $CDCl_3$) 31.9 (CH_2, C-10), 34.3 (CH_2, C-11), 55.2 (CH_3, C-19), 61.5 (C, C-9), 114.0 (2CH, C-17), 122.5 (CH, C2/5), 122.7 (CH, C2/5), 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; $C_{20}H_{17}NNaO_2$ (MNa^+) Requires 326.1151 (-0.3 ppm error), Found: 304.1330; $C_{20}H_{18}NO_2$ (MH^+) Requires 304.1332 (0.6 ppm error).

Lab notebook reference: MJJ1/81 + WPU/2134

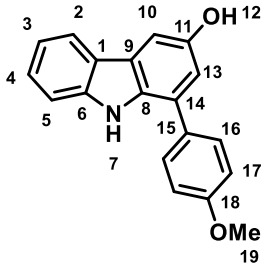
2-Methoxyspiro[cyclopent[2]ene-1,3'-indol]-4-one (84s)



To a 0 °C solution of Et_2NH (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. $NH_4Cl_{(aq)}$ (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine, dried ($MgSO_4$), 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; ν_{max} (cm^{-1}) 1691, 1595, 1251, 749; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 40.3 (CH_2, C-10), 59.4 (CH_3, 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; $C_{13}H_{11}NNaO_2$ (MNa^+) Requires 236.0682 (0.1 ppm error), Found: 214.0859; $C_{13}H_{12}NO_2$ (MH^+) Requires 214.0863 (1.8 ppm error).

Lab notebook reference: MJJ2/36

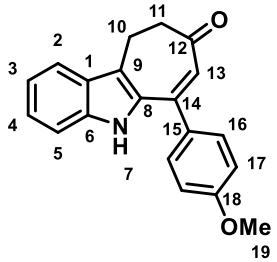
1-(4-Methoxyphenyl)-9*H*-carbazol-3-ol (85a)



Synthesised using **general procedure 2C** with ynone **83a** (58 mg, 0.2 mmol) and $(Ph_3P)AuNTf_2$·½PhMe (15.7 mg, 0.02 mmol) in CH_2Cl_2 (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; ν_{max} (cm^{-1}) 3368, 1609, 1517, 1495, 1317, 1237, 1174, 1152, 830, 728; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 55.3 (CH_3, 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; $C_{19}H_{15}NNaO_2$ (MNa^+) Requires 312.0995 (0.8 ppm error), Found: 290.1173; $C_{19}H_{16}NO_2$ (MH^+) Requires 290.1176 (1.0 ppm error).

Lab notebook reference: MJJ6/2

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

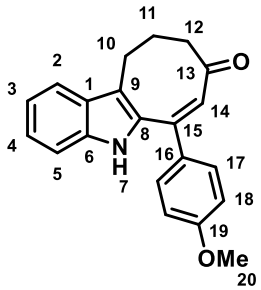


Synthesised using **general procedure 2C** with ynone **83q** (61 mg, 0.2 mmol) and $(Ph_3P)AuNTf_2$·½PhMe (31 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at 40 °C for 24 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **85q** (51 mg, 84%) as a yellow solid, mp 209–211 °C; ν_{max} (cm^{-1}) 3318, 1625, 1604, 1509, 1331, 1248, 1177, 735; δ_H (400 MHz, $CDCl_3$) 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

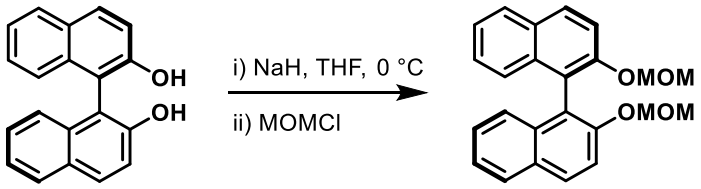
6-(4-Methoxyphenyl)-5*H*,8*H*,9*H*,10*H*,11*H*-cycloocta[b]indol-8-one (85r)



Synthesised using **general procedure 2C** with ynone **83r** (48 mg, 0.15 mmol) and $(Ph_3P)AuNTf_2$·½PhMe (24 mg, 0.03 mmol) in CH_2Cl_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; ν_{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)

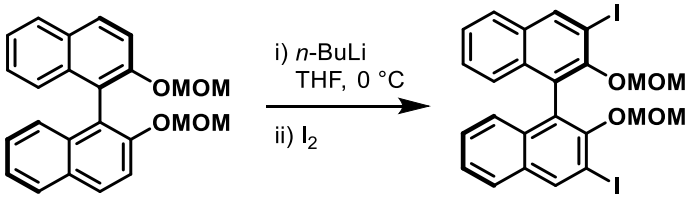


To a suspension of NaH (307 m, 7.68 mmol, 60% wt.) in THF (12 mL) under argon at 0 °C was added a solution of (*R*)-BINOL (1.00 g, 3.49 mmol) in THF (5 mL). The mixture was stirred for 1 h under argon at 0 °C, then MOMCl (0.66 mL, 8.73 mmol) was added dropwise. The mixture was stirred for a further 1 h under argon at RT, then quenched with the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried ($MgSO_4$) 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.[138] 98–100 °C); $[\alpha]_D^{20}$ = +91.7 (c 1.0, $CHCl_3$) [lit.[138] $[\alpha]_D^{25}$ = +95.0 (c 1.0, THF)]; ν_{max} (cm^{-1}) 1592, 1506, 1238, 1147, 1031, 1012, 810, 750; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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)



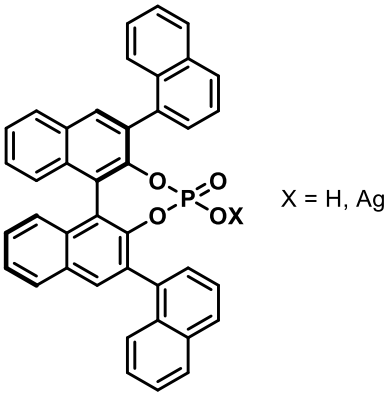
To a solution of 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**116**) (475 mg, 1.27 mmol) in THF (11.4 mL) under argon at 0 °C was added *n*-BuLi (1.52 mL, 3.81 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C and iodine (967 mg, 3.81 mmol) was added in one portion. The mixture was allowed to warm to RT and stirred for 1.5 h, then poured into sat. $NH_4Cl_{(aq)}$ (15 mL) and extracted with EtOAc (3 × 20 mL). The organics were combined, washed with $Na_2S_2O_3$ (15 mL), brine (15 mL), dried ($MgSO_4$) 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); $[\alpha]_D^{20}$ = −35.6 (c 1.0, $CHCl_3$)

[lit.[139] $[\alpha]_D^{20} = -9.3$ (c 0.98, THF)]; ν_{max} (cm^{-1}) 1382, 1345, 1232, 1202, 1158, 1085, 995, 955, 905, 748; δ_H (400 MHz, $CDCl_3$) 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_C (100 MHz, $CDCl_3$) 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.[139]

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

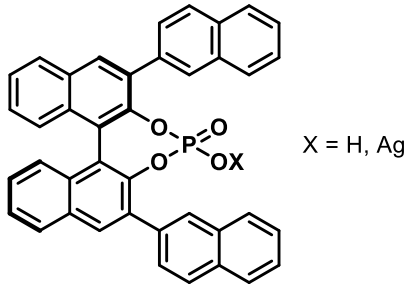


Synthesised using **general procedure 2E** with naphthalen-1-ylboronic acid (66 mg, 0.384 mmol). Purification by column chromatography (CH_2Cl_2, then 9:1 CH_2Cl_2:MeOH) afforded the *title compound* **114b** (57 mg, 59%) as an off white solid; $[\alpha]_D^{20} = -120.7$ (c 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 6.83–8.03 (24H, m); δ_p (162 MHz, $CDCl_3$) 3.1 (br s). **Ag-114b** synthesised using **general procedure 2H** using CPA **114b** (56 mg, 0.0932 mmol), Ag_2CO_3 (12.9 mg, 0.0466 mmol), CH_2Cl_2 (0.9 mL) and H_2O (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.[140]

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

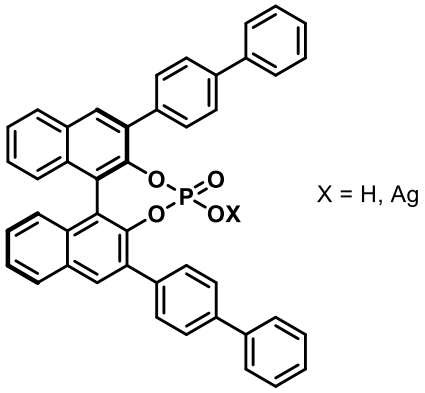


Synthesised using **general procedure 2E** with naphthalen-2-ylboronic acid (66 mg, 0.384 mmol). Purification by column chromatography (CH_2Cl_2, then 9:1 CH_2Cl_2:MeOH) afforded the *title compound* **114c** (78 mg, 81%) as an off white solid; $[\alpha]_D^{20}$ = −268.3 (c 1.0, $CHCl_3$) [lit.[141] $[\alpha]_D^{25}$ = −265.0 (c 0.2, $CHCl_3$)]; ν_{max} (cm^{-1}) 1252, 1102, 857, 747; δ_H (400 MHz, $CDCl_3$) 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); δ_p (162 MHz, $CDCl_3$) 0.3 (br s). **Ag-114c** synthesised using **general procedure 2H** using CPA **114c** (78 mg, 0.130 mmol), Ag_2CO_3 (18 mg, 0.065 mmol), CH_2Cl_2 (1.3 mL) and H_2O (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)



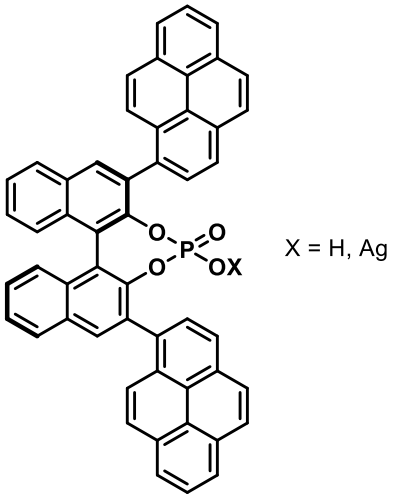
Synthesised using **general procedure 2E** with [1,1'-biphenyl]-4-ylboronic acid (76 mg, 0.384 mmol). Purification by column chromatography (CH_2Cl_2, then 39:1 CH_2Cl_2:MeOH) afforded the *title compound* **114d** (54 mg, 50%) as a white solid; $[\alpha]_D^{20}$ = −204.1 (c 1.0, $CHCl_3$) [lit.[140] $[\alpha]_D^{21}$ = −335.6 (c 1.2, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 6.89–7.64 (24H, m) 7.74–7.89 (2H, m), 7.91–8.08 (2H, m); δ_p (162 MHz, $CDCl_3$) 1.5 (br s). **Ag-114d** synthesised using **general**

procedure 2H using CPA **114d** (44 mg, 0.0674 mmol), Ag_2CO_3 (8.3 mg, 0.0337 mmol), CH_2Cl_2 (1.0 mL) and H_2O (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]

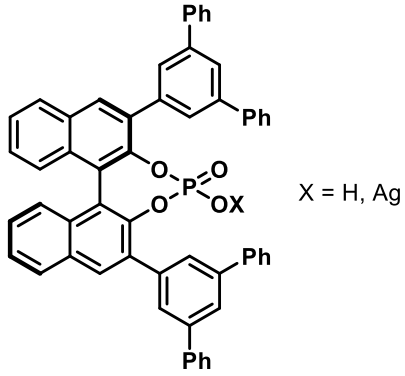
(*R*)-4-Hydroxy-2,6-di(pyren-1-yl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide (114e)



Synthesised using **general procedure 2E** with pyren-1-ylboronic acid (95 mg, 0.384 mmol). Purification by column chromatography (CH_2Cl_2, then 20:1 CH_2Cl_2:MeOH) afforded the *title compound* **114e** (24 mg, 20%) as a yellow solid; $[\alpha]_D^{20}$ = −90.0 (c 1.0, $CHCl_3$); ν_{max} (cm^{-1}) 1437, 1182, 1119, 1096, 906, 842, 719, 693, 538; δ_H (400 MHz, $CDCl_3$) 7.20–8.20 (28H, m); δ_p (162 MHz, $CDCl_3$) 29.9 (s). **Ag-114e** synthesised using **general procedure 2H** using CPA **114e** (23 mg, 0.0307 mmol), Ag_2CO_3 (4.2 mg, 15.4 μmol), CH_2Cl_2 (0.5 mL) and H_2O (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-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide (114f)

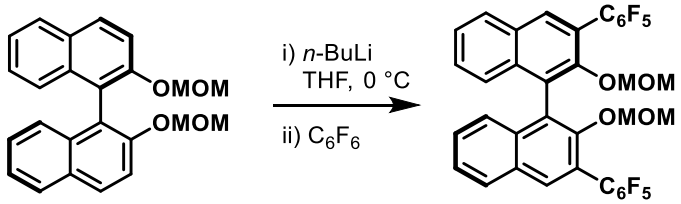


Synthesised using **general procedure 2E** with [1,1':3',1"-terphenyl]-5'-ylboronic acid (105 mg, 0.384 mmol). Purification by column chromatography (CH_2Cl_2, then 20:1 CH_2Cl_2:MeOH) afforded the *title compound* **114f** (121 mg, 94%) as a white solid; $[\alpha]_D^{20}$ = −202.3 (c 1.0, $CHCl_3$) [lit.[142] (*S* enantiomer) $[\alpha]_D^{32}$ = 247.1 (c 1.0, $CHCl_3$)]; ν_{max} (cm^{-1}) 1594, 1437, 1261, 1182, 1104, 758, 723, 696, 542; δ_H (400 MHz, $CDCl_3$) 7.03–7.14 (3H, m), 7.15–7.51 (27H, m), 7.89–8.04 (6H, m); δ_C (100 MHz, $CDCl_3$) 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; δ_P (162 MHz, $CDCl_3$) 4.5 (br s). **Ag-114f** synthesised using **general procedure 2H** using CPA **114f** (121 mg, 0.150 mmol), Ag_2CO_3 (21 mg, 0.075 mmol), CH_2Cl_2 (2 mL) and H_2O (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)



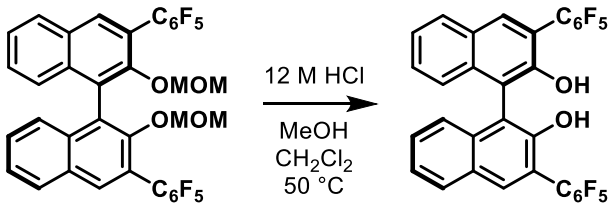
To a solution of (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (**117**) (475 mg, 1.27 mmol) in THF (11.4 mL) under argon at 0 °C was added *n*-BuLi (1.52 mL, 3.81 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C and hexafluorobenzene (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. $NH_4Cl_{(aq)}$ (15 mL) and extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine (15 mL),

dried ($MgSO_4$) 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; $[\alpha]_D^{20}$ = −19.1 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) −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)

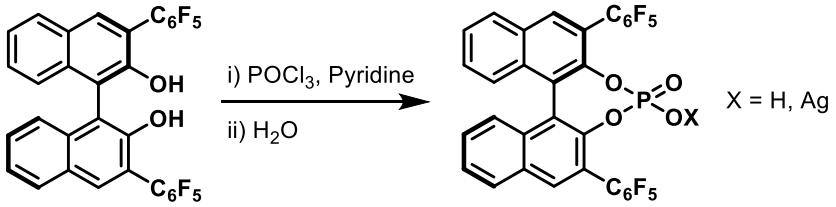


To a stirred solution of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(perfluorophenyl)-1,1'-binaphthalene (**118g**) (710 mg, 1.00 mmol) in MeOH (7 mL) and CH_2Cl_2 (1.5 mL) was added 12 M $HCl_{(aq)}$ (0.22 mL, 2.60 mmol). The mixture was stirred for 16 h at 50 °C, then poured into sat. $NaHCO_{3\ (aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* **119g** (613 mg, 99%) without further purification as a white solid, mp 122–124 °C; $[\alpha]_D^{20}$ = +87.5 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) −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)

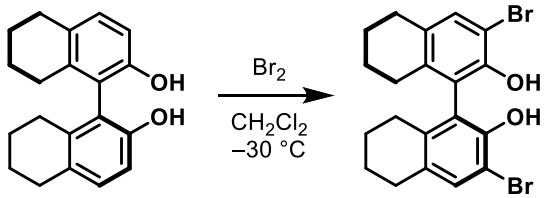


To a stirred solution of (*R*)-3,3'-bis(perfluorophenyl)-[1,1'-binaphthalene]-2,2'-diol (**119g**) (592 mg, 0.98 mmol) in pyridine (2.1 mL) was added $POCl_3$ (0.18 mL, 1.91 mmol) was added dropwise. The mixture was stirred for 16 h under argon at RT then cooled to 0 °C and 12 M $HCl_{(aq)}$ (2 mL) was added. The mixture was stirred for a further 5 h at RT then poured into 10% $HCl_{(aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were then washed with 10% $HCl_{(aq)}$ (5 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 CH_2Cl_2:MeOH) 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 *title compound* **114g** (612 mg, 93%) as a white powder; $[\alpha]_D^{20}$ = −236.0 (c 1.0, $CHCl_3$) [lit.[143] $[\alpha]_D^{24}$ = −164.5 (c 1.0, $CHCl_3$)]; δ_H (400 MHz, DMSO-d_6) 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); δ_F (376 MHz, DMSO-d_6) −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); δ_P (162 MHz, DMSO-d_6) 4.24. **Ag-114g** synthesised using **general procedure 2H** using CPA **114g** (50 mg, 0.0735 mmol), Ag_2CO_3 (10 mg, 0.037 mmol), CH_2Cl_2 (0.7 mL) and H_2O (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)



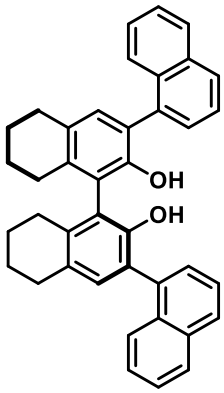
To a solution of (*S*)-(H_8)-BINOL (500 mg, 1.70 mmol) in CH_2Cl_2 (9.5 mL) under argon at −30 °C was added bromine (0.19 mL, 3.74 mmol) dropwise. The mixture was stirred for 40 min at −30 °C, then quenched with sat. $Na_2S_2O_{3\ (aq)}$ (10 mL) and allowed to warm to room temperature. The organics were separated, washed with sat. $NaHCO_{3\ (aq)}$ (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, $CHCl_3$)]; ν_{max} (cm^{-1}) 3511, 1930, 1450, 1265, 1211, 1179, 1159, 909, 731; δ_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); δ_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)

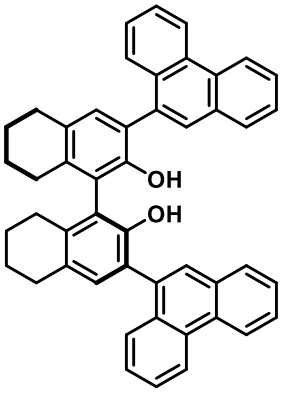


Synthesised using **general procedure 2F** with (*S*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol **121** (100 mg, 0.221 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), di(1-adamantyl)-*n*-butylphosphine (3.9 mg, 0.011 mmol), naphthalen-1-ylboronic acid (95 mg, 0.553 mmol), DME (2.2 mL) and 1 M $K_2CO_{3\ (aq)}$ (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, $CHCl_3$)]; ν_{max} (cm^{-1}) 3527, 2928, 1449, 1234, 802, 778, 753; δ_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)

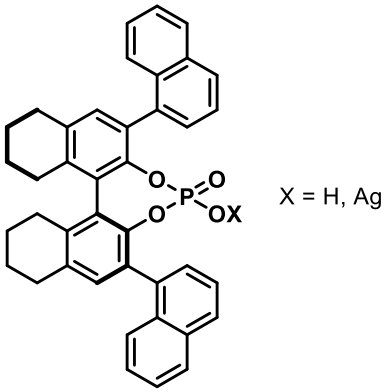


Synthesised using **general procedure 2F** with (*S*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol **121** (100 mg, 0.221 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), di(1-adamantyl)-*n*-butylphosphine (3.9 mg, 0.011 mmol), phenanthren-9-ylboronic acid (123 mg, 0.553 mmol), DME (2.2 mL) and 1 M $K_2CO_{3\ (aq)}$ (1.1 mL). Purification by column chromatography (silica gel, hexane to 7:3 hexane:CH_2Cl_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, $CHCl_3$)]; ν_{max} (cm^{-1}) 3528, 2928, 1450, 1227, 771, 747, 726; δ_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)

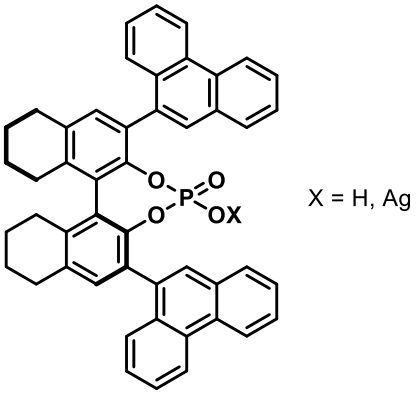


Synthesised using **general procedure 2G** with diol **122a** (129 mg, 0.236 mmol), pyridine (1 mL) and $POCl_3$ (0.04 mL, 0.429 mmol). Then DMAP (3 mg, 0.022 mmol), 2 M $NaOH_{(aq)}$ (1 mL) and THF (1 mL). Purification by column chromatography (19:1 CH_2Cl_2:MeOH then 9:1 CH_2Cl_2:MeOH) afforded the *title compound* **123a** (125 mg, 87%) as an off white solid, $[\alpha]_D^{20}$ = 65.0 (c 0.5, $CHCl_3$) [lit.[147] (*R* enantiomer) $[\alpha]_D^{18}$ = −146.5 (c 1.0, CH_2Cl_2)]); ν_{max} (cm^{-1}) 2929, 1261, 1089, 1017, 801, 778; δ_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); δ_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_2CO_3 (27.6 mg, 0.100 mmol), CH_2Cl_2 (2 mL) and H_2O (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)

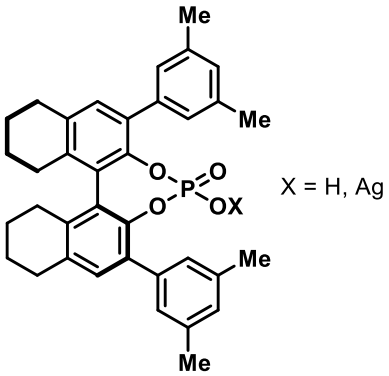


Synthesised using **general procedure 2G** with diol **122b** (140 mg, 0.216 mmol), pyridine (0.5 mL) and $POCl_3$ (0.04 mL, 0.429 mmol). Then DMAP (3 mg, 0.022 mmol), 2 M $NaOH_{(aq)}$ (1 mL) and THF (1 mL). Purification by column chromatography (19:1 CH_2Cl_2:MeOH) afforded the *title compound* **123b** (142 mg, 93%) as a white solid, $[\alpha]_D^{20}$ = +26.5 (c 1.0, $CHCl_3$); ν_{max} (cm^{-1}) 2931, 1423, 1243, 1101, 1087, 749, 727; δ_H (400 MHz, DMSO-d_6) 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); δ_p (162 MHz, DMSO-d_6) 0.39 (br s). **Ag-123b** synthesised using **general procedure 2H** using CPA **123b** (132 mg, 0.186 mmol) Ag_2CO_3 (26 mg, 0.0931 mmol), CH_2Cl_2 (2 mL) and H_2O (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.[150]

(*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)

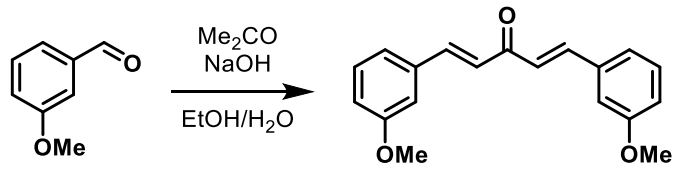


Synthesised using **general procedure 2G** with (*S*)-3,3'-bis(3,5-dimethylphenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (102 mg, 0.203 mmol), pyridine (0.5

mL) and $POCl_3$ (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 CH_2Cl_2:MeOH) afforded the *title compound* **123c** (38 mg, 33%) as a pale yellow solid; $[\alpha]_D^{20}$ = +260.8 (c 1.0, CH_2Cl_2); ν_{max} (cm^{-1}) 2925, 1260, 1234, 1098, 1082, 1019, 845, 801, 713; δ_H (400 MHz,CD_2Cl_2) 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); δ_C (100 MHz, CD_2Cl_2) 21.4 (CH_3), 23.3 (CH_2), 23.4 (CH_2), 28.3 (CH_2), 29.7 (CH_2), 30.3 (CH_2), 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); δ_p (162 MHz, $CDCl_3$) −0.24 (br s); HRMS ($APCI^+$): Found: 565.2481; $C_{36}H_{38}O_4P$ (MH^+) Requires 565.2502 (3.8 ppm error). **Ag-123c** synthesised using **general procedure 2H** using CPA **123c** (31 mg, 0.0549 mmol), Ag_2CO_3 (7.6 mg, 0.0275 mmol), CH_2Cl_2 (0.6 mL) and H_2O (0.6 mL) to afford the silver salt as an off white solid (17 mg, 46%).

Lab notebook reference: MJJ2/15 + MJJ2/18

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

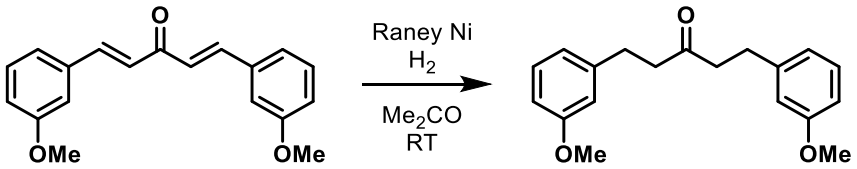


To a solution of NaOH (15 g, 375 mmol) in EtOH/H_2O (264 mL, 1:1 v/v) was added drop-wise a solution of *m*-anisaldehyde (20 g, 147 mmol) in acetone (5.4 mL, 73.4 mmol) and EtOH (20 mL). The mixture was stirred for 2 h at RT. The mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The organics were combined, dried ($MgSO_4$) 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; ν_{max} (cm^{-1}) 1652, 1619, 1577, 1594, 1253, 1184, 1157, 1041, 982, 783; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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)

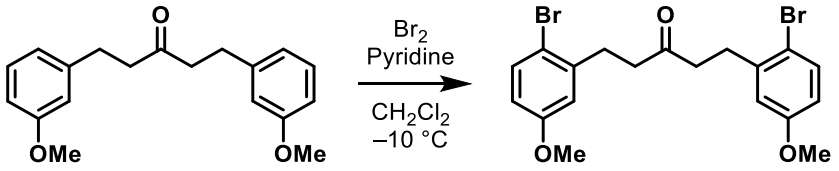


To a suspension of Raney Ni (34 mL, volume of solid in undisturbed suspension) in acetone (40 mL) was added a solution of dienone **128** (5.32 g, 18.1 mmol) in acetone (85 mL). The mixture was stirred for 16 h at RT under H_2. The reaction mixture was carefully decanted through celite, ensuring the 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 H_2. 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 CH_2Cl_2 (3 × 100 mL). The organics were dried ($MgSO_4$) 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, $CDCl_3$) 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, $CDCl_3$) 29.7, 44.3, 55.1, 111.4, 114.0, 120.6, 129.4, 142.6, 159.7, 209.0.

Lab notebook reference: MJJ2/75

Spectroscopic data matched those reported in the literature.[69]

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



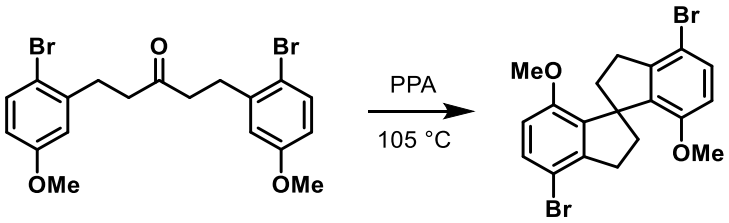
To a solution of ketone **129** (9.35 g, 31.3 mmol) in CH_2Cl_2 (172 mL) and pyridine (9.39 mL, 116 mmol) at −10 °C was added Br_2 (4.01 mL, 78.3 mmol) dropwise. Upon complete addition the reaction mixture was allowed to warm to RT and stirred for 4 h. The mixture was poured into $Na_2S_2O_{3\,(aq)}$ (200 mL), the organics were collected, washed with 10% $HCl_{(aq)}$ (100 mL) and water (100 mL). The organics were dried ($MgSO_4$) 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, $CDCl_3$)) 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); δ_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)

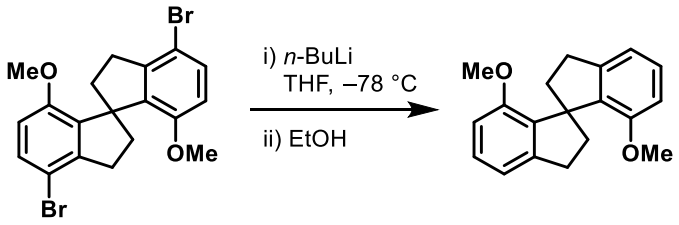


Ketone **130** (13.05 g, 28.6 mmol) was dissolved in PPA (115 g) and stirred for 6 h at 105 °C. The mixture was carefully poured into water (500 mL) and extracted with CH_2Cl_2 (5 × 500 mL). The organics were dried onto silica gel and eluted through a pad of silica gel with hexane:EtOAc (9:1). The filtrate was concentrated *in vacuo* to afford the *title compound* **131** (crude, 9.53 g, 76%) as a yellow solid; ν_{max} (cm^{-1}) 2934, 1471, 1262, 1081, 798; δ_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); δ_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)



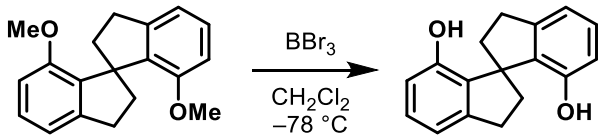
To a solution of **131** (9.53 g, 21.7 mmol) in THF (190 mL) at −78 °C was added *n*-BuLi (34.7 mL, 86.8 mmol, 2.5 M in hexanes) drop-wise. The mixture was stirred for 1 h at −78 °C then quenched with the slow addition of EtOH (8 mL). The mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (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; ν_{max} (cm^{-1}) 2931, 1586, 1475, 1232, 1097, 1085, 1061, 773; δ_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); δ_C (100 MHz, $CDCl_3$) 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)

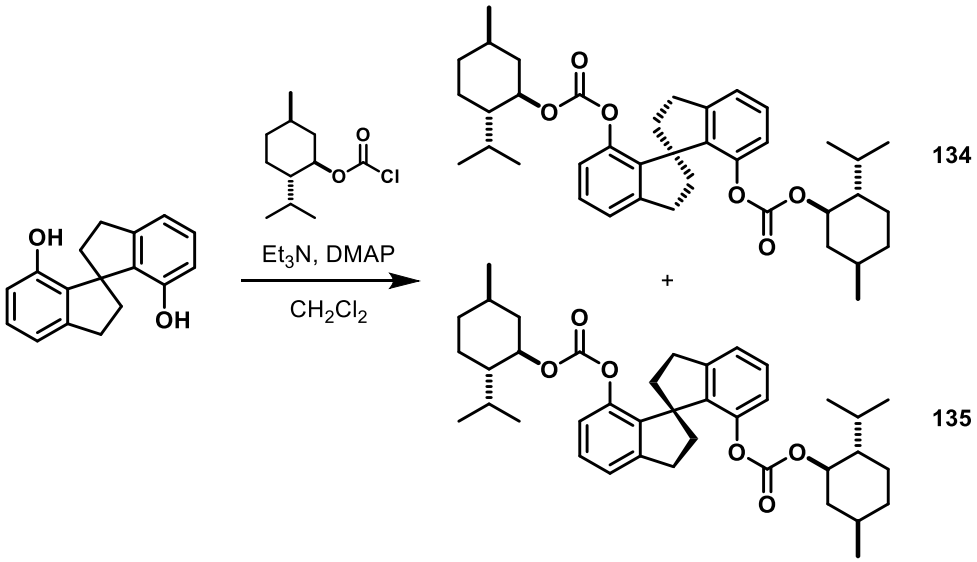


To a solution of **132** (6.10 g, 22.8 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added drop-wise BBr_3 (52.4 mL, 52.5 mmol, 1M in CH_2Cl_2). Upon complete addition the mixture was allowed to warm to RT and stirred overnight. The reaction mixture was carefully poured into water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organics were combined, dried ($MgSO_4$) 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); ν_{max} (cm^{-1}) 3516, 2936, 1586, 1463, 1278, 1231, 1181, 995, 777, 734; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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-menthyloxy-carbonyloxy)-1,1'-spiorbiindane (134 and 135)

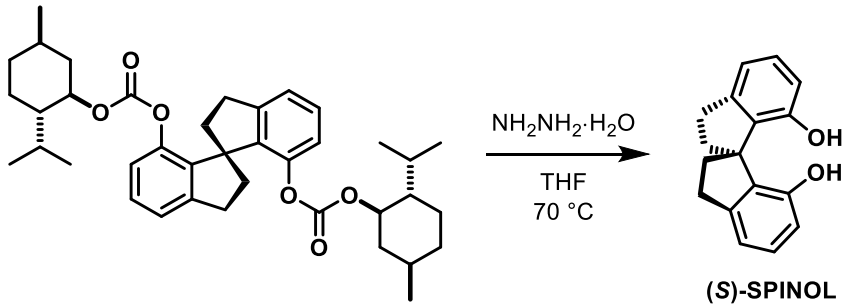


To a solution of **133** (3.14 g, 12.4 mmol), Et_3N (6.47 mL, 46.4 mmol) and DMAP (152 mg, 1.24 mmol) in CH_2Cl_2 (124 mL) was added L-menthyl chloroformate (6.45 mL, 30.1 mmol). The mixture was stirred for 16 h at RT. The mixture was washed with water (100 mL), 10% $HCl_{(aq)}$ (100 mL) and brine (100 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (3% Et_2O 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); ν_{max} (cm^{-1}) 2951, 1753, 1267, 1258, 1236; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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)

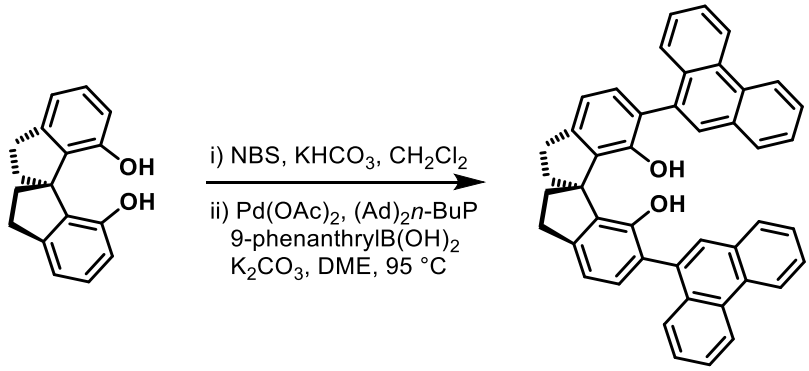


To a solution of **135** (731 mg, 1.19 mmol) in THF (8 mL) was added $NH_2NH_2{\cdot}H_2O$ (0.41 mL). The mixture was stirred for 2 h at 70 °C under argon. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 10% $HCl_{(aq)}$ (20 mL) and water (20 mL). The organics were dried ($MgSO_4$) and 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.[69] 155–156 °C); $[\alpha]_D^{20} = -24.9$ (c 1.0, $CHCl_3$) [lit.[69] $[\alpha]_D^{25} = -32.7$ (c 1.0, $CHCl_3$)]; ν_{max} (cm^{-1}) 3516, 2936, 1586, 1463, 1278, 1231, 1181, 995, 777, 734; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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)



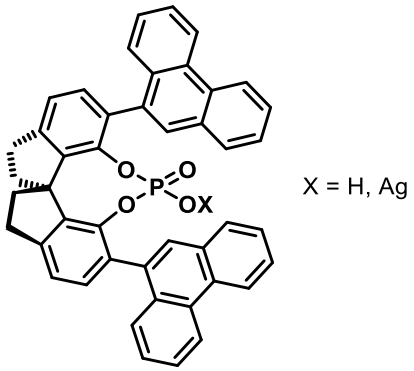
To a solution of **136** (25 mg, 0.10 mmol), $KHCO_3$ (20 mg, 0.20 mmol) in CH_2Cl_2 (0.5 mL) at −30 °C was added a solution of NBS (36.5 mg, 0.205 mmol) in CH_2Cl_2 (2 mL) over 30 min. The mixture was stirred for 4 h at −30 °C. The mixture was poured into 10% $HCl_{(aq)}$ (5 mL) and extracted with CH_2Cl_2 (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), $(Ad)_2$*n*-BuP (0.9 mg, 2.5 μmol), phenanthren-9-ylboronic acid (39 mg, 0.175 mmol) in 1 M $K_2CO_{3\ (aq)}$ (0.25 mL) and DME (0.5 mL). The mixture was purged by alternating vaccum and argon three times. The mixture was stirred for 16 h under argon at 95 °C, then poured into sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with CH_2Cl_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; $[\alpha]_D^{20} = -37.9$ (c 1.0, $CHCl_3$); ν_{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).

Lab notebook reference: MJJ3/27 + MJJ3/32

Spectroscopic data matched those reported in the literature.[151]

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

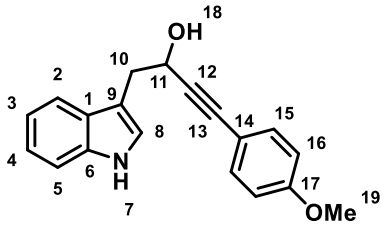


Synthesised using **general procedure 2G** with diol **126** (12 mg, 0.020 mmol), pyridine (0.2 mL) and $POCl_3$ (0.01 mL, 0.040 mmol). Then DMAP (0.24 mg, 2 μmol), 2 M $NaOH_{(aq)}$ (0.2 mL) and THF (0.2 mL) for 2 days. Purification by column chromatography (CH_2Cl_2 then 9:1 CH_2Cl_2:MeOH) afforded the *title compound* **126** (12 mg, 90%) as a colourless oil; $[\alpha]_D^{20} = -297.6$ (c 1.0, $CHCl_3$); ν_{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_2CO_3 (2.5 mg, 9 μmol), CH_2Cl_2 (0.2 mL) and H_2O (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]

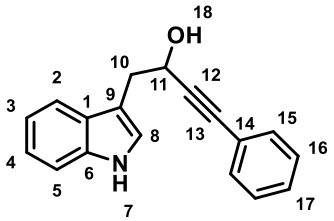
1-(1*H*-Indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-ol (144a)



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; ν_{max} (cm^{-1}) 3412, 1605, 1509, 1248, 1029, 832, 744; δ_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); δ_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-(1*H*-Indol-3-yl)-4-phenylbut-3-yn-2-ol (114b)

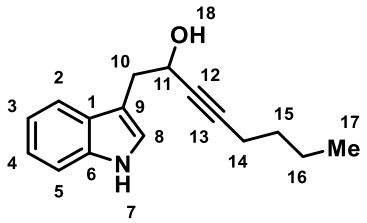


Synthesised using **general procedure 2I** with ynone **83b** (250 mg, 0.96 mmol), $NaBH_4$ (140 mg, 3.70 mmol) and MeOH (19 mL). Purified by column chromatography (7:3 petrol:EtOAc) afford the *title compound* **144b** (230 mg, 92%) as a yellow oil; ν_{max} (cm^{-1}) 3413, 1489, 1457, 1070, 1029, 743, 691; δ_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); δ_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, C8), 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

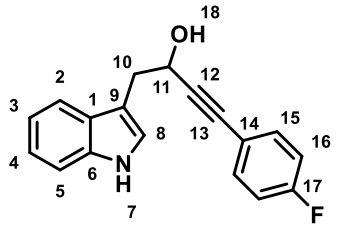
1-(1*H*-Indol-3-yl)oct-3-yn-2-ol (144c)



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; ν_{max} (cm^{-1}) 3410, 2930, 1457, 1027, 1010, 738; δ_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); δ_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; $C_{16}H_{19}NNaO$ (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

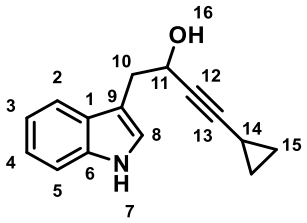
4-(4-Fluorophenyl)-1-(1*H*-indol-3-yl)but-3-yn-2-ol (144d)



Synthesised using **general procedure 2I** with ynone **83d** (2.06 g, 7.43 mmol), MeOH (150 mL) and $NaBH_4$ (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; ν_{max} (cm^{-1}) 3411, 1601, 1506, 1229, 1011, 836, 743; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 34.0 (CH_2, 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); δ_F (376 MHz, $CDCl_3$) −110.6–−110.8 (1F, m); HRMS (ESI^+): Found: 302.0937; $C_{18}H_{14}FNNaO$ (MNa^+) Requires 302.0952 (4.7 ppm error), Found: 280.1121; $C_{18}H_{15}FNO$ (MH^+) Requires 280.1132 (4.0 ppm error).

