Cascade Reactions of Heterocycle-tethered Ynones for the Selective Synthesis of Heterocycles and Spirocycles

Nantachai Inprung

PhD

University of York

Chemistry

September 2023

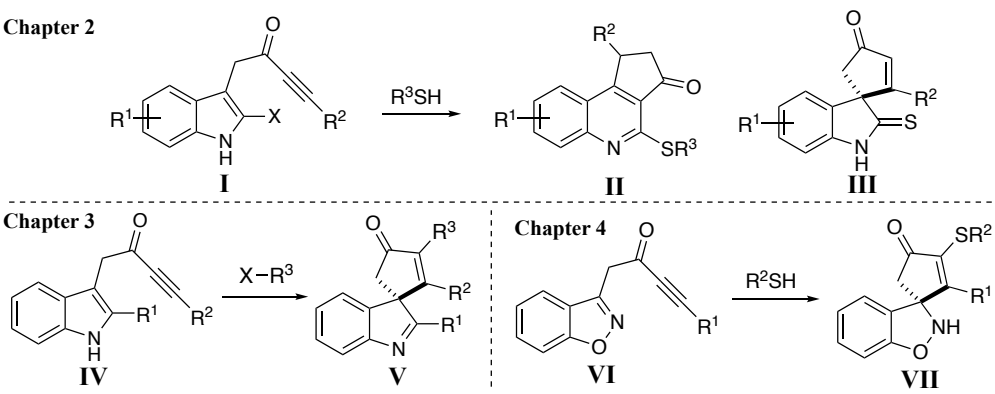
Abstract

This thesis describes the developments of a series of cascade reactions of heterocycle-tethered ynones. Chapter 1 provides an introduction to cascade reactions and photocatalysis. Key studies involving photocatalysed spirocyclisation cascade reactions are also discussed.

Chapter 2 describes the transformation of C2-halo indole-tethered ynones **I** to functionalised quinolines **II** via thiol-mediated cascade reactions. The reactions were promoted by thiol reagents involving three steps 1) dearomatising spirocyclisation, 2) nucleophilic substitution and 3) ring expansion. The reaction conditions developed operate under simple and mild conditions, and proceed in excellent yields in most cases. The synthesis of thio-oxindoles **III** was also discovered by serendipity.

Chapter 3 describes the developments of radical-based dearomatising spirocyclisation cascade reactions of indole-tethered ynones **IV**. Synthetic protocols for cyanomethylation, sulfonylation, trifluoromethylation, stannylation and borylation were developed, making use of photoredox catalysis, EDA complex-based initiation and thermolysis of AIBN. These methods allowed to synthesise spirocycles **V**. A general reaction mechanism was proposed based on a luminescence study.

Finally, Chapter 4 describes the reactivity of benzisoxaole-tethered ynones **VI**. The radical-based spirocyclisation cascade reactions between benzisoxazole-tethered ynones and thiyl radicals were successful to access functionalised spirocycles **VII**. Subsequent N–O bond cleavage and cyclisation led to the formation of other spirocyclic frameworks.



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Acknowledgements

First and foremost, I would like to deeply thank my supervisors; Richard Taylor, William Unsworth and Michael James, for providing me a great opportunity to join their groups and study at University of York. You always give me guidance, support and encouragement for my study. I have gained a lot of valuable experiences and knowledge throughout my PhD journey.

My research would not be completed without staff and members of the Department of Chemistry. I also especially thank to NMR Centre, Centre of Excellence in Mass Spectrometry and X-ray Diffraction Service for the excellent analysis.

I also would like to thank RJKT, WPU and MJJ lab members, who are amazing people, for kindly sharing research ideas and discussions. It was a great experience to work and collaborate with you.

My special thanks go to all my friends in York who always listen to me and push me up when I feel down. Thanks for making a memorable and fantastic time in York.

Next, I would like to thank the Development and Promotion of Science and Technology Talents Project (DPST) and the Royal Government of Thailand for the financial support throughout the PhD study.

Last but not least, it was a difficult time to study far away from my family and home country. I would like to warmly thank my beloved family for always giving me a big support and encouragement.

Declaration

The work presented in this Thesis was carried out at the Department of Chemistry, University of York between October 2019 and September 2023. This work is, to the best of my knowledge, original except where due reference has been made to other works.

Some of this work has also been reported in 3 recent publications, which can be found in the Appendices.

