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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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.

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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 \( \pi \)-system, with the number of delocalised \( \pi \)-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, dearomatization of these molecules is typically a challenging process. Despite this, a number of powerful dearomatization 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 dearomatization include oxidation, cycloaddition, inter-/intramolecular alkylation, alkylation, arylation and halogenation reactions.\(^2\)\(^-\)\(^5\) As shown in Scheme 1, a number of these dearomatization strategies have been utilised in the total synthesis of natural products.\(^6\)

![Scheme 1. Examples of dearomatisation strategies used in total synthesis.](image-url)
Corey and co-workers employed an alkylation dearomatisation strategy in the total synthesis of the natural product cedrane 3 (Scheme 1A).\textsuperscript{7} Phenol 1 was deprotonated under basic conditions to generate the corresponding phenolate which then underwent intramolecular \textit{para}-alkylation to access spirocycle 2 as a mixture of \textit{cis} and \textit{trans}-forms. Upon exposure to methanolic sodium methoxide the \textit{cis/trans}-mixture was converted largely into the more stable \textit{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).\textsuperscript{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 \textit{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;\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.

![Figure 1. Natural products (12 and 13) and drug molecules (14 and 15) containing spirocyclic cores.](image-url)
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, 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. 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). 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).

(A) Dearomatisation via arylation - You (2012)

(B) Dearomatisation via alkylation - Rainier (2006)

(C) Dearomatisation via cycloaddition - Qin (2009)

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), 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.
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 \(40\). 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 *Leucaetta* alkaloid 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.](image)

**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. The You group have made significant advances in this field, which has also been well reviewed. Inspired by initial CADA allylation protocols developed by Trost and Quancard, the You group have developed a series of intramolecular asymmetric allylic alkylation reactions (Scheme 7). 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.
The use of transition metals in the activation of alkynes is commonly used to exploit their versatile reactivity, facilitating many synthetic transformations, including the dearomatization 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 $\delta$-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 $\pi$-system and computational analyses indicate that approximately half of the total bonding force is actually electrostatic in nature.$^{37}$

![Orbital interactions between metal centre and alkyne ligand.](image)

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

With overall depletion of electron density from the $\pi$-system, due to the dominant $\sigma$-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 $\pi$-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 ($53 \rightarrow 54$), 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 alkenes have only recently been reported in the literature following the first isolation of spirocyclic indolenine products by the You group in 2010. In the majority of cases, the spirocyclic products are often formed as minor side products during other transformations. 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). The annulated indole product 59 was also isolated in 25% yield resulting from a 1,2-migration process.
Carbery and co-workers also observed small amounts of spirocyclic indolenine formation when exploring the gold-catalysed annulation of indoles (Scheme 9B); 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). 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. 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.

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 yrones 67 was reported by Van der Eycken and co-workers in 2017 (Scheme 10).
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.

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 AlCl₃·6H₂O 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).
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.

Pleasingly, it was found that treatment of anisole-tethered ynone 82 with stoichiometric SnCl₂·2H₂O 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 12. Retrosynthesis routes to spirobacillene A 76 and B 79 devised by Taylor/Unsworth group.
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.\textsuperscript{55,56} For details regarding the optimisation of the SnCl$_2$·2H$_2$O-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).\textsuperscript{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. Dearomatic 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. 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 ynone 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](image)

Scheme 18. Divergent synthesis of carbazoles 107, spirocycles 71 and quinolines 75 from indole-tethered ynone 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 ynone 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 ynone via π-acidic alkyne activation. Density functional theory (DFT) calculations are also reported which suggest an unusual C-3 nucleophilicity of the pyrrole-tethered ynone.

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, 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 and following their work, several comprehensive reviews and textbooks emerged. 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.

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. AgNO₃ immobilised on silica (AgNO₃·SiO₂) was first introduced as a chromatographic medium for the separation of olefins, however, its use as a synthetic reagent is becoming more prevalent. One of the earliest reports of
AgNO$_3$·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$_3$·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 $\rightarrow$ 111) exemplifies this transformation (Scheme 20).$^{75}$

**Scheme 20. Use of AgNO$_3$·SiO$_2$ in total synthesis of kallolide B.**

Another efficient furan synthesis using AgNO$_3$·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$_3$·SiO$_2$ reported by Knight et al.**

The Knight group have since extended the intramolecular cyclisation of π-systems using AgNO$_3$·SiO$_2$ to synthesise pyrroles from propargylic glycinites.$^{77}$ 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.

\[ R^4 \text{OH} \xrightarrow{\text{AgNO}_3 \cdot \text{SiO}_2 (10 \text{ wt%), 10 mol\%)} \text{CH}_2\text{Cl}_2, \text{RT}, 16 \text{ h}} \quad \text{HN} \quad R^1 \quad R^2 \quad \text{R}^3\quad R^4 \]

\[ \text{R}^1 = \text{Boc, CO}_2\text{Me, Ns} \\
\text{R}^2 = \text{Me, Et, Ph, CH}_2\text{OTBS, CO}_2\text{Me} \\
\text{R}^3 = \text{H, Me, i-Pr, Ph} \\
\text{R}^4 = \text{H, Me, } n\text{-Bu, Ph, CH}_2\text{OTBS} \]

Scheme 22. General synthesis of substituted pyrroles using AgNO₃·SiO₂.

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% AgNO₃·SiO₂ (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

\[ \text{HO} \quad \text{HO} \quad \text{HO} \quad \text{R} \quad \text{AgNO}_3 \cdot \text{SiO}_2 (10 \text{ wt%), 10 mol\%)} \text{CH}_2\text{Cl}_2, \text{RT}, 3 \text{ h} \]

\[ \text{HN} \quad \text{CO}_2\text{Me} \]

\[ \text{R} = \]

\[ \text{HO}_2\text{C} \quad \text{HO}_2\text{C} \quad \text{HN} \]

Scheme 23. Use of AgNO₃·SiO₂ 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 AgBF₄ and Bu₄NBH₄...
generated AgNPs in situ, and these promoted the cycloaddition reaction of hydroxylchalcone 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 AgBF₄, Bu₄NBH₄ 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 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.


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).
**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 MgI₂. 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 Ag₂O, no reaction was observed, and in the presence of other metal salts such as AgOTf, AgBF₄ 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). 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 Ag₂O, AgNO₃ 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). 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.
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. Indeed, it is also possible that previous protocols describing the use of AgNO$_3$·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.

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, it was realised that a supported silver catalyst could also be used to effect the same spirocyclisation ($84 \rightarrow 85$), albeit using a stoichiometric amount of catalyst (Scheme 29).

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.\textsuperscript{55}

\begin{center}
\includegraphics[width=\textwidth]{Scheme30.pdf}
\end{center}

Scheme 30. Preparation of model ynone system 136a.

The catalyst loading (mol\%) in the reaction and AgNO\textsubscript{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\textsubscript{3} loading on silica takes into account the total weight of AgNO\textsubscript{3} and therefore the actual loading of silver metal on silica is lower than this value. For example, a loading of 1 wt\% AgNO\textsubscript{3} immobilised on silica equates to just 0.63 wt\% Ag based on the stoichiometry of AgNO\textsubscript{3}. Commercially available 10 wt\% AgNO\textsubscript{3}·SiO\textsubscript{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.\textsuperscript{62,69,93} The silver salt (AgNO\textsubscript{3} or AgOTf) was added to a vigorously stirred silica slurry in deionised water. This mixture was then stirred for 15 minutes, concentrated \textit{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.
A range of both catalyst loadings (0.1–10 mol%) and AgNO₃ 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 AgNO₃ on silica to 0.1 wt% (Entry 6) but a longer reaction time was required to reach completion. 1 wt% AgOTf·SiO₂ also displayed comparable efficiency to 1 wt% AgNO₃·SiO₂ 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% AgNO₃ 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% AgNO₃·SiO₂ 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 AgNO₃ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading / AgNO₃ loading / Time</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol% 30 wt% 10 min</td>
<td>100 (100)</td>
</tr>
<tr>
<td>2b</td>
<td>10 mol% 10 wt% 10 min</td>
<td>100 (98)</td>
</tr>
<tr>
<td>3</td>
<td>1 mol% 30 wt% 24 h</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>1 mol% 10 wt% 6 h</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>1 mol% 1 wt% 30 min</td>
<td>100 (98)</td>
</tr>
<tr>
<td>6</td>
<td>1 mol% 0.1 wt% 1.5 h</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>0.1 mol% 1 wt% 2 d</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>0.1 mol% 0.1 wt% 5 d</td>
<td>45</td>
</tr>
<tr>
<td>9c</td>
<td>1 mol% - 6 h</td>
<td>100</td>
</tr>
<tr>
<td>10d</td>
<td>1 mol% - 2 h</td>
<td>100</td>
</tr>
<tr>
<td>11e</td>
<td>1 mol% - 1 h</td>
<td>100 (88)</td>
</tr>
<tr>
<td>12f</td>
<td>- - 24 h</td>
<td>Trace</td>
</tr>
</tbody>
</table>

All reactions were performed in CH₂Cl₂ at RT and isolated yields are reported in parentheses.

*Conversions calculated by analysis of starting material:product ratio in the unpurified ¹H NMR spectra. bCommercial 10 wt% AgNO₃·SiO₂ used. cAgNO₃ used. dAgNO₃ and SiO₂ added separately. e1 wt% AgOTf·SiO₂ used. fHeat-treated (140 °C) SiO₂ added.

Table 1. Catalyst optimisation results.
and expected values could be due to experimental error or the quality of commercial AgNO₃ 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 AgNO₃ 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, and the progress of each reaction was monitored by thin layer chromatography (TLC).

![Diagram of the spirolactone formation reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/support</th>
<th>Ag content / wt %</th>
<th>Time</th>
<th>Conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgNO₃/silica</td>
<td>0.63</td>
<td>30 min</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>AgNO₃/Celite</td>
<td>0.63</td>
<td>24 h</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Ag₂CO₃/Celite</td>
<td>0.63</td>
<td>24 h</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>AgNO₃/alumina</td>
<td>0.63</td>
<td>24 h</td>
<td>Trace</td>
</tr>
</tbody>
</table>

*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, AgNO₃ supported on Celite (Entry 2) promoted full conversion of ynone 136a into spiroycyle 137a, although it appeared to be less active than AgNO₃ supported on silica as a prolonged reaction time of 24 hours was required. In contrast, AgNO₃ immobilised on alumina (Entry 4) performed the worst out of the catalysts tested; only trace amounts of spiroycyle 137a were observed in the ¹H NMR spectrum of the unpurified reaction mixture after 24 hours. In conclusion, AgNO₃ immobilised on silica remained the best supported catalyst for the spiroycycilation, with full conversion of ynone 136a to spiroycyle 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 spiroycycilation proceeded well in the majority of solvents tested; a range of polar and non-polar aprotic solvents furnished the spiroycyclic product 137a in 6 hours or less.
Table 3. Solvent optimisation results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversiona / % 30 min</th>
<th>Conversion / % 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TBME</td>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>2-MeTHF</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>50</td>
<td>&gt;95</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td>6</td>
<td>EtOAc</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>Et2O</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Hexane</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>MeOH</td>
<td>60</td>
<td>100b</td>
</tr>
<tr>
<td>10</td>
<td>DCE</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>Acetone</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>EtOH</td>
<td>90</td>
<td>100b</td>
</tr>
<tr>
<td>13</td>
<td>Toluene</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>CHCl3</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>CH2Cl2</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

All reactions performed on 0.08 mmol of ynone 136a using 1 wt% AgNO3·SiO2 at RT. aConversions calculated by analysis of starting material:product ratio in the unpurified 1H NMR spectra. bMixture of products observed by 1H NMR spectroscopy but all starting material consumed.

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 CHCl3 and CH2Cl2 clearly outperformed all other solvents with full conversion of ynone 136a into spirocycle 137a observed in the first 30 minutes (Entries 14 and 15); CH2Cl2 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.](image)

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.](image)

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

![Scheme 33. Weinreb amides prepared using T3P coupling procedure.](image)

*Previously synthesised by Michael James.*

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28
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$_2$CO$_3$ and Pd(PPh$_3$)$_4$ to generate the dimeric Weinreb amide 135i.

![Scheme 34. Preparation of Weinreb amide 135i via Suzuki cross-coupling.](image)

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).
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.

---

"Synthesised via in situ generation of lithium acetylide. Previously synthesised by Michael James."
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 NaBH₄.⁹⁴

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 AgNO₃ 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 AgNO₃·SiO₂ (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.

"Prepared by Michael James."⁹²

Scheme 36. Preparation of propargyl alcohol substrates 141 and 142.
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\(_3\)-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\(_3\)-SiO\(_2\) and unsupported AgNO\(_3\) was observed. Not only were shorter reaction times and enhanced isolated yields obtained when using AgNO\(_3\)-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-2H/3H-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 dearomatiation and spirocyclisation at the C-2 position of pyrroles affording spiro-2H-pyrroles\(^ {55,97,98}\) and reports on C-3 pyrrole spirocyclisations are particularly rare.\(^ {99,100}\) Firstly, the spirocyclisation of 2-pyrrole yrones \(136h-k\) was explored using both supported and unsupported \(\text{AgNO}_3\) and the results are shown in Scheme 38.

![Scheme 38. Supported and unsupported spirocyclisations of 2-pyrrole yrones.](image)

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

As can be seen from Scheme 38, all spiro-2H-pyrroles were generated in excellent yields of 90% or above when using the supported \(\text{AgNO}_3\cdot\text{SiO}_2\) catalyst. Once again, unsupported \(\text{AgNO}_3\) 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 \(\text{AgNO}_3\cdot\text{SiO}_2\) and unsupported \(\text{AgNO}_3\) and will be discussed later on in the Thesis (see Section 2.7). Characteristic \(^1\text{H}\) and \(^{13}\text{C}\) NMR signals could be used to identify the presence of the spirocyclic pyrrole products; imine protons H-2 had a chemical shift around 8.3 ppm in the \(^1\text{H}\) NMR spectrum and the spirocyclic carbon centres C-4 had a particularly key chemical shift at 89 ppm in the \(^{13}\text{C}\) NMR spectrum (Figure 3).
Figure 3. Characteristic $^1$H and $^{13}$C NMR chemical shifts in spiro-$2H$-pyrroles.

It was then envisaged that the same supported AgNO$_3$·SiO$_2$ spirocyclisation conditions could be applied to 3-pyrrole ynone precursors to furnish valuable spiro-$3H$-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-$3H$-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$_3$·SiO$_2$ and pleasingly complete conversion and quantitative isolation of spirocycles 147l–n was achieved (Scheme 40).
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$_3$·SiO$_2$. The quantitative synthesis of spirocyclic pyrroline systems 147i–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$_3$·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$_3$. 

![Scheme 40. Spirocyclisation of 3-pyrrole ynones.](image-url)
Trace amounts of ring-opened tautomer observed in $^1$H NMR spectrum. 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$_3$·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).

Scheme 42. Synthesis of dibenzofuran product 151 via 1,2-migration.
2.5.4 Propargyl alcohol spirocyclisations

Although the compatibility of a variety of yrones 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 \( \text{AgNO}_3 \cdot \text{SiO}_2 \) to furnish spirocycle 154 in a quantitative yield (Scheme 43).

\[
\begin{align*}
\text{OH} & \\
\text{Ph} & \\
\text{N} & \\
\text{Ph} & \\
\text{HO} & \\
\text{N} & \\
\text{Ph} & \\
\end{align*}
\]

(A) \( \text{AgNO}_3 \cdot \text{SiO}_2 \) (1 wt%, 10 mol%) \( \text{CH}_2\text{Cl}_2 \), RT

(B) \( \text{AgNO}_3 \) (10 mol%) \( \text{CH}_2\text{Cl}_2 \), RT

\begin{align*}
\text{HO} & \\
\text{N} & \\
\text{Ph} & \\
\end{align*}

\( \text{154} \)

\( \text{24 h, 100\% (1:6:1 \text{ dr})} \)

\( \text{24 h, 95\% conv.}^a \)

\( ^a\text{Conversion calculated by analysis of starting material:product ratio in the unpurified } ^1\text{H NMR spectrum.} \)

Scheme 43. Spirocyclisation of propargyl alcohol 142.

It is interesting to note that the reaction in Scheme 43 took hours to reach completion using \( \text{AgNO}_3 \cdot \text{SiO}_2 \) 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 \( \text{AgNO}_3 \) also displayed comparable reactivity to \( \text{AgNO}_3 \cdot \text{SiO}_2 \), 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 \( \text{AgNO}_3 \cdot \text{SiO}_2 \). However, propargyl alcohol 141 was not converted cleanly into the desired spirocycle 156. The major product of the reaction when using \( \text{AgNO}_3 \cdot \text{SiO}_2 \) (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 \( ^1\text{H NMR} \) spectrum and identification of the spirocycle was challenging.
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 44. Spirocyclisation of propargyl alcohol 141.

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, 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.

![Scheme 46. Additives tested in robustness screen.](image-url)
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 sp³-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 CH₂Cl₂, dried under vacuum and then used in the subsequent spirocyclisations. The product isolated from each spirocyclisation reaction was analysed by ¹H NMR spectroscopy.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Cycle no.</th>
<th>Conversion / %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>86</td>
</tr>
</tbody>
</table>

All reactions were carried out on 0.38 mmol of ynone 136a in CH₂Cl₂ (0.1 M) at RT. <sup>a</sup>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 AgNO₃·SiO₂ 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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sample</th>
<th>Ag content in 137a / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spirocycle 137a after cycle 1</td>
<td>0.0067</td>
</tr>
<tr>
<td>2</td>
<td>Spirocycle 137a after cycle 8</td>
<td>0.0056</td>
</tr>
</tbody>
</table>

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 CH₂Cl₂ (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

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ag content in 137a / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0.0058</td>
</tr>
<tr>
<td>2</td>
<td>Acetone</td>
<td>0.1360</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

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 AgNO₃ (see Section 2.5), a mechanistic study was initiated in an attempt to identify why AgNO₃·SiO₂ 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).

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).

*aAll ReactIR™ experiments were performed in CH₂Cl₂ at RT using 1 mol% of AgNO₃·SiO₂ (1 wt%) or AgNO₃ catalyst.
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, AgNO₃ 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 AgNO₃·SiO₂ (blue line) and unsupported AgNO₃ 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 AgNO₃.

The observation of sigmoidal kinetics and induction periods can be indicative of the in situ formation of nanoparticles. 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 AgNO₃ 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. AgNO₃ was stirred in CH₂Cl₂ 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. Ynone 136a was then added to the pre-stirred AgNO₃ solution and the reaction was monitored by ReactIR™ (grey line, Figure 6).
Figure 6. ReactIR™ plot for the spirocyclisation reaction using pre-stirred AgNO₃ (grey line) and unsupported AgNO₃ (purple line).

Evidently, pre-stirring AgNO₃ 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 AgNO₃ was comparable to the unsupported AgNO₃ 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 AgNO₃ with silica added separately to the reaction mixture 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. 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. AgNO₃) 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.

![Graph showing ReactIR™ plot for the spirocyclisation reaction using unsupported AgNO₃ (purple line) and the mercury drop test experiment (red line).](image)

**Figure 7.** ReactIR™ plot for the spirocyclisation reaction using unsupported AgNO₃ (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 AgNO₃ 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. AgNO₃ was stirred in CH₂Cl₂ 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 CH₂Cl₂ had evaporated was then analysed by TEM (Figure 8).
As anticipated, the images shown in Figure 8 indicate the presence of silver nanoparticles after pre-stirring AgNO$_3$ in CH$_2$Cl$_2$. 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$_3$·SiO$_2$ catalyst before (Figure 9) and after (Figure 10) use in the spirocyclisation reaction were obtained.
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 protodemetalation (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 AgNO₃ 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 protodemetalation 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 protodemetalation 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 protodemetalation 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.

![Scheme 48. Silanol groups facilitating protodemetalation step in spirocyclisation.](image)
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.](image)

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 AgNO₃ 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 AgNO₃·SiO₂ (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 CH₂Cl₂ 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.

Figure 11. ReactIR™ plot for the spirocyclisation reaction of ynone 136a using AgNO₃·SiO₂ 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 AgNO₃ was used as the catalyst in this experiment rather than AgNO₃·SiO₂ 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.

![ReactIR plot for the spirocyclisation reaction of ynone 136a using AgNO₃ (purple line) and AgNO₃ with the addition of spirocycle 137a (pink line).](image)

“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 AgNO₃ (purple line) and AgNO₃ 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 AgNO₃ was used instead as there was not an induction
period observed in this reaction (Figure 13).

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 AgNO₃-SiO₂ 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

\(^{0.5}\text{equiv. of spirocyclic imine } 137\text{a added at the beginning of the reaction.}\)

**Figure 13. ReactIR™ plot for the spirocyclisation reaction of ynone 136a using pre-
stirred AgNO₃ (grey line) and AgNO₃ with spirocycle 137a (pink line).**
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.\textsuperscript{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.\textsuperscript{114}

Silica-supported AgNPs were prepared using two different literature procedures reported by Waite\textsuperscript{114} and Porco Jr.\textsuperscript{84} and their performance in the standard indole spirocyclisation reaction was investigated. The aim was to compare the results obtained with our AgNO\textsubscript{3}·SiO\textsubscript{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\textsubscript{3} with NaBH\textsubscript{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\textsubscript{3})\textsubscript{2}]\textsuperscript{+} complex prior to reduction. In comparison, Porco Jr.’s method used AgBF\textsubscript{4} as their Ag(I) source and Bu\textsubscript{4}NBH\textsubscript{4} as the reductant without any ligand additive.

![Scheme 51](image)

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 AgNO₃·SiO₂ typically used for this transformation; this highlights the superior activity of the nanoparticles present in our AgNO₃·SiO₂ 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. 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. In view of this, a multi-gram spirocyclisation was performed using a continuous FlowSyn™ reactor, whereby a solution containing ynone 136a in CH₂Cl₂ 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% AgNO₃·SiO₂ 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.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (conc.)</th>
<th>Time / h</th>
<th>Catalyst loading&lt;sup&gt;a&lt;/sup&gt; / mol%</th>
<th>Spirocycle produced / g</th>
<th>Full conversion at end of reaction?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; (0.5 M)</td>
<td>12</td>
<td>0.43</td>
<td>6.90</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Toluene (0.1 M)</td>
<td>51</td>
<td>0.12</td>
<td>23.6</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 wt% AgNO<sub>3</sub>·SiO<sub>2</sub> catalyst was used for each flow reaction. At the end of each reaction the products were concentrated in vacuo and analysed by <sup>1</sup>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<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>·SiO<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> and the flow rate was increased to 0.3 mL/min to offset these more dilute conditions. The same amount of AgNO<sub>3</sub>·SiO<sub>2</sub> 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% AgNO₃·SiO₂ 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 AgNO₃ 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™ 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 AgNO₃·SiO₂ with unsupported AgNO₃ has been described throughout and a significant difference in their reactivity has been established. In all cases, AgNO₃·SiO₂ was superior to unsupported AgNO₃ 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).
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).\textsuperscript{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).

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

![Scheme 52. Natural products containing spirocyclic dienone motif and ipso-cyclisation strategies.](image-url)
3.2 Project background

During work towards the synthesis of the natural product spirobacillene A, it was found that treating anisole-tethered ynone 82 with five equivalents of SnCl$_2$·2H$_2$O at RT in CH$_2$Cl$_2$ resulted in efficient conversion into the spirocyclic dienone 83 (Scheme 53).

\[
\text{Scheme 53. Sn(II)-mediated synthesis of spirocyclic dienone 83.}
\]

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$_2$·2H$_2$O 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$_2$·2H$_2$O 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.
“5 equiv. of SnCl₂·2H₂O used. “0.1 equiv. of Cu(OTf)₂ used. “Reaction performed at 50 °C.
Conversions calculated by analysis of starting material:product ratio in the unpurified ¹H NMR spectra.

Scheme 54. Spirocyclisation of anisole-tethered ynones using SnCl₂·2H₂O (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).
Low isolated yield due to a lactone-forming side reaction.

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

Reaction performed by Dr. John Liddon. Reaction performed by BSc student Jack Partington.

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

Generally, the isolated yields for these phenol-tethered yrones 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 AgNO₃·SiO₂-catalysed spirocyclisations of para-substituted phenol-tethered yrones were examined first, delivering the corresponding spirocyclic dienone frameworks 198a–h in excellent yields (Scheme 58). Once again AgNO₃·SiO₂ proved to be a much more reactive catalyst system than unsupported AgNO₃; yrones 197a–c, 197e–f, 197h did not react in the
presence of AgNO₃ and only 7% conversion into the desired spirocyclic dienone 198g was observed for ynone 197g.