Lab notebook reference: BSC

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

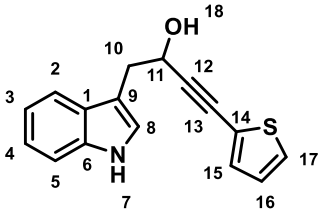


Synthesised using **general procedure 2J** with Weinreb **81a** (500 mg, 2.29 mmol), ethynylcyclopropane (0.58 mL, 6.87 mmol), *n*-BuLi (2.29 mL, 5.73 mmol, 2.5 M in hexanes) and THF (7 mL + 21 mL). Then $NaBH_4$ (346 mg, 9.16 mmol) and MeOH (46 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the *title compound* **144e** (384 mg, 74%) as a yellow oil; ν_{max} (cm^{-1}) 3408, 2236, 1456, 1027, 1010, 740; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) −0.6 (CH, C-14), 8.0 ($2CH_2$, C-15), 34.3 (CH_2, 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; $C_{15}H_{15}NNaO$ (MNa^+) Requires 248.1046 (−0.3 ppm error).

Lab notebook reference: MJJ5/14

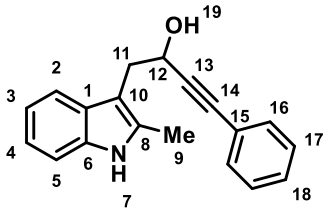
1-(1*H*-Indol-3-yl)-4-(thiophen-2-yl)but-3-yn-2-ol (144f)



Synthesised using **general procedure 2I** with ynone **83i** (186 mg, 0.701 mmol), $NaBH_4$ (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; ν_{max} (cm^{-1}) 3411, 2221, 1456, 1033, 1010, 743, 704; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 33.8 (CH_2, 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; $C_{16}H_{13}NNaOS$ (MNa^+) Requires 290.0610 (−0.3 ppm error), Found: 268.0782; $C_{16}H_{14}NOS$ (MH^+) Requires 268.0791 (3.3 ppm error).

Lab notebook reference: MJJ4/94

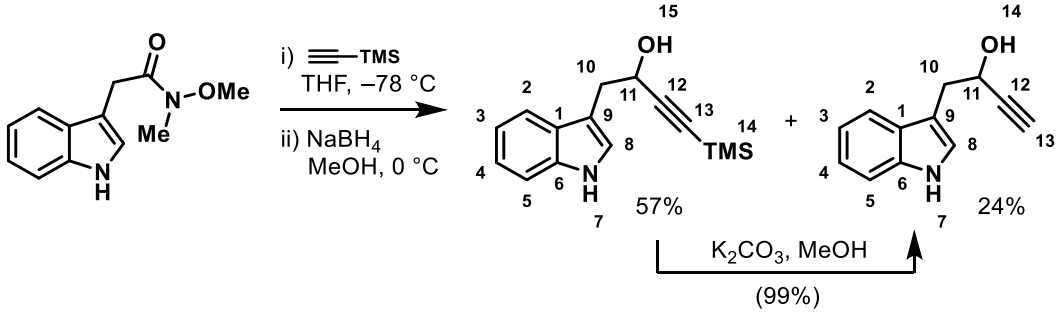
1-(2-Methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-ol (144g)



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 $NaBH_4$ (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; ν_{max} (cm^{-1}) 3400, 1489, 1462, 1041, 1011, 908, 739, 691; δ_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, d, *J* = 8.0 Hz, H-2), 7.92 (1H, br s, H-7); δ_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, CAr), 121.1 (CH, CAr), 122.6 (C, C-15), 128.17 (2CH, C-17), 128.23 (CH, CAr), 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-(1*H*-Indol-3-yl)-4-(trimethylsilyl)but-3-yn-2-ol (144h) & 1-(1*H*-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 $NaBH_4$ (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.

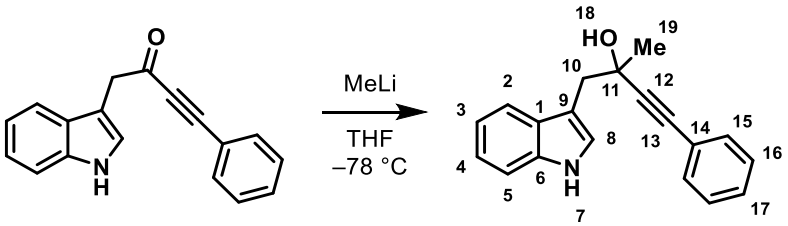
Data for **144h**: ν_{max} (cm^{-1}) 3412, 1457, 1249, 838, 737; δ_H (400 MHz, $CDCl_3$) 0.19 (9H, s, H-14), 2.27 (1H, d, *J* = 5.5 Hz, H-15), 3.17 (1H, dd, *J* = 14.5, 7.0 Hz, H-10a), 3.25 (1H, dd, *J* = 14.5, 5.5 Hz, H-10b), 4.62–4.71 (1H, m, H-11), 7.06 (1H, d, *J* = 2.0 Hz, H-8), 7.16 (1H, dd, *J* = 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); δ_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; $C_{15}H_{19}NNaOSi$ (MNa^+) Requires 280.1128 (2.7 ppm error), Found: 258.1303; $C_{15}H_{20}NOSi$ (MH^+) Requires 258.1309 (2.2 ppm error).

Data for **144i**: ν_{max} (cm^{-1}) 3408, 3281, 1457, 1025, 1010, 742, 647; δ_H (400 MHz, $CDCl_3$) 2.28 (1H, br d, *J* = 3.0 Hz, H-14), 2.49 (1H, d, *J* = 2.0 Hz, H-13), 3.19 (1H, dd, *J* = 14.5, 7.0 Hz, H-10a), 3.27 (1H, dd, *J* = 14.5, 5.5 Hz, H-10b), 4.64–4.73 (1H, m, H-11), 7.12 (1H, d, *J* = 2.0 Hz, H-8), 7.17 (1H, dd, *J* = 7.5, 7.0 Hz, H-3), 7.25 (1H, dd, *J* = 7.5, 7.0 Hz, H-4), 7.37 (1H, d, *J* = 7.5 Hz, H-5), 7.69 (1H, d, *J* = 7.5 Hz, H-2), 8.15 (1H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 33.7 (CH_2, C-10), 62.2 (CH, C-11), 73.2 (CH, C-13), 84.7 (C, C-12), 110.1 (C, C-9), 111.2 (CH, C-5), 118.9 (CH, C-2), 119.5 (CH, C-3), 122.1 (CH, C-4), 123.5 (CH, C-8), 127.5 (C, C-1), 136.1 (C, C-6); HRMS (ESI^+): Found: 208.0735; $C_{12}H_{11}NNaO$ (MNa^+) Requires 208.0733 (−0.8 ppm error).

Propargyl alcohol **144i** was also synthesised by adding K_2CO_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_2O (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-(1*H*-Indol-3-yl)-2-methyl-4-phenylbut-3-yn-2-ol (144j)

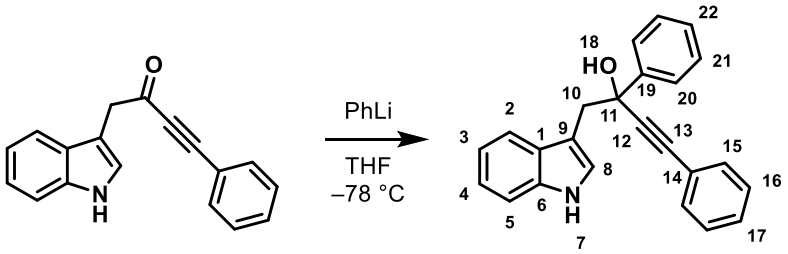


To a solution of ynone **83b** (200 mg, 0.771 mmol) in THF (7.7 mL) at −78 °C under argon was added drop-wise MeLi (1.93 mL, 3.08 mmol, 1.6 M in Et_2O) and the mixture was stirred for 4 h at −78 °C. The mixture was quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL)

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 ($MgSO_4$) 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; ν_{max} (cm^{-1}) 3411, 1489, 1456, 1104, 742, 691; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, s, H-19), 2.42 (1H, br s, H-18), 3.20 (1H, d, *J* = 14.0 Hz, H-10a), 3.33 (1H, d, *J* = 14.0 Hz, H-10b), 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); δ_C (100 MHz, $CDCl_3$) 29.4 (CH_3, C-19), 39.6 (CH_2, 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; $C_{19}H_{17}NNaO$ (MNa^+) Requires 298.1202 (0.6 ppm error).

Lab notebook reference: MJJ4/11

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

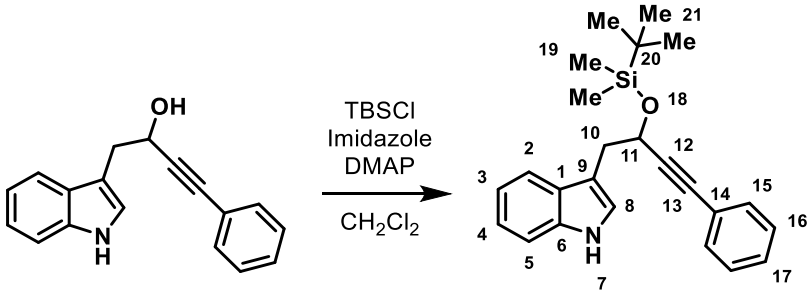


To a solution of ynone **83b** (159 mg, 0.613 mmol) in THF (6.1 mL) at −78 °C under argon was added drop-wise PhLi (1.29 mL, 2.45 mmol, 1.9 M in Bu_2O) and the mixture was stirred for 5 h at −78 °C. The mixture was quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and diluted with EtOAc (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 ($MgSO_4$) 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; ν_{max} (cm^{-1}) 3416, 1490, 1456, 1070, 1010, 756, 742, 692; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 42.2 (CH_2, 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; $C_{24}H_{19}NNaO$ (MNa^+) Requires 360.1359 (1.1 ppm error).

Lab notebook reference: MJJ4/93

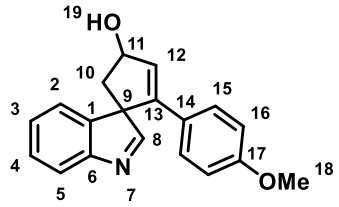
3-(2-((*tert*-Butyldimethylsilyl)oxy)-4-phenylbut-3-yn-1-yl)-1*H*-indole (144l)



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 CH_2Cl_2 (4 mL) was added TBSCl (115 mg, 0.766 mmol). The mixture was stirred for 16 h, then filtered through Celite, washing with CH_2Cl_2 (20 mL). The collected filtrate was washed with 10% $HCl_{(aq)}$ (10 mL) and water (10 mL) successively. The organics were collected, dried ($MgSO_4$) 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; ν_{max} (cm^{-1}) 3420, 2958, 2927, 2856, 1490, 1457, 1253, 1081, 837, 778, 756, 740; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) −5.0 (CH_3, C-19a), −4.8 (CH_3, C-19b), 18.3 (C, C-20), 25.8 ($3CH_3$, C-21), 34.9 (CH_2, 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; $C_{24}H_{29}NNaOSi$ (MNa^+) Requires 398.1911 (4.8 ppm error).

Lab notebook reference: MJJ4/53

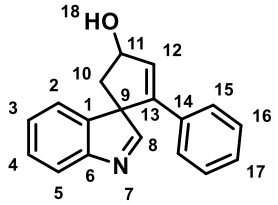
2-(4-Methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-ol (145a)



Synthesised using **general procedure 2K** with alcohol **144a** (81 mg, 0.278 mmol), Ag_2O (3.2 mg, 0.0139 mmol), $AgNO_3$ (4.7 mg, 0.0278 mmol) and CH_2Cl_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; ν_{max} (cm^{-1}) 3295, 2930, 1606, 1510, 1251, 1180, 1032, 908, 828, 756, 730; δ_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 (2 H, 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, dd, *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*); δ_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), 132.2 (CH), 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: MJJ4/46

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

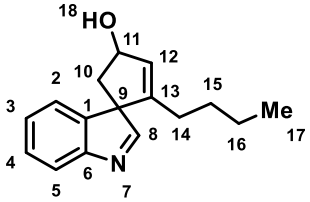


Synthesised using **general procedure 2K** with alcohol **144b** (100 mg, 0.383 mmol), Ag_2O (4.4 mg, 0.0192 mmol), $AgNO_3$ (6.5 mg, 0.0383 mmol) and CH_2Cl_2 (3.8 mL). Purification by column chromatography (2%→10% MeOH in DCM) afforded the *title compound* **145b** (96 mg, 96%, 54:46 *dr*) as a brown oil; ν_{max} (cm^{-1}) 3294, 1549, 1455, 1445, 1075, 1014, 907, 776,

752, 731, 692; δ_H (400 MHz, $CDCl_3$) 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, *minor*), 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, $CDCl_3$) 42.5 (CH_2), 43.6 (CH_2), 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; $C_{18}H_{16}NO$ (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)

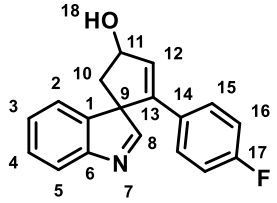


Synthesised using **general procedure 2K** with alcohol **144c** (154 mg, 0.638 mmol), Ag_2O (7.4 mg, 0.0319 mmol), $AgNO_3$ (10.8 mg, 0.0638 mmol) and CH_2Cl_2 (6.4 mL). Purification by column chromatography (2%→10% MeOH in DCM) afforded the *title compound* **145c** (141 mg, 92%, 53:47 *dr*) as a brown oil; ν_{max} (cm^{-1}) 3315, 2956, 2828, 2871, 1551, 1455, 1048, 1022, 751; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 13.7 ($2CH_3$), 22.2 ($2CH_2$), 26.7 (CH_2), 26.9 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 40.7 (CH_2), 41.6 (CH_2), 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; $C_{16}H_{19}NNaO$ (MNa^+) Requires 264.1359 (−1.8 ppm error), Found: 242.1546; $C_{16}H_{20}NO$ (MH^+) Requires 242.1539 (−2.8 ppm error).

Lab notebook reference: MJJ4/55

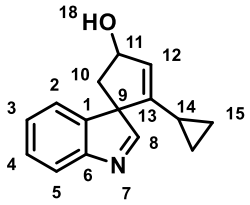
2-(4-Fluorophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-ol (145d)



Synthesised using **general procedure 2K** with alcohol **144d** (95 mg, 0.340 mmol), Ag_2O (3.9 mg, 0.0170 mmol), $AgNO_3$ (5.8 mg, 0.0340 mmol) and CH_2Cl_2 (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; ν_{max} (cm^{-1}) 3330, 2928, 1673, 1600, 1507, 1259, 1233, 1160, 1023, 832, 732; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 42.4 (CH_2), 43.6 (CH_2), 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, $CDCl_3$) −112.6–−112.7 (1F, m, *minor*), −112.7–−112.8 (1F, m, *major*); HRMS (ESI^+): Found: 302.0948; $C_{18}H_{14}FNNaO$ (MNa^+) Requires 302.0952 (1.2 ppm error), Found: 280.1125; $C_{18}H_{15}FNO$ (MH^+) Requires 280.1132 (2.6 ppm error).

Lab notebook reference: MJJ4/31

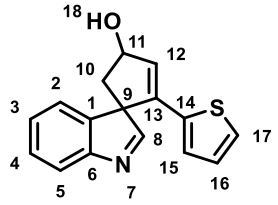
2-Cyclopropylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (145e)



Synthesised using **general procedure 2K** with alcohol **144e** (152 mg, 0.675 mmol), Ag_2O (7.8 mg, 0.0338 mmol), $AgNO_3$ (11.5 mg, 0.0675 mmol) and CH_2Cl_2 (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; ν_{max} (cm^{-1}) 3305, 1456, 1020, 752, 733; δ_H (400 MHz, $CDCl_3$) 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*); δ_C (100 MHz, $CDCl_3$) 7.5 (CH_2), 7.7 (CH_2), 8.1 (CH), 8.2 (CH), 8.35 (CH_2), 8.37 (CH_2), 40.7 (CH_2), 41.7 (CH_2), 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; $C_{15}H_{15}NNaO$ (MNa^+) Requires 248.1046 (1.4 ppm error), Found: 226.1224; $C_{15}H_{16}NO$ (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)

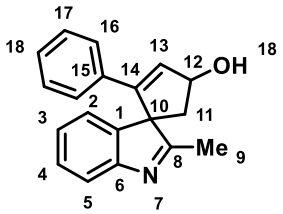


Synthesised using **general procedure 2K** with alcohol **144f** (68 mg, 0.254 mmol), Ag_2O (2.9 mg, 0.0127 mmol), $AgNO_3$ (4.3 mg, 0.0254 mmol) and CH_2Cl_2 (2.5 mL). Purification by column chromatography (2→10% MeOH in DCM) afforded the *title compound* **145f** (65 mg, 96%, 59:41 *dr*) as a pale brown oil; ν_{max} (cm^{-1}) 3307, 1455, 1046, 754, 731, 701; δ_H (400

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, *minor*), 2.81 (1H, dd, *J* = 14.0, 7.0 Hz, H-10b, *major*), 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_2), 43.0 (CH_2), 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)

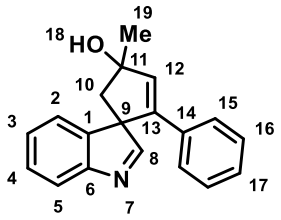


Synthesised using **general procedure 2K** with alcohol **144g** (106 mg, 0.385 mmol), Ag_2O (4.5 mg, 0.0193 mmol), $AgNO_3$ (6.5 mg, 0.0385 mmol) and CH_2Cl_2 (3.9 mL). Purification by column chromatography (1→10% MeOH in DCM) afforded the *title compound* **145g** (102 mg, 96%, 50:50 *dr*) as a yellow oil; ν_{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

(CH), 143.1 (C), 143.8 (C), 145.1 (C), 145.7 (C), 153.8 (C), 154.0 (C), 185.5 (C), 186.0 (C); HRMS (ESI^+): Found: 276.1377; $C_{19}H_{18}NO$ (MH^+) Requires 276.1383 (2.3 ppm error).

Lab notebook reference: MJ4/60

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

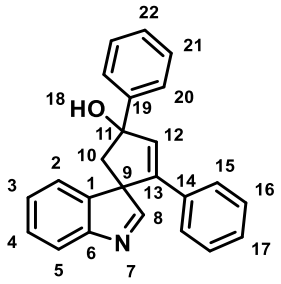


Synthesised using **general procedure 2K** with alcohol **144j** (40 mg, 0.134 mmol), Ag_2O (1.7 mg, 7.26 μmol), $AgNO_3$ (2.5 mg, 0.0145 mmol) and CH_2Cl_2 (1.7 mL). Purification by column chromatography (2→10% MeOH in DCM) afforded the *title compound* **145j** (38 mg, 95%, 50:50 *dr*) as a brown oil; 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

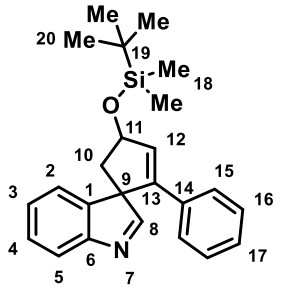
2,4-Diphenylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (145k)



Synthesised using **general procedure 2K** with alcohol **144k** (69 mg, 0.205 mmol), Ag_2O (2.4 mg, 0.0103 mmol), $AgNO_3$ (3.5 mg, 0.0205 mmol) and CH_2Cl_2 (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; ν_{max} (cm^{-1}) 3255, 3058, 1491, 1446, 906, 754, 727, 695; δ_H (400 MHz, $CDCl_3$) 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, *major*), 2.85 (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*); δ_C (100 MHz, $CDCl_3$) 49.0 (CH_2), 51.1 (CH_2), 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; $C_{24}H_{20}NO$ (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)

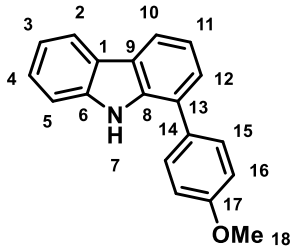


Synthesised using **general procedure 2K** with alcohol **144l** (44 mg, 0.117 mmol), Ag_2O (1.4 mg, 5.85 μmol), $AgNO_3$ (2.0 mg, 0.0117 mmol) and CH_2Cl_2 (1.1 mL). Purification by column

chromatography (8:2 hexane:EtOAc) afforded the *title compound* **145l** (41 mg, 93%, 52:48 *dr*) as a colourless oil; ν_{max} (cm^{-1}) 2954, 2928, 2856, 1252, 1087, 1089, 836, 776, 751, 692; δ_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* = 13.0, 4.0 Hz, H-10a, *minor*), 2.38 (1H, dd, *J* = 13.0, 6.0 Hz, H-10b, *minor*), 2.72 (1H, dd, *J* = 13.5, 6.5 Hz, H-10b, *major*), 5.14–5.19 (1H, m, H-11, *major*), 5.22–5.28 (1H, m, H-11, *minor*), 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*), 7.16–7.27 (3H, 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*); δ_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)-9*H*-carbazole (146a)



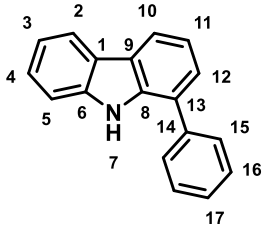
Synthesised using **general procedure 2L** with alcohol **144a** (70 mg, 0.240 mmol), AgOTf (6.2 mg, 0.024 mmol) and THF (2.4 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **146a** (64 mg, 98%) as a white solid, mp 134–136 °C; ν_{max} (cm^{-1}) 3418, 1924, 1611, 1515, 1456, 1246, 750; δ_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); δ_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; $C_{19}H_{16}NO$ (MH^+) Requires 274.1226 (−2.7 ppm error).

Lab notebook reference: MJJ4/47

Spectroscopic data matched those reported in the literature.[152]

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



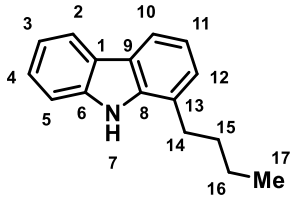
Synthesised using **general procedure 2L** with alcohol **144b** (92 mg, 0.352 mmol), AgOTf (9.0 mg, 0.0352 mmol) and THF (3.5 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **146b** (72 mg, 84%) as a white solid, mp 124–126 °C; ν_{max} (cm^{-1}) 3435, 3057, 2923, 1456, 1413, 1232, 749, 734, 701; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 110.7 (CH, C-5), 119.46 (CH, C-2/3/10/11), 119.52 (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; $C_{18}H_{14}N$ (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]

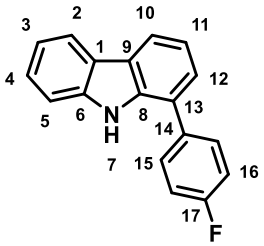
1-*n*-Butyl-9*H*-carbazole (146c)



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; ν_{max} (cm^{-1}) 3429, 2955, 2927, 1501, 1455, 1425, 1325, 1232, 748; δ_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); δ_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, C6/8), 139.3 (C, C-6/8); HRMS (ESI^+): Found: 246.1250; $C_{16}H_{17}NNa$ (MNa^+) Requires 246.1253 (1.4 ppm error), Found: 224.1432; $C_{16}H_{17}N$ (MH^+) Requires 224.1434 (0.8 ppm error).

Lab notebook reference: MJJ4/56

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

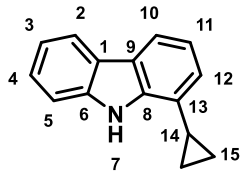


Synthesised using **general procedure 2L** with alcohol **144d** (96 mg, 0.344 mmol), AgOTf (8.8 mg, 0.0344 mmol) and THF (3.4 mL). Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **146d** (86 mg, 96%) as a white solid, mp 155–157 °C; ν_{max} (cm^{-1}) 3468, 1603, 1509, 1455, 1314, 1222, 1156, 840, 749, 738; δ_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); δ_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; $C_{18}H_{13}FN$ (MH^+) Requires 262.1027 (4.3 ppm error).

Lab notebook reference: MJJ4/32

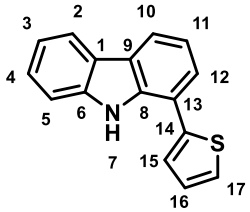
1-Cyclopropyl-9*H*-carbazole (146e)



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, 1422, 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; $C_{15}H_{14}NO$ (MH^+) Requires 208.1121 (−1.5 ppm error).

Lab notebook reference: MJJ5/20

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

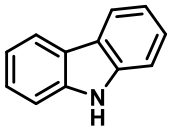


Synthesised using **general procedure 2L** with alcohol **144f** (77 mg, 0.288 mmol), AgOTf (7.4 mg, 0.0288 mmol) and THF (2.9 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the *title compound* **146f** (20 mg, 28%) as an off white semi-solid; ν_{max} (cm^{-1}) 3430, 1493, 1455, 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 Hz, H-12), 8.06 (1H, d, *J* = 8.0 Hz, H-2/10), 8.10 (1H, d, *J* = 8.0 Hz, H-2/10), 8.54 (1H, br s, H-7); δ_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, C1/9), 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; $C_{16}H_{12}NS$ (MH^+) Requires 250.0685 (0.1 ppm error).

Lab notebook reference: MJJ5/3

9*H*-Carbazole (146i)



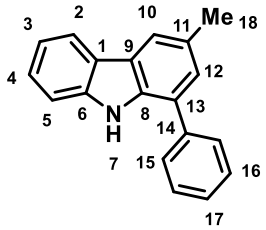
Synthesised using **general procedure 2L** with alcohol **144i** (70 mg, 0.378 mmol), AgOTf (9.7 mg, 0.0378 mmol) and THF (3.8 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **146i** (62 mg, 98%) as an off-white solid, mp 242–243 °C; ν_{max} (cm^{-1}) 3416, 1450, 746, 722, 573; δ_H (400 MHz, DMSO-d_6) 7.15 (2H, dd, *J* = 7.5, 7.5 Hz), 7.38 (2H, dd, *J* = 8.0, 7.5 Hz), 7.49 (2H, d, *J* = 8.0 Hz), 8.11 (2H, d, *J* = 7.5 Hz), 11.26 (1H, br s); δ_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; $C_{12}H_{10}N$ (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: MJJ4/36 + 4/38

Spectroscopic data matched those reported in the literature.[154]

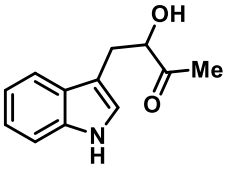
3-Methyl-1-phenyl-9*H*-carbazole (146j):



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; ν_{max} (cm^{-1}) 3435, 3031, 2919, 1608, 1499, 1488, 1452, 1317, 1235, 776, 734, 703, 578; δ_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); δ_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)



To a solution of alcohol **144i** (112 mg, 0.605 mmol) in CH_2Cl_2 (6.1 mL) was added sequentially Ag_2O (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; ν_{max} (cm^{-1}) 3408, 1710, 1457, 1355, 1093, 744; δ_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); δ_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),

127.4 (C), 136.0 (C), 209.8 (C); HRMS (ESI^+): Found: 226.0833; $C_{12}H_{13}NNaO_2$ (MNa^+) Requires 226.0838 (2.3 ppm error).

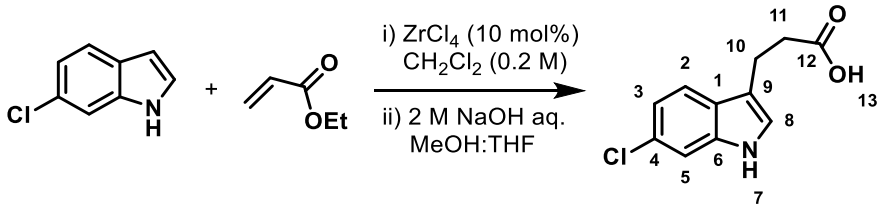
Compound **162** also synthesised using alcohol **144h** (45 mg, 0.175 mmol), CH_2Cl_2 (1.8 mL), Ag_2O (2.0 mg, 8.75 μmol) and $AgNO_3$ (3.0 mg, 0.0175 mmol). After stirring for 24 h the reaction mixture was stirred was purified by column chromatography (3:2 hexane:EtOAc then EtOAc) to afford the *title 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

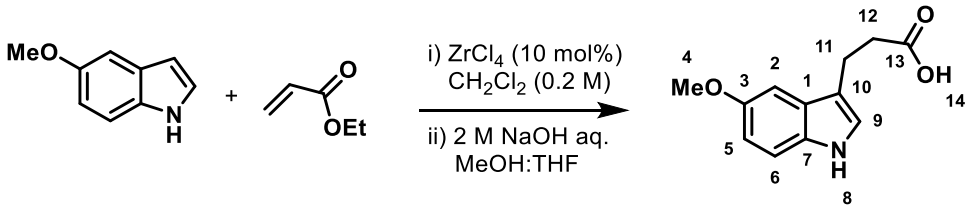
3-(6-Chloro-1*H*-indol-3-yl)propanoic acid (80i)



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_2Cl_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 *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 *in vacuo*, the crude material was dissolved in H_2O (50 mL) and washed with CH_2Cl_2 (2 × 50 mL). The organics were discarded and the aqueous was acidified to pH 1 with 10% $HCl_{(aq)}$ and extracted with CH_2Cl_2 (3 × 50 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* **80i** (1.86 g, 63%) as an off-white solid, mp 94–96 °C; ν_{max} (cm^{-1}) 3438, 1705, 1410, 1279, 1205, 804, 463; δ_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); δ_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; $C_{11}H_{10}{}^{35}ClNNaO_2$ (MNa^+) Requires 246.0292 (−3.1 ppm error).

Lab notebook reference: MJJ7/48

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

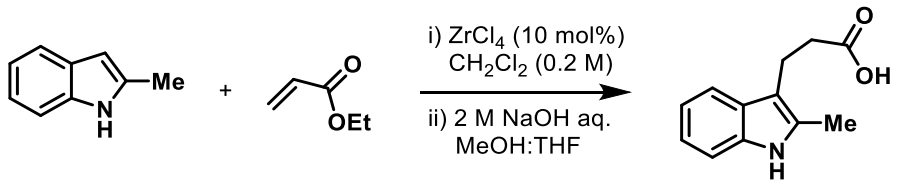


Synthesised according to a modified literature procedure.[109] To a solution of 5-methoxyindole (2.00 g, 13.6 mmol), ethyl acrylate (1.77 mL, 16.3 mmol) in anhydrous CH_2Cl_2 (68 mL) under argon was added $ZrCl_4$ (317 mg, 1.36 mmol) in one portion. The mixture was stirred at RT

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 $NaOH_{(aq)}$ (68 mL) was added. The mixture was stirred at RT for 18 h then concentrated *in vacuo*, the crude material was dissolved in H_2O (50 mL) and washed with CH_2Cl_2 (2 × 50 mL). The organics were discarded and the aqueous was acidified to pH 1 with 10% $HCl_{(aq)}$ and extracted with CH_2Cl_2 (3 × 50 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* **80j** (2.36 g, 79%) as a white solid, mp 132–134 °C; ν_{max} (cm^{-1}) 3343, 1714, 1488, 1211, 1177, 1018, 797, 640, 621, 541; δ_H (400 MHz, DMSO-d_6) 2.58 (2H, t, *J* = 7.5 Hz, H-12), 2.89 (2H, t, *J* = 7.5 Hz, H-11), 3.76 (3H, s, H-4), 6.71 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.99 (1H, d, *J* = 2.5 Hz, H-2), 7.07 (1H, d, *J* = 2.0 Hz, H-9), 7.22 (1H, d, *J* = 8.5 Hz, H-6), 10.62 (1H, br s, H-8), 12.08 (1H, br s, H-14); δ_C (100 MHz, DMSO-d_6) 20.4 (CH_2, C-11), 34.5 (CH_2, C-12), 55.3 (CH_3, C-4), 100.0 (CH, C-2), 111.1 (CH, C-5), 112.0 (CH, C-6), 113.2 (C, C-10), 122.9 (CH, C-9), 127.2 (C, C-1), 131.4 (C, C-7), 153.0 (C, C-3), 174.4 (C, C-13); HRMS (ESI^+): Found: 242.0789; $C_{12}H_{13}NNaO_3$ (MNa^+) Requires 242.0788 (−0.7 ppm error), Found: 220.0970; $C_{12}H_{14}NO_3$ (MH^+) Requires 220.0968 (−0.8 ppm error).

Lab notebook reference: MJJ7/46

3-(2-Methyl-1*H*-indol-3-yl)propanoic acid (S1)



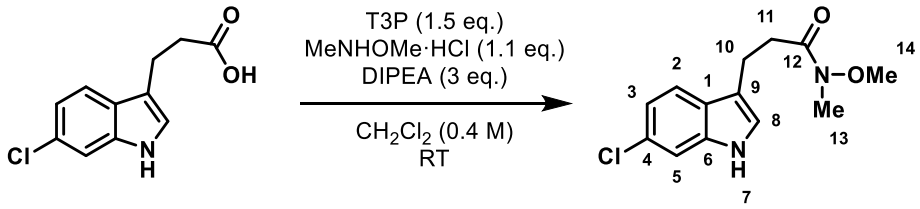
Synthesised according to a modified literature procedure.[109] To a solution of 2-methylindole (2.67 g, 20.4 mmol), ethyl acrylate (2.65 mL, 24.5 mmol) in anhydrous CH_2Cl_2 (102 mL) under argon was added $ZrCl_4$ (475 mg, 2.04 mmol) in one portion. The mixture was stirred at RT under argon for 24 h then concentrated *in vacuo*. The crude ester was then dissolved in MeOH:THF (1:1 v/v, 408 mL) and 2 M $NaOH_{(aq)}$ (102 mL) was added. The mixture was stirred at RT for 18 h then concentrated *in vacuo*, the crude material was dissolved in H_2O (50 mL) and washed with CH_2Cl_2 (2 × 50 mL). The organics were discarded and the aqueous was acidified to pH 1 with 10% $HCl_{(aq)}$ and extracted with CH_2Cl_2 (3 × 50 mL). The organics were dried ($MgSO_4$) 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); ν_{max} (cm^{-1}) 1464, 1405, 1306, 1295, 1211; δ_H (400 MHz, DMSO-d_6) 2.31 (3H, s); 2.45 (2H, t, *J* = 7.5 Hz), 2.87 (2H, t, *J* = 7.5 Hz), 6.91 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz), 6.97 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz), 7.21 (1H, br d, *J* = 7.5 Hz), 7.39 (1H, br d, *J* = 7.5 Hz), 10.68 (1H, s), 12.01 (1H, br s); δ_C (100 MHz, DMSO-d_6)

11.2 (CH_3), 19.4 (CH_2), 35.1 (CH_2), 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]

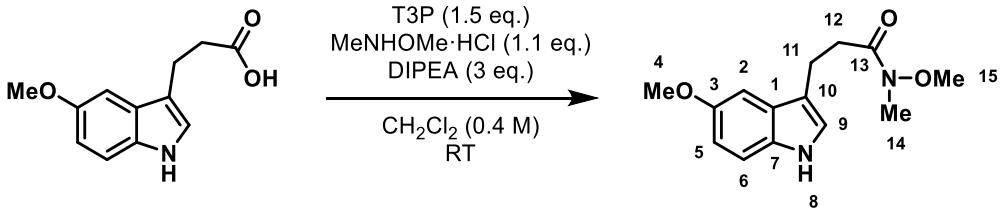
3-(6-Chloro-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylpropanamide (81i)



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 CH_2Cl_2 (21 mL) afforded the *title compound* **81i** (1.92 g, 87%) as a pale brown solid, mp 104–106 °C; ν_{max} (cm^{-1}) 3281, 1641, 1457, 803; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.1 (CH_2, C-10), 32.2 (CH_3, C-13), 32.5 (CH_2, C-11), 61.2 (CH_3, 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; $C_{13}H_{15}{}^{35}ClN_2NaO_2$ (MNa^+) Requires 289.0714 (0.5 ppm error), Found: 267.0896; $C_{13}H_{16}{}^{35}ClN_2O_2$ (MH^+) Requires 267.0895 (−0.5 ppm error).

Lab notebook reference: MJJ7/55

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

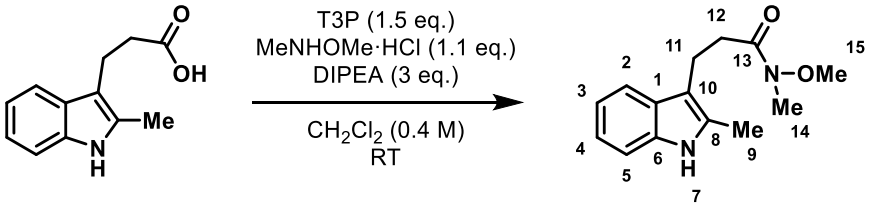


Synthesised using **general procedure 2A** with **80j** (2.36 g, 8.31 mmol), T3P 50% in EtOAc (8.59 g, 13.5 mmol), DIPEA (4.70 mL, 27.0 mmol) and MeNHOMe·HCl (965 mg, 9.90 mmol) in CH_2Cl_2 (23 mL) afforded the *title compound* **81j** (2.31 g, 82%) as a brown oil; ν_{max} (cm^{-1}) 3301, 2967, 1639, 1485, 1440, 1214, 1062, 797; δ_H (400 MHz, $CDCl_3$) 2.84 (2H, t, *J* =

7.5 Hz, H-12), 3.10 (2H, t, *J* = 7.5 Hz, H-11), 3.21 (3H,s, H-14), 3.60 (3H, s, H-15), 3.87 (3H, s, H-4), 6.86 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.01 (1H, d, *J* = 2.0 Hz, H-9), 7.08 (1H, d, *J* = 2.5 Hz, H-2), 7.24 (1H, d, *J* = 8.5 Hz, H-6), 8.15 (1H, br s, H-8); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2, C-11), 32.1 (CH_3, C-14), 32.5 (CH_2, C-12) , 55.9 (CH_3, C-4), 61.1 (CH_3, C-15), 100.4 (CH, C-2), 111.8 (CH, C-5/6), 112.0 (CH, C-5/6), 115.0 (C, C-10), 122.4 (CH, C-9), 127.5 (C, C-1), 131.4 (C, C-7), 153.8 (C, C-3), 174.2 (C, C-13); HRMS (ESI^+): Found: 285.1212; $C_{14}H_{18}N_2NaO_3$ (MNa^+) Requires 285.1210 (−0.7 ppm error), Found: 263.1387; $C_{14}H_{19}N_2O_3$ (MH^+) Requires 263.1390 (1.3 ppm error).