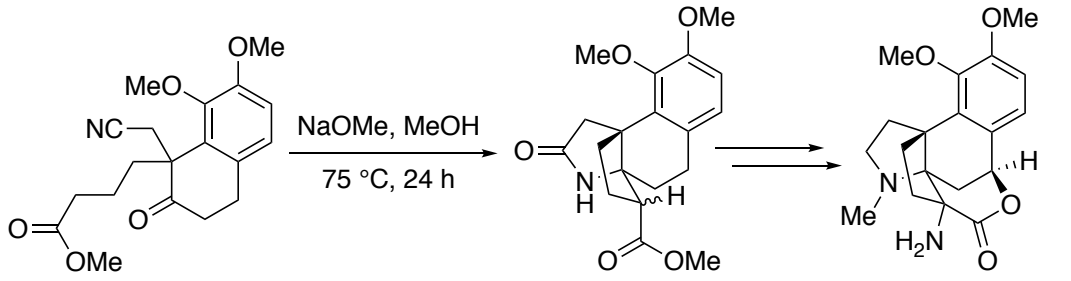
Nantachai Inprung

September 2023

Chapter 1: Introduction

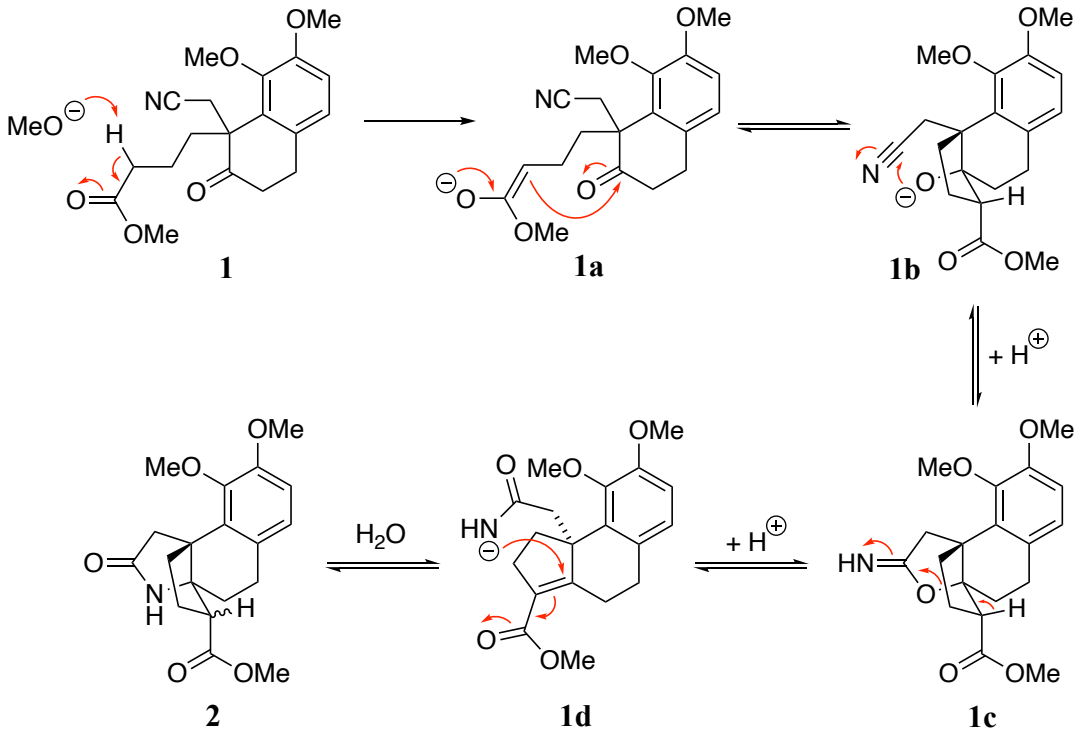
1.1 Cascade reactions and spirocyclic indole scaffolds

Cascade reactions, also known as sequential, domino, tandem and one-pot reactions, are important tools for synthetic chemists, which enable multiple transformations to occur in a single-step operation.[1-4] Cascade reactions can be developed through designed sequences, but also discovered by serendipity. Due to the power of cascade reactions to assemble complex structures very quickly, cascade strategies are often utilised to synthesise fused, bridged, and spirocyclic frameworks found in bioactive natural products.[5, 6] Cascade reactions may include electrophilic, nucleophilic, radical, metal-catalysed and pericyclic steps. For example, Trauner and co-workers used a cascade reaction in the total synthesis of natural product stephadiamine **3** (Scheme 1).[7] In this work, an impressive aldol addition cascade reaction converted bicycle **1** into the corresponding tetracycle **2** in excellent yield. The cascade reaction began with the deprotonation of saturated ester **1** to form ester enolate **1a** (Scheme 2), which then underwent intramolecular aldol addition to afford alkoxide intermediate **1b**. Next, nucleophilic addition of the alkoxide anion to the adjacent nitrile generated five-membered ring intermediate **1c**. However, deprotonation resulted in ring opening and the formation of intermediate **1d**, which subsequently underwent aza-Michael addition to furnish lactam **2**.