Reactions were performed using 10 mol% catalyst. *Reactions were performed at 40 °C. †Reaction performed by Dr. John Liddon. Conversions calculated by analysis of starting material:product ratio in the unpurified ¹H 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).
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. 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$_3$·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.

![Scheme 61. Asymmetric spirocyclisation of ynone 197k using Ag-CPAs.](image)

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

Scheme 62. Asymmetric spirocyclisation of ynone 197n.

Unfortunately, once again only low enantioselectivities (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. Unfortunately, neither the BINAP nor the phosphoramidite 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. 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 and B, 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. Spirobacillene A 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. 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 Ag₂O as a single electron transfer agent (Scheme 63). Our group used a dearomatization and ipso-cyclisation strategy requiring five equivalents of SnCl₂·2H₂O to furnish the key spirocyclic dienone intermediate 83 (Scheme 63).

![Scheme 63](image)

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 AgNO₃·SiO₂-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).

(A) Alkyne synthesis

With phenol-tethered ynone 209 in hand, spirocyclisation was performed on this substrate using our AgNO₃·SiO₂ 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.

(B) Ynone formation

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

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 ynone 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 AgNO₃·SiO₂ 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. 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

Figure 14. Biologically important indole derivatives.

The biological importance of substituted indoles has stimulated much research into new synthetic strategies to access such frameworks. 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). Other classical indole syntheses developed include the Bartoli, Larock, Gassman, Reissert and Leimgruber-Batcho methods, some of which are summarised in Scheme 66. Typically, these methods construct the indole framework via the annulation of a pyrrole ring onto a pre-functionalised benzene precursor.
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.\textsuperscript{145–148}

**Scheme 66. Classical indole syntheses.**

**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$_3$·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$_3$·SiO$_2$.](image)

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading / mol%</th>
<th>Reaction time / h</th>
<th>SM 214a</th>
<th>Conversion$^{a}$ / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgNO$_3$·SiO$_2$</td>
<td>1</td>
<td>4</td>
<td>65</td>
<td>23 (23)</td>
</tr>
<tr>
<td>2</td>
<td>AgNO$_3$·SiO$_2$</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>80 (80)</td>
</tr>
<tr>
<td>3</td>
<td>AgNO$_3$</td>
<td>1</td>
<td>6</td>
<td>78</td>
<td>22 (22)</td>
</tr>
<tr>
<td>4</td>
<td>AgNO$_3$</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>100 (97)</td>
</tr>
</tbody>
</table>

$^{a}$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$_3$·SiO$_2$.

Table 8. Optimisation of benzannulation conditions.
As can be seen from the results in Table 8, with AgNO$_3$·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$_3$·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 benzannulation 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 pyroles 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.](image)

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.](image)

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). 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.](image)

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.](image)

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.](image)

A range of 3-pyrrole-tethered yrones 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.

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Pyrrole-tethered ynones incorporating substituents in the C-2 and C-3 positions were also prepared using a variety of literature procedures,\textsuperscript{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 initial Pd-catalysed steps were also reported by the Trost group.\textsuperscript{152} Standard conditions were used for the hydrolysis, T3P coupling and ynone formation steps; these conditions are described in Scheme 72 and Scheme 74.
Isolated yields for ynone forming step only.

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).
Monitoring these cyclisations by TLC was difficult due to many of the starting ynone and indole products having coincident R<sub>f</sub> values. It was also difficult to monitor these reactions by <sup>1</sup>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<sup>-1</sup>) 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 <sup>13</sup>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 <sup>13</sup>C NMR spectra.

*Only 10 mol% AgNO<sub>3</sub> used. <sup>b</sup>5 mol% AgNO<sub>3</sub> and 2.5 mol% Ag<sub>2</sub>O used.

**Scheme 76. Benzannulations of pyrrole-tethered ynone**
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. 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 trisubstituted 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 an Ag₂O 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).](image)
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 \textbf{238}. TMS-protected ynone \textbf{214I} failed to react in the presence of AgNO$_3$ and efforts to isolate the corresponding deprotected ynone \textbf{239} were also unsuccessful. Hence, it was decided to focus on the \textit{in situ} deprotection and immediate reaction of the terminal ynone \textbf{239} to afford 5-hydroxy indole \textbf{238}. Pleasantly, \textit{in situ} TMS deprotection promoted by borax (Na$_2$B$_4$O$_7$·10H$_2$O), followed by the addition of 10 mol\% AgNO$_3$ at RT afforded 5-hydroxy indole \textbf{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 NaBH₄ reduction (conditions B in Scheme 78) to prepare propargyl alcohol substrates 240a–f for screening in the benzannulation reaction.

Scheme 78. Reduction of 3-pyrrole ynones using organometallic reagents or NaBH₄.

Propargyl alcohols 240d and 240e were obtained in high yields following NaBH₄ 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 NaBH₄ reduction and K₂CO₃-mediated deprotection, provided propargyl alcohol 240f in an 83% yield (Scheme 79).
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.

Not only did the propargyl alcohol substrates require higher catalyst loadings in comparison to the pyrrole ynone substrates described earlier, but in some cases, AgNO₃ alone was not able to promote full conversion into the indole products. Previously, our group have shown that a combination of AgNO₃ and Ag₂O can be effective in the cyclisation of indole-tethered propargyl alcohols; it appeared that a Ag₂O 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 Ag₂O

\[ ^{15} \text{AgNO}_3 \text{ used. Conversions calculated by analysis of starting material:product ratios in the unpurified } ^1H \text{ NMR spectra.} \]

**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, AgNO₃ alone was not able to promote full conversion into the indole products. Previously, our group have shown that a combination of AgNO₃ and Ag₂O can be effective in the cyclisation of indole-tethered propargyl alcohols; it appeared that a Ag₂O 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 Ag₂O
additive is not known, but when trying to promote the cyclisation of ynone 240d using 15 mol% Ag₂O no reaction was observed. Therefore, it appears that Ag₂O does not catalyse the reaction directly, but may work by buffering the reaction mixture. Unfortunately, the combination of AgNO₃ and Ag₂O were less successful conditions for the formation of substituted indoles 241b and 241c. In these two cases, switching to the AgNO₃·SiO₂ 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 protodemetalation 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 protodemetalation 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 AgNO₃ and Ag₂O, 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 AgNO₃ is unclear and can not be accurately modelled by DFT. However, the reaction of AgOTf with an equivalent of PPh₃ results in the formation of a known complex Ag(OTf)PPh₃,¹⁵⁵,¹⁵⁶ 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)PPh₃ (formed \textit{in situ} by mixing AgOTf and PPh₃ in CH₂Cl₂), 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)PPh₃ 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 ($\Delta G_{298} = -223$ kJ mol$^{-1}$) and that spirocycle 216 would be a kinetic product from this reaction ($\Delta G_{298} = -58$ 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$_2$Cl$_2$.

**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 \textbf{214a} and \textbf{237a} were then modelled by DFT using [Ag(PPh\textsubscript{3})\textsuperscript{+}] as the catalyst system (Scheme 84b). In the case of the cyclisation reaction of unsubstituted pyrrole \textbf{214a}, two transition states for C-C bond formation were calculated. Transition state \textbf{ts\textsubscript{BC}} is best represented as nucleophilic attack through the C-3 position leading to the vinyl silver spirocycle \textbf{C}. The second transition state, \textbf{ts\textsubscript{BD}} corresponds to C-C bond formation through the C-2 position leading to \textbf{D} where subsequent tautomerisation and protodemetalation would give indole product \textbf{215a}. Although the formation of \textbf{C} will occur more rapidly than \textbf{D}, the former is, at best, isoenergetic with \textbf{A}, and will be in rapid equilibrium with \textbf{B}. As \textbf{D} is significantly lower in energy (–33 kJ mol\textsuperscript{-1}), indole \textbf{215a} would be the expected product from the reaction rather than spirocycle \textbf{216}. In the case of substituted pyrrole ynone \textbf{237a} the situation is different with corresponding complex \textbf{C} now lower in energy than both \textbf{B} and \textbf{A}. As \textbf{C} will have a significant population in this case, it may then undergo protodemetalation to give spirocyclic product \textbf{246a}, consistent with it being a kinetic product formed from the lower lying transition state \textbf{ts\textsubscript{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 \textbf{C} is significantly lower than complex \textbf{B}; the spirocyclic intermediate \textbf{C} is not in equilibrium with the ring-opened species \textbf{B} and therefore ring closure via C-2 does not occur.

\textbf{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 CH₂Cl₂, 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 ¹³C 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, δH 7.27 and δC 77.0 for CDCl₃, δH 2.50 and δC 39.5 for (CD₃)₂SO, δH 3.31 and δC 49.1 for CD₃OD, δH 2.05 and δC 29.8 for (CD₃)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 CH₂Cl₂ or CDCl₃. 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 60F₂₅₄ 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 (SiO₂), 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.% AgNO₃·SiO₂ catalyst

Based on procedures reported by Smith and Li. 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 AgNO₃ (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 AgNO₃·SiO₂. 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.% AgNO₃ on Celite catalyst

Based on a procedure reported by McKillop, 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 AgNO₃ (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.% AgNO₃ on alumina catalyst

Based on a procedure reported by Smith, AgNO₃ (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.% Ag₂CO₃ on Celite catalyst

Based on a procedure reported by McKillop, 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 Ag₂CO₃ (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™ studies

All ReactIR™ experiments were performed using a Mettler Toledo ReactIR™ 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™ experiment shown as dark blue line in Figures 4, 5 and 11

To a shallow boiling tube charged with a stirrer bar was added CH₂Cl₂ (3.9 mL). Ynone 136a (100 mg, 0.386 mmol) was then added followed by the addition of 1 wt.% AgNO₃·SiO₂ (65.6 mg, 3.86 μmol) and the reaction mixture was stirred at RT for 1 h.

Procedure for ReactIR™ 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 CH₂Cl₂ (3.9 mL). Ynone 136a (100 mg, 0.386 mmol) was then added followed by the addition of AgNO₃ (0.66 mg, 3.86 μmol) and the reaction mixture was stirred at RT for 6 h.

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

To a shallow boiling tube charged with a stirrer bar was added CH₂Cl₂ (3.9 mL). Ynone 136a (100 mg, 0.386 mmol) was then added followed by the addition of AgNO₃ (0.66 mg, 3.86 μmol) and SiO₂ (65.6 mg) and the reaction mixture was stirred at RT for 3 h.

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

To a shallow boiling tube charged with a stirrer bar and aged AgNO₃ (0.66 mg, 3.86 μmol) in CH₂Cl₂ (3.9 mL) was added ynone 136a (100 mg, 0.386 mmol). The reaction mixture was stirred at RT for 3 h.

Note: Aged AgNO₃ was prepared by stirring AgNO₃ in CH₂Cl₂ for 24 h under air at RT.

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

To a shallow boiling tube charged with a stirrer bar was added CH₂Cl₂ (7.7 mL). Ynone 136a (200 mg, 0.771 mmol) was then added followed by the addition of AgNO₃ (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 CH₂Cl₂ (3.9 mL). Ynone 136a (100 mg, 0.386 mmol) was then added followed by the addition of AgNO₃ (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 CH₂Cl₂ (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 AgNO₃ (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 HNO₃ (TraceSelect® HNO₃ 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 HNO₃ 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 AgNO₃·SiO₂ 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.% AgNO₃·SiO₂ 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. 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 and dispersion effects modelled with Grimme’s D3 method.
6.8 General procedures

General procedure A: Weinreb amide formation

\[
\begin{align*}
R^1 & \quad \text{OH} \quad \text{O} \\
\text{CH}_2\text{Cl}_2 & \quad \text{RT} \\
\text{MeNH(OMe)}\cdot\text{HCl} & \quad \text{DIPEA} \\
\text{T3P, DIPEA} & \quad \text{MeNH(OMe)}\cdot\text{HCl} \\
\text{酸} & \quad \text{T3P, DIPEA} \quad \text{MeNH(OMe)}\cdot\text{HCl} \\
R^1 & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

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\textsubscript{2}Cl\textsubscript{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\textsubscript{4} and concentrated in vacuo to afford the Weinreb amide product.

General procedure B: Ynone formation

\[
\begin{align*}
R^2 & \quad \text{Li} \\
\text{THF} & \quad \text{RT} \\
R^1 & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\end{align*}
\]

To a stirred solution of alkyne (48.0 mmol) in THF (48 mL) at −78 °C under argon was added \text{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\textsubscript{4}Cl (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\textsubscript{4}, concentrated in vacuo and purified by column chromatography to afford the ynone product.
General procedure C: Spirocyclisation using AgNO$_3$·SiO$_2$

To a solution of ynone (1 mmol) in CH$_2$Cl$_2$ (10 mL) was added AgNO$_3$·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$_2$Cl$_2$ (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 AgNO₃

![Diagram of General procedure E]

To a solution of ynone (1 mmol) in CH₂Cl₂ (10 mL) was added AgNO₃ (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 AgNO₃ and Ag₂O

![Diagram of General procedure F]

To a solution of ynone (1 mmol) in CH₂Cl₂ (10 mL) was added AgNO₃ (0.05–0.10 equiv.) and Ag₂O (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 AgNO₃ and Ag₂O

![Diagram of General procedure G]

To a solution of propargyl alcohol (1 mmol) in CH₂Cl₂ (10 mL) was added AgNO₃ (0.10 equiv.) and Ag₂O (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.
To a solution of propargyl alcohol (1 mmol) in CH₂Cl₂ (10 mL) was added AgNO₃·SiO₂ (0.10 equiv.). The mixture was stirred at RT until completion was observed by TLC. The reaction mixture was filtered, then concentrated \textit{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-(1H-Indol-3-yl)-N-methoxy-N-methylacetamide (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 CH₂Cl₂ (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; R₇ 0.14 (1:1 hexane:EtOAc); ν_max (thin film)/cm⁻¹: 3296, 2936, 1643, 1458, 1426, 1008, 743; δ_H (400 MHz, CDCl₃) 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, CDCl₃) 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-(1H-pyrrol-2-yl)acetate (S2)

To a stirred solution of pyrrole S1 (1.34 g, 20.0 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added ethyl diazoadetate (3.02 mL, 25.0 mmol, 87 wt.% in CH₂Cl₂) 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 CH₂Cl₂ (2 x 100 mL). The organics were combined, dried over MgSO₄ 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%); Rf 0.57 (1:1 hexane:EtOAc); ν\text{max} (thin film)/cm\(^{-1}\) 3388, 2983, 1727, 1370, 1243, 1157, 1028, 720; δ\text{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\text{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-(1H-Pyrrol-2-yl)acetic acid (134e)

![Diagram of 2-(1H-Pyrrol-2-yl)acetic acid (134e)]

To a solution of ethyl 2-(1H-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 \textit{in vacuo} to afford the title compound 134e without further purification as an off white solid (621 mg, 95%); mp 77–79 °C; Rf 0.36 (1:1 hexane:EtOAc); ν\text{max} (thin film)/cm\(^{-1}\) 3341, 3325, 3119, 2910, 1696, 1415, 1243, 1209, 745; δ\text{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\text{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)**

Synthesised using general procedure A with 2-(1H-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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3322, 2938, 1646, 1432, 1386, 1175, 1002, 723; $\delta_{\text{H}}$ (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); $\delta_{\text{C}}$ (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$_8$H$_{12}$N$_2$NaO$_2$ (MNa$^+$) Requires 191.0791 (0.1 ppm error), Found: 169.0977; C$_8$H$_{13}$N$_2$O$_2$ (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-1H-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 bromoacetate 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$_4$Cl (70 mL) and the aqueous layer was extracted with diethyl ether (50 mL). The combined organics were washed with sat. aq. NH$_4$Cl (50 mL),
dried over MgSO₄ 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%); Rₕ 0.71 (1:1 hexane:EtOAc); νₓmax (thin film)/cm⁻¹ 3374, 2980, 2922, 1725, 1178, 1031, 783; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₀H₁₅NNaO₂ (MNa⁺) Requires 204.0995 (1.5 ppm error), Found: 182.1176; C₁₀H₁₆NO₂ (MH⁺) Requires 182.1176 (−0.2 ppm error).

Lab notebook reference: akc05-30

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

![Chemical structure diagram]

To a solution of ethyl 2-(2,5-dimethyl-1H-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 MgSO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ 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 MgSO₄ and concentrated in vacuo to afford the title compound 135f without further purification as a brown oil (823 mg, 74%); Rₕ 0.49 (7:3 EtOAc:hexane); νₓmax (thin film)/cm⁻¹ 3222, 2932, 1638, 1437, 1380, 1178, 1003, 787; δH (400 MHz, CDCl₃) 1.71–2.22 (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); δC (100 MHz, CDCl₃) 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; \(\text{C}_{10}\text{H}_{16}\text{N}_{2}\text{NaO}_{2}\) (\(\text{MNa}^{+}\)) Requires 219.1104 (−3.4 ppm error), Found: 197.1286; \(\text{C}_{10}\text{H}_{17}\text{N}_{2}\text{O}_{2}\) (\(\text{MH}^{+}\)) Requires 197.1285 (−0.7 ppm error).

Lab notebook reference: akc05-31/32

\(\text{2-(Benzofuran-3-yl)-N-methoxy-N-methylacetamide (135g)}\)

![Diagram of 135g]

Synthesised using general procedure A with 2-(benzofuran-3-yl)acetic acid \(\text{134g}^{*198}\) (514 mg, 2.92 mmol), T3P 50% in EtOAc (2.78 g, 4.38 mmol), DIPEA (1.52 mL, 8.75 mmol) and MeNH(O)Me-HCl (313 mg, 3.21 mmol) in \(\text{CH}_{2}\text{Cl}_{2}\) (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); \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 1659, 1452, 1093, 1001, 742; \(\delta_{\text{H}}\) (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); \(\delta_{\text{C}}\) (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; \(\text{C}_{12}\text{H}_{13}\text{NNO}_{3}\) (\(\text{MNa}^{+}\)) Requires 242.0788 (−3.1 ppm error), Found: 220.0970; \(\text{C}_{12}\text{H}_{14}\text{NO}_{3}\) (\(\text{MH}^{+}\)) 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)**

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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2937, 1658, 1455, 1173, 1007, 743; $\delta_H$ (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); $\delta_C$ (100 MHz, CDCl$_3$) 12.2 (C-8), 28.2 (C-10), 32.3 (C-12), 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.\textsuperscript{55}

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

Weinreb amide 135a (1.00 g, 4.58 mmol) was stirred in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3244, 2935, 1641, 1450, 1425, 1338, 1176, 1002, 742; $\delta_H$ (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); $\delta_C$ (100 MHz, CDCl$_3$) 29.7 (C-10), 32.3 (C-12), 61.2 (C-13), 108.7 (C-9), 109.7 (C-8), 171.5 (C-11)
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; \(\text{C}_{12}\text{H}_{13}\text{BrN}_{2}\text{NaO}_{2}\) (\(\text{MNa}^{+}\)) Requires 319.0053 (4.7 ppm error), Found: 297.0227; \(\text{C}_{12}\text{H}_{14}\text{BrN}_{2}\text{O}_{2}\) (\(\text{MH}^{+}\)) Requires 297.0233 (2.1 ppm error).

Lab notebook reference: akc02-82

\[
\text{2,2'}-(2,2'-\text{(1,4-Phenylene)}\text{bis(1H-indole-3,2-diyl)})\text{bis(N-methoxy-N-methylacetamide)}
\]

(135i)

\[
\begin{array}{c}
\text{benzene-1,4-diboronic acid} \\
\text{LiCl, Na}_{2}\text{CO}_{3}, \text{Pd(PPh}_{3}\text{)}_{4} \\
\text{PhMe/EtOH/H}_{2}\text{O}
\end{array}
\]

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), \(\text{Na}_{2}\text{CO}_{3}\) (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 \(\text{Pd(PPh}_{3}\text{)}_{4}\) (118 mg, 0.102 mmol). The reaction mixture was then stirred overnight at 80 \(^\circ\)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 \textit{in vacuo} to afford the \textit{title compound} \(135i\) without further purification as a yellow solid (240 mg, 46\%); mp 227–229 \(^\circ\)C; \(R_f\) 0.19 (1:1 hexane:EtOAc); \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 3252, 2932, 1636, 1455, 1002, 731; \(\delta_{\text{H}}\) (400 MHz, (CD\(_3\))\(_2\)SO) 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); \(\delta_{\text{C}}\) (100 MHz, (CD\(_3\))\(_2\)SO) 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; \(\text{C}_{30}\text{H}_{36}\text{N}_{4}\text{NaO}_{4}\) (\(\text{MNa}^{+}\)) Requires 533.2159 (4.4 ppm error).

Lab notebook reference: akc02-83
1-(1H-Indol-3-yl)-4-phenylbut-3-yn-2-one (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, 1666, 1083, 743; δ_H (400 MHz, CDCl₃) 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, CDCl₃) 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; C₁₈H₁₃NNaO (MNa⁺) Requires 282.0889 (2.8 ppm error), Found: 260.1066; C₁₈H₁₄NO (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-(1H-Indol-3-yl)pent-3-yn-2-one (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. NH₄Cl (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 MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) to afford the title compound 136b as an orange oil (398 mg, 88%); Rf 0.52 (3:2 hexane:EtOAc); v max (thin film)/cm⁻¹ 3406, 2215, 1661, 1457, 1244, 742; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₃H₁₁NNaO (M⁺Na⁺) Requires 220.0733 (2.9 ppm error), Found: 198.0905; C₁₃H₁₂NO (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)

Synthesised using general procedure B with phenylacetylene (0.43 mL, 3.87 mmol), THF (10 mL), N-methoxy-N-methyl-2-(2-methyl-1H-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; Rf 0.60 (1:1 hexane:EtOAc); v max (thin film)/cm⁻¹ 3398, 2202, 1660, 1462, 1302, 1117, 1093, 742; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; \text{C}_{19}\text{H}_{15}\text{NNaO} (\text{MNa}^+) \text{ Requires } 296.1046 \text{ (3.4 ppm error)}; \text{Found: } 274.1227; \text{C}_{19}\text{H}_{16}\text{NO} (\text{MH}^+) \text{ Requires } 274.1226 \text{ (–0.4 ppm error)}.

Lab notebook reference: akc01-53

*Material made by M. James

\textbf{1-(5-Bromo-1H-indol-3-yl)-4-phenylbut-3-yn-2-one (136d)}

\begin{center}
\includegraphics[width=0.2\textwidth]{136d}
\end{center}

Synthesised using general procedure B with phenylacetylene (0.16 mL, 1.46 mmol), THF (3.9 mL), \textit{2-(5-bromo-1H-indol-3-yl)-N-methoxy-N-methylacetamide 135c} \footnote{Material made by M. James} (145 mg, 0.488 mmol) and \textit{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 \textit{title compound 136d} as an orange solid (85.2 mg, 51\%); \textit{mp }124–126 °C; \textit{R_f }0.44 (1:1 hexane:EtOAc); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3419, 2201, 1660, 1489, 1458, 1284, 1096, 791, 757, 687; $\delta_H$ (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); $\delta_C$ (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); \textit{HRMS (ESI$^+$): Found: }359.9984; \textit{C}_{18}\text{H}_{12}^{79}\text{BrNNaO (MNa}^+) \text{ Requires } 359.9994 \text{ (2.8 ppm error)}.

Lab notebook reference: akc01-63

*Material made by M. James
5-(1H-Indol-3-yl)-1-phenylpent-1-yn-3-one (136e)

Synthesised using general procedure B with phenylacetylene (0.71 mL, 6.46 mmol), THF (17.3 mL), 3-(1H-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; Rf 0.62 (1:1 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3413, 3057, 2202, 1661, 1489, 1457, 1095, 758, 742; \( \delta_H \) (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); \( \delta_C \) (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\(^+\)) R\(_{\text{equ}}\) 296.1046 (−2.4 ppm error).

Lab notebook reference: akc01-76

*Material made by M. James

1,1’-(2,2’-(1,4-Phenylene)bis(1H-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. NH₄Cl (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 MgSO₄ 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; Rf 0.66 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹: 3438, 2199, 1668, 1457, 1279, 1190, 1090, 847, 767, 752, 689; δH (400 MHz, (CD3)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); δC (100 MHz, (CD3)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; C42H28N2NaO2 (MNa⁺) Requires 615.2043 (3.9 ppm error).