Lab notebook reference: MJJ7/53

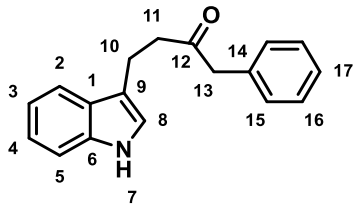
_N_-Methoxy-_N_-methyl-3-(2-methyl-1_H_-indol-3-yl)propanamide (S2)



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_2Cl_2 (36 mL) afforded the *title compound* **S2** (3.28 g, 92%) as a brown oil; ν_{max} (cm^{-1}) 3300, 1640, 1463, 1439, 742; δ_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); δ_C (100 MHz, $CDCl_3$) 11.5 (CH_3, C-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; $C_{14}H_{18}N_2NaO_2$ (MNa^+) Requires 269.1260 (2.7 ppm error), Found: 247.1450; $C_{14}H_{19}N_2O_2$ (MH^+) Requires 247.1441 (−3.5 ppm error).

Lab notebook reference: MJJ7/94

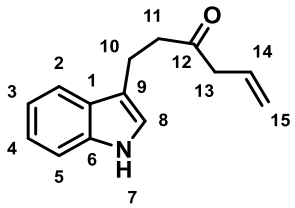
4-(1*H*-Indol-3-yl)-1-phenylbutan-2-one (192a)



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; ν_{max} (cm^{-1}) 3310, 1708, 745; δ_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); δ_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-(1*H*-Indol-3-yl)hex-5-en-3-one (S3)

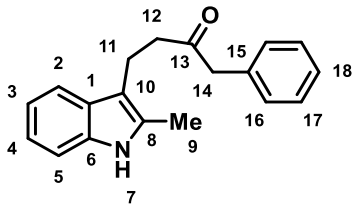


Synthesised using **general procedure 3A** with Weinreb amide **81b** (978 mg, 4.21 mmol), AllylMgBr (16.8 mL, 16.8 mmol, 1.0 M in Et_2O) and THF (30 mL). Purification by column chromatography (7:3 hexane:EtOAc) afforded the *title compound* **S3** (840 mg, 94%) as a white solid, mp 60–62 °C; ν_{max} (cm^{-1}) 3410, 1708, 1457, 743; δ_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-15*trans*), 5.17 (1H, dd, *J* = 10.5, 1.5 Hz, H-15*cis*), 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); δ_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; $C_{14}H_{15}NNaO$ (MNa^+) Requires 236.1046 (−2.0 ppm error), Found: 214.1226; $C_{14}H_{16}NO$ (MH^+) Requires 214.1226 (0.3 ppm error).

Lab notebook reference: MJJ7/23

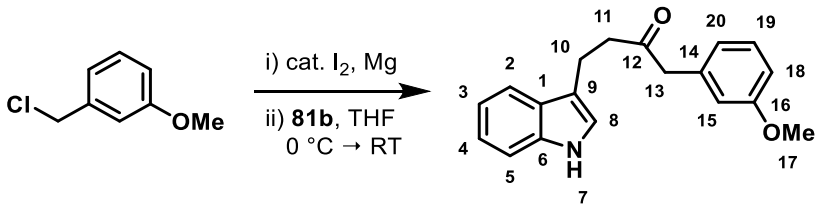
4-(2-Methyl-1*H*-indol-3-yl)-1-phenylbutan-2-one (S4)



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; ν_{max} (cm^{-1}) 3398, 1708, 1462, 741, 700; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, H-9), 2.80 (2H, t, *J* = 7.5 Hz, H-12), 2.97 (2H, t, *J* = 7.5 Hz, H-11), 3.63 (2H, s, H-14), 7.05–7.16 (4H, m, ArH), 7.22–7.34 (4H, m, ArH), 7.41 (1H, d, *J* = 8.0 Hz, H-2), 7.74 (1H, br s, H-7); δ_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; $C_{19}H_{19}NNaO$ (MNa^+) Requires 300.1359 (1.1 ppm error), Found: 278.1531; $C_{19}H_{20}NO$ (MH^+) Requires 278.1539 (−3.9 ppm error).

Lab notebook reference: MJJ9/16

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

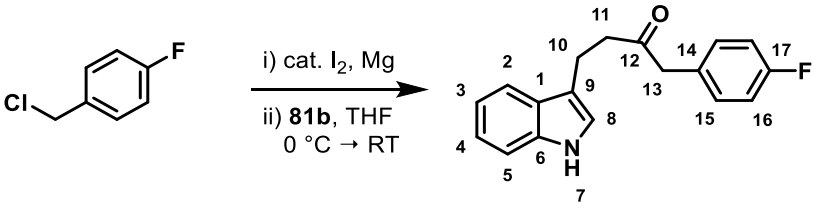


Iodine (2 crystals) was sublimed over freshly crushed magnesium turnings (836 mg, 34.4 mmol) under argon by heating the solids with a heat gun (30 seconds). THF (4 mL) was then added, followed by 3-methoxybenzyl chloride (0.10 mL, 0.69 mmol), once a dark grey colour change was observed the mixture was 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. $NH_4Cl_{(aq)}$ (30 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried ($MgSO_4$), 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; ν_{max} (cm^{-1}) 3409, 2920, 1711, 1598, 1490, 1457, 1260, 744; δ_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), 3.65 (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); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2, C-10), 42.3 (CH_2, C-11), 50.4 (CH_2, C-13), 55.1 (CH_3, 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; $C_{19}H_{19}NNaO$ (MNa^+) Requires 316.1308 (0.8 ppm error).

Lab notebook reference: MJJ7/26

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

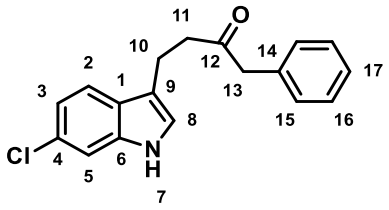


Iodine (2 crystals) was sublimed over freshly crushed magnesium turnings (1.67 g, 68.8 mmol) under argon by heating the solids with a heat gun (30 seconds). THF (5 mL) was then added, followed by 4-fluorobenzyl chloride (0.10 mL, 0.83 mmol), once a dark grey colour change was observed the mixture was 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. $NH_4Cl_{(aq)}$ (30 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (35% EtOAc in

hexane) to afford the *title compound* **192c** (1.39 g, 57%) as a white solid, mp 111–113 °C; ν_{max} (cm^{-1}) 3379, 1714, 1509, 1221, 743; δ_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); δ_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); δ_F (376 MHz, $CDCl_3$) −115.7–−115.8 (1F, m); HRMS (ESI^+): Found: 304.1105; $C_{18}H_{16}FNNaO$ (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

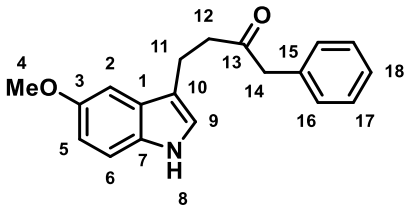
4-(6-Chloro-1*H*-indol-3-yl)-1-phenylbutan-2-one (192d)



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; ν_{max} (cm^{-1}) 3367, 1710, 1454, 1060, 804, 700; δ_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); δ_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-1/4), 127.0 (CH, C-17), 127.9 (C, C-1/4), 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; $C_{18}H_{16}{}^{35}ClNNaO$ (MNa^+) Requires 320.0813 (−3.5 ppm error).

Lab notebook reference: MJJ7/56

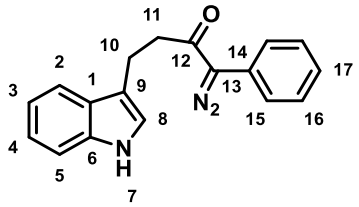
4-(5-Methoxy-1*H*-indol-3-yl)-1-phenylbutan-2-one (192e)



Synthesised using **general procedure 3A** with Weinreb amide **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, mp 48–50 °C; ν_{max} (cm^{-1}) 3407, 1709, 1485, 1454, 1214, 1058, 700; δ_H (400 MHz, $CDCl_3$) 2.87 (2H, t, *J* = 7.5 Hz, H-12), 3.01 (2H, t, *J* = 7.5 Hz, H-11), 3.68 (2H, s, H-14), 3.86 (3H, s, H-4), 6.86 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.90 (1H, d, *J* = 2.0 Hz, H-9), 6.97 (1H, d, *J* = 2.5 Hz, H-2), 7.17 (2H, d, *J* = 7.0 Hz, H-16), 7.21–7.35 (4H, m, H-6,17,18), 7.85 (1H, br s, H-8); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2, C-11), 42.2 (CH_2, C-12), 50.4 (CH_2, C-14), 55.9 (CH_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$^+$): Found: 316.1301; $C_{19}H_{19}NNaO_2$ (MNa^+) Requires 316.1308 (2.1 ppm error).

Lab notebook reference: MJJ7/59

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

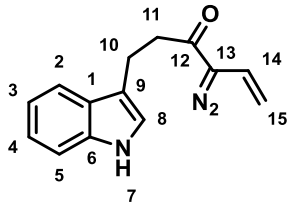


Synthesised using **general procedure 3B** with benzyl ketone **192a** (527 mg, 2.00 mmol), *p*-ABSA (576 mg, 2.40 mmol), DBU (0.42 mL, 2.80 mmol) and MeCN (6 mL). Purification by column chromatography (70:27:3 hexane:EtOAc:Et_3N) afforded the *title compound* **188a** (426 mg, 74%) as a yellow solid, mp 105–106 °C (decomposition); ν_{max} (cm^{-1}) 3406, 2925, 2074, 1640, 744; δ_H (400 MHz, CD_2Cl_2) 2.98 (2H, t, *J* = 7.5 Hz, H-11), 3.16 (2H, t, *J* = 7.5 Hz, H-10), 7.05 (1H, d, *J* = 2.0 Hz, H-8), 7.08 (1H, dd, *J* = 8.0, 7.0 Hz, H-3), 7.17 (1H, dd, *J* = 8.0, 7.0 Hz, H-4), 7.24 (1H, dd, *J* = 7.5, 7.5 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 Hz, H-2), 8.10 (1H, br s, H-7); δ_C (100 MHz, CD_2Cl_2) 20.7 (CH_2, C-10), 40.3 (CH_2, C-11), 72.7 (C, C-13), 111.7 (CH, C-5), 115.3 (C, C-9), 119.1 (CH,

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; $C_{18}H_{15}N_3NaO$ (MNa^+) Requires 312.1107 (−1.2 ppm error).

Lab notebook reference: MJJ6/8

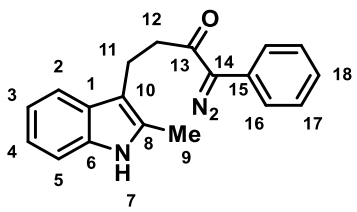
4-Diazo-1-(1*H*-indol-3-yl)hex-5-en-3-one (207)



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_3N) afforded the *title compound* **207** (466 mg, 57%) as a pale orange solid, mp 102–104 °C (decomposition); ν_{max} (cm^{-1}) 3410, 2078, 1635, 1609, 1292, 742; δ_H (400 MHz, CD_2Cl_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*trans*), 5.17 (1H, d, *J* = 11.0 Hz, H-15*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); δ_C (100 MHz, CD_2Cl_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; $C_{14}H_{13}N_3NaO$ (MNa^+) Requires 262.0951 (−2.9 ppm error).

Lab notebook reference: MJJ7/25

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

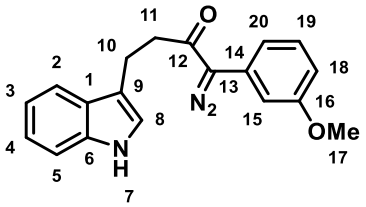


Synthesised using **general procedure 3B** with benzyl ketone **S4** (359 mg, 1.29 mmol), *p*-ABSA (372 mg, 1.55 mmol), DBU (0.27 mL, 1.81 mmol) and MeCN (4 mL). Purification by

column chromatography (70:27:3 hexane:EtOAc:Et_3N) afforded the *title compound* **223** (136 mg, 35%) as a yellow solid, mp 77–79 °C (decomposition); ν_{max} (cm^{-1}) 3400, 2071, 1630, 1462, 742, 693; δ_H (400 MHz, CD_2Cl_2) 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); δ_C (100 MHz, CD_2Cl_2) 11.8 (CH_3, C-9), 20.0 (CH_2, C-11), 40.4 (CH_2, 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; $C_{19}H_{17}N_3NaO$ (MNa^+) Requires 326.1264 (−0.8 ppm error).

Lab notebook reference: MJJ9/18

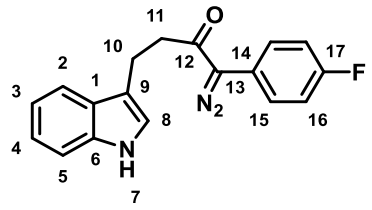
1-Diazo-4-(1*H*-indol-3-yl)-1-(3-methoxyphenyl)butan-2-one (188b)



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:Et_3N) afforded the *title compound* **188b** (455 mg, 73%) as a yellow solid, mp 87–89 °C (decomposition); ν_{max} (cm^{-1}) 3408, 2075, 1632, 1601, 1231, 743; δ_H (400 MHz, CD_2Cl_2) 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); δ_C (100 MHz, CD_2Cl_2) 20.7 (CH_2, C-10), 40.4 (CH_2, C-11), 55.8 (CH_3, 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; $C_{19}H_{17}N_3NaO_2$ (MNa^+) Requires 342.1213 (1.1 ppm error).

Lab notebook reference: MJJ7/30

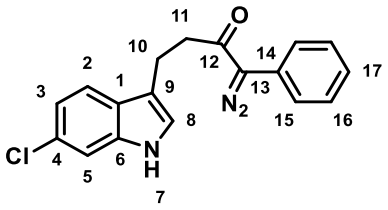
1-Diazo-1-(4-fluorophenyl)-4-(1*H*-indol-3-yl)butan-2-one (188c)



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:Et_3N) afforded the *title compound* **188c** (1.09 g, 75%) as a yellow solid, mp 95–97 °C (decomposition); ν_{max} (cm^{-1}) 3316, 2075, 1636, 1508, 1226, 1200, 832, 739; δ_H (400 MHz, CD_2Cl_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); δ_C (100 MHz, CD_2Cl_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); δ_F (376 MHz, $CDCl_3$) −114.5–−116.5 (1F, m); HRMS (ESI^+): Found: 330.1009; $C_{18}H_{14}FN_3NaO$ (MNa^+) Requires 330.1013 (1.2 ppm error).

Lab notebook reference: MJJ7/52

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

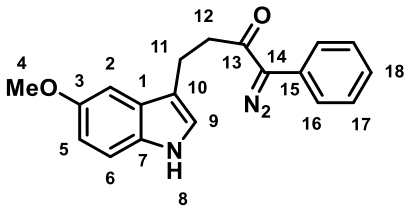


Synthesised using **general procedure 3B** with benzyl ketone **192d** (774 mg, 2.60 mmol), *p*-ABSA (749 mg, 3.12 mmol), DBU (0.54 mL, 3.64 mmol) and MeCN (8 mL). Purification by column chromatography (57:40:3 hexane:EtOAc:Et_3N) afforded the *title compound* **188d** (496 mg, 59%) as a yellow solid, mp 110–112 °C (decomposition); ν_{max} (cm^{-1}) 3343, 2074, 1621, 1203, 803, 698; δ_H (400 MHz, CD_2Cl_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); δ_C (100 MHz, CD_2Cl_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; $C_{18}H_{14}{}^{35}ClN_3NaO$ (MNa^+) Requires 346.0718 (−1.0 ppm error).

Lab notebook reference: MJJ7/63

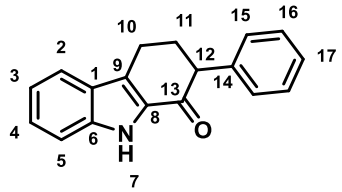
1-Diazo-4-(5-methoxy-1*H*-indol-3-yl)-1-phenylbutan-2-one (188e)



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:Et_3N) 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, CD_2Cl_2) 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, CD_2Cl_2) 20.8 (CH_2, C-11), 40.3 (CH_2, C-12), 56.2 (CH_3, 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; $C_{19}H_{17}N_3NaO_2$ (MNa^+) Requires 342.1218 (4.4 ppm error).

Lab notebook reference: MJJ7/65

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

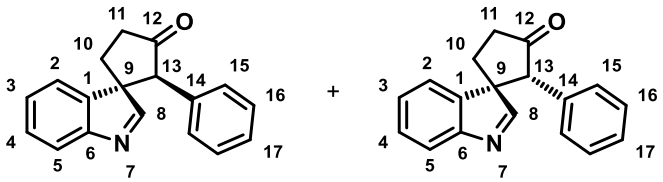


Synthesised using **general procedure 3H** with α-diazocarbonyl **188a** (43 mg, 0.149 mmol), silica gel (34 mg) and CH_2Cl_2 (1.5 mL). Purification by column chromatography (40% Et_2O in hexane) afforded the *title compound* **193a** (28 mg, 72%) as a white solid, mp 169–171 °C; ν_{max} (cm^{-1}) 3275, 1642, 739; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2, C-10), 33.4 (CH_2, 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; $C_{18}H_{15}NNaO$ (MNa^+) Requires 284.1046 (3.4 ppm error), Found: 262.1216; $C_{18}H_{16}NO$ (MH^+) Requires 262.1226 (3.9 ppm error).

Lab notebook reference: 6/92

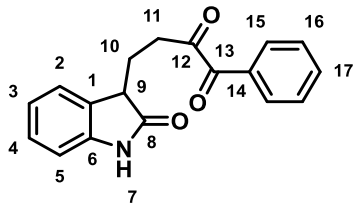
2-Phenylspiro[cyclopentane-1,3'-indol]-3-one (190a)



Synthesised using **general procedure 3C** with α-diazocarbonyl **188a** (29 mg, 0.1 mmol), Rh_2oct_4 (3.9 mg, 5.0 μmol) and deoxygenated $CHCl_3$ (1 mL). Purification by column chromatography (40→60% EtOAc in hexane, positive pressure of N_2) afforded the *title compound* **190a** (24 mg, 92%, 54:45 *dr*) as a colourless oil; ν_{max} (cm^{-1}) 1745, 1453, 734, 699; δ_H (400 MHz, $CDCl_3$) 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*); δ_C (100 MHz, $CDCl_3$) 26.7 (CH_2), 28.2 (CH_2), 36.5 (CH_2), 38.1 (CH_2), 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; $C_{18}H_{16}NO$ (MH^+) Requires 262.1226 (−1.7 ppm error).

Lab notebook reference: MJJ6/99

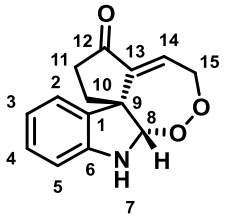
4-(2-Oxoindolin-3-yl)-1-phenylbutane-1,2-dione (198a)



To α-diazocarbonyl **188a** (57 mg, 0.197 mmol) and Rh_2oct_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; ν_{max} (cm^{-1}) 1695, 1667, 1470, 749, 691; δ_H (400 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 Hz, H-9), 6.88 (1H, d, *J* = 8.0 Hz, H-5), 7.06 (1H, dd, *J* = 8.0, 7.5 Hz, H-3), 7.20–7.30 (2H, m, H-2,4), 7.48 (2H, dd, *J* = 7.5, 7.5 Hz, H-16), 7.63 (1H, dd, *J* = 7.5, 7.5 Hz, H-17), 7.91–7.99 (3H, m, H-7,15); δ_C (100 MHz, $CDCl_3$) 23.3 (CH_2, C-10), 34.5 (CH_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; $C_{18}H_{15}NNaO_3$ (MNa^+) Requires 316.0950 (−1.6 ppm error).

Lab notebook reference: MJJ6/21

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

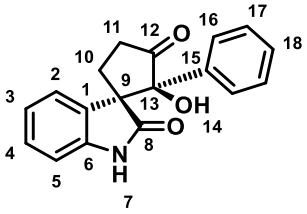


To α-diazocarbonyl **207** (53 mg, 0.221 mmol) and Rh_2oct_4 (8.6 mg, 11.1 μmol) in a flask open to air was added $CHCl_3$ (4.4 mL). The mixture was stirred at RT for 24 h then purified by column chromatography (35% EtOAc in hexane) to afford the *title compound* **208** (10 mg, 19%) as a white solid, mp 151–153 °C; ν_{max} (cm^{-1}) 3401, 2918, 1721, 1652, 1483, 1206, 1049, 745; δ_H (400 MHz, $CDCl_3$) 2.10–2.25 (2H, m, H-10), 2.58 (1H, ddd, *J* = 18.5, 7.5, 2.5 Hz, H-11a), 2.69–2.82 (1H, m, H-11b), 4.58 (1H, ddd, *J* = 20.0, 2.5, 2.0 Hz, H-15a), 4.78–4.86 (1H, m, H-7), 5.02 (1H, dd, *J* = 20.0, 2.0 Hz, H-15b), 5.51 (1H, d, *J* = 2.5 Hz, H-8), 6.68–6.76 (3H, m, H-3,5,14), 6.83 (1H, d, *J* = 7.0 Hz, H-2), 7.11 (1H, dd, *J* = 7.5, 7.5 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 35.3 (CH_2, C-10), 36.0 (CH_2, C-11), 55.5 (C, C-9), 75.2 (CH_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; $C_{14}H_{13}NNaO_3$ (MNa^+) Requires 266.0788 (2.5 ppm error).

Lab notebook reference: MJJ8/6

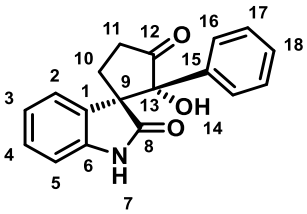
syn-2-Hydroxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (212a)



Synthesised using **general procedure 3D** with α-diazocarbonyl **188a** (29 mg, 0.1 mmol), Rh_2oct_4 (1.6 mg, 2.0 μmol) and $CHCl_3$ (2 mL) for 1 h then TFA (23 μL, 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; ν_{max} (cm^{-1}) 3257, 1746, 1703, 729, 699; δ_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); δ_C (100 MHz, $CDCl_3$) 27.4 (CH_2, C-10), 34.4 (CH_2, C-11), 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; $C_{18}H_{15}NNaO_3$ (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)

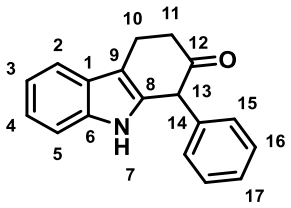


Synthesised using **general procedure 3E** with α-diazocarbonyl **188a** (29 mg, 0.1 mmol), Rh_2oct_4 (1.6 mg, 2.0 μmol) and $CHCl_3$ (2 mL) for 1 h then *t*-BuOK (34 mg, 0.3 mmol) and THF (1 mL) for 2 h. Purification by column chromatography (30→40% EtOAc in hexane) afforded the *title compound* **214a** (17 mg, 58%) as a white solid, mp 184–186 °C; ν_{max} (cm^{-1})

3276, 1742, 1697, 1471, 740; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2, C-10), 34.3 (CH_2, C-11), 61.0 (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; $C_{18}H_{15}NNaO_3$ (MH^+) Requires 316.0944 (1.0 ppm error).

Lab notebook reference: MJJ7/7

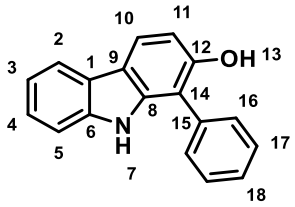
1-Phenyl-3,4-dihydro-1*H*-carbazol-2(9*H*)-one (199a)



Synthesised using **general procedure 3F** with α-diazocarbonyl **188a** (57 mg, 0.197 mmol), $Pd(MeCN)_4(BF_4)_2$ (4.4 mg, 9.85 μmol) and $CHCl_3$ (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; ν_{max} (cm^{-1}) 3395, 1713, 1455, 1236, 741; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2, C-10), 36.8 (CH_2, 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; $C_{18}H_{16}NO$ (MH^+) Requires 262.1226 (−4.6 ppm error).

Lab notebook reference: MJJ6/35

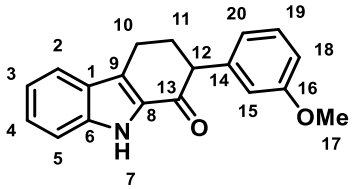
1-Phenyl-9*H*-carbazol-2-ol (200a)



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; ν_{max} (cm^{-1}) 3389, 1460, 1175, 739; δ_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); δ_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), 130.05 (2CH, C-16/17), 130.09 (2CH, C-16/17), 133.0 (C, C-6/8/15), 139.0 (C, C-6/8/15), 139.4 (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-1*H*-carbazol-1-one (193b)

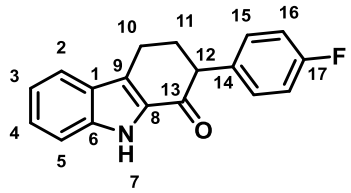


Synthesised using **general procedure 3H** with α-diazocarbonyl **188b** (32 mg, 0.10 mmol), silica gel (32 mg) and CH_2Cl_2 (1 mL). Purification by column chromatography (50% Et_2O in hexane) afforded the *title compound* **193b** (19 mg, 65%) as a white solid, mp 146–148 °C; ν_{max} (cm^{-1}) 3279, 1646, 1251, 739; δ_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); δ_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; $C_{19}H_{18}NO_2$ (MH^+) Requires 292.1332 (3.8 ppm error).

Lab notebook reference: MJJ7/37

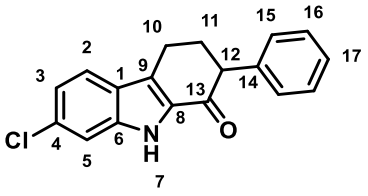
2-(4-Fluorophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (193c)



Synthesised using **general procedure 3H** with α-diazocarbonyl **188c** (61 mg, 0.2 mmol), silica gel (61 mg) and CH_2Cl_2 (2 mL). Purification by column chromatography (40% Et_2O in hexane) afforded the *title compound* **193c** (28 mg, 50%) as an off-white solid, mp 185–187 °C; ν_{max} (cm^{-1}) 3277, 1640, 1510, 1228, 742; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.6 (CH_2, C-10), 33.5 (CH_2, 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); δ_F (376 MHz, $CDCl_3$) −115.7–−115.9 (1F, m); HRMS (ESI^+): Found: 302.0954; $C_{18}H_{14}FNNaO$ (MNa^+) Requires 302.0952 (−0.9 ppm error), Found: 280.1133; $C_{18}H_{15}FNO$ (MH^+) Requires 280.1132 (−0.2 ppm error).

Lab notebook reference: MJJ7/57

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

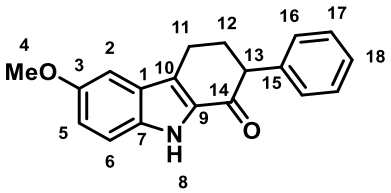


Synthesised using **general procedure 3H** with α-diazocarbonyl **188d** (65 mg, 0.2 mmol), silica gel (65 mg) and CH_2Cl_2 (2 mL). Purification by column chromatography (0→1% MeOH in CH_2Cl_2) afforded the *title compound* **193d** (44 mg, 75%) as a white solid, mp 230–232 °C; ν_{max} (cm^{-1}) 3241, 1649, 1636, 936, 737, 698; δ_H (400 MHz, DMSO-d_6) 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); δ_C (100 MHz, DMSO-d_6) 20.2 (CH_2, C-10), 33.0 (CH_2, 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; $C_{18}H_{14}{}^{35}ClNNaO$ (MNa^+) Requires 318.0656 (−0.6 ppm error), Found: 296.0837; $C_{18}H_{15}{}^{35}ClNO$ (MH^+) Requires 296.0837 (0.0 ppm error).

Lab notebook reference: MJJ7/67

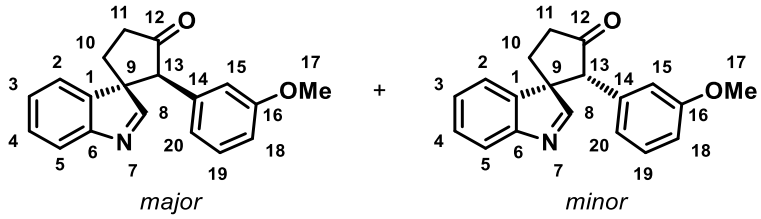
7-Chloro-2-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (193e)



Synthesised using **general procedure 3H** with α-diazocarbonyl **188e** (64 mg, 0.2 mmol), silica gel (64 mg) and CH_2Cl_2 (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 CH_2Cl_2:Et_2O (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; ν_{max} (cm^{-1}) 3268, 1638, 1483, 1215; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2, C-11), 33.4 (CH_2, C-12), 53.7 (CH, C-13), 55.7 (CH_3, 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; $C_{19}H_{17}NNaO_2$ (MNa^+) Requires 314.1151 (−1.1 ppm error).

Lab notebook reference: MJJ7/80

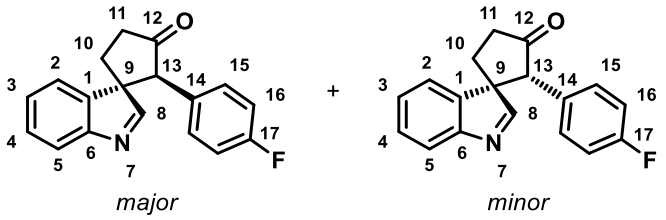
2-(3-Methoxyphenyl)spiro[cyclopentane-1,3'-indol]-3-one (190b)



Synthesised using **general procedure 3C** with α-diazocarbonyl **188b** (48 mg, 0.15 mmol), Rh_2oct_4 (5.8 mg, 7.5 μmol) and deoxygenated $CHCl_3$ (1.5 mL). Purification by column chromatography (40→70% EtOAc in hexane, positive pressure of N_2) afforded the *title compound* **190b** (31 mg, 71%, 78:22 *dr*) as a colourless oil; ν_{max} (cm^{-1}) 1740, 1600, 1455, 1248, 733; δ_H (400 MHz, $CDCl_3$) 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*); δ_C (100 MHz, $CDCl_3$) 26.8 (CH_2), 28.2 (CH_2), 36.4 (CH_2), 38.2 (CH_2), 55.0 ($2CH_3$), 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; $C_{19}H_{17}NNaO_2$ (MNa^+) Requires 314.1151 (−0.0 ppm error).

Lab notebook reference: MJJ7/64

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

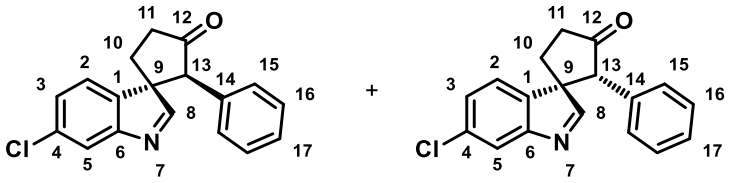


Synthesised using **general procedure 3C** with α-diazocarbonyl **188c** (61 mg, 0.199 mmol), Rh_2oct_4 (7.7 mg, 9.95 μmol) and deoxygenated $CHCl_3$ (2 mL). Purification by column

chromatography (40→70% EtOAc in hexane, positive pressure of N_2) afforded the *title compound* **190c** (37 mg, 66%, 61:39 *dr*) as a pale brown oil; ν_{max} (cm^{-1}) 1742, 1511, 1225, 733; δ_H (400 MHz, $CDCl_3$) 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*); δ_C (100 MHz, $CDCl_3$) 26.4 (CH_2), 27.9 (CH_2), 36.2 (CH_2), 37.9 (CH_2), 59.1 (CH), 61.8 (CH), 65.9 (C), 66.1 (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); δ_F (376 MHz, $CDCl_3$) −114.03–−114.14 (1F, m, *major*), −114.3–−114.4 (1F, m, *minor*); HRMS (ESI^+): Found: 280.1125; $C_{18}H_{15}FNO$ (MH^+) Requires 280.1132 (2.4 ppm error).

Lab notebook reference: MJJ7/66

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



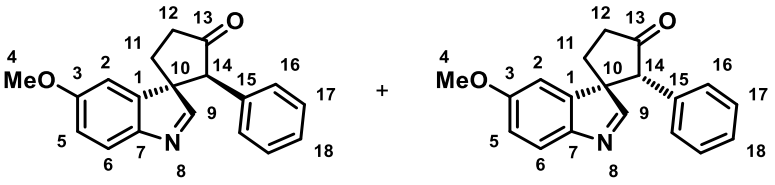
major *minor*

Synthesised using **general procedure 3C** with α-diazocarbonyl **188d** (49 mg, 0.15 mmol), Rh_2oct_4 (5.8 mg, 7.5 μmol) and deoxygenated $CHCl_3$ (4.5 mL). Purification by column chromatography (40→70% EtOAc in hexane, positive pressure of N_2) afforded the *title compound* **190d** (24 mg, 54%, 58:42 *dr*) as a pale brown oil; ν_{max} (cm^{-1}) 1745, 1453, 735, 699; δ_H (400 MHz, $CDCl_3$) 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*); δ_C (100 MHz, $CDCl_3$) 26.7 (CH_2), 28.1 (CH_2), 36.5 (CH_2), 38.0 (CH_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; $C_{18}H_{14}{}^{35}ClNNaO$ (MNa^+) Requires 318.0656 (−2.9 ppm error), Found: 296.0831; $C_{18}H_{15}{}^{35}ClNO$ (MH^+) Requires 296.0837 (1.8 ppm error).

Lab notebook reference: MJJ7/88

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

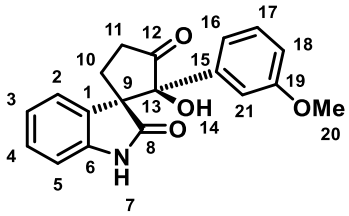


major *minor*

Synthesised using **general procedure 3C** with α-diazocarbonyl **188e** (64 mg, 0.20 mmol), Rh_2oct_4 (7.8 mg, 10.0 μmol) and deoxygenated $CHCl_3$ (2 mL). Purification by column chromatography (40→80% EtOAc in hexane, positive pressure of N_2) afforded the *title compound* **190e** (34 mg, 59%, 63:37 *dr*) as a colourless oil; ν_{max} (cm^{-1}) 1744, 1470, 1284, 1027, 734, 699; δ_H (400 MHz, $CDCl_3$) 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* = 13.0, 9.5, 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*); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 28.6 (CH_2), 36.5 (CH_2), 38.1 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 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; $C_{19}H_{18}NO_2$ (MH^+) Requires 292.1332 (−2.5 ppm error).

Lab notebook reference: MJJ7/89

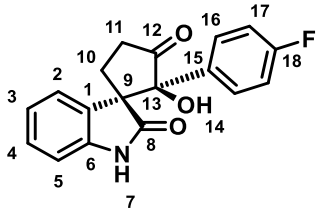
***syn*-2-Hydroxy-2-(3-methoxyphenyl)spiro[cyclopentane-1,3'-indoline]-2',3-dione (212b)**



Synthesised using **general procedure 3D** with α-diazocarbonyl **188b** (48 mg, 0.15 mmol), Rh_2oct_4 (2.3 mg, 3.0 μmol) and $CHCl_3$ (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, $CDCl_3$) 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, $CDCl_3$) 27.3 (CH_2, C-10), 34.4 (CH_2, C-11), 55.2 (CH_3, 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; $C_{19}H_{17}NNaO_4$ (MNa^+) 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)**

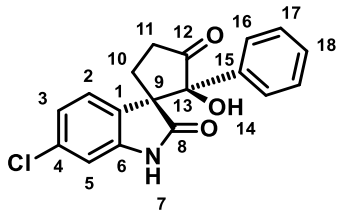


Synthesised using **general procedure 3D** with α-diazocarbonyl **188c** (61 mg, 0.20 mmol), Rh_2oct_4 (3.1 mg, 4.0 μmol) and $CHCl_3$ (4 mL) for 1 h then TFA (46 μL, 0.60 mmol) and THF (2 mL) for 4 h. Purification by column chromatography (50% EtOAc in hexane) afforded the *title compound* **212c** (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, $CDCl_3$) 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-

5), 6.96–7.03 (2H, m, H-17), 7.08–7.14 (2H, m, H-16), 7.18 (1H, dd, *J* = 8.0, 8.0 Hz, H-4), 7.72 (1H, br s); δ_C (100 MHz, $CDCl_3$) 27.3 (CH_2, C-10), 34.2 (CH_2, C-11), 59.7 (C, C-9), 84.1 (C, C-13), 110.1 (CH, C-5), 115.0 (2CH, d, *J* = 22.0 Hz, C-17), 122.1 (CH, C-3), 125.1 (CH, C-2), 127.8 (C, C-1), 128.7 (2CH, d, *J* = 8.5 Hz, C-16), 128.8 (CH, C-4), 133.1 (C, d, *J* = 4.0 Hz, C-15), 141.1 (C, C-6), 162.5 (C, d, *J* = 248 Hz, C-18), 180.3 (C, C-8), 215.2 (C, C-12); δ_F (376 MHz, $CDCl_3$) –112.8–−112.9 (1F, m); HRMS (ESI^+): Found: 334.0857; $C_{18}H_{14}FNNaO_3$ (MNa^+) Requires 334.0850 (−2.2 ppm error).

Lab notebook reference: MJJ7/61

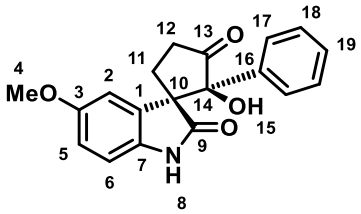
syn-6'-Chloro-2-hydroxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (212d)



Synthesised using **general procedure 3D** with α-diazocarbonyl **188d** (65 mg, 0.20 mmol), Rh_2oct_4 (3.1 mg, 4.0 μmol) and $CHCl_3$ (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; ν_{max} (cm^{-1}) 3258, 1743, 1702, 1207, 744, 696; δ_H (400 MHz, DMSO-d_6) 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); δ_C (100 MHz, DMSO-d_6) 26.5 (CH_2, C-10), 34.5 (CH_2, 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; $C_{18}H_{14}{}^{35}ClNNaO_3$ (MNa^+) Requires 350.0554 (−3.8 ppm error).

Lab notebook reference: MJJ7/71

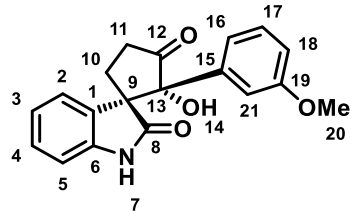
syn-2-Hydroxy-5'-methoxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (212e)



Synthesised using **general procedure 3D** with α-diazocarbonyl **188e** (64 mg, 0.20 mmol), Rh_2oct_4 (3.1 mg, 4.0 μmol) and $CHCl_3$ (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_{max} (cm^{-1}) 3262, 1739, 1690, 1489, 1205, 700, 615; δ_H (400 MHz, DMSO-d_6) 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_C (100 MHz, DMSO-d_6) 27.0 (CH_2, C-11), 34.5 (CH_2, C-12), 54.9 (CH_3, 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; $C_{19}H_{17}NNaO_4$ (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)

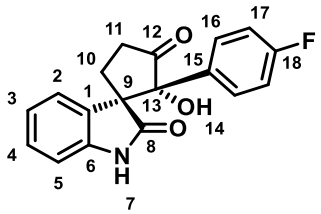


Synthesised using **general procedure 3E** with α-diazocarbonyl **188b** (48 mg, 0.15 mmol), Rh_2oct_4 (2.3 mg, 3.0 μmol) and $CHCl_3$ (3 mL) for 1 h then *t*-BuOK (51 mg, 0.45 mmol) and THF (1.5 mL) for 2 h. Purification by column chromatography (40% EtOAc in hexane) afforded the *title compound* **214b** (21 mg, 54%) as a white solid, mp 208–210 °C; ν_{max} (cm^{-1}) 3348, 3240, 1745, 1685, 1211, 760, 691; δ_H (400 MHz, DMSO-d_6) 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_C (100 MHz, DMSO-d_6) 27.7 (CH_2, C-10), 33.5 (CH_2, C-11), 54.6 (CH_3, C-20),

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; $C_{19}H_{17}NNaO_4$ (MNa^+) Requires 346.1050 (0.9 ppm error), Found: 324.1230; $C_{19}H_{18}NO_4$ (MH^+) Requires 324.1230 (0.2 ppm error).