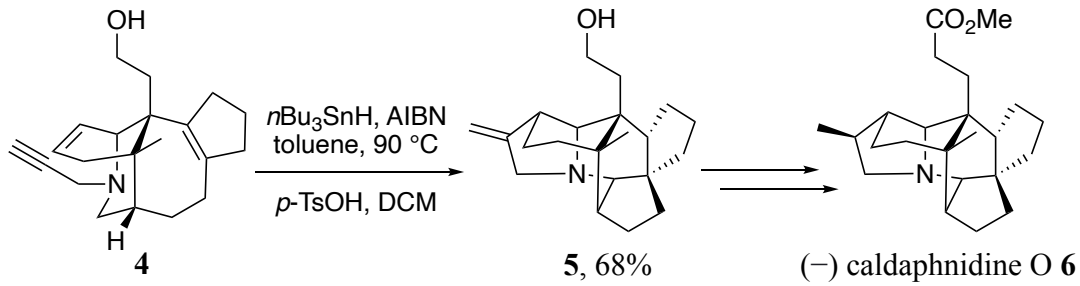
1 **2**, 99% (±) stephadiamine **3**

Scheme 1. Aldol addition cascade reaction by Trauner and co-workers

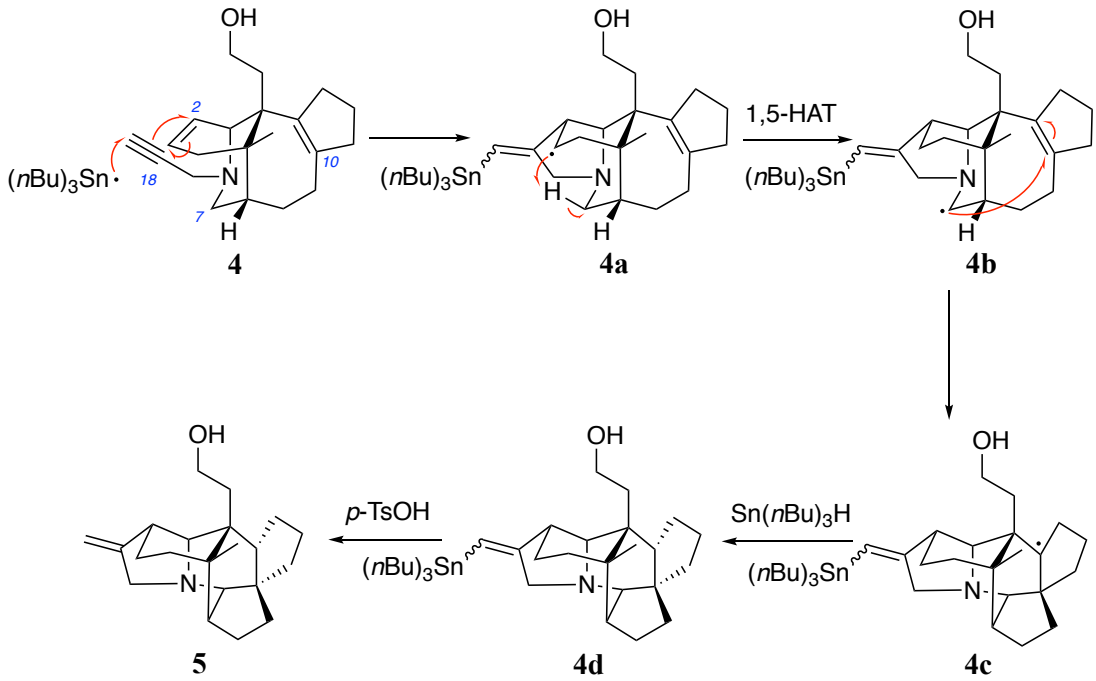


Scheme 2. Proposed mechanism for aldol-type cascade reaction

Another interesting application was described by Xu and co-workers in the enantioselective total synthesis of alkaloid caldaphnidine O **6** (Scheme 3).[8] The radical cyclisation cascade reaction of dienyne **4** led to the formation of hexacyclic core **5**. The construction of the core structure of caldaphnidine O started with the radical addition of tributyltin radical to dienyne **4** (Scheme 4), promoting C_{18} – C_2 radical cyclisation to form vinyltin intermediate **4a**. Then, 1,5-HAT (hydrogen atom transfer) generated α-amino radical intermediate **4b** at the C-7 position, which triggered C_7 – C_{10} radical cyclisation followed by radical trapping to afford hexacyclic skeleton **4d**. Finally, hydrolysis of vinyltin by acid workup provided the corresponding product **5**.



Scheme 3. Radical cascade reaction by Xu and co-workers



Scheme 4. Proposed mechanism for radical cascade reaction

Cascade reactions are also commonly used to synthesise spirocyclic indole derivatives such as spiroindolenines, which are an important class of spirocyclic compounds that are prevalent in many naturally occurring bioactive alkaloids. It is well-known that spirocyclic compounds are typically relatively rigid and have well-defined three-dimensional geometrical properties. Derived from the parent indole **7**, a generic spiroindolenine scaffold **8** is shown in Figure 1; the indole ring is connected to another ring via a single common atom at its C3-position. If the bond between the C2-position of indole and nitrogen is unsaturated, this makes it an indolenine, while the analogous saturated derivatives are called indolines **9**. Spiroindolenines are known to possess a wide range of biological properties that are important in the pharmaceutical and medicinal industries; for example compounds **10** – **13**, that have proven biological activity such as anti-tumour, anti-inflammatory and analgesic activity.[9]