Lab notebook reference: akc02-84

4-Phenyl-1-(1H-pyrrol-2-yl)but-3-yn-2-one (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; Rf 0.62 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹: 3354, 2203, 1667, 1444, 1282, 1091, 725, 690; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C14H12NNaO (MNa⁺) Requires 232.0733 (−1.2 ppm error), Found: 210.0912; C14H12NO (MH⁺) Requires 210.0913 (0.7 ppm error).

Lab notebook reference: akc01-56
4-(4-Fluorophenyl)-1-(1H-pyrrol-2-yl)but-3-yn-2-one (136j)

Synthesised using general procedure B with 1-ethyl-1-4-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, CDCl₃) 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, J_{HH} = 8.5 Hz, J_{HF} 8.5 Hz, H-12), 7.54 (2 H, dd, J_{HH} = 8.5 Hz, J_{HF} = 5.0 Hz, H-11), 8.58 (1 H, br s, H-1); δ_{C} (100 MHz, CDCl₃) 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, J_{CF} = 3.0 Hz, C-10), 116.2 (d, J_{CF} = 23.0 Hz, C-12), 118.3 (C-2/3/4), 122.6 (C-5), 135.5 (d, J_{CF} = 10.0 Hz, C-11), 164.1 (d, J_{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-(1H-Pyrrol-2-yl)oct-3-yn-2-one (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, CDCl₃) 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, CDCl₃) 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; \(\text{C}_{12}\text{H}_{15}\text{NNaO (MNa\(^+\))}\) Requires 212.1046 (−2.6 ppm error), Found: 190.1221; \(\text{C}_{12}\text{H}_{16}\text{NO (MH\(^+\))}\) Requires 190.1226 (2.9 ppm error).

Lab notebook reference: akc05-05

1-(2,5-Dimethyl-1\textit{H}-pyrrol-3-yl)-4-phenylbut-3-yn-2-one (136\textit{l})

Synthesised using general procedure B with phenylacetylene (0.42 mL, 3.82 mmol), THF (10 mL), Weinreb amide 135\textit{f} (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 136\textit{l} as a yellow oil (164 mg, 54%); R\(_f\) 0.83 (1:1 hexane:EtOAc); \(\nu\)\(_{\text{max}}\) (thin film)/cm\(^{-1}\) 3370, 2918, 2203, 1659, 1489, 1288, 1071, 758, 689; \(\delta\)\(_{\text{H}}\) (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); \(\delta\)\(_{\text{C}}\) (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; \(\text{C}_{16}\text{H}_{15}\text{NNaO (MNa\(^+\))}\) Requires 260.1046 (0.8 ppm error), Found: 238.1219; \(\text{C}_{16}\text{H}_{16}\text{NO (MH\(^+\))}\) Requires 238.1226 (3.0 ppm error).

Lab notebook reference: akc05-33
1-(2,5-Dimethyl-1H-pyrrol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one (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%); Rf 0.57 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3369, 2919, 2203, 1656, 1599, 1505, 1224, 1066, 837; δH (400 MHz, CDCl₃) 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, 3JHH = 8.5 Hz, 3JHF = 8.5 Hz, H-14), 7.49–7.55 (2 H, m, H-13), 7.68 (1 H, br s, H-3); δc (100 MHz, CDCl₃) 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, 2JCF = 23.0 Hz, C-14), 116.3 (d, 2JCF = 4.0 Hz, C-12), 124.2 (C-1/7), 125.7 (C-4), 135.2 (d, 1JCF = 8.5 Hz, C-13), 163.8 (d, 1JCF = 253 Hz, C-15), 186.1 (C-9); HRMS (ESI⁺): Found: 278.0944; C₁₆H₁₄FNNaO (MNa⁺) Requires 278.0952 (2.7 ppm error), Found: 256.1127; C₁₆H₁₃FNO (MH⁺) Requires 256.1132 (2.2 ppm error).

Lab notebook reference: akc05-42

1-(2,5-Dimethyl-1H-pyrrol-3-yl)oct-3-yn-2-one (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%); Rf 0.62 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3372, 2958, 2931, 2872, 2211,
1658, 1243, 1171, 781; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₄H₁₉NNaO (MNa⁺) Requires 240.1359 (−0.2 ppm error), Found: 218.1539; C₁₄H₁₈NO (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)

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; Rf 0.29 (10:1 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm⁻¹ 3062, 2921, 2202, 1669, 1456, 1282, 1251, 1174, 1113, 1078, 746; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₉H₁₉NaO₂ (MNa⁺) Requires 297.0886 (1.5 ppm error), Found: 275.1074; C₁₉H₁₈O₂ (MH⁺) Requires 275.1067 (−2.8 ppm error).

Lab notebook reference: akc03-21

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1-(Benzofuran-3-yl)-4-phenylbut-3-yn-2-one (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%); Rf 0.49 (9:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 2202, 1669, 1453, 1097, 1081, 746; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₈H₁₂NaO₂ (MNa⁺) Requires 283.0730 (2.9 ppm error), Found: 261.0898; C₁₈H₁₃O₂ (MH⁺) Requires 261.0910 (4.6 ppm error).

Lab notebook reference: akc03-30

1-(1H-Indol-3-yl)but-3-yn-2-ol (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. NH₄Cl (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 MgSO₄ and concentrated in vacuo. The crude material was then dissolved in MeOH (45 mL),
cooled to 0 °C and NaBH₄ (347 mg, 9.16 mmol) was added portionwise. The mixture was stirred for 30 min at RT and then K₂CO₃ (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. NH₄Cl (20 mL) and diluted with CH₂Cl₂ (50 mL). The organics were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over MgSO₄, 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%); Rₚ 0.21 (7:3 hexane:EtOAc); ν}$/max$(thin film)/cm⁻¹ 3409, 3282, 1457, 1027, 1010, 743, 649; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₂H₁₁NNaO (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)

Method 1. Synthesised using general procedure C with ynone 136a (100 mg, 0.386 mmol), AgNO₃·SiO₂ (65.5 mg, 3.86 μmol) in CH₂Cl₂ (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), AgNO₃ (0.66 mg, 3.86 μmol) in CH₂Cl₂ (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%).
mp 138–140 °C; Rf 0.31 (1:1 hexane:EtOAc); ν\text{max} (thin film)/cm\textsuperscript{-1} 3068, 1701, 1591, 757; δ\text{H} (400 MHz, CDCl\textsubscript{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\text{C} (100 MHz, CDCl\textsubscript{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-23), 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\textsuperscript{+}): Found: 282.0885; C\textsubscript{18}H\textsubscript{13}NNaO (MNa\textsuperscript{+}) Requires 282.0889 (1.5 ppm error), Found: 260.1068; C\textsubscript{18}H\textsubscript{14}NO (MH\textsuperscript{+}) Requires 260.1070 (0.9 ppm error).

Spectroscopic data matched those previously reported in the literature.\textsuperscript{55}

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

\[
\begin{align*}
\text{Method 1. Synthesised using general procedure C with ynone 136b (112 mg, 0.568 mmol),} \\
\text{AgNO}_3\cdot\text{SiO}_2 (96.5 mg, 5.68 μmol) \text{ in CH}_2\text{Cl}_2 (5.7 mL) \text{ at RT for 35 min. Afforded the title compound 137b without further purification as a yellow solid (106 mg, 95%).}
\end{align*}
\]

Lab notebook reference: akc02-67

\[
\begin{align*}
\text{Method 2. Synthesised using general procedure D with ynone 136b (114 mg, 0.578 mmol),} \\
\text{AgNO}_3 (0.98 mg, 5.78 μmol) \text{ in CH}_2\text{Cl}_2 (5.8 mL) \text{ at RT for 5 h. Purification by column} \\
\text{chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) afforded the title compound 137b as a yellow solid (100 mg, 88%).}
\end{align*}
\]

Lab notebook reference: akc02-68

mp 109–111 °C; Rf 0.23 (1:1 hexane:EtOAc); ν\text{max} (thin film)/cm\textsuperscript{-1} 1713, 1689, 1619, 1550, 1455, 1295, 1192, 849, 773, 758; δ\text{H} (400 MHz, CDCl\textsubscript{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\text{C} (100 MHz, CDCl\textsubscript{3}) 14.6 (C-14), 40.4 (C-10), 113
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_{19}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)

Method 1. Synthesised using general procedure C with ynone 136c (100 mg, 0.366 mmol), AgNO₃·SiO₂ (62.2 mg, 3.66 μmol) in CH₂Cl₂ (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), AgNO₃ (0.62 mg, 3.66 μmol) in CH₂Cl₂ (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

R₉ 0.22 (1:1 hexane:EtOAc); νₖ max (thin film)/cm⁻¹ 3063, 1723, 1694, 1568, 1447, 1264, 1240, 1198, 861, 764; δ_H (400 MHz, CDCl₃) 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, CDCl₃) 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)

Method 1. Synthesised using general procedure C with ynone 136d (100 mg, 0.297 mmol), AgNO$_3$·SiO$_2$ (50.4 mg, 2.97 μmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3061, 1697, 1591, 1569, 1446, 1258, 777; $\delta_{\text{H}}$ (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); $\delta_{\text{C}}$ (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$_{12}$BrNNaO (MNa$^+$) Requires 359.9994 (1.9 ppm error).
1-Phenylspiro[cyclohex[6]ene-2,3'-indol]-5-one (137e)

Synthesised using general procedure C with ynone 136e (99.7 mg, 0.365 mmol), AgNO₃·SiO₂ (620 mg, 0.0365 mmol) in CH₂Cl₂ (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; Rf 0.27 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3057, 2930, 1670, 1445, 1331, 1262, 749, 698; δH (400 MHz, (CD₃)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); δC (100 MHz, (CD₃)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; C₁₉H₁₉NNaO (MNa⁺) Requires 296.1046 (3.5 ppm error), Found: 274.1217; C₁₉H₁₆NO (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)

Synthesised using general procedure C with 5-((1H-indol-3-yl)-1-(4-methoxyphenyl)pent-1-yn-3-one 136fs⁵⁵ (100 mg, 0.330 mmol), AgNO₃·SiO₂ (560 mg, 0.0330 mmol) in CH₂Cl₂ (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%); Rf 0.35 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 2934, 2838, 1666, 1604, 1510, 1242, 1181, 1031, 831, 758; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl3) 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; C20H17NNaO2 (MNa⁺) Requires 326.1151 (−0.3 ppm error), Found: 304.1330; C20H18NO2 (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}-[cyclopentane-1,3'indol]-2-en-4-one (137g)

\[\text{Ph} = \text{C} = \text{O} \]

\[\text{N} \]

\[\text{H} \]

\[\text{Ph} \]

\[\text{AgNO}_3 \cdot \text{SiO}_2 \]

CH₂Cl₂

To a solution of ynone 136g (24.5 mg, 41.3 µmol) in CH₂Cl₂ (0.8 mL) was added AgNO₃·SiO₂ (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; Rf 0.52 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3070, 2925, 1720, 1587, 1260, 863, 759; δH (400 MHz, CDCl₃) 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, m, H-15/16/17/2/3, 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); δC (100 MHz, CD₃SO) 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_{2}O_{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)

Synthesised using general procedure C with ynone 136h (100 mg, 0.477 mmol), AgNO_{3}·SiO_{2} (405 mg, 0.0239 mmol) in CH_{2}Cl_{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); \nu_{\text{max}} (thin film)/cm^{-1} 3064, 1694, 1593, 1570, 1492, 1340, 1237, 1199, 766; \delta_{\text{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); \delta_{\text{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)

Synthesised using general procedure C with 4-(4-methoxyphenyl)-1-(1H-pyrrol-2-yl)but-3-yn-2-one 136i*55 (19.7 mg, 0.0823 mmol), AgNO₃·SiO₂ (70.0 mg, 4.11 μmol) in CH₂Cl₂ (1 mL) at RT for 2 h. Afforded the title compound 143i without further purification as a brown oil (17.9 mg, 91%); Rᵢ 0.12 (1:1 hexane:EtOAc); ν max (thin film)/cm⁻¹ 1689, 1604, 1589, 1509, 1251, 1179, 1027, 833, 772; δH (400 MHz, CDCl₃) 2.66 (1 H, d, J = 18.0 Hz, H-5a), 2.90 (1 H, d, J = 18.0 Hz, H-5b), 3.79 (1 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); δC (100 MHz, CDCl₃) 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; C₁₅H₁₃NNaO₂ (MNa⁺) Requires 262.0838 (2.4 ppm error), Found: 240.1018; C₁₅H₁₄NO₂ (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)

Synthesised using general procedure C with ynone 136j (20.6 mg, 0.0907 mmol), AgNO₃·SiO₂ (77.0 mg, 4.54 μmol) in CH₂Cl₂ (1 mL) at RT for 2 h min. Afforded the title compound 143j without further purification as a brown oil (19.7 mg, 96%); Rᵢ 0.15 (1:1
hexane:EtOAc); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1694, 1603, 1506, 1199, 1162, 837, 773; $\delta_H$ (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); $\delta_C$ (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$_3$-SiO$_2$ (443 mg, 0.0261 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2958, 2931, 1719, 1695, 1615, 1196, 771; $\delta_H$ (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); $\delta_C$ (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$_{15}$FNNaO (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)

Synthesised using general procedure C with 1-(2,5-dimethyl-1H-pyrrol-3-yl)-4-phenylbut-3-yn-2-one 136i (46.3 mg, 0.195 mmol), AgNO₃·SiO₂ (33.1 mg, 1.95 μmol) in CH₂Cl₂ (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; Rₓ 0.17 (2:1 hexane:EtOAc); νₓ (thin film)/cm⁻¹ 1723, 1693, 1591, 1445, 1279, 1254, 770; δₓ (H, CDCl₃) 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); δₓ (C, CDCl₃) 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; C₁₆H₁₆NO (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)

Synthesised using general procedure C with 1-(2,5-dimethyl-1H-pyrrol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one 136m (66.0 mg, 0.259 mmol), AgNO₃·SiO₂ (43.9 mg, 2.59 μmol) in CH₂Cl₂ (2.6 mL) at RT for 15 min. Afforded the title compound 147m without further purification as a yellow oil (66.0 mg, 100%); Rₓ 0.21 (1:1 hexane:EtOAc); νₓ (thin film)/cm⁻¹ 1717, 1694, 1601, 1574, 1509, 1238, 1163, 836, 809; δₓ (H, CDCl₃) 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); δₓ (C, CDCl₃) 15.2 (C-2), 16.3 (C-4), 41.3 (C-7), 69.3 (C-6), 116.2 (d, ³J_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)

Synthesised using general procedure C with 1-(2,5-dimethyl-1H-pyrrol-3-yl)oct-3-yn-2-one 136n (39.5 mg, 0.182 mmol), AgNO$_3$·SiO$_2$ (30.9 mg, 1.82 μmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2964, 2931, 1720, 1701, 1611; $\delta_H$ (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); $\delta_C$ (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


To a solution of ynone 136o (130 mg, 0.472 mmol) in CH$_2$Cl$_2$ (4.7 mL) was added AgNO$_3$·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%); Rf 0.25 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3358, 2932, 1686, 1598, 1478, 1175, 757; HRMS (ESI⁺): Found: 315.0984; C₁₉H₁₆NaO₃ (MNa⁺) Requires 315.0992 (2.5 ppm error).

NMR data for the major diastereoisomer 148: δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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: δH (400 MHz, CDCl₃) 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)

To a solution of ynone 136p (22.6 mg, 86.8 μmol) in CH₂Cl₂ (0.9 mL) was added AgNO₃·SiO₂ (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%); Rf 0.31 (8:2 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3359, 1449, 1406, 1171, 773, 748; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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), 128.1 (C).
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; C₁₈H₁₃NaO₂ (MNa⁺) Requires 283.0730 (2.6 ppm error), Found: 261.0922;
C₁₈H₁₁O₂ (MH⁺) Requires 261.0910 (~4.6 ppm error).

Lab notebook reference: akc03-31

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

Synthesised using general procedure C with 1-(1H-indol-3-yl)-4-phenylbut-3-yn-2-ol 142
(77.4 mg, 0.293 mmol), AgNO₃·SiO₂ (497 mg, 2.93 μmol) in CH₂Cl₂ (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%); Rₓ 0.19 (1:1 hexane:EtOAc); νₘₐₓ (thin
film)/cm⁻¹ 3291, 1549, 1455, 1445, 1076, 1043, 1014, 906, 752, 730, 692; δH (400 MHz,
CDCl₃) 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); δC (100
MHz, CDCl₃) 42.4 (CH₂), 43.6 (CH₂), 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), 154.6 (C), 154.8 (2C), 176.9 (CH), 177.0 (CH); HRMS (ESI⁺):
Found: 284.1043; C₁₈H₁₅NNaO (MNa⁺) Requires 284.1046 (1.2 ppm error), Found: 262.1223;
C₁₈H₁₆NO (MH⁺) Requires 262.1226 (1.5 ppm error).

Lab notebook reference: akc02-81

*Material made by M. James
3-Hydroxy-4-(1H-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$_2$Cl$_2$ (4.2 mL) was added AgNO$_3$·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$_2$Cl$_2$: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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3350, 1707, 1457, 1355, 1091, 742; $\delta_H$ (400 MHz, CDCl$_3$) 3.01 (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), 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); $\delta_C$ (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$^+$/MNa)$^+$: 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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3405, 1707, 1457, 1355, 1091, 742; $\delta_H$ (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); $\delta_C$ (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-(1H-indol-3-yl)butan-2-one (155)

To a solution of alcohol 141 (19.5 mg, 0.105 mmol) in CH\(_2\)Cl\(_2\) (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)-1H-indole (158)

To a solution of alcohol 141 (94.7 mg, 0.511 mmol) in CH\(_2\)Cl\(_2\) (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 \textit{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; \nu_{\text{max}} \text{(thin film)/cm}^{-1}: 3420, 3308, 2928, 2856, 1457, 1251, 1081, 834, 777, 738; \delta_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); \delta_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}NaNOSi (MNa\(^+\)) Requires 322.1598 (−2.0 ppm error).

Lab notebook reference: akc03-103
4-Phenyl-1-(1-deutero-1H-indol-3-yl)but-3-yn-2-one (187) and 1-(1H-Indol-3-yl)-4-phenylbut-3-yn-2-one (136a)

Ynone 136a (130 mg, 0.501 mmol) was stirred in dry CD$_3$OD (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3273, 3045, 2493, 2202, 1652; $\delta_H$ (400 MHz, CDCl$_3$) 4.11 (4 H, s, H-$\text{-10}$, D+H compound), 7.15–7.21 (2 H, m, H-$\text{-3}$, D+H compound), 7.21–7.28 (4 H, m, H-$\text{-4,8}$, D+H compound), 7.29–7.45 (12 H, m, H-$\text{-5,15,16,17}$, D+H compound), 7.69 (2 H, br d, $J = 8.0$ Hz, H-$\text{-2}$, D+H compound), 8.22 (1 H, br s, H-$\text{-7}$, H compound); $\delta_C$ (100 MHz, CDCl$_3$) 42.0 (C-$\text{-10}$, D+H compounds), 88.0 (C-$\text{-12}$, D+H compounds), 92.0 (C-$\text{-13}$, D+H compounds), 107.5 (C-$\text{-9}$, D compound), 107.6 (C-$\text{-9}$, H compound), 111.2 (C-$\text{-5}$, D compound), 111.3 (C-$\text{-5}$, H compound), 118.9 (C-$\text{-2}$, D+H compounds), 119.8 (C-$\text{-3}$, D+H compounds), 119.9 (C-$\text{-14}$, D+H compounds), 122.3 (C-$\text{-4}$, D+H compounds), 123.5 (C-$\text{-8}$, D compound), 123.7 (C-$\text{-8}$, H compound), 127.4 (C-$\text{-1}$, D compound), 128.5 (C-$\text{-15/16}$, D+H compounds), 130.6 (C-$\text{-17}$, D+H compounds), 133.1 (C-$\text{-15/16}$, D+H compounds), 136.0 (C-$\text{-6}$, D compound), 136.1 (C-$\text{-6}$, H compound), 185.6 (C-$\text{-11}$, 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 ynone 187:136a (130 mg, 0.499 mmol), AgNO₃ (8.48 mg, 4.99 μmol), in CH₂Cl₂ (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; Rₛ 0.42 (1:1 hexane:EtOAc); νₘₚₓ (thin film)/cm⁻¹ 3064, 1698, 1548, 1224, 750; δₜₜ (400 MHz, CDCl₃) 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); δₛ (100 MHz, CDCl₃) 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; C₁₈H₁₂DNaO (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)

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 CH₂Cl₂ (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; Rₓ 0.58 (9:1 EtOAc:hexane); νₓ max (thin film)/cm⁻¹ 3264, 1631, 1614, 1594, 1515, 1446, 1233, 1172, 1002, 798; δₓ (400 MHz, CDCl₃) 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); δₓ (100 MHz, CDCl₃) 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; C₁₀H₁₃NNaO₃ (MNa⁺) Requires 218.0788 (−0.3 ppm error), Found: 196.0975; C₁₀H₁₃NO₃ (MH⁺) Requires 196.0968 (−3.2 ppm error).

Lab notebook reference: akc-bsc-01

2-(3-Hydroxyphenyl)-N-methoxy-N-methylacetamide (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 CH₂Cl₂ (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; Rₓ 0.27 (1:1 EtOAc:hexane); νₓ max (thin film)/cm⁻¹ 3261, 2939, 1632, 1597, 1586, 1485, 1454, 1387, 1155, 998, 772; δₓ (400 MHz, CDCl₃) 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, 6.10–6.12 (1 H, d, J = 8.5 Hz, H-1), 6.14–6.16 (1 H, s, H-2), 6.18–6.20 (1 H, s, H-6), 6.23–6.26 (1 H, d, J = 8.5 Hz, H-3), 6.27–6.30 (1 H, d, J = 8.5 Hz, H-4); δₓ (100 MHz, CDCl₃) 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: 196.0968; C₁₀H₁₃NO₃ (MH⁺) Requires 196.0968 (−0.3 ppm error), Found: 196.0975; C₁₀H₁₃NO₃ (MH⁺) Requires 196.0968 (−3.2 ppm error).
H-6), 7.15 (1 H, dd, \( J = 8.0, 8.0 \) Hz, H-2), 7.59 (1 H, br s, H-5); \( \delta_c \) (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)

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)_2·HCl (1.41 g, 14.6 mmol) in CH\(_2\)Cl\(_2\) (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); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3260, 1628, 1596, 1456, 1246, 1000, 753; \( \delta_h \) (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); \( \delta_c \) (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)

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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3316, 2939, 1639, 1514, 1432, 1271, 1200, 1151, 1033; $\delta_H$ (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); $\delta_C$ (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)

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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3242, 2938, 1627, 1601, 1518, 1444, 1388, 1280, 1260, 1194, 1115, 1004, 797; $\delta_H$ (400 MHz, CDCl$_3$) 3.23 (3 H, s, H-11), 3.62 (3 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); $\delta_C$ (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
133.4 (C-3/5), 144.3 (C-3/5), 173.7 (C-10); HRMS (ESI+): Found: 234.0734; C_{10}H_{13}NaO_{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)

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); v_{max} (thin film)/cm^{-1} 3368, 2202, 1655, 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_{10}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)

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; Rf 0.62 (1:1 hexane:EtOAc); νmax (thin film)/cm−1 3353, 2195, 1651, 1600, 1510, 1254, 1170, 1076, 834; δH (400 MHz, CDCl3) 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); δC (100 MHz, CDCl3) 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), 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)**

Synthesised using general procedure B with tert-butyl but-3-yn-1-yl(methyl)carbamate*\(^{\text{52}}\) (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%); Rf 0.62 (1:1 hexane:EtOAc); νmax (thin film)/cm−1 3331, 2977, 2212, 1663, 1515, 1395, 1366, 1225, 1145, 730; δH (400 MHz, CDCl3) 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); δC (100 MHz, CDCl3) 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 1H 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)

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; Rf 0.59 (1:1 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3367, 2201, 1647, 1514, 1222; \( \delta_{\text{H}} \) (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); \( \delta_{\text{C}} \) (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)

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%); Rf 0.74 (1:1 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1} \) 3376, 2961, 2871, 2205, 1650, 1514, 1224, 1172; \( \delta_{\text{H}} \) (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); \( \delta_{\text{C}} \) (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; C₁₅H₁₆NaO₂ (MNa⁺) Requires 251.1043 (0.7 ppm error).

