Dearomatisation Reactions and a Novel Route to Substituted Indoles

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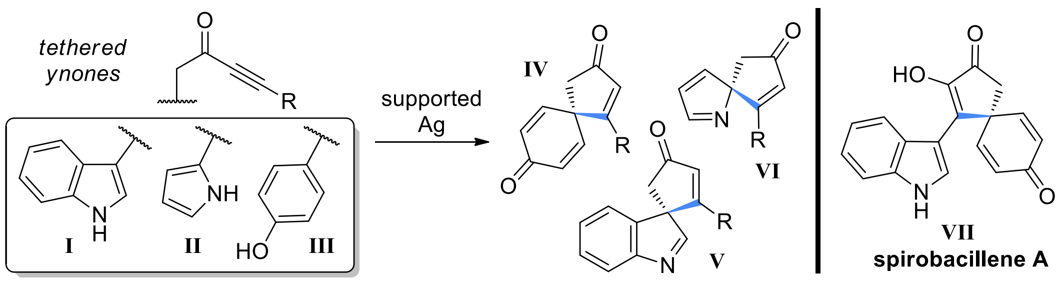
Abstract

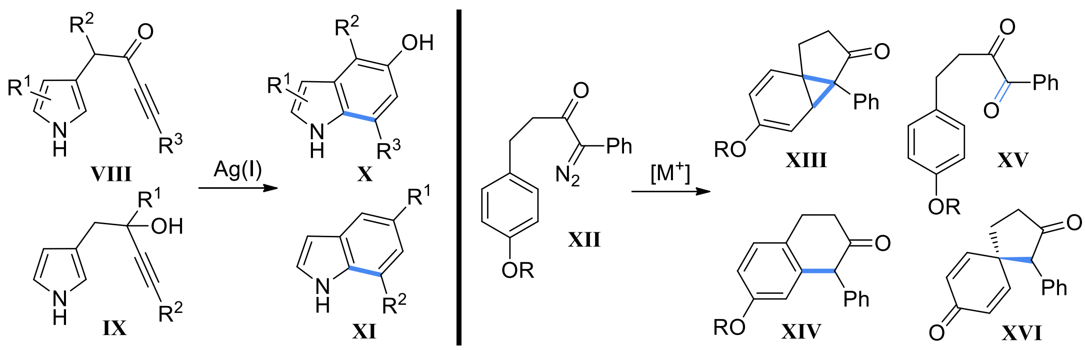
This Thesis describes the development of silver-catalysed dearomatising spirocyclisation reactions of alkyne-tethered aromatic and heteroaromatic systems. An overview of dearomatisation methodologies and spirocyclisation strategies involving alkyne activation are discussed in Chapter 1.

Chapter 2 describes a novel silica-supported silver-catalysed spirocyclisation method. This strategy was applied to a range of aromatic ynone systems (for example **I** and **II**) and mechanistic information suggesting the involvement of silver nanoparticles in the spirocyclisation process is also reported. This silica-supported spirocyclisation reaction was then applied to a range of phenol-tethered ynones **III** furnishing spirocyclic dienone products **IV** which is the focus of Chapter 3. Some preliminary asymmetric spirocyclisation studies using silver salts of chiral phosphoric acids (CPAs) are also described as well as a formal synthesis of the natural product spirobacillene A **VII**.



A novel Ag(I)-catalysed synthesis of substituted indoles **X/XI** using pyrrole-tethered alkynes **VIII/IX** is detailed in Chapter 4. Density functional theory (DFT) calculations are described which suggest that benzannulation proceeds initially *via* spirocyclisation at the pyrrole C-3 position before undergoing subsequent rearrangement to deliver the indole products.

Chapter 5 describes the divergent reactivity of phenol-/anisole-tethered α-diazocarbonyls **XII**. Four products (cyclopropanes **XIII**, tetralones **XIV**, 1,2-dicarbonyls **XV** and spirocycle **XVI**) were accessed through distinct reaction pathways in which the outcome was dependent on the catalyst used and the nature of the aromatic oxygen substituent.



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Finally, a heartfelt thanks goes my family, who have provided constant love, support and encouragement, for which I am extremely grateful.

Declaration

The work presented in this Thesis is my own and was carried out at the University of York between January 2015 and March 2018. This work is, to the best of my knowledge, original except where due reference has been made to other workers. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references.

Some of this work has also been reproduced in 5 recent publications, copies of which can be found in the Appendices.

Aimee Clarke

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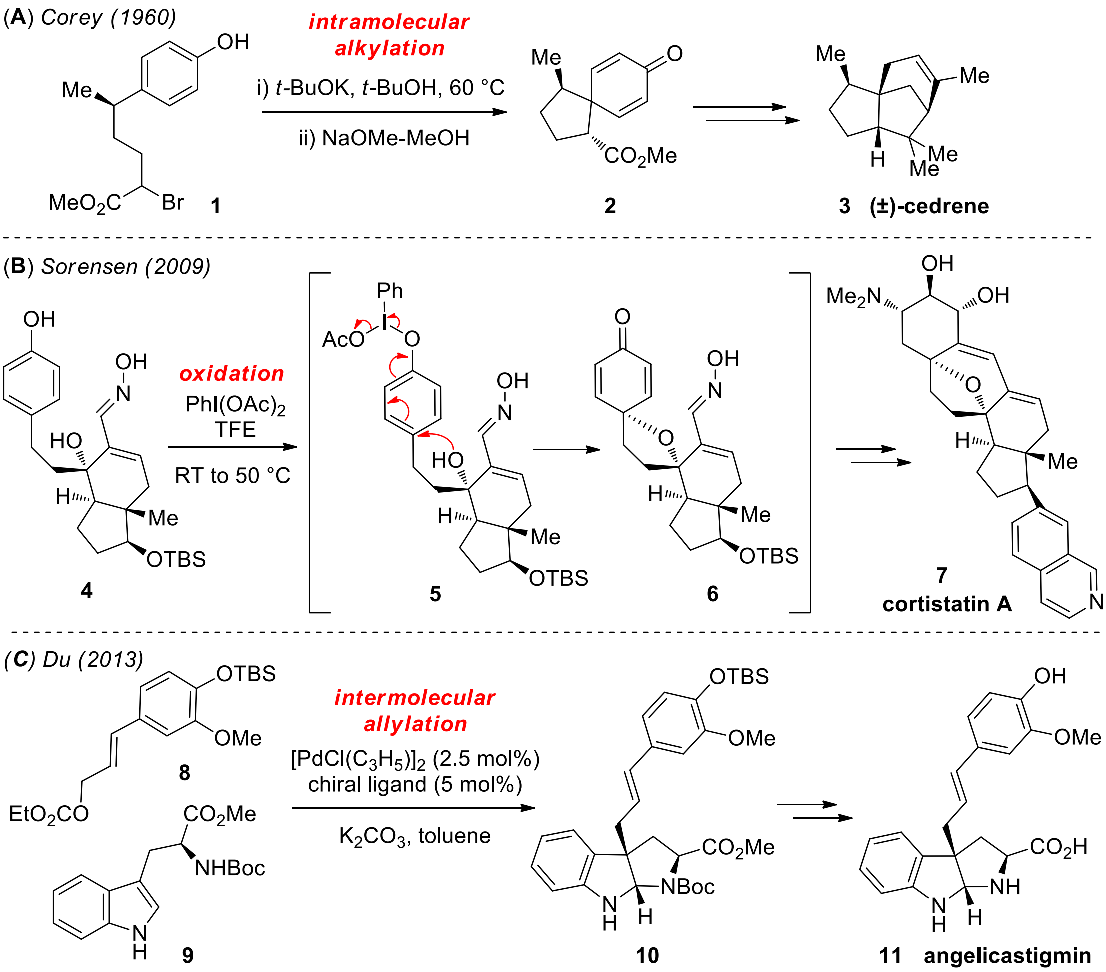
Chapter 1. Introduction

1.1 Introduction to dearomatisation and spirocyclic scaffolds

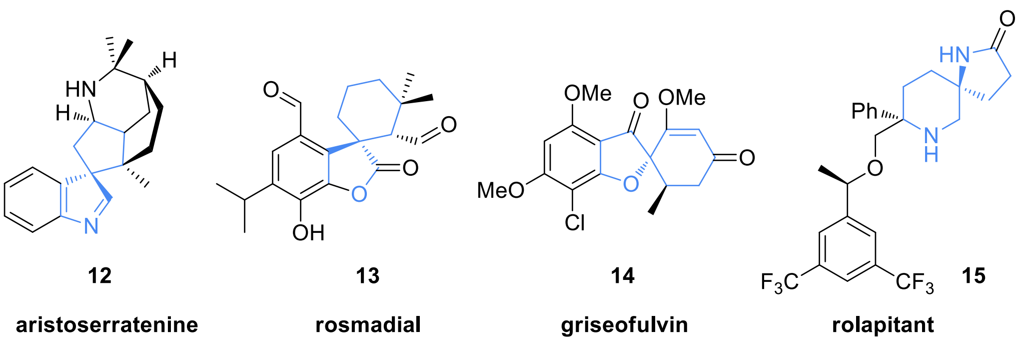
Aromatic compounds are cyclic, planar structures consisting of a fully conjugated π-system, with the number of delocalised π-electrons obeying Hückel's rule (4n + 2, where n is zero or any positive integer).[1] Due to their high resonance energies, aromatic compounds are generally stable, and consequently, dearomatisation of these molecules is typically a challenging process. Despite this, a number of powerful dearomatisation reactions have been designed, which provide access to valuable fused, bridged and spiro-compounds from relatively simple aromatic precursors. Furthermore, the more complex three-dimensional structures obtained from such reactions are often reactive species themselves, further extending their synthetic utility. Approaches used to achieve dearomatisation include oxidation, cycloaddition, inter-/intramolecular alkylation, allylation, arylation and halogenation reactions.[2–5] As shown in Scheme 1, a number of these dearomatisation strategies have been utilised in the total synthesis of natural products.[6]



Scheme 1. Examples of dearomatisation strategies used in total synthesis.

Corey and co-workers employed an alkylative dearomatisation strategy in the total synthesis of the natural product cedrane **3** (Scheme 1A).[7] Phenol **1** was deprotonated under basic conditions to generate the corresponding phenolate which then underwent intramolecular *para*-alkylation to access spirocycle **2** as a mixture of *cis* and *trans*-forms. Upon exposure to methanolic sodium methoxide the *cis*/*trans*-mixture was converted largely into the more stable *trans*-stereoisomer. An impressive cascade process triggered by intramolecular oxidative dearomatisation was reported by Sorensen and co-workers in 2009 for construction of the core of cortistatin A **7** (Scheme 1B).[8] Exposure of phenol **4** to the hypervalent iodine reagent, phenyliodine diacetate (PIDA), led to phenol activation followed by nucleophilic attack of the proximate tertiary alcohol *via* intermediate **5**. Oxidation of the oxime moiety in **6** then generated the nitrile oxide which initiated an intramolecular [3+2]-dipolar cycloaddition to further construct another ring present in the core structure of cortistatin A **7**. Finally, Du and Liu used a Pd-catalysed intermolecular allylation dearomatisation reaction to construct the bicyclic core of angelicastigmin **11**;[9] this natural product was accessed in a succinct manner in just four steps (Scheme 1C).

Dearomatisation is also an attractive method used to access valuable spirocyclic scaffolds which are prevalent in many natural products and biologically active molecules (Figure 1).[10–13] Spirocyclic compounds have attracted a significant amount of interest in recent years due to their rigid, three-dimensional shape, which allows them to access areas of chemical space that currently are thought to be under-explored.[14,15] Probing new areas of chemical space is fundamental in the development of new lead compounds in drug discovery and therefore the design of methodologies to access spirocyclic structures is an area of synthetic interest.



12 — **aristoserratenine** — *isolated from Aristotelia serrata*

13 — **rosmadial** — *isolated from Rosmarinus officinalis*

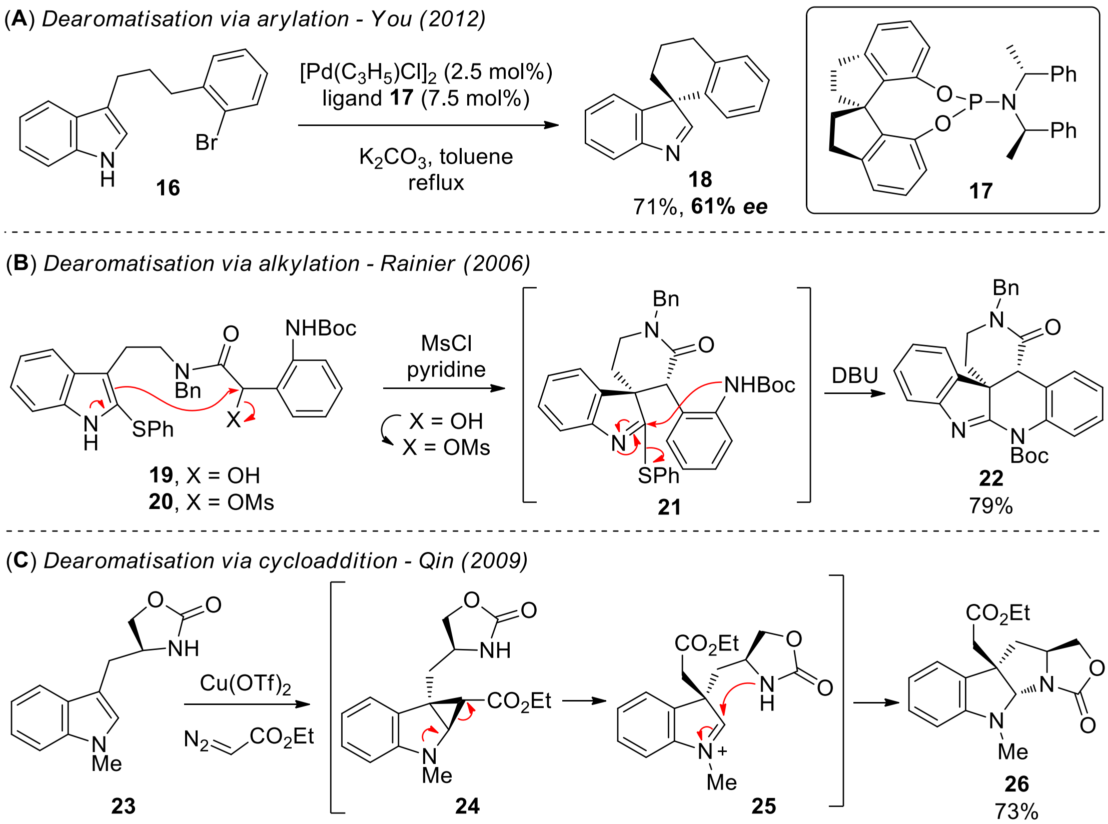
14 — **griseofulvin** — *antifungal*

15 — **rolapitant** — *NK_1 receptor antagonist*

Figure 1. Natural products (12 and 13) and drug molecules (14 and 15) containing spirocyclic cores.

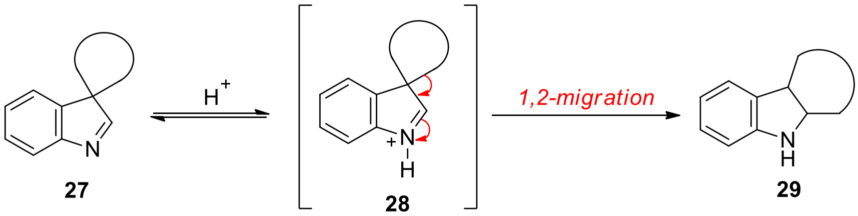
1.2 Dearomatisation of aromatic and heteroaromatic systems

The dearomatisation of indoles has been studied extensively; they are the most frequently utilised substrates in published dearomatisation studies, providing convenient access to complex nitrogen-containing skeletons. A recent review by Roche *et al*. gives a broad and detailed overview of this topic,[4] describing the dearomatisation of indoles through a range of alkylation, cycloaddition and arylation reactions, with selected examples illustrating these strategies shown in Scheme 2. In all three of these examples, dearomatisation proceeds *via* nucleophilic attack through the C-3 position of the indole ring onto an electrophile, generating a spirocyclic indolenine or derivative thereof. The simplest example of spirocyclic indolenine formation is illustrated in a recent example by the You group (Scheme 2A), whereby alkyl bromide **16** was successfully converted into indolenine **18** using a Pd-catalysed arylation reaction.[16] Although indolenine **18** was isolated in 71% yield in You's procedure, spirocyclic indolenines are often difficult to isolate due to their relatively high reactivity, and instead they are often used as reactive intermediates to access other scaffolds. This is exemplified in Rainier's procedure in which the indolenine intermediate **21** was trapped with an amine nucleophile to generate the stable pentacycle **22** in 79% yield (Scheme 2B).[17] Another example, reported by Qin *et al.* describes the intramolecular trapping of intermediate **25** with a carbamate tether to furnish fused polycyclic product **26** (Scheme 2C).[18]



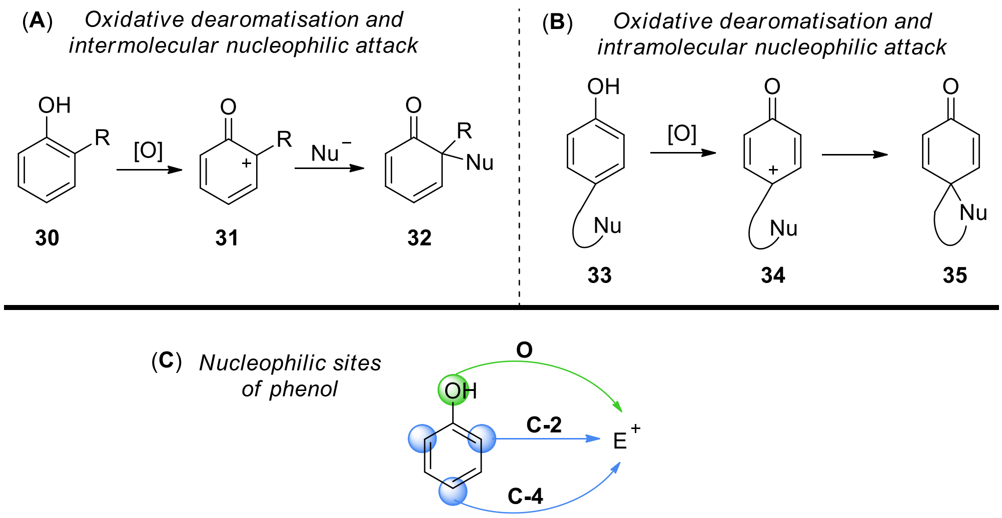
Scheme 2. Indole dearomatisation strategies.

The reactive nature of spirocyclic indolenines and their derivatives can be useful, given that manipulations can often be performed in a straightforward manner, allowing transformation into other privileged scaffolds such as indolines, oxindoles and carbazoles. However, their reactivity can also present some synthetic challenges with regards to their isolation and handling. In particular, it is well-known that spirocyclic indolenines of the form **27** have a propensity to undergo 1,2-migrations under acidic conditions (Scheme 3),[19] resulting in the formation of more stable aromatic indole products **29**. An appreciation of how to avoid this reactivity is required if isolation of the spirocyclic indolenine framework is desired.



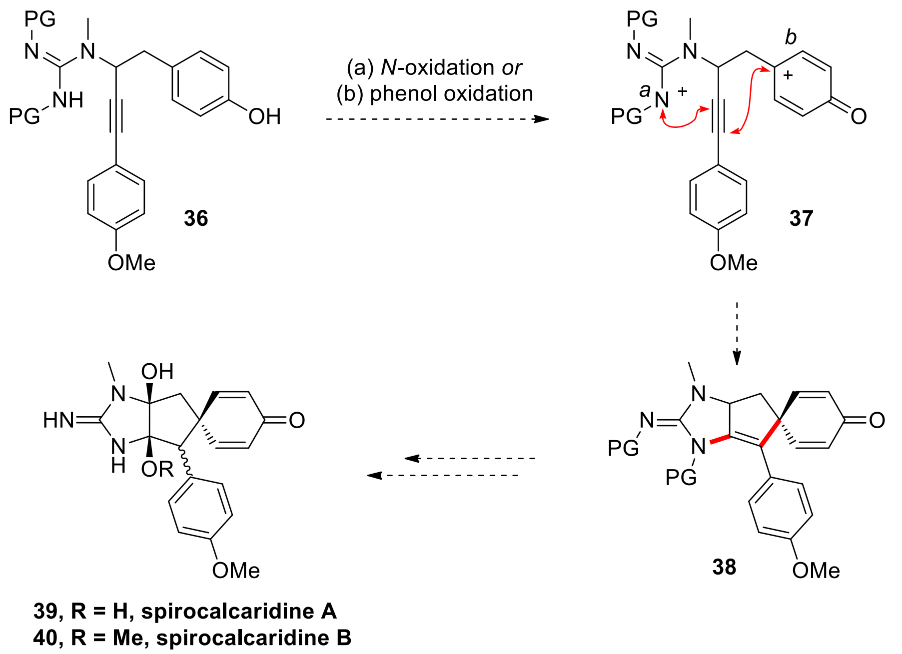
Scheme 3. Reactivity of spirocyclic indolenines.

In addition to indole dearomatisation, other aromatic systems including pyridine, quinolines and pyrroles have also been explored and similar dearomatisation strategies have been developed.[20,21] Dearomatisation reactions of phenols have also been studied widely since they provide access to synthetically useful cyclohexadienone compounds; as a class of electron-rich arenes with a hydroxyl group directly bound to the aromatic ring, phenols are readily oxidised and therefore dearomatisation strategies tend to focus on oxidative processes.[22–24] Following oxidation of the phenol ring, often achieved using hypervalent iodine reagents,[25,26] intermolecular nucleophilic attack can take place (at C-2 or C-4 depending on the position of substitution) furnishing the cyclohexadienone compounds **32** (Scheme 4A). It is also possible to achieve *ipso*-cyclisation affording spirocyclic dienone products **35** instead by employing phenols incorporating a tethered nucleophile (Scheme 4B).[27] Non-oxidative dearomatisation processes of phenols have also been reported,[24,28] these methods utilise the nucleophilic sites of phenol shown in Scheme 4C, but key to the success of these dearomatisation reactions is whether *C*-alkylation can be preferentially promoted over *O*-alkylation.



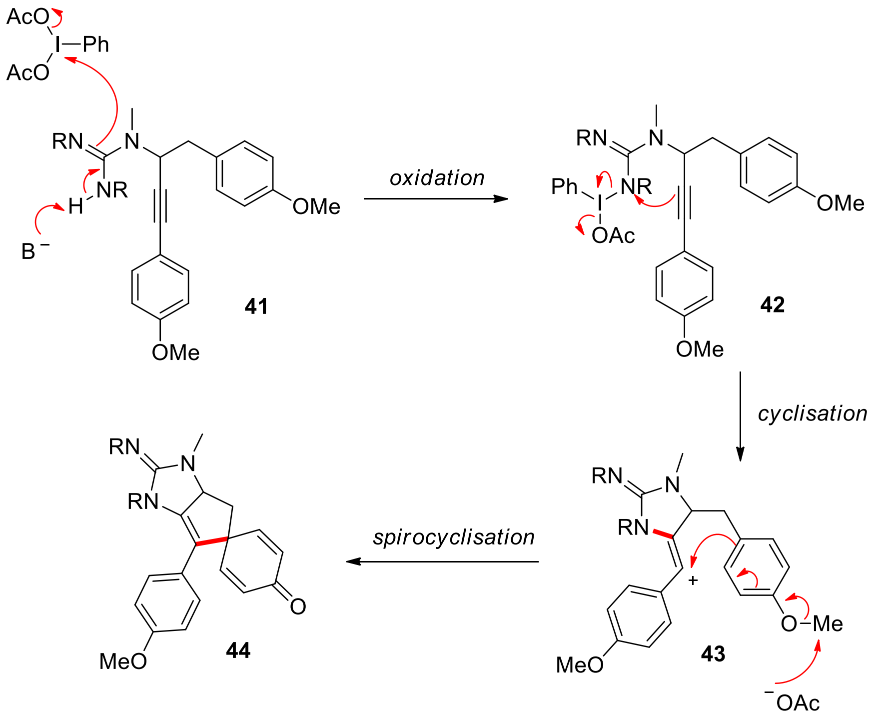
Scheme 4. Oxidative dearomatisation of phenol and its nucleophilic sites.

A recent oxidative tandem dearomatising spirocyclisation of anisole-tethered propargyl guanidines was reported by the Lovely group in a project directed towards the total synthesis of spirocalcaridine A **39** and B **40**.[29] They proposed that oxidation of either a phenol or guanidine unit, as shown in Scheme 5, could trigger the cyclisation/spirocyclisation sequence required to access the tricyclic core of the *Leucetta* alkaloid natural products.



Scheme 5. Cyclisation/spirocyclisation approach to spirocalcaridine natural products.

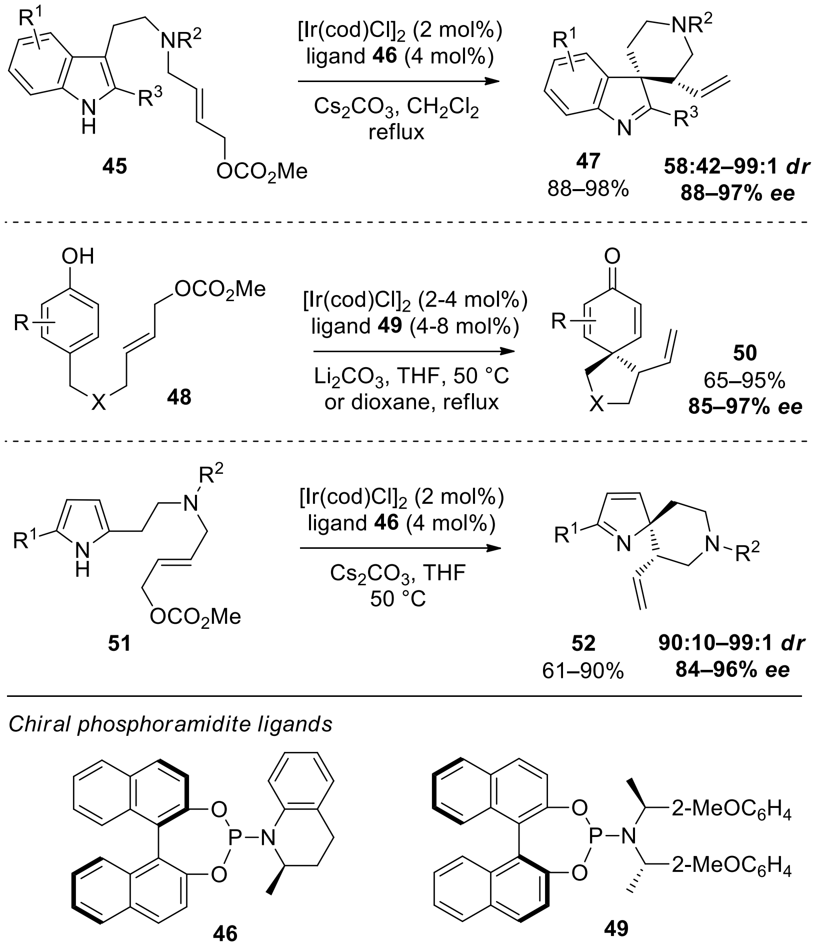
Given the large number of phenol oxidations reported in the literature, Lovely and co-workers evaluated this approach first but unfortunately, a complex mixture of cyclohexadienone products were formed. Instead, oxidation of the guanidine unit successfully promoted clean conversion into the desired cyclohexadienone products **44** in good isolated yields. The authors propose that the reaction sequence proceeds *via* PIDA activation to form electrophilic species **42**, followed by intramolecular cyclisation of the alkyne to deliver the vinylic cation **43**, which then undergoes *ipso*-cyclisation with the electron-rich anisole ring to furnish the final dearomatised cyclohexadienone products **44**.



Scheme 6. Tandem oxidative dearomatising spirocyclisation reported by Lovely and co-workers.[29]

1.3 Catalytic asymmetric dearomatisation (CADA) reactions

Most published dearomatisation protocols give rise to racemic products, with enantioselective variants being less common. However, more recently several catalytic asymmetric dearomatisation (CADA) reactions have been developed, generating enantiopure and dearomatised products of high synthetic value.[24,30,31] The You group have made significant advances in this field, which has also been well reviewed.[24,30,32] Inspired by initial CADA allylation protocols developed by Trost and Quancard,[33] the You group have developed a series of intramolecular asymmetric allylic alkylation reactions (Scheme 7).[21,34–36] Allylic carbonates tethered to aromatic systems including indoles **45**, phenols **48** and pyrroles **51** were employed in these reactions and treated with an iridium complex incorporating chiral phosphoramidite ligands, which successfully furnished highly enantiomerically enriched dearomatised products. This strategy was originally applied to electron-rich aromatics but has since been developed further and applied to other electron-deficient systems including pyridines, pyrazines, quinolines and isoquinolines.[21]



Scheme 7. CADA allylic alkylation reactions reported by the You group.

1.4 Alkyne activation

The use of transition metals in the activation of alkynes is commonly used to exploit their versatile reactivity, facilitating many synthetic transformations, including the dearomatisation of aromatic systems. Alkyne activation using platinum and the coinage metals (copper, silver and gold) has been studied in detail and the use of π-activated alkynes in nucleophilic addition reactions is commonly reported.[37–40] The bonding between the π-system of an alkyne and a transition metal centre can be viewed as several donor-acceptor interactions based on the Dewar-Chatt-Duncanson (DCD) model.[41] According to the DCD model, an in-plane σ-donor interaction is formed by overlap of a π-bonding orbital of the alkyne with a vacant d-orbital at the metal centre (Figure 2A), which is in combination with an in-plane π-accepting interaction, resulting through back-donation of electron density from an occupied metal d-orbital into a vacant antibonding π* orbital of the alkyne (Figure 2B).[37,40,42] Two out-of-plane interactions can also contribute to the bonding, a π-donor interaction (Figure 2C), which is particularly important in complexes when alkyne ligands serve as a four-electron donor, and an additional back-donating interaction from a filled metal d-orbital into an empty π* orbital of the alkyne (Figure 2D). This latter interaction, has δ-symmetry, which results in weak orbital overlap and therefore provides minimal contribution to the bonding. There is also an electrostatic component to bonding between the metal centre and the electron rich π-system and computational analyses indicate that approximately half of the total bonding force is actually electrostatic in nature.[37]

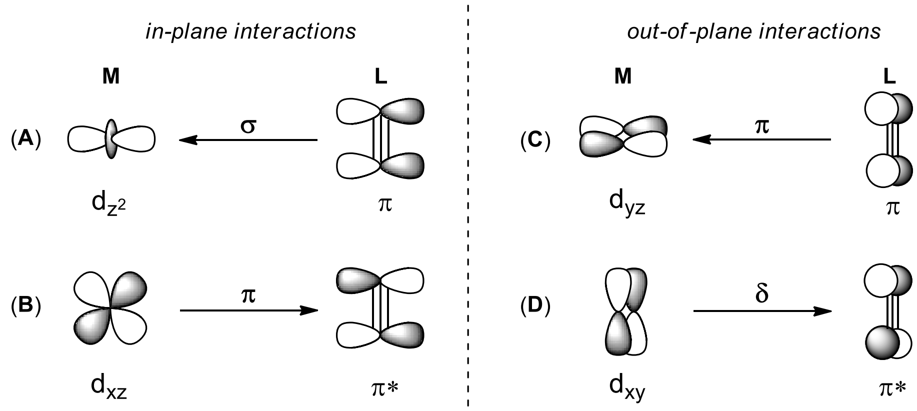
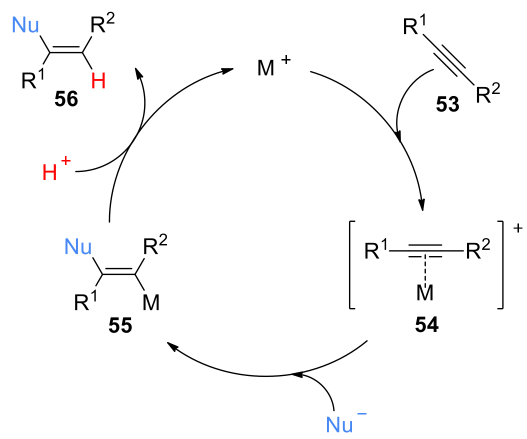


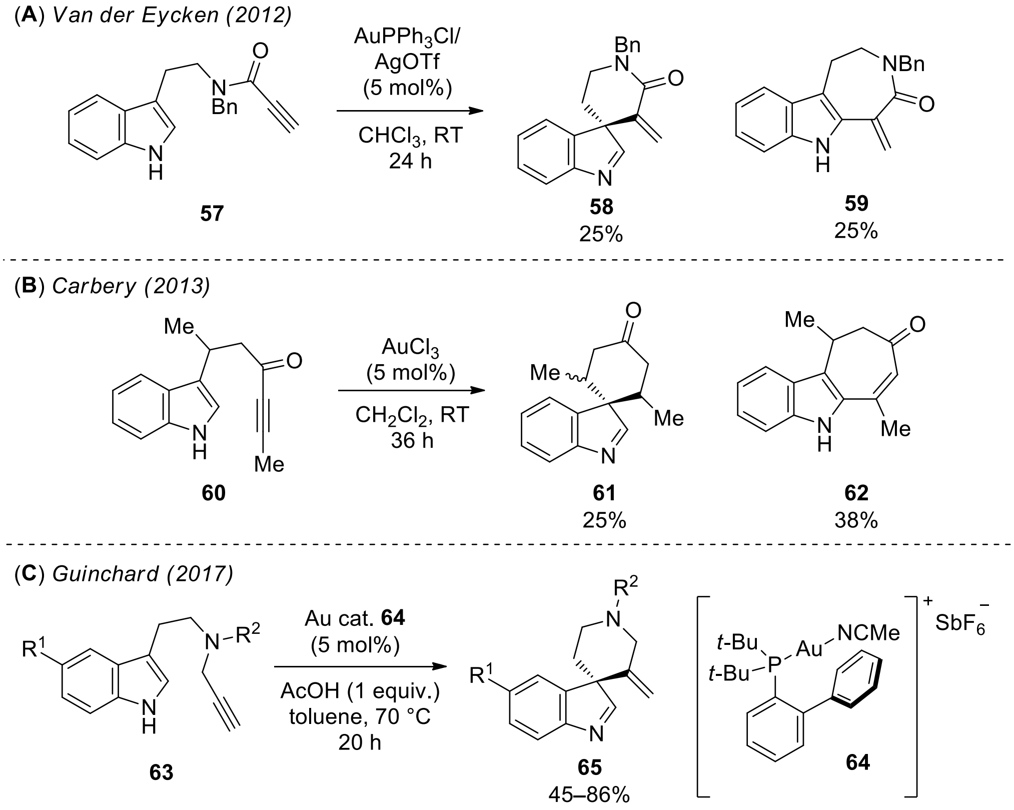
Figure 2. Orbital interactions between metal centre and alkyne ligand.

With overall depletion of electron density from the π-system, due to the dominant σ-donor interaction (Figure 2A),[43] the alkyne ligand becomes electrophilic, and is susceptible to nucleophilic attack from a variety of inter- and intramolecular nucleophiles. Complexation and activation of the alkyne π-system constitutes the first step of the chemical transformation, and the steps that generally follow alkyne activation in a nucleophilic addition reaction are shown in Scheme 8. After activation with a suitable metal catalyst (**53** → **54**), nucleophilic attack occurs onto the now electrophilic alkyne to form vinyl metal species **55**, which then undergoes protodemetallation to furnish the alkene product **56**. It is important to note that there is often no physical evidence for the formation of the putative intermediates (such as **54** and **55**) and therefore mechanisms are often based on reaction outcomes and theoretical calculations.



Scheme 8. Nucleophilic addition to alkyne activated by transition-metal species.

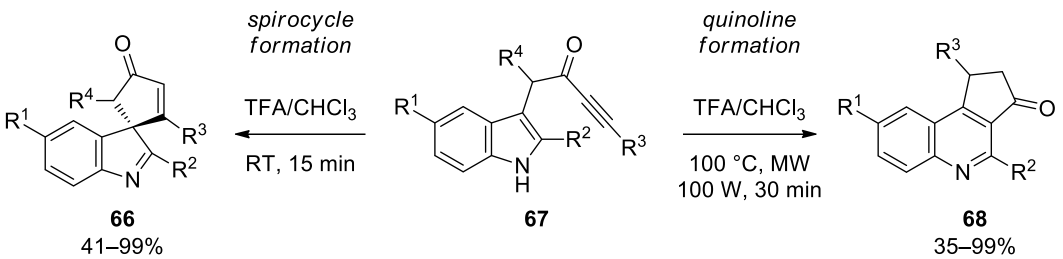
Spirocyclisation reactions of indole utilising the electrophilic activation of tethered alkynes have only recently been reported in the literature following the first isolation of spirocyclic indolenine products by the You group in 2010.[34] In the majority of cases, the spirocyclic products are often formed as minor side products during other transformations.[44–46] An early example of spirocyclisation facilitated by alkyne activation was reported by Van der Eycken and co-workers, in which they described the formation of spirocyclic indolenine **58** during the gold-catalysed cyclisation of propargylic amide **57** (Scheme 9A).[45] The annulated indole product **59** was also isolated in 25% yield resulting from a 1,2-migration process.



Scheme 9. Gold-catalysed syntheses of spirocyclic indolenines.

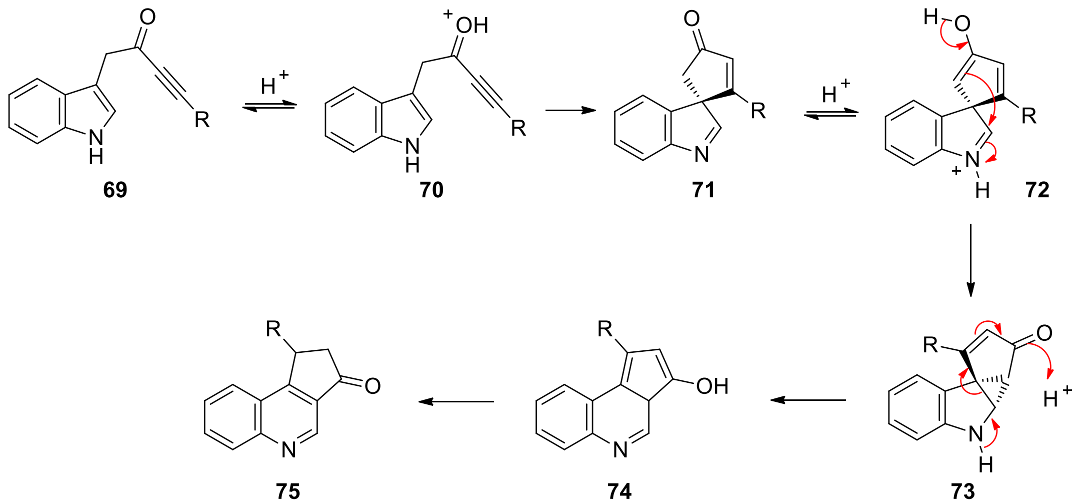
Carbery and co-workers also observed small amounts of spirocyclic indolenine formation when exploring the gold-catalysed annulation of indoles (Scheme 9B);[46] in a single example, indolenine **61** was isolated in 25% yield and annulated indole **62** was isolated as the major product in 38% yield. More recently, Guinchard and co-workers also published a gold-catalysed process for the dearomatisation of *N*-propargyl tryptamines **63** (Scheme 9C).[47] The isolated yields for the spirocyclic indolenine products **65** generated using this procedure are noticeably higher (45–86%) which is particularly impressive given that the C-2 position is unsubstituted; this position is often deliberately substituted in related work, in order to minimise the impact of competing 1,2-migration processes.[48] In addition to gold-catalysed dearomatisation processes reported above, there are also several reports on the use of palladium-catalysed alkyne activation methods to access spirocyclic indolenines.[28,49,50]

Whilst conducting the work described in this Thesis, more recent spirocyclisation efforts employing electrophilic activation of alkynes have since been published. A Brønsted acid-promoted selective synthesis of spirocyclic indolenines **66** and quinolines **68** from indole-tethered ynones **67** was reported by Van der Eycken and co-workers in 2017 (Scheme 10).[51]



Scheme 10. Temperature switchable synthesis of spirocyclic indolenines and quinolines from indole-tethered ynones.

It was found that selective synthesis of each product could be controlled by the temperature at which the reactions were performed; when performing the reaction at RT the spirocyclic indolenines **66** were generated but performing the reactions at higher temperatures facilitated a rearrangement process (shown in Scheme 11) leading to the formation of quinoline structures **68** instead.



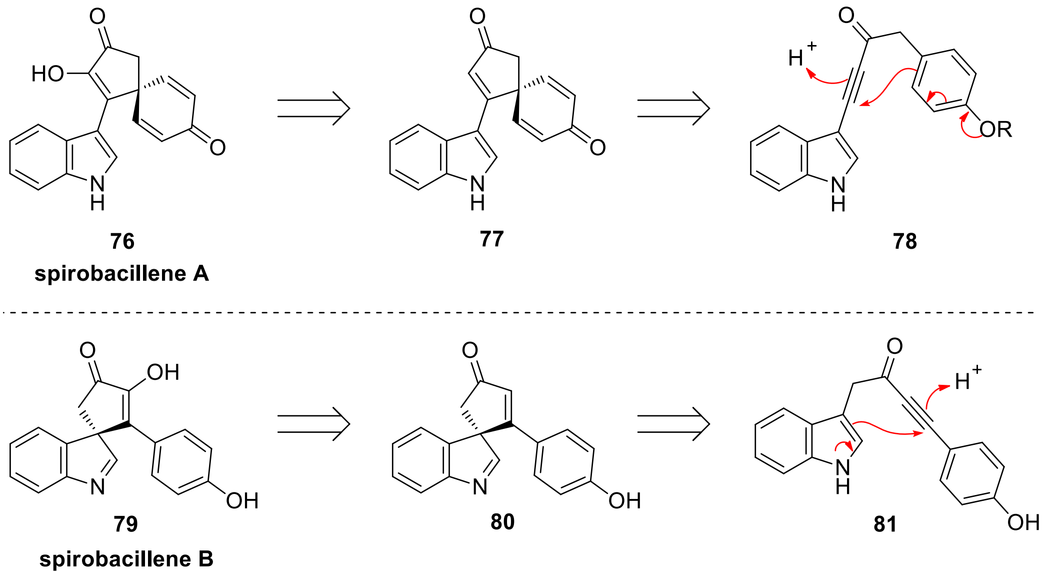
Scheme 11. Proposed rearrangement pathway leading to quinoline formation.

This procedure is very similar to an earlier report on the divergent synthesis of spirocycles, carbazoles and quinolines by the Taylor/Unsworth group. In this earlier work, Taylor and co-workers describe the use of $AlCl_3{\cdot}6H_2O$ instead of a Brønsted acid to catalyse the same rearrangement process seen in Van der Eycken's study. This Lewis acid-catalysed procedure presumably proceeds *via* the same mechanism and this work is discussed in more detail in Section 1.5.3 (Scheme 18).[52]

1.5 Taylor/Unsworth group methodologies

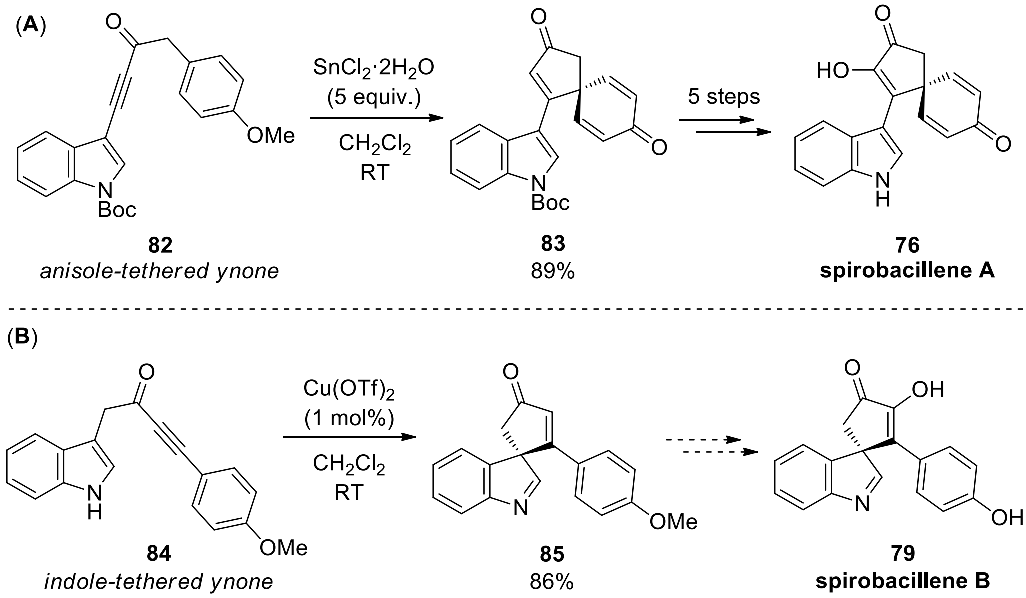
1.5.1 Spirobacillenes A and B

The chemistry described in this Thesis has its origins in a total synthesis project. Following the isolation of natural products spirobacillene A **76** and B **79** from acidic coal mine drainage in 2012,[53] the Taylor/Unsworth group decided to attempt their total synthesis. Retrosynthetic routes for each natural product were devised, focusing on phenol/anisole- and indole-tethered ynones **78** and **81** which had not been widely explored before this time (Scheme 12). It was envisaged that under acidic conditions, the ynone precursors **78** and **81** would undergo an intramolecular nucleophilic *ipso*-cyclisation to provide the enone intermediates **77** and **80**, respectively. Following this, it was hoped that oxidation of each enone framework would then deliver the desired natural products spirobacillene A **76** and B **79**.



Scheme 12. Retrosynthesis routes to spirobacillene A 76 and B 79 devised by Taylor/Unsworth group.

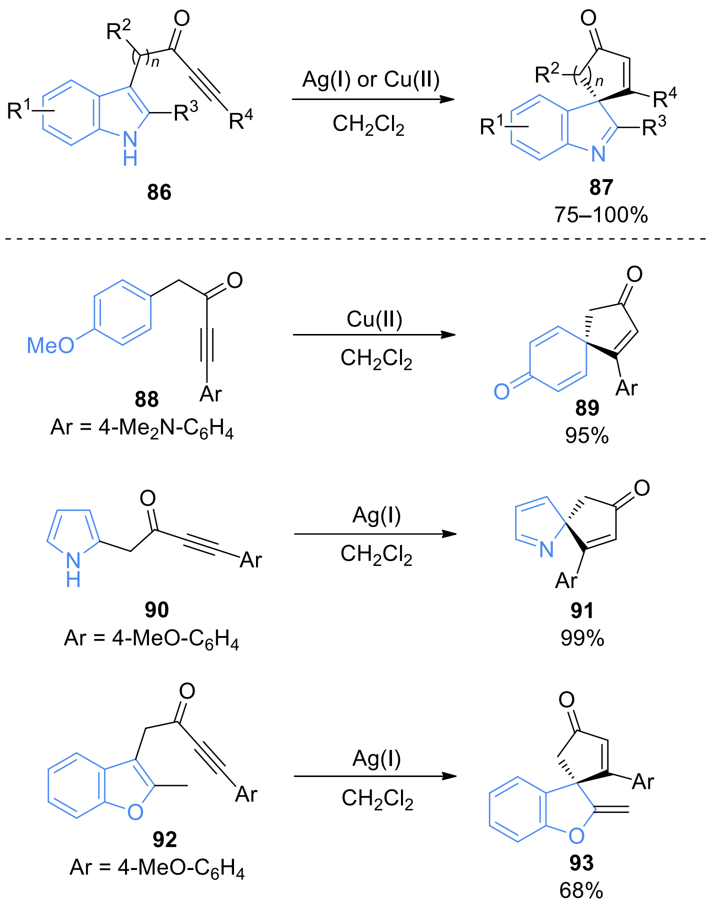
Pleasingly, it was found that treatment of anisole-tethered ynone **82** with stoichiometric $SnCl_2{\cdot}2H_2O$ did indeed promote spirocyclisation and hydrolysis to furnish spirocyclic enone **83** (Scheme 13A), which could then be converted into spirobacillene A **76** in just five steps.[54] In addition, it was also found that indole-tethered ynone **84** could undergo a similar spirocyclisation, upon reaction with catalytic $Cu(OTf)_2$, to yield the key spirocyclic enone intermediate **85** towards the natural product spirobacillene B **79** (Scheme 13B), although to date, the final steps in the total synthesis of spirobacillene B have not been completed.



Scheme 13. Spirocyclisation of ynones 82 and 84 forming key spirocyclic intermediates in natural product synthesis.

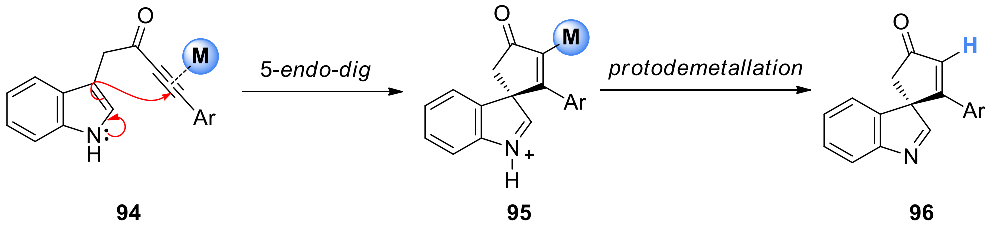
1.5.2 Dearomatising spirocyclisation methodology involving alkyne activation

Each of the initial spirocyclisation reactions (shown in Scheme 13) were then further optimised and developed into full methodologies, which is important given the rarity of high-yielding spirocyclisation reactions using alkyne activation reported in the literature.[55,56] For details regarding the optimisation of the $SnCl_2·2H_2O$-mediated spirocyclisation reaction used in the total synthesis of spirobacillene A **76**, see Chapter 3. Following optimisation studies based on the initial Cu(OTf)$_2$-catalysed spirocyclisation reaction of indole-tethered ynone **84** (Scheme 13B), a novel dearomatisation spirocyclisation methodology was developed which efficiently converted a range of aromatic-tethered ynone precursors into their spirocyclic scaffolds using Ag(I) or Cu(II) catalysis (Scheme 14).[55] This methodology was applied to other indole-tethered ynone precursors of the form **86**, generating spirocyclic indolenine products **87** in 75–100% yields, and in addition, several other ynone-tethered systems including anisole **88**, pyrrole **90** and benzofuran **92** were also explored furnishing their spirocyclic products **89**, **91** and **93** in similarly high yields.



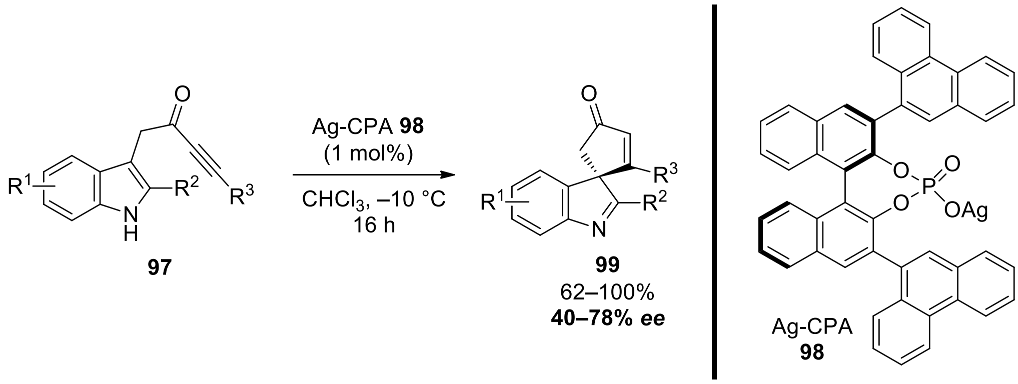
Scheme 14. Dearomative spirocyclisation methodology developed in the Taylor/Unsworth group.

As illustrated in Scheme 15 using indole-tethered ynone **94** as an example, it is believed that the spirocyclisation first proceeds *via* Ag(I)/Cu(II) alkyne coordination. This coordination increases the electrophilicity of the alkyne and subsequently facilitates nucleophilic attack by the indole ring through its C-3 position to generate the vinyl metal species **95** *via* a 5-*endo*-*dig* cyclisation.[57] The vinyl metal intermediate **95** then undergoes rapid protodemetallation to furnish the desired spirocyclic product **96**.



Scheme 15. Proposed mechanism for spirocyclisation.

Preliminary asymmetric studies were also performed on the indole-tethered ynone systems **97** using Ag(I) salts of chiral phosphoric acids (CPAs) as catalysts (Scheme 16). It was found that a combination of increasing the steric bulk around the BINOL backbone (see Ag-CPA catalyst **98**), switching the reaction solvent to chloroform and performing the reaction at −10 °C significantly improved the enantioselectivity up to 78% *ee*.

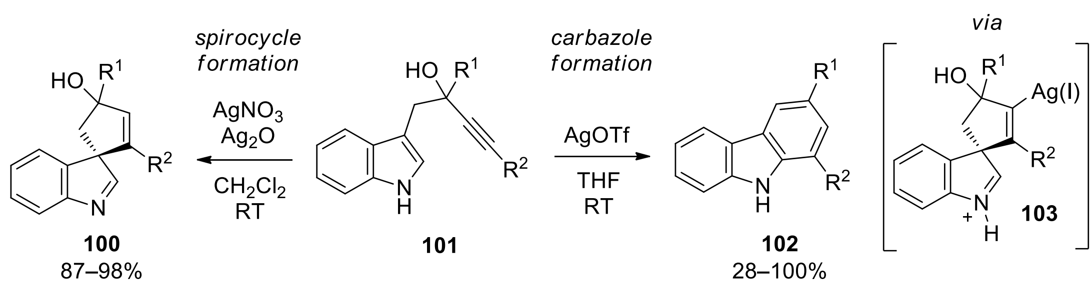


Scheme 16. Asymmetric indole-tethered ynone spirocyclisations.

1.5.3 Extension of Taylor/Unsworth group methodologies

The research and methodologies discussed up until this point describe the state of the dearomatising spirocyclisation project at the time I joined the Taylor group, and following the success of this work, the initial goal in this PhD was to develop heterogeneous variants of the groups' spirocyclisation reactions (see Section 1.6 for Project Aims). However, whilst carrying out the research described in this Thesis, several other related projects have been explored by colleagues, and details of these projects are provided below.

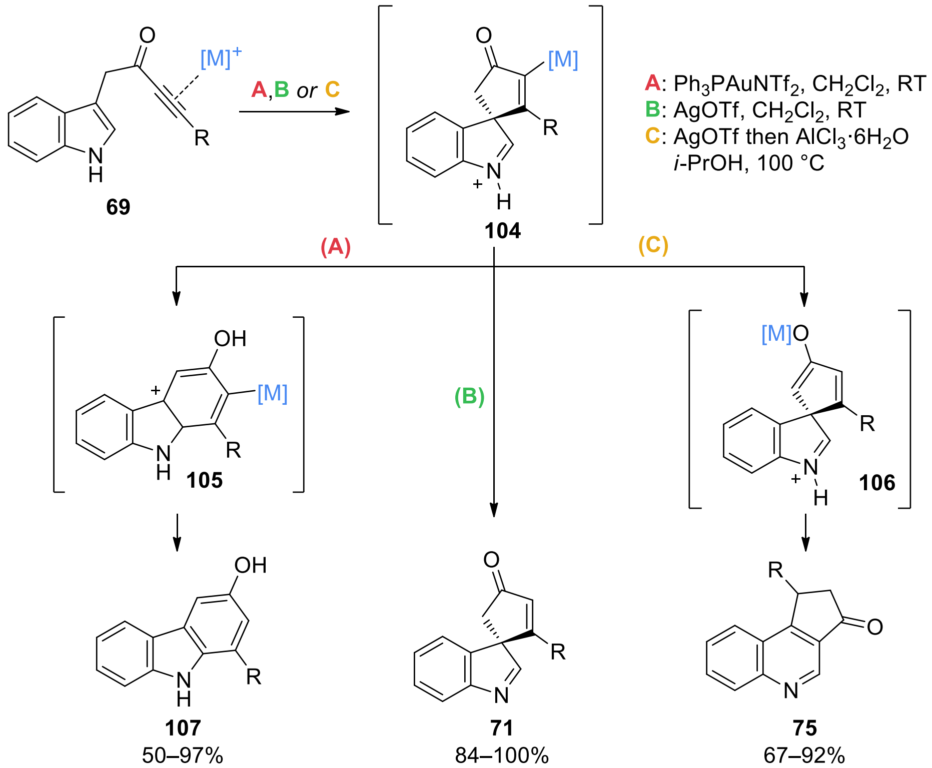
As described previously (see Scheme 3), spirocyclic indolenines have the propensity to undergo 1,2-migration. In a subsequent study within the Taylor/Unsworth group, reaction conditions were sought that could selectively deliver either spirocyclic indolenines **100** or the corresponding 1,2-migration products (carbazoles **102**) by modulating the acidity of the reaction medium. A generally high-yielding and divergent approach, capable of generating two products selectively from a common indole-tethered propargyl alcohol precursor **101** was developed and is shown in Scheme 17.



Scheme 17. Divergent synthesis of spirocyclic indolenines 100 and carbazoles 102.

It was proposed that the divergent reactivity observed was due to the presence of adventitious Brønsted acid, likely to be present in the AgOTf reagent, facilitating a 1,2-migration process of the spirocyclic vinyl silver intermediates **103** to furnish the carbazole products **102**. This theory was put to the test by performing the AgOTf reaction in the presence of triethylamine; the expectation here was that in the presence of a basic additive the reactivity would be switched so spirocyclic indolenine formation was promoted rather than carbazole formation. This was indeed the case; the triethylamine additive appeared to quench any adventitious acid, promoting spirocyclisation instead of carbazole formation. It had been suggested previously that the electron-withdrawing carbonyl group present in ynones is needed to reduce the migratory aptitude of the alkene in the spirocyclic products and prevent 1,2-migration, but this study showed that this is not a requirement providing suitable reaction conditions are used.

The divergent reactivity of spirocyclic vinyl-metal intermediates has been further explored by the Taylor/Unsworth group. It was found by varying the metal catalyst used, the nature and reactivity of the vinyl metal intermediates **104** could be altered, enabling the formation of multiple products by different rearrangement reactions (Scheme 18).[52] Indole-tethered ynone starting materials **69** were converted into carbazoles **107** *via* intermediate **105** using Au(I), spirocyclic indolenines **71** using Ag(I) and quinolines **75** *via* enolate **106** using Ag(I)/Al(III) in high yields, by simple catalytic processes.



Scheme 18. Divergent synthesis of carbazoles 107, spirocycles 71 and quinolines 75 from indole-tethered ynones 69.

1.6 Project aims

The overriding goal of this PhD research was to develop new heterogeneous spirocyclisation methodologies. Building on the previous work described in this Introduction, we were keen to focus on Ag(I)/Cu(II)-catalysed procedures, especially those able to generate biologically important scaffolds. It was also planned to undertake mechanistic studies to better understand the underlying catalysis in any successful procedures.

Chapter 2 describes the development of a silica-supported silver-catalysed spirocyclisation reaction. The application of this methodology in the spirocyclisation of a variety of aromatic and heteroaromatic systems is reported and mechanistic studies using ReactIR™ technology are also described.

Chapter 3 focuses on the use of phenol-tethered ynones in the silica-supported spirocyclisation reaction. Some preliminary asymmetric studies are reported as well as the application of this methodology in the formal synthesis of spirobacillene A.

Chapter 4 describes a new method for the synthesis of substituted indoles using pyrrole-tethered ynones *via* π-acidic alkyne activation. Density functional theory (DFT) calculations are also reported which suggest an unusual C-3 nucleophilicity of the pyrrole-tethered ynones.

Finally, **Chapter 5** explores the divergent reactivity of α-diazocarbonyl compounds and describes how four distinct product classes were accessed from closely related phenol- and anisole-tethered α-diazocarbonyl precursors.

Chapter 2. Preparation of spirocyclic scaffolds using silica-supported silver nitrate

2.1 Organic synthesis using supported reagents

Although organic synthesis employing supported reagents and catalysts has recently received increased attention from synthetic chemists,[58–60] the concept of utilising heterogeneous catalysis to promote chemical transformations is not new. Seminal work by Fetizon and Golfier introduced the use of silver carbonate on a Celite support in oxidation reactions back in 1968[61] and following their work, several comprehensive reviews and textbooks emerged.[62–65] Originally, supported reagents were designed to disperse reagents over a support, providing a high surface area to enhance reagent activity and little attention was paid at the time to additional benefits. Now there is more of an appreciation for the many advantages accompanying the use of supported reagents and catalysts; whilst improving reactivity they can also help simplify product purification, facilitate catalyst recovery and enhance synthetic procedures by enabling scale-up and improved safety profiles. A particularly noteworthy factor in favour of using supported reagents and catalysts is their recyclability, which often provides a more environmentally friendly alternative to conventional reagents.

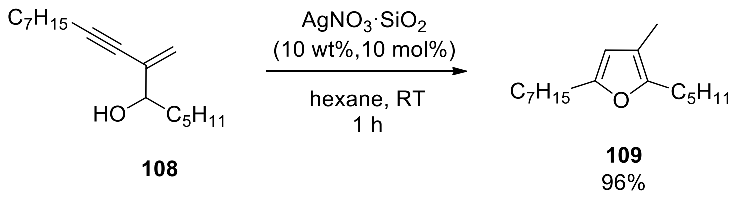
Although both organic and inorganic supports are routinely used, inorganic supports are more commonly employed. Certain materials have found more widespread use than others and silica is one of the most common, primarily due to its excellent stability, porosity, easy handling and the ability to chemically modify its surface. These advantages have led to the immobilisation of a wide range of reagents and catalysts onto silica over the years.[66–68]

2.1.1 Silica-supported silver catalysts

Silica supports can take a variety of different forms including: hydrated and anhydrous crystalline, microcrystalline and amorphous solids; the latter is most generally used due to its high surface area and increased porosity. The surface of amorphous silicas consists of siloxane (Si-O-Si) and silanol (Si-OH) groups which contribute to its weakly acidic and hydrophilic properties. The groups present on the silica surface can serve as reactive sites, enabling chemical modifications and immobilisation of reagents to take place, which can tune the surface acidity and other properties of the silica.

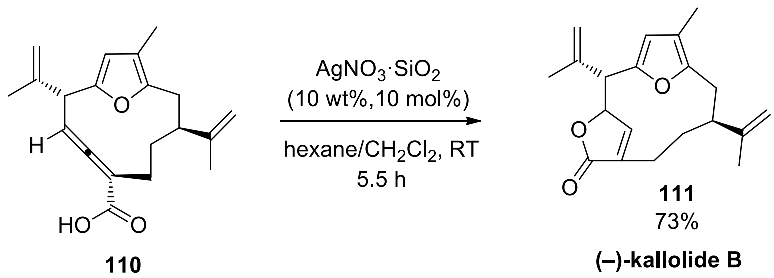
Supported silver catalysts enable the selective activation of π-systems with an uncomplicated recovery of catalyst and purification of products. $AgNO_3$ immobilised on silica ($AgNO_3 \cdot SiO_2$) was first introduced as a chromatographic medium for the separation of olefins,[69–71] however, its use as a synthetic reagent is becoming more prevalent. One of the earliest reports of

$AgNO_3{\cdot}SiO_2$ being used as a catalytic reagent was in the synthesis of furans, reported by Marshall *et al*. in 1995 and a representative example of their work is shown in Scheme 19, whereby Ag(I) initiates cyclisation through π-coordination to the alkyne.[72]



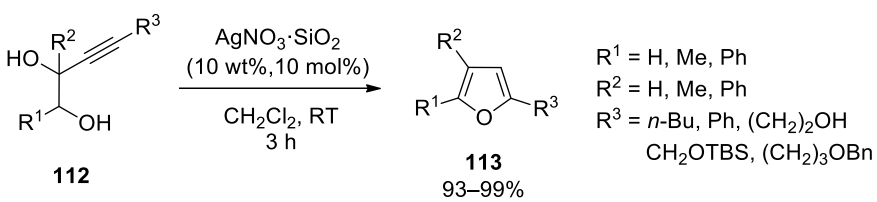
Scheme 19. Synthesis of furan 109 using $AgNO_3{\cdot}SiO_2$ reported by Marshall *et al*.

$AgNO_3$ immobilised on silica served as a suitable catalyst for the conversion of β-alkynyl allylic alcohol **108** into furan **109**. The supported catalyst could also be recycled and reused, albeit with a reduced yield and prolonged reaction time of 2 hours. Following this initial report, the methodology was then applied to a range of allenones and allenic acids;[73,74] the final step in the total synthesis of kallolide B (**110** → **111**) exemplifies this transformation (Scheme 20).[75]



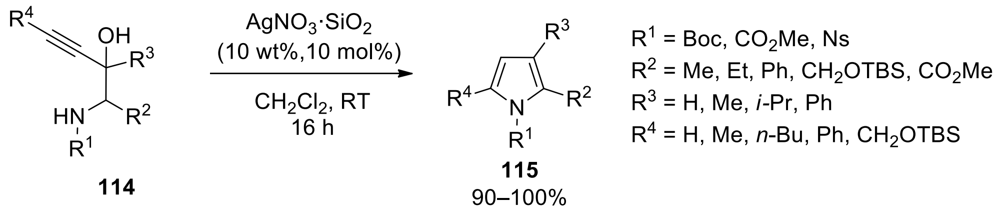
Scheme 20. Use of $AgNO_3{\cdot}SiO_2$ in total synthesis of kallolide B.

Another efficient furan synthesis using $AgNO_3{\cdot}SiO_2$ to promote 5-*endo-dig* cyclisations of 3-alkyne-1,2-diols **112** was reported by the Knight group in 2007.[76] In this publication, a more extensive substrate scope than was previously described by Marshall *et al*. is reported, with a variety of different furan substitution patterns accessible in high yields (Scheme 21).



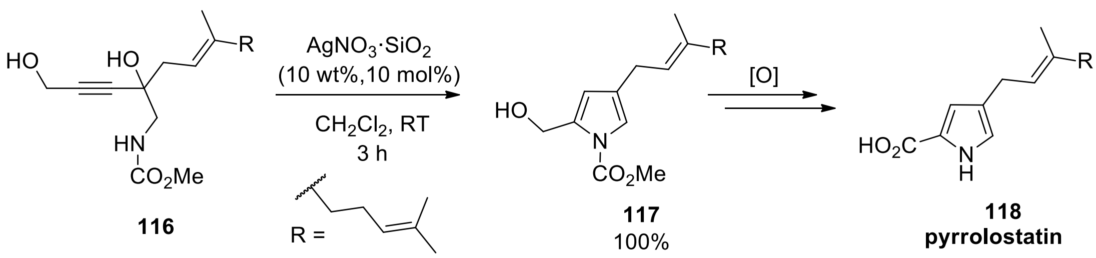
Scheme 21. General furan synthesis using $AgNO_3{\cdot}SiO_2$ reported by Knight *et al*.

The Knight group have since extended the intramolecular cyclisation of π-systems using $AgNO_3{\cdot}SiO_2$ to synthesise pyrroles from propargylic glycinates.[77] The impressive efficiency of this procedure was exemplified during the synthesis of a range of multi-substituted pyrroles **115** in near-quantitative yields at ambient temperature (Scheme 22). Terminal alkynes and a range of *N*-protecting groups were tolerated in this protocol, as well as alkyl and aryl substituents on the propargylic glycinate precursors.



Scheme 22. General synthesis of substituted pyrroles using $AgNO_3 \cdot SiO_2$.

This strategy was then applied in the total synthesis of pyrrolostatin **118** in 2016,[78] whereby a key pyrrole intermediate **117** was obtained in quantitative yield through the cyclisation of diol **116** using 10 mol% $AgNO_3 \cdot SiO_2$ (Scheme 23); this result was a significant improvement upon the pyrrole-forming step used in a previous synthesis of pyrrolostatin **118**, which suffered from a low yield of 18%.[79]



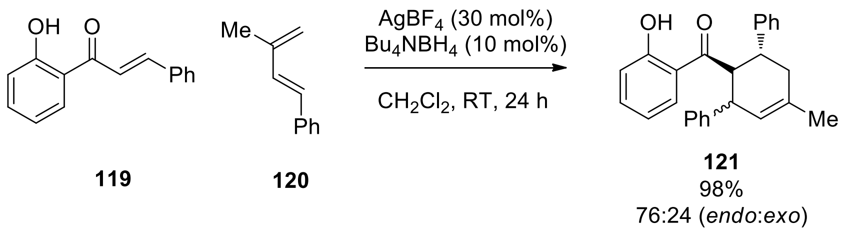
Scheme 23. Use of $AgNO_3 \cdot SiO_2$ in the total synthesis of pyrrolostatin 118.

2.1.2 Silica-supported silver nanoparticles

Since the pioneering work on silica-supported silver catalysts by the groups of Marshall and Knight, the field of heterogeneous silver catalysis has begun to incorporate the use of solid-supported silver nanoparticles (AgNPs).[80–82] Nanoparticles possess unique chemical properties and are promising heterogeneous catalysts due to their high surface area and nanoscale size, although their application in organic synthesis has often been limited to previously known transformations.[83] The immobilisation of AgNPs on heterogeneous supports such as silica is still at a relatively early stage in development but research exploring the catalytic activity of AgNPs has increased significantly in recent years.

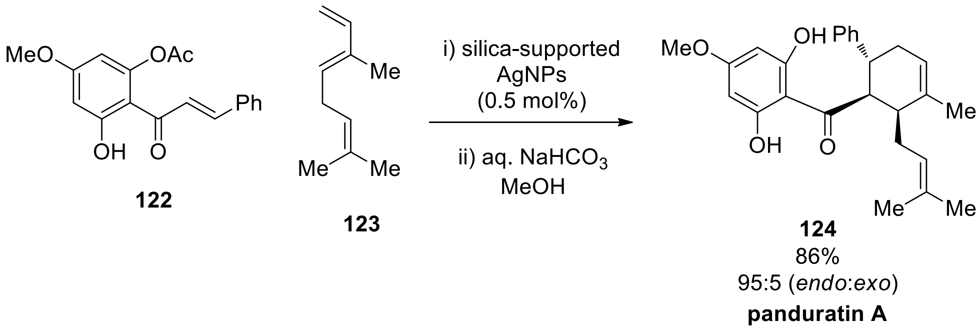
The first example of a metal nanoparticle-catalysed Diels-Alder cycloaddition was reported by Porco Jr. *et al.* in 2010 and this contributed greatly to the development of nanosilver-promoted natural product synthesis.[84] Initial studies revealed that a combination of $AgBF_4$ and Bu_4NBH_4

generated AgNPs *in situ*, and these promoted the cycloaddition reaction of hydroxychalcone **119** and diene **120**, favouring the *endo* Diels-Alder product **121** in high yield as illustrated in Scheme 24. The authors observed little or no reactivity when using just $AgBF_4$, Bu_4NBH_4 or commercially available Ag powder.



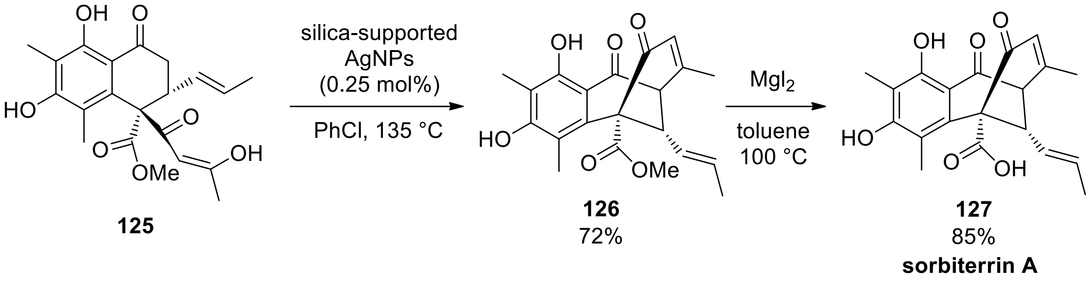
Scheme 24. AgNP-catalysed Diels-Alder cycloaddition reaction.

Encouraged by these results, Porco Jr. *et al.* then went on to develop a heterogeneous and reusable catalyst by immobilising the AgNPs onto a silica support. Cycloadditions were also successfully catalysed by the silica-supported AgNPs, generally favouring the *endo* Diels-Alder products again, in high yields using low catalyst loadings. The synthetic utility of this silica-supported AgNP-catalysed Diels-Alder reaction was exemplified in the total synthesis of two natural products, panduratin A **124**[84] and sorocenol B[85] (a key step in synthesis of panduratin A is shown in Scheme 25), in which the authors propose that the silver nanoparticles serve as an electron shuttle during the cycloaddition process.



Scheme 25. Synthesis of panduratin A 124 by Porco Jr. *et al*.

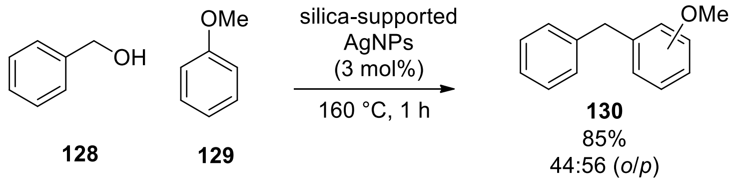
Porco Jr. *et al.* were also able to use their silica-supported AgNPs to promote a key intramolecular aldol condensation/dehydration reaction whilst working towards the synthesis of natural product sorbiterrin A **127** (Scheme 26).[86]



Scheme 26. Synthesis of sorbiterrin A 127 *via* aldol condensation and dehydration.

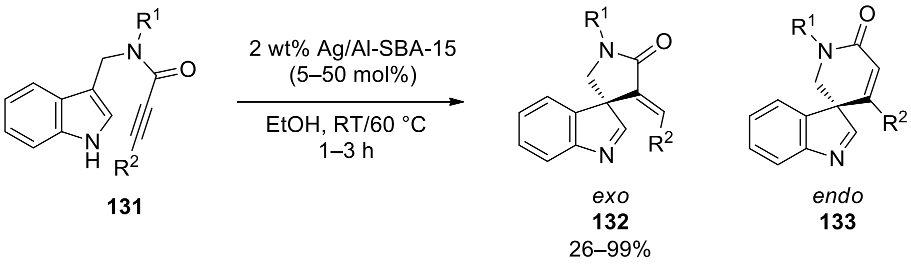
The AgNP-catalysed reaction of enol **125** generated the cyclised product **126** in a 72% yield which could subsequently be converted into sorbiterrin A **127** by treatment with MgI_2. The unique reactivity of the AgNPs in the aldol reaction was established when a series of other conditions failed to promote formation of the desired aldol product **126**. In the absence of silver or when using Ag_2O, no reaction was observed, and in the presence of other metal salts such as AgOTf, $AgBF_4$ and $Cu(OTf)_2$ the starting material **125** decomposed.

In 2010, Shimizu and co-workers described a novel Friedel-Crafts alkylation reaction employing silica-supported silver nanoparticles as an effective catalyst (Scheme 27).[87] The alkylation of anisole **129** with benzyl alcohol **128** was performed, exploiting partially oxidised AgNPs formed *via* a calcination process, to furnish the diphenylmethane product **130** in an 85% yield. Alternative silver catalysts were evaluated in the reaction and it was found that Ag_2O, $AgNO_3$ and Ag powder were completely ineffective.



Scheme 27. Friedel-Crafts alkylation catalysed by silica-supported AgNPs.

Recently, in 2016 during this PhD, a silver nanoparticle-catalysed dearomatisation of indoles towards the synthesis of spirocyclic indolenines was reported by the Van der Eycken group (Scheme 28).[88] It was found that supporting AgNPs on an aluminium-containing mesoporous silica (Al-SBA-15) was an effective catalyst system in converting a range of indole-tethered alkynes **131** into their spirocyclic indolenines **132**. Substrates bearing terminal alkynes showed good reactivity, resulting in the formation of 5-*exo*-*dig* products **132** in generally high yields. However, internal alkynes required higher temperatures, longer reaction times and almost equimolar amounts of catalyst to achieve complete reactions; a mixture of *endo*- and *exo*-cyclisation products were also formed when using internal alkynes which could not be separated.

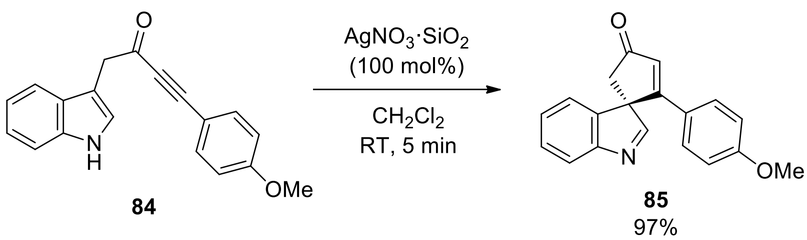


Scheme 28. AgNP-catalysed spiroindolenine formation.

In addition to the applications of silica-supported AgNPs in organic synthesis which have been discussed above, there are also a few examples in the literature employing silica-supported AgNPs in oxidations/reductions and hydrogenation reactions.[89,90] Indeed, it is also possible that previous protocols describing the use of $AgNO_3 \cdot SiO_2$ and other supported silver reagents may also involve AgNPs, without the researchers realising their importance. It is however particularly challenging to determine whether a reaction is proceeding *via* homo- or heterogeneous catalysis; a detailed review by Widegren and Finke explores the difficulties behind this and also describes experiments which can be used to identify whether nanoparticles may be catalysing a chemical reaction.[91]

2.2 Preliminary results

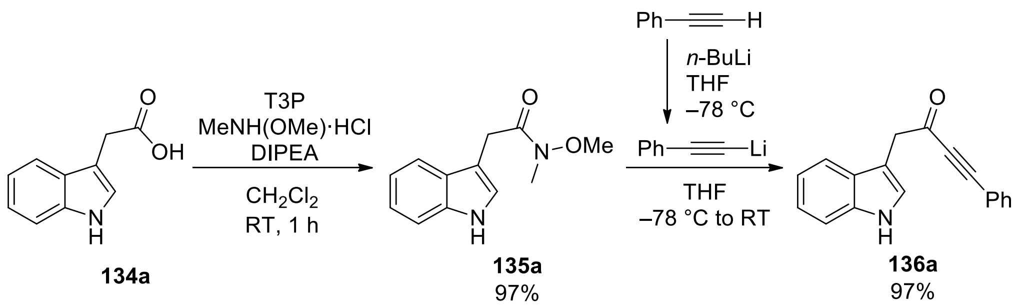
As the use of heterogeneous catalysis in organic synthesis continues to grow, it was desirable to extend Taylor and Unsworth's spirocyclisation methodology (see Scheme 14 in Chapter 1) to a heterogeneous variant, whereby the catalyst for the reaction is immobilised on a solid support. During some preliminary studies carried out by Michael James,[92] it was realised that a supported silver catalyst could also be used to effect the same spirocyclisation (**84** → **85**), albeit using a stoichiometric amount of catalyst (Scheme 29).



Scheme 29. Preliminary heterogeneous spirocyclisation reaction carried out by Michael James.

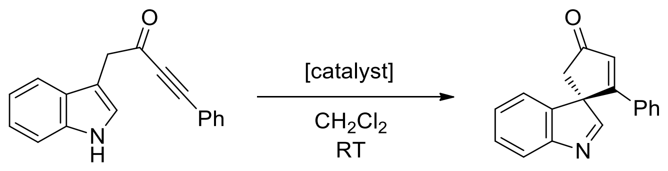
2.3 Reaction optimisation studies

The success of the preliminary heterogeneous spirocyclisation reaction (Scheme 29) prompted further optimisation of the reaction conditions. Consideration of both the catalyst loading and reaction solvent was necessary before moving on to any substrate scoping studies. All optimisation reactions were performed on a model phenyl ynone system **136a**, prepared in a two-step protocol starting from the commercially available carboxylic acid **134a** (Scheme 30). Firstly, carboxylic acid **134a** was converted into Weinreb amide **135a** *via* a simple T3P coupling reaction; T3P is a particularly useful coupling reagent as the by-product generated is water-soluble and therefore can easily be removed by an aqueous work-up. Weinreb amide **135a** was then treated with lithiated phenylacetylene to furnish the desired phenyl ynone **136a** in a near-quantitative yield.[55]



Scheme 30. Preparation of model ynone system 136a.

The catalyst loading (mol%) in the reaction and $AgNO_3$ loading on the silica (wt%) were the first parameters to be investigated in the spirocyclisation reaction (Table 1). It should be noted that the $AgNO_3$ loading on silica takes into account the total weight of $AgNO_3$ and therefore the actual loading of silver metal on silica is lower than this value. For example, a loading of 1 wt% $AgNO_3$ immobilised on silica equates to just 0.63 wt% Ag based on the stoichiometry of $AgNO_3$. Commercially available 10 wt% $AgNO_3 \cdot SiO_2$ from Aldrich was purchased and tested in the spirocyclisation reaction (Entry 2) but all other catalysts used in the optimisation studies were prepared in-house. Preparation of the silica-supported catalysts were very straightforward and were based on procedures described by McKillop, Smith and Li.[62,69,93] The silver salt ($AgNO_3$ or AgOTf) was added to a vigorously stirred silica slurry in deionised water. This mixture was then stirred for 15 minutes, concentrated *in vacuo* at 60 °C and dried further by heating to 140 °C under a high vacuum for 4–5 hours to provide the supported catalysts as free-flowing powders.



136a **137a**

Entry	Catalyst loading / mol%	$AgNO_3$ loading / wt%	Time	Conversion[a] / %
1	10	30	10 min	100 (100)
2[b]	10	10	10 min	100 (98)
3	1	30	24 h	57
4	1	10	6 h	80
5	**1**	**1**	**30 min**	**100 (98)**
6	1	0.1	1.5 h	100
7	0.1	1	2 d	80
8	0.1	0.1	5 d	45
9[c]	1	-	6 h	100
10[d]	1	-	2 h	100
11[e]	1	-	1 h	100 (88)
12[f]	-	-	24 h	Trace

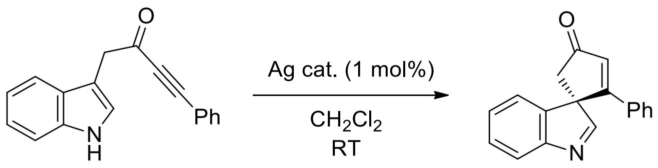
All reactions were performed in CH_2Cl_2 at RT and isolated yields are reported in parentheses. [a]Conversions calculated by analysis of starting material:product ratio in the unpurified ^1H NMR spectra. [b]Commercial 10 wt% $AgNO_3 \cdot SiO_2$ used. [c]$AgNO_3$ used. [d]$AgNO_3$ and SiO_2 added separately. [e]1 wt% $AgOTf \cdot SiO_2$ used. [f]Heat-treated (140 °C) SiO_2 added.

Table 1. Catalyst optimisation results.

A range of both catalyst loadings (0.1–10 mol%) and $AgNO_3$ loadings on silica (0–30 wt%) were tested in the spirocyclisation reaction of ynone **136a**. Interestingly, lowering the relative amount of silver immobilised on silica from 30 wt% (Entry 3) to 1 wt% (Entry 5) significantly improved the efficiency of the reaction. Full conversion could still be achieved when lowering the loading of $AgNO_3$ on silica to 0.1 wt% (Entry 6) but a longer reaction time was required to reach completion. 1 wt% $AgOTf \cdot SiO_2$ also displayed comparable efficiency to 1 wt% $AgNO_3 \cdot SiO_2$ promoting full conversion to spirocycle **137a** in 1 hour (Entry 11), however, a lower isolated yield was obtained using this catalyst system. As highlighted in Table 1, 1 mol% catalyst loading and 1 wt% $AgNO_3$ loading on silica (Entry 5) enabled the efficient conversion of phenyl ynone **136a** to spirocycle **137a** in a near-quantitative isolated yield and these were the catalyst conditions taken on into solvent optimisation studies.

Inductively Coupled Plasma Mass Spectrometry (ICP-MS) was used to verify the incorporation of silver in our 1 wt% $AgNO_3 \cdot SiO_2$ catalyst. ICP-MS analysis of the silver concentration in our catalyst before use gave a reading of 4990 ppm which equates to 0.49 wt% Ag. For a $AgNO_3$ loading of 1 wt% immobilised on silica you would expect a value of 0.63 wt% Ag as explained previously; the small difference observed between the measured and expected values could be due to experimental error or the quality of commercial $AgNO_3$ used. There is minimal loss of silver during preparation of the catalyst as neither filtration nor an aqueous work-up is involved and therefore theoretically full silver incorporation should be achieved.

After establishing the optimal combination of catalyst loading in the reaction and $AgNO_3$ loading on silica, some alternative solid supports for the immobilisation of silver were also explored (Table 2). Ynone **136a** was treated with 1 mol% of each supported catalyst, prepared according to literature procedures,[62,69,93] and the progress of each reaction was monitored by thin layer chromatography (TLC).



136a **137a**

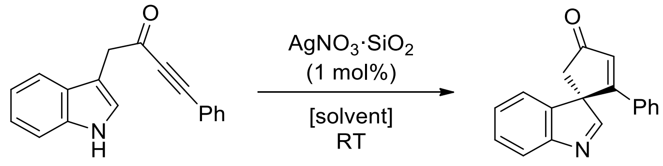
Entry	Catalyst/support	Ag content / wt %	Time	Conversion[a] / %
1	$AgNO_3$/silica	0.63	30 min	100
2	$AgNO_3$/Celite	0.63	24 h	100
3	Ag_2CO_3/Celite	0.63	24 h	50
4	$AgNO_3$/alumina	0.63	24 h	Trace

[a]Conversions calculated by analysis of starting material:product ratio in the unpurified ^1H NMR spectra.

Table 2. Spirocyclisation using alternative solid supports.

As can be seen in Table 2, $AgNO_3$ supported on Celite (Entry 2) promoted full conversion of ynone **136a** into spirocycle **137a**, although it appeared to be less active than $AgNO_3$ supported on silica as a prolonged reaction time of 24 hours was required. In contrast, $AgNO_3$ immobilised on alumina (Entry 4) performed the worst out of the catalysts tested; only trace amounts of spirocycle **137a** were observed in the ^1H NMR spectrum of the unpurified reaction mixture after 24 hours. In conclusion, $AgNO_3$ immobilised on silica remained the best supported catalyst for the spirocyclisation, with full conversion of ynone **136a** to spirocycle **137a** observed in just 30 minutes.

After the most suitable catalyst system had been found, a variety of solvents were examined (Table 3). Pleasingly, the spirocyclisation proceeded well in the majority of solvents tested; a range of polar and non-polar aprotic solvents furnished the spirocyclic product **137a** in 6 hours or less.



Entry	Solvent	Conversion[a] / % 30 min	Conversion / % 6 h
1	DMF	0	0
2	TBME	8	60
3	2-MeTHF	10	60
4	THF	50	>95
5	MeCN	>95	>95
6	EtOAc	25	100
7	Et_2O	30	100
8	Hexane	35	100
9	MeOH	60	100[b]
10	DCE	80	100
11	Acetone	88	100
12	EtOH	90	100[b]
13	Toluene	90	100
14	$CHCl_3$	100	-
15	**CH_2Cl_2**	**100**	**-**

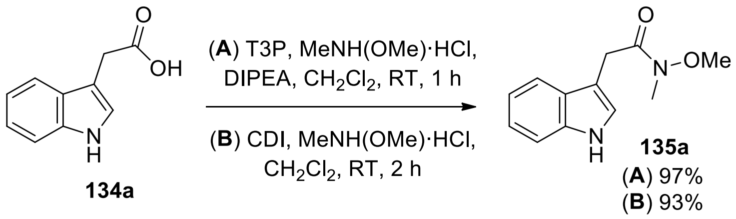
All reactions performed on 0.08 mmol of ynone **136a** using 1 wt% $AgNO_3·SiO_2$ at RT. [a]Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra. [b]Mixture of products observed by ^{1}H NMR spectroscopy but all starting material consumed.

Table 3. Solvent optimisation results.

The formation of spirocycle **137a** in the presence of polar protic solvents such as MeOH and EtOH was observed in the first 30 minutes (Entries 9 and 12); however, as the reaction proceeded the spirocycle appeared to decompose leading to a complex mixture of products after 6 hours. Both $CHCl_3$ and CH_2Cl_2 clearly outperformed all other solvents with full conversion of ynone **136a** into spirocycle **137a** observed in the first 30 minutes (Entries 14 and 15); CH_2Cl_2 was chosen as the solvent for the spirocyclisation due to its compatibility with other transformations, ease of removal and consistency with other spirocyclisation conditions previously used in the group.

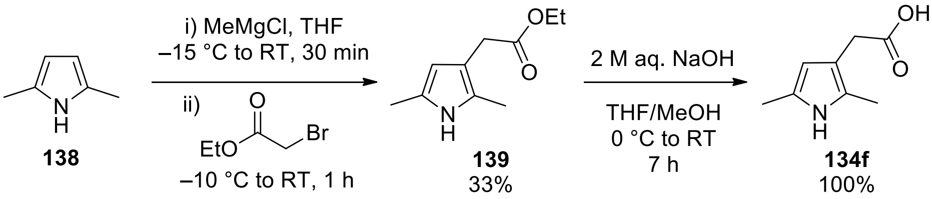
2.4 Preparation of spirocyclisation precursors

As mentioned previously, ynone precursors for the spirocyclisation methodology can be accessed *via* a two-step procedure using commercially available carboxylic acid starting materials in the majority of cases. The initial coupling reaction can be performed using either T3P (conditions A in Scheme 31) or CDI (conditions B in Scheme 31) as the coupling agent. T3P was used for all couplings except when large quantities of Weinreb amide **135a** were required (see Flow Chemistry Section 2.9); in this case CDI was favoured as a cheaper alternative.



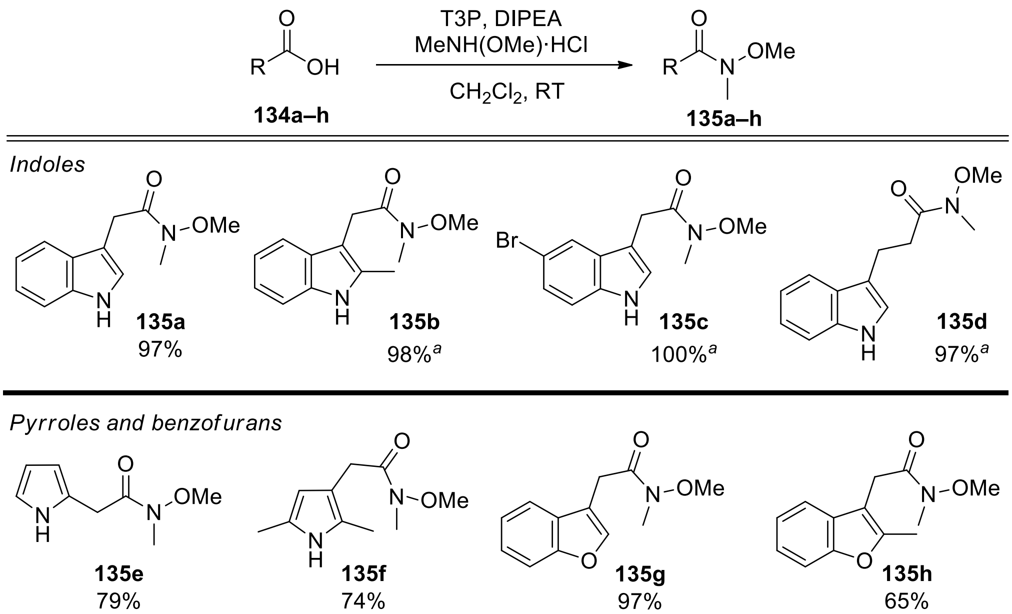
Scheme 31. Conditions used for (A) T3P and (B) CDI couplings.

Pyrrole carboxylic acid **134f** was not commercially available and was prepared *via* a two-step procedure starting from 2,5-dimethylpyrrole **138** (Scheme 32).



Scheme 32. Preparation of pyrrole carboxylic acid 134f.

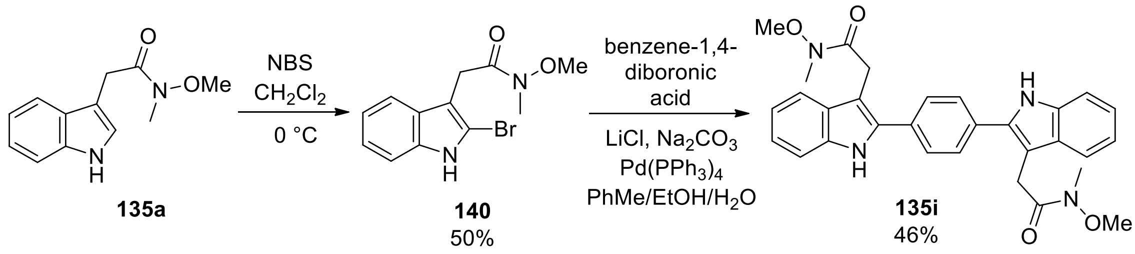
A range of Weinreb amides were then prepared using the T3P coupling conditions, all of which are shown in Scheme 33.



[a]Previously synthesised by Michael James.[92]

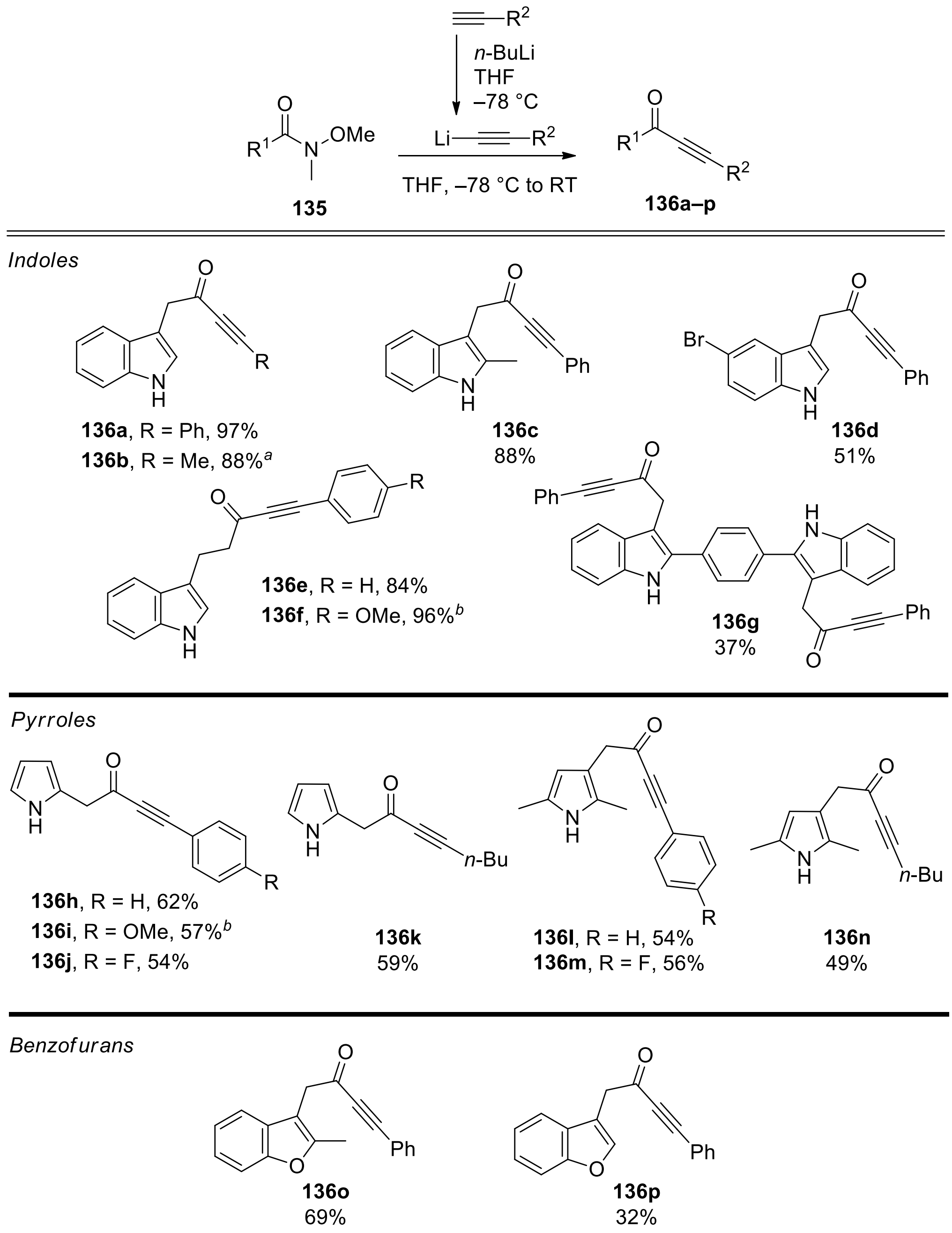
Scheme 33. Weinreb amides prepared using T3P coupling procedure.

In addition to the substrates shown in Scheme 33, dimeric Weinreb amide **135i** was prepared using a Suzuki cross-coupling reaction (Scheme 34). The standard Weinreb amide **135a** was brominated using NBS to provide a handle for the cross-coupling reaction. The brominated Weinreb amide **140** was then treated with benzene-1,4-diboronic acid in the presence of LiCl, Na_2CO_3 and $Pd(PPh_3)_4$ to generate the dimeric Weinreb amide **135i**.



Scheme 34. Preparation of Weinreb amide 135i *via* Suzuki cross-coupling.

All of the Weinreb amides were then used to access various ynone precursors by treatment with a range of different lithium acetylides. An excess of lithiated alkyne (2.5 equivalents) was required during the formation of indole and pyrrole-tethered ynones as one equivalent was consumed during deprotonation of the heterocycle. A range of indole-tethered ynones, as well as, other heterocyclic systems including pyrrole and benzofuran-tethered ynones, were prepared (Scheme 35).

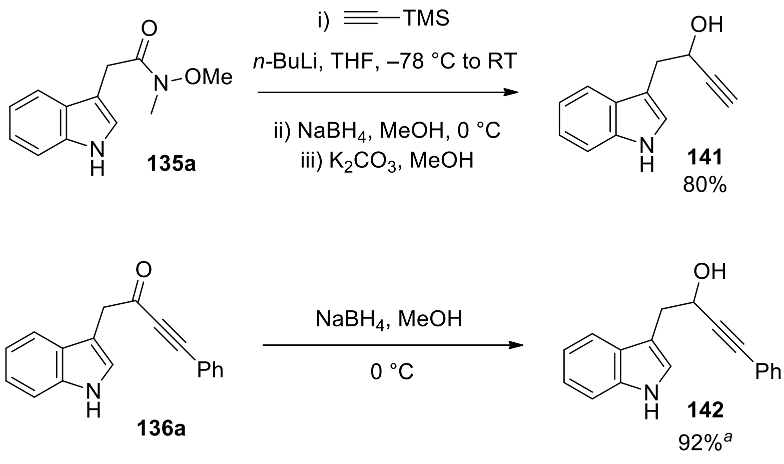


[a]Synthesised *via in situ* generation of lithium acetylide. [b]Previously synthesised by Michael James.[92]

Scheme 35. Ynones prepared *via* addition of lithium acetylides.

The preparation of ynones using this procedure was generally very efficient and high-yielding for the indole substrates with slightly lower isolated yields obtained for the pyrrole- and benzofuran-tethered ynones. Solubility issues were encountered during the isolation of bis-ynone **136g** which subsequently led to its lower isolated yield.

In addition to the ynone precursors shown in Scheme 35, propargyl alcohol substrates **141** and **142** were also prepared (Scheme 36) with the aim of demonstrating the versatility of the spirocyclisation reaction.



[a]Prepared by Michael James.[92]

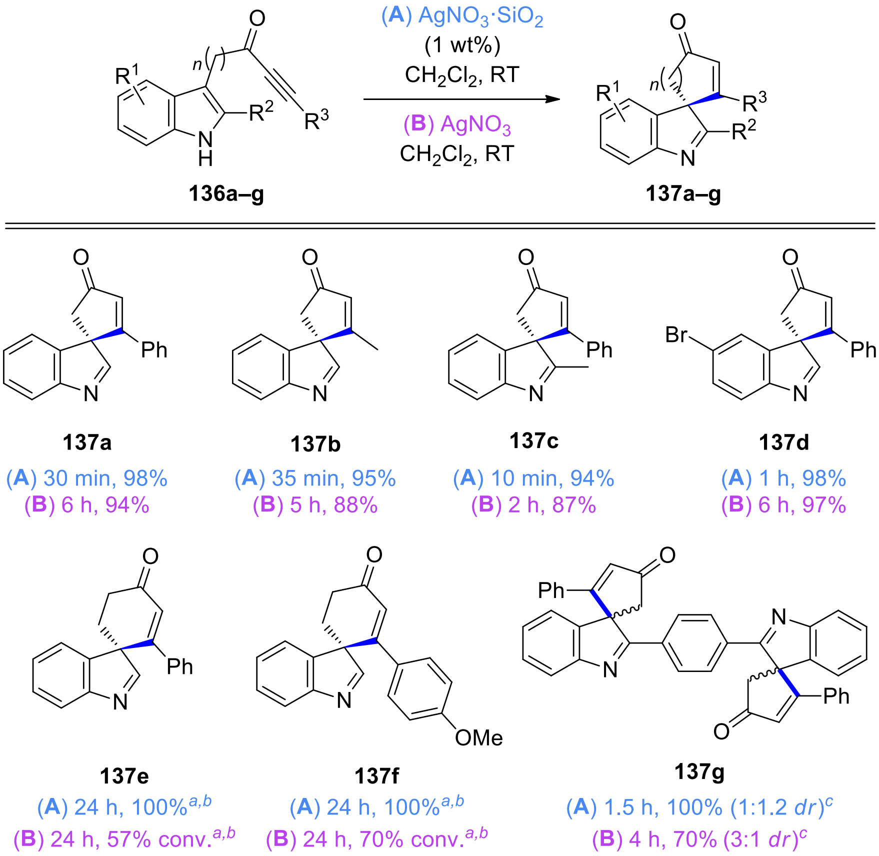
Scheme 36. Preparation of propargyl alcohol substrates 141 and 142.