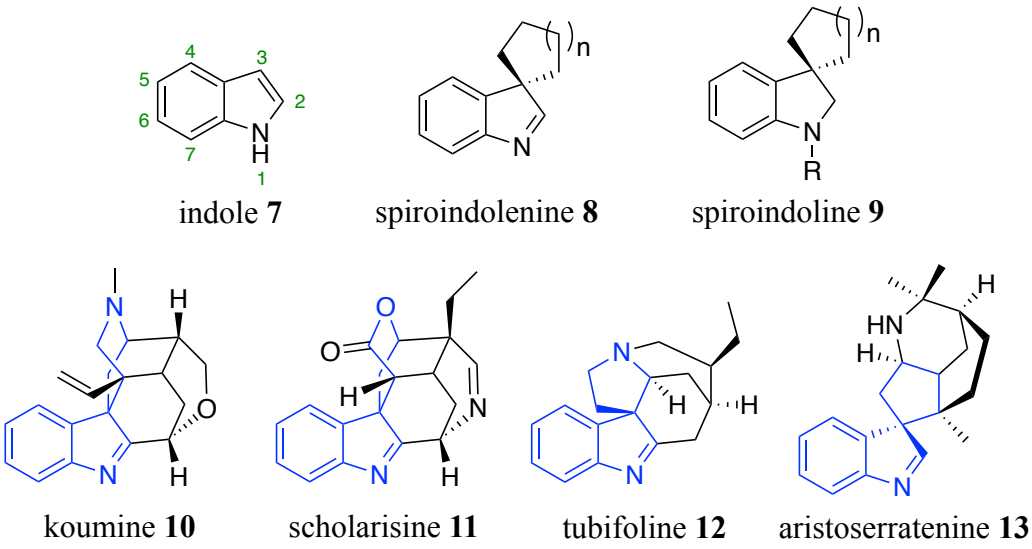
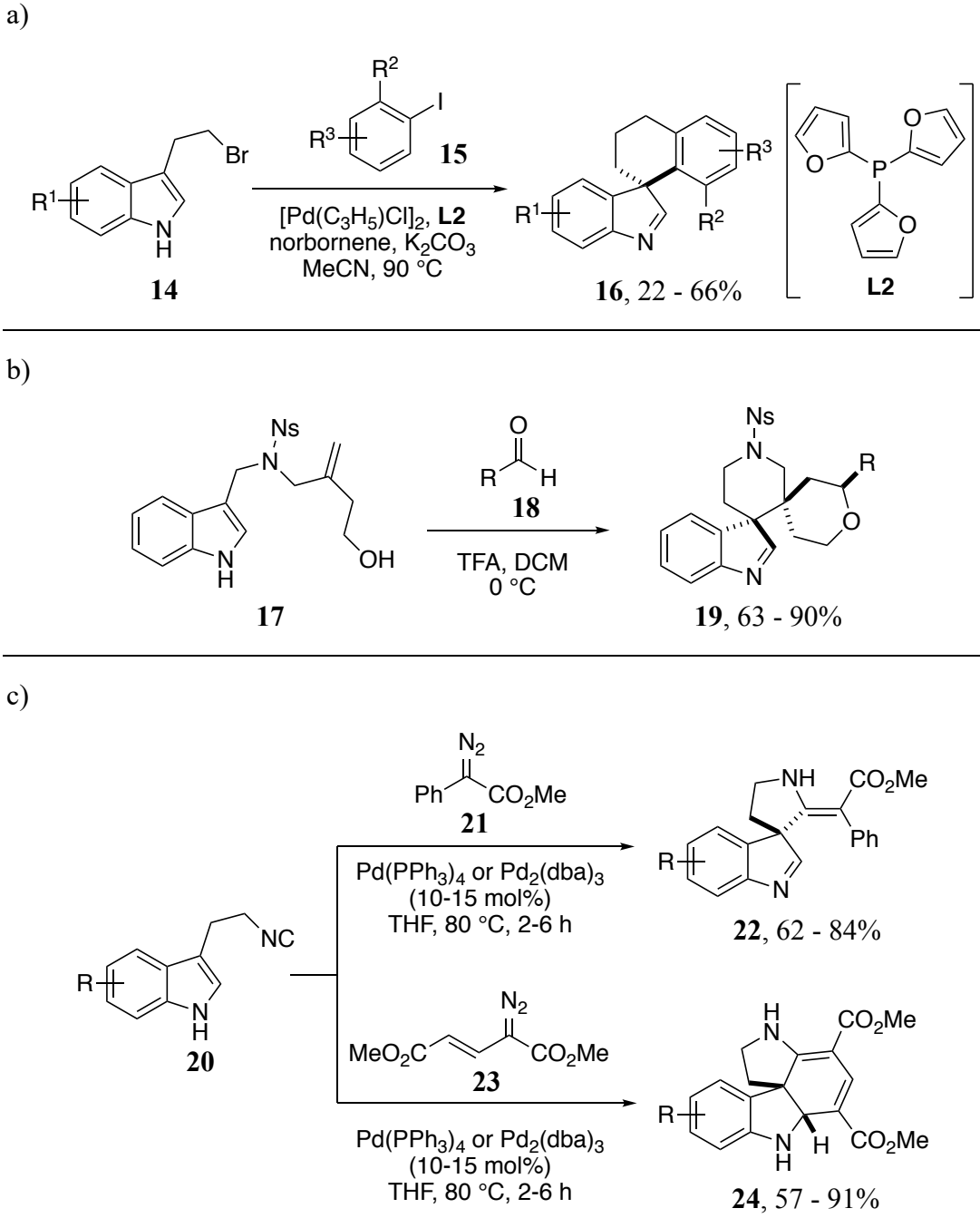