Lab notebook reference: akc04-81

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

Synthesised using general procedure B with hex-1-yn (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%); Rf 0.76 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3373, 2959, 2933, 2209, 1652, 1514, 1224, 796; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₄H₁₄NaO₂ (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)

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; Rf 0.20 (7:3 hexane:EtOAc); νmax (thin film)/cm\(^{-1}\) 3437, 2195, 1655, 1601, 1509, 1254, 1237, 1170; δ\(_{\text{H}}\) (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\(_{\text{C}}\) (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)

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; Rf 0.81 (8:2 EtOAc:hexane); νmax (thin film)/cm\(^{-1}\) 3369, 2202, 1648, 1607, 1519, 1444, 1286, 1191, 1114, 1083, 758; δ\(_{\text{H}}\) (400 MHz, (CD\(_3\))\(_3\)CO) 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\(_{\text{C}}\) (100 MHz, (CD\(_3\))\(_3\)CO) 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)

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%); Rf 0.57 (6:4 hexane:EtoAc); νmax (thin film)/cm−1 3371, 2202, 1655, 1589, 1489, 1456, 1284, 1078, 758; δH (400 MHz, CDCl3) 3.89 (2 H, s, H-8), 5.44–5.51 (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); δC (100 MHz, CDCl3) 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; C16H12NaO2 (MNa+) Requires 259.0730 (−0.5 ppm error), Found: 237.0916; C16H13O2 (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)

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; Rf 0.67 (6:4 hexane:EtoAc); νmax (thin film)/cm−1 3333, 2982, 2202, 1661, 1489, 1458, 1156, 753; δH (400 MHz, CDCl3) 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); δC (100 MHz, CDCl3) 47.5 (C-8), 87.8 (C-10), 94.0 (C-11), 138
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)

![Chemical Structure of 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); v_{max} (thin film)/cm^{-1} 3364, 2193, 1645, 1599, 1508, 1254, 1080, 834; δ_H (400 MHz, CDCl₃) 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, CDCl₃) 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)

![Chemical Structure of 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; Rf 0.46 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3357, 2203, 1651, 1598, 1485, 1234, 838, 754; δH (400 MHz, CDCl₃) 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), 7.18–7.25 (2 H, m, H-3/4/5/6), 5.1 (2 H, dd, 3JHH = 8.5 Hz, 3JHF 8.5 Hz, H-14), 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); δC (100 MHz, CDCl₃) −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: 277.0628; C16H11FNaO₂ (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)

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; Rf 0.87 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3369, 2202, 1649, 1458, 1269, 755; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) −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; C13H11NaO2 (MNa⁺) Requires 223.0730 (−3 ppm error), Found: 201.0918; C13H10O2 (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)

Synthesised using general procedure C with ynone 197a (100 mg, 0.423 mmol), AgNO$_3$·SiO$_2$ (719 mg, 0.0423 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3068, 1693, 1658, 1592, 859, 764; $\delta_H$ (400 MHz, CDCl$_3$) 2.80 (2 H, s, H-5), 6.49 (2 H, d, $J = 10.0$ Hz, H-2), 6.71 (1 H, s, H-7), 6.96 (2 H, d, $J = 10.0$ Hz, H-10/11), 7.49–7.54 (2 H, m, H-10/11); $\delta_C$ (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), 134.8 (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)

Synthesised using general procedure C with ynone 197b (100 mg, 0.376 mmol), AgNO$_3$·SiO$_2$ (638 mg, 0.0376 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1691, 1659, 1602, 1586, 1509, 1251, 1179, 1027, 860, 833; $\delta_H$ (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); $\delta_C$ (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; \(\text{C}_{17}\text{H}_{14}\text{NaO}_3\) (MNa\(^+\)) Requires 289.0835 (0.1 ppm error), Found: 267.1009; \(\text{C}_{17}\text{H}_{15}\text{O}_3\) (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)**

![Diagram of 198c](image)

Synthesised using general procedure C with ynone 197c (73.5 mg, 0.232 mmol), AgNO\(_3\)-SiO\(_2\) (394 mg, 0.0232 mmol) in CH\(_2\)Cl\(_2\) (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); \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 2975, 1720, 1688, 1662, 1624, 1615, 1392, 1365, 1165, 1144, 860; \(\delta_H\) (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); \(\delta_C\) (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; \(\text{C}_{18}\text{H}_{23}\text{NNaO}_4\) (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)

Synthesised using general procedure C with ynone 197e (101 mg, 0.504 mmol), AgNO$_3$·SiO$_2$ (857 mg, 0.0504 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1689, 1666, 1624, 1605, 1401, 1252, 860; $\delta$H (400 MHz, CDCl$_3$) 0.77–0.82 (2 H, m, H$_{-10}$a), 1.11–1.17 (2 H, m, H$_{-10}$b), 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); $\delta$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 (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)

Synthesised using general procedure C with ynone 197f (60.2 mg, 0.264 mmol), AgNO$_3$·SiO$_2$ (448 mg, 0.0264 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 2958, 1697, 1657, 1621, 1609, 1403, 1249, 864; $\delta$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); $\delta$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_{13}H_{16}NaO_2 (MNa^+) Requires 251.1043 (3.9 ppm error), Found: 229.1215; C_{13}H_{15}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)**

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

Synthesised using general procedure C with ynone 197g (85.4 mg, 0.395 mmol), AgNO_3·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); v_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 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, t, 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_{15}O_2 (MH^+) Requires 217.1223 (2.0 ppm error).

Lab notebook reference: akc04-75

Spectroscopic data matched those previously reported in the literature.¹⁰⁴

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

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

Synthesised using general procedure C with ynone 197h (59.0 mg, 0.199 mmol), AgNO_3·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%); Rf 0.14 (1:1 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 1691, 1664, 1636, 1603, 1587, 1509, 1258, 1208, 1177, 831; \( \delta_{\text{H}} \) (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), 3.68 (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); \( \delta_{\text{C}} \) (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-4a,5,6,7-tetrahydrocyclopenta[d]quinoline-3,9(4H,10H)-dione (199)

To a stirred solution of spirocyclic dienone 198c (64.2 mg, 0.202 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (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%); Rf 0.47 (9:1 EtOAc:MeOH); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2790, 1709, 1684, 1632, 1209; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 2.23–2.32 (4 H, m, H-7, CH\(_2\)H\(^{\prime}\)), 2.45–2.54 (2 H, m, H-6, CHH\(^{\prime}\)), 2.58–2.75 (4 H, m, CH\(_3\), CHH\(^{\prime\prime}\) (×2)), 2.87 (1 H, dd, \( J = 16.0, 2.5 \) Hz, CHH\(^{\prime}\)), 3.10 (1 H, ddd, \( J = 11.0, 5.5, 2.5 \) Hz, CHH\(^{\prime\prime}\)), 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); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 29.7 (CH\(_3\)), 40.0 (CH\(_2\)), 42.1 (C-7), 45.9 (CH\(_2\)), 49.4 (C-1), 56.7 (CH\(_3\)), 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)

Synthesised using general procedure C with ynone 197k (115 mg, 0.487 mmol), AgNO$_3$·SiO$_2$ (826 mg, 0.0487 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1694, 1659, 1595, 1195, 760; $\delta_{\text{H}}$ (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); $\delta_{\text{C}}$ (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: 259.0730 (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)

Synthesised using general procedure C with ynone 197l (50 mg, 0.188 mmol), AgNO$_3$·SiO$_2$ (319 mg, 0.0188 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1689, 1659, 1602, 1587, 1510, 1262, 1179, 1026, 833, 731; $\delta_{\text{H}}$ (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); \( \delta_C \) (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)

Synthesised using general procedure C with ynone 197m (98.8 mg, 0.389 mmol), AgNO\(_3\)-SiO\(_2\) (661 mg, 0.0389 mmol) in CH\(_2\)Cl\(_2\) (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); \( \nu_{max} \) (thin film)/cm\(^{-1}\) 1694, 1659, 1601, 1582, 1508, 1238, 1193, 1163, 836; \( \delta_H \) (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, \( J_{HH} = 8.5 \) Hz, \( J_{HF} = 8.5 \) Hz, H-13), 7.25–7.29 (1 H, m, Ar-H), 7.29–7.34 (2 H, m, H-12); \( \delta_C \) (100 MHz, CDCl\(_3\)) 48.4 (C-7), 60.5 (C-6), 116.2 (d, \( J_{CF} = 22.0 \) Hz, C-13), 121.9 (CH), 126.5 (CH), 128.6 (d, \( J_{CF} = 3.0 \) Hz, C-11), 129.2 (C-9), 129.5 (d, \( J_{CF} = 8.5 \) Hz, C-12), 142.4 (CH), 144.3 (C-5), 164.3 (d, \( J_{CF} = 254 \) Hz, C-14), 172.3 (C-10), 200.1 (C-1), 204.3 (C-8); HRMS (ESI\(^+\)): Found: 277.0642; C\(_{16}\)F\(_{11}\)NaO\(_2\) (MNa\(^+\)) Requires 277.0635 (−2.4 ppm error), Found: 255.0818; C\(_{16}\)F\(_{12}\)O\(_2\) (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)

Synthesised using general procedure C with ynone 197n (108 mg, 0.538 mmol), AgNO₃·SiO₂ (915 mg, 0.0538 mmol) in CH₂Cl₂ (5.4 mL) at RT for 2 h. Afforded the title compound 201n without further purification as a yellow oil (104 mg, 96%); Rₛ 0.34 (1:1 hexane:EtOAc); νₖₑₑₙ (thin film)/cm⁻¹ 1694, 1660, 1632, 1607, 1557, 1200, 862; δₜₜ (400 MHz, CDCl₃) 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); δₑ (100 MHz, CDCl₃) 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; C₁₃H₁₂NaO₂ (MNa⁺) Requires 223.0730 (−1.3 ppm error), Found: 201.0907; C₁₃H₁₀O₂ (MH⁺) Requires 201.0910 (1.3 ppm error).

Lab notebook reference: akc04-68

tert-Butyl 3-iodo-1H-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. Na₂S₂O₃ (100 mL), extracted with diethyl ether (3 x 100 mL), dried over MgSO₄ and concentrated in vacuo. The crude material was then dissolved in CH₂Cl₂ (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
CH₂Cl₂ (100 mL), washed with water (70 mL), dried over MgSO₄ 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%); Rₛ 0.78 (7:3 hexane:EtOAc); νₚₑ₅₈ (thin film)/cm⁻¹ 2978, 1735, 1448, 1369, 1310, 1246, 1154, 1052, 744; δₜₜ₆ (400 MHz, CDCl₃) 1.68 (9 H, s, H₉₋₁₁), 7.30–7.44 (3 H, m, Ar-H), 7.74 (1 H, s, H₇), 8.14 (1 H, br d, J = 8.0 Hz, Ar-H); δₙ₉ (100 MHz, CDCl₃) 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₋₁₁/₆), 135.0 (C₋₁₋₁/₆), 148.8 (C₋₉).

Note: Some peaks broadened in ¹H and ¹³C 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-1H-indole-1-carboxylate (208)

![Chemical structure of tert-Butyl 3-ethynyl-1H-indole-1-carboxylate (208)](attachment)

A solution of tert-butyl 3-iodo-1H-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(PPh₃)₂Cl₂ (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 × 50 mL), dried over MgSO₄ 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. NH₄Cl (50 mL), extracted with diethyl ether (3 × 50 mL), dried over MgSO₄ 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%); Rₛ 0.63 (10:1 hexane:EtOAc); νₚₑ₅₈ (thin film)/cm⁻¹ 3292, 2980, 1734, 1451, 1358, 1227, 1148, 1081, 745; δₜ₉ (400 MHz, CDCl₃) 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₋₁₁/₆).
10), 8.17 (1 H, d, J = 8.0 Hz, Ar-H); δc (100 MHz, CDCl₃) 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)-1H-indole-1-carboxylate (209)**

![Diagram](image)

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%); Rf 0.37 (7:3 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3374, 2980, 2188, 1743, 1369, 1232, 1150, 1072; \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 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); \( \delta_{\text{C}} \) (100 MHz, CDCl₃) 28.2 (C-10), 51.2 (C-15), 85.3 (C-19), 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; C₂₃H₂₁NNaO₄ (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)-1H-indole-1-carboxylate (83)**

Synthesised using general procedure C with ynone 209 (68.4 mg, 0.182 mmol), AgNO$_3$·SiO$_2$ (310 mg, 0.0182 mmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 1742, 1694, 1662, 1595, 1370, 1351, 1228, 1148, 1109, 861, 732; $\delta_H$ (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); $\delta_C$ (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-(1H-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. NH₄Cl (100 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL), organics were combined, washed with brine (50 mL), dried over MgSO₄ 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; Rf 0.22 (2:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3300, 2983, 1732, 1509, 1422, 1261, 1235, 1072; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₈H₉NNaO₃ (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-(1H-pyrrol-3-yl)acetate (222)

To a rbf under argon containing ethyl 2-oxo-2-(1H-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 NaH₂PO₄·H₂O (11.8 g, 110 mmol) in H₂O (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 NaH₂PO₄·H₂O (11.8 g, 110 mmol) in H₂O (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 MgSO₄ 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%); Rf 0.51 (2:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3393, 2982, 1725, 1279, 1148, 1061; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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)-1H-pyrrol-3-yl)acetate (225)**

To a stirred solution of TIPS-pyrrole 220 (3.00 g, 13.4 mmol) in CH₂Cl₂ (67 mL) at 0 °C was added ethyl diazoacetate (2.03 mL, 16.8 mmol, 87 wt.% in CH₂Cl₂) 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 CH₂Cl₂ (2 x 50 mL). The organics were combined, washed with brine (50 mL), dried over MgSO₄ 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%); Rf 0.65 (6:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 2946, 2868, 1737, 1464, 1096; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₇H₃₁NNaO₂S𝑖 (MNa⁺) Requires 332.2016 (1.2 ppm error), Found: 310.2191; C₁₇H₃₂NO₂S𝑖 (MH⁺) Requires 310.2197 (1.9 ppm error).

Lab notebook reference: akc05-19
**N-Methoxy-N-methyl-2-(1H-pyrrol-3-yl)acetamide (218a)**

![Chemical structure]

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 MgSO₄ 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 MgSO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ 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 MgSO₄ 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*ₜ 0.43 (5:1 EtOAc:hexane); *ν* max (thin film)/cm⁻¹ 3314, 2937, 1641, 1435, 1384, 1071, 1004, 768; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₈H₁₃N₂NaO₂ (MNa⁺) Requires 191.0791 (−0.4 ppm error), Found: 169.0979; C₈H₁₃N₂O₂ (MH⁺) Requires 169.0972 (−4.6 ppm error).

Lab notebook reference: akc05-20/22/23
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. NH₄Cl (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 MgSO₄, 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 × 10 mL). The organic layer was dried over MgSO₄ 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 × 20 mL). The organics were combined, washed with brine (20 mL), dried over MgSO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ layer was removed and the aqueous extracted with EtOAc (2 × 20 mL). The organics were combined, washed with brine (20 mL), dried over MgSO₄ 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%); Rf 0.36 (1:1 EtOAc:hexane); νmax (thin film)/cm⁻¹ 3313, 2972, 2935, 1640, 1384, 1071, 989, 769; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃)
MHz, CDCl₃) 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; C₉H₁₄N₂NaO₂ (MNa⁺) Requires 205.0947 (3.8 ppm error), Found: 183.1121; C₉H₅N₂O₂ (MH⁺) Requires 183.1128 (−4.1 ppm error).

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

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

![Chemical Structure](image)


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 CH₂Cl₂ (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, CDCl₃) 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, CDCl₃) 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; C₉H₁₀N₂NaO₂ (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-1H-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 MgSO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ layer was removed and the aqueous extracted with EtOAc (2 x 20 mL). The organics were combined, washed with brine (10 mL), dried over MgSO₄ 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%); *Rf* 0.14 (6:4 hexane:EtOAc); *ν*<sub>max</sub> (thin film)/cm<sup>-1</sup> 2937, 1655, 1507, 1419, 1379, 1160, 1006, 764; δ<sub>H</sub> (400 MHz, CDCl₃) 3.20 (3 H, s, H<sub>-8</sub>), 3.61 (5 H, s, H<sub>-1/6</sub>), 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<sub>C</sub> (100 MHz, CDCl₃) 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<sup>+</sup>): Found: 205.0941; C₉H₁₄N₂NaO₂ (MNa<sup>+</sup>) Requires 205.0947 (3.3 ppm error).

Lab notebook reference: akc07-76
4-Phenyl-1-(1H-pyrrol-3-yl)but-3-yn-2-one (214a)

Syrthesised 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, CDCl₃) 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, CDCl₃) 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; C₁₄H₁₁NNaO (MNa⁺) Requires 232.0733 (−2.8 ppm error), Found: 210.0920; C₁₄H₁₂NO (MH⁺) Requires 210.0913 (−3.1 ppm error).

Lab notebook reference: akc05-24

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

Syrthesised using general procedure B with 1-ethyl-1-4-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, CDCl₃) 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, 3_J_HH = 8.5 Hz, 3_J_HF 8.5 Hz, H-12), 7.52 (2 H, dd, 3_J_HH = 8.5 Hz, 4_J_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-((1H-pyrrol-3-yl)but-3-yn-2-one (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_{10}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-(1H-pyrrolo-3-yl)but-3-yn-2-one (214d)

Synthesised using general procedure B with 1-(benzyloxy)-4-ethynylbenzene* (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; Rf 0.23 (5:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3392, 2197, 1659, 1601, 1508, 1250, 1078, 1058, 833, 698; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₂₁H₁₇NNaO₂ (MNa⁺) Requires 338.1151 (2.2 ppm error), Found: 316.1331; C₂₁H₁₆NO₂ (MH⁺) Requires 316.1332 (0.5 ppm error).

Lab notebook reference: akc05-62

*Material made by W. Unsworth

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

Synthesised using general procedure B with hex-1-yn (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%); Rf 0.75 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3394, 2959, 2933, 2873, 2210, 1665, 1235, 1071, 765; δH (400 MHz, CDCl₃) 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); δc (100 MHz, CDCl₃) 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; C₁₂H₁₅NNaO (MNa⁺) Requires 212.1046 (−0.4 ppm error), Found: 190.1229; C₁₂H₁₆NO (MH⁺) Requires 190.1226 (−1.4 ppm error).

Lab notebook reference: akc05-58

**tert-Butyl methyl(5-oxo-6-(1H-pyrrol-3-yl)hex-3-y1)carbamate (214f)**

![](image)

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%); Rf 0.67 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3334, 2976, 2935, 2211, 1669, 1481, 1393, 1366, 1168, 1145; δH (400 MHz, CDCl₃) 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); δc (100 MHz, CDCl₃) 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; C₁₆H₂₃N₂NaO₃ (MNa⁺) Requires 313.1523 (0.6 ppm error).

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

Lab notebook reference: akc05-76

*Material made by J. Liddon*
7-Chloro-1-(1H-pyrrol-3-yl)hept-3-yn-2-one (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); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3392, 2924, 2211, 1665, 1234, 1071, 765; \( \delta_{\text{H}} \) (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); \( \delta_{\text{C}} \) (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\(_{12}\)ClN\(_2\)O (MNa\(^+\)) Requires 232.0500 (1.2 ppm error).

Lab notebook reference: akc05-74

5-Methyl-1-(1H-pyrrol-3-yl)hex-5-en-3-yn-2-one (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); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3393, 2923, 2195, 2165, 1660, 1296, 1118, 764; \( \delta_{\text{H}} \) (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); \( \delta_{\text{C}} \) (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), 162
127.5 (C-11), 186.3 (C-7); HRMS (ESI⁺): Found: 196.0729; C₁₁H₁₁NNaO (MNa⁺) Requires 196.0733 (2.2 ppm error).

Lab notebook reference: akc05-66

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

Synthesised using general procedure B with 1-methoxy-4-(prop-2-yn-1-yl)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%); Rf 0.66 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3395, 2910, 2217, 1672, 1506, 1206, 1039, 826; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₆H₁₅NNaO₃ (MNa⁺) Requires 292.0944 (0.2 ppm error), Found: 270.1116; C₁₆H₁₅NO₃ (MH⁺) Requires 270.1125 (3.1 ppm error).

Lab notebook reference: akc05-63
1-Phenyl-4-(1H-pyrrol-3-yl)pent-1-yn-3-one (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%); Rtf 0.75 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3392, 2975, 2196, 1651, 1489, 1443, 1287, 1122, 1069, 1042, 970, 756, 687; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₅H₁₃NNaO (MNa⁺) Requires 246.0889 (1.5 ppm error), Found: 224.1067; C₁₅H₁₄NO (MH⁺) Requires 224.1070 (−1.4 ppm error).

Lab notebook reference: akc06-20

1-(1-Methyl-1H-pyrrol-3-yl)-4-phenylbut-3-yn-2-one (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%); Rf 0.89 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 2201, 1661, 1489, 1286, 1160, 1071, 756; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 36.2 (C-1), 44.0 (C-6), 88.0 (C-8), 91.5 (C-9), 164
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; \(\text{C}_{15}\text{H}_{13}\text{NNaO (MNa}^+\) - Requires 246.0889 (−2.1 ppm error).

Lab notebook reference: akc07-77

1-(1\(H\)-Pyrrl-3-yl)-4-(trimethylsilyl)but-3-yn-2-one (214l)

\[
\begin{align*}
\text{Synthesised using general procedure B with ethynyltrimethylsilane (0.30 mL, 2.19 mmol),} \\
\text{THF (6 mL), Weinreb amide 218a (123 mg, 0.731 mmol) and n-BuLi (0.73 mL, 1.83 mmol,} \\
\text{2.5 M in hexanes) stirring at RT for 30 min. Purification by column chromatography (9:1} \\
\text{hexane:EtOAc) afforded the title compound 214l as a yellow oil (79.5 mg, 53%); R\(_f\) 0.20 (9:1} \\
\text{hexane:EtOAc); }\nu_{\max} (\text{thin film})/\text{cm}^{-1} 3399, 2962, 2151, 1668, 1252, 1095, 845, 760; \delta_H (400} \\
\text{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); \delta_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; \(\text{C}_{11}\text{H}_{15}\text{NNaOSi (MNa}^+\) Requires} \\
228.0815 (1.7 ppm error), Found: 206.0996; \(\text{C}_{11}\text{H}_{15}\text{NOSi (MH}^+)\) Requires 206.0996} \\
(−0.1 ppm error).

Lab notebook reference: akc05-88
Methyl 4-((tert-butoxycarbonyl)amino)but-2-ynoate (231)


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 CH₂Cl₂ (16 mL) was added to afford a homogeneous, light yellow reaction mixture that was cooled to 0 °C. After 5 min, freshly distilled NEt₃ (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. NaHCO₃ (20 mL). The organics were separated, washed with sat. aq. NaHCO₃ (3 x 20 mL), dried over MgSO₄ 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 Et₂O (2 x 20 mL). The organics were combined, washed with brine, dried over MgSO₄ 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; Rf 0.17 (6:1 hexane:EtOAc); νmax (thin film)/cm⁻¹: 3354, 2980, 2243, 1716, 1514, 1249, 1166; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₀H₁₅NNaO₄ (MNa⁺) Requires 236.0893 (0.2 ppm error).
Spectroscopic data matched those previously reported in the literature.\textsuperscript{152}

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


**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$_2$Cl$_2$:Et$_2$O (15 mL), filtered through a short pad of Florosil eluting with CH$_2$Cl$_2$:Et$_2$O (1:1, 2 x 20 mL) and then Et$_2$O (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); $\nu_{max}$ (thin film)/cm$^{-1}$ 2980, 2952, 1732, 1341, 1252, 1149, 769, 698; $\delta_H$ (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); $\delta_C$ (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).
Spectroscopic data matched those previously reported in the literature.\(^{152}\)

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

![Chemical structure](image)


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); \(v_{\text{max}}\) (thin film)/cm\(^{-1}\) 3376, 2951, 1724, 1607, 1515, 1455, 1436, 1263, 1196, 1155, 1123, 978, 760; \(\delta_H\) (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); \(\delta_C\) (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-1H-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 MgSO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ layer was removed and the aqueous extracted with EtOAc (2 x 10 mL). The organics were combined, dried with 10% aq. HCl (10 mL), brine (10 mL), dried over MgSO₄ 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%); Rf 0.43 (7:3 EtOAc:hexane); νmax (thin film)/cm⁻¹ 3299, 2939, 1638, 1607, 1513, 1458, 1384, 1004, 764; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₄H₁₆N₂NaO₂ (MNa⁺) Requires 267.1104 (1.4 ppm error).