Due to the instability of terminal ynones, it was necessary to access propargyl alcohol **141** *via* a one-pot reaction incorporating ynone formation, reduction and deprotection. Propargyl alcohol **142** was previously prepared in the group by Michael James *via* the reduction of phenyl ynone **136a** with $NaBH_4$.[94]

2.5 Scope of spirocyclisation reaction

2.5.1 Indole-ynone spirocyclisations

After suitable reaction conditions were established and a range of precursors prepared, the scope of the spirocyclisation using silica-supported $AgNO_3$ was examined. The substrate scoping studies began with indole-tethered ynones **136a–g** encompassing substituents around the indole ring, extended ynone tethers and various alkyne functionalities; pleasingly, all ynones **136a–g** were converted into their corresponding spirocycles **137a–g** in excellent isolated yields using $AgNO_3{\cdot}SiO_2$ (Scheme 37). Substrates incorporating extended ynone tethers (**136e** and **136f**), and therefore furnishing 6-membered spirocycles **137e** and **137f**, required an increased catalyst loading of 10 mol% and elevated temperatures to ensure full conversion was achieved.



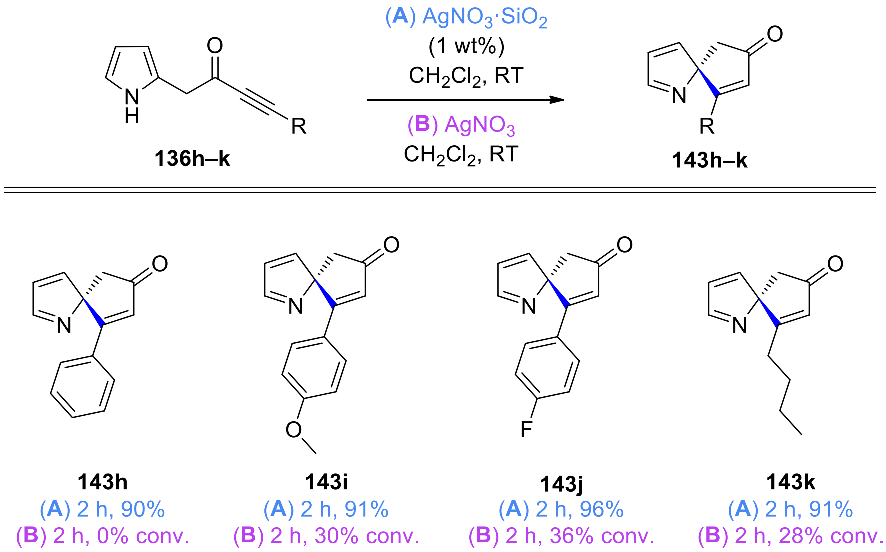
Reactions were performed using 1 mol% catalyst unless stated otherwise. [a]10 mol% catalyst used. [b]Reaction performed at 45 °C. [c]2 mol% catalyst used. Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra.

Scheme 37. Spirocyclisation of indole-tethered ynones.

As well as performing the spirocyclisation reactions using $AgNO_3{\cdot}SiO_2$ (conditions A in Scheme 37) the analogous unsupported reactions were also examined (conditions B in Scheme 37) and a clear difference in the reactivity of $AgNO_3{\cdot}SiO_2$ and unsupported $AgNO_3$ was observed. Not only were shorter reaction times and enhanced isolated yields obtained when using $AgNO_3{\cdot}SiO_2$, but the spirocyclisation reactions of ynones **136e** and **136f** failed to reach completion when using unsupported $AgNO_3$, even with a much higher (10 mol%) $AgNO_3$ loading being employed in these reactions. It was envisaged that bis-ynone **136g** was going to perform poorly in the spirocyclisation due to its limited solubility. In fact, quite the opposite was observed; the supported spirocyclisation (conditions A in Scheme 37) afforded spirocycle **137g** quantitatively, as a mixture of diastereoisomers, in just 1.5 hours. In contrast, the unsupported reaction (conditions B in Scheme 37) did not proceed as efficiently or as cleanly as the supported reaction, further demonstrating the benefits of the silica-supported catalyst.

2.5.2 *Pyrrole-ynone spirocyclisations*

The dearomatising spirocyclisation reactions of pyrrole-tethered ynones providing spiro-2*H*/3*H*-pyrroles were of particular interest due to the lack of literature focusing on the synthesis of these structures and also due to the occurrence of their derivatives in natural products.[95,96] There are only a few reports in the literature which describe the dearomatisation and spirocyclisation at the C-2 position of pyrroles affording spiro-2*H*-pyrroles[55,97,98] and reports on C-3 pyrrole spirocyclisations are particularly rare.[99,100] Firstly, the spirocyclisation of 2-pyrrole ynones **136h–k** was explored using both supported and unsupported $AgNO_3$ and the results are shown in Scheme 38.



Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra.

Scheme 38. Supported and unsupported spirocyclisations of 2-pyrrole ynones.

As can be seen from Scheme 38, all spiro-2*H*-pyrroles were generated in excellent yields of 90% or above when using the supported $AgNO_3{\cdot}SiO_2$ catalyst. Once again, unsupported $AgNO_3$ was an inferior catalyst, promoting only low levels of spirocyclisation or in the case of phenyl ynone **136h** not promoting any reaction at all. These results emphasise the significant difference in reactivity between $AgNO_3{\cdot}SiO_2$ and unsupported $AgNO_3$ and will be discussed later on in the Thesis (see Section 2.7). Characteristic ^{1}H and ^{13}C NMR signals could be used to identify the presence of the spirocyclic pyrroline products; imine protons H-2 had a chemical shift around 8.3 ppm in the ^{1}H NMR spectrum and the spirocyclic carbon centres C-4 had a particularly key chemical shift at 89 ppm in the ^{13}C NMR spectrum (Figure 3).

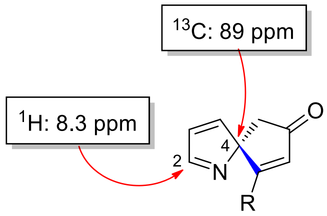
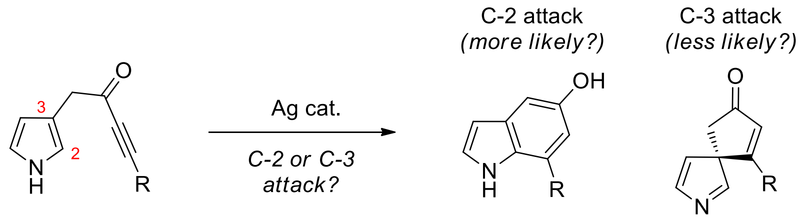


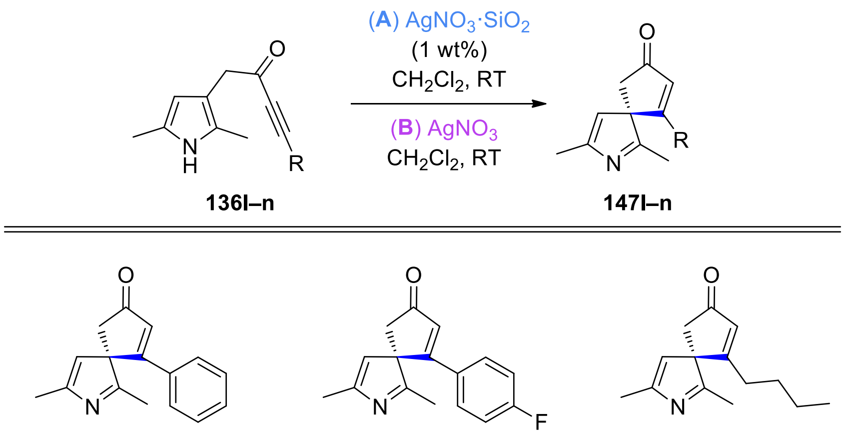
Figure 3. Characteristic ^{1}H and ^{13}C NMR chemical shifts in spiro-2*H*-pyrroles.

It was then envisaged that the same supported $AgNO_3{\cdot}SiO_2$ spirocyclisation conditions could be applied to 3-pyrrole ynone precursors to furnish valuable spiro-3*H*-pyrroles. This is a more challenging transformation; although indoles readily form C-3 spirocycles due to the inherent nucleophilicity of their C-3 position, in contrast, it is well-known that pyrroles are more nucleophilic at their C-2 position. Therefore, it may be expected that pyrrole-tethered ynones of the form **144** would react *via* C-2 attack to generate indole products **145** rather than the desired C-3 spirocycles **146** as shown in Scheme 39.



Scheme 39. Proposed indole formation using 3-pyrrole ynones 144.

For this reason, it was proposed that if the 2-position of the pyrrole ring was blocked, direct C-2 attack could be avoided, allowing spiro-3*H*-pyrroles to be accessed. Thus, 2,5-dimethylpyrrole-tethered ynones (**136l–n**) were prepared using the standard two-step procedure shown previously in Scheme 35. Each ynone precursor was reacted with 1 mol% $AgNO_3{\cdot}SiO_2$ and pleasingly complete conversion and quantitative isolation of spirocycles **147l–n** was achieved (Scheme 40).



147l	147m	147n
(A) 20 min, 100%	(A) 15 min, 100%	(A) 10 min, 100%
(B) 20 min, 89% conv.	(B) 15 min, 20% conv.	(B) 10 min, 89% conv.

Reactions were performed using 1 mol% catalyst. Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra.

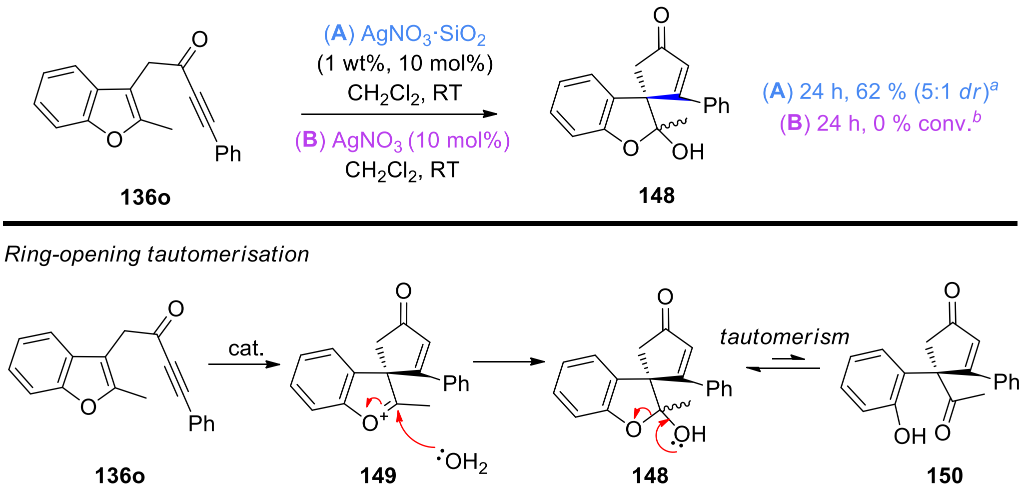
Scheme 40. Spirocyclisation of 3-pyrrole ynones.

In contrast, while unsupported $AgNO_3$ promoted spirocyclisation in all three cases, it did not perform as efficiently as $AgNO_3{\cdot}SiO_2$. The quantitative synthesis of spirocyclic pyrroline systems **147l–n** is especially noteworthy given the lack of dearomatisation methods currently available to make these scaffolds. As can be seen from the remarkably short reaction times, the 3-pyrrole ynones are a very reactive class of compounds; in fact, they appeared to be the most reactive of all ynones tested.

The reactivity of unsubstituted 3-pyrrole ynones in the presence of our $AgNO_3{\cdot}SiO_2$ catalyst is discussed in Chapter 4, Section 4.2.

2.5.3 Benzofuran-ynone spirocyclisations

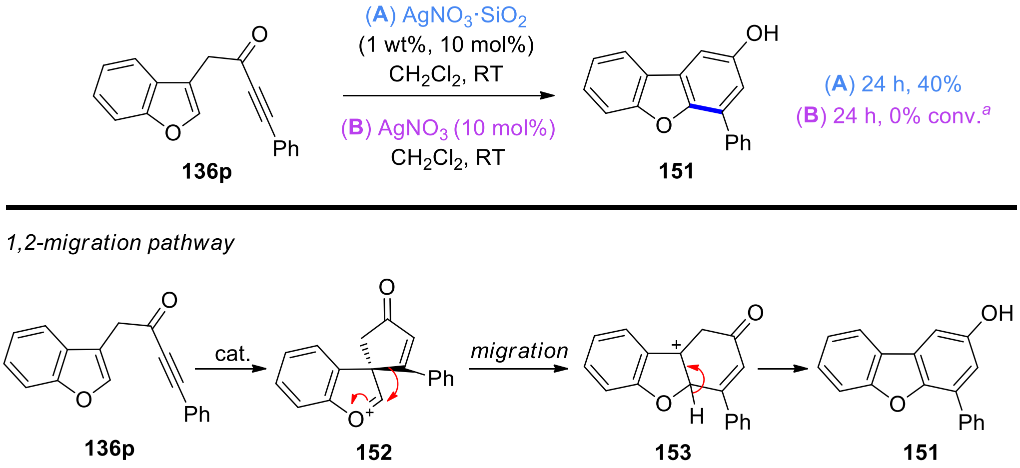
Next, the spirocyclisation conditions were applied to benzofuran substrate **136o** (Scheme 41). Silica-supported $AgNO_3$ afforded the hydrated spirocyclic product **148** in a 5:1 *dr*; small amounts of ring-opening also took place during the reaction and this is believed to have lowered the isolated yield. It is proposed that the presence of small amounts of water in the silica-based catalyst facilitates the formation of the ring-opened by-product **150** as illustrated in Scheme 41. Benzofuran-tethered ynone **136o** was another heterocyclic substrate which failed to react in the presence of unsupported $AgNO_3$.



[a]Trace amounts of ring-opened tautomer observed in ^{1}H NMR spectrum. [b]Conversion calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectrum.

Scheme 41. Spirocyclisation of benzofuran-tethered ynone 136o and ring-opening pathway.

We next studied the 2-desmethyl analogue **136p** to see what effect this would have on the ring-opening and spirocyclisation processes. Unfortunately, using the demethylated analogue **136p** facilitated a 1,2-migration process instead, leading to the formation of the dibenzofuran product **151** (Scheme 42). Although this particular reaction did not reach completion when using $AgNO_3 \cdot SiO_2$ (conditions A in Scheme 42), ynone **136p** failed to react at all in the presence of unsupported $AgNO_3$ (conditions B in Scheme 42).

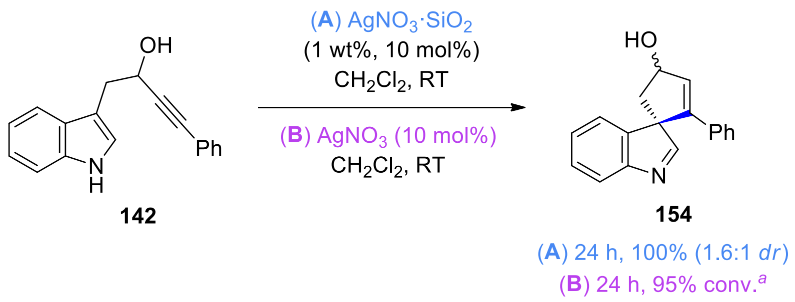


[a]Conversion calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectrum.

Scheme 42. Synthesis of dibenzofuran product 151 *via* 1,2-migration.

2.5.4 Propargyl alcohol spirocyclisations

Although the compatibility of a variety of ynones in the spirocyclisation reaction has been demonstrated, the ynone functionality is not essential for the spirocyclisation reaction to proceed, as demonstrated by the methodology being extended to propargyl alcohol systems. The spirocyclisation of propargyl alcohol **142** proceeded cleanly using $AgNO_3{\cdot}SiO_2$ to furnish spirocycle **154** in a quantitative yield (Scheme 43).

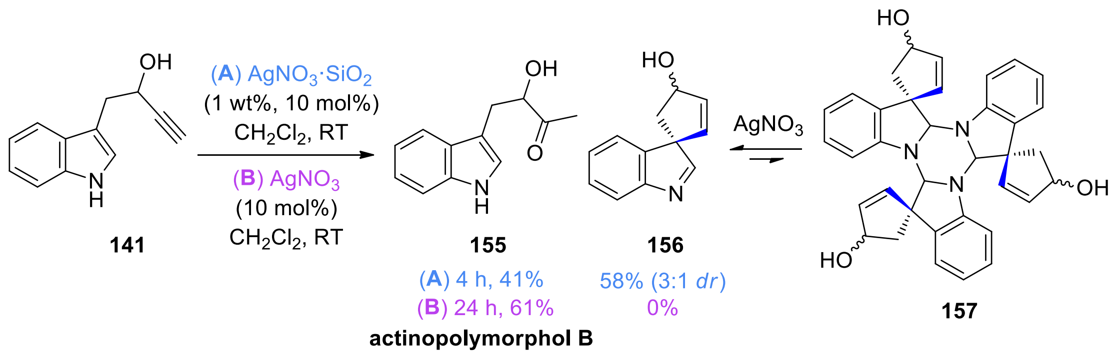


[a]Conversion calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectrum.

Scheme 43. Spirocyclisation of propargyl alcohol 142.

It is interesting to note that the reaction in Scheme 43 took hours to reach completion using $AgNO_3{\cdot}SiO_2$ which was significantly longer than its respective ynone **136a** requiring just 30 minutes. The decreased reactivity of propargyl alcohol **142** could be attributed to the removal of ynone functionality; it is believed that the ynone moiety is involved in electrophilic activation making the alkyne more susceptible to nucleophilic attack from the indole. Unsupported $AgNO_3$ also displayed comparable reactivity to $AgNO_3{\cdot}SiO_2$, leading to 95% conversion into the desired spirocycle **154** in 24 hours.

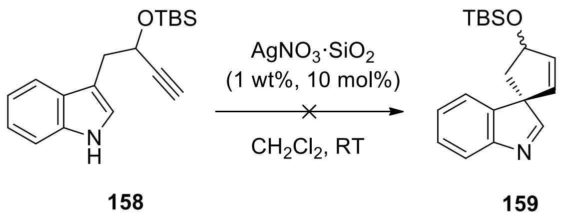
Next, propargyl alcohol **141** bearing a terminal alkyne was assessed in the supported and unsupported spirocyclisation reactions (Scheme 44). Different reaction outcomes were observed depending on the catalyst system used. The use of a terminal ynone appeared to make the alcohol more reactive as all of the ynone **141** was consumed in just 4 hours when using $AgNO_3{\cdot}SiO_2$. However, propargyl alcohol **141** was not converted cleanly into the desired spirocycle **156**. The major product of the reaction when using $AgNO_3{\cdot}SiO_2$ (conditions A in Scheme 44) was the desired spirocyclic product **156** but this was not recognised initially as the existence of an equilibrium between spirocycle **156** and trimer **157** complicated the ^{1}H NMR spectrum and identification of the spirocycle was challenging.



Scheme 44. Spirocyclisation of propargyl alcohol 141.

Previously when trimer formation has been observed in the Taylor group it has been interrupted by introducing an acid, which can protonate the imine and remove its ability to react with another imine centre. Here, the ^{1}H NMR spectrum was simplified by stirring the spirocyclic monomer:trimer mixture with one equivalent of $AgNO_3$; presumably the silver coordinates to the nitrogen lone pair; this facilitated identification and characterisation of spirocycle **156**. The other product isolated in a 41% yield from the supported reaction was the hydroxy ketone **155**, which is the natural product actinopolymorphol B.[101] It is believed that this natural product is formed as a result of alkyne hydration[102,103] and its isolation has previously been reported by the Taylor group, albeit in a low yield.[94] In contrast, when employing unsupported $AgNO_3$, only the hydroxy ketone **155** was isolated in a 61% yield without the formation of any spirocycle **156**.

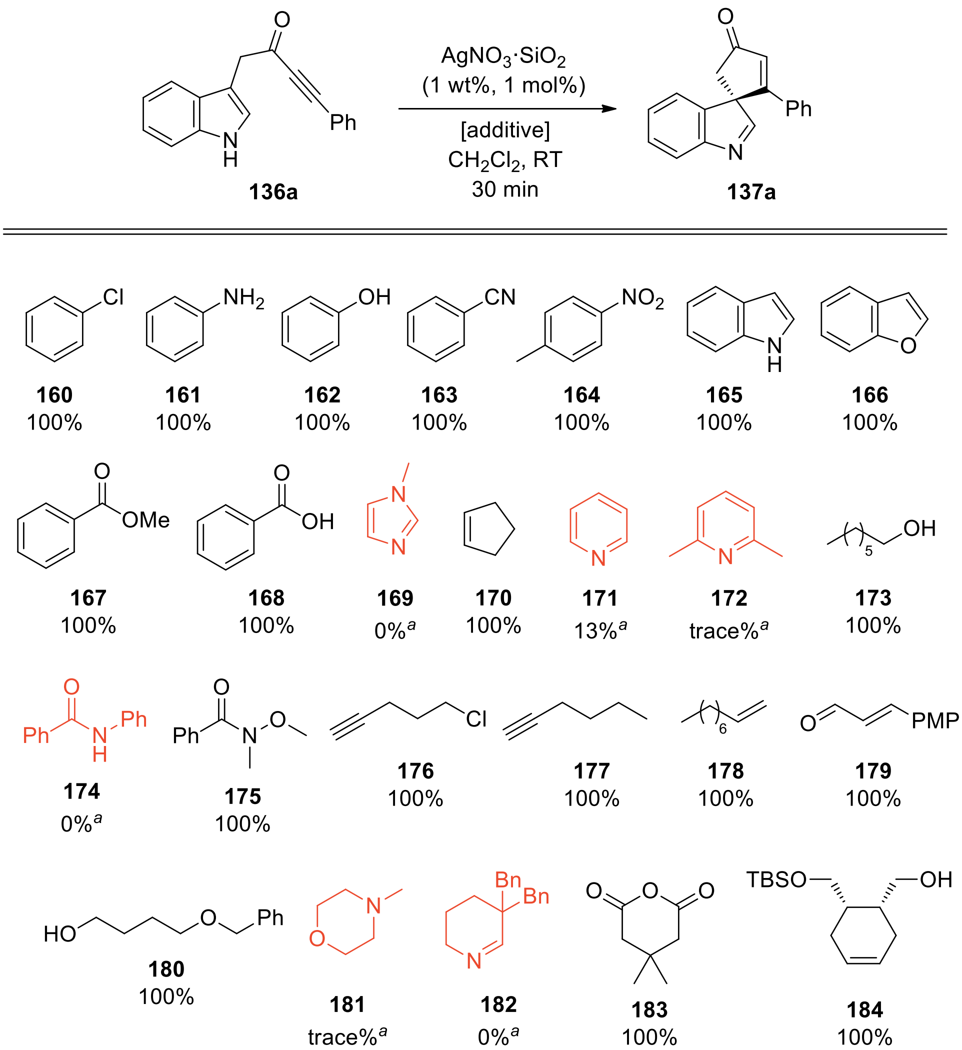
In an attempt to favour the selective formation of spirocycle **156** using the supported reaction conditions, a TBS-protected alcohol **158** was prepared and tested in the spirocyclisation (Scheme 45). Unfortunately, the presence of the TBS group did not improve the selectivity of the reaction and instead led to the formation of three uncharacterisable compounds.



Scheme 45. Spirocyclisation using TBS-protected alcohol 158.

2.5.5 *Robustness screen*

In addition to the substrate scope described, a robustness screen was also performed to corroborate the functional group tolerance of the spirocyclisation reaction. The robustness screening method, first introduced by Glorius in 2013,[104] is an efficient way to assess the functional group tolerance of a process; this is performed by screening the reaction in the presence of a range of additives representing different chemical functionalities. If the reaction proceeds as normal in the presence of the additive, this indicates that the method is tolerant of the functional groups present in the additive. The robustness screen was performed on the standard spirocyclisation reaction of phenyl ynone **136a** and the results can be seen in Scheme 46.



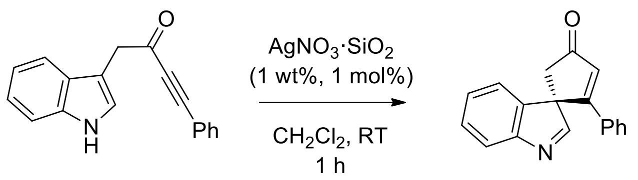
Each additive (1 equiv.) was added at the start of the reaction before catalyst addition. Results quoted as conversions which were calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra. [a]Reaction was left for 2 hours.

Scheme 46. Additives tested in robustness screen.

The results from this screen further demonstrate the high functional group compatibility of the ynone spirocyclisation reaction. Full conversion within the standard reaction time of 30 minutes was observed in the presence of halides, amines, alcohols, phenols, aldehydes, esters, carboxylic acids, acid anhydrides, alkenes, alkynes and silyl ethers. The reaction was, however, sensitive to additives containing a basic nitrogen (see additives **169**, **171**, **172**, **174**, **181**, **182** in Scheme 24), which is somewhat surprising considering all of the indole-derived spirocyclic products contain an sp^2-nitrogen as part of the imine functionality. A strong indication of whether the additive was going to retard the reaction could be seen almost instantly after additive addition; a colour change from a bright orange to a dark brown reaction mixture was observed in all cases where the reaction failed. Proposing a rationale as to why certain nitrogen-containing additives shut down the reaction is difficult, but it is possible that some of the nitrogen-containing additives may chelate to the catalyst rendering it inactive and steric factors may also play a role.

2.6 Catalyst recycling

One of the advantages of using a supported silver catalyst is the ability to recover and reuse the same catalyst for several consecutive reactions. To test this, the spirocyclisation of **136a** was performed multiple times, using catalyst recovered from the previous reaction, until a reduction in activity was observed (Table 4). After each cycle the catalyst was simply removed by filtration, washed with CH_2Cl_2, dried under vacuum and then used in the subsequent spirocyclisations. The product isolated from each spirocyclisation reaction was analysed by ^1H NMR spectroscopy.



136a **137a**

Cycle no.	Conversion / %^{a}
1	100
2	100
3	100
4	100
5	100
6	99
7	94
8	86

All reactions were carried out on 0.38 mmol of ynone **136a** in CH_2Cl_2 (0.1 M) at RT. ^{a}Conversions were calculated by analysis of the starting material:product ratio in the unpurified ^1H NMR spectra.

Table 4. Catalyst recycling experiments.

As can be seen in Table 4, five repeat cycles using the same batch of recovered catalyst were completed without any reduction in activity. Although full conversion was not achieved after the fifth spirocyclisation, high conversions were still observed in subsequent reactions demonstrating the long-lasting activity of the $AgNO_3 \cdot SiO_2$ catalyst.

As catalyst leaching from solid supports is a well-known phenomenon, the silver content of the spirocyclic products isolated from the first and eighth recycling experiments were analysed by ICP-MS to monitor the levels of silver leaching (Table 5).

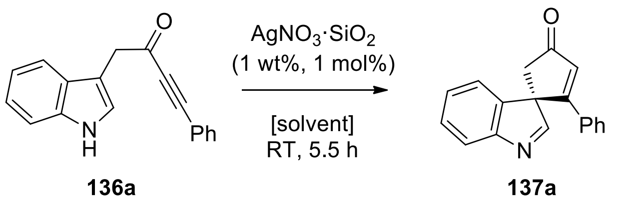
Entry	Sample	Ag content in 137a / %
1	Spirocycle **137a** after cycle 1	0.0067
2	Spirocycle **137a** after cycle 8	0.0056

Each ICP-MS sample was run three times and the mean silver content is shown.

Table 5. ICP-MS results from analysis of products from recycling experiments.

The reason for the gradual decrease in catalytic activity seen in Table 4 appeared to be caused by minor amounts of silver leaching; ICP-MS analysis revealed that the products from the first and eighth reactions contained 67 ppm and 56 ppm silver, respectively (Entries 1 and 2). These relatively low values are promising, since neither column chromatography nor aqueous work-ups were used during product isolation (although presumably these methods could be utilised in the future should it be necessary to completely remove silver from the spirocyclic products).

Additionally, it was also discovered that by simply changing the reaction solvent to a less polar variant significantly reduced the levels of silver leaching. As can be seen in Table 6, the silver content of the spirocyclic product **137a** was reduced to just 5 ppm by simply performing the reaction in toluene (Entry 3). This resulted in over ten times less silver leaching when compared to using CH_2Cl_2 (58 ppm) and is particularly significant given that it is below the acceptable limit of silver in any drug product or substance (17 ppm).[105]



Entry	Solvent	Ag content in 137a / %
1	CH_2Cl_2	0.0058
2	Acetone	0.1360
3	Toluene	0.0005

All reactions were performed using 0.38 mmol of ynone **136a** in the appropriate solvent (0.1 M) at RT.

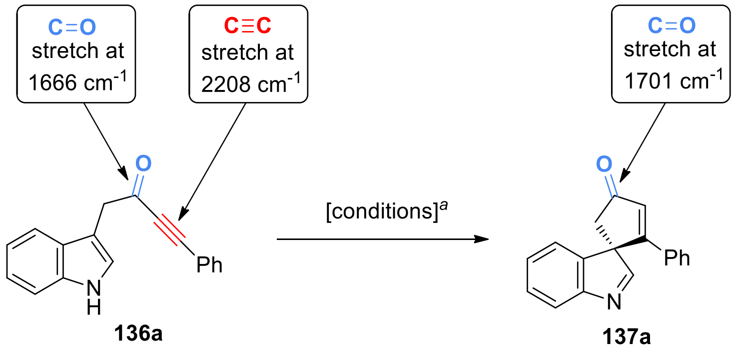
Table 6. ICP-MS results when performing spirocyclisation in different solvents.

2.7 *Mechanistic studies*

In view of the marked differences in reactivity observed when using supported and unsupported $AgNO_3$ (see Section 2.5), a mechanistic study was initiated in an attempt to identify why $AgNO_3 \cdot SiO_2$ is a superior spirocyclisation catalyst.

2.7.1 *ReactIR™*

ReactIR™ technology was used to quantitatively monitor the progress of the spirocyclisation reactions. *In situ* infrared spectra were recorded every minute over a given time period, thus enabling the analysis of characteristic infrared peaks throughout the duration of the reaction. The conversion of ynone **136a** was chosen as the standard system for all ReactIR™ experiments and the progress of each reaction was monitored by observing changes in intensities of key IR stretches (Scheme 47).



[a]All ReactIR™ experiments were performed in CH_2Cl_2 at RT using 1 mol% of $AgNO_3 \cdot SiO_2$ (1 wt%) or $AgNO_3$ catalyst.

Scheme 47. IR stretches observed in standard spirocyclisation reaction using ReactIR™.

The C≡C stretch at 2208 cm^{-1} in the IR spectrum of ynone **136a** is the most reliable signal for reaction monitoring as it is in a clear region of the spectrum. The C=O stretches present in the IR spectrum of ynone **136a** (at 1666 cm^{-1}) and spirocycle **137a** (at 1701 cm^{-1}) could also be seen decreasing (for **136a**) and increasing (for **137a**) as the reaction progressed, but due to partial overlap they were not used in the ReactIR™ analysis.

The first ReactIR™ experiments performed were the standard supported and unsupported reactions (Figure 4).

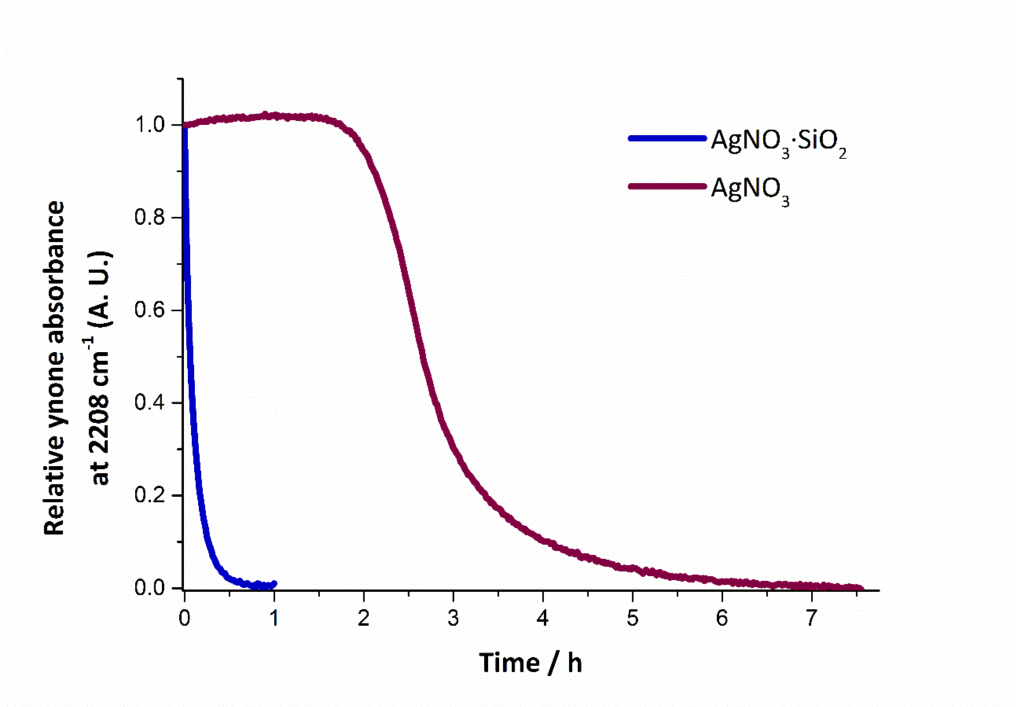


Figure 4. ReactIR™ plot for the conversion of ynone 136a into spirocycle 137a using $AgNO_3 \cdot SiO_2$ (blue line) and unsupported $AgNO_3$ (purple line).

The supported reaction (blue line, Figure 4) started immediately after catalyst addition and reached completion in just over 30 minutes. In contrast, an induction period of approximately 2 hours was seen in the unsupported reaction (purple line, Figure 4), which consequently led to a prolonged reaction time of ~6.5 hours. It was also possible to see how the rates of reaction differed when using the supported and unsupported catalyst systems by inspecting the gradients of each line; following the induction period, the unsupported reaction progressed notably slower than the supported reaction.

In the next ReactIR™ experiment, $AgNO_3$ and silica were added to the reaction mixture as separate components but in the same quantities as present in the standard supported reaction (orange line, Figure 5). The unsupported and supported reactions were also plotted for comparison.

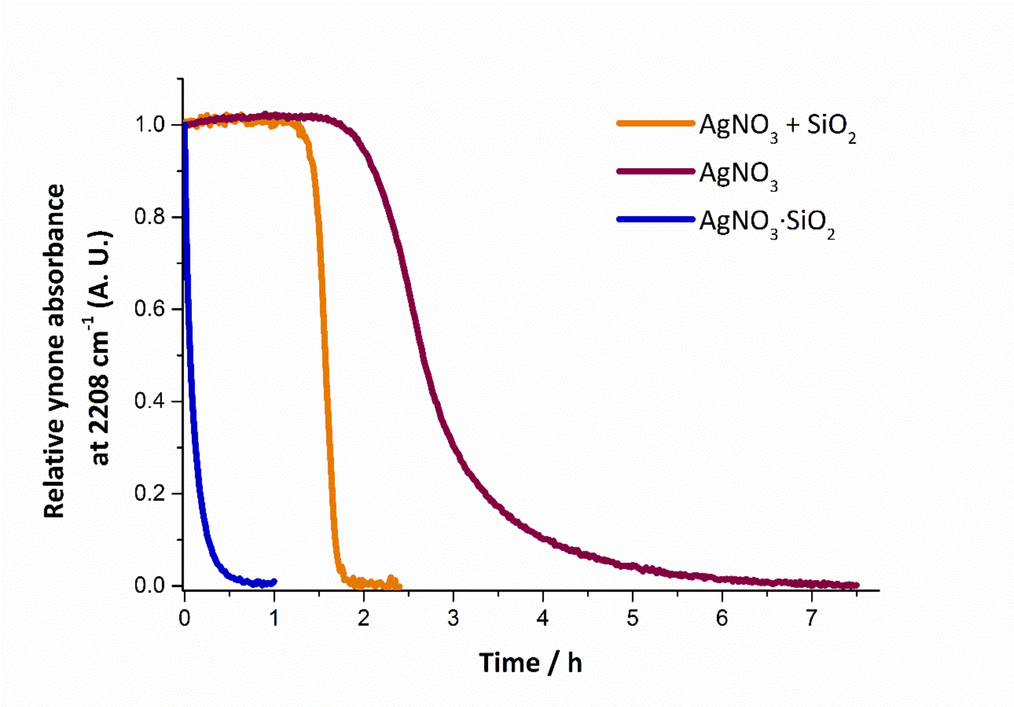


Figure 5. ReactIR™ plot for the spirocyclisation reaction using $AgNO_3{\cdot}SiO_2$ (blue line) and unsupported $AgNO_3$ in the presence of silica (orange line) and in the absence of silica (purple line).

Although an induction period was still observed when silica was added separately (orange line, Figure 5), the rate of reaction was comparable to the supported reaction (once consumption of ynone **136a** began, the reaction was complete in around 30 minutes) and was faster than the unsupported reaction (purple line, Figure 5). From this result, it was concluded that silica clearly increases the rate of reaction and that the induction period is related to the use of unsupported $AgNO_3$.

The observation of sigmoidal kinetics and induction periods can be indicative of the *in situ* formation of nanoparticles.[91] Therefore, it was proposed that the induction period seen in the unsupported reaction was associated with the *in situ* formation of silver nanoparticles (AgNPs), with $AgNO_3$ acting as a pre-catalyst in the reaction. To test this hypothesis, a further ReactIR™ experiment was performed which explored the potential formation of AgNPs during the induction period of the unsupported reaction. $AgNO_3$ was stirred in CH_2Cl_2 under air for 24 hours and the initial colourless solution turned yellow during this period. Several reports in the literature describe the observation of a yellow "solution" after the formation of AgNPs.[82,106] Ynone **136a** was then added to the pre-stirred $AgNO_3$ solution and the reaction was monitored by ReactIR™ (grey line, Figure 6).

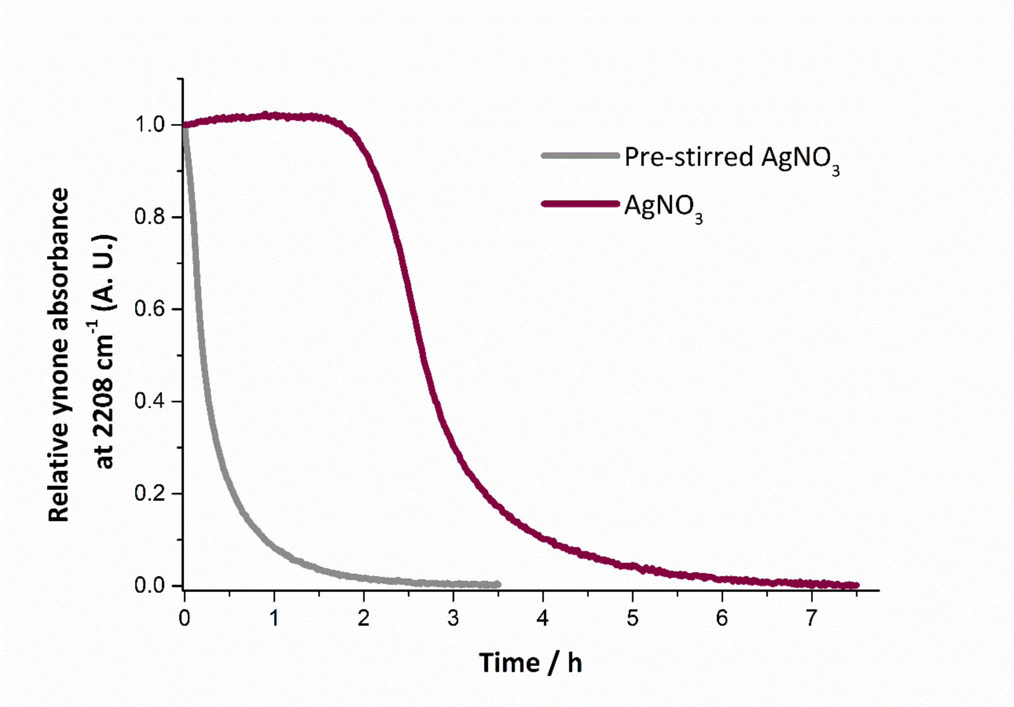


Figure 6. ReactIR™ plot for the spirocyclisation reaction using pre-stirred $AgNO_3$ (grey line) and unsupported $AgNO_3$ (purple line).

Evidently, pre-stirring $AgNO_3$ changes the catalytic species present in the reaction mixture as the induction period was completely removed and the reaction started to proceed as soon as ynone **136a** was added. This supports the idea that AgNPs were formed in advance of the reaction and therefore negated the induction period. The rate of reaction using pre-stirred $AgNO_3$ was comparable to the unsupported $AgNO_3$ reaction (purple line, Figure 6); this was expected as both reactions were conducted in the absence of silica. It is worth noting that the spirocyclisation using pre-stirred $AgNO_3$ with silica added separately to the reaction mixure led to an increase in the rate of reaction; although not monitored by ReactIR™, the reaction was complete within 30 minutes and had a similar rate to the standard supported reaction.

Although providing unambiguous evidence for heterogeneous catalysis is difficult, and often requires several cross-over experiments, the mercury drop test is commonly used as a starting point when investigating the potential involvement of heterogeneous particles in a reaction.[91] The theory of this experiment is that a large excess of mercury is added to the reaction mixture, and if heterogeneous particles such as nanoparticles are present, the mercury will coat the heterogeneous species, rendering them inactive and terminate the reaction. Conversely, if the reaction is proceeding *via* homogeneous catalysis the addition of mercury should not affect the reaction. The unsupported reaction was performed as normal using ReactIR™ to monitor its progress, when approximately 50% consumption of ynone **136a** was reached, 200 equivalents of mercury (w.r.t. $AgNO_3$) was added to the reaction mixture (red line, Figure 7). This almost instantly shut down the reaction, which provides additional support for the idea of heterogeneous nanoparticles catalysing the reaction.

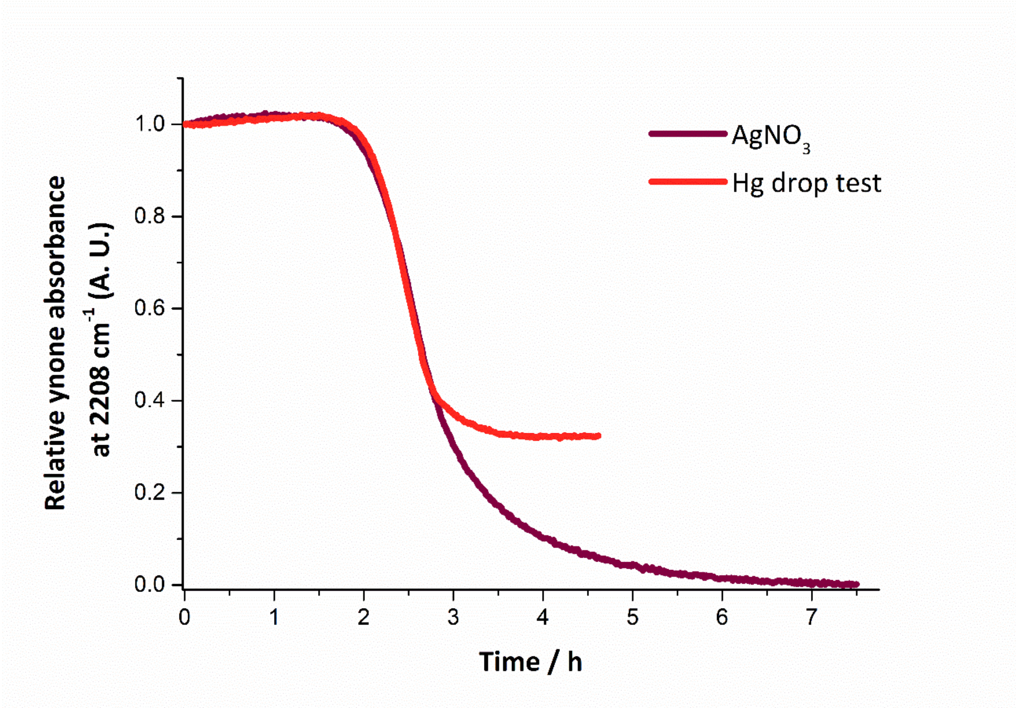


Figure 7. ReactIR™ plot for the spirocyclisation reaction using unsupported $AgNO_3$ (purple line) and the mercury drop test experiment (red line).

2.7.2 Transmission electron microscopy (TEM)

In order to provide further evidence for the presence of AgNPs and their involvement in catalysis, their characterisation in the unsupported reaction was attempted. As it was previously shown that pre-stirring $AgNO_3$ appeared to change the catalytic species present and removed the induction period, this catalyst system was chosen for initial TEM studies as it was considered likely that AgNPs would be present. $AgNO_3$ was stirred in CH_2Cl_2 for 24 hours and an aliquot of this solution was removed and dropped onto a copper TEM grid. The deposit remaining on the grid after the CH_2Cl_2 had evaporated was then analysed by TEM (Figure 8).

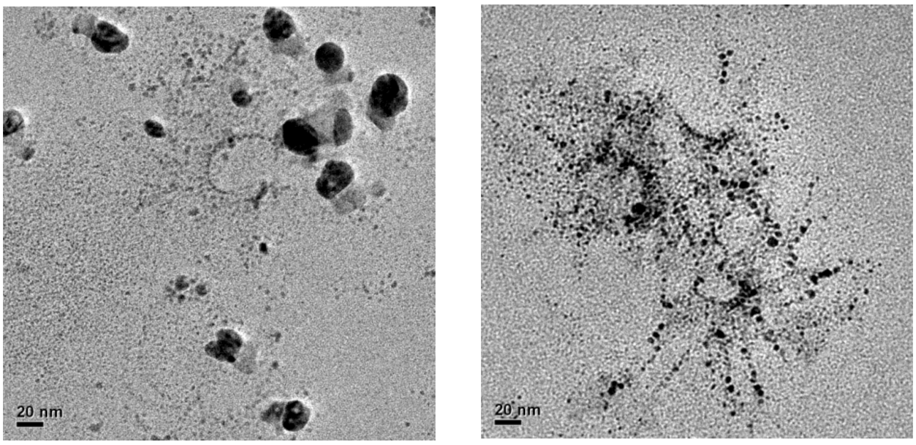


Figure 8. TEM images of AgNPs after pre-stirring $AgNO_3$ in CH_2Cl_2.

As anticipated, the images shown in Figure 8 indicate the presence of silver nanoparticles after pre-stirring $AgNO_3$ in CH_2Cl_2. A large variation in nanoparticle size can be seen in these images with some particularly large particles measuring over 20 nm. The large variation in particle size could be attributed to the fact that these particles do not have any support or capping agent present to control their growth and aggregation.[107,108]

After identifying the potentially active catalytic species in the unsupported reaction, attention was drawn to the supported reaction to see whether AgNPs were also present on the surface of the silica support. In the literature, several procedures describe the immobilisation of silver nanoparticles on solid supports[84,86,109] and in view of the above results, it was considered likely that AgNPs were also present in the supported catalytic system. TEM images of the $AgNO_3 \cdot SiO_2$ catalyst before (Figure 9) and after (Figure 10) use in the spirocyclisation reaction were obtained.

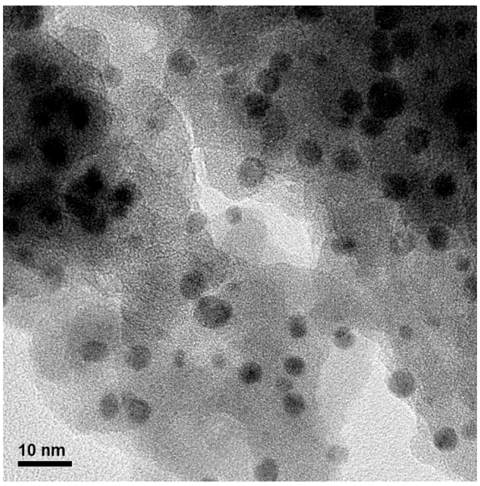


Figure 9. TEM image of $AgNO_3 \cdot SiO_2$ before use in spirocyclisation reaction.

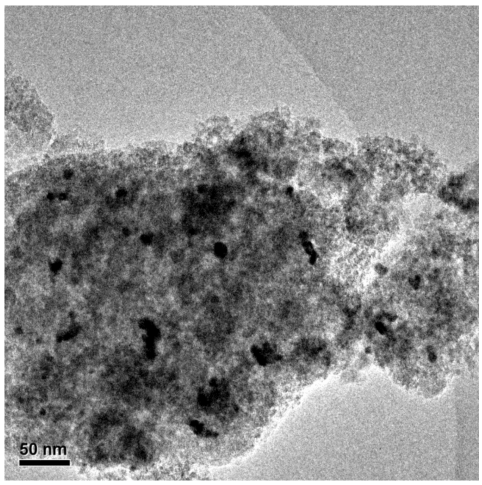


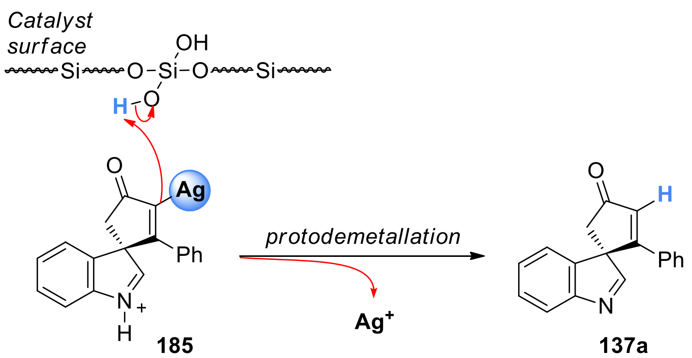
Figure 10. TEM image of $AgNO_3 \cdot SiO_2$ after use in spirocyclisation reaction.

The TEM images shown above in Figure 9 and Figure 10 confirm the presence of crystalline AgNPs on the surface of the silica. There is little difference in the distribution and size of the nanoparticles before and after use which is surprising, but may be why the same batch of catalyst can perform so well after being recycled (see Section 2.6).

In conclusion, the presence of silica clearly enhances the rate of reaction; this could be attributed to faster protodemetallation (see Scheme 48) and/or its role may be to support the formation of AgNPs and modulate their growth/aggregation/stability. It appears that AgNPs are involved in the catalysis of both the supported and unsupported spirocyclisation reactions, and that $AgNO_3$ itself could act as a pre-catalyst in the formation of these nanoparticles. It is also possible that the AgNPs themselves are converted back into Ag^+ as part of a catalytic cycle but further studies are needed to confirm this. Unambiguously establishing the exact species responsible for spirocyclisation is clearly a difficult process given the complexity of this system and identification of the catalytically active species remains ambiguous. Nonetheless, the obvious synthetic benefits of the catalyst system in terms of its improved reactivity over related Ag(I) catalysts and AgNPs are much clearer.

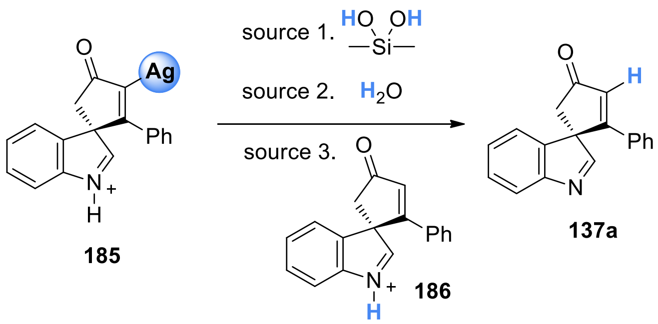
2.7.3 Deuterium-labelling studies

As previously described, the postulated mechanism for the spirocyclisation reaction proceeds *via* a 5-*endo*-*dig* cyclisation followed by protodemetallation to yield the spirocyclic products (see Scheme 15). As ReactIR™ results discussed earlier revealed an increase in the rate of spirocyclisation in the presence of silica, the possibility of silanol groups facilitating the final protodemetallation step was considered. Silanol groups on the silica surface may deliver protons to the vinyl silver species **185**, thus releasing the silver for further catalysis and increasing the rate of reaction (Scheme 48). Silica-accelerated protodemetallation has previously been described by Toste *et al*., where they propose the surface acidity of the silica enhances the protodeauration of a vinyl gold intermediate.[110]



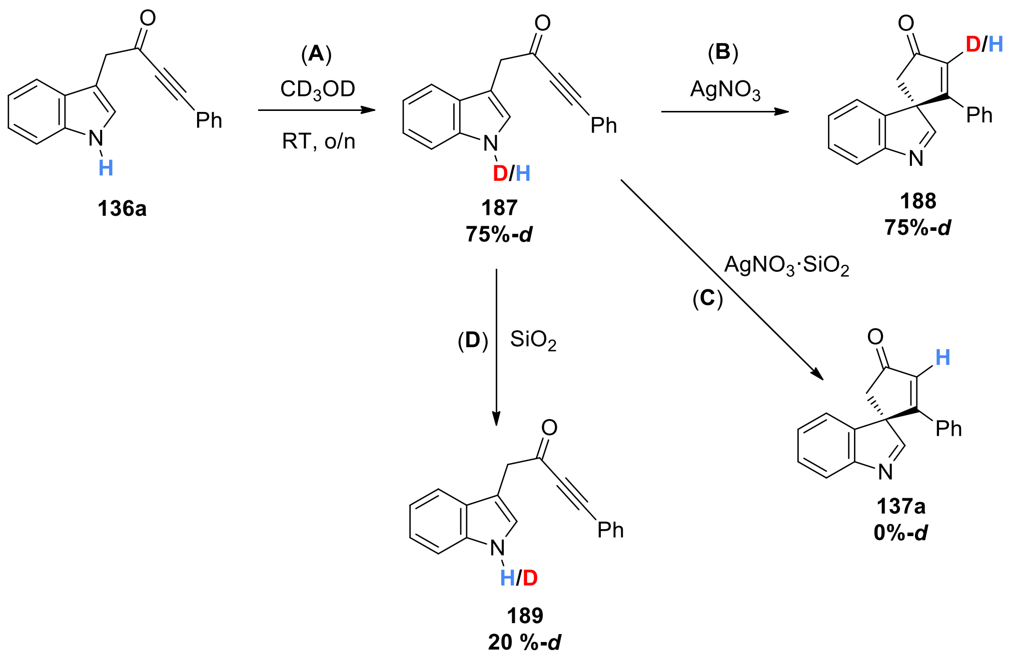
Scheme 48. Silanol groups facilitating protodemetallation step in spirocyclisation.

Although this is a plausible theory, obtaining additional evidence proved to be particularly challenging as there are a variety of potential proton sources which could be involved in this step. For example, protons could originate from either the silanol groups or residual water present in the silica support, or alternatively the iminium functionality present in the spirocyclic intermediate **186** could act as a proton shuttle (Scheme 49).



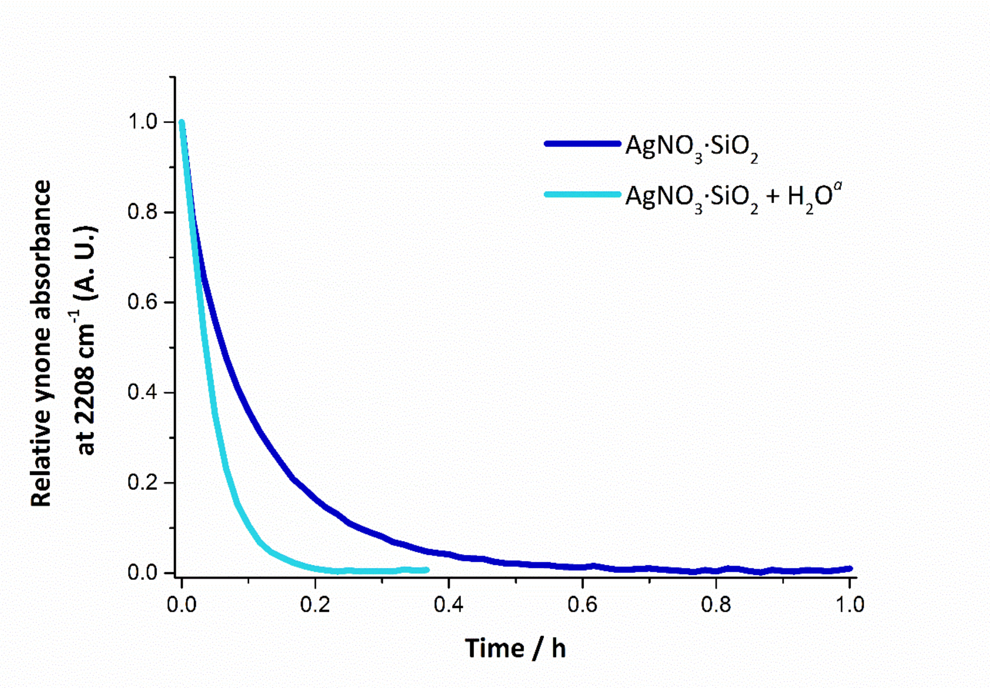
Scheme 49. Potential proton sources in the supported spirocyclisation reaction.

Deuterium-labelling experiments were utilised to try and determine the source of protons in the protodemetallation step (Scheme 50). Ynone **136a** was stirred in deuterated methanol under an inert atmosphere to generate deuterated ynone **187** (step A in Scheme 50). When spirocyclisation using unsupported $AgNO_3$ was performed on deuterated ynone **187** (step B in Scheme 50), the same deuterium content was incorporated in the spirocyclic product **188** as expected. The spirocyclisation was then performed using the silica-supported catalyst to see if silica had any involvement in the protodemetallation step. When spirocyclisation was performed using $AgNO_3{\cdot}SiO_2$ (step C in Scheme 50), deuterium was not observed in spirocyclic product **137a**. Initially, it was thought that the silanol groups on the silica surface were providing the protons for protodemetallation in this reaction (source 1 in Scheme 49), however, when deuterated ynone **187** was simply stirred in CH_2Cl_2 in the presence of silica (step D in Scheme 50) its deuterium content dropped to just 20%, suggesting the deuterium in ynone **187** was exchanging with protons in the silanol groups before spirocyclisation. As a result, firm conclusions about the source of protons used in the protodemetallation step could not be made from these experiments.



Scheme 50. Deuterium-labelling experiments performed on ynone 136a.

In addition to the deuterium experiments described above, two ReactIR™ experiments were performed to explore the effects of water (Figure 11) and spirocyclic imine **137a** (Figure 12) in the spirocyclisation reaction as these were also identified as potential proton sources/proton shuttles in the protodemetallation step.

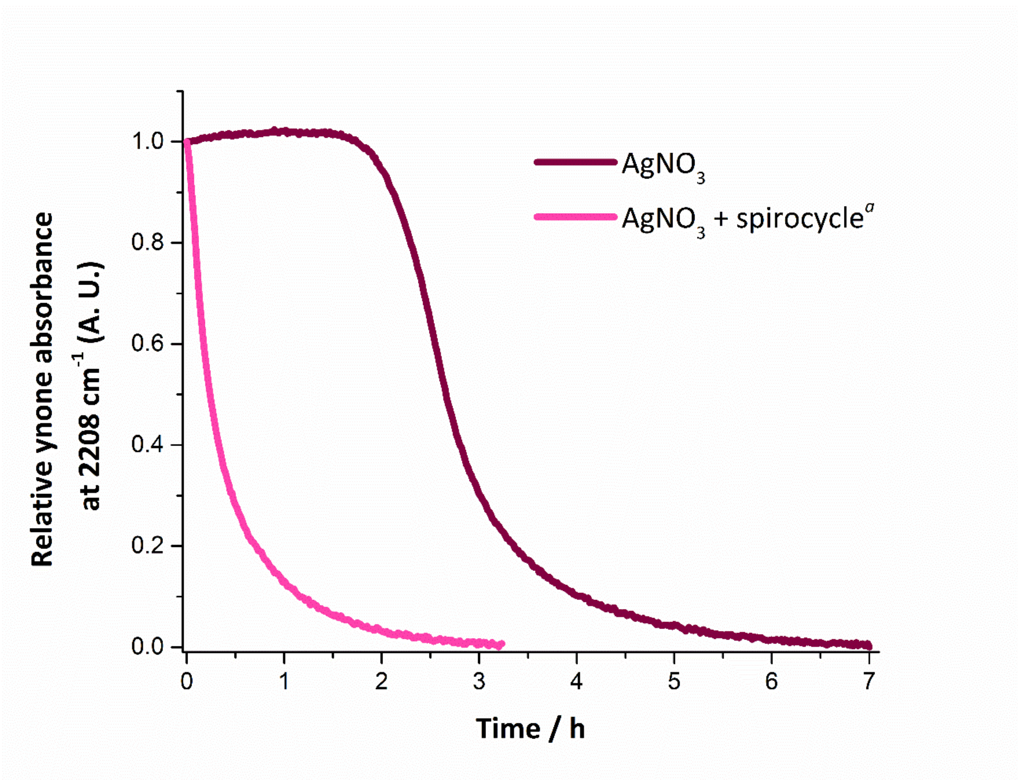


[a]1.0 equiv. of H_2O added to CH_2Cl_2 solvent system.

Figure 11. ReactIR™ plot for the spirocyclisation reaction of ynone 136a using $AgNO_3$·SiO_2 with water (light blue line) and without water (dark blue line).

The addition of water clearly increased the rate of reaction and subsequently led to complete conversion of ynone **136a** in under 15 minutes (light blue line, Figure 11). Although this rate of reaction was favourable, the isolated yield of the spirocyclic product **137a** was reduced. This result suggests that water could be involved in the protodemetallation step (source 2 in Scheme 49), thus explaining the observed increase in the rate of reaction.

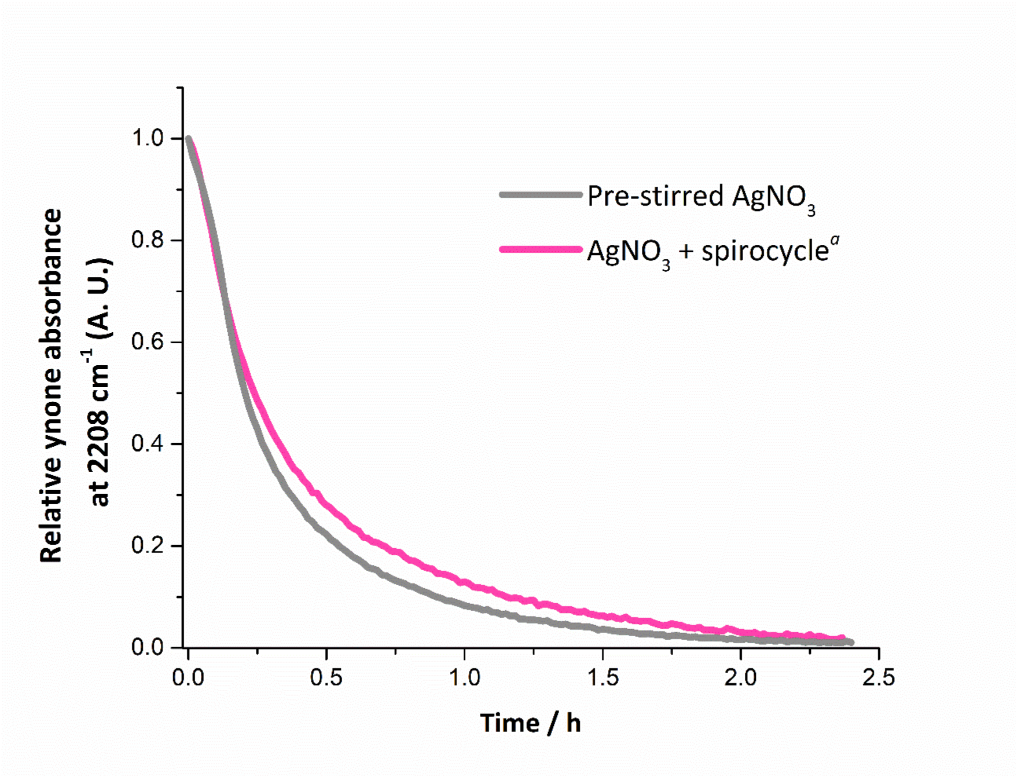
A further ReactIR™ experiment investigating whether the addition of spirocyclic imine **137a** had an effect on the rate of protodemetallation was performed; this compared the unsupported spirocyclisation reaction (purple line, Figure 12) with the unsupported spirocyclisation reaction and the addition of spirocyclic imine **137a** (pink link, Figure 12). Unsupported $AgNO_3$ was used as the catalyst in this experiment rather than $AgNO_3{\cdot}SiO_2$ in order to remove any protodemetallation rate enhancements from the silica support. It was anticipated that if spirocyclic imine **137a** was involved in the protodemetallation step, the rate of reaction would be faster and a steeper reaction profile would be observed.



[a]0.5 equiv. of spirocyclic imine **137a** added at the beginning of the reaction.

Figure 12. ReactIR™ plot for the spirocyclisation reaction of ynone 136a using $AgNO_3$ (purple line) and $AgNO_3$ with the addition of spirocycle 137a (pink line).

Since discovering the heterogeneous nature of the unsupported reaction and the likely formation of nanoparticles during the induction period, it was surprising to see that the addition of imine **137a** at the beginning of the unsupported reaction removed the induction period completely (pink line, Figure 12). To aid comparison of reaction rates, the ReactIR™ reaction profile when using pre-stirred $AgNO_3$ was used instead as there was not an induction period observed in this reaction (Figure 13).



[a]0.5 equiv. of spirocyclic imine **137a** added at the beginning of the reaction.

Figure 13. ReactIR™ plot for the spirocyclisation reaction of ynone 136a using pre-stirred $AgNO_3$ (grey line) and $AgNO_3$ with spirocycle 137a (pink line).

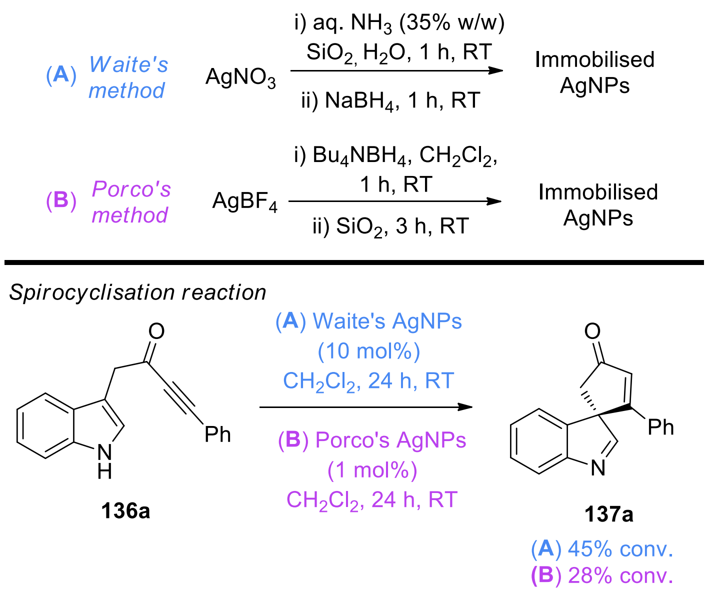
On inspection of the reaction profiles shown in Figure 13 it appears that the addition of spirocyclic imine **137a** did not increase the rate of reaction and is therefore unlikely to be involved in the protodemetallation step (source 3, Scheme 49). Although the exact role of imine **137a** is still unclear, this result does suggest that the formation of the spirocyclic product itself affects the reaction in some way and could be involved in the formation of nanoparticles as the induction period was removed on addition of this species.

In summary, it is clear that there is an important synergistic relationship between the silica support and the AgNPs which renders $AgNO_3 \cdot SiO_2$ an effective catalyst for the spirocyclisation methodology. Evidence obtained from ReactIR™ studies and TEM images suggests that AgNPs are the active catalytic species in the reaction and it is also believed that the nanoparticles are formed during catalyst preparation. The silica support appears to be involved in enhancing the rate of reaction; although silica does not promote spirocyclisation on its own, the increased rate of reaction observed when in the presence of silica could be due to augmented levels of protodemetallation and hence more effective catalyst turnover. In addition to this, silica also provides a surface for the AgNPs which could help to control their growth and aggregation, ultimately prolonging their reactivity.

2.8 Silica-supported AgNPs prepared using literature methods

There are a variety of methods available to the synthetic chemist for the impregnation of AgNPs onto silica, the most common of which is the chemical reduction of a Ag(I) species using a reducing agent.[111–113] It is reported that the strength of reducing agent used in the preparation affects the characteristics of the AgNPs and the addition of ligands during impregnation can influence the silver loading of AgNP-impregnated silica.[114]

Silica-supported AgNPs were prepared using two different literature procedures reported by Waite[114] and Porco Jr.[84] and their performance in the standard indole spirocyclisation reaction was investigated. The aim was to compare the results obtained with our $AgNO_3{\cdot}SiO_2$ catalyst and see if there was any difference in the reactivity of the AgNPs prepared using literature methods. Waite and co-workers generated their silica-supported AgNPs by treating $AgNO_3$ with $NaBH_4$ in an aqueous ammonia medium (Scheme 51). They suggested the role of the ammonia was not just to act as a base, adjusting the pH of the system, but to also act as a ligand to form a $[Ag(NH_3)_2]^+$ complex prior to reduction. In comparison, Porco Jr.'s method used $AgBF_4$ as their Ag(I) source and Bu_4NBH_4 as the reductant without any ligand additive.

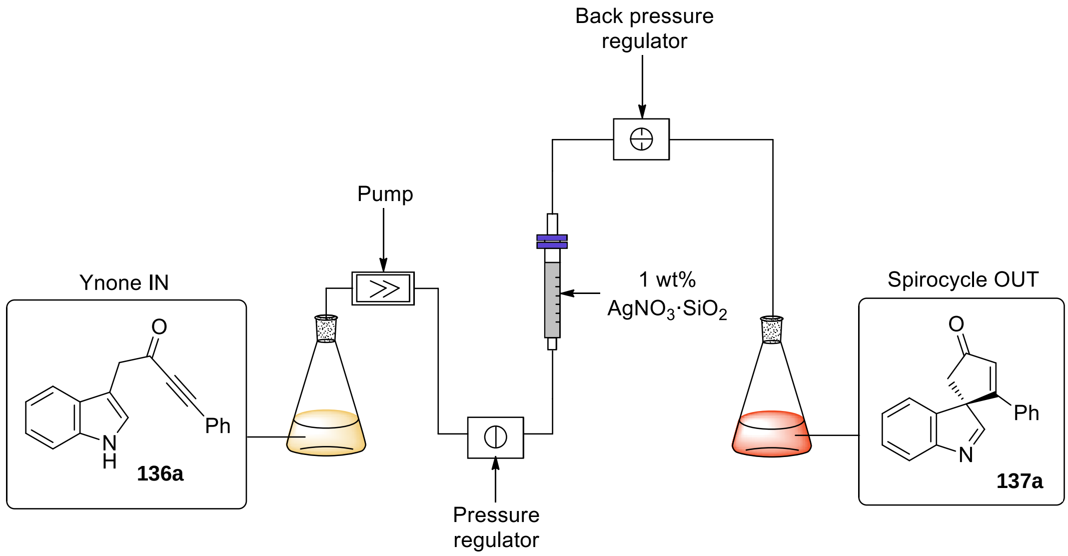


Scheme 51. Preparation of AgNPs using literature methods and their use in the standard spirocyclisation reaction.

The literature procedures reported by Waite and Porco Jr. were followed to prepare two separate batches of silica-supported AgNPs which were then tested in the transformation of ynone **136a** into spirocycle **137a**. Neither of the two batches of AgNPs prepared were able to promote complete conversion into the desired spirocycle **137a**; only 45% and 28% conversion was observed for Waite's and Porco Jr.'s nanoparticles, respectively. It is particularly important to note that 10 mol% of Waite's AgNPs were used in the spirocyclisation reaction which is significantly more than the 1 mol% of $AgNO_3 \cdot SiO_2$ typically used for this transformation; this highlights the superior activity of the nanoparticles present in our $AgNO_3 \cdot SiO_2$ system. These results also provide additional support for the intermediacy of AgNPs in our process.

2.9 Flow chemistry

Although organic synthesis has traditionally been performed in batch reactors, flow chemistry is a rapidly growing research area, attracting much recent interest due to the benefits associated with it including: safer reactions, simplified scale-up, cleaner products and faster reaction optimisation.[115] Supported reagents and catalysts have been used extensively in batch organic syntheses as such reagents can provide clean products without the need of traditional work-up procedures and/or chromatography; in recent years, focus has moved towards their use in flow chemistry and is now also well documented in the literature.[116,117] In view of this, a multi-gram spirocyclisation was performed using a continuous FlowSyn™ reactor, whereby a solution containing ynone **136a** in CH_2Cl_2 was converted into spirocycle **137a** over a 12 hour period (Table 7, Entry 1). The ynone solution was simply passed through a reactor column packed with 1.9 g of 1 wt% $AgNO_3 \cdot SiO_2$ and TLC was used to monitor the reaction as the product solution emerged from the flow machine; when full conversion stopped taking place the reaction was terminated. A flow rate of 0.1 mL/min was chosen, giving the ynone approximately 1 hour on the column which enabled complete spirocyclisation to take place.



Entry	Solvent (conc.)	Time / h	Catalyst loading[a] / mol%	Spirocycle produced / g	Full conversion at end of reaction?
1	CH_2Cl_2 (0.5 M)	12	0.43	6.90	No
2	Toluene (0.1 M)	51	0.12	23.6	Yes

[a]1 wt% $AgNO_3{\cdot}SiO_2$ catalyst was used for each flow reaction. At the end of each reaction the products were concentrated *in vacuo* and analysed by ^{1}H NMR spectroscopy.

Table 7. Flow chemistry results and representation of flow set-up.

Our first attempt at performing this continuous flow spirocyclisation reaction in CH_2Cl_2 was a success, generating 6.90 g of spirocycle **137a** in just 12 hours. In comparison to the equivalent batch spirocyclisation process using 1 mol% $AgNO_3{\cdot}SiO_2$ (Scheme 37), a lower catalyst loading of 0.43 mol% was used in this flow reaction. Although the catalyst's reactivity was gradually reduced during the flow process resulting in incomplete conversion at the end of the reaction, it was envisaged that switching reaction solvent to a less polar alternative would suppress levels of silver leaching (see ICP-MS results in Table 6) and therefore increase the catalyst turnover significantly. This was indeed the case, using toluene as the reaction solvent facilitated quantitative conversion of 23.6 g of ynone **136a** into spirocycle **137a** in 51 hours (Table 7, Entry 2). Full conversion of ynone was still being achieved at the end of this reaction which suggested further spirocyclisation could have been performed if more ynone was available. A more dilute reaction mixture was required as the ynone was less soluble in toluene than in CH_2Cl_2 and the flow rate was increased to 0.3 mL/min to offset these more dilute conditions. The same amount of $AgNO_3{\cdot}SiO_2$ catalyst (1.9 g, equating to *ca*. 10 mg of silver), was used in this >20 g reaction resulting in an impressive catalyst loading of just 0.12 mol%.

2.10 Summary

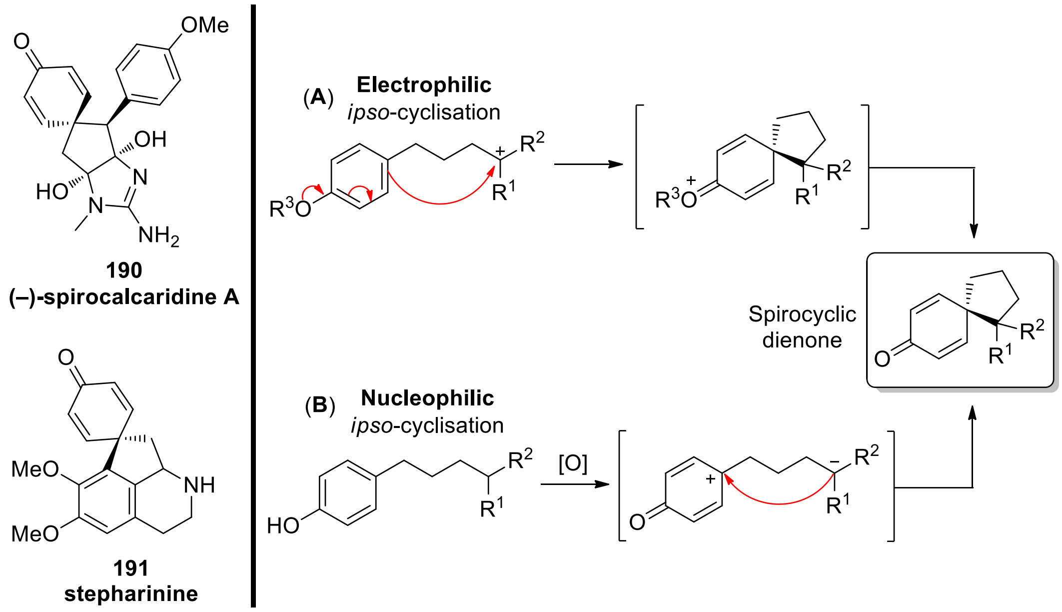
The application of 1 wt% $AgNO_3{\cdot}SiO_2$ in the dearomatising spirocyclisation methodology has successfully been demonstrated providing a range of spirocyclic products from their alkyne-tethered precursors. The facile isolation and recovery of our heterogeneous catalyst system has also been exploited through catalyst recycling studies and large-scale flow experiments; the same batch of silica-supported $AgNO_3$ can be used repeatedly in over five spirocyclisation reactions or in a continuous flow reaction converting over 20 g of an ynone precursor without any significant loss in activity. The mechanistic aspects of the spirocyclisation reaction and determination of the active catalytic species have also been explored. A combination of ReactIR^{TM} experiments and TEM studies not only revealed the presence of the AgNPs but also recognised the importance of the silica support itself in enhancing the reactivity of the catalyst. A comparison of $AgNO_3{\cdot}SiO_2$ with unsupported $AgNO_3$ has been described throughout and a significant difference in their reactivity has been established. In all cases, $AgNO_3{\cdot}SiO_2$ was superior to unsupported $AgNO_3$ and it was also more reactive than silica-supported AgNPs made using literature procedures.

The work described in this Chapter was reported in *Angewandte Chemie* (see Appendix I).[118]

Chapter 3. Dearomatisation of phenols and the synthesis of spirocyclic dienone frameworks

3.1 *Introduction*

The spirocyclic dienone framework incorporating a quaternary carbon centre and cyclohexadiene moiety, is a common motif in bioactive natural products (Scheme 52).[53,119] This abundance in nature has helped to propagate the development of a variety of methods which generate key spirocyclic dienone structures. Several of these methods proceed *via ipso*-cyclisation of a substituted phenol or anisole derivative which is typically achieved in one of two ways, either *via* electrophilic (A) or nucleophilic (B) activation modes (Scheme 52).

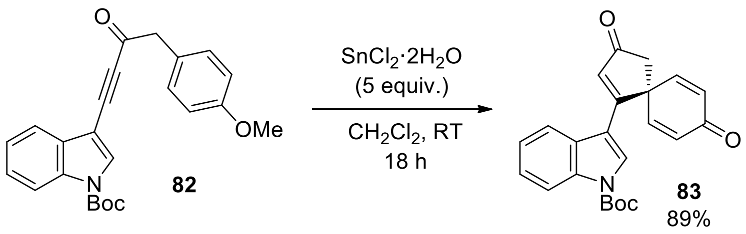


Scheme 52. Natural products containing spirocyclic dienone motif and *ipso*-cyclisation strategies.

The activation of alkene, alkyne, and allene moieties provides the driving force for a large number of electrophilic *ipso*-cyclisations (Scheme 52A).[120–122] Transition-metal catalysts are commonly used in these cyclisations to activate the π-system, increasing its electrophilicity towards reaction with the nucleophilic phenol derivative.[35,123–125] Alternatively, the flow of electrons can be reversed and nucleophilic *ipso*-cyclisations can be utilised (Scheme 52B).[126–128] This is achieved through the oxidation of a substituted phenol, typically using hypervalent iodine reagents such as $PhI(OAc)_2$,[27,129–131] followed by interception of the now electrophilic phenol with various nucleophiles, affording the spirocyclic dienones.

3.2 Project background

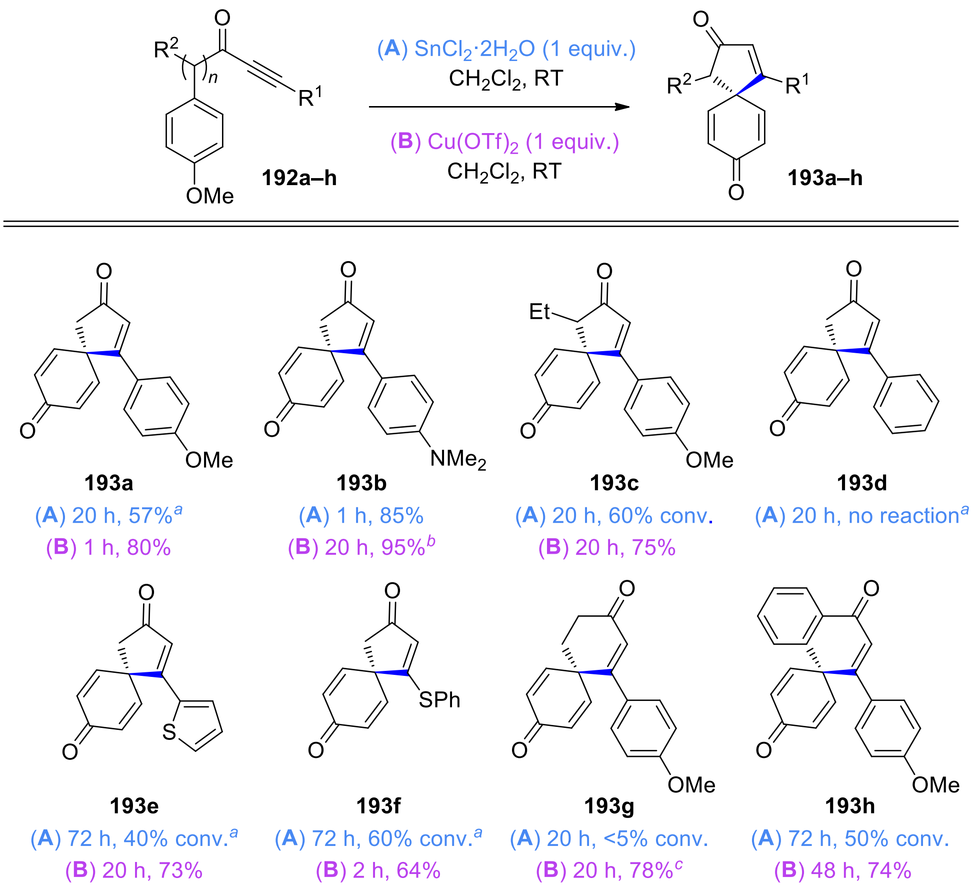
During work towards the synthesis of the natural product spirobacillene A **76**, it was found that treating anisole-tethered ynone **82** with five equivalents of $SnCl_2 \cdot 2H_2O$ at RT in CH_2Cl_2 resulted in efficient conversion into the spirocyclic dienone **83** (Scheme 53).[54]



Scheme 53. Sn(II)-mediated synthesis of spirocyclic dienone 83.

At the time of publication, this was the only reported reaction of this type and therefore it was decided to further optimise this process and explore the substrate scope. During optimisation studies carried out by Dr. Will Unsworth and James Cuthbertson, it was established that switching from $SnCl_2 \cdot 2H_2O$ to $Cu(OTf)_2$ significantly improved the efficiency of the reaction. A range of anisole-tethered ynones were prepared and tested in both the Sn(II)- and Cu(II)-mediated spirocyclisations and the results obtained from this study are shown in Scheme 54.

The dearomatisation and spirocyclisation reaction worked well on a range of substrates, although the reaction failed if electron-donating groups were not present at the terminal alkyne position (see ynone **192d**). $Cu(OTf)_2$ outperformed $SnCl_2 \cdot 2H_2O$ in all cases; however, stoichiometric quantities of $Cu(OTf)_2$ were still required for the reactions to reach completion. The requirement of electron-rich ynones and relatively large quantities of Sn(II)/Cu(II) reagents were therefore identified as areas for improvement.[56]

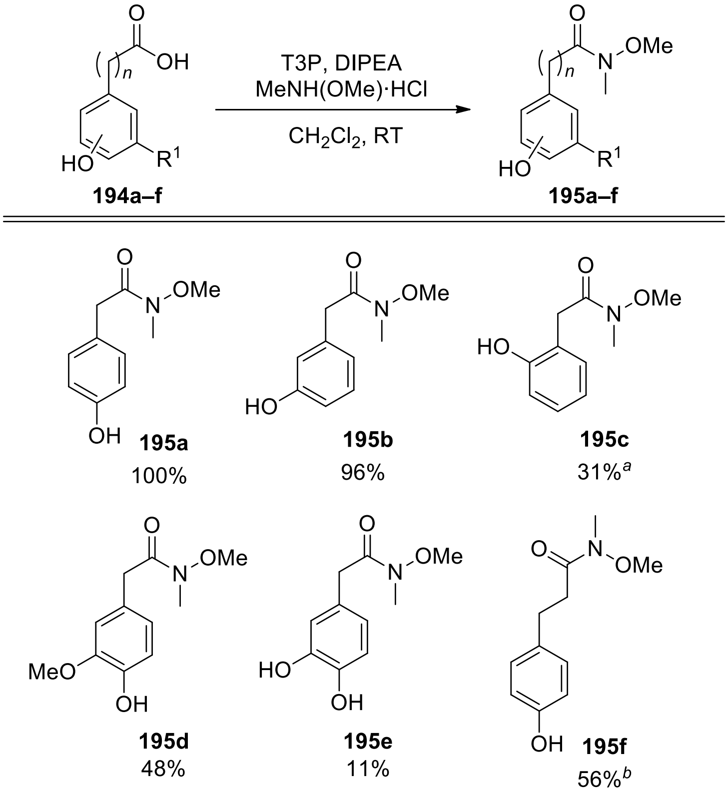


[a]5 equiv. of $SnCl_2 \cdot 2H_2O$ used. [b]0.1 equiv. of $Cu(OTf)_2$ used. [c]Reaction performed at 50 °C. Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra.

Scheme 54. Spirocyclisation of anisole-tethered ynones using $SnCl_2 \cdot 2H_2O$ (A) and $Cu(OTf)_2$ (B).

3.3 Spirocyclisation of phenol-tethered ynones

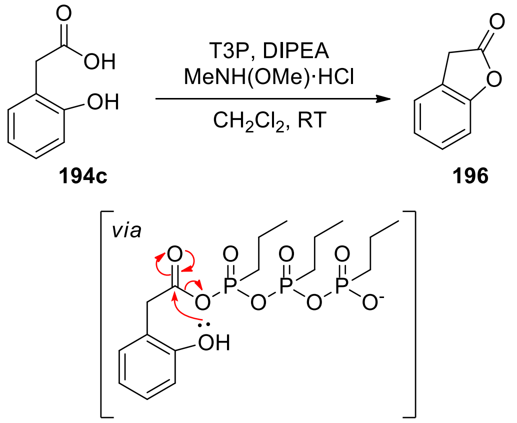
It was reasoned that switching from an anisole system to a more reactive phenol system may address the limitations associated with the previous Sn(II)/Cu(II)-mediated spirocyclisation protocol. The following study began by synthesising a range of phenol-tethered Weinreb amides using the standard T3P coupling procedure (Scheme 55).



[a]Low isolated yield due to a lactone-forming side reaction. [b]Reaction performed by BSc student Jack Partington.

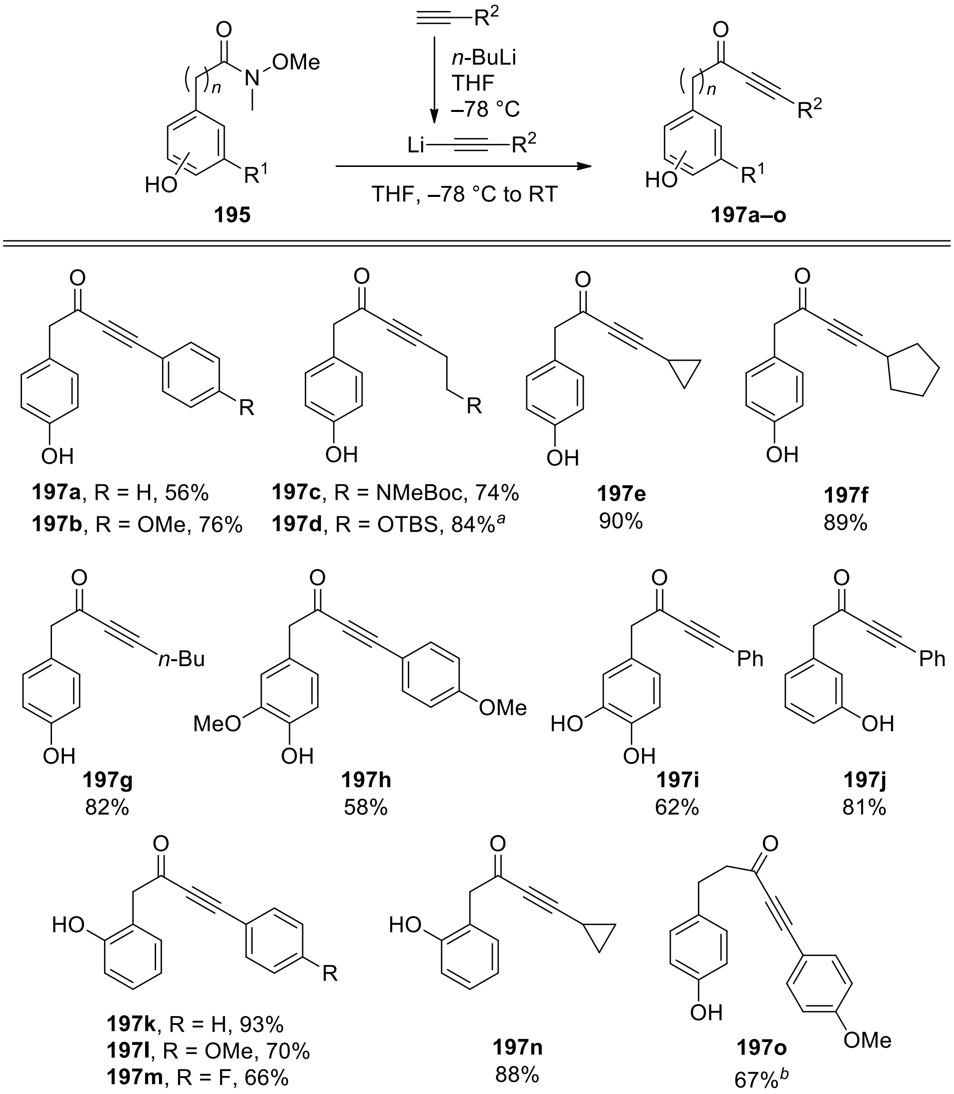
Scheme 55. Phenol-tethered Weinreb amides prepared using T3P coupling.

Ortho-, *meta*- and *para*-substituted Weinreb amides **195a–f** were prepared with varying levels of efficiency, depending on the substitution pattern around the phenol ring. The preparation of *ortho*-substituted Weinreb amide **195c** unfortunately suffered from the formation of an appreciable amount of lactone **196** which consequently lowered the isolated yield (Scheme 56). Dihydroxylated Weinreb amide **195e** was also obtained in a low yield due to difficulties regarding its isolation using the standard acid/base work-up procedure.



Scheme 56. Lactone-forming side reaction

Phenol-tethered ynones **197a–o** were then prepared from their respective Weinreb amides upon treatment with the relevant lithiated alkynes as described previously (Scheme 57).

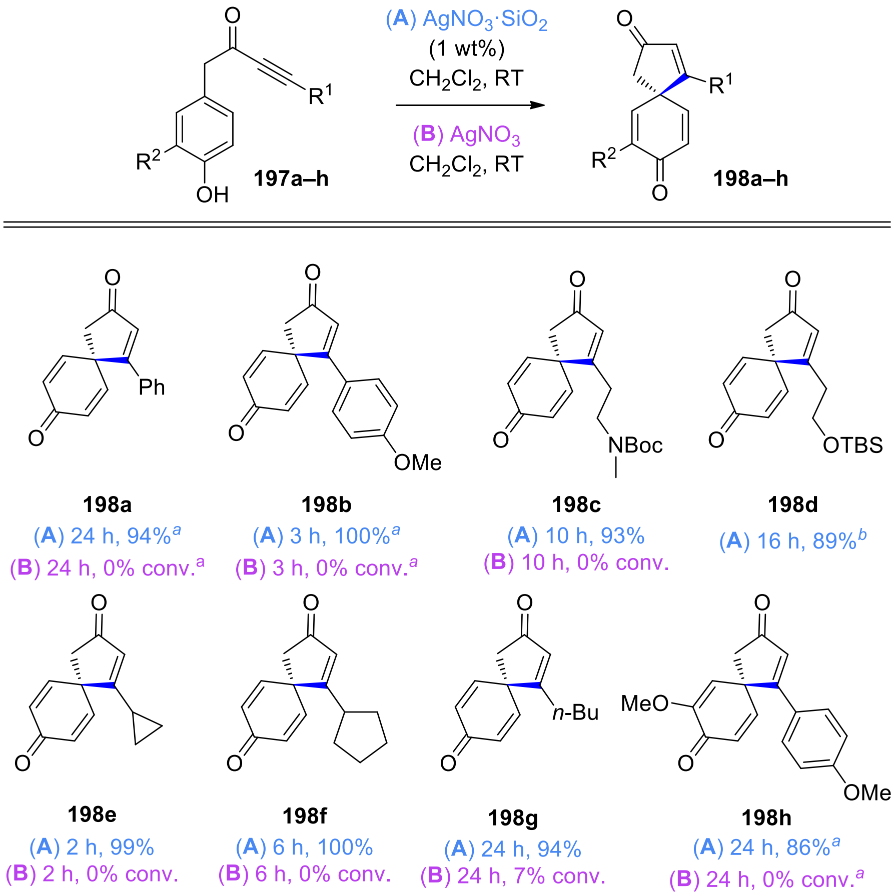


[a]Reaction performed by Dr. John Liddon. [b]Reaction performed by BSc student Jack Partington.

Scheme 57. Phenol-tethered ynones prepared by treatment with various lithium acetylides.

Generally, the isolated yields for these phenol-tethered ynones were high, with a range of electron-rich, electron-neutral and electron-poor aromatics, saturated cyclic and alkyl functional groups incorporated into the ynone tethers.

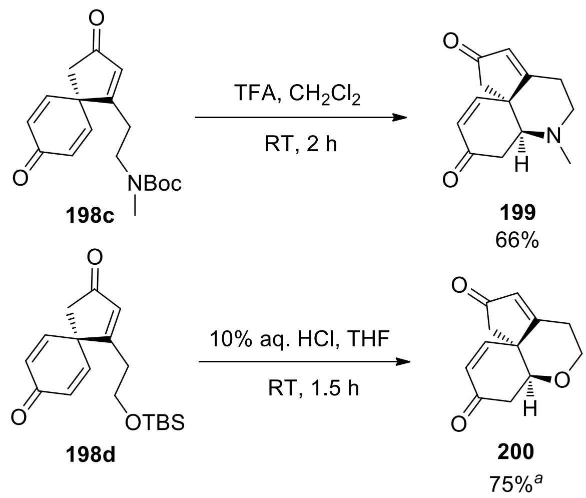
The $AgNO_3{\cdot}SiO_2$-catalysed spirocyclisations of *para*-substituted phenol-tethered ynones were examined first, delivering the corresponding spirocyclic dienone frameworks **198a–h** in excellent yields (Scheme 58). Once again $AgNO_3{\cdot}SiO_2$ proved to be a much more reactive catalyst system than unsupported $AgNO_3$; ynones **197a–c**, **197e–f, 197h** did not react in the presence of $AgNO_3$ and only 7% conversion into the desired spirocyclic dienone **198g** was observed for ynone **197g**.



Reactions were performed using 10 mol% catalyst. [a]Reactions were performed at 40 °C. [b]Reaction performed by Dr. John Liddon. Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra.

Scheme 58. Spirocyclisations of *para*-substituted ynones

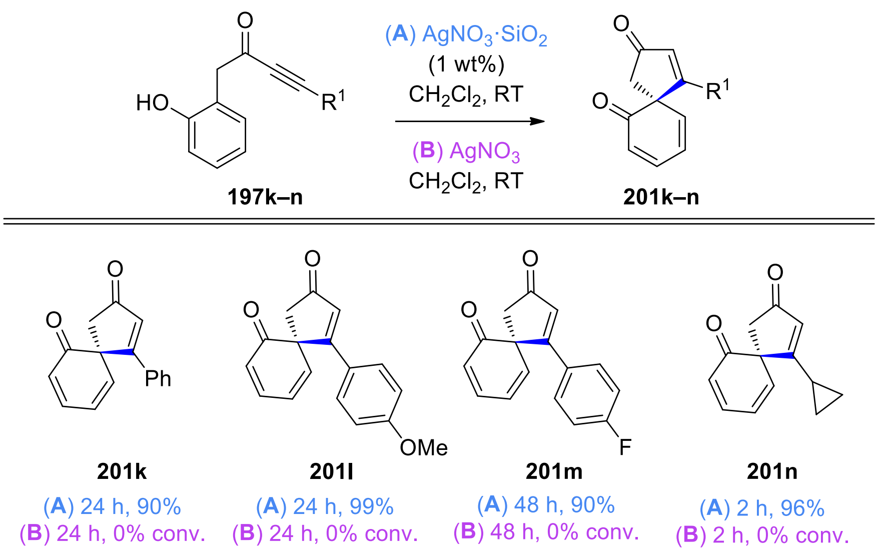
As can be seen from the results in Scheme 58, it is not necessary to use electron-rich ynones in this procedure; simple alkyl chains along with electron-rich and electron-neutral aromatic ynones were all tolerated, providing spirocyclic dienones **198a–d** and **198g–h** in high yields. The incorporation of cyclopropane and cyclopentane rings appeared to increase ynone reactivity; spirocyclisations of ynones **197e** and **197f** reached completion in just 2 h and 6 h, respectively, to give spirocyclic products **198e** and **198f**, which is notably faster than the majority of reactions performed in this study. Ynones **197c** and **197d** bearing protected amine and alcohol functionalities reacted smoothly to generate their corresponding spirocyclic dienones **198c** and **198d**; the value of these products was demonstrated by performing deprotection and subsequent cyclisation of the protected functional groups in one-pot to generate novel tricyclic structures **199** and **200**, as single diastereomers in reasonable un-optimised yields (Scheme 59).



[a]Reaction performed by Dr. John Liddon.

Scheme 59. One-pot deprotection and cyclisation of spirocyclic dienones.

Ortho-substituted phenols also underwent efficient spirocyclisation, delivering chiral spirocyclic products **201k–n** in isolated yields of 90% or above (Scheme 60). Electron-rich, electron-neutral and electron-deficient aromatic ynone substituents were tolerated, as well as cyclopropane-substituted ynone **197n**, which delivered spirocyclic dienone **201n** in an efficient manner. The ability of these *ortho*-substituted phenols to undergo spirocyclisation was particularly pleasing as there are relatively few literature examples of dearomatisation and *ipso*-cyclisation of *ortho*-substituted phenols.[3,27,31,132,133] These results also opened up avenues for asymmetric catalysis to be explored.