Figure 1. Indole and some spirocyclic indole derivatives

The applications of cascade reactions towards the synthesis of spiroindolenine skeletons have been explored by synthetic chemists.[10-12] For example, Liang and co-workers introduced the palladium-catalysed dearomatising spirocyclisation of indoles (Scheme 5a).[13] The cross-coupling reaction between indoles **14** and aryl iodides **15** was promoted by norbornene-mediated palladium catalysis, which provided spiroindolenines **16** in 22 – 66% yields. Reddy and co-workers demonstrated the construction of spiroindolenines via a Prins/Friedel-Crafts spirocyclisation cascade (Scheme 5b).[14] The cascade reaction of indole derivative **17** and aldehyde **18** in the presence of TFA was performed under relatively mild conditions, affording the corresponding spirocycles **19** in 63 – 90 % yields. Another interesting spirocyclisation cascade reaction was reported by Liu and co-workers to access spiroindolenines **22** and polycyclic spiroindolines **24** (Scheme 5c).[15] In this approach, tryptamine-derived isocycanide **20** was reacted with diazo acetate **21** in the presence of a palladium(0) catalyst to form spiroindolenines **22** in 62 – 84% yields. Moreover, the reaction with diazo acetate **23** led to the formation of polycyclic spiroindolines **24** in 57 – 91% yields.



Scheme 5. Spirocyclisation cascade reaction towards spiroindolenine scaffolds

1.2 Photoredox catalysis

Photocatalysis has become an increasingly powerful tool for organic chemistry in the last decade, and used by synthetic chemists as an effective method for bond formation in the construction of biologically active compounds, natural products, drugs and other organic materials.[16-18] In simple terms, the use of photoredox catalysts in synthetic chemistry enables radical intermediates to be generated under mild reaction conditions using light (usually visible light). Common photoredox catalysts include polypyridyl complexes of ruthenium(II) and iridium(III) and organic dyes (Figure 2).[19, 20]

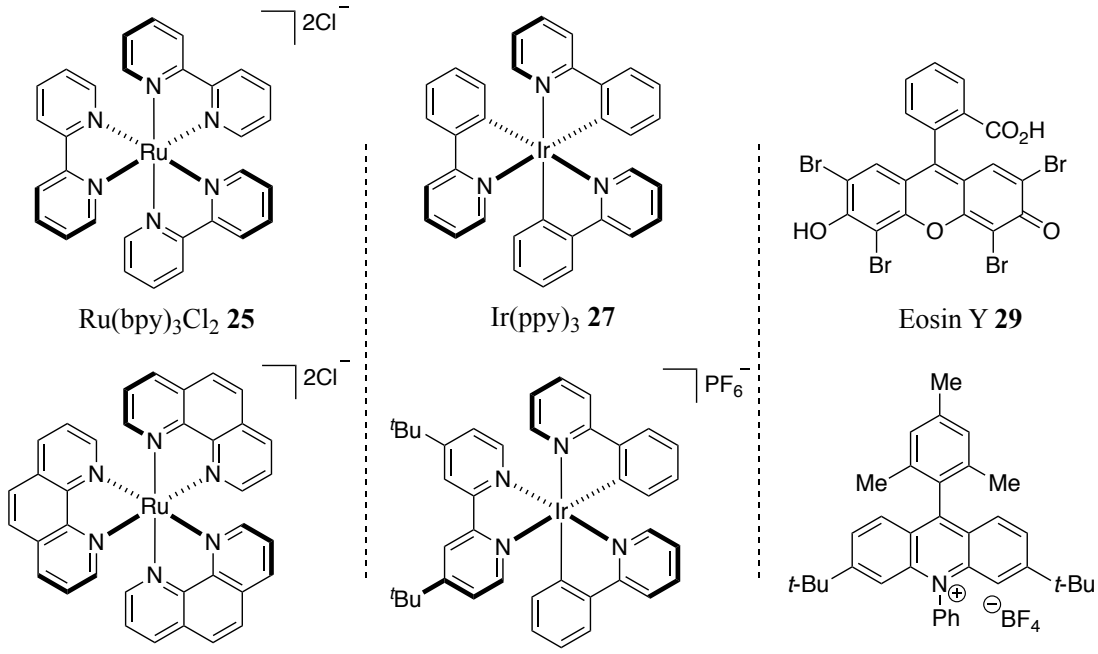


Figure 2. Common photocatalysts a) Ru(II) complexes b) Ir(III) complexes c) organic dyes