Lab notebook reference: akc07-33/37
4-Phenyl-1-(5-phenyl-1H-pyrrol-3-yl)but-3-yn-2-one (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%); RF 0.72 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3380, 3058, 2202, 1660, 1489, 1282, 758, 689; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 43.9 (C-10), 88.0 (C-12), 92.0 (C-13), 107.3 (C-1/8), 116.3 (C), 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; C₂₀H₁₅NNaO (MNa⁺) Requires 308.1046 (−4.8 ppm error), Found: 286.1218; C₂₀H₁₆NO (MH⁺) Requires 286.1226 (2.9 ppm error).

Lab notebook reference: akc07-38

1-(5-Phenyl-1H-pyrrol-3-yl)oct-3-yn-2-one (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%); RF 0.81 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3382, 2958, 2869, 2210, 1663, 1607, 1514, 1455, 1239, 1119, 763; δH (400 MHz, CDCl₃) 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
(Z)-Methyl 3-(((tert-butoxycarbonyl)amino)methyl)-5-phenylpent-2-en-4-ynoate (234)


**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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3386, 2978, 2208, 1710, 1606, 1199, 1170, 1118, 758; $\delta_H$ (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); $\delta_C$ (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; C₁₈H₂₁NNaO₄ (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-1H-pyrrole-1-carboxylate (235)

![Chemical structure of 235](image)


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), PdCl₂ (9.17 mg, 51.7 µmol), CuCl₂·2H₂O (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 MgSO₄, 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%); Rₖ 0.41 (6:1 hexane:EtOAc); νₘₐₓ (thin film)/cm⁻¹ 2930, 1736, 1436, 1367, 1255, 1152, 1004, 992, 851, 767; δₜₜ (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₂₄H₂₃NNaO₄ (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-1H-pyrrol-3-yl)acetate (236)


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%); Rf 0.19 (5:1 hexane:EtOAc); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3372, 2954, 2925, 2855, 1729, 1603, 1457, 1436, 1157, 767, 698; \( \delta_{\text{H}} \) (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); \( \delta_{\text{C}} \) (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; \( \text{C}_{19}\text{H}_{23}\text{NNaO}_{2} \) (MNa\(^+\)) Requires 320.1621 (4.0 ppm error), Found: 298.1792; \( \text{C}_{19}\text{H}_{24}\text{NO}_{2} \) (MH\(^+\)) Requires 298.1802 (–3.4 ppm error)

Lab notebook reference: akc07-55
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 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 MgSO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ layer was removed and the aqueous extracted with EtOAc (2 x 10 mL). The organics were combined, brine (10 mL), dried over MgSO₄ 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. NH₄Cl (5 mL). The organics were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over MgSO₄ 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%); Rₜ 0.49 (5:2 hexane:EtOAc); νₜₐₘₓ (thin film)/cm⁻¹ 3373, 2955, 2925, 2855, 2201, 1660, 1489, 1072, 688; δₜ (400 MHz, CDCl₃) 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, s, 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); δₐ (100 MHz, CDCl₃) 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), 174
126.6 (CH), 127.2 (CH), 128.5 (CH), 129.6 (CH), 130.6 (CH), 132.0 (C-5), 133.1 (CH), 133.3 (C), 186.6 (C-17); HRMS (ESI+): Found: 368.2019; C\textsubscript{26}H\textsubscript{26}NO (MH\textsuperscript{+}) Requires 368.2009 (−2.7 ppm error).

Lab notebook reference: akc07-57/58/59

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

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\textsubscript{4} and concentrated \textit{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\textsubscript{2}Cl\textsubscript{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\textsubscript{2}Cl\textsubscript{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\textsubscript{4} and concentrated \textit{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\textsubscript{4}Cl (5 mL). The organics were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organics were combined, washed with brine (10 mL), dried over MgSO\textsubscript{4} and concentrated \textit{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%); Rf 0.71 (3:2 hexane:EtOAc); ν\textsubscript{max} (thin film)/cm\textsuperscript{-1} 3370, 2961, 2927, 2873, 2211, 1667, 1604, 1165, 767, 698; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}): Found: 348.2313; C\textsubscript{24}H\textsubscript{29}NO (MH\textsuperscript{+}) Requires 348.2322 (−2.6 ppm error).

Lab notebook reference: akc07-61/62/64

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

![Image of the structure of 215a]

Method 1: Synthesised using general procedure E with ynone 214a (81.2 mg, 0.388 mmol), AgNO\textsubscript{3} (3.30 mg, 19.4 µmol) in CH\textsubscript{2}Cl\textsubscript{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

![Image of the reaction scheme for 215a]

Method 2: A solution of AgOTf (6.1 mg, 23.9 µmol) and PPh\textsubscript{3} (6.3 mg, 23.9 µmol) in CH\textsubscript{2}Cl\textsubscript{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$_2$Cl$_2$ (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); $\nu_{max}$ (thin film)/cm$^{-1}$ 3432, 1591, 1485, 1416, 1162, 1132, 890, 758; $\delta$$_H$ (400 MHz, CDCl$_3$) 4.65 (1 H, br s, H-8), 6.50–6.53 (1 H, m, H-2/3), 6.84 (1 H, d, $J$ = 2.5 Hz, H-6/9), 7.07 (1 H, d, $J$ = 2.5 Hz, H-6/9), 7.19–7.23 (1 H, m, H-2/3), 7.42 (1 H, t, $J$ = 7.5 Hz, H-14), 7.52 (2 H, dd, $J$ = 7.5, 7.5 Hz, H-13), 7.63 (2 H, d, $J$ = 7.5 Hz, H-12), 8.29 (1 H, br s, H-1); $\delta$$_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)-1H-indol-5-ol (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$_2$Cl$_2$ (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); $\nu_{max}$ (thin film)/cm$^{-1}$ 3435, 1607, 1504, 1223, 1159, 1133, 835, 803, 731; $\delta$$_H$ (400 MHz, CDCl$_3$) 4.85 (1 H, br s, H-8), 6.49–6.54 (1 H, m, H-2/3), 6.78 (1 H, d, $J$ = 2.5 Hz, H-6/9), 7.06 (1 H, d, $J$ = 2.5 Hz, H-6/9), 7.15–7.23 (3 H, m, H-2/3,13), 7.56 (1 H, dd, $^3$J$_{IH}$ = 8.5 Hz, $^3$J$_{HF}$ = 5.5 Hz, H-12), 8.21 (1 H, br s, H-1); $\delta$$_C$ (100 MHz, CDCl$_3$) 102.6 (C-2/3), 104.3 (C-6/9), 111.6 (C-6/9), 116.1 (d, $^2$J$_{CF}$ = 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, $^3$J$_{CF}$ = 8.0 Hz, C-12), 134.7 (d, $^4$J$_{CF}$ = 3.0 Hz, C-11), 149.8 (C-7), 162.3 (d, $^1$J$_{CF}$ = 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)-1H-indol-5-ol (215c)

Synthesised using general procedure E with ynone 214c (55.6 mg, 0.232 mmol), AgNO₃ (1.97 mg, 11.6 μmol) in CH₂Cl₂ (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%); Rᵢ 0.11 (6:1 hexane:EtOAc); ν max (thin film)/cm⁻¹ 3393, 2928, 1610, 1506, 1286, 1246, 1179, 1163, 1134, 833, 725; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₅H₁₄NO₂ (MH⁺) Requires 240.1019 (4.5 ppm error).

Lab notebook reference: ake05-73

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

Synthesised using general procedure E with ynone 214d (85.5 mg, 0.271 mmol), AgNO₃ (2.30 mg, 13.6 μmol) in CH₂Cl₂ (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; Rᵢ 0.78 (1:1 hexane:EtOAc); ν max (thin film)/cm⁻¹ 3435, 1608, 1505, 1240, 1162, 1133, 832, 732; δH (400 MHz, CDCl₃) 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); \( \delta_c \) (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)

Synthesised using general procedure E with ynone 214e (69.3 mg, 0.366 mmol), AgNO\(_3\) (3.11 mg, 18.3 μmol) in CH\(_2\)Cl\(_2\) (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); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 3418, 3340, 2956, 2929, 2859, 1595, 1430, 1138, 840, 725; \( \delta_h \) (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); \( \delta_c \) (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](image)

Synthesised using general procedure E with ynone **214f** (72.4 mg, 0.249 mmol), AgNO₃ (2.12 mg, 12.5 μmol) in CH₂Cl₂ (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%); Rₜ 0.67 (1:1 hexane:EtOAc); νₘₚ (thin film)/cm⁻¹ 3316, 2977, 2933, 1662, 1484, 1431, 1396, 1367, 1165, 1142, 727; δ_H (400 MHz, CDCl₃) 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, CDCl₃) 28.5 (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; C₁₆H₂₂N₂O₃ (MNa⁺) Requires 313.1523 (0.7 ppm error), Found: 291.699; C₁₆H₂₃N₂O₃ (M⁺) Requires 291.1703 (1.3 ppm error).

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

Lab notebook reference: akc05-79

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

![215g](image)

Synthesised using general procedure E with ynone **214g** (32.4 mg, 0.155 mmol), AgNO₃ (1.31 mg, 7.73 μmol) in CH₂Cl₂ (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%); Rₜ 0.37 (3:1 hexane:EtOAc); νₘₚ (thin film)/cm⁻¹ 3417, 2927,
2855, 1595, 1494, 1430, 1138, 840, 727; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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, 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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}): Found: 210.0684; C\textsubscript{11}H\textsubscript{13}ClNO (MH\textsuperscript{+}) Requires 210.0680 (−1.6 ppm error).

Lab notebook reference: akc05-77

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

Synthesised using general procedure E with ynone 214h (52.1 mg, 0.301 mmol), AgNO\textsubscript{3} (2.56 mg, 15.0 μmol) in CH\textsubscript{2}Cl\textsubscript{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\textsubscript{f} 0.33 (4:1 hexane:EtOAc); \upsilon\textsubscript{max} (thin film)/cm\textsuperscript{-1} 3428, 1590, 1491, 1422, 1306, 1139, 724; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{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\textsubscript{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}): Found: 196.0728; C\textsubscript{11}H\textsubscript{12}NNaO (MNa\textsuperscript{+}) Requires 196.0733 (2.2 ppm error), Found: 174.0914; C\textsubscript{11}H\textsubscript{12}NO (MH\textsuperscript{+}) Requires 174.0913 (−0.4 ppm error).

Lab notebook reference: akc05-71
7-((4-Methoxyphenoxy)methyl)-1H-indol-5-ol (215i)

![Chemical Structure](image)

Synthesised using general procedure E with ynone 214i (69.2 mg, 0.257 mmol), AgNO₃ (2.18 mg, 12.8 μmol) in CH₂Cl₂ (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%); Rₛ 0.68 (1:1 hexane:EtOAc); νₘₐₓ (thin film)/cm⁻¹ 3421, 2929, 1506, 1439, 1222, 1142, 1033, 825; δₜ (400 MHz, CDCl₃) 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); δₑ (100 MHz, CDCl₃) 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; C₁₆H₁₅NNaO₃ (MN⁺) Requires 292.0944 (0.7 ppm error), Found: 270.1129; C₁₆H₁₅NO₃ (MH⁺) Requires 270.1125 (1.5 ppm error).

Lab notebook reference: akc05-65

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

![Chemical Structure](image)

To a solution of ynone 214j (51.0 mg, 0.228 mmol) in CH₂Cl₂ (2.3 mL) at RT was added AgNO₃ (1.94 mg, 11.4 μmol) and Ag₂O (1.32 mg, 5.71 μmol). The reaction mixture was stirred at RT for 24 h. A further portion of both AgNO₃ (1.94 mg, 11.4 μmol ) and Ag₂O (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%); Rₛ 0.33 (8:2 hexane:EtOAc); νₘₐₓ (thin film)/cm⁻¹ 3436, 2922, 2852, 1598,
1491, 1388, 1346, 1095, 850, 763, 724, 705; δH (400 MHz, CDCl3) 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); δC (100 MHz, CDCl3) 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_{13}NO (MH\') Requires 224.1070 (1.4 ppm error).

Lab notebook reference: akc06-62

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

Synthesised using general procedure E with ynone 214k (50.3 mg, 0.225 mmol), AgNO₃ (3.80 mg, 22.5 μmol) in CH₂Cl₂ (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%); Rf 0.84 (1:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3344, 1605, 1586, 1485, 1409, 1165, 1139, 1098, 993, 810, 770; δH (400 MHz, CDCl3) 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); δC (100 MHz, CDCl3) 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-1H-indol-5-ol (215l)

Synthesised using general procedure F with ynone 233a (30.9 mg, 0.108 mmol), AgNO₃ (1.84 mg, 10.8 µmol) and Ag₂O (1.25 mg, 5.40 µmol) in CH₂Cl₂ (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; Rₚ 0.53 (7:3 hexane:EtOAc); νₘₐₓ (thin film)/cm⁻¹ 3466, 3350, 3057, 1594, 1480, 1191, 1156, 907, 845, 759, 733, 704; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₂₀H₁₅NNaO (MNa⁺) Requires 308.1046 (−4.3 ppm error), Found: 286.1218; C₂₀H₁₄NO (MH⁺) Requires 286.1226 (2.8 ppm error).

Lab notebook reference: akc07-40

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

Synthesised using general procedure F with ynone 233b (46.2 mg, 0.174 mmol), AgNO₃ (1.48 mg, 8.71 µmol) and Ag₂O (1.00 mg, 4.35 µmol) in CH₂Cl₂ (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%); Rₚ 0.54 (7:3 hexane:EtOAc); νₘₐₓ (thin film)/cm⁻¹ 3353, 2955, 2928, 2859, 1617, 1599, 1452, 1375, 1245, 1138, 842, 763, 746; δH (400 MHz, CDCl₃) 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); $\delta$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

1H-Indol-5-ol (238)

![Chemical structure](https://via.placeholder.com/150)

To a solution of ynone 214I (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); $\nu$$_{\text{max}}$ (thin film)/cm$^{-1}$ 3408, 1627, 1583, 1487, 1455, 1341, 1219, 1145, 1129, 947, 802, 757, 726; $\delta$H (400 MHz, (CD$_3$)$_2$SO) 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); $\delta$C (100 MHz, (CD$_3$)$_2$SO) 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.$^{209}$
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. NH₄Cl (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 MgSO₄ 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%); Rf 0.32 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3392, 2980, 2930, 1598, 1489, 1059, 756, 738, 691; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₅H₁₅NNaO (MNa⁺) Requires 248.1046 (2.1 ppm error).

Lab notebook reference: akc06-02

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. NH₄Cl (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-(1H-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; C₁₈H₂₁NNaO (MNa⁺) Requires 290.1515 (0.8 ppm error).

Lab notebook reference: akc06-46/52

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

![Reaction Scheme]

To a stirred solution of ynone 214b (155 mg, 0.682 mmol) in MeOH (14 mL) at 0 °C was added NaBH₄ (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. NH₄Cl (10 mL) at 0 °C and the aqueous layer extracted with EtOAc (3 × 10 mL). The organics were combined, dried over MgSO₄ 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; Rₓ 0.53 (1:1 hexane:EtOAc); ν max (thin film)/cm⁻¹ 3396, 2929, 2204, 1657, 1599, 1506, 1232, 1157, 1059, 837; δH (400 MHz, CDCl₃) 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, 3JHH = 8.5 Hz, 3JHF 8.5 Hz, H-13), 7.39–7.46 (2 H, m, H-12), 8.20 (1 H, br s, H-2); δC (100 MHz, CDCl₃) 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, 3JC = 22.0 Hz, C-13), 117.1 (C-1/3/4), 117.5 (C-5), 118.3 (C-1/3/4), 118.8 (d, 3JC = 4.0 Hz, C-11), 133.5 (d, 3JC = 8.5 Hz, C-12), 162.5 (d, 1JC = 249 Hz, C-14); HRMS (ESI⁺): Found: 252.0798; C₁₄H₁₃FNNaO (MNa⁺) Requires 252.0795 (−1.3 ppm error), Found: 230.0975; C₁₄H₁₃FNO (MH⁺) Requires 230.0976 (0.5 ppm error)

Lab notebook reference: akc06-66
1-(1H-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 NaBH₄ (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. NH₄Cl (10 mL) at 0 °C and the aqueous layer extracted with CH₂Cl₂ (3 × 10 mL). The organics were combined, dried over MgSO₄ 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%); Rf 0.13 (8:2 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3394, 2957, 2931, 2872, 1488, 1466, 1431, 1380, 1061, 1034, 999, 774, 711; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₂H₁₇NNaO (MNa⁺) Requires 214.1202 (0.6 ppm error).

Lab notebook reference: akc06-31

1-(1H-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. NH₄Cl (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 MgSO₄ and concentrated in vacuo. The crude material was then dissolved in MeOH (15 mL), cooled to 0 °C and NaBH₄ (114 mg, 3.02 mmol) was added portionwise. The mixture was stirred for a further 5 h at RT. The reaction was quenched by the addition of sat. aq. NH₄Cl (20 mL) and diluted with CH₂Cl₂ (50 mL). The organics were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organics were combined, washed with brine (20 mL), dried over MgSO₄, 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%); Rf 0.25 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3392, 3285, 2919, 1430, 1025, 780, 732, 643; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₈H₉NO (M⁺) Requires 135.0684 (−2.2 ppm error).

Lab notebook reference: akc05-88/89

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

Synthesised using general procedure G with propargyl alcohol 240a (75 mg, 0.333 mmol), AgNO₃ (5.66 mg, 33.3 µmol) and Ag₂O (3.86 mg, 16.7 µmol) in CH₂Cl₂ (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%); Rf 0.76 (7:3 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3433, 3029, 2918, 1592, 1477, 1413, 1325, 1305, 1136, 850, 758, 702; δH (400 MHz, CDCl₃) 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); δC (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)

Synthesised using general procedure H with propargyl alcohol 240b (25.2 mg, 0.123 mmol), AgNO$_3$·SiO$_2$ (209 mg, 12.3 μmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3420, 2956, 2928, 2859, 1593, 1480, 1455, 1411, 1342, 1116, 845, 723; $\delta_{\text{H}}$ (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); $\delta_{\text{C}}$ (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-1H-indole (241c)

Synthesised using general procedure H with propargyl alcohol 240c (68.5 mg, 0.256 mmol), AgNO$_3$·SiO$_2$ (435 mg, 25.6 μmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3431, 2955, 2927, 2857, 1598, 1470, 1444, 1347, 1324, 1115, 870, 760, 725, 698; $\delta$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); $\delta$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)-1H-indole (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$_2$O (2.5 mg, 10.9 μmol) in CH$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3428, 1603, 1519, 1503, 1485, 1412, 1330, 1220, 1158, 840, 793, 729; $\delta$H (400 MHz, CDCl$_3$)
6.64–6.69 (1 H, m, H-2/3), 7.18–7.26 (5 H, m, H-2/3,6/7,12), 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); δC (100 MHz, CDCl₃) 103.2 (CH), 116.0 (d, 2JCF = 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, 3JCF = 7.5 Hz, C-11), 133.7 (C-4/5/9), 135.2 (d, 4JCF = 3.0 Hz, C-10), 162.2 (d, 1JCF = 247 Hz, C-13); HRMS (ESI⁺): Found: 212.0863; C₁₄H₁₁FN (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-1H-indole (241e)

Synthesised using general procedure G with propargyl alcohol 240e (20.7 mg, 0.108 mmol), AgNO₃ (1.84 mg, 10.8 µmol) and Ag₂O (1.25 mg, 6.41 µmol) in CH₂Cl₂ (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%); Rf 0.68 (8:2 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3425, 2956, 2926, 2855, 1465, 1432, 1342, 1110, 970, 726; δH (400 MHz, (CDCl₃) 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); δC (100 MHz, (CDCl₃) 14.0 (C-13), 14.0 (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; C₁₂H₁₀N (MH⁺) Requires 174.1277 (−2.6 ppm error).

Lab notebook reference: akc06-59
1H-Indole (241f)

Synthesised using general procedure G with propargyl alcohol 240f (77.6 mg, 0.574 mmol), AgNO₃ (9.75 mg, 57.4 µmol) and Ag₂O (6.65 mg, 28.7 µmol) in CH₂Cl₂ (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, CDCl₃) 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, CDCl₃) 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)

To a solution of ynone 237a (16.9 mg, 0.046 mmol) in CH₂Cl₂ (0.5 mL) at RT was added AgNO₃ (0.78 mg, 4.60 µmol) and Ag₂O (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, 1445, 769, 698; δ_H (400 MHz, CDCl₃) 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); δc (100 MHz, CDCl3) 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 (CH), 133.0 (C), 134.1 (C), 135.7 (C), 151.5 (C), 173.6 (C-13), 173.7 (C), 204.3 (C-16); HRMS (ESI+): Found: 368.1996; C26H26NO (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 CH2Cl2 (0.7 mL) at RT was added AgNO3 (1.14 mg, 6.73 µmol) and Ag2O (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%); Rf 0.20 (4:1 hexane:EtOAc); v max (thin film)/cm⁻¹ 2956, 2927, 2871, 1717, 1692, 1610, 1445, 1186, 771, 699; δH (400 MHz, CDCl3) 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, 7.5 Hz, H-11), 7.73 (2 H, d, J = 7.5 Hz, H-10), 7.82 (1 H, s, H-13); δc (100 MHz, CDCl3) 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; C24H30NO (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)

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$_2$Cl$_2$ (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); $\delta_H$ (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); $\delta_C$ (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)

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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3263, 2938, 1632, 1614, 1593, 1515, 1446, 1388, 1266, 1228, 1172, 987; $\delta_H$ (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); $\delta_C$ (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
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. NH₄Cl (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 MgSO₄ 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, CDCl₃) 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, CDCl₃) 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; C₁₇H₁₈NaO₂ (MNa⁺) Requires 277.1199 (−3.7 ppm error).

Lab notebook reference: akc07-82
**4-(4-Hydroxyphenyl)-1-phenylbutan-2-one (274b)**

![Chemical Structure](image)


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. NH₄Cl (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 MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) to afford the title compound 274b as a white solid (1.51 g, 86%); mp 112–114 °C; Rₓ0.46 (6:4 hexane:EtOAc); νₓmax (thin film)/cm⁻¹ 3387, 3027, 2929, 1707, 1614, 1515, 1451, 1362, 1221, 833, 741, 699; δₓH (400 MHz, CD₃OD) 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); δₓC (100 MHz, CD₃OD) 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; C₁₆H₁₆NaO₂ (MNa⁺) Requires 263.1043 (+3.4 ppm error).

Lab notebook reference: akc08-17

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

![Chemical Structure](image)


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% Et₃N as a basic additive) to afford the title compound 275a as a yellow solid (797
mg, 74%); mp 79–81 °C; Rf 0.73 (7:3 hexane:EtOAc); νmax (thin film)/cm\(^{-1}\) 3009, 2951, 2836, 2074, 1631, 1611, 1497, 1362, 1246, 1176, 1034, 821, 753; δH (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); δC (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\(_2\)O\(_2\) (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 anhydrous DMF (11.5 mL) was added imidazole (590 mg, 8.66 mmol) at 0 °C. TBSCI (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\(_2\)O (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; Rf 0.51 (9:1 hexane:EtOAc); νmax (thin film)/cm\(^{-1}\) 2955, 2931, 2859, 1708, 1510, 1255, 910, 839, 779, 732; δH (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); δC (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\(_2\)Si (MNa\(^+\)) Requires 377.1907 (0.7 ppm error), Found: 355.2084; C\(_{22}\)H\(_{31}\)O\(_2\)Si (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)


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% Et₃N as a basic additive) to afford the title compound 275c as an orange oil (109 mg, 68%); Rₛ 0.49 (9:1 hexane:EtOAc); ν<sub>max</sub> (thin film)/cm⁻¹ 2955, 2929, 2857, 2067, 1648, 1509, 1497, 1252, 1204, 912, 838, 780, 1176, 1034, 821, 753; δ<sub>H</sub> (400 MHz, CDCl₃) 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-1), 7.46 (2 H, d, J = 8.0 Hz, H-13); δ<sub>C</sub> (100 MHz, CDCl₃) −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<sup>+</sup>): Found: 403.1816; C₂₂H₂₈N₂NaO₂Si (MNa<sup>+</sup>) 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 Et₂O (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo to afford the title compound 275b without further purification as a yellow solid (509 mg, 93%);
mp 77–79 °C; Rf 0.63 (6:4 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3361, 2077, 1612, 1515, 1497, 1448, 1370, 1205, 830, 756; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₆H₁₄N₂O₂ (MNa⁺) Requires 289.0947 (−1.3 ppm error).