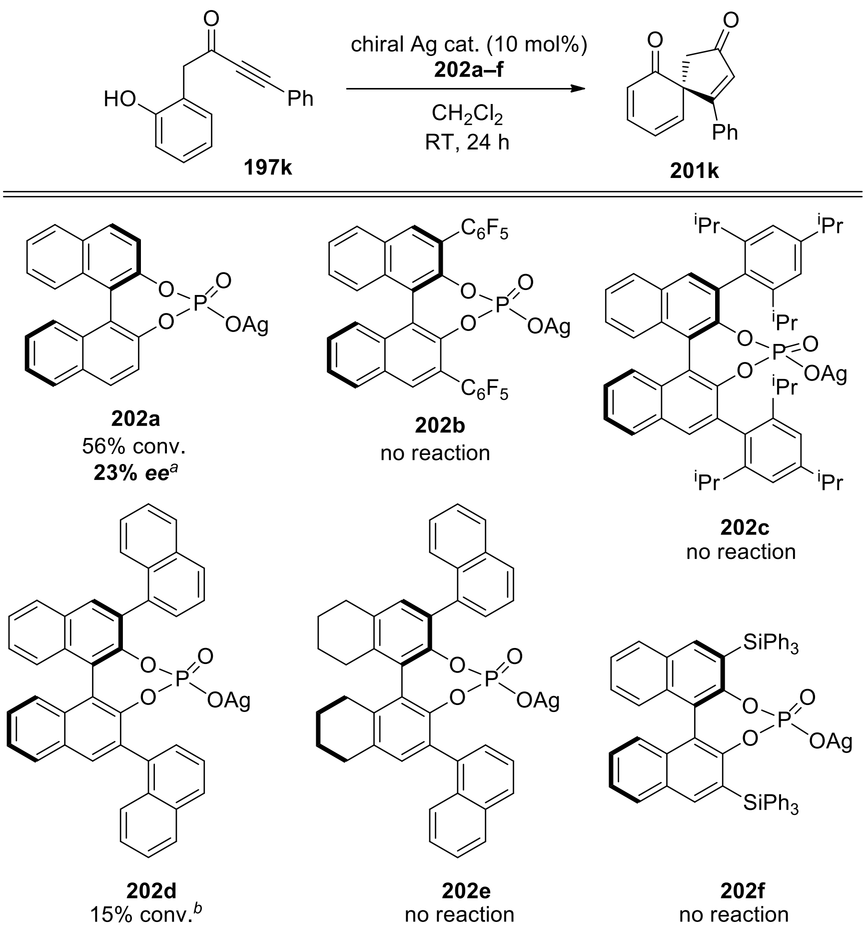
Reactions were performed using 10 mol% catalyst. Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra.

Scheme 60. Spirocyclisations of *ortho*-substituted ynones.

Dihydroxylated ynone **197i**, *meta*-substituted phenol ynone **197j** and extended phenol ynone **197o** (shown in Scheme 57) were also subjected to the $AgNO_3 \cdot SiO_2$ spirocyclisation conditions but unfortunately all of these substrates failed to react at both RT and 40 °C and the starting ynones were recovered in all cases.

3.4 Preliminary asymmetric studies

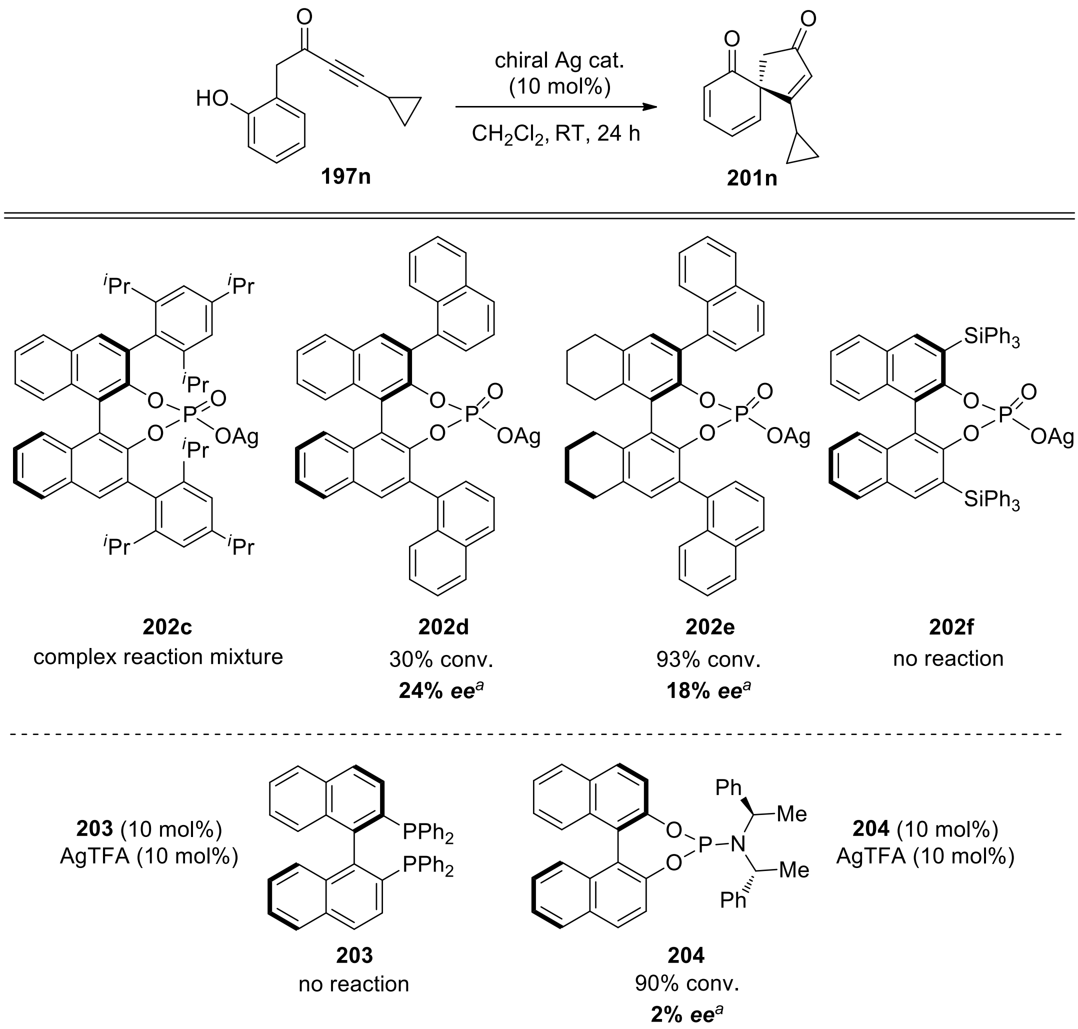
As the spirocyclisation reaction on *ortho*-substituted phenol-tethered ynones successfully furnished chiral spirocyclic dienones, it was envisaged that the development of an asymmetric variant may be possible. Silver salts of chiral phosphoric acids (Ag-CPAs) have previously been identified as useful chiral catalysts in related asymmetric reactions[55,134] and were chosen for our initial asymmetric studies. Phenyl-substituted ynone **197k** was used as the test substrate, the results of which are shown in Scheme 61. Chiral HPLC was used to obtain the *ee* values presented, with rac-**201k** used to establish the best HPLC conditions for *ee* determination.



[a]Determined using CSP-HPLC: Chiralpak ID column, eluting with 20% IPA in hexanes, [b]Unable to isolate product for chiral separation. Conversions calculated by analysis of starting material:product ratio in the unpurified ^1H NMR spectra. Ag-CPA catalysts previously prepared by Michael James.[55,92]

Scheme 61. Asymmetric spirocyclisation of ynone 197k using Ag-CPAs.

Unfortunately, all the catalysts tested in this study performed poorly, with four out of the six Ag-CPAs failing to promote any spirocyclisation. The unsubstituted BINOL framework seen in Ag-CPA **202a** performed the best, providing spirocycle **201k** in 23% *ee*. In view of the low conversions observed a more active cyclopropane-substituted ynone system **197n** was chosen for additional asymmetric studies, again using Ag-CPAs, as well as two Ag(I) complexes formed using chiral phosphine ligands (Scheme 62).



[a]Determined using CSP-HPLC: Chiralpak ID column, eluting with 20% IPA in hexanes. Conversions calculated by analysis of starting material:product ratio in the unpurified ^{1}H NMR spectra. Ag-CPA catalysts previously prepared by Michael James.[55,92]

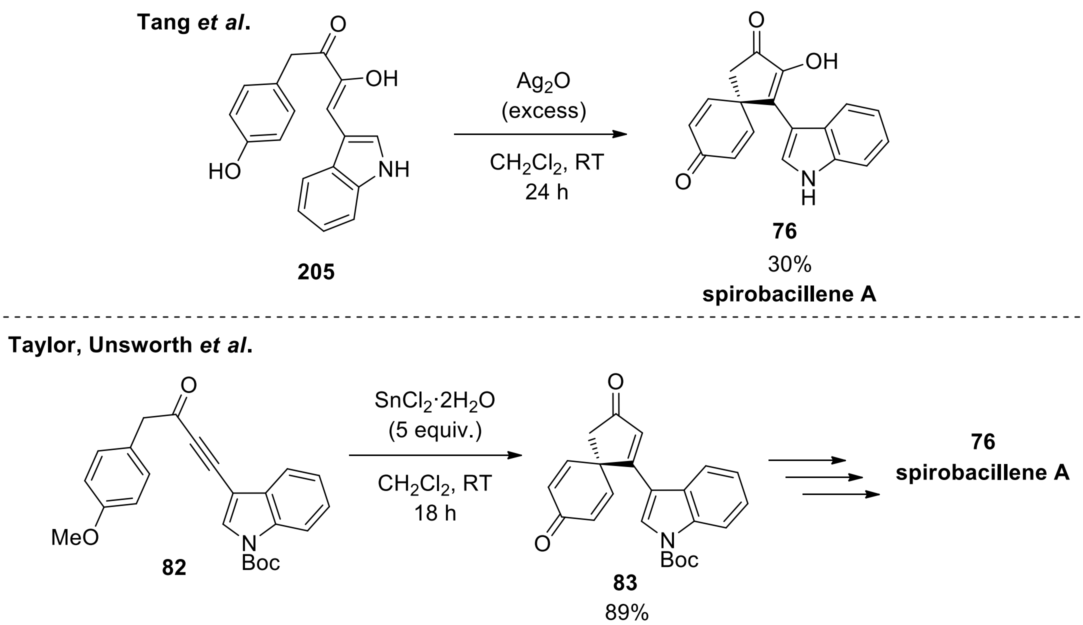
Scheme 62. Asymmetric spirocyclisation of ynone 197n.

Unfortunately, once again only low enantioselectivites (18–24%) were observed when using Ag-CPAs in the spirocyclisation of cyclopropane-substituted ynone **197n**, with little improvement over the previous results obtained. Silver salts in combination with commercially available chiral phosphine ligands were evaluated in the spirocyclisation of ynone **197n** as there are numerous literature reports describing the use of these conditions in enantioselective silver-catalysed transformations.[135] Unfortunately, neither the BINAP **203** nor the phosphoramidite **204** ligand showed signs of asymmetric induction.

Previous work has showed that increasing the steric bulk around the BINOL backbone of the chiral phosphoric acid increases enantioselectivity during the spirocyclisation of indole-tethered ynones.[55] Unfortunately, the same trend was not observed for phenol-tethered ynones and there is clearly a different mode of asymmetric induction involved. It is possible that coordination and hydrogen-bonding of the phenol moiety, within the Ag-CPA cavity, could be dictating the levels of asymmetric induction observed rather than unfavourable steric interactions.

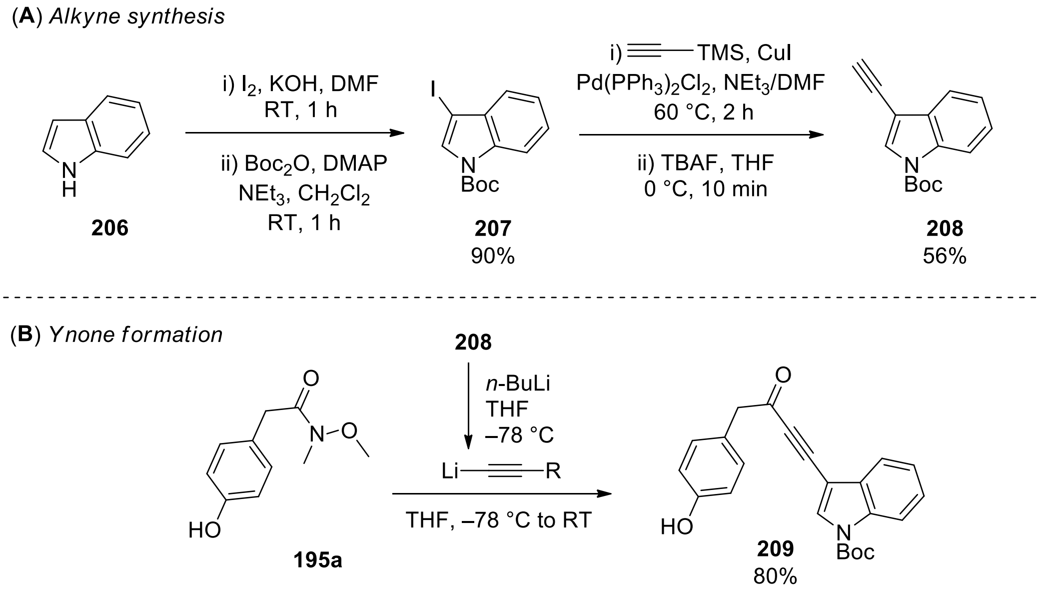
3.5 Formal synthesis of spirobacillene A

The indole alkaloids, spirobacillene A **76** and B **79**, were isolated from the broth culture of *L. Fusiformis*, a strain of bacteria found in acidic coal mine drainage contaminated with iron-rich heavy metals.[53] Spirobacillene A **76** is a particularly attractive target, in part due to its inhibitory activity against the production of nitric oxide and reactive oxygen species. Since its isolation in 2012, there have been two reported total syntheses, both of which were published in quick succession in 2013.[54,136] A phenol-enol oxidative coupling reaction was developed by Tang and co-workers which they used in the final step of their total synthesis, employing Ag_2O as a single electron transfer agent (Scheme 63). Our group used a dearomatisation and *ipso*-cyclisation strategy requiring five equivalents of $SnCl_2{\cdot}2H_2O$ to furnish the key spirocyclic dienone intermediate **83** (Scheme 63).



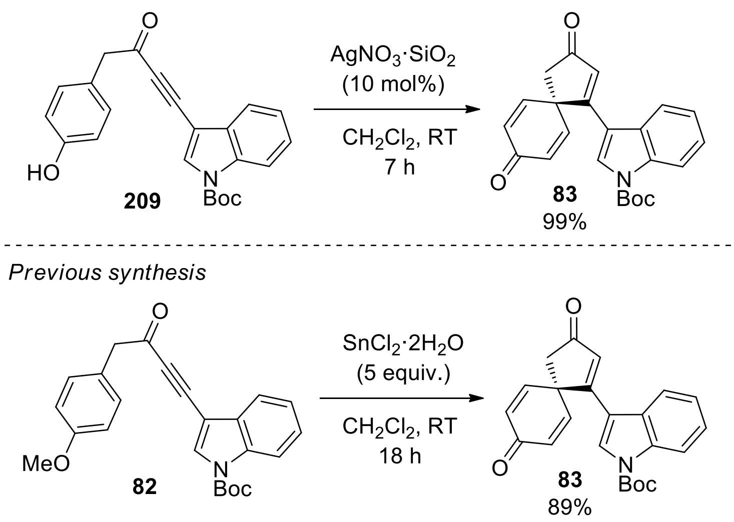
Scheme 63. Key steps in previous reported total syntheses of spirobacillene A 76.

It was realised that the key spirocyclic dienone intermediate **83** used as a precursor to spirobacillene A **76** could be accessed using our $AgNO_3{\cdot}SiO_2$-catalysed spirocyclisation methodology from phenol-tethered ynone **209**. Ynone **209** was prepared using the standard lithiation conditions, although the indole-tethered alkyne **208** required for this was not commercially available and was prepared in two steps prior to ynone formation (Scheme 64).



Scheme 64. Preparation of alkyne 208 (A) and ynone formation (B).

With phenol-tethered ynone **209** in hand, spirocyclisation was performed on this substrate using our $AgNO_3{\cdot}SiO_2$ catalyst (Scheme 65). An extremely successful spirocyclisation was achieved, furnishing key spirocyclic dienone **83** in a near-quantitative yield in just 7 h. This result was a significant improvement on previous reported syntheses, providing a more scalable and catalytic route towards the synthesis of spirobacillene A **76**.



Scheme 65. Previous and improved routes to key spirobacillene A precursor 83.

3.6 Summary

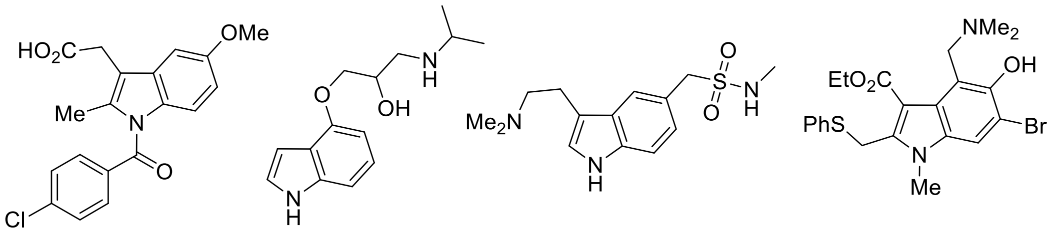
Mild and efficient spirocyclisation conditions have been applied to a range of phenol-tethered ynones to generate spirocyclic dienones, which are important frameworks present in a broad array of natural products. The tolerance of *ortho*-substituted phenols in the methodology is also valuable, given that chiral spirocyclic products are generated, and preliminary asymmetric studies have shown that spirocyclisation can be achieved with low levels of asymmetric induction. Optimisation of these reaction conditions and modification of the catalyst has the potential to improve upon these initial results in future work. Finally, an efficient formal synthesis of the natural product spirobacillene A **76** has been completed; catalytic quantities of silver in the form of $AgNO_3{\cdot}SiO_2$ efficiently provided the key spirocyclic dienone precursor **83** in a near-quantitative yield.

The work described in this Chapter was reported in *Organic and Biomolecular Chemistry* (see Appendix 2).[56]

Chapter 4. Pyrrole benzannulations: The synthesis of substituted indoles

4.1 Introduction

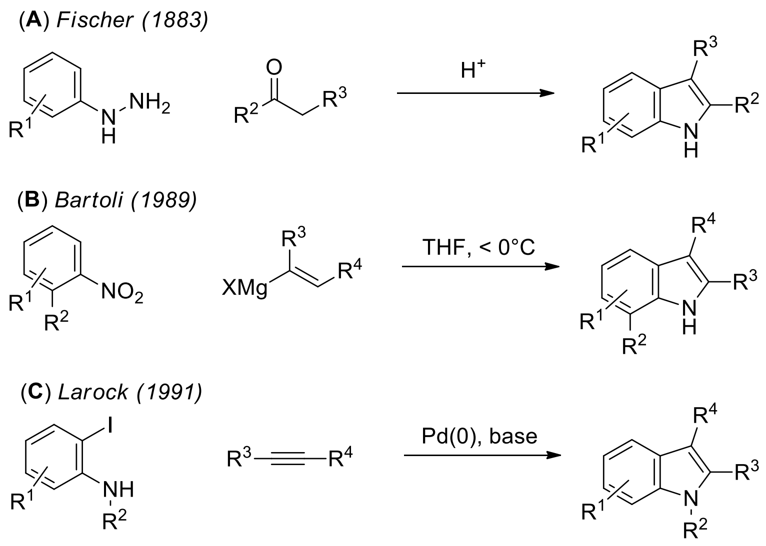
Functionalised indole subunits are privileged heterocyclic structures; they are found in a range of natural products, agrochemicals, dyes and biologically active pharmaceuticals.[137,138] Their importance in biomedical applications is highlighted by their presence in the neurotransmitter serotonin and natural amino acid tryptophan, as well as in a variety of marketed drugs including: indomethacin **210**, pindolol **211**, sumatriptan **212** and arbidol **213** (Figure 14).[138]



210 **indomethacin** *anti-inflammatory* | **211** **pindolol** *anti-hypertensive* | **212** **sumatriptan** *migraine* | **213** **arbidol** *influenza*

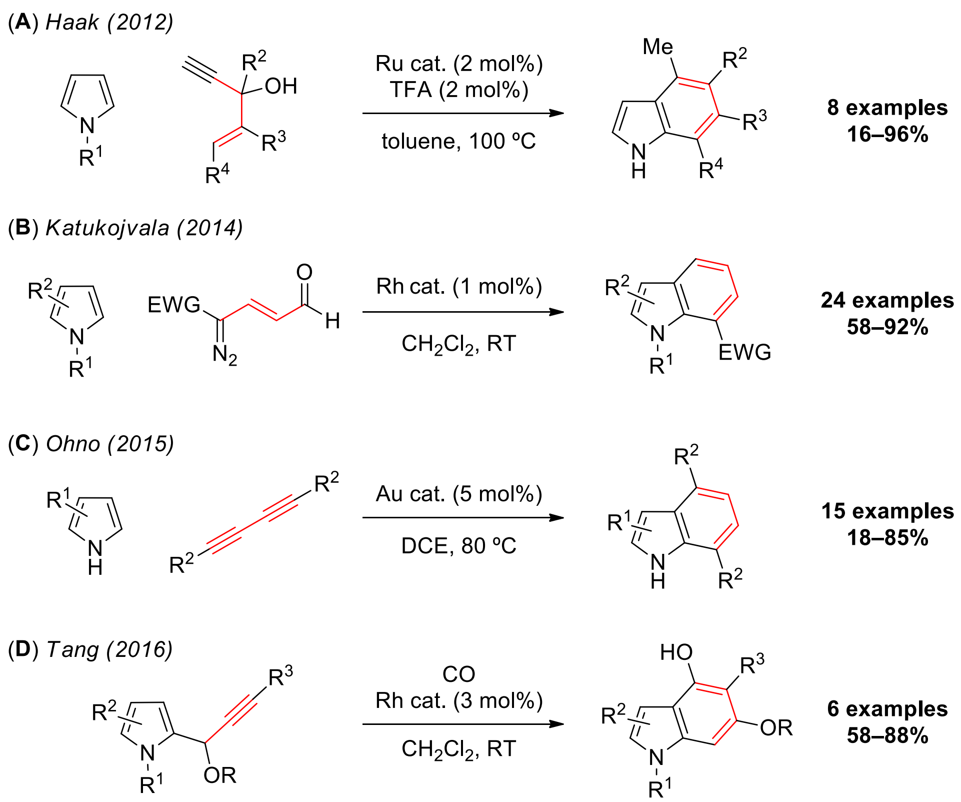
Figure 14. Biologically important indole derivatives.

The biological importance of substituted indoles has stimulated much research into new synthetic strategies to access such frameworks.[139,140] Since its discovery in 1883, the Fischer indole synthesis, (the treatment of phenylhydrazines with aldehydes or ketones under acidic conditions), has been widely used to prepare substituted indole frameworks (Scheme 66A).[141,142] Other classical indole syntheses developed include the Bartoli, Larock, Gassman, Reissert and Leimgruber-Batcho methods, some of which are summarised in Scheme 66.[143,144] Typically, these methods construct the indole framework *via* the annulation of a pyrrole ring onto a pre-functionalised benzene precursor.



Scheme 66. Classical indole syntheses.

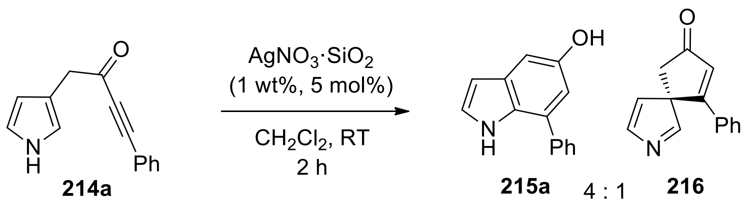
More recently, there have been scattered reports of routes to substituted indoles proceeding through the functionalisation of pyrrole precursors, whereby the substituted benzenoid ring is constructed during the synthesis, although there are far fewer indole syntheses of this type. Selected examples are included below (Scheme 67), although it should be noted that the reported methods are generally quite substrate specific with little scope for substituent variation.[145–148]



Scheme 67. Indole syntheses starting from pyrrole precursors.

4.2 *Preliminary results*

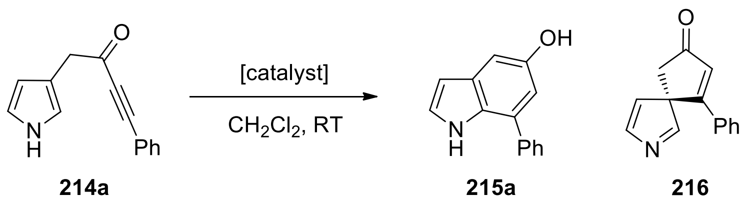
Whilst examining the spirocyclisation of 3-pyrrole ynones it was realised that treatment of pyrrole-tethered ynone **214a** with 5 mol% $AgNO_3 \cdot SiO_2$ led to the formation of indole **215a** and spirocycle **216** in a 4:1 ratio (Scheme 68). Although we had initially hoped to isolate the spirocycle in this reaction, the formation of the indole product was not entirely unexpected, considering the known tendency for pyrroles to react through their C-2 position. This preliminary result prompted further investigation into the possibility of preparing a range of substituted indole frameworks from simple pyrrole precursors using silver catalysis.



Scheme 68. Treatment of pyrrole-tethered ynone 214a with $AgNO_3 \cdot SiO_2$.

4.3 *Reaction optimisation*

Before the scope of this methodology could be examined, the reaction conditions were optimised to ensure full and clean conversion of the pyrrole ynones into their indole products. Catalyst optimisation studies were performed on pyrrole-tethered ynone **214a** and the results are summarised in Table 8.



Entry	Catalyst	Catalyst loading / mol%	Reaction time / h	Conversion[a] / % SM 214a	Indole 215a	Spiro 216
1	$AgNO_3 \cdot SiO_2$[b]	1	4	65	23	12
2	$AgNO_3 \cdot SiO_2$[b]	5	2	0	80	20
3	$AgNO_3$	1	6	78	22	0
4	$AgNO_3$	5	3	0	100 (97)	0

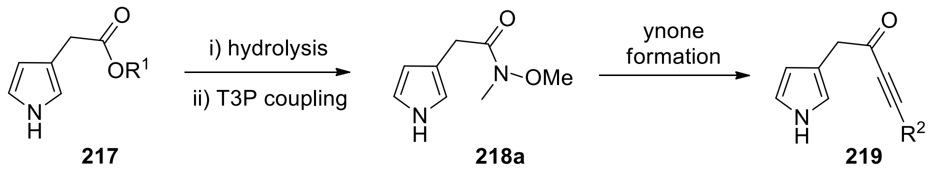
[a]Conversions calculated by analysis of starting material:product ratios in the unpurified ^{1}H NMR spectra and isolated yields reported in parentheses. [b]Reactions performed using 1 wt% $AgNO_3 \cdot SiO_2$.

Table 8. Optimisation of benzannulation conditions.

As can be seen from the results in Table 8, with $AgNO_3 \cdot SiO_2$ the formation of spirocycle **216** could not be avoided, and consequently, the conversion into the indole product **215a** was lower (Entries 1 and 2). It was also realised during these reactions that full conversion of ynone **214a** into 5-hydroxy indole **215a** was crucial in enabling clean isolation of the indole product, as any remaining ynone starting material could not be separated by column chromatography. Fortunately, it was found that simply switching from the $AgNO_3 \cdot SiO_2$ catalyst to unsupported $AgNO_3$ enabled the pyrrole benzannulation to proceed cleanly to indole **215a**, without the formation of spirocycle **216** (Entry 3). Using 5 mol% $AgNO_3$, pyrrole ynone **214a** underwent full and clean benzannulation furnishing 5-hydroxy indole **215a** in a 97% isolated yield (Entry 4). The mild reaction conditions used in this transformation and the near-quantitative yield obtained suggested that the synthesis of indoles *via* this $AgNO_3$-catalysed benzannulation procedure could be competitive with current literature methods.

4.4 Synthesis of pyrrole-tethered ynone precursors

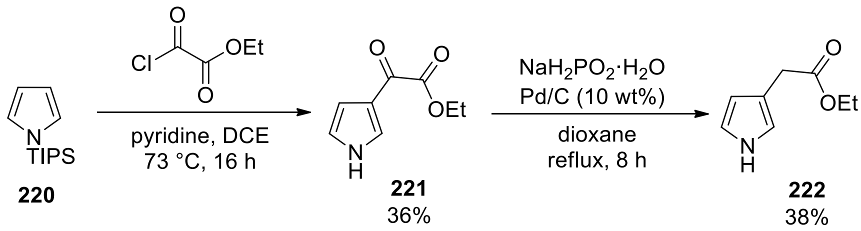
Before the scope of this benzannualation process could be explored, a suitable method of preparing 3-pyrrole-tethered ynones **219** had to be established. Provided that a route to 3-substituted pyrroles **217** incorporating an ester/carboxylic acid group in the tether could be found, it was envisaged that the desired 3-pyrrole-tethered ynones **219** could be accessed using hydrolysis, T3P coupling and ynone formation reactions that have previously been used in the preparation of similar substrates (Scheme 69).



Scheme 69. Proposed route to 3-pyrrole-tethered ynones.

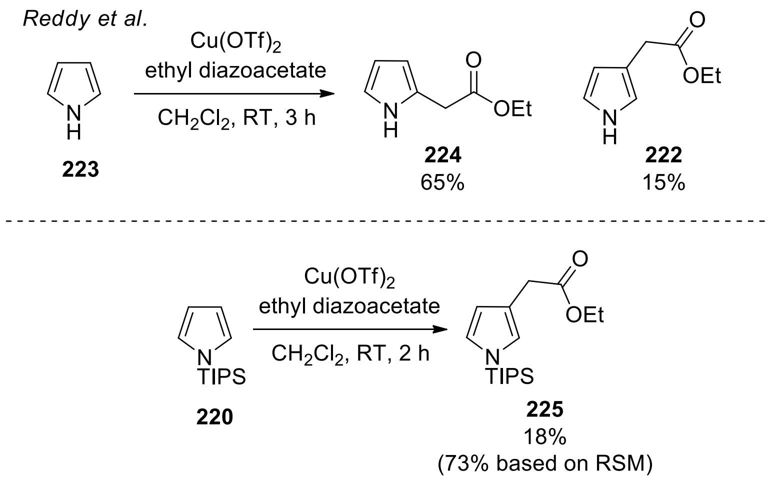
Following a literature search, it was found that there were only two synthetic procedures describing the synthesis of pyrrole-tethered ynones of the form **219**. Both these literature procedures were repeated in order to test their reproducibility, in the hope that one of these methods could be used as a viable route towards 3-pyrrole-tethered ynones **219**.

Firstly, a route comprising of two literature steps, a Friedel-Crafts reaction[149] and hydrogenolysis,[150] was used to access pyrrole-tethered ethyl ester **222** (Scheme 70). The literature yields reported for the Friedel-Crafts and hydrogenolysis steps were 60% and 54%, respectively; unfortunately, when repeating both these literature procedures, neither of the reported yields were reproducible in our hands, and purification following the Friedel-Crafts reaction was particularly challenging and cumbersome, and thus an alternative strategy was explored.



Scheme 70. Synthesis of ethyl ester 222 *via* Friedel-Crafts and hydrogenolysis.

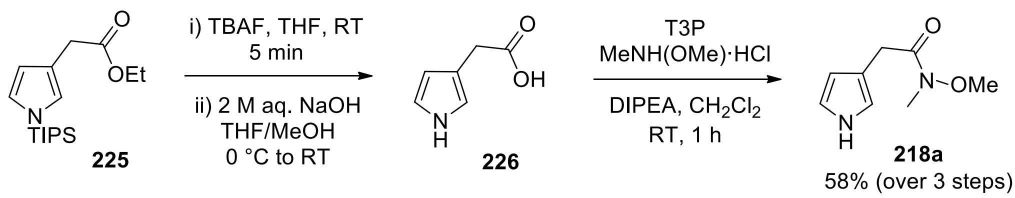
Previously, a Cu-catalysed alkylation reaction reported by Reddy and co-workers was used to access 2-substituted pyrrole-tethered ethyl ester **224** in 65% yield, as well as a smaller amount of 3-substituted pyrrole **222** (Scheme 71).[151] It was anticipated that if a bulky *N*-protecting group was used to sterically hinder the 2-position of pyrrole (this concept was employed in the Friedel Crafts reaction seen in Scheme 70), the same reaction could be employed to access a greater proportion of the 3-substituted pyrrole-tethered ethyl ester **222**. When performing the Cu-catalysed alkylation reaction on TIPS-protected pyrrole **220**, unfortunately pyrrole-tethered ethyl ester **225** was only isolated in an 18% yield (Scheme 71). This reaction not only suffered from incomplete consumption of starting material **220** and dimerisation of ethyl diazoacetate (EDA), but also led to the formation of multiple alkylation products as the TIPS protecting group was not sufficiently bulky to prevent C-2 alkylation.



Scheme 71. Synthesis of pyrrole-tethered ethyl esters 222 and 225.

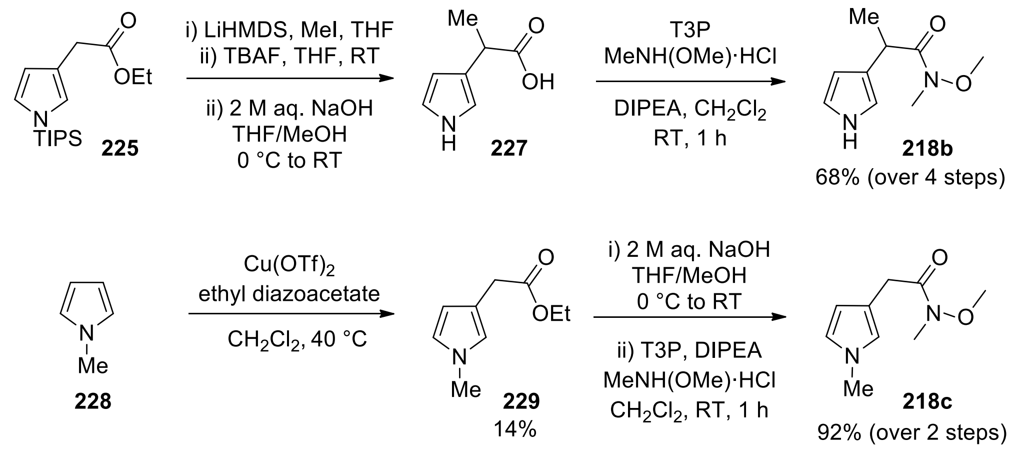
A variety of metal catalysts were screened in the alkylation reaction of TIPS-protected pyrrole **220**, and other reaction parameters (including solvent, temperature, stoichiometry of reagents and rate of EDA addition) were varied, but unfortunately full and clean conversion into the monoalkylated ethyl ester **225** could not be achieved. Nonetheless, while the isolated yield was low, recovery of the TIPS-protected pyrrole starting material **220** was straightforward and the reaction could be performed in just 2 hours, which were advantages over the previous two-step procedure described in Scheme 70. Thus, while the preparation of pyrrole-tethered ethyl ester **225** was not entirely satisfactory, it was sufficient for us to progress with the next phase of the project.

Weinreb amide **218a** was then prepared in three simple steps from TIPS-protected pyrrole-tethered ethyl ester **225** (Scheme 72). TIPS deprotection was achieved using tetrabutylammonium fluoride (TBAF) and the hydrolysis and T3P coupling reactions were performed using standard conditions previously used within the group.



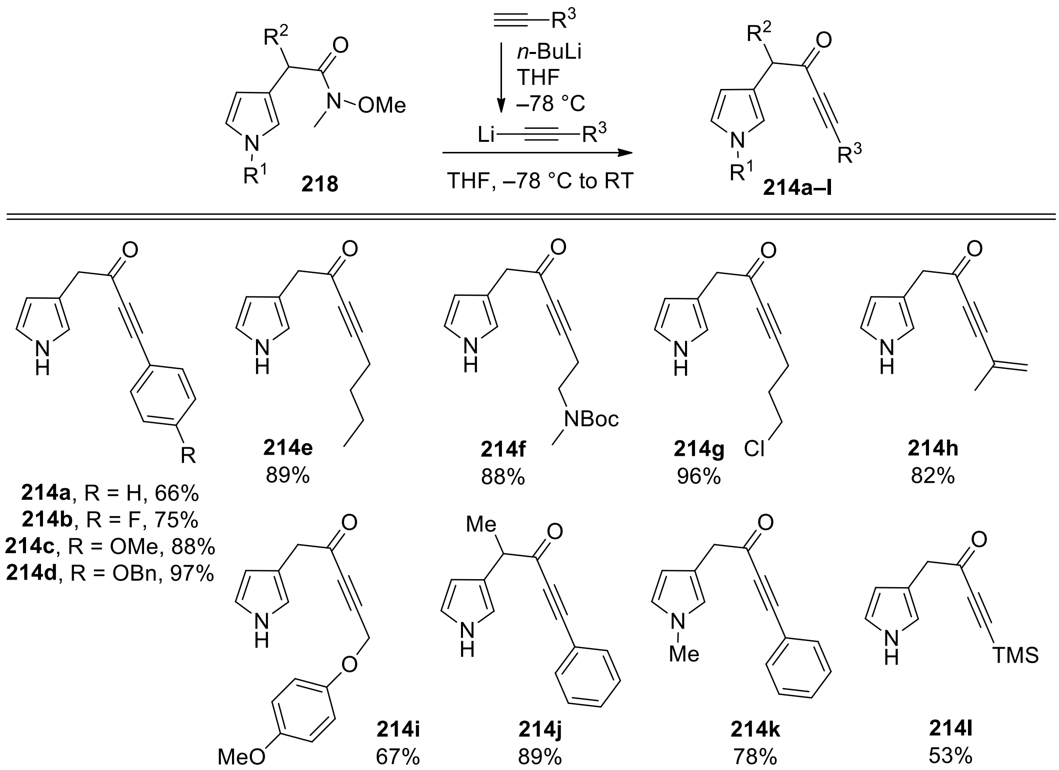
Scheme 72. Formation of Weinreb amide 218a from TIPS-protected ethyl ester 225.

Two additional Weinreb amides (**218b** and **218c**) were also prepared *via* alkylation reactions starting from TIPS-protected pyrrole-tethered ethyl ester **225** and commercially available *N*-methyl pyrrole **228** (Scheme 73).



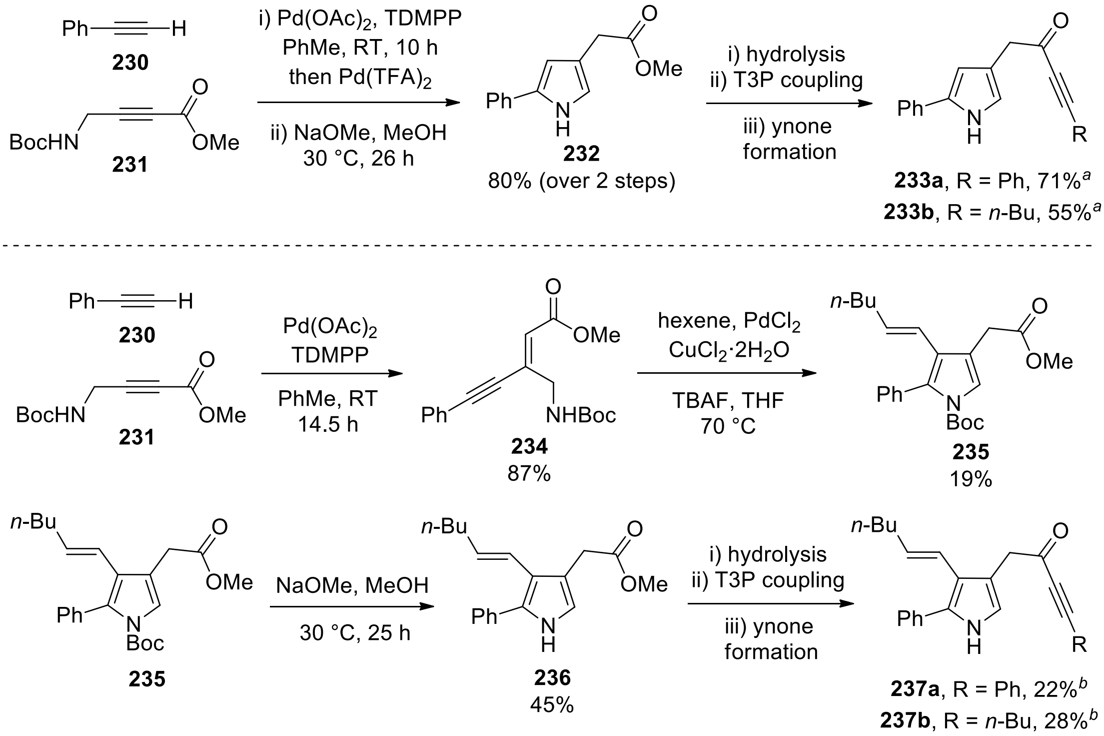
Scheme 73. Preparation of Weinreb amides 218b and 218c.

A range of 3-pyrrole-tethered ynones were then prepared from their respective Weinreb amides using standard lithiation reaction conditions (Scheme 74). The yields of these ynone-forming reactions were generally high across all substrates; the lowest isolated yield was obtained for TMS-protected ynone **214l** which is not surprising, given the lability of the TMS functional group.



Scheme 74. 3-pyrrole-tethered ynones prepared.

Pyrrole-tethered ynones incorporating substituents in the C-2 and C-3 positions were also prepared using a variety of literature procedures,[152–154] some of which had to be modified to generate the desired products (Scheme 75). A literature procedure by Trost *et al.* was used to prepare the starting propargyl amine **231** which was used in both syntheses; the intial Pd-catalysed steps were also reported by the Trost group.[152] Standard conditions were used for the hydrolysis, T3P coupling and ynone formation steps; these conditions are described in Scheme 72 and Scheme 74.



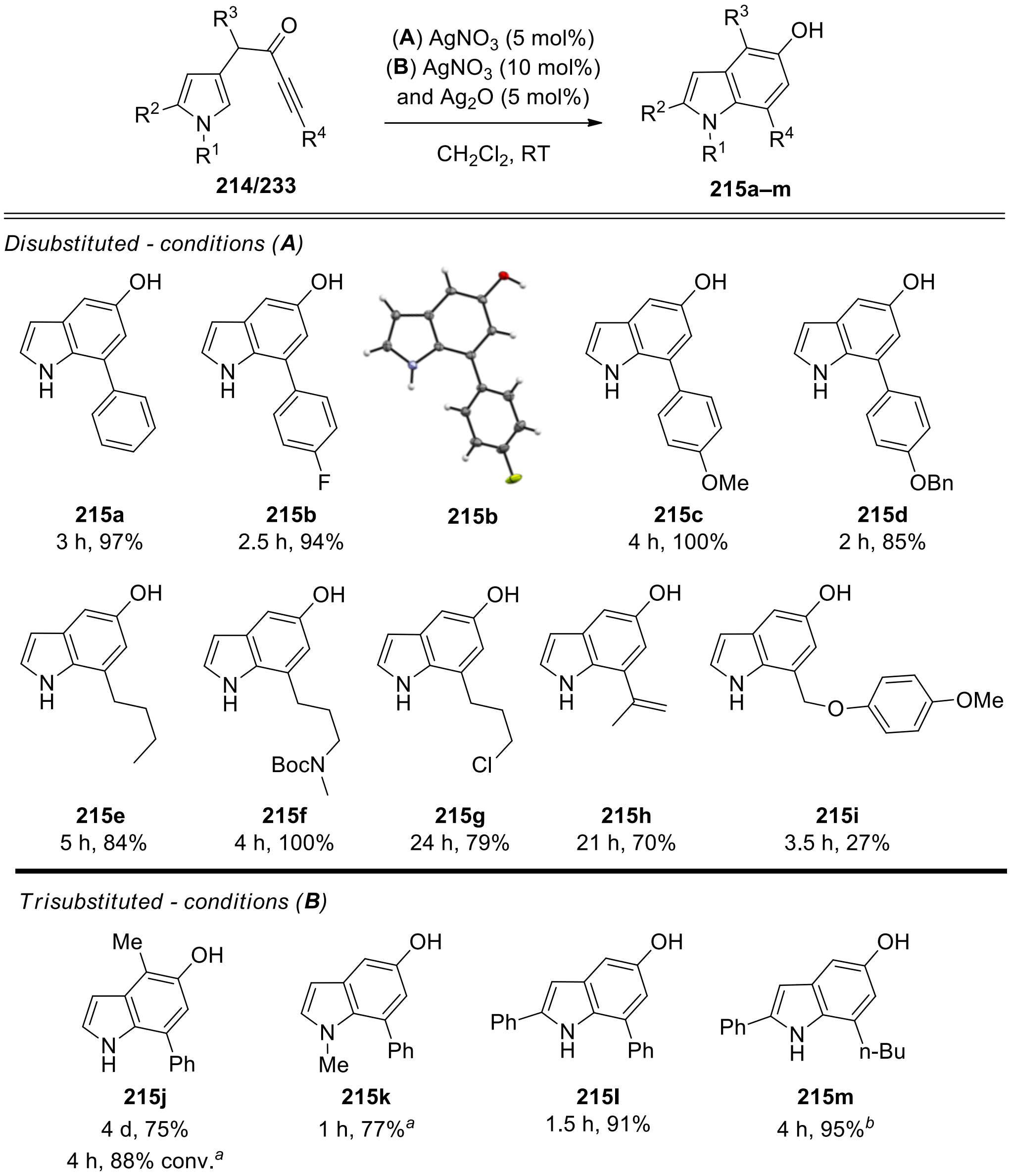
[a]Isolated yields for ynone forming step only. [b]Isolated yields reported over three steps (hydrolysis, T3P coupling and ynone formation).

Scheme 75. Formation of C-2/3 substituted ynones.

C-2 substituted ynones **233a** and **233b** were isolated in good yields from their respective Weinreb amides. Ynones **237a** and **237b** incorporating C-2 and C-3 substituents were prepared in three consecutive steps from pyrrole-tethered methyl ester **236**; the use of the unpurified material in each step is likely to have led to the low overall isolated yields observed.

4.5 Pyrrole benzannulations using ynone precursors

With a range of pyrrole-tethered ynones in hand, the scope of the benzannulation was explored. Attention was initially focused on the benzannulation of 3-pyrrole-tethered ynones which furnished a range of 5-hydroxy indole products (Scheme 76).



[a]Only 10 mol% $AgNO_3$ used. [b]5 mol% $AgNO_3$ and 2.5 mol% Ag_2O used.

Scheme 76. Benzannulations of pyrrole-tethered ynones.

Monitoring these cyclisations by TLC was difficult due to many of the starting ynones and indole products having coincident R_f values. It was also difficult to monitor these reactions by ^{1}H NMR spectroscopy as there were few characteristic peaks allowing identification of the indole products. Therefore, the disappearance of the alkyne stretch (at *ca*. 2200 cm^{-1}) in the IR spectra of the reaction mixtures was generally used to monitor the progress of these reactions. In some cases it was also possible to use the highly fluorescent properties of the 5-hydroxy indole products, as the ynone starting materials themselves did not fluoresce under UV light. A characteristic ^{13}C NMR signal for C-OH was also used to confirm the isolation of the 5-hydroxy indole products; the C-OH carbon environment had a chemical shift at around 149 ppm in the ^{13}C NMR spectra.

The majority of pyrrole ynones were converted into their corresponding 5-hydroxy indoles in good yields. This was particularly pleasing given that the 5-hydroxy indole motif, and derivatives thereof, feature in numerous natural products and biologically active molecules.[138,140] A range of alkyl and aromatic groups were tolerated in the C-7 position and an amine tether bearing a Boc-protecting group was also shown to be compatible, providing indole **215f** in quantitative yield. Ynones **214g** and **214h** incorporating a chloro group and an alkene moiety appeared to be less reactive and both required over 20 h for the reaction to reach completion; their hydroxy indoles **215g** and **215h** are particularly useful though, containing functional groups amenable to further modification. Four trisubtituted indoles **215j**–**m** were also generated, demonstrating the compatibility of *N*-protected pyrrole ynones and C-2/4 substituents in this procedure. Indole products **215j**, **215l** and **215m** required a Ag_2O additive for the benzannulation to proceed to completion, but nonetheless, the indole products were isolated in good yields using these modified conditions.

The regioselectivity of the benzannulation procedure was confirmed by both nOe experiments and X-ray crystallography. Indole **215b** was the only product isolated from the reaction of ynone **214b**; it was obtained as a crystalline solid and its structure was determined by crystallography (shown in Scheme 76 and Figure 15). Additionally, nOe experiments were performed on the phenyl-substituted indole **215a** and the results were supportive of the regioisomer **215a-A** shown in Scheme 76 rather than regioisomer **215a-B**; an enhancement in the phenyl proton signal (labelled b) was observed when the amine proton signal (labelled a) was irradiated (Figure 16).

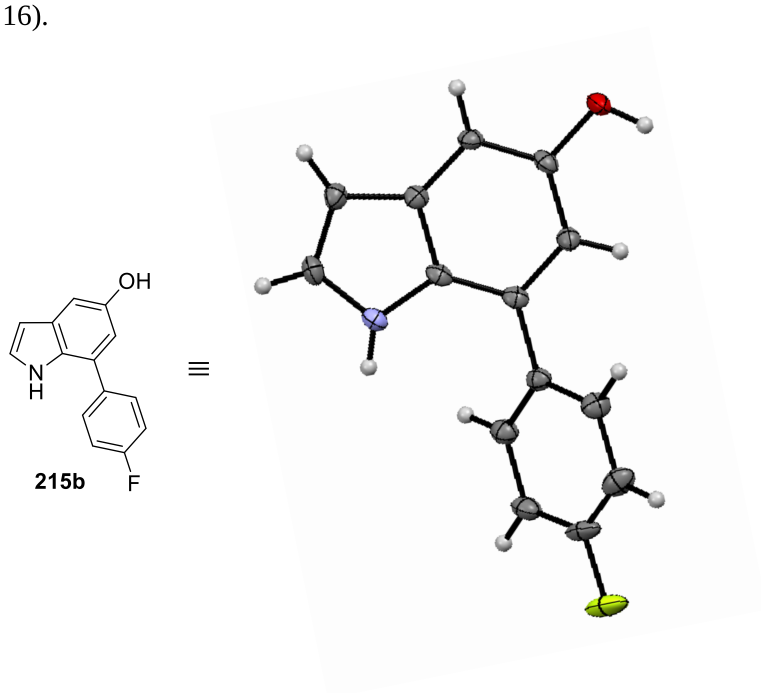


Figure 15. X-ray structure of indole 215b with thermal ellipsoids shown at 50% (CCDC 1554901).

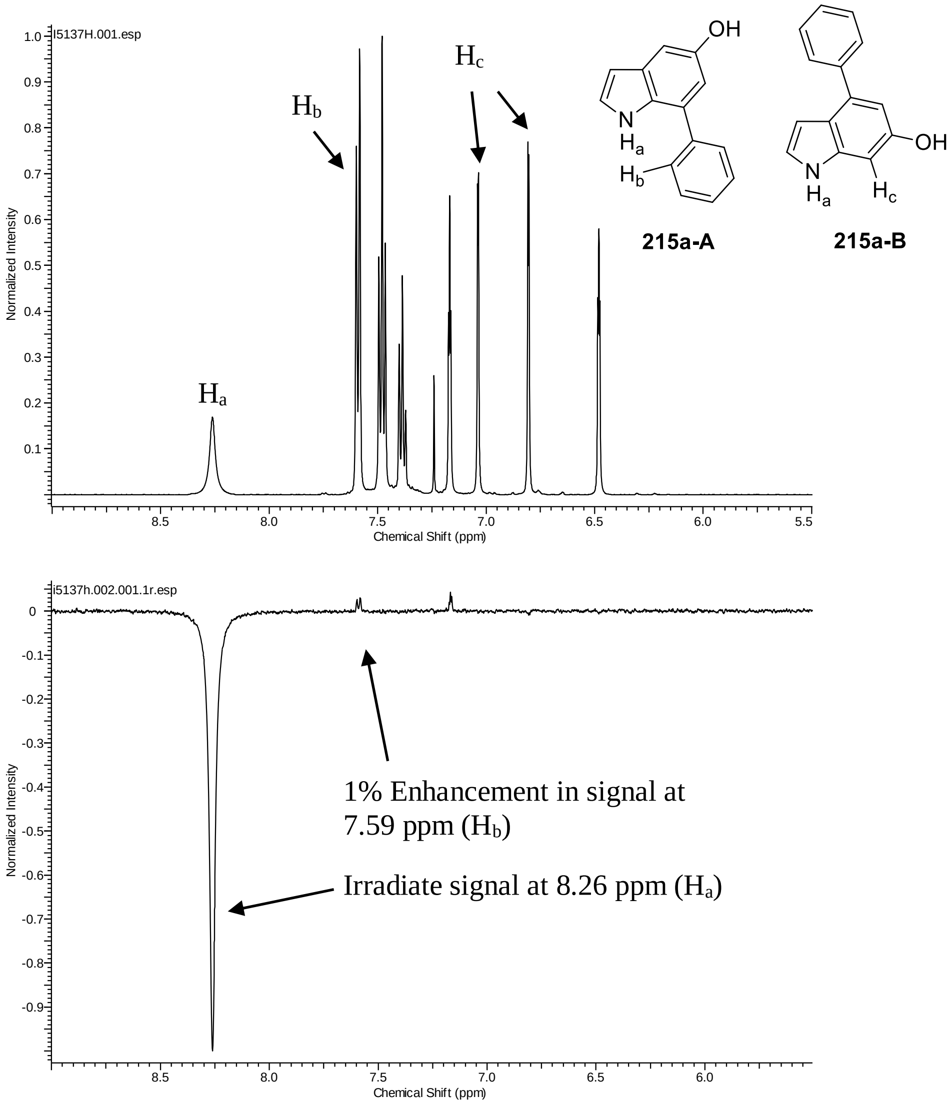
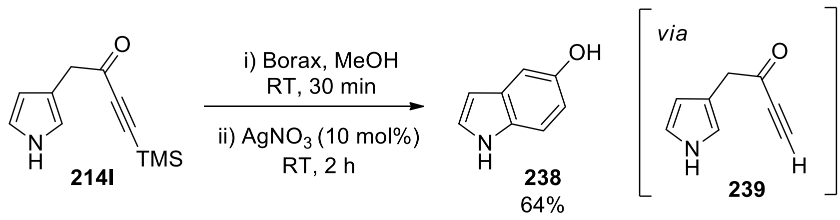


Figure 16. Regioselectivity confirmation using nOe experiments.

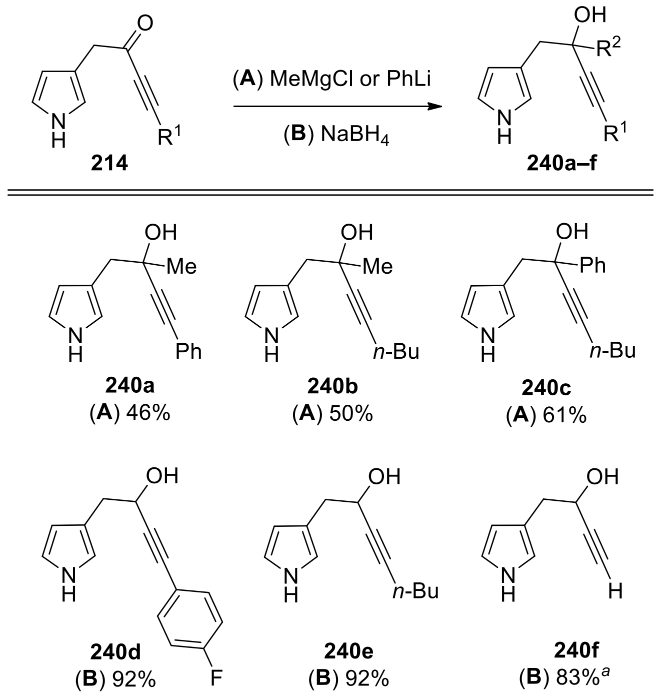
In addition to demonstrating the tolerance of various functional groups in the C-7 position of the indole framework, it was also desirable to synthesise the unsubstituted 5-hydroxy indole **238**. TMS-protected ynone **214l** failed to react in the presence of $AgNO_3$ and efforts to isolate the corresponding deprotected ynone **239** were also unsuccessful. Hence, it was decided to focus on the *in situ* deprotection and immediate reaction of the terminal ynone **239** to afford 5-hydroxy indole **238**. Pleasingly, *in situ* TMS deprotection promoted by borax ($Na_2B_4O_7{\cdot}10H_2O$), followed by the addition of 10 mol% $AgNO_3$ at RT afforded 5-hydroxy indole **238** in 64% yield (Scheme 77).



Scheme 77. One-pot deprotection and cyclisation of TMS-protected ynone 214l.

4.6 Pyrrole benzannulations using propargyl alcohols

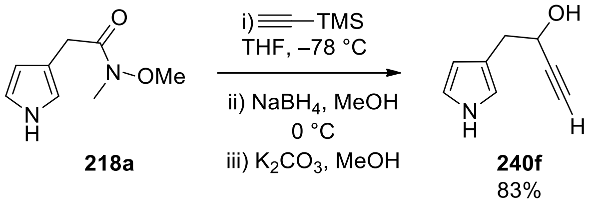
A selection of 3-pyrrole ynones were then transformed using either Grignard/organolithium addition (conditions A in Scheme 78) or $NaBH_4$ reduction (conditions B in Scheme 78) to prepare propargyl alcohol substrates **240a–f** for screening in the benzannulation reaction.



[a]Isolated yield over three steps.

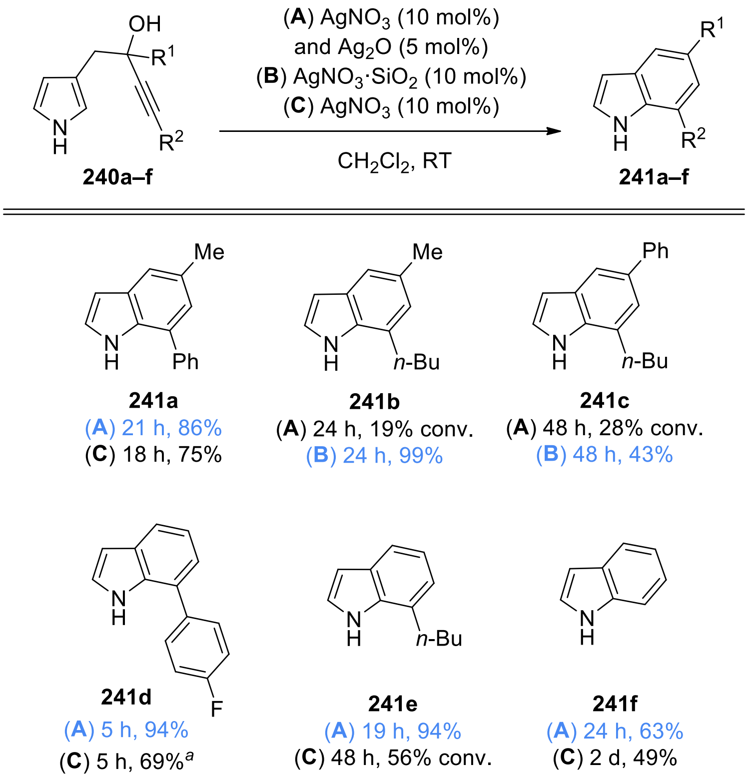
Scheme 78. Reduction of 3-pyrrole ynones using organometallic reagents or $NaBH_4$.

Propargyl alcohols **240d** and **240e** were obtained in high yields following $NaBH_4$ reduction, but the Grignard/organolithium reductions typically did not proceed to completion, which could be due to the presence of enolisable protons in these systems. Terminal propargyl alcohol **240f** was prepared from Weinreb amide **218a** in three steps; ynone formation followed by $NaBH_4$ reduction and K_2CO_3-mediated deprotection, provided propargyl alcohol **240f** in an 83% yield (Scheme 79).



Scheme 79. Formation of terminal propargyl alcohol 240f from Weinreb amide 218a.

Propargyl alcohol substrates **240a–f** were then examined in the benzannulation process, furnishing a range of substituted indole frameworks, the results of which are shown in Scheme 80.



[a]15 mol% $AgNO_3$ used. Conversions calculated by analysis of starting material:product ratios in the unpurified ^1H NMR spectra.

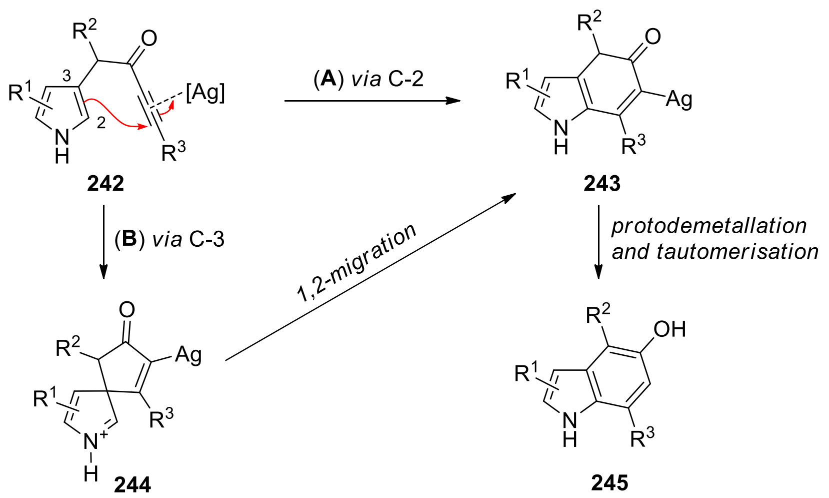
Scheme 80. Benzannulation reactions using propargyl alcohol substrates.

Not only did the propargyl alcohol substrates require higher catalyst loadings in comparison to the pyrrole ynone substrates described earlier, but in some cases, $AgNO_3$ alone was not able to promote full conversion into the indole products. Previously, our group have shown that a combination of $AgNO_3$ and Ag_2O can be effective in the cyclisation of indole-tethered propargyl alcohols;[94] it appeared that a Ag_2O additive (conditions A in Scheme 80) also had a beneficial role in the cyclisation of pyrrole-tethered propargyl alcohols, leading to increased conversions and enhanced isolated yields for indoles **241a,d–f**. The exact role of the Ag_2O

additive is not known, but when trying to promote the cyclisation of ynone **240d** using 15 mol% Ag_2O no reaction was observed. Therefore, it appears that Ag_2O does not catalyse the reaction directly, but may work by buffering the reaction mixture. Unfortunately, the combination of $AgNO_3$ and Ag_2O were less successful conditions for the formation of substituted indoles **241b** and **241c**. In these two cases, switching to the $AgNO_3 \cdot SiO_2$ catalyst previously developed within the group, promoted cyclisation of propargyl alcohols **240b** and **240c** and the desired indole products **241b** and **241c** were isolated in 99% and 43% yields, respectively.

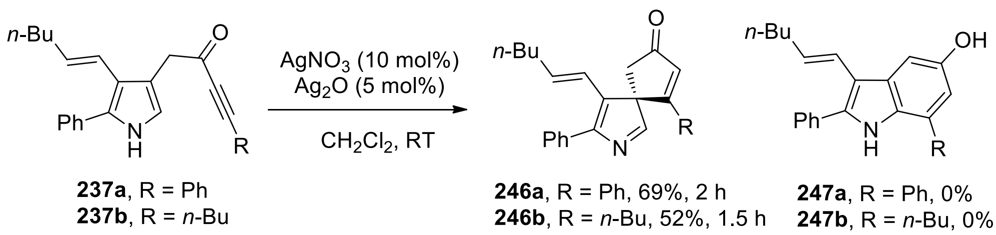
4.7 Mechanistic insight and density functional theory (DFT) calculations

Two possible mechanistic pathways were considered for the benzannulation of pyrrole-tethered ynones, both of which are depicted in Scheme 81. Coordination of the alkyne to the silver(I) catalyst increases its electrophilicity and activates it towards attack from the electron-rich pyrrole ring. This nucleophilic attack can occur through either the pyrrole C-2 position (route A, Scheme 81) or C-3 position (route B, Scheme 81). It was considered likely that attack would occur *via* the most nucleophilic C-2 position, giving rise to intermediate enone **243** which then undergoes protodemetallation and tautomerisation to generate the 5-hydroxy indole product **245**. Alternatively, it is possible that attack could occur *via* the less nucleophilic C-3 position to form spirocyclic intermediate **244**, which then undergoes a 1,2-migration followed by protodemetallation and tautomerisation as seen in pathway A. The propargyl alcohol series are also expected to undergo one of these described pathways, except the tautomerisation step is replaced by the elimination of water.



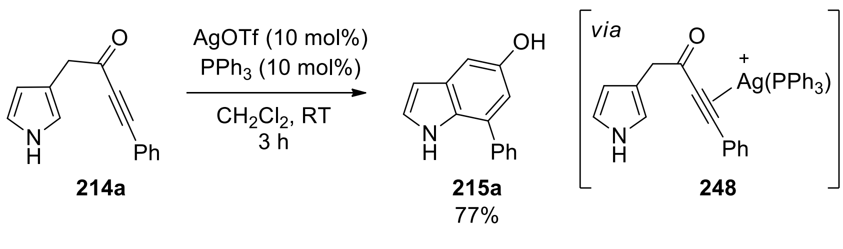
Scheme 81. Possible mechanistic pathways for benzannulation.

Although it was considered most likely that the benzannulation would occur *via* C-2 attack, this original notion was questioned following attempts to cyclise substituted ynones **237a** and **237b** (Scheme 82). When treating each ynone with a mixture of $AgNO_3$ and Ag_2O, none of the expected indole products (**247a** and **247b**) were formed and instead spirocyclic structures **246a** and **246b** were isolated. These results were surprising, not only because dearomatisation of pyrroles through the C-3 position is rare, but also because this had taken place in preference to C-2 annulation.



Scheme 82. Attempted benzannulation of ynones 237a and 237b.

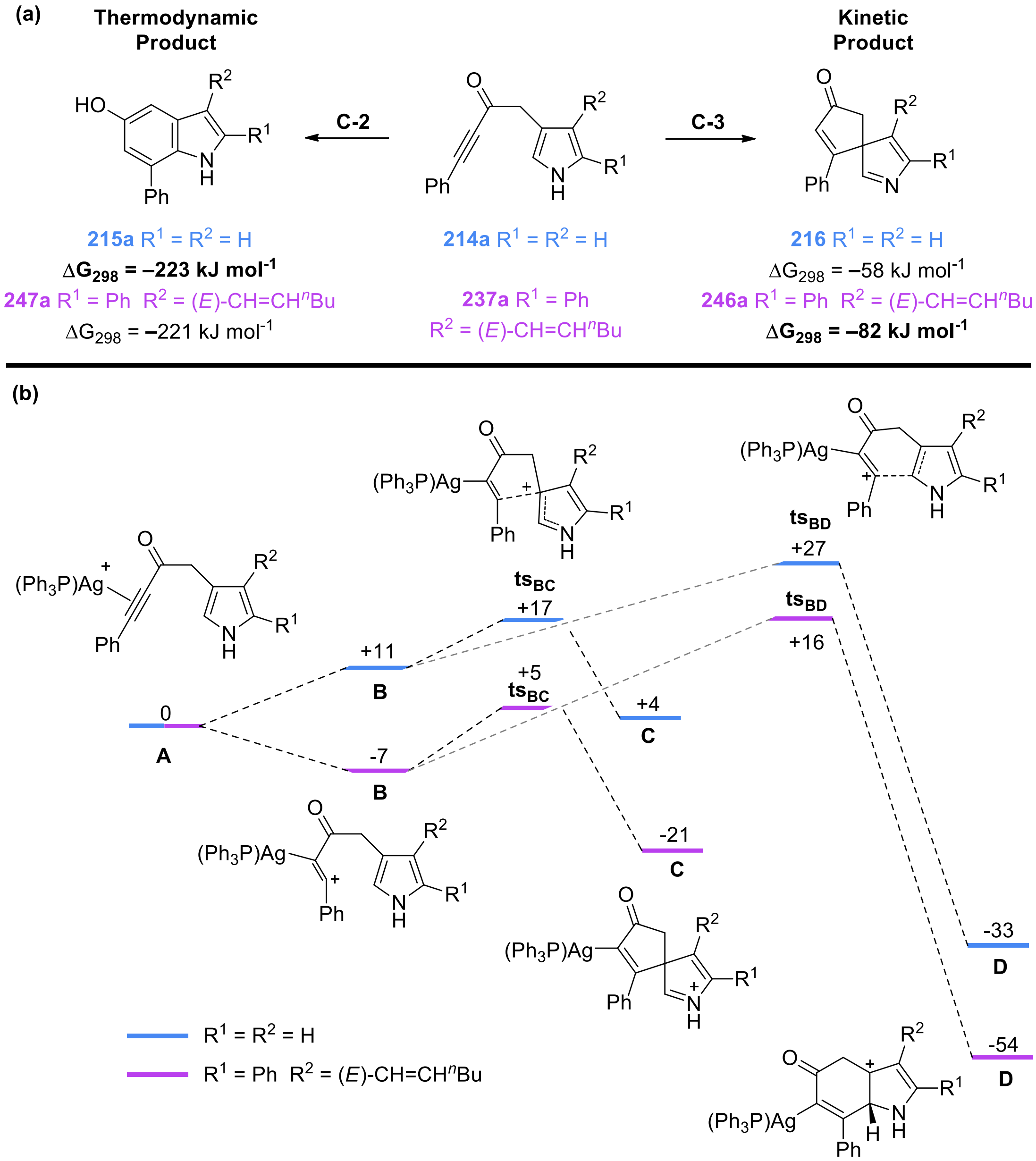
In view of these surprising results, density functional theory was used to try and gain an understanding of the factors underpinning the mechanism, by probing possible pathways for C-C bond formation. Before the cyclisations of selected pyrrole ynones could be modelled by DFT, a suitable catalyst system that could be modelled effectively had to be established. Due to the kinetic lability of silver(I) complexes, the precise nature of the active species of $AgNO_3$ is unclear and can not be accurately modelled by DFT. However, the reaction of AgOTf with an equivalent of PPh_3 results in the formation of a known complex $Ag(OTf)PPh_3$,[155,156] and it was anticipated that ynone substrates would displace the weakly bound OTf ligand in this complex to give a cationic silver(I) phosphine species **248** that could be modelled by DFT. The feasibility of this catalyst system was evaluated by treating pyrrole ynone **214a** with a solution of $Ag(OTf)PPh_3$ (formed *in situ* by mixing AgOTf and PPh_3 in CH_2Cl_2), pleasingly it was found to be a viable catalyst system resulting in the formation of indole **215a** in 77% isolated yield (Scheme 83).



Scheme 83. Benzannulation of pyrrole ynone 214a using $Ag(OTf)PPh_3$ complex.

All the DFT calculations were carried out by Dr. Jason Lynam at the University of York. Firstly, the Gibbs energies for the transformations shown in Scheme 84a (**214a** into **216** and

215a, **237a** into **246a** and **247a**) were calculated using DFT. It was found that indole **215a** was the thermodynamic product of the reaction when using unsubstituted pyrrole ynone **214a** (ΔG_{298} = –223 kJ mol^{-1}) and that spirocycle **216** would be a kinetic product from this reaction (ΔG_{298} = –58 kJ mol^{-1}). Although, employing substituted pyrrole ynone **237a** changed the outcome of the experimental reaction (see Scheme 82), it did not significantly alter this picture with the indole product **247a** being more stable than spirocycle **246a**, indicating that this reaction is instead under kinetic control.



All DFT calculations were performed by Dr. Jason Lynam. Energies are Gibbs energies at 298 K at the D3-PBE0/def2-TZVPP//BP86/SVP(P) level with COSMO solvent correction in CH_2Cl_2.

Scheme 84. DFT-calculated energies for (a) formation of compounds 215a/247a and 216/246a from 214a/237a and (b) silver-catalysed C-C bond formation from alkyne complex A.

The cyclisation of ynones **214a** and **237a** were then modelled by DFT using $[Ag(PPh_3)^+]$ as the catalyst system (Scheme 84b). In the case of the cyclisation reaction of unsubstituted pyrrole **214a**, two transition states for C-C bond formation were calculated. Transition state $\mathbf{ts_{BC}}$ is best represented as nucleophilic attack through the C-3 position leading to the vinyl silver spirocycle **C**. The second transition state, $\mathbf{ts_{BD}}$ corresponds to C-C bond formation through the C-2 position leading to **D** where subsequent tautomerisation and protodemetallation would give indole product **215a**. Although the formation of **C** will occur more rapidly than **D**, the former is, at best, isoenergetic with **A**, and will be in rapid equilibrium with **B**. As **D** is significantly lower in energy (–33 kJ mol^{-1}), indole **215a** would be the expected product from the reaction rather than spirocycle **216**. In the case of substituted pyrrole ynone **237a** the situation is different with corresponding complex **C** now lower in energy than both **B** and **A**. As **C** will have a significant population in this case, it may then undergo protodemetallation to give spirocyclic product **246a**, consistent with it being a kinetic product formed from the lower lying transition state $\mathbf{ts_{BC}}$.

In summary of these DFT studies, we propose that the cyclisation of pyrrole ynones is likely to proceed *via* initial nucleophilic attack through the C-3 position of pyrrole due to the lower lying transition state associated with this transformation. Therefore, it is believed that C-3 spirocycles are transiently formed in all reactions, but the formation of the C-2 annulated products are isolated in the majority of cases due to them being the more thermodynamically stable species. The kinetic spirocyclic products are formed in cases when the energy of the spirocyclic intermediate **C** is significantly lower than complex **B**; the spirocyclic intermediate **C** is not in equilibrium with the ring-opened species **B** and therefore ring closure *via* C-2 does not occur.

4.8 Summary

The use of the pyrrole benzannulation methodology in the synthesis of various substituted indole frameworks has been established using silver(I) catalysis. The substrate scoping studies began with pyrrole-tethered ynones in which a range of substituted 5-hydroxy indole products were isolated in high yields. The benzannulation procedure was also extended to propargyl alcohol substrates with varying levels of success, and slight modification of the initial reaction conditions was required to access some indole frameworks. Insight into the mechanistic pathway was provided by DFT calculations; these studies suggest that the reactions proceed *via* initial nucleophilic attack through the pyrrole C-3 position, going against the generally accepted view that pyrroles are most nucleophilic through C-2. The C-2 annulated products are formed in the majority of cases, likely *via* ring-opening of a spirocyclic intermediate and re-closing through C-2 attack.

Chapter 5. Divergent reactivity of phenol- and anisole-tethered donor-acceptor α-diazocarbonyls

Chapter 6. Experimental

6.1 General experimental details

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2, toluene, acetonitrile 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. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.27 and δ_C 77.0 for $CDCl_3$, δ_H 2.50 and δ_C 39.5 for $(CD_3)_2SO$, δ_H 3.31 and δ_C 49.1 for CD_3OD, δ_H 2.05 and δ_C 29.8 for $(CD_3)_2CO$ were used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplets), tt (triplet of triplets), qt (quartet of triplets), m (multiplet). Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. 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 (high-resolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 µm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector. Numbering schemes on compounds refer to NMR assignments and not to compound naming.

6.2 *Preparation of supported catalysts*

Preparation of 1 wt.% $AgNO_3 \cdot SiO_2$ catalyst

Based on procedures reported by Smith and Li.[69,93] To a stirred slurry of Fluka silica gel (9.90 g, pore size 60 Å, 220–440 mesh particle size) in deionised water (27 mL) was added $AgNO_3$ (100 mg) and the resulting mixture was stirred vigorously for 15 min. The catalyst mixture was then concentrated *in vacuo* (water bath at 60 °C) to form free-flowing $AgNO_3 \cdot SiO_2$. The catalyst was then dried further by heating to 140 °C under a high vacuum for 4-5 h. After preparation, the catalyst was stored in the dark at RT

Preparation of 1 wt.% $AgNO_3$ on Celite catalyst

Based on a procedure reported by McKillop,[62] Celite was first purified by washing successively with MeOH containing 10% aq. HCl and then with distilled water until neutral pH was reached. The Celite was then dried by heating to 120 °C under a high vacuum for 1 h. To a stirred slurry of purified Celite (990 mg) in water (7.5 mL) was added $AgNO_3$ (10 mg) and the resulting mixture was stirred vigorously for 15 min. The catalyst mixture was then concentrated *in vacuo* (water bath at 60 °C) and then dried further by heating to 140 °C under a high vacuum for 4-5 h. After preparation the catalyst was stored in the dark at RT.

Preparation of 1 wt.% $AgNO_3$ on alumina catalyst

Based on a procedure reported by Smith,[93] $AgNO_3$ (10 mg) was added to a stirred slurry of alumina (990 mg) in water (3 mL) and the resulting mixture was stirred vigorously for 15 min. The catalyst mixture was then concentrated *in vacuo* (water bath at 60 °C) and then dried further by heating to 140 °C under a high vacuum for 4-5 h. After preparation the catalyst was stored in the dark at RT.

Preparation of 0.8 wt.% Ag_2CO_3 on Celite catalyst

Based on a procedure reported by McKillop,[62] Celite was purified by washing successively with MeOH containing 10% aq. HCl and then with distilled water until neutral pH was reached. The Celite was then dried by heating to 120 °C under a high vacuum for 1 h. To a stirred slurry of purified Celite (992 mg) in water (3 mL) was added Ag_2CO_3 (8 mg) and the resulting mixture was stirred vigorously for 15 min. The catalyst mixture was then concentrated/dried *in vacuo* (water bath at 55 °C) for 2 h. After preparation the catalyst was stored in the dark at RT.

6.3 ReactIR^{TM} studies

All ReactIR^{TM} experiments were performed using a Mettler Toledo ReactIR^{TM} spectrometer with a silicon probe and K6 conduit/R4 (mirror arm). IR spectra were taken in real-time every 60 seconds between 4000 and 649 cm^{-1}, with a spectral resolution of 4 cm^{-1}. The probe was fitted to a shallow glass boiling tube containing a magnetic stirrer bar to provide agitation and all reactions were performed under air at RT.

Procedure for ReactIR^{TM} experiment shown as dark blue line in Figures 4, 5 and 11

To a shallow boiling tube charged with a stirrer bar was added CH_2Cl_2 (3.9 mL). Ynone **136a** (100 mg, 0.386 mmol) was then added followed by the addition of 1 wt.% $AgNO_3 \cdot SiO_2$ (65.6 mg, 3.86 μmol) and the reaction mixture was stirred at RT for 1 h.

Procedure for ReactIR^{TM} experiment shown as purple line in Figures 4, 5, 6, 7 and 12

To a shallow boiling tube charged with a stirrer bar was added CH_2Cl_2 (3.9 mL). Ynone **136a** (100 mg, 0.386 mmol) was then added followed by the addition of $AgNO_3$ (0.66 mg, 3.86 μmol) and the reaction mixture was stirred at RT for 6 h.

Procedure for ReactIR^{TM} experiment shown as orange line in Figure 5

To a shallow boiling tube charged with a stirrer bar was added CH_2Cl_2 (3.9 mL). Ynone **136a** (100 mg, 0.386 mmol) was then added followed by the addition of $AgNO_3$ (0.66 mg, 3.86 μmol) and SiO_2 (65.6 mg) and the reaction mixture was stirred at RT for 3 h.

Procedure for ReactIR^{TM} experiment shown as grey line in Figures 6 and 13

To a shallow boiling tube charged with a stirrer bar and aged $AgNO_3$ (0.66 mg, 3.86 μmol) in CH_2Cl_2 (3.9 mL) was added ynone **136a** (100 mg, 0.386 mmol). The reaction mixture was stirred at RT for 3 h.

Note: Aged $AgNO_3$ was prepared by stirring $AgNO_3$ in CH_2Cl_2 for 24 h under air at RT.

Procedure for ReactIR^{TM} experiment shown as red line in Figure 7

To a shallow boiling tube charged with a stirrer bar was added CH_2Cl_2 (7.7 mL). Ynone **136a** (200 mg, 0.771 mmol) was then added followed by the addition of $AgNO_3$ (1.32 mg, 7.71 μmol) and the reaction mixture was stirred at RT for 2 h 40 min before the addition of Hg (22.8 μL, 1.54 mmol). The reaction mixture was stirred vigorously until cessation of the reaction was clearly observed.

Procedure for ReactIR™ experiment shown as light blue line in Figure 11

To a shallow boiling tube charged with a stirrer bar was added CH_2Cl_2 (3.9 mL). Ynone **136a** (100 mg, 0.386 mmol) was then added followed by the addition of $AgNO_3$ (0.66 mg, 3.86 μmol) and the reaction mixture was stirred at RT for 20 min.

Procedure for ReactIR™ experiment shown as pink line in Figures 12 and 13

To a shallow boiling tube charged with a stirrer bar was added CH_2Cl_2 (3.5 mL). Ynone **136a** (90 mg, 0.347 mmol) was then added followed by the addition of spirocyclic imine **137a** (45 mg, 0.174 mmol) and $AgNO_3$ (0.59 mg, 3.47 μmol) and the reaction mixture was stirred at RT for 3 h.

6.4 TEM imaging

Solid samples for TEM imaging were crushed between two glass slides and pressed onto 3 mm holey carbon coated copper grids (300 mesh) supplied by Agar Scientific. TEM images were obtained using a JEOL 2011 transmission electron microscope operated at 200 kV accelerating voltage. CCD images were extracted using Gatan Digital Micrograph software. Particle size distributions of nanoparticles were evaluated by averaging the diameter of > 30 particles from a TEM image.

6.5 ICP-MS analysis

Sample preparation: To a glass sample tube charged with a magnetic stirrer bar was added 10 mg of material to be analysed. 5 mL of HNO_3 (TraceSelect® HNO_3 99.999% trace metal basis, lot no. SHBF1444V, supplied by Sigma Aldrich) was then added and the mixture was heated to 110 °C for 3 h. A glass block was placed on top of the sample tube to avoid HNO_3 evaporation. After 3 h, the mixture was left to cool to RT and carefully poured into a 100 mL volumetric flask containing approx. 50 mL Milli-Q® water. Milli-Q® water was then added to make up a 100 mL solution for analysis.

Determination of the silver content in samples using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) was performed using an Agilent 7700x spectrometer and the analysis was run under helium. Each sample was run three times and the overall mean value of silver in ppm was obtained.

6.6 Flow chemistry

Flow reactions were performed using a Uniqsis FlowSyn™ platform fitted with a 7 bar back pressure regulator and PTFE flow paths were used. The $AgNO_3 \cdot SiO_2$ catalyst was packed into a 10 mm id x 100 mm OMNIFIT® column reactor and a flow rate of 0.3 mL/min was used.

Procedure for > 20g scale flow reaction

To a reagent vessel was added ynone **136a** (23.6 g, 91.0 mmol) and toluene (900 mL) which was stirred for 1 h to ensure all of the ynone had dissolved. The 1 wt.% $AgNO_3 \cdot SiO_2$ catalyst (1.93 g, 0.114 mmol) was packed inside the column reactor and toluene was flushed through the flow path before starting the reaction. The flow reaction was performed continuously over 51 h using a flow rate of 0.3 mL/min. All fractions from the flow reaction were combined and concentrated *in vacuo* to afford spirocycle **137a** (23.6 g, 100%).

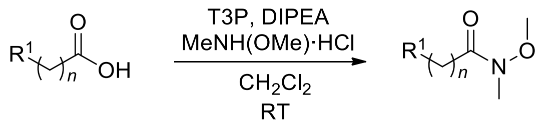
6.7 Computational chemistry

All calculations were performed using the TURBOMOLE V6.4 package using the resolution of identity (RI) approximation.[183–190]

Initial optimisations were performed at the (RI-)BP86/SV(P) level, followed by frequency calculations at the same level. Transition states were located by initially performing a constrained minimisation (by freezing internal coordinates that change most during the reaction) of a structure close to the anticipated transition state. This was followed by a frequency calculation to identify the transition vector to follow during a subsequent transition state optimisation. A final frequency calculation was then performed on the optimised transition-state structure. All minima were confirmed as such by the absence of imaginary frequencies and all transition states were identified by the presence of only one imaginary frequency. Dynamic Reaction Coordinate analysis confirmed that transition states were connected to the appropriate minima. Single-point calculations on the (RI-)BP86/SV(P) optimised geometries were performed using the hybrid PBE0 functional and the flexible def2-TZVPP basis set. The (RI-)PBE0/def2-TZVPP SCF energies were corrected for their zero point energies, thermal energies and entropies (obtained from the (RI-)BP86/SV(P)-level frequency calculations). A 28 electron quasi-relativistic ECP replaced the core electrons of Ag. No symmetry constraints were applied during optimisations. Solvent corrections were applied with the COSMO dielectric continuum model[191] and dispersion effects modelled with Grimme's D3 method.[192,193]

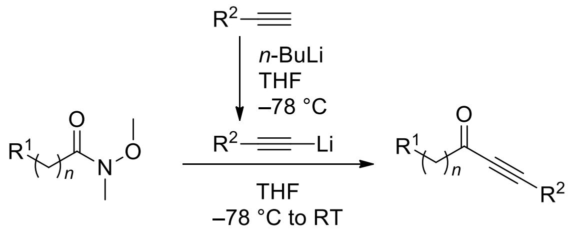
6.8 General procedures

General procedure A: Weinreb amide formation



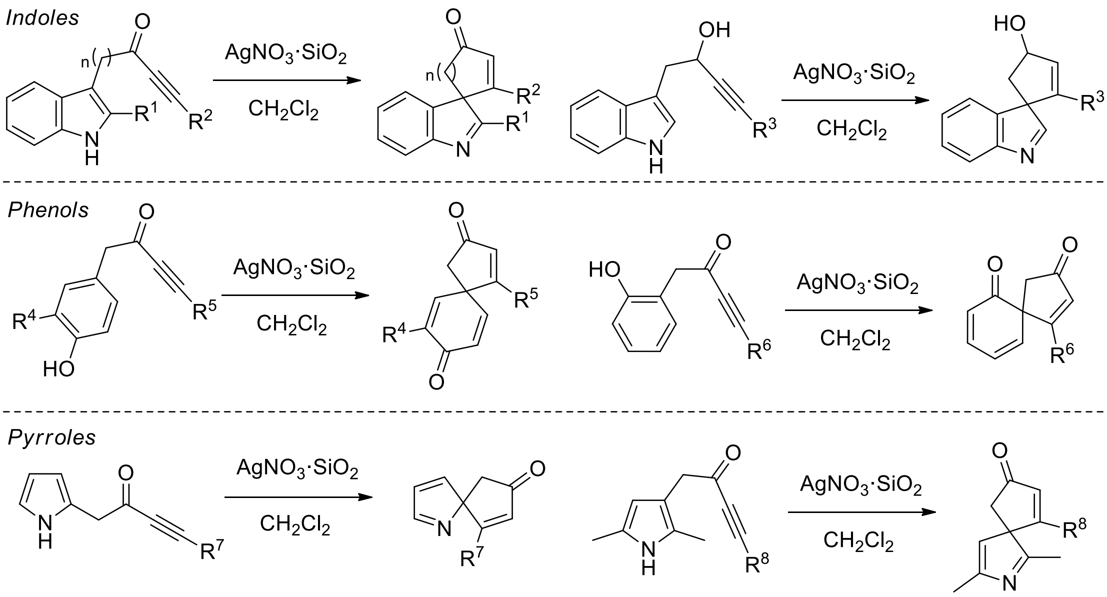
To a stirred solution of acid (1.00 mmol), MeNH(OMe)·HCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH_2Cl_2 (2.5 mL) was added T3P 50% in EtOAc (955 mg, 1.50 mmol). The solution was stirred at RT until completion was observed by TLC. The reaction mixture was poured into water (20 mL) and acidified using 10% aq. HCl (5 mL). The organics were collected and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with aq. 2 M NaOH (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the Weinreb amide product.

General procedure B: Ynone formation



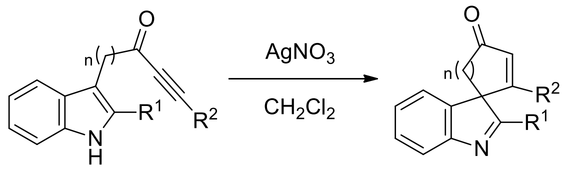
To a stirred solution of alkyne (48.0 mmol) in THF (48 mL) at −78 °C under argon was added *n*-BuLi (16.0 mL, 40.0 mmol, 2.5 M in hexanes) dropwise. The mixture was stirred for 30 min at −78 °C and then transferred *via* cannula to a −78 °C solution of Weinreb amide (16.0 mmol) in THF (80 mL). Upon complete transfer the mixture was warmed to RT and stirred for the specified amount of time. The reaction was quenched by the careful addition of sat. aq. NH_4Cl (100 mL). The organics were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organics were combined, washed with brine (100 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography to afford the ynone product.

General procedure C: Spirocyclisation using $AgNO_3 \cdot SiO_2$



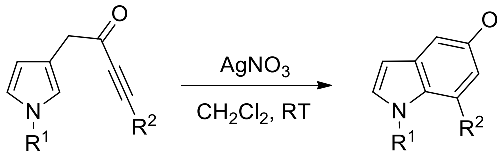
To a solution of ynone (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3 \cdot SiO_2$ (0.01–0.1 equiv., 1 wt.% $AgNO_3$ on SiO_2). The mixture was stirred at the specified temperature until completion was observed by TLC. The reaction mixture was filtered, washing the catalyst with EtOAc (10 mL), then concentrated *in vacuo* to afford the spirocyclic product.

General procedure D: Spirocyclisation using $AgNO_3$



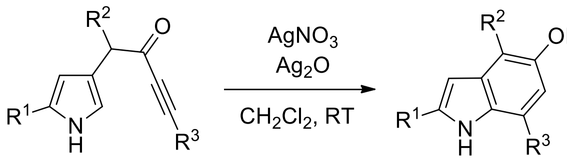
To a solution of ynone (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3$ (0.01–0.1 equiv.). The mixture was stirred at the specified temperature until completion was observed by TLC. The reaction mixture was concentrated *in vacuo* and then purified by column chromatography to afford the spirocyclic product.

General procedure E: Pyrrole annulation of ynones using $AgNO_3$



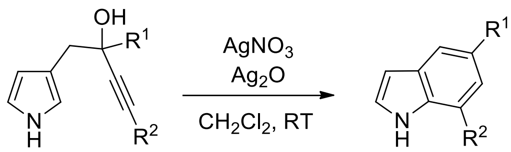
To a solution of ynone (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3$ (0.05–0.10 equiv.). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was concentrated *in vacuo* and then purified by column chromatography to afford the benzannulated product.

General procedure F: Pyrrole annulation of ynones using $AgNO_3$ and Ag_2O



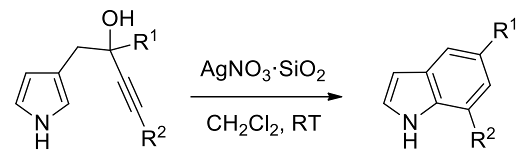
To a solution of ynone (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3$ (0.05–0.10 equiv.) and Ag_2O (0.025–0.05 equiv.). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was concentrated *in vacuo* and then purified by column chromatography to afford the benzannulated product.

General procedure G: Pyrrole annulation of propargyl alcohols using $AgNO_3$ and Ag_2O



To a solution of propargyl alcohol (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3$ (0.10 equiv.) and Ag_2O (0.05 equiv.). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was concentrated *in vacuo* and then purified by column chromatography to afford the benzannulated product.

General procedure H: Pyrrole annulation of propargyl alcohols using $AgNO_3 \cdot SiO_2$

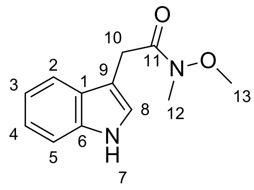


To a solution of propargyl alcohol (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3 \cdot SiO_2$ (0.10 equiv.). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was filtered, then concentrated *in vacuo* and then purified by column chromatography to afford the benzannulated product.

6.9 Reaction procedures and compound characterisation

6.9.1 Chapter 2

2-(1*H*-Indol-3-yl)-*N*-methoxy-*N*-methylacetamide (135a)



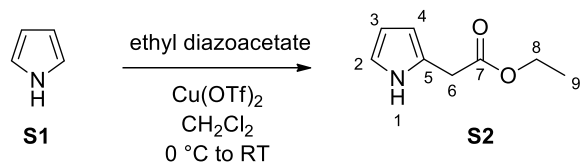
135a

Synthesised using general procedure A with indole-3-acetic acid **134a** (15.0 g, 85.6 mmol), T3P 50% in EtOAc (81.7 g, 128 mmol), DIPEA (44.7 mL, 257 mmol) and MeNH(OMe)·HCl (9.18 g, 94.1 mmol) in CH_2Cl_2 (214 mL) at RT for 1 h. Afforded the *title compound* **135a** without further purification as a pale brown solid (18.1 g, 97%); mp 122–124 °C; R_f 0.14 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3296, 2936, 1643, 1458, 1426, 1008, 743; δ_H (400 MHz, $CDCl_3$) 3.23 (3 H, s, H-12), 3.67 (3 H, s, H-13), 3.93 (2 H, s, H-10), 7.09–7.21 (3 H, m, H-3/4/8), 7.33 (1 H, d, *J* = 8.0 Hz, H-5), 7.67 (1 H, d, *J* = 8.0 Hz, H-2), 8.27 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 29.1 (C-10), 32.5 (C-12), 61.4 (C-13), 109.1 (C-9), 111.1 (C-5), 118.8 (C-2), 119.5 (C-3), 122.0 (C-4), 123.1 (C-8), 127.6 (C-1), 136.2 (C-6), 173.3 (C-11).

Lab notebook reference: akc01-67

Spectroscopic data matched those previously reported in the literature.[194]

Ethyl 2-(1*H*-pyrrol-2-yl)acetate (S2)



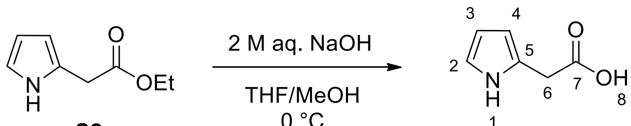
To a stirred solution of pyrrole **S1** (1.34 g, 20.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added ethyl diazoacetate (3.02 mL, 25.0 mmol, 87 wt.% in CH_2Cl_2) and $Cu(OTf)_2$ (362 mg, 1.00 mmol). The reaction mixture was then warmed to RT and stirred for 1 h. The reaction mixture was then quenched with water (100 mL). The organics were separated and the aqueous extracted with CH_2Cl_2 (2 x 100 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (20:1 hexane:EtOAc, then 10:1 hexane:EtOAc) to afford the *title compound* **S2** as a pale yellow oil

(836 mg, 27%); R_f 0.57 (1:1 hexane:EtOAc); ν_{max} (thin film)/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, H-9), 3.68 (2 H, s, H-6), 4.19 (2 H, q, J = 7.0 Hz, H-8), 6.02–6.05 (1 H, m, H-4), 6.14–6.18 (1 H, m, H-2/3), 6.76–6.79 (1 H, m, H-2/3), 8.76 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 14.1 (C-9), 33.2 (C-6), 61.1 (C-8), 107.2 (C-4), 108.2 (C-2/3), 117.7 (C-2/3), 123.3 (C-5), 171.2 (C-7).

Lab notebook reference: akc01-91

Spectroscopic data matched those previously reported in the literature.[195]

2-(1*H*-Pyrrol-2-yl)acetic acid (134e)

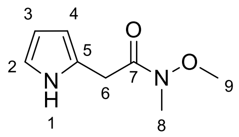


To a solution of ethyl 2-(1*H*-pyrrol-2-yl)acetate **S2** (804 mg, 5.25 mmol) in THF (37 mL) and MeOH (3.7 mL) at 0 °C was added 2 M aq. NaOH (30 mL) dropwise. The reaction mixture was warmed to RT and stirred for 1 h 20 min. Water (20 mL) was added and the aqueous layer was washed with EtOAc (20 mL). The organic extract was discarded. The aqueous layer was acidified with 10% aq. HCl (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* **134e** without further purification as an off white solid (621 mg, 95%); mp 77–79 °C; R_f 0.36 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3341, 3325, 3119, 2910, 1696, 1415, 1243, 1209, 745; δ_H (400 MHz, $CDCl_3$) 3.74 (2 H, s, H-6), 6.07–6.11 (1 H, m, H-4), 6.17–6.20 (1 H, m, H-2/3), 6.77–6.80 (1 H, m, H-2/3), 8.57 (1 H, br s, H-1), 10.67 (1 H, br s, H-8); δ_C (100 MHz, $CDCl_3$) 33.1 (C-6), 107.9 (C-4), 108.5 (C-2/3), 118.1 (C-2/3), 122.2 (C-5), 177.3 (C-7).

Lab notebook reference: akc01-92

Spectroscopic data matched those previously reported in the literature.[196]

N-Methoxy-N-methyl-2-(1H-pyrrol-2-yl)acetamide (135e)



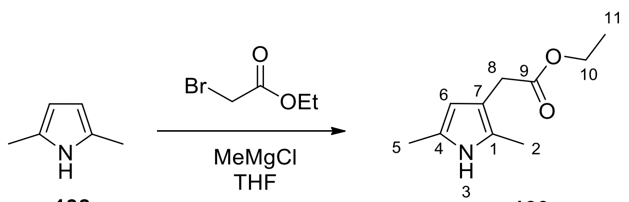
135e

Synthesised using general procedure A with 2-(1*H*-pyrrol-2-yl)acetic acid **134e** (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* **135e** without further purification as a pale brown solid (633 mg, 79%); mp 63–65 °C; R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/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 (C-6), 32.0 (C-8), 61.5 (C-9), 107.0 (C-4), 107.9 (C-2/3), 117.5 (C-2/3), 124.3 (C-5), 171.6 (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

Spectroscopic data matched those previously reported in the literature.[55]

Ethyl 2-(2,5-dimethyl-1H-pyrrol-3-yl)acetate (139)

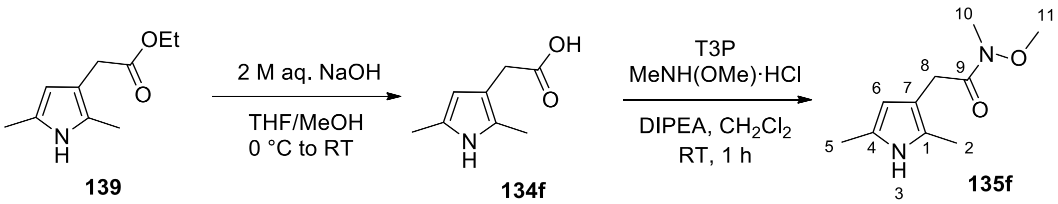


Procedure adapted from that of Schloemer *et al.*, *J. Org. Chem.*, 1994, **59**, 5230–5234.[197]

To a stirred solution of 2,5-dimethyl-1*H*-pyrrole **138** (4.50 g, 47.3 mmol) in THF (71 mL) at −15 °C was added methylmagnesium chloride (15.1 mL, 45.4 mmol, 3 M solution in THF). The cooling bath was removed, the solution was warmed to RT and stirred for 30 min. The solution was then cooled to −10 °C and ethyl bromoacatate was added quickly (2.09 mL, 18.9 mmol). The reaction mixture was then warmed to RT again and stirred for 1 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (70 mL) and the aqueous layer was extracted with diethyl ether (50 mL). The combined organics were washed with sat. aq. NH_4Cl (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by fractional distillation (bp 150–160 °C at 0.2 Torr) to afford the *title compound* **139** as a yellow oil (1.13 g, 33%); R_f 0.71 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3374, 2980, 2922, 1725, 1257, 1178, 1031, 783; δ_H (400 MHz, $CDCl_3$) 1.27 (3 H, t, *J* = 7.5 Hz, H-11), 2.18 (3 H, s, H-2), 2.21 (3 H, s, H-5), 3.36 (2 H, s, H-8), 4.14 (2 H, q, *J* = 7.5 Hz, H-10), 5.75–5.78 (1 H, m, H-6), 7.51 (1 H, br s, H-3); δ_C (100 MHz, $CDCl_3$) 11.0 (C-2), 12.9 (C-5), 14.2 (C-11), 32.2 (C-8), 60.5 (C-10), 107.2 (C-6), 111.3 (C-1/7), 123.3 (C-1/7), 125.3 (C-4), 172.7 (C-9); HRMS (ESI$^+$): Found: 204.0992; $C_{10}H_{15}NNaO_2$ (MNa^+) Requires 204.0995 (1.5 ppm error), Found: 182.1176; $C_{10}H_{16}NO_2$ (MH^+) Requires 182.1176 (−0.2 ppm error).

Lab notebook reference: akc05-30

2-(2,5-Dimethyl-1*H*-pyrrol-3-yl)-*N*-methoxy-*N*-methylacetamide (135f)



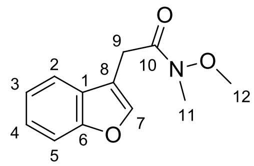
To a solution of ethyl 2-(2,5-dimethyl-1*H*-pyrrol-3-yl)acetate **139** (1.12 g, 6.18 mmol) in THF (43 mL) and MeOH (4.3 mL) at 0 °C was added 2 M aq. NaOH (34 mL). The reaction mixture was warmed to RT and stirred for 7 h. Water (30 mL) was added and the aqueous layer was washed with EtOAc (30 mL). The organic extract was discarded. The aqueous layer was acidified with 10% aq. HCl (30 mL) until pH = 1 and then extracted with EtOAc (2 x 30 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude pyrrole acid **134f** as a brown oil (1.01 g, 100%).