Lab notebook reference: MJJ7/44

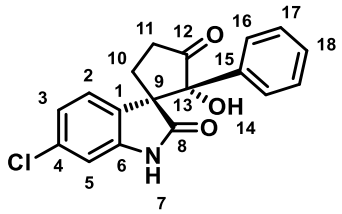
anti-2-(4-Fluorophenyl)-2-hydroxyspiro[cyclopentane-1,3'-indoline]-2',3-dione (214c)



Synthesised using **general procedure 3E** with α-diazocarbonyl **188c** (61 mg, 0.20 mmol), Rh_2oct_4 (3.1 mg, 4.0 μmol) and $CHCl_3$ (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; ν_{max} (cm^{-1}) 3416, 1748, 1698, 1470, 1219, 824, 759, 750, 538, 526; δ_H (400 MHz, DMSO-d_6) 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-d_6) 28.1 (CH_2, C-10), 33.9 (CH_2, 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-d_6) –114.8–−114.9 (1F, m); HRMS (ESI^+): Found: 334.0838; $C_{18}H_{14}FNNaO_3$ (MNa^+) Requires 334.0850 (3.7 ppm error).

Lab notebook reference: MJJ7/62

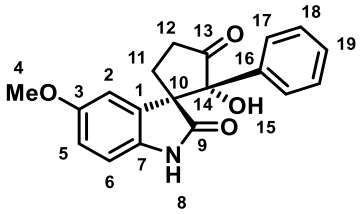
***anti*-6'-Chloro-2-hydroxy-2-phenylspiro[cyclopentane-1,3'-indoline]-2',3-dione (214d)**



Synthesised using **general procedure 3E** with α-diazocarbonyl **188d** (49 mg, 0.15 mmol), Rh_2oct_4 (2.3 mg, 3.0 μmol) and $CHCl_3$ (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; ν_{max} (cm^{-1}) 3237, 1737, 1698, 1617, 749, 694; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2, C-10), 34.2 (CH_2, 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; $C_{18}H_{14}{}^{35}ClNNaO_3$ (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)**

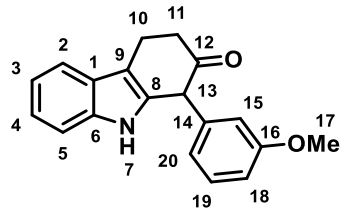


Synthesised using **general procedure 3E** with α-diazocarbonyl **188e** (64 mg, 0.20 mmol), Rh_2oct_4 (3.1 mg, 4.0 μmol) and $CHCl_3$ (4 mL) for 1 h then *t*-BuOK (67 mg, 0.60 mmol) and THF (2 mL) for 2 h. Purification by column chromatography (50% EtOAc in hexane) afforded the *title compound* **214e** (26 mg, 40%) as an off-white solid, mp 194–196 °C; ν_{max} (cm^{-1}) 3221, 1742, 1684, 1491, 1201, 1032, 751, 696; δ_H (400 MHz, DMSO-d_6) 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); δ_C (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; $C_{19}H_{17}NNaO_4$ (MNa^+) Requires 346.1050 (1.0 ppm error).

Lab notebook reference: MJJ7/84

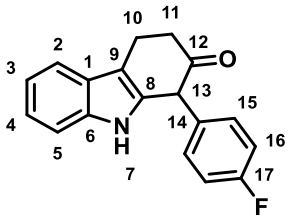
1-(3-Methoxyphenyl)-3,4-dihydro-1*H*-carbazol-2(9*H*)-one (199b)



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, 1454, 1260, 1236, 737; δ_H (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); δ_C (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; $C_{19}H_{17}NNaO_2$ (MNa^+) 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

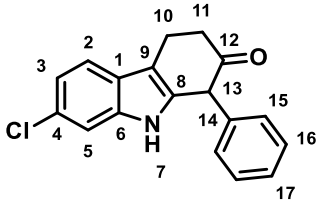
1-(4-Fluorophenyl)-3,4-dihydro-1*H*-carbazol-2(9*H*)-one (199c)



Synthesised using **general procedure 3F** with α-diazocarbonyl **188c** (61 mg, 0.20 mmol), $Pd(MeCN)_4(BF_4)_2$ (4.4 mg, 10 μmol) and $CHCl_3$ (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; ν_{max} (cm^{-1}) 3394, 1714, 1505, 1224, 741; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2, C-10), 36.7 (CH_2, 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); δ_F (376 MHz, $CDCl_3$) −114.2–−114.3 (1F, m); HRMS (ESI^+): Found: 280.1142; $C_{18}H_{15}FNO$ (MH^+) Requires 280.1132 (−3.4 ppm error).

Lab notebook reference: MJJ7/58

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

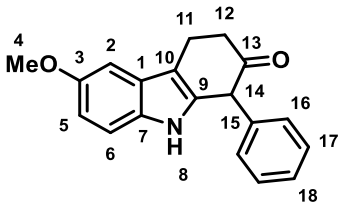


Synthesised using **general procedure 3F** with α-diazocarbonyl **188d** (65 mg, 0.20 mmol), $Pd(MeCN)_4(BF_4)_2$ (4.4 mg, 10 μmol) and $CHCl_3$ (2 mL). Purification by column chromatography (20% EtOAc in hexane) afforded the *title compound* **199d** (38 mg, 64%) as a white solid, mp 222–224 °C; ν_{max} (cm^{-1}) 3353, 1712, 1465, 1453, 909, 735, 705; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 20.1 (CH_2, C-10), 36.6 (CH_2, 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; $C_{18}H_{14}{}^{35}ClNNaO$ (MNa^+) Requires 318.0656 (0.9 ppm error), Found: 296.0843; $C_{18}H_{15}{}^{35}ClNO$ (MH^+) Requires 296.0837 (−2.2 ppm error).

Lab notebook reference: MJJ7/68

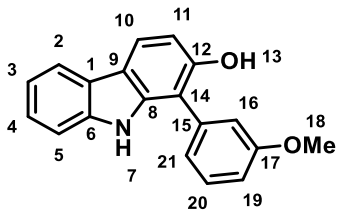
6-Methoxy-1-phenyl-3,4-dihydro-1*H*-carbazol-2(9*H*)-one (199e)



Synthesised using **general procedure 3F** with α-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; ν_{max} (cm^{-1}) 3395, 1714, 1485, 1456, 1217; δ_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); δ_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)

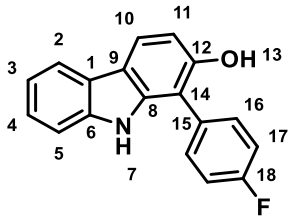


Synthesised using **general procedure 3G** with α-diazocarbonyl **188b** (48 mg, 0.15 mmol), $Cu(OTf)_2$ (10.9 mg, 30 μmol) and $CHCl_3$ (3 mL). Purification by column chromatography (20→30% EtOAc in hexane) afforded the *title compound* **200b** (31 mg, 71%) as an off-white

solid, mp 146–148 °C; ν_{max} (cm^{-1}) 3409, 1604, 1460, 1413, 1219, 1178, 1166, 737; δ_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); δ_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; $C_{19}H_{15}NNaO_2$ (MNa^+) 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

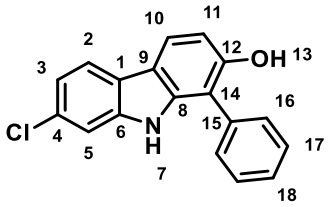
1-(4-Fluorophenyl)-9*H*-carbazol-2-ol (200c)



Synthesised using **general procedure 3G** with α-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; ν_{max} (cm^{-1}) 3457, 1603, 1459, 1222, 1157, 840, 737; δ_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); δ_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); δ_F (376 MHz, $CDCl_3$) −112.5–−112.6 (1F, m); HRMS (ESI^+): Found: 300.0810; $C_{18}H_{12}FNNaO$ (MNa^+) Requires 300.0795 (−4.9 ppm error), Found: 278.0971; $C_{18}H_{13}FNO$ (MH^+) Requires 278.0976 (1.6 ppm error).

Lab notebook reference: MJJ7/60

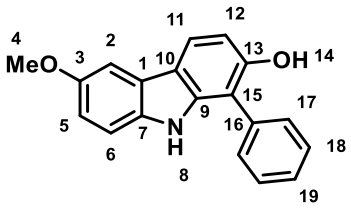
7-Chloro-1-phenyl-9*H*-carbazol-2-ol (200d)



Synthesised using **general procedure 3G** with α-diazocarbonyl **188d** (65 mg, 0.20 mmol), $Cu(OTf)_2$ (14.5 mg, 40 μmol) and $CHCl_3$ (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, $CDCl_3$) 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, $CDCl_3$) 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; $C_{18}H_{12}{}^{35}ClNNaO$ (MNa^+) Requires 316.0500 (0.3 ppm error), Found: 294.0681; $C_{18}H_{13}{}^{35}ClNO$ (MH^+) Requires 294.0680 (−0.2 ppm error).

Lab notebook reference: MJJ7/69

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



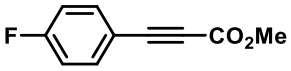
Synthesised using **general procedure 3G** with α-diazocarbonyl **188e** (64 mg, 0.20 mmol), $Cu(OTf)_2$ (14.5 mg, 40 μmol) and $CHCl_3$ (4 mL). Purification by column chromatography (30% EtOAc in hexane) afforded the *title compound* **200e** (20 mg, 35%) as a brown oil; ν_{max} (cm^{-1}) 3415, 1612, 1483, 1288, 1165; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 56.0 (CH_3, 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

(C, C-7/9/16), 134.2 (C, C-7/9/16), 139.8 (C, C-7/9/16), 151.0 (C, C-13), 154.0 (C, C-3); 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)

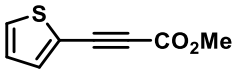


To a solution of 1-ethynyl-4-fluorobenzene (533 mg, 4.44 mmol) in THF (44 mL) at −78 °C was added *n*-BuLi (1.95 mL, 4.88 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.38 mL, 4.88 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL) and diluted with Et_2O (20 mL). The organics were separated and the aqueous extracted with Et_2O (3 × 30 mL). The organics were combined, washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0 → 5% Et_2O in hexane) to afford the *title compound* **269a** (494 mg, 62%) as a white solid, mp 57–59 °C (lit.[156] 57–59 °C); ν_{max} (cm^{-1}) 2224, 1708, 1304, 1203, 833; δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s), 7.08 (2H, dd, *J* = 8.5, 8.0 Hz), 7.59 (2H, dd, *J* = 8.5, 5.5 Hz); δ_C (100 MHz, $CDCl_3$) 52.8 (CH_3), 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); δ_F (376 MHz, $CDCl_3$) −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)

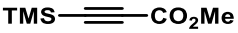


To a solution of 2-ethynylthiophene (0.5 mL, 4.99 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.20 mL, 5.49 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.42 mL, 5.49 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (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 ($MgSO_4$), 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); ν_{max} (cm^{-1}) 2207, 1709, 1269, 1221, 1160; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 52.8 (CH_3), 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)

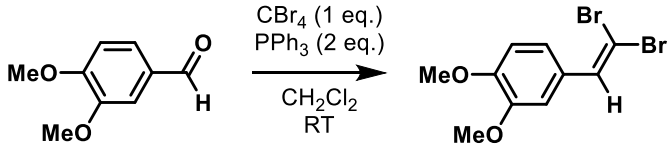


To a solution of ethynyltrimethylsilane (0.5 mL, 3.62 mmol) in THF (36 mL) at −78 °C was added *n*-BuLi (1.59 mL, 3.98 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred at −78 °C for 30 min before methyl chloroformate (0.31 mL, 3.98 mmol) was added dropwise. The mixture was stirred at −78 °C for a further 2 h before being quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (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 ($MgSO_4$), 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; δ_H (400 MHz, $CDCl_3$) 0.25 (9H, s), 3.78 (3H, s); δ_C (100 MHz, $CDCl_3$) −0.9 ($3CH_3$), 52.7 (CH_3), 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)



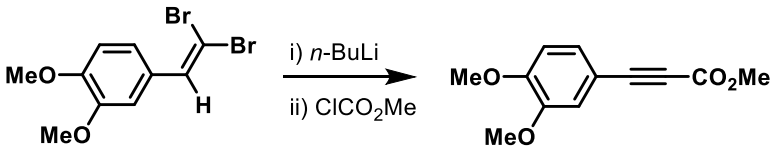
To a suspension of CBr_4 (20.0 g, 60.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added PPh_3 (31.6 g, 120.4 mmol) portionwise and the mixture was stirred at 0 °C for 30 min. 3,4-dimethoxybenzaldehyde (10 g, 60.2 mmol) was then added and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture 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 CH_2Cl_2:hexane (2 × 100 mL) and the organics were combined, dried ($MgSO_4$) 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; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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)

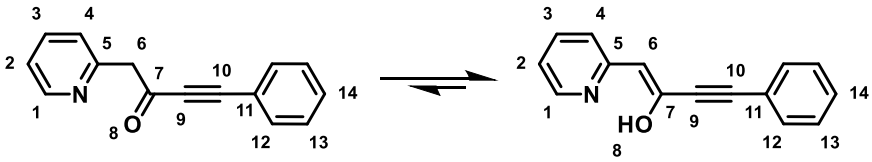


To a solution of dibromide **271** (15.3 g, 47.5 mmol) in THF (190 mL) at −78 °C was added *n*-BuLi (62 mL, 99.8 mmol, 2.5 M in hexanes) dropwise and the mixture was stirred at −78 °C for 45 min then at 0 °C for 45 min. The mixture was then recooled to −78 °C and methylchloroformate (3.67 mL, 97.5 mmol) was added dropwise. The mixture was stirred at 0 °C for 2h then quenched with sat. $NH_4Cl_{(aq)}$ (100 mL) and the organics were separated. The aqueous was further extracted with Et_2O (2 × 100 mL) and the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by successive recystallisations (EtOAc:hexane, washing with cold hexane and Et_2O) 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); ν_{max} (cm^{-1}) 2211, 1708, 1515, 1252, 1232, 1157, 1137, 1023; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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)

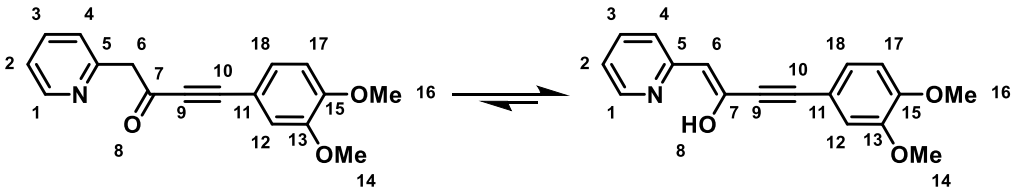


Synthesised using **general procedure 4A** with DIPA (0.60 mL, 4.26 mmol), *n*-BuLi (1.70 mL, 4.26 mmol, 2.5 M in hexanes), 2-methylpyridine (0.20 mL, 2.03 mmol), methyl phenylpropiolate (0.31 mL, 2.13 mmol) and THF (30 mL). Purification by column

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; ν_{max} (cm^{-1}) 1741, 1694, 1491, 1388, 1366, 1160; δ_H (400 MHz, $CDCl_3$) 4.19 (2H, s, H-6, *keto*), 5.90 (1H, s, H-6, *enol*), 6.97–7.06 (2H, m, H-2,4 *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, ddd, *J* = 8.0, 8.0, 2.0 Hz, H-3, *enol*), 7.71 (1H, ddd, *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*); ^{13}C NMR data of enol tautomer δ_C (100 MHz, $CDCl_3$) 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 ^{13}C NMR data of keto tautomer δ_C (100 MHz, $CDCl_3$) 54.3 (CH_2, C-6); HRMS (ESI^+): Found: 222.0915; $C_{15}H_{12}NO$ (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)

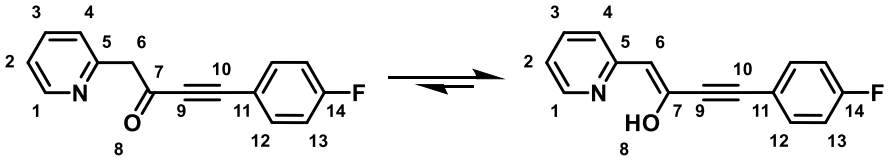


Synthesised using **general procedure 4A** with DIPA (2.94 mL, 21.0 mmol), *n*-BuLi (8.4 mL, 21.0 mmol, 2.5 M in hexanes), 2-methylpyridine (0.99 mL, 10.0 mmol) in THF (100 mL) and a solution of ester **269d** (2.31 g, 10.5 mmol) in THF (50 mL). Purification by column chromatography (40% EtOAc in hexane) afforded the *title compound* **228b** (2.11 g, 75%, 77:23 *enol*:*keto*) as a yellow solid, mp 78–80 °C; ν_{max} (cm^{-1}) 2200, 1595, 113, 1252, 1023, 808; δ_H (400 MHz, $CDCl_3$) 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*); ^{13}C NMR data of enol tautomer δ_C (100 MHz, $CDCl_3$) 55.86 (CH_3, C-14/16), 55.89 (CH_3, 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 δ_C (100 MHz, $CDCl_3$) 54.2 (CH_2, C-6); HRMS (ESI$^+$): Found: 304.0944; $C_{17}H_{15}NNaO_3$ (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

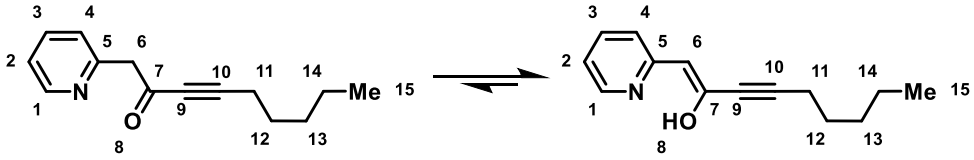
4-(4-Fluorophenyl)-1-(pyridin-2-yl)but-3-yn-2-one (228c)



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; ν_{max} (cm^{-1}) 1620, 1597, 1507, 1374, 1224, 834, 801; δ_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 δ_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 δ_C (100 MHz, $CDCl_3$) 54.3 (CH_2, C-6); δ_F (376 MHz, $CDCl_3$) −105.7–−105.8 (1F, m, *keto*), −109.4–−109.5 (1F, m, *enol*); HRMS (ESI$^+$): Found: 240.0810; $C_{15}H_{11}FNO$ (MH^+) Requires 240.0819 (4.0 ppm error).

Lab notebook reference: MJJ8/56

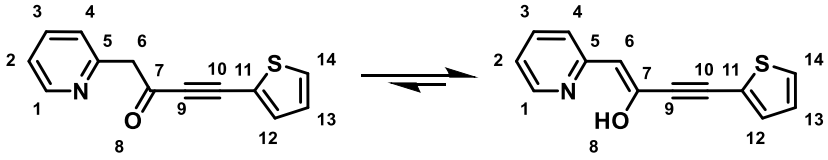
1-(Pyridin-2-yl)non-3-yn-2-one (228d)



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%, 67:37 *enol*:*keto*) as a yellow oil; ν_{max} (cm^{-1}) 2930, 2228, 1618, 1594, 1550, 1470, 1361, 1151, 805, 739; δ_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, ddd, *J* = 8.0, 8.0, 1.5 Hz, H-3, *enol*), 7.68 (1H, ddd, *J* = 8.0, 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 δ_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 δ_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: MJJ8/44

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

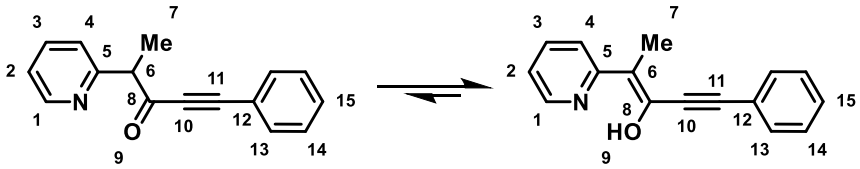


Synthesised using **general procedure 4A** with DIPA (0.30 mL, 2.12 mmol), *n*-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyridine (0.1 mL, 1.01 mmol) in THF (10 mL) and a solution of methyl ester **269b** (176 mg, 1.06 mmol) in THF (5 mL). Purification by column chromatography (20% EtOAc in 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.); ν_{max} (cm^{-1}) 2198, 1615, 1552, 1472, 705; δ_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 δ_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 δ_C (100 MHz, $CDCl_3$) 54.0 (CH_2, C-6); HRMS (ESI^+): Found: 228.0470; $C_{13}H_{10}NOS$ (MH^+) Requires 228.0478 (3.5 ppm error).

Lab notebook reference: MJJ8/60

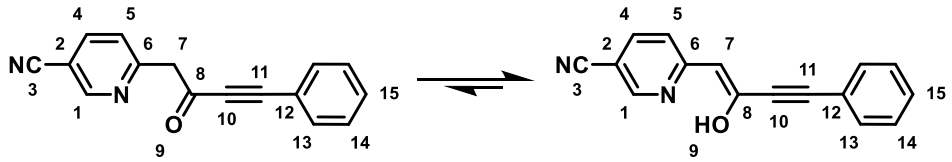
1-Phenyl-4-(pyridin-2-yl)pent-1-yn-3-one (228f)



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.); ν_{max} (cm^{-1}) 1589, 1551, 1488, 1461, 755, 690; ^{1}H NMR data of enol tautomer δ_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 δ_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 δ_C (100 MHz, $CDCl_3$) 56.9 (CH, C-6); HRMS (ESI^+): Found: 258.0887 $C_{16}H_{13}NNaO$ (MNa^+) Requires 258.0889 (0.7 ppm error), Found: 236.1078; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (−3.5 ppm error).

Lab notebook reference: MJJ8/52

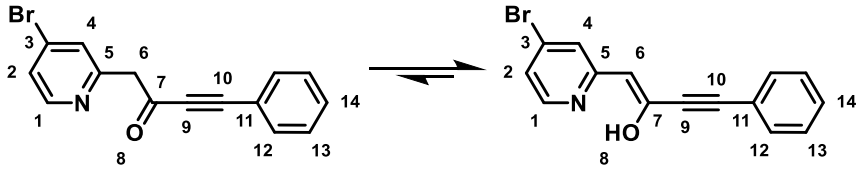
6-(2-Oxo-4-phenylbut-3-yn-1-yl)nicotinonitrile (228g)



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; ν_{max} (cm^{-1}) 2227, 2196, 1638, 1587, 1521, 1162, 837, 749, 688, 551; ^{1}H NMR of enol tautomer δ_H (400 MHz, $CDCl_3$) 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); ^{13}C NMR data of enol tautomer δ_C (100 MHz, $CDCl_3$) 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 ^{13}C NMR data of keto tautomer δ_C (100 MHz, $CDCl_3$) 54.1 (CH_2, C-7); HRMS (ESI^+): Found: 247.0869; $C_{16}H_{11}N_2O$ (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)

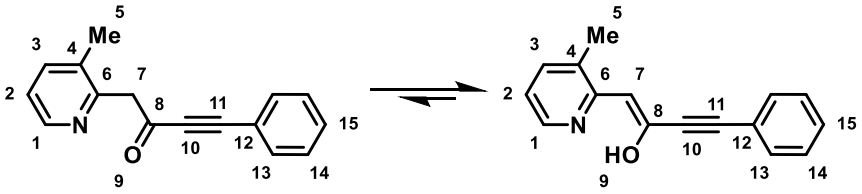


Synthesised using **general procedure 4A** with DIPA (0.25 mL, 1.76 mmol), *n*-BuLi (0.70 mL, 1.76 mmol, 2.5 M in hexanes), 4-bromo-2-methylpyridine (0.10 mL, 0.84 mmol), methyl phenylpropiolate (0.14 mL, 0.92 mmol) and THF (13 mL). Purification by column chromatography (10% EtOAc in hexane) afforded the *title compound* **228h** (221 mg, 88%, 76:24 *enol*:*keto*) as a yellow solid, mp 93–95 °C; ν_{max} (cm^{-1}) 2202, 1616, 1573, 1531, 756, 690; δ_H (400 MHz, $CDCl_3$) 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*); ^{13}C NMR data of enol tautomer δ_C (100 MHz, $CDCl_3$) 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

(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 δ_C (100 MHz, $CDCl_3$) 53.8 (CH_2); HRMS (ESI^+): Found: 300.0006; $C_{15}H_{11}{}^{79}BrNO$ (MH^+) Requires 300.0019 (4.3 ppm error).

Lab notebook reference: MJJ8/33

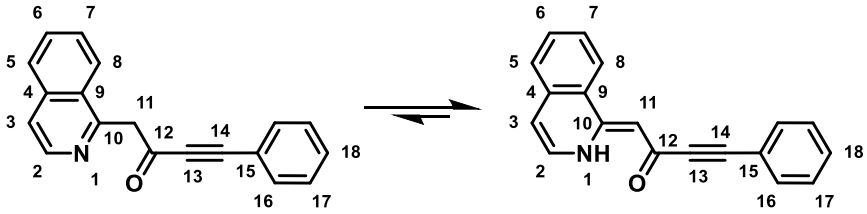
1-(3-Methylpyridin-2-yl)-4-phenylbut-3-yn-2-one (228i)



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; ν_{max} (cm^{-1}) 2202, 1589, 1562, 1435, 757, 690; δ_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 δ_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 δ_C (100 MHz, $CDCl_3$) 52.6 (CH_2, C-7); HRMS (ESI^+): Found: 236.1062; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (3.3 ppm error).

Lab notebook reference: MJJ8/64

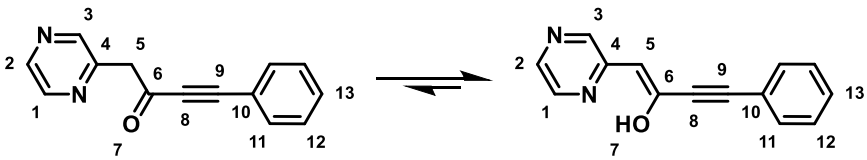
1-(Isoquinolin-1-yl)-4-phenylbut-3-yn-2-one (228j)



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; ν_{max} (cm^{-1}) 1588, 1550, 1493, 1250, 1207, 1143; δ_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); δ_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)

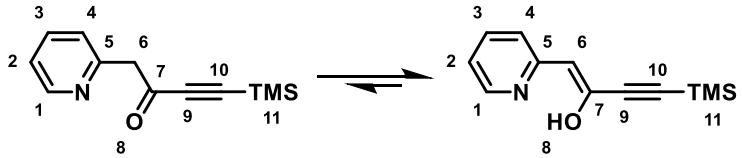


Synthesised using **general procedure 4A** with DIPA (0.30 mL, 2.12 mmol), *n*-BuLi (0.85 mL, 2.12 mmol, 2.5 M in hexanes), 2-methylpyrazine (0.09 mL, 1.01 mmol), methyl phenylpropiolate (0.16 mL, 1.06 mmol) and THF (15 mL) (**Note:** Reaction stirred at −78 °C for 1 h after the addition of the methyl 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; ν_{max} (cm^{-1}) 1618, 1506, 1117, 755; ^{1}H NMR data of enol tautomer δ_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 δ_C (100 MHz, $CDCl_3$) 85.1 (C, C-8),

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 δ_C (100 MHz, $CDCl_3$) 51.5 (CH_2, C-5); HRMS (ESI^+): Found: 245.0692; $C_{14}H_{10}N_2NaO$ (MNa^+) Requires 245.0685 (−2.6 ppm error).

Lab notebook reference: MJJ8/43

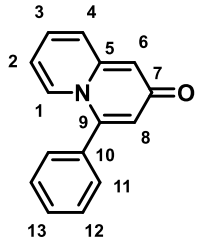
1-(Pyridin-2-yl)-4-(trimethylsilyl)but-3-yn-2-one (228l)



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; ν_{max} (cm^{-1}) 1617, 1595, 1552, 1472, 1249, 1149, 932, 843; δ_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, 1.5 Hz, H-3, *enol*), 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 δ_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 δ_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

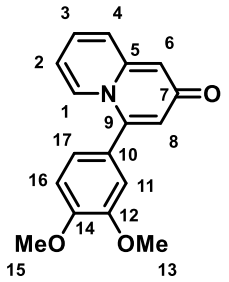
4-Phenyl-2*H*-quinolizin-2-one (229a)



Synthesised using **general procedure 4B** with pyridine-ynone **228a** (66 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 → 20% MeOH in EtOAc) afforded the *title compound* **229a** (64 mg, 97%) as a pale brown solid, mp 174–176 °C; ν_{max} (cm^{-1}) 3378, 1620, 1576, 1505, 749, 703; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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; $C_{15}H_{11}NNaO$ (MNa^+) Requires 244.0733 (−2.1 ppm error), Found: 222.0923; $C_{15}H_{12}NO$ (MH^+) Requires 222.0913 (−4.5 ppm error).

Lab notebook reference: MJJ8/51

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

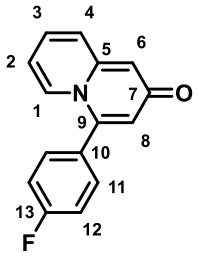


Synthesised using **general procedure 4B** with pyridine-ynone **228b** (2.11 g, 7.50 mmol), $AgNO_3$ (25.5 mg, 0.15 mmol) in DCE (37.5 mL) and EtOH (37.5 mL) for 4 h. Purification by column chromatography (5 → 20% MeOH in EtOAc) afforded the *title compound* **229b** (2.09 g, 99%) as a pale brown solid, mp 211–213 °C; ν_{max} (cm^{-1}) 3379, 1622, 1576, 1516, 1491, 1263, 1022, 756; δ_H (400 MHz, $CDCl_3$) 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

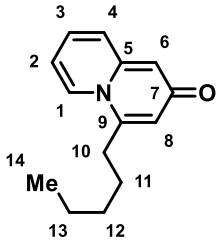
4-(4-Fluorophenyl)-2*H*-quinolizin-2-one (229c)



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; ν_{max} (cm^{-1}) 3380, 1623, 1577, 1515, 1486; δ_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); δ_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); δ_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

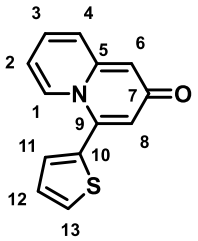
4-Pentyl-2*H*-quinolizin-2-one (229d)



Synthesised using **general procedure 4B** with pyridine-ynone **228d** (153 mg, 0.711 mmol), $AgNO_3$ (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; ν_{max} (cm^{-1}) 3369, 1622, 1574, 1489, 1177, 726; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 13.8 (CH_3, C-14), 22.3 (CH_2, C-12/13), 26.2 (CH_2, C-11), 31.3 (CH_2, C-12/13), 32.4 (CH_2, C-10), 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; $C_{14}H_{18}NO$ (MH^+) Requires 216.1383 (1.1 ppm error).

Lab notebook reference: MJJ8/46

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

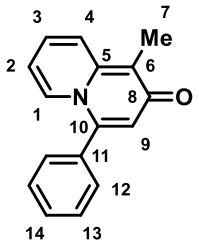


Synthesised using **general procedure 4B** with pyridine-ynone **228e** (80 mg, 0.352 mmol), $AgNO_3$ (1.2 mg, 7.0 μmol) in DCE (1.8 mL) and EtOH (1.8 mL) for 9 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **229e** (47 mg, 59%) as a brown oil; ν_{max} (cm^{-1}) 3379, 1618, 1577, 1485, 754; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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; $C_{13}H_{10}NOS$ (MH^+) Requires 228.0478 (1.7 ppm error).

Lab notebook reference: MJJ8/61

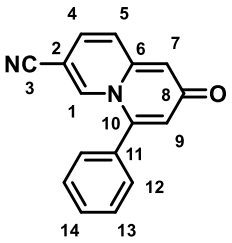
1-Methyl-4-phenyl-2*H*-quinolizin-2-one (229f)



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; ν_{max} (cm^{-1}) 3401, 1622, 1560, 1508, 761, 703; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, H-7), 6.41 (1H, ddd, *J* = 7.5, 7.0, 1.5 Hz, H-2), 6.80 (1H, s, H-9), 7.11 (1H, dd, *J* = 9.0, 7.0 Hz, H-3), 7.37–7.43 (2H, m, H-12/13), 7.47 (1H, d, *J* = 9.0 Hz, H-4), 7.51–7.57 (3H, m, H-12/13,14), 7.68 (1H, d, *J* = 7.5 Hz, H-1); δ_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; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (−0.3 ppm error).

Lab notebook reference: MJJ8/54

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

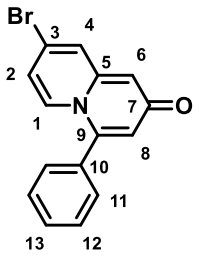


Synthesised using **general procedure 4B** with pyridine-ynone **228g** (74 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 3 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **229g** (61 mg, 82%) as a pale yellow solid, mp 243–245 °C; ν_{max} (cm^{-1}) 2230, 1628, 1602, 1585, 1519,

1306; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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 $C_{16}H_{10}N_2NaO$ (MNa^+) Requires 269.0685 (−3.1 ppm error), Found: 247.0872; $C_{16}H_{11}N_2O$ (MH^+) Requires 247.0866 (−2.6 ppm error).

Lab notebook reference: MJJ8/38

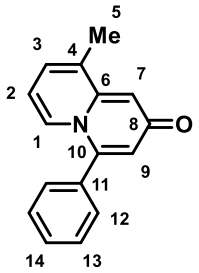
8-Bromo-4-phenyl-2*H*-quinolizin-2-one (229h)



Synthesised using **general procedure 4B** with pyridine-ynone **228h** (90 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** (90 mg, 82%) as a yellow solid, mp >300 °C; ν_{max} (cm^{-1}) 1625, 1578, 1505, 752; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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; $C_{15}H_{11}{}^{79}BrNO$ (MH^+) Requires 300.0019 (−1.2 ppm error).

Lab notebook reference: MJJ8/35

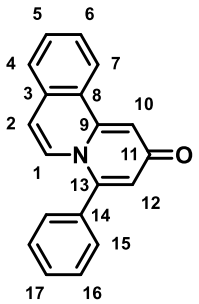
9-Methyl-4-phenyl-2*H*-quinolizin-2-one (229i)



Synthesised using **general procedure 4B** with pyridine-ynone **228i** (71 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 → 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, $CDCl_3$) 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, $CDCl_3$) 19.6 (CH_3, 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; $C_{16}H_{14}NO$ (MH^+) Requires 236.1070 (2.0 ppm error).

Lab notebook reference: MJJ8/65

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

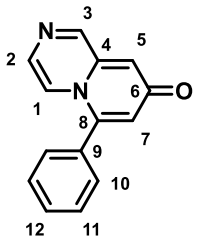


Synthesised using **general procedure 4B** with ynone **228j** (81 mg, 0.3 mmol), $AgNO_3$ (1.0 mg, 6.0 μmol) in DCE (1.5 mL) and EtOH (1.5 mL) for 20 h. Purification by column chromatography (5 → 10% MeOH in EtOAc) afforded the *title compound* **229j** (58 mg, 70%) as a pale yellow solid, mp 139–141 °C; ν_{max} (cm^{-1}) 1626, 1601, 1572, 1582; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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

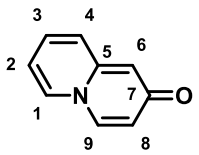
6-Phenyl-8*H*-pyrido[1,2-a]pyrazin-8-one (229k)



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; ν_{max} (cm^{-1}) 3400, 1619, 1600, 1567, 1505; δ_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), 7.52–7.63 (3H, m, H-10/11,12), 8.65 (1H, s, H-3); δ_C (100 MHz, $CDCl_3$) 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), 129.6 (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; $C_{14}H_{10}N_2NaO$ (MNa^+) Requires 245.0685 (2.9 ppm error), Found: 223.0865; $C_{14}H_{11}N_2O$ (MH^+) Requires 223.0866 (0.4 ppm error).

Lab notebook reference: MJJ8/45

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

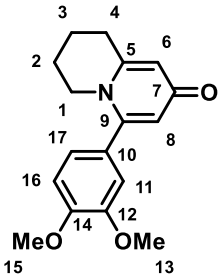


To a solution of TMS-ynone **228l** (98 mg, 0.451 mmol) in acetone (4.5 mL) was added $AgNO_3$ (15.3 mg, 90.2 μmol). The reaction mixture was stirred at rt for 19 h then concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 and purified by column chromatography (5 → 20% MeOH in EtOAc) to afford the *title compound* **229l** (54 mg, 82%) as a brown solid, mp 38–40 °C; ν_{max} (cm^{-1}) 3301, 1649, 1571, 1513, 1486, 1427, 851; δ_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,

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

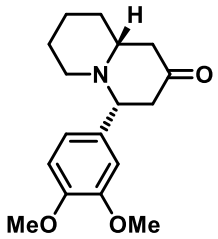
6-(3,4-Dimethoxyphenyl)-3,4-dihydro-1*H*-quinolizin-8(2*H*)-one (273)



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-1*H*-quinolizin-2(6*H*)-one (274)



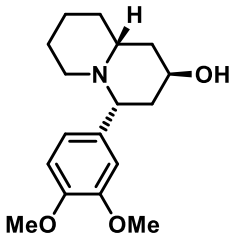
To a solution of quinolizidine **229b** (1.05 g, 3.73 mmol) in AcOH (0.64 mL, 11.2 mmol) and EtOH (37 mL) was added PtO_2 (254 mg, 1.12 mmol). The mixture was evacuated *in vacuo* and backfilled with nitrogen three times then evacuated *in vacuo* and backfilled with hydrogen three times. The mixture was stirred at rt for 4 days before being filtered through Celite®, eluting with EtOAc. The filtrate was poured into sat. $NaCHO_{3\ (aq)}$ (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 ($MgSO_4$), 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 CH_2Cl_2 (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 CH_2Cl_2 (19 mL) was added. The mixture was stirred at −78 °C for 1 h, then Et_3N (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 CH_2Cl_2 (20 mL). The organics were separated and the aqueous extracted with CH_2Cl_2 (3 × 60 mL). The organics were combined, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0 → 2% MeOH in CH_2Cl_2) to afford the *title compound* **274** (730 mg, 68%) as a yellow oil; ν_{max} (cm^{-1}) 2932, 1722, 1516, 1263, 1028; δ_H (400 MHz, $CDCl_3$) 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, dd, *J* = 12.5, 3.0 Hz), 3.88 (3H, s), 3.91 (3H, s), 6.79–6.87 (2H, m), 6.91 (1H, br s); δ_C (100 MHz, $CDCl_3$) 24.2 (CH_2), 25.8 (CH_2), 34.3 (CH_2), 48.7 (CH_2), 50.9 (CH_2), 52.8 (CH_2), 55.8 (CH_3), 56.0 (CH_3), 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; $C_{17}H_{24}NO_3$ (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)

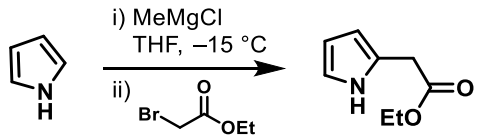


To a solution of ketone **274** (724 mg, 2.50 mmol) in THF (25 mL) at −78 °C was added L-Selectride® (5.0 mL, 5.00 mmol, 1.0 M in THF) dropwise. The mixture was stirred at −78 °C for 3 h then warmed to 0 °C before being quenched by the careful addition of sat. $NaHCO_{3\,(aq)}$ (25 mL). The suspension 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 ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (10 → 20 → 30% MeOH in CH_2Cl_2) to afford the *title compound* **235** (527 mg, 72%) as an off-white foam, mp 41–43 °C; ν_{max} (cm^{-1}) 2930, 1516, 1261, 1230, 1136, 1028; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 24.8 (CH_2), 26.1 (CH_2), 33.6 (CH_2), 40.3 (CH_2), 42.7 (CH_2), 53.2 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 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; $C_{17}H_{26}NO_3$ (MH^+) Requires 292.1907 (−3.6 ppm error).