Lab notebook reference: akc08-33

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

A flame-dried rbf was charged with α-diazocarbonyl 275a (100 mg, 0.357 mmol) and Ag₂O (1.7 mg, 7.13 µmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (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%); Rf 0.33 (9:1 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3028, 2934, 2829, 1745, 1715, 1489, 1446, 1416, 1219, 1167, 1109, 1020, 816, 756; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₁₇H₁₆NaO₂ (MNa⁺) Requires 275.1043 (−0.9 ppm error), Found: 253.1222; C₁₇H₁₇O₂ (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-dihyronaphthalen-2(1H)-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 CH₂Cl₂ (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, CDCl₃) 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, d, 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, CDCl₃) 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}NaO₂ (MNa⁺) Requires 275.1043 (0.4 ppm error), Found: 253.1232; C_{17}H_{16}O₂ (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%); Rf 0.21 (7:3 hexane:EtOAc); vmax (thin film)/cm⁻¹ 2952, 1713, 1653, 1626, 1435, 1265, 1211, 1111, 1058, 1007, 915, 728; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₂₃H₂₂NaO₆ (MNa⁺) Requires 417.1309 (−1.8 ppm error), Found: 395.1485; C₂₃H₂₃O₆ (MH⁺) Requires 395.1489 (1.0 ppm error).

Lab notebook reference: akc08-82

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

A heterogeneous solution of Au(PPh₃)₃Cl (2.65 mg, 5.35 µmol) and AgSbF₆ (1.84 mg, 5.35 µmol) in CH₂Cl₂ (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 CH₂Cl₂ (0.5 mL) was then added to the catalyst mixture at 0 °C, the vial containing diazo solution was rinsed with CH₂Cl₂ (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%); Rf 0.32 (9:1 hexane:EtOAc); vmax (thin film)/cm⁻¹ 2934, 2836, 1711, 1670, 1596, 1449, 1245, 1177, 1033, 825, 689; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 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; C₂₃H₂₂NaO₆ (MNa⁺) Requires 417.1309 (−1.8 ppm error), Found: 395.1485; C₂₃H₂₃O₆ (MH⁺) Requires 395.1489 (1.0 ppm error).
CDCl₃) 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; C₁₇H₁₆NaO₃ (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 CH₂Cl₂ (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 MgSO₄ 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; Rf 0.21 (6:4 hexane:EtOAc); νmax (thin film)/cm⁻¹ 3035, 1746, 1663, 1622, 1499, 1135, 868, 700; δH (400 MHz, CDCl₃) 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); δC (100 MHz, CDCl₃) 31.4 (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; C₁₆H₁₂NaO₂ (MNa⁺) Requires 261.0886 (−4.2 ppm error), Found: 239.1057; C₁₆H₁₃O₂ (MH⁺) Requires 239.1067 (−4.1 ppm error).
A flame-dried rbf was charged with α-diazocarbonyl 275c (150 mg, 0.394 mmol) and Ag₂O (4.57 mg, 19.7 µmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (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%); Rᵣ 0.42 (9:1 hexane:EtOAc); νₓ(max) (thin film)/cm⁻¹ 2955, 2929, 2857, 1747, 1407, 1252, 1202, 1183, 1110, 900, 873, 837, 781, 749; δH (400 MHz, CDCl₃) −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); δc (100 MHz, CDCl₃) −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; C₂₂H₂₉O₂Si (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-dihyronaphthalen-2(1H)-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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (thin film)/cm$^{-1}$ 3372, 3027, 1704, 1612, 1587, 1493, 1450, 1342, 1297, 1232, 1153, 821; $\delta_H$ (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); $\delta_C$ (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)


A heterogeneous solution of Au(PPh$_3$)$_3$Cl (32.5 mg, 65.7 µmol) and AgSbF$_6$ (22.5 mg, 65.7 µmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$
(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); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2955, 2930, 2858, 1713, 1672, 1509, 1253, 912, 838, 781; \( \delta_H \) (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); \( \delta_C \) (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

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

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); \( \nu_{\text{max}} \) (thin film)/cm\(^{-1}\) 2953, 2858, 1714, 1651, 1625, 1435, 1342, 1303, 1256, 1225, 1204, 1110, 1061, 913, 864, 839, 785; \( \delta_H \) (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\text{C} (100 MHz, CDCl\textsubscript{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\textsuperscript{+}): Found: 517.2017; C\textsubscript{28}H\textsubscript{34}NaO\textsubscript{6}Si (M\textsubscript{Na}+\textsuperscript{+}) Requires 517.2017 (−0.1 ppm error), Found: 495.2195; C\textsubscript{28}H\textsubscript{35}O\textsubscript{6}Si (MH\textsuperscript{+}) 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-1H-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\textsubscript{4} and concentrated \textit{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\text{f} 0.66 (1:1 hexane:EtOAc); ν\textsubscript{max} (thin film)/cm\textsuperscript{−1} 2953, 1718, 1626, 1435, 1333, 1270, 1218, 1115, 1064, 729, 718; δ\text{H} (400 MHz, CDCl\textsubscript{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\text{C} (100 MHz, CDCl\textsubscript{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; \(\text{C}_{22}\text{H}_{20}\text{NaO}_{6}\) (MNa\(^+\)) Requires 403.1152 (−1.5 ppm error),
Found: 381.1335; \(\text{C}_{22}\text{H}_{21}\text{O}_{6}\) (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 \(\text{CH}_2\text{Cl}_2\) (3.2 ml) under argon. The solution was cooled to 0 °C and 
BF\(_3\)·Et\(_2\)O (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 \(\text{CH}_2\text{Cl}_2\) (3 x 10 ml). The organics were combined, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The crude material was purified 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); \(\nu_{\text{max}}\) (thin film)/cm\(^{-1}\) 3416, 3027, 2932, 1712, 1669, 1596, 1515, 1449, 1254; \(\delta_H\) (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); \(\delta_C\) (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; \(\text{C}_{16}\text{H}_{14}\text{NaO}_{3}\) (MNa\(^+\)) Requires 277.0835 (0.6 ppm error).

Lab notebook reference: akc08-85
Appendices

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

Aimee K. Clarke, Michael J. James, Peter O'Brien, Richard J. K. Taylor,* and William P. Unsworth*

Abstract: Silica-supported AgNO₃ (AgNO₃-SiO₂) catalyzes the dearomatizing spirocyclization of alkynetherlated aromatics far more effectively than the analogue unsupported reagent. In many cases, reactions which fail using unsupported AgNO₃ proceed effectively with AgNO₃-SiO₂. Mechanistic studies indicate that this is a consequence of silver nanoparticle formation on the silica surface combined with a synergistic effect caused by the silica support itself. The remarkable ease with which the reagent can be prepared and used is likely to be of much synthetic importance, in particular by making nanoparticle catalysis more accessible to non-specialists.

Preceded in the 1980s, silica-supported AgNO₃ (AgNO₃-SiO₂) is well-known for its use as a support in the separation of E- and Z-alkynes by column chromatography. However, the synthetic potential of AgNO₃-SiO₂ as a catalyst has been mostly over-looked, with just a handful of reports on its use as a reagent in organic synthesis. To the best of our knowledge, examples are limited to syntheses of 5-membered heterocycles from alkynes and allenes, reported by Marshall[1] and Knight.[2] As part of a wider program on dearomatizing spirocyclization reactions,[3,4] we decided to investigate the catalytic potential of AgNO₃-SiO₂ due to its limited previous use in synthesis and with the intention of exploiting the practical benefits of using a solid-supported reagent.[5,6] To our surprise, we found that AgNO₃-SiO₂ offers vastly superior reactivity compared to unsupported AgNO₃ in dearomatizing spirocyclization reactions of alkynetherlated heteroaromatics of the type shown in Figure 1.[7,8]

Of much significance, several dearomatization reactions that previously failed with unsupported AgNO₃ can now be carried out in high yield with the AgNO₃-SiO₂ catalyst. These unexpected findings prompted a mechanistic investigation which ultimately, via the combined use of in situ infrared spectroscopy (via ReactIR) and TEM, implicated a key role for silver nanoparticles (Ag-NPs) formed during the preparation of AgNO₃-SiO₂, together with a synergistic effect from the silica support itself. Pre-prepared Ag-NPs have been used as catalysts previously,[7,8] but to the best of our knowledge, the catalytic role of Ag-NPs formed while supporting silver salts on silica has not been documented. In this paper, we highlight AgNO₃-SiO₂ as an easily prepared and highly active catalyst for dearomatizing spirocyclizations (Figure 1), showing the methodology with the AgNO₃-SiO₂-mediated synthesis of 25,6, e 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 alkynecatalyst pathway that could have much more synthetic scope for alkynecatalyst functionalization.

To start, we examined the conversion of ynone 1a into spirocyclic indoline 2a.[9,10] Commercial AgNO₃-SiO₂ (10 wt% AgNO₃ 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” AgNO₃-SiO₂ with a reduced AgNO₃ loading of 1 wt% was an even more effective catalyst; stirring ynone 1a at RT in CH₂Cl₂ with catalytic (1 mol%) 1 wt% AgNO₃-SiO₂ led to the formation of spirocycle 2a in 95% isolated yield in 30 minutes (Scheme 1, conditions A). Interestingly, this is significantly faster than the same reaction with unsupported AgNO₃ (6 h, conditions B).[12] Even more dramatic differences were seen in the reactions of ynonestherto other aromatics; phenol 3a, pyrrole 5a and benzofuran 7 were reacted with both catalyst systems, and while spirocycle products 4a, 6a, and 8 were isolated in high yields with 1 wt% AgNO₃-SiO₂, was used, AgNO₃ alone led to no reaction in all three cases (Scheme 1).[13]

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 (2288 cm⁻¹) to monitor reaction progress. Using 1 mol% of the 1 wt% AgNO₃-SiO₂ catalyst, ynone 1a was converted into spirocycle 2a in 30 min (blue line, A, Figure 2),
fully consistent with the synthetic reaction. In contrast, as expected from the synthetic work, the unsupported AgNO₃ reaction was much slower, requiring > 6 h to reach completion (purple line, B); interestingly, there was a clear induction period of around 2 h, and even after this time the reaction was slower.

To explore the role of silica, AgNO₃ and silica were both added to a solution of 1a in CH₂Cl₂ (i.e. the AgNO₃ was not supported on the silica in advance). In this experiment (pink line, C), an induction period was still observed (around 90 min), but once this period had passed, the reaction proceeded at a similar rate to the standard AgNO₃-SiO₂ reaction (blue line, A). Silica is not able to promote spirocyclization on its own (stirring ynone 1a in silica in CH₂Cl₂ led to no reaction after several days) but clearly its presence significantly increases the rate of the Ag-mediated spirocyclization reaction. We suggest that this may be due to accelerated protodemetalation:¹² silanediol groups on the silica surface might be expected to facilitate this step, thus releasing the silver for further catalysis and increasing the turnover rate.

Our results also indicate a clear difference between the supported AgNO₃-SiO₂ catalyst and unsupported AgNO₃ in the presence of silica (which should have the same elemental composition). This led us to propose that AgNO₃ is a pre-catalyst in the unsupported reaction and that the induction period is connected to the time taken for Ag-NPs to form in situ. To test this, unsupported AgNO₃ was “aged” by stirring the standard reaction dose in CH₂Cl₂ for 24 h before adding ynone 1a; the expectation was that by ageing the catalyst, Ag-NPs would form in advance and alter the reaction profile.¹¹ The initially colorless solution became yellow during the ageing process, which is indicative of Ag-NP formation,²³ and the aged catalyst did indeed perform differently (gray line, D). The reaction proceeded at a similar rate to the standard AgNO₃ reaction (purple line, B), but crucially there was no induction period. A mercury drop test was also performed which led to the complete cessation of the reaction,²⁴ adding additional support to the idea that Ag-NPs are the true catalyst. Further supporting evidence was obtained using transmission electron microscopy (TEM): AgNO₃ was stirred for 24 h at RT in CH₂Cl₂, and an aliquot of the solution (> 5 μL) was removed and dropped onto a copper TEM grid. The deposit that remained after the CH₂Cl₂ had evaporated was then analyzed using TEM, and Ag-NPs were found to be present (Figure 3).

In view of the above results, we considered it likely that Ag-NPs were also present in our standard supported AgNO₃-SiO₂ (1 wt%) catalyst system, as they could potentially form during the preparation of the supported reagent. This was confirmed by TEM imaging of the supported catalyst: crystalline Ag-NPs were observed (Figure 4) and the electron diffraction pattern enabled the identification of a cubic silver crystal phase (space group Fm3m) and showed that the particles had a spacing of around 0.205 nm, which is representative of cubic silver.²⁵ Thus, it appears that in both the supported and unsupported systems, Ag-NPs rather than AgNO₃ 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 protodemetalation, and hence more effective catalyst turnover and/or its role may also be to adsorb the Ag-NPs and control their growth/aggregation.
Next, to more fully evaluate the synthetic utility of our AgNO₃·SiO₂ catalyst, the optimized spirocyclization conditions were applied to other alkene-tethered aromatics, and compared to unsupported AgNO₃ in each case (Scheme 2). Indolyl spirocyclic products 2a–e were all obtained in excellent yields (94–100%), with AgNO₃·SiO₂ promoting a faster transformation than with unsupported AgNO₃ in all cases. More pronounced differences in reactivity were observed for 2- and 4-phenyl derivatives 3a–f; these substrates did not react at all using unsupported AgNO₃, but using AgNO₃·SiO₂, spirocyclic dienes 4a–f were all formed in high yield, notably including compound 4f, an advanced intermediate in a published route to spiroracene A. Pryrole derivatives 5a–g are also well tolerated, with AgNO₃·SiO₂ superior to unsupported AgNO₃ in all examples. The quantitative formation of spirocycles 6a–g is especially noteworthy, given the rarity of deoxametated products derived from 3-pyrroles. 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.

Finally, the use of our AgNO₃·SiO₂ catalyst in a continuous flow reaction has been demonstrated. A 0.1 M solution of ynone 1a in toluene was simply passed through a 1 cm diameter column packed with 1.93 g of our standard 1 wt% catalyst (19.3 mg of AgNO₃) at a flow rate of 0.3 mL/min, concentrated in vacuo, and analyzed using 1H 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 boiling of 0.12 mol% and an NMR aliquot measured after 51 h showed that the product was still being formed cleanly, indicating that the catalyst remained active.

In summary, 1 wt% AgNO₃·SiO₂ is a very effective catalyst for the deoxametated spirocyclization of alkene-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 AgNO₃, and in our hands, it is also more reactive than silica-supported Ag-NPs made by literature methods in which the Ag-NPs were prepared separately. In contrast to existing methods to prepare supported...
Back Pressure Regulator (7 bar)

AgNO(SO)2 (1 wt. %)

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Scheme 3. How silylization of ynone 1a.

**Communications**

Ag-NPs[1,2,3] our catalyst is easy to prepare with full silver incorporation into the supported catalyst and it can be stored in the dark for RT for several months with no loss of activity.[23] 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.[9] ICP-MS analysis confirmed that silyl ether 2a was formed under the standard conditions contains ca. 60% 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 CHCl3, silver contamination in the product could be reduced to just 2 ppm, which is significantly below the 17 ppm limit set by the FDA for the permissible amount in a drug.[22] 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(SO)2 also benefited from the presence of Ag-NPs while moving forwards, AgNO(SO)2 may also represent a more convenient source of Ag-NPs than those prepared by conventional methods.

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**Keywords:** deamination · flow chemistry · heterogeneous catalysis · silver nanoparticles · silyl ethers

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[9] Ynone 1a (9.1 mmol) was stirred with 10 mol% of AgNO(SO)2 (10 wt%, Sigma-Aldrich, 248782) in CHCl3 for 10 min, resulting in full conversion into silyl ether 2a. 1 wt% AgNO(SO)2 was prepared by adding AgNO3 (100 mg) to a slurry of Filsa silica gel (9.9 g, pore size 60 Å, 220-440 mesh particle size) in deionized water (27 mL). The mixture was stirred at 13 min, concentrated in vacuo at 60°C to form a free-flowing powder and dried by heating to 140°C under high vacuum for 4-6 h, and reference therein.
[18] The reaction of ynone 1a with unsupported AgNO₃ was allowed to proceed to ca. 30% conversion, before mercury was added (200 equivalents with respect to AgNO₃), which stopped any further reaction.
[19] Qualitatively, the supported Ag-NPs appear to be much more uniform in size than those obtained from aged AgNO₃ in CH₃Cl; more detailed studies will be required in future to probe this observation and its implications more rigorously.
[23] Silica-supported Ag-NPs synthesized by literature methods (references [16a] and [10b]) were tested in the transformation of ynone 1a into spirocycle 2a, resulting in 45% and 25% conversion into 2a, respectively, with unsupported 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

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. 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 nucleophile ipso-cyclisation reaction can take place with a range of C-nucleophiles including alkenes/alkynes, nitriles, activated alkenes, activated aryl halides, propargyl bromides/carbonates, activated allyl/allenes and allylic carbonates have all been reported.

![Diagram of natural products containing spirocyclic dienone motifs](image)

Scheme 1. General methods for spirocyclic dienone synthesis.
In this manuscript, two complementary protocols which generate spirocyclic dienes are outlined (Scheme 1C), with both methods promoted by the activation of a tethered alkyne moiety. The first approach focuses on the spirocyclisation of para-substituted ansiloates using either SnCl₂·2H₂O or Cu(OtBu)₂ to activate the alkyne towards nucleophilic attack, while the second uses silica-supported AgNO₃ to generate similar scaffolds from analogous phenol precursors with greater efficiency and scope. Substrate scope studies are described for each reaction series, while comparisons between the two reaction types, synthetic extensions and preliminary symmetric results are also outlined.

Results and discussion

This research program began during a project to synthesise the spirocyclic natural product spinobacillene A (6, Fig. 1). In this published work, it was found that treating ansiloate-tethered ynone 7 with five equivalents of SnCl₂·2H₂O at RT in CH₂Cl₂ resulted in its efficient conversion into spirocyclic diene 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 spinobacillene A, which was published in 2013.

This initial discovery inspired the development of a number of other classes of deoxamomising spirocyclisation reactions in our group in the following years. However, prior to this publication, the conversion of ynone 7 into spirocycle 8 remained the only reported reaction of its type in the literature, hence it was decided to further optimise this process and to evaluate its scope.

Initial results were disappointing, with unsubstituted and allyl substituted ynones 9a and 9b both failing to react with SnCl₂·2H₂O under the conditions used during the total synthesis of spinobacillene 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 ansiloate-substituted ynone 9d; under the standard SnCl₂·2H₂O mediated conditions, a more respectable 75% conversion into spirocyclic diene 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(OtBu)₂ promoted the complete cyclisation of ynone 9d within 1 h, with spirocycle 10d isolated in 86% isolated yield (entry 6). However, Cu(OtBu)₂ did not lead to any improvement in the reactivity of substrates 9a-9c, forcing us to conclude that an electron donating group on the alkyne terminus is a requirement for this transformation.

With this in mind, a series of ansiloate tethered to electron-rich ynones (9d-1) were made and tested using both SnCl₂·2H₂O and Cu(OtBu)₂ to activate the alkyne (Table 2). Spirocyclo 10e was formed in just 1 h from alkynyl-substituted ynone 9e using one equivalent of SnCl₂·2H₂O. Alternatively, the same product could be made using catalytic Cu(OtBu)₂ (0.1 equivalents), albeit with a longer reaction time. Thiophene-substituted ynone 9f reacted more slowly; the cyclisation was incomplete following treatment with SnCl₂·2H₂O at room temperature for 3 days, but proceeded more efficiently with Cu(OtBu)₂ to afford 10f in a 73% yield. Substitution around either ring system is well tolerated, evidenced by the efficient syntheses of compounds 10g-1. Vinyl sulfide product 10h could also be isolated in a reasonable yield using Cu(OtBu)₂ demonstrating compatibility with non-aromatic-tethered ynones.

Additionally, the reaction is not limited to the synthesis of spirocyclic cyclophosphorinones; spirocyclic cyclophosphorins 10f and 10h 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 ansiloates tethered to electron-rich ynones can be converted into spirocyclic dienes 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 spirocyclisations of anilsle-tethered yrones using SnCl₂:2H₂O (A) and Cu(OtTf)₂ (B)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Product</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂₆</td>
<td>Oₙ</td>
<td>H</td>
<td>MeO</td>
<td>10g</td>
<td>(A) 20 h, 66% conv.</td>
</tr>
<tr>
<td>CH₂₆</td>
<td>Oₙ</td>
<td>H</td>
<td>Ome</td>
<td>10h</td>
<td>(A) 20 h, 64% conv.</td>
</tr>
<tr>
<td>CH₂₆</td>
<td>Oₙ</td>
<td>H</td>
<td>Ph</td>
<td>10i</td>
<td>(A) 20 h, 68% conv.</td>
</tr>
</tbody>
</table>

*All reactions were performed in CH₂Cl₂ (0.1 M) at RT with 1 equiv. of reagent unless specified. Where stated, reaction conversions were measured by analysis of the ¹H NMR spectra of the unpurified reaction mixture. ¹ equiv. of SnCl₂:2H₂O used. 0.1 equiv. of Cu(OtTf)₂ used.

Table 3: Substrate scope of AgNO₃:SO₂-catalysed dimerisation/ spirocyclisations

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Product</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂₆</td>
<td>Oₙ</td>
<td>H</td>
<td>MeO</td>
<td>11c,d,m,v</td>
<td>(A) 2 h, 55%</td>
</tr>
<tr>
<td>CH₂₆</td>
<td>Oₙ</td>
<td>H</td>
<td>Ome</td>
<td>10d,m-r</td>
<td>(A) 2 h, 64%</td>
</tr>
<tr>
<td>CH₂₆</td>
<td>Oₙ</td>
<td>H</td>
<td>Ph</td>
<td>10e</td>
<td>(A) 20 h, 68% conv.</td>
</tr>
</tbody>
</table>

*All reactions were performed using 1 w% AgNO₃:SO₂ in CH₂Cl₂ (0.1 M) at RT unless specified otherwise. ¹ Reaction performed at 80 °C. Compositions highlighted with a * were featured in our earlier publication (see ref. 36e); all other examples are novel.

reaction conditions are the most pleasing aspects of this method, although the use of relatively large quantities of Sn(II) and Cu(i) reagents and the requirement to use electron-rich yrones 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 alkynie activation processes, but disappointingly, the Ag(i) catalysts tested were ineffective for the spirocyclisation of anilsle system 9d. However, by switching the nucleophilic component in the starting material from an anile to the analogous phenol, the desired spinoyclic 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 AgNO₃ (10 mol%) in CH₂Cl₂ at RT was found to be a particularly active and convenient catalytic system and was chosen for the substrate scope studies, which were performed on yrone tethered phenols (11e,d,m,v). For clarity, five of these examples (denoted in the table with a *) were included in an earlier publication, while the other seven substrates are novel examples (Table 3). It should also be noted that AgNO₃:SO₂ is a much more reactive catalyst than unsupported AgNO₃, and only a 7% conversion to spinoyclic dimer 10m was observed for yrone 11m when using unsupported AgNO₃.

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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 allyl chains and aromatic substituents in the 12 position were all well tolerated, generating spirocyclic diene products 10c, 10d, 10e in high yields. Allyl substituted ynone bearing protected amine and alcohol groups (10o and 10p) also reacted smoothly to furnish their corresponding spirocyclic dienes (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 pheno1s 11s-v; there are relatively few literature examples of deamidisation and cyclo-arylation reactions of ortho-substituted pheno1s, and so the efficient synthesis of chiral spirocyclic products 12s-v in 90-99% yields are especially pleasing.

The superior reactivity of the Ag(I) mediated reaction system compared to the earlier Sn(II)/Cul)2 reactions is best demonstrated by a direct comparison. Thus, our published synthesis of spirocyclic diene 8, which is a key intermediate on route to spirabacillene A, required five equivalents of SnCl2·2H2O and 18 h to generate the product in 69% yield. In contrast, the same product was generated from phenol 13 in near-quantitative yield in just 7 h using 10 mol% AgNO3/SiO2 (Scheme 3).

The potential of the spirocyclic diene products to undergo additional complexity generating reactions has also been briefly demonstrated; 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, un-optimised yields (Scheme 4).

Finally, having shown that ortho-substituted pheno1s can be converted into chiral spirocyclic dienes, 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 (R)-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 should lead to improve enantioreactivity in this process.

Conclusions

In summary, two mild and effective methods for the synthesis of spirocyclic dienes are described. Both were briefly introduced by our group in previous publications, but the significantly expanded substrate scope and 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 AgNO3/SiO2 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.