To a stirred solution of crude pyrrole acid **134f** (872 mg, 5.70 mmol), MeNH(OMe)·HCl (611 mg, 6.27 mmol) and DIPEA (2.98 mL, 17.1 mmol) in CH_2Cl_2 (28 mL) was added T3P 50% in EtOAc (5.44 g, 8.54 mmol). The solution was stirred at RT for 1.5 h. Water (15 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 20 mL). The organics were combined, washed with 10% aq. HCl (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **135f** without further purification as a brown oil (823 mg, 74%); R_f 0.49 (7:3 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3322, 2932, 1638, 1437, 1380, 1178, 1003, 787; δ_H (400 MHz, $CDCl_3$) 2.17–2.22 (6 H, m, H-2,5), 3.19 (3 H, s, H-10), 3.50 (2 H, s, H-8), 3.67 (3 H, s, H-11), 5.76 (1 H, s, H-6), 7.53 (1 H, br s, H-3); δ_C (100 MHz, $CDCl_3$) 11.0 (C-2), 12.9

(C-5), 30.1 (C-8), 32.2 (C-10), 61.1 (C-11), 107.2 (C-6), 111.8 (C-1/7), 123.2 (C-1/7), 125.2 (C-4), 173.6 (C-9); HRMS (ESI$^+$): Found: 219.1111; $C_{10}H_{16}N_2NaO_2$ (MNa^+) Requires 219.1104 (−3.4 ppm error), Found: 197.1286; $C_{10}H_{17}N_2O_2$ (MH^+) Requires 197.1285 (−0.7 ppm error).

Lab notebook reference: akc05-31/32

2-(Benzofuran-3-yl)-*N*-methoxy-*N*-methylacetamide (135g)



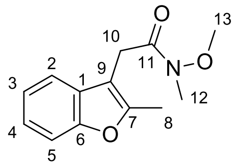
135g

Synthesised using general procedure A with 2-(benzofuran-3-yl)acetic acid **134g***[198] (514 mg, 2.92 mmol), T3P 50% in EtOAc (2.78 g, 4.38 mmol), DIPEA (1.52 mL, 8.75 mmol) and MeNH(OMe)·HCl (313 mg, 3.21 mmol) in CH_2Cl_2 (15 mL) at RT for 1.5 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **135g** as a yellow oil (622 mg, 97%); R_f 0.46 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1659, 1452, 1093, 1001, 742; δ_H (400 MHz, $CDCl_3$) 3.23 (3 H, s, H-11), 3.71 (3 H, s, H-12), 3.85 (2 H, s, H-9), 7.23–7.33 (2 H, m, H-3,4), 7.48 (1 H, d, *J* = 8.0 Hz, H-5), 7.63 (1 H, d, *J* = 8.0 Hz, H-2), 7.65 (1 H, s, H-7); δ_C (100 MHz, $CDCl_3$) 27.5 (C-9), 32.2 (C-11), 61.3 (C-12), 111.4 (C-5), 113.6 (C-8), 119.8 (C-2), 122.5 (C-3/4), 124.3 (C-3/4), 127.9 (C-1), 142.9 (C-7), 155.1 (C-6), 171.2 (C-10); HRMS (ESI$^+$): Found: 242.0795; $C_{12}H_{13}NNaO_3$ (MNa^+) Requires 242.0788 (−3.1 ppm error), Found: 220.0970; $C_{12}H_{14}NO_3$ (MH^+) Requires 220.0968 (−0.9 ppm error).

Lab notebook reference: akc03-29

*Material made by M. James

N-Methoxy-N-methyl-2-(2-methylbenzofuran-3-yl)acetamide (135h)



135h

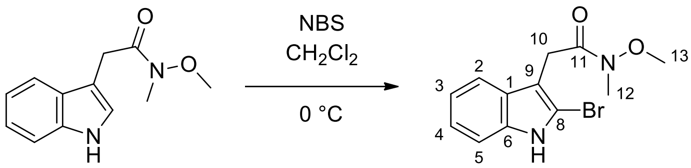
Synthesised using general procedure A with 2-(2-methylbenzofuran-3-yl)acetic acid **134h***[199] (872 mg, 4.58 mmol), T3P 50% in EtOAc (4.38 g, 6.88 mmol), DIPEA (2.39 mL, 13.8 mmol) and MeNH(OMe)·HCl (492 mg, 5.04 mmol) in CH_2Cl_2 (20 mL) at RT for 1 h. Purification by column chromatography (5:3 hexane:EtOAc) afforded the *title compound* **135h** as a pale yellow oil (698 mg, 65%); R_f 0.48 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2937, 1658, 1455, 1173, 1007, 743; δ_H (400 MHz, $CDCl_3$) 2.46 (3 H, s, H-8), 3.21 (3 H, s, H-12), 3.66 (3 H, s, H-13), 3.76 (2 H, s, H-10), 7.18–7.22 (2 H, m, H-2/3/4/5), 7.36–7.40 (1 H, m, H-2/3/4/5), 7.52–7.55 (1 H, m, H-2/3/4/5); δ_C (100 MHz, $CDCl_3$) 12.2 (C-8), 28.2 (C-10), 32.3 (C-12), 61.2 (C-13), 108.2 (C-9), 110.5 (C-2/3/4/5), 119.2 (C-2/3/4/5), 122.3 (C-2/3/4/5), 123.2 (C-2/3/4/5), 129.3 (C-1), 152.3 (C-7), 153.8 (C-6), 171.5 (C-11).

Lab notebook reference: akc03-20

*Material made by G. Coulthard

Spectroscopic data matched those previously reported in the literature.[55]

2-(2-Bromo-1H-indol-3-yl)-N-methoxy-N-methylacetamide (140)

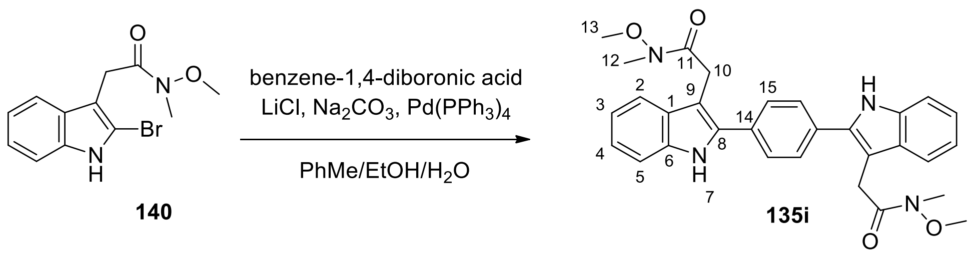


135a 7 **140**

Weinreb amide **135a** (1.00 g, 4.58 mmol) was stirred in CH_2Cl_2 (20 mL) at 0 °C and N-bromosuccinimide (815 mg, 4.58 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min. The crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the *title compound* **140** as a pale yellow solid (677 mg, 50%); mp 98–100 °C; R_f 0.49 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3244, 2935, 1641, 1450, 1425, 1338, 1176, 1002, 742; δ_H (400 MHz, $CDCl_3$) 3.23 (3 H, s, H-12), 3.68 (3 H, s, H-13), 3.89 (2 H, s, H-10), 7.07–7.16 (2 H, m, H-3,4), 7.17–7.22 (1 H, m, H-5), 7.61 (1 H, d, J = 7.5 Hz, H-2), 8.39 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 29.7 (C-10), 32.3 (C-12), 61.2 (C-13), 108.7 (C-9), 109.7 (C-8), 110.5 (C-5), 118.6 (C-2), 120.1 (C-3), 122.2 (C-4), 127.7 (C-1), 136.1 (C-6), 171.8 (C-11); HRMS (ESI$^+$): Found: 319.0038; $C_{12}H_{13}{}^{79}BrN_2NaO_2$ (MNa$^+$) Requires 319.0053 (4.7 ppm error), Found: 297.0227; $C_{12}H_{14}{}^{79}BrN_2O_2$ (MH$^+$) Requires 297.0233 (2.1 ppm error).

Lab notebook reference: akc02-82

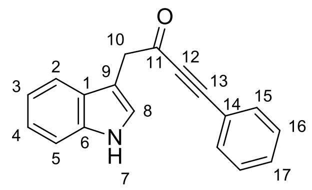
2,2'-(2,2'-(1,4-Phenylene)bis(1*H*-indole-3,2-diyl))bis(*N*-methoxy-*N*-methylacetamide) (135i)



To a dry two-neck flask was charged Weinreb amide **140** (670 mg, 2.25 mmol), benzene-1,4-diboronic acid (170 mg, 1.02 mmol), LiCl (174 mg, 4.10 mmol), Na_2CO_3 (541 mg, 5.10 mmol), toluene (5.6 mL), EtOH (5.6 mL) and water (3.4 mL). Argon was bubbled through the mixture for 10 min before the addition of $Pd(PPh_3)_4$ (118 mg, 0.102 mmol). The reaction mixture was then stirred overnight at 80 °C. The reaction mixture was cooled to RT and poured into water (20 mL), the aqueous was washed with EtOAc (2 x 20 mL). The organics were combined and extracted with water (10 mL) and brine (10 mL). All aqueous layers were combined and extracted with $CHCl_3$ (3 x 50 mL). (The organic product was soluble in the aqueous layer in this procedure.) The $CHCl_3$ layers were combined, washed with brine (20 mL) and concentrated *in vacuo* to afford the *title compound* **135i** without further purification as a yellow solid (240 mg, 46%); mp 227–229 °C; R_f 0.19 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3252, 2932, 1636, 1455, 1002, 731; δ_H (400 MHz, $(CD_3)_2SO$) 3.15 (6 H, s, H-12), 3.67 (6 H, s, H-13), 4.00 (4 H, s, H-10), 7.02 (2 H, dd, J = 8.0, 7.5 Hz, H-3/4), 7.13 (2 H, dd, J = 8.0, 7.5 Hz, H-3/4), 7.40 (2 H, d, J = 8.0 Hz, H-2/5), 7.52 (2 H, d, J = 8.0 Hz, H-2/5), 7.77 (4 H, s, H-15), 11.37 (2 H, s, H-7); δ_C (100 MHz, $(CD_3)_2SO$) 28.2 (C-10), 32.2 (C-12), 61.3 (C-13), 105.7 (C-1/9), 111.2 (C-2/5), 118.9 (C-2/5), 119.0 (C-3/4), 121.8 (C-3/4), 128.1 (C-15), 129.2 (C-1/9), 131.7 (C-14), 135.4 (C-8/9), 136.1 (C-1/6), 172.0 (C-11); HRMS (ESI$^+$): Found: 533.2136; $C_{30}H_{30}N_4NaO_4$ (MNa$^+$) Requires 533.2159 (4.4 ppm error).

Lab notebook reference: akc02-83

1-(1*H*-Indol-3-yl)-4-phenylbut-3-yn-2-one (136a)



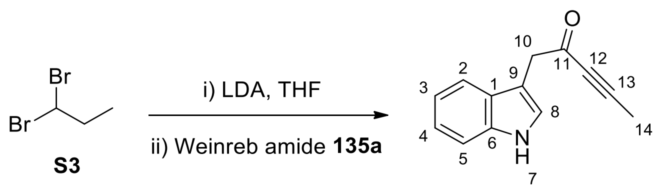
136a

Synthesised using general procedure B with phenylacetylene (22.6 mL, 0.206 mol), THF (550 mL), Weinreb amide **135a** (15.0 g, 68.7 mmol) and *n*-BuLi (68.7 mL, 0.172 mol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 5:1 hexane:EtOAc) afforded the *title compound* **136a** as a brown solid (17.3 g, 97%); mp 90–92 °C; R_f 0.54 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3409, 2208, 1666, 1083, 743; δ_H (400 MHz, $CDCl_3$) 4.10 (2 H, s, H-10), 7.15–7.21 (1 H, m, H-3), 7.21–7.28 (2 H, m, H-4,8), 7.29–7.45 (6 H, m, H-5,15,16,17), 7.69 (1 H, br d, *J* = 7.5 Hz, H-2), 8.18 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 42.0 (C-10), 88.0 (C-12), 92.1 (C-13), 107.6 (C-9), 111.3 (C-5), 118.9 (C-2), 119.8 (C-3), 119.9 (C-14), 122.3 (C-4), 123.7 (C-8), 127.4 (C-1), 128.5 (C-15/16), 130.6 (C-17), 133.1 (C-15/16), 136.1 (C-6), 185.7 (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: akc02-13/akc03-09

Spectroscopic data matched those previously reported in the literature.[55]

1-(1*H*-Indol-3-yl)pent-3-yn-2-one (136b)



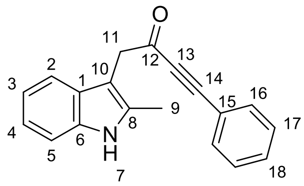
136b

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 **S3** (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 −78 °C solution of Weinreb amide **135a** (500 mg, 2.29 mmol) in THF (33 mL). Upon complete transfer the reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL). The organics were separated and the aqueous extracted with EtOAc (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ 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* **136b** as an orange oil (398 mg, 88%); R_f 0.52 (3:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3406, 2215, 1661, 1457, 1244, 1168, 742; δ_H (400 MHz, $CDCl_3$) 1.96 (3 H, s, H-14), 3.99 (2 H, s, H-10), 7.12–7.15 (2 H, m, H-3,8), 7.19–7.25 (1 H, m, H-4), 7.38 (1 H, d, *J* = 8.0 Hz, H-5), 7.61 (1 H, d, *J* = 8.0 Hz, H-2), 8.17 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 4.1 (C-14), 42.0 (C-10), 80.2 (C-12), 91.3 (C-13), 107.3 (C-9), 111.3 (C-5), 118.7 (C-2), 119.6 (C-3), 122.1 (C-4), 123.6 (C-8), 127.2 (C-1), 136.0 (C-6), 185.7 (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: akc02-65

Spectroscopic data matched those previously reported in the literature.[55]

1-(2-Methyl-1H-indol-3-yl)-4-phenylbut-3-yn-2-one (136c)



136c

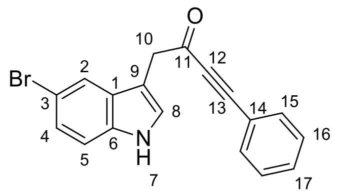
Synthesised using general procedure B with phenylacetylene (0.43 mL, 3.87 mmol), THF (10 mL), *N*-methoxy-*N*-methyl-2-(2-methyl-1*H*-indol-3-yl)acetamide **135b***[55] (300 mg, 1.29 mmol) and *n*-BuLi (1.29 mL, 3.23 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **136c** as a yellow solid (310 mg, 88%); mp 102–104 °C; R_f 0.60 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3398, 2202, 1660, 1462, 1302, 1117, 1093, 742; δ_H (400 MHz, $CDCl_3$) 2.47 (3 H, s, H-9), 4.00 (2 H, s, H-11), 7.11–7.19 (2 H, m, Ar-H), 7.28–7.34 (5 H, m, Ar-H), 7.37–7.43 (1 H, m, Ar-H), 7.59–7.62 (1 H, m, Ar-H), 7.96 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 11.8 (C-9), 41.1 (C-11), 88.0 (C-13), 91.6 (C-14), 103.4 (C-10), 110.4 (C-5), 118.1 (C-2), 119.7 (C-3/4), 119.9 (C-15), 121.3 (C-3/4), 128.4 (C-16/17), 128.6 (C-1), 130.5 (C-18), 133.0 (C-16/17), 133.5 (C-8), 135.5 (C-6), 185.3 (C-12); HRMS (ESI$^+$): Found:

296.1036; $C_{19}H_{15}NNaO$ (MNa^+) Requires 296.1046 (3.4 ppm error), Found: 274.1227; $C_{19}H_{16}NO$ (MH^+) Requires 274.1226 (−0.4 ppm error).

Lab notebook reference: akc01-53

*Material made by M. James

1-(5-Bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (136d)



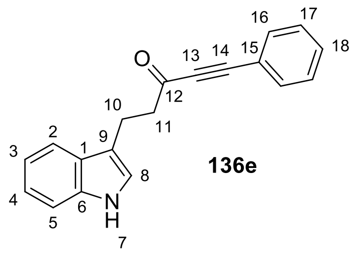
136d

Synthesised using general procedure B with phenylacetylene (0.16 mL, 1.46 mmol), THF (3.9 mL), 2-(5-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **135c***[55] (145 mg, 0.488 mmol) and *n*-BuLi (0.49 mL, 1.22 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **136d** as an orange solid (85.2 mg, 51%); mp 124–126 °C; R_f 0.44 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3419, 2201, 1660, 1489, 1458, 1284, 1096, 791, 757, 687; δ_H (400 MHz, $CDCl_3$) 4.06 (2 H, s, H-10), 7.19–7.22 (1 H, d, *J* = 2.5 Hz, H-8), 7.25 (1 H, d, *J* = 8.5 Hz, H-5), 7.31 (1 H, dd, *J* = 8.5, 2.0 Hz, H-4), 7.32–7.38 (2 H, m, H-15/16), 7.41–7.47 (3 H, m, H-15/16,17), 7.83 (1 H, d, *J* = 2.0 Hz, H-2), 8.30 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 41.8 (C-10), 87.9 (C-12), 92.4 (C-13), 107.3 (C-9), 112.8 (C-5), 113.2 (C-3), 119.7 (C-14), 121.6 (C-2), 124.9 (C-8), 125.2 (C-4), 128.6 (C-15/16), 129.1 (C-1), 130.8 (C-17), 133.1 (C-15/16), 134.7 (C-6), 185.1 (C-11); HRMS (ESI^+): Found: 359.9984; $C_{18}H_{12}{}^{79}BrNNaO$ (MNa^+) Requires 359.9994 (2.8 ppm error).

Lab notebook reference: akc01-63

*Material made by M. James

5-(1*H*-Indol-3-yl)-1-phenylpent-1-yn-3-one (136e)



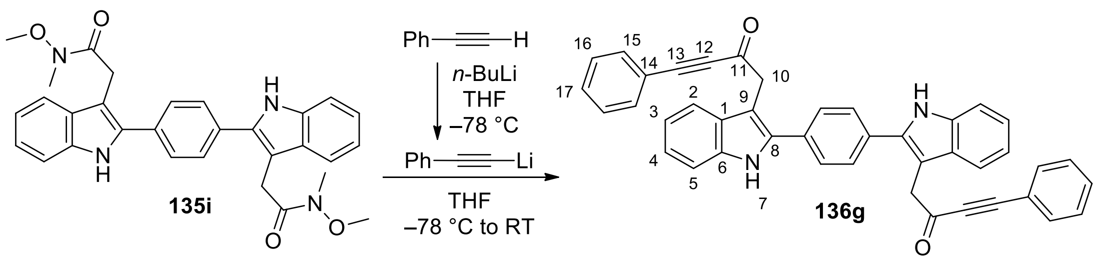
136e

Synthesised using general procedure B with phenylacetylene (0.71 mL, 6.46 mmol), THF (17.3 mL), 3-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methylpropanamide **135d***[55] (500 mg, 2.15 mmol) and *n*-BuLi (2.15 mL, 5.38 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **136e** as a pale yellow solid (491 mg, 84%); mp 74–76 °C; R_f 0.62 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3413, 3057, 2202, 1661, 1489, 1457, 1095, 758, 742; δ_H (400 MHz, $CDCl_3$) 3.08–3.15 (2 H, m, H-11), 3.21–3.28 (2 H, m, H-10), 7.03–7.07 (1 H, m, H-8), 7.13–7.19 (1 H, m, H-3), 7.20–7.26 (1 H, m, H-4), 7.35–7.42 (3 H, m, H-5,16/17), 7.43–7.50 (1 H, m, H-18), 7.52–7.58 (2 H, m, H-16/17), 7.66 (1 H, d, *J* = 8.0 Hz, H-2), 8.01 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 19.7 (C-10), 45.9 (C-11), 87.8 (C-13), 91.1 (C-14), 111.2 (C-5), 114.6 (C-9), 118.6 (C-2), 119.3 (C-3), 119.9 (C-15), 121.6 (C-8), 122.1 (C-4), 127.1 (C-1), 128.6 (C-16/17), 130.7 (C-18), 133.0 (C-16/17), 136.3 (C-6), 187.7 (C-12); HRMS (ESI^+): Found: 296.1053; $C_{19}H_{15}NNaO$ (MNa^+) Requires 296.1046 (−2.4 ppm error).

Lab notebook reference: akc01-76

*Material made by M. James

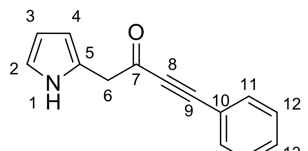
1,1'-(2,2'-(1,4-Phenylene)bis(1*H*-indole-3,2-diyl))bis(4-phenylbut-3-yn-2-one) (136g)



To a stirred solution of phenylacetylene (0.13 mL, 1.18 mmol) in THF (1.8 mL) at −78 °C under argon was added *n*-BuLi (0.39 mL, 0.979 mmol, 2.5 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 **135i** (100 mg, 0.196 mmol) in THF (2 mL). Upon complete transfer the mixture was warmed to RT and stirred for 1 hr. The reaction was quenched by the careful addition of sat. aq. NH_4Cl (10 mL). The organics were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 6:4 hexane:EtOAc) to afford the *title compound* **136g** as a yellow solid (43.4 mg, 37%); mp 196–198 °C; R_f 0.66 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3438, 2199, 1668, 1457, 1279, 1190, 1090, 847, 767, 752, 689; δ_H (400 MHz, $(CD_3)_2SO$) 4.29 (4 H, s, H-10), 7.09 (2 H, dd, *J* = 8.0, 7.5 Hz, H-3), 7.19 (2 H, dd, *J* = 7.5, 7.0 Hz, H-4), 7.30–7.35 (4 H, m, H-15), 7.35–7.41 (4 H, dd, *J* = 8.0, 8.0 Hz, H-16), 7.43–7.51 (4 H, m, H-5,17), 7.68 (2 H, d, *J* = 8.0 Hz, H-2), 7.88 (4 H, s, H-19), 11.60 (2 H, s, H-7); δ_C (100 MHz, $(CD_3)_2SO$) 41.6 (C-10), 88.1 (C-12), 91.1 (C-13), 103.8 (C-9), 111.4 (C-5), 118.9 (C-14), 119.0 (C-2), 119.4 (C-3), 122.2 (C-4), 128.0 (C-19), 129.0 (C-16), 129.1 (C-1), 131.3 (C-17), 131.5 (C-18), 132.8 (C-15), 135.7 (C-8), 136.2 (C-6), 185.2 (C-11); HRMS (ESI$^+$): Found: 615.2019; $C_{42}H_{28}N_2NaO_2$ (MNa$^+$) Requires 615.2043 (3.9 ppm error).

Lab notebook reference: akc02-84

4-Phenyl-1-(1*H*-pyrrol-2-yl)but-3-yn-2-one (136h)

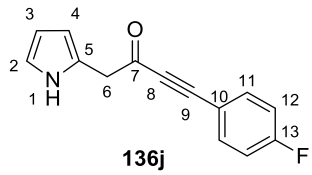


136h

Synthesised using general procedure B with phenylacetylene (0.98 mL, 8.92 mmol), THF (24 mL), Weinreb amide **135e** (500 mg, 2.97 mmol) and *n*-BuLi (2.97 mL, 7.43 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the *title compound* **136h** as a black solid (387 mg, 62%); mp 75–77 °C; R_f 0.62 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3354, 2203, 1667, 1444, 1282, 1091, 725, 690; δ_H (400 MHz, $CDCl_3$) 4.02 (2 H, s, H-6), 6.12–6.16 (1 H, m, H-2/3/4), 6.19–6.24 (1 H, m, H-2/3/4), 6.79–6.83 (1 H, m, H-2/3/4), 7.36–7.42 (2 H, m, H-12), 7.45–7.51 (1 H, m, H-13), 7.53–7.58 (2 H, m, H-11), 8.60 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 43.8 (C-6), 87.6 (C-8), 92.9 (C-9), 108.3 (C-4), 108.6 (C-2/3), 118.2 (C-2/3), 119.6 (C-10), 122.7 (C-5), 128.6 (C-11/12), 131.0 (C-11/12), 133.2 (C-13), 184.7 (C-7); HRMS (ESI$^+$): Found: 232.0736; $C_{14}H_{11}NNaO$ (MNa$^+$) Requires 232.0733 (−1.2 ppm error), Found: 210.0912; $C_{14}H_{12}NO$ (MH$^+$) Requires 210.0913 (0.7 ppm error).

Lab notebook reference: akc01-56

4-(4-Fluorophenyl)-1-(1*H*-pyrrol-2-yl)but-3-yn-2-one (136j)

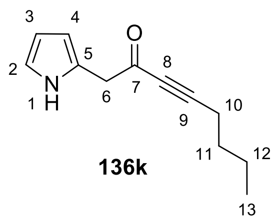


136j

Synthesised using general procedure B with 1-ethynyl-4-fluorobenzene (602 mg, 5.01 mmol), THF (13 mL), Weinreb amide **135e** (280 mg, 1.67 mmol) and *n*-BuLi (1.67 mL, 4.18 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **136j** as a brown solid (206 mg, 54%); mp 72–74 °C; R_f 0.43 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3360, 2205, 1668, 1598, 1506, 1095, 843, 725; δ_H (400 MHz, $CDCl_3$) 4.01 (2 H, s, H-6), 6.12–6.15 (1 H, m, H-2/3/4), 6.21 (1 H, dd, *J* = 6.0, 2.5 Hz, H-2/3/4), 6.79–6.83 (1 H, m, H-2/3/4), 7.09 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-12), 7.54 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HF}$ = 5.0 Hz, H-11), 8.58 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 43.7 (C-6), 87.5 (C-8), 91.9 (C-9), 108.3 (C-2/3/4), 108.6 (C-2/3/4), 115.7 (d, $^4J_{CF}$ = 3.0 Hz, C-10), 116.2 (d, $^2J_{CF}$ = 23.0 Hz, C-12), 118.3 (C-2/3/4), 122.6 (C-5), 135.5 (d, $^3J_{CF}$ = 10.0 Hz, C-11), 164.1 (d, $^1J_{CF}$ = 254 Hz, C-13), 184.6 (C-7); HRMS (ESI$^+$): Found: 250.0638; $C_{14}H_{10}FNNaO$ (MNa^+) Requires 250.0639 (0.2 ppm error).

Lab notebook reference: akc04-93

1-(1*H*-Pyrrol-2-yl)oct-3-yn-2-one (136k)

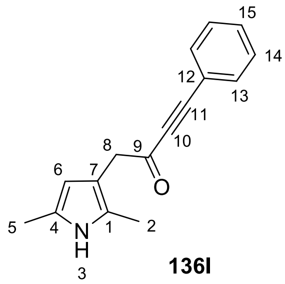


136k

Synthesised using general procedure B with with hex-1-yne (1.02 mL, 8.92 mmol), THF (24 mL), Weinreb amide **135e** (500 mg, 2.97 mmol) and *n*-BuLi (2.97 mL, 7.43 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the *title compound* **136k** as a brown oil (329 mg, 59%); R_f 0.61 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3386, 2959, 2933, 2873, 2211, 1666, 1237, 718; δ_H (400 MHz, $CDCl_3$) 0.94 (3 H, t, *J* = 7.5 Hz, H-13), 1.42 (2 H, app. sextet, *J* = 7.5 Hz, H-12), 1.56 (2 H, app. pentet, *J* = 7.5 Hz, H-11), 2.38 (2 H, t, *J* = 7.5 Hz, H-10), 3.89 (2 H, s, H-6), 6.02–6.05 (1 H, m, H-2/3/4), 6.17 (1 H, dd, *J* = 5.5, 3.0 Hz, H-2/3/4), 6.73–6.76 (1 H, m, H-2/3/4), 8.59 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 13.4 (C-13), 18.7 (C-10), 21.9 (C-12), 29.6 (C-11), 43.8 (C-6), 80.7 (C-8), 96.6 (C-9), 107.9 (C-2/3/4), 108.4 (C-2/3/4), 118.0 (C-2/3/4), 122.8 (C-5), 184.8 (C-7); HRMS (ESI$^+$): Found: 212.1051; $C_{12}H_{15}NNaO$ (MNa^+) Requires 212.1046 (−2.6 ppm error), Found: 190.1221; $C_{12}H_{16}NO$ (MH^+) Requires 190.1226 (2.9 ppm error).

Lab notebook reference: akc05-05

1-(2,5-Dimethyl-1*H*-pyrrol-3-yl)-4-phenylbut-3-yn-2-one (136l)

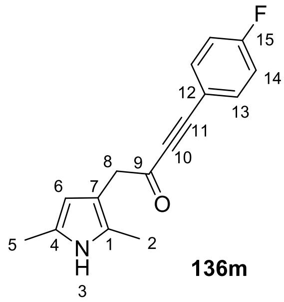


136l

Synthesised using general procedure B with phenylacetylene (0.42 mL, 3.82 mmol), THF (10 mL), Weinreb amide **135f** (250 mg, 1.27 mmol) and *n*-BuLi (1.27 mL, 3.18 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 2:1 hexane:EtOAc) afforded the *title compound* **136l** as a yellow oil (164 mg, 54%); R_f 0.83 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3370, 2918, 2203, 1659, 1489, 1288, 1071, 758, 689; δ_H (400 MHz, $CDCl_3$) 2.22 (3 H, s, H-2), 2.23 (3 H, s, H-5), 3.69 (2 H, s, H-8), 5.78–5.81 (1 H, m, H-6), 7.35–7.41 (2 H, m, H-13/14), 7.42–7.47 (1 H, m, H-15), 7.51–7.55 (2 H, m, H-13/14), 7.60 (1 H, br s, H-3); δ_C (100 MHz, $CDCl_3$) 11.1 (C-2), 12.9 (C-5), 43.2 (C-8), 88.2 (C-10), 91.1 (C-11), 107.6 (C-6), 110.1 (C), 120.3 (C), 124.2 (C), 125.7 (C), 128.5 (C-13/14), 130.5 (C-15), 133.0 (C-13/14), 186.2 (C-9); HRMS (ESI$^+$): Found: 260.1044; $C_{16}H_{15}NNaO$ (MNa^+) Requires 260.1046 (0.8 ppm error), Found: 238.1219; $C_{16}H_{16}NO$ (MH^+) Requires 238.1226 (3.0 ppm error).

Lab notebook reference: akc05-33

1-(2,5-Dimethyl-1*H*-pyrrol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one (136m)

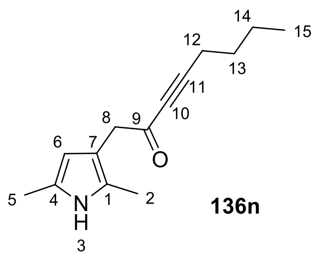


136m

Synthesised using general procedure B with 1-ethynyl-4-fluorobenzene (450 mg, 3.75 mmol), THF (10 mL), Weinreb amide **135f** (245 mg, 1.25 mmol) and *n*-BuLi (1.25 mL, 3.13 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **136m** as a yellow oil (178 mg, 56%); R_f 0.57 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3369, 2919, 2203, 1656, 1599, 1505, 1224, 1066, 837; δ_H (400 MHz, $CDCl_3$) 2.22 (3 H, s, H-2), 2.23 (3 H, s, H-5), 3.69 (2 H, s, H-8), 5.78–5.81 (1 H, m, H-6), 7.07 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-14), 7.49–7.55 (2 H, m, H-13), 7.68 (1 H, br s, H-3); δ_C (100 MHz, $CDCl_3$) 11.0 (C-2), 12.9 (C-5), 43.1 (C-8), 88.0 (C-10), 90.1 (C-11), 107.5 (C-6), 110.0 (C-1/7), 116.0 (d, $^2J_{CF}$ = 23.0 Hz, C-14), 116.3 (d, $^4J_{CF}$ = 4.0 Hz, C-12), 124.2 (C-1/7), 125.7 (C-4), 135.2 (d, $^3J_{CF}$ = 8.5 Hz, C-13), 163.8 (d, $^1J_{CF}$ = 253 Hz, C-15), 186.1 (C-9); HRMS (ESI^+): Found: 278.0944; $C_{16}H_{14}FNNaO$ (MNa^+) Requires 278.0952 (2.7 ppm error), Found: 256.1127; $C_{16}H_{15}FNO$ (MH^+) Requires 256.1132 (2.2 ppm error).

Lab notebook reference: akc05-42

1-(2,5-Dimethyl-1*H*-pyrrol-3-yl)oct-3-yn-2-one (136n)

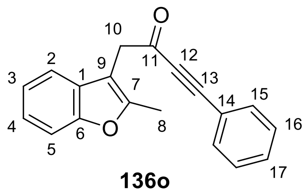


136n

Synthesised using general procedure B with with hex-1-yne (0.40 mL, 3.45 mmol), THF (9 mL), Weinreb amide **135f** (226 mg, 1.15 mmol) and *n*-BuLi (1.15 mL, 2.88 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **136n** as a yellow oil (123 mg, 49%); R_f 0.62 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3372, 2958, 2931, 2872, 2211, 1658, 1243, 1171, 781; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, t, *J* = 7.5 Hz, H-15), 1.41 (2 H, app. sextet, *J* = 7.5 Hz, H-14), 1.54 (2 H, app. pentet, *J* = 7.5 Hz, H-13), 2.17 (3 H, s, H-2), 2.21 (3 H, s, H-5), 2.35 (2 H, t, *J* = 7.5 Hz, H-12), 3.57 (2 H, s, H-8), 5.71–5.74 (1 H, m, H-6), 7.70 (1 H, br s, H-3); δ_C (100 MHz, $CDCl_3$) 10.9 (C-2), 12.8 (C-5), 13.4 (C-15), 18.6 (C-12), 21.8 (C-14), 29.6 (C-13), 43.2 (C-8), 81.0 (C-10), 94.7 (C-11), 107.3 (C-6), 110.1 (C-1/7), 123.9 (C-1/7), 125.4 (C-4), 186.5 (C-9); HRMS (ESI^+): Found: 240.1359; $C_{14}H_{19}NNaO$ (MNa^+) Requires 240.1359 (−0.2 ppm error), Found: 218.1539; $C_{14}H_{20}NO$ (MH^+) Requires 218.1539 (0.1 ppm error).

Lab notebook reference: akc05-38

1-(2-Methylbenzofuran-3-yl)-4-phenylbut-3-yn-2-one (136o)

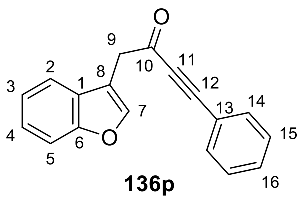


136o

Synthesised using general procedure B with phenylacetylene (0.87 mL, 7.92 mmol), THF (20 mL), Weinreb amide **135h** (616 mg, 2.64 mmol) and *n*-BuLi (2.64 mL, 6.60 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (10:1 hexane:EtOAc, then 8:1 hexane:EtOAc) afforded the *title compound* **136o** as a yellow solid (499 mg, 69%); mp 34–36 °C; R_f 0.29 (10:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3062, 2921, 2202, 1669, 1456, 1282, 1251, 1174, 1113, 1078, 746; δ_H (400 MHz, $CDCl_3$) 2.50 (3 H, s, H-8), 3.92 (2 H, s, H-10), 7.21–7.29 (2 H, m, H-2/3/4/5), 7.30–7.38 (4 H, m, H-15,16), 7.41–7.46 (2 H, m, H-2/3/4/5,17), 7.50–7.54 (1 H, m, H-2/3/4/5); δ_C (100 MHz, $CDCl_3$) 12.2 (C-8), 40.4 (C-10), 87.7 (C-12), 92.4 (C-13), 107.1 (C-9), 110.7 (C-2/3/4/5), 118.9 (C-2/3/4/5), 119.6 (C-14), 122.5 (C-2/3/4/5), 123.5 (C-2/3/4/5), 128.6 (C-15/16), 129.1 (C-1), 130.8 (C-17), 133.1 (C-15/16), 153.3 (C-7), 154.0 (C-6), 184.0 (C-11); HRMS (ESI^+): Found: 297.0882; $C_{19}H_{14}NaO_2$ (MNa^+) Requires 297.0886 (1.5 ppm error), Found: 275.1074; $C_{19}H_{15}O_2$ (MH^+) Requires 275.1067 (−2.8 ppm error).

Lab notebook reference: akc03-21

1-(Benzofuran-3-yl)-4-phenylbut-3-yn-2-one (136p)

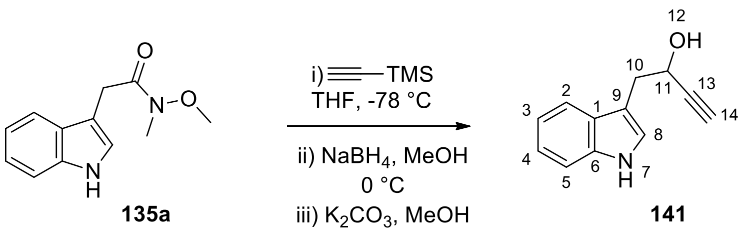


136p

Synthesised using general procedure B with phenylacetylene (0.81 mL, 7.35 mmol), THF (20 mL), Weinreb amide **135g** (537 mg, 2.45 mmol) and *n*-BuLi (2.45 mL, 6.12 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **136p** as a yellow oil (201 mg, 32%); R_f 0.49 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2202, 1669, 1453, 1097, 1081, 746; δ_H (400 MHz, $CDCl_3$) 4.04 (2 H, s, H-9), 7.27–7.31 (1 H, m, H-3), 7.32–7.39 (3 H, m, H-4,14/15), 7.40–7.47 (3 H, m, H-14/15,16), 7.53 (1 H, d, *J* = 8.0 Hz, H-5), 7.61 (1 H, d, *J* = 8.0 Hz, H-2), 7.71 (1 H, s, H-7); δ_C (100 MHz, $CDCl_3$) 40.2 (C-9), 87.6 (C-11), 92.6 (C-12), 111.6 (C-5), 112.5 (C-8), 119.6 (C-13), 119.7 (C-2), 122.8 (C-3), 124.6 (C-4), 127.7 (C-1), 128.6 (C-14/15), 130.9 (C-16), 133.1 (C-14/15), 143.4 (C-7), 155.2 (C-6), 183.8 (C-10); HRMS (ESI$^+$): Found: 283.0721; $C_{18}H_{12}NaO_2$ (MNa^+) Requires 283.0730 (2.9 ppm error), Found: 261.0898; $C_{18}H_{13}O_2$ (MH^+) Requires 261.0910 (4.6 ppm error).

Lab notebook reference: akc03-30

1-(1*H*-Indol-3-yl)but-3-yn-2-ol (141)



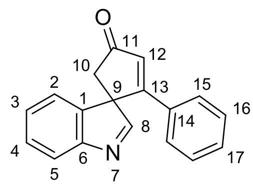
135a **141**

To a stirred solution of TMS acetylene (0.98 mL, 6.87 mmol) in THF (20 mL) at −78 °C under argon was added *n*-BuLi (2.29 mL, 5.73 mmol, 2.5 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 **135a** (500 mg, 2.29 mmol) in THF (11 mL). Upon complete transfer the mixture was warmed to RT and stirred for 40 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL). The organics were separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then dissolved in MeOH (45 mL), cooled to 0 °C and $NaBH_4$ (347 mg, 9.16 mmol) was added portionwise. The mixture was stirred for 30 min at RT and then K_2CO_3 (633 mg, 4.58 mmol) was added. The mixture was stirred for a further 6 h at RT. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL) and diluted with CH_2Cl_2 (50 mL).The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (7:3 hexane:EtOAc, then 3:2 hexane:EtOAc) to afford the *title compound* **141** as a brown oil (338 mg, 80%); R_f 0.21 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3409, 3282, 1457, 1027, 1010, 743, 649; δ_H (400 MHz, $CDCl_3$) 2.09 (1 H, br d, *J* = 5.5 Hz, H-12), 2.48 (1 H, d, *J* = 2.5 Hz, H-14), 3.19 (1 H, dd, *J* = 14.5, 7.0 Hz, H-10a), 3.28 (1 H, dd, *J* = 14.5, 5.5 Hz, H-10b), 4.65–4.72 (1 H, m, H-11), 7.13–7.19 (2 H, m, H-3,8), 7.23 (1 H, ddd, *J* = 8.0, 7.5, 1.0 Hz, H-4), 7.39 (1 H, br d, *J* = 8.0 Hz, H-5), 7.69 (1 H, br d, *J* = 8.0 Hz, H-2), 8.13 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 33.8 (C-10), 62.2 (C-11), 73.1 (C-14), 84.7 (C-13), 110.3 (C-9), 111.2 (C-5), 118.9 (C-2), 119.6 (C-3), 122.2 (C-4), 123.4 (C-8), 127.5 (C-1), 136.2 (C-6); HRMS (ESI$^+$): Found: 208.0730; $C_{12}H_{11}NNaO$ (MNa^+) Requires 208.0733 (1.5 ppm error).

Lab notebook reference: akc03-11

Spectroscopic data matched those previously reported in the literature.[94]

2-Phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one (137a)



137a

Method 1. Synthesised using general procedure C with ynone **136a** (100 mg, 0.386 mmol), $AgNO_3 \cdot SiO_2$ (65.5 mg, 3.86 μmol) in CH_2Cl_2 (3.9 mL) at RT for 30 min. Afforded the *title compound* **137a** without further purification as a brown solid (98.2 mg, 98%).

Lab notebook reference: akc02-30

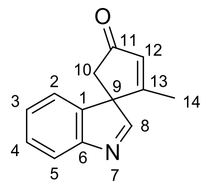
Method 2. Synthesised using general procedure D with ynone **136a** (100 mg, 0.386 mmol), $AgNO_3$ (0.66 mg, 3.86 μmol) in CH_2Cl_2 (3.9 mL) at RT for 6 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **137a** as a brown solid (94.4 mg, 94%).

Lab notebook reference: akc02-34

mp 138–140 °C; R_f 0.31 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3068, 1701, 1591, 757; δ_H (400 MHz, $CDCl_3$) 2.69 (1 H, d, J = 19.0 Hz, H-10a), 3.06 (1 H, d, J = 19.0 Hz, H-10b), 6.85 (1 H, s, H-12), 6.96–7.01 (2 H, m, H-15), 7.16–7.23 (2 H, m, H-16), 7.24–7.34 (3 H, m, H-2,3,17); 7.46 (1 H, ddd, J = 8.0, 7.5, 1.5 Hz, H-4), 7.78 (1 H, d, J = 8.0 Hz, H-5), 8.22 (1 H, s, H-8); δ_C (100 MHz, $CDCl_3$) 42.4 (C-10), 65.9 (C-9), 121.5 (C-2/3), 122.1 (C-5), 126.8 (C-15), 127.7 (C-2/3), 128.9 (C-16), 129.1 (C-4), 130.8 (C-12), 131.4 (C-17), 132.4 (C-14), 140.8 (C-1), 154.8 (C-6), 172.0 (C-13), 174.1 (C-8), 204.4 (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).

Spectroscopic data matched those previously reported in the literature.[55]

2-Methylspiro[cyclopent[2]ene-1,3'-indol]-4-one (137b)



137b

Method 1. Synthesised using general procedure C with ynone **136b** (112 mg, 0.568 mmol), $AgNO_3·SiO_2$ (96.5 mg, 5.68 μmol) in CH_2Cl_2 (5.7 mL) at RT for 35 min. Afforded the *title compound* **137b** without further purification as a yellow solid (106 mg, 95%).

Lab notebook reference: akc02-67

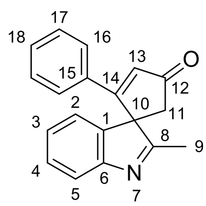
Method 2. Synthesised using general procedure D with ynone **136b** (114 mg, 0.578 mmol), $AgNO_3$ (0.98 mg, 5.78 μmol) in CH_2Cl_2 (5.8 mL) at RT for 5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **137b** as a yellow solid (100 mg, 88%).

Lab notebook reference: akc02-68

mp 109–111 °C; R_f 0.23 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1713, 1689, 1619, 1550, 1455, 1295, 1192, 849, 773, 758; δ_H (400 MHz, $CDCl_3$) 1.57 (3 H, s, H-14), 2.67 (1 H, d, J = 19.0 Hz, H-10a), 2.94 (1 H, d, J = 19.0 Hz, H-10b), 6.27–6.30 (1 H, m, H-12), 7.22 (1 H, br d, J = 7.0 Hz, H-2), 7.30–7.35 (1 H, m, H-3), 7.44 (1 H, ddd, J = 8.0, 8.0, 1.5 Hz, H-4), 7.71 (1 H, br d, J = 8.0 Hz, H-5), 7.96 (1 H, s, H-8); δ_C (100 MHz, $CDCl_3$) 14.6 (C-14), 40.4 (C-10), 67.8 (C-9), 121.5 (C-2), 127.7 (C-5), 127.4 (C-3), 129.0 (C-4), 132.8 (C-12), 139.1 (C-1), 155.6 (C-6), 173.1 (C-8), 175.6 (C-13), 205.5 (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).

Spectroscopic data matched those previously reported in the literature.[55]

2'-Methyl-2-phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one (137c)



137c

Method 1. Synthesised using general procedure C with ynone **136c** (100 mg, 0.366 mmol), $AgNO_3 \cdot SiO_2$ (62.2 mg, 3.66 μmol) in CH_2Cl_2 (3.7 mL) at RT for 10 min. Afforded the *title compound* **137c** without further purification as a yellow oil (93.8 mg, 94%).

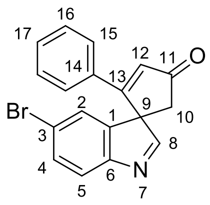
Lab notebook reference: akc01-55

Method 2. Synthesised using general procedure D with ynone **136c** (100 mg, 0.366 mmol), $AgNO_3$ (0.62 mg, 3.66 μmol) in CH_2Cl_2 (3.7 mL) at RT for 2 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **137c** as a yellow oil (86.7 mg, 87%).

Lab notebook reference: akc02-59

R_f 0.22 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3063, 1723, 1694, 1568, 1447, 1264, 1240, 1198, 861, 764; δ_H (400 MHz, $CDCl_3$) 2.22 (3 H, s, H-9), 2.75 (1 H, d, *J* = 19.0 Hz, H-11a), 2.84 (1 H, d, *J* = 19.0 Hz, H-11b), 6.88 (1 H, s, H-13), 6.96–7.02 (2 H, m, Ar-H), 7.17–7.24 (4 H, m, Ar-H), 7.29–7.35 (1 H, m, Ar-H), 7.38–7.44 (1 H, m, Ar-H), 7.66 (1 H, d, *J* = 8.0 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 15.8 (C-9), 45.1 (C-11), 66.6 (C-10), 120.8 (C-2/5), 121.7 (C-2/5), 126.6 (C-3/4), 126.9 (C-16/17), 129.0 (C-3/4), 129.0 (C-16/17), 130.9 (C-13), 131.4 (C-18), 132.1 (C-15), 141.7 (C-1), 154.6 (C-6), 172.8 (C-14), 182.9 (C-8), 204.7 (C-12); HRMS (ESI$^+$): Found: 296.1037; $C_{19}H_{15}NNaO$ (MNa^+) Requires 296.1046 (3.2 ppm error), Found: 274.1220; $C_{19}H_{16}NO$ (MH^+) Requires 274.1226 (2.3 ppm error).

5'-Bromo-2-phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one (137d)



137d

Method 1. Synthesised using general procedure C with ynone **136d** (100 mg, 0.297 mmol), $AgNO_3{\cdot}SiO_2$ (50.4 mg, 2.97 μmol) in CH_2Cl_2 (3 mL) at RT for 1 h. Afforded the *title compound* **137d** without further purification as an orange solid (98.8 mg, 98%).

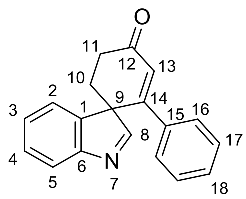
Lab notebook reference: akc02-53

Method 2. Synthesised using general procedure D with ynone **136d** (100 mg, 0.297 mmol), $AgNO_3$ (0.50 mg, 2.97 μmol) in CH_2Cl_2 (3 mL) at RT for 6 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **137d** as an orange solid (97.5 mg, 97%).

Lab notebook reference: akc02-54

mp 189–191 °C; R_f 0.29 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3061, 1697, 1591, 1569, 1446, 1258, 777; δ_H (400 MHz, $CDCl_3$) 2.67 (1 H, d, *J* = 19.0 Hz, H-10a), 3.05 (1 H, d, *J* = 19.0 Hz, H-10b), 6.86 (1 H, s, H-12), 6.97–7.02 (2 H, m, H-15/16), 7.20–7.26 (2 H, m, H-15/16), 7.32–7.38 (1 H, m, H-17), 7.38 (1 H, d, *J* = 2.0 Hz, H-2), 7.58 (1 H, dd, *J* = 8.0, 2.0 Hz, H-4), 7.64 (1 H, d, *J* = 8.0 Hz, H-5), 8.21 (1 H, s, H-8); δ_C (100 MHz, $CDCl_3$) 42.2 (C-10), 66.1 (C-9), 121.6 (C-3), 123.4 (C-5), 125.0 (C-2), 126.7 (C-15/16), 129.1 (C-15/16), 131.0 (C-12), 131.6 (C-17), 132.1 (C-14), 132.3 (C-4), 143.0 (C-1), 153.8 (C-6), 171.0 (C-13), 174.4 (C-8), 203.5 (C-11); HRMS (ESI$^+$): Found: 359.9988; $C_{18}H_{12}{}^{79}BrNNaO$ (MNa^+) Requires 359.9994 (1.9 ppm error).

1-Phenylspiro[cyclohex[6]ene-2,3'-indol]-5-one (137e)

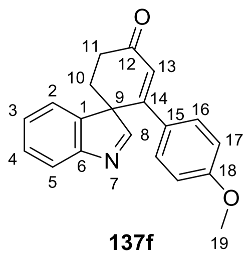


137e

Synthesised using general procedure C with ynone **136e** (99.7 mg, 0.365 mmol), $AgNO_3{\cdot}SiO_2$ (620 mg, 0.0365 mmol) in CH_2Cl_2 (3.7 mL) at 45 °C for 24 h. Afforded the *title compound* **137e** without further purification as a white solid (99.3 mg, 100%); mp 139–141 °C; R_f 0.27 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3057, 2930, 1670, 1445, 1331, 1262, 749, 698; δ_H (400 MHz, $(CD_3)_2SO$) 1.88–2.02 (1 H, m, H-10a), 2.32–2.43 (1 H, m, H-10b), 2.68–2.83 (2 H, m, H-11), 6.33 (1 H, s, H-13), 6.75–6.83 (2 H, m, H-16/17), 7.10–7.18 (2 H, m, H-16/17), 7.19–7.30 (2 H, m, H-3,18), 7.40 (1 H, ddd, *J* = 8.0, 7.5, 1.0 Hz, H-4), 7.48 (1 H, d, *J* = 7.5 Hz, H-2), 7.64 (1 H, d, *J* = 8.0 Hz, H-5), 8.60 (1 H, s, H-8); δ_C (100 MHz, $(CD_3)_2SO$) 31.1 (C-10), 34.7 (C-11), 61.5 (C-9), 121.6 (C-5), 123.2 (C-2), 125.6 (C-16/17), 126.7 (C-3), 128.3 (C-16/17), 128.8 (C-4), 129.2 (C-18), 129.8 (C-13), 137.8 (C-15), 141.2 (C-1), 155.1 (C-6), 157.3 (C-14), 176.2 (C-8), 197.4 (C-12); HRMS (ESI$^+$): Found: 296.1035; $C_{19}H_{15}NNaO$ (MNa^+) Requires 296.1046 (3.5 ppm error), Found: 274.1217; $C_{19}H_{16}NO$ (MH^+) Requires 274.1226 (3.6 ppm error).

Lab notebook reference: akc02-46

1-(4-Methoxyphenyl)spiro[cyclohex[6]ene-2,3'-indol]-5-one (137f)



137f

Synthesised using general procedure C with 5-(1*H*-indol-3-yl)-1-(4-methoxyphenyl)pent-1-yn-3-one **136f***[55] (100 mg, 0.330 mmol), $AgNO_3{\cdot}SiO_2$ (560 mg, 0.0330 mmol) in CH_2Cl_2 (3.3 mL) at 45 °C for 24 h. Afforded the *title compound* **137f** without further purification as a dark green oil (100 mg, 100%); R_f 0.35 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2934, 2838, 1666, 1604, 1510, 1242, 1181, 1031, 831, 758; δ_H (400 MHz, $CDCl_3$) 1.78 (1 H, dt, *J* = 13.5, 5.0 Hz, H-10a), 2.55–2.66 (1 H, m, H-10b), 2.71 (1 H, dt, *J* = 18.0, 5.0 Hz, H-11a), 2.81–2.93

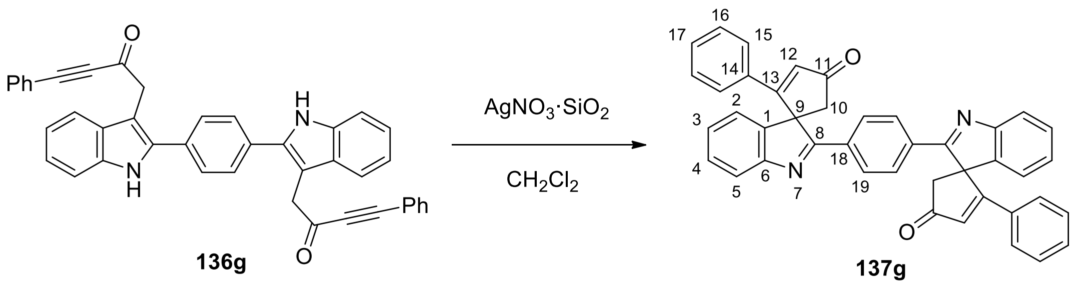
(1 H, m, H-11b) 3.72 (3 H, s, H-19), 6.47 (1 H, s, H-13), 6.63–6.69 (2 H, m, H-17), 6.69–6.76 (2 H, m, H-16), 7.30 (1 H, dd, *J* = 7.5, 7.5 Hz, H-3), 7.37 (1 H, d, *J* = 7.5 Hz, H-2), 7.45–7.52 (1 H, m, H-4), 7.78 (1 H, d, *J* = 7.5 Hz, H-5), 8.21 (1 H, br s, H-8); δ_C (100 MHz, $CDCl_3$) 32.0 (C-10), 34.3 (C-11), 55.2 (C-19), 61.6 (C-9), 114.1 (C-17), 122.5 (C-2/5), 122.8 (C-2/5), 127.0 (C-3), 127.3 (C-16), 128.4 (C-13), 129.2 (C-4), 129.6 (C-15), 140.6 (C-1), 154.7 (C-6), 157.2 (C-14), 161.0 (C-18), 176.7 (C-8), 197.8 (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: akc02-48

*Material made by M. James

Spectroscopic data matched those previously reported in the literature.[55]

2'-(4-(4-Oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-2'-yl)phenyl)-2-phenylspiro[cyclopentane-1,3'indol]-2-en-4-one (137g)

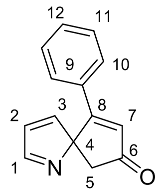


To a solution of ynone **136g** (24.5 mg, 41.3 μmol) in CH_2Cl_2 (0.8 mL) was added $AgNO_3{\cdot}SiO_2$ (14.1 mg, 0.827 μmol). The mixture was stirred at RT for 1.5 h. The reaction mixture was filtered, washing the catalyst with EtOAc (5 mL), then concentrated *in vacuo* to afford the *title compound* **137g** without further purification as a yellow solid (1:1.2 mixture of diastereoisomers A:B, 24.5 mg, 100%); mp 128–130 °C; R_f 0.52 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3070, 2925, 1720, 1692, 1587, 1260, 863, 759; δ_H (400 MHz, $CDCl_3$) 2.66 (2 H, d, *J* = 19.0 Hz, H-10a, A), 2.68 (2 H, d, *J* = 18.5 Hz, H-10a, B), 3.06 (2 H, d, *J* = 18.5 Hz, H-10b, B), 3.09 (2 H, d, *J* = 19.0 Hz, H-10b, A), 6.98 (2 H, s, H-12, A/B), 7.00 (2 H, s, H-12, A/B), 7.01–7.07 (8 H, m, H-15/16/17/2/3, A+B), 7.11–7.30 (20 H, m, H-15/16/17/2/3, A+B), 7.43–7.49 (4 H, m, H-4, A+B), 7.81 (2 H, d, *J* = 8.0 Hz, H-5, A/B), 7.82 (2 H, d, *J* = 8.0 Hz, H-5, A/B), 7.98 (4 H, s, H-19, A/B), 7.99 (4 H, s, H-19, A/B); δ_C (100 MHz, $(CD_3)_2SO$) 46.5 (C-10, A+B), 64.6 (C-9, A+B), 121.1 (CH, A+B), 121.7 (CH, A+B), 126.8 (CH, A+B), 127.6 (CH, A+B), 128.1 (CH, A+B), 129.1 (CH, A+B), 129.3 (CH, A+B), 130.7 (CH, A+B), 131.4

(CH, A+B), 132.3 (C, A+B), 134.2 (C, A+B), 143.5 (C, A+B), 153.3 (C, A+B), 172.4 (C, A+B), 172.0 (C, A+B), 204.1 (C-11, A+B); HRMS (ESI$^+$): Found: 593.2248; $C_{42}H_{29}N_2O_2$ (MH^+) Requires 593.2224 (−4.1 ppm error).

Lab notebook reference: akc02-88

9-Phenyl-1-azaspiro[4.4]nona-1,3,8-trien-7-one (143h)

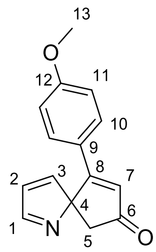


143h

Synthesised using general procedure C with ynone **136h** (100 mg, 0.477 mmol), $AgNO_3\cdot SiO_2$ (405 mg, 0.0239 mmol) in CH_2Cl_2 (4.8 mL) at RT for 2 h. Afforded the *title compound* **143h** without further purification as a brown oil (90.2 mg, 90%); R_f 0.12 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3064, 1694, 1593, 1570, 1492, 1340, 1237, 1199, 766; δ_H (400 MHz, $CDCl_3$) 2.72 (1 H, d, *J* = 18.0 Hz, H-5a), 2.95 (1 H, d, *J* = 18.0 Hz, H-5b), 6.61 (1 H, d, *J* = 5.0 Hz, H-2), 6.62 (1 H, s, H-7), 7.19–7.24 (2 H, m, H-10/11), 7.25–7.31 (2 H, m, H-10/11), 7.33–7.39 (1 H, m, H-12), 7.48 (1 H, d, *J* = 5.0 Hz, H-3), 8.28 (1 H, s, H-1); δ_C (100 MHz, $CDCl_3$) 40.8 (C-5), 88.8 (C-4), 126.7 (C-10/11), 128.4 (C-10/11), 128.5 (C-2), 130.6 (C-12), 131.6 (C-7), 133.3 (C-9), 157.3 (C-3), 166.2 (C-1), 172.9 (C-8), 203.9 (C-6); HRMS (ESI$^+$): Found: 232.0732; $C_{14}H_{11}NNaO$ (MNa^+) Requires 232.0733 (0.2 ppm error), Found: 210.0916; $C_{14}H_{12}NO$ (MH^+) Requires 210.0913 (−1.4 ppm error).

Lab notebook reference: akc01-101

9-(4-Methoxyphenyl)-1-azaspiro[4.4]nona-1,3,8-trien-7-one (143i)



143i

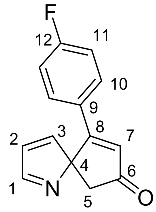
Synthesised using general procedure C with 4-(4-methoxyphenyl)-1-(1*H*-pyrrol-2-yl)but-3-yn-2-one **136i***[55] (19.7 mg, 0.0823 mmol), $AgNO_3 \cdot SiO_2$ (70.0 mg, 4.11 μmol) in CH_2Cl_2 (1 mL) at RT for 2 h. Afforded the *title compound* **143i** without further purification as a brown oil (17.9 mg, 91%); R_f 0.12 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1689, 1604, 1589, 1509, 1251, 1179, 1027, 833, 772; δ_H (400 MHz, $CDCl_3$) 2.66 (1 H, d, *J* = 18.0 Hz, H-5a), 2.90 (1 H, d, *J* = 18.0 Hz, H-5b), 3.79 (3 H, s, H-13), 6.59 (1 H, s, H-7), 6.63 (1 H, d, *J* = 5.0 Hz, H-2/3), 6.78 (2 H, d, *J* = 8.5 Hz, H-10/11), 7.19 (2 H, d, *J* = 8.5 Hz, H-10/11), 7.50 (2 H, d, *J* = 5.0 Hz, H-2/3), 8.31 (1 H, s, H-1); δ_C (100 MHz, $CDCl_3$) 40.9 (C-5), 55.3 (C-13), 88.8 (C-4), 113.8 (C-10/11), 125.8 (C-9), 128.1 (C-2/3), 128.6 (C-10/11), 129.5 (C-7), 158.1 (C-2/3), 161.7 (C-12), 166.1 (C-1), 171.7 (C-8), 203.7 (C-6); HRMS (ESI$^+$): Found: 262.0832; $C_{15}H_{13}NNaO_2$ (MNa^+) Requires 262.0838 (2.4 ppm error), Found: 240.1018; $C_{15}H_{14}NO_2$ (MH^+) Requires 240.1019 (0.4 ppm error).

Lab notebook reference: akc04-94

*Material made by M. James

Spectroscopic data matched those previously reported in the literature.[55]

9-(4-Fluorophenyl)-1-azaspiro[4.4]nona-1,3,8-trien-7-one (143j)



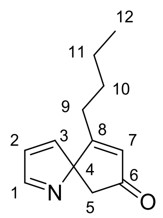
143j

Synthesised using general procedure C with ynone **136j** (20.6 mg, 0.0907 mmol), $AgNO_3 \cdot SiO_2$ (77.0 mg, 4.54 μmol) in CH_2Cl_2 (1 mL) at RT for 2 h min. Afforded the *title compound* **143j** without further purification as a brown oil (19.7 mg, 96%); R_f 0.15 (1:1

hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1603, 1506, 1237, 1199, 1162, 837, 773; δ_H (400 MHz, $CDCl_3$) 2.70 (1 H, d, *J* = 18.5 Hz, H-5a), 2.93 (1 H, d, *J* = 18.5 Hz, H-5b), 6.58 (1 H, s, H-7), 6.62 (1 H, d, *J* = 4.5 Hz, H-2/3), 6.96 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-11), 7.21 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HF}$ 5.5 Hz, H-10), 7.47 (1 H, d, *J* = 4.5 Hz, H-2/3), 8.29 (1 H, s, H-1); δ_C (100 MHz, $CDCl_3$) 40.7 (C-5), 88.7 (C-4), 115.6 (d, $^2J_{CF}$ = 22.0 Hz, C-11), 128.6 (C-7), 128.9 (d, $^3J_{CF}$ = 8.5 Hz, C-10), 129.4 (d, $^4J_{CF}$ = 4.0 Hz, C-9), 131.5 (C-2/3), 157.4 (C-2/3), 164.0 (d, $^1J_{CF}$ = 252 Hz, C-12), 166.4 (C-1), 171.4 (C-8), 203.5 (C-6); HRMS (ESI$^+$): Found: 250.0635; $C_{14}H_{10}FNNaO$ (MNa^+) Requires 250.0639 (1.5 ppm error), Found: 228.0818; $C_{14}H_{11}FNO$ (MH^+) Requires 228.0819 (0.5 ppm error).

Lab notebook reference: akc05-02

9-Butyl-1-azaspiro[4.4]nona-1,3,8-trien-7-one (143k)

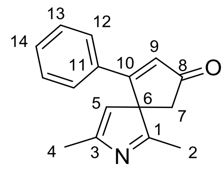


143k

Synthesised using general procedure C with ynone **136k** (98.6 mg, 0.521 mmol), $AgNO_3\cdot SiO_2$ (443 mg, 0.0261 mmol) in CH_2Cl_2 (5.2 mL) at RT for 2 h. Afforded the *title compound* **143k** without further purification as a brown oil (89.9 mg, 91%); R_f 0.18 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2958, 2931, 1719, 1695, 1615, 1196, 771; δ_H (400 MHz, $CDCl_3$) 0.85 (3 H, t, *J* = 7.5 Hz, H-12), 1.26 (2 H, app. sextet, *J* = 7.5 Hz, H-11), 1.37–1.51 (2 H, m, H-10), 1.59–1.70 (1 H, m, H-9a), 1.73–1.83 (1 H, m, H-9b), 2.61 (1 H, d, *J* = 18.5 Hz, H-5a), 2.86 (1 H, d, *J* = 18.5 Hz, H-5b), 6.20 (1 H, s, H-7), 6.58 (1 H, d, *J* = 4.5 Hz, H-2/3), 7.21 (1 H, d, *J* = 4.5 Hz, H-2/3), 8.24 (1 H, s, H-1); δ_C (100 MHz, $CDCl_3$) 13.7 (C-12), 22.2 (C-11), 26.5 (C-9), 29.6 (C-10), 39.2 (C-5), 89.4 (C-4), 128.7 (C-2/3), 130.6 (C-7), 155.8 (C-2/3), 166.0 (C-1), 179.8 (C-8), 205.0 (C-6); HRMS (ESI$^+$): Found: 212.1044; $C_{12}H_{15}NNaO$ (MNa^+) Requires 212.1046 (1.0 ppm error), Found: 190.1225; $C_{12}H_{16}NO$ (MH^+) Requires 190.1226 (0.9 ppm error).

Lab notebook reference: akc05-08

1,3-Dimethyl-9-phenyl-2-azaspiro[4.4]nona-1,3,8-trien-7-one (147l)

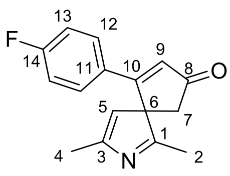


147l

Synthesised using general procedure C with 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)-4-phenylbut-3-yn-2-one **136l** (46.3 mg, 0.195 mmol), $AgNO_3{\cdot}SiO_2$ (33.1 mg, 1.95 μmol) in CH_2Cl_2 (2 mL) at RT for 20 min. Afforded the *title compound* **147l** without further purification as a brown solid (46.3 mg, 100%); mp 98–100 °C; R_f 0.17 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1723, 1693, 1591, 1568, 1445, 1279, 1254, 770; δ_H (400 MHz, $CDCl_3$) 2.09 (3 H, s, H-2/4), 2.21 (3 H, s, H-2/4), 2.54 (1 H, d, *J* = 19.0 Hz, H-7a), 2.75 (1 H, d, *J* = 19.0 Hz, H-7b), 5.84–5.87 (1 H, m, H-5), 6.67 (1 H, s, H-9), 7.24 (2 H, d, *J* = 7.5 Hz, H-12), 7.33 (2 H, dd, *J* = 7.5, 7.5 Hz, H-13), 7.38–7.43 (1 H, m, H-14); δ_C (100 MHz, $CDCl_3$) 15.2 (C-2/4), 16.3 (C-2/4), 41.3 (C-7), 69.4 (C-6), 124.2 (C-5), 126.6 (C-12), 129.0 (C-13), 130.0 (C-9), 131.4 (C-14), 132.9 (C), 153.6 (C), 173.0 (C), 184.7 (C-1), 204.7 (C-8); HRMS (ESI$^+$): Found: 238.1225; $C_{16}H_{16}NO$ (MH^+) Requires 238.1226 (0.5 ppm error).

Lab notebook reference: akc05-34

9-(4-Fluorophenyl)-1,3-dimethyl-2-azaspiro[4.4]nona-1,3,8-trien-7-one (147m)



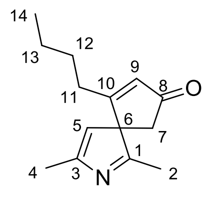
147m

Synthesised using general procedure C with 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one **136m** (66.0 mg, 0.259 mmol), $AgNO_3{\cdot}SiO_2$ (43.9 mg, 2.59 μmol) in CH_2Cl_2 (2.6 mL) at RT for 15 min. Afforded the *title compound* **147m** without further purification as a yellow oil (66.0 mg, 100%); R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1717, 1694, 1601, 1574, 1509, 1238, 1163, 836, 809; δ_H (400 MHz, $CDCl_3$) 2.08 (3 H, s, H-2), 2.22 (3 H, s, H-4), 2.54 (1 H, d, *J* = 19.0 Hz, H-7a), 2.75 (1 H, d, *J* = 19.0 Hz, H-7b), 5.84–5.87 (1 H, m, H-5), 6.63 (1 H, s, H-9), 7.02 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-13), 7.21–7.27 (2 H, m, H-12); δ_C (100 MHz, $CDCl_3$) 15.2 (C-2), 16.3 (C-4), 41.3 (C-7), 69.3 (C-6), 116.2 (d, $^2J_{CF}$ = 22.0 Hz, C-13), 124.2 (C-5), 128.9 (d, $^3J_{CF}$ = 8.5 Hz, C-12), 129.1 (d,

$^4J_{CF}$ = 4.0 Hz, C-11), 129.8 (C-9), 153.8 (C-3), 164.5 (d, $^1J_{CF}$ = 254 Hz, C-14), 171.5 (C-10), 184.7 (C-1), 204.4 (C-8); HRMS (ESI$^+$): Found: 256.1136; $C_{16}H_{15}FNO$ (MH$^+$) Requires 256.1132 (−1.3 ppm error).

Lab notebook reference: akc05-45

9-Butyl-1,3-dimethyl-2-azaspiro[4.4]nona-1,3,8-trien-7-one (147n)

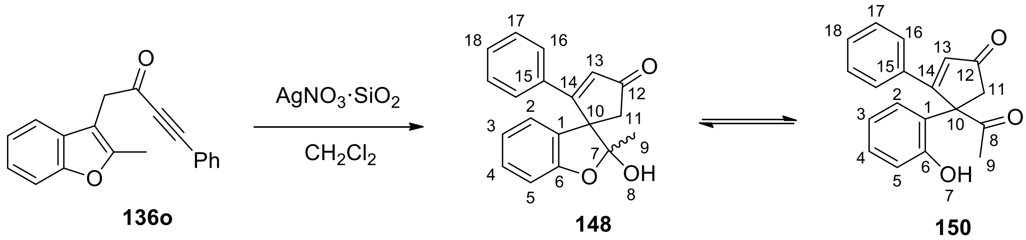


147n

Synthesised using general procedure C with 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)oct-3-yn-2-one **136n** (39.5 mg, 0.182 mmol), $AgNO_3 \cdot SiO_2$ (30.9 mg, 1.82 μmol) in CH_2Cl_2 (1.8 mL) at RT for 10 min. Afforded the *title compound* **147n** without further purification as a yellow oil (39.4 mg, 100%); R$_f$ 0.27 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2964, 2931, 1720, 1701, 1611; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* = 7.5 Hz, H-14), 1.24–1.35 (2 H, m, H-13), 1.46 (2 H, app. pentet, *J* = 7.5 Hz, H-12), 1.72–1.83 (1 H, m, H-11a), 1.83–1.92 (1 H, m, H-11b), 2.01 (3 H, s, H-2), 2.18 (3 H, s, H-4), 2.45 (1 H, d, *J* = 19.0 Hz, H-7a), 2.61 (1 H, d, *J* = 19.0 Hz, H-7b), 5.59–5.63 (1 H, m, H-5), 6.16 (1 H, s, H-9); δ_C (100 MHz, $CDCl_3$) 13.7 (C-14), 14.9 (C-2), 16.2 (C-4), 22.3 (C-13), 28.1 (C-11), 29.4 (C-12), 39.3 (C-7), 71.3 (C-6), 122.1 (C-5), 130.1 (C-9), 154.6 (C-3), 182.0 (C-10), 182.9 (C-1), 206.2 (C-8); HRMS (ESI$^+$): Found: 218.1547; $C_{14}H_{20}NO$ (MH$^+$) Requires 218.1539 (−3.5 ppm error).

Lab notebook reference: akc05-41

2-Hydroxy-2-methyl-2'-phenyl-2*H*-spiro[benzofuran-3,1'-cyclopent[2]en]-4'-one (148)



136o **148** **150**

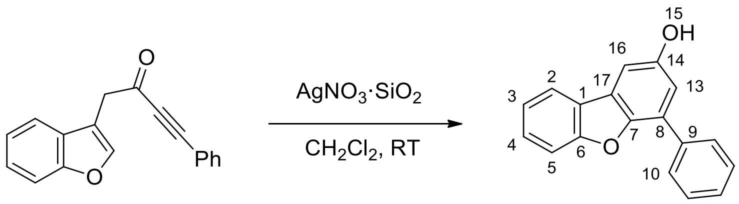
To a solution of ynone **136o** (130 mg, 0.472 mmol) in CH_2Cl_2 (4.7 mL) was added $AgNO_3 \cdot SiO_2$ (803 mg, 0.0472 mmol). The mixture was stirred at RT for 24 h. The reaction mixture was filtered, washing the catalyst with EtOAc (5 mL), then concentrated *in vacuo* to afford the crude material. Purification by column chromatography (10:1 hexane:EtOAc, then 8:3 hexane:EtOAc) afforded the *title compound* **148** as a pale yellow oil (approximately 5:1 ratio of diastereoisomers A:B and containing trace amounts of ring-opened compound **150**, 86.2 mg, 62%); R_f 0.25 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3358, 2932, 1686, 1598, 1478, 1175, 757; HRMS (ESI$^+$): Found: 315.0984; $C_{19}H_{16}NaO_3$ (MNa$^+$) Requires 315.0992 (2.5 ppm error).

NMR data for the major diastereoisomer **148**: δ_H (400 MHz, $CDCl_3$) 1.50 (3 H, s, H-9), 2.94 (1 H, d, *J* = 19.5 Hz, H-11a), 3.32–3.33 (1 H, m, H-8), 3.49 (1 H, d, *J* = 19.5 Hz, H-11b), 6.28 (1 H, s, H-13), 6.73 (2 H, d, *J* = 8.0 Hz, Ar-H), 6.90 (1 H, d, *J* = 8.0 Hz, Ar-H), 6.99–7.41 (9 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 22.7 (C-9), 44.3 (C-11), 63.2 (C-10), 110.8 (C-7), 111.0 (CH), 122.6 (CH), 124.0 (CH), 127.3 (C-16/17), 128.5 (C-16/17), 130.0 (CH), 130.1 (CH), 130.4 (C-1/15), 132.2 (C-13), 135.2 (C-1/15), 157.8 (C-6), 176.4 (C-14), 206.4 (C-12).

Characteristic NMR data for the minor diastereoisomer **148**: δ_H (400 MHz, $CDCl_3$) 2.73 (1 H, d, *J* = 18.5 Hz, H-11a), 3.14 (1 H, d, *J* = 18.5 Hz, H-11b), 6.49 (1 H, s, H-13).

Lab notebook reference: akc03-25

4-Phenyldibenzo[b,d]furan-2-ol (151)

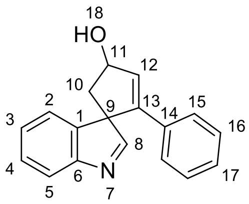


136p **151**

To a solution of ynone **136p** (22.6 mg, 86.8 μmol) in CH_2Cl_2 (0.9 mL) was added $AgNO_3 \cdot SiO_2$ (148 mg, 8.68 μmol). The mixture was stirred at RT for 24 h. The reaction mixture was filtered, washing the catalyst with EtOAc (5 mL), then concentrated *in vacuo* to afford the crude material. Purification by column chromatography (8:3 hexane:EtOAc) afforded the *title compound* **151** as a yellow oil (9.0 mg, 40%); R_f 0.31 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3359, 1449, 1406, 1171, 773, 748; δ_H (400 MHz, $CDCl_3$) 4.91 (1 H, br s, H-15), 7.14 (1 H, d, *J* = 2.5 Hz, H-13/16), 7.34 (1 H, dd, *J* = 7.5 Hz, *J* = 7.5 Hz, Ar-H), 7.38 (1 H, d, *J* = 2.5 Hz, H-13/16), 7.42–7.50 (2 H, m, Ar-H), 7.52–7.60 (3 H, m, H-10/11,Ar-H), 7.88–7.95 (3 H, m, H-10/11,Ar-H); δ_C (100 MHz, $CDCl_3$) 105.3 (C-13/16), 111.9 (CH), 114.8 (C-13/16), 120.7 (CH), 122.5 (CH), 124.2 (C), 125.7 (C), 126.4 (C), 127.4 (CH), 128.0 (CH), 128.7 (C-10/11), 128.7 (C-10/11), 136.0 (C), 148.3 (C), 151.7 (C), 156.9 (C); HRMS (ESI$^+$): Found: 283.0722; $C_{18}H_{12}NaO_2$ (MNa$^+$) Requires 283.0730 (2.6 ppm error), Found: 261.0922; $C_{18}H_{13}O_2$ (MH$^+$) Requires 261.0910 (−4.6 ppm error).

Lab notebook reference: akc03-31

2-Phenylspiro[cyclopent[2]ene-1,3'-indol]-4-ol (154)



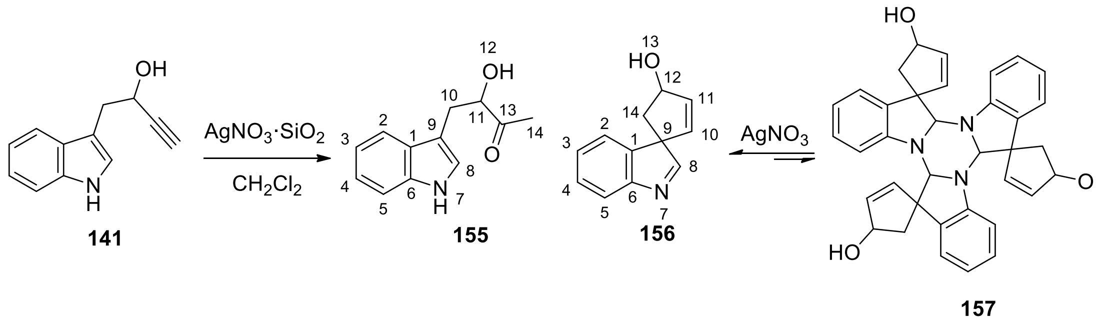
154

Synthesised using general procedure C with 1-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-ol **142***[94] (77.4 mg, 0.293 mmol), $AgNO_3 \cdot SiO_2$ (497 mg, 2.93 μmol) in CH_2Cl_2 (2.9 mL) at RT for 24 h. Afforded the *title compound* **154** without further purification as an orange oil (approximately 1.6:1 ratio of diastereoisomers A:B, 78.5 mg, 100%); R_f 0.19 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3291, 1549, 1455, 1445, 1076, 1043, 1014, 906, 752, 730, 692; δ_H (400 MHz, $CDCl_3$) 2.09 (1 H, dd, *J* = 14.0, 4.0 Hz, H-10a, B), 2.35 (1 H, dd, *J* = 13.5, 4.0 Hz, H-10a, A), 2.48 (1 H, dd, *J* = 13.5, 6.5 Hz, H-10b, A), 2.57 (2 H, br s, H-18, A+B), 2.80 (1 H, dd, *J* = 14.0, 7.0 Hz, H-10b, B), 5.23–5.29 (1 H, m, H-11, B), 5.31–5.38 (1 H, m, H-11, A), 6.58 (1 H, d, *J* = 2.5 Hz, H-12, B), 6.59 (1 H, d, *J* = 2.5 Hz, H-12, A), 6.78–6.84 (4 H, m, H-15, A+B), 7.03–7.16 (6 H, m, H-16,17, A+B), 7.18–7.26 (3 H, m, H-2,3, 2 H from A and 1 H from B), 7.35-7.41 (2 H, m, H-4, A+B), 7.45 (1 H, d, *J* = 7.5 Hz, H-2, B), 7.70 (1 H, d, *J* = 8.5 Hz, H-5, B), 7.72 (1 H, d, *J* = 8.0 Hz, H-5, A), 8.11 (1 H, s, H-8, B), 8.25 (1 H, s, H-8, A); δ_C (100 MHz, $CDCl_3$) 42.4 (CH_2), 43.6 (CH_2), 69.6 (C), 69.9 (C), 74.9 (CH), 74.9 (CH), 121.3 (CH), 121.6 (CH), 121.7 (CH), 123.0 (CH), 125.7 (2CH), 125.8 (2CH), 126.9 (CH), 127.1 (CH), 128.3 (3CH), 128.3 (2CH), 128.4 (3CH), 133.9 (2C), 134.0 (CH), 134.2 (CH), 141.9 (C), 142.3 (C), 145.1 (C), 145.6 (C), 154.8 (2C), 176.9 (CH), 177.0 (CH); HRMS (ESI$^+$): Found: 284.1043; $C_{18}H_{15}NNaO$ (MNa$^+$) Requires 284.1046 (1.2 ppm error), Found: 262.1223; $C_{18}H_{16}NO$ (MH$^+$) Requires 262.1226 (1.5 ppm error).

Lab notebook reference: akc02-81

*Material made by M. James

3-Hydroxy-4-(1*H*-indol-3-yl)butan-2-one (155) and Spiro[cyclopent[2]ene-1,3'-indol]-4-ol (156)



To a solution of alcohol **141** (77.2 mg, 0.417 mmol) in CH_2Cl_2 (4.2 mL) was added $AgNO_3 \cdot SiO_2$ (708 mg, 0.0417 mmol). The mixture was stirred at RT for 4 h. The reaction mixture was poured directly onto silica and purified by column chromatography (1:1 hexane:EtOAc, then 9:1 CH_2Cl_2:MeOH) to afford the *title compound* **155** as an off-white oil (34.7 mg, 41%) and *title compound* **156** as a brown foam (3:1 mixture of diastereoisomers A:B and trace amounts trimer **157**, 45.2 mg, 58%); to simplify the NMR spectra from a monomer:trimer mixture the purified material was dissolved in $CDCl_3$ and 1 equiv. $AgNO_3$ was added and the monomer:trimer mixture was stirred for 1 h. Data of the resultant monomer **156**: R_f 0.19 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3350, 1456, 1339, 1013, 908, 729; δ_H (400 MHz, $CDCl_3$) 2.01 (1 H, dd, *J* = 14.0, 4.0 Hz, H-14a, B), 2.31 (1 H, dd, *J* = 14.5, 2.5 Hz, H-14a, A), 2.44 (1 H, dd, *J* = 14.5, 6.5 Hz, H-14b, A), 2.74 (1 H, dd, *J* = 14.0, 7.0 Hz, H-14b, B), 5.22 (2 H, m, H-12, A+B), 5.34 (1 H, d, *J* = 5.5 Hz, H-10, B), 5.40 (1 H, d, *J* = 5.5 Hz, H-10, A), 6.32 (1 H, dd, *J* = 5.5, 1.5 Hz, H-11, B), 6.37 (1 H, dd, *J* = 5.5, 2.0 Hz, H-11, A), 7.22–7.41 (5 H, m, Ar-H, 3 H from A and 2 H from B), 7.49 (1 H, d, *J* = 7.5 Hz, Ar-H, B), 7.63–7.69 (2 H, m, Ar-H, A+B), 8.22 (1 H, s, H-8, B), 8.45 (1 H, s, H-8, A); δ_C (100 MHz, $CDCl_3$) 39.9 (C-14, B), 40.7 (C-14, A), 68.8 (C-9, A), 69.2 (C-9, B), 76.9 (C-12, A), 77.2 (C-12, B), 120.4 (CH, B), 120.6 (CH, A) 122.4 (CH, A), 123.6 (CH, B), 127.7 (CH, A), 127.8 (CH, B), 128.5 (CH, A), 128.6 (CH, B), 131.0 (C-10, B), 132.2 (C-10, A), 140.0 (C-11, A), 140.1 (C-11, B), 141.1 (C-1, A), 141.2 (C-1, B), 152.6 (C-6, B), 152.7 (C-6, A), 180.4 (C-8, B), 181.0 (C-8, A); HRMS (ESI$^+$): Found: 208.0733; $C_{12}H_{11}NNaO$ (MNa^+) Requires 208.0733 (−0.1 ppm error), Found: 186.0912; $C_{12}H_{12}NO$ (MH^+) Requires 186.0913 (1.0 ppm error).

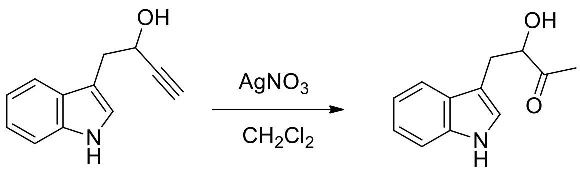
Data for **155**: R_f 0.51 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3405, 1707, 1457, 1355, 1091, 742; δ_H (400 MHz, $CDCl_3$) 2.21 (3 H, s, H-14), 3.14 (1 H, dd, *J* = 15.0, 6.5 Hz, H-10a), 3.33 (1 H, dd, *J* = 15.0, 4.5 Hz, H-10b), 3.50 (1 H, br d, *J* = 4.5 Hz, H-12), 4.50–4.56 (1 H, m, H-11), 7.09 (1 H, br d, *J* = 2.0 Hz, H-8), 7.15 (1 H, dd, *J* = 7.5, 7.0 Hz, H-3), 7.22 (1 H, dd, *J* = 8.0, 7.0 Hz, H-4), 7.36 (1 H, d, *J* = 8.0 Hz, H-5), 7.68 (1 H, d, *J* = 8.0 Hz, H-2), 8.15 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 25.8 (C-14), 29.5 (C-10), 77.1 (C-11), 110.3 (C-9), 111.2 (C-

5), 118.6 (C-2), 119.6 (C-3), 122.2 (C-4), 122.9 (C-8), 127.4 (C-1), 136.0 (C-6), 209.8 (C-13); HRMS (ESI$^+$): Found: 226.0846; $C_{12}H_{13}NNaO_2$ (MNa^+) Requires 226.0838 (−3.5 ppm error).

Lab notebook reference: akc03-43

Spectroscopic data matched those previously reported in the literature.[200]

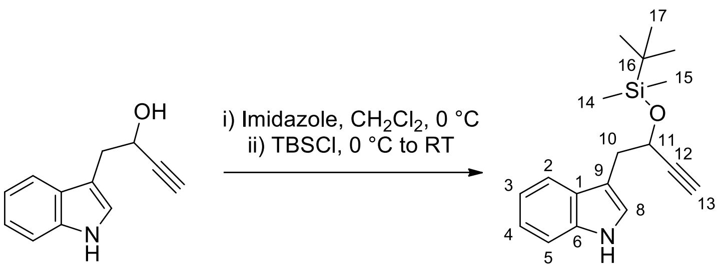
3-Hydroxy-4-(1*H*-indol-3-yl)butan-2-one (155)



To a solution of alcohol **141** (19.5 mg, 0.105 mmol) in CH_2Cl_2 (1 mL) was added $AgNO_3$ (1.79 mg, 0.0105 mmol). The mixture was stirred at RT for 24 h. The reaction mixture was poured directly onto silica and purified by column chromatography (3:2 hexane:EtOAc) to afford the *title compound* **155** as a brown oil (13.1 mg, 61%). Data for compound **155** reported above.

Lab notebook reference: akc03-28

3-(2-((*tert*-Butyldimethylsilyl)oxy)but-3-yn-1-yl)-1*H*-indole (158)

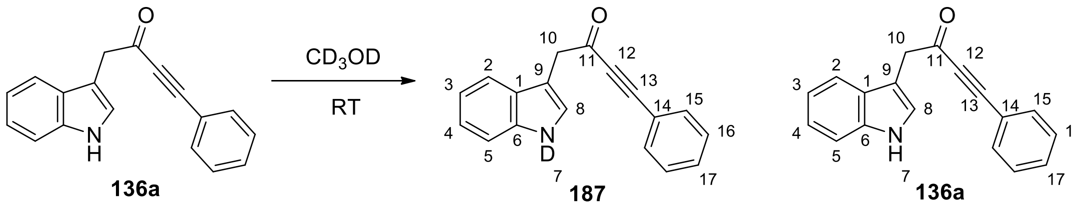


To a solution of alcohol **141** (94.7 mg, 0.511 mmol) in CH_2Cl_2 (2 mL) was added imidazole (52.2 mg, 0.767 mmol) at 0 °C. TBSCl (84.8 mg, 0.562 mmol) was then added at 0 °C and then the reaction was warmed to RT and stirred for 1.5 h. The reaction mixture was filtered through a pad of silica, washed with EtOAc (20 mL) and concentrated *in vacuo* to afford the crude material. Purification by column chromatography (10:1 hexane:EtOAc) afforded the *title compound* **158** as an pale brown solid (116 mg, 76%); mp 63–65 °C; R_f 0.76 (2:1

hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3420, 3308, 2928, 2856, 1457, 1251, 1081, 834, 777, 738; δ_H (400 MHz, $CDCl_3$) 0.00 (3 H, s, H-14/15), 0.04 (3 H, s, H-14/15), 0.91 (9 H, s, H-17), 2.43 (1 H, br d, *J* = 2.0 Hz, H-13), 3.18 (1 H, dd, *J* = 14.0, 7.5 Hz, H-10a/10b), 3.23 (1 H, dd, *J* = 14.0, 6.5 Hz, H-10a/10b), 4.63 (1 H, ddd, *J* = 7.0, 6.5, 2.0 Hz, H-11), 7.12–7.19 (2 H, m, H-3,8), 7.23 (1 H, dd, *J* = 8.0, 7.5 Hz, H-4), 7.37 (1 H, d, *J* = 8.0 Hz, H-5), 7.66 (1 H, d, *J* = 8.0 Hz, H-2), 8.02 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) −5.2 (C-14/15), −5.0 (C-14/15), 18.2 (C-16), 25.7 (C-17), 34.8 (C-10), 63.5 (C-11), 72.4 (C-13), 85.7 (C-12), 111.1 (C-5), 111.5 (C-9), 118.8 (C-2), 119.3 (C-3), 121.8 (C-4), 123.2 (C-8), 127.7 (C-1), 135.9 (C-6); HRMS (ESI$^+$): Found: 322.1604; $C_{18}H_{25}NNaOSi$ (MNa^+) Requires 322.1598 (−2.0 ppm error).

Lab notebook reference: akc03-103

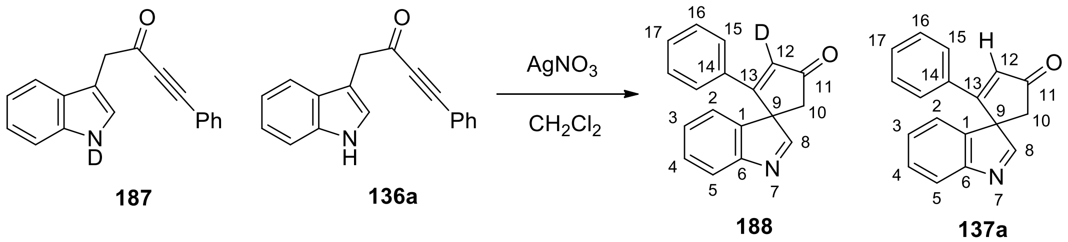
4-Phenyl-1-(1-deutero-1*H*-indol-3-yl)but-3-yn-2-one (187) and 1-(1*H*-Indol-3-yl)-4-phenylbut-3-yn-2-one (136a)



Ynone **136a** (130 mg, 0.501 mmol) was stirred in dry CD_3OD (3.5 mL) at RT overnight under an argon atmosphere. The reaction mixture was then concentrated *in vacuo* to afford the *title compounds* **187** and **136a** as an orange solid (approximately 4:1 ratio of **187**:**136a** product, 129 mg, 99%); mp 86–88 °C; R_f 0.60 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3273, 3045, 2493, 2202, 1652; δ_H (400 MHz, $CDCl_3$) 4.11 (4 H, s, H-10, D+H compound), 7.15–7.21 (2 H, m, H-3, D+H compound), 7.21–7.28 (4 H, m, H-4,8, D+H compound); 7.29–7.45 (12 H, m, H-5,15,16,17, D+H compound), 7.69 (2 H, br d, *J* = 8.0 Hz, H-2, D+H compound), 8.22 (1 H, br s, H-7, H compound); δ_C (100 MHz, $CDCl_3$) 42.0 (C-10, D+H compounds), 88.0 (C-12, D+H compounds), 92.0 (C-13, D+H compounds), 107.5 (C-9, D compound), 107.6 (C-9, H compound), 111.2 (C-5, D compound), 111.3 (C-5, H compound), 118.9 (C-2, D+H compounds), 119.8 (C-3, D+H compounds), 119.9 (C-14, D+H compounds), 122.3 (C-4, D+H compounds), 123.5 (C-8, D compound), 123.7 (C-8, H compound), 127.4 (C-1, D compound), 127.4 (C-1, H compound), 128.5 (C-15/16, D+H compounds), 130.6 (C-17, D+H compounds), 133.1 (C-15/16, D+H compounds), 136.0 (C-6, D compound), 136.1 (C-6, H compound), 185.6 (C-11, D+H compounds); HRMS (ESI$^+$): Found: 282.0887; $C_{18}H_{11}DNNaO$ (MNa^+) Requires 282.0874 (−4.6 ppm error).

Lab notebook reference: akc02-62/66

2-Phenyl-3-deuterospiro[cyclopent[2]ene-1,3'-indol]-4-one (188) and 2-Phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one (137a)

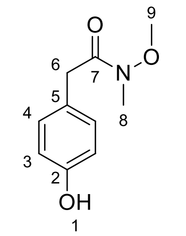


Synthesised using general procedure D with a 4:1 mixture of ynones **187:136a** (130 mg, 0.499 mmol), $AgNO_3$ (8.48 mg, 4.99 µmol), in CH_2Cl_2 (5 mL) at RT for 30 min. Afforded the *title compounds* **188** and **137a** without further purification as an orange solid (approximately 4:1 ratio of **188:137a**, 107 mg, 85%); mp 143–145 °C; R_f 0.42 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3064, 1698, 1548, 1224, 750; δ_H (400 MHz, $CDCl_3$) 2.68 (2 H, d, *J* = 18.5 Hz, H-10a, D+H compounds), 3.05 (2 H, d, *J* = 18.5 Hz, H-10b, D+H compounds), 6.85 (1 H, s, H-12, H compound), 6.95–7.01 (4 H, m, H-15, D+H compounds), 7.16–7.23 (4 H, m, H-16, D+H compounds), 7.23–7.34 (6 H, m, H-2,3,17, D+H compounds); 7.45 (2 H, ddd, *J* = 8.0, 7.5, 1.5 Hz, H-4, D+H compounds), 7.77 (2 H, d, *J* = 8.0 Hz, H-5, D+H compounds), 8.22 (2 H, s, H-8, D+H compounds); δ_C (100 MHz, $CDCl_3$) 42.4 (C-10, D+H compounds), 65.9 (C-9, D+H compounds), 121.5 (C-2/3, D+H compounds), 122.1 (C-5, D+H compounds), 126.8 (C-15, D+H compounds), 127.7 (C-2/3, D+H compounds), 128.9 (C-16, D+H compounds), 129.1 (C-4, D+H compounds), 130.8 (C-12, D+H compounds), 131.4 (C-17, D+H compounds), 132.4 (C-14, D compound), 132.4 (C-14, H compound), 140.8 (C-1, D+H compounds), 154.8 (C-6, D+H compounds), 171.9 (C-13, D compound) 172.0 (C-13, H compound), 174.1 (C-8, D+H compounds), 204.4 (C-11, D+H compounds); HRMS (ESI$^+$): Found: 283.0958; $C_{18}H_{12}DNNaO$ (MNa^+) Requires 283.0952 (−2.2 ppm error).

Lab notebook reference: akc02-69

6.9.2 Chapter 3

2-(4-)-*N*-methoxy-*N*-methylacetamide (195a)

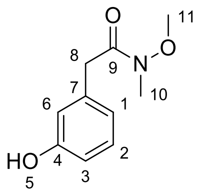


195a

Synthesised using general procedure A with 2-(4-hydroxyphenyl)acetic acid **194a** (2.40 g, 15.8 mmol), T3P 50% in EtOAc (15.1 g, 23.7 mmol), DIPEA (8.3 mL, 47.4 mmol) and MeNH(OMe)·HCl (1.66 g, 17.4 mmol) in CH_2Cl_2 (40 mL) at RT for 1 h. Afforded the *title compound* **195a** without further purification as a white solid (3.00 g, 100%); mp 110–112 °C; R_f 0.58 (9:1 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3264, 1631, 1614, 1594, 1515, 1446, 1233, 1172, 1002, 798; δ_H (400 MHz, $CDCl_3$) 3.22 (3 H, s, H-8), 3.65 (3 H, s, H-9), 3.70 (2 H, s, H-6), 6.68 (2 H, d, *J* = 8.5 Hz, H-3), 7.07 (2 H, d, *J* = 8.5 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 32.3 (C-8), 38.2 (C-6), 61.3 (C-9), 115.6 (C-3), 125.9 (C-5), 130.4 (C-4), 155.2 (C-2), 173.3 (C-7); HRMS (ESI$^+$): Found: 218.0788; $C_{10}H_{13}NNaO_3$ (MNa^+) Requires 218.0788 (−0.3 ppm error), Found: 196.0975; $C_{10}H_{14}NO_3$ (MH^+) Requires 196.0968 (−3.2 ppm error).

Lab notebook reference: akc-bsc-01

2-(3-Hydroxyphenyl)-*N*-methoxy-*N*-methylacetamide (195b)



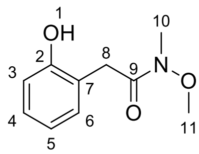
195b

Synthesised using general procedure A with 2-(3-hydroxyphenyl)acetic acid **194b** (925 mg, 6.08 mmol), T3P 50% in EtOAc (5.81 g, 9.12 mmol), DIPEA (3.2 mL, 18.2 mmol) and MeNH(OMe)·HCl (652 g, 6.68 mmol) in CH_2Cl_2 (15 mL) at RT for 1 h. Afforded the *title compound* **195b** without further purification as a white solid (1.14 g, 96%); mp 59–61 °C; R_f 0.27 (1:1 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3261, 2939, 1632, 1597, 1586, 1485, 1454, 1387, 1155, 998, 772; δ_H (400 MHz, $CDCl_3$) 3.22 (3 H, s, H-10), 3.59 (3 H, s, H-11), 3.75 (2 H, s, H-8), 6.71–6.75 (1 H, m, H-1/3), 6.77 (1 H, d, *J* = 8.0 Hz, H-1/3), 6.93–6.95 (1 H, br s, H-6), 7.15 (1 H, dd, *J* = 8.0, 8.0 Hz, H-2), 7.59 (1 H, br s, H-5); δ_C (100 MHz, $CDCl_3$) 32.3 (C-10), 39.2 (C-8), 61.4 (C-11), 114.3 (C-1/3), 116.0 (C-6), 121.0 (C-1/3), 129.6 (C-2), 135.8 (C-7), 156.8 (C-4), 172.8 (C-9); HRMS (ESI^+): Found: 218.0783; $C_{10}H_{13}NNaO_3$ (MNa^+) Requires 218.0788 (2.0 ppm error), Found: 196.0966; $C_{10}H_{14}NO_3$ (MH^+) Requires 196.0968 (1.3 ppm error).

Lab notebook reference: akc-bsc-02-6

Spectroscopic data matched those previously reported in the literature.[201]

2-(2-Hydroxyphenyl)-*N*-methoxy-*N*-methylacetamide (195c)

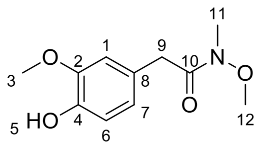


195c

Synthesised using general procedure A with 2-(2-hydroxyphenyl)acetic acid **194c** (2.00 g, 13.1 mmol), T3P 50% in EtOAc (12.6 g, 19.7 mmol), DIPEA (6.9 mL, 39.4 mmol) and MeNH(OMe)·HCl (1.41 g, 14.6 mmol) in CH_2Cl_2 (33 mL) at RT for 1.5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **195c** as a white solid (788 mg, 31%); mp 63–65 °C; R_f 0.39 (1:1 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3260, 1628, 1596, 1456, 1246, 1000, 753; δ_H (400 MHz, $CDCl_3$) 3.24 (3 H, s, H-10), 3.80 (3 H, s, H-11), 3.87 (2 H, s, H-8), 6.85 (1 H, dd, *J* = 8.0, 7.5 Hz, H-2), 6.99 (1 H, d, *J* = 8.0 Hz, H-4), 7.09 (1 H, d, *J* = 7.5 Hz, H-1), 7.19 (1 H, dd, *J* = 8.0, 8.0 Hz, H-3), 9.50 (1 H, s, H-6); δ_C (100 MHz, $CDCl_3$) 32.0 (C-10), 35.1 (C-8), 62.0 (C-11), 118.2 (C-4), 120.2 (C-2), 120.9 (C-7), 129.1 (C-3), 130.9 (C-6), 156.8 (C-5), 173.5 (C-9); HRMS (ESI^+): Found: 218.0794; $C_{10}H_{13}NNaO_3$ (MNa^+) Requires 218.0788 (−3.0 ppm error), Found: 196.0967; $C_{10}H_{14}NO_3$ (MH^+) Requires 196.0968 (−0.8 ppm error).