In the case of $[Ru(bpy)_3]^{2+}$ (Figure 3), the irradiation with visible light from a simple household light, or a blue coloured LED bulb (around 450 nm), stimulates an electronic transition of an electron from a metal t_{2g} orbital to a ligand π^* orbital, which is a process usually referred to as metal-to-ligand charge transfer (MLCT). Then, the excited electron of the initially formed singlet excited state undergoes intersystem crossing (ISC), passing to a triplet excited state which extends the lifetime of the

excited state species, enabling it to take part in useful chemical transformations. The excited triplet state complex is a reactive open-shell photoredox catalyst which has the ability to act as either (or both) a single electron oxidant and/or reductant. Additional advantages of this chemistry are that the reactions usually require a very low amount of catalyst, *e.g.* 1 – 2 mol%, and can often be performed at room temperature.[21]

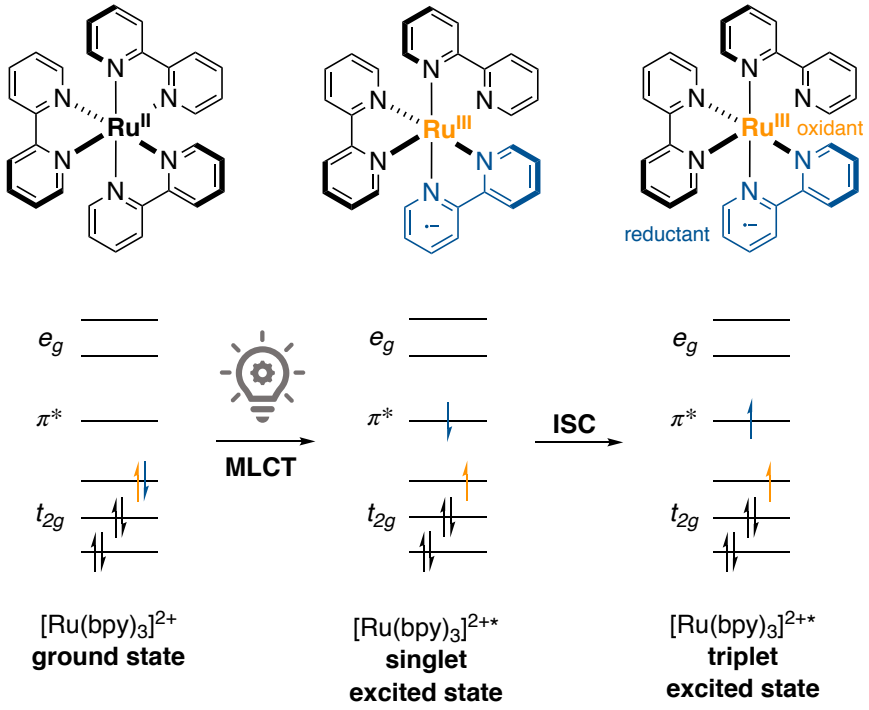


Figure 3. Simplified molecular orbital of $[Ru(bpy)_3]^{2+}$

Similar principles apply to various other commonly used photoredox catalysts, depicted in more general terms in Figure 4 for a generic photocatalyst denoted **PC**. Such photocatalytic processes start with visible light irradiation of the ground state photocatalyst (**PC**) which is excited to an excited state (**PC***). In this state, **PC*** is generally both more oxidising and more reducing than **PC**. By virtue of this special property, the excited species can react via either an oxidative or reductive quenching pathway. In the oxidative quenching cycle, **PC*** acts as a reductant, which reduces an electron acceptor (**A**) via single-electron-transfer (SET) resulting in the formation of oxidised photocatalyst ($\mathbf{PC}^+$) and radical anion ($\mathbf{A}^{\cdot-}$). Therefore, **A** is said to be an oxidative quencher of the photocatalyst. Common examples of oxidative quenchers are species like viologens, CHX_3, Ar-NO_2, Ar-CN and Ar-N_2^+. Then, $\mathbf{PC}^+$, which will

usually now be a strong oxidant, can accept an electron from an electron donor (**D**) generating the radical cation ($\mathbf{D}^{\cdot+}$) and returning **PC** to the catalytic cycle.

In the same fashion, **PC*** can also act as an oxidant in a reductive quenching cycle. It accepts an electron from an electron donor (**D**), which is often called a reductive quencher, to give the reduced photocatalyst ($\mathbf{PC}^{-}$) and a radical cation ($\mathbf{D}^{\cdot+}$). Finally, a strong reductant $\mathbf{PC}^{-}$ is oxidised by an electron acceptor (**A**) to form the radical anion ($\mathbf{A}^{\cdot-}$) and the ground state photocatalyst (**PC**). An important class of reductive quenchers are tertiary amines. In both cases of quenching cycle, the reduction potential of **PC***, **D** and **A** are critically important for the catalytic cycle.