Lab notebook reference: MJJ8/75

Spectroscopic data matched those reported in the literature.[6]

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



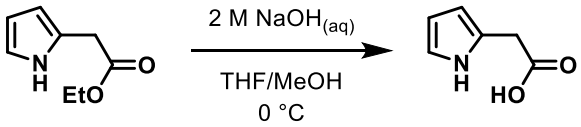
To a solution of pyrrole (13.9 mL, 200 mmol) in THF (300 mL) at ~−15 °C was slowly added MeMgCl (64 mL, 192 mmol, 3.0 M in THF). The reaction mixture was allowed to warm to RT and stirred for 30 min. The reaction mixture was then recooled to ~−10 °C and ethyl bromoacetate (8.85 mL, 80 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 30 min and then quenched with $NH_4Cl_{(aq)}$ (200 mL). The organics were separated and the aqueous was extracted with Et_2O (2 x 200 mL). The organics were combined, dried over $MgSO_4$ 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%); ν_{max} (cm^{-1}) 3388, 2983, 1727, 1370, 1243, 1157, 1028, 720; δ_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); δ_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-(1*H*-Pyrrol-2-yl)acetic acid (277)

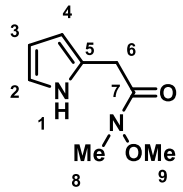


To a solution of ethyl 2-(1*H*-pyrrol-2-yl)acetate **276** (804 mg, 5.25 mmol) in THF (37 mL) and MeOH (3.7 mL) at 0 °C was added 2 M $NaOH_{(aq)}$ (30 mL) dropwise. The reaction mixture was warmed to RT and stirred for 1 h 20 min. Water (20 mL) was added and the aqueous layer was washed with EtOAc (20 mL). The organic extract was discarded. The aqueous layer was acidified with 10% $HCl_{(aq)}$ (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; ν_{max} (cm^{-1}) 3341, 3325, 3119, 2910, 1696, 1415, 1243, 1209, 745; δ_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); δ_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-(1_H_-pyrrol-2-yl)acetamide (278)

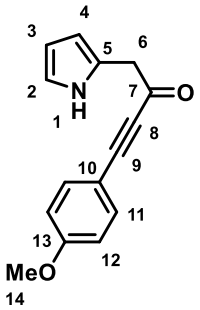


Synthesised using **general procedure 2A** with 2-(1*H*-pyrrol-2-yl)acetic acid **277** (596 mg, 4.76 mmol), T3P 50% in EtOAc (4.55 g, 7.14 mmol), DIPEA (2.49 mL, 14.3 mmol) and MeNH(OMe)·HCl (511 mg, 5.24 mmol) in CH_2Cl_2 (24 mL) at RT for 1.5 h. Afforded the *title compound* **278** without further 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, $CDCl_3$) 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, $CDCl_3$) 30.4 (CH_2, C-6), 32.0 (CH_3, C-8), 61.5 (CH_3, 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; $C_8H_{12}N_2NaO_2$ (MNa^+) Requires 191.0791 (0.1 ppm error), Found: 169.0977; $C_8H_{13}N_2O_2$ (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-(1_H_-pyrrol-2-yl)but-3-yn-2-one (231a)

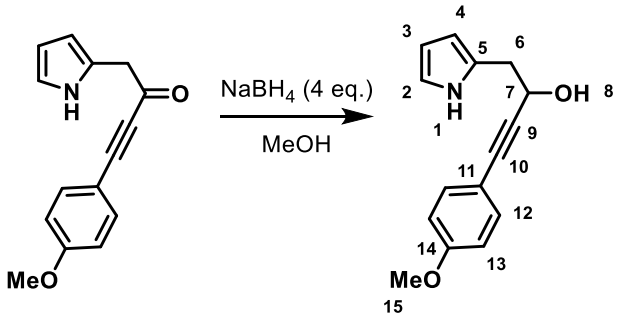


Synthesised using **general procedure 2B** with 4-ethynylanisole (919 mg, 6.96 mmol), THF (15 + 10 mL), Weinreb amide **278** (390 mg, 2.32 mmol) and *n*-BuLi (2.32 mL, 5.80 mmol, 2.5M in hexanes). Purification by column chromatography (10:1 hexane:EtOAc, then 2:1 hexane:EtOAc) afforded the *title compound* **231a** as a pale yellow solid (314 mg, 57%); mp 112–114 °C; ν_{max} (cm^{-1}) 3337, 2198, 1655, 1597, 1508, 1253, 1089, 1023, 839, 798, 739; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 43.6 (CH_2, C-6), 55.4 (CH_3, 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; $C_{15}H_{13}NNaO_2$ (MNa^+) Requires 262.0838 (1.9 ppm error), Found: 240.1022; $C_{15}H_{14}NO_2$ (MH^+) Requires 240.1019 (−1.9 ppm error).

Lab notebook reference: WPU

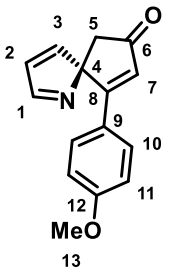
4-(4-Methoxyphenyl)-1-(1*H*-pyrrol-2-yl)but-3-yn-2-ol (279a)



Synthesised using **general procedure 2I** with pyrrole-ynone **231a** (76 mg, 0.318 mmol), $NaBH_4$ (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, $CDCl_3$) 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, $CDCl_3$) 36.1 (CH_2, C-6), 55.2 (CH_3, 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; $C_{15}H_{15}NNaO_2$ (MNa^+) Requires 264.0995 (3.8 ppm error), Found: 242.1168; $C_{15}H_{16}NO_2$ (MH^+) Requires 242.1176 (3.2 ppm error).

Lab notebook reference: MJJ3/74

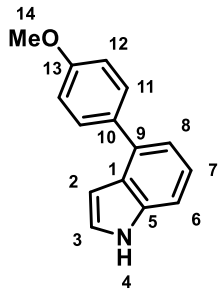
9-(4-Methoxyphenyl)-1-azaspiro[4.4]nona-1,3,8-trien-7-one (280a)



To a solution of ynone **231a** (23.9 mg, 0.100 mmol) in CH_2Cl_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%); ν_{max} (cm^{-1}) 3337, 2198, 1655, 1597, 1508, 1253, 1089, 1023, 839, 798, 739; δ_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); δ_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)-1*H*-indole (281a)



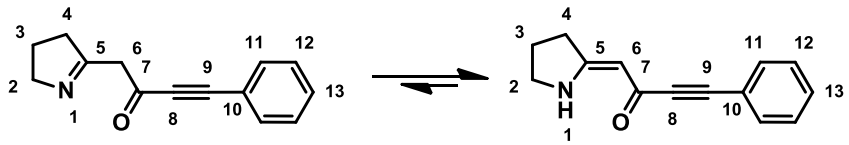
Synthesised using **general procedure 2L** with alcohol **279a** (47 mg, 0.195 mmol), $AgNO_3$ (3.3 mg, 19.5 µmol) and CH_2Cl_2 (2 mL). Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **281a** (36 mg, 83%) as a colourless oil; ν_{max} (cm^{-1}) 3412, 1608, 1518, 1492, 1244, 1178, 1031, 836, 753; δ_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); δ_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; $C_{15}H_{13}NNaO$ (MNa^+) Requires 246.0889 (3.3 ppm error).

Lab notebook reference: MJJ3/80

Spectroscopic data matched those reported in the literature.[161]

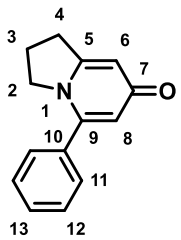
1-(3,4-Dihydro-2*H*-pyrrol-5-yl)-4-phenylbut-3-yn-2-one (283a)



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 phenylpropiolate (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; ν_{max} (cm^{-1}) 1593, 1532, 1507, 1295, 1270, 1134, 759, 691; δ_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); δ_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; $C_{14}H_{14}NO$ (MH^+) Requires 212.1070 (−1.4 ppm error).

Lab notebook reference: MJJ9/33

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



Synthesised using **general procedure 4B** with pyrroline-ynone **283a** (21 mg, 0.1 mmol), $AgNO_3$ (0.33 mg, 2.0 μmol) 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; ν_{max} (cm^{-1}) 1629, 1536; δ_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); δ_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

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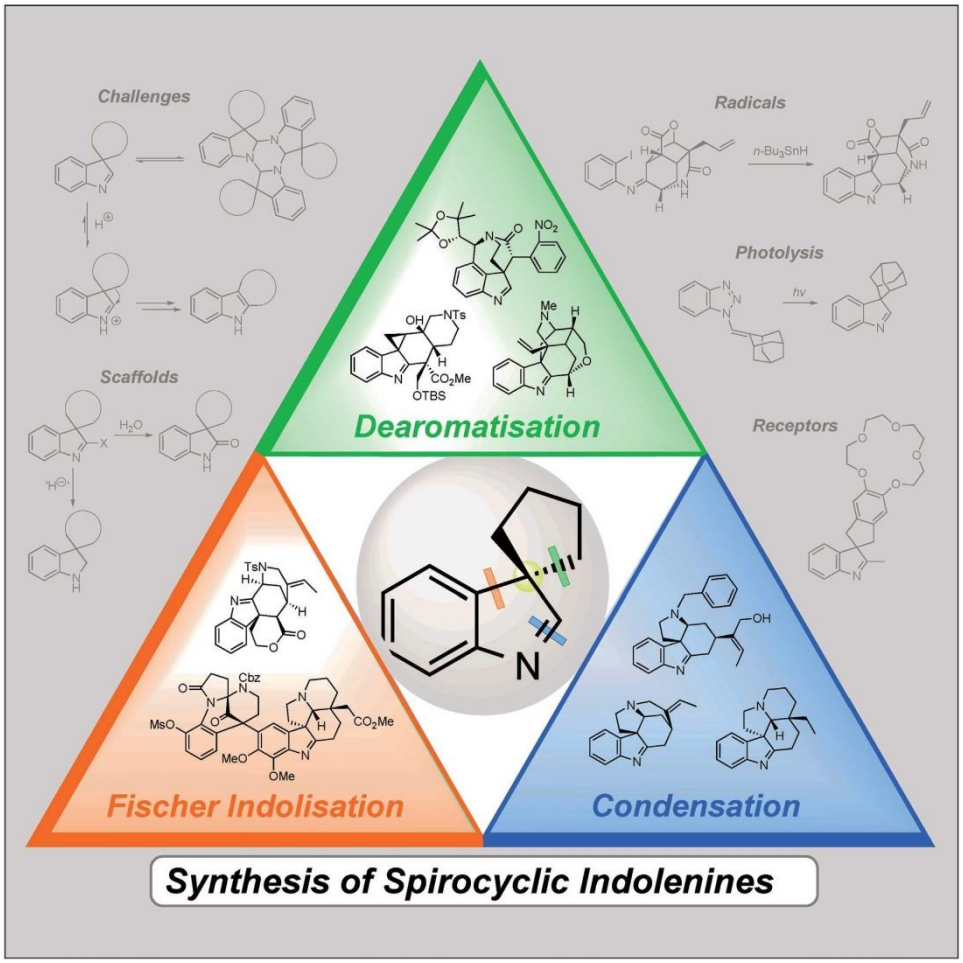
Organic Chemistry

Synthesis of Spirocyclic Indolenines

Michael J. James, Peter O'Brien, Richard J. K. Taylor, and William P. Unsworth*[a]



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Abstract: This Review provides an in-depth account of the synthesis of spirocyclic indolenines. 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, dearomatisation 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.[1] 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.[2–4] Spirocyclic indolenines (sometimes referred to as spiroindolenines or spirocyclic 3*H*-indoles), compounds which fall into both of these categories, are therefore important; the spirocyclic indolenine 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,[5] including indolines, oxindoles, carbazoles, indoles and others (Figure 2). Considering this, an in-depth account of the various strategies used for the direct synthesis of spirocyclic indolenines 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 indolenines 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) dearomatisation 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 indolenines, involving at least one C–C or C–heteroatom bond that is integral to the spirocyclic indolenine 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

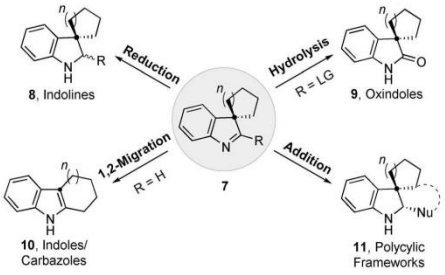


Figure 2. Spirocyclic indolenines as precursors for other heterocyclic scaffolds.

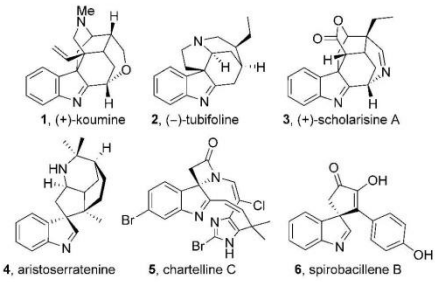
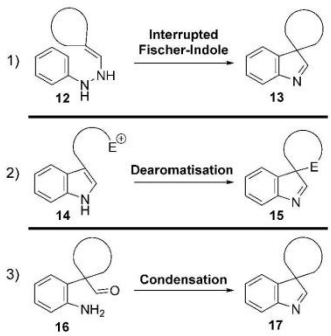


Figure 1. Spirocyclic indolenine natural products.



Scheme 1. Spirocyclic indolenine synthetic strategies.

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indolenines are not covered here.[6–11] Likewise, the synthesis of related spirocyclic compounds at the oxindole oxidation level, including oxindoles, imidates and thioimidates are not covered, and have been reviewed previously elsewhere.[12–19]

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 protic 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 indolenine 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 particular to the 3,3′-disubstituted indolenine motif (Scheme 2). First, this framework is known for its propensity to undergo 1,2-migrations under acidic conditions;[20–22] 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 trimer form (**22**↔**23**). This equilibrium may not always affect their subsequent reactivity (as the trimer **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).[23–25] 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.[23] In addition to these factors, the usual steric, stereoelectronic and stereochemical issues concerning the generation of quaternary carbon centres 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 Indolisations

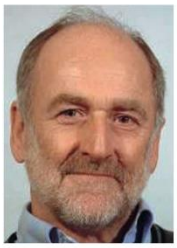
The interrupted Fischer indolisation constitutes, to the best of our knowledge, the oldest reported synthesis of a spirocyclic indolenine. One of the challenges associated with this approach is preventing the acid catalysed 1,2-migration described above (Scheme 2). The first example of this strategy,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

Michael J. James carried out his undergraduate studies and obtained an M Chem. at the University of York in 2013 (including a one-year industrial placement at GlaxoSmithKline, Stevenage). Currently, he is undertaking his Ph.D. studies under the joint supervision of Prof. Peter O'Brien and Prof. Richard J. K. Taylor, investigating the development of novel spirocyclisation methodology and applying this to natural product synthesis.

William P. Unsworth studied chemistry at the University of Oxford, where he remained to complete his Ph.D. studies, in the group of Prof. Jeremy Robertson. He completed his Ph.D. in 2010 and then began work at the University of York, first as a postdoctoral research associate in the group of Prof. Richard J. K. Taylor, before being appointed to a Research and Teaching Fellowship in 2013. His current research interests include the construction of diverse spirocyclic scaffolds, cascade reactions, macrocylisation and total synthesis.

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 (2007) and has been an Associate Editor for Tetrahedron since 1998. His research focuses on asymmetric synthesis of nitrogen heterocycles using organolithium 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.



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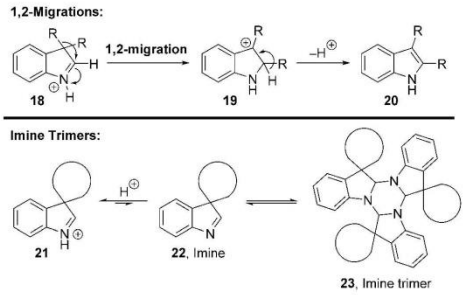
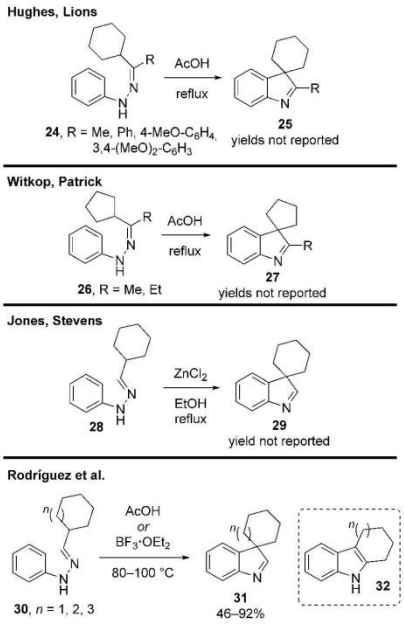


Scheme 2. General synthetic challenges associated with spirocyclic indolenine synthesis.



Scheme 3. Interrupted Fischer indolisations for the synthesis of simple carbocyclic spirocycles (Hughes, Lions;[26] Witkop, Patrick;[27] Jones, Stevens;[28] Rodríguez et al.[20]).

further synthetic investigations by several other research groups (Scheme 3).[26] In a similar fashion Witkop and Patrick briefly explored the synthesis of cyclopentyl spirocyclic indolenines **27** under the same conditions.[27] A common feature of the early work of both Hughes/Lions and Witkop/Patrick 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 indolenine **29** without a substituent on the indole 2-position.[28] This was achieved using Lewis acid catalysis, as opposed to the previously used Brønsted 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 cycloalkyl spirocyclic indolenines **31** from the corresponding hydrazones **30**.[20] 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 spirocycles **31** in modest to excellent yield. More recently, Rodríguez, García-Mera and co-workers expanded upon these works with welcome additions to the substrate scope.[29,30]

The incorporation of heterocyclic frameworks into interrupted 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 piperidine **35** in excellent yield, with the reaction promoted by either acetic acid or $ZnCl_2$ (Scheme 4).[31] Other early work into the synthesis of similar spirocyclic piperidines was carried out by Wang, who synthesised benzo-fused **37** as a precursor towards a fused indole-azepine motif.[32] More recently, Tian and co-workers reported a select range of heterocyclic spirocyclic indolenines **39**, under the typical acid-catalysed conditions.[33] The vast majority of heterocyclic spirocyclic indolenines 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.[34–43]

Another interesting example of a heterocyclic Fischer indolisation spirocyclisation was reported by Dobeneck and co-workers (Scheme 5).[44] 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 syntheses. 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 regioisomeric enamines is formed 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 enamine regioisomers, with an illustrative example of this being found in Stork and Dolfini's total synthesis of aspidospermidine (Scheme 6).[45] In 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 enamine **46** rather than **45**. Stork and Dolfini did not report an isolated

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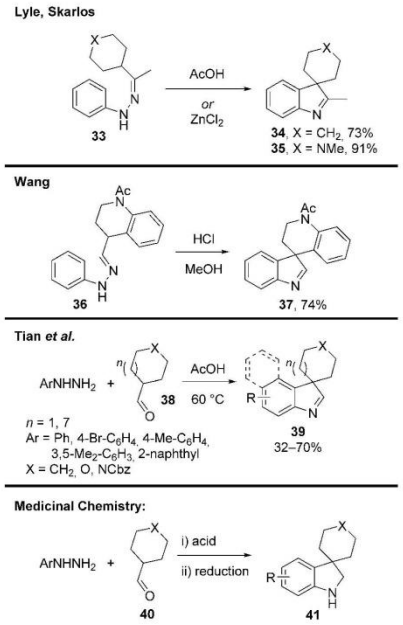
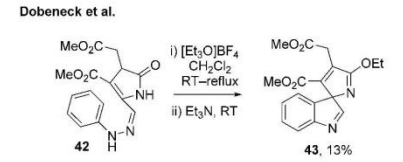


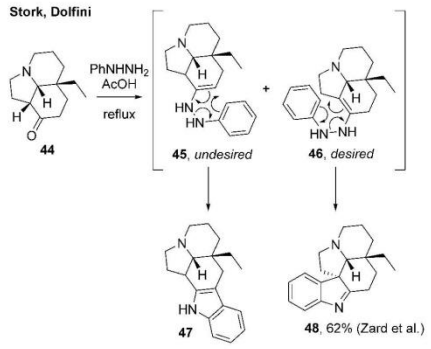
Scheme 4. Interrupted Fischer indolisations for the synthesis of simple heterocyclic spirocycles (Lyle, Skarloes;[31] Wang;[32] Tian et al.[33]).



Scheme 5. Interrupted Fischer indolisations promoted by Meerwein's salt (Dobeneck et al.[44]).

yield for this process, but its efficacy and selectivity has been demonstrated by others since,[46–49] for example, Zard and co-workers reported the formation of **48** in 62% yield using this procedure.[46]

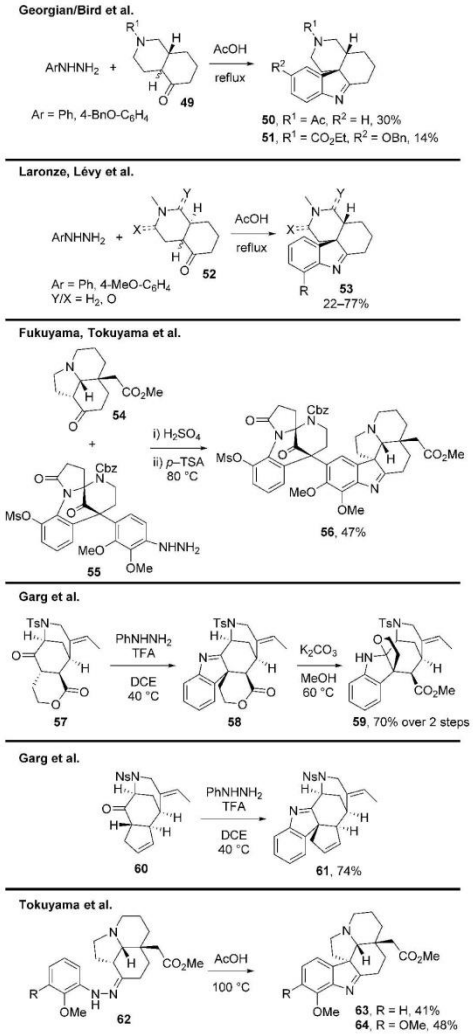
In another synthesis of a fused ring system, Bird and co-workers (who were inspired by the earlier work of Georgian)[50] described the formation of compounds **50** and **51** to evaluate their biological properties (Scheme 7).[51] Similarly Laronze, Lévy and co-workers described the synthesis of spirocycles **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.[52] Fu-



Scheme 6. Interrupted Fischer indolisations applied to natural product studies and potential regioselectivity issues (Stork, Dolfini[45] and Zard et al.[46]).

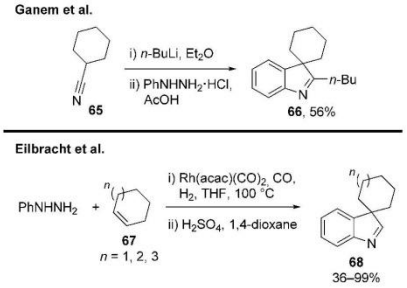
kuyama, Tokuyama and co-workers also utilised this strategy in their impressive total synthesis of (+)-haplophytine. The key precursor **56** was formed in 47% yield under acidic conditions, although the yield was reduced by the formation of the unwanted Fischer indole regioisomer (not shown).[53] Next, Garg and co-workers described an elegant high yielding two step procedure to access compound **59**, a key precursor in their total synthesis of (±)-aspidophylline A;[54] a TFA-mediated interrupted Fischer indolisation cleanly delivered the spirocyclic indolenine **58**, which was subsequently treated with potassium carbonate and methanol to promote lactone methanolysis and *N,O*-acetal formation. Later, Garg and co-workers applied the same method to make complex pentacycle **61** during their total synthesis of picrinine.[55] Finally, Tokuyama and co-workers used an interrupted Fischer indolisation in their total synthesis of (−)-aspidophytine and its congeners, (+)-cimicidine and (+)-cimicine.[56] This reaction was performed in the typical way, by treating the hydrazones **62** with acetic acid at 100 °C to afford spirocyclic indolenines **63** and **64** in 41 and 48% yield, respectively.

In most cases, the hydrazone intermediates required for these interrupted Fischer indolisations are generated through a standard condensation reaction between a hydrazine derivative and an aldehyde or ketone, but a small number of alternative methods have also been reported. First, Ganem and co-workers, reported a single example of spirocyclic indolenine synthesis from nitrile **65** by a two-step protocol (Scheme 8).[57] This process is initiated by organolithium addition to the nitrile to form an imine species, which was then treated directly with phenyl hydrazine to form a hydrazone, before its treatment with acetic acid completed the interrupted Fischer indolisation, furnishing spirocycle **66** in modest yield. Second, Eilbracht and co-workers reported a tandem rhodium-catalysed hydroformylation-Fischer indolisation sequence. In this process alkene **67** was hydroformylated and then reacted under the typical acidic Fischer-indolisation conditions, to afford the desired spirocycles **68** in modest to excellent yield.[58]

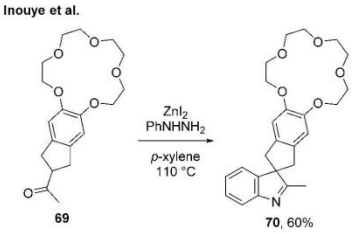


Scheme 7. Interrupted Fischer indolisations in other natural product studies (Georgian,[56] Bird et al.;[51] Laronze, Levy et al.;[52] Fukuyama, Tokuyama et al.;[53] Garg et al.;[55] Tokuyama et al.[56]).

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;[59] spiro-crown ether **70** was synthesised in good yield from ketone **69** using ZnI_2 as the catalyst (Scheme 9).

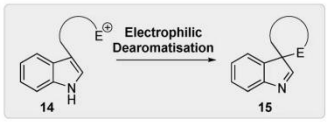


Scheme 8. Alternative hydrazone formations used in interrupted Fischer indolisations (Ganem et al.;[57] Eilbracht et al.[58]).



Scheme 9. Spirocyclic crown ether synthesis by Fischer indolisation (Inouye et al.[59]).

4. Indole Dearomatisations



Probably the most popular method to access spirocyclic indolenines today is through the dearomatisation of an indole precursor.[60,61] 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.[60,62] 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 indolenine intermediates (e.g., **73**) are known intermediates in these pro-

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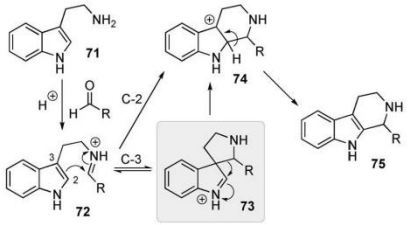
cesses (Scheme 10). In a traditional Pictet–Spengler reaction, the desired tetrahydro-β-carboline product **75** is formed in situ from this spirocyclic intermediate, either via a 1,2-migration-elimination sequence (**73**→**74**→**75**) or regeneration of the iminium intermediate **72** followed by direct C-2 attack (**72**→**74**→**75**).[63] Thus, the challenge in the context of spirocyclic indolenine synthesis is to design a process in which the initial spirocyclisation step (**72**→**73**) proceeds, but then no further reaction takes place.

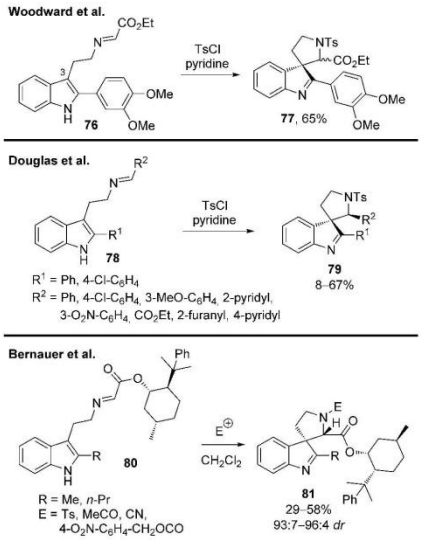


Scheme 10. Overview of Pictet–Spengler mechanistic possibilities.

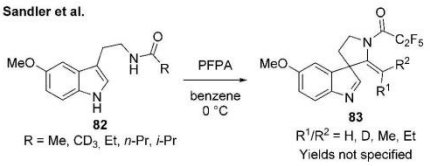
This strategy was first demonstrated in the pioneering work of Woodward and co-workers in their seminal total synthesis of strychnine (Scheme 11).[64] In this process, spirocyclisation was initiated by the activation of imine **76** with tosyl chloride to form a more electrophilic *N*-sulfonyliminium ion; subsequent nucleophilic attack from the indole C-3 position afforded the desired spirocycles **77** in good yield. Inspired by this approach, Douglas and co-workers sought to apply this methodology to a wider range of substrates in order to investigate their pharmacological properties (**78**→**79**, Scheme 11).[65] A diastereoselective variant of this strategy has also been developed by Bernauer and co-workers, who found that spirocyclic indolenines **81** could be formed with high diastereoselectivities by using a menthyl ester derivative **80**.[66] Other activating agents (including other sulfonyl chlorides, acyl chlorides, chloroformates and cyanogen bromide) were also shown to promote this reaction, demonstrating that the activating agent is not limited to tosyl chloride.

A similar strategy was devised by Sandler and co-workers, who implemented the reaction of pentafluoropropionic anhydride (PFPA) and amide **82**, presumably to form a reactive imidate or *N*-acylimidate ion primed to undergo an addition–dehydration sequence (Scheme 12).[67] 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 polymerisation.

Another method to access reactive iminium ion species for spirocyclic indolenine synthesis is by an in situ amine-aldehyde condensation. This approach was first described by Kuehne and co-workers, who treated indole **84** and aldehyde **85** with BF_3·OEt_2 to furnish the impressive tetracyclic framework **86** in



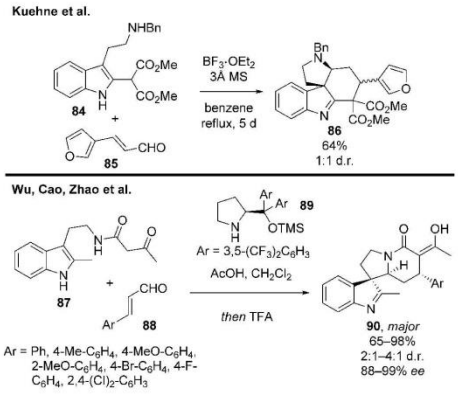
Scheme 11. Spirocyclisation induced by electrophilic activation of an imine (Woodward et al.;[64] Douglas et al.;[65] Bernauer et al.[66]).



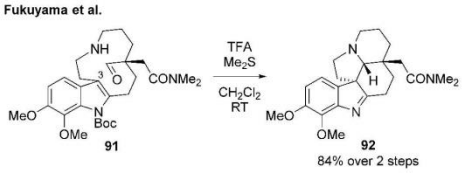
Scheme 12. Activated amide induced spirocyclisation (Sandler et al.[67]).

good yield, as a 1:1 mixture of two diastereoisomers.[68] 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).[69] The Jørgensen–Hayashi catalyst **89**[70] was used to promote a condensation–spirocyclisation sequence between α,β-unsaturated aldehydes **88** and β-ketoamide-indoles **87** to form spirocycles **90**, in excellent yield and with high enantioselectivity.

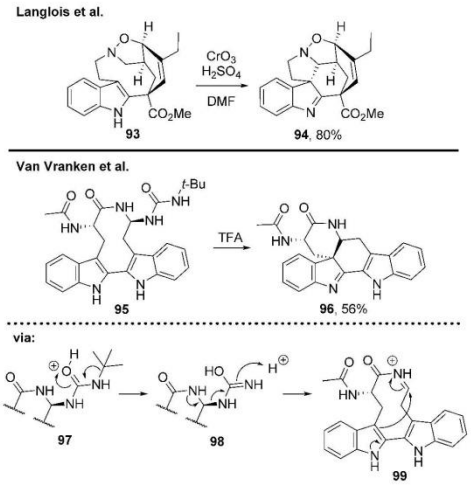
Fukuyama and co-workers demonstrated an elegant intramolecular variant of an in situ aldehyde condensation–spirocyclisation sequence.[71] TFA was used to catalyse both the imine formation and the Boc cleavage, with the removal of the Boc group, thus increasing the nucleophilicity of the indole C-3 position and promoting spirocyclisation. This resulted in the formation of the impressive pentacyclic framework **92** in



Scheme 13. Spirocyclisation by addition to an iminium species formed by an intermolecular condensation (Kuehne et al.;[68] Wu, Cao, Zhao et al.[69]).



Scheme 14. Spirocyclisation by addition to an iminium ion formed by an intramolecular condensation (Fukuyama et al.[71]).



Scheme 15. Polycyclic scaffold formation by transannular spirocyclisation (Langlois et al.;[72] Van Vranken et al.[73]).

excellent yield, which was subsequently used as a precursor in the total synthesis of (−)-aspidophytine (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 ion intermediate (Scheme 15). For example, Langlois and co-workers used the Jones oxidation of hydroxylamine **93**;[72] 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 ditryptophan **95** with TFA to form a reactive *N*-acyl iminium species **99** that either undergoes spirocyclisation or *N*-alkylation, depending on which diastereoisomer is used.[73] This overall transformation formed the ring-fused indolenine **96** in 56% yield.

Finally, the most recent example of spirocyclic indolenine synthesis by iminium ion trapping was reported by Xu, Sun and co-workers, who described an intriguing intermolecular spirocyclisation sequence between a range of indoles **101** and amino-benzaldehydes **100** (Scheme 16).[74] 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 spirocycle. 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 Alkylations

Spirocyclic indolenine frameworks can also be accessed by a dearomatising 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 tryptophol tosylate **105** with potassium *tert*-butoxide afforded spirocyclic cyclopropane **106**.[75] This process was later reported with more experimental detail by Rapoport, where an analogous tryptophol bromide underwent intramolecular alkylation in the presence of potassium carbonate in refluxing acetonitrile.[76] Homologues of this reaction class to afford spirocyclic cyclopentyl and cyclohexyl systems were first reported by Jackson and co-workers,[23,24] 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 spirocycle **110** in modest yield for use in mechanistic studies, by treating benzyl bromide derivative **109** with sodium hydride.[77] An intriguing example

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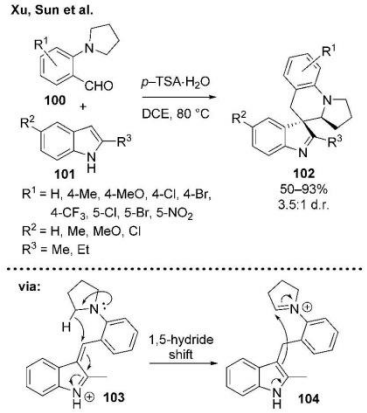
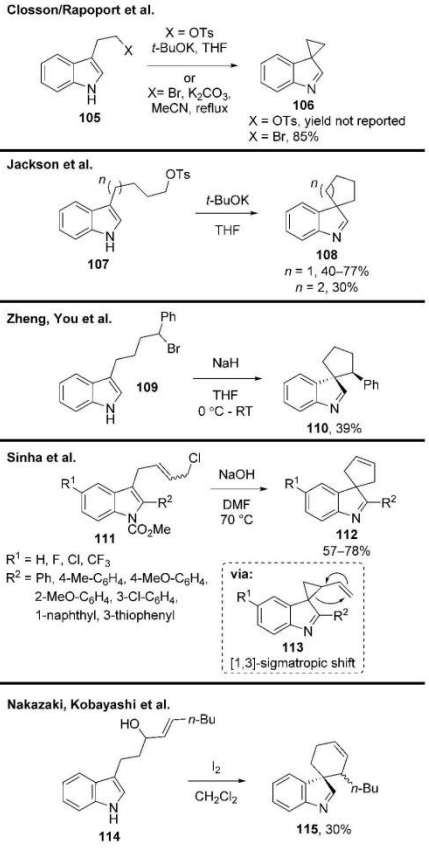


Scheme 16. Spirocyclisation by addition to an iminium formed by 1,5-hydride shift (Xu, Sun et al.).[74]

of intramolecular S_N2' alkylation followed by a [1,3]-sigmatropic rearrangement was demonstrated by Sinha and co-workers;[78] it was found that a wide variety of substrates **111** undergo this reaction to afford spirocyclic cyclopentenyl indolenines **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_N2' alkylation as a side product during their synthesis of spirocyclic oxindoles,[79] 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, Rao and Kamiya in their synthesis of desethylibogamine;[80] 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 koumidine **118** via a two-step mesylation-alkylation sequence, forming the intriguing ring system **119** in good yield.[81] Rubiralta and co-workers demonstrated the utility of dithiane indole derivatives in the synthesis of aspidospermidine; the final precursor was accessed by an in situ tosylation–alkyation of **120** to furnish the skeleton of aspidospermidine **121**.[82] This strategy to access the *Aspidosperma* alkaloid framework was also used by Rawal 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.[83,84]



Scheme 17. Alkylations for the synthesis of simple carbocyclic spirocycles (Closson/Rapoport et al.;[75,76] Jackson et al.;[23,24] Zheng, You et al.;[77] Sinha et al.;[78] Nakazaki, Kobayashi et al.[79]).

Spirocycle formation was also reported by Muniz and co-workers, as side-products **126**, during a study directed towards the formation of azetidones **125** (Scheme 19).[85] Later, Smith and co-workers utilised the phosphazene base BTPP to promote the mesylate displacement of **127**, to furnish spirocyclic scaffold **128**, an advanced precursor of (+)-scholarisine A.[86] Next, Fukuyama and co-workers reported the impressive alkylation of bromoacetamide **129** with caesium carbonate to form the chartelline C skeleton **130** in excellent yield.[87] 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.[88]

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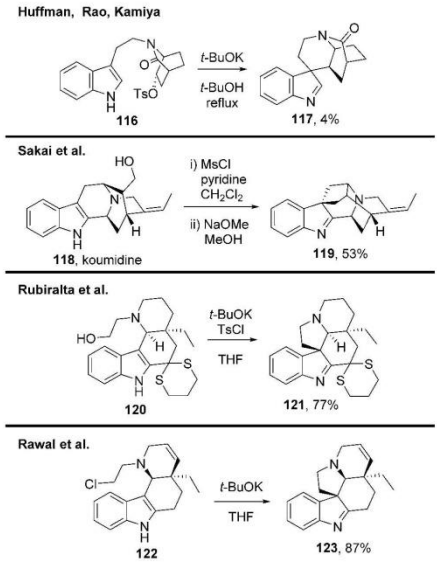
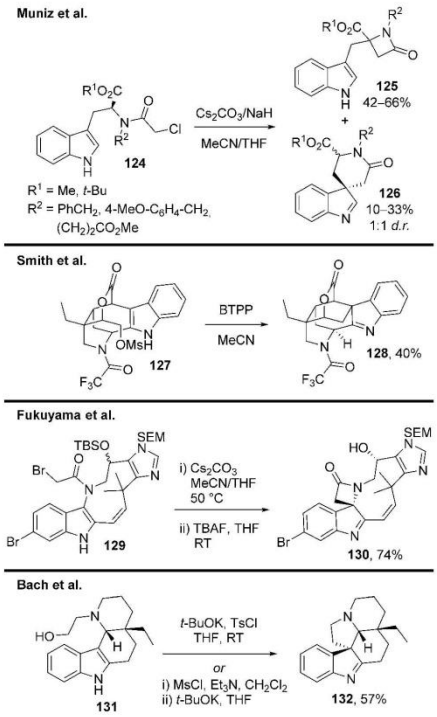


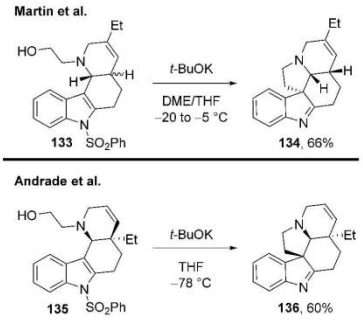
Scheme 18. Alkylations found in natural product studies (Huffman, Rao, Kamiya;[80] Sakai et al.;[81] Rubiralta et al.;[82] Rawal et al.[83,84]).

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, Rubiralta and co-workers.[89] Martin and co-workers first used this protocol to furnish pentacycle **134**, a key intermediate towards the synthesis of (±)-pseudotabersonine,[90] and Andrade and co-workers later used the same method in their synthesis of the *Aspidosperma* alkaloid precursor **136** (Scheme 20).[91]

Another popular alkylation strategy is the use of Ag^{I} 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 aspidospermidine; a Finkelstein reaction of chloroacetamide **137** and subsequent treatment with AgOTf afforded the desired indolenine **138** in excellent yield.[92] Andrade and co-workers used a similar strategy to dearomatise bromoacetamide derivative **139**, which upon treatment with AgOTf and a weak base underwent a facile spirocyclisation to afford indolenine **140** in excellent yield. This indolenine was then used in a novel intramolecular aza-Baylis–Hillman reaction to furnish the tetracyclic natural product framework **141**.[93] Inspired by this approach, Kwon and co-workers implemented this strategy in their synthesis of (+)-ibophyllidine, utilising a similar telescoped spirocyclisation-aza-Baylis–Hillman reaction sequence to afford the pentacyclic skeleton **144** (a precursor to (+)-ibophyllidine) in excellent yield.[94] Banwell and co-workers also used a AgOTf promoted alkylation of **145** in their total synthesis of (±)-limaspermidine



Scheme 19. Alkylations from natural product studies (Muniz et al.;[85] Smith et al.;[86] Fukuyama et al.;[87] Bach et al.[88]).