Lab notebook reference: akc-bsc-06 and akc04-61

2-(4-Hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (195d)

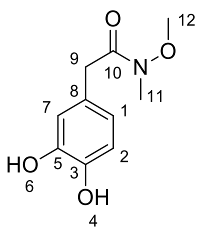


195d

Synthesised using general procedure A with 2-(4-hydroxy-3-methoxyphenyl)acetic acid **194d** (1.15 g, 6.34 mmol), T3P 50% in EtOAc (6.05 g, 9.50 mmol), DIPEA (3.3 mL, 19.0 mmol) and MeNH(OMe)·HCl (679 mg, 6.97 mmol) in CH_2Cl_2 (15 mL) at RT for 1 h. Afforded the *title compound* **195d** without further purification as a clear and colourless oil (810 mg, 48%); R_f 0.21 (1:1 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3316, 2939, 1639, 1514, 1432, 1271, 1200, 1151, 1033; δ_H (400 MHz, $CDCl_3$) 3.19 (3 H, s, H-11), 3.62 (3 H, s, H-12), 3.70 (2 H, s, H-9), 3.87 (3 H, s, H-3), 5.35 (1 H, br s, H-5), 6.75 (1 H, d, J = 8.0 Hz, H-7), 6.82–6.86 (2 H, m, H-1/6); δ_C (100 MHz, $CDCl_3$) 32.2 (C-11), 38.8 (C-9), 55.8 (C-3), 61.3 (C-12), 111.7 (C-1), 114.2 (C-6), 122.1 (C-7), 126.5 (C-8), 144.5 (C-4), 146.5 (C-2), 172.7 (C-10); HRMS (ESI$^+$): Found: 248.0884; $C_{11}H_{15}NNaO_4$ (MNa^+) Requires 248.0893 (3.7 ppm error), Found: 226.1070; $C_{11}H_{16}NO_4$ (MH^+) Requires 226.1074 (1.6 ppm error).

Lab notebook reference: akc-bsc-04

2-(3,4-Dihydroxyphenyl)-*N*-methoxy-*N*-methylacetamide (195e)



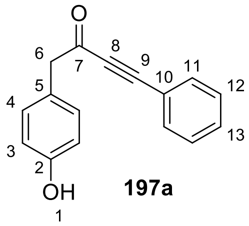
195e

Synthesised using general procedure A with 2-(3,4-dihydroxyphenyl)acetic acid **194e** (1.00 g, 5.95 mmol), T3P 50% in EtOAc (5.68 g, 8.92 mmol), DIPEA (3.1 mL, 17.8 mmol) and MeNH(OMe)·HCl (638 mg, 6.54 mmol) in CH_2Cl_2 (15 mL) at RT for 1 h. Afforded the *title compound* **195e** without further purification as a clear and colourless oil (139 mg, 11%); R_f 0.35 (8:2 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3242, 2938, 1627, 1601, 1518, 1444, 1388, 1280, 1260, 1194, 1115, 1004, 797; δ_H (400 MHz, $CDCl_3$) 3.23 (3 H, s, H-11), 3.62 (3 H, s, H-12), 3.67 (2 H, s, H-9), 6.39 (1 H, br s, H-4/6), 6.59 (1 H, d, J = 7.5 Hz, H-1/2), 6.72 (1 H, d, J = 7.5 Hz, H-1/2), 6.86 (1 H, s, H-7), 7.89 (1 H, br s, H-4/6); δ_C (100 MHz, $CDCl_3$) 32.4 (C-11), 38.4 (C-9), 61.4 (C-12), 115.0 (C-1/2), 116.0 (C-7), 121.4 (C-1/2), 125.9 (C-8), 143.6

(C-3/5), 144.3 (C-3/5), 173.7 (C-10); HRMS (ESI$^+$): Found: 234.0734; $C_{10}H_{13}NNaO_4$ (MNa$^+$) Requires 234.0737 (1.1 ppm error).

Lab notebook reference: akc-bsc-06

1-(4-Hydroxyphenyl)-4-phenylbut-3-yn-2-one (197a)

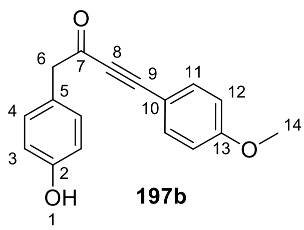


197a

Synthesised using general procedure B with phenylacetylene (0.34 mL, 3.07 mmol), THF (8.2 mL), Weinreb amide **195a** (200 mg, 1.02 mmol) and *n*-BuLi (1.02 mL, 2.56 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **197a** as a pale yellow solid (135 mg, 56%); mp 96–98 °C; R_f 0.51 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3368, 2202, 1655, 1514, 1224, 1079, 758, 688; δ_H (400 MHz, $CDCl_3$) 3.87 (2 H, s, H-6), 5.42 (1 H, br s, H-1), 6.83–6.88 (2 H, m, H-3), 7.16–7.21 (2 H, m, H-4), 7.33–7.39 (2 H, m, H-11/12), 7.42–7.50 (3 H, m, H-11/12,13); δ_C (100 MHz, $CDCl_3$) 51.3 (C-6), 87.7 (C-8), 93.3 (C-9), 115.7 (C-3), 119.7 (C-10), 125.1 (C-5), 128.6 (C-11/12), 130.9 (C-13), 131.1 (C-4), 133.1 (C-11/12), 155.1 (C-2), 186.1 (C-7); HRMS (ESI$^+$): Found: 259.0731; $C_{16}H_{12}NaO_2$ (MNa$^+$) Requires 259.0730 (−0.6 ppm error), Found: 237.0919; $C_{16}H_{13}O_2$ (MH$^+$) Requires 237.0910 (−3.8 ppm error).

Lab notebook reference: akc03-08

1-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (197b)



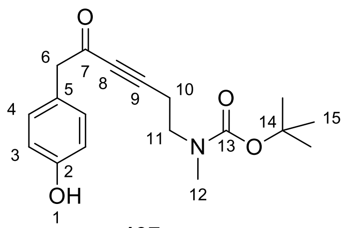
197b

Synthesised using general procedure B with 1-ethynyl-4-methoxybenzene (983 mg, 7.44 mmol), THF (18 mL), Weinreb amide **195a** (484 mg, 2.48 mmol) and *n*-BuLi (2.48 mL, 6.20

mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197b** as a yellow solid (502 mg, 76%); mp 86–88 °C; R_f 0.62 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3353, 2195, 1651, 1600, 1510, 1254, 1170, 1076, 834; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s, H-14), 3.85 (2 H, s, H-6), 5.52 (1 H, br s, H-1), 6.86 (4 H, m, H-3,12), 7.17 (2 H, d, *J* = 8.0 Hz, H-4), 7.41 (2 H, d, *J* = 8.5 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 51.1 (C-6), 55.4 (C-14), 87.8 (C-8), 94.7 (C-9), 111.5 (C-10), 114.3 (C-3/12), 115.6 (C-3/12), 125.4 (C-5), 131.1 (C-4), 135.2 (C-11), 155.1 (C-2), 161.7 (C-13), 186.3 (C-7); HRMS (ESI$^+$): Found: 289.0839; $C_{17}H_{14}NaO_3$ (MNa^+) Requires 289.0835 (−1.4 ppm error).

Lab notebook reference: akc-bsc-07

tert-Butyl (6-(4-hydroxyphenyl)-5-oxohex-3-yn-1-yl)(methyl)carbamate (197c)



197c

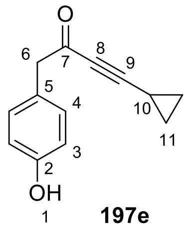
Synthesised using general procedure B with *tert*-butyl but-3-yn-1-yl(methyl)carbamate*[52] (568 mg, 3.10 mmol), THF (8 mL), Weinreb amide **195a** (202 mg, 1.03 mmol) and *n*-BuLi (1.03 mL, 2.58 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **197c** as a yellow oil (241 mg, 74%); R_f 0.62 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3331, 2977, 2212, 1663, 1515, 1395, 1366, 1225, 1145, 730; δ_H (400 MHz, $CDCl_3$) 1.47 (9 H, s, H-15), 2.54 (2 H, t, *J* = 7.0 Hz, H-10/11), 2.86 (3 H, s, H-12), 3.36 (2 H, t, *J* = 7.0 Hz, H-10/11), 3.71 (2 H, s, H-6), 6.07 (1 H, br s, H-1), 6.81 (2 H, d, *J* = 8.0 Hz, H-3/4), 7.08 (2 H, d, *J* = 8.0 Hz, H-3/4); δ_C (100 MHz, $CDCl_3$) 18.6 (C-10/11), 28.4 (C-15), 35.0 (C-12), 47.2 (C-10/11), 51.2 (C-6), 80.3 (C-14), 81.7 (C-8), 92.9 (C-9), 115.8 (C-3/4), 124.8 (C-5), 130.9 (C-3/4), 155.6 (C-2), 155.6 (C-13), 185.4 (C-7); HRMS (ESI$^+$): Found: 340.1522; $C_{18}H_{23}NNaO_4$ (MNa^+) Requires 340.1519 (−0.9 ppm error).

Note: Majority of peaks broadened in ^{1}H NMR spectrum due to presence of rotamers.

Lab notebook reference: akc04-73

*Material made by J. Liddon

4-Cyclopropyl-1-(4-hydroxyphenyl)but-3-yn-2-one (197e)

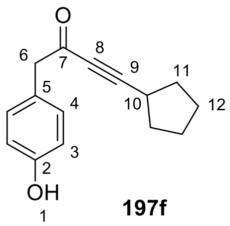


197e

Synthesised using general procedure B with ethynylcyclopropane (0.40 mL, 4.61 mmol), THF (20 mL), Weinreb amide **195a** (300 mg, 1.54 mmol) and *n*-BuLi (1.54 mL, 3.84 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **197e** as a white solid (276 mg, 90%); mp 81–83 °C; R_f 0.59 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3367, 2201, 1647, 1514, 1222; δ_H (400 MHz, $CDCl_3$) 0.80–0.85 (2 H, m, H-11a), 0.92–0.98 (2 H, m, H-11b), 1.31–1.39 (1 H, m, H-10), 3.71 (2 H, s, H-6), 5.30 (1 H, br s, H-1), 6.80 (2 H, d, *J* = 8.0 Hz, H-3), 7.09 (2 H, d, *J* = 8.0 Hz, H-4); δ_C (100 MHz, $CDCl_3$) −0.3 (C-10), 9.9 (C-11), 51.1 (C-6), 76.5 (C-8), 101.6 (C-9), 115.5 (C-3), 125.3 (C-5), 130.9 (C-4), 154.9 (C-2), 186.0 (C-7); HRMS (ESI$^+$): Found: 223.0734; $C_{13}H_{12}NaO_2$ (MNa^+) Requires 223.0730 (−2.1 ppm error), Found: 201.0906; $C_{13}H_{13}O_2$ (MH^+) Requires 201.0910 (1.9 ppm error).

Lab notebook reference: akc04-55

4-Cyclopentyl-1-(4-hydroxyphenyl)but-3-yn-2-one (197f)



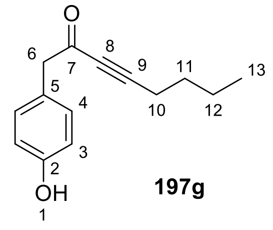
197f

Synthesised using general procedure B with ethynylcyclopentane (0.36 mL, 3.07 mmol), THF (8 mL), Weinreb amide **195a** (200 mg, 1.02 mmol) and *n*-BuLi (1.02 mL, 2.55 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197f** as a pale yellow oil (207 mg, 89%); R_f 0.74 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3376, 2961, 2871, 2205, 1650, 1514, 1224, 1172; δ_H (400 MHz, $CDCl_3$) 1.50–1.76 (6 H, m, H-11/12), 1.83–1.97 (2 H, m, H-11/12), 2.73 (1 H, tt, *J* = 7.5, 7.5 Hz, H-10), 3.74 (2 H, s, H-6), 5.49 (1 H, br s, H-1), 6.80 (2 H, d, *J* = 8.0 Hz, H-3), 7.10 (2 H, d, *J* = 8.0 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 25.1 (C-11/12), 30.0 (C-10), 33.0 (C-11/12), 51.3 (C-6), 80.2 (C-8), 101.3 (C-9), 115.5 (C-3), 125.2

(C-5), 130.9 (C-4), 154.9 (C-2), 186.6 (C-7); HRMS (ESI$^+$): Found: 251.1041; $C_{15}H_{16}NaO_2$ (MNa$^+$) Requires 251.1043 (0.7 ppm error).

Lab notebook reference: akc04-81

1-(4-Hydroxyphenyl)oct-3-yn-2-one (197g)

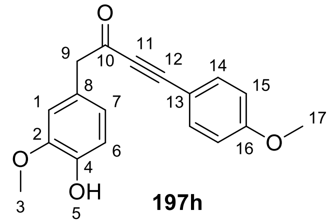


197g

Synthesised using general procedure B with hex-1-yne (0.35 mL, 3.07 mmol), THF (8 mL), Weinreb amide **195a** (200 mg, 1.02 mmol) and *n*-BuLi (1.02 mL, 2.55 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197g** as a yellow oil (181 mg, 82%); R_f 0.76 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3373, 2959, 2933, 2209, 1652, 1514, 1224, 796; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.5 Hz, H-13), 1.35 (2 H, qt, *J* = 7.5, 7.5 Hz, H-12), 1.48 (2 H, tt, *J* = 7.5, 7.0 Hz, H-11), 2.32 (2 H, t, *J* = 7.0 Hz, H-10), 3.74 (2 H, s, H-6), 5.93 (1 H, br s, H-1), 6.80 (2 H, d, *J* = 8.0 Hz, H-3/4), 7.09 (2 H, d, *J* = 8.0 Hz, H-3/4); δ_C (100 MHz, $CDCl_3$) 13.4 (C-13), 18.6 (C-10), 21.8 (C-12), 29.5 (C-11), 51.3 (C-6), 80.7 (C-8), 97.3 (C-9), 115.6 (C-3/4), 124.9 (C-5), 130.9 (C-3/4), 155.1 (C-2), 186.7 (C-7); HRMS (ESI$^+$): Found: 239.1050; $C_{14}H_{16}NaO_2$ (MNa$^+$) Requires 239.1043 (−3.2 ppm error).

Lab notebook reference: akc04-74

1-(4-Hydroxy-3-methoxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (197h)



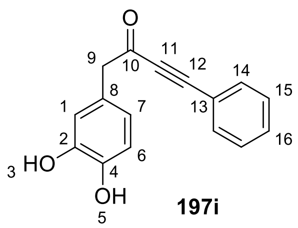
197h

Synthesised using general procedure B with 1-ethynyl-4-methoxybenzene (880 mg, 6.66 mmol), THF (18 mL), Weinreb amide **195d** (500 mg, 2.22 mmol) and *n*-BuLi (2.22 mL, 5.55 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1

hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197h** as a yellow solid (443 mg, 58%); mp 61–63 °C; R_f 0.20 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3437, 2195, 1655, 1601, 1509, 1254, 1237, 1170; δ_H (400 MHz, $CDCl_3$) 3.84 (5 H, s, H-9,3/17), 3.89 (3 H, s, H-3/17), 5.63 (1 H, br s, H-5), 6.78–6.95 (5 H, m, Ar-H), 7.43 (2 H, d, J = 8.5 Hz, H-14/15); δ_C (100 MHz, $CDCl_3$) 51.7 (C-9), 55.4 (C-3/17), 55.9 (C-3/17), 87.7 (C-11), 94.1 (C-12), 111.6 (C-13), 112.0 (C-1/7), 114.3 (C-14/15), 114.5 (C-6), 122.8 (C-1/7), 125.2 (C-8), 135.1 (C-14/15), 144.9 (C-4), 146.6 (C-2/16), 161.7 (C-2/16), 185.7 (C-10); HRMS (ESI$^+$): Found: 319.0939; $C_{18}H_{16}NaO_4$ (MNa^+) Requires 319.0941 (0.7 ppm error).

Lab notebook reference: akc-bsc-011

1-(3,4-Dihydroxyphenyl)-4-phenylbut-3-yn-2-one (197i)

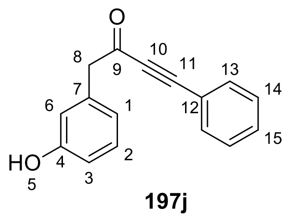


197i

Synthesised using general procedure B with phenylacetylene (0.26 mL, 2.33 mmol), THF (8 mL), Weinreb amide **195e** (123 mg, 0.582 mmol) and *n*-BuLi (0.81 mL, 2.04 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **197i** as a white solid (91 mg, 62%); mp 117–119 °C; R_f 0.81 (8:2 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3369, 2202, 1648, 1607, 1519, 1444, 1286, 1191, 1114, 1083, 758; δ_H (400 MHz, $(CD_3)_2CO$) 2.93 (1 H, s, H-3/5), 3.79 (2 H, s, H-9), 6.70 (1 H, dd, J = 8.0, 2.0 Hz, H-7), 6.82 (1 H, d, J = 8.0 Hz, H-6), 6.86 (1 H, d, J = 2.0 Hz, H-1), 7.42–7.48 (2 H, m, Ar-H), 7.50–7.58 (3 H, m, Ar-H), 7.92 (1 H, br s, H-3/5); δ_C (100 MHz, $(CD_3)_2CO$) 52.0 (C-9), 88.3 (C-11), 91.8 (C-12), 116.2 (C-6), 117.7 (C-1), 120.7 (C-8/13), 122.2 (C-7), 126.0 (C-8/13), 129.7 (C-14/15/16), 131.8 (C-14/15/16), 133.7 (C-14/15/16), 145.3 (C-2/5), 146.0 (C-2/5), 185.6 (C-10); HRMS (ESI$^+$): Found: 275.0678; $C_{16}H_{12}NaO_3$ (MNa^+) Requires 275.0679 (0.4 ppm error).

Lab notebook reference: akc04-59

1-(3-Hydroxyphenyl)-4-phenylbut-3-yn-2-one (197j)

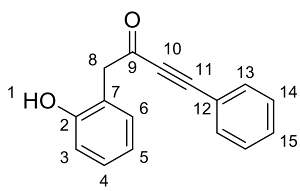


197j

Synthesised using general procedure B with phenylacetylene (0.34 mL, 3.07 mmol), THF (8.2 mL), Weinreb amide **195b** (200 mg, 1.02 mmol) and *n*-BuLi (1.02 mL, 2.56 mmol, 2.5 M in hexanes) stirring at RT for 45 min. Purification by column chromatography (10:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197j** as an orange oil (195 mg, 81%); R_f 0.57 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3371, 2202, 1655, 1589, 1489, 1456, 1284, 1078, 758; δ_H (400 MHz, $CDCl_3$) 3.89 (2 H, s, H-8), 5.44–5.61 (1 H, m, H-5), 6.78–6.84 (2 H, m, H-1/3,6), 6.89 (1 H, d, *J* = 8.0 Hz, H-1/3), 7.24 (1 H, dd, *J* = 8.0, 8.0 Hz, H-2), 7.32–7.40 (2 H, m, Ar-H), 7.42–7.50 (3 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 51.9 (C-8), 87.6 (C-10), 93.5 (C-11), 114.5 (C-1/3/6), 116.8 (C-1/3/6), 120.0 (C-7/12), 122.2 (C-1/3), 128.6 (C-13/14), 129.9 (C-2), 130.9 (C-15), 133.2 (C-13/14), 134.7 (C-4), 156.0 (C-4), 185.5 (C-9); HRMS (ESI$^+$): Found: 259.0731; $C_{16}H_{12}NaO_2$ (MNa^+) Requires 259.0730 (−0.5 ppm error), Found: 237.0916; $C_{16}H_{13}O_2$ (MH^+) Requires 237.0910 (−2.4 ppm error).

Lab notebook reference: akc-bsc-06-5

1-(2-Hydroxyphenyl)-4-phenylbut-3-yn-2-one (197k)

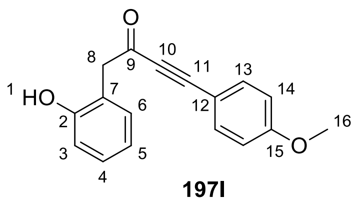


197k

Synthesised using general procedure B with phenylacetylene (2.0 mL, 18.1 mmol), THF (78 mL), Weinreb amide **195c** (1.18 g, 6.04 mmol) and *n*-BuLi (6.04 mL, 15.1 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197k** as a yellow solid (1.33 g, 93%); mp 106–108 °C; R_f 0.67 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3333, 2982, 2202, 1661, 1489, 1458, 1156,753; δ_H (400 MHz, $CDCl_3$) 4.01 (2 H, s, H-8), 6.27 (1 H, br s, H-1), 6.94–6.98 (2 H, m, Ar-H), 7.19–7.26 (2 H, m, Ar-H), 7.39 (2 H, m, H-13/14), 7.45–7.50 (1 H, m, Ar-H), 7.51–7.55 (2 H, m, H-13/14); δ_C (100 MHz, $CDCl_3$) 47.5 (C-8), 87.8 (C-10), 94.0 (C-11), 116.8 (CH), 119.6 (C-7/12), 120.4 (C-7/12), 121.0 (CH), 128.6 (C-13/14), 129.3 (CH), 131.1 (CH), 131.5 (CH), 133.3 (C-13/14), 154.8 (C-2), 187.0 (C-9); HRMS (ESI$^+$): Found: 259.0722; $C_{16}H_{12}NaO_2$ (MNa$^+$) Requires 259.0730 (3.1 ppm error), Found: 237.0914; $C_{16}H_{13}O_2$ (MH$^+$) Requires 237.0910 (−1.5 ppm error).

Lab notebook reference: akc04-13

1-(2-Hydroxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (197l)

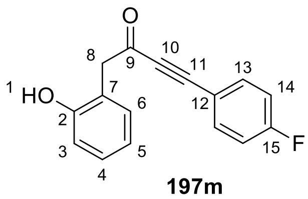


197l

Synthesised using general procedure B with 1-ethynyl-4-methoxybenzene (1.01 g, 7.68 mmol), THF (20 mL), Weinreb amide **195c** (500 mg, 2.56 mmol) and *n*-BuLi (2.56 mL, 6.40 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197l** as a yellow solid (478 mg, 70%); mp 108–110 °C; R_f 0.29 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3364, 2193, 1645, 1599, 1508, 1254, 1080, 834; δ_H (400 MHz, $CDCl_3$) 3.85 (3 H, s, H-16), 3.99 (2 H, s, H-8), 6.64 (1 H, s, H-1), 6.87–6.96 (4 H, m, Ar-H), 7.17–7.24 (2 H, m, H-3/4/5,6), 7.49 (2 H, d, J = 8.0 Hz, H-13/14); δ_C (100 MHz, $CDCl_3$) 47.6 (C-8), 55.4 (C-16), 87.0 (C-10), 95.8 (C-11), 111.2 (C-12), 114.4 (C-13/14), 117.1 (C-3/4/5), 120.7 (C-7), 121.0 (C-3/4/5), 129.2 (C-3/4/5), 131.5 (C-6), 135.5 (C-13/14), 154.9 (C-2), 162.0 (C-15), 187.2 (C-9); HRMS (ESI$^+$): Found: 289.0833; $C_{17}H_{14}NaO_3$ (MNa$^+$) Requires 289.0835 (0.6 ppm error).

Lab notebook reference: akc-bsc-011

4-(4-Fluorophenyl)-1-(2-hydroxyphenyl)but-3-yn-2-one (197m)

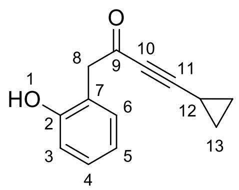


197m

Synthesised using general procedure B with 1-ethynyl-4-fluorobenzene (923 mg, 7.68 mmol), THF (20 mL), Weinreb amide **195c** (500 mg, 2.56 mmol) and *n*-BuLi (2.56 mL, 6.40 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **197m** as a yellow solid (430 mg, 66%); mp 115–117 °C; R_f 0.46 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3357, 2203, 1651, 1598, 1505, 1458, 1234, 1082, 838, 754; δ_H (400 MHz, $CDCl_3$) 3.99 (2 H, s, H-8), 6.25 (1 H, s, H-1), 6.89–6.97 (2 H, m, H-3/4/5), 7.08 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-14), 7.18–7.25 (2 H, m, H-3/4/5,6), 7.51 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HF}$ = 5.5 Hz, H-13); δ_C (100 MHz, $CDCl_3$) 47.4 (C-8), 87.7 (C-10), 92.8 (C-11), 115.7 (d, $^4J_{CF}$ = 4.0 Hz, C-12), 116.2 (d, $^2J_{CF}$ = 22.0 Hz, C-14), 116.8 (C-3/4/5), 120.4 (C-7), 121.1 (C-3/4/5), 129.3 (C-3/4/5), 131.5 (C-6), 135.6 (d, $^3J_{CF}$ = 8.5 Hz, C-13), 154.7 (C-2), 164.1 (d, $^1J_{CF}$ = 255 Hz, C-15), 186.8 (C-9); HRMS (ESI$^+$): Found: 277.0628; $C_{16}H_{11}FNaO_2$ (MNa^+) Requires 277.0635 (2.5 ppm error).

Lab notebook reference: akc-bsc-011

4-Cyclopropyl-1-(2-hydroxyphenyl)but-3-yn-2-one (197n)

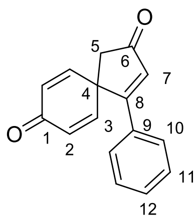


197n

Synthesised using general procedure B with ethynylcyclopropane (0.65 mL, 7.68 mmol), THF (35 mL), Weinreb amide **195c** (500 mg, 2.56 mmol) and *n*-BuLi (2.56 mL, 6.40 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **197n** as an off-white solid (452 mg, 88%); mp 98–100 °C; R_f 0.78 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3369, 2202, 1649, 1458, 1269, 755; δ_H (400 MHz, $CDCl_3$) 0.87–0.92 (2 H, m, H-13a), 0.97–1.04 (2 H, m, H-13b), 1.37–1.45 (1 H, m, H-12), 3.85 (2 H, s, H-8), 6.70 (1 H, br s, H-1), 6.88–6.93 (2 H, m, H-3,5), 7.11 (1 H, app. d, J = 7.5 Hz, H-6), 7.19 (1 H, app. dd, J = 8.0, 8.0 Hz, H-4); δ_C (100 MHz, $CDCl_3$) −0.1 (C-12), 10.2 (C-13), 47.5 (C-8), 76.8 (C-10), 103.2 (C-11), 117.1 (C-3/5), 120.6 (C-7), 120.9 (C-3/5), 129.2 (C-4), 131.3 (C-6), 154.9 (C-2), 187.2 (C-9); HRMS (ESI$^+$): Found: 223.0738; $C_{13}H_{12}NaO_2$ (MNa^+) Requires 223.0730 (−3.6 ppm error), Found: 201.0918; $C_{13}H_{13}O_2$ (MH^+) Requires 201.0910 (−3.8 ppm error).

Lab notebook reference: akc04-64

4-Phenylspiro[4.5]deca-3,6,9-triene-2,8-dione (198a)



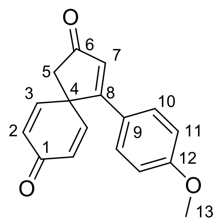
198a

Synthesised using general procedure C with ynone **197a** (100 mg, 0.423 mmol), $AgNO_3{\cdot}SiO_2$ (719 mg, 0.0423 mmol) in CH_2Cl_2 (4.2 mL) at 40 °C for 24 h. Afforded the *title compound* **198a** without further purification as a pale brown solid (94.0 mg, 94%); mp 124–126 °C; R_f 0.31 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3068, 1693, 1658, 1592, 1251, 859, 764; δ_H (400 MHz, $CDCl_3$) 2.80 (2 H, s, H-5), 6.49 (2 H, d, *J* = 10.0 Hz, H-2/3), 6.71 (1 H, s, H-7), 6.96 (2 H, d, *J* = 10.0 Hz, H-2/3), 7.34–7.40 (2 H, m, H-10/11), 7.42–7.48 (1 H, m, H-12), 7.49–7.54 (2 H, m, H-10/11); δ_C (100 MHz, $CDCl_3$) 46.9 (C-5), 51.2 (C-4), 127.4 (C-10/11), 129.0 (C-10/11), 129.9 (C-2/3/7), 130.0 (C-2/3/7), 131.6 (C-12), 132.9 (C-9), 151.4 (C-2/3), 173.9 (C-8), 184.7 (C-1), 203.3 (C-6); HRMS (ESI$^+$): Found: 259.0732; $C_{16}H_{12}NaO_2$ (MNa^+) Requires 259.0730 (−0.9 ppm error).

Lab notebook reference: akc02-27

Spectroscopic data matched those previously reported in the literature.[202]

4-(4-Methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (198b)



198b

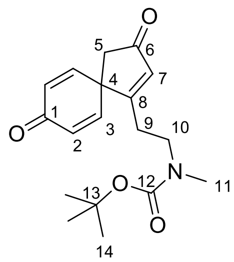
Synthesised using general procedure C with ynone **197b** (100 mg, 0.376 mmol), $AgNO_3{\cdot}SiO_2$ (638 mg, 0.0376 mmol) in CH_2Cl_2 (3.8 mL) at 40 °C for 3 h. Afforded the *title compound* **198b** without further purification as a brown solid (100 mg, 100%); mp 135–137 °C; R_f 0.33 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1691, 1659, 1602, 1586, 1509, 1251, 1179, 1027, 860, 833; δ_H (400 MHz, $CDCl_3$) 2.77 (2 H, s, H-5), 3.83 (3 H, s, H-13), 6.49 (2 H, d, *J* = 10.0 Hz, H-2), 6.64 (1 H, s, H-7), 6.87 (2 H, d, *J* = 8.0 Hz, H-10/11), 6.97 (2 H, d, *J* = 10.0 Hz, H-3), 7.50 (2 H, d, *J* = 8.0 Hz, H-10/11); δ_C (100 MHz, $CDCl_3$) 46.8 (C-5), 51.0 (C-4), 55.4 (C-

13), 114.4 (C-10/11), 125.3 (C-9), 127.5 (C-7), 129.5 (C-10/11), 129.7 (C-2), 152.0 (C-3), 162.4 (C-12), 173.1 (C-8), 184.8 (C-1), 203.1 (C-6); HRMS (ESI$^+$): Found: 289.0835; $C_{17}H_{14}NaO_3$ (MNa$^+$) Requires 289.0835 (0.1 ppm error), Found: 267.1009; $C_{17}H_{15}O_3$ (MH$^+$) Requires 267.1016 (2.4 ppm error).

Lab notebook reference: akc-bsc-010

Spectroscopic data matched those previously reported in the literature.[203]

tert-Butyl (2-(3,8-dioxospiro[4.5]deca-1,6,9-trien-1-yl)ethyl)(methyl)carbamate (198c)



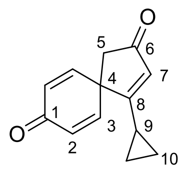
198c

Synthesised using general procedure C with ynone **197c** (73.5 mg, 0.232 mmol), $AgNO_3 \cdot SiO_2$ (394 mg, 0.0232 mmol) in CH_2Cl_2 (2.3 mL) at RT for 10 h. Afforded the *title compound* **198c** without further purification as a pale yellow oil (68.5 mg, 93%); R_f 0.22 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2975, 1720, 1688, 1662, 1624, 1615, 1392, 1365, 1165, 1144, 860; δ_H (400 MHz, $CDCl_3$) 1.43 (9 H, s, H-14), 2.31 (2 H, t, *J* = 7.0 Hz, H-9/10), 2.62 (2 H, s, H-5), 2.81 (3 H, s, H-11), 3.39 (2 H, t, *J* = 7.0 Hz, H-9/10), 6.20 (1 H, s, H-7), 6.43 (2 H, d, *J* = 9.5 Hz, H-2/3), 6.65–6.73 (2 H, br m, H-2/3); δ_C (100 MHz, $CDCl_3$) 27.2 (C-9/10), 28.4 (C-14), 34.2 (C-11), 45.1 (C-5), 47.1 (C-9/10), 52.8 (C-4), 80.0 (C-13), 130.9 (C-2/3), 132.0 (C-7), 149.4 (C-2/3), 155.5 (C-12), 176.9 (C-8), 184.5 (C-1), 203.8 (C-6); HRMS (ESI$^+$): Found: 340.1522; $C_{18}H_{23}NNaO_4$ (MNa$^+$) Requires 340.1519 (−0.8 ppm error).

Note: Majority of peaks broadened in ^{1}H NMR spectrum due to presence of rotamers.

Lab notebook reference: akc04-79/80

4-Cyclopropylspiro[4.5]deca-3,6,9-triene-2,8-dione (198e)

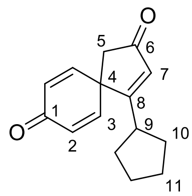


198e

Synthesised using general procedure C with ynone **197e** (101 mg, 0.504 mmol), $AgNO_3 \cdot SiO_2$ (857 mg, 0.0504 mmol) in CH_2Cl_2 (5.0 mL) at RT for 2 h. Afforded the *title compound* **198e** without further purification as a white solid (100 mg, 99%); mp 109–111 °C; R_f 0.45 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1689, 1666, 1624, 1605, 1401, 1252, 860; δ_H (400 MHz, $CDCl_3$) 0.77–0.82 (2 H, m, H-10a), 1.11−1.17 (2 H, m, H-10b), 1.18−1.24 (1 H, m, H-9), 2.64 (2 H, s, H-5), 5.75 (1 H, s, H-7), 6.45 (2 H, d, J = 10.0 Hz, H-2), 6.72 (2 H, d, J = 10.0 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 11.0 (C-9), 13.8 (C-10), 45.0 (C-5), 52.8 (C-4), 123.5 (C-7), 130.6 (C-2), 150.0 (C-3), 184.9 (C-8), 185.6 (C-6), 204.2 (C-1); HRMS (ESI$^+$): Found: 223.0733; $C_{13}H_{12}NaO_2$ (MNa^+) Requires 223.0730 (−1.7 ppm error), Found: 201.0906; $C_{13}H_{13}O_2$ (MH^+) Requires 201.0910 (2.2 ppm error).

Lab notebook reference: akc04-60

4-Cyclopentylspiro[4.5]deca-3,6,9-triene-2,8-dione (198f)



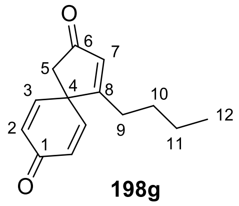
198f

Synthesised using general procedure C with ynone **197f** (60.2 mg, 0.264 mmol), $AgNO_3 \cdot SiO_2$ (448 mg, 0.0264 mmol) in CH_2Cl_2 (2.6 mL) at RT for 6 h. Afforded the *title compound* **198f** without further purification as a white solid (60.0 mg, 100%); mp 129–131 °C; R_f 0.43 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2958, 1697, 1657, 1621, 1609, 1403, 1249, 864; δ_H (400 MHz, $CDCl_3$) 1.37–1.50 (2 H, m, H-10/11), 1.52−1.67 (2 H, m, H-10/11), 1.68–1.82 (2 H, m, H-10/11), 1.83−1.95 (2 H, m, H-10/11), 2.30 (1 H, tt, J = 8.0, 8.0 Hz, H-5), 2.64 (2 H, s, H-5), 6.22 (1 H, s, H-7), 6.44 (2 H, d, J = 10.0 Hz, H-2/3), 6.69 (2 H, d, J = 10.0 Hz, H-2/3); δ_C (100 MHz, $CDCl_3$) 25.5 (C-10/11), 34.8 (C-10/11), 40.2 (C-9), 45.0 (C-5), 53.0 (C-4), 129.0 (C-7), 130.5 (C-2), 150.0 (C-3), 185.0 (C-1), 186.8 (C-8), 204.7 (C-6); HRMS (ESI$^+$): Found:

251.1033; $C_{15}H_{16}NaO_2$ (MNa^+) Requires 251.1043 (3.9 ppm error), Found: 229.1215; $C_{15}H_{17}O_2$ (MH^+) Requires 229.1223 (3.7 ppm error).

Lab notebook reference: akc04-82

4-Butylspiro[4.5]deca-3,6,9-triene-2,8-dione (198g)



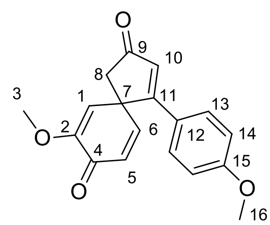
198g

Synthesised using general procedure C with ynone **197g** (85.4 mg, 0.395 mmol), $AgNO_3{\cdot}SiO_2$ (671 mg, 0.0395 mmol) in CH_2Cl_2 (4.0 mL) at RT for 24 h. Afforded the *title compound* **198g** without further purification as a pale yellow solid (80.3 mg, 94%); mp 100–102 °C; R_f 0.35 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2959, 2929, 2875, 2857, 1720, 1696, 1657, 1614, 1599, 1255, 1232, 862; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* = 7.5 Hz, H-12), 1.33 (2 H, qt, *J* = 7.5, 7.5 Hz, H-11), 1.52 (2 H, tt, *J* = 7.5, 7.5 Hz, H-10), 2.10 (2 H, t, *J* = 7.5 Hz, H-9), 2.65 (2 H, s, H-5), 6.22 (1 H, s, H-7), 6.45 (2 H, d, *J* = 9.0 Hz, H-2/3), 6.66 (2 H, d, *J* = 9.0 Hz, H-2/3); δ_C (100 MHz, $CDCl_3$) 13.7 (C-12), 22.2 (C-11), 28.8 (C-9), 29.5 (C-10), 45.0 (C-5), 52.6 (C-4), 130.58 (C-2/3), 130.61 (C-7), 150.0 (C-2/3), 181.6 (C-8), 184.9 (C-1), 204.6 (C-6); HRMS (ESI$^+$): Found: 239.1043; $C_{14}H_{16}NaO_2$ (MNa^+) Requires 239.1043 (−0.3 ppm error), Found: 217.1219; $C_{14}H_{17}O_2$ (MH^+) Requires 217.1223 (2.0 ppm error).

Lab notebook reference: akc04-75

Spectroscopic data matched those previously reported in the literature.[204]

7-Methoxy-4-(4-methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (198h)

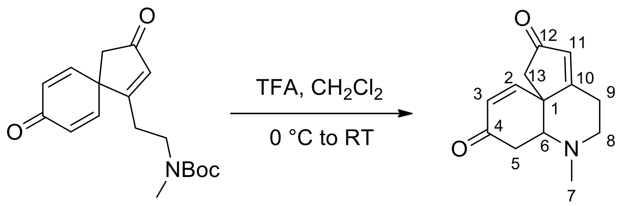


198h

Synthesised using general procedure C with ynone **197h** (59.0 mg, 0.199 mmol), $AgNO_3{\cdot}SiO_2$ (338 mg, 0.0199 mmol) in CH_2Cl_2 (2.0 mL) at 40 °C for 24 h. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **198h** an off-white oil (50.9 mg, 86%); R_f 0.14 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1691, 1664, 1636, 1603, 1587, 1509, 1258, 1208, 1177, 831; δ_H (400 MHz, $CDCl_3$) 2.78 (1 H, d, *J* = 18.5 Hz, H-8a), 2.86 (1 H, d, *J* = 18.5 Hz, H-8b), 3.66 (3 H, s, H-3/16), 3.83 (3 H, s, H-3/16), 5.86 (1 H, d, *J* = 2.5 Hz, H-1), 6.50 (1 H, d, *J* = 9.5 Hz, H-5), 6.61 (1 H, s, H-10), 6.85 (2 H, d, *J* = 8.5 Hz, H-13/14), 6.97 (1 H, dd, *J* = 9.5, 2.5 Hz, H-6), 7.48 (2 H, d, *J* = 8.5 Hz, H-13/14); δ_C (100 MHz, $CDCl_3$) 48.0 (C-8), 51.6 (C-7), 55.2 (C-3/16), 55.4 (C-3/16), 114.3 (C-13/14), 119.4 (C-1), 125.3 (C-12), 127.1 (C-10), 129.0 (C-5), 129.4 (C-13/14), 151.7 (C-2/15), 152.4 (C-6), 162.2 (C-2/15), 173.7 (C-11), 180.1 (C-4), 203.4 (C-9); HRMS (ESI$^+$): Found: 319.0947; $C_{18}H_{16}NaO_4$ (MNa^+) Requires 319.0941 (−2.0 ppm error).

Lab notebook reference: akc04-41

5-Methyl-4*a*,5,6,7-tetrahydrocyclopenta[*d*]quinoline-3,9(4*H*,10*H*)-dione (199)

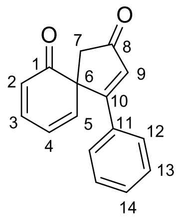


198c **199**

To a stirred solution of spirocyclic dienone **198c** (64.2 mg, 0.202 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added TFA (0.2 mL) dropwise. The mixture was warmed to RT and stirred for 2 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 EtOAc:MeOH) to afford the *title compound* **199** as a colourless oil (29.2 mg, 66%); R_f 0.47 (9:1 EtOAc:MeOH); ν_{max} (thin film)/cm^{-1} 2790, 1709, 1684, 1632, 1209; δ_H (400 MHz, $CDCl_3$) 2.23–2.32 (4 H, m, H-7, C*H*H′), 2.45–2.54 (2 H, m, H-6, C*H*H′), 2.58–2.75 (4 H, m, CH_2, CH*H′* (×2)), 2.87 (1 H, dd, *J* = 16.0, 2.5 Hz, C*H*H′), 3.10 (1 H, ddd, *J* = 11.0, 5.5, 2.5 Hz, CH*H′*), 6.00 (1 H, s, H-11), 6.09 (1 H, d, *J* = 10.0 Hz, H-3), 6.41 (1 H, dd, *J* = 10.0, 2.5 Hz, H-2); δ_C (100 MHz, $CDCl_3$) 29.7 (CH_2), 40.0 (CH_2), 42.1 (C-7), 45.9 (CH_2), 49.4 (C-1), 56.7 (CH_2), 70.2 (C-6), 127.7 (C-11), 129.2 (C-3), 149.8 (C-2), 181.3 (C-10), 196.1 (C-4/12), 204.9 (C-4/12); HRMS (ESI$^+$): Found: 218.1170; $C_{13}H_{16}NO_2$ (MH^+) Requires 218.1176 (2.5 ppm error).

Lab notebook reference: akc05-11

4-Phenylspiro[4.5]deca-3,7,9-triene-2,6-dione (201k)

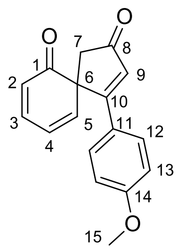


201k

Synthesised using general procedure C with ynone **197k** (115 mg, 0.487 mmol), $AgNO_3 \cdot SiO_2$ (826 mg, 0.0487 mmol) in CH_2Cl_2 (4.9 mL) at RT for 24 h. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **201k** a pale yellow oil (103 mg, 90%); R_f 0.22 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1659, 1595, 1195, 760; δ_H (400 MHz, $CDCl_3$) 2.54 (1 H, d, *J* = 18.0 Hz, H-7a), 2.78 (1 H, d, *J* = 18.0 Hz, H-7b), 6.34 (1 H, d, *J* = 10.0 Hz, H-2/4), 6.44–6.49 (2 H, m, Ar-H), 6.77 (1 H, s, H-9), 7.24–7.30 (1 H, m, H-2/3/4), 7.30–7.38 (4 H, m, H-12,13), 7.38–7.44 (1 H, m, H-14); δ_C (100 MHz, $CDCl_3$) 48.3 (C-7), 60.5 (C-6), 121.8 (C-2/3/4), 126.5 (C-2/4), 127.3 (C-12/13), 129.0 (C-12/13), 129.5 (C-9), 131.5 (C-14), 132.3 (C-11), 142.3 (C-2/3/4), 144.6 (C-5), 173.7 (C-10), 200.2 (C-1), 204.6 (C-8); HRMS (ESI$^+$): Found: 259.0723; $C_{16}H_{12}NaO_2$ (MNa^+) Requires 259.0730 (2.5 ppm error), Found: 237.0906; $C_{16}H_{13}O_2$ (MH^+) Requires 237.0910 (1.9 ppm error).

Lab notebook reference: akc04-76

4-(4-Methoxyphenyl)spiro[4.5]deca-3,7,9-triene-2,6-dione (201l)

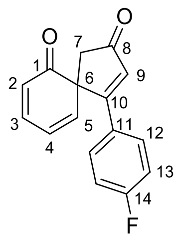


201l

Synthesised using general procedure C with ynone **197l** (50 mg, 0.188 mmol), $AgNO_3 \cdot SiO_2$ (319 mg, 0.0188 mmol) in CH_2Cl_2 (1.8 mL) at RT for 24 h. Afforded the *title compound* **201l** without further purification as a yellow oil (49.5 mg, 99%); R_f 0.25 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1689, 1659, 1602, 1587, 1510, 1262, 1179, 1026, 833, 731; δ_H (400 MHz, $CDCl_3$) 2.51 (1 H, d, *J* = 18.0 Hz, H-7a), 2.75 (1 H, d, *J* = 18.0 Hz, H-7b), 3.81 (3 H, s, H-15), 6.34 (1 H, d, J = 9.5 Hz, Ar-H), 6.45–6.47 (2 H, m, Ar-H), 6.68 (1 H, s, H-9), 6.85 (2 H, d, J = 8.5 Hz, H-12/13), 7.25–7.31 (3 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 48.3 (C-7), 55.4 (C-15), 60.4 (C-6), 114.4 (C-12/13), 121.5 (CH), 124.8 (C-11), 126.5 (CH), 127.2 (CH), 129.2 (C-12/13), 142.3 (CH), 145.0 (CH), 162.2 (C-14), 173.4 (C-10), 200.5 (C-1), 204.5 (C-8); HRMS (ESI^+): Found: 289.0834; $C_{17}H_{14}NaO_3$ (MNa^+) Requires 289.0835 (0.4 ppm error), Found: 267.1004; $C_{17}H_{15}O_3$ (MH^+) Requires 267.1016 (4.2 ppm error).

Lab notebook reference: akc-bsc-012

4-(4-Fluorophenyl)spiro[4.5]deca-3,7,9-triene-2,6-dione (201m)

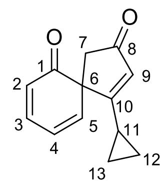


201m

Synthesised using general procedure C with ynone **197m** (98.8 mg, 0.389 mmol), $AgNO_3\cdot SiO_2$ (661 mg, 0.0389 mmol) in CH_2Cl_2 (3.9 mL) at RT for 48 h. Purification by column chromatography (8:2 EtOAc:hexane) afforded the *title compound* **201m** a yellow oil (88.7 mg, 90%); R_f 0.36 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1659, 1601, 1582, 1508, 1238, 1193, 1163, 836; δ_H (400 MHz, $CDCl_3$) 2.53 (1 H, d, J = 18.0 Hz, H-7a), 2.76 (1 H, d, J = 18.0 Hz, H-7b), 6.33 (1 H, d, J = 9.5 Hz, H-2/4), 6.42–6.50 (2 H, m, Ar-H), 6.70 (1 H, s, H-9), 7.03 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-13), 7.25–7.29 (1 H, m, Ar-H), 7.29–7.34 (2 H, m, H-12); δ_C (100 MHz, $CDCl_3$) 48.4 (C-7), 60.5 (C-6), 116.2 (d, $^2J_{CF}$ = 22.0 Hz, C-13), 121.9 (CH), 126.5 (CH), 128.6 (d, $^4J_{CF}$ = 3.0 Hz, C-11), 129.2 (C-9), 129.5 (d, $^3J_{CF}$ = 8.5 Hz, C-12), 142.4 (CH), 144.3 (C-5), 164.3 (d, $^1J_{CF}$ = 254 Hz, C-14), 172.3 (C-10), 200.1 (C-1), 204.3 (C-8); HRMS (ESI^+): Found: 277.0642; $C_{16}H_{11}FNaO_2$ (MNa^+) Requires 277.0635 (−2.4 ppm error), Found: 255.0818; $C_{16}H_{12}FO_2$ (MH^+) Requires 255.0816 (−0.7 ppm error).

Lab notebook reference: akc04-42

4-Cyclopropylspiro[4.5]deca-3,7,9-triene-2,6-dione (201n)

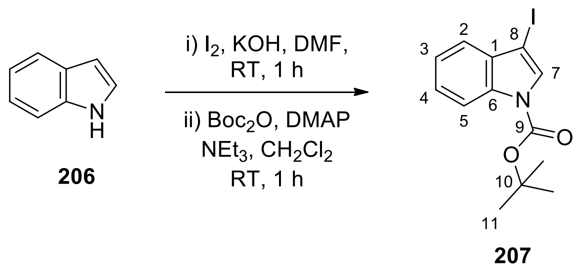


201n

Synthesised using general procedure C with ynone **197n** (108 mg, 0.538 mmol), $AgNO_3 \cdot SiO_2$ (915 mg, 0.0538 mmol) in CH_2Cl_2 (5.4 mL) at RT for 2 h. Afforded the *title compound* **201n** without further purification as a yellow oil (104 mg, 96%); R_f 0.34 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1660, 1632, 1607, 1557, 1200, 862; δ_H (400 MHz, $CDCl_3$) 0.68–0.79 (2 H, m, H-12/13), 0.97−1.09 (2 H, m, H-12/13), 1.20−1.28 (1 H, m, H-11), 2.39 (1 H, d, *J* = 18.0 Hz, H-7a), 2.77 (1 H, d, *J* = 18.0 Hz, H-7b), 5.72 (1 H, s, H-9), 6.23 (1 H, d, *J* = 9.5 Hz, H-2), 6.28 (1 H, d, *J* = 9.0 Hz, H-5), 6.47 (1 H, dd, *J* = 9.0, 5.5 Hz, H-4), 7.19 (1 H, ddd, *J* = 9.5, 5.5, 1.5 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 11.0 (C-11), 11.9 (C-12/13), 13.2 (C-12/13), 46.8 (C-7), 62.7 (C-6), 122.8 (C-4), 123.9 (C-9), 126.7 (C-2), 142.5 (C-3/5), 142.8 (C-3/5), 184.5 (C-10), 200.3 (C-1), 206.2 (C-8); HRMS (ESI$^+$): Found: 223.0732; $C_{13}H_{12}NaO_2$ (MNa^+) Requires 223.0730 (−1.3 ppm error), Found: 201.0907; $C_{13}H_{13}O_2$ (MH^+) Requires 201.0910 (1.3 ppm error).

Lab notebook reference: akc04-68

***tert*-Butyl 3-iodo-1*H*-indole-1-carboxylate (207)**



To a solution of indole **206** (1.00 g, 8.54 mmol) in DMF (20 mL) was added KOH (1.20 g, 21.3 mmol) followed by the addition of iodine (2.17 g, 8.54 mmol). The reaction mixture was stirred at RT for 1 h. The resulting brown solution was quenched with sat. aq. $Na_2S_2O_3$ (100 mL), extracted with diethyl ether (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then dissolved in CH_2Cl_2 (44 mL) and triethylamine (3.6 mL) followed by the sequential addition of dimethylaminopyridine (104 mg, 0.854 mmol) and di-*tert*-butyl dicarbonate (2.24 g, 10.2 mmol). The reaction was stirred at RT for 1 h, diluted with

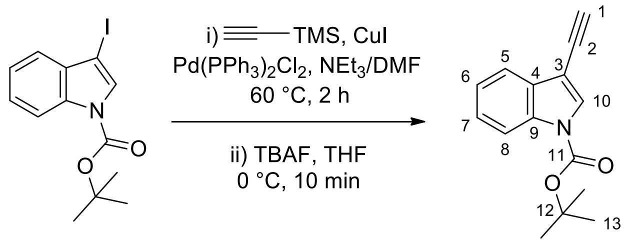
CH_2Cl_2 (100 mL), washed with water (70 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the *title compound* **207** as a clear and colourless oil (2.64 g, 90%); R_f 0.78 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2978, 1735, 1448, 1369, 1310, 1246, 1154, 1052, 744; δ_H (400 MHz, $CDCl_3$) 1.68 (9 H, s, H-11), 7.30–7.44 (3 H, m, Ar-H), 7.74 (1 H, s, H-7), 8.14 (1 H, br d, *J* = 8.0 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 28.2 (C-11), 65.4 (C-8), 84.3 (C-10), 115.1 (CH), 121.6 (CH), 123.4 (CH), 125.4 (CH), 130.2 (C-7), 132.3 (C-1/6), 135.0 (C-1/6), 148.8 (C-9).

Note: Some peaks broadened in ^{1}H and ^{13}C NMR spectra due to presence of rotamers.

Lab notebook reference: akc04-83

Spectroscopic data matched those previously reported in the literature.[205]

***tert*-Butyl 3-ethynyl-1*H*-indole-1-carboxylate (208)**



207 208

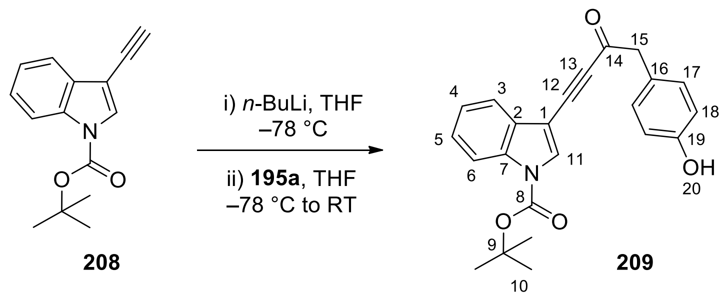
A solution of *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate **207** (2.63 g, 7.66 mmol) in triethylamine (7.7 mL) and DMF (7.7 mL) was degassed in a sonic bath for 30 min. $Pd(PPh_3)_2Cl_2$ (108 mg, 0.153 mmol) and CuI (58.4 mg, 0.307 mmol) were added, followed by ethynyltrimethylsilane (1.62 mL, 11.5 mmol) and the resulting solution was stirred at 60 °C for 2 h. The reaction mixture was cooled to RT, quenched with water (50 mL), extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then passed through a short plug of silica (10:1 hexane:EtOAc), concentrated and redissolved in THF (77 mL). The solution was then cooled to 0 °C, before adding TBAF (9.19 mL, 9.19 mmol, 1 M solution in THF) and stirring at 0 °C for 10 min. The reaction was then quenched by the addition of sat. aq. NH_4Cl (50 mL), extracted with diethyl ether (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (20:1 hexane:EtOAc, then 10:1 hexane:EtOAc) to afford the *title compound* **208** as a yellow oil (1.04 g, 56%); R_f 0.63 (10:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3292, 2980, 1734, 1451, 1358, 1227, 1148, 1081, 745; δ_H (400 MHz, $CDCl_3$) 1.70 (9 H, s, H-13), 3.25 (1 H, s, H-1), 7.29–7.41 (2 H, m, Ar-H), 7.70 (1 H, d, *J* = 8.0 Hz, Ar-H), 7.83 (1 H, s, H-

10), 8.17 (1 H, d, J = 8.0 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 28.1 (C-13), 75.8 (C-2/3), 80.7 (C-1), 84.4 (C-12), 102.3 (C-2/3), 115.2 (CH), 120.0 (CH), 123.2 (CH), 125.2 (CH), 129.9 (C-10), 130.4 (C-4/9), 134.5 (C-4/9), 149.0 (C-11).

Lab notebook reference: akc04-85

Spectroscopic data matched those previously reported in the literature.[54]

***tert*-Butyl 3-(4-(4-hydroxyphenyl)-3-oxobut-1-yn-1-yl)-1*H*-indole-1-carboxylate (209)**

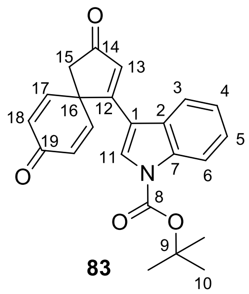


Synthesised using general procedure B with alkyne **208** (738 mg, 3.06 mmol), THF (8 mL), Weinreb amide **195a** (199 mg, 1.02 mmol) and *n*-BuLi (1.02 mL, 2.54 mmol, 2.5 M in hexanes) stirring at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the *title compound* **209** as a yellow oil (306 mg, 80%); R_f 0.37 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3374, 2980, 2188, 1743, 1369, 1232, 1150, 1072; δ_H (400 MHz, $CDCl_3$) 1.70 (9 H, s, H-10), 3.89 (2 H, s, H-15), 4.98 (1 H, br s, H-20), 6.87 (2 H, d, J = 8.0 Hz, Ar-H), 7.23 (2 H, d, J = 8.0 Hz, Ar-H), 7.32 (1 H, dd, J = 8.0, 7.5 Hz, H-4/5), 7.38 (1 H, dd, J = 8.0, 7.5 Hz, H-4/5), 7.51 (1 H, d, J = 8.0 Hz, Ar-H), 7.91 (1 H, s, H-11), 8.14 (1 H, d, J = 8.0 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 28.2 (C-10), 51.2 (C-15), 85.3 (C-1/9), 86.8 (C-1/9), 92.4 (C-12/13), 100.5 (C-12/13), 115.5 (CH), 115.8 (CH), 120.1 (C-3/6), 123.8 (C-4/5), 125.7 (C-4/5), 125.8 (C-16), 129.9 (C-2/7), 131.2 (C-17/18), 133.1 (C-11), 134.8 (C-2/7), 148.6 (C-8), 155.2 (C-19), 185.3 (C-14); HRMS (ESI$^+$): Found: 398.1357; $C_{23}H_{21}NNaO_4$ (MNa^+) Requires 398.1363 (1.5 ppm error).

Note: Some peaks broadened in ^{13}C NMR spectrum due to presence of rotamers.

Lab notebook reference: akc04-86

***tert*-Butyl 3-(3-oxo-5-(4-oxocyclohexa-2,5-dien-1-yl)cyclopent-1-en-1-yl)-1*H*-indole-1-carboxylate (83)**



83

Synthesised using general procedure C with ynone **209** (68.4 mg, 0.182 mmol), $AgNO_3{\cdot}SiO_2$ (310 mg, 0.0182 mmol) in CH_2Cl_2 (1.8 mL) at RT for 7 h. Afforded the *title compound* **83** without further purification as a pale brown solid (67.9 mg, 99%); mp 190–192 °C; R_f 0.46 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 1742, 1694, 1662, 1595, 1370, 1351, 1228, 1148, 1109, 861, 732; δ_H (400 MHz, $CDCl_3$) 1.63 (9 H, s, H-10), 2.76 (2 H, s, H-15), 6.50 (2 H, d, *J* = 9.5 Hz, H-17/18), 6.91 (1 H, s, H-13), 6.97 (2 H, d, *J* = 9.5 Hz, H-17/18), 7.34–7.45 (2 H, m, H-4,5), 7.78 (1 H, d, *J* = 8.0 Hz, H-3/6), 7.93 (1 H, s, H-11), 8.25 (1 H, d, *J* = 8.0 Hz, H-3/6); δ_C (100 MHz, $CDCl_3$) 28.0 (C-10), 45.6 (C-15), 51.9 (C-16), 85.4 (C-9), 114.0 (C), 115.7 (C-3/6), 120.3 (C-3/6), 124.2 (C-4/5), 125.7 (C-4/5), 127.8 (C), 128.2 (C-11/13), 128.4 (C-11/13), 129.7 (C-17/18), 135.8 (C), 148.4 (C), 151.9 (C-17/18), 165.9 (C), 184.3 (C-19), 203.4 (C-14).

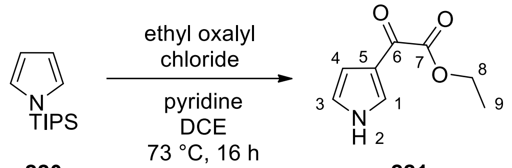
Note: Some peaks broadened in ^{13}C NMR spectrum due to presence of rotamers.

Lab notebook reference: akc04-87

Spectroscopic data matched those previously reported in the literature.[54]

6.9.3 Chapter 4

Ethyl 2-oxo-2-(1*H*-pyrrol-3-yl)acetate (221)

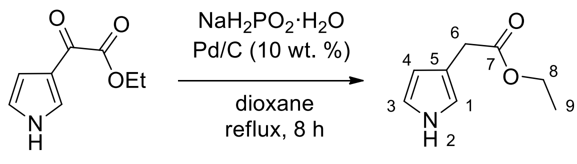


To a stirred solution of TIPS-pyrrole **220** (13.0 g, 58.2 mmol) in anhydrous 1,2-DCE (100 mL) at RT was added ethyl oxalyl chloride (19.5 mL, 175 mmol) and pyridine (14.1 mL, 175 mmol). The reaction mixture was then heated to 73 °C and stirred for 16 h. The reaction mixture was then cooled to RT and quenched with sat. aq. NH_4Cl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), organics were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (5:1 hexane:EtOAc, then 2:1 hexane:EtOAc) to afford the *title compound* **221** as a brown solid (3.53 g, 36%); mp 80–82 °C; R_f 0.22 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3300, 2983, 1732, 1641, 1509, 1422, 1261, 1235, 1072; δ_H (400 MHz, $CDCl_3$) 1.40 (3 H, t, *J* = 7.0 Hz, H-9), 4.39 (2 H, q, *J* = 7.0 Hz, H-8), 6.82–6.86 (2 H, m, H-1/3/4), 7.85–7.89 (1 H, m, H-1/3/4); δ_C (100 MHz, $CDCl_3$) 14.1 (C-9), 62.1 (C-8), 110.2 (C-1/3/4), 120.2 (C-1/3/4), 121.7 (C-5), 128.4 (C-1/3/4), 163.0 (C-7), 178.9 (C-6); HRMS (ESI$^+$): Found: 190.0480; $C_8H_9NNaO_3$ (MNa^+) Requires 190.0475 (−3.0 ppm error).

Lab notebook reference: akc05-52

Spectroscopic data matched those previously reported in the literature.[149]

Ethyl 2-(1*H*-pyrrol-3-yl)acetate (222)

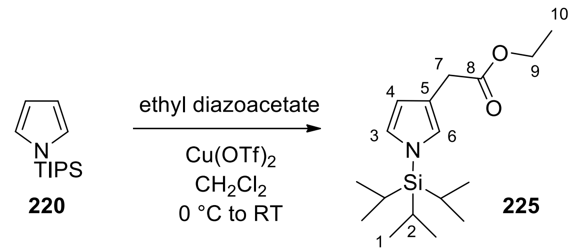


To a rbf under argon containing ethyl 2-oxo-2-(1*H*-pyrrol-3-yl)acetate **221** (3.53 g, 21.1 mmol) at RT was added Pd/C (706 mg, 6.63 mmol, 10 wt.%), followed by 1,4-dioxane (64 mL). A solution of $NaH_2PO_2{\cdot}H_2O$ (11.8 g, 110 mmol) in H_2O (11 mL) was then added and the reaction mixture was heated to 110 °C and stirred for 4 h. The mixture was cooled to RT and a second solution of $NaH_2PO_2{\cdot}H_2O$ (11.8 g, 110 mmol) in H_2O (11 mL) was added, the mixture was heated to 110 °C and stirred for 4 h. The reaction mixture was cooled to RT, filtered through Celite washing with several portions of diethyl ether. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude material. Purification by column chromatography (2:1 hexane:EtOAc) afforded the *title compound* **222** as a brown oil (1.23 g, 38%); R_f 0.51 (2:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3393, 2982, 1725, 1279, 1148, 1061; δ_H (400 MHz, $CDCl_3$) 1.28 (3 H, t, *J* = 7.0 Hz, H-9), 3.53 (2 H, s, H-6), 4.17 (2 H, q, *J* = 7.0 Hz, H-8), 6.18–6.22 (1 H, m, H-1/3/4), 6.73–6.77 (2 H, m, H-1/3/4), 8.17 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 14.2 (C-9), 33.0 (C-6), 60.6 (C-8), 109.2 (C-1/3/4), 115.6 (C-5), 116.5 (C-1/3/4), 118.0 (C-1/3/4), 172.6 (C-7).

Lab notebook reference: akc05-53

Spectroscopic data matched those previously reported in the literature.[151,206]

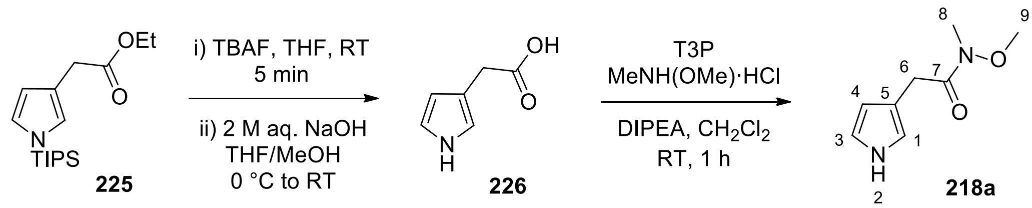
Ethyl 2-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)acetate (225)



To a stirred solution of TIPS-pyrrole **220** (3.00 g, 13.4 mmol) in CH_2Cl_2 (67 mL) at 0 °C was added ethyl diazoacetate (2.03 mL, 16.8 mmol, 87 wt.% in CH_2Cl_2) and $Cu(OTf)_2$ (486 mg, 1.34 mmol). The reaction mixture was then warmed to RT and stirred for 2 h. The reaction mixture was then quenched with water (50 mL). The organics were separated and the aqueous extracted with CH_2Cl_2 (2 x 50 mL). The organics were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (20:1 hexane:EtOAc) to afford the *title compound* **225** as a colourless oil (756 mg, 18%); R_f 0.65 (6:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2946, 2868, 1737, 1464, 1096; δ_H (400 MHz, $CDCl_3$) 1.10 (18 H, d, *J* = 7.5 Hz, H-1), 1.26 (3 H, t, *J* = 7.0 Hz, H-10), 1.43 (3 H, septet, *J* = 7.5 Hz, H-2), 3.51 (2 H, s, H-7), 4.15 (2 H, q, *J* = 7.0 Hz, H-9), 6.24–6.27 (1 H, m, H-4/6), 6.68–6.73 (2 H, m, H-3,4/6); δ_C (100 MHz, $CDCl_3$) 11.6 (C-2), 14.2 (C-10), 17.8 (C-1), 33.2 (C-7), 60.4 (C-9), 111.2 (C-4/6), 117.5 (C-5), 122.6 (C-4/6), 124.2 (C-3), 172.6 (C-8); HRMS (ESI^+): Found: 332.2012; $C_{17}H_{31}NNaO_2Si$ (MNa^+) Requires 332.2016 (1.2 ppm error), Found: 310.2191; $C_{17}H_{32}NO_2Si$ (MH^+) Requires 310.2197 (1.9 ppm error).

Lab notebook reference: akc05-19

N-Methoxy-N-methyl-2-(1H-pyrrol-3-yl)acetamide (218a)

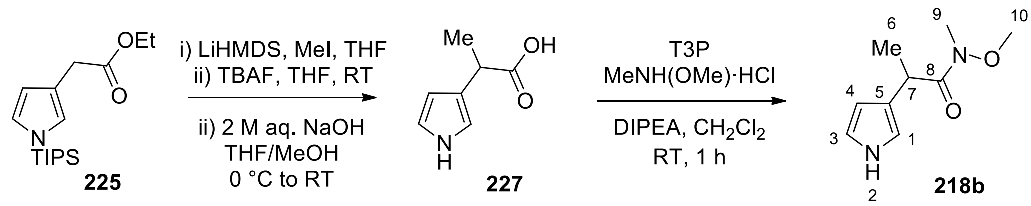


To a solution of ethyl ester **225** (740 mg, 2.39 mmol) in THF (7 mL) at RT was added TBAF (2.39 mL, 2.39 mmol, 1 M solution in THF). The reaction mixture was stirred for 5 min at RT. EtOAc was added (10 mL) and the organic layer washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude deprotected pyrrole as a brown oil. To a solution of the crude material (554 mg, 3.62 mmol) in THF (25 mL) and MeOH (2.5 mL) at 0 °C was added 2 M aq. NaOH (20 mL). The reaction mixture was warmed to RT and stirred for 4 h. 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% aq. HCl (15 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 crude pyrrole acid **226** as a brown oil (332 mg, 73%).

To a stirred solution of crude pyrrole acid **226** (332 mg, 2.65 mmol), MeNH(OMe)·HCl (284 mg, 2.92 mmol) and DIPEA (1.38 mL, 7.95 mmol) in CH_2Cl_2 (13 mL) was added T3P 50% in EtOAc (2.53 g, 3.98 mmol). The solution was stirred at RT for 1 h. Water (20 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 30 mL). The organics were combined, washed with 10% aq. HCl (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude material. Purification by column chromatography (9:1 hexane:EtOAc, then 5:1 EtOAc:hexane) afforded the *title compound* **218a** as a colourless oil (232 mg, 52%); R_f 0.43 (5:1 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3314, 2937, 1641, 1435, 1384, 1071, 1004, 768; δ_H (400 MHz, $CDCl_3$) 3.21 (3 H, s, H-8), 3.66 (2 H, s, H-6), 3.68 (3 H, s, H-9), 6.17–6.21 (1 H, m, H-1/3/4), 6.71–6.76 (2 H, m, H-1/3/4), 8.25 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 30.8 (C-6), 32.2 (C-8), 61.2 (C-9), 109.3 (C-1/3/4), 116.2 (C-5), 116.6 (C-1/3/4), 117.8 (C-1/3/4), 173.4 (C-7); HRMS (ESI$^+$): Found: 191.0792; $C_8H_{12}N_2NaO_2$ (MNa$^+$) Requires 191.0791 (−0.4 ppm error), Found: 169.0979; $C_8H_{13}N_2O_2$ (MH$^+$) Requires 169.0972 (−4.6 ppm error).

Lab notebook reference: akc05-20/22/23

N-Methoxy-N-methyl-2-(1H-pyrrol-3-yl)propanamide (218b)



To a solution of ethyl ester **225** (500 mg, 1.62 mmol) in THF (8 mL) at −78 °C was added LiHMDS (2.42 mL, 2.42 mmol, 1 M solution in THF) dropwise. The resulting solution was then stirred at 0 °C for 30 min. The solution was then recooled to −78 °C and MeI (0.30 mL, 4.85 mmol) was added dropwise. The reaction mixture was warmed to RT and stirred for 2 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL). The organics were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo* to afford the crude alkylated product as a yellow oil (522 mg, 100%).

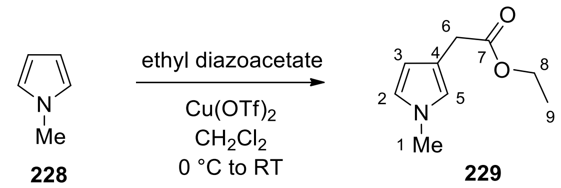
To a solution of the crude alkylated product (518 mg, 1.60 mmol) in THF (5 mL) at RT was added TBAF (1.60 mL, 1.60 mmol, 1 M solution in THF). The reaction mixture was stirred for 5 min at RT. EtOAc was added (10 mL) and the organic layer washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude deprotected pyrrole as a brown oil. To a solution of the crude material (447 mg, 2.92 mmol) in THF (20 mL) and MeOH (2 mL) at 0 °C was added 2 M aq. NaOH (16 mL). The reaction mixture was warmed to RT and stirred for 21 h. 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% aq. HCl (15 mL) until pH = 1 and then extracted with EtOAc (3 x 20 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude pyrrole acid **227** as a brown oil (191 mg, 86%).

To a stirred solution of crude pyrrole acid **227** (187 mg, 1.34 mmol), MeNH(OMe)·HCl (144 mg, 1.48 mmol) and DIPEA (0.70 mL, 4.03 mmol) in CH_2Cl_2 (7 mL) was added T3P 50% in EtOAc (1.28 g, 2.01 mmol). The solution was stirred at RT for 1 h. Water (10 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude material. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 EtOAc:hexane) afforded the *title compound* **218b** as a pale orange oil (201 mg, 82%); R_f 0.36 (1:1 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3313, 2972, 2935, 1640, 1460, 1384, 1071, 989, 769; δ_H (400 MHz, $CDCl_3$) 1.44 (3 H, d, J = 7.5 Hz, H-6), 3.19 (3 H, s, H-9), 3.62 (3 H, s, H-10), 4.12–4.22 (1 H, m, H-7), 6.16–6.22 (1 H, m, H-1/3/4), 6.67–6.74 (2 H, m, H-1/3/4), 8.24 (1 H, br s, H-2); δ_C (100

MHz, $CDCl_3$) 19.3 (C-6), 32.3 (C-9), 33.9 (C-7), 61.3 (C-10), 107.7 (C-1/3/4), 115.1 (C-1/3/4), 117.7 (C-1/3/4), 123.9 (C-5), 176.5 (C-8); HRMS (ESI$^+$): Found: 205.0940; $C_9H_{14}N_2NaO_2$ (MNa$^+$) Requires 205.0947 (3.8 ppm error), Found: 183.1121; $C_9H_{15}N_2O_2$ (MH$^+$) Requires 183.1128 (−4.1 ppm error).

Lab notebook reference: akc06-12/13/14/16

Ethyl 2-(1-methyl-1*H*-pyrrol-3-yl)acetate (229)



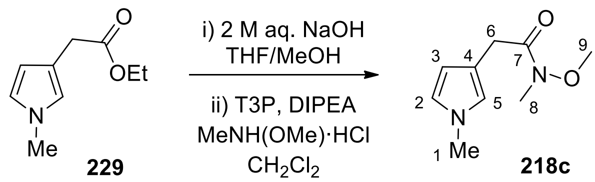
Procedure based on *US Pat.*, US2004192720A1, 2004.

To a 100 mL rbf was added *N*-methyl pyrrole **228** (6.87 g, 84.7 mmol) and $Cu(OTf)_2$ (160 mg, 0.44 mmol). This mixture was heated to 40 °C and ethyl diazoacetate (25 mL, 29.4 mmol, 15% in toluene) was added dropwise over 2.5 h. After addition was complete the reaction mixture was maintained at 50 °C for a further 15 min. The reaction mixture was then filtered through a short pad of Celite, washed through with CH_2Cl_2 (50 mL) and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 85:15 hexane:EtOAc) to afford the *title compound* **229** as a yellow oil (682 mg, 14%); R_f 0.44 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2981, 1733, 1508, 1300, 1267, 1241, 1164, 1033, 764; δ_H (400 MHz, $CDCl_3$) 1.28 (3 H, t, *J* = 7.0 Hz, H-9), 3.47 (2 H, s, H-6), 3.62 (3 H, s, H-1), 4.16 (2 H, q, *J* = 7.0 Hz, H-8), 6.06–6.10 (1 H, m, H-3), 6.52–6.58 (2 H, m, H-2,5); δ_C (100 MHz, $CDCl_3$) 14.2 (C-9), 33.1 (C-6), 36.1 (C-1), 60.5 (C-8), 108.9 (C-3), 115.6 (C-4), 120.5 (C-2/5), 121.7 (C-2/5), 172.6 (C-7); HRMS (ESI$^+$): Found: 190.0846; $C_9H_{13}NNaO_2$ (MNa$^+$) Requires 190.0838 (3.7 ppm error).

Lab notebook reference: akc07-72

Spectroscopic data matched those previously reported in the literature.[207]

_N_-Methoxy-_N_-methyl-2-(1-methyl-1_H_-pyrrol-3-yl)acetamide (218c)

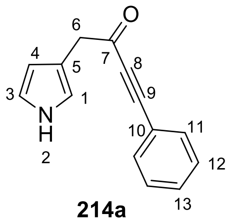


To a solution of ethyl ester **229** (359 mg, 2.15 mmol) in THF (15.1 mL) and MeOH (1.5 mL) at 0 °C was added 2 M aq. NaOH (11.8 mL). The reaction mixture was warmed to RT and stirred for 3.5 h. Water (20 mL) was added and the aqueous layer was washed with EtOAc (20 mL). The organic extract was discarded. The aqueous layer was acidified with 10% aq. HCl (8 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 crude pyrrole acid as a brown oil (372 mg, 100%).

To a stirred solution of crude pyrrole acid (372 mg, 2.67 mmol), MeNH(OMe)·HCl (286 mg, 2.94 mmol) and DIPEA (1.4 mL, 8.01 mmol) in CH_2Cl_2 (13 mL) was added T3P 50% in EtOAc (2.55 g, 4.01 mmol). The solution was stirred at RT for 1 h. Water (15 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 20 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the *title compound* **218c** as a clear and colourless oil (360 mg, 74%); R_f 0.14 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2937, 1655, 1507, 1419, 1379, 1160, 1006, 764; δ_H (400 MHz, $CDCl_3$) 3.20 (3 H, s, H-8), 3.61 (5 H, s, H-1/6), 3.69 (3 H, s, H-9), 6.04–6.09 (1 H, m, H-3), 6.51–6.54 (1 H, m, H-2/5), 6.55–6.58 (1 H, m, H-2/5); δ_C (100 MHz, $CDCl_3$) 30.8 (C-1/6), 32.2 (C-8), 36.0 (C-1/6), 61.2 (C-9), 109.0 (C-3), 116.2 (C-4), 120.5 (C-2/5), 121.5 (C-2/5), 173.4 (C-7); HRMS (ESI^+): Found: 205.0941; $C_9H_{14}N_2NaO_2$ (MNa^+) Requires 205.0947 (3.3 ppm error).

Lab notebook reference: akc07-76

4-Phenyl-1-(1*H*-pyrrol-3-yl)but-3-yn-2-one (214a)

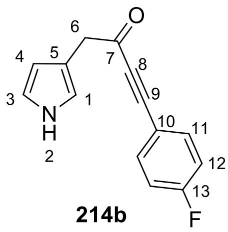


214a

Synthesised using general procedure B with phenylacetylene (0.44 mL, 4.02 mmol), THF (11 mL), Weinreb amide **218a** (225 mg, 1.34 mmol) and *n*-BuLi (1.34 mL, 3.35 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 7:1 hexane:EtOAc) afforded the *title compound* **214a** as a yellow oil (186 mg, 66%); R_f 0.74 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3389, 2200, 1657, 1489, 1285, 1070, 1058, 756, 687; δ_H (400 MHz, $CDCl_3$) 3.85 (2 H, s, H-6), 6.23–6.27 (1 H, m, H-1/3/4), 6.78–6.82 (2 H, m, H-1/3/4), 7.35–7.40 (2 H, m, H-11/12), 7.42–7.48 (1 H, m, H-13), 7.51–7.56 (2 H, m, H-11/12), 8.27 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 43.9 (C-6), 87.9 (C-8), 91.7 (C-9), 109.6 (C-1/4), 114.5 (C-5), 117.2 (C-1/4), 118.3 (C-3), 120.1 (C-10), 128.5 (C-11/12), 130.6 (C-13), 133.0 (C-11/12), 186.3 (C-7); HRMS (ESI$^+$): Found: 232.0739; $C_{14}H_{11}NNaO$ (MNa^+) Requires 232.0733 (−2.8 ppm error), Found: 210.0920; $C_{14}H_{12}NO$ (MH^+) Requires 210.0913 (−3.1 ppm error).

Lab notebook reference: akc05-24

4-(4-Fluorophenyl)-1-(1*H*-pyrrol-3-yl)but-3-yn-2-one (214b)



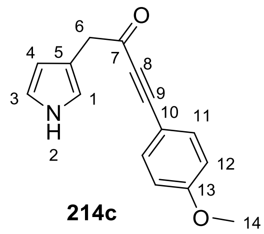
214b

Synthesised using general procedure B with 1-ethynyl-4-fluorobenzene (1.39 mg, 1.16 mmol), THF (3.2 mL), Weinreb amide **218a** (65.0 mg, 0.386 mmol) and *n*-BuLi (0.39 mL, 0.966 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 6:1 hexane:EtOAc) afforded the *title compound* **214b** as a pale brown solid (65.6 mg, 75%); mp 67–69 °C; R_f 0.59 (3:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3393, 2203, 1655, 1599, 1505, 1232, 1156, 1071, 1058, 838; δ_H (400 MHz, $CDCl_3$) 3.83 (2 H, s, H-6), 6.21–6.26 (1 H, m, H-1/3/4), 6.77–6.83 (2 H, m, H-1/3/4), 7.07 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-12), 7.52 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HF}$ 5.5 Hz, H-11), 8.24 (1 H, br s, H-2);

δ_C (100 MHz, $CDCl_3$) 43.8 (C-6), 87.9 (C-8), 90.6 (C-9), 109.7 (C-1/3/4), 114.5 (C-5), 116.1 (d, $^2J_{CF}$ = 22.0 Hz, C-12), 116.2 (d, $^4J_{CF}$ = 4.0 Hz, C-10), 117.2 (C-1/3/4), 118.3 (C-1/3/4), 135.3 (d, $^3J_{CF}$ = 8.5 Hz, C-11), 163.9 (d, $^1J_{CF}$ = 253 Hz, C-13), 186.2 (C-7); HRMS (ESI$^+$): Found: 250.0635; $C_{14}H_{10}FNNaO$ (MNa$^+$) Requires 250.0639 (1.4 ppm error).

Lab notebook reference: akc05-60

4-(4-Methoxyphenyl)-1-(1*H*-pyrrol-3-yl)but-3-yn-2-one (214c)

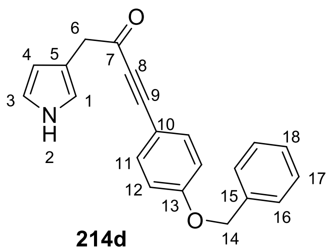


214c

Synthesised using general procedure B with 1-ethynyl-4-methoxybenzene (177 mg, 1.34 mmol), THF (3.6 mL), Weinreb amide **218a** (75 mg, 0.446 mmol) and *n*-BuLi (0.45 mL, 1.12 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 5:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded the *title compound* **214c** as a yellow solid (93.5 mg, 88%); mp 82–84 °C; R_f 0.78 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3393, 2193, 1655, 1600, 1508, 1251, 1169, 1070, 1057, 1025, 833; δ_H (400 MHz, $CDCl_3$) 3.83 (2 H, s, H-6), 3.84 (3 H, s, H-14), 6.23–6.26 (1 H, m, H-1/3/4), 6.77–6.82 (2 H, m, H-1/3/4), 6.88 (2 H, d, *J* = 8.5 Hz, H-11), 7.48 (2 H, d, *J* = 8.5 Hz, H-12), 8.25 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 43.8 (C-6), 55.4 (C-14), 87.9 (C-8), 92.9 (C-9), 109.7 (C-1/4), 111.9 (C-10), 114.3 (C-11), 114.8 (C-5), 117.1 (C-1/4), 118.2 (C-3), 135.1 (C-12), 161.5 (C-13), 186.4 (C-7); HRMS (ESI$^+$): Found: 262.0839; $C_{15}H_{13}NNaO_2$ (MNa$^+$) Requires 262.0838 (0.0 ppm error), Found: 240.1024; $C_{15}H_{14}NO_2$ (MH$^+$) Requires 240.1019 (−2.2 ppm error).

Lab notebook reference: akc05-72

4-(4-(Benzyloxy)phenyl)-1-(1*H*-pyrrol-3-yl)but-3-yn-2-one (214d)



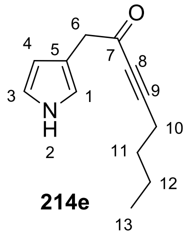
214d

Synthesised using general procedure B with 1-(benzyloxy)-4-ethynylbenzene*[208] (260 mg, 1.25 mmol), THF (3.4 mL), Weinreb amide **218a** (70.0 mg, 0.416 mmol) and *n*-BuLi (0.42 mL, 1.04 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (7:1 hexane:EtOAc, then 5:1 hexane:EtOAc) afforded the *title compound* **214d** as a pale brown solid (127 mg, 97%); mp 82–84 °C; R_f 0.23 (5:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3392, 2197, 1659, 1601, 1508, 1250, 1170, 1078, 1058, 833, 698; δ_H (400 MHz, $CDCl_3$) 3.83 (2 H, s, H-6), 5.10 (2 H, s, H-14), 6.22–6.27 (1 H, m, H-1/3/4), 6.77–6.83 (2 H, m, H-1/3/4), 6.96 (2 H, d, *J* = 8.5 Hz, H-11/12), 7.33–7.45 (5 H, m, H-16,17,18), 7.48 (2 H, d, *J* = 8.5 Hz, H-11/12), 8.24 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 43.8 (C-6), 70.1 (C-14), 87.9 (C-8), 92.8 (C-9), 109.7 (C-1/3/4), 112.2 (C-10/15), 114.8 (C-5), 115.1 (C-11/12), 117.1 (C-1/3/4), 118.2 (C-1/3/4), 127.5 (C-16/17), 128.2 (C-18), 128.7 (C-16/17), 135.1 (C-11/12), 136.1 (C-10/15), 160.7 (C-13), 186.4 (C-7); HRMS (ESI$^+$): Found: 338.1144; $C_{21}H_{17}NNaO_2$ (MNa^+) Requires 338.1151 (2.2 ppm error), Found: 316.1331; $C_{21}H_{18}NO_2$ (MH^+) Requires 316.1332 (0.5 ppm error).

Lab notebook reference: akc05-62

*Material made by W. Unsworth

1-(1*H*-Pyrrol-3-yl)oct-3-yn-2-one (214e)



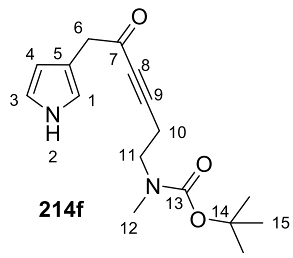
214e

Synthesised using general procedure B with hex-1-yne (0.16 mL, 1.43 mmol), THF (3.8 mL), Weinreb amide **218a** (80.0 mg, 0.476 mmol) and *n*-BuLi (0.48 mL, 1.19 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the *title compound* **214e** as a yellow oil

(80.5 mg, 89%); R_f 0.75 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3394, 2959, 2933, 2873, 2210, 1665, 1235, 1071, 765; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.5 Hz, H-13), 1.40 (2 H, app. sextet, J = 7.5 Hz, H-12), 1.54 (2 H, app. pentet, J = 7.5 Hz, H-11), 2.35 (2 H, t, J = 7.5 Hz, H-10), 3.72 (2H, s, H-6), 6.15–6.20 (1 H, m, H-1/3/4), 6.71–6.74 (1 H, m, H-1/3/4), 6.75–6.79 (1 H, m, H-1/3/4), 8.22 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 13.5 (C-13), 18.7 (C-10), 21.8 (C-12), 29.7 (C-11), 43.9 (C-6), 80.9 (C-8), 95.2 (C-9), 109.5 (C-1/3/4), 114.6 (C-5), 117.0 (C-1/3/4), 118.1 (C-1/3/4), 186.5 (C-7); HRMS (ESI$^+$): Found: 212.1047; $C_{12}H_{15}NNaO$ (MNa^+) Requires 212.1046 (−0.4 ppm error), Found: 190.1229; $C_{12}H_{16}NO$ (MH^+) Requires 190.1226 (−1.4 ppm error).

Lab notebook reference: akc05-58

tert-Butyl methyl(5-oxo-6-(1_H_-pyrrol-3-yl)hex-3-yn-1-yl)carbamate (214f)



214f

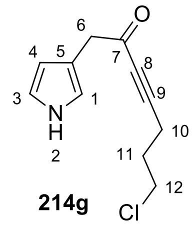
Synthesised using general procedure B with _tert_-butyl but-3-yn-1-yl(methyl)carbamate*[52] (262 mg, 1.43 mmol), THF (3.9 mL), Weinreb amide **218a** (80.0 mg, 0.476 mmol) and _n_-BuLi (0.48 mL, 1.19 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded the _title compound_ **214f** as a yellow oil (121 mg, 88%); R_f 0.67 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3334, 2976, 2935, 2211, 1669, 1481, 1393, 1366, 1168, 1145; δ_H (400 MHz, $CDCl_3$) 1.47 (9 H, s, H-15), 2.52–2.60 (2 H, m, H-10), 2.87 (3 H, s, H-12), 3.35–3.42 (2 H, m, H-11), 3.70 (2H, s, H-6), 6.11–6.15 (1 H, m, H-1/3/4), 6.68–6.72 (1 H, m, H-1/3/4), 6.72–6.77 (1 H, m, H-1/3/4), 8.42 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 18.5 (C-10), 28.4 (C-15), 35.0 (C-12), 43.9 (C-6), 47.3 (C-11), 79.9 (C-14), 81.8 (C-8), 91.6 (C-9), 109.5 (C-1/3/4), 114.5 (C-5), 117.1 (C-1/3/4), 118.1 (C-1/3/4), 155.4 (C-13), 185.8 (C-7); HRMS (ESI$^+$): Found: 313.1521; $C_{16}H_{22}N_2NaO_3$ (MNa^+) Requires 313.1523 (0.6 ppm error).

Note: Majority of peaks broadened in ^{1}H NMR spectrum due to presence of rotamers.

Lab notebook reference: akc05-76

*Material made by J. Liddon

7-Chloro-1-(1*H*-pyrrol-3-yl)hept-3-yn-2-one (214g)

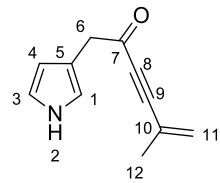


214g

Synthesised using general procedure B with 5-chloropent-1-yne (0.13 mL, 1.25 mmol), THF (3.3 mL), Weinreb amide **218a** (70.0 mg, 0.416 mmol) and *n*-BuLi (0.42 mL, 1.25 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded the *title compound* **214g** as an orange oil (84.0 mg, 96%); R_f 0.34 (3:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3392, 2924, 2211, 1665, 1234, 1071, 765; δ_H (400 MHz, $CDCl_3$) 1.98 (2 H, app. pentet, *J* = 6.5 Hz, H-11), 2.54 (2 H, t, *J* = 6.5 Hz, H-10), 3.56 (2 H, t, *J* = 6.5 Hz, H-12), 3.71 (2H, s, H-6), 6.14–6.20 (1 H, m, H-1/3/4), 6.71–6.75 (1 H, m, H-1/3/4), 6.75–6.80 (1 H, m, H-1/3/4), 8.26 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 16.4 (C-10), 30.3 (C-11), 43.2 (C-12), 43.8 (C-6), 81.4 (C-8), 92.7 (C-9), 109.5 (C-1/3/4), 114.5 (C-5), 117.1 (C-1/3/4), 118.2 (C-1/3/4), 186.3 (C-7); HRMS (ESI$^+$): Found: 232.0497; $C_{11}H_{12}{}^{35}ClNNaO$ (MNa^+) Requires 232.0500 (1.2 ppm error).

Lab notebook reference: akc05-74

5-Methyl-1-(1*H*-pyrrol-3-yl)hex-5-en-3-yn-2-one (214h)



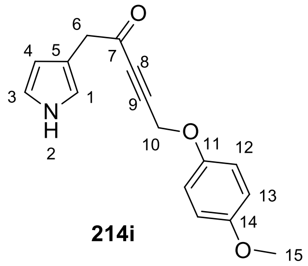
214h

Synthesised using general procedure B with 2-methylbut-1-en-3-yne (0.12 mL, 1.25 mmol), THF (3. mL), Weinreb amide **218a** (70.0 mg, 0.416 mmol) and *n*-BuLi (0.42 mL, 1.04 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 5:1 hexane:EtOAc) afforded the *title compound* **214h** as an orange oil (59.0 mg, 82%); R_f 0.77 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3393, 2923, 2195, 2165, 1660, 1296, 1118, 764; δ_H (400 MHz, $CDCl_3$) 1.92 (3 H, s, H-12), 3.77 (2H, s, H-6), 5.48–5.53 (1 H, m, H-11a), 5.54–5.58 (1 H, m, H-11b), 6.17–6.22 (1 H, m, H-1/3/4), 6.72–6.81 (1 H, m, H-1/3/4), 8.23 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 22.4 (C-12), 43.8 (C-6), 86.7 (C-8), 92.5 (C-9), 109.6 (C-1/3/4), 114.5 (C-5), 117.1 (C-1/3/4), 118.2 (C-1/3/4), 124.9 (C-10),

127.5 (C-11), 186.3 (C-7); HRMS (ESI$^+$): Found: 196.0729; $C_{11}H_{11}NNaO$ (MNa^+) Requires 196.0733 (2.2 ppm error).

Lab notebook reference: akc05-66

5-(4-Methoxyphenoxy)-1-(1*H*-pyrrol-3-yl)pent-3-yn-2-one (214i)

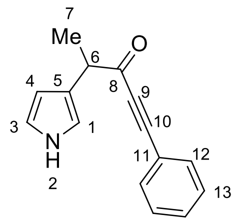


214i

Synthesised using general procedure B with 1-methoxy-4-(prop-2-yn-1-yloxy)benzene (203 mg, 1.25 mmol), THF (3.3 mL), Weinreb amide **218a** (70.0 mg, 0.416 mmol) and *n*-BuLi (0.42 mL, 1.04 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (7:1 hexane:EtOAc, then 5:1 hexane:EtOAc) afforded the *title compound* **214i** as an orange oil (75.1 mg, 67%); R_f 0.66 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3395, 2910, 2217, 1672, 1506, 1206, 1039, 826; δ_H (400 MHz, $CDCl_3$) 3.72 (2 H, s, H-6), 3.80 (3 H, s, H-15), 4.77 (2 H, s, H-16), 6.09–6.13 (1 H, m, H-1/3/4), 6.62–6.66 (1 H, m, H-1/3/4), 6.71–6.75 (1 H, m, H-1/3/4), 6.83–6.93 (4 H, m, H-12,13), 8.20 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 43.7 (C-6), 55.7 (C-15), 56.6 (C-16), 85.6 (C-8), 87.3 (C-9), 109.5 (C-1/3/4), 113.7 (C-5), 114.6 (C-12/13), 116.3 (C-12/13), 117.2 (C-1/3/4), 118.2 (C-1/3/4), 151.4 (C-11/14), 154.7 (C-11/14), 185.3 (C-7); HRMS (ESI$^+$): Found: 292.0944; $C_{16}H_{15}NNaO_3$ (MNa^+) Requires 292.0944 (0.2 ppm error), Found: 270.1116; $C_{16}H_{16}NO_3$ (MH^+) Requires 270.1125 (3.1 ppm error).

Lab notebook reference: akc05-63

1-Phenyl-4-(1*H*-pyrrol-3-yl)pent-1-yn-3-one (214j)

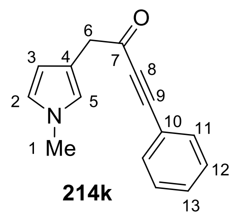


214j

Synthesised using general procedure B with phenylacetylene (0.34 mL, 3.08 mmol), THF (8 mL), Weinreb amide **218b** (187 mg, 1.03 mmol) and *n*-BuLi (1.03 mL, 2.57 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **214j** as an orange oil (204 mg, 89%); R_f 0.75 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3392, 2975, 2196, 1651, 1489, 1443, 1287, 1122, 1069, 1042, 970, 756, 687; δ_H (400 MHz, $CDCl_3$) 1.57 (3 H, d, *J* = 7.5 Hz, H-7), 3.92 (1 H, q, *J* = 7.5 Hz, H-6), 6.24–6.29 (1 H, m, H-1/3/4), 6.75–6.82 (2 H, m, H-1/3/4), 7.33–7.39 (2 H, m, H-13), 7.41–7.47 (1 H, m, H-14), 7.51–7.54 (2 H, m, H-12), 8.23 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 16.8 (C-7), 47.3 (C-6), 87.3 (C-9), 92.0 (C-10), 108.1 (C-1/3/4), 115.9 (C-1/3/4), 118.2 (C-1/3/4), 120.3 (C-11), 121.5 (C-5), 128.5 (C-13), 130.5 (C-14), 133.0 (C-12), 189.5 (C-8); HRMS (ESI$^+$): Found: 246.0886; $C_{15}H_{13}NNaO$ (MNa^+) Requires 246.0889 (1.5 ppm error), Found: 224.1067; $C_{15}H_{14}NO$ (MH^+) Requires 224.1070 (−1.4 ppm error).

Lab notebook reference: akc06-20

1-(1-Methyl-1*H*-pyrrol-3-yl)-4-phenylbut-3-yn-2-one (214k)

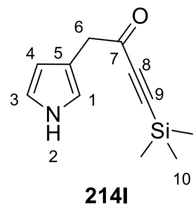


214k

Synthesised using general procedure B with phenylacetylene (0.30 mL, 2.77 mmol), THF (10 mL), Weinreb amide **218c** (252 mg, 1.38 mmol) and *n*-BuLi (0.83 mL, 2.07 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the *title compound* **214k** as a yellow oil (239 mg, 78%); R_f 0.89 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2201, 1661, 1489, 1286, 1160, 1071, 756; δ_H (400 MHz, $CDCl_3$) 3.65 (3 H, s, H-1), 3.81 (2 H, s, H-6), 6.11–6.15 (1 H, m, H-3), 6.57–6.62 (2 H, m, H-2,5), 7.35–7.42 (2 H, m, H-11/12), 7.42–7.48 (1 H, m, H-13), 7.53–7.58 (2 H, m, H-11/12); δ_C (100 MHz, $CDCl_3$) 36.2 (C-1), 44.0 (C-6), 88.0 (C-8), 91.5 (C-9), 109.4 (C-3), 114.4 (C-4), 120.2 (C-10), 121.1 (C-2/5), 122.0 (C-2/5), 128.5 (C-11/12), 130.5 (C-13), 133.0 (C-11/12), 186.2 (C-7); HRMS (ESI$^+$): Found: 246.0884; $C_{15}H_{13}NNaO$ (MNa^+) Requires 246.0889 (−2.1 ppm error).

Lab notebook reference: akc07-77

1-(1*H*-Pyrrol-3-yl)-4-(trimethylsilyl)but-3-yn-2-one (214l)

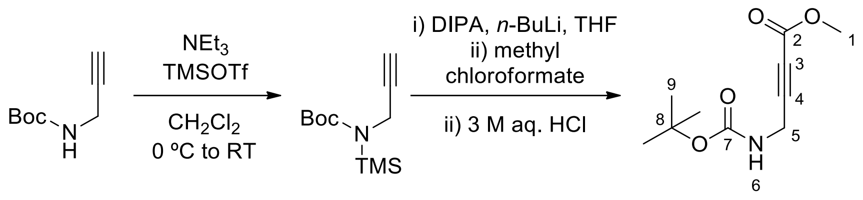


214l

Synthesised using general procedure B with ethynyltrimethylsilane (0.30 mL, 2.19 mmol), THF (6 mL), Weinreb amide **218a** (123 mg, 0.731 mmol) and *n*-BuLi (0.73 mL, 1.83 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **214l** as a yellow oil (79.5 mg, 53%); R_f 0.20 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3399, 2962, 2151, 1668, 1252, 1095, 845, 760; δ_H (400 MHz, $CDCl_3$) 0.23 (9 H, s, H-10), 3.75 (2 H, s, H-6), 6.15–6.19 (1 H, m, H-1/3/4), 6.72–6.75 (1 H, m, H-1/3/4), 6.75–6.80 (1 H, m, H-1/3/4), 8.22 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) −0.8 (C-10), 43.7 (C-6), 98.7 (C-9), 102.1 (C-8), 109.6 (C-1/3/4), 114.2 (C-5), 117.1 (C-1/3/4), 118.1 (C-1/3/4), 185.9 (C-7); HRMS (ESI$^+$): Found: 228.0811; $C_{11}H_{15}NNaOSi$ (MNa^+) Requires 228.0815 (1.7 ppm error), Found: 206.0996; $C_{11}H_{16}NOSi$ (MH^+) Requires 206.0996 (−0.1 ppm error).