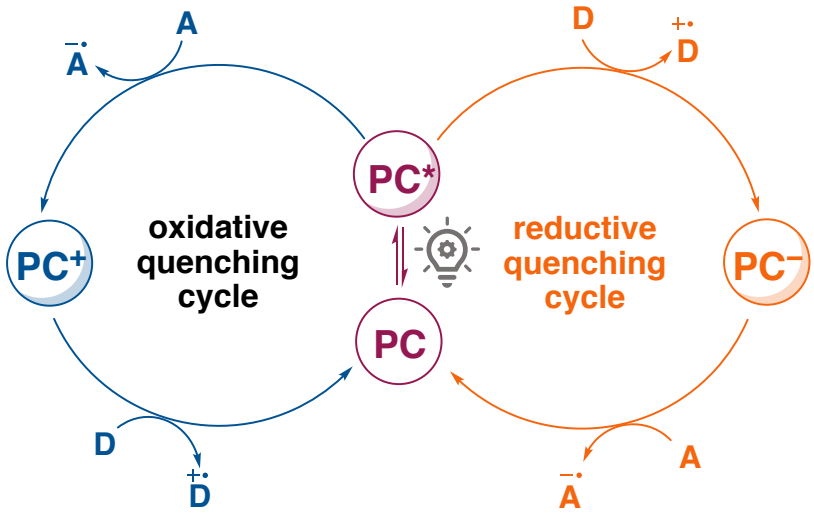
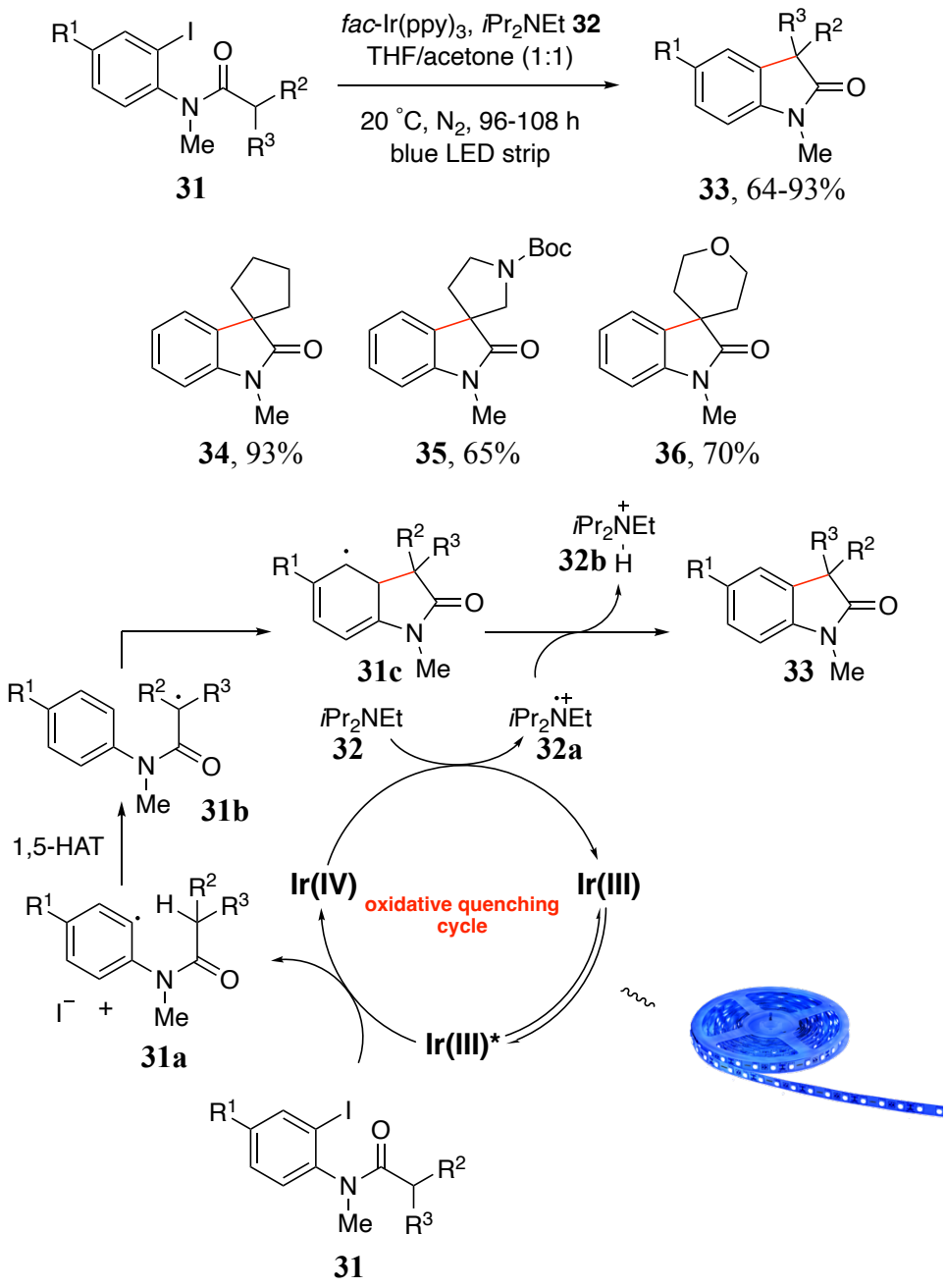