(A) Previous work

(B) This work

Scheme 3 Previous and improved routes to spirabacillene A precursor 8.
1H NMR and 13C NMR spectra were recorded on a JEOI ECA-400 or JEOL ECS-400 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, δ4 = 7.26 and δ6 = 77.0 for CDCl3, and δ4 = 2.50 and δ6 = 39.5 for DMSO-d6. 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, HMQC, and HSQC experiments, where required. Infrared (IR) spectra were recorded on a Perkin-Elmer UATR 2 Spectrometer as a thin film dispersed from either CH2Cl2 or CDCl3, 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, Microtof spectrometer. Melting points were determined using a Gallenkamp apparatus and are uncorrected. Reactions were monitored using thin layer chromatography (TLC), which was carried out on Merek silica gel 60F254 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 alumina packed Fluka silica gel (SiO2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Compounds 9a⁶⁸⁸ and 9b⁶⁸⁸ 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(OH)MeHCl (107 mg, 1.10 mmol) and stirring continued for a further 2 h. The crude reaction mixture was then poured into water (16 mL) and basified to 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 MgSO4, and concentrated in vacuo, affording the Weinreb amide product which was used without further purification.

General procedure A2: Weinreb amide synthesis II

To a stirred solution of acid (1.00 mmol), MeNH(OH)MeHCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH2Cl2 (2.5 mL) was added TSP (50% in EtOAc) (957 mg, 1.50 mmol). The solution was stirred at RT until complete reaction 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 2 M aq. NaOH (10 mL), brine (10 mL), dried over MgSO4, 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 (0.873 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 recooled to −78 °C and quenched with sat. aq. NH4Cl (30 mL), allowed to warm to RT, diluted with water (70 mL), extracted with EtOAc (3 × 100 mL), dried over MgSO4, 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. NH4Cl (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 MgSO4, concentrated in vacuo and purified by flash column chromatography to afford the ynone product.

General procedure C: spinoxydination using Sn(0)/Cu(0)

To a solution of ynone (1.00 mmol) in CH2Cl2 (10 mL) was added an acid catalyst (0.1–0.5 equiv.). The resulting suspension was stirred at the specified temperature until complete reaction was observed by TLC, before adding an excess of solid K2CO3 and stirring for an additional 10 min. The mixture was then filtered, rinsed with CH2Cl2, and concentrated in vacuo. Purification by flash column chromatography afforded the spinoxydine product.

General procedure C2: spinoxydination using AgNO3/SiO2

To a solution of ynone (1 mmol) in CH2Cl2 (10 mL) was added AgNO3/SiO2 (0.60–0.80 equiv., 1 wt% AgNO3 on SiO2). The mixture was stirred at the specified temperature until complete conversion was observed by TLC. The reaction mixture was filtered, washing the catalyst with EtOAc (10 mL), then concentrated in vacuo to afford the spinoxydine product.

Compound synthesis

1,4-(Methoxyphenyl)spino[4.5]deca-3,6,9-triene-2,8-dione (16d). Synthesized using general procedure C from ynone 9d (32.3 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 16d as a brown solid (19 mg, 80%), mp. 115–117 °C,
See the main text for the full content.
6.5(4-methoxybenzyl)piperidin-1-yl]piperidin-4-ylpenta-3,6-diene-1,4-dione (10). Synthesized using general procedure C from 4-ethylphenylacetone (386 mg, 2.04 mmol) and copper(triﬂate [0.04 mg, 0.250 mmol] for 2 h at RT. Purification by flash column chromatography (1:1 petrol:EtOAc) afforded the title compound 10 as a yellow solid (96 mg, 46%).

9. (4-Methoxphenyl)piperidin-4-ylpenta-3,6-diene-1,4-dione (9). Synthesized using general procedure B from 4-ethylphenylacetone (386 mg, 2.04 mmol) and copper(triﬂate [0.04 mg, 0.250 mmol] for 2 h at RT. Purification by flash column chromatography (1:1 petrol:EtOAc) afforded the title compound 9 as a yellow solid (96 mg, 46%).
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Synthesized using general procedure B2 from ethynyl-1-propanol (0.35 ml, 3.07 mmol) and Weintrab amide S3 (208 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<sub>f</sub> 0.76 (1:1 hexane:EtOAc) v<sub>max</sub> <sub>cm</sub> <sub>-1</sub> 3737, 2959, 2933, 2209, 1652, 1514, 1224, 796 <delta> (400 MHz, CDCl<sub>3</sub>), 0.89 (1 H, t, J = 7.5), 1.35 (2 H, q, J = 7.5, 7.5), 1.84 (2 H, t, J = 7.0, 7.0), 2.22 (2 H, t, J = 7.0), 3.74 (2 H, s), 5.98 (1 H, br s), 6.80 (2 H, d, J = 8.0), 7.09 (2 H, d, J = 8.0); <delta> (100 MHz, CDCl<sub>3</sub>) 13.4, 18.6, 21.8, 29.5, 51.3, 88.7, 97.3, 115.6, 129.4, 130.9, 151.5, 186.7; HRMS [ESI]: Found: 239.0600; C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> [M+Na]<sup>+</sup> Requi...
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; Rf 0.59 (1:1 hexane:EtOAc); t_{R,1}\text{R,1} (thin film) cm^-1 3367, 2201, 1647, 1514, 1222; δ_{(400 MHz, CDCl3)} (400 MHz, CDCl3) 0.01–0.05 (2 H, m), 0.92–0.98 (2 H, m), 1.31–1.39 (1 H, m), 3.71 (2 H, m), 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, CDCl3) 0.3–0.9, 9.5, 51.1, 76.5, 101.6, 115.5, 125.3, 130.9, 1514, 186.0; HRMS (ESI): Found: 223.0734; C_{6}H_{10}NO_{2} (M{+}H\text{}^{+}) Requires 223.0730 (+0.3 ppm error). Found: 210.0910 (1.9 ppm error).

4-Cyclopropyl[1,4]-digea-3,6,9,10-tetra-2,8-dione (10q).
Synthesised using general procedure C2 from ynone 11q (101 mg, 0.504 mmol) and AgNO_{3}-SO_{3} (857 mg, 0.0501 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; Rf 0.65 (1:1 hexane:EtOAc); t_{R,1}\text{R,1} (thin film) cm^-1 1699, 1666, 1624, 1665, 1401, 1252, 880; δ_{(400 MHz, CDCl3)} 0.77–0.82 (2 H, m), 1.11–1.17 (2 H, m), 1.18–1.24 (2 H, m), 2.64 (2 H, m), 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, CDCl3) 11.0, 12.8, 45.0, 52.8, 123.5, 130.6, 150.0, 184.9, 185.7, 204.2; HRMS (ESI): Found: 223.0733; C_{6}H_{10}NO_{2} (M{+}Na\text{}^{+}) Requires 223.0730 (+1.7 ppm error). Found: 210.0906; C_{6}H_{10}O_{2} (M{+}H\text{}^{+}) Requires 210.0910 (2.2 ppm error).

4-Cyclopentyli-1-(4-hydroxyphenyl)buty-3-yn-2-one (11r).
Synthesised using general procedure B2 from ethynylcyclohexene (6.36 mL, 3.07 mmol) and Weinreb amide S3 (500 mg, 2.56 mmol) stirring at RT for 45 min. Purification by flash column chromatography (1:1 hexane:EtOAc) afforded the title compound 11r as an off-white solid (452 mg, 88%); mp 98–100 °C; Rf 0.78 (1:1 hexane:EtOAc); t_{R,1}\text{R,1} (thin film) cm^-1 1369, 2203, 1649, 1548, 1269, 75; δ_{(100 MHz, CDCl3)} 0.87–0.92 (2 H, m), 9.07–10.0 (2 H, m), 1.37–1.45 (1 H, m), 3.85 (2 H, s), 6.70 (1 H, br, s), 6.98–6.93 (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, CDCl3) 6.1, 19.2, 47.5, 76.8, 103.2, 117.1, 126.0, 129.1, 129.3, 131.3, 134.9, 187.2; HRMS (ESI): Found: 233.0738; C_{6}H_{10}NO_{2} (M{+}Na\text{}^{+}) Requires 233.0730 (+3.6 ppm error). Found: 210.0918; C_{6}H_{10}O_{2} (M{+}H\text{}^{+}) Requires 210.0910 (+3.8 ppm error).

4-Cyclopentyl[1,4]-digea-3,6,9,10-tetra-2,8-dione (11s).
Synthesised using general procedure C2 from ynone 11s (108 mg, 0.538 mmol) and AgNO_{3}-SO_{3} (915 mg, 6.0838 mmol) for 2 h at RT. Afforded the title compound 11s without further purification as an yellow oil (104 mg, 96%); Rf 0.34 (1:1 hexane:EtOAc); t_{R,1}\text{R,1} (thin film) cm^-1 1694, 1660, 1632, 1607, 1537, 1200, 862; δ_{(400 MHz, CDCl3)} 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), 6.32 (1 H, d, J = 9.5), 6.28 (1 H, d, J = 9.0), 6.47 (1 H, app, d, J = 9.5, 5.5); 7.19 (1 H, app, d, J = 9.5, 5.5); 9.5, 5.5, 13.5; δ_{c} (100 MHz, CDCl3) 11.0, 11.9, 13.2, 46.8, 62.7, 122.8, 123.9, 126.7, 142.5, 143.8, 184.5, 200.5, 206.2; HRMS (ESI): Found: 233.0732; C_{6}H_{10}NO_{2} (M{+}Na\text{}^{+}) Requires 233.0730 (+1.3 ppm error). Found: 210.0907; C_{6}H_{10}O_{2} (M{+}H\text{}^{+}) Requires 210.0910 (1.3 ppm error).

1-(4-Hydroxyphenyl)buty-3-yn-2-one (11t).
Synthesised using general procedure B2 from phenylacrylate (2.0 mL, 181 mmol) and Weinreb amide S5 (11.8 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 oil (1.33 g, 99%); mp 106–108 °C; Rf 0.67 (6:4 hexane:EtOAc); t_{R,1}\text{R,1} (thin film) cm^-1 3333, 2982, 2202, 1611, 1489, 1458, 1156, 753; δ_{(100 MHz, CDCl3)} 4.04 (2 H, s), 8.27 (1 H, br, s), 6.94–6.98 (2 H, m), 7.19–7.26 (2 H, m), 7.39 (1 H, br, s), 7.45–7.50 (1 H, m), 7.54–7.55 (2 H, m); δ_{c} (100 MHz, CDCl3) 47.5, 87.8, 94.0, 116.8, 119.6, 120.4, 121.0, 128.6, 129.3, 131.1, 131.5, 154.8, 187.0; HRMS (ESI): Found: 259.8722; C_{6}H_{10}NO_{2} (M{+}Na\text{}^{+}) Requires 259.8722.
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259.07(0) (3.1 ppm error). Found: 237.0914; C$_{11}$H$_{10}$O$_{2}$ (M+H) requires 237.0910 (1.5 ppm error).

4-(4-Fluorophenyl)-4-ethyl-3,6-dicarbethoxy-2,6-dione (12c). Prepared as described for compound 12b from ethyl-3,6-dicarbethoxy-2,6-dione. Found: 259.0703 (2.6 ppm error). Requires: 259.0701 (1.9 ppm error).

The title compound was also prepared in an anion-rich form using CPA 1615 (50% crude, 21% ee, see Scheme 4).

4-(4-Methoxyphenyl)-4-(4-methoxyphenyl)-1,2-dimethoxy-1-benzene (11b). Prepared using general procedure B from 1,2-dimethoxy-1,2-diphenylethane-1,2-diol (50 mmol, 2.56 mmol) in the presence of 4-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1,2-dimethoxy-1-benzene (11b). Requires: 289.0835 (0.6 ppm error).

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Note: some peaks broadened in 1H NMR spectrum due to presence of rotamers. Spectroscopic data matched those previously reported in the literature.

5-Methyl-4a,5,6,7-tetrahydrocyclopenta[d]furo[3,2-b]pyrrole-3,4(1H,10H)-
dione (14). To a stirred solution of tert-butyldimethylsilyl[4(4,6-dimethyl-3,5-phenyl)2,7-diene (2.6 mg; 0.32 mmol) in CH₂Cl₂ (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. NaHCO₃ (5 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 × 5 mL). The organics were combined, washed with brine, dried over MgSO₄, 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%).

6. 4a,4b,6,7-Tetrahydro-3H-cyclopenta[d]furo[3,2-b]pyrrole-3,4(1H,10H)-
dione (15). To a 10 mL reaction vial containing 4a,4b,6,7-tetrahydrocyclopenta[d]furo[3,2-b]pyrrole-3,4(1H,10H)-dione (10 mg, 0.06 mmol) in THF (1 mL) was added 10% aqueous HCl (1.0 mL) and the reaction stirred under argon at RT. After 1.5 h, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL), extracted successively with EtOAc (3 × 10 mL), the combined organics washed with brine (10 mL), dried over Na₂SO₄ and concentrated to yield a crude product. The product was purified by flash column chromatography (8:2 hexane:EtOAc; then 8:2 EtOAc:hexanes) to afford the title compound 15 as an off-white solid (15.0 mg, 75%).

Notes and references

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12 This refers to the direct conversion of an alkene-tethered ynone into a spirocyclic diene.

13 AgNO$_3$-SO$_2$ is also a far more efficient catalyst than Cu(0), on this reaction system, with no reaction observed when ynone $\text{He}$ was treated with 10 mol% Cu(0), at RT for 3d. The reactions were not performed in the dark and to the best of our knowledge, are insensitive to light.


Appendix III. Divergent Reactivity of Phenol- and Anisole-Tethered Donor-Acceptor α-Diazoketones

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 (cyclopropynes, tertolones and 1,2-diazoketones) while phenols selectively produce spirocyclic dimotes.

1. Introduction

α-Diazocarbonyl compounds are a versatile compound class able to undergo a variety of synthetic transformations to generate multiple products. Their diverse reactivity is well-known in the literature and is a consequence of the many reactive intermediates they can form, including carbones, carbeneoids, ylides and diazo- nium 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. The versatile reactivity of α-diazocarbonyl compounds means that they are well-suited for use in diversity-oriented synthesis, especially for research focused on the synthesis of multiple product classes from the same starting material. Such processes are particularly useful if the chemoselectivity can be controlled, for example, by variation of the reaction conditions or reagents. In our groups, we are interested in developing divergent reaction systems in which the outcome is controlled by the choice of catalyst. Such 'catalyst selective synthesis' 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 group 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). 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, Scheme 1B). There were no reports concerning the reactions of diazo compounds of this type prior to this study, 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 bromoacetic 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). Theaza nucleophile was promoted by copper(I) chloride to generate spirocycles (e.g. 10 → 11, Scheme 2B); indeed, Mander et al. had previously

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2. Results and discussion

2.1. Anisole-tethered α-diazoketones

We initiated our study by treating anisole-tethered α-diazo-ketone 3a with a range of metal-based catalysts. The expectation was that by forming different metal carbonyl 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 CH2Cl2 (0.1 M) at RT unless stated, with the product ratios determined by integration of the unsaturated 1H NMR spectra. As expected, many of the conditions produced mixtures of products, although three

shown that spirocycles of this type could be prepared using BF3·OEt2 to promote the reaction, albeit with competing diastereo- 
phenol rearrangement products being formed in some cases.13 Apart from these works, surprisingly little is known about the re-
actions of phenol-tethered α-diazoketones, although Harada, 
Nemoto and co-workers recently published a powerful strategy for the 
conversion of structurally related α-diazocoumarins 12 into 
spirocyclic diamines 13 in high yield and exo-stereoisomeric 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 McKeown 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, (acceptor-
acceptor) diazo compounds, for example, the anisole annihilation 
method developed by Doyle and co-workers, depicted in Scheme 3B. Interestingly, 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 is often easier than in less 
stable 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.20 Our interest in these systems was further piqued by the fact 
that, to the best of our knowledge, there has been no report 
concerning the reactions of any phenol/anisole-tethered α-diazo-
ketones of this type (3) prior to this study.20 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.

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major identifiable products were observed in most cases: these were subsequently isolated and the structures assigned as cyclopropane 4a, tetraene 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 ratios 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(COD), Cu(OAc) and Pd(dba) catalysts (Table 1, entries 1–3), with AgOTf producing this product with the highest purity of the catalysts screened (entry 4). Conversely, more Lewis acidic catalysts Cu(OAc)2 and AgOTf furnished tetraene 5a as the major product with good chemoselectivity (entries 5 and 6), whereas Pd(PPh3)3Cl2 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 tetraene 5a. Presumably, following metal-mediated dioxo decomposition, Buchner cyclopropanation of the electron-rich aniline ring takes place to form cyclopropane 4a which is in dynamic equilibrium with cyclopropane 4a* arising from reversible electrocyclic ring opening. Under certain conditions (e.g. Table 1, entries 1–4) the cyclopropane/cyclopropane equilibrating mixture 4a*/4a is isolable, but under more acidic conditions (for example, in the presence of comparatively Lewis acidic catalysts such as Cu(OAc)2 or AgOTf, see Table 1, entries 5 and 6) we propose that Lewis acid-mediated ring expansion and tautomerisation (4a → 20 → 5a) results in its conversion into tetraene 5a.\(^\text{13}\)\(^\text{14}\) In support of this, it was observed that a purified sample of cyclopropane 4a can be converted into tetraene 5a smoothly upon treatment under our standard AgOTf-mediated conditions (cf. Table 1, entry 6).

Attention next turned to further optimising each of the three individual processes. Pleasingly, the selective formation of cyclopropane 4a and tetraene 5a required little additional optimisation; changes to the reaction solvents and catalyst loadings were broadly examined, and optimal conditions were uncovered that enabled each product to be isolated in 83% and 79% yield respectively, using either 2 mol% AgOTf or 10 mol% AgOTf both in CH2Cl2 at room temperature (Scheme 5). We were also able to perform a subsequent Dieck–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 nорcaradiene-like in character.

In our initial catalyst screen, the most effective catalyst for the preparation of 1,2-dicarbonyl 6a was Pd(PPh3)3Cl2, but after further optimisation, we were unable to get full and clean conversion into this product, with unwanted side products (especially tetraene 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 under conditions originally reported by Toste et al., thus, 1,2-dicarboxy 6a was isolated in 90% yield following treatment with a mixed AgOTf/AgOTf catalyst system in the presence of diphenyl disulfide (Scheme 6).\(^\text{15}\)\(^\text{16}\)

2.2. Phenol-tethered a-diaxoketones

Given that para-anisole derivatives have been successfully used\(^\text{17}\) in deaminating spirocyclisation reactions to make spirocyclic dienes via either electrophilic activation modes, we were

![Image](https://example.com/image.png)
somewhat surprised that none of the catalysts tested on anisole 3a delivered spirocycle 7. However, based on precedent for the formation of spirocyclic dimines from related phenol derivatives, we were optimistic that shifting focus to the analogous phenol-tethered diazoketone 3b would facilitate access to this medicinally important compound class. Thus, the same metal catalysts previously used on anisole 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 CuOTf/RT, thus, the treatment of diazoketone 3b with 5 mol% CuOTf for 3 h at RT in CH2Cl2 afforded spirocycle 7, which was isolated in 70% yield (Scheme 7). The selective formation of this highly functionalized product nicely complements the anisole studies outlined above (Schemes 3–5).

2.3. Spiroprotected d-diazoketones

As shown above, each of products 4a–6a can be selectively obtained from anisole-tethered d-diazoketone 3a, while phenol-tethered d-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 the analogous system in which the tethered phenol is protected with a tert-butylimidethylsilyl (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 desilylations would enable phenol derivatives 4b–6b to be isolated. Thus, TBS-protected spirocycle 3c was reacted under the optimised conditions for the preparation of 4a–6a (Scheme 8). First, the AgO catalysts delivered the expected Buchner cyclopropane product 4c (as before, in dynamic equilibrium with its cyclopropenone form) in good yield. Next, the AgOTf conditions also worked well, but proceeded with concomitant desilylation, affording phenol-tethered 3b 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, 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 d-diazoketone starting material 3b. Compound 4c is a good Diels–Alder substrate, reacting with dimethyl acrylamidomethoxylate 21 to form 22c in high yield, and subsequent TBS-decavage 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, TFA) but decomposition of starting material 6c into a mixture of uncharacterizable products was commonly observed. The best conditions we uncovered involved reacting 6c with BF3·Et2O in CH2Cl2 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 d-diazoketones has been
performed. In total, four distinct products classes have been shown to react 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 products types C, clopropanes, 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 8. 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 3-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.1,2

4. Experimental aspects

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 CHCl₃, toluene, MeCN and DMF were obtained from an Innovative Technology Inc. Pure-Solv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzenophenone ketyl immediately before use.¹H NMR and ¹³C NMR spectra were recorded on a Jeol JEO 4040 or Jeol EC 400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 25 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δH 7.27 and δC 77.0 for CDCl₃ and δH 3.31 and δC 49.1 for CDOD 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, HMRG and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer GAAT 2 Spectrometer as a thin film dispersed either from CHCl₃ or CDCl₃. Mass spectra (high-resolution) were obtained by the University of York Mass Spectrometry Centre. Using Electrospray ionisation (ESI) or Liquid Injection Field Desorption (LIFD) on a Bruker Daltonics, Micro-TOF spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. This layer chromatography was carried out on Merck silica gel 60F₂₅₄ 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 slurried packed Fluka silica gel (SiO₂), 35–70 μm, 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(OEt)·HCl (107 mg, 1.50 mmol) and DPEA (0.52 mL, 3.00 mmol) in CHCl₃ (2.5 mL) was added TFA·H₂O (0.95 mg, 15.00 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 a 2 M NaOH (20 mL), brine (20 mL), dried over MgSO₄ and concentrated in vacuo to afford the Weinreb amide product.

4.3. Experimental procedures

4.3.1. N-methoxy-2-(4-methoxyphenyl)-N-methylpropanamide

Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid (7.00 g, 38.4 mmol), T3P 50% in EtOAc (37.0 g, 58.3 mmol), DPEA (20.3 mL, 116 mmol) and MeNH(OEt)·HCl (4.20 g, 42.7 mmol) in CH₂Cl₂ (100 mL) at RT for 1 h, afforded the title compound without further purification as a yellow oil (8.70 g, 100%). Rf 0.46 (1:1 hexane:EDAc); δH (400 MHz, CDCl₃) 2.71 (2H, t, J = 7.3 Hz), 2.91 (2H, t, J = 7.3 Hz), 3.8 (3H, s), 3.61 (3H, s), 6.84 (2H, d, J = 8.0 Hz), 7.25 (2H, d, J = 8.0 Hz); δC (100 MHz, CDCl₃) 29.8, 32.1, 34.0, 55.2, 61.2, 113.8, 129.3, 133.4, 157.9, 157.1, 173.7; HRMS (ESI+): Found: 246.1007; C₁₀H₁₄NO₂ (M⁺) Requires: 246.1010. Found: 224.1277; C₈H₆NO (MH⁺) Requires: 224.1281. Spectroscopic data matched those previously reported in the literature.¹

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 (50 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 with stirring with sat. aq. NaCl (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 MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 2:1 hexane:EtOAc) to afford the title compound as a clear and colourless oil (1.76 g, 77%); δH (7.3 hexane:EtOAc) 7.48 (3H, d, J = 8.0 Hz); δC (100 MHz, CDCl₃) 28.5, 43.7, 50.4, 55.2, 113.8, 127.8, 128.7, 129.2, 132.6, 135.4, 137.2, 145.7, 157.8, 157.6, 157.5, 157.3; HRMS (ESI+): Found: 277.1889; C₁₀H₉NO (M⁺) Requires: 277.1999.

4.3.3. 1-(3-Azido-4-(4-methoxyphenyl)-1-phenylbutan-2-one [3a]

To a solution of 4-(4-methoxyphenyl)-1-phenylbutan-2-one (177 mg, 3.84 mmol) and p-ABSA (113 g, 461 mmol) in MeCN (11.5 mL) at RT under argon was added DIBU (1.08 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% EtOH as a basic additive) to afford the title compound 3a as a yellow solid (797 mg, 74%); mp 79–81°C; δH (7.3 hex- ane:EtOAc) 7.48 (3H, d, J = 8.0 Hz); δC (CDCl₃) 28.7 (2H, t, J = 7.5 Hz), 2.91 (2H, t, J = 7.5 Hz), 3.97 (3H, s), 6.84 (2H, d, J = 8.5 Hz), 7.31 (2H, d, J = 8.5 Hz), 7.27 (2H, t, J = 7.5 Hz), 7.41 (2H, d, J = 8.0 Hz), 7.51 Hz, 7.47 (2H, d, J = 8.0 Hz); δC (100 MHz, CDCl₃) 28.4, 41.1, 55.2, 72.3, 113.9, 125.4, 126.2, 127.8, 129.0, 129.6, 132.7, 158.1, 192.2; HRMS (ESI+): Found: 280.1212; C₁₀H₉NO (M⁺) Requires: 280.1212.