Lab notebook reference: akc05-88

Methyl 4-((*tert*-butoxycarbonyl)amino)but-2-ynoate (231)



Prepared according to literature procedure: B. M. Trost, J.-P. Lumb and J. M. Azzarelli, *J. Am. Chem. Soc.*, 2011, **133**, 740–743

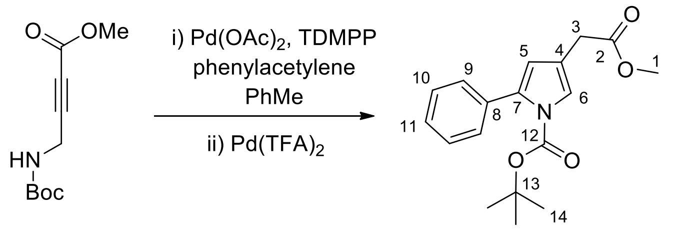
An oven-dried flask was charged with Boc-protected propargyl amine **S4** (1.25 g, 8.05 mmol) and purged with a steady stream of argon for 5 min, at which point dry CH_2Cl_2 (16 mL) was added to afford a homogeneous, light yellow reaction mixture that was cooled to 0 °C. After 5 min, freshly distilled NEt_3 (2.24 mL, 16.1 mmol) was added, followed by the dropwise addition of TMSOTf (1.89 mL, 10.5 mmol). After 5 min the reaction mixture was warmed to RT, stirred for 15 min and then quenched by the addition of sat. aq. $NaHCO_3$ (20 mL). The organics were separated, washed with sat. aq. $NaHCO_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

An oven-dried flask was charged with THF (11 mL) followed by diisopropylamine (0.84 mL, 6.0 mmol) and the resulting mixture was cooled to 0 °C. To this mixture was added *n*-BuLi (2.31 mL, 5.76 mmol, 2.5 M in hexanes) and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was then cooled to −78 °C and the crude material **S5** (1.05 g, 4.61 mmol) was added as a solution in THF (6 mL) which was then stirred at −78 °C for 1 h. Methyl chloroformate (0.39 mL, 5.07 mmol) was added as a solution in THF (3 mL, 3 mL rinse) *via* cannula. The reaction mixture was then allowed to warm to RT over the course of 16 h. The reaction mixture was then removed from the cooling bath and stirred at RT for an additional 2 h, quenched by the addition of 10% aq. HCl (20 mL) and the resulting solution was stirred at RT for 1 h. The organic phase was separated and the aqueous phase was washed with Et_2O (2 x 20 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (6:1 hexane:EtOAc, then 3:1 hexane:EtOAc) to afford the *title compound* **231** as a pale orange solid (585 mg, 60%); mp 33–35 °C; R_f 0.17 (6:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3354, 2980, 2243, 1716, 1514, 1249, 1166; δ_H (400 MHz, $CDCl_3$) 1.46 (9 H, s, H-9), 3.78 (3 H, s, H-1), 4.07 (2 H, br d, *J* = 4.5 Hz, H-5), 4.78 (1 H, br s, H-6); δ_C (100 MHz, $CDCl_3$) 28.3 (C-9), 30.3 (C-5), 52.8 (C-1), 74.6 (C-3/4/8), 80.5 (C-3/4/8), 84.1 (C-3/4/8), 153.6 (C-2/7), 155.0 (C-2/7); HRMS (ESI$^+$): Found: 236.0893; $C_{10}H_{15}NNaO_4$ (MNa$^+$) Requires 236.0893 (0.2 ppm error).

Lab notebook reference: akc07-15/16

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

tert-Butyl 4-(2-methoxy-2-oxoethyl)-2-phenyl-1_H_-pyrrole-1-carboxylate (S6)



231 **S6**

Prepared according to literature procedure: B. M. Trost, J.-P. Lumb and J. M. Azzarelli, *J. Am. Chem. Soc.*, 2011, **133**, 740–743

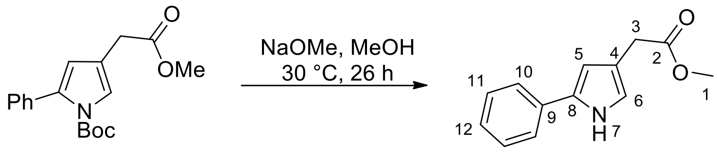
Generation of 0.007 M 1:1 $Pd(OAc)_2$ and TDMPP catalyst solution: A rbf was charged with $Pd(OAc)_2$ (5.0 mg, 22.3 µmol), TDMPP (9.8 mg, 22.3 µmol) and toluene (3.01 mL). The resulting mixture was then stirred rapidly for 15 min to afford a bright orange/red, homogeneous mixture.

To a rbf under argon was added propargyl amine **231** (518 mg, 2.43 mmol). To this was added an aliquot of the pre-formed catalyst solution (2.38 mL, 0.167 mmol, 0.007 M, which corresponds to the addition of 0.75 mol% of both the $Pd(OAc)_2$ and TDMPP components). The resulting homogeneous, orange solution was stirred at RT for 10 min before the addition of phenylacetylene (0.27 mL, 2.43 mmol). The reaction mixture was then stirred at RT for 10 h before the addition of $Pd(TFA)_2$ (16.2 mg, 48.6 µmol) in one portion. The reaction mixture was then stirred at RT overnight, diluted with a 1:1 mixture of CH_2Cl_2:Et_2O (15 mL), filtered through a short pad of Florosil eluting with CH_2Cl_2:Et_2O (1:1, 2 x 20 mL) and then Et_2O (1 x 30 mL). The reaction mixture was then concentrated *in vacuo* and the crude material was purified by column chromatography (9:1 hexane:EtOAc, then 6:1 hexane:EtOAc) to afford the *title compound* **S6** as a pale yellow oil (547 mg, 74%); R_f 0.40 (6:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2980, 2952, 1732, 1341, 1252, 1149, 769, 698; δ_H (400 MHz, $CDCl_3$) 1.35 (9 H, s, H-14), 3.49 (2 H, s, H-3), 3.73 (3 H, s, H-1), 6.16 (1 H, d, J = 1.5 Hz, H-5/6), 7.26–7.36 (6 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 27.6 (C-14), 32.6 (C-3), 52.0 (C-1), 83.5 (C-13), 115.5 (C-5/6), 117.7 (C-4/7/8), 120.8 (CH), 127.2 (CH), 127.5 (CH), 129.1 (CH), 134.1 (C-4/7/8), 135.3 (C-4/7/8), 149.1 (C-12), 172.0 (C-2); HRMS (ESI$^+$): Found: 338.1350; $C_{18}H_{21}NNaO_4$ (MNa^+) Requires 338.1363 (3.9 ppm error).

Lab notebook reference: akc07-21/25

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

Methyl 2-(5-phenyl-1*H*-pyrrol-3-yl)acetate (232)

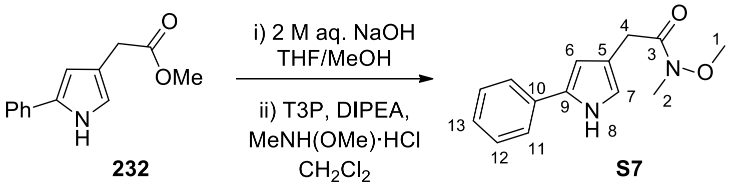


Procedure adapted from literature procedure: K. Ravinder, A. V. Reddy, K. C. Mahesh, M. Narasimhulu and Y. Venkateswarlu, *Synth. Commun.*, 2007, **37**, 281–287

To a solution of Boc-protected pyrrole methyl ester **S6** (495 mg, 1.57 mmol) in dry MeOH (12 mL) was added NaOMe (93 mg, 1.72 mmol) in one portion. The reaction mixture was stirred for 26 h at 30 °C. The mixture was then diluted with water (15 mL) and extracted with EtOAc (2 x 15 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) to afford the *title compound* **232** as a pale yellow oil (289 mg, 86%); R_f 0.31 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3376, 2951, 1724, 1607, 1515, 1455, 1436, 1263, 1196, 1155, 1123, 978, 760; δ_H (400 MHz, $CDCl_3$) 3.56 (2 H, s, H-3), 3.73 (3 H, s, H-1), 6.48 (1 H, s, H-5/6), 6.79 (1 H, s, H-5/6), 7.21 (1 H, t, *J* = 7.5 Hz, H-12), 7.36 (2 H, dd, *J* = 8.0, 8.0 Hz, H-11), 7.46 (2 H, d, *J* = 8.0 Hz, H-10), 8.36 (1 H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 32.9 (C-3), 52.0 (C-1), 106.9 (C-5/6), 117.3 (C-4/8/9), 117.6 (C-5/6), 123.8 (C-10), 126.3 (C-12), 128.8 (C-11), 132.3 (C-4/8/9), 132.5 (C-4/8/9), 172.8 (C-2); HRMS (ESI$^+$): Found: 216.1018; $C_{13}H_{14}NO_2$ (MH^+) Requires 216.1019 (0.7 ppm error).

Lab notebook reference: akc07-28/31

_N_-Methoxy-_N_-methyl-2-(5-phenyl-1_H_-pyrrol-3-yl)acetamide (S7)

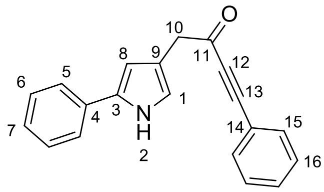


To a solution of methyl ester **232** (277 mg, 1.29 mmol) in THF (9 mL) and MeOH (0.9 mL) at 0 °C was added 2 M aq. NaOH (7.1 mL). The reaction mixture was warmed to RT and stirred for 5.5 h. Water (10 mL) was added and the aqueous layer was washed with EtOAc (10 mL). The organic extract was discarded. The aqueous layer was acidified with 10% aq. HCl (5 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 crude pyrrole acid as a dark purple solid (246 mg, 95%).

To a stirred solution of crude pyrrole acid (244 mg, 1.21 mmol), MeNH(OMe)·HCl (130 mg, 1.33 mmol) and DIPEA (0.63 mL, 3.63 mmol) in CH_2Cl_2 (6 mL) was added T3P 50% in EtOAc (1.16 g, 1.82 mmol). The solution was stirred at RT for 1.5 h. Water (15 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 10 mL). The organics were combined, washed with 10% aq. HCl (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (8:2 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the *title compound* **S7** as a pale brown oil (286 mg, 97%); R_f 0.43 (7:3 EtOAc:hexane); ν_{max} (thin film)/cm^{-1} 3299, 2939, 1638, 1607, 1513, 1458, 1384, 1004, 764; δ_H (400 MHz, $CDCl_3$) 3.22 (3 H, s, H-2), 3.68 (2 H, s, H-4), 3.70 (3 H, s, H-1), 6.49 (1 H, s, H-6/7), 6.78 (1 H, s, H-6/7), 7.19 (1 H, t, *J* = 7.5 Hz, H-13), 7.34 (2 H, dd, *J* = 8.0, 8.0 Hz, H-12), 7.46 (2 H, d, *J* = 8.0 Hz, H-11), 8.47 (1 H, br s, H-8); δ_C (100 MHz, $CDCl_3$) 30.8 (C-4), 32.2 (C-2), 61.3 (C-1), 107.0 (C-6/7), 117.7 (C-6/7), 118.0 (C-5/9/10), 123.7 (C-11), 126.1 (C-13), 128.8 (C-12), 132.1 (C-5/9/10), 132.7 (C-5/9/10), 173.2 (C-3); HRMS (ESI$^+$): Found: 267.1100; $C_{14}H_{16}N_2NaO_2$ (MNa^+) Requires 267.1104 (1.4 ppm error).

Lab notebook reference: akc07-33/37

4-Phenyl-1-(5-phenyl-1*H*-pyrrol-3-yl)but-3-yn-2-one (233a)

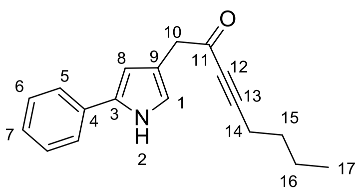


233a

Synthesised using general procedure B with phenylacetylene (0.17 mL, 1.58 mmol), THF (4.2 mL), Weinreb amide **S7** (129 mg, 0.526 mmol) and *n*-BuLi (0.53 mL, 1.32 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (6:1 hexane:EtOAc, then 7:3 hexane:EtOAc) afforded the *title compound* **233a** as an orange oil (107 mg, 71%); R_f 0.72 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3380, 3058, 2202, 1660, 1489, 1282, 1076, 758, 689; δ_H (400 MHz, $CDCl_3$) 3.87 (2 H, s, H-10), 6.53 (1 H, s, H-1/8), 6.84 (1 H, s, H-1/8), 7.22 (1 H, t, *J* = 7.5 Hz, H-7/17), 7.32–7.40 (4 H, m, Ar-H), 7.41–7.50 (3 H, m, Ar-H), 7.53 (2 H, d, *J* = 7.5 Hz, H-5/15), 8.50 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 43.9 (C-10), 88.0 (C-12), 92.0 (C-13), 107.3 (C-1/8), 116.3 (C), 118.30 (C-1/8), 118.30 (C) 120.0 (C), 123.7 (CH), 126.3 (C-7/17), 128.5 (CH), 128.8 (CH), 130.6 (CH), 132.5 (C), 133.1 (C-5/15), 186.2 (C-11); HRMS (ESI^+): Found: 308.1031; $C_{20}H_{15}NNaO$ (MNa^+) Requires 308.1046 (−4.8 ppm error), Found: 286.1218; $C_{20}H_{16}NO$ (MH^+) Requires 286.1226 (2.9 ppm error).

Lab notebook reference: akc07-38

1-(5-Phenyl-1*H*-pyrrol-3-yl)oct-3-yn-2-one (233b)



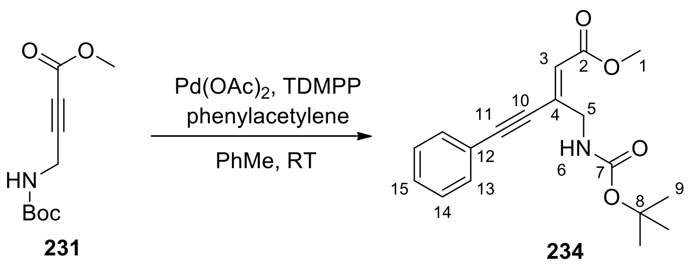
233b

Synthesised using general procedure B with hex-1-yne (0.23 mL, 2.02 mmol), THF (5.4 mL), Weinreb amide **S7** (151 mg, 0.673 mmol) and *n*-BuLi (0.67 mL, 1.68 mmol, 2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **233b** as a brown oil (97.7 mg, 55%); R_f 0.81 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3382, 2958, 2869, 2210, 1663, 1607, 1514, 1455, 1239, 1119, 763; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.5 Hz, H-17), 1.40 (2 H, app. sextet, *J* = 7.5 Hz, H-16), 1.54 (2 H, app. pentet, *J* = 7.5 Hz, H-15), 2.36 (2 H, t, *J* = 7.0 Hz, H-14), 3.73

(2H, s, H-10), 6.46 (1 H, s, H-1/8), 6.78 (1 H, s, H-1/8), 7.21 (1 H, t, *J* = 7.0 Hz, H-7), 7.36 (2 H, dd, *J* = 8.0, 7.5 Hz, H-6), 7.46 (2 H, d, *J* = 8.0 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 13.5 (C-17), 18.7 (C-14), 21.9 (C-16), 29.7 (C-15), 43.9 (C-10), 80.9 (C-12), 95.5 (C-13), 107.2 (C-1/8), 116.5 (C-3/4/9), 118.1 (C-1/8), 123.7 (C-5), 126.3 (C-7), 128.8 (C-6), 132.4 (C-3/4/9), 132.5 (C-3/4/9), 186.3 (C-11); HRMS (ESI$^+$): Found: 288.1351; $C_{18}H_{19}NNaO$ (MNa^+) Requires 288.1359 (2.7 ppm error), Found: 266.1532; $C_{18}H_{20}NO$ (MH^+) Requires 266.1539 (−2.6 ppm error).

Lab notebook reference: akc07-41

(*Z*)-Methyl 3-(((*tert*-butoxycarbonyl)amino)methyl)-5-phenylpent-2-en-4-ynoate (234)



Prepared according to literature procedure: B. M. Trost, J.-P. Lumb and J. M. Azzarelli, *J. Am. Chem. Soc.*, 2011, **133**, 740–743

Generation of 0.007 M 1:1 $Pd(OAc)_2$ and TDMPP catalyst solution: A rbf was charged with $Pd(OAc)_2$ (5.0 mg, 22.3 μmol), TDMPP (9.8 mg, 22.3 μmol) and toluene (3.01 mL). The resulting mixture was then stirred rapidly for 15 min to afford a bright orange/red, homogeneous mixture.

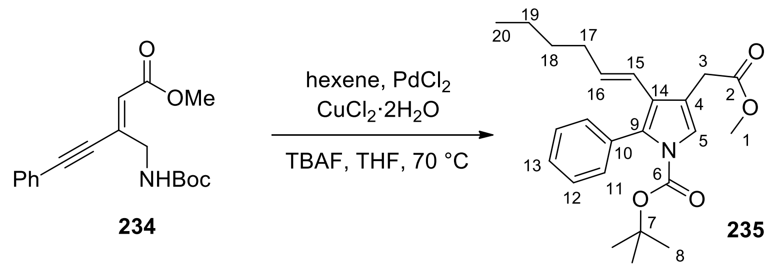
To a rbf under argon was added propargyl amine **231** (300 mg, 1.41 mmol). To this was added an aliquot of the pre-formed catalyst solution (1.57 mL, 0.011 mmol, 0.007 M, which corresponds to the addition of 0.75 mol% of both the $Pd(OAc)_2$ and TDMPP components). The resulting homogeneous, orange solution was stirred at RT for 10 min before the addition of phenylacetylene (0.15 mL, 1.41 mmol). The reaction mixture was stirred at RT for 14.5 h, concentrated *in vacuo* and the crude material was purified by column chromatography (9:1 hexane:EtOAc, then 6:1 hexane:EtOAc) to afford the *title compound* **234** as an off-white solid (388 mg, 87%); R_f 0.25 (6:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3386, 2978, 2208, 1710, 1606, 1199, 1170, 1118, 758; δ_H (400 MHz, $CDCl_3$) 1.44 (9 H, s, H-9), 3.75 (3 H, s, H-1), 4.44 (2 H, br d, *J* = 6.0 Hz, H-5), 5.14 (1 H, br s, H-6), 6.22 (1 H, s, H-3), 7.32–7.40 (3 H, m, Ar-H), 7.48–7.52 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 28.4 (C-9), 41.1 (C-5), 51.6 (C-1), 79.5 (C-8), 88.0 (C-10/11), 97.2 (C-10/11), 122.0 (C-12), 124.0 (C-3), 128.4 (CH), 129.3

(CH), 132.1 (CH), 140.8 (C-4), 155.8 (C-7), 166.0 (C-2); HRMS (ESI$^+$): Found: 338.1347; $C_{18}H_{21}NNaO_4$ (MNa^+) Requires 338.1363 (−4.8 ppm error).

Lab notebook reference: akc07-47

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

(*E*)-*tert*-Butyl 3-(hex-1-en-1-yl)-4-(2-methoxy-2-oxoethyl)-2-phenyl-1*H*-pyrrole-1-carboxylate (235)

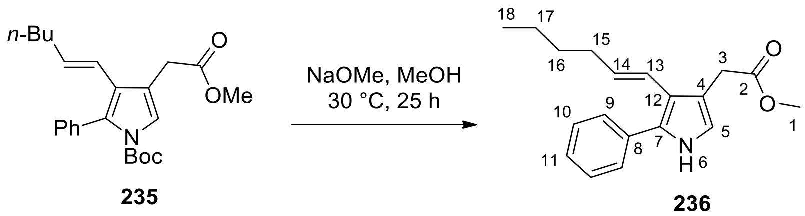


Procedure adapted from literature procedure: A. Yasuhara, Y. Takeda, N. Suzuki and T. Sakamoto, *Chem. Pharm. Bull.*, 2002, **50**, 235–238

To a rbf under argon was added Boc-protected amine **234** (326 mg, 1.03 mmol) and THF (20 mL). To this was added hex-1-ene (0.2 mL, 1.55 mmol), $PdCl_2$ (9.17 mg, 51.7 µmol), $CuCl_2·2H_2O$ (386 mg, 2.27 mmol) and TBAF (1.24 mL, 1.24 mmol, 1 M solution in THF). The resulting solution was heated to 70 °C and stirred for 1.5 h. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organics were combined, dried over $MgSO_4$, concentrated *in vacuo* and the crude material was purified by column chromatography (8:1 hexane:EtOAc) to afford the *title compound* **235** as a yellow oil (60.5 mg, 19%); R_f 0.41 (6:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2930, 1736, 1436, 1367, 1255, 1152, 1004, 992, 851, 767; δ_H (400 MHz, $CDCl_3$) 0.85 (3 H, t, *J* = 7.0 Hz, H-20), 1.22–1.30 (13 H, m, H-8,18,19), 1.96–2.05 (2 H, m, H-17), 3.60 (2 H, s, H-3), 3.74 (3 H, s, H-1), 5.63 (1 H, dt, *J* = 16.5, 7.5 Hz, H-16), 5.92 (1 H, d, *J* = 16.5 Hz, H-15), 7.22–7.41 (6 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 13.9 (C-20), 22.0 (C-18/19), 27.5 (C-8), 31.6 (C-18/19), 32.3 (C-3), 33.4 (C-17), 52.0 (C-1), 83.3 (C-7), 116.4 (C), 120.9 (C-5/13/15), 121.4 (C-5/13/15), 123.8 (C), 127.3 (C-5/13), 127.6 (C-11/12), 130.6 (C-11/12), 131.1 (C), 132.2 (C-16), 133.7 (C), 149.1 (C-6), 172.1 (C-2); HRMS (ESI$^+$): Found: 420.2128; $C_{24}H_{31}NNaO_4$ (MNa^+) Requires 420.2145 (4.2 ppm error).

Lab notebook reference: akc07-49/51

(*E*)-Methyl 2-(4-(hex-1-en-1-yl)-5-phenyl-1*H*-pyrrol-3-yl)acetate (236)

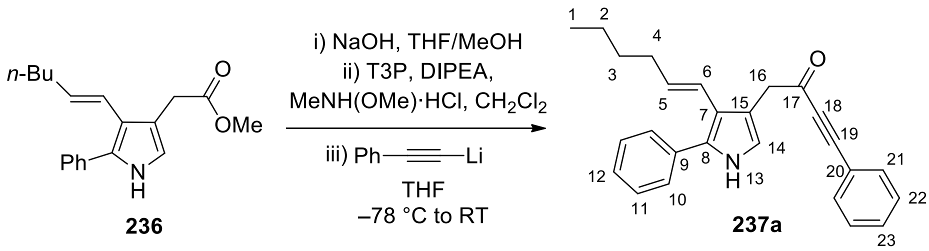


Procedure adapted from literature procedure: K. Ravinder, A. V. Reddy, K. C. Mahesh, M. Narasimhulu and Y. Venkateswarlu, *Synth. Commun.*, 2007, **37**, 281–287

To a solution of Boc-protected pyrrole methyl ester **235** (446 mg, 1.41 mmol) in dry MeOH (11 mL) was added NaOMe (115 mg, 2.12 mmol) in one portion. The reaction mixture was stirred for 19 h at 30 °C followed by the addition of a further portion of NaOMe (38 mg, 0.703 mmol). The reaction mixture was then stirred for a further 6 h at 30 °C. The mixture was concentrated *in vacuo* and the crude material was purified by column chromatography (7:1 hexane:EtOAc) to afford the *title compound* **236** as a pale yellow oil (188 mg, 45%); R_f 0.19 (5:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3372, 2954, 2925, 2855, 1729, 1603, 1457, 1436, 1157, 767, 698; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, t, *J* = 7.5 Hz, H-18), 1.33–1.46 (4 H, m, H-16,17), 2.13–2.20 (2 H, m, H-15), 3.64 (2 H, s, H-3), 3.73 (3 H, s, H-1), 5.77 (1 H, dt, *J* = 16.0, 7.0 Hz, H-14), 6.34 (1 H, d, *J* = 16.0 Hz, H-13), 6.76–6.80 (1 H, m, H-5), 7.24–7.29 (1 H, m, H-11), 7.36–7.42 (2 H, dd, *J* = 7.5, 7.5 Hz, H-10), 7.45 (2 H, d, *J* = 7.5 Hz, H-9), 8.13 (1 H, br s, H-6); δ_C (100 MHz, $CDCl_3$) 14.0 (C-18), 22.2 (C-16/17), 31.8 (C-3/16/17), 32.2 (C-3/16/17), 33.4 (C-15), 51.9 (C-1), 115.4 (C-4/7), 117.7 (C-5), 118.4 (C-12), 122.3 (C-13), 126.5 (C-11), 127.3 (C-9/10), 128.6 (C-9/10), 129.5 (C-4/7/8), 131.6 (C-14), 133.3 (C-4/7/8), 173.0 (C-2); HRMS (ESI$^+$): Found: 320.1608; $C_{19}H_{23}NNaO_2$ (MNa^+) Requires 320.1621 (4.0 ppm error), Found: 298.1792; $C_{19}H_{24}NO_2$ (MH^+) Requires 298.1802 (−3.4 ppm error)

Lab notebook reference: akc07-55

(*E*)-1-(4-(Hex-1-en-1-yl)-5-phenyl-1*H*-pyrrol-3-yl)-4-phenylbut-3-yn-2-one (237a)



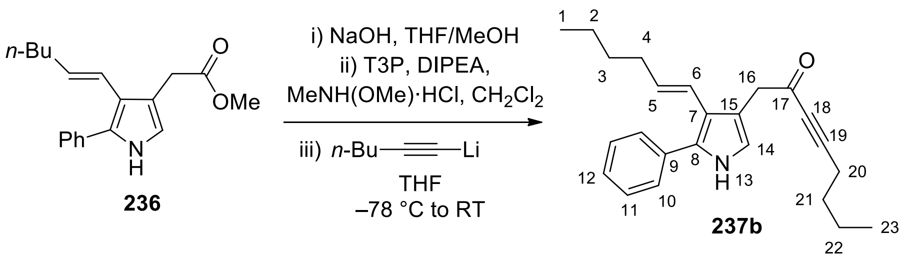
To a solution of methyl ester **236** (163 mg, 0.548 mmol) in THF (3.8 mL) and MeOH (0.4 mL) at 0 °C was added 2 M aq. NaOH (3 mL). The reaction mixture was warmed to RT and stirred for 23 h. Water (10 mL) was added and the aqueous layer was aqueous layer was acidified with 10% aq. HCl (2 mL) until pH = 1. The aqueous layer was then extracted with EtOAc (3 x 20 mL), the organics were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude pyrrole acid as a brown oil (156 mg, 100%).

To a stirred solution of crude pyrrole acid (155 mg, 0.547 mmol), MeNH(OMe)·HCl (58.7 mg, 0.602 mmol) and DIPEA (0.29 mL, 1.64 mmol) in CH_2Cl_2 (3 mL) was added T3P 50% in EtOAc (522 mg, 0.821 mmol). The solution was stirred at RT for 1 h. Water (10 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 10 mL). The organics were combined, brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude Weinreb amide as a brown oil (179 mg, 100%).

To a stirred solution of phenylacetylene (0.18 ml, 1.64 mmol) in THF (1.6 mL) at −78 °C under argon was added *n*-BuLi (0.55 mL, 1.37 mmol, 2.5 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 crude Weinreb amide (178 mg, 0.547 mmol) in THF (2.6 mL). Upon complete transfer the mixture was warmed to RT and stirred for 1 h. The reaction was quenched by the careful addition of sat. aq. NH_4Cl (5 mL). The organics were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude material. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 4:1 hexane:EtOAc) to afford the *title compound* **237a** as a yellow oil (44.4 mg, 22%); R_f 0.49 (5:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3373, 2955, 2925, 2855, 2201, 1660, 1489, 1072, 758, 688; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.5 Hz, H-1), 1.31–1.46 (4 H, m, H-2,3), 2.14–2.17 (2 H, m, H-4), 3.94 (2 H, s, H-16), 5.82 (1 H, dt, *J* = 16.0, 7.0 Hz, H-5), 6.37 (1 H, d, *J* = 16.0 Hz, H-6), 6.81–6.85 (1 H, m, H-14), 7.25–7.31 (1 H, m, Ar-H), 7.33–7.53 (9 H, m, Ar-H), 8.20 (1 H, br s, H-13); δ_C (100 MHz, $CDCl_3$) 14.0 (C-1), 22.2 (C-2/3), 31.8 (C-2/3), 33.4 (C-4), 43.0 (C-16), 88.2 (C-18), 91.9 (C-19), 114.8 (C), 118.4 (C-14), 118.8 (C), 120.1 (C), 122.3 (C-6), 126.6 (CH), 127.2 (CH), 128.5 (CH), 128.6 (CH), 129.6 (C), 130.6 (CH), 132.0 (C-5), 133.1 (CH), 133.3 (C), 186.6 (C-17); HRMS (ESI$^+$): Found: 368.2019; $C_{26}H_{26}NO$ (MH$^+$) Requires 368.2009 (−2.7 ppm error).

Lab notebook reference: akc07-57/58/59

(*E*)-1-(4-(Hex-1-en-1-yl)-5-phenyl-1*H*-pyrrol-3-yl)oct-3-yn-2-one (237b)



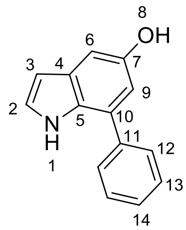
To a solution of methyl ester **236** (188 mg, 0.632 mmol) in THF (4.4 mL) and MeOH (0.44 mL) at 0 °C was added 2 M aq. NaOH (3.5 mL). The reaction mixture was warmed to RT and stirred for 22.5 h. Water (10 mL) was added and the aqueous layer was aqueous layer was acidified with 10% aq. HCl (2.5 mL) until pH = 1. The aqueous layer was then extracted with EtOAc (3 x 20 mL), the organics were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude pyrrole acid as a brown oil (239 mg, 100%).

To a stirred solution of crude pyrrole acid (239 mg, 0.843 mmol), MeNH(OMe)·HCl (90.5 mg, 0.928 mmol) and DIPEA (0.44 mL, 2.53 mmol) in CH_2Cl_2 (4.2 mL) was added T3P 50% in EtOAc (804 mg, 1.26 mmol). The solution was stirred at RT for 1 h. Water (10 mL) was added and basified using aq. 2 M NaOH until pH = 10. The CH_2Cl_2 layer was removed and the aqueous extracted with EtOAc (2 x 10 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude Weinreb amide as a brown oil (202 mg, 73%).

To a stirred solution of hex-1-yne (0.21 ml, 1.86 mmol) in THF (1.9 mL) at −78 °C under argon was added *n*-BuLi (0.62 mL, 1.55 mmol, 2.5 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 crude Weinreb amide (202 mg, 0.619 mmol) in THF (3.1 mL). Upon complete transfer the mixture was warmed to RT and stirred for 1 h. The reaction was quenched by the careful addition of sat. aq. NH_4Cl (5 mL). The organics were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude material. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 4:1 hexane:EtOAc) to afford the *title compound* **237b** as a yellow oil (59.2 mg, 28%); R_f 0.71 (3:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3370, 2961, 2929, 2873, 2211, 1667, 1604, 1458, 1165, 767, 698; δ_H (400 MHz, $CDCl_3$) 0.85–0.97 (6 H, m, H-1,23), 1.31–1.45 (6 H, m, H-2,3,22), 1.46–1.56 (2 H, m, H-21), 2.11–2.19 (2 H, m, H-4), 2.33 (2 H, t, *J* = 7.0 Hz, H-20), 3.79 (2 H, s, H-16), 5.73 (1 H, dt, *J* = 16.0, 7.0 Hz, H-5), 6.30 (1 H, d, *J* = 16.0 Hz, H-6), 6.74 (1 H, d, *J* = 2.5 Hz, H-14), 7.25 (1 H, t, *J* = 7.0 Hz, H-12), 7.38 (2 H, dd, *J* = 7.5, 7.0 Hz, H-11), 7.44 (2 H, d, *J* = 7.5 Hz, H-10), 8.15 (1 H, br s, H-13); δ_C (100 MHz, $CDCl_3$) 13.5 (C-1/23), 14.0 (C-1/23), 18.7 (C-20), 21.8 (C-2/3/22), 22.2 (C-2/3/22), 29.6 (C-21), 31.8 (C-2/3/22), 33.4 (C-4), 43.0 (C-16), 81.1 (C-18), 95.3 (C-19), 114.8 (C-7/8/9/15), 118.3 (C-14), 118.6 (C-7/8/9/15), 122.3 (C-6), 126.5 (C-12), 127.2 (C-10/11), 128.6 (C-10/11), 129.5 (C-7/8/9/15), 131.8 (C-5), 133.3 (C-7/8/9/15), 186.7 (C-17); HRMS (ESI$^+$): Found: 348.2313; $C_{24}H_{30}NO$ (MH^+) Requires 348.2322 (−2.6 ppm error).

Lab notebook reference: akc07-61/62/64

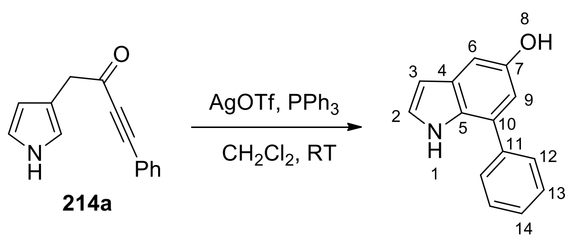
7-Phenyl-1*H*-indol-5-ol (215a)



215a

Method 1: Synthesised using general procedure E with ynone **214a** (81.2 mg, 0.388 mmol), $AgNO_3$ (3.30 mg, 19.4 μmol) in CH_2Cl_2 (3.9 mL) at RT for 3 h. Purification by column chromatography (1:1 hexane:EtOAc) afforded the *title compound* **215a** as a yellow oil (78.8 mg, 97%).

Lab notebook reference: akc05-57

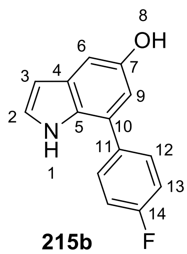


Method 2: A solution of AgOTf (6.1 mg, 23.9 µmol) and PPh_3 (6.3 mg, 23.9 µmol) in CH_2Cl_2 (1.2 mL) was stirred for 1 h at RT. To this pre-mixed catalyst solution was added a solution of

ynone **214a** (50 mg, 0.239 mmol) in CH_2Cl_2 (1.2 mL). The reaction mixture was then stirred at RT for 3 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the *title compound* **215a** as a yellow oil (38.3 mg, 77%).

R_f 0.80 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3432, 1591, 1485, 1416, 1162, 1132, 890, 758; δ_H (400 MHz, $CDCl_3$) 4.65 (1 H, br s, H-8), 6.50–6.53 (1 H, m, H-2/3), 6.84 (1 H, d, J = 2.5 Hz, H-6/9), 7.07 (1 H, d, J = 2.5 Hz, H-6/9), 7.19–7.23 (1 H, m, H-2/3), 7.42 (1 H, t, J = 7.5 Hz, H-14), 7.52 (2 H, dd, J = 7.5, 7.5 Hz, H-13), 7.63 (2 H, d, J = 7.5 Hz, H-12), 8.29 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 102.4 (C-2/3), 104.3 (C-6/9), 111.6 (C-6/9), 125.4 (C-2/3), 126.3 (C-4/10/11), 127.6 (C-14), 128.1 (C-12), 129.0 (C-4/10/11), 129.15 (C-13), 129.13 (C-4/10/11), 138.7 (C-5), 149.9 (C-7); HRMS (ESI$^+$): Found: 210.0909; $C_{14}H_{12}NO$ (MH^+) Requires 210.0913 (2.1 ppm error).

7-(4-Fluorophenyl)-1*H*-indol-5-ol (215b)

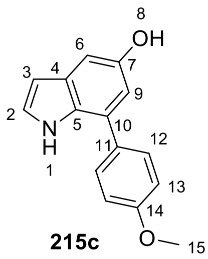


215b

Synthesised using general procedure E with ynone **214b** (49.0 mg, 0.216 mmol), $AgNO_3$ (1.83 mg, 10.8 μmol) in CH_2Cl_2 (2.2 mL) at RT for 2.5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 7:1 hexane:EtOAc) afforded the *title compound* **215b** as a yellow oil (46.3 mg, 94%); R_f 0.70 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3435, 1607, 1504, 1223, 1159, 1133, 835, 803, 731; δ_H (400 MHz, $CDCl_3$) 4.85 (1 H, br s, H-8), 6.49–6.54 (1 H, m, H-2/3), 6.78 (1 H, d, J = 2.5 Hz, H-6/9), 7.06 (1 H, d, J = 2.5 Hz, H-6/9), 7.15–7.23 (3 H, m, H-2/3,13), 7.56 (1 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 5.5 Hz, H-12), 8.21 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 102.6 (C-2/3), 104.5 (C-6/9), 111.7 (C-6/9), 116.1 (d, $^2J_{CF}$ = 21.0 Hz, C-13), 125.2 (C-4/5/10), 125.5 (C-2/3), 129.0 (C-4/5/10), 129.1 (C-4/5/10), 129.7 (d, $^3J_{CF}$ = 8.0 Hz, C-12), 134.7 (d, $^4J_{CF}$ = 3.0 Hz, C-11), 149.8 (C-7), 162.3 (d, $^1J_{CF}$ = 247 Hz, C-14); HRMS (ESI$^+$): Found: 228.0820; $C_{14}H_{11}FNO$ (MH^+) Requires 228.0819 (−0.4 ppm error).

Lab notebook reference: akc05-61

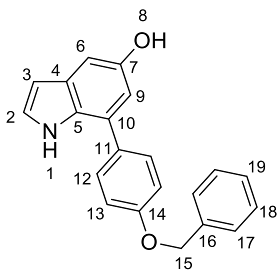
7-(4-Methoxyphenyl)-1*H*-indol-5-ol (215c)



Synthesised using general procedure E with ynone **214c** (55.6 mg, 0.232 mmol), $AgNO_3$ (1.97 mg, 11.6 μmol) in CH_2Cl_2 (2.3 mL) at RT for 4 h. Purification by column chromatography (9:1 hexane:EtOAc, then 5:1 hexane:EtOAc) afforded the *title compound* **215c** as a yellow oil (55.6 mg, 100%); R_f 0.11 (6:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3393, 2928, 1610, 1506, 1286, 1246, 1179, 1163, 1134, 833, 725; δ_H (400 MHz, $CDCl_3$) 3.89 (3 H, s, H-15), 4.72 (1 H, br s, H-8), 6.48–6.52 (1 H, m, H-2/3), 6.77–6.81 (1 H, m, H-6/9), 7.02–7.08 (3 H, m, H-6/9,11/12), 7.18–7.22 (1 H, m, H-2/3), 7.55 (2 H, d, *J* = 8.5 Hz, H-11/12), 8.26 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 55.4 (C-15), 102.4 (C-2/3), 103.9 (C-6/9), 111.4 (C-6/9), 114.6 (C-12/13), 125.3 (C-2/3), 126.0 (C), 128.9 (C), 129.19 (C-12/13), 129.23 (C), 131.1 (C), 149.9 (C-7), 159.1 (C-14); HRMS (ESI$^+$): Found: 240.1008; $C_{15}H_{14}NO_2$ (MH^+) Requires 240.1019 (4.5 ppm error).

Lab notebook reference: akc05-73

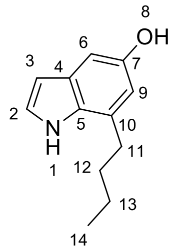
7-(4-(Benzyloxy)phenyl)-1*H*-indol-5-ol (215d)



Synthesised using general procedure E with ynone **214d** (85.5 mg, 0.271 mmol), $AgNO_3$ (2.30 mg, 13.6 μmol) in CH_2Cl_2 (2.7 mL) at RT for 2 h. Purification by column chromatography (9:1 hexane:EtOAc, then 4:1 hexane:EtOAc) afforded the *title compound* **215d** as a white solid (72.5 mg, 85%); mp 122–124 °C; R_f 0.78 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3435, 1608, 1505, 1240, 1162, 1133, 832, 732; δ_H (400 MHz, $CDCl_3$) 4.60 (1 H, s, H-8), 5.15 (2 H, s, H-15), 6.48–6.52 (1 H, m, H-2/3), 6.79 (1 H, d, *J* = 2.0 Hz, H-6/9), 7.03 (1 H, d, *J* = 2.0 Hz, H-6/9), 7.12 (2 H, d, *J* = 8.5 Hz, H-12/13), 7.18–7.22 (1 H, m, H-2/3), 7.33–7.40 (1 H, m, H-19), 7.43 (2 H, dd, *J* = 7.5, 7.5 Hz, H-18), 7.49 (2 H, d, *J* = 7.5 Hz, H-17), 7.55 (2 H, d, *J* = 8.5 Hz, H-12/13), 8.25 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 70.1 (C-15), 102.4 (C-2/3), 103.9 (C-6/9), 111.4 (C-6/9), 115.5 (C-12/13), 125.3 (C-2/3), 126.0 (C), 127.5 (C-17/18), 128.1 (C-19), 128.7 (C-17/18), 128.9 (C), 129.2 (C-12/13), 131.4 (C), 136.8 (C), 149.9 (C-7), 158.4 (C-14); HRMS (ESI^+): Found: 316.1324; $C_{21}H_{18}NO_2$ (MH^+) Requires 316.1332 (2.6 ppm error).

Lab notebook reference: akc05-64

7-Butyl-1*H*-indol-5-ol (215e)

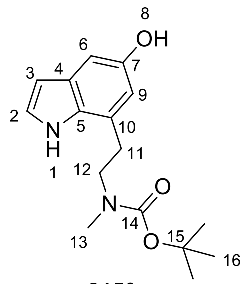


215e

Synthesised using general procedure E with ynone **214e** (69.3 mg, 0.366 mmol), $AgNO_3$ (3.11 mg, 18.3 μmol) in CH_2Cl_2 (3.7 mL) at RT for 5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 6:1 hexane:EtOAc) afforded the *title compound* **215e** as a pale yellow oil (57.9 mg, 84%); R_f 0.16 (7:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3418, 3340, 2956, 2929, 2859, 1595, 1430, 1138, 840, 725; δ_H (400 MHz, $CDCl_3$) 0.97 (3 H, t, *J* = 7.5 Hz, H-14), 1.43 (2 H, app. sextet, *J* = 7.5 Hz, H-13), 1.72 (2 H, app. pentet, *J* = 7.5 Hz, H-12), 2.79 (2 H, t, *J* = 7.5 Hz, H-11), 4.71 (1 H, br s, H-8), 6.43–6.47 (1 H, m, H-2/3), 6.64 (1 H, d, *J* = 2.0 Hz, H-6/9), 6.92 (1 H, d, *J* = 2.0 Hz, H-6/9), 7.16–7.21 (1 H, m, H-2/3), 8.02 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 13.9 (C-14), 22.6 (C-13), 30.9 (C-11), 31.6 (C-12), 102.3 (C-2/3), 102.5 (C-6/9), 111.4 (C-6/9), 124.7 (C-2/3), 126.2 (C-4/5/10), 128.1 (C-4/5/10), 130.2 (C-4/5/10), 149.5 (C-7); HRMS (ESI^+): Found: 190.1235; $C_{12}H_{16}NO$ (MH^+) Requires 190.1226 (−4.5 ppm error).

Lab notebook reference: akc05-59

tert-Butyl (2-(5-hydroxy-1H-indol-7-yl)ethyl)(methyl)carbamate (215f)



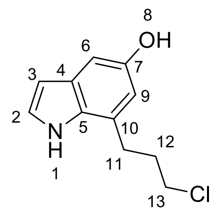
215f

Synthesised using general procedure E with ynone **214f** (72.4 mg, 0.249 mmol), $AgNO_3$ (2.12 mg, 12.5 μmol) in CH_2Cl_2 (2.5 mL) at RT for 4 h. Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded the *title compound* **215f** as a pale yellow oil (72.4 mg, 100%); R_f 0.67 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3316, 2977, 2933, 1662, 1484, 1431, 1396, 1367, 1165, 1142, 727; δ_H (400 MHz, $CDCl_3$) 1.54 (9 H, s, H-16), 2.92 (3 H, s, H-13), 2.99–3.08 (2 H, m, H-11), 3.46–3.53 (2 H, m, H-12), 5.60 (1 H, br s, H-8), 6.38–6.45 (1 H, m, H-2/3/6), 6.59–6.65 (1 H, m, H-9), 6.95–7.01 (1 H, m, H-2/3/6), 7.16–7.22 (1 H, m, H-2/3/6), 9.88 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 28.5 (C-16), 31.1 (C-11), 35.3 (C-13), 49.6 (C-12), 80.1 (C-15), 101.7 (C-2/3/6), 103.5 (C-2/3/6), 111.9 (C-9), 122.5 (C-4/5/10), 125.4 (C-2/3/6), 128.7 (C-4/5/10), 130.9 (C-4/5/10), 149.7 (C-7), 156.5 (C-14); HRMS (ESI$^+$): Found: 313.1514; $C_{16}H_{22}N_2NaO_3$ (MNa^+) Requires 313.1523 (2.7 ppm error), Found: 291.699; $C_{16}H_{23}N_2O_3$ (MH^+) Requires 291.1703 (1.3 ppm error).

Note: Majority of peaks broadened in ^{1}H NMR spectrum due to presence of rotamers.

Lab notebook reference: akc05-79

7-(3-Chloropropyl)-1H-indol-5-ol (215g)

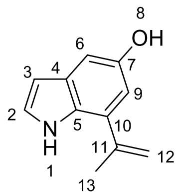


215g

Synthesised using general procedure E with ynone **214g** (32.4 mg, 0.155 mmol), $AgNO_3$ (1.31 mg, 7.73 μmol) in CH_2Cl_2 (1.5 mL) at RT for 24 h. Purification by column chromatography (9:1 hexane:EtOAc, then 3:1 hexane:EtOAc) afforded the *title compound* **215g** as a pale yellow oil (25.5 mg, 79%); R_f 0.37 (3:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3417, 2927, 2855, 1595, 1494, 1430, 1138, 840, 727; δ_H (400 MHz, $CDCl_3$) 2.18 (2 H, app. pentet, *J* = 7.0 Hz, H-12), 2.97 (2 H, t, *J* = 7.0 Hz, H-11), 3.58 (2 H, t, *J* = 7.0 Hz, H-13), 4.75 (1 H, br s, H-8), 6.43–6.49 (1 H, m, H-2/3), 6.63 (1 H, d, *J* = 2.0 Hz, H-6/9), 6.94 (1 H, d, *J* = 2.0 Hz, H-6/9), 7.17–7.22 (1 H, m, H-2/3), 8.21 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 27.7 (C-11), 32.5 (C-12), 44.7 (C-13), 102.4 (C-2/3), 103.2 (C-6/9), 111.6 (C-6/9), 124.1 (C-10), 125.1 (C-2/3), 128.5 (C-4/5), 130.4 (C-4/5), 149.6 (C-7); HRMS (ESI$^+$): Found: 210.0684; $C_{11}H_{13}{}^{35}ClNO$ (MH^+) Requires 210.0680 (−1.6 ppm error).

Lab notebook reference: akc05-77

7-(Prop-1-en-2-yl)-1*H*-indol-5-ol (215h)

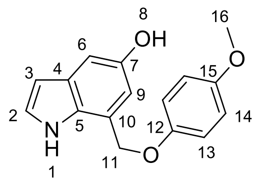


215h

Synthesised using general procedure E with ynone **214h** (52.1 mg, 0.301 mmol), $AgNO_3$ (2.56 mg, 15.0 μmol) in CH_2Cl_2 (3.0 mL) at RT for 21 h. Purification by column chromatography (9:1 hexane:EtOAc, then 4:1 hexane:EtOAc) afforded the *title compound* **215h** as a yellow oil (36.5 mg, 70%); R_f 0.33 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3428, 1590, 1491, 1422, 1306, 1139, 724; δ_H (400 MHz, $CDCl_3$) 2.22 (3 H, s, H-13), 4.68 (1 H, br s, H-8), 5.33–5.46 (2 H, m, H-12), 6.40–6.51 (1 H, m, H-2/3), 6.71–6.78 (1 H, m, H-9), 6.93–7.04 (1 H, m, H-6), 7.16–7.25 (1 H, m, H-2/3), 8.34 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 23.4 (C-13), 102.3 (C-2/3), 104.2 (C-6), 109.8 (C-9), 114.1 (C-12), 125.0 (C-2/3), 127.0 (C-10/11), 128.6 (C-4/5), 128.8 (C-4/5), 142.4 (C-10/11), 149.4 (C-7); HRMS (ESI$^+$): Found: 196.0728; $C_{11}H_{11}NNaO$ (MNa^+) Requires 196.0733 (2.2 ppm error), Found: 174.0914; $C_{11}H_{12}NO$ (MH^+) Requires 174.0913 (−0.4 ppm error).

Lab notebook reference: akc05-71

7-((4-Methoxyphenoxy)methyl)-1*H*-indol-5-ol (215i)

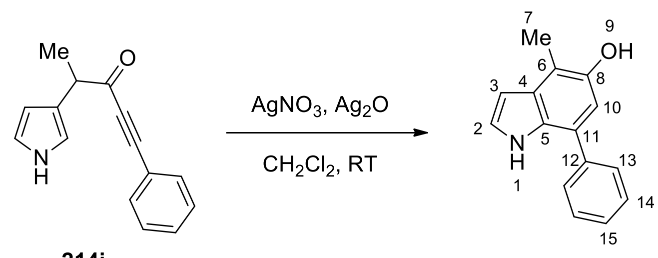


215i

Synthesised using general procedure E with ynone **214i** (69.2 mg, 0.257 mmol), $AgNO_3$ (2.18 mg, 12.8 μmol) in CH_2Cl_2 (2.6 mL) at RT for 3.5 h. Purification by column chromatography (9:1 hexane:EtOAc, then 5:1 hexane:EtOAc) afforded the *title compound* **215i** as a white oil (19.0 mg, 27%); R_f 0.68 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3421, 2929, 1506, 1439, 1222, 1142, 1033, 825; δ_H (400 MHz, $CDCl_3$) 3.77 (3 H, s, H-16), 4.77 (1 H, br s, H-8), 5.28 (2 H, s, H-11), 6.43–6.47 (1 H, m, H-2/3), 6.70–6.76 (1 H, m, H-6/9), 6.84 (2 H, d, *J* = 9.0 Hz, H-13/14), 6.96 (2 H, d, *J* = 9.0 Hz, H-13/14), 7.01–7.04 (1 H, m, H-6/9), 7.18–7.21 (1 H, m, H-2/3), 8.63 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 55.7 (C-16), 69.9 (C-11), 101.9 (C-2/3), 105.0 (C-6/9), 110.5 (C-6/9), 114.8 (C-13/14), 115.9 (C-13/14), 120.9 (C-4/5/10), 125.4 (C-2/3), 129.1 (C-4/5/10), 129.8 (C-4/5/10), 149.2 (C-7), 152.5 (C-12/15), 154.3 (C-12/15); HRMS (ESI$^+$): Found: 292.0942; $C_{16}H_{15}NNaO_3$ (MNa^+) Requires 292.0944 (0.7 ppm error), Found: 270.1129; $C_{16}H_{16}NO_3$ (MH^+) Requires 270.1125 (−1.5 ppm error).

Lab notebook reference: akc05-65

4-Methyl-7-phenyl-1*H*-indol-5-ol (215j)

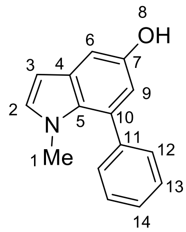


214j **215j**

To a solution of ynone **214j** (51.0 mg, 0.228 mmol) in CH_2Cl_2 (2.3 mL) at RT was added $AgNO_3$ (1.94 mg, 11.4 μmol) and Ag_2O (1.32 mg, 5.71 μmol). The reaction mixture was stirred at RT for 24 h. A further portion of both $AgNO_3$ (1.94 mg, 11.4 μmol) and Ag_2O (1.32 mg, 5.71 μmol) were added and the mixture was stirred for 3 days. The reaction mixture was concentrated *in vacuo* and the crude material was purified by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) to afford the *title compound* **215j** as a yellow oil (38.2 mg, 75%); R_f 0.33 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3436, 2922, 2852, 1598, 1491, 1388, 1346, 1095, 850, 763, 724, 705; δ_H (400 MHz, $CDCl_3$) 2.50 (3 H, s, H-7), 4.58 (1 H, br s, H-9), 6.56–6.59 (1 H, m, H-2/3), 6.83 (1 H, s, 10), 7.20–7.23 (1 H, m, H-2/3), 7.37–7.43 (1 H, m, H-15), 7.47–7.53 (2 H, m, H-13/14), 7.59–7.64 (2 H, m, H-13/14), 8.32 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 11.8 (C-7), 101.3 (C-2/3), 111.8 (C-10), 112.8 (C-6), 123.6 (C-4/5/11/12), 124.8 (C-2/3), 127.4 (C-15), 128.1 (C-13/14), 128.7 (C-4/5/11/12), 129.1 (C-13/14), 129.3 (C-4/5/11/12), 138.8 (C-4/5/11/12), 147.1 (C-8); HRMS (ESI^+): Found: 246.0889; $C_{15}H_{13}NNaO$ (MNa^+) Requires 246.0889 (−0.2 ppm error), Found: 224.1067; $C_{15}H_{14}NO$ (MH^+) Requires 224.1070 (1.4 ppm error).

Lab notebook reference: akc06-62

1-Methyl-7-phenyl-1*H*-indol-5-ol (215k)

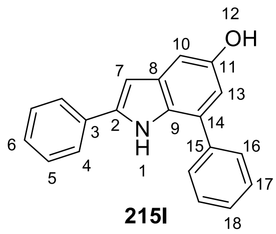


215k

Synthesised using general procedure E with ynone **214k** (50.3 mg, 0.225 mmol), $AgNO_3$ (3.80 mg, 22.5 μmol) in CH_2Cl_2 (2.3 mL) at RT for 1 h. Purification by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) afforded the *title compound* **215k** as a yellow oil (38.5 mg, 77%); R_f 0.84 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3344, 1605, 1586, 1485, 1409, 1165, 1139, 1098, 993, 810, 770; δ_H (400 MHz, $CDCl_3$) 3.26 (3 H, s, H-1), 4.67 (1 H, br s, H-8), 6.42 (1 H, d, J = 3.0 Hz, H-2/3), 6.63 (1 H, d, J = 3.0 Hz, H-6/9), 6.96 (1 H, d, J = 3.0 Hz, H-2/3), 7.05 (1 H, d, J = 3.0 Hz, H-6/9), 7.40–7.46 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 36.7 (C-1), 100.3 (C-2/3), 104.3 (C-6/9), 113.8 (C-6/9), 127.3 (C-14), 127.5 (C), 127.6 (C-12/13), 129.7 (C), 129.9 (C-12/13), 130.4 (C), 131.8 (C-2/3), 139.8 (C-10/11), 148.6 (C-7); HRMS (ESI^+): Found: 224.1063; $C_{15}H_{14}NO$ (MH^+) Requires 224.1070 (−3.2 ppm error).

Lab notebook reference: akc07-78

2,7-Diphenyl-1*H*-indol-5-ol (215l)

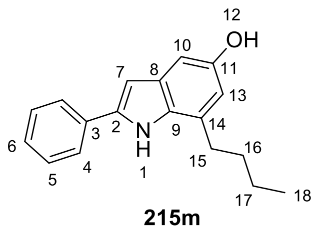


215l

Synthesised using general procedure F with ynone **233a** (30.9 mg, 0.108 mmol), $AgNO_3$ (1.84 mg, 10.8 µmol) and Ag_2O (1.25 mg, 5.40 µmol) in CH_2Cl_2 (1.1 mL) at RT for 1.5 h. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **215l** as a brown solid (28.1 mg, 91%); mp 133–135 °C; R_f 0.53 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3466, 3350, 3057, 1594, 1480, 1191, 1156, 907, 845, 759, 733, 704; δ_H (400 MHz, $CDCl_3$) 4.60 (1 H, br s, H-12), 6.78 (1 H, d, *J* = 2.5 Hz, H-7), 6.82 (1 H, d, *J* = 2.5 Hz, H-10/13), 7.04 (1 H, d, *J* = 2.5 Hz, H-10/13), 7.29–7.35 (1 H, m, H-6/18), 7.40–7.48 (3 H, m, H-6/8,5/17), 7.56 (2 H, dd, *J* = 8.0, 7.5 Hz, H-5/17), 7.63 (2 H, d, *J* = 8.0 Hz, H-4/16), 7.68 (2 H, d, *J* = 7.5 Hz, H-4/16), 8.39 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 99.9 (C-7), 104.2 (C-10/13), 111.9 (C-10/13), 125.2 (C-4/16), 126.2 (C), 127.7 (C-6/18), 127.8 (C-6/18), 128.1 (C-4/5/16/17), 129.0 (C-4/5/16/17), 129.3 (C-4/5/16/17), 130.1 (C), 130.4 (C), 132.2 (C), 138.7 (C), 139.2 (C), 150.1 (C-11); HRMS (ESI$^+$): Found: 308.1032; $C_{20}H_{15}NNaO$ (MNa^+) Requires 308.1046 (−4.3 ppm error), Found: 286.1218; $C_{20}H_{16}NO$ (MH^+) Requires 286.1226 (2.8 ppm error).

Lab notebook reference: akc07-40

7-Butyl-2-phenyl-1*H*-indol-5-ol (215m)



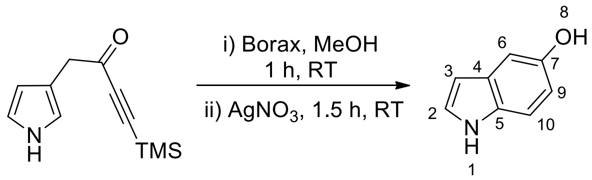
215m

Synthesised using general procedure F with ynone **233b** (46.2 mg, 0.174 mmol), $AgNO_3$ (1.48 mg, 8.71 µmol) and Ag_2O (1.00 mg, 4.35 µmol) in CH_2Cl_2 (1.7 mL) at RT for 4 h. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **215m** as a yellow oil (44.0 mg, 95%); R_f 0.54 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3353, 2955, 2928, 2859, 1617, 1599, 1452, 1375, 1245, 1138, 842, 763, 746; δ_H (400 MHz, $CDCl_3$) 0.99 (3 H, t, *J* = 7.5 Hz, H-18), 1.47 (2 H, app. sextet, *J* = 7.5 Hz, H-17), 1.77 (2 H, app.

pentet, J = 7.5 Hz, H-16), 2.83 (2 H, t, J = 8.0 Hz, H-15), 4.49 (1 H, br s, H-12), 6.64 (1 H, d, J = 2.0 Hz, H-10/13), 6.72 (1 H, d, J = 2.0 Hz, H-7), 6.90 (1 H, d, J = 2.0 Hz, H-10/13), 7.34 (1 H, t, J = 7.5 Hz, H-6), 7.46 (2 H, dd, J = 8.0, 8.0 Hz, H-5), 7.68 (2 H, d, J = 7.5 Hz, H-4), 8.11 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 14.0 (C-18), 22.7 (C-17), 30.8 (C-15), 31.6 (C-16), 100.0 (C-7), 102.5 (C-10/13), 111.7 (C-10/13), 125.1 (C-4), 126.1 (C), 127.6 (C-6), 129.0 (C-5), 129.6 (C), 131.2 (C), 132.5 (C), 138.4 (C), 149.9 (C-11); HRMS (ESI$^+$): Found: 288.1348; $C_{18}H_{19}NNaO$ (MNa^+) Requires 288.1359 (3.7 ppm error), Found: 266.1528; $C_{18}H_{20}NO$ (MH^+) Requires 266.1539 (4.4 ppm error).

Lab notebook reference: akc07-48

1*H*-Indol-5-ol (238)



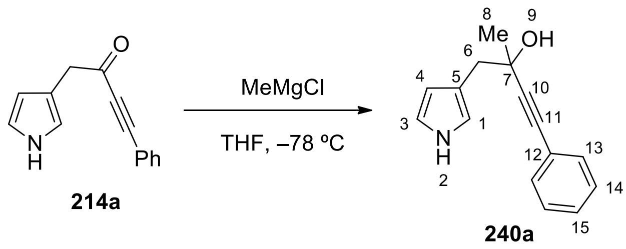
214l **238**

To a solution of ynone **214l** (80 mg, 0.390 mmol) in MeOH (3.9 mL) at RT was added a solution of Borax (0.39 mL, 3.90 μmol, 0.01 M solution in water). The reaction mixture was stirred at RT for 1 h, followed by the addition of $AgNO_3$ (6.63 mg, 39.0 μmol) at RT. The mixture was then stirred for a further 1.5 h at RT until completion was observed by TLC. Brine (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the *title compound* **238** as an white solid (33.2 mg, 64%); mp 95–97 °C; R_f 0.22 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3408, 1627, 1583, 1487, 1455, 1341, 1219, 1145, 1129, 947, 802, 757, 726; δ_H (400 MHz, $(CD_3)_2SO$) 6.16–6.27 (1 H, m, H-2/3), 6.59 (1 H, d, J = 8.5 Hz, H-9/10), 6.81–6.86 (1 H, m, H-2/3), 7.16 (1 H, d, J = 8.5 Hz, H-9/10), 7.19–7.22 (1 H, m, H-6), 8.58 (1 H, br s, H-8), 10.74 (1 H, br s, H-1); δ_C (100 MHz, $(CD_3)_2SO$) 100.1 (C-2/3), 103.8 (C-2/3), 111.2 (C-9/10), 111.5 (C-9/10), 125.4 (C-6), 128.3 (C-4/5), 130.4 (C-4/5), 150.4 (C-7).

Lab notebook reference: akc06-19

Spectroscopic data matched those previously reported in the literature.[209]

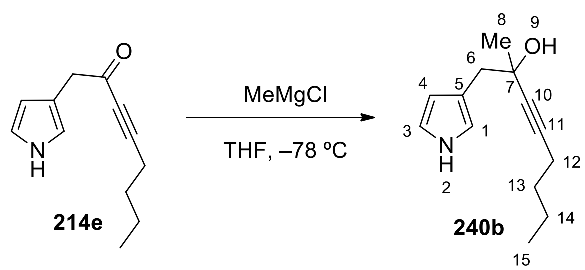
2-Methyl-4-phenyl-1-(1*H*-pyrrol-3-yl)but-3-yn-2-ol (240a)



To a stirred solution of ynone **214a** (50.6 mg, 0.242 mmol) in THF (3.6 mL) at −78 °C under argon was added MeMgCl (0.40 mL, 1.21 mmol, 3.0 M in THF). The mixture was stirred for 1 h at −78 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and left to stir for 5 min whilst warming to RT. The organics were separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The organics were combined, washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) to afford the *title compound* **240a** as a pale yellow oil (25.1 mg, 46%); R_f 0.32 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3392, 2980, 2930, 1598, 1489, 1059, 756, 738, 691; δ_H (400 MHz, $CDCl_3$) 1.65, (3 H, s, H-8), 2.40 (1 H, br s, H-9), 2.88 (1 H, d, *J* = 14.0 Hz, H-6a), 3.06 (1 H, d, *J* = 14.0 Hz, H-6b), 6.30–6.34 (1 H, m, H-1/3/4), 6.77–6.83 (2 H, m, H-1/3/4), 7.28–7.36 (3 H, m, H-13/14,15), 7.40–7.46 (2 H, m, H-13/14), 8.24 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 29.1 (C-8), 41.7 (C-6), 67.9 (C-7), 83.1 (C-10), 93.5 (C-11), 110.5 (C-1/3/4), 117.5 (C-5), 117.6 (C-1/3/4), 118.0 (C-1/3/4), 123.0 (C-12), 128.1 (C-15), 128.2 (C-13/14), 131.6 (C-13/14); HRMS (ESI$^+$): Found: 248.1041; $C_{15}H_{15}NNaO$ (MNa^+) Requires 248.1046 (2.1 ppm error).

Lab notebook reference: akc06-02

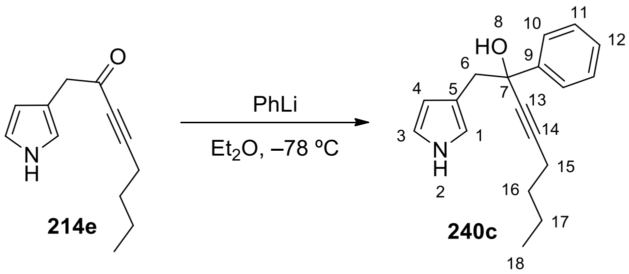
2-Methyl-1-(1*H*-pyrrol-3-yl)oct-3-yn-2-ol (240b)



To a stirred solution of ynone **214e** (92.4 mg, 0.488 mmol) in THF (7.3 mL) at −78 °C under argon was added MeMgCl (0.81 mL, 2.44 mmol, 3.0 M in THF). The mixture was stirred vigorously for 1.5 h at −78 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and left to stir for 5 min whilst warming to RT. The organics were separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) to afford the *title compound* **240b** as an orange oil (50.4 mg, 50%); R_f 0.31 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3396, 2957, 2931, 2872, 1431, 1456, 1374, 1353, 1060, 937, 784, 738; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, t, *J* = 7.5 Hz, H-15), 1.35–1.44 (2 H, m, H-13/14), 1.44–1.50 (2 H, m, H-13/14), 1.51 (3 H, s, H-8), 2.21 (2 H, t, *J* = 7.0 Hz, H-12), 2.78 (1 H, d, *J* = 14.0 Hz, H-6a), 2.92 (1 H, d, *J* = 14.0 Hz, H-6b), 6.23–6.27 (1 H, m, H-1/3/4), 6.72–6.79 (2 H, m, H-1/3/4), 8.24 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 13.6 (C-15), 18.3 (C-12), 21.9 (C-13/14), 29.5 (C-8), 30.8 (C-13/14), 41.8 (C-6), 67.5 (C-7), 83.6 (C-10/11), 84.4 (C-10/11), 110.5 (C-1/3/4), 117.5 (C-1/3/4), 117.7 (C-5), 117.8 (C-1/3/4); HRMS (ESI$^+$): Found: 228.1357; $C_{13}H_{19}NNaO$ (MNa^+) Requires 228.1359 (0.7 ppm error).

Lab notebook reference: akc06-30

2-Phenyl-1-(1*H*-pyrrol-3-yl)oct-3-yn-2-ol (240c)

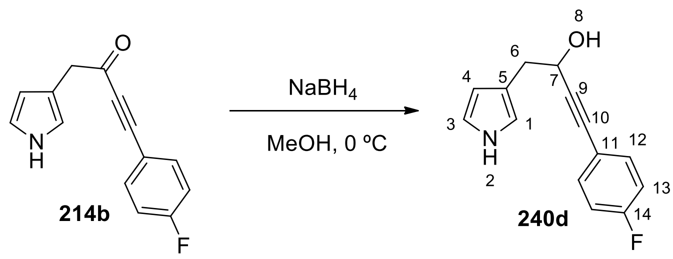


To a stirred solution of ynone **214e** (87.4 mg, 0.462 mmol) in Et_2O (2.5 mL) at −78 °C under argon was added PhLi (0.73 mL, 1.39 mmol, 1.9 M in Et_2O). The mixture was warmed to RT and stirred vigorously for 4 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and left to stir for 5 min. The organics were separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (8:2 hexane:EtOAc) to afford the *title compound* **240c** as a pale yellow oil (75.1 mg, 61%); R_f 0.26 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3399, 2956, 2930, 2871, 1448, 1060, 1032, 767, 699; δ_H (400 MHz, $CDCl_3$) 0.94 (3 H, t, *J* = 7.5 Hz, H-18), 1.44 (2 H, sextet, *J* = 7.5 Hz, H-17), 1.55 (2 H, pentet, *J* = 7.5 Hz, H-16), 2.29 (2 H, t, *J* = 7.5 Hz, H-15), 2.65 (1 H, s, H-8), 3.02 (1 H, d, *J* = 14.0 Hz, H-6a), 3.12 (1 H, d, *J* = 14.0 Hz, H-6b), 6.10–6.16 (1 H, m, H-1/3/4), 6.62–6.68 (1 H, m, H-1/3/4), 6.70–6.76 (1 H, m, H-1/3/4), 7.30 (1 H, t, *J* = 7.5 Hz, H-12), 7.36 (2 H, dd, *J* = 7.5, 7.5 Hz, H-11), 7.66 (2 H, d, *J* = 7.5 Hz, H-10), 8.16 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 13.6 (C-8), 18.5 (C-15), 22.0 (C-17), 30.7 (C-16), 44.2 (C-6), 72.4 (C-7), 83.1

(C-13/14), 86.3 (C-13/14), 110.6 (C-1/3/4), 117.2 (C-5), 117.7 (C-1/3/4), 117.8 (C-1/3/4), 125.5 (C-10), 127.2 (C-12), 127.9 (C-11), 145.1 (C-7); HRMS (ESI$^+$): Found: 290.1513; $C_{18}H_{21}NNaO$ (MNa^+) Requires 290.1515 (0.8 ppm error).

Lab notebook reference: akc06-46/52

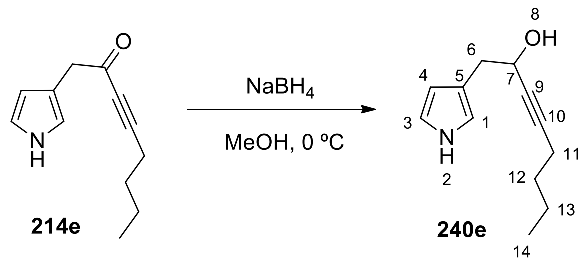
4-(4-Fluorophenyl)-1-(1*H*-pyrrol-3-yl)but-3-yn-2-ol (240d)



To a stirred solution of ynone **214b** (155 mg, 0.682 mmol) in MeOH (14 mL) at 0 °C was added $NaBH_4$ (103 mg, 2.73 mmol) portionwise. The mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) at 0 °C and the aqueous layer extracted with EtOAc (3 × 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the *title compound* **240d** as a pale yellow solid (144 mg, 92%); mp 81–83 °C; R_f 0.53 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3396, 2929, 2204, 1657, 1599, 1506, 1232, 1157, 1059, 837; δ_H (400 MHz, $CDCl_3$) 2.12 (1 H, d, J = 6.0 Hz, H-8), 2.98 (1 H, dd, J = 14.0, 6.0 Hz, H-6a), 3.05 (1 H, dd, J = 14.0, 6.0 Hz, H-6b), 4.72 (1 H, dd, J = 6.0, 6.0, 6.0 Hz, H-7), 6.22–6.28 (1 H, m, H-1/3/4), 6.76–6.83 (2 H, m, H-1/3/4), 7.01 (2 H, dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ 8.5 Hz, H-13), 7.39–7.46 (2 H, m, H-12), 8.20 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 35.7 (C-6), 63.1 (C-7), 83.7 (C-9/10), 89.8 (C-9/10), 109.5 (C-1/3/4), 115.5 (d, $^2J_{CF}$ = 22.0 Hz, C-13), 117.1 (C-1/3/4), 117.5 (C-5), 118.3 (C-1/3/4), 118.8 (d, $^4J_{CF}$ = 4.0 Hz, C-11), 133.5 (d, $^3J_{CF}$ = 8.5 Hz, C-12), 162.5 (d, $^1J_{CF}$ = 249 Hz, C-14); HRMS (ESI$^+$): Found: 252.0798; $C_{14}H_{12}FNNaO$ (MNa^+) Requires 252.0795 (−1.3 ppm error), Found: 230.0975; $C_{14}H_{13}FNO$ (MH^+) Requires 230.0976 (0.5 ppm error)

Lab notebook reference: akc06-66

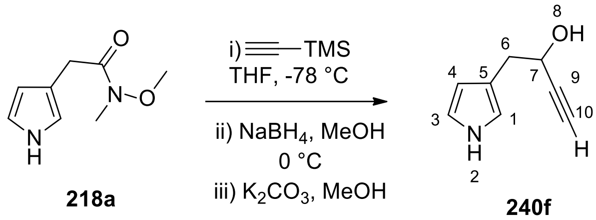
1-(1*H*-Pyrrol-3-yl)oct-3-yn-2-ol (240e)



To a stirred solution of ynone **214e** (86.1 mg, 0.455 mmol) in MeOH (9 mL) at 0 °C was added $NaBH_4$ (68.8 mg, 1.82 mmol) portionwise. The mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) at 0 °C and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 7:3 hexane:EtOAc) to afford the *title compound* **240e** as a pale yellow oil (79.8 mg, 92%); R_f 0.13 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3394, 2957, 2931, 2872, 1488, 1466, 1431, 1380, 1061, 1034, 999, 964, 774, 711; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, t, *J* = 7.0 Hz, H-14), 1.36–1.44 (2 H, m, H-12/13), 1.45–1.55 (2 H, m, H-12/13), 2.00 (1 H, d, *J* = 5.5 Hz, H-8), 2.24 (2 H, td, *J* = 7.0, 2.0 Hz, H-11), 2.85 (1 H, dd, *J* = 14.0, 5.5 Hz, H-6a), 2.94 (1 H, dd, *J* = 14.0, 5.5 Hz, H-6b), 4.45–4.53 (1 H, m, H-7), 6.17–6.22 (1 H, m, H-1/3/4), 6.70–6.74 (1 H, m, H-1/3/4), 6.75–6.80 (1 H, m, H-1/3/4), 8.21 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 13.6 (C-14), 18.4 (C-11), 21.9 (C-12/13), 30.7 (C-12/13), 36.1 (C-6), 63.0 (C-7), 81.0 (C-9/10), 85.4 (C-9/10), 109.4 (C-1/3/4), 116.9 (C-1/3/4), 118.0 (C-5), 118.2 (C-1/3/4); HRMS (ESI$^+$): Found: 214.1201; $C_{12}H_{17}NNaO$ (MNa^+) Requires 214.1202 (0.6 ppm error).

Lab notebook reference: akc06-31

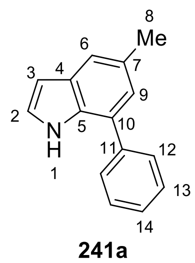
1-(1*H*-Pyrrol-3-yl)but-3-yn-2-ol (240f)



To a stirred solution of TMS acetylene (0.31 mL, 2.27 mmol) in THF (2.5 mL) at −78 °C under argon was added *n*-BuLi (0.76 mL, 1.88 mmol, 2.5 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 **218a** (127 mg, 0.755 mmol) in THF (4 mL). Upon complete transfer the mixture was warmed to RT and stirred for 30 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL). The organics were separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then dissolved in MeOH (15 mL), cooled to 0 °C and $NaBH_4$ (114 mg, 3.02 mmol) was added portionwise. The mixture was stirred for 30 min at RT and then K_2CO_3 (209 mg, 1.51 mmol) was added. The mixture was stirred for a further 5 h at RT. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL) and diluted with CH_2Cl_2 (50 mL).The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (9:1 hexane:EtOAc, then 6:4 hexane:EtOAc) to afford the *title compound* **240f** as an orange oil (84.4 mg, 83%); R_f 0.25 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3392, 3285, 2919, 1430, 1025, 780, 732, 643; δ_H (400 MHz, $CDCl_3$) 2.04–2.15 (1 H, m, H-8), 2.47 (1 H, d, *J* = 2.0 Hz, H-10), 2.90 (1 H, dd, *J* = 14.0, 6.5 Hz, H-6a), 2.98 (1 H, dd, *J* = 14.0, 5.5 Hz, H-6b), 4.48–4.56 (1 H, m, H-7), 6.19–6.23 (1 H, m, H-1/3/4), 6.72–6.80 (2 H, m, H-1/3/4), 8.22 (1 H, br s, H-2); δ_C (100 MHz, $CDCl_3$) 35.5 (C-6), 62.5 (C-7), 72.8 (C-10), 84.8 (C-9), 109.5 (C-1/3/4), 117.1 (C-1/3/4), 117.3 (C-5), 118.3 (C-1/3/4); HRMS (EI$^+$): Found: 135.0681; C_8H_9NO (M^+) Requires 135.0684 (−2.2 ppm error).

Lab notebook reference: akc05-88/89

5-Methyl-7-phenyl-1*H*-indole (241a)



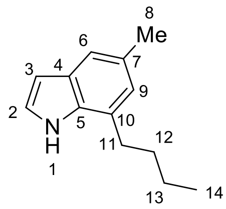
241a

Synthesised using general procedure G with propargyl alcohol **240a** (75 mg, 0.333 mmol), $AgNO_3$ (5.66 mg, 33.3 µmol) and Ag_2O (3.86 mg, 16.7 µmol) in CH_2Cl_2 (3.3 mL) at RT for 21 h. Purification by column chromatography (9:1 hexane:EtOAc, then 6:4 hexane:EtOAc) afforded the *title compound* **241a** as a pale yellow oil (64.3 mg, 86%); R_f 0.76 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3433, 3029, 2918, 1592, 1477, 1413, 1325, 1305, 1136, 850, 758, 702; δ_H (400 MHz, $CDCl_3$) 2.53 (3 H, s, H-8), 6.54–6.60 (1 H, m, H-2/3), 7.09 (1 H, s, H-6/9), 7.18–7.22 (1 H, m, H-2/3), 7.42 (1 H, t, *J* = 7.5 Hz, H-14), 7.46 (1 H, s, H-6/9), 7.53 (2 H, dd, *J* = 7.5, 7.5 Hz, H-13), 7.66 (2 H, d, *J* = 7.5 Hz, H-12), 8.33 (1 H, br s, H-1); δ_C (100

MHz, $CDCl_3$) 21.4 (C-8), 102.5 (C-2/3), 119.7 (C-6/9), 123.5 (C-6/9), 124.4 (C-2/3), 125.2 (C), 127.3 (C-14), 128.2 (C-12), 128.6 (C), 129.1 (C-13), 129.5 (C-7), 132.0 (C), 139.3 (C); HRMS (ESI^+): Found: 208.1122; $C_{15}H_{14}N$ (MH^+) Requires 208.1121 (−0.5 ppm error).

Lab notebook reference: akc07-17

7-Butyl-5-methyl-1*H*-indole (241b)

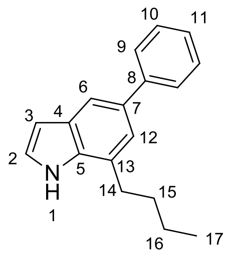


241b

Synthesised using general procedure H with propargyl alcohol **240b** (25.2 mg, 0.123 mmol), $AgNO_3 \cdot SiO_2$ (209 mg, 12.3 μmol) in CH_2Cl_2 (1.2 mL) at RT for 24 h. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **241b** as a dark brown oil (22.8 mg, 99%); R_f 0.63 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3420, 2956, 2928, 2859, 1593, 1480, 1455, 1411, 1342, 1116, 845, 723; δ_H (400 MHz, $CDCl_3$) 0.98 (3 H, t, J = 7.5 Hz, H-14), 1.45 (2 H, sextet, J = 7.5 Hz, H-13), 1.74 (2 H, pentet, J = 7.5 Hz, H-12), 2.45 (3 H, s, H-8), 2.81 (2 H, t, J = 7.5 Hz, H-11), 6.47–6.51 (1 H, m, H-2/3), 6.84–6.89 (1 H, m, H-6/9), 7.15–7.20 (1 H, m, H-2/3), 7.28–7.33 (1 H, m, H-6/9), 8.03 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 14.0 (C-14), 21.4 (C-8), 22.8 (C-13), 31.1 (C-11), 31.9 (C-12), 102.5 (C-2/3), 118.0 (C-6/9), 123.2 (C-6/9), 123.7 (C-2/3), 124.8 (C-5/10), 127.9 (C-4), 129.1 (C-7), 133.2 (C-5/10); HRMS (ESI^+): Found: 188.1427; $C_{13}H_{18}N$ (MH^+) Requires 188.1434 (3.4 ppm error).

Lab notebook reference: akc06-39

7-Butyl-5-phenyl-1*H*-indole (241c)

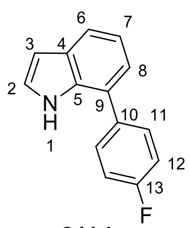


241c

Synthesised using general procedure H with propargyl alcohol **240c** (68.5 mg, 0.256 mmol), $AgNO_3 \cdot SiO_2$ (435 mg, 25.6 µmol) in CH_2Cl_2 (2.6 mL) at RT for 48 h. Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **241c** as a pale brown oil (29.5 mg, 43%); R_f 0.54 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3431, 2955, 2927, 2857, 1598, 1470, 1444, 1347, 1324, 1115, 870, 760, 725, 698; δ_H (400 MHz, $CDCl_3$) 0.99 (3 H, t, *J* = 7.5 Hz, H-17), 1.48 (2 H, sextet, *J* = 7.5 Hz, H-16), 1.80 (2 H, pentet, *J* = 7.5 Hz, H-15), 2.91 (2 H, t, *J* = 7.5 Hz, H-14), 6.61–6.65 (1 H, m, H-2/3), 7.24–7.27 (1 H, m, H-2/3), 7.28–7.35 (2 H, m, H-6/12,11), 7.45 (2 H, dd, *J* = 8.0, 8.0 Hz, H-10), 7.67 (2 H, d, *J* = 8.0 Hz, H-9), 7.73 (1 H, s, H-6/12), 8.14 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 14.0 (C-17), 22.8 (C-16), 31.2 (C-14), 31.8 (C-15), 103.4 (C-2/3), 117.0 (C-6/12), 121.5 (C-6/12), 124.4 (C-2/3), 125.3 (C), 126.2 (C-11), 127.4 (C-9), 128.1 (C), 128.6 (C-10), 133.6 (C), 134.4 (C), 142.8 (C); HRMS (ESI$^+$): Found: 272.1415; $C_{18}H_{19}NNa$ (MNa^+) Requires 272.1410 (2.1 ppm error), Found: 250.1595; $C_{18}H_{20}N$ (MH^+) Requires 250.1590 (1.8 ppm error).

Lab notebook reference: akc06-54

7-(4-Fluorophenyl)-1*H*-indole (241d)



241d

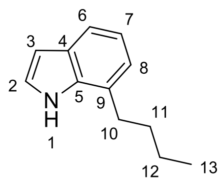
Synthesised using general procedure G with propargyl alcohol **240d** (50.0 mg, 0.218 mmol), $AgNO_3$ (3.7 mg, 21.8 µmol) and Ag_2O (2.5 mg, 10.9 µmol) in CH_2Cl_2 (2.2 mL) at RT for 5 h. Purification by column chromatography (8:2 hexane:EtOAc) afforded the *title compound* **241d** as a pale yellow oil (43.3 mg, 94%); R_f 0.58 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3428, 1603, 1519, 1503, 1485, 1412, 1330, 1220, 1158, 840, 793, 729; δ_H (400 MHz, $CDCl_3$)

6.64–6.69 (1 H, m, H-2/3), 7.18–7.26 (5 H, m, H-2/3,6/8,7,12), 7.58–7.65 (2 H, m, H-11), 7.69 (1 H, d, J = 8.0 Hz, H-6/8), 8.33 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 103.2 (CH), 116.0 (d, $^2J_{CF}$ = 21.0 Hz, C-12), 120.1 (CH), 120.3 (CH), 121.9 (CH), 124.4 (CH), 124.6 (C-4/5/9), 128.3 (C-4/5/9), 129.8 (d, $^3J_{CF}$ = 7.5 Hz, C-11), 133.7 (C-4/5/9), 135.2 (d, $^4J_{CF}$ = 3.0 Hz, C-10), 162.2 (d, $^1J_{CF}$ = 247 Hz, C-13); HRMS (ESI$^+$): Found: 212.0863; $C_{14}H_{11}FN$ (MH$^+$) Requires 212.0870 (−3.4 ppm error).

Lab notebook reference: akc06-69

Spectroscopic data matched those previously reported in the literature.[210]

7-Butyl-1*H*-indole (241e)

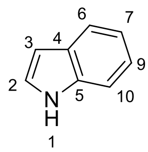


241e

Synthesised using general procedure G with propargyl alcohol **240e** (20.7 mg, 0.108 mmol), $AgNO_3$ (1.84 mg, 10.8 µmol) and Ag_2O (1.25 mg, 6.41 µmol) in CH_2Cl_2 (1 mL) at RT for 19 h. Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **241e** as a pale yellow oil (17.6 mg, 94%); R_f 0.68 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3425, 2956, 2926, 2855, 1465, 1432, 1342, 1110, 970, 726; δ_H (400 MHz, ($CDCl_3$) 1.00 (3 H, t, J = 7.5 Hz, H-13), 1.47 (2 H, sextet, J = 7.5 Hz, H-12), 1.77 (2 H, pentet, J = 7.5 Hz, H-11), 2.87 (2 H, t, J = 7.5 Hz, H-10), 6.56–6.64 (1 H, m, H-2/3), 7.05 (1 H, d, J = 7.5 Hz, H-6/8), 7.11 (1 H, dd, J = 7.5, 7.5 Hz, H-7), 7.19–7.24 (1 H, m, H-2/3), 7.55 (1 H, d, J = 7.5 Hz, H-6/8), 8.10 (1 H, br s, H-1); δ_C (100 MHz, ($CDCl_3$) 14.0 (C-13), 22.8 (C-12), 31.0 (C-10), 31.8 (C-11), 103.0 (C-2/3), 118.4 (C-6/8), 119.9 (C-7), 121.4 (C-6/8), 123.7 (C-2/3), 125.1 (C-4/5/9), 127.6 (C-4/5/9), 134.9 (C-4/5/9); HRMS (ESI$^+$): Found: 174.1273; $C_{12}H_{16}N$ (MH$^+$) Requires 174.1277 (−2.6 ppm error).

Lab notebook reference: akc06-59

1*H*-Indole (241f)



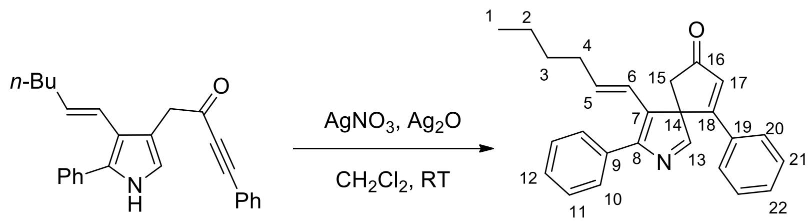
241f

Synthesised using general procedure G with propargyl alcohol **240f** (77.6 mg, 0.574 mmol), $AgNO_3$ (9.75 mg, 57.4 μmol) and Ag_2O (6.65 mg, 28.7 μmol) in CH_2Cl_2 (5.7 mL) at RT for 24 h. Purification by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **241f** as a white solid (48.8 mg, 63%); mp 42–44 °C; R_f 0.60 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3401, 3051, 1456, 1416, 1353, 1337, 1247, 1091, 745, 723; δ_H (400 MHz, $CDCl_3$) 6.60 (1 H, s, Ar-H), 7.16 (1 H, d, *J* = 7.0 Hz, Ar-H), 7.20–7.26 (2 H, m, Ar-H), 7.42 (1 H, d, *J* = 8.0 Hz, Ar-H), 7.69 (1 H, d, *J* = 8.0 Hz, Ar-H), 8.13 (1 H, br s, H-1); δ_C (100 MHz, $CDCl_3$) 102.6 (CH), 111.0 (CH), 119.8 (CH), 120.7 (CH), 122.0 (CH), 124.1 (CH), 127.8 (C-4/5), 135.7 (C-4/5).

Lab notebook reference: akc07-18

Spectroscopic data matched those previously reported in the literature.[210]

(*E*)-4-(Hex-1-en-1-yl)-3,9-diphenyl-2-azaspiro[4.4]nona-1,3,8-trien-7-one (246a)

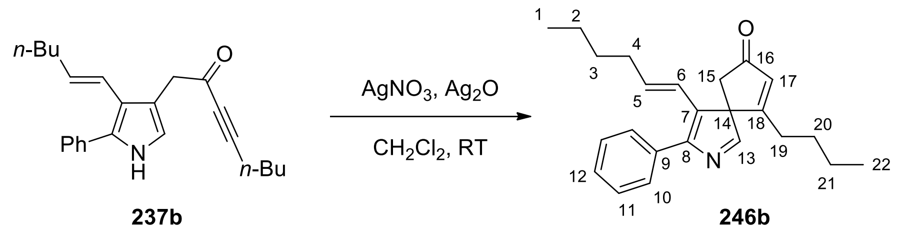


237a **246a**

To a solution of ynone **237a** (16.9 mg, 0.046 mmol) in CH_2Cl_2 (0.5 mL) at RT was added $AgNO_3$ (0.78 mg, 4.60 μmol) and Ag_2O (0.53 mg, 2.30 μmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by column chromatography (5:1 hexane:EtOAc, then 2:1 hexane:EtOAc) to afford the *title compound* **246a** as a brown oil (11.6 mg, 69%); R_f 0.10 (5:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956, 2926, 2856, 1694, 1590, 1569, 1445, 769, 698; δ_H (400 MHz, $CDCl_3$) 0.81 (3 H, t, *J* = 7.0 Hz, H-1), 1.01–1.19 (2 H, m, H-2/3), 1.19–1.30 (2 H, m, H-2/3), 1.97–2.13 (2 H, m, H-4), 2.87 (2 H, s, H-15), 5.67 (1 H, dt, *J* = 16.5, 7.0 Hz, H-5), 6.52 (1 H, d, *J* = 16.5 Hz, H-6), 6.75 (1 H, s, H-17), 7.23–7.33 (4 H, m, Ar-H), 7.37–7.43 (2 H, m, Ar-H), 7.49 (2 H, dd, *J* = 7.5, 7.5 Hz, H-11/21), 7.72 (2 H, d, *J* = 7.5 Hz, H-10/20), 8.13 (1 H, s, H-13); δ_C (100 MHz, $CDCl_3$) 13.8 (C-1), 22.0 (C-2/3), 31.3 (C-2/3), 33.5 (C-4), 42.0 (C-15), 70.1 (C-14), 121.2 (C-6), 126.6 (C-10/11/20/21), 128.4 (CH), 128.5 (C-10/11/20/21), 128.7 (C-10/11/20/21), 129.0 (C-10/11/20/21), 130.2 (C-17), 131.5 (CH), 133.0 (C), 134.1 (C), 134.3 (C), 135.7 (C-5), 151.5 (C), 173.6 (C-13), 173.7 (C), 204.3 (C-16); HRMS (ESI$^+$): Found: 368.1996; $C_{26}H_{26}NO$ (MH^+) Requires 368.2009 (3.5 ppm error).

Lab notebook reference: akc07-60

(*E*)-9-Butyl-4-(hex-1-en-1-yl)-3-phenyl-2-azaspiro[4.4]nona-1,3,8-trien-7-one (246b)

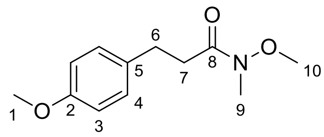


To a solution of ynone **237b** (23.4 mg, 0.0673 mmol) in CH_2Cl_2 (0.7 mL) at RT was added $AgNO_3$ (1.14 mg, 6.73 µmol) and Ag_2O (0.78 mg, 3.37 µmol). The reaction mixture was stirred at RT for 1.5 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by column chromatography (4:1 hexane:EtOAc) to afford the *title compound* **246b** as a brown oil (12.2 mg, 52%); R_f 0.20 (4:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2956, 2927, 2871, 1717, 1692, 1610, 1445, 1186, 771, 699; δ_H (400 MHz, $CDCl_3$) 0.82–0.92 (6 H, m, H-1,22), 1.23–1.41 (6 H, m, H-2,3,21), 1.50 (2 H, quintet, *J* = 7.5 Hz, H-20), 1.76–1.86 (1 H, m, H-19a), 1.93–2.04 (1 H, m, H-19b), 2.09–2.17 (2 H, m, H-4), 2.72 (1 H, d, *J* = 19.0 Hz, H-15a), 2.81 (1 H, d, *J* = 19.0 Hz, H-15b), 5.56 (1 H, dt, *J* = 16.0, 7.0 Hz, H-5), 6.28 (1 H, s, H-17), 6.58 (1 H, d, *J* = 16.0 Hz, H-6), 7.40 (1 H, t, *J* = 7.5 Hz, H-12), 7.48 (2 H, dd, *J* = 7.5, 7.5 Hz, H-11), 7.73 (2 H, d, *J* = 7.5 Hz, H-10), 7.82 (1 H, s, H-13); δ_C (100 MHz, $CDCl_3$) 13.7 (C-1/22), 13.9 (C-1/22), 22.2 (C-2/3/21), 22.3 (C-2/3/21), 28.7 (C-19), 29.0 (C-20), 31.5 (C-2/3/21), 33.6 (C-4), 40.0 (C-15), 71.9 (C-14), 121.5 (C-6), 128.45 (C-12), 128.47 (C-11), 128.8 (C-10), 130.7 (C-17), 132.3 (C-7), 134.0 (C-9), 134.6 (C-5), 152.4 (C-8), 172.6 (C-13), 182.0 (C-18), 205.6 (C-16); HRMS (ESI$^+$): Found: 348.2311; $C_{24}H_{30}NO$ (MH^+) Requires 348.2322 (3.2 ppm error).

Lab notebook reference: akc07-65

6.9.4 Chapter 5

N-Methoxy-3-(4-methoxyphenyl)-N-methylpropanamide (273a)



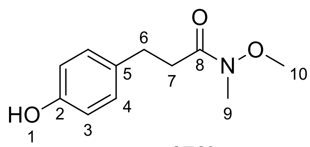
273a

Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid **272a** (7.00 g, 38.8 mmol), T3P 50% in EtOAc (37.0 g, 58.3 mmol), DIPEA (20.3 mL, 116 mmol) and MeNH(OMe)·HCl (4.20 g, 42.7 mmol) in CH_2Cl_2 (100 mL) at RT for 1 h. Afforded the *title compound* **273a** without further purification as a yellow oil (8.70 g, 100%); R_f 0.46 (1:1 hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 2.71 (2 H, t, J = 7.5 Hz, H-6/7), 2.91 (2 H, t, J = 7.5 Hz, H-6/7), 3.18 (3 H, s, H-9), 3.61 (3 H, s, H-10), 6.84 (2 H, d, J = 8.0, H-3), 7.15 (2 H, d, J = 8.0 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 29.8 (C-6/7), 32.1 (C-9), 34.0 (C-6/7), 55.2 (C-1), 61.2 (C-10), 113.8 (C-3), 129.3 (C-4), 133.4 (C-5), 157.9 (C-2), 173.7 (C-8); HRMS (ESI^+): Found: 246.1097; $C_{12}H_{17}NNaO_3$ (MNa^+) Requires 246.1101 (−1.6 ppm error), Found: 224.1277; $C_{12}H_{18}NO_3$ (MH^+) Requires 224.1281 (1.9 ppm error).

Lab notebook reference: akc07-74

Spectroscopic data matched those previously reported in the literature.[211]

3-(4-Hydroxyphenyl)-N-methoxy-N-methylpropanamide (273b)



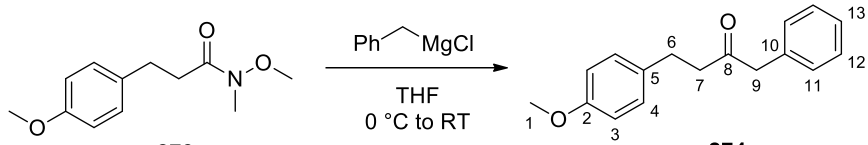
273b

Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid **272b** (7.00 g, 42.1 mmol), T3P 50% in EtOAc (40.2 g, 63.2 mmol), DIPEA (22.0 mL, 126 mmol) and MeNH(OMe)·HCl (4.50 g, 46.3 mmol) in CH_2Cl_2 (105 mL) at RT for 1 h. Afforded the *title compound* **273b** without further purification as a yellow oil (7.61 g, 86%); R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3263, 2938, 1632, 1614, 1593, 1515, 1446, 1388, 1266, 1228, 1172, 987; δ_H (400 MHz, $CDCl_3$) 2.72 (2 H, t, J = 7.5 Hz, H-6/7), 2.90 (2 H, t, J = 7.5 Hz, H-6/7), 3.19 (3 H, s, H-9), 3.61 (3 H, s, H-10), 5.85 (1 H, br s, H-1), 6.77 (2 H, d, J = 8.0, H-3), 7.08 (2 H, d, J = 8.0 Hz, H-4); δ_C (100 MHz, $CDCl_3$) 29.8 (C-6/7), 32.2 (C-9), 34.0 (C-6/7), 61.2 (C-10), 115.3 (C-3), 129.5 (C-4), 133.0 (C-5), 154.3 (C-2), 173.9 (C-8); HRMS

(ESI$^+$): Found: 232.09591; $C_{11}H_{15}NNaO_3$ (MNa$^+$) Requires 232.0944 (2.8 ppm error), Found: 210.1127; $C_{11}H_{16}NO_3$ (MH$^+$) Requires 210.1125 (−1.2 ppm error).

Lab notebook reference: akc07-73

4-(4-Methoxyphenyl)-1-phenylbutan-2-one (274a)



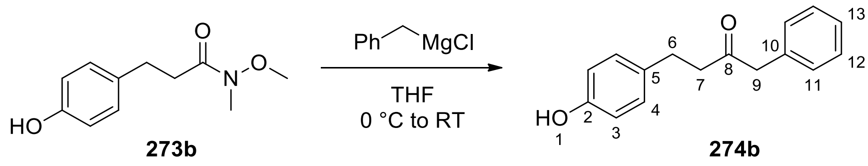
273a **274a**

Procedure based on: Taylor *et al.*, *Angew. Chem. Int. Ed.*, 2016, **55**, 9671–9675.[173]

To a solution of Weinreb amide **273a** (2.00 g, 8.96 mmol) in THF (90 mL) at 0 °C under argon was added benzylmagnesium chloride (13.4 mL, 26.9 mmol, 2.0 M in THF) dropwise using a syringe pump. The resulting solution was warmed to RT and stirred for 1.5 h. The reaction was then cooled to 0 °C, quenched with sat. aq. NH_4Cl (20 mL), diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) to afford the *title compound* **274a** as a clear and colourless oil (1.76 g, 77%); R_f 0.70 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2908, 1712, 1512, 1245, 1178, 1033, 830, 735, 699; δ_H (400 MHz, $CDCl_3$) 2.72–2.78 (2 H, m, H-6/7), 2.79–2.86 (2 H, m, H-6/7), 3.67 (2 H, s, H-9), 3.79 (3 H, s, H-1), 6.81 (2 H, d, J = 8.0 Hz, H-3/4), 7.06 (2 H, d, J = 8.0 Hz, H-3/4), 7.18 (2 H, d, J = 7.0 Hz, H-11), 7.25–7.36 (3 H, m, H-12,13); δ_C (100 MHz, $CDCl_3$) 28.9 (C-6/7), 43.7 (C-6/7), 50.4 (C-9), 55.2 (C-1), 113.8 (C-3/4), 127.0 (C-13), 128.7 (CH), 129.2 (CH), 129.4 (CH), 132.9 (C-5), 134.1 (C-10), 157.9 (C-2), 207.6 (C-8); HRMS (ESI$^+$): Found: 277.1189; $C_{17}H_{18}NaO_2$ (MNa$^+$) Requires 277.1199 (−3.7 ppm error).

Lab notebook reference: akc07-82

4-(4-Hydroxyphenyl)-1-phenylbutan-2-one (274b)

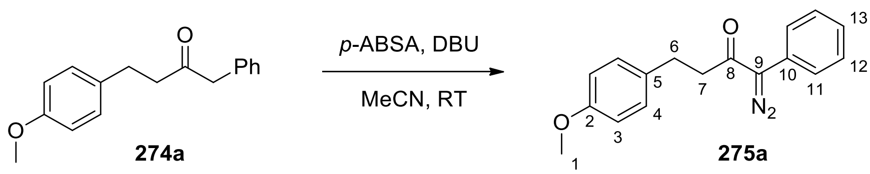


Procedure based on: Taylor *et al.*, *Angew. Chem. Int. Ed.*, 2016, **55**, 9671–9675.[173]

To a solution of Weinreb amide **273b** (1.53 g, 7.31 mmol) in THF (70 mL) at 0 °C under argon was added benzylmagnesium chloride (14.6 mL, 29.2 mmol, 2.0 M in THF) dropwise using a syringe pump. The resulting solution was warmed to RT and stirred for 2 h. The reaction was then cooled to 0 °C, quenched with sat. aq. NH_4Cl (20 mL), diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ 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* **274b** as a white solid (1.51 g, 86%); mp 112–114 °C; R_f 0.46 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3387, 3027, 2929, 1707, 1614, 1515, 1451, 1362, 1221, 833, 741, 699; δ_H (400 MHz, CD_3OD) 2.68–2.81 (4 H, m, H-6,7), 3.68 (2 H, s, H-9), 6.66 (2 H, d, *J* = 8.0 Hz, H-3/4), 6.93 (2 H, d, *J* = 8.0 Hz, H-3/4), 7.11–7.17 (2 H, m, Ar-H), 7.19–7.33 (3 H, m, Ar-H); δ_C (100 MHz, CD_3OD) 30.2 (C-6/7), 44.9 (C-6/7), 51.0 (C-9), 116.3 (C-3/4), 128.0 (C-13), 129.7 (CH), 130.4 (CH), 130.7 (CH), 133.2 (C-5), 136.0 (C-10), 156.8 (C-2), 210.7 (C-8); HRMS (ESI$^+$): Found: 263.1034; $C_{16}H_{16}NaO_2$ (MNa^+) Requires 263.1043 (−3.4 ppm error).