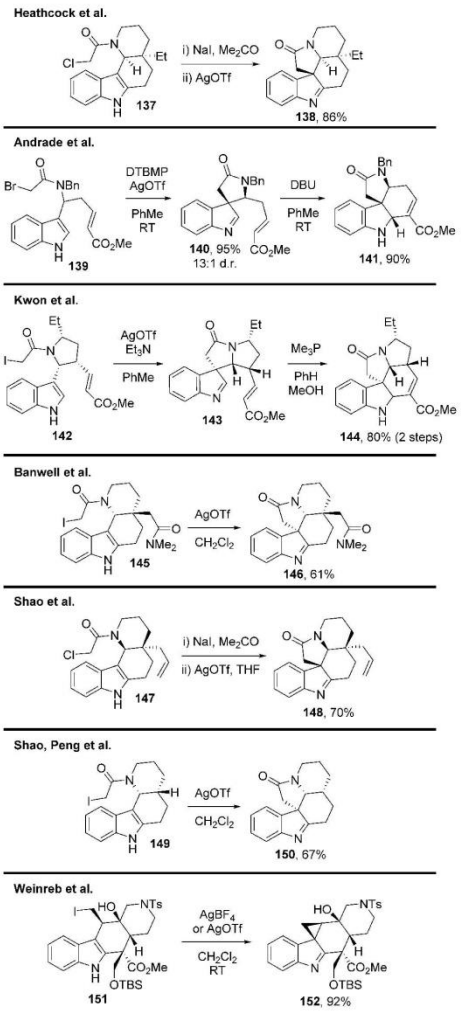
Scheme 20. One-pot *N*-desulfonylation/*O*-sulfonylation protocols (Martin et al.;[90] Andrade et al.[91]).

and (±)-1-acetylaspidoalbidine precursor **146**.[95] Shao, Peng and co-workers have also applied this strategy in natural product synthesis, to form similar pentacyclic frameworks **148** and **150** in good yields.[96,97] Finally Weinreb and co-workers reported the cyclopropanation spirocyclisation of **151**, which upon treatment with either AgOTf or $AgBF_4$, afforded the spirocyclic indolenine **152** in excellent yield.[98]

Intramolecular Mitsunobu reactions have also been shown to be effective for spirocyclic indolenine synthesis (Scheme 22). This method was first reported by Magnus and co-workers as the final step of their total synthesis of (+)-koumine (**154**), which was completed by reacting the *E*- and *Z*-isomers of allylic alcohol **153** under classical Mitsunobu reaction conditions in the presence of sodium hydride, to promote an S_N2' reaction.[99] Similarly, Bajtos and co-workers reported the cyclopropanation of indole **155** under standard Mitsunobu conditions, furnishing spirocycle **156** in moderate yield.[100] In a related fashion, Weinreb and co-workers demonstrated the high yielding cyclopropanation of indole **157**.[98]

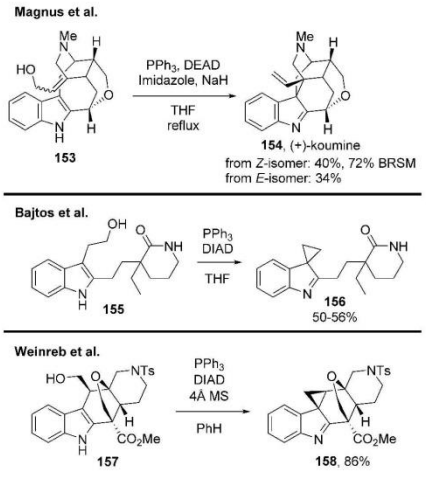
4.3 Addition to π-allyl intermediates

Some of the most impressive routes to spirocyclic indolenines proceed by nucleophilic addition reactions involving electrophilic π-allyl intermediates, which are usually derived from allylic acetates or carbonates (Scheme 23). Sakai and co-workers reported the first example of this class of reaction in their biosynthetic studies of koumine; it was proposed that the treatment of an allylic acetate/carbonate (**159**) with palladium(II) acetate and triphenylphosphine formed the reactive π-allyl species, which following attack from the indole C-3 position, furnished spirocyclic indolenine **160** in modest yield.[101] Next, You and co-workers expanded this strategy, utilising allylic carbonate **161** and $[Ir(COD)Cl]_2$ with chiral phosphoramidite ligand **162** to furnish an array of spirocyclic indolenines **163** in excellent yield and also with high enantioselectivity and diastereoselectivity.[102] 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 indolenines were generated as part of this work, only one indolenine **166** was isolated as a discrete product; in general, the spirocyclic indolenine intermediates **166** were immediately converted into the respective indolines **168** or tetrahydrocarbazoles **167** (via an acid-mediated 1,2-migration)[22] and isolated at this stage. The conversion of indolenine 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 ruthenium-catalysed approach using ruthenium 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.[103]



Scheme 21. Ag^{I} promoted alkyations of pendant halides (Heathcock et al.;[92] Andrade et al.;[93] Kwon et al.;[94] Banwell et al.;[95] Shao et al.;[96] Shao, Peng et al.;[97] Weinreb et al.[98]).

Reactive π-allyl intermediates can also be generated from propargyl carbonates **172**, as first demonstrated by Hamada and co-workers as an extension of their phenol dearomatisation spirocyclisation methodology (Scheme 24).[104] This reaction is proposed to proceed by the formation of a η^3-π-allenyl-palladium complex **178**, which following nucleophilic attack from the indole C-3 position and a protonation–elimination

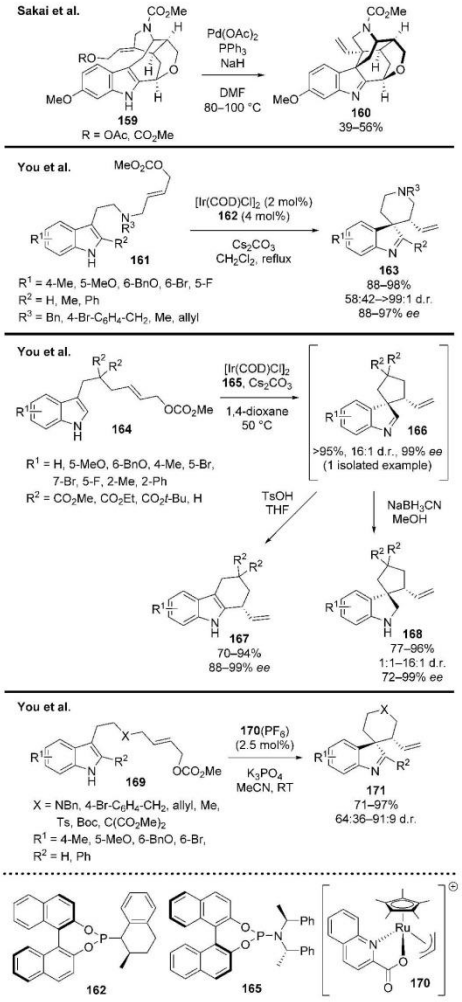


Scheme 22. Mitsunobu reactions in alkylative spirocyclisations (Magnus et al.;[99] Bajtos et al.;[100] Weinreb et al.[98]).

sequence, furnishes spirocyclic indolenines **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 using in situ nucleophilic substitution with a primary amine.[105] Furthermore, although they were not the desired targets in this study, they also reported the isolation of numerous spirocyclic indolenines **175** as side-products, some being formed in good yield.

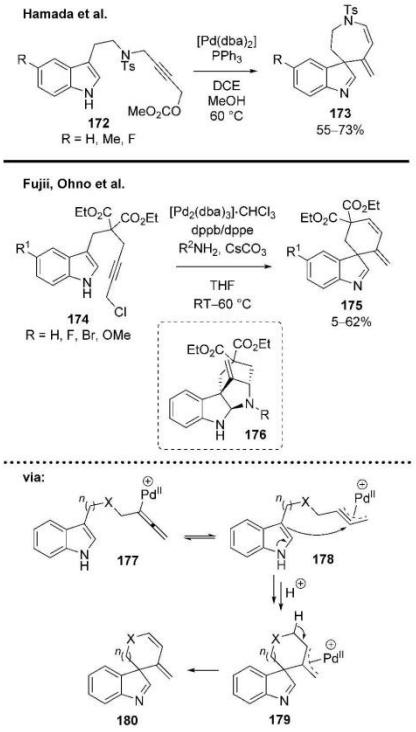
A similar strategy, which was developed around the same time by the You and Rawal groups, is the use of propargyl carbonates in intermolecular reactions;[106,107] these reactions are proposed to proceed first by the interception of a typical η^3-π-allenylpalladium species by a nucleophile tethered onto the indole, before undergoing a protonation–spirocyclisation sequence to form the spirocyclic indolenine products (Scheme 25). The contribution by You and co-workers concerns the reaction of malonates **182** with methyl propargyl carbonate, $[Pd_2(dba)_3]$ and an appropriate phosphine ligand, to afford spirocyclic indolenines **183** in moderate to excellent yield, with preliminary results suggesting that an asymmetric variant is possible using (*R*)-segphos or related derivatives.[106] Meanwhile, Rawal and co-workers reported the reaction of a variety of indole-tethered pro-nucleophiles, $[Pd_2(dba)_3]$, xantphos, and in some cases a base, to furnish an impressive variety of spirocyclic indolenines **185**/**186**, generally in good yield.[107] 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 indolenines **189** in good to excellent yield and with high enantioselectivity.[108]

Finally, Liu and co-workers described an intriguing spirocyclisation methodology;[109] using a chiral palladium complex with

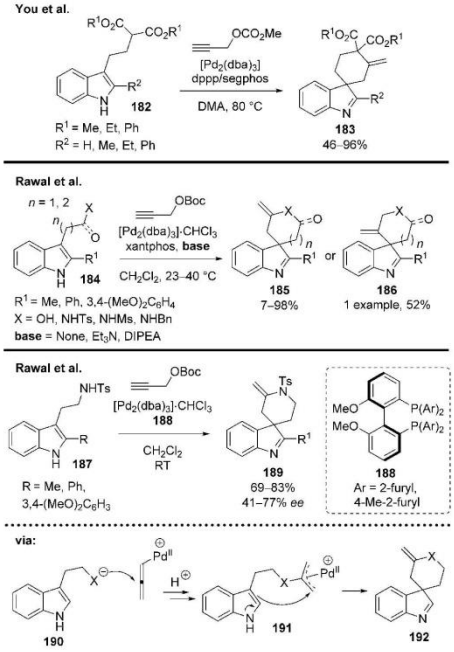


Scheme 23. Intramolecular addition to π-allyl intermediates generated from allylic carbonates/acetates (Sakai et al.;[101] You et al.[22,102,103]).

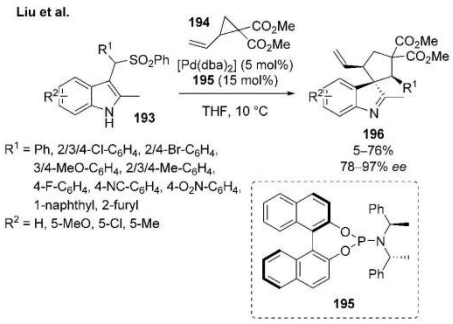
vinyl cyclopropane **194**, a reactive 1,3-dipole is formed in situ, which then undergoes a formal [3+2]-cycloaddition with the β-unsaturated indolenine (afforded by the extrusion of phenyl sulfinic acid from sulfone **193**) to furnish the spirocycles **196**. A range of substrates were well tolerated, generating spirocyclic indolenines as single diastereoisomers, typically in good yield and with excellent enantioselectivity (Scheme 26).



Scheme 24. Intramolecular addition to π-allyl intermediates generated from propargylic systems (Hamada et al.,[104] Fujii, Ohno et al.[105]).



Scheme 25. Intermolecular addition to π-allyl intermediates generated from propargylic systems (You et al.;[106] Rawal et al.[107,108]).



Scheme 26. Intermolecular addition to π-allyl intermediates generated from a vinyl cyclopropane system (Liu et al.[109]).

4.4 Addition to alkenes, alkynes and allenes

To the best of our knowledge, the only examples of spirocyclic indolenine synthesis by the electrophilic activation of a simple alkene were reported recently by Tang, Shi and co-workers;[110] AgOTf was used to activate the strained indolylcyclopropene **197**, promoting spirocyclisation and the formation of indolenines **198**, generally in good yields (Scheme 27). A single example of allene activation for spirocyclic indolenine synthesis was also reported by Bandini and co-workers; who used Au^{I} catalysis with allenamide **199** to afford the vinyl spirocycle **200** in excellent yield and with good diastereoselectivity.

In recent years, the electrophilic activation of alkynes has received considerable interest from the synthetic community,[112,113] and accordingly the majority of the examples in this reaction class are based on alkyne activation. These cyclisations typically proceed by activation of the alkyne by a π-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 indolenines **202** as a side-product in their synthesis of ring-fused indole **203** (Scheme 28).[114] Using a typical Au^{I}/Ag^{I} catalyst system, an array of the desired ring-fused indoles were furnished in high yield; however, the submission of terminal propargyl amide **201** to these reaction conditions afforded

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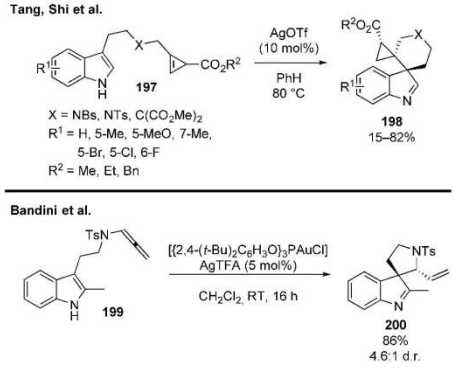
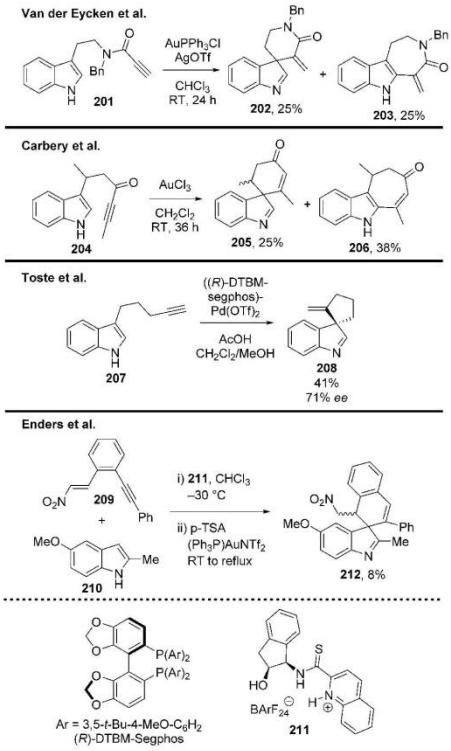


Scheme 27. Spirocyclisation by addition to a pendant alkene/allene (Tang, Shi et al.;[110] Bandindi et al.[111]).



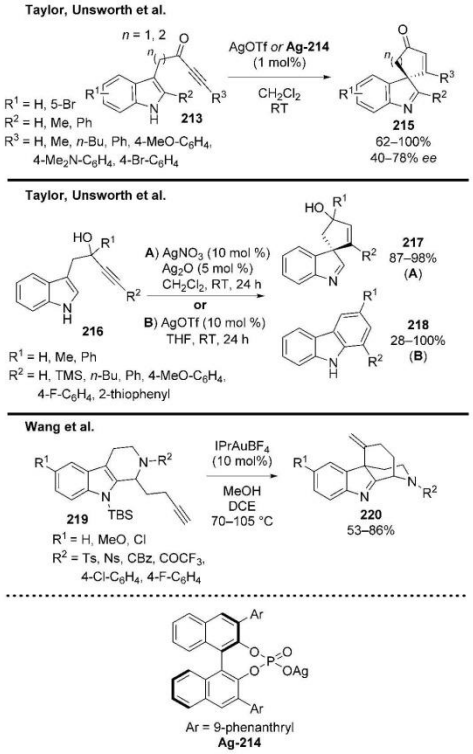
Scheme 28. Spirocyclisation by addition to a pendant alkyne (Van der Eycken et al.;[114] Carbery et al.;[115] Toste et al.;[116] Enders et al.[117]).

only a 1:1 mixture of the desired indole **203** and spirocycle **202** (which is likely an intermediate en route to **203**). Similarly, Carbery and co-workers reported an example of spirocyclisation of indole **204** in their mechanistic studies of a Au^{III} catalysed synthesis of the fused indole framework **206**.[115] As in the Van der Eycken study, the spirocycle **205** was a side-product in this reaction, with the major fused indole products **206** presumably being formed via a 1,2-migration of spirocycle **205**. Next, Toste and co-workers reported a single example of a Pd^{II} catalysed spirocyclisation in their studies towards the synthesis of the kopsifoline.[116] Submission of alkyne **207** to the asymmetric Pd^{II} conditions furnished the spirocycle **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 indolenine **212** as a mechanistic probe.

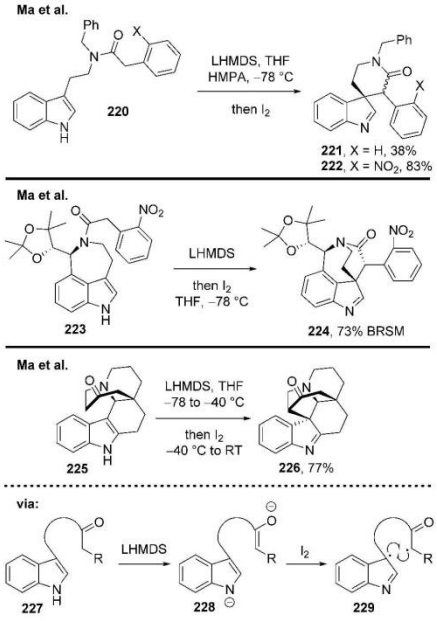
In a study that directly targeted spirocyclic products (rather than their ring-annulated analogues) our own group reported the first high yielding examples of this reaction class, using catalytic AgOTf in DCM at RT to activate ynones **213** to form spirocyclic indolenines **215**.[118] This work was well informed by the approach of Carbery and co-workers,[115] who showed that similar indolylynones **204** spirocyclised under π-acidic conditions, but it was found that the use of AgOTf rather than a Au^{III} 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 chiral phosphoric 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 propargylic alcohol substrates **216** also undergo spirocyclisation effectively, forming indolenines **217** in high yields.[119] 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^{I} catalysed approach to form tetracyclic spirocycles **220**.[120] In this process the authors noted a key difference in chemoselectivity between C–N and C–C cyclisation 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. MRSA) 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 indolenine synthesis in their total synthesis of (−)-communesin F.[121] This approach, along with other related processes (initiated by Baran and co-



Scheme 29. Spirocyclisation by addition to a pendant alkyne (Taylor, Unsworth et al.;[118,119] Wang et al.[120]).



Scheme 30. Spirocyclisation by oxidative coupling (Ma et al.[121,126,127]).

workers),[122–125] are proposed to proceed by a double deprotonation reaction to form a dianion (**227**→**228**), which is then oxidised with iodine to form a highly reactive diradical species **229** which undergoes radical–radical coupling to generate the spirocyclic indolenine. Ma and co-workers found that the incorporation of the *ortho*-nitro group into the benzyl amide **220** significantly increased the yield of this reaction, presumably due to the associated increase in acidity increasing the ease with which the dianion forms. Later, Ma and co-workers used a similar approach in their total synthesis of communesins A and B with indole **223** to good effect, forming compound **224** in good yield, based on recovered starting material.[126] Ma and co-workers also applied this strategy to the total synthesis of the methyl (+)-*N*-decarbomethoxychanofruticosinate natural product framework **226** in good yield.[127]

Inspired by this approach, Higuchi and co-workers applied this methodology in their synthesis of the scholarisine A framework (Scheme 31).[128] After screening a variety of oxidants, it was found that NIS could also be used in place of I_2 to form complex scaffold **231** in good yield. Finally, one of the most recent examples of the oxidative coupling approach to spirocyclic indolenine 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).[129–131] Employing the typical oxidative coupling conditions and a PPTS-MeOH quench they promoted tandem oxidative coupling, cleavage of the TES protecting group, autoxidation 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).[132] In this process, dilauroyl 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 **238**, followed by cyclisation onto the adjacent vinyl amide; the resultant α-nitrogen radical **239** is then thought be oxidised by dilauroyl 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.[133]

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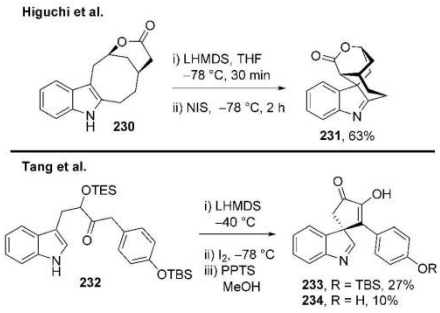
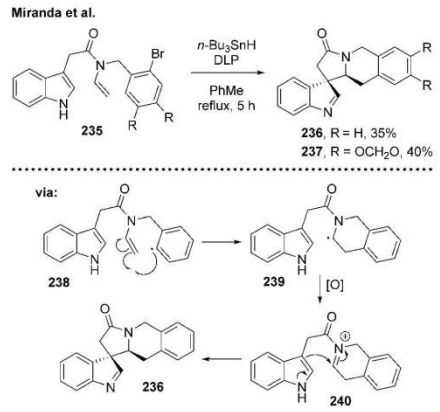


Scheme 31. Spirocyclisation by oxidative coupling (Higuchi et al.;[128] Tang et al.[129]).

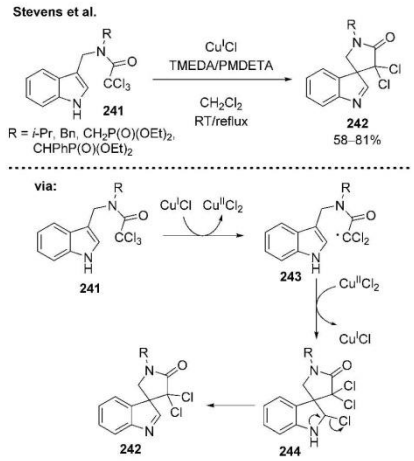
One of the most recent examples of a radical spirocyclisation was reported by Stevens and co-workers, who employed a CuCl-mediated atom transfer radical cyclisation (ATRC, Scheme 33);[134] a small selection of indolyl trichloroacetamides **241** were treated with CuCl and either TMEDA or PMDETA (*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine) to furnish the spirocyclic indolenines **242**, generally in excellent yield.

4.6 Conjugate additions

A lesser utilised strategy to access spirocyclic indolenines is to harness the nucleophilicity of the indole moiety in a conjugate addition reaction. One of the earliest examples of this was demonstrated by Noland and Hammer;[135] an attempted acylation of bis-indole **245** with maleic anhydride **246** unexpectedly resulted in the formation of spirocyclic indolenine **247** in low



Scheme 32. Tributyltin hydride radical mediated spirocyclisation (Miranda et al.[132]).

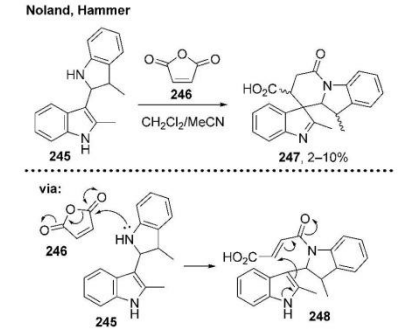


Scheme 33. Spirocyclisation by ATRC (Stevens et al.[134]).

yield (Scheme 34). This reaction presumably proceeds by *N*-acylation followed by conjugate addition into the resultant acrylamide **248**.

Later, Takeuchi and co-workers reported a curious conjugate addition of nitrodienamine **250** with a bis-indole species **252** formed upon the reaction of indole with TFA (Scheme 35).[136] The overall yield for this process is modest, but it is nonetheless impressive, given the significant increase in complexity of the spirocyclic indolenine **251** compared with the starting materials.

One of the first high-yielding examples of this strategy was demonstrated by Angle and co-workers (Scheme 36).[137] Ag_2O was used to oxidise electron-rich phenol **256** to the



Scheme 34. Spirocyclisation by conjugate addition (Noland and Hammer[135]).

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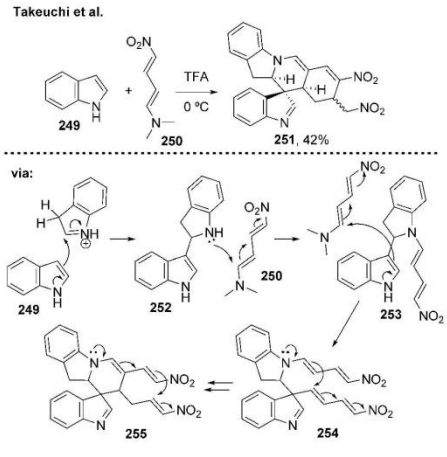
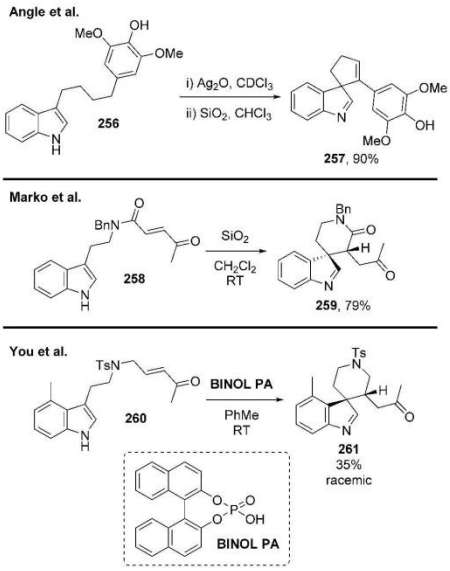


Scheme 35. Spirocyclisation by conjugate addition (Takeuchi et al.[136]).

corresponding quinone methide, which following conjugate addition and another oxidation-rearomatisation 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 indolenine **259** in excellent yield.[138] 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 oximes **261** was used to promote formal nucleophilic substitution at the oxime sp^2 nitrogen, affording spirocycles **262** in good to excellent yield (Scheme 37). In a similar fashion, Nishikawa, Isobe and co-workers treated O-nosylated hydroxamic acids **263** with LHMDS to afford the synthetically challenging spirocyclic β-lactam framework **264**, found in the chartelline natural products.[139] Finally, Kundu and co-workers reported an unusual $SnCl_2{\cdot}2\,H_2O$-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**.[140]



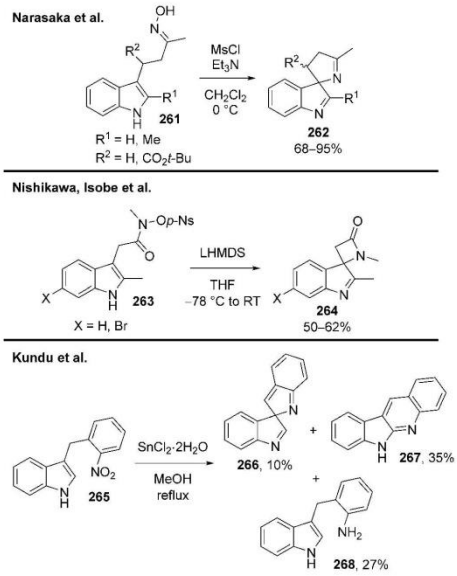
Scheme 36. Spirocyclisation by conjugate addition (Angle et al.;[137] Markó et al.;[138] You et al.[77]).

4.8 Addition to thio/oxo-carbenium ions

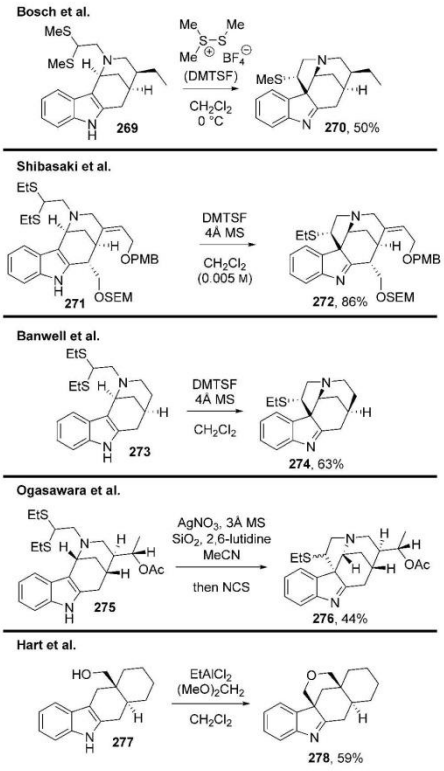
In a strategy pioneered by Bosch and co-workers, dithioacetal **269** was treated with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) to generate a thionium ion, which is subsequently attacked by the nucleophilic indole to deliver the spirocyclic indolenine **270** in good yield (Scheme 38).[143–146] This method was further adapted by Shibasaki and co-workers who found that by incorporating molecular sieves and decreasing the reaction concentration they could access a similar framework (**272**) in excellent yield.[147,148] These conditions were also employed by Banwell and co-workers to good effect in the synthesis of polycyclic framework **274**.[149] An alternative to the DMTSF-mediated conditions was demonstrated by Ogasawara and co-workers,[150] using a combination of $AgNO_3$ and NCS in two step protocol, which was originally developed by Nicolaou and co-workers for a related process.[151,152] 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 dimethoxymethane and ethylaluminum dichloride 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.[153]

4.9 Harley-Mason rearrangements

Another approach to the spirocyclic indolenine framework was developed by Harley-Mason and co-workers, whereby indole



Scheme 37. Spirocyclisation by addition to an electrophilic nitrogen species (Narasaka et al.;[141] Nishikawa, Isobe et al.;[142] Kundu et al.[140]).



Scheme 38. Intramolecular addition to a thio/oxo-carbenium ion (Bosch et al.;[143–146] Shibasaki et al.;[147,148] Banwell et al.;[149] Ogasawara et al.;[150] Hart et al.[153]).

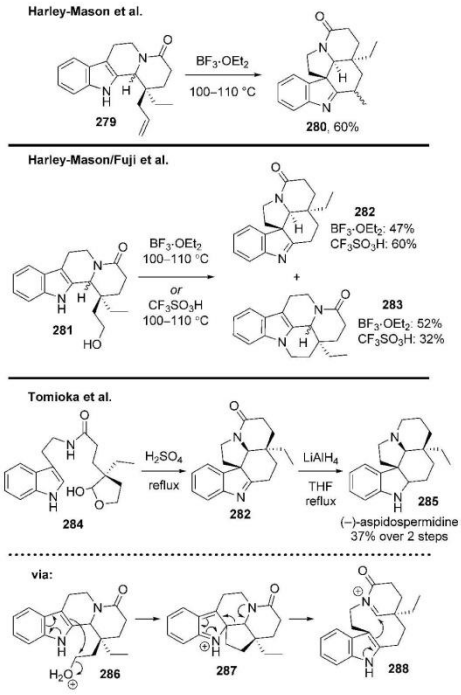
279 was heated in neat $BF_3{\cdot}OEt_2$ to initiate a rearrangement sequence to afford the spirocyclic indolenine **280** in good yield.[154] Later, Harley-Mason and co-workers effected the same rearrangement in the synthesis of (±)-aspidospermidine, using alcohol **281** and either sulfuric acid or boron trifluoride etherate.[155] Further work by Fuji and co-workers replicated this reactivity using high temperatures and either boron trifluoride etherate or triflic acid to synthesise the spirocyclic indolenine **282** in modest to good yield.[156,157] A more recent and elegant example of this reaction was demonstrated by Tomioka and co-workers,[158] who utilised chiral acetal **284** and acidic conditions to promote a sequential one-pot Pictet–Spengler reaction and Harley-Mason rearrangement, to afford the spirocyclic indolenine **282**, which was further reduced in situ to afford (−)-aspidospermidine **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**).[159]

4.10 Addition to nitriles/isonitriles

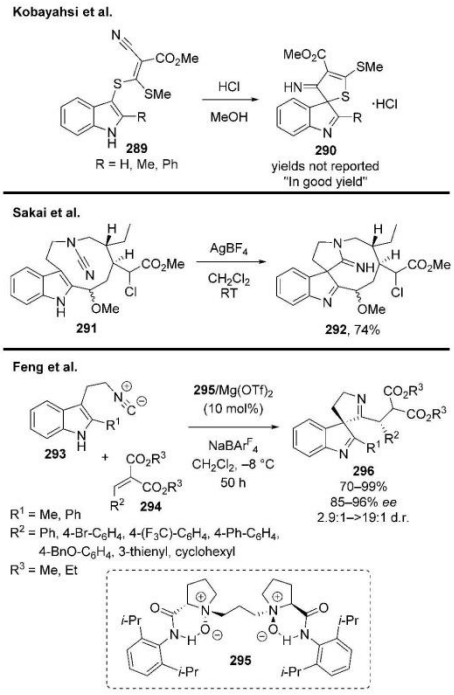
Nucleophilic addition into nitriles has also been utilised in spirocyclic indolenine synthesis, as first demonstrated by Kobayashi and co-workers;[160] the treatment of nitriles **289** with hydrochloric acid led to the formation of spirocycles **290** in unreported yield. Sakai and co-workers further proved the efficacy of this strategy when they reported a single example of an $AgBF_4$ mediated nucleophilic addition to a pendant nitrile **291**, affording amidine **292** in 74% yield (Scheme 40).[161] More recently, Feng and co-workers utilised an intriguing intermolecular Michael/Fridel–Crafts/Mannich cascade sequence between isonitrile **293** and alkylidene malonate **294**.[162] This process was catalysed by a combination of $Mg(OTf)_2$ with ligand **295** to afford a variety of spirocyclic indolenines **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 Pd^0-catalysed dearomative arylation of indoles (Scheme 41).[163] This reaction is proposed to proceed by Pd^0 oxidative addition into an aryl bromide **297**, followed by intramolecular carbopalladation on the indole 3-position and subsequent reductive elimination. Using this strategy, an impres-



Scheme 39. Spirocyclic indolenine synthesis by Harley-Mason rearrangements (Harley-Mason et al.;[154,155] Fuji et al.;[156,157] Tomioka et al.[158]).

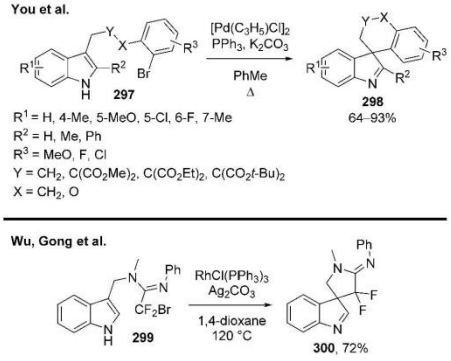


Scheme 40. Spirocyclisation by addition to a nitrile/isonitrile (Kobayashi et al.;[160] Sakai et al.;[161] Feng et al.[162]).

sive range of spirocyclic indolenines **298** can be formed in good to excellent yield. In similar vein, Wu, Gong and co-workers later described a single example of spirocyclic indolenine synthesis in their studies of the difluoromethylenative dearomatisation of phenols.[164] The reaction is proposed to proceed through oxidative addition of a transition metal complex (in this case Wilkinson's catalyst) into a pendant bromide **299**, intramolecular indole carbometallation and reductive elimination to afford the spirocyclic indolenine **300** in good yield.

4.12 Miscellaneous dearomatisation reactions

Other dearomatisation reactions which do not fit into a clearly defined theme are described in this section. One of the oldest examples of spirocyclic indolenine synthesis was detailed in 1965 by Schumann and Schmid, who used platinum oxide and an atmosphere of oxygen to generate (−)-tubifoline **302** from indole precursor **301** in good yield (Scheme 42).[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.[166–168]



Scheme 41. Spirocyclisation by dearomative cross-coupling (You et al.;[163] Wu, Gong et al.[164]).

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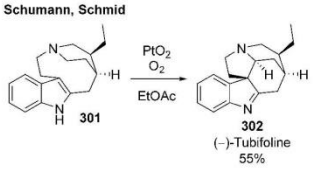
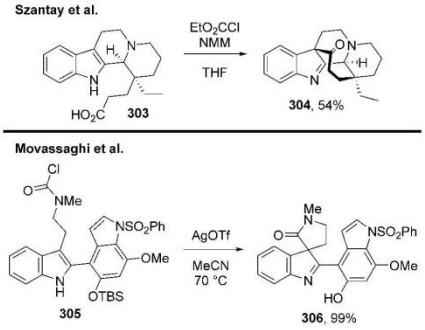


Scheme 42. Platinum oxide mediated spirocyclisation (Schumann and Schmid[165]).

The generation of a spirocyclic indolenine through an acylation reaction was first described by Szantay and co-workers (Scheme 43).[169] The treatment of acid **303** with ethyl chloroformate is proposed to form a mixed anyhydride, which following indole C-3 addition furnished the spirocyclic indolenine **304** in moderate yield. Later, Movassaghi and co-workers reported the near-quantitative formation of spirocyclic indolenine **306** upon the treatment of carbamoyl chloride **305** with AgOTf at 70 °C in acetonitrile.[170]

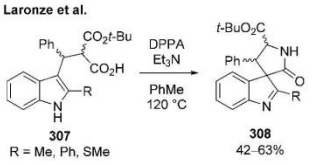


Scheme 43. Spirocyclisation by intramolecular acylation (Szantay et al.;[169] Movassaghi et al.[170]).

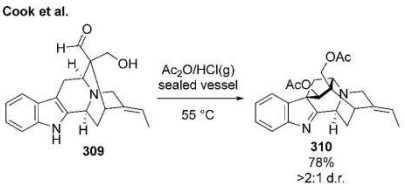
The Curtius rearrangement has also been employed in spirocyclic indolenine synthesis as demonstrated by Laronze and co-workers; the treatment of acid **307** with DPPA at 120 °C affords the typical isocyanate intermediate, which is trapped in situ by the indole by attack through its 3-position, forming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

Cook and co-workers demonstrated spirocyclisation by addition to an aldehyde (Scheme 45). Utilising an indole C-3 addition to a pendant aldehyde **309** and trapping the resultant alcohol with acetic anhydride afforded the spirocyclic indolenine **310** in good yield.[172]

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).[173] This process was initiated by the thermal



Scheme 44. The Curtius rearrangement applied to spirocyclic indolenine synthesis (Laronze et al.[171]).



Scheme 45. Intramolecular addition to a pendant aldehyde (Cook et al.[172]).

cleavage of the Boc protecting group of indole **311**, followed by treatment with NBS, which is proposed to form a highly reactive 3-bromo indolenine **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 chartelline C skeleton.[174]

In other synthetic studies geared towards the synthesis of the chartelline marine natural products, Nishikawa and co-workers reported the unexpected synthesis of spirocyclic indolenine **318** (Scheme 47).[175] 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 DME to afford the spirocycle **318** in improved yield.

Finally, Jiang, Zhou and co-workers recently reported that the combination of sulfone **319** and sulfur ylides **320** under basic conditions afforded a variety of spirocyclic indolenines **321** in good to excellent yield and with high diastereoselectivity (Scheme 48).[176] The reaction presumably proceeds via the conjugate addition of a sulfur ylide into an unsaturated intermediate **322** (itself formed via the extrusion of tolyl sulfinic acid from sulfone **319**) to access a reactive sulfonium species **324** which then quickly undergoes cyclopropanation to furnish the spirocyclic indolenine **321**.