4.3.4. 5-Methoxy-3-phenyl-3b,5-dihydroxy-3H-cyclopenta[1,3]dicycloprop[2,benzimidazol]-2(1H)-one [4a]

A flame-dried, round-bottomed flask was charged with 1: diac Idaho-3-(4-methoxyphenyl)-1-phenylbutan-2-one 3a (100 mg, 0.357 mmol) and Ac₂O (1.7 mg, 0.03 mmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (3.6 mL) was degassed with argon for 20 min before adding the diac/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 (7.45 g, 8523); Rf 0.33 (hexane:EtOAc = 1:1) [thin film (cm) 1 3028, 2934, 2829, 1745, 1674, 1496, 1446, 1416, 1219, 1167, 1109, 1020, 815, 756; δ 400 MHz, CDCl3] 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), 3.57 (1H, br d, J = 8.5 Hz), 5.60 (1H, d, J = 8.0 Hz), 5.87 (1H, d, J = 8.5 Hz), 6.53 (1H, d, J = 8.0 Hz), 7.14 - 7.24 (3H, m, δ (ppm) (100 MHz, CDCl3) 27.3, 34.8, 54.6, 90.0, 119.5, 123.3, 126.9, 127.5, 128.5, 136.6, 157.2, 175.7; HRMS (ESI+) Found: 2755.104; C10H14Na2O2 (M+Na+) Requires 2755.1043. Found: 253.1222. C6H8Na2O2 (M+) Requires 253.1223. Note: 11C NMR signal was not observed, presumably due to peak broadening arising from the Buchler rearrangement.

4.3.5. 1-[4-[(4-fluorophenoxy)phenyl]-N-methyl-N-(4-methylphenyl)propan-2-amine [2a] (100 mg, 0.515 mmol) in toluene (0.5 ml) under argon, dimethyl acetylenedicarboxylate [2b] (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 (9:1 hexane:EtOAc to afford the title compound 4a as an oil (275 mg, 90%); Rf 0.32 (9:1 hexane:EtOAc) [thin film (cm) 1 2934, 2829, 1717, 1670, 1596, 1449, 1420, 1377, 1033, 825, 685; δ 400 MHz, CDCl3] 3.00 (2H, t, J = 7.5 Hz), 3.21 (2H, t, J = 7.5 Hz), 3.79 (2H, s), 6.83 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 7.5 Hz), 7.48 (2H, d, J = 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.5 Hz); δ (ppm) (100 MHz, CDCl3) 27.8, 30.4, 55.2, 113.2, 119.2, 129.4, 130.2, 131.8, 133.1, 134.6, 158.1, 191.2, 202.4; HRMS (ESI+) Found: 290.0990; C10H11NaO2 (M+) Requires 290.0992.

4.3.6. 3-(4-Hydroxyphenyl)-N-methyl-N-(4-methylphenyl)propan-2-amine [3b] (700 mg, 4.21 mmol) T3P 50% in EtOAc (40.2 g, 63.2 mmol), DIFMA (22.0 g, 126 mmol) and MeOH/NH4Cl (4.50, 483.6 mmol) in ClCH2Cl (105 ml) at RT for 1 h. The title compound was purified using further precipitation as a yellow oil (75 g, 860); Rf 0.21 (1:3 hexane:EtOAc) [thin film (cm) 1 3263, 2538, 1632, 1614, 1593, 1515, 1468, 1388, 1266, 1228, 1172, 987; δ 400 MHz, CDCl3] 2.90 (2H, t, J = 7.5 Hz), 7.09 (2H, t, J = 7.5 Hz), 7.19 (3H, s), 3.01 (3H, s, δ (ppm) (100 MHz, CDCl3) 29.2, 32.2, 40.0, 61.2, 113.5, 129.3, 154.3, 179.3; HRMS (ESI+) Found: 232.09591; C7H8NaO2 (M+) Requires 232.09544. Found: 210.1127; C6H8Na2O2 (M+) Requires 210.1125.

4.3.7. 4-[4-(4-hydroxyphenyl)-1-phenylbutan-2-one] [4a] (4.3 g, 7.31 mol) in THF (70 ml) at 0 °C under argon was added benzylmagnesium chloride (146.6 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. NH4Cl (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 MgSO4 and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) to afford the title compound as a white solid (15 g, 865); mp 112-114 °C; Rf 0.46 (4:1 hexane:EtOAc) [thin film (cm) 1 1387, 3027, 2929, 1007, 1614, 1155, 1451, 1362, 1221, 833, 741, 699; δ 400 MHz, CDCl3) 2.68 - 2.81 (4H, m), 3.58 (2H, s, δ (ppm) (100 MHz, CDCl3) 6.93 (2H, d, J = 8.0 Hz) 7.11 - 7.17 (3H, m), 7.10 - 7.47 (4H, m); δ (ppm) (100 MHz, CDCl3) 30.2, 44.9, 510, 156.3, 128.0, 128.7, 136.4, 139.7, 131.3, 136.0, 156.8, 210.7; HRMS (ESI+) Found: 263.3034; C10H11NaO2 (M+) Requires 263.3043.

4.3.8. 4-[4-(4-tert-Butyldimethylsilyl)phenyl]-1-phenylbutan-2-one To a solution of 4-(4-hydroxyphenyl)-1-phenylbutan-2-one (139 g, 5.77 mmol) in anhydrous DMF (113 ml) was added imidazole (500 mg, 8.66 mmol) at 0 °C. TBCI (130 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 EtO (20 ml) and the organic layer was washed with water (3 x 30 ml). The organic was then washed with brine (20 ml) over MgSO4 and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc) afforded the title compound as a white solid (153 g, 792); mp 64 - 66 °C; δ (ppm) (100 MHz, CDCl3) 27.8, 30.4, 55.2, 113.2, 119.2, 129.4, 130.2, 131.8, 133.1, 134.6, 207.7; HRMS (ESI+) Found: 377.1905; C10H11NaO2Si (M+) Requires 377.1907. Found:
3.4.3. 1-1-Phenylobutan-2-one (10 mg, 0.043 mmol) and p-ABSA (122 mg, 0.508 mmol) in MeCN (15 mL) at RT under argon was added DIBU (88.5 µL, 0.590 mmol) and the resulting solution was stirred for 1 h before being concentrated in vacuo. The crude material was purified by column chromatography (23:1 hexane:EtOAc; then 1:1 hexane:EtOAc) to afford the title compound 7 as a yellow solid (168 mg, 67%).

3.4.4. 1-1-Phenylobutan-2-one (10 mg, 0.043 mmol) and p-ABSA (45.7 mg, 0.17 µmol) and p-ABSA (0.40 mL, 3.9 mol) was degassed with argon for 10 min in the diol/catalyst mixture. The reaction mixture was then stirred at RT for 1 h after 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 4 as an orange oil (110 mg, 643%).

3.4.5. 1-1-Phenylobutan-2-one (10 mg, 0.043 mmol) and p-ABSA (122 mg, 0.508 mmol) in MeCN (15 mL) at RT under argon was added DIBU (88.5 µL, 0.590 mmol) and the resulting solution was stirred for 1 h before being concentrated in vacuo. The crude material was purified by column chromatography (23:1 hexane:EtOAc; then 1:1 hexane:EtOAc) to afford the title compound 7 as a yellow solid (168 mg, 67%).

A flame-dried round-bottomed flask was charged with 4-(1-1-Phenylobutan-2-one) (10 mg, 0.043 mmol) and p-ABSA (45.7 mg, 0.17 µmol) and p-ABSA (0.40 mL, 3.9 mol) was degassed with argon for 20 min before adding to the diol/catalyst mixture. The reaction mixture was then stirred at RT for 6 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 4 as an orange oil (110 mg, 643%).

3.5.2. 1-1-Phenylobutan-2-one (10 mg, 0.043 mmol) and p-ABSA (122 mg, 0.508 mmol) in MeCN (15 mL) at RT under argon was added DIBU (88.5 µL, 0.590 mmol) and the resulting solution was stirred for 1 h before being concentrated in vacuo. The crude material was purified by column chromatography (23:1 hexane:EtOAc; then 1:1 hexane:EtOAc) to afford the title compound 7 as a yellow solid (168 mg, 67%).

A flame-dried round-bottomed flask was charged with 4-(1-1-Phenylobutan-2-one) (10 mg, 0.043 mmol) and p-ABSA (45.7 mg, 0.17 µmol) and p-ABSA (0.40 mL, 3.9 mol) was degassed with argon for 20 min before adding to the diol/catalyst mixture. The reaction mixture was then stirred at RT for 6 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 4 as an orange oil (110 mg, 643%).

3.4.5. 1-1-Phenylobutan-2-one (10 mg, 0.043 mmol) and p-ABSA (122 mg, 0.508 mmol) in MeCN (15 mL) at RT under argon was added DIBU (88.5 µL, 0.590 mmol) and the resulting solution was stirred for 1 h before being concentrated in vacuo. The crude material was purified by column chromatography (23:1 hexane:EtOAc; then 1:1 hexane:EtOAc) to afford the title compound 7 as a yellow solid (168 mg, 67%).

A flame-dried round-bottomed flask was charged with 4-(1-1-Phenylobutan-2-one) (10 mg, 0.043 mmol) and p-ABSA (45.7 mg, 0.17 µmol) and p-ABSA (0.40 mL, 3.9 mol) was degassed with argon for 20 min before adding to the diol/catalyst mixture. The reaction mixture was then stirred at RT for 6 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 4 as an orange oil (110 mg, 643%).
A round-bottomed flask was charged with cyclopropene 4c (591 mg, 0.54 mmol) in toluene (13 mL) under argon and dimethyl acetylenedicarboxylate 21 (0.13 mL, 1.68 mmol) was added and the reaction mixture stirred at 80 °C for 3 h. The crude material was purified by column chromatography (62:8 hexane:EtOAc) and then recrystallised from hexane:EtOAc:thf (9:1) to afford the title compound 22c as a yellow oil (171 mg, 21%).

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.L), and the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-013, W.P.L) 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.2020.02.003.

References


3. For a powerful example in activity directed synthesis, see: (a) Karapetian G. Warriner S. Nolan A. Nat. Chem. 2014;6:737.

that it is in both a lemma and an aromatic ring.

15. For the first report of Bucherer ring expansion, see: (a) Bucher E, Curtius T. Ber Black Chem Soc. 1885;18:2597. For early reports on intramolecular Bucherer
reaction, see:
18. For an excellent review, including a detailed section on acceptor-acceptor
diacyl compounds, see reference 9. Our recent examples of their use in synthe-
(g) Lloyd MG, Taylor JJ. J Org Chem. 2016;81:9671.
19. Starting material 1a was prepared using a two-step procedure: GPnG addition into a Wessner amide followed by diacyl transfer reaction using the
method based on a previous publication from our group, see reference 1a.)
21. It is also possible that the rearrangement may be catalyzed by Wilson’s benzoxadiazole acid catalyst, see: (a) Tang TT, Borch J, Hennestad L. J Org Chem. 2011;76:9331.
Appendix IV. Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones

Synthetic Methods

Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones

John T. R. Liddon, Michael J. James, Aimee K. Clarke, Peter O’Brien, Richard J. K. Taylor,* and William P. Unsworth†§

Abstract: Medicinally relevant spirocyclic indolines, 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 deaminating spirocyclisation reaction to generate an intermediate vinyl-metal species, which then rearranges selectively by careful choice of catalyst and reaction conditions.

The synthesis of structurally diverse compounds is central to the discovery of pharmaceutical lead compounds. However, the formation of distinct compound sets usually requires multiple synthetic routes, which is time-consuming and labour-intensive; therefore, strategies capable of selectively forming multiple products from common starting materials are of high value. The concept underpinning our approach is the formation of a common reactive intermediate (from a simple, inexpensive starting material), which depending on the catalyst used can rearrange into different scaffolds (e.g., spirocyles, 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,13,16 such methods have mainly focused on the formation of products with similar frameworks (e.g., redox iso- mers, 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.

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 deaminating spirocyclisation16 of ynones 1 into spirocyclic indolines 3 can be catalysed by AgOTf, with vinylsilver species 2 (IM) → Ag as likely intermediates.10 A key design feature of our strategy was the idea that varying the catalyst would alter the nature and reactivity of the vinyl-metal intermediate 2 in a programmable way, such that alternative products could be formed by different rearrangement reactions. Herein, we report the successful realisation of this approach. Notably, by judicious choice of catalyst, simple, inexpensive ynone starting materials 1 can be converted into spirocyclic indolines13 3 using Ag, carbazoles 5 using Au, and quinolines 7 using Ag/Ag2O in high yield, each by...
a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetra cyclic scaffolds **B** can be formed with complete diastereoselectivity, by a telescoped spirocyclisation/ nuclophilic addition sequence, which was performed using a chiral Ag^+ salt to furnish an enantioenrich product.

The spirocyclisation of 1a using AgOTf formed indolene 3a in quantitative yield (Scheme 2).

![Scheme 2. Formation of spirocyclic Indolene 3a.](image)

The spirocyclisation of 1a using AgOTf formed indolene 3a in quantitative yield (Scheme 2). The mild reaction conditions are believed to play a key role in this process, stabilising the spirocycle with respect to further reactions. However, in the proposed scaffold diversity approach, in which the synthesis of carbazole 5a was an initial goal, the challenge was to deliberately promote 1,2-migration\(^\text{a}\) in a controlled manner.\(^\text{a}\) A Ph/PNNT catalyst was chosen based on the prediction that the \(\alpha\)-acidic gold) 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-carbonyl species.\(^\text{a}\) This idea was validated (94%) yield of 5a) with a likely reaction mechanism depicted in Scheme 3; the ring enlargement is believed to proceed either via cyclopropane intermediate 9a, or by a direct 1,2-migration reaction 2a-Au → 10a based on related precedents.\(^\text{a}\) 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/PNNT, under the same conditions.

Next we 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 AICl₃·6H₂O and subsequent heating in a microwave gave quinoline 7a in high yield (Scheme 4).\(^\text{a}\)\(^\text{a}\) Following Ag-

![Scheme 4. Formation of quinoline 7a: X = O or N0.](image)

mediated spirocyclisation, it is thought that the \(\text{Ag}^+\) 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 LiHMDS 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\(^\text{a}\)\(^\text{a}\) with AICl₃·6H₂O did not result in quinoline formation. Instead, 1,2 migration of the allenyl group took place, furnishing carbazole 15 following tetrahydroxylation and dehydration (Scheme 5).

![Scheme 5. Base-mediated formation of quinoline 7a and the contrasting reactivity of spirocyclic cyclopentenol 14.](image)

To probe the scope of all three reaction manifolds, various functionailised indole-tethered yrones 1a–1m were prepared, substituted in several positions with electron-rich and -poor aromatics, alkyl substituents, O- and N-protected alkyl groups and PMS.\(^\text{a}\)\(^\text{a}\) First, using the AgOTf-mediated spirocyclisation...
Table 1. Reaction scope for the formation of spirocyclic indolines, carbazoles and quinolines.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
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<tr>
<td>n-BuLi (1.1 M) in i-PrOH, 0 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>74%</td>
<td>67%</td>
<td>82%</td>
</tr>
<tr>
<td>1b</td>
<td>75%</td>
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<td>84%</td>
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<tr>
<td>1c</td>
<td>78%</td>
<td>78%</td>
<td>86%</td>
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</table>

(a) AgOTf (1 mol%) in CH₂Cl₂ (0.1 M) at RT for 0.1–1.5 h; (b) Ph₃P/Ph₂NZ (2.5 mol%) in CH₂Cl₂ (0.1 M) at RT for 0.1–1.5 h; (c) AgOTf (1 mol%) in i-PrOH (0.1 M) at RT for 0.1–1.5 h; then ACl₃;H₂O (0.1 molar) at 100 °C for 1 h; (d) reaction performed in toluene; (e) AgOTf (1 molar%) in CH₂Cl₂ (0.1 M) at RT for 0.1–1.5 h; then solvent swap for i-PrOH (0.1 M) then ACl₃;H₂O (0.1 M) at 100 °C for 1 h, PMP = para-methoxyphenyl.

Methodology: substrates 1a-1m were cleanly converted into the corresponding spirocyclic indolines 3a-3m, all in excellent yields (Table 1, conditions A). The Ph₃P/Ph₂NZ-mediated carbazole-forming reaction was similarly broad in scope (conditions B); some reactions were less efficient than the analogous spirocyclic formations, and ynone 1d did not produce any of the desired product (instead stalling at the formation 3d), but the majority of the carbazole products 5a-5j were isolated in very good yields. Finally, the quinoline-forming reaction sequence was also found to be very general (conditions C). For ynoles 1a-1e, 1g-1l, the sequential AgOTf spirocyclisation and ACl₃;H₂O mediated rearrangement steps could both be performed in i-PrOH in one-pot as described, whereas for ynone with more sensitive functional groups (1f, 1h, 1i, 1j, 1m), the process benefited from a solvent swap, with the spirocyclisation first being performed in CH₂Cl₂, before concentration and addition of i-PrOH prior to the ACl₃;H₂O step. The ACl₃;H₂O reactions were typically performed under microwave irradiation at 120 °C, but they were also shown to proceed well on a gram scale with conventional heating, albeit with a longer reaction time being required. The structure of quinoline 4f was confirmed by X-ray crystallography.

Another strand of scaffold diversity starting from more functionalised ynoles 1h-1j was briefly explored. Tetracyclic scaffolds 8h-8j equipped with additional complexity, were easily obtained following reaction of ynoles 1h-1j with AgOTf and subsequent acid-mediated protecting group cleavage in one pot (Scheme 6, and see the Supporting information for details). The tetracycles were formed as the single diastereoisomers shown, and in addition, (S)-8h was prepared in enantiomerically enriched form (93:11 e.e.) by utilising (9R,10S)-exo-salt 16a in place of AgOTf. 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. In summary, readily available indolyl ynoles have been shown to be versatile starting materials for the synthesis of spirocyclic indolines 3a-m, carbazoles 5a-j, quinolines 7a-m and tetracyclic compounds 8h-8j using a catalyst-driven scaff-
241


Appendix V. Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives

Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives


Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

Supporting Information

ABSTRACT: The deamination of 2-haloindole precursors allows access to indoleninyl halides, a hitherto underexplored functional handle with broad synthetic utility. Indoleninyl halides 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 deamination 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 underexplored functional handle for the synthesis of a broad array of spirocyclic indole derivatives. Simple deamination methods 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. 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 or putative intermediates in previous synthetic protocols and were found to hydrolyze readily in situ, generating quinolines. 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 a-acidic catalysts in the expectation of promoting deamination spirocyclization and in situ hydrolysis to generate spirocyclic indoles (e.g., 6 → 7 → 8; Scheme 1). However, when ynone 6a (R = Ph) was reacted with 10 mol % Cu(OAc)₂ in DCM at rt, the only product isolated after workup and column chromatography was spirocyclic indolene 7a in quantitative yield. None of the expected quinolide 8 was isolated, and spirocycle 7a proved to be surprisingly stable; it appears to be insensitive to air.

Scheme 1. Indoleninyl Halide Substitute Synthesis

![Chemical structure](image)

Figure 1. Preparation and reactions of indoleninyl halides.
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 AgNO3/SiO2 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.6 Indolensyl iodides 7b–d, as well as indolensyl 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 indolensyl halides established, the next step decided to examine their reactivity. Indolensyl 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 different 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, indolensyl iodide 7a was hydrolyzed using aqueous HCl in THF, affording spirocyclic esterone 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 indolensyl derivatives 9–13 in high yields (Scheme 2B).

With spirocycle 7a acting as a vinyl halide surrogate, cross-coupling reactions were performed (Scheme 2C). Sonogashira reactions using arylboronic acids afforded phenyl-2- naphtyl derivatives 14 and 15 in good yields. Likewise, Stille coupling reactions allowed furan (18), pyridine (19), thiophene (20), and olefin groups (21) to be added at the indolensyl 2-position, all in good yields. Finally, alcohol derivative 22 was prepared in quantitative yield with 85:15 de following a chemo- and diastereoselective Luche reduction of the enone moiety of 7a, leaving the indolensyl halide moiety intact (Scheme 2D). In terms of the reduction step, hydrolyde 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 indolensyl halides derived from yeast 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 deacetylation procedures to previously untested 2-halogenated starting materials, beginning with an eschweiler- cleve-catalyzed aliphatic deacetylation procedure developed by You and co-workers.6 Thus, 2-iodoindole precursor 23 was prepared and reacted with bis(1,5-cyclooctadiene)dipicridium dichloride and commercially available chiral phosphinate ligand 27.25 Plausibly, indolensyl iodide 24 was produced in near-quantitative yield with >95:5 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.6 Its subsequent deacetylation 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, indolensyl iodide 30 was prepared from imine 29 and iodide 28. These were treated with the peptidyl coupling agent TFP and (IPr)NiEt at rt, using the direct imine acylation (DiA) method developed by our group.6
furnishing spirocycle 30 with 83.17% dr. The relative stereochemistry of 30 was assigned on the basis of analogy to related compounds.14 This scaffold was again amenable to additional functionalization either by nucleophlic substitution with benzyl mercaptan or by hydrolysis, forming products 31 and 32, respectively (Scheme 4).

Scheme 4. Indoleninyl Isodole via Direct Amine Acylation

![Diagram](image)

"50, benzyl mercaptan, Cs2CO3, MeCN, 3.5 h. 51, 10% HCl(aq), THF, rt, 3 h.

In addition, cyclopropyl substrate 34 was prepared in high yield by a Mitsunobo-type reaction of indole-tethered alcohol 33. Functionalization by nucleophile displacement [5] and cross-coupling [6] again demonstrated the synthetic utility of the indoleninyl isodole substructure (Scheme 5).

Scheme 5. Indoleninyl Isodole via a Mitsunobo Reaction

![Diagram](image)

"54, benzyl mercaptan, Cs2CO3, MeCN, 33 h. 55, phenylcyclohexene, Cs2CO3, PdCl2(PPh3)2, Cat, THF, rt, 5 h.

Finally, it was found that indolomethyl 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 indolines were shown to rearrange to form quinoline derivatives upon treatment with either strong base or Lewis acid.15 It was found that treating spirocyclic indolene 7a with LHMDS in THF at 0 °C promoted its conversion into 2-isoquinoline 37 in 78% yield via a similar process (Scheme 6 for mechanistic speculation, see our earlier publication16). Of course, 2-isoquinolines are valuable, versatile building blocks in their own right, and to demonstrate this, derivatization reactions similar to those performed on indoleninyl isodole 7a were also explored. These results are summarised in Scheme 6.

First, it was found that quinoline 37 could be hydrolyzed with aqueous HCl, affording 2-quinoline 38 in quantitative yield (Scheme 6A). A chemo- and diastereoselective reduction was also performed using NaBH4 to yield alcohol 39 in good yield, with reduction presumably occurring anti to the adjacent phenyl substituent (Scheme 6B). A selection of S2Ar 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), Sondhi (47–48), and Stille (49) cross-coupling reactions all proceeding well in good yields (Scheme 6D).

In summary, we have demonstrated that indolomethyl iodides are readily accessible via the deamination of 2-indolinone 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 indolomethyl iodides to quickly become established as valuable intermediates and reagents. Their utility as precursors to easily functionalized 2-isoquinolines has also been demonstrated, further expanding their synthetic utility. Finally, while this work has focused largely on indolomethyl iodides, we have also demonstrated that indolomethyl bromide and chloride analogues can also be prepared using similar methods, and in future work the reactivity of these systems will also be examined.
### Abbreviations

<table>
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<tr>
<td>Ac</td>
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<tr>
<td>acac</td>
<td>acetylacetonate</td>
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<td>AgNPs</td>
<td>silver nanoparticles</td>
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</tr>
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<td>EDG</td>
<td>electron donating group</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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equiv. equivalents
ESI electrospray ionisation
Et ethyl
Et₂O 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 diisopropylamide
LIFDI liquid injection field desorption ionisation
m multiplet
M molar
Me methyl
min minute(s)
mp melting point
Ms mesyl
NBS N-bromosuccinimide
NEt₃ triethylamine
NMR nuclear magnetic resonance
nOe nuclear Overhauser effect
[O] oxidation
OAc acetate
oct octanoate
p-ABSA 4-acetamidobenzensulfonyl 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-butylmethylsilyl
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
References


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