Lab notebook reference: akc08-17

1-Diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one (275a)

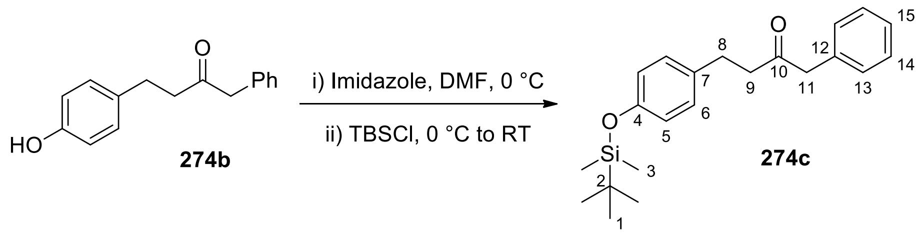


Procedure based on: Taylor *et al.*, *Angew. Chem. Int. Ed.*, 2016, **55**, 9671–9675.[173]

To a solution of benzyl ketone **274a** (977 mg, 3.84 mmol) and *p*-ABSA (1.11 g, 4.61 mmol) in MeCN (11.5 mL) at RT under argon was added DBU (0.8 mL, 5.38 mmol) dropwise. The resulting solution was stirred for 50 min before being concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 7:3 hexane:EtOAc with 3% Et_3N as a basic additive) to afford the *title compound* **275a** as a yellow solid (797 mg, 74%); mp 79–81 °C; R_f 0.73 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3009, 2951, 2836, 2074, 1631, 1611, 1511, 1497, 1362, 1246, 1176, 1034, 821, 753; δ_H (400 MHz, $CDCl_3$) 2.87 (2 H, t, *J* = 7.5 Hz, H-6/7), 2.99 (2 H, t, *J* = 7.5 Hz, H-6/7), 3.97 (3 H, s, H-1), 6.84 (2 H, d, *J* = 8.5 Hz, H-3/4), 7.13 (2 H, d, *J* = 8.5 Hz, H-3/4), 7.27 (1 H, t, *J* = 7.5 Hz, H-13), 7.41 (2 H, dd, *J* = 8.0, 7.5 Hz, H-12), 7.47 (2 H, d, *J* = 8.0 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 29.8 (C-6/7), 41.1 (C-6/7), 55.2 (C-1), 72.3 (C-9), 113.9 (C-3/4), 125.4 (C-10), 126.1 (C-11), 127.0 (C-13), 129.0 (C-12), 129.4 (C-3/4), 132.7 (C-5), 158.1 (C-2), 192.0 (C-8); HRMS (LIFDI$^+$): Found: 280.1211; $C_{17}H_{16}N_2O_2$ (M^+) Requires 280.1212 (−0.4 ppm error).

Lab notebook reference: akc07-87

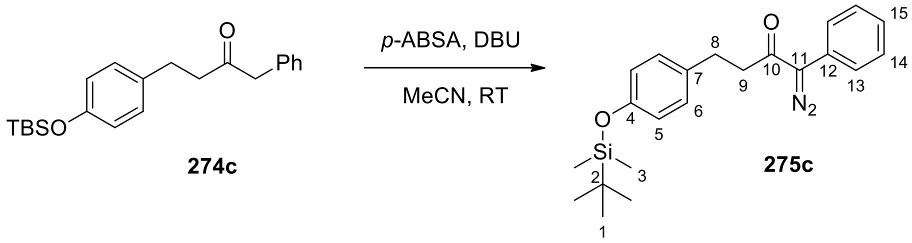
4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-phenylbutan-2-one (274c)



To a solution of alcohol **274b** (1.39 g, 5.77 mmol) in anyhrous DMF (11.5 mL) was added imidazole (590 mg, 8.66 mmol) at 0 °C. TBSCl (1.30 g, 8.66 mmol) was then added at 0 °C and then the reaction was warmed to RT and stirred for 2 h. The reaction mixture was then diluted with Et_2O (20 mL) and the organic layer was washed with water (3 x 30 mL). The organic layer was then washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc) afforded the *title compound* **274c** as a white solid (1.53 g, 75%); mp 64–66 °C; R_f 0.51 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2931, 2859, 1708, 1510, 1255, 910, 839, 779, 732; δ_H (400 MHz, $CDCl_3$) 0.19 (6 H, s, H-3), 0.99 (9 H, s, H-1), 2.71–2.77 (2 H, m, H-8/9), 2.78–2.84 (2 H, m, H-8/9), 3.66 (2 H, s, H-11), 6.74 (2 H, d, *J* = 8.0 Hz, H-5/6), 6.99 (2 H, d, *J* = 8.0 Hz, H-5/6), 7.17 (2 H, d, *J* = 7.5 Hz, H-13), 7.24–7.36 (3 H, m, H-14,15); δ_C (100 MHz, $CDCl_3$) −4.5 (C-3), 18.2 (C-2), 25.7 (C-1), 29.0 (C-8/9), 43.7 (C-8/9), 50.4 (C-11), 120.0 (C-5/6), 127.0 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 133.5 (C-7/12), 134.1 (C-7/12), 153.9 (C-4), 207.7 (C-10); HRMS (ESI$^+$): Found: 377.1905; $C_{22}H_{30}NaO_2Si$ (MNa^+) Requires 377.1907 (0.7 ppm error), Found: 355.2084; $C_{22}H_{31}O_2Si$ (MH^+) Requires 355.2088 (1.1 ppm error).

Lab notebook reference: akc08-20

4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one (275c)

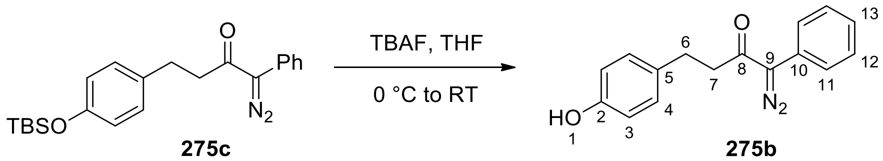


Procedure based on: Taylor *et al.*, *Angew. Chem. Int. Ed.*, 2016, **55**, 9671–9675.[173]

To a solution of benzyl ketone **274c** (150 mg, 0.423 mmol) and *p*-ABSA (122 mg, 0.508 mmol) in MeCN (1.5 mL) at RT under argon was added DBU (88.5 µL, 0.592 mmol) dropwise. The resulting solution was stirred for 1 h before being concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 hexane:EtOAc with 3% Et_3N as a basic additive) to afford the *title compound* **275c** as an orange oil (109 mg, 68%); R_f 0.49 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2929, 2857, 2067, 1648, 1509, 1497, 1252, 1204, 912, 838, 780, 1176, 1034, 821, 753; δ_H (400 MHz, $CDCl_3$) 0.19 (6 H, s, H-3), 0.98 (9 H, s, H-1), 2.86 (2 H, t, *J* = 7.5 Hz, H-8/9), 2.97 (2 H, t, *J* = 7.5 Hz, H-8/9), 6.76 (2 H, d, *J* = 8.0 Hz, H-5/6), 7.06 (2 H, d, *J* = 8.0 Hz, H-5/6), 7.24–7.29 (1 H, m, H-15), 7.41 (2 H, dd, *J* = 8.0, 7.5 Hz, H-14), 7.46 (2 H, d, *J* = 8.0 Hz, H-13); δ_C (100 MHz, $CDCl_3$) −4.5 (C-3), 18.2 (C-2), 25.7 (C-1), 30.1 (C-8/9), 41.0 (C-8/9), 72.4 (C-11), 120.1 (C-5/6), 124.1 (C-7/12), 126.1 (C-13), 127.1 (C-15), 129.0 (C-14), 129.3 (C-5/6), 133.2 (C-7/12), 154.1 (C-4), 192.1 (C-10); HRMS (ESI$^+$): Found: 403.1816; $C_{22}H_{28}N_2NaO_2Si$ (MNa^+) Requires 403.1812 (−0.9 ppm error).

Lab notebook reference: akc08-22

1-Diazo-4-(4-hydroxyphenyl)-1-phenylbutan-2-one (275b)

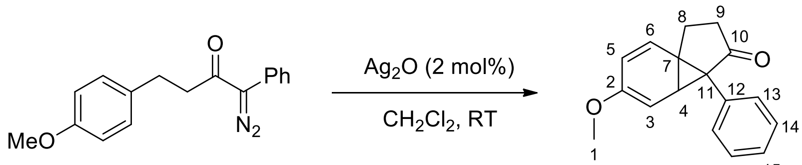


To a solution of α-diazocarbonyl **275c** (785 mg, 2.06 mmol) in THF (4 mL) at 0 °C was added TBAF (3.09 mL, 3.09 mmol, 1 M solution in THF). The resulting solution was warmed to RT and stirred for 30 min. The reaction mixture was then diluted with Et_2O (10 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **275b** without further purification as a yellow solid (509 mg, 93%);

mp 77–79 °C; R_f 0.63 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3361, 2077, 1612, 1515, 1497, 1448, 1370, 1205, 830, 756; δ_H (400 MHz, $CDCl_3$) 2.86 (2 H, t, *J* = 7.5 Hz, H-6/7), 2.97 (2 H, t, *J* = 7.5 Hz, H-6/7), 4.70 (1 H, br s, H-1), 6.76 (2 H, d, *J* = 8.5 Hz, H-3/4), 7.08 (2 H, d, *J* = 8.5 Hz, H-3/4), 7.24–7.29 (1 H, m, H-13), 7.41 (2 H, dd, *J* = 8.0, 7.5 Hz, H-12), 7.47 (2 H, d, *J* = 7.5 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 30.0 (C-6/7), 41.1 (C-6/7), 72.6 (C-9), 115.4 (C-3/4), 125.4 (C-5/10), 126.2 (C-11/12), 127.2 (C-13), 129.0 (C-11/12), 129.5 (C-3/4), 132.5 (C-5/10), 154.2 (C-2), 192.4 (C-8); HRMS (ESI$^+$): Found: 289.0951; $C_{16}H_{14}N_2NaO_2$ (MNa^+) Requires 289.0947 (−1.3 ppm error).

Lab notebook reference: akc08-33

5-Methoxy-3a-phenyl-3a,3b-dihydro-1*H*-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2*H*)-one (279a)



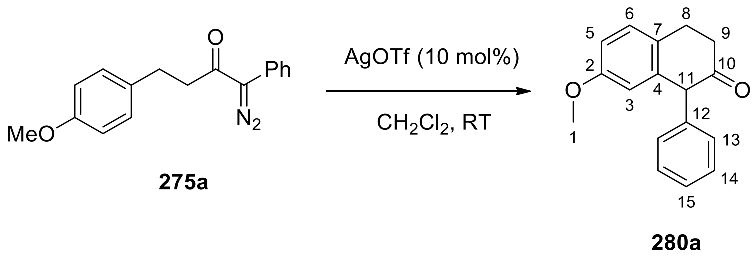
275a **279a**

A flame-dried rbf was charged with α-diazocarbonyl **275a** (100 mg, 0.357 mmol) and Ag_2O (1.7 mg, 7.13 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.6 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 22.5 h before being concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the *title compound* **279a** as a pale yellow oil (74.5 mg, 83%); R_f 0.33 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3028, 2934, 2829, 1745, 1715, 1647, 1489, 1446, 1416, 1219, 1167, 1109, 1020, 816, 756; δ_H (400 MHz, $CDCl_3$) 2.33–2.45 (1 H, m, H-8a/9a), 2.55–2.67 (1 H, m, H-8b/9b), 2.72–2.82 (1 H, m, H-8a/9a), 2.83–2.95 (1 H, m, H-8b/9b), 3.41 (3 H, s, H-1), 5.07 (1 H, br d, *J* = 8.5 Hz, H-4), 5.60 (1 H, d, *J* = 8.0 Hz, H-5/6), 5.87 (1 H, d, *J* = 8.5 Hz, H-3), 6.38 (1 H, d, *J* = 8.0 Hz, H-5/6), 7.14–7.24 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 27.4 (C-8/9), 34.8 (C-8/9), 54.6 (C-1), 109.1 (C-5/6), 115.5 (C-3), 123.3 (C-5/6), 126.9 (C-13/14), 127.7 (C-13/14,C-4/15), 128.5 (C-4/15,C-7/11), 136.6 (C-11/12), 157.2 (C-2), 215.7 (C-10); HRMS (ESI$^+$): Found: 275.1040; $C_{17}H_{16}NaO_2$ (MNa^+) Requires 275.1043 (−0.9 ppm error), Found: 253.1222; $C_{17}H_{17}O_2$ (MH^+) Requires 253.1223 (−0.4 ppm error).

Lab notebook reference: akc08-26

Note: Missing 1 x C peak (C-7/11) due to Buchner ring expansion equilibrium.[179]

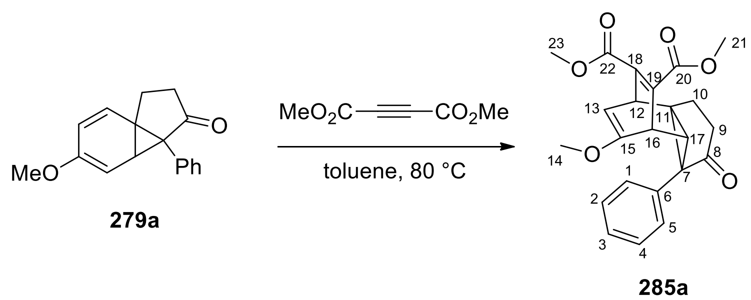
7-Methoxy-1-phenyl-3,4-dihydronaphthalen-2(1*H*)-one (280a)



A flame-dried rbf was charged with α-diazocarbonyl **275a** (100 mg, 0.357 mmol) and AgOTf (9.2 mg, 35.7 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.6 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the *title compound* **280a** as a yellow oil (71.1 mg, 79%); R_f 0.38 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2940, 2844, 1714, 1611, 1502, 1450, 1260, 1156, 1037, 729; δ_H (400 MHz, $CDCl_3$) 2.52–2.61 (1 H, m, H-9a), 2.72 (1 H, ddd, *J* = 17.0, 6.5, 6.0 Hz, H-9b), 2.93–3.11 (2 H, m, H-8a,8b), 3.75 (3 H, s, H-1), 4.72 (1 H, s, H-11), 6.56 (1 H, d, *J* = 2.5 Hz, H-3), 6.84 (1 H, dd, *J* = 8.0, 2.5 Hz, H-5), 7.12 (2 H, d, *J* = 7.5 Hz, H-13), 7.21 (1 H, d, *J* = 8.0 Hz, H-6), 7.24–7.34 (3 H, m, H-14,15); δ_C (100 MHz, $CDCl_3$) 27.2 (C-8), 37.2 (C-9), 55.2 (C-1), 59.9 (C-11), 113.0 (C-5), 114.6 (C-3), 127.2 (C-15), 128.56 (C-13/14), 128.64 (C-13/14), 128.8 (C-6), 129.0 (C-4/7/12), 137.3 (C-4/7/12), 137.6 (C-4/7/12), 158.7 (C-2), 209.6 (C-10); HRMS (ESI$^+$): Found: 275.1044; $C_{17}H_{16}NaO_2$ (MNa^+) Requires 275.1043 (0.4 ppm error), Found: 253.1232; $C_{17}H_{17}O_2$ (MH^+) Requires 253.1223 (3.4 ppm error).

Lab notebook reference: akc08-32

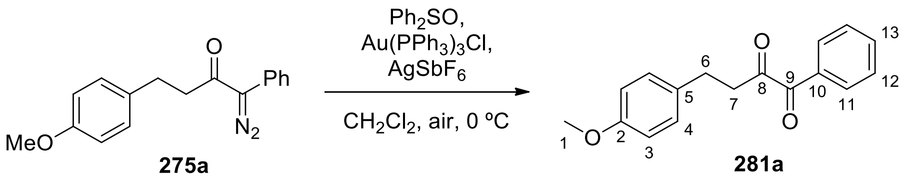
(3bR,4R,7R,7aR)-Dimethyl 8-methoxy-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1H-4,7-ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (285a)



A rbf was charged with cyclopropane **279a** (65 mg, 0.258 mmol) in toluene (0.5 mL) under argon. Dimethyl acetylenedicarboxylate (63 µL, 0.515 mmol) was added and the reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was then cooled to RT and concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the *title compound* **285a** as a clear and colourless oil (83.4 mg, 82%); R_f 0.21 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2952, 1713, 1653, 1626, 1435, 1265, 1211, 1111, 1058, 1007, 915, 728; δ_H (400 MHz, $CDCl_3$) 1.83 (1 H, d, *J* = 4.0 Hz, H-17), 2.17–2.31 (2 H, m, H-9/10), 2.36–2.49 (5 H, m, H-9/10,14), 3.80 (3 H, s, H-21/23), 3.85 (3 H, s, H-21/23), 4.09–4.13 (2 H, m, H-12,16), 4.33 (1 H, dd, *J* = 7.0, 3.0 Hz, H-13), 6.89–6.93 (1 H, m, Ar-H), 7.12 (1 H, d, *J* = 7.5 Hz, Ar-H), 7.15–7.23 (2 H, m, Ar-H), 7.29–7.34 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 27.1 (C-9/10), 33.6 (C-17), 35.4 (C-9/10), 44.0 (C-12/16), 44.7 (C-12/16), 52.3 (C-21/23), 52.4 (C-21/23), 52.8 (C-11), 54.6 (C-14), 60.2 (C-7), 99.1 (C-13), 126.5 (CH), 127.3 (CH), 128.1 (CH), 130.1 (CH), 130.5 (CH), 133.7 (C-6), 144.0 (C-15/18/19), 152.9 (C-15/18/19), 160.6 (C-15/18/19), 165.0 (C-20/22), 167.2 (C-20/22), 211.8 (C-8); HRMS (ESI$^+$): Found: 417.1316; $C_{23}H_{22}NaO_6$ (MNa^+) Requires 417.1309 (−1.8 ppm error), Found: 395.1485; $C_{23}H_{23}O_6$ (MH^+) Requires 395.1489 (1.0 ppm error).

Lab notebook reference: akc08-82

4-(4-Methoxyphenyl)-1-phenylbutane-1,2-dione (281a)



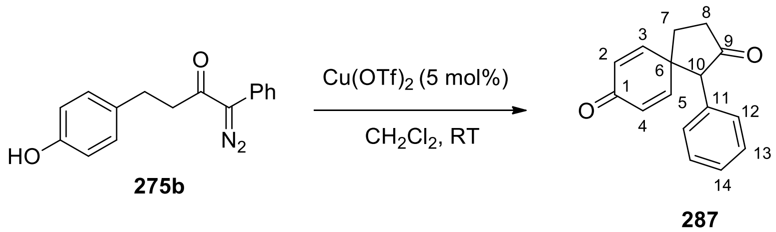
Procedure based on: Toste *et al*., *J. Am. Chem. Soc*., 2007, **129**, 5838–5839.[181]

A heterogeneous solution of $Au(PPh_3)_3Cl$ (2.65 mg, 5.35 µmol) and $AgSbF_6$ (1.84 mg, 5.35 µmol) in CH_2Cl_2 (0.5 mL) was stirred for 5 min under air and cooled to 0 °C. A solution of α-diazocarbonyl **275a** (30 mg, 0.107 mmol) and diphenyl sulfoxide (86.6 g, 0.428 mmol) in CH_2Cl_2 (0.5 mL) was then added to the catalyst mixture at 0 °C, the vial containing diazo solution was rinsed with CH_2Cl_2 (0.2 mL). The reaction mixture was stirred under air at 0 °C for 2 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the *title compound* **281a** as a yellow oil (25.9 mg, 90%); R_f 0.32 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2934, 2836, 1711, 1670, 1596, 1449, 1245, 1177, 1033, 825, 689; δ_H (400 MHz, $CDCl_3$) 3.00 (2 H, t, *J* = 7.5 Hz, H-6/7), 3.21 (2 H, t, *J* = 7.5 Hz, H-6/7), 3.79 (3 H, s, H-1), 6.83 (2 H, d, *J* = 8.5 Hz, H-3/4), 7.15 (2 H, d, *J* = 8.5 Hz, H-3/4), 7.48 (2 H, dd, *J* = 7.5, 7.5 Hz, H-12), 7.64 (1 H, t, *J* = 7.5 Hz, H-13), 7.91 (2 H, d, *J* = 7.5 Hz, H-14); δ_C (100 MHz,

$CDCl_3$) 28.0 (C-6/7), 40.4 (C-6/7), 55.2 (C-1), 113.9 (C-3/4), 128.7 (C-3/4/12), 129.4 (C-3/4/12), 130.2 (C-11), 131.8 (C-5/10), 132.1 (C-5/10), 134.6 (C-13), 158.1 (C-2), 192.1 (C-8/9), 202.4 (C-8/9); HRMS (ESI$^+$): Found: 291.0990; $C_{17}H_{16}NaO_3$ (MNa$^+$) Requires 291.0992 (0.5 ppm error).

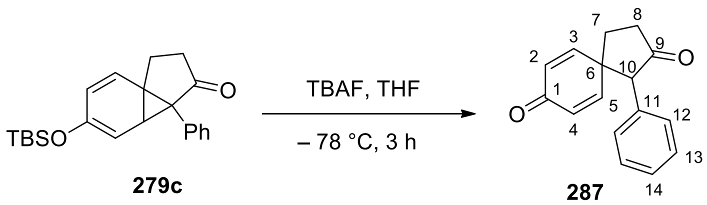
Lab notebook reference: akc08-69

1-Phenylspiro[4.5]deca-6,9-diene-2,8-dione (287)



Method 1: A flame-dried rbf was charged with α-diazocarbonyl **275b** (38 mg, 0.143 mmol) and $Cu(OTf)_2$ (2.6 mg, 7.14 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (1.4 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 3 h before being concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the *title compound* **287** as a white solid (23.4 mg, 70%)

Lab notebook reference: akc08-41-2

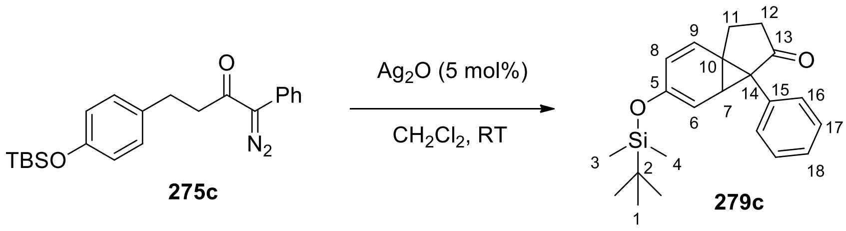


Method 2: To a solution of cyclopropane **279c** (36.8 mg, 0104 mmol) in THF (0.6 mL) at −78 °C was added TBAF (0.16 mL, 0.156 mmol, 1 M solution in THF) dropwise to afford an orange solution. The resulting solution was stirred at −78 °C for 3 h. The reaction mixture was then quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the *title compound* **287** as a white solid (16.6 mg, 67%)

Lab notebook reference: akc08-76

mp 135–137 °C; R_f 0.21 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3035, 1746, 1663, 1622, 1499, 1135, 868, 700; δ_H (400 MHz, $CDCl_3$) 2.17 (1 H, ddd, *J* = 13.5, 8.5, 2.5 Hz, H-7a/8a), 2.32–2.42 (1 H, m, H-7b/8b), 2.64–2.84 (2 H, m, H-7/8), 3.75 (1 H, s, H-10), 6.14 (1 H, dd, *J* = 10.0, 2.0 Hz, H-2/3/4/5), 6.32 (1 H, dd, *J* = 10.0, 2.0 Hz, H-2/3/4/5), 6.86 (1 H, dd, *J* = 10.0, 3.0 Hz, H-2/3/4/5), 6.93–6.97 (2 H, m, Ar-H), 7.00 (1 H, dd, *J* = 10.0, 3.0 Hz, H-2/3/4/5), 7.21–7.29 (3 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 31.4 (C-7/8), 35.3 (C-7/8), 51.4 (C-6), 65.5 (C-10), 127.9 (C-14), 128.3 (C-12/13), 129.4 (C-12/13), 130.1 (C-2/3/4/5), 130.5 (C-2/3/4/5), 132.5 (C-11), 147.5 (C-2/3/4/5), 152.4 (C-2/3/4/5), 185.3 (C-1), 213.1 (C-9); HRMS (ESI$^+$): Found: 261.0875; $C_{16}H_{14}NaO_2$ (MNa^+) Requires 261.0886 (−4.2 ppm error), Found: 239.1057; $C_{16}H_{15}O_2$ (MH^+) Requires 239.1067 (−4.1 ppm error).

5-((*tert*-Butyldimethylsilyl)oxy)-3a-phenyl-3a,3b-dihydro-1*H*-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one (279c)

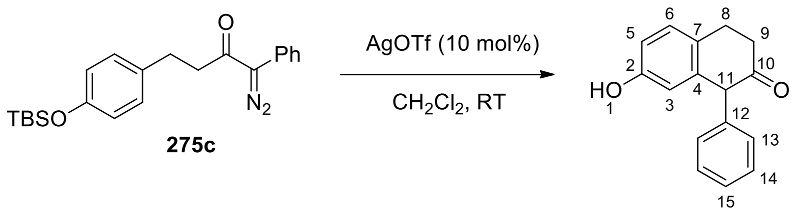


A flame-dried rbf was charged with α-diazocarbonyl **275c** (150 mg, 0.394 mmol) and Ag_2O (4.57 mg, 19.7 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.9 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (10:1 hexane:EtOAc) to afford the *title compound* **279c** as a yellow oil (110 mg, 79%); R_f 0.42 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2929, 2857, 1747, 1622, 1407, 1252, 1202, 1183, 1110, 900, 873, 837, 781, 749; δ_H (400 MHz, $CDCl_3$) −0.36 (3 H, s, H-3/4), −0.27 (3 H, s, H-3/4), 0.77 (9 H, s, H-1), 2.38 (1 H, ddd, *J* = 18.0, 9.0, 6.5 Hz, H-11a/12a), 2.64 (1 H, ddd, *J* = 18.0, 11.0, 7.0 Hz, H-11b/12b), 2.80–3.03 (2 H, m, H-11/12), 5.41 (1 H, d, *J* = 9.5 Hz, H-7), 5.76 (1 H, d, *J* = 7.5 Hz, H-8/9), 5.98 (1 H, d, *J* = 9.5 Hz, H-6), 6.41 (1 H, d, *J* = 7.5 Hz, H-8/9), 7.11–7.21 (3 H, m, Ar-H), 7.21–7.26 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) −5.4 (C-3/4), −5.1 (C-3/4), 17.8 (C-2), 25.4 (C-1), 27.3 (C-11/12), 35.3 (C-11/12), 56.9 (C-10/14), 114.0 (C-7), 116.1 (C-8/9), 122.4 (C-8/9), 123.8 (C-6), 127.1 (C-8), 127.74 (C-16/17), 127.79 (C-16/17), 137.4 (C-15), 153.2 (C-5), 216.0 (C-13); HRMS (ESI$^+$): Found: 353.1939; $C_{22}H_{29}O_2Si$ (MH^+) Requires 353.1931 (−2.1 ppm error).

Lab notebook reference: akc08-70

Note: Missing 1 x C peak (C-10/14) due to Buchner ring expansion equilibrium.[179]

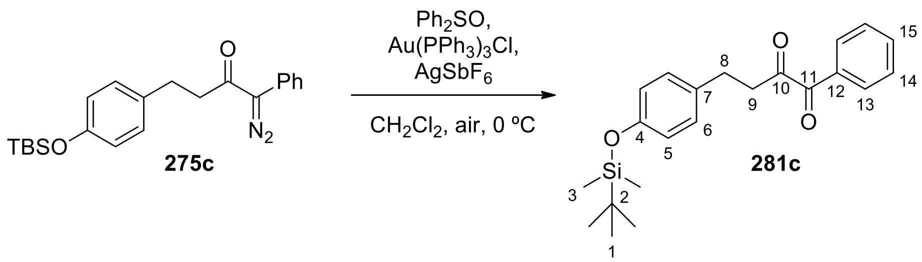
7-Hydroxy-1-phenyl-3,4-dihydronaphthalen-2(1*H*)-one (280b)



A flame-dried rbf was charged with α-diazocarbonyl **275c** (150 mg, 0.394 mmol) and AgOTf (10.1 mg, 39.4 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.9 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the *title compound* **280b** as an orange oil (80.9 mg, 86%); R_f 0.38 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3372, 3027, 1704, 1612, 1587, 1493, 1450, 1342, 1297, 1232, 1153, 821; δ_H (400 MHz, $CDCl_3$) 2.57 (1 H, ddd, J = 17.0, 6.5, 6.5 Hz, H-8a/9a), 2.70 (1 H, ddd, *J* = 17.0, 6.5, 6.5 Hz, H-8b/9b), 2.91–3.09 (2 H, m, H-8/9), 4.66 (1 H, s, H-11), 5.63 (1 H, br s, H-1), 6.46 (1 H, d, *J* = 2.5 Hz, H-3), 6.76 (1 H, dd, *J* = 8.0, 2.5 Hz, H-5), 7.10 (2 H, d, *J* = 7.0 Hz, H-13), 7.14 (1 H, d, *J* = 8.0 Hz, H-6), 7.25–7.33 (3 H, m, H-14,15); δ_C (100 MHz, $CDCl_3$) 27.3 (C-8/9), 37.3 (C-8/9), 59.7 (C-11), 114.5 (C-5), 116.0 (C-3), 127.3 (C-15), 128.69 (C-13/14), 128.71 (C-13/14), 128.8 (C-4/7/12), 129.1 (C-6), 137.2 (C-4/7/12), 137.7 (C-4/7/12), 154.9 (C-2), 210.5 (C-10); HRMS (ESI$^+$): Found: 261.0885; $C_{16}H_{14}NaO_2$ (MNa^+) Requires 261.0886 (0.2 ppm error).

Lab notebook reference: akc08-65

4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-phenylbutane-1,2-dione (281c)



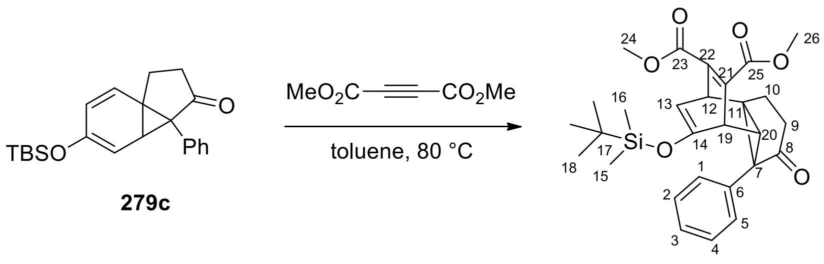
Procedure based on: Toste *et al.*, *J. Am. Chem. Soc.*, 2007, **129**, 5838–5839.[181]

A heterogeneous solution of $Au(PPh_3)_3Cl$ (32.5 mg, 65.7 µmol) and $AgSbF_6$ (22.5 mg, 65.7 µmol) in CH_2Cl_2 (6 mL) was stirred for 5 min under air and cooled to 0 °C. A solution of α-diazocarbonyl **275c** (500 mg, 1.31 mmol) and diphenyl sulfoxide (1.06 g, 5.24 mol) in CH_2Cl_2

(6 mL) was then added to the catalyst mixture at 0 °C and the reaction mixture was stirred under air for 1.5 h. The reaction mixture was then concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (20:1 hexane:EtOAc) to afford the *title compound* **281c** as a yellow oil (294 mg, 61%); R_f 0.70 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2930, 2858, 1713, 1672, 1509, 1253, 912, 838, 781; δ_H (400 MHz, $CDCl_3$) 0.18 (6 H, s, H-3), 0.98 (9 H, s, H-1), 2.98 (2 H, t, *J* = 7.5 Hz, H-8), 3.21 (2 H, t, *J* = 7.5 Hz, H-9), 6.76 (2 H, d, *J* = 8.0 Hz, H-5), 7.08 (2 H, d, *J* = 8.0 Hz, H-6), 7.48 (2 H, dd, *J* = 7.5, 7.5 Hz, H-14), 7.64 (1 H, t, *J* = 7.5 Hz, H-15), 7.91 (2 H, d, *J* = 7.5 Hz, H-13); δ_C (100 MHz, $CDCl_3$) −4.5 (C-3), 18.2 (C-2), 25.7 (C-1), 28.1 (C-8), 40.4 (C-9), 120.1 (C-5), 128.8 (C-14), 129.3 (C-6), 130.2 (C-13), 131.8 (C-7/12), 132.7 (C-7/12), 134.6 (C-15), 154.1 (C-4), 192.1 (C-11), 202.5 (C-10); HRMS (ESI$^+$): Found: 391.1705; $C_{22}H_{28}NaO_3Si$ (MNa^+) Requires 391.1700 (−1.2 ppm error).

Lab notebook reference: akc08-75

(3bR,4S,7R,7aR)-Dimethyl 9-((*tert*-butyldimethylsilyl)oxy)-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1*H*-4,7-ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (285c)

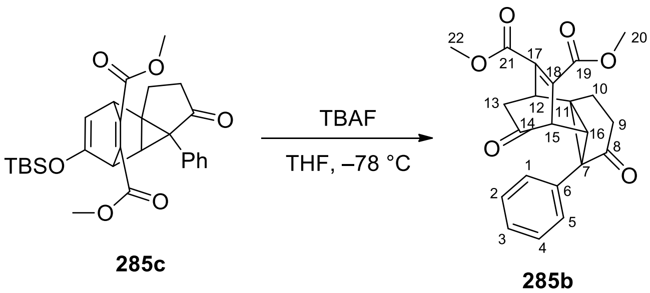


A rbf was charged with cyclopropane **279c** (191 mg, 0.541 mmol) in toluene (1.1 mL) under argon. Dimethyl acetylenedicarboxylate (0.13 mL, 1.08 mmol) was added and the reaction mixture was stirred at 80 °C for 30 h. The reaction mixture was then cooled to RT and concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (20:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the *title compound* **285c** as a clear and colourless oil (220 mg, 82%); R_f 0.58 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2953, 2858, 1714, 1651, 1625, 1435, 1342, 1303, 1256, 1225, 1204, 1110, 1061, 913, 864, 839, 785; δ_H (400 MHz, $CDCl_3$) −0.32 (3 H, s, H-15/16), −0.19 (3 H, s, H-15/16), 0.75 (9 H, s, H-18), 1.80 (1 H, d, *J* = 4.0 Hz, H-20), 2.13–2.33 (2 H, m, H-9/10), 2.34–2.49 (2 H, m, H-9/10), 3.81 (3 H, s, H-24/26), 3.83 (3 H, s, H-24/26), 3.91–3.95 (1 H, m, H-19), 4.07 (1 H, d, *J* = 6.5 Hz, H-12), 4.49 (1 H, dd, *J* = 6.5, 3.0 Hz, H-13), 6.82 (1 H, d, *J* = 7.5 Hz, Ar-

H), 7.11–7.22 (3 H, m, Ar-H), 7.24–7.29 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) −5.4 (C-15/16), −4.7 (C-15/16), 17.9 (C-17), 25.4 (C-18), 27.2 (C-9/10), 34.0 (C-20), 35.4 (C-9/10), 44.7 (C-12), 47.0 (C-19), 52.3 (C-24/26), 52.4 (C-24/26), 52.9 (C-11), 60.4 (C-7), 106.9 (C-13), 126.5 (CH), 127.5 (CH), 128.2 (CH), 130.0 (CH), 130.6 (CH), 133.8 (C-6), 146.1 (C-14/21/22), 151.0 (C-14/21/22), 156.7 (C-14/21/22), 165.7 (C-23/25), 166.8 (C-23/25), 212.2 (C-8); HRMS (ESI^+): Found: 517.2017; $C_{28}H_{34}NaO_6Si$ (MNa^+) Requires 517.2017 (−0.1 ppm error), Found: 495.2195; $C_{28}H_{35}O_6Si$ (MH^+) Requires 495.2197 (0.5 ppm error).

Lab notebook reference: akc08-94

(3bR,4S,7R,7aR)-Dimethyl 9-hydroxy-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1*H*-4,7-ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (285b)

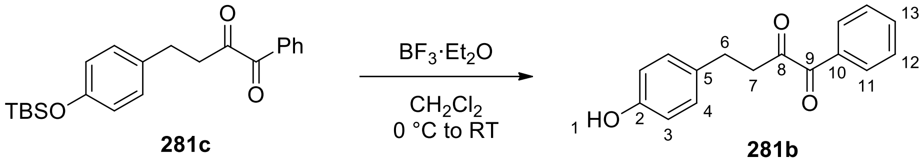


A rbf was charged with TBS-protected alcohol **285c** (35 mg, 0.0708 mmol) in THF (0.5 mL) at −78 °C and TBAF (0.11 mL, 0.106 mmol, 1 M solution in THF) was added dropwise leading to the formation of a pale yellow milky solution. The reaction mixture was then stirred at −78 °C for 3 h. The reaction mixture was then quenched by the addition of water (2 mL) at −78 °C and extracted with EtOAc (3 x 5 mL). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the *title compound* **285b** as a clear and colourless oil (23 mg, 85%); R_f 0.66 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2953, 1718, 1626, 1435, 1333, 1270, 1218, 1115, 1064, 729, 718; δ_H (400 MHz, $CDCl_3$) 1.82 (1 H, dd, *J* = 19.0, 3.0 Hz, H-13a), 2.06–2.14 (2 H, m, H-13b,15), 2.24–2.36 (2 H, m, H-9/10), 2.36–2.49 (2 H, m, H-9/10), 3.72–3.75 (1 H, m, H-12), 3.82 (3 H, s, H-20/22), 3.87 (3 H, s, H-20/22), 4.16 (1 H, d, *J* = 4.0 Hz, H-16), 7.09 (1 H, dd, *J* = 6.0, 2.0 Hz, Ar-H), 7.22–7.37 (4 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 27.5 (C-9/10), 33.1 (C-9/10), 34.1 (C-15), 37.2 (C-13), 41.0 (C-12), 47.6 (C-11), 51.8 (C-16), 52.7 (C-20/22), 52.8 (C-20/22), 57.7 (C-7), 128.3 (CH), 128.7 (CH), 128.8 (CH), 131.2 (C-6), 131.3 (CH), 132.5 (CH), 136.9 (C-17/18), 150.5 (C-17/18), 164.0 (C-19/21), 166.4 (C-19/21), 204.8 (C-14), 211.1 (C-8);

HRMS (ESI$^+$): Found: 403.1158; $C_{22}H_{20}NaO_6$ (MNa$^+$) Requires 403.1152 (−1.5 ppm error), Found: 381.1335; $C_{22}H_{21}O_6$ (MH$^+$) Requires 381.1333 (−0.5 ppm error).

Lab notebook reference: akc08-92

4-(4-Hydroxyphenyl)-1-phenylbutane-1,2-dione (281b)



A flame-dried round-bottomed flask was charged with 1,2-dicarbonyl **281c** (118 mg, 0.320 mmol) in anhydrous CH_2Cl_2 (3.2 ml) under argon. The solution was cooled to 0 °C and $BF_3{\cdot}Et_2O$ (0.4 ml, 3.20 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 1 h before warming to RT and stirring for another 4.5 h. The reaction mixture was then quenched by the addition of water (10 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The organics were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purififed by column chromatography (8:2 hexane:EtOAc) to afford the title compound **281b** as a yellow oil (17.1 mg, 21%);

R_f 0.27 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3416, 3027, 2932, 1712, 1669, 1596, 1515, 1449, 1254; δ_H (400 MHz, $CDCl_3$) 2.98 (2 H, t, *J* = 7.5 Hz, H-6/7), 3.20 (2 H, t, *J* = 7.5 Hz, H-6/7), 4.90 (1 H, br s, H-1), 6.76 (2 H, d, *J* = 8.0 Hz, H-3/4), 7.10 (2 H, d, *J* = 8.0 Hz, H-3/4), 7.48 (2 H, dd, *J* = 8.0, 7.5 Hz, H-12), 7.64 (1 H, t, *J* = 7.5 Hz, H-13), 7.91 (2 H, d, *J* = 7.5 Hz, H-11); δ_C (100 MHz, $CDCl_3$) 28.0 (C-6/7), 40.4 (C-6/7), 115.3 (C-3/4), 128.8 (C-12), 129.6 (C-3/4), 130.2 (C-11), 131.8 (C-5/10), 132.3 (C-5/10), 134.6 (C-13), 154.0 (C-2), 192.1 (C-9), 202.5 (C-8); HRMS (ESI$^+$): Found: 277.0837; $C_{16}H_{14}NaO_3$ (MNa$^+$) Requires 277.0835 (0.6 ppm error).

Lab notebook reference: akc08-85

Appendicies

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

Supported Catalysts

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German Edition: DOI: 10.1002/ange.201608263

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.*

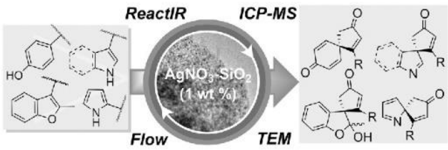

Figure 1. $AgNO_3$–SiO_2 mediated dearomatizing spirocyclization.

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.

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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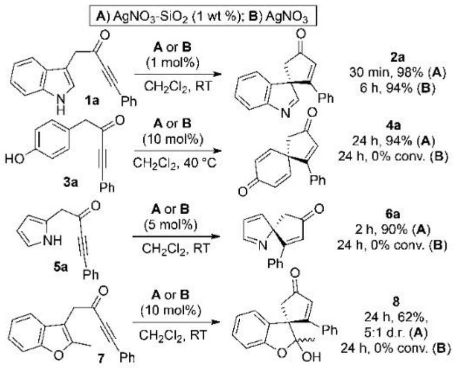


Scheme 1. Supported and unsupported Ag^{I}-catalyzed spirocyclization.

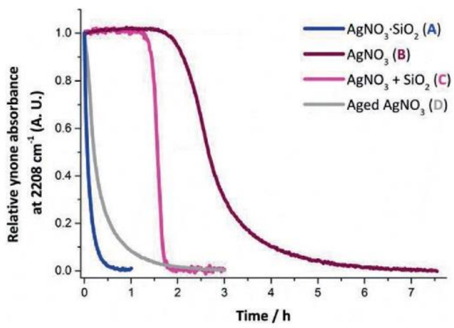


Figure 2. 2D ReactIR plots of the conversion of **1a** into **2a** using catalysts **A–D** (1 mol%) in CH_2Cl_2 at RT.

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).

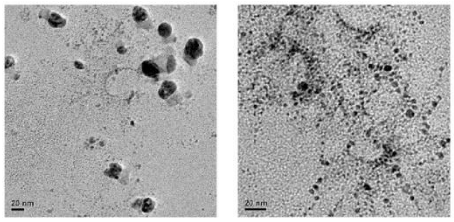


Figure 3. TEM images for $AgNO_3$ "aged" in CH_2Cl_2.

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 *Fm*3*m*) 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.

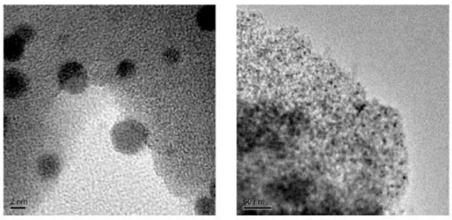
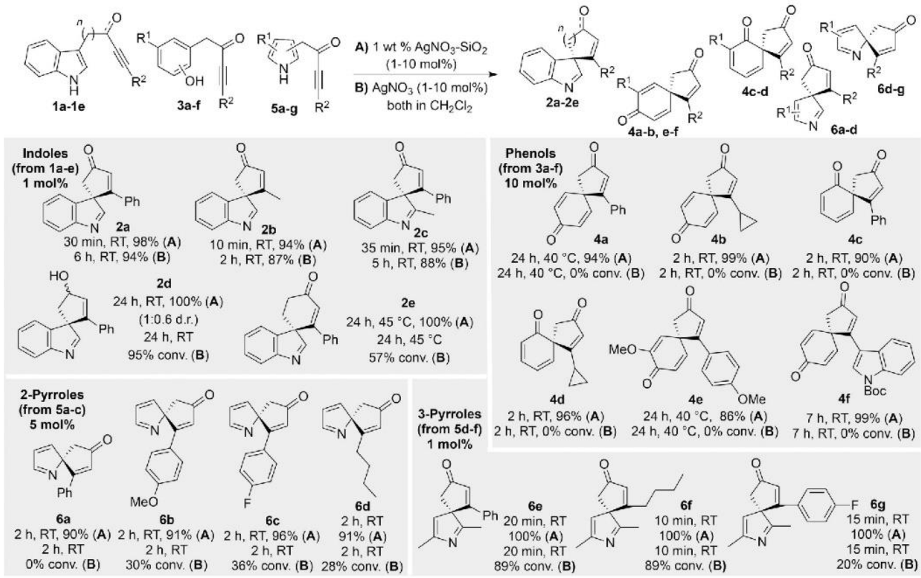


Figure 4. TEM images for $AgNO_3$–SiO_2.

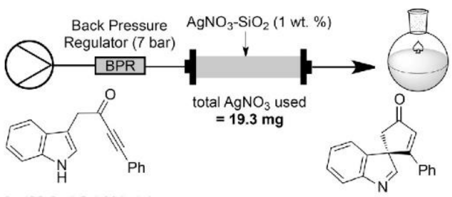
Next, to more fully evaluate the synthetic utility of our $AgNO_3$–SiO_2 catalyst, the optimized spirocyclization conditions were applied to other alkyne-tethered aromatics, and compared to unsupported $AgNO_3$ in each case (Scheme 2). Indolyl spirocyclic products **2a–e** were all obtained in excellent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



1a (23.6 g) 0.1 M in toluene **2a**, 100% (23.6 g)

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.

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

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[11] Ynone **1a** (0.1 mmol) was stirred with 10 mol% of $AgNO_3$-SiO_2 (10 wt%, Sigma Aldrich, 248762) in CH_2Cl_2 for 10 min, resulting in full conversion into spirocycle **2a**.

[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 II. Dearomatisation Approaches to Spirocyclic Dienones via the Electrophilic Activation of Alkynes

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Dearomatisation approaches to spirocyclic dienones *via* the electrophilic activation of alkynes†

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Two complementary dearomatising spirocyclisation protocols to generate spirocyclic dienones from anisole and phenol-tethered ynones are described, each proceeding *via* electrophilic alkyne activation. The first approach focuses on the spirocyclisation of *para*-substituted anisoles using either $SnCl_2 \cdot 2H_2O$ or $Cu(OTf)_2$. The second approach, which enables the spirocyclisation of both *ortho*- and *para*-substituted phenols, uses silica-supported $AgNO_3$ to generate similar scaffolds with much greater efficiency. Initial asymmetric studies are also outlined.

Introduction

Spirocyclic dienones are key structural features in numerous bioactive natural products isolated from a variety of trees, plants and bacteria, with representative examples **1–6** shown in Fig. 1.[1a–e]

A popular approach to synthesise spirocyclic dienones is *via* the dearomatisation and *ipso*-cyclisation of a phenol or anisole derivative, with this typically achieved using one of two methods (Scheme 1). The most common method is based on the oxidation of a substituted phenol (Scheme 1a); following oxidation of the phenol, an intramolecular nucleophilic *ipso*-cyclisation reaction can take place with a range of C-nucleophiles including alkenes/alkynes,[2a] enamides,[2b] allyl silanes,[2c,d] enols/enolates,[2e] aromatics,[2f] nitro compounds[2g] and diazo compounds.[2h,i] Alternatively, the flow of electron density can be reversed and a substituted phenol/anisole can react directly with a tethered electrophilic species (Scheme 1b); examples of electrophilic *ipso*-cyclisation with sulfonates,[3a–c] nitriles,[3d] epoxides,[3e] activated allenes,[3f] activated aryl halides,[3g] propargyl bromides/carbonates,[3h] activated alkynes/alkenes[3i–k] and allylic carbonates[3l,m] have all been reported.

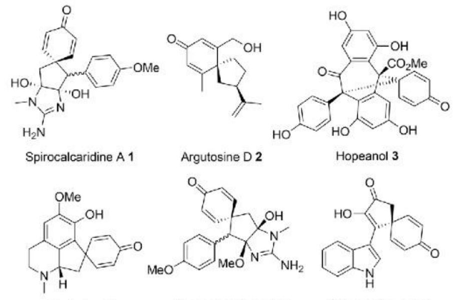
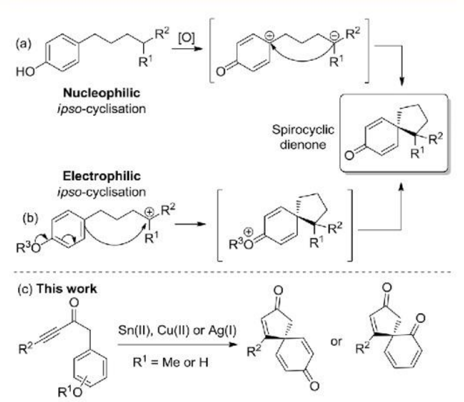


Fig. 1 Natural products containing spirocyclic dienone motifs.



Scheme 1 General methods for spirocyclic dienone synthesis.

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†Electronic supplementary information (ESI) available: Optimisation table and NMR spectra. See DOI: 10.1039/c6ob02426b

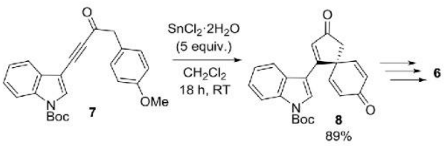
In this manuscript, two complementary protocols which generate spirocyclic dienones are outlined (Scheme 1c), with both methods promoted by the activation of a tethered alkyne moiety.[4] The first approach focuses on the spirocyclisation of *para*-substituted anisoles using either $SnCl_2{\cdot}2H_2O$ or $Cu(OTf)_2$ to activate the alkyne towards nucleophilic attack, while the second uses silica-supported $AgNO_3$ to generate similar scaffolds from analogous phenol precursors with greater efficiency and scope. Substrate scoping studies are described for each reaction series, while comparisons between the two reaction types, synthetic extensions and preliminary asymmetric results are also outlined.

Results and discussion

This research program began during a project to synthesise the spirocyclic natural product spirobacillene A (**6**, Fig. 1).[5,6] In this published work, it was found that treating anisole-tethered ynone **7** with five equivalents of $SnCl_2{\cdot}2H_2O$[7] at RT in CH_2Cl_2 resulted in its efficient conversion into spirocyclic dienone **8**, which was isolated in 89% yield (Scheme 2). The ease and scalability of this key step was instrumental in allowing us to complete the synthesis of spirobacillene A **6**, which was published in 2013.[5,8]

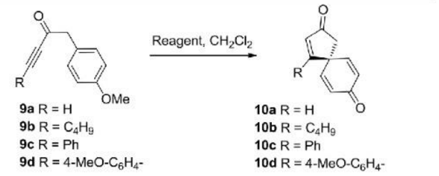
This initial discovery inspired the development of a number of other classes of dearomatising spirocyclisation reactions[9] in our group in the following years.[10,11] However, prior to this publication, the conversion of ynone **7** into spirocycle **8** remained the only reported reaction of its type in the literature,[12] hence it was decided to further optimise this process and to evaluate its scope.

Initial results were disappointing, with unsubstituted and alkyl substituted ynones **9a** and **9b** both failing to react with $SnCl_2{\cdot}2H_2O$ under the conditions used during the total synthesis of spirobacillene A (Table 1, entries 1 and 2). Phenyl substituted ynone **9c** also failed to react at room temperature (entry 3), although a small amount of cyclisation was observed upon heating at reflux (entry 4). A plausible explanation for this poor reactivity is that the more electron-rich the alkyne, the more readily it can interact with acidic additives, promoting spirocyclisation. Support for this theory was found when examining the cyclisation of anisole-substituted ynone **9d**; under the standard $SnCl_2{\cdot}2H_2O$ mediated conditions, a more respectable 75% conversion into spirocyclic dienone **10d** was observed (entry 5, 57% isolated yield). Pleasingly, the spirocyclisation was improved significantly by changing the catalyst; full details of reaction optimisation are included in the ESI,† with the highlight being the discovery that $Cu(OTf)_2$ promoted the complete cyclisation of ynone **9d** within 1 h, with spirocycle **10d** isolated in 80% isolated yield (entry 6). However, $Cu(OTf)_2$ did not lead to any improvement in the reactivity of substrates **9a–9c**, forcing us to concede that an electron donating group on the alkyne terminus is a requirement for this transformation.



Scheme 2 Sn(II)-mediated synthesis of spirobacillene A.

Table 1 Optimisation of the spirocyclisation of anisole-tethered ynones



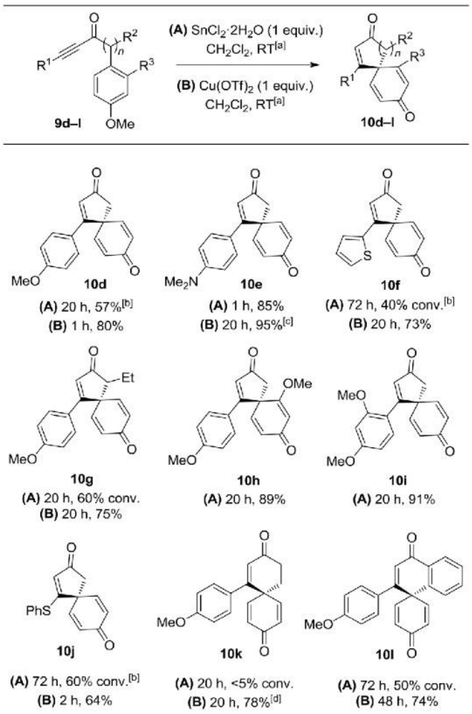
Entry	Ynone	Reagent	Equiv./time [h]/temp. [°C]	Conversion[a,b] (isolated yield in brackets)
1	**9a**	$SnCl_2{\cdot}2H_2O$	5/20/RT or 45	No reaction
2	**9b**	$SnCl_2{\cdot}2H_2O$	5/20/RT or 45	No reaction
3	**9c**	$SnCl_2{\cdot}2H_2O$	5/20/RT	No reaction
4	**9c**	$SnCl_2{\cdot}2H_2O$	5/20/45	10%
5	**9d**	$SnCl_2{\cdot}2H_2O$	5/20/RT	75% (57%)
6	**9d**	$Cu(OTf)_2$	1/1/RT	>95% (80%)

[a] All reactions were performed using 0.09–0.20 mmol of the ynone **9a–d** in CH_2Cl_2 (0.1 M). [b] Conversion measured by analysis of the ^1H NMR spectra of the unpurified reaction mixture.

With this in mind, a series of anisoles tethered to electron-rich ynones (**9d–l**) were made and tested using both $SnCl_2{\cdot}2H_2O$ and $Cu(OTf)_2$ to activate the alkyne (Table 2). Spirocycle **10e** was formed in just 1 h from aniline-substituted ynone **9e** using one equivalent of $SnCl_2{\cdot}2H_2O$. Alternatively, the same product could be made using catalytic $Cu(OTf)_2$ (0.1 equivalents), albeit with a longer reaction time. Thiophene-substituted ynone **9f** reacted more slowly; the cyclisation was incomplete following treatment with $SnCl_2{\cdot}2H_2O$ at room temperature for 3 days, but proceeded more efficiently with $Cu(OTf)_2$ to afford **10f** in a 73% yield. Substitution around either ring system is well tolerated, evidenced by the efficient syntheses of compounds **10g–i**. Vinyl sulfide product **10j** could also be isolated in a reasonable yield using $Cu(OTf)_2$, demonstrating compatibility with non-aromatic-tethered ynones. Additionally, the reaction is not limited to the synthesis of spirocyclic cyclopentenones; spirocyclic cyclohexenones **10k** and **10l** were both formed in good yields, although the reactions were slower and thus required additional heating or a longer reaction time.

To summarise this reaction series, *para*-substituted anisoles tethered to electron-rich ynones can be converted into spirocyclic dienones in high yield using either a Sn(II) or Cu(II) reagent. The simplicity of the synthetic procedure and mild

Table 2 Substrate scope of spirocyclisation of anisole-tethered ynones using $SnCl_2{\cdot}2H_2O$ (A) and $Cu(OTf)_2$ (B)

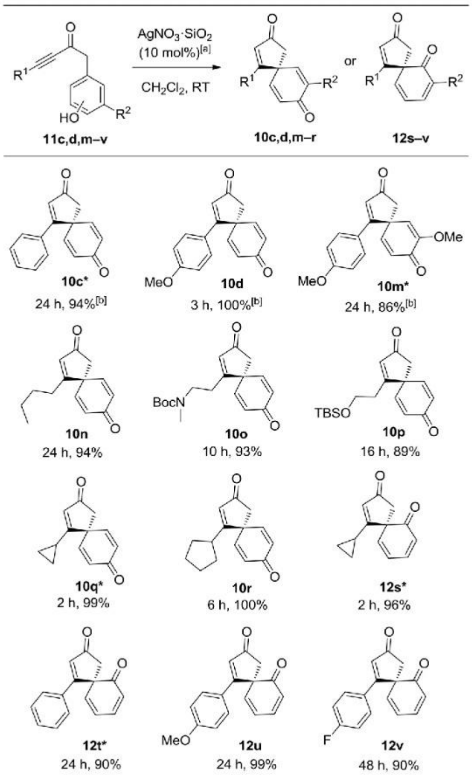


[a] All reactions were performed in CH_2Cl_2 (0.1 M) at RT with 1 equiv. of reagent unless specified. Where stated, reaction conversions were measured by analysis of the ^{1}H NMR spectra of the unpurified reaction mixture. [b] 5 equiv. of $SnCl_2{\cdot}2H_2O$ used. [c] 0.1 equiv. of $Cu(OTf)_2$ used. [d] Reaction performed at 50 °C.

reaction conditions are the most pleasing aspects of this method, although the use of relatively large quantities of Sn(II) and Cu(II) reagents and the requirement to use electron-rich ynones were both identified as areas with potential for improvement.

It was reasoned that both of the above limitations might be addressed by using a more active catalyst. Silver(I) catalysts were identified as particularly promising candidates, given that they have generally been found to be the best catalyst class in related alkyne activation processes,[10] but disappointingly, the Ag(I) catalysts tested were ineffective for the spirocyclisation of anisole system **9d**. However, by switching the nucleophilic component in the starting material from an anisole to the analogous phenol, the desired spirocyclic product **10d** could indeed be formed, and with Ag(I) catalysts now viable for this transformation, significant improvements in the scope and efficiency soon emerged. The use of silica-supported $AgNO_3$ (10 mol%) in CH_2Cl_2 at RT was found to be a particularly active and convenient catalyst system and was chosen for the substrate scoping studies, which were performed on ynone tethered phenols (**11c,d,m–v**). For clarity, five of these examples (denoted in the table with a *) were included in an earlier publication,[10c] while the other seven substrates are novel examples (Table 3). It should also be noted that $AgNO_3{\cdot}SiO_2$ is a much more reactive catalyst than unsupported $AgNO_3$; ynones **11c,d,m,o,q–v** did not react in the presence of unsupported $AgNO_3$ and only a 7% conversion to spirocyclic dienone **10n** was observed for ynone **11n** when using unsupported $AgNO_3$.[13]

Table 3 Substrate scope of $AgNO_3{\cdot}SiO_2$-catalysed dearomatisation/spirocyclisations



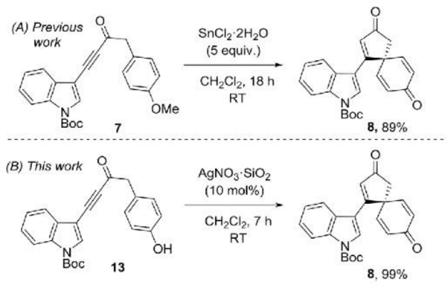
[a] All reactions were performed using 1 wt% $AgNO_3{\cdot}SiO_2$ in CH_2Cl_2 (0.1 M) at RT unless specified otherwise. [b] Reaction performed at 40 °C. Compounds highlighted with a * were featured in our earlier publication (see ref. 10*c*); all other examples are novel.

It quickly became apparent that by changing the catalyst and starting material, the requirement for an electron-donating substituent on the ynone had been removed; simple alkyl chains and aromatic substituents in the R^1 position were all well tolerated, generating spirocyclic dienone products **10c**, **10d**, **10n** in high yields. Alkyl substituted ynones bearing protected amine and alcohol groups (**11o** and **11p**) also reacted smoothly to furnish their corresponding spirocyclic dienones (**10o** and **10p**). The incorporation of terminal cyclopropane and cyclopentane rings appeared to increase the reactivity of the ynone; dienones **10q** and **10r** were produced in near-quantitative yields in 2–6 h which is notably faster than most of the other reactions explored in this study. Pleasingly, we were also able to perform the spirocyclisation on *ortho*-substituted phenols **11s–v**; there are relatively few literature examples of dearomatisation and *ipso*-cyclisation reactions of *ortho*-substituted phenols, and so the efficient syntheses of chiral spirocyclic products **12s–v** in 90–99% yields are especially pleasing.[2d,14]

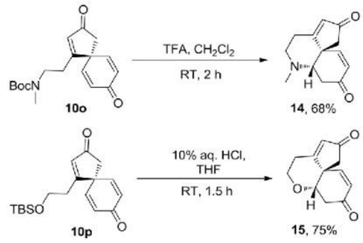
The superior reactivity of the Ag(I) mediated reaction system compared to the earlier Sn(II)/Cu(II) reactions is best demonstrated by a direct comparison. Thus, our published synthesis of spirocyclic dienone **8**, which is a key intermediate *en route* to spirobacillene A, required five equivalents of $SnCl_2{\cdot}2H_2O$ and 18 h to generate the product in 89% yield.[5] In contrast, the same product was generated from phenol **13** in near-quantitative yield in just 7 h using 10 mol% $AgNO_3{\cdot}SiO_2$ (Scheme 3).

The potential of the spirocyclic dienone products to undergo additional complexity generating reactions has also been briefly demostrated; spirocyclic products **10o** and **10p** were each found to undergo protecting group cleavage and cyclisation in one-pot to furnish novel tricyclic products **14** and **15** as single diastereomers and in reasonable, unoptimised yields (Scheme 4).

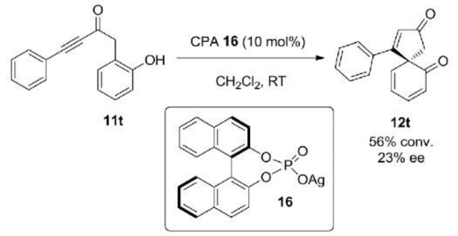
Finally, having shown that *ortho*-substituted phenols can be converted into chiral spirocyclic dienones, the possibility of performing this reaction asymmetrically has also been briefly examined. Preliminary studies show that spirocyclisation can be achieved with a modest amount of asymmetric induction (23% ee) using the BINOL-based chiral phosphoric acid silver(I) salt **16** (Scheme 5). It is envisaged that optimisation of the reaction conditions and the nature of the silver(I) catalyst[15] should lead to improve enatioselectivity in this process.



Scheme 3 Previous and improved routes to spirobacillene A precursor **8**.



Scheme 4 One-pot deprotection and cyclisation of spirocyclic dienones **10o** and **10p**.



Scheme 5 Asymmetric spirocyclisation reaction using silver salt of CPA **16**.

Conclusions

In summary, two mild and efficient methods for the synthesis of spirocyclic dienones are described. Both were briefly introduced by our group in previous publications, but the significantly expanded substrate scoping studies outlined in this manuscript mean that each can now be considered as general and versatile synthetic approach to this important compound class. Both methods work well on a variety of easy-to-synthesise ynone precursors. The use of catalytic $AgNO_3{\cdot}SiO_2$ to promote the spirocyclisation of ynone tethered phenols is likely to be of particular interest, in view of the excellent isolated yields in this series, the simple product purification and the capacity to recover the active catalyst by filtration.

Experimental

Except where stated, all reagents were purchased from commercial sources and used without further purification.

^{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 respectively. All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ and δ_H 2.50 and δ_C 39.5 for DMSO-d_6. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 Spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$ and are reported in wavenumbers (cm^{-1}). 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 and are uncorrected. Reactions were monitored using thin layer chromatography (TLC), which was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 µm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Compounds **9d**[16] and **9e**[10a] were prepared according to literature procedures.

General experimental

General procedure A: Weinreb amide synthesis I

To a suspension of acid (1.00 mmol) in DCM (2 mL) at RT was added CDI (220 mg, 1.20 mmol). A homogeneous solution quickly formed, and was stirred at RT for 1 h, after which time MeNH(OMe)·HCl (107 mg, 1.10 mmol) and stirring continued for a further 2 h. The crude reaction mixture was then poured into water (10 mL) and basified to *ca.* pH 10 with 2 M aq. NaOH extracted with EtOAc (3 × 30 mL) and washed with 10% aq. HCl (15 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*, affording the Weinreb amide product which was used without further purification.

General procdure A2: Weinreb amide synthesis II

To a stirred solution of acid (1.00 mmol), MeNH(OMe)·HCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH_2Cl_2 (2.5 mL) was added T3P 50% in EtOAc (955 mg, 1.50 mmol). The solution was stirred at RT until completion was observed by TLC. The reaction mixture was poured into water (10 mL) and acidified using 10% aq. HCl (5 mL). The organics were collected and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with aq. 2 M NaOH (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the Weinreb amide product which was used without further purification.

General procedure B: ynone formation I

To a solution of terminal alkyne (1.50 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.875 mL, 1.4 mmol, 1.6 M in hexanes). The resulting yellow solution was stirred at −78 °C for 30 min, then transferred *via* cannula to a cooled (−78 °C) solution of Weinreb amide (1.00 mmol) in THF (5 mL). The mixture was stirred at −78 °C for 5 min then warmed to −10 °C and stirred for a further 1 h. The reaction was then re-cooled to −78 °C and quenched with sat. aq. NH_4Cl (30 mL), allowed to warm to RT, diluted with water (70 mL), extracted with EtOAc (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (10 : 1 petrol : EtOAc to elute the excess alkyne, then 5 : 1 petrol : EtOAc to elute the product) afforded the ynone product.

General procedure B2: ynone formation II

To a stirred solution of alkyne (3.00 mmol) in THF (3 mL) at −78 °C under argon was added *n*-BuLi (1.00 mL, 2.5 mmol, 2.5 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 (1.00 mmol) in THF (5 mL). Upon complete transfer the mixture was warmed to RT and stirred for the specified amount of time. The reaction was quenched with sat. aq. NH_4Cl (30 mL), diluted with water (70 mL) and extracted with EtOAc (3 × 100 mL). The organics were combined, washed with brine (100 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography to afford the ynone product.

General procedure C: spirocyclisation using Sn(II)/Cu(II)

To a solution of ynone (1.00 mmol) in CH_2Cl_2 (10 mL) was added an acid catalyst (0.1–5.0 equiv.). The resulting suspension was stirred at the specified temperature until completion was observed by TLC, before adding an excess of solid K_2CO_3 and stirring for an additional 10 min. The mixture was then filtered, rinsed with CH_2Cl_2 and concentrated *in vacuo*. Purification by flash column chromatography afforded the spirocyclic product.

General procedure C2: spirocyclisation using $AgNO_3 \cdot SiO_2$

To a solution of ynone (1 mmol) in CH_2Cl_2 (10 mL) was added $AgNO_3 \cdot SiO_2$ (0.01–0.1 equiv., 1 wt% $AgNO_3$ on SiO_2). The mixture was stirred at the specified temperature until completion was observed by TLC. The reaction mixture was filtered, washing the catalyst with EtOAc (10 mL), then concentrated *in vacuo* to afford the spirocyclic product.

Compound synthesis

4-(4-Methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10d). Synthesised using general procedure C from ynone **9d** (25.0 mg, 0.0892 mmol) and copper(II) triflate (32.3 mg, 0.0892 mmol) for 1 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc) afforded the *title compound* **10d** as a brown solid (19 mg, 80%); mp. 135–137 °C;

R_f 0.20 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1669, 1639, 1579, 1541, 1488, 1234, 1163, 1013, 848, 822; δ_H (400 MHz, $CDCl_3$) 2.75 (2 H, s), 3.81 (3 H, s), 6.46 (2 H, d, *J* = 10.0), 6.62 (1 H, s), 6.85 (2 H, d, *J* = 9.0), 6.95 (2 H, d, *J* = 10.0), 7.48 (2 H, d, *J* = 9.0); δ_C (100 MHz, $CDCl_3$) 46.8, 51.0, 55.4, 114.3, 125.3, 127.5, 129.4, 130.0, 152.0, 162.3, 173.1, 184.7, 203.0; HRMS (ESI^+): Found: 289.0825; $C_{17}H_{14}NaO_3$ (MH^+) Requires 289.0835 (3.5 ppm error). Spectroscopic data matched those previously reported in the literature.[16]

4-(4-(Dimethylamino)phenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10e). Synthesised using general procedure C from ynone **9e** (32 mg, 0.109 mmol) and $SnCl_2{\cdot}2H_2O$ (2.5 mg, 0.0109 mmol) for 20 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc) afforded the *title compound* **10e** as a yellow solid (29 mg, 95%); mp. 199–201 °C; R_f 0.20 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1656, 1636, 1581, 1548, 1500, 1353, 1182, 1156, 719; δ_H (400 MHz, $CDCl_3$) 2.72 (2 H, s), 3.02 (6 H, s), 6.46 (2 H, d, *J* = 10.0), 6.55 (1 H, s), 6.58 (2 H, d, *J* = 9.0), 6.98 (2 H, d, *J* = 10.0), 7.43 (2 H, d, *J* = 9.0); δ_C (100 MHz, $CDCl_3$) 39.9, 46.7, 50.9, 111.3, 119.9, 124.0, 129.2, 129.5, 152.3, 152.9, 173.3, 185.0, 203.0; HRMS (ESI^+): Found: 280.1334; $C_{18}H_{18}NO_2$ (MH^+) Requires 280.1332 (0.8 ppm error). Spectroscopic data matched those previously reported in the literature.[10a]

1-(4-Methoxyphenyl)-4-(thiophen-2-yl)but-3-yn-2-one (9f). Synthesised using general procedure B from 2-ethynylthiophene[17] (303 mg, 2.80 mmol) and *N*-methoxy-2-(4-methoxyphenyl)-*N*-methylacetamide[18] (391 mg, 1.87 mmol). Purification by flash column chromatography afforded the *title compound* **9f** as a pale yellow oil (310 mg, 65%); R_f 0.73 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2148, 1636, 1586, 1489, 1230, 1019, 704; δ_H (400 MHz, $CDCl_3$) 3.80 (3 H, s), 3.85 (2 H, s), 6.90 (2 H, d, *J* = 8.5), 7.03 (1 H, dd, *J* = 5.0, 3.5) 7.22 (2 H, d, *J* = 8.5), 7.40 (1 H, d, *J* = 3.5), 7.47 (1 H, d, *J* = 5.0); δ_C (100 MHz, $CDCl_3$) 50.9, 55.2, 86.7, 92.4, 114.1, 119.6, 125.1, 127.6, 130.8, 131.8, 136.7, 158.9, 189.1; HRMS (ESI^+): Found: 257.0625; $C_{15}H_{13}O_2S$ (MH^+) Requires 257.0631 (1.7 ppm error).

4-(Thiophen-2-yl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10f). Synthesised using general procedure C from ynone **9f** (40 mg, 0.156 mmol) and copper(II) triflate (56.4 mg, 0.156 mmol) for 20 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc) afforded the *title compound* **10f** as a pale yellow oil (28 mg, 73%); R_f 0.50 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1691, 1661, 1576, 1246, 1027, 907, 859, 724; δ_H (400 MHz, $CDCl_3$) 2.77 (2 H, s), 6.49 (2 H, d, *J* = 10.0), 6.58 (1 H, s), 6.92 (2 H, d, *J* = 10.0), 7.03 (1 H, dd, *J* = 4.5, 3.5) 7.32 (1 H, d, *J* = 3.5), 7.52 (1 H, d, *J* = 4.5); δ_C (100 MHz, $CDCl_3$) 46.3, 50.9, 127.3, 128.7, 130.2, 130.5, 131.4, 135.8, 150.9, 166.3, 184.7, 202.6; HRMS (ESI^+): Found: 243.0480; $C_{14}H_{11}O_2S$ (MH^+) Requires 243.0474 (−2.3 ppm error).

***N*-Methoxy-2-(4-methoxyphenyl)-*N*-methylbutanamide (S1).** Synthesised using general procedure A from 2-(4-methoxyphenyl)butanoic acid[19] (1.07 g, 5.51 mmol) affording the *title compound* **S1** as a colourless oil (1.31 g, 100%); ν_{max} (thin film)/cm^{-1} 1656, 1510, 1461, 1380, 1247, 1178, 997, 822; δ_H (400 MHz, $CDCl_3$) 0.85 (3 H, t, *J* = 7.5), 1.64–1.75 (1 H, m), 1.98–2.10 (1 H, m), 3.14 (3 H, s), 3.49 (3 H, s), 3.76 (3 H, s), 3.78–3.86 (1 H, m), 6.82 (2 H, d, *J* = 8.5), 7.23 (2 H, d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) 12.2, 27.2, 32.1, 48.3, 55.1, 61.2, 113.8, 129.1, 132.2, 158.4, 175.0; HRMS (ESI^+): Found: 238.1438; $C_{13}H_{20}NO_3$ (MH^+) Requires 238.1438 (0 ppm error).

1,4-Bis(4-methoxyphenyl)hex-1-yn-3-one (9g). Synthesised using general procedure B from 4-ethynyl-anisole (0.41 mL, 3.17 mmol) and Weinreb amide **S1** (500 mg, 2.11 mmol). Purification by flash column chromatography afforded the *title compound* **9g** as a yellow oil (482 mg, 74%); R_f 0.71 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2188, 1658, 1601, 1508, 1248, 1058, 1027, 831, 540; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, t, *J* = 7.5), 1.77–1.89 (1 H, m), 2.16–2.27 (1 H, m), 3.63–3.67 (1 H, m), 3.79 (3 H, s), 3.82 (3 H, s), 6.85 (2 H, d, *J* = 9.0), 6.89 (2 H, d, *J* = 9.0), 7.24 (2 H, d, *J* = 9.0), 7.41 (2 H, d, *J* = 9.0); δ_C (100 MHz, $CDCl_3$) 12.0, 24.8, 55.2, 55.4, 61.7, 87.5, 93.5, 111.9, 114.1, 114.2, 129.7, 130.0, 135.0, 158.9, 161.5, 188.4; HRMS (ESI^+): Found: 309.1490; $C_{20}H_{21}O_3$ (MH^+) Requires 309.1485 (−1.6 ppm error).

1-Ethyl-4-(4-methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10g). Synthesised using general procedure C from ynone **9g** (60.0 mg, 0.195 mmol) and copper(II) triflate (70.5 mg, 0.195 mmol) for 20 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc) afforded the *title compound* **10g** as a pale brown oil (43 mg, 75%); R_f 0.50 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1696, 1661, 1590, 1509, 1257, 1177, 1030, 908, 832, 725; δ_H (400 MHz, $CDCl_3$) 0.97 (3 H, t, *J* = 7.5), 1.25–1.35 (1 H, m), 1.75–1.84 (1 H, m), 2.66 (1 H, t, *J* = 7.0), 3.81 (3 H, s), 6.47 (1 H, dd, *J* = 10.0, 1.5), 6.56 (1 H, s), 6.56 (1 H, dd, *J* = 10.0, 1.5), 6.80 (1 H, dd, *J* = 10.0, 3.0), 6.84 (2 H, d, *J* = 9.0), 6.96 (1 H, dd, *J* = 10.0, 3.0), 7.44 (2 H, d, *J* = 9.0); δ_C (100 MHz, $CDCl_3$) 12.6, 20.0, 55.4, 55.8, 58.9, 114.3, 125.6, 126.9, 129.3, 130.0, 131.6, 151.0, 152.2, 162.1, 171.5, 185.3, 205.1; HRMS (ESI^+): Found: 295.1324; $C_{19}H_{19}O_3$ (MH^+) Requires 295.1329 (1.6 ppm error).

2-(2,4-Dimethoxyphenyl)-*N*-methoxy-*N*-methylacetamide (S2). Synthesised using general procedure A from 2-(2,4-dimethoxyphenyl)acetic acid (981 mg, 5.00 mmol) affording the *title compound* **S2** as a pale yellow oil (1.13 g, 91%); ν_{max} (thin film)/cm^{-1} 1641, 1590, 1486, 1442, 1273, 1191, 1139, 1021; δ_H (400 MHz, $CDCl_3$) 3.19 (3 H, s), 3.67 (3 H, s), 3.69 (2 H, s), 3.78 (6 H, s), 6.42–6.47 (2 H, m), 7.07–7.11 (1 H, m); δ_C (100 MHz, $CDCl_3$) 32.4, 32.7, 55.3, 55.4, 61.1, 98.5, 104.1, 116.1, 131.1, 158.2, 159.8, 173.0; HRMS (ESI^+): Found: 240.1232; $C_{12}H_{18}NO_4$ (MH^+) Requires 240.1230 (1.0 ppm error).

1-(2,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (9h). Synthesised using general procedure B from 4-ethynyl-anisole (741 mg, 5.61 mmol) and Weinreb amide **S2** (894 mg, 3.74 mmol). Purification by trituration with ether afforded the *title compound* **9h** as a pale yellow crystalline solid (789 mg, 68%); mp. 102–104 °C; R_f 0.68 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2184, 1664, 1601, 1589, 1508, 1256, 1211, 1124, 1071, 1027, 835, 786, 575; δ_H (400 MHz, $CDCl_3$) 3.77–3.84 (11 H, m), 6.46–6.50 (2 H, m), 6.84 (2 H, d, *J* = 8.5), 7.11 (1 H, d, *J* = 8.5), 7.37 (2 H, d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) 46.0, 55.3, 55.3, 55.4, 87.7, 92.7, 98.5, 104.2, 111.9, 114.2, 115.1, 131.7, 135.1, 158.7, 160.4, 161.5, 186.2; HRMS (ESI$^+$): Found: 311.1284; $C_{19}H_{19}O_4$ (MH$^+$) Requires 311.1278 (2.1 ppm error).

6-Methoxy-4-(4-methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10h). Synthesised using general procedure C from ynone **9h** (60.3 mg, 0.200 mmol) and $SnCl_2 \cdot 2H_2O$ (78 mg, 0.200 mmol) for 20 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc, then 1 : 1 petrol : EtOAc) afforded the *title compound* **10h** as a white solid (51 mg, 89%); mp. 169–171 °C; R_f 0.19 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1689, 1652, 1588, 1360, 1244, 1177, 1027, 989, 858, 840; δ_H (400 MHz, $CDCl_3$) 2.61 (1 H, d, J = 18.0), 2.86 (1 H, d, J = 18.0), 3.65 (3 H, s), 3.79 (3 H, s), 5.76 (1 H, d, J = 1.5), 6.34 (1 H, dd, J = 10.0, 1.5), 6.61 (1 H, s), 6.64 (1 H, d, J = 10.0), 6.83 (2 H, d, J = 9.0), 7.43 (2 H, d, J = 9.0); δ_C (100 MHz, $CDCl_3$) 47.7, 52.5, 55.4, 56.2, 103.4, 114.3, 125.1, 128.3, 128.4, 128.9, 147.4, 162.1, 171.6, 175.5, 187.2, 203.6; HRMS (ESI$^+$): Found: 297.1112; $C_{18}H_{17}O_4$ (MH$^+$) Requires 297.1121 (1.9 ppm error).

4-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)but-3-yn-2-one (9i). Synthesised using general procedure B from 1-ethynyl-2,4-dimethoxybenzene[20] (420 mg, 2.59 mmol) and *N*-methoxy-2-(4-methoxyphenyl)-*N*-methylacetamide[21] (361 mg, 1.73 mmol). Purification by flash column chromatography afforded the *title compound* **9i** as a pale yellow oil (340 mg, 63%); R_f 0.60 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2185, 1652, 1600, 1505, 1296, 1244, 1210, 1026, 819; δ_H (400 MHz, $CDCl_3$) 3.79 (3 H, s), 3.82 (3 H, s), 3.84–3.87 (5 H, m), 6.39 (1 H, d, J = 2.0), 6.45 (1 H, dd, J = 8.5, 2.0), 6.86 (2 H, d, J = 8.5), 7.25 (2 H, d, J = 8.5), 7.34 (1 H, d, J = 8.5); δ_C (100 MHz, $CDCl_3$) 51.3, 55.2, 55.5, 55.7, 91.3, 91.9, 98.2, 101.5, 105.4, 114.0, 125.6, 130.9, 136.5, 158.7, 163.2, 163.6, 185.5; HRMS (ESI$^+$): Found: 311.1272; $C_{19}H_{19}O_4$ (MH$^+$) Requires 311.1278 (1.9 ppm error).

4-(2,4-Dimethoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10i). Synthesised using general procedure C from ynone **9i** (55.0 mg, 0.177 mmol) and $SnCl_2 \cdot 2H_2O$ (40.0 mg, 0.177 mmol) for 20 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc, then 1 : 1 petrol : EtOAc) afforded the *title compound* **10i** as a pale brown solid (48 mg, 91%); mp. 172–174 °C; R_f 0.19 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1688, 1660, 1605, 1551, 1233, 1213, 1026, 859; δ_H (400 MHz, $CDCl_3$) 2.67 (2 H, s), 3.80 (3 H, s), 3.84 (3 H, s), 6.37 (1 H, dd, J = 8.5, 2.5), 6.40 (2 H, d, J = 10.0), 6.46 (1 H, d, J = 2.5), 6.95 (2 H, d, J = 10.0), 6.97 (1 H, s), 7.26 (1 H, d, J = 8.5); δ_C (100 MHz, $CDCl_3$) 46.1, 52.4, 55.4, 55.5, 98.9, 104.4, 115.0, 129.2, 130.2, 131.6, 152.9, 160.1, 163.2, 168.8, 184.9, 204.7; HRMS (ESI$^+$): Found: 297.1113; $C_{18}H_{17}O_4$ (MH$^+$) Requires 297.1121 (2.6 ppm error).

1-(4-Methoxyphenyl)-4-(phenylthio)but-3-yn-2-one (9j). Synthesised using general procedure B from ethynyl(phenyl) sulfane[22] (671 mg, 5.00 mmol) and *N*-methoxy-2-(4-methoxyphenyl)-*N*-methylacetamide[21] (697 mg, 3.33 mmol). Purification by flash column chromatography afforded the *title compound* **9j** as a yellow oil (313 mg, 33%); R_f 0.81 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2115, 1651, 1510, 1246, 1176, 1120, 738, 686; δ_H (400 MHz, $CDCl_3$) 3.79 (2 H, s), 3.80 (3 H, s), 6.89 (2 H, d, J = 8.5), 7.17–7.35 (7 H, m); δ_C (100 MHz, $CDCl_3$) 50.2, 55.2, 87.6, 100.7, 114.2, 125.0, 127.0, 127.8, 129.5, 129.6, 130.9, 158.9, 183.3; HRMS (ESI$^+$): Found: 283.0786; $C_{17}H_{15}O_2S$ (MH$^+$) Requires 283.0787 (0.1 ppm error).

4-(Phenylthio)spiro[4.5]deca-3,6,9-triene-2,8-dione (10j). Synthesised using general procedure C from ynone **9j** (70.6 mg, 0.250 mmol) and copper(II) triflate (90.4 mg, 0.250 mmol) for 2 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc, then 1 : 1 petrol : EtOAc) afforded the *title compound* **10j** as a pale orange solid (43 mg, 64%); mp. 113–115 °C; R_f 0.25 (1 : 1 petrol : ethyl acetate); ν_{max} (thin film)/cm^{-1} 1687, 1665, 1548, 860, 752; δ_H (400 MHz, $CDCl_3$) 2.74 (2 H, s), 5.63 (1 H, s), 6.47 (2 H, d, J = 10.0), 6.79 (2 H, d, J = 10.0), 7.42–7.49 (5 H, m); δ_C (100 MHz, $CDCl_3$) 46.2, 51.3, 125.8, 128.4, 130.2, 130.4, 130.6, 134.5, 149.2, 182.5, 184.5, 199.8; HRMS (ESI$^+$): Found: 269.0621; $C_{16}H_{13}O_2S$ (MH$^+$) Requires 269.0631 (3.0 ppm error).

1,5-Bis(4-methoxyphenyl)pent-1-yn-3-one (9k). Synthesised using general procedure B from 4-ethynylanisole (488 mg, 3.70 mmol) and *N*-methoxy-3-(4-methoxyphenyl)-*N*-methylpropanamide[23] (550 mg, 2.46 mmol). Purification by flash column chromatography afforded the *title compound* **9k** as a yellow solid (500 mg, 69%); mp. 58–60 °C; R_f 0.80 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2185, 1659, 1601, 1508, 1293, 1245, 117, 1084, 1026, 830; δ_H (400 MHz, $CDCl_3$) 2.92–3.02 (4 H, m), 3.78 (3 H, s), 3.83 (3 H, s), 6.83 (2 H, d, J = 8.5), 6.89 (2 H, d, J = 8.5), 7.14 (2 H, d, J = 8.5), 7.51 (2 H, d, J = 8.5); δ_C (100 MHz, $CDCl_3$) 29.2, 47.1, 55.2, 55.4, 87.7, 92.3, 111.6, 113.9, 114.3, 129.3, 132.4, 135.1, 158.0, 161.6, 187.1; HRMS (ESI$^+$): Found: 295.1317; $C_{19}H_{19}O_3$ (MH$^+$) Requires 295.1329 (3.7 ppm error).

7-(4-Methoxyphenyl)spiro[5.5]undeca-1,4,7-triene-3,9-dione (10k). Synthesised using general procedure C from ynone **9k** (62.0 mg, 0.204 mmol) and copper(II) triflate (73.7 mg, 0.204 mmol) for 20 h at 50 °C. Purification by flash column chromatography (1 : 1 petrol : EtOAc) afforded the *title compound* **10k** as a pale yellow solid (46 mg, 78%); mp. 165–167 °C; R_f 0.25 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1657, 1623, 1603, 1510, 1243, 1178, 1030, 859, 731; δ_H (400 MHz, $CDCl_3$) 2.25 (2 H, t, J = 6.5), 2.68 (2 H, t, J = 6.5), 3.78 (3 H, s), 6.30 (1 H, s), 6.42 (2 H, d, J = 10.0), 6.79 (2 H, d, J = 9.0), 7.06 (2 H, d, J = 10.0), 7.19 (2 H, d, J = 9.0); δ_C (100 MHz, $CDCl_3$) 34.0, 37.7, 45.5, 55.3, 114.0, 127.7, 128.1, 130.1, 130.4, 152.6, 159.2, 161.0, 184.7, 196.9; HRMS (ESI$^+$): Found: 281.1179; $C_{18}H_{17}O_3$ (MH$^+$) Requires 281.1172 (2.5 ppm error).

1-(4′-Methoxybiphenyl-2-yl)-3-(4-methoxyphenyl)prop-2-yn-1-one (9l). Synthesised using general procedure B from 4-ethynylanisole (190 mg, 1.44 mmol) and *N*,4′-dimethoxy-*N*-methyl-[1,1′-biphenyl]-2-carboxamide[24] (260 mg, 0.958). Purification by flash column chromatography (10 : 1 petrol : EtOAc, then 5 : 1 petrol : EtOAc) afforded the *title compound* **9l** as a pale yellow oil (141 mg, 43%); R_f 0.70 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 2184, 1620, 1599, 1508, 1289, 1248, 1027, 999, 830, 760; δ_H (400 MHz, $CDCl_3$) 3.77 (3 H, s), 3.80 (3 H, s), 6.79 (2 H, d, J = 9.0), 6.94 (2 H, d, J = 8.5), 7.22 (2 H, d, J = 9.0), 7.35 (2 H, d, J = 8.5), 7.40–7.45 (2 H, m), 7.53–7.58 (1 H, m), 7.92 (1 H, d, J = 7.5); δ_C (100 MHz, $CDCl_3$) 55.3, 55.4, 88.9, 94.9, 112.0, 113.8, 114.0, 127.0, 129.9, 130.7, 130.9, 131.9, 132.9, 135.0, 138.1, 142.3, 159.4, 161.4, 180.8; HRMS (ESI$^+$): Found: 343.1324; $C_{23}H_{19}O_3$ (MH$^+$) Requires 343.1329 (1.0 ppm error).

2′-(4-Methoxyphenyl)-4′*H*-spiro[cyclohexa[2,5]diene-1,1′-naphthalene]-4,4′-dione (10l). Synthesised using general procedure C from ynone **9l** (66.0 mg, 0.193 mmol) and copper(II) triflate (69.6 mg, 0.193 mmol) for 48 h at RT. Purification by flash column chromatography (2 : 1 petrol : EtOAc) afforded the *title compound* **10l** as a pale yellow oil (47 mg, 74%); R_f 0.25 (1 : 1 petrol : EtOAc); ν_{max} (thin film)/cm^{-1} 1655, 1602, 1510, 1331, 1251, 1031, 836; δ_H (400 MHz, $CDCl_3$) 3.797 (3 H, s), 6.44 (2 H, d, *J* = 9.5), 6.72 (1 H, s), 6.74 (2 H, d, *J* = 9.5), 6.82 (2 H, d, *J* = 9.0), 7.25–7.29 (3 H, m), 7.48–7.57 (2 H, m), 8.25 (1 H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 50.7, 55.3, 113.7, 127.3, 128.2, 128.7, 128.9, 129.6, 130.0, 130.0, 130.2, 133.2, 138.3, 150.0, 156.0, 160.6, 183.6, 185.2; HRMS (ESI$^+$): Found: 329.1170; $C_{22}H_{17}O_3$ (MH$^+$) Requires 329.1172 (0.8 ppm error).

2-(4-)-*N*-Methoxy-*N*-methylacetamide (S3). Synthesised using general procedure A2 from 2-(4-hydroxyphenyl)acetic acid (2.40 g, 15.8 mmol) stirring at RT for 1 h. Afforded the *title compound* **S3** as a white solid (3.00 g, 100%); mp 110–112 °C; R_f 0.58 (9 : 1 EtOAc : hexane); ν_{max} (thin film)/cm^{-1} 3264, 1631, 1614, 1594, 1515, 1446, 1233, 1172, 1002, 798; δ_H (400 MHz, $CDCl_3$) 3.22 (3 H, s), 3.65 (3 H, s), 3.70 (2 H, s), 6.68 (2 H, d, *J* = 8.5), 7.07 (2 H, d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) 32.3, 38.2, 61.3, 115.6, 125.9, 130.4, 155.2, 173.3; HRMS (ESI$^+$): Found: 218.0788; $C_{10}H_{13}NNaO_3$ (MNa$^+$) Requires 218.0788 (−0.3 ppm error), Found: 196.0975; $C_{10}H_{14}NO_3$ (MH$^+$) Requires 196.0968 (−3.2 ppm error).

1-(4-Hydroxyphenyl)-4-phenylbut-3-yn-2-one (11c). Synthesised using general procedure B2 from phenylacetylene (0.34 mL, 3.07 mmol) and Weinreb amide **S3** (200 mg, 1.02 mmol) stirring at RT for 30 min. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 1 : 1 hexane : EtOAc) afforded the *title compound* **11c** as a pale yellow solid (135 mg, 56%); mp 96–98 °C; R_f 0.51 (6 : 4 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3368, 2202, 1655, 1514, 1224, 1079, 758, 688; δ_H (400 MHz, $CDCl_3$) 3.87 (2 H, s), 5.42 (1 H, br s), 6.83–6.88 (2 H, m), 7.16–7.21 (2 H, m), 7.33–7.39 (2 H, m), 7.42–7.50 (3 H, m); δ_C (100 MHz, $CDCl_3$) 51.3, 87.7, 93.3, 115.7, 119.7, 125.1, 128.6, 130.9, 131.1, 133.1, 155.1, 186.1; HRMS (ESI$^+$): Found: 259.0731; $C_{16}H_{12}NaO_2$ (MNa$^+$) Requires 259.0730 (−0.6 ppm error), Found: 237.0919; $C_{16}H_{13}O_2$ (MH$^+$) Requires 237.0910 (−3.8 ppm error).

4-Phenylspiro[4.5]deca-3,6,9-triene-2,8-dione (10c). Synthesised using general procedure C2 from ynone **11c** (100 mg, 0.423 mmol) and $AgNO_3{\cdot}SiO_2$ (719 mg, 0.0423 mmol) for 24 h at 40 °C. Afforded the *title compound* **10c** without further purification as a pale brown solid (94.0 mg, 94%); mp 124–126 °C; R_f 0.31 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3068, 1693, 1658, 1592, 1251, 859, 764; δ_H (400 MHz, $CDCl_3$) 2.80 (2 H, s), 6.49 (2 H, d, *J* = 10.0), 6.71 (1 H, s), 6.96 (2 H, d, *J* = 10.0), 7.34–7.40 (2 H, m), 7.42–7.48 (1 H, m), 7.49–7.54 (2 H, m); δ_C (100 MHz, $CDCl_3$) 46.9, 51.2, 127.4, 129.0, 129.9, 130.0, 131.6, 132.9, 151.4, 173.9, 184.7, 203.3; HRMS (ESI$^+$): Found: 259.0732; $C_{16}H_{12}NaO_2$ (MNa$^+$) Requires 259.0730 (−0.9 ppm error). Spectroscopic data matched those previously reported in the literature.[25]

1-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (11d). Synthesised using general procedure B from 1-ethynyl-4-methoxybenzene (983 mg, 7.44 mmol) and Weinreb amide **S3** (484 mg, 2.48 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11d** as a yellow solid (502 mg, 76%); mp 86–88 °C; R_f 0.62 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3353, 2195, 1651, 1600, 1510, 1254, 1170, 1076, 834; δ_H (400 MHz, $CDCl_3$) 3.83 (3 H, s), 3.85 (2 H, s), 5.52 (1 H, br s), 6.86 (4 H, m), 7.17 (2 H, d, *J* = 8.0), 7.41 (2 H, d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) 51.1, 55.4, 87.8, 94.7, 111.5, 114.3, 115.6, 125.4, 131.1, 135.2, 155.1, 161.7, 186.3; HRMS (ESI$^+$): Found: 289.0839; $C_{17}H_{14}NaO_3$ (MNa$^+$) Requires 289.0835 (−1.4 ppm error).

4-(4-Methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10d). Synthesised using general procedure C2 from ynone **11d** (100 mg, 0.376 mmol) and $AgNO_3{\cdot}SiO_2$ (638 mg, 0.0376 mmol) for 3 h at 40 °C. Afforded the *title compound* **10d** without further purification as a brown solid (100 mg, 100%). Data for this compound is reported above.

2-(4-Hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylacetamide (S4). Synthesised using general procedure A2 from 2-(4-hydroxy-3-methoxyphenyl)acetic acid (1.15 g, 6.34 mmol) stirring at RT for 1 h. Afforded the *title compound* **S4** as a clear and colourless oil (810 mg, 48%); R_f 0.21 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3316, 2939, 1639, 1514, 1432, 1271, 1200, 1151, 1033; δ_H (400 MHz, $CDCl_3$) 3.19 (3 H, s), 3.62 (3 H, s), 3.70 (2 H, s), 3.87 (3 H, s), 5.35 (1 H, br s), 6.75 (1 H, d, *J* = 8.0), 6.82–6.86 (2 H, m); δ_C (100 MHz, $CDCl_3$) 32.2, 38.8, 55.8, 61.3, 111.7, 114.2, 122.1, 126.5, 144.5, 146.5, 172.7; HRMS (ESI$^+$): Found: 248.0884; $C_{11}H_{15}NNaO_4$ (MNa$^+$) Requires 248.0893 (3.7 ppm error), Found: 226.1070; $C_{11}H_{16}NO_4$ (MH$^+$) Requires 226.1074 (1.6 ppm error).

1-(4-Hydroxy-3-methoxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (11m). Synthesised using general procedure B2 from 1-ethynyl-4-methoxybenzene (880 mg, 6.66 mmol) and Weinreb amide **S4** (500 mg, 2.22 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11m** as a yellow solid (443 mg, 58%); mp 61–63 °C; R_f 0.20 (7 : 3 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3437, 2195, 1655, 1601, 1509, 1254, 1237, 1170; δ_H (400 MHz, $CDCl_3$) 3.84 (5 H, s), 3.89 (3 H, s), 5.63 (1 H, br s), 6.78–6.95 (5 H, m), 7.43 (2 H, d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) 51.7, 55.4, 55.9, 87.7, 94.1, 111.6, 112.0, 114.3, 114.5, 122.8, 125.2, 135.1, 144.9, 146.6, 161.7, 185.7; HRMS (ESI$^+$): Found: 319.0939; $C_{18}H_{16}NaO_4$ (MNa$^+$) Requires 319.0941 (0.7 ppm error).

7-Methoxy-4-(4-methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10m). Synthesised using general procedure C2 from ynone **11m** (59.0 mg, 0.199 mmol) and $AgNO_3{\cdot}SiO_2$ (338 mg, 0.0199 mmol) for 24 h at 40 °C. Purification by flash column chromatography (8 : 2 hexane : EtOAc) afforded the *title compound* **10m** an off-white oil (50.9 mg, 86%); R_f 0.14 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1691, 1664, 1636, 1603, 1587, 1509, 1258, 1208, 1177, 831; δ_H (400 MHz, $CDCl_3$) 2.78 (1 H, d, *J* = 18.5), 2.86 (1 H, d, *J* = 18.5), 3.66 (3 H, s), 3.83 (3 H, s), 5.86 (1 H, d, *J* = 2.5), 6.50 (1 H, d, *J* = 9.5), 6.61 (1 H, s), 6.85 (2 H, d, *J* = 8.5), 6.97 (1 H, dd, *J* = 9.5, 2.5), 7.48 (2 H, d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) 48.0, 51.6, 55.2, 55.4, 114.3, 119.4, 125.3, 127.1, 129.0, 129.4, 151.7, 152.4, 162.2, 173.7, 180.1, 203.4; HRMS (ESI^+): Found: 319.0947; $C_{18}H_{16}NaO_4$ (MNa^+) Requires 319.0941 (−2.0 ppm error).

1-(4-Hydroxyphenyl)oct-3-yn-2-one(11n). Synthesised using general procedure B2 from hex-1-yne (0.35 mL, 3.07 mmol) and Weinreb amide **S3** (200 mg, 1.02 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11n** as a yellow oil (181 mg, 82%); R_f 0.76 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3373, 2959, 2933, 2209, 1652, 1514, 1224, 796; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* = 7.5), 1.35 (2 H, qt, *J* = 7.5, 7.5), 1.48 (2 H, tt, *J* = 7.5, 7.0), 2.32 (2 H, t, *J* = 7.0), 3.74 (2 H, s), 5.93 (1 H, br s), 6.80 (2 H, d, *J* = 8.0), 7.09 (2 H, d, *J* = 8.0); δ_C (100 MHz, $CDCl_3$) 13.4, 18.6, 21.8, 29.5, 51.3, 80.7, 97.3, 115.6, 124.9, 130.9, 155.1, 186.7; HRMS (ESI^+): Found: 239.1050; $C_{14}H_{16}NaO_2$ (MNa^+) Requires 239.1043 (−3.2 ppm error).

4-Butylspiro[4.5]deca-3,6,9-triene-2,8-dione(10n). Synthesised using general procedure C2 from ynone **11n** (85.4 mg, 0.395 mmol) and $AgNO_3{\cdot}SiO_2$ (671 mg, 0.0395 mmol) for 24 h at RT. Afforded the *title compound* **10n** without further purification as a pale yellow solid (80.3 mg, 94%); mp 100–102 °C; R_f 0.35 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 2959, 2929, 2875, 2857, 1720, 1696, 1657, 1614, 1599, 1255, 1232, 862; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* = 7.5), 1.33 (2 H, qt, *J* = 7.5, 7.5), 1.52 (2 H, tt, *J* = 7.5, 7.5), 2.10 (2 H, t, *J* = 7.5), 2.65 (2 H, s), 6.22 (1 H, s), 6.45 (2 H, d, *J* = 9.0), 6.66 (2 H, d, *J* = 9.0); δ_C (100 MHz, $CDCl_3$) 13.7, 22.2, 28.8, 29.5, 45.0, 52.6, 130.58, 130.61, 150.0, 181.6, 184.9, 204.6; HRMS (ESI^+): Found: 239.1043; $C_{14}H_{16}NaO_2$ (MNa^+) Requires 239.1043 (−0.3 ppm error), Found: 217.1219; $C_{14}H_{17}O_2$ (MH^+) Requires 217.1223 (2.0 ppm error). Spectroscopic data matched those previously reported in the literature.[26]

***tert*-Butyl (6-(4-hydroxyphenyl)-5-oxohex-3-yn-1-yl)(methyl) carbamate (11o).** Synthesised using general procedure B2 from *tert*-butyl but-3-yn-1-yl(methyl)carbamate[10d] (568 mg, 3.10 mmol) and Weinreb amide **S3** (202 mg, 1.03 mmol) stirring at RT for 2.5 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 1 : 1 hexane : EtOAc) afforded the *title compound* **11o** as a yellow oil (241 mg, 74%); R_f 0.62 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3331, 2977, 2212, 1663, 1515, 1395, 1366, 1225, 1145, 730; δ_H (400 MHz, $CDCl_3$) 1.47 (9 H, s), 2.54 (2 H, t, *J* = 7.0), 2.86 (3 H, s), 3.36 (2 H, t, *J* = 7.0), 3.71 (2 H, s), 6.07 (1 H, br s), 6.81 (2 H, d, *J* = 8.0), 7.08 (2 H, d, *J* = 8.0); δ_C (100 MHz, $CDCl_3$) 18.6, 28.4, 35.0, 47.2, 51.2, 80.3, 81.7, 92.9, 115.8, 124.8, 130.9, 155.6, 155.6, 185.4; HRMS (ESI^+): Found: 340.1522; $C_{18}H_{23}NNaO_4$ (MNa^+) Requires 340.1519 (−0.9 ppm error). Note: majority of peaks broadened in ^{1}H NMR spectrum due to presence of rotamers.