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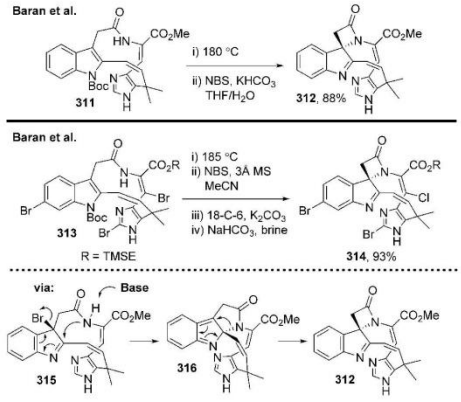
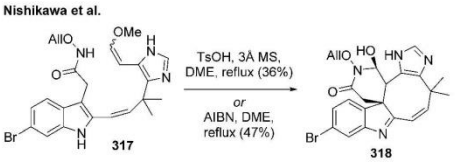
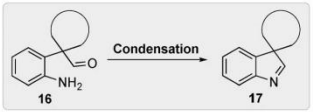


Scheme 46. NBS promoted spirocyclisation (Baran et al.[173,174]).

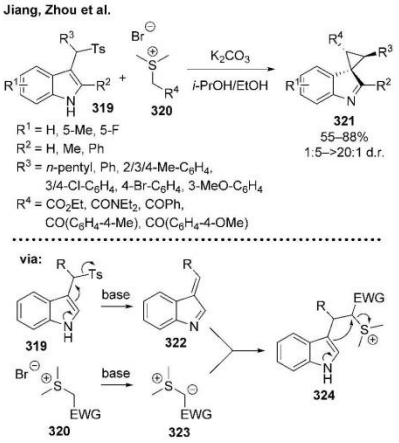


Scheme 47. Potential radical-mediated spirocyclisation (Nishikawa et al.[175]).

5. Condensation Reactions



Spirocyclic indolenine 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 unveiling 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 elegant cationic aza-Cope rearrangement sequence to reveal the requisite ketone for condensation (Scheme 49). The first examples were performed by treating cyclic hemiaminals **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 aniline to furnish a small selection of spirocyclic indolenines **326** in good to quantitative yield.[177] The same group further demonstrated the power of this protocol by treating hemiaminal **327** under the same reaction conditions,[178] 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 (±)-deoxoapodine, (±)-meloscine, (±)-epimeloscine, and the formal synthesis of (±)-1-acetylaspidoalbidine. Finally, Overman and co-workers applied this reaction sequence in the synthesis of (±)-dehydrotubifoline.[179] 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 (±)-dehydrotubifoline **331** in excellent yield.



Scheme 48. Sulfur ylide cyclopropanation (Jiang, Zhou et al.[176]).

Another elegant multistep sequence was developed by Bonjoch, Bosch and co-workers in their synthesis of (±)-dehydrotubifoline;[180] the key tandem cross-coupling, nitro reduction and condensation sequence was realised by employing a Ni^0 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.[181] This powerful methodology has also been used to complete the total synthesis of both (±)-akuammicine and (±)-norfluorocurarine.[182]

Finally, another multistep one-pot procedure was reported by Zhu and co-workers who utilised their iORC (integrated oxidation/reduction/cyclisation) process for the synthesis of (±)-1,2-dehydroaspidospermidine **339** (Scheme 51).[183] This process proceeds through a sequential one-pot ozonolysis, nosyl 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, (±)-aspidospermidine and (±)-vincadifformine.

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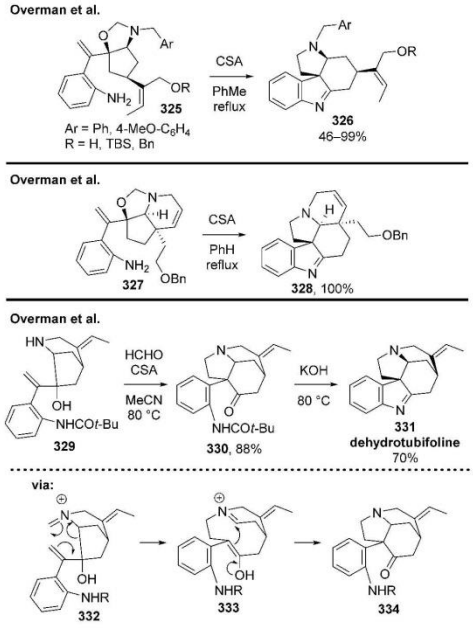
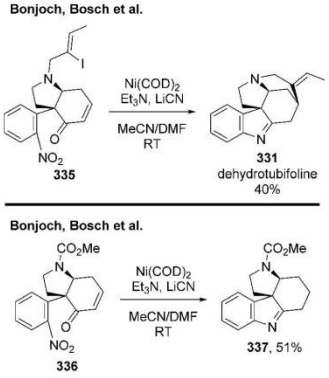


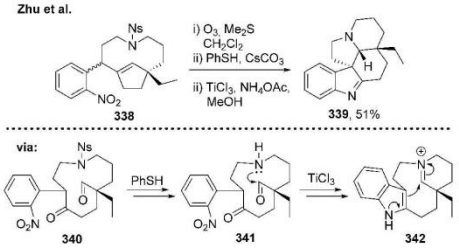
Scheme 49. Spirocyclisation mediated by an aza-Cope rearrangement (Overman et al.[177–179]).



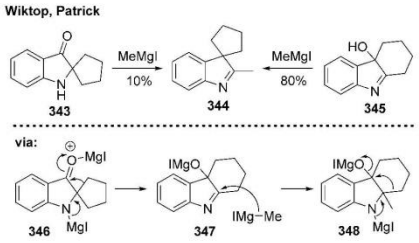
Scheme 50. Ni^0-promoted tandem cross-coupling, nitro reduction and condensation (Bonjoch, Bosch et al.[180–182]).

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, Witkop and Patrick reported the Wagner–Meerwein rearrangement of both **343** and **345** upon reaction with methyl magnesium iodide, with the rearrangement of indolenine **345** affording the spirocyclic indolenine **344** in good yield (Scheme 52).[27]



Scheme 51. Integrated oxidation, reduction and cyclisation protocol (Zhu et al.[183]).

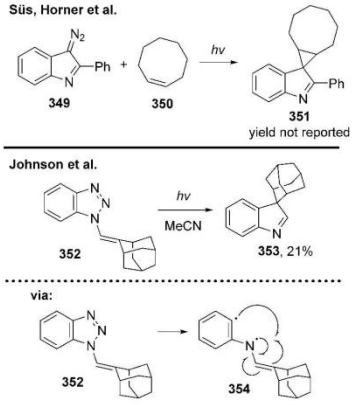


Scheme 52. Spirocyclic indolenine synthesis by the Wagner–Meerwein rearrangement (Wiktop and Patrick[27]).

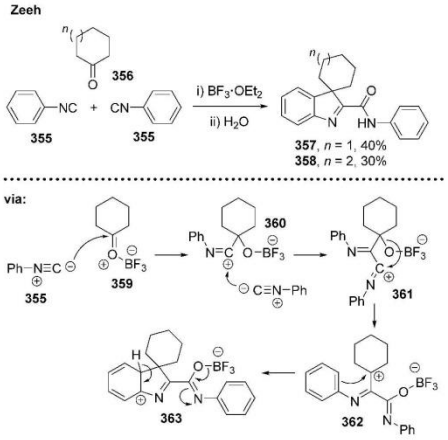
Photolysis has also briefly featured in spirocyclic indolenine synthesis (Scheme 53). First, Süs, Horner and co-workers described the photolysis of diazoindolenine **349** in cyclooctene **350** to furnish a product that was tentatively assigned as being spirocyclic cyclopropane **351**, in an undisclosed 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 indolenine **353** in low yield.[184]

Zeeh reported an unusual two step procedure, combining arylisocyanides **355** with cyclic ketones **356** in $BF_3{\cdot}OEt_2$ to furnish spirocyclic indolenines **357** and **358** in modest yield. This reaction was proposed to proceed through a multistep process, as depicted below in Scheme 54.[186]

An interesting S_NAr reaction was reported by Ong and co-workers in attempts to access the medicinally important spirocyclic piperidine framework (Scheme 55).[188] The treatment of nitrile **364** with phenyl magnesium bromide afforded only the unusual biphenyl spirocyclic indolenine **365** in low yield. The authors propose that the reaction proceeds by nucleophilic



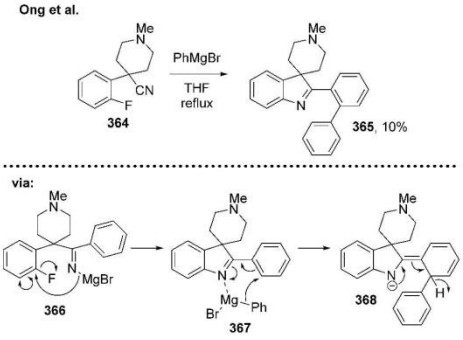
Scheme 53. Photochemistry in spirocyclic indolenine synthesis (Süs, Horner et al.;[185] Johnson et al.[184]).



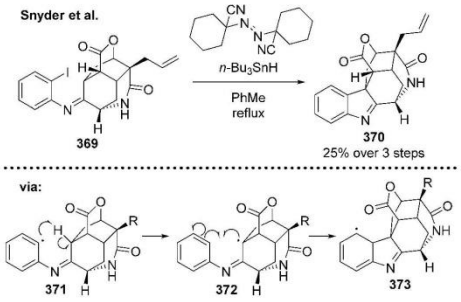
Scheme 54. Multicomponent spirocyclic indolenine synthesis (Zeeh[187]).

attack of the Grignard reagent into the nitrile, followed by an S_NAr reaction to displace the fluoride and then another Grignard addition into intermediate **367** which then rearomatises by eliminating hydride.

Snyder and co-workers reported one of the more recent spirocyclic indolenine preparations in their impressive total synthesis of (+)-scholarisine A.[189] This reaction is proposed to proceed by tributyltin radical halogen abstraction of **369**, 1,5-H transfer, cyclisation into the phenyl ring and then a radical terminating oxidation-rearomatisation sequence to form the spirocyclic indolenine **370** (Scheme 56).



Scheme 55. S_NAr-promoted spirocyclic indolenine synthesis (Ong et al.[188]).



Scheme 56. Spirocyclic indolenine synthesis through a radical process (Snyder et al.[189]).

Finally, Driver and co-workers recently reported an intriguing tandem reduction and cyclisation of nitrostyrenes **374** to afford spirocyclic indolenines **375** in good yields.[190] 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 intermediate **376** (Scheme 57).

7. Summary and Outlook

In this review, a wide range of impressive methodologies for the synthesis of spirocyclic indolenines are described. As is evident from the number of examples included, indole dearomatisation reactions are by far the most popular method for spirocyclic indolenine synthesis. However, we believe that there are still several under-utilised and under-developed strategies, for example the condensation strategy, which in our opinion, contains some of most elegant examples of spirocyclic indolenine synthesis, notably, those reported by Overman and

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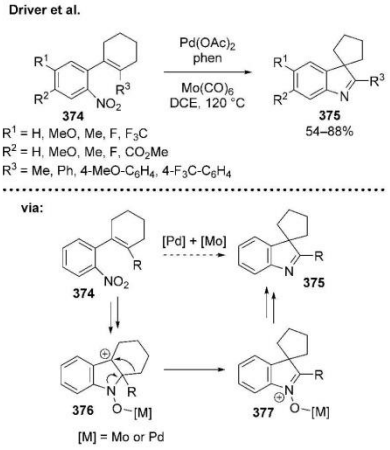

Scheme 57. Spirocyclic indolenine synthesis through a tandem reduction and cyclisation of nitrostyrenes (Driver et al.[190]).

co-workers. The impressive iORC approach of Zhu and co-workers further demonstrates the power of the condensation approach. Another area of current interest, which has only briefly appeared in spirocyclic indolenine synthesis are photochemical methods, and we envisage that a photoredox strategy might find application in spirocyclic indolenine synthesis in the future. At present, there are relatively few efficient catalytic asymmetric protocols for the synthesis of spirocyclic indolenines, which is a key area in need of further developments. For inspiration in this area, the work performed in π-allyl cyclisations by the You group and others represents the current state-of-the-art.[22,102] Our own contributions into this field using electrophilic activation of alkynes also demonstrate the potential for the development of other asymmetric reaction modes.[118] It is likely that over time, many 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 indolenine synthesis.[191] Overall, we trust that this review will serve to inform researchers wishing to synthesise spirocyclic indolenines, draw attention to the synthetic utility of the products themselves and encourage further growth in this area.

Acknowledgements

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Keywords: 3*H*-indoles · dearomatisation · indolenines · spirocycles · spiroindolenines

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Appendix II. Silver(I)- or Copper(II)-Mediated Dearomatization of Aromatic Ynones:

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Spirocycles

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Silver(I)- or Copper(II)-Mediated Dearomatization of Aromatic Ynones: Direct Access to Spirocyclic Scaffolds**

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 that contain ynone substituents, including indole, anisole, pyrrole, and benzofuran derivatives, into functionalized spirocyclic scaffolds. A high-yielding asymmetric variant furnishes spirocyclic indolenines in up to 89:11 e.r.*

Dearomatizing spirocyclization reactions[1] 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.[2] The dearomatization strategy described herein is based on the conversion of aromatic ynone derivatives into spirocycles through alkyne activation with a simple Lewis or π-acidic catalyst, illustrated by the conversion of indole derivative **1** into 3,3-substituted spirocyclic indolenine **2** (Figure 1a).[3,4] A significant problem with this type of transformation is the proclivity 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 indolenines. An illustrative example was recently reported by Van der Eycken (Figure 1b):[5] spirocyclic indolenine **4a** was formed in low yield when alkyne **3** was treated with $AuPPh_3Cl/AgOTf$, the other major product being the rearomatized indole **4b**. Indeed, while processes involving the electrophilic activation of alkynes have been well studied in recent years,[6] 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;[7] in related processes, rearomatized products such as compound **4b** are reported far more often (not only with indoles, but across a range of heteroaromatics).[7,8]

The new methods described herein provide a general, high-yielding strategy for the conversion of a range of achiral heteroaromatics (left in Figure 2) into complex, spirocyclic

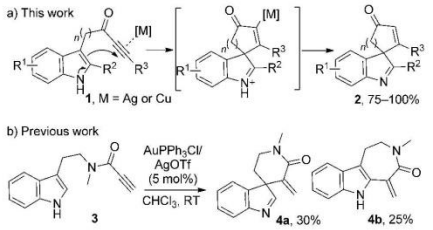

Figure 1. Dearomatizing spirocyclization through electrophilic alkyne activation.

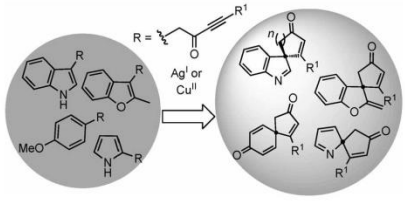

Figure 2. Dearomatizing spirocyclization.

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 enone 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 spirocycle **6a** using a range of Brønsted, Lewis, and π acids to activate the alkyne. 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 $Cu(OTf)_2$, $AgNO_3$, and AgOTf (Table 1), while surprisingly, standard gold π -acids[9] were ineffective,[10] as was triflic acid (Table 1, entry 2).[11] The dearomatizing spirocyclization reaction of indole **5a** can be performed efficiently under a range of conditions (Table 1, entries 3–7),[12] with the use of 0.01 equivalents of AgOTf in dichloromethane at room

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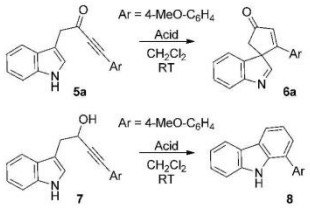
Table 1: Optimization of acid-catalyzed indole/alkyne spirocyclization.



Entry	Starting material	Acid (equiv)	t [h]	Product	Yield [%][a]
1	**5a**	–	20		–
2	**5a**	TfOH (0.01)	1	**6a**	trace
3	**5a**	$Cu(OTf)_2$ (1)	20	**6a**	80
4	**5a**	$Cu(OTf)_2$ (0.01)	8.5	**6a**	89
5	**5a**	$AgNO_3$ (0.01)	2.5	**6a**	97
6	**5a**	AgOTf (0.1)	1	**6a**	95
7	**5a**	AgOTf (0.01)	0.5	**6a**	100
8	**7**	AgOTf (0.1)	1	**8**	80

[a] All reactions performed in CH_2Cl_2 (0.1 M) at RT.

temperature being optimal, furnishing spirocyclic indolenine **6a** in quantitative yield (entry 7, for X-ray crystallographic data see the Supporting Information).[13] 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.[8] 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 indolenines **6a**–**6d** in very good yields with short reaction times at room temperature (Table 2, entries 1–4). Alkyl-substituted ynones **5e** and **5f** were similarly good substrates, furnishing indolenines **6e** and **6f**, respectively, in excellent yields under the same conditions (Table 2, entries 5 and 6).[15] Additional substitution around the indole system is also well tolerated: for example, benzyl- and bromo-substituted spirocycles **6g** and **6h** were each formed in high yields (Table 2, entries 7 and 8). Indolenines **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). Indolenine **10**[15] was also synthesized, through a desilylation/spirocyclization sequence, by

Table 2: Substrate scope of indole/ynone spirocyclization.[a]

Entry	Starting material	t [h]	Isolated product	Yield [%]
1	**5a** Ar = 4-MeO-C_6H_4	0.5	**6a** Ar = 4-MeO-C_6H_4	100[b]
2	**5b** Ar = Ph	0.5	**6b** Ar = Ph	100[b]
3	**5c** Ar = 4-Me_2N-C_6H_4	0.3	**6c** Ar = 4-Me_2N-C_6H_4	97[b]
4	**5d** Ar = 4-Br-C_6H_4	1.5	**6d** Ar = 4-Br-C_6H_4	100
5	**5e** R = Me	2	**6e** R = Me	95[b]
6	**5f** R = *n*Bu	3.5	**6f** R = *n*Bu	100[b]
7	**5g** Ar = 4-MeO-C_6H_4	0.5	**6g** Ar = 4-MeO-C_6H_4	95[c]
8	**5h** Ar = 4-MeO-C_6H_4	1	**6h** Ar = 4-MeO-C_6H_4	100
9	**5i** Ar = 4-MeO-C_6H_4	0.2	**6i** Ar = 4-MeO-C_6H_4	100
10	**5j** Ar = 4-MeO-C_6H_4	0.1	**6j** Ar = 4-MeO-C_6H_4	84
11[d]	**5k** Ar = 4-MeO-C_6H_4	16	**6k** Ar = 4-MeO-C_6H_4	75
12[e]	**9**	16	**10**	93

[a] All reactions performed using 0.01 equiv AgOTf as catalyst in CH_2Cl_2 (0.1 M) at RT, unless otherwise stated. [b] Compounds **6a**–**c** and **6e**–**f** can also be formed using 0.01 equiv $Cu(OTf)_2$ (see the Supporting Information). [c] d.r. = 55:45. [d] Reaction performed using 0.1 equiv AgOTf as catalyst at 35 °C. [e] Reaction performed in acetone using $AgNO_3$ (0.2 equiv) as catalyst.

stirring ynone **9** with 0.2 equivalents of $AgNO_3$[16] in acetone at room temperature for 16 h, affording spirocyclic cyclopentenone **10**, 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

TMS = H) required to access spirocycle **10** in the standard way is unstable and could not be isolated.

Promising preliminary studies have also been performed using Ag^I salts of chiral phosphoric acids (CPAs) as catalysts for the indole/ynone spirocyclization (Figure 3). Six catalysts

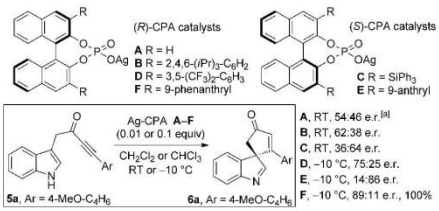


Figure 3. Asymmetric spirocyclization of **5a**. All reactions were performed using 0.09–0.30 mmol of **5a** in chloroform (0.1 M) and 0.01 equiv of the specified CPA catalyst. The reaction mixtures were stirred at either RT or −10°C for 16 h, unless otherwise stated. Enantiomeric ratios were measured by HPLC using a Chiralpak IB column, eluting with 10% IPA in hexane, and the major enantiomer formed using the (*R*)-CPA catalysts **A**, **B**, **D**, and **F** is shown. [a] Reaction was performed in CH_2Cl_2 using 0.1 equiv of catalyst **A** for 5 min. IPA = isopropanol.

were screened, all of which are simple Ag^I salts of commercially available BINOL-based CPAs.[17] 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.r.). 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.r. observed using 9-phenanthryl derivative **F**, which furnished spirocycle **6a** in quantitative yield, in 89:11 e.r.

These conditions were then applied to other ynone substrates. Pleasingly, in all cases the spirocyclic products were isolated in high yields (**6b**, **6d**,**e**, **6h**,**i**, 62–100%) and with consistently good enantioselectivity (e.r. 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.r. of compounds **6a** and **6d** could be easily increased (98:2 e.r.) following recrystallization from ethyl acetate/hexane. The fact that good enantiomeric ratios were achieved by testing a relatively small number of commercially available CPAs augurs well that further optimization will lead to greater improvements.[18] The major enantiomer formed in reactions using (*R*)-CPA catalysts is the (*S*)-spirocycle (as shown in Figures 3 and 4) based on X-ray crystallographic data of spirocycle **6d**.[13,19] A tentative mechanism consistent with this outcome is included in the Supporting Information.

Finally, preliminary studies demonstrate that a wider range of aromatic ynones undergo dearomatizing spirocyclization, expanding the potential scope of the method (Table 3). Anisole-substituted ynone **11** furnished spirocyclic dienone **12**[20,21] upon treatment with 0.1 equivalents of $Cu(OTf)_2$, 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 dearomatizing 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.

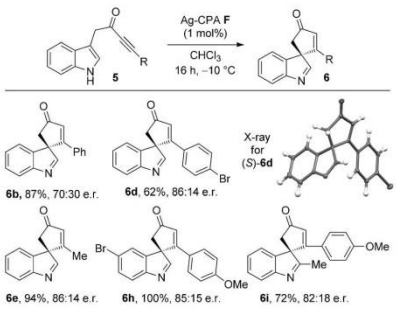


Figure 4. Asymmetric spirocyclization reactions. All reactions were performed using 0.09–0.30 mmol of ynone in chloroform (0.1 M) and 0.01 equiv of catalyst **F**. The reaction mixtures were stirred at −10°C for 16 h. Enantiomeric ratios were measured by HPLC using a Chiralpak IB column, eluting with 10% IPA in hexane.

Table 3: Alternative spirocyclization reaction systems.[a]

Entry	Starting material	*t* [h]	Isolated product	Yield [%]
1[b]	**11** Ar = 4-Me_2N-C_6H_4	1	**12** Ar = 4-Me_2N-C_6H_4	95
2[c]	**13** Ar = 4-MeO-C_6H_4	0.5	**14** Ar = 4-MeO-C_6H_4	99
3[d]	**15** Ar = 4-MeO-C_6H_4	18	**16** Ar = 4-MeO-C_6H_4	68

[a] Reactions performed in CH_2Cl_2 (0.1 M) at RT. [b] 0.1 equiv $Cu(OTf)_2$ used as catalyst. [c] 0.1 equiv $AgNO_3$ used as catalyst. [d] 0.01 equiv AgOTf used as catalyst.

Keywords: asymmetric catalysis · dearomatization · indolenines · silver · spirocycles

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Angew. Chem. **2015**, *127*, 7750–7753

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[9] A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; *Angew. Chem.* **2007**, *119*, 3478.

[10] A complex mixture of products was formed when the mixed $AuPPh_3Cl/AgOTf$ catalyst system used in the work of Van der Eycken (see Figure 1b and reference [5]) was tested.

[11] The unpurified reaction mixture (Table 1, entry 2) contained approximately 90% unreacted **5a**, along with other unidentified impurities and only trace amounts of spirocycle **6a**. This appears to rule out the possibility that the successful reactions using AgOTf or $Cu(OTf)_2$ are catalyzed by adventitious triflic acid through "hidden Brønsted acid catalysis". See: T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353.

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

[13] CCDC 1023667 (**6a**) and 1049165 (**6d**) 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/cif.

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[15] Compounds **6f** and **10** exist as equilibrating mixtures of indolenine and imine trimers in $CDCl_3$. To simplify its NMR spectra, compound **10** was characterized as its salt with TFA. See: J. S. L. Ibaceta-Lizana, A. H. Jackson, N. Prasitpan, P. V. R. Shannon, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1221.

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[18] SPINOL-based CPA catalysts have been shown to improve the e.r. of related processes. See: C.-H. Xing, Y.-X. Liao, J. Ng, Q.-S. Hu, *J. Org. Chem.* **2011**, *76*, 4125, and references therein.

[19] A sample of spirocycle **6d** was enriched to 98:2 e.r. by recrystallization from ethyl acetate/hexane, before a single crystal was then grown by slow crystallization from ethyl acetate/hexane, with the heavy Br atom allowing the absolute configuration to be determined. The specific crystal used to obtain the X-ray data was confirmed as being the major enantiomer using HPLC.

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

Organic LETTERS

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

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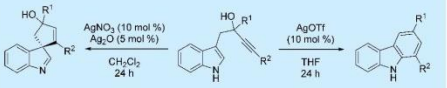
Supporting Information

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 (±)-actinopolymorphol B is also reported.



The indole subunit can be found in numerous biologically active natural products and pharmaceutical compounds.[1] For example, benzo-fused indoles (carbazoles) have well established, broad therapeutic potential, with prominent examples exhibiting anticancer, anti-HIV, and antimalarial properties (**1**–**3**, Figure 1).[2] Spirocyclic indolenines have also

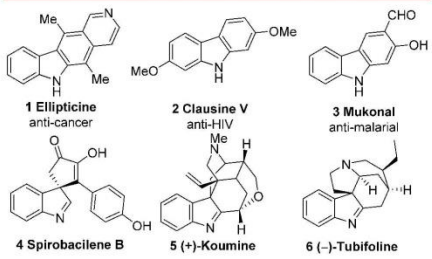
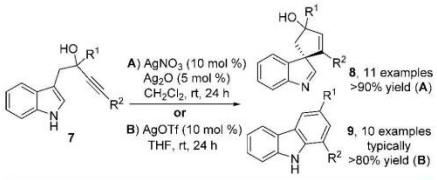


Figure 1. Carbazole and indolenine natural products.

attracted attention in recent years, in view of their presence in various natural products (**4**–**6**, Figure 1)[3] and their ability to act as precursors for other privileged heterocycles such as indolines and oxindoles[4] and as scaffolds to evaluate under-explored regions of chemical space in a range of bioassays.[5] New methods that expedite the synthesis of each of these scaffolds are therefore 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,[6] we reported a single example of a novel carbazole-forming reaction, based on the activation of an indole-derived propargyl alcohol[7] with AgOTf. This transformation was proposed to proceed via an initial Ag(I)-catalyzed spirocyclisation (*cf.* **7** → **8**), before undergoing 1,2-migration[8] and subsequent elimination *in situ*,

Scheme 1. Divergent Synthesis of Spirocyclic Indolenines and Carbazoles



furnishing a carbazole product (*cf.* **9**). In this study, it was planned to identify reaction conditions that would deliver either spirocyclic indolenine **8** or carbazole **9** selectively. The known propensity for related spirocyclic alkenes to undergo the aforementioned 1,2-migration[9] 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. Optimized 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 $AgNO_3$ as catalyst (Table 1). First, compound **7a** was treated with 10 mol % AgOTf in CH_2Cl_2 at rt for 24 h (entry 1) and the major component of the unpurified reaction mixture was carbazole **9a** (90%), although a small amount of spirocyclic indolenine **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 $AgNO_3$, the selectivity was reversed under otherwise identical conditions; in each of the three solvents tested, the only product formed was the spirocyclic indolenine **8a**, as a

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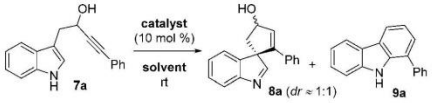
Table 1. Ag(I)-Mediated Reactions of Alkyne 7a



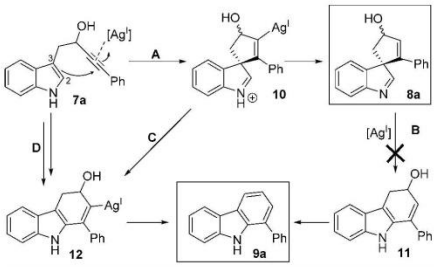
				proportion, %[d]		
entry	catalyst[a]	solvent	additive	7a	8a	9a
1	AgOTf	CH_2Cl_2	–	–	10	90
2	**AgOTf**	**THF**	–	–	–	**100**
3	AgOTf	PhMe	–	–	–	100
4	$AgNO_3$	CH_2Cl_2	–	trace	>95	–
5	$AgNO_3$	THF	–	10	90	–
6	$AgNO_3$	PhMe	–	90	10	–
7	AgOTf	THF	Et_3N[b]	55	45	–
8	$AgNO_3$	CH_2Cl_2	*p*-TSA[c]	20	40	40
9	**$AgNO_3$**	**CH_2Cl_2**	**Ag_2O[b]**	–	**100**	–

[a]Reactions performed with 0.1–0.2 mmol of **7a** and 10 mol % catalyst in the stated solvent (0.1 M) at rt. [b]5 mol %. [c]2 mol %. [d]Calculated using the ^{1}H NMR spectrum of the unpurified reaction mixture, rounded to the nearest 5%.

roughly 1:1 mixture of diastereoisomers (entries 4–6). One theory to 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 forming reactions.[10] 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 indolenine 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 $AgNO_3$ in CH_2Cl_2 (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 $AgNO_3$ in order to establish a reliable synthetic procedure for spirocycle formation; several additives were trialled, and the addition of 5 mol % of Ag_2O 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 scoping 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 π-acidic Ag(I) catalyst[11] presumably promotes spirocyclization via nucleophilic attack of the indole 3-position (route **A**; **7a** → **10**) before protodemetalation reveals the indolenine product (**10** → **8a**). The formation of carbazole **9a** is more complicated. One possibility is that indolenine **8a** is an intermediate en 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 indolenine **8a** to the optimal carbazole-forming reaction conditions (10 mol % AgOTf in 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

Scheme 2. Mechanistic Possibilities



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 nucleophilic 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.[8,9,12] 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 these reactions, indicating that this step may by mediated by a Brønsted acid, rather than the Ag(I) catalyst itself.[9] 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**, that undergoes the key 1,2-migration is intriguing and is expected to be instructive during future endeavors in the field of Ag-catalysis.

The scope of each of the two reaction modes was examined using the optimized conditions, beginning with the spirocyclization procedure (Figure 2).[12,13] Good reactivity was observed for electron-neutral (**8a**), electron-rich (**8c**), and electron-poor (**8d**) aromatic examples, and silyl protection on the alcohol is also well tolerated (**8b**). Similarly, simple alkyl (**8e**) and cyclopropyl (**8f**) spirocycles were furnished 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 thiophene group in product **8i** indicates that other heterocycles can be used in this method. Finally, indoles substituted on their 2-position are also suitable substrates, with indolenine **8j** being formed in quantitative yield under the standard conditions. There was no diastereocontrol in any of the reactions (all products were isolated as aproximately 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.[9] Previously, it was suggested that an electron-withdrawing carbonyl group is needed to reduce the migratory aptitude of the alkene product,[6] 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

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Org. Lett. 2015, 17, 4372–4375

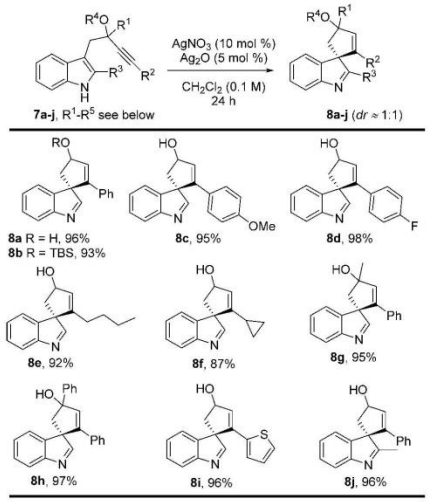


Figure 2. Ag(I) mediated dearomatizing spirocyclization to form spirocyclic indolenines.

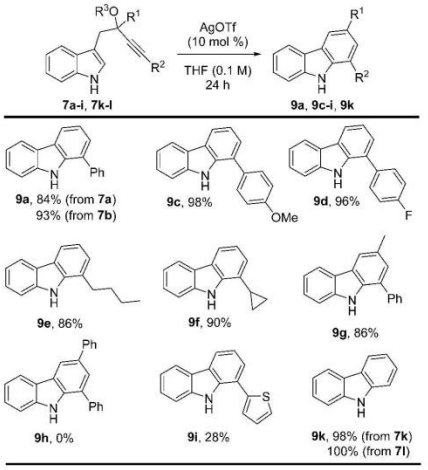
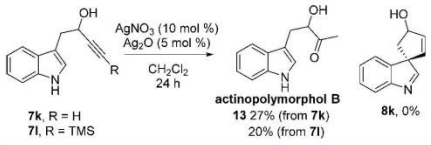


Figure 3. Ag(I) mediated carbazole synthesis.

of other dearomatization reactions involving electrophilic alkyne activation.

The only substrates tested which failed to deliver the desired spirocyclic indolenines are shown in Scheme 3. The terminal

Scheme 3. Synthesis of Actinopolymorphol B 13



alkyne starting material **7k** and its trimethylsilyl-substituted analogue **7l**[14] were each treated under the standard conditions for indolenine 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 (±)-actinopolymorphol B **13**.[15] Alkyne hydration reactions of this type have traditionally been performed under acidic conditions using a Hg(II) catalyst,[16] although, more recently, Ag(I) and Au(I) variants have also been reported;[17] 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.[18] 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.[19] Also, carbazole **9i** was isolated in much lower yield in this series, with the majority of the material recovered being spirocycle **8i**, indicating that there is a higher energy barrier to the 1,2-migration pathway in this system. However, in contrast to the indolenine 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.[20] Note that the carbazole product was formed as a single regioisomer in all cases, with the regiochemical outcome being consistent with the 1,2-migration of the alkenyl 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,[21] 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 indolenines 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 alkyne tethered indoles. The results accrued shed light on the mechanism of each process, indicating that the spirocyclization step is Ag(I)-catalyzed, whereas the 1,2-migration step, which appears to proceed via a vinyl silver intermediate, could be promoted by an adventitious Brønsted acid. Finally, the natural product (±)-actinopolymorphol B was synthesized unexpectedly when the standard indolenine-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 optimization other silver-mediated hydration con-

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ditions may be uncovered, for use in the improved synthesis of hydroxyl ketone **13** and related natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02216.

Experimental procedures, spectroscopic data, and X-ray data (PDF)

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Notes

The authors declare no competing financial interest.

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(20) The contrasting reactivity of substrates **7k**/**7l** under the two sets of reaction conditions is surprising; further studies are planned to probe this effect.

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Appendix IV. Silica-Supported Silver Nitrate as a Highly Active Dearomatizing Spirocyclization Catalyst: Synergistic Alkyne Activation by Silver Nanoparticles and Silica

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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 $AgNO_3$ ($AgNO_3$–SiO_2) catalyzes the dearomatizing spirocyclization of alkyne-tethered aromatics far more effectively than the analogous unsupported reagent; in many cases, reactions which fail using unsupported $AgNO_3$ proceed effectively with $AgNO_3$–SiO_2. 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.*

Pioneered in the 1960s, silica-supported $AgNO_3$ ($AgNO_3$–SiO_2) is well-known for its use as a support in the separation of *E*- and *Z*-alkenes by column chromatography.[1] However, the synthetic potential of $AgNO_3$–SiO_2 as a catalyst has been mostly over-looked, with just a handful of reports on its use as a reagent in organic synthesis.[2] To the best of our knowledge, examples are limited to syntheses of 5-membered heterocycles from alkynes and allenes, reported by Marshall[2a] and Knight.[2b,c] As part of a wider program on dearomatizing spirocyclization reactions,[3,4] we decided to investigate the catalytic potential of $AgNO_3$–SiO_2 due to its limited previous use in synthesis and with the intention of exploiting the practical benefits of using a solid-supported reagent.[5] To our surprise, we found that $AgNO_3$–SiO_2 offers vastly superior reactivity compared with unsupported $AgNO_3$ in dearomatizing spirocyclization reactions[3] of alkyne-tethered heteroaromatics of the type shown in Figure 1.[4]

Of much significance, several dearomatization reactions that previously failed with unsupported $AgNO_3$ can now be carried out in high yield with the $AgNO_3$–SiO_2 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)[6] formed during the preparation of $AgNO_3$–SiO_2 together with a synergistic effect from the silica support itself. Pre-prepared Ag-NPs have been used as catalysts previously,[7–9] 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 $AgNO_3$–SiO_2 as an easily prepared and highly active catalyst for dearomatizing spirocyclizations (Figure 1), showcasing the methodology with the $AgNO_3$–SiO_2-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.

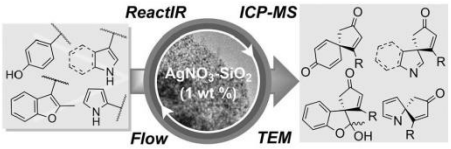

Figure 1. $AgNO_3$–SiO_2 mediated dearomatizing spirocyclization.

To start, we examined the conversion of ynone **1a** into spirocyclic indolenine **2a**.[10] Commercial $AgNO_3$–SiO_2 (10 wt% $AgNO_3$ on silica) was found to effect this transformation with reasonable efficiency,[11] and following additional optimization (see Supporting Information) it was discovered that "home-made"[12] $AgNO_3$–SiO_2 with a reduced $AgNO_3$ loading of 1 wt% was an even more effective catalyst; stirring ynone **1a** at RT in CH_2Cl_2 with catalytic (1 mol%) 1 wt% $AgNO_3$–SiO_2 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 $AgNO_3$ (6 h, conditions B).[4a] Even more dramatic differences were seen in the reactions of ynones tethered to other aromatics; phenol **3a**, pyrrole **5a** and benzofuran **7** were reacted with both catalyst systems, and while spirocyclic products **4a**, **6a**, and **8** were isolated in high yields when 1 wt% $AgNO_3$–SiO_2 was used, $AgNO_3$ alone led to no reaction in all three cases (Scheme 1).[13,14]

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% $AgNO_3$–SiO_2 catalyst, ynone **1a** was converted into spirocycle **2a** in 30 min (blue line, **A**, Figure 2),

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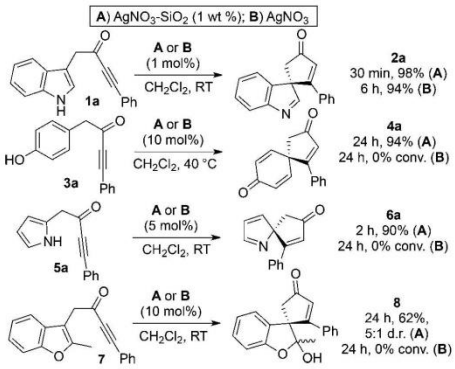


Scheme 1. Supported and unsupported Ag^{I}-catalyzed spirocyclization.

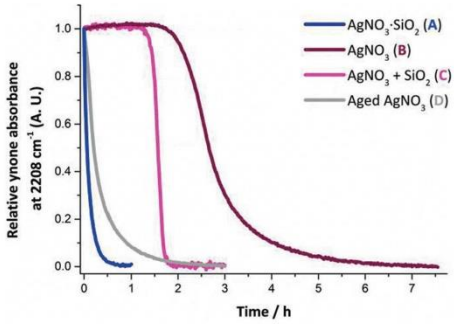


Figure 2. 2D ReactIR plots of the conversion of **1a** into **2a** using catalysts **A**–**D** (1 mol%) in CH_2Cl_2 at RT.

fully consistent with the synthetic reaction. In contrast, as expected from the synthetic work, the unsupported $AgNO_3$ 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, $AgNO_3$ and silica were both added to a solution of **1a** in CH_2Cl_2 (i.e. the $AgNO_3$ 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 $AgNO_3$–SiO_2 reaction (blue line, **A**). Silica is not able to promote spirocyclization on its own (stirring ynone **1a** in silica in CH_2Cl_2 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 protodemetallation;[15] 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 $AgNO_3$–SiO_2 catalyst and unsupported $AgNO_3$ in the presence of silica (which should have the same elemental composition). This led us to propose that $AgNO_3$ 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 $AgNO_3$ was "aged" by stirring the standard reaction dose in CH_2Cl_2 for 24 h before adding ynone **1a**; the expectation was that by ageing the catalyst, Ag-NPs would form in advance and alter the reaction profile.[16] The initially colorless solution became yellow during the ageing process, which is indicative of Ag-NP formation,[17] and the aged catalyst did indeed perform differently (gray line, **D**). The reaction proceeded at a similar rate to the standard $AgNO_3$ 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,[18] adding additional support to the idea that Ag-NPs are the true catalyst. Further supporting evidence was obtained using transmission electron microscopy (TEM); $AgNO_3$ was stirred for 24 h at RT in CH_2Cl_2 and an aliquot of the solution (≈5 μL) was removed and dropped onto a copper TEM grid. The deposit that remained after the CH_2Cl_2 had evaporated was then analyzed using TEM, and Ag-NPs were found to be present (Figure 3).