Figure 4. General photoredox catalytic process

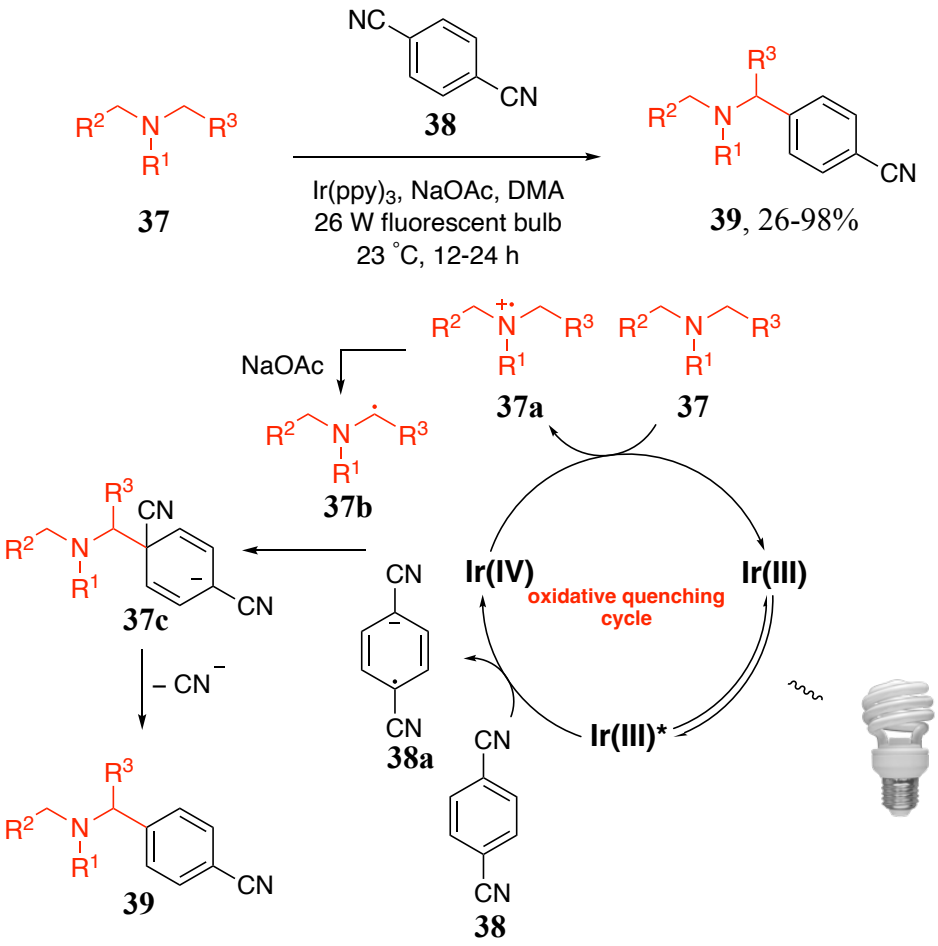
In the last decade, the number of reports on visible light photoredox catalysis being used in organic chemistry, and the number of review articles, has grown enormously.[21-23] Herein, representative examples of visible light photoredox reactions proceeding via oxidative and reductive quenching cycles are summarised. To begin with, the synthesis of oxindole **33** by intramolecular cyclisation reported by Xu and co-workers is summarised in Scheme 6.[24] The reaction of aryl iodide **31**, Ir(III) complex and *i*Pr$_2$Net **32** under irradiation of blue LED strips operated via an oxidative quenching pathway. After the Ir(III) complex was excited by visible light, the excited state species Ir(III)* complex acted as a reductant, ($E_{1/2(IV/III^*)} = -1.73$ V vs SCE),[19] donating an electron to aryl iodide **31**. Thus, an Ir(IV) complex and aryl radical **31a** were generated and the

latter underwent 1,5-HAT followed by cyclisation to form radical intermediate **31c**. After that, *i*Pr$_2$NEt **32** behaved as a terminal quencher to convert Ir(IV) complex back into the ground state Ir(III) complex and form cation radical **32a**. Finally, HAT between intermediate **31c** and radical **32a** provided oxindole **33**. In the case of substrates containing a cyclic group at the α-carbon, the reaction afforded spirocyclic oxindoles **34** – **36** in 65 – 93% yields.