***tert*-Butyl (2-(3,8-dioxospiro[4.5]deca-1,6,9-trien-1-yl)ethyl) (methyl)carbamate (10o).** Synthesised using general procedure C2 from ynone **11o** (73.5 mg, 0.232 mmol) and $AgNO_3{\cdot}SiO_2$ (394 mg, 0.0232 mmol) for 10 h at RT. Afforded the *title compound* **10o** without further purification as a pale yellow oil (68.5 mg, 93%); R_f 0.22 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 2975, 1720, 1688, 1662, 1624, 1615, 1392, 1365, 1165, 1144, 860; δ_H (400 MHz, $CDCl_3$) 1.43 (9 H, s), 2.31 (2 H, t, *J* = 7.0), 2.62 (2 H, s), 2.81 (3 H, s), 3.39 (2 H, t, *J* = 7.0), 6.20 (1 H, s), 6.43 (2 H, d, *J* = 9.5), 6.65–6.73 (2 H, br m); δ_C (100 MHz, $CDCl_3$) 27.2, 28.4, 34.2, 45.1, 47.1, 52.8, 80.0, 130.9, 132.0, 149.4, 155.5, 176.9, 184.5, 203.8; HRMS (ESI^+): Found: 340.1522; $C_{18}H_{23}NNaO_4$ (MNa^+) Requires 340.1519 (−0.8 ppm error). Note: majority of peaks broadened in ^{1}H NMR spectrum due to presence of rotamers.

6-((*tert*-Butyldimethylsilyl)oxy)-1-(4-hydroxyphenyl)hex-3-yn-2-one (11p). To an oven-dried 100 mL round-bottom flask containing (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane[27] (753 mg, 4.09 mmol) and freshly distilled THF (15 mL) at −78 °C under argon was added *n*-BuLi (1.3 mL, 4.3 mmol, 2.5 M in hexanes) drop-wise over 10 min. After stirring at −78 °C for 60 min, the alkyne solution was transferred *via* cannula into an oven-dried round-bottom flask containing Weinreb amide **S3** (266 mg, 1.36 mmol) in THF (15 mL) and stirred at −78 °C for 10 min. The resulting suspension was warmed to RT, quenched with saturated aqueous NH_4Cl (20 mL), extracted successively with EtOAc (3 × 15 mL), and the combined organics washed with brine (20 mL), dried ($MgSO_4$), and concentrated under vacuum to yield a crude product. The crude product was purified by flash column chromatography (9 : 1 hexane : EtOAc, then 6 : 4 hexane : EtOAc) to afford the *title compound* **11p** as a yellow oil (367 mg, 84%); R_f 0.56 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3379, 2953, 2929, 2857, 2213, 1670, 1514, 1253, 1106, 836, 795, 778; δ_H (400 MHz, $CDCl_3$) 0.06 (6 H, s), 0.88 (9 H, s), 2.53 (2 H, t, *J* = 7.0), 3.71 (2 H, t, *J* = 7.0), 3.73 (2 H, s), 6.77 (2 H, app. d, *J* = 8.5), 7.06 (2 H, app. d, *J* = 8.5); δ_C (100 MHz, $CDCl_3$) −5.2, 18.4, 23.5, 25.9, 51.3, 60.8, 81.5, 93.7, 115.7, 124.8, 131.0, 155.2, 186.3; HRMS (ESI^+): Found: 341.1536; $C_{18}H_{26}NaO_3Si$ (MNa^+) Requires 341.1543 (2.3 ppm error).

4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (10p). Synthesised using general procedure C2 from ynone **11p** (55.0 mg, 0.170 mmol) and $AgNO_3{\cdot}SiO_2$ (293 mg, 0.0170 mmol) 16 h at RT. Purification by flash column chromatography (8 : 2 hexane : EtOAc, then 1 : 1 hexane : EtOAc) afforded the *title compound* **10p** as an orange solid (49.0 mg, 89%); R_f 0.42 (1 : 1 hexane : EtOAc); mp 76–80 °C; ν_{max} (thin film)/cm^{-1} 2928, 2857, 1721, 1698, 1657, 1621, 1254, 1102, 864, 834, 775; δ_H (400 MHz, $CDCl_3$) 0.01 (6 H, s), 0.85 (9 H, s), 2.28 (2 H, dt, *J* = 6.0, 1.5), 2.26 (2 H, s), 3.75 (2 H, t, *J* = 6.0), 6.31 (1 H, t, *J* = 1.5), 6.42 (2 H, app. d, *J* = 10.0), 6.64 (2 H, app. d, *J* = 10.0); δ_C (100 MHz, $CDCl_3$) −5.35, 18.3, 25.9, 32.3, 44.9, 52.7, 60.6, 130.8, 132.0, 149.8, 178.0, 184.9, 204.8; HRMS (ESI^+): Found: 341.1541; $C_{18}H_{26}NaO_3Si$ (MNa^+) Requires 341.1543 (0.7 ppm error).

4-Cyclopropyl-1-(4-hydroxyphenyl)but-3-yn-2-one (11q). Synthesised using general procedure B2 from ethynylcyclopropane (0.40 mL, 4.61 mmol) and Weinreb amide **S3** (300 mg, 1.54 mmol) stirring at RT for 1 h. Purification by flash column chromatography (1 : 1 hexane : EtOAc) afforded the *title compound* **11q** as a white solid (276 mg, 90%); mp 81–83 °C; R_f 0.59 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3367, 2201, 1647, 1514, 1222; δ_H (400 MHz, $CDCl_3$) 0.80–0.85 (2 H, m), 0.92–0.98 (2 H, m), 1.31–1.39 (1 H, m), 3.71 (2 H), 5.30 (1 H, br s), 6.80 (2 H, d, J = 8.0), 7.09 (2 H, d, J = 8.0); δ_C (100 MHz, $CDCl_3$) −0.3, 9.9, 51.1, 76.5, 101.6, 115.5, 125.3, 130.9, 154.9, 186.0; HRMS (ESI$^+$): Found: 223.0734; $C_{13}H_{12}NaO_2$ (MNa$^+$) Requires 223.0730 (−2.1 ppm error), Found: 201.0906; $C_{13}H_{13}O_2$ (MH$^+$) Requires 201.0910 (1.9 ppm error).

4-Cyclopropylspiro[4.5]deca-3,6,9-triene-2,8-dione (10q). Synthesised using general procedure C2 from ynone **11q** (101 mg, 0.504 mmol) and $AgNO_3{\cdot}SiO_2$ (857 mg, 0.0504 mmol) for 2 h at RT. Afforded the *title compound* **10q** without further purification as a white solid (100 mg, 99%); mp 109–111 °C; R_f 0.45 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1689, 1666, 1624, 1605, 1401, 1252, 860; δ_H (400 MHz, $CDCl_3$) 0.77–0.82 (2 H, m), 1.11–1.17 (2 H, m), 1.18–1.24 (1 H, m), 2.64 (2 H, s), 5.75 (1 H, s), 6.45 (2 H, d, J = 10.0), 6.72 (2 H, d, J = 10.0); δ_C (100 MHz, $CDCl_3$) 11.0, 13.8, 45.0, 52.8, 123.5, 130.6, 150.0, 184.9, 185.6, 204.2; HRMS (ESI$^+$): Found: 223.0733; $C_{13}H_{12}NaO_2$ (MNa$^+$) Requires 223.0730 (−1.7 ppm error), Found: 201.0906; $C_{13}H_{13}O_2$ (MH$^+$) Requires 201.0910 (2.2 ppm error).

4-Cyclopentyl-1-(4-hydroxyphenyl)but-3-yn-2-one (11r). Synthesised using general procedure B2 from ethynylcyclopentane (0.36 mL, 3.07 mmol) and Weinreb amide **S3** (200 mg, 1.02 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11r** as a pale yellow oil (207 mg, 89%); R_f 0.74 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3376, 2961, 2871, 2205, 1650, 1514, 1224, 1172; δ_H (400 MHz, $CDCl_3$) 1.50–1.76 (6 H, m), 1.83–1.97 (2 H, m), 2.73 (1 H, tt, J = 7.5, 7.5), 3.74 (2 H, s), 5.49 (1 H, br s), 6.80 (2 H, d, J = 8.0), 7.10 (2 H, d, J = 8.0); δ_C (100 MHz, $CDCl_3$) 25.1, 30.0, 33.0, 51.3, 80.2, 101.3, 115.5, 125.2, 130.9, 154.9, 186.6; HRMS (ESI$^+$): Found: 251.1041; $C_{15}H_{16}NaO_2$ (MNa$^+$) Requires 251.1043 (0.7 ppm error).

4-Cyclopentylspiro[4.5]deca-3,6,9-triene-2,8-dione (10r). Synthesised using general procedure C2 from ynone **11r** (60.2 mg, 0.264 mmol) and $AgNO_3{\cdot}SiO_2$ (448 mg, 0.0264 mmol) for 6 h at RT. Afforded the *title compound* **10r** without further purification as a white solid (60.0 mg, 100%); mp 129–131 °C; R_f 0.43 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 2958, 1697, 1657, 1621, 1609, 1403, 1249, 864; δ_H (400 MHz, $CDCl_3$) 1.37–1.50 (2 H, m), 1.52–1.67 (2 H, m), 1.68–1.82 (2 H, m), 1.83–1.95 (2 H, m), 2.30 (1 H, tt, J = 8.0, 8.0), 2.64 (2 H, s), 6.22 (1 H, s), 6.44 (2 H, d, J = 10.0), 6.69 (2 H, d, J = 10.0); δ_C (100 MHz, $CDCl_3$) 25.5, 34.8, 40.2, 45.0, 53.0, 129.0, 130.5, 150.0, 185.0, 186.8, 204.7; HRMS (ESI$^+$): Found: 251.1033; $C_{15}H_{16}NaO_2$ (MNa$^+$) Requires 251.1043 (3.9 ppm error), Found: 229.1215; $C_{15}H_{17}O_2$ (MH$^+$) Requires 229.1223 (3.7 ppm error).

2-(2-Hydroxyphenyl)-*N*-methoxy-*N*-methylacetamide (S5). Synthesised using general procedure A2 from 2-(2-hydroxyphenyl)acetic acid (2.00 g, 13.1 mmol) stirring at RT for 1.5 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 1 : 1 hexane : EtOAc) afforded the *title compound* **S5** as a white solid (788 mg, 31%); mp 63–65 °C; R_f 0.39 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3260, 1628, 1596, 1456, 1246, 1000, 753; δ_H (400 MHz, $CDCl_3$) 3.24 (3 H, s), 3.80 (3 H, s), 3.87 (2 H, s), 6.85 (1 H, dd, J = 8.0, 7.5), 6.99 (1 H, d, J = 8.0), 7.09 (1 H, d, J = 7.5), 7.19 (1 H, dd, J = 8.0, 8.0), 9.50 (1 H, s); δ_C (100 MHz, $CDCl_3$) 32.0, 35.1, 62.0, 118.2, 120.2, 120.9, 129.1, 130.9, 156.8, 173.5; HRMS (ESI$^+$): Found: 218.0794; $C_{10}H_{13}NNaO_3$ (MNa$^+$) Requires 218.0788 (−3.0 ppm error), Found: 196.0967; $C_{10}H_{14}NO_3$ (MH$^+$) Requires 196.0968 (−0.8 ppm error).

4-Cyclopropyl-1-(2-hydroxyphenyl)but-3-yn-2-one (11s). Synthesised using general procedure B2 from ethynylcyclopropane (0.65 mL, 7.68 mmol) and Weinreb amide **S5** (500 mg, 2.56 mmol) stirring at RT for 45 min. Purification by flash column chromatography (1 : 1 hexane : EtOAc) afforded the *title compound* **11s** as an off-white solid (452 mg, 88%); mp 98–100 °C; R_f 0.78 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3369, 2202, 1649, 1458, 1269, 755; δ_H (400 MHz, $CDCl_3$) 0.87–0.92 (2 H, m), 0.97–1.04 (2 H, m), 1.37–1.45 (1 H, m), 3.85 (2 H, s), 6.70 (1 H, br s), 6.88–6.93 (2 H, m), 7.11 (1 H, app. d, J = 7.5), 7.19 (1 H, app. dd, J = 8.0, 8.0); δ_C (100 MHz, $CDCl_3$) −0.1, 10.2, 47.5, 76.8, 103.2, 117.1, 120.6, 120.9, 129.2, 131.3, 154.9, 187.2; HRMS (ESI$^+$): Found: 223.0738; $C_{13}H_{12}NaO_2$ (MNa$^+$) Requires 223.0730 (−3.6 ppm error), Found: 201.0918; $C_{13}H_{13}O_2$ (MH$^+$) Requires 201.0910 (−3.8 ppm error).

4-Cyclopropylspiro[4.5]deca-3,7,9-triene-2,6-dione (12s). Synthesised using general procedure C2 from ynone **11s** (108 mg, 0.538 mmol) and $AgNO_3{\cdot}SiO_2$ (915 mg, 0.0538 mmol) for 2 h at RT. Afforded the *title compound* **12s** without further purification as a yellow oil (104 mg, 96%); R_f 0.34 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1660, 1632, 1607, 1557, 1200, 862; δ_H (400 MHz, $CDCl_3$) 0.68–0.79 (2 H, m), 0.97–1.09 (2 H, m), 1.20–1.28 (1 H, m), 2.39 (1 H, d, J = 18.0), 2.77 (1 H, d, J = 18.0), 5.72 (1 H, s), 6.23 (1 H, d, J = 9.5), 6.28 (1 H, d, J = 9.0), 6.47 (1 H, dd, J = 9.0, 5.5), 7.19 (1 H, ddd, J = 9.5, 5.5, 1.5); δ_C (100 MHz, $CDCl_3$) 11.0, 11.9, 13.2, 46.8, 62.7, 122.8, 123.9, 126.7, 142.5, 142.8, 184.5, 200.3, 206.2; HRMS (ESI$^+$): Found: 223.0732; $C_{13}H_{12}NaO_2$ (MNa$^+$) Requires 223.0730 (−1.3 ppm error), Found: 201.0907; $C_{13}H_{13}O_2$ (MH$^+$) Requires 201.0910 (1.3 ppm error).

1-(2-Hydroxyphenyl)-4-phenylbut-3-yn-2-one (11t). Synthesised using general procedure B2 from phenylacetylene (2.0 mL, 18.1 mmol) and Weinreb amide **S5** (1.18 g, 6.04 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11t** as a yellow solid (1.33 g, 93%); mp 106–108 °C; R_f 0.67 (6 : 4 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3333, 2982, 2202, 1661, 1489, 1458, 1156, 753; δ_H (400 MHz, $CDCl_3$) 4.01 (2 H, s), 6.27 (1 H, br s), 6.94–6.98 (2 H, m), 7.19–7.26 (2 H, m), 7.39 (2 H, m), 7.45–7.50 (1 H, m), 7.51–7.55 (2 H, m); δ_C (100 MHz, $CDCl_3$) 47.5, 87.8, 94.0, 116.8, 119.6, 120.4, 121.0, 128.6, 129.3, 131.1, 131.5, 133.3, 154.8, 187.0; HRMS (ESI$^+$): Found: 259.0722; $C_{16}H_{12}NaO_2$ (MNa$^+$) Requires

259.0730 (3.1 ppm error), Found: 237.0914; $C_{16}H_{13}O_2$ (MH^+) Requires 237.0910 (−1.5 ppm error).

4-Phenylspiro[4.5]deca-3,7,9-triene-2,6-dione (12t). Synthesised using general procedure C2 from ynone **11t** (115 mg, 0.487 mmol) and $AgNO_3$·SiO_2 (826 mg, 0.0487 mmol) for 24 h at RT. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 1 : 1 hexane : EtOAc) afforded the *title compound* **12t** a pale yellow oil (103 mg, 90%); R_f 0.22 (7 : 3 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1659, 1595, 1195, 760; δ_H (400 MHz, $CDCl_3$) 2.54 (1 H, d, J = 18.0), 2.78 (1 H, d, J = 18.0), 6.34 (1 H, d, J = 10.0), 6.44–6.49 (2 H, m), 6.77 (1 H, s), 7.24–7.30 (1 H, m), 7.30–7.38 (4 H, m), 7.38–7.44 (1 H, m); δ_C (100 MHz, $CDCl_3$) 48.3, 60.5, 121.8, 126.5, 127.3, 129.0, 129.5, 131.5, 132.3, 142.3, 144.6, 173.7, 200.2, 204.6; HRMS (ESI^+): Found: 259.0723; $C_{16}H_{12}NaO_2$ (MNa^+) Requires 259.0730 (2.5 ppm error), Found: 237.0906; $C_{16}H_{13}O_2$ (MH^+) Requires 237.0910 (1.9 ppm error).

The *title compound* was also prepared in an enantioenriched form using CPA **16**[15] (56% conv., 23% ee, see Scheme 4); $[\alpha]_D^{21}$ = +5.6 (c = 0.2, $CHCl_3$).

1-(2-Hydroxyphenyl)-4-(4-methoxyphenyl)but-3-yn-2-one (11u). Synthesised using general procedure B2 from 1-ethynyl-4-methoxybenzene (1.01 g, 7.68 mmol) and Weinreb amide **S5** (500 mg, 2.56 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11u** as a yellow solid (478 mg, 70%); mp 108–110 °C; R_f 0.29 (7 : 3 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3364, 2193, 1645, 1599, 1508, 1254, 1080, 834; δ_H (400 MHz, $CDCl_3$) 3.85 (3 H, s), 3.99 (2 H, s), 6.64 (1 H, s), 6.87–6.96 (4 H, m), 7.17–7.24 (2 H, m), 7.49 (2 H, d, J = 8.0); δ_C (100 MHz, $CDCl_3$) 47.6, 55.4, 87.0, 95.8, 111.2, 114.4, 117.1, 120.7, 121., 129.2, 131.5, 135.5, 154.9, 162.0, 187.2; HRMS (ESI^+): Found: 289.0833; $C_{17}H_{14}NaO_3$ (MNa^+) Requires 289.0835 (0.6 ppm error).

4-(4-Methoxyphenyl)spiro[4.5]deca-3,7,9-triene-2,6-dione (12u). Synthesised using general procedure C2 from ynone **11u** (50 mg, 0.188 mmol) and $AgNO_3$·SiO_2 (319 mg, 0.0188 mmol) for 24 h at RT. Afforded the *title compound* **12u** without further purification as a yellow oil (49.5 mg, 99%); R_f 0.25 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1689, 1659, 1602, 1587, 1510, 1262, 1179, 1026, 833, 731; δ_H (400 MHz, $CDCl_3$) 2.51 (1 H, d, J = 18.0), 2.75 (1 H, d, J = 18.0), 3.81 (3 H, s), 6.34 (1 H, d, J = 9.5), 6.45–6.47 (2 H, m), 6.68 (1 H, s), 6.85 (2 H, d, J = 8.5), 7.25–7.31 (3 H, m); δ_C (100 MHz, $CDCl_3$) 48.3, 55.4, 60.4, 114.4, 121.5, 124.8, 126.5, 127.2, 129.2, 142.3, 145.0, 162.2, 173.4, 200.5, 204.5; HRMS (ESI^+): Found: 289.0834; $C_{17}H_{14}NaO_3$ (MNa^+) Requires 289.0835 (0.4 ppm error), Found: 267.1004; $C_{17}H_{15}O_3$ (MH^+) Requires 267.1016 (4.2 ppm error).

4-(4-Fluorophenyl)-1-(2-hydroxyphenyl)but-3-yn-2-one (11v). Synthesised using general procedure B2 from 1-ethynyl-4-fluorobenzene (923 mg, 7.68 mmol) and Weinreb amide **S5** (500 mg, 2.56 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 7 : 3 hexane : EtOAc) afforded the *title compound* **11v** as a yellow solid (430 mg, 66%); mp 115–117 °C; R_f 0.46 (7 : 3 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3357, 2203, 1651, 1598, 1505, 1458, 1234, 1082, 838, 754; δ_H (400 MHz, $CDCl_3$) 3.99 (2 H, s), 6.25 (1 H, s), 6.89–6.97 (2 H, m), 7.08 (2 H, dd, $^3J_{HH}$ = 8.5, $^3J_{HF}$ 8.5), 7.18–7.25 (2 H, m), 7.51 (2 H, dd, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.5); δ_C (100 MHz, $CDCl_3$) 47.4, 87.7, 92.8, 115.7 (d, $^4J_{CF}$ = 4.0), 116.2 (d, $^2J_{CF}$ = 22.0), 116.8, 120.4, 121.1, 129.3, 131.5, 135.6 (d, $^3J_{CF}$ = 8.5), 154.7, 164.1 (d, $^1J_{CF}$ = 255), 186.8; HRMS (ESI^+): Found: 277.0628; $C_{16}H_{11}FNaO_2$ (MNa^+) Requires 277.0635 (2.5 ppm error).

4-(4-Fluorophenyl)spiro[4.5]deca-3,7,9-triene-2,6-dione (12v). Synthesised using general procedure C2 from ynone **11v** (98.8 mg, 0.389 mmol) and $AgNO_3$·SiO_2 (661 mg, 0.0389 mmol) for 48 h at RT. Purification by flash column chromatography (8 : 2 EtOAc : hexane) afforded the *title compound* **12v** a yellow oil (88.7 mg, 90%); R_f 0.36 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1694, 1659, 1601, 1582, 1508, 1238, 1193, 1163, 836; δ_H (400 MHz, $CDCl_3$) 2.53 (1 H, d, J = 18.0), 2.76 (1 H, d, J = 18.0), 6.33 (1 H, d, J = 9.5), 6.42–6.50 (2 H, m), 6.70 (1 H, s), 7.03 (2 H, dd, $^3J_{HH}$ = 8.5, $^3J_{HF}$ 8.5), 7.25–7.29 (1 H, m), 7.29–7.34 (2 H, m); δ_C (100 MHz, $CDCl_3$) 48.4, 60.5, 116.2 (d, $^2J_{CF}$ = 22.0), 121.9, 126.5, 128.6 (d, $^4J_{CF}$ = 3.0), 129.2, 129.5 (d, $^3J_{CF}$ = 8.5), 142.4, 144.3, 164.3 (d, $^1J_{CF}$ = 254), 172.3, 200.1, 204.3; HRMS (ESI^+): Found: 277.0642; $C_{16}H_{11}FNaO_2$ (MNa^+) Requires 277.0635 (−2.4 ppm error), Found: 255.0818; $C_{16}H_{12}FO_2$ (MH^+) Requires 255.0816 (−0.7 ppm error).

***tert*-Butyl 3-(4-(4-hydroxyphenyl)-3-oxobut-1-yn-1-yl)-1*H*-indole-1-carboxylate (13).** Synthesised using general procedure B2 from *tert*-butyl 3-ethynyl-1*H*-indole-1-carboxylate[5] (738 mg, 3.06 mmol) and Weinreb amide **S3** (199 mg, 1.02 mmol) stirring at RT for 1 h. Purification by flash column chromatography (9 : 1 hexane : EtOAc, then 8 : 2 hexane : EtOAc) afforded the *title compound* **13** as a yellow oil (306 mg, 80%); R_f 0.37 (7 : 3 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 3374, 2980, 2188, 1743, 1369, 1232, 1150, 1072; δ_H (400 MHz, $CDCl_3$) 1.70 (9 H, s), 3.89 (2 H, s), 4.98 (1 H, br s), 6.87 (2 H, d, J = 8.0), 7.23 (2 H, d, J = 8.0), 7.32 (1 H, dd, J = 8.0, 7.5), 7.38 (1 H, dd, J = 8.0, 7.5), 7.51 (1 H, d, J = 8.0), 7.91 (1 H, s), 8.14 (1 H, d, J = 8.0); δ_C (100 MHz, $CDCl_3$) 28.2, 51.2, 85.3, 86.8, 92.4, 100.5, 115.5, 115.8, 120.1, 123.8, 125.7, 125.8, 129.9, 131.2, 133.1, 134.8, 148.6, 155.2, 185.3; HRMS (ESI^-): Found: 398.1357; $C_{23}H_{21}NNaO_4$ (MNa^+) Requires 398.1363 (1.5 ppm error). Note: some peaks broadened in ^{13}C NMR spectrum due to presence of rotamers.

***tert*-Butyl 3-(3-oxo-5-(4-oxocyclohexa-2,5-dien-1-yl)cyclopent-1-en-1-yl)-1*H*-indole-1-carboxylate (8).** Synthesised using general procedure C2 from ynone **13** (68.4 mg, 0.182 mmol) and $AgNO_3$·SiO_2 (310 mg, 0.0182 mmol) for 7 h at RT. Afforded the *title compound* **8** without further purification as a pale brown solid (67.9 mg, 99%); mp 190–192 °C; R_f 0.46 (1 : 1 hexane : EtOAc); ν_{max} (thin film)/cm^{-1} 1742, 1694, 1662, 1595, 1370, 1351, 1228, 1148, 1109, 861, 732; δ_H (400 MHz, $CDCl_3$) 1.63 (9 H, s), 2.76 (2 H, s), 6.50 (2 H, d, J = 9.5), 6.91 (1 H, s), 6.97 (2 H, d, J = 9.5), 7.34–7.45 (2 H, m), 7.78 (1 H, d, J = 8.0), 7.93 (1 H, s), 8.25 (1 H, d, J = 8.0); δ_C (100 MHz, $CDCl_3$) 28.0, 45.6, 51.9, 85.4, 114., 115.7, 120.3, 124.2, 125.7, 127.8, 128.2, 128.4, 129.7, 135.8, 148.4, 151.9, 165.9, 184.3, 203.4.

Note: some peaks broadened in ^{13}C NMR spectrum due to presence of rotamers. Spectroscopic data matched those previously reported in the literature.[5]

5-Methyl-4a,5,6,7-tetrahydrocyclopenta[*d*]quinoline-3,9(4*H*,10*H*)-dione(14). To a stirred solution of *tert*-butyl (2-(3,8-dioxospiro[4.5]deca-1,6,9-trien-1-yl)ethyl)(methyl)carbamate **10o** (64.2 mg, 0.202 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added TFA (0.2 mL) dropwise. The mixture was warmed to RT and stirred for 2 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9 : 1 EtOAc : MeOH) to afford the *title compound* **14** as a colourless oil (29.2 mg, 66%); R_f 0.47 (9 : 1 EtOAc : MeOH); ν_{max} (thin film)/cm^{-1} 2790, 1709, 1684, 1632, 1209; δ_H (400 MHz, $CDCl_3$) 2.23–2.32 (4 H, m), 2.45–2.54 (2 H, m), 2.58–2.75 (4 H, m), 2.87 (1 H, dd, J = 16.0, 2.5), 3.10 (1 H, ddd, J = 11.0, 5.5, 2.5), 6.00 (1 H, s), 6.09 (1 H, d, J = 10.0), 6.41 (1 H, dd, J = 10.0, 2.5); δ_C (100 MHz, $CDCl_3$) 29.7, 40.0, 42.1, 45.9, 49.4, 56.7, 70.2, 127.7, 129.2, 149.8, 181.3, 196.1, 204.9; HRMS (ESI$^+$): Found: 218.1170; $C_{13}H_{16}NO_2$ (MH$^+$) Requires 218.1176 (2.5 ppm error).

4,4a,6,7-Tetrahydro-3*H*-cyclopenta[*d*]chromene-3,9(10*H*)-dione (15). To a 10 mL reaction vial containing 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)spiro[4.5]deca-3,6,9-triene-2,8-dione **10p** (31.0 mg, 0.097 mmol) in THF (3 mL) was added 10% aqueous HCl (0.1 mL) and the reaction stirred under argon at RT. After 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted successively with EtOAc (3 × 10 mL), the combined organics washed with brine (10 mL), dried over Na_2SO_4 and concentrated to yield a crude product. The product was purified by flash column chromatography (8 : 2 hexane : EtOAc, then 8 : 2 EtOAc : hexane) to afford the *title compound* **15** as an off-white solid (15.0 mg, 75%); R_f 0.47 (EtOAc); mp 115–120 °C; ν_{max} (thin film)/cm^{-1} 3564, 2961, 2925, 2856, 1706, 1682, 1629, 1404, 1234, 1204, 1060, 1009, 781, 701; δ_H (400 MHz, $CDCl_3$) 2.40 (1 H, d, J = 18.5), 2.55 (1 H, d, J = 18.5), 2.60–2.75 (4 H, m), 3.50 (1 H, dt, J = 11.5, 3.0), 3.81–3.83 (1 H, m), 4.22 (1 H, ddd, J = 11.5, 5.5, 2.5), 6.08 (1 H, d, J = 1.5), 6.13 (1 H, d, J = 10.0), 6.42 (1 H, dd, J = 10.0, 3.0); δ_C (100 MHz, $CDCl_3$) 30.1, 41.5, 44.3, 48.9, 68.1, 81.5, 128.8, 129.7, 148.2, 179.5, 195.1, 204.3; HRMS (ESI$^+$): Found: 227.0680; $C_{12}H_{12}NaO_3$ (MNa$^+$) Requires 227.0679 (−0.6 ppm error).

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Appendix III. Divergent Reactivity of Phenol- and Anisole-Tethered Donor-Acceptor α-Diazoketones

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Divergent reactivity of phenol- and anisole-tethered donor-acceptor α-diazoketones

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ABSTRACT

The first study of the divergent reactivity of phenol/anisole-tethered donor-acceptor α-diazoketones is described. Four distinct product classes were shown to be accessible from closely related α-diazoketone precursors, with the reaction outcome dependent on the nature of the oxygen substituent on the phenol/anisole ring and the catalyst used to decompose the diazo group. Anisole and TBS-protected derivatives selectively produce three products types (cyclopropanes, tetralones and 1,2-dicarbonyls) while phenols selectively produce spirocyclic dienones.

1. Introduction

α-Diazocarbonyl compounds are a versatile compound class able to undergo a variety of synthetic transformations to generate multiple products.[1,2] Their diverse reactivity is well-known in the literature and is a consequence of the many reactive intermediates they can form, including carbenes, carbenoids, ylides and diazonium cations. An excellent review by Maguire, McKervey and co-workers details the importance of α-diazocarbonyl compounds in modern organic synthesis, and demonstrates their utility in a range of C-H insertion, cyclopropanation, cycloaddition and ylide-forming reactions.[1d]

The versatile reactivity of α-diazocarbonyl compounds means that they are well-suited for use in diversity-oriented synthesis,[3] especially for research focused on the synthesis of multiple product classes from the same starting material.[4,5] Such processes are particularly useful if the chemoselectivity can be controlled, for example, by variation of the reaction conditions or reagents. In our groups,[5a,6] we are interested in developing divergent reaction systems in which the outcome is controlled by the choice of catalyst. Such 'catalyst selective synthesis'[7,8] has the power to significantly streamline the synthesis of diverse compounds, whilst also advancing our knowledge of the catalysis that underpins the divergent reactivity. An instructive example of the power of this approach was published by our groups in 2016, in which we demonstrated that by careful choice of catalyst and reaction conditions we could selectively generate six distinct products from single indolyl α-diazoketone precursors of the form **1** (Scheme 1A).[5a] To the best of our knowledge, this represents the highest number of distinct products selectively accessible from a single precursor by varying the catalyst and reaction conditions reported date.

In this manuscript, we describe efforts to extend this catalyst selective synthesis approach to phenol-/anisole-tethered α-diazoketones of the form **3** (i.e. 'donor-acceptor' diazoketones,[9] Scheme 1B). There were no reports concerning the reactions of diazo compounds of this type prior to this study,[10] although we drew inspiration from earlier studies detailing the reactivity of related classes of phenol-tethered α-diazoketones. For example, one of the first published intramolecular cyclisation reactions of such a compound was reported by Mander et al. in 1974, in which either Brønsted or Lewis acids were used to promote the displacement of nitrogen from simple α-diazoketones of the form **8**, leading to the formation of bridged tricyclic systems (*e.g.* **8** → **9**, Scheme 2A).[11] Iwata and co-workers later reported that similar transformations could be promoted with copper(I) chloride to generate spirocycles (*e.g.* **10** → **11**, Scheme 2B)[12]; indeed, Mander et al. had previously

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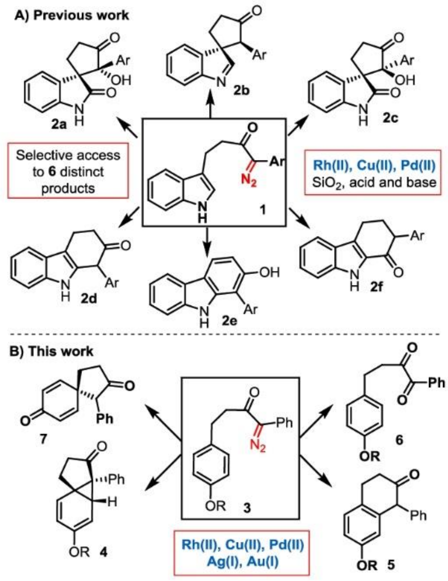
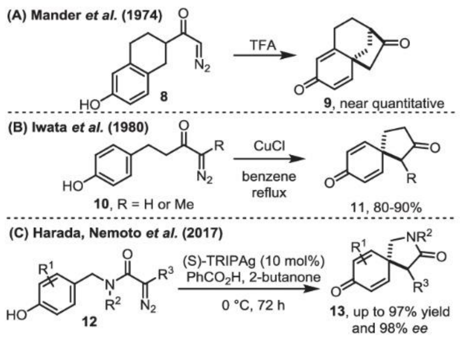


Scheme 1. Catalyst selective synthesis using α-diazoketones.



Scheme 2. Use of related phenol-tethered α-diazocarbonyl compounds in the literature.

shown that spirocycles of this type could be prepared using $BF_3.OEt_2$ to promote the reaction, albeit with competing dienone-phenol rearrangement products being formed in some cases.[13] Apart from these works, surprisingly little is known about the reactions of phenol-tethered α-diazoketones, although Harada, Nemoto and co-workers recently published a powerful strategy for the conversion of structurally related α-diazoacetamides **12** into spirocyclic dienones **13** in high yield and enantiomeric excess using chiral silver(I) salts (Scheme 2C).[14] Encouragingly for us, divergent reactivity was observed during initial catalyst screening in this study, with ring-annulated and C–H insertion products also observed to some degree when other catalysts were used.

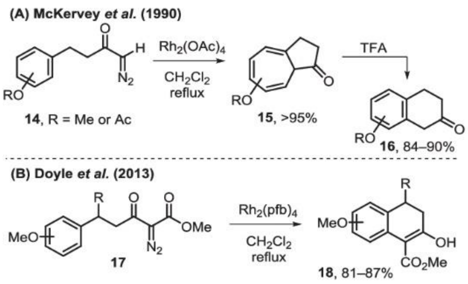
Compared to phenol-tethered systems, more is known about the reactivity of α-diazoketones tethered to anisoles, particularly in the well-established Buchner reaction (*e.g.* Scheme 3A).[15] Various mechanistic and kinetic studies have been performed, most notably by McKervey and Maguire,[16] with much of this work focused on the reactions of H-/Me-substituted α-diazoketones. More recently, related reactions on α-diazoketones substituted with electron-withdrawing substituents have also emerged[17] ('acceptor-acceptor' diazo compounds), for example, the anisole annulation method developed by Doyle and co-workers, depicted in Scheme 3B.[17a] Notably, the reaction outcomes in these studies typically differ to those observed in the analogous phenol systems, in which spirocyclic products usually dominate.

Our previous work in this area (Scheme 1A) focused on systems in which the diazo group is flanked on either side by both a ketone and an aromatic ring (see **1**, Scheme 1); controlling the reactivity of such 'donor-acceptor' diazo systems[9] is often easier than in less stabilised diazo systems, and it was decided to retain this feature in the current study (*e.g.* **3**) in the hope that it would allow us to impart similar chemoselectivity to that achieved in our earlier work.[5a] Our interest in these systems was further piqued by the fact that, to the best of our knowledge, there have been no reports concerning the reactions of any phenol/anisole-tethered α-diazoketones of this type (**3**) prior to this study.[10] Thus, herein, we describe our initial catalyst-screening, reaction optimisation and provide mechanistic proposals for a new, catalyst-driven divergent reaction series, that enables cyclopropane, tetralone, 1,2-dicarbonyl and spirocyclic products (**4–7**) to be selectively prepared from structurally related α-diazoketone precursors of the form **3**.

2. Results and discussion

2.1. Anisole-tethered α-diazoketones

We initiated our study by treating anisole-tethered α-diazoketone **3a**[18] with a range of metal-based catalysts. The expectation was that by forming different metal carbenoid species, different reactive pathways would be accessed, resulting in the preparation of multiple products. Selected screening results are shown in Table 1, with details of the full screen included in the Supporting Information. All catalysts were tested at 10 mol% loading in CH_2Cl_2 (0.1 M) at RT unless stated, with the product ratios determined by integration of their unpurified ^1H NMR spectra. As expected, many of the conditions produced mixtures of products, although three



Scheme 3. Use of related anisole-tethered α-diazocarbonyl compounds in the literature.

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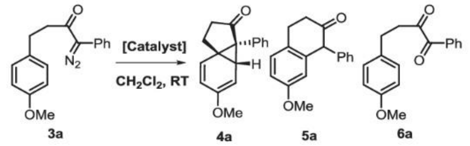
Table 1
Catalyst screening on diazoketone **3a**.[a]



Entry	Catalyst	3a: 4a: 5a: 6a[b]
1[c]	$Rh_2(OAc)_4$	15: **65**: 0: 20
2	CuCl	5: **85**: 0: 10
3	$Pd(OAc)_2$	0: **80**: 0: 20
4	Ag_2O	0: **95**: 0: 5
5	$Cu(OTf)_2$	10: 0: **90**: 0
6	AgOTf	0: 0: **100**: 0
7	$Pd(PhCN)_2Cl_2$	0: 0: 15: **85**[d]

[a] Reactions were performed with 0.1 mmol of diazoketone **3a** and 10 mol% catalyst in CH_2Cl_2 (0.1 M) under argon at RT for 16 h unless stated otherwise.
[b] Product ratio was calculated using the ^1H NMR spectrum of the unpurified reaction mixture, rounded to nearest 5%.
[c] 5 mol% catalyst used.
[d] Other minor impurities (unidentified) were observed in this case.

major identifiable products were observed in most cases: these were subsequently isolated and the structures assigned as cyclopropane **4a**, tetralone **5a** and 1,2-dicarbonyl **6a**. Other minor products were also observable by ^1H NMR spectroscopy in some cases, but these could not be obtained cleanly, hence the subsequent discussion is focused on the ratio of the three major products **4a**–**6a**. Cyclopropane **4a**, which was formed using the widest array of catalysts (via the Buchner reaction), was the major product produced using Rh(II), Cu(I) and Pd(II) catalysts (Table 1, entries 1–3), with Ag_2O producing this product with the highest purity of the catalysts screened (entry 4). Conversely, more Lewis acidic catalysts $Cu(OTf)_2$ and AgOTf furnished tetralone **5a** as the major product with good chemoselectivity (entries 5 and 6), whereas $Pd(PhCN)_2Cl_2$ unexpectedly formed 1,2-dicarbonyl **6a** as the major component (entry 7).

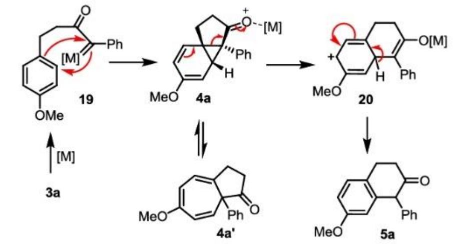
Thus, these initial screening reactions uncovered three complementary metal-catalysed processes to access three distinct products. It is likely that products **4a** and **5a** are mechanistically related; Scheme 4 shows a proposed mechanistic pathway through which cyclopropane **4a** could be converted into tetralone **5a**. Presumably, following metal-mediated diazo decomposition, Buchner cyclopropanation of the electron-rich anisole ring takes place to form cyclopropane **4a** which is in dynamic equilibrium with cycloheptatriene **4a'** arising from reversible electrocyclic ring opening.[19] Under certain conditions (*e.g.* Table 1, entries 1–4) the cyclopropane/cycloheptatriene equilibrating mixture **4a**/**4a'** is isolable, but under more acidic conditions (for example, in the presence of comparatively Lewis acidic catalysts such as $Cu(OTf)_2$ or AgOTf, see Table 1, entries 5 and 6) we propose that Lewis acid-mediated[20] ring expansion and tautomerisation (**4a** → **20** → **5a**) results in its conversion into tetralone **5a**.[16b,21] In support of this, it was observed that a purified sample of cyclopropane **4a** can be converted into tetralone **5a** smoothly upon treatment under our standard Ag(I)-mediated conditions (c.f. Table 1, entry 6).

Attention next turned to further optimising each of the three individual processes. Pleasingly, the selective formation of cyclopropane **4a** and tetralone **5a** required little additional optimisation; changes to the reaction solvents and catalyst loadings were briefly examined, and optimal conditions were uncovered that enabled each product to be isolated in 83% and 79% yield respectively, using either 2 mol% Ag_2O or 10 mol% AgOTf, both in CH_2Cl_2 at room temperature (Scheme 5). We were also able to perform a subsequent Diels–Alder reaction on cyclopropane product **4a** with dimethyl acetylenedicarboxylate **21** to generate compound **22a** in good yield. This adds support to the notion that compound **4a** is norcaradiene-like in character.

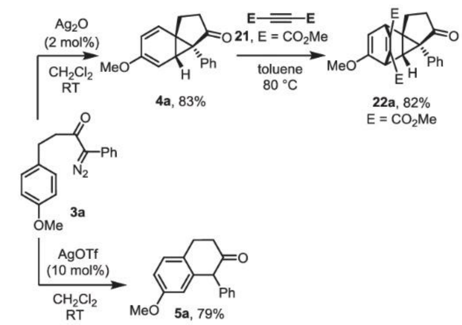
In our initial catalyst screen, the most effective catalyst for the preparation of 1,2-dicarbonyl **6a** was $Ph(PhCN)_2Cl_2$, but after further optimisation, we were unable to get full and clean conversion into this product, with unwanted side products (especially tetralone **5a**) contaminating the desired product in all cases. Of course, this reaction is a formal oxidation process, but with no obvious oxidant present in the reaction, we reasoned that adventitious impurities (in particular oxygen and water), may be required for this transformation. However, changes to the solvent and reagent quantities failed to deliver an improved procedure; the addition of 1 equivalent of water, performing the reaction open to air and purging the reaction solvent with oxygen failed to improve the yield of this oxidation process. Pleasingly however, we found that we could access this third product more reliably using conditions originally reported by Toste et al.; thus, 1,2-diketone **6a** was isolated in 90% yield following treatment with a mixed Ag(I)/Au(I) catalyst system in the presence of diphenyl sulfoxide (Scheme 6).[22]

2.2. Phenol-tethered α-diazoketones

Given that *para*-anisole derivatives have been successfully used[23] in dearomatising spirocyclisation[24] reactions to make spirocyclic dienones via other electrophilic activation modes, we were



Scheme 4. Buchner cyclisation and rearrangement.



Scheme 5. Formation of cyclopropane **4a** and tetralone **5a**.

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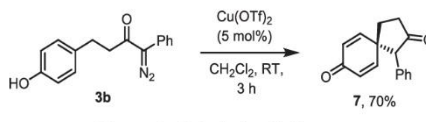
Scheme 6. Synthesis of 1,2-dicarbonyl **6a**.

somewhat surprised that none of the catalysts tested on anisole **3a** delivered spirocycle **7**. However, based on precedent for the formation of spirocyclic dienones from related phenol derivatives,[11–13,25] we were optimistic that shifting focus to the analogous phenol-tethered α-diazoketone **3b** would facilitate access to this medicinally important compound class.[26] Thus, the same metal catalysts previously used on anisole system **3a**, were tested on the new phenol substrate **3b**, with full screening results included in the Supporting Information. As we hoped, many of the catalysts screened delivered spirocycle **7** as the major product, along with 1,2-dicarbonyl **6a** and other unidentified minor impurities in some cases. The most effective catalyst at promoting spirocyclisation was $Cu(OTf)_2$; thus, the treatment of α-diazoketone **3b** with 5 mol% $Cu(OTf)_2$ for 3 h at RT in CH_2Cl_2 afforded spirocycle **7**, which was isolated in 70% yield (Scheme 7). The selective formation of this forth structural class nicely complements the anisole studies outlined above (Schemes 3–5).

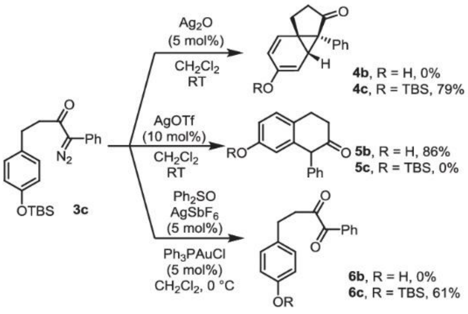
2.3. Silyl-protected α-diazoketones

As shown above, each of products **4a**–**6a** can be selectively obtained from anisole-tethered α-diazoketone **3a**, while phenol-tethered α-diazoketone **3b** delivers spirocycle **7** in good yield, but there is no crossover between the two series, meaning that the phenol analogues of anisole products **4a**–**6a**, (*i.e.* **4b**–**6b**) were inaccessible at this stage. To address this, it was decided to examine a third α-diazoketone starting material (**3c**) in which the tethered phenol is protected with a *t*-butyldimethylsilyl (TBS) group. The expectation here was that this compound **3c** would react similarly to its anisole analogue **3a** (to form TBS-protected products **4c**–**6c**), and that subsequent desilylation would enable phenol derivatives **4b**–**6b** to be isolated. Thus, TBS-protected α-diazoketone **3c** was reacted under the optimised conditions for the preparation of **4a**–**6a** (Scheme 8). First, the Ag_2O-catalysed conditions delivered the expected Buchner cyclopropane product **4c** (as before, in dynamic equilibrium with its cyclohepatriene form) in good yield. Next, the AgOTf conditions also worked well, but proceeded with concomitant desilylation, affording phenol-tetralone **5b** directly in 86% yield, with none of its TBS-protected analogue **5c** observable. Finally, the oxidative conditions proceeded as expected, to deliver 1,2-diketone **6c** in 61% yield, with the TBS group still in place.

At this point, all that remained was to test whether desilylation of products **4c** and **6c** could be achieved. Interestingly, treating cyclopropane **4c** with TBAF in THF at −78 °C, did not lead to the formation of its phenol analogue **4b**, but instead promoted desilylation and rearrangement to form spirocycle **7** in 67% yield,



Scheme 7. Synthesis of spirocyclic dienone **7**.



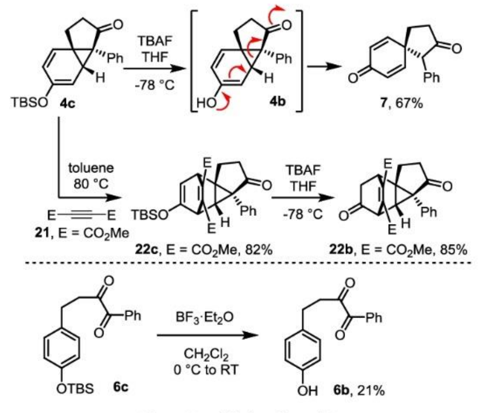
Scheme 8. Divergent reactivity of α-diazoketone **3c**.

presumably via the mechanism shown in Scheme 9. Thus, it appears that cyclopropane **4b** is unstable with respect to collapse to spirocycle **7**, which certainly helps to explain why we were unable to isolate any products other than **7** from the phenol-tethered α-diazoketone starting material **3b**. Compound **4c** is a good Diels–Alder substrate, reacting with dimethyl acetylenedicarboxylate **21** to form **22c** in high yield, and subsequent TBS-cleavage with TBAF afforded its ketone derivative **22b** in 85% yield.

The desilylation of **6c** was more challenging; a variety of deprotection conditions were tested on this substrate (TBAF at −78 °C and at RT, TFA, $TiCl_4$) but decomposition of starting material **6c** into a mixture of uncharacterisable products was commonly observed. The best conditions we uncovered involved reacting **6c** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at RT; deprotected diketone **6b** was successfully formed using this method, although several impurities were still obtained during this reaction, hence the isolated yield (21%) is relatively low.

3. Conclusion

In conclusion, the first study of the divergent reactivity of phenol/anisole-tethered donor-acceptor α-diazoketones has been



Scheme 9. Desilylation of **4c** and **6c**.

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performed. In total, four distinct products classes have been shown to be accessible, with the reaction outcome dependent on the nature of the aromatic oxygen substituent and the catalyst used to activate the diazo group. Anisole and TBS derivatives **3a** and **3c** were both able to selectively produce three products types (cyclopropanes, tetralones and 1,2-dicarbonyls **4**–**6**) while phenol derivative **3b** produced only spirocycle **7**, with this difference believed to be a consequence of the instability of the phenol Buchner cyclisation product **4b**. These results are likely to be useful from a synthetic standpoint, especially in diversity-oriented synthesis. Furthermore, the insight gleaned from studying a class of phenol/anisole-tethered α-diazoketones that has previously not been examined is expected to be of value to those interested in the study of diazo compounds and metal carbenoids, complementing the important studies of related systems summarised in the introduction.[11–17]

4. Experimental

4.1. General aspects

Except where stated, all reagents were purchased from commercial sources and used without further purification and all experimental procedures were carried out under an atmosphere of argon unless stated otherwise. Anhydrous CH_2Cl_2, toluene, MeCN and DMF were obtained from an Innovative Technology Inc. Pure-Solv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.27 and δ_C 77.0 for $CDCl_3$ and δ_H 3.31 and δ_c 49.1 for CD_3OD were used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. 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 (high-resolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) or Liquid Injection Field Desorption Ionisation (LIFDI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 µm, 60 Å, under a slight positive pressure, eluting with the specified solvent system.

4.2. General procedure A: preparation of Weinreb amides

To a stirred solution of acid (1.00 mmol), MeNH(OMe)·HCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH_2Cl_2 (2.5 mL) was added T3P 50% in EtOAc (955 mg, 1.50 mmol). The solution was stirred at RT until completion was observed by TLC. The reaction mixture was poured into water (20 mL) and acidified using 10% aq. HCl (5 mL). The organics were collected and the aqueous extracted with EtOAc (3 × 30 mL). The organics were combined, washed with aq. 2 M NaOH (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the Weinreb amide product.

4.3. Experimental procedures

4.3.1. N-methoxy-3-(4-methoxyphenyl)-N-methylpropanamide

Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid (7.00 g, 38.8 mmol), T3P 50% in EtOAc (37.0 g, 58.3 mmol), DIPEA (20.3 mL, 116 mmol) and MeNH(OMe)·HCl (4.20 g, 42.7 mmol) in CH_2Cl_2 (100 mL) at RT for 1 h. Afforded the title compound without further purification as a yellow oil (8.70 g, 100%); R_f 0.46 (1:1 hexane:EtOAc); δ_H (400 MHz, $CDCl_3$) 2.71 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 3.18 (3H, s), 3.61 (3H, s), 6.84 (2H, d, J = 8.0), 7.15 (2H, d, J = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 29.8, 32.1, 34.0, 55.2, 61.2, 113.8, 129.3, 133.4, 157.9, 173.7; HRMS (ESI$^+$): Found: 246.1097; $C_{12}H_{17}NNaO_3$ (MNa^+) Requires 246.1101, Found: 224.1277; $C_{12}H_{18}NO_3$ (MH^+) Requires 224.1281. Spectroscopic data matched those previously reported in the literature.[27]

4.3.2. 4-(4-Methoxyphenyl)-1-phenylbutan-2-one

To a solution of N-methoxy-3-(4-methoxyphenyl)-N-methylpropanamide (2.00 g, 8.96 mmol) in THF (90 mL) at 0 °C under argon was added benzylmagnesium chloride (13.4 mL, 26.9 mmol, 2.0 M in THF) dropwise using a syringe pump. The resulting solution was warmed to RT and stirred for 1.5 h. The reaction was then cooled to 0 °C, quenched with sat. aq. NH_4Cl (20 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) to afford the title compound as a clear and colourless oil (1.76 g, 77%); R_f 0.70 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2908, 1712, 1512, 1245, 1178, 1033, 830, 735, 699; δ_H (400 MHz, $CDCl_3$) 2.72–2.78 (2H, m), 2.79–2.86 (2H, m), 3.67 (2H, s), 3.79 (3H, s), 6.81 (2H, d, J = 8.0 Hz), 7.06 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 7.0 Hz), 7.25–7.36 (3H, m); δ_C (100 MHz, $CDCl_3$) 28.9, 43.7, 50.4, 55.2, 113.8, 127.0, 128.7, 129.2, 129.4, 132.9, 134.1, 157.9, 207.6; HRMS (ESI$^+$): Found: 277.1189; $C_{17}H_{18}NaO_2$ (MNa^+) Requires 277.1199.

4.3.3. 1-Diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one (3a)

To a solution of 4-(4-methoxyphenyl)-1-phenylbutan-2-one (977 mg, 3.84 mmol) and p-ABSA (1.11 g, 4.61 mmol) in MeCN (11.5 mL) at RT under argon was added DBU (0.8 mL, 5.38 mmol) dropwise. The resulting solution was stirred for 50 min before being concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 7:3 hexane:EtOAc with 3% Et_3N as a basic additive) to afford the title compound **3a** as a yellow solid (797 mg, 74%); mp 79–81 °C; R_f 0.73 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3009, 2951, 2836, 2074, 1631, 1611, 1511, 1497, 1362, 1246, 1176, 1034, 821, 753; δ_H (400 MHz, $CDCl_3$) 2.87 (2H, t, J = 7.5 Hz), 2.99 (2H, t, J = 7.5 Hz), 3.97 (3H, s), 6.84 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 7.41 (2H, dd, J = 8.0, 7.5 Hz), 7.47 (2H, d, J = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 29.8, 41.1, 55.2, 72.3, 113.9, 125.4, 126.1, 127.0, 129.0, 129.4, 132.7, 158.1, 192.0; HRMS (LIFDI$^+$): Found: 280.1211; $C_{17}H_{16}N_2O_2$ (M^+) Requires 280.1212.

4.3.4. 5-Methoxy-3a-phenyl-3a,3b-dihydro-1H-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one (4a)

A flame-dried round-bottomed flask was charged with 1-diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one **3a** (100 mg, 0.357 mmol) and Ag_2O (1.7 mg, 7.13 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.6 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 22.5 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1

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hexane:EtOAc) to afford the title compound **4a** as a pale yellow oil (74.5 mg, 83%); R_f 0.33 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3028, 2934, 2829, 1745, 1715, 1647, 1489, 1446, 1416, 1219, 1167, 1109, 1020, 816, 756; δ_H (400 MHz, $CDCl_3$) 2.33–2.45 (1H, m), 2.55–2.67 (1H, m), 2.72–2.82 (1H, m), 2.83–2.95 (1H, m), 3.41 (3H, s), 5.07 (1H, br d, J = 8.5 Hz), 5.60 (1H, d, J = 8.0 Hz), 5.87 (1H, d, J = 8.5 Hz), 6.38 (1H, d, J = 8.0 Hz), 7.14–7.24 (5H, m); δ_C (100 MHz, $CDCl_3$) 27.4, 34.8, 54.6, 109.1, 115.5, 123.3, 126.9, 127.7, 128.5, 136.6, 157.2, 215.7; HRMS (ESI$^+$): Found: 275.1040; $C_{17}H_{16}NaO_2$ (MNa$^+$) Requires 275.1043, Found: 253.1222; $C_{17}H_{17}O_2$ (MH$^+$) Requires 253.1223. Note: 1 ^{13}C NMR signal was not observed, presumably due to peak broadening arising from the Buchner rearrangement.

*4.3.5. (3bR,4R,7R,7aR)-dimethyl 8-methoxy-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1H-4,7-ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (**22a**)*

A round-bottomed flask was charged with cyclopropane **4a** (65 mg, 0.258 mmol) in toluene (0.5 mL) under argon. dimethyl acetylenedicarboxylate **21** (63 µL, 0.515 mmol) was added and the reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was then cooled to RT and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the title compound **22a** as a clear and colourless oil (83.4 mg, 82%); R_f 0.21 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2952, 1713, 1653, 1626, 1435, 1265, 1211, 1111, 1058, 1007, 915, 728; δ_H (400 MHz, $CDCl_3$) 1.83 (1H, d, J = 4.0 Hz), 2.17–2.31 (2H, m), 2.36–2.49 (5H, m), 3.80 (3H, s), 3.85 (3H, s), 4.09–4.13 (2H, m), 4.33 (1H, dd, J = 7.0, 3.0 Hz), 6.89–6.93 (1H, m), 7.12 (1H, d, J = 7.5 Hz), 7.15–7.23 (2H, m), 7.29–7.34 (1H, m); δ_C (100 MHz, $CDCl_3$) 27.1, 33.6, 35.4, 44.0, 44.7, 52.3, 52.4, 52.8, 54.6, 60.2, 99.1, 126.5, 127.3, 128.1, 130.1, 130.5, 133.7, 144.0, 152.9, 160.6, 165.0, 167.2, 211.8; HRMS (ESI$^+$): Found: 417.1316; $C_{23}H_{22}NaO_6$ (MNa$^+$) Requires 417.1309, Found: 395.1485; $C_{23}H_{23}O_6$ (MH$^+$) Requires 395.1489.

*4.3.6. 7-Methoxy-1-phenyl-3,4-dihydronaphthalen-2(1H)-one (**5a**)*

A flame-dried round-bottomed flask was charged with 1-diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one **3a** (100 mg, 0.357 mmol) and AgOTf (9.2 mg, 35.7 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.6 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the title compound **5a** as a yellow oil (71.1 mg, 79%); R_f 0.38 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2940, 2844, 1714, 1611, 1502, 1450, 1260, 1156, 1037, 729; δ_H (400 MHz, $CDCl_3$) 2.52–2.61 (1H, m), 2.72 (1H, ddd, J = 17.0, 6.5, 6.0 Hz), 2.93–3.11 (2H, m), 3.75 (3H, s), 4.72 (1H, s), 6.56 (1H, d, J = 2.5 Hz), 6.84 (1H, dd, J = 8.0, 2.5 Hz), 7.12 (2H, d, J = 7.5 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.24–7.34 (3H, m); δ_C (100 MHz, $CDCl_3$) 27.2, 37.2, 55.2, 59.9, 113.0, 114.6, 127.2, 128.56, 128.64, 128.8, 129.0, 137.3, 137.6, 158.7, 209.6; HRMS (ESI$^+$): Found: 275.1044; $C_{17}H_{16}NaO_2$ (MNa$^+$) Requires 275.1043, Found: 253.1232; $C_{17}H_{17}O_2$ (MH$^+$) Requires 253.1223.

*4.3.7. 4-(4-Methoxyphenyl)-1-phenylbutane-1,2-dione (**6a**)*

To a solution of 1-diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one **3a** (30.0 mg, 0.107 mmol) in CH_2Cl_2 (0.5 mL) was added diphenyl sulfoxide (86.6 mg, 0.428 mmol). This solution was then added to a premixed solution of Ph_3PAuCl (2.65 mg, 5.35 µmol) and $AgSbF_6$ (1.84 mg, 5.35 µmol) in CH_2Cl_2 (0.5 mL) cooled to 0 °C, the vial containing diazo solution was also rinsed with CH_2Cl_2 (0.2 mL). The reaction mixture was stirred at 0 °C for 2 h. The crude mixture was concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the title compound **6a** as a yellow oil (25.9 mg, 90%); R_f 0.32 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2934, 2836, 1711, 1670, 1596, 1449, 1245, 1177, 1033, 825, 689; δ_H (400 MHz, $CDCl_3$) 3.00 (2H, t, J = 7.5 Hz), 3.21 (2H, t, J = 7.5 Hz), 3.79 (3H, s), 6.83 (2H, d, J = 8.5 Hz), 7.15 (2 H, d, J = 8.5 Hz), 7.48 (2 H, dd, J = 7.5, 7.5 Hz), 7.64 (1 H, t, J = 7.5 Hz), 7.91 (2 H, d, J = 7.5 Hz); δ_C (100 MHz, $CDCl_3$) 28.0, 40.4, 55.2, 113.9, 128.7, 129.4, 130.2, 131.8, 132.1, 134.6, 158.1, 192.1, 202.4; HRMS (ESI$^+$): Found: 291.0990; $C_{17}H_{16}NaO_3$ (MNa$^+$) Requires 291.0992.

4.3.8. 3-(4-Hydroxyphenyl)-N-methoxy-N-methylpropanamide

Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid (7.00 g, 42.1 mmol), T3P 50% in EtOAc (40.2 g, 63.2 mmol), DIPEA (22.0 mL, 126 mmol) and MeNH(OMe)·HCl (4.50 g, 46.3 mmol) in CH_2Cl_2 (105 mL) at RT for 1 h. Afforded the title compound without further purification as a yellow oil (7.61 g, 86%); R_f 0.21 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3263, 2938, 1632, 1614, 1593, 1515, 1446, 1388, 1266, 1228, 1172, 987; δ_H (400 MHz, $CDCl_3$) 2.72 (2H, t, J = 7.5 Hz), 2.90 (2H, t, J = 7.5 Hz), 3.19 (3H, s), 3.61 (3H, s), 5.85 (1H, br s), 6.77 (2H, d, J = 8.0), 7.08 (2H, d, J = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 29.8, 32.2, 34.0, 61.2, 115.3, 129.5, 133.0, 154.3, 173.9; HRMS (ESI$^+$): Found: 232.09591; $C_{11}H_{15}NNaO_3$ (MNa$^+$) Requires 232.0944, Found: 210.1127; $C_{11}H_{16}NO_3$ (MH$^+$) Requires 210.1125.

4.3.9. 4-(4-Hydroxyphenyl)-1-phenylbutan-2-one

To a solution of 3-(4-hydroxyphenyl)-N-methoxy-N-methylpropanamide (1.53 g, 7.31 mmol) in THF (70 mL) at 0 °C under argon was added benzylmagnesium chloride (14.6 mL, 29.2 mmol, 2.0 M in THF) dropwise using a syringe pump. The resulting solution was warmed to RT and stirred for 2 h. The reaction was then cooled to 0 °C, quenched with sat. aq. NH_4Cl (20 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 30 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$ 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 as a white solid (1.51 g, 86%); mp 112–114 °C; R_f 0.46 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3387, 3027, 2929, 1707, 1614, 1515, 1451, 1362, 1221, 833, 741, 699; δ_H (400 MHz, CD_3OD) 2.68–2.81 (4H, m), 3.68 (2H, s), 6.66 (2H, d, J = 8.0 Hz), 6.93 (2H, d, J = 8.0 Hz), 7.11–7.17 (2H, m), 7.19–7.33 (3H, m); δ_C (100 MHz, CD_3OD) 30.2, 44.9, 51.0, 116.3, 128.0, 129.7, 130.4, 130.7, 133.2, 136.0, 156.8, 210.7; HRMS (ESI$^+$): Found: 263.1034; $C_{16}H_{16}NaO_2$ (MNa$^+$) Requires 263.1043.

4.3.10. 4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-1-phenylbutan-2-one

To a solution of 4-(4-hydroxyphenyl)-1-phenylbutan-2-one (1.39 g, 5.77 mmol) in anhyrous DMF (11.5 mL) was added imidazole (590 mg, 8.66 mmol) at 0 °C. TBSCl (1.30 g, 8.66 mmol) was then added at 0 °C and then the reaction was warmed to RT and stirred for 2 h. The reaction mixture was then diluted with Et_2O (20 mL) and the organic layer was washed with water (3 × 30 mL). The organic layer was then washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc) afforded the title compound as a white solid (1.53 g, 75%); mp 64–66 °C; R_f 0.51 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2931, 2859, 1708, 1510, 1255, 910, 839, 779, 732; δ_H (400 MHz, $CDCl_3$) 0.19 (6H, s), 0.99 (9H, s), 2.71–2.77 (2H, m), 2.78–2.84 (2H, m), 3.66 (2H, s), 6.74 (2H, d, J = 8.0 Hz), 6.99 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 7.5 Hz), 7.24–7.36 (3H, m); δ_C (100 MHz, $CDCl_3$) −4.5, 18.2, 25.7, 29.0, 43.7, 50.4, 120.0, 127.0, 128.7, 129.2, 129.4, 133.5, 134.1, 153.9, 207.7; HRMS (ESI$^+$): Found: 377.1905; $C_{22}H_{30}NaO_2Si$ (MNa$^+$) Requires 377.1907, Found:

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355.2084; $C_{22}H_{31}O_2Si$ (MH^+) Requires 355.2088.

*4.3.11. 4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one (**3c**)*

To a solution of 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-phenylbutan-2-one (150 mg, 0.423 mmol) and p-ABSA (122 mg, 0.508 mmol) in MeCN (1.5 mL) at RT under argon was added DBU (88.5 µL, 0.592 mmol) dropwise. The resulting solution was stirred for 1 h before being concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc with 3% Et_3N as a basic additive) to afford the title compound **3c** as an orange oil (109 mg, 68%); R_f 0.49 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2929, 2857, 2067, 1648, 1509, 1497, 1252, 1204, 912, 838, 780, 1176, 1034, 821, 753; δ_H (400 MHz, $CDCl_3$) 0.19 (6H, s), 0.98 (9H, s), 2.86 (2H, t, *J* = 7.5 Hz), 2.97 (2H, t, *J* = 7.5 Hz), 6.76 (2H, d, *J* = 8.0 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 7.24–7.29 (1H, m), 7.41 (2H, dd, *J* = 8.0, 7.5 Hz), 7.46 (2H, d, *J* = 8.0 Hz); δ_C (100 MHz, $CDCl_3$) −4.5, 18.2, 25.7, 30.1, 41.0, 72.4, 120.1, 124.1, 126.1, 127.1, 129.0, 129.3, 133.2, 154.1, 192.1; HRMS (ESI$^+$): Found: 403.1816; $C_{22}H_{28}N_2NaO_2Si$ (MNa^+) Requires 403.1812.

*4.3.12. 1-Diazo-4-(4-hydroxyphenyl)-1-phenylbutan-2-one (**3b**)*

To a solution of 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one **3c** (785 mg, 2.06 mmol) in THF (4 mL) at 0 °C was added TBAF (3.09 mL, 3.09 mmol, 1 M solution in THF). The resulting solution was warmed to RT and stirred for 30 min. The reaction mixture was then diluted with Et_2O (10 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford the title compound **3b** without further purification as a yellow solid (509 mg, 93%); mp 77–79 °C; R_f 0.63 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3361, 2077, 1612, 1515, 1497, 1448, 1370, 1205, 830, 756; δ_H (400 MHz, $CDCl_3$) 2.86 (2H, t, *J* = 7.5 Hz), 2.97 (2H, t, *J* = 7.5 Hz), 4.70 (1H, br s), 6.76 (2H, d, *J* = 8.5 Hz), 7.08 (2H, d, *J* = 8.5 Hz), 7.24–7.29 (1H, m), 7.41 (2H, dd, *J* = 8.0, 7.5 Hz), 7.47 (2H, d, *J* = 7.5 Hz); δ_C (100 MHz, $CDCl_3$) 30.0, 41.1, 72.6, 115.4, 125.4, 126.2, 127.2, 129.0, 129.5, 132.5, 154.2, 192.4; HRMS (ESI$^+$): Found: 289.0951; $C_{16}H_{14}N_2NaO_2$ (MNa^+) Requires 289.0947.

*4.3.13. 1-Phenylspiro[4.5]deca-6,9-diene-2,8-dione (**7**)*

Method 1: A flame-dried round-bottomed flask was charged with 1-diazo-4-(4-hydroxyphenyl)-1-phenylbutan-2-one **3b** (38 mg, 0.143 mmol) and $Cu(OTf)_2$ (2.6 mg, 7.14 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (1.4 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 3 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the title compound **7** as a yellow solid (23.4 mg, 70%); mp 135–137 °C; R_f 0.21 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3035, 1746, 1663, 1622, 1499, 1135, 868, 700; δ_H (400 MHz, $CDCl_3$) 2.17 (1H, ddd, *J* = 13.5, 8.5, 2.5 Hz), 2.32–2.42 (1H, m), 2.64–2.84 (2H, m), 3.75 (1H, s), 6.14 (1H, dd, *J* = 10.0, 2.0 Hz), 6.32 (1H, dd, *J* = 10.0, 2.0 Hz), 6.86 (1H, dd, *J* = 10.0, 3.0 Hz), 6.93–6.97 (2H, m), 7.00 (1H, dd, *J* = 10.0, 3.0 Hz), 7.21–7.29 (3H, m); δ_C (100 MHz, $CDCl_3$) 31.4, 35.3, 51.4, 65.5, 127.9, 128.3, 129.4, 130.1, 130.5, 132.5, 147.5, 152.4, 185.3, 213.1; HRMS (ESI$^+$): Found: 261.0875; $C_{16}H_{14}NaO_2$ (MNa^+) Requires 261.0886, Found: 239.1057; $C_{16}H_{15}O_2$ (MH^+) Requires 239.1067.

Method 2: To a solution of 5-((*tert*-butyldimethylsilyl)oxy)-3a-phenyl-3a,3b-dihydro-1H-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one **4c** (36.8 mg, 0.104 mmol) in THF (0.6 mL) at −78 °C was added TBAF (0.16 mL, 0.156 mmol, 1 M solution in THF) dropwise to afford an orange solution. The resulting solution was stirred at −78 °C for 3 h. The reaction mixture was then quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the title compound **7** as a yellow solid (16.6 mg, 67%).

*4.3.14. 5-((tert-Butyldimethylsilyl)oxy)-3a-phenyl-3a,3b-dihydro-1H-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one (**4c**)*

A flame-dried round-bottomed flask was charged with 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one **3c** (150 mg, 0.394 mmol) and Ag_2O (4.57 mg, 19.7 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.9 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (10:1 hexane:EtOAc) to afford the title compound **4c** as a yellow oil (110 mg, 79%); R_f 0.42 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2929, 2857, 1747, 1622, 1407, 1252, 1202, 1183, 1110, 900, 873, 837, 781, 749; δ_H (400 MHz, $CDCl_3$) −0.36 (3H, s), −0.27 (3H, s), 0.77 (9H, s), 2.38 (1H, ddd, *J* = 18.0, 9.0, 6.5 Hz), 2.64 (1H, ddd, *J* = 18.0, 11.0, 7.0 Hz), 2.80–3.03 (2H, m), 5.41 (1H, d, *J* = 9.5 Hz), 5.76 (1H, d, *J* = 7.5 Hz), 5.98 (1H, d, *J* = 9.5 Hz), 6.41 (1H, d, *J* = 7.5 Hz), 7.11–7.21 (3H, m), 7.21–7.26 (2H, m); δ_C (100 MHz, $CDCl_3$) −5.4, −5.1, 17.8, 25.4, 27.3, 35.3, 56.9, 114.0, 116.1, 122.4, 123.8, 127.1, 127.74, 127.79, 137.4, 153.2, 216.0; HRMS (ESI$^+$): Found: 353.1939; $C_{22}H_{29}O_2Si$ (MH^+) Requires 353.1931. Note: 1 ^{13}C NMR signal was not observed, presumably due to peak broadening arising from the Buchner rearrangement.

*4.3.15. 7-Hydroxy-1-phenyl-3,4-dihydronaphthalen-2(1H)-one (**5b**)*

A flame-dried round-bottomed flask was charged with 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one **3c** (150 mg, 0.394 mmol) and AgOTf (10.1 mg, 39.4 µmol) and purged with argon for 10 min. Anhydrous CH_2Cl_2 (3.9 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the title compound **5b** as an orange oil (80.9 mg, 86%); R_f 0.38 (7:3 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3372, 3027, 1704, 1612, 1587, 1493, 1450, 1342, 1297, 1232, 1153, 821; δ_H (400 MHz, $CDCl_3$) 2.57 (1H, ddd, *J* = 17.0, 6.5, 6.5 Hz), 2.70 (1H, ddd, *J* = 17.0, 6.5, 6.5 Hz), 2.91–3.09 (2H, m), 4.66 (1H, s), 5.63 (1H, br s), 6.46 (1H, d, *J* = 2.5 Hz), 6.76 (1H, dd, *J* = 8.0, 2.5 Hz), 7.10 (2H, d, *J* = 7.0 Hz), 7.14 (1H, d, *J* = 8.0 Hz), 7.25–7.33 (3H, m); δ_C (100 MHz, $CDCl_3$) 27.3, 37.3, 59.7, 114.5, 116.0, 127.3, 128.69, 128.71, 128.8, 129.1, 137.2, 137.7, 154.9, 210.5; HRMS (ESI$^+$): Found: 261.0885; $C_{16}H_{14}NaO_2$ (MNa^+) Requires 261.0886.

*4.3.16. 4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-1-phenylbutane-1,2-dione (**6c**)*

A heterogeneous solution of Ph_3PAuCl (32.5 mg, 65.7 µmol) and $AgSbF_6$ (22.5 mg, 65.7 µmol) in CH_2Cl_2 (6 mL) was stirred for 5 min under air and cooled to 0 °C. A solution of 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one **3c** (500 mg, 1.31 mmol) and diphenyl sulfoxide (1.06 g, 5.24 mol) in CH_2Cl_2 (6 mL) was then added to the catalyst mixture at 0 °C and the reaction mixture was stirred under air for 1.5 h. The reaction mixture was then concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (20:1 hexane:EtOAc) to afford the title compound **6c** as a yellow oil (294 mg, 61%); R_f 0.70 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2955, 2930, 2858, 1713, 1672, 1509, 1253, 912, 838, 781; δ_H

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(400 MHz, $CDCl_3$) 0.18 (6H, s), 0.98 (9H, s), 2.98 (2H, t, J = 7.5 Hz), 3.21 (2H, t, J = 7.5 Hz), 6.76 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.48 (2H, dd, J = 7.5, 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.5 Hz); δ_C (100 MHz, $CDCl_3$) −4.5, 18.2, 25.7, 28.1, 40.4, 120.1, 128.8, 129.3, 130.2, 131.8, 132.7, 134.6, 154.1, 192.1, 202.5; HRMS (ESI^+): Found: 391.1705; $C_{22}H_{28}NaO_3Si$ (MNa^+) Requires 391.1700.

*4.3.17. (3bR,4S,7R,7aR)-dimethyl 9-((tert-butyldimethylsilyl)oxy)-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1H-4,7-ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (**22c**)*

A round-bottomed flask was charged with cyclopropane **4c** (191 mg, 0.541 mmol) in toluene (1.1 mL) under argon and dimethyl acetylenedicarboxylate **21** (0.13 mL, 1.08 mmol) was added and the reaction mixture stirred at 80 °C for 30 h. The reaction mixture was then cooled to RT and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (20:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the title compound **22c** as a clear and colourless oil (220 mg, 82%); R_f 0.58 (6:4 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2953, 2858, 1714, 1651, 1625, 1435, 1342, 1303, 1256, 1225, 1204, 1110, 1061, 913, 864, 839, 785; δ_H (400 MHz, $CDCl_3$) −0.32 (3H, s), −0.19 (3H, s), 0.75 (9H, s), 1.80 (1H, d, J = 4.0 Hz), 2.13–2.33 (2H, m), 2.34–2.49 (2H, m), 3.81 (3H, s), 3.83 (3H, s), 3.91–3.95 (1H, m), 4.07 (1H, d, J = 6.5 Hz), 4.49 (1H, dd, J = 6.5, 3.0 Hz), 6.82 (1H, d, J = 7.5 Hz), 7.11–7.22 (3H, m), 7.24–7.29 (1H, m); δ_C (100 MHz, $CDCl_3$) −5.4, −4.7, 17.9, 25.4, 27.2, 34.0, 35.4, 44.7, 47.0, 52.3, 52.4, 52.9, 60.4, 106.9, 126.5, 127.5, 128.2, 130.0, 130.6, 133.8, 146.1, 151.0, 156.7, 165.7, 166.8, 212.2; HRMS (ESI^+): Found: 517.2017; $C_{28}H_{34}NaO_6Si$ (MNa^+) Requires 517.2017, Found: 495.2195; $C_{28}H_{35}O_6Si$ (MH^+) Requires 495.2197.

*4.3.18. (3bR,4S,7R,7aR)-dimethyl 9-hydroxy-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1H-4,7-ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (**22b**)*

A round-bottomed flask was charged with Diels–Alder adduct **22c** (35 mg, 0.0708 mmol) in THF (0.5 mL) at −78 °C and TBAF (0.11 mL, 0.106 mmol, 1 M solution in THF) was added dropwise leading to the formation of a pale yellow milky solution. The reaction mixture was then stirred at −78 °C for 3 h. The reaction mixture was then quenched by the addition of water (2 mL) at −78 °C and extracted with EtOAc (3 × 5 mL). The organics were combined, dried over $MgSO_4$ and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the title compound **22b** as a clear and colourless oil (23 mg, 85%); R_f 0.66 (1:1 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 2953, 1718, 1626, 1435, 1333, 1270, 1218, 1115, 1064, 729, 718; δ_H (400 MHz, $CDCl_3$) 1.82 (1H, dd, J = 19.0, 3.0 Hz), 2.06–2.14 (2H, m), 2.24–2.36 (2H, m), 2.36–2.49 (2H, m), 3.72–3.75 (1H, m), 3.82 (3H, s), 3.87 (3H, s), 4.16 (1H, d, J = 4.0 Hz), 7.09 (1H, dd, J = 6.0, 2.0 Hz), 7.22–7.37 (4H, m); δ_C (100 MHz, $CDCl_3$) 27.5, 33.1, 34.1, 37.2, 41.0, 47.6, 51.8, 52.7, 52.8, 57.7, 128.3, 128.7, 128.8, 131.2, 131.3, 132.5, 136.9, 150.5, 164.0, 166.4, 204.8, 211.1; HRMS (ESI^+): Found: 403.1158; $C_{22}H_{20}NaO_6$ (MNa^+) Requires 403.1152, Found: 381.1335; $C_{22}H_{21}O_6$ (MH^+) Requires 381.1333.

*4.3.19. 4-(4-Hydroxyphenyl)-1-phenylbutane-1,2-dione (**6b**)*

A flame-dried round-bottomed flask was charged with 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-phenylbutane-1,2-dione **6c** (118 mg, 0.320 mmol) in anhydrous CH_2Cl_2 (3.2 mL) under argon. The solution was cooled to 0 °C and $BF_3 \cdot Et_2O$ (0.4 mL, 3.20 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 1 h before warming to RT and stirring for another 4.5 h. The reaction mixture was then quenched by the addition of water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography (8:2 hexane:EtOAc) to afford the title compound **6b** as a yellow oil (17.1 mg, 21%); R_f 0.27 (8:2 hexane:EtOAc); ν_{max} (thin film)/cm^{-1} 3416, 3027, 2932, 1712, 1669, 1596, 1515, 1449, 1254; δ_H (400 MHz, $CDCl_3$) 2.98 (2H, t, J = 7.5 Hz), 3.20 (2H, t, J = 7.5 Hz), 4.90 (1H, br s), 6.76 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 7.48 (2H, dd, J = 8.0, 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.5 Hz); δ_C (100 MHz, $CDCl_3$) 28.0, 40.4, 115.3, 128.8, 129.6, 130.2, 131.8, 132.3, 134.6, 154.0, 192.1, 202.5; HRMS (ESI^+): Found: 277.0837; $C_{16}H_{14}NaO_3$ (MNa^+) Requires 277.0835.

Dedication

In recognition of the many contributions of Sir Derek Barton, not least his memorable lectures on 'The Invention of Chemical Reactions'.

Acknowledgements

The authors would like to thank the University of York (A.K.C., W.P.U.) and the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-013, W.P.U.) for financial support. Dr Michael J. James is thanked for useful advice.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.02.003.

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Synthetic Methods

Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones

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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.

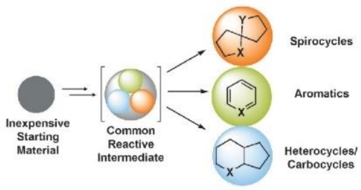
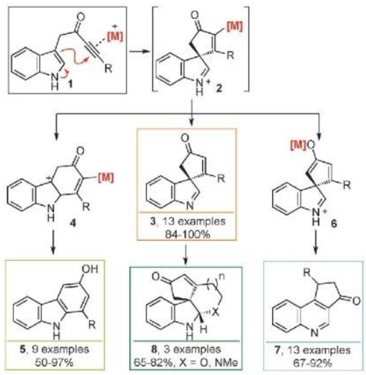


Figure 1. Catalyst-driven scaffold diversity.

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 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



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

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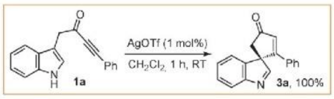
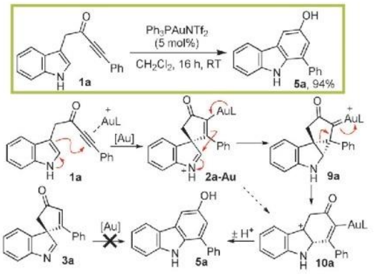
a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetracyclic scaffolds **8** can be formed with complete diastereoselectivity, by a telescoped spirocyclisation/nucleophilic addition sequence, which was performed using a chiral Ag^{I} salt to furnish an enantiopure product.

The spirocyclisation of **1a** using AgOTf formed indolenine **3a** in quantitative yield (Scheme 2);[5] the mild reaction condi-



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

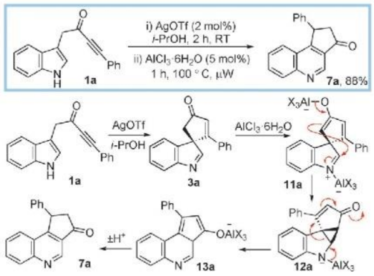
tions are believed to play a key role in this process, stabilising the spirocycle with respect to further reactions. However, in the proposed scaffold diversity approach, in which the synthesis of carbazole **5a** was an initial goal, the challenge was to deliberately promote 1,2-migration[7] in a controlled 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 en-



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

largement 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.

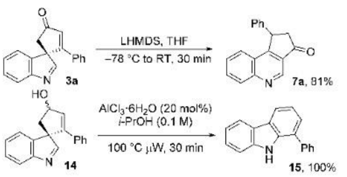
We next examined whether we could initiate an alternative rearrangement commencing from ynone **1a**, by seeking to promote cyclopropanation of an enolate from the less substituted branch of the cyclopentenone; more oxophilic catalysts were chosen for this task, as it was thought that they would better 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 $AlCl_3·6H_2O$ and subsequent heating in a microwave gave quinoline **7a** in high yield (Scheme 4).[10] Following Ag^{I}-



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

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).

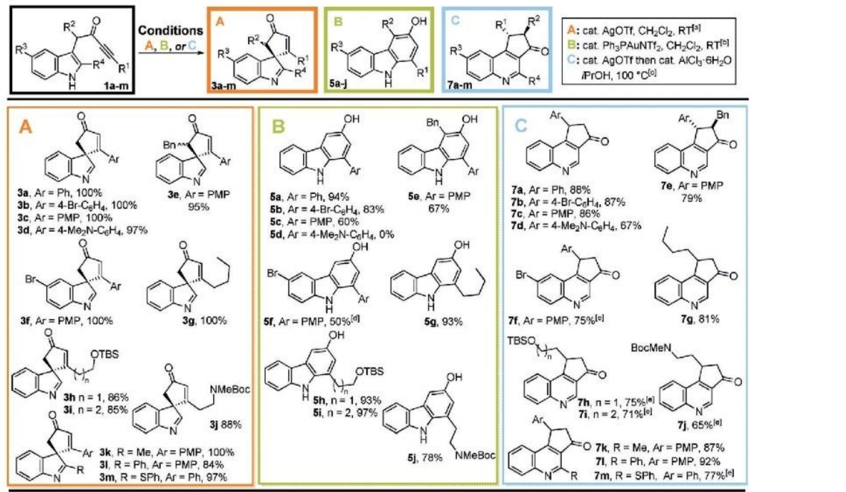
Supporting evidence for this unprecedented rearrangement was obtained: treatment of spirocycle **3a** with LHMDS in THF (i.e. conditions which almost certainly would result in enolate formation) also led to the formation of quinoline **7a**, in 81% yield. Furthermore, the importance of the carbonyl group was shown by the fact that treatment of known cyclopentenol **14**[11] with $AlCl_3·6H_2O$ 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

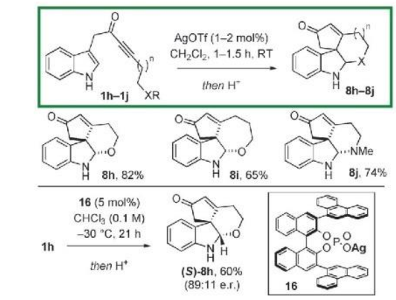
Table 1. Reaction scope for the formation of spirocyclic indolenines, carbazoles and quinolones.



[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 scaffold 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

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Keywords: carbazoles · catalysis · diversity · quinolines · spirocycles

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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 V. Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives

Organic LETTERS

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Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives

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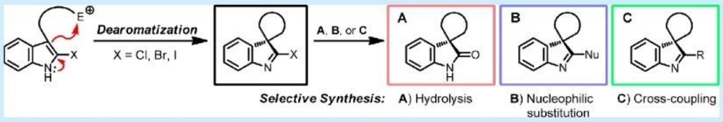
Supporting Information



ABSTRACT: The dearomatization of 2-haloindole precursors allows access to indoleninyl halides, a hitherto underexploited functional handle with broad synthetic utility. Indoleninyl iodides have been shown to react via three distinct modes: hydrolysis, nucleophilic substitution, and cross-coupling. This allows a broad array of functionalized spirocyclic indole derivatives to be generated from a common starting material. They are also useful precursors to functionalized quinolines following migratory rearrangement and subsequent derivatization reactions.

Structural motifs that pair high stability with versatile reactivity are of great value in organic synthesis. Moreover, such motifs are particularly useful if they are easy to prepare and can be incorporated into biologically significant frameworks, rendering them important in pharmaceutical and agrochemical research programs. Herein we detail the synthesis and subsequent reactions of indoleninyl halides **2**, a vastly underexploited functional handle for the synthesis of a broad array of spirocyclic indole derivatives. Simple dearomative methods[1] for their generation (**1** → **2**) and a series of procedures for their subsequent reaction (via three distinct reaction modes, **1** → **3**, **4**, or **5**) are outlined (Figure 1). In view of their ease of formation, high stability, and diverse reactivity, indoleninyl halides are expected to be of broad utility in synthesis.

Indoleninyl halides are surprisingly rare in the chemical literature, with very little reported about their stability and reactivity.[2] Initially, we postulated that indoleninyl halides **2** would behave similarly to acid chlorides and react readily with nucleophiles. This notion is supported by literature precedent; indoleninyl chlorides and bromides have each been proposed as short-lived[3] or putative intermediates[4] in previous synthetic protocols and were found to hydrolyze readily in situ, generating oxindoles.[5] It was this precedent that prompted us to initiate the research program described herein, in which it was planned to react readily available 2-haloindole precursors of the form **6** with π-acidic catalysts in the expectation of promoting dearomatizing spirocyclization[6,7] and in situ hydrolysis to generate spirocyclic oxindoles (e.g., **6** → **7** → **8**; Scheme 1). However, when ynone **6a** (R = Ph) was reacted with 10 mol % $Cu(OTf)_2$ in DCM at rt, the only product isolated after workup and column chromatography was spirocyclic indolenine **7a** in quantitative yield. None of the expected oxindole **8** was isolated, and spirocycle **7a** proved to be surprisingly stable; it appears to be insensitive to air and

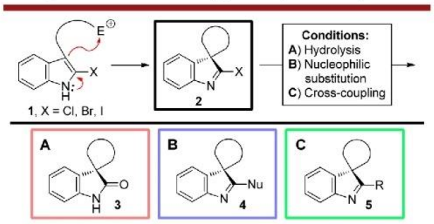
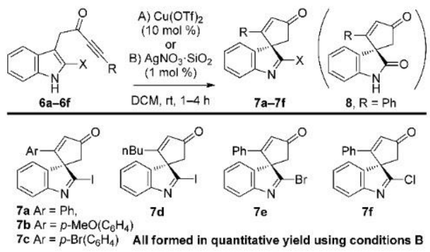


Figure 1. Preparation and reactions of indoleninyl halides.

Scheme 1. Indoleninyl Halide Substrate Synthesis



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moisture and can be stored in a freezer for several months with no evidence of decomposition.

While this Cu(II)-mediated spirocyclization worked well, a brief examination of other catalysts revealed that $AgNO_3 \cdot SiO_2$ was an even more convenient catalyst system for this transformation, enabling spirocycle **7a** to be isolated in quantitative yield at just 1 mol % catalyst loading.[8] Indoleninyl iodides **7b–d**, as well as indoleninyl bromide **7e** and chloride **7f**, were also prepared in quantitative yield using the same procedure and were found to have comparable stability.

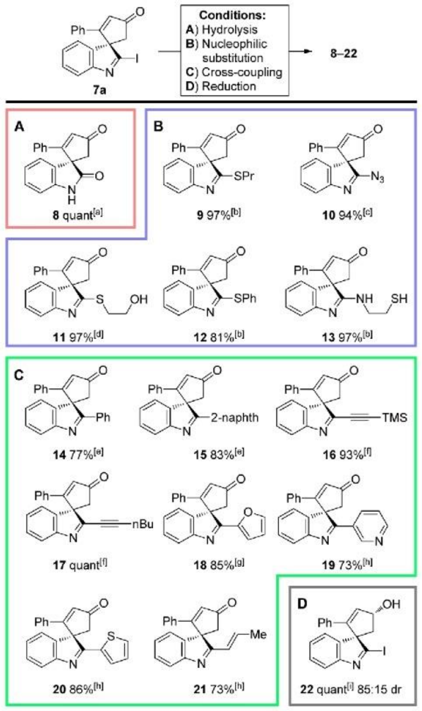
With a simple method to generate spirocyclic indoleninyl halides established, it was next decided to examine their reactivity. Indoleninyl iodide **7a**, an easy-to-handle solid product that could be readily prepared on a gram scale, was chosen as the main test substrate. Its reactivity with a range of nucleophilic reagents was investigated, with three distinct reaction modes [hydrolysis (**8**), nucleophilic substitution (**9–13**), and transition-metal-catalyzed cross-coupling (**14–21**)] all being demonstrated. These results are summarized in Scheme 2.

To begin, indoleninyl iodide **7a** was hydrolyzed using aqueous HCl in THF, affording spirocyclic oxindole **8** in quantitative yield (Scheme 2A). Next, a selection of nucleophilic substitution reactions were performed with sulfur and nitrogen nucleophiles, leading to the formation of indolenine derivatives **9–13** in high yields (Scheme 2B). With spirocycle **7a** acting as a vinyl halide surrogate, cross-coupling reactions were performed (Scheme 2C). Suzuki reactions using arylboronic acids afforded phenyl and 2-naphthyl derivatives **14** and **15** in good yields. Likewise, Sonogashira cross-couplings yielded alkyne derivatives **16** and **17**, and Stille coupling reactions allowed furan (**18**), pyridine (**19**), thiophene (**20**), and olefin groups (**21**) to be added at the indolenine 2-position, all in good yields. Finally, alcohol derivative **22** was prepared in quantitative yield with 85:15 dr following a chemo- and diastereoselective Luche reduction of the enone moiety of **7a**, leaving the indoleninyl halide moiety intact (Scheme 2D). In terms of the reduction step, hydride attack presumably occurs predominantly via the most accessible face of the molecule, i.e., anti to the indole unit.

Having successfully demonstrated the synthesis and utility of indoleninyl halides derived from ynone precursors, it was then decided to examine whether the same functional handle could be installed and used in a much broader range of indole systems. This was done by applying established indole dearomatization procedures to previously untested 2-halogenated starting materials, beginning with an enantioselective iridium-catalyzed allylic dearomatization procedure[10a] developed by You and co-workers.[10] Thus, 2-iodoindole precursor **23** was prepared and reacted with bis(1,5-cyclooctadiene)-diiridium(I) dichloride and commercially available chiral phosphoramidite ligand **27**.[10a] Pleasingly, indoleninyl iodide **24** was produced in near-quantitative yield with >9:1 dr and 86:14 er based on NMR and chiral HPLC data respectively, with its absolute stereochemistry assigned on the basis of comparison to literature precedent.[10a] Its subsequent derivatization was also achieved successfully, with both cross-coupling and nucleophilic substitution reactions being performed to produce spirocycles **25** and **26** in good yields (Scheme 3).

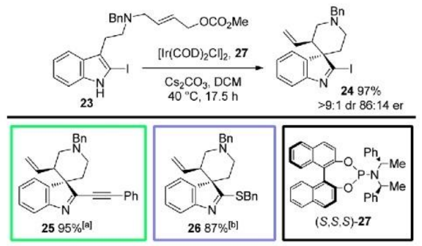
In another application, indoleninyl iodide **30** was prepared from imine **29** and indole **28**. These were treated with the peptide coupling agent T3P and iPr_2NEt at rt, using the direct imine acylation (DIA) method developed by our group,[11]

Scheme 2. Indoleninyl Iodide 7a Diversification



[a]10% HCl(aq), THF, rt, 4 h. [b]Thiol, Cs_2CO_3, MeCN, rt, 2–4 h. [c]NaN_3, DMF, 60 °C, 1.5 h. [d]2-Mercaptoethanol, Et_3N, MeCN, rt, 22 h. [e]Arylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene/H_2O, 80 °C, 16–20 h. [f]RC≡CH, iPr_2NH, $PdCl_2(PPh_3)_2$, CuI, THF, rt, 1.5 h. [g]2-(Tributylstannyl)furan, $Pd(PPh_3)_4$, dioxane, 100 °C, 21 h. [h]Stannane, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$,[9] toluene or dioxane, 100–130 °C, 17–48 h. [i]$CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, rt, 90 min.

Scheme 3. Indoleninyl Iodide via Allylic Dearomatization



[a]**24**, phenylacetylene, iPr_2NH, $PdCl_2(PPh_3)$, CuI, THF, rt, 1.5 h. [b]**24**, benzyl mercaptan, Cs_2CO_3, MeCN, 1.5 h.

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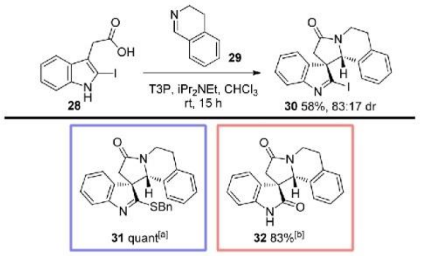
furnishing spirocycle **30** with 83:17 dr. The relative stereochemistry of **30** was assigned on the basis of analogy to related compounds.[11a] This scaffold was again amenable to additional functionalization either by nucleophilic substitution with benzyl mercaptan or by hydrolysis, forming products **31** and **32**, respectively (Scheme 4).

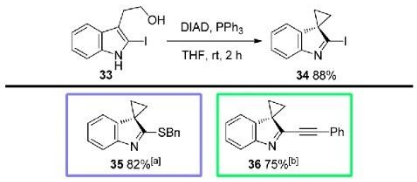
Scheme 4. Indoleninyl Iodide via Direct Imine Acylation



^{a}**30**, benzyl mercaptan, Cs_2CO_3, MeCN, 3.5 h. ^{b}**30**, 10% HCl(aq), THF, rt, 3 h.

In addition, cyclopropyl substrate **34** was prepared in high yield by a Mitsunobu-type reaction of indole-tethered alcohol **33**. Functionalization by nucleophilic displacement (**35**) and cross-coupling (**36**) again demonstrated the synthetic utility of the indoleninyl iodide substructure (Scheme 5).

Scheme 5. Indoleninyl Iodide via a Mitsunobu Reaction

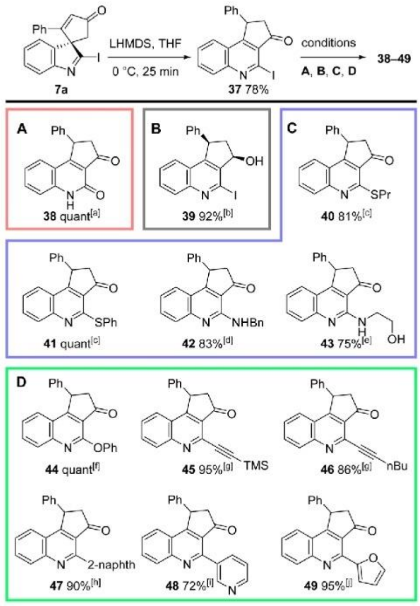


^{a}**34**, benzyl mercaptan, Cs_2CO_3, MeCN, 3.5 h. ^{b}**34**, phenylacetylene, Cs_2CO_3, $PdCl_2(PPh_3)$, CuI, THF, rt, 5 h.

Finally, it was found that indoleninyl halide **7a** rearranges to form quinoline **37** under basic conditions. A related rearrangement reaction was reported by our group in a 2016 study, in which non-halogenated spirocyclic indolenines were shown to rearrange to form quinoline derivatives upon treatment with either strong base or Lewis acid.[6c] It was found that treating spirocyclic indolenine **7a** with LHMDS in THF at 0 °C promoted its conversion into 2-iodoquinoline **37** in 78% yield via a similar process (Scheme 6; for mechanistic speculation, see our earlier publication[6c]). Of course, 2-iodoquinolines are valuable, versatile building blocks in their own right, and to demonstrate this, derivatization reactions similar to those performed on indoleninyl iodide **7a** were also explored. These results are summarized in Scheme 6.

First, it was found that quinoline **37** could be hydrolyzed with aqueous HCl, affording 2-quinolone **38** in quantitative yield (Scheme 6A). A chemo- and diastereoselective reduction was also performed using $NaBH_4$ to yield alcohol **39** in good

Scheme 6. 2-Iodoquinoline 37 Diversification



^{a}10% HCl(aq), 100 °C, 16 h. ^{b}$NaBH_4$, MeOH, rt, 3.5 h. ^{c}Thiol, Cs_2CO_3, MeCN, rt, 3–6 h. ^{d}Benzylamine, rt, 15 h. ^{e}2-Aminoethanol, rt, 5 h. ^{f}Phenol, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$,[9] Cs_2CO_3, toluene, 100 °C, 2 h. ^{g}RC≡CH, Et_3N, $PdCl_2(PPh_3)$, CuI, DMF, rt, 2–3 h. ^{h}2-Naphthylboronic acid, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, toluene/ethanol/H_2O, 80 °C, 16 h. ^{i}3-Pyridinylboronic acid, *trans*-PdBr(*N*-Succ)-$(PPh_3)_2$,[9] LiCl, Na_2CO_3, toluene/ethanol/H_2O, 100 °C, 24 h. ^{j}2-(Tributylstannyl)furan, $Pd(PPh_3)_4$, LiCl, THF, 85 °C, 16 h.

yield, with reduction presumably occurring anti to the adjacent phenyl substituent (Scheme 6B).[12] A selection of S_NAr derivatizations with sulfur (**40**–**41**) and amine nucleophiles (**42**–**43**) were also demonstrated (Scheme 6C). Finally, various cross-coupling protocols were also tested, with Buchwald–Hartwig (**44**), Sonogashira (**45**–**46**), Suzuki (**47**–**48**), and Stille (**49**) cross-coupling reactions all proceeding well in good yields (Scheme 6D).

In summary, we have demonstrated that indoleninyl iodides are readily accessible via the dearomatization of 2-iodoindole derivatives and that they can be used to synthesize a range of diverse spirocyclic indole derivatives. In view of their ability to react via three distinct reaction modes (hydrolysis, nucleophilic substitution, and cross-coupling), we expect indoleninyl iodides to quickly become established as valuable intermediates and reagents. Their utility as precursors to easily functionalized 2-iodoquinolines has also been demonstrated, further expanding their synthetic utility. Finally, while this work has focused largely on indoleninyl iodides, we have also demonstrated that indoleninyl bromide and chloride analogues can also be prepared using similar methods, and in future work the reactivity of these systems will also be examined.

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, spectroscopic data, NMR spectra, and further discussion of stereochemical assignments (PDF)

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(12) For further information regarding the assignment of the stereochemistry of substrate **39**, see the Supporting Information.

Abbreviations

Ac	acetyl
acac	acetylacetonate
AgNPs	silver nanoparticles
app.	apparent
aq.	aqueous
Ar	aryl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
CADA	catalytic asymmetric dearomatisation
CCDC	Cambridge crystallographic data centre
CDI	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
CSP-HPLC	chiral stationary phase high-performance liquid chromatography
δ	chemical shift
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarisation transfer
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
dr	diastereomeric ratio
EDA	ethyl diazoacetate
EDG	electron donating group
ee	enantiomeric excess

equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
Et_2O	diethyl ether
EWG	electron withdrawing group
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
ICP-MS	inductively coupled mass spectrometry
IR	infrared
LDA	lithium diispropylamide
LIFDI	liquid injection field desorption ionisation
m	multiplet
M	molar
Me	methyl
min	minute(s)
mp	melting point
Ms	mesyl
NBS	*N*-bromosuccinimide
NEt_3	triethylamine
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
[O]	oxidation
OAc	acetate
oct	octanoate
p-ABSA	4-acetamidobenzenesulfonyl azide
Ph	phenyl
ppm	parts per million
Pr	propyl

q	quartet
R_f	retention factor
$Rh_2[oct]_4$	$[Rh[CH_3(CH_2)_6CO_2]_2]_2$
RT	room temperature
s	singlet
sat.	saturated
t	triplet
TBME	*tert*-butyl methyl ether
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TDMPP	tris-(2,6-dimethoxyphenyl)phosphine
TEM	transmission electron microscopy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilane
TLC	thin layer chromatography
T3P	propylphosphonic anhydride
TPA	triphenylacetate

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