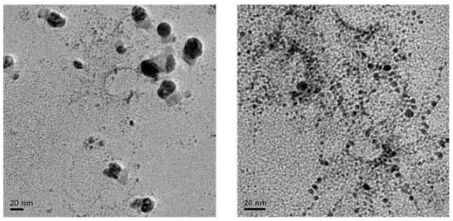


Figure 3. TEM images for $AgNO_3$ "aged" in CH_2Cl_2.

In view of the above results, we considered it likely that Ag-NPs were also present in our standard supported $AgNO_3$–SiO_2 (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.[19]

Thus, it appears that in both the supported and unsupported systems, Ag-NPs rather than $AgNO_3$ are predominantly 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 protodemetallation, and hence more effective catalyst turnover and/or its role may also be to adsorb the Ag-NPs and control their growth/aggregation.

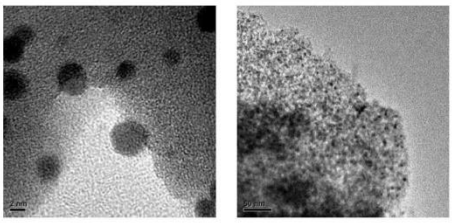


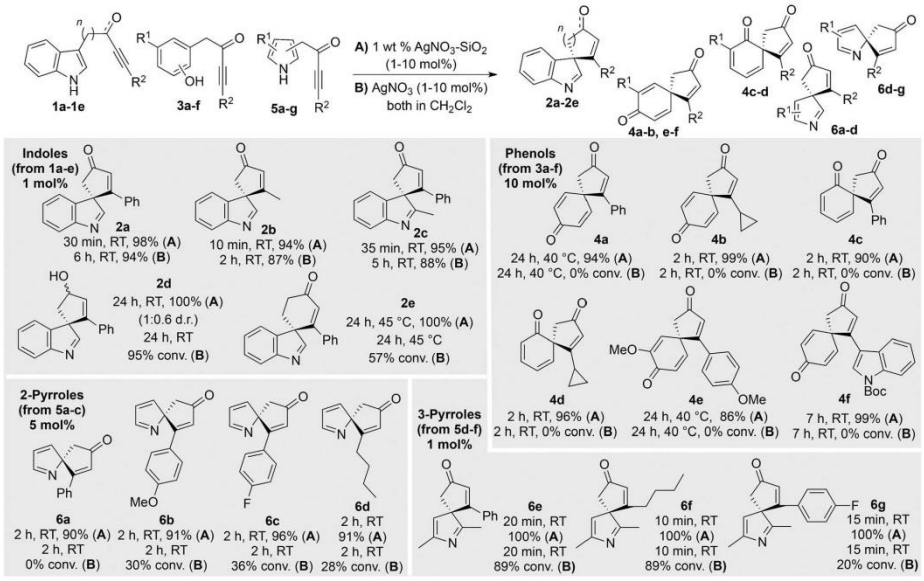
Figure 4. TEM images for $AgNO_3$–SiO_2.

Next, to more fully evaluate the synthetic utility of our $AgNO_3$–SiO_2 catalyst, the optimized spirocyclization conditions were applied to other alkyne-tethered aromatics, and compared to unsupported $AgNO_3$ in each case (Scheme 2).

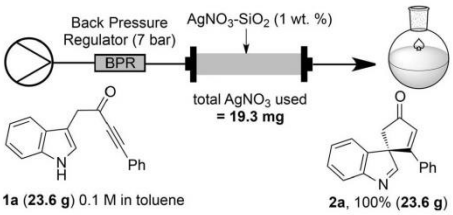
Indolyl spirocyclic products **2a–e** were all obtained in excellent yields (94–100%), with $AgNO_3$–SiO_2 promoting a faster transformation than with unsupported $AgNO_3$ in all cases. More pronounced differences in reactivity were observed for 2- and 4-phenol derivatives **3a–f**; these substrates did not react at all using unsupported $AgNO_3$, but using $AgNO_3$–SiO_2 spirocyclic dienones **4a–f** were all formed in high yield, notably including compound **4f**, an advanced intermediate in a published route to spirobacillene A.[14a] Pyrrole derivatives **5a–g** are also well tolerated, with $AgNO_3$–SiO_2 superior to unsupported $AgNO_3$ in all examples. The quantitative formation of spirocycles **6e–g** is especially noteworthy, given the rarity of dearomatized products derived from 3-pyrroles.[20] 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.[21]

Finally, the use of our $AgNO_3$–SiO_2 catalyst in a continuous flow reaction[22] 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 $AgNO_3$) at a flow rate of 0.3 mL min^{-1}, concentrated in vacuo, and analyzed using ^{1}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% $AgNO_3$–SiO_2 is a very effective catalyst for the dearomatizing spirocyclization of alkyne-tethered heteroaromatics, with its efficacy believed to stem from a synergistic relationship between the silica support and Ag-NPs formed during its preparation. It is much more reactive than unsupported $AgNO_3$, 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.[23] In contrast to existing methods to prepare supported



Scheme 2. Supported and unsupported Ag^I-catalyzed spirocyclization. Isolated yields (following catalyst removal) are quoted, or for incomplete reactions, conversion (conv.) was calculated based on analysis of the ^{1}H NMR spectrum on the unpurified product mixture.



Scheme 3. Flow spirocyclization of ynone **1a**.

Ag-NPs,[6a,8b] our catalyst is easy to prepare with full silver incorporation into the supported catalyst and it can be stored in the dark at RT for several months with no loss of activity.[12] The reactions are easy to perform and are purified simply by removing the supported catalyst by filtration, which can then be reused five times with no apparent loss of activity.[24] ICP-MS analysis confirmed that spirocycle **2a** formed under the standard conditions contains ca. 60 ppm silver (which is pleasing given that no aqueous work-up or chromatography was performed on the analyzed samples), and by performing the same reaction in toluene rather than CH_2Cl_2, silver contamination in the product could be reduced to just 5 ppm, which is significantly below the 17 ppm limit set by the FDA for the permissible amount in a drug.[25] All of these findings have potential implications in both previous and future work; it may now be considered that the processes previously described by Marshall and Knight using $AgNO_3$–SiO_2 also benefitted from the presence of Ag-NPs, while moving forwards, $AgNO_3$–SiO_2 may also represent a more convenient source of Ag-NPs than those prepared by conventional methods.

Acknowledgements

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Keywords: dearomatization · flow chemistry · heterogeneous catalysis · silver nanoparticles · spirocycles

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[12] 1 wt % $AgNO_3$–SiO_2 was prepared by adding $AgNO_3$ (100 mg) to a slurry of Fluka silica gel (9.90 g, pore size 60 Å, 220–440 mesh particle size) in deionized water (27 mL). The mixture was stirred for 15 min, concentrated in vacuo at 60 °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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[19] Qualitatively, the supported Ag-NPs appear to be much more uniform in size than those obtained from aged $AgNO_3$ in CH_2Cl_2; more detailed studies will be required in future to probe this observation and its implications more rigorously.
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[23] Silica-supported Ag-NPs synthesized by literature methods (references [6a] and [8b]) 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

John T. R. Liddon, Michael J. James, Aimee K. Clarke, Peter O'Brien, Richard J. K. Taylor,* and William P. Unsworth*[a]

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 dearomatising 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.[1] 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/carbocycles; Figure 1). This approach has the potential to significantly streamline existing synthetic methods, and lead to a broader understanding of catalysis and reaction mechanisms. Although there have been numerous examples of catalyst variation leading to different products in recent years,[2,3] such methods have mainly focused on the formation of products with similar frameworks (e.g., redox isomers, regioisomers 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.

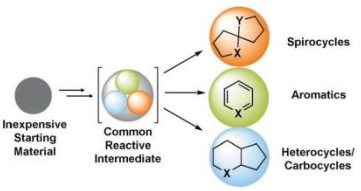
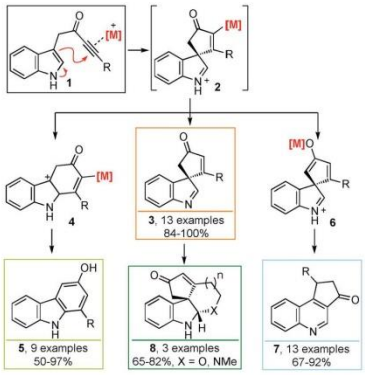


Figure 1. Catalyst-driven scaffold diversity.

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



Scheme 1. Divergent synthesis of spirocycles **3**, carbazoles **5**, quinolines **7** and tetracyclic scaffolds **8** from indolyl ynones **1**.

demonstrated that the dearomatising spirocyclisation[4] of ynones **1** into spirocyclic indolenines **3** can be catalysed by AgOTf, with vinyl–silver species **2** ([M] = Ag) as likely intermediates.[5] 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[6] **3** using Ag^{I}, carbazoles **5** using Au^{I} and quinolines **7** using Ag^{I}/Al^{III} in high yield, each by

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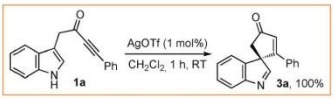
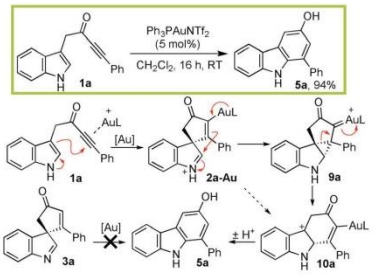
a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetracyclic scaffolds **8** can be formed with complete diastereoselectivity, by a telescoped spirocyclisation/nucleophilic addition sequence, which was performed using a chiral Ag^{I} salt to furnish an enantiopure product.

The spirocyclisation of **1a** using AgOTf formed indolenine **3a** in quantitative yield (Scheme 2);[5] the mild reaction conditions 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[7] in a controlled manner.[8] A $Ph_3PAuNTf_2$ catalyst was chosen based on the prediction that the π-acidic gold(I) 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–carbenoid species.[9] 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.[7,9] 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 $Ph_3PAuNTf_2$ under the same conditions.

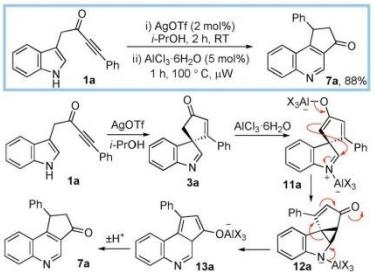


Scheme 2. Formation of spirocyclic indolenine **3a**.



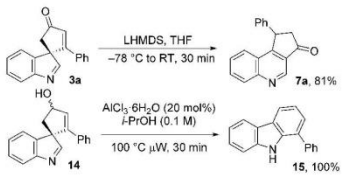
Scheme 3. Formation of carbazole **5a**; [Au] = $Ph_3PAuNTf_2$, L = ligand.

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 cyclopentenone; 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 $AlCl_3{\cdot}6H_2O$ and subsequent heating in a microwave gave quinoline **7a** in high yield (Scheme 4).[10] Following Ag^{I}-mediated spirocyclisation, it is thought that the Al^{III} 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).



Scheme 4. Formation of quinoline **7a**; X = Cl or *i*PrO.

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 cyclopentenol **14**[11] with $AlCl_3{\cdot}6H_2O$ did not result in quinoline formation. Instead, 1,2-migration of the alkenyl group took place, furnishing carbazole **15** following tautomerisation and dehydration (Scheme 5).



Scheme 5. Base-mediated formation of quinoline **7a** and the contrasting reactivity of spirocyclic cyclopentenol **14**.

To probe the scope of all three reaction manifolds, various functionalised indole-tethered ynones **1a**–**1m** were prepared, substituted in several positions with electron-rich and -poor aromatics, alkyl substituents, *O*- and *N*-protected alkyl groups and PhS.[12] First, using the AgOTf-mediated spirocyclisation

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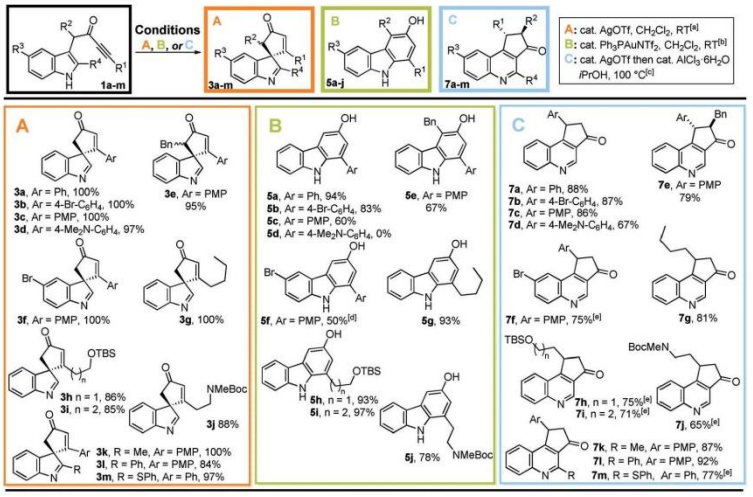
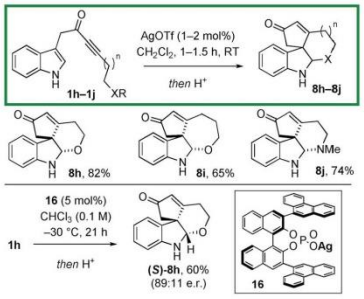
Table 1. Reaction scope for the formation of spirocyclic indolenines, carbazoles and quinolones.



[a] AgOTf (1 mol%) in CH_2Cl_2 (0.1 M) at RT for 0.1–3.5 h. [b] $Ph_3PAuNTf_2$ (2–5 mol%) in CH_2Cl_2 (0.1 M) at RT for 7–18 h. [c] AgOTf (1 mol%) in *i*PrOH (0.1 M) at RT for 1–3 h, then $AlCl_3{\cdot}6H_2O$ (5–10 mol%) at 100 °C μW for 1–2 h. [d] Reaction performed in toluene. [e] AgOTf (1 mol%) in CH_2Cl_2 (0.1 M) at RT for 1–3 h, then solvent swap for *i*PrOH (0.1 M) then $AlCl_3{\cdot}6H_2O$ (5–10 mol%) at 100 °C μW for 1–2 h. PMP = *para*-methoxyphenyl.

methodology, substrates **1a–1m** were cleanly converted into the corresponding spirocyclic indolenines **3a–3m**, all in excellent yields (Table 1, conditions A). The $Ph_3PAuNTf_2$-mediated carbazole-forming reaction was similarly broad in scope (conditions B); some reactions were less efficient than the analogous spirocycle 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.[13] Finally, the quinoline-forming reaction sequence was also found to be very general (conditions C). For ynones **1a–1e**,**1g**,**1k–1l**, the sequential AgOTf spirocyclisation and $AlCl_3{\cdot}6H_2O$ mediated rearrangement steps could both be performed in *i*PrOH in one-pot as described, whereas for ynones with more sensitive functional groups (**1f**, **1h**, **1i**, **1j**, **1m**), the process benefited from a solvent swap, with the spirocyclisation first being performed in CH_2Cl_2 before concentration and addition of *i*PrOH prior to the $AlCl_3{\cdot}6H_2O$ step. The $AlCl_3{\cdot}6H_2O$ 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.[14] The structure of quinoline **7f** was confirmed by X-ray crystallography.[15]

Another strand of scaffold diversity starting from more functionalised ynones **1h–1j** was briefly explored. Tetracyclic scaffolds **8h–j**, equipped with additional complexity, were easily obtained following reaction of ynones **1h–1j** with AgOTf and subsequent acid-mediated protecting group cleavage in one pot (Scheme 6, and see the Supporting Information for details).[16] The tetracycles were formed as the single diastereoisomers shown, and in addition, **(*S*)-8h** was prepared in enantioenriched form (89:11 e.r.) by utilising (*R*)-CPA silver(I) salt **16** in place of AgOTf.[17] The e.r. of **(*S*)-8h** could be increased to ≈100:0 by recrystallisation from ethanol, and its structure was confirmed by X-ray crystallography (see the Supporting Information).[15]



Scheme 6. One-pot spirocyclisation/trapping to form tetracycles **8h–8j**.

In summary, readily available indolyl ynones have been shown to be versatile starting materials for the synthesis of spirocyclic indolenines **3a–m**, carbazoles **5a–j**, quinolines **7a–m** and tetracyclic compounds **8h–j** using a catalyst-driven scaf-

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fold diversity approach. The reactions are typically high yielding, work on a wide range of indolyl ynone substrates, are operationally simple and can all be performed with no effort to exclude air or moisture. All of the procedures are thought to proceed by an initial dearomatising spirocyclisation to form a key vinyl–metal intermediate before diverging at this point depending on the nature of the catalyst used. The synthetic methods are expected to be of value both in target synthesis projects[18] and to enable the rapid generation of compound libraries for biological screening.

Acknowledgements

The authors wish to thank the EPSRC (J.T.R.L. EP/M018601/01) and the University of York (M.J.J., A.K.C. and W.P.U.) for funding and Dr A. C. Whitwood (University of York) for X-ray crystallography.

Keywords: carbazoles · catalysis · diversity · quinolines · spirocycles

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[12] Ynones **1a–g** and **1k–l** were prepared as described in reference [5], while ynones **1h–j** and **1m** were synthesised for the first time in this work (see Supporting Information for preparative details).

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[14] Ynone **1a** (3.8 mmol) was converted into quinoline **7a** in 82% yield upon conventional heating with $AlCl_3{\cdot}6H_2O$ at reflux under an air atmosphere for 8 h (see the Supporting Information for full details).

[15] CCDC 1453490 (**7f**) and 1453491 (**(*S*)-8h**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Appendix VI. Selective Synthesis of Six Products from a Single Indolyl α-Diazocarbonyl Precursor

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Selective Synthesis of Six Products from a Single Indolyl α-Diazocarbonyl Precursor

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

Abstract: *Indolyl α-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^{II}, Pd^{II}, and Cu^{II}, 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.[1] In most cases, such compounds are generated using organic synthesis, and over the years, a number of reliable and predictable methods have emerged.[1,2] The importance of such methods cannot be over-stated, but nonetheless, there is also value in the examination of reaction systems which react less predictably.[3] 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 α-diazocarbonyl compounds.[4] The utility of diazo precursors in diversity-orientated synthesis was elegantly demonstrated by Warriner, Nelson and co-worker in 2014,[3] who exploited the unpredictable reactivity of α-diazoamides to generate product mixtures for bioassays. 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.[5] Most reported methods of this type allow the selective synthesis of two distinct products,[6] with protocols able to deliver three or more products being much more rare.[7] However, herein we report the catalyst-selective synthesis of six structurally distinct cyclic scaffolds from a single α-diazocarbonyl, of the form **1**, 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).

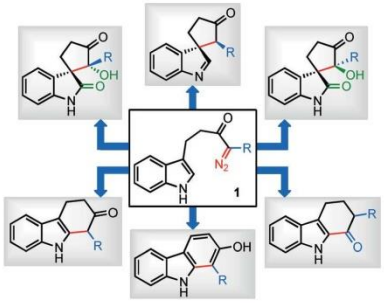

Figure 1. Catalyst-selective synthesis: six scaffolds from one precursor.

Our studies began with the three-step synthesis of the α-diazocarbonyl **1a** from the commercially available acid **2a** (Table 1),[8] which was then treated with a range of potential catalysts (10 mol%) in CH_2Cl_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 spirocyclic indolenine **3a** and α,β-dicarbonyl **4a** (group A), C2 annulated indole **5a** and carbazole **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, more promising catalysts were also found and they enabled the selective synthesis of group A products **3a** and **4a** [Rh_2oct_4)], group B redox isomers **5a** and **6a** [$Pd(MeCN)_4(BF_4)_2$ 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_2oct_4]-catalyzed procedure[9] to form **3a** represents the first reported synthesis of a spirocyclic indolenine[10] from a diazocarbonyl precursor, although C3 functionalization of indoles using diazocarbonyl compounds has been reported,[11,12] so this outcome was not wholly unexpected.[13] However, the formation of the oxidized

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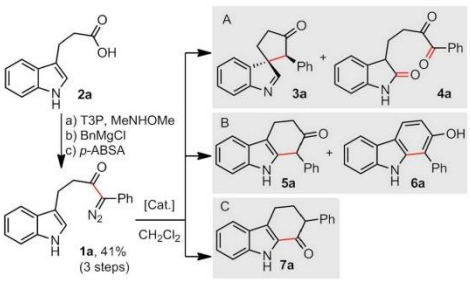
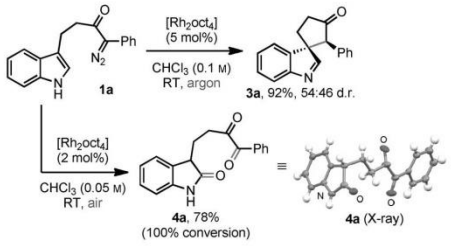
Table 1: Initial catalyst screening.



Entry		Catalyst[a]	Product composition [%][b]					
			1a	3a	4a	5a	6a	7a
1	mix	$[Rh_2(OAc)_4]$	–	–	50	20	15	15
2		$[Rh_2esp_2]$	–	10	55	15	–	20
3		$Cu(MeCN)_4OTf$	–	20	–	60	20	–
4		$Cu(MeCN)_4PF_6$	15	65	20	–	–	–
5	A	$[Rh_2oct_4]$	–	95	5	–	–	–
6	B	$Pd(MeCN)_4(BF_4)_2$	–	–	–	95	5	–
7		$Cu(OTf)_2$	–	–	–	70	30	–
8	C	SiO_2 (1 g/g)	–	–	–	–	–	>90

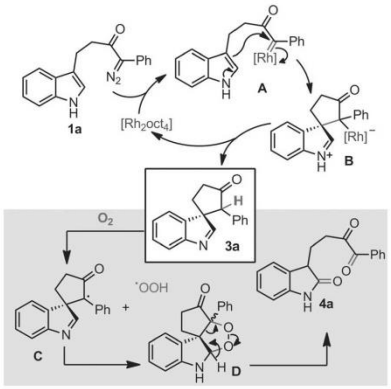
[a] Reactions performed with 0.05 mmol of **2a** and 10 mol% catalyst in CH_2Cl_2 (0.1 M) under argon at RT for 16 h. [b] Calculated using the ^1H NMR spectrum of the unpurified reaction mixture. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate, oct = octanoate, *p*-ABSA = *p*-acetamidobenzenesulfonyl azide, T3P = propane phosphonic acid anhydride, Tf = trifluoromethanesulfonyl.

product **4a** was much more surprising, with the structure of this product confirmed by X-ray crystallography.[14] It was found that the selective synthesis of either product could be achieved, with the reaction outcome being dependent on the presence of air in the reaction. By switching the reaction solvent from CH_2Cl_2 to chloroform, reducing catalyst loading to 5 mol%, and performing the reaction under oxygen-free conditions, **3a** was isolated in 92% yield (Scheme 1). Furthermore, carrying out the same reaction in a flask open to air was sufficient to completely switch the selectivity to efficiently furnish **4a**.



Scheme 1. Selective synthesis of **3a** and **4a**.

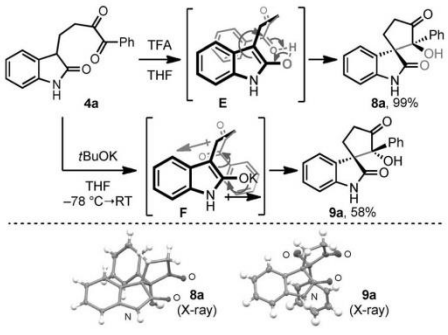
We propose that both reactions start with the formation of the rhodium carbenoid **A**,[15] which then reacts with the nucleophilic indole to form the spirocycle **B**, before undergoing protodemetallation to furnish **3a** (Scheme 2). Then, in



Scheme 2. Proposed mechanism for the formation of **3a** and **4a**.

the presence of oxygen, we propose that **3a** forms the intermediate endoperoxide **D**,[8a] possibly by a radical rebound process (**3a**→**C**→**D**),[16] 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.

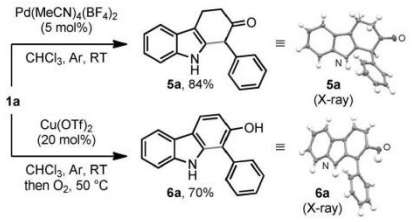
While **4a** could be isolated in good yield, it was found to be relatively short-lived as it degraded during silica gel chromatography and upon storage, but pleasingly, we were able to exploit its high reactivity to deliver two new oxindole scaffolds, **8a** and **9a** (Scheme 3). Thus, two highly diastereoselective intramolecular aldol-type reactions were developed using either Brønsted-acidic or Brønsted-basic conditions.



Scheme 3. Stereoselective formation of **8a** and **9a**.

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 *t*BuOK. Under acidic conditions **4a** was selectively converted into the *syn*-diastereoisomer **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*-diastereoisomer **9a** was formed, and we propose that it results from a reactive conformation of the form **F**, in which the destabilizing steric interactions are lower than those in **E**, and the carbonyl dipoles are opposed. Both product structures were confirmed by X-ray analysis.[14]

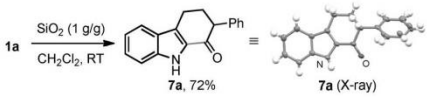
Next, the palladium(II)- and copper(II)-catalyzed reactions were optimized, thus allowing selective formation of the C2-annulated product **5a** and carbazole **6a** using $Pd(MeCN)_4(BF_4)_2$ (5 mol%) and $Cu(OTf)_2$ (20 mol%), respectively (Scheme 4).[18,19] A key difference between these reactions is



Scheme 4. Selective formation of **5a** and **6a**. TFA = trifluoroacetic acid, THF = tetrahydrofuran.

that it is necessary to perform the carbazole-forming 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,[20] and the observation that **3a** can be converted into a mixture of **5a** and **6a** upon reaction with $Cu(OTf)_2$, 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 SiO_2 in CH_2Cl_2 (Scheme 5). The reaction likely



Scheme 5. Synthesis of **7a**.

proceeds by a Wolff rearrangement, induced by the mildly acidic silica,[21] and trapping by the nucleophilic indole (either by direct C2 attack or by an initial C3 attack followed by a 1,2-migration). To the best of our knowledge, only one other example of a C2-annulation reaction of this type has been reported.[22]

Finally, the scope of all six procedures was tested on five diazocarbonyl substrates (**1a–e**), thus delivering 30 discrete 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 **8a–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.[23]

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,[5–8] 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,[24,25] 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,[26] we believe that the same principles apply in catalyst-selective synthesis.

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Keywords: cyclizations · diazo compounds · indoles · spirocycles · synthetic methods

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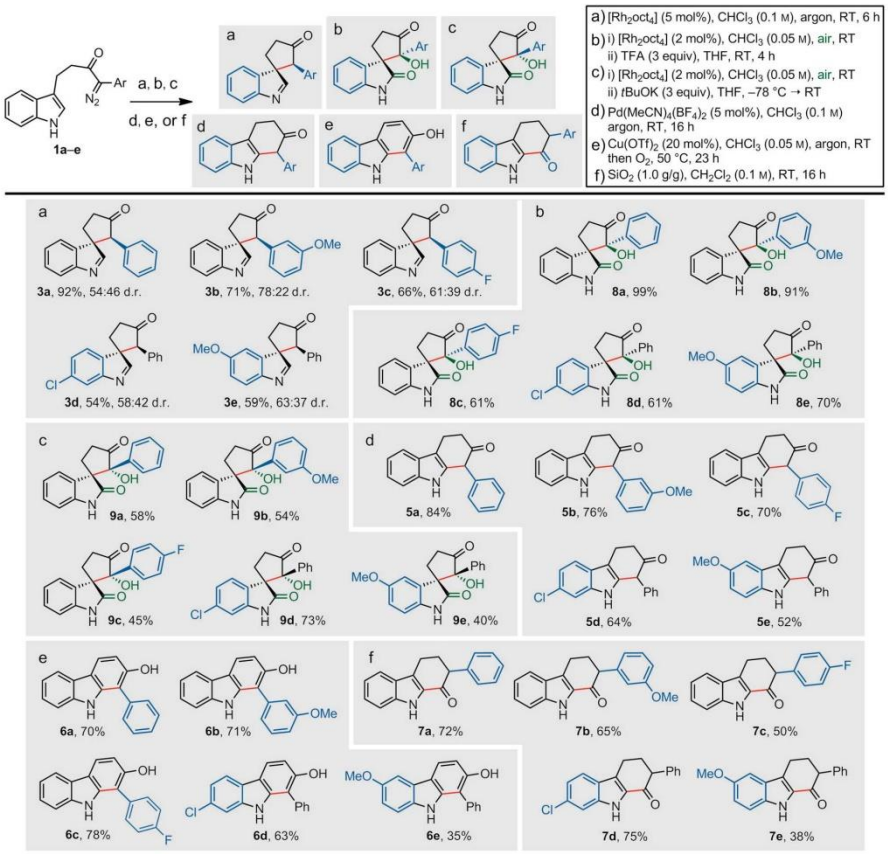

Scheme 6. Catalyst-selective synthesis of six products from a single indolyl α-diazocarbonyl precursor (yields are those of products isolated after column chromatography).

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Appendix VII. Catalytic Dearomatization Approach to Quinolizidine Alkaloids: Five Step Total Synthesis of (±)-Lasubine II

Organic LETTERS

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Catalytic Dearomatization Approach to Quinolizidine Alkaloids: Five Step Total Synthesis of (±)-Lasubine II

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Supporting Information

ABSTRACT: A series of high-yielding silver(I)-catalyzed cyclization reactions of pyridine-, isoquinoline-, and pyrazine-ynones are described. The operationally simple and mild reaction conditions are a significant improvement over previously reported thermal cyclizations. The quinolizinone products 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.[1] 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),[2] which makes them highly attractive synthetic targets.

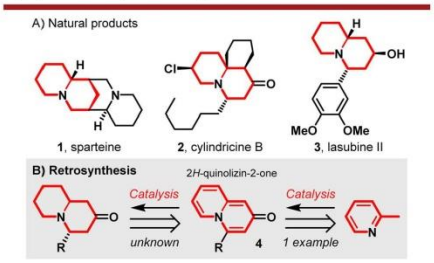
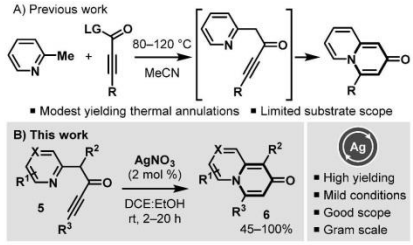


Figure 1. (A) Natural products containing the saturated quinolizidine framework; (B) proposed dearomative retrosynthesis.

An unexplored and expedient strategy by which to access these bicyclic frameworks is by the dearomatization of a 2*H*-quinolizin-2-one system **4** (Figure 1B). Dearomatization reactions are important transformations as they enable high value spiro-[3] or bridged-compounds[4] to be formed from inexpensive and readily available aromatic feedstocks.[5] However, current methods for the synthesis of 2*H*-quinolizin-2-ones are limited, relying primarily on harsh thermal conditions,[6] with catalytic examples being rare.[7] Seeking to address this limitation, an opportunity to build upon our recent work on the catalytic dearomatization/cyclization of aromatic alkynes was indentified.[8] This previous work is based on the activation of alkynes with π-acidic catalysts[9] to promote cyclization to generate spirocyclic/annulated products, and based on this, it was considered that pyridine-ynones would serve as useful precursors to 2*H*-quinolizin-2-ones. The viability of a related cyclization protocol had already been briefly demonstrated by both Katritzky and Natarajan (Scheme 1A);[6d,e] 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-, isoquinoline-, and pyrazine-ynones **5** can all be cyclized into annulated products **6** at room temperature using mild silver(I)-catalyzed conditions (Scheme 1B).

Scheme 1. Pyridine-ynone Cyclizations



Using this new method, a diverse array of quinolizinone products has 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,

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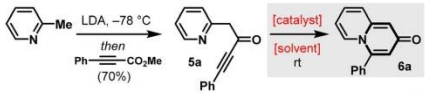
an efficient five-step synthesis of 0.53 g of the alkaloid lasubine II has also been developed, including a catalytic dearomatization of a quinolizinone product as a key step.

Our studies began with the preparation of pyridine-ynone **5a** via the deprotonation and acylation 2-picoline with methyl phenylpropiolate (Table 1). Ynone **5a** was then reacted with

Table 1. Optimization of the Pyridine-Ynone Cyclization



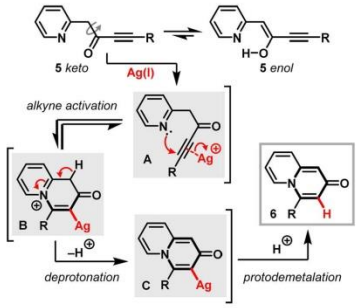
entry	[catalyst][a] (equiv)	[solvent]	time (h)	conv (%)[b]
1	$Cu(MeCN)_4PF_6$ (0.1)	CH_2Cl_2	16	0
2	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	16	0
3	$Ph_3PAuNTf_2$ (0.1)	CH_2Cl_2	16	0
4	AgOTf (0.1)	CH_2Cl_2	16	>95
5	AgOTf (0.02)	CH_2Cl_2	2	90
6	$AgSbF_6$ (0.02)	CH_2Cl_2	2	25
7	$AgNO_3$ (0.02)	CH_2Cl_2	2	>95
8	$AgNO_3$ (0.01)	CH_2Cl_2	0.5	50

[a]Reactions performed with 0.2 mmol of **5a** and catalyst in the stated solvent (0.1 M) at rt. [b]Calculated by measuring the ratio of starting material to product in the ^1H NMR spectrum of the unpurified reaction mixture, rounded to the nearest 5%.

four π-acidic catalysts in dichloromethane (Table 1, entries 1–4), of which only AgOTf was effective for the formation of quinolizinone **6a**. This prompted further scrutiny of other silver(I) catalysts, and of those tested, $AgNO_3$ 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

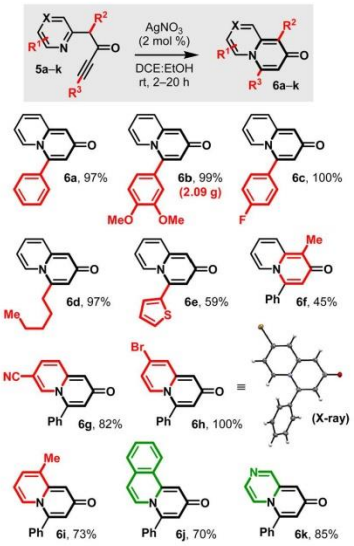
Scheme 2. Proposed Mechanism for the Silver(I)-Catalyzed Cyclization



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 π-acidic silver(I) catalyst (**A**), promoting nucleophilic attack from the pyridine lone pair to form pyridinium species **B** (which is likely a reversible process).[10] 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 quinolizinone 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-dichloroethane (see ref 12 for details) and 2 mol % of $AgNO_3$ 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 aryl ynone subunit were varied to afford quinolizinones **6a–c** in quantitative/near-quantitative yield. Pleasingly, these reactions were equally effective on gram scale; for example, 2.09 g of quinolizinone **6b** were prepared in a single reaction in 99% yield. The aliphatic quinolizinone **6d** was also afforded in near-quantitative yield. Thiophene-substituted and methylated-quinolizinones **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 quinolizinones **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.[11] Finally, this methodology was also demonstrated on other heteroaromatic systems, to afford isoquinoline and pyrazine derived products **6j** and **6k** in excellent yield. The fully unsubstituted quinolizinone **6l** was also synthesized in excellent yield from TMS-ynone **5l** by using 20 mol % $AgNO_3$ and acetone to promote a one-pot desilylation–cyclization sequence (Scheme 4).[13,14] This reaction is particularly pleasing,

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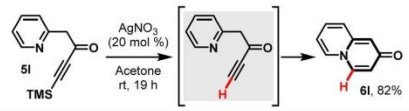
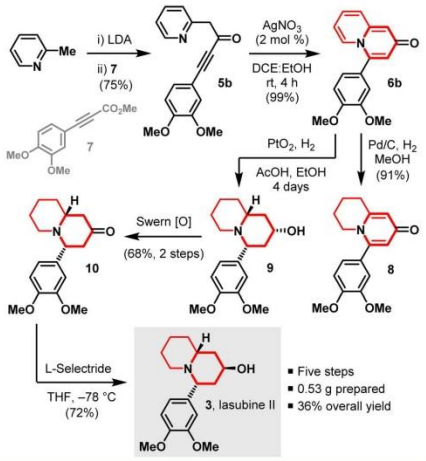
as the TMS ynone **5l** is completely unreactive under the previously reported thermal conditions.[6e]

Scheme 4. Tandem Ag(I)-Catalyzed Desilylation–Cyclization



The ease of formation of these quinolizinone products is likely to be of significant value in target synthesis projects, especially given the prevalence of saturated quinolizidine frameworks in Nature.[2] This was demonstrated in the five-step dearomative synthesis of (±)-lasubine II (Scheme 5).

Scheme 5. Five-Step Total Synthesis of (±)-Lasubine II



The synthesis began with the LDA-mediated deprotonation and acylation of 2-picoline with methyl ester **7**[15] 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 hydrogenated with either Pd/C or PtO_2 to form products **8** and **9** respectively.[16] The unpurified quinolizidine **9** was then oxidized under Swern conditions to form ketone **10** in excellent yield over the two-step sequence.[17] Finally, the known L-Selectride reduction of ketone **10** afforded 0.53 g of (±)-lasubine II **3** in 36% overall yield.[18,19]

In summary, we have developed a mild and operationally simple protocol for the high-yielding catalytic synthesis of quinolizinones. Furthermore, we demonstrated the synthetic utility of the products by preparing 0.53 g of (±)-lasubine II in just five steps and 36% overall yield from 2-picoline. The development of a protocol for the asymmetric hydrogenation of quinolizinones remains the focus of future work,[20] in hopes of enabling the enantioselective synthesis of lasubine 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.orglett.6b03017.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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Abbreviations

Ac	acetyl
acac	acetylacetone
Ad	adamantyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionisation
aq	aqueous
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
CADA	catalytic asymmetric dearomatisation
CCDC	Cambridge crystallographic data centre
CDI	1,1'-carbonyldiimidazole
COD	cyclooctadiene
COSY	correlation spectroscopy
CPA	chiral phosphoric acid
CSA	camphorsulfonic acid
CSP	chiral stationary phase
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
DTBM-SEGPHOS	5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
EDG	electron donating group
ee	enantiomeric excess
ESI	electrospray ionisation
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
EWG	electron withdrawing group
h	hour(s)
H_8-BINOL	5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-2-naphthol
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum coherence
IBX	2-iodoxybenzoic acid
Im	imidazole
IPr	1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
LA	Lewis acid
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
m-CPBA	*meta*-Chloroperoxybenzoic acid

Me	methyl
MOM	methoxymethyl ether
Ms	mesyl
NBS	N-bromosuccinimide
NMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
oct	octanoate
p-ABSA	4-acetamidobenzenesulfonyl azide
Ph	phenyl
PMP	*para*-methoxyphenyl
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
p-TSA	*para*-toluenesulfonic acid
Raney-Ni	Raney nickel
RT	room temperature
s	singlet
SPINOL	1,1′-spirobiindane-7,7′-diol
t	triplet
T3P	propylphosphonic anhydride
TBAF	tetrabutylammonium fluoride
TBME	methyl *tert*-butyl ether
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPA	triphenylacetate
Ts	tosyl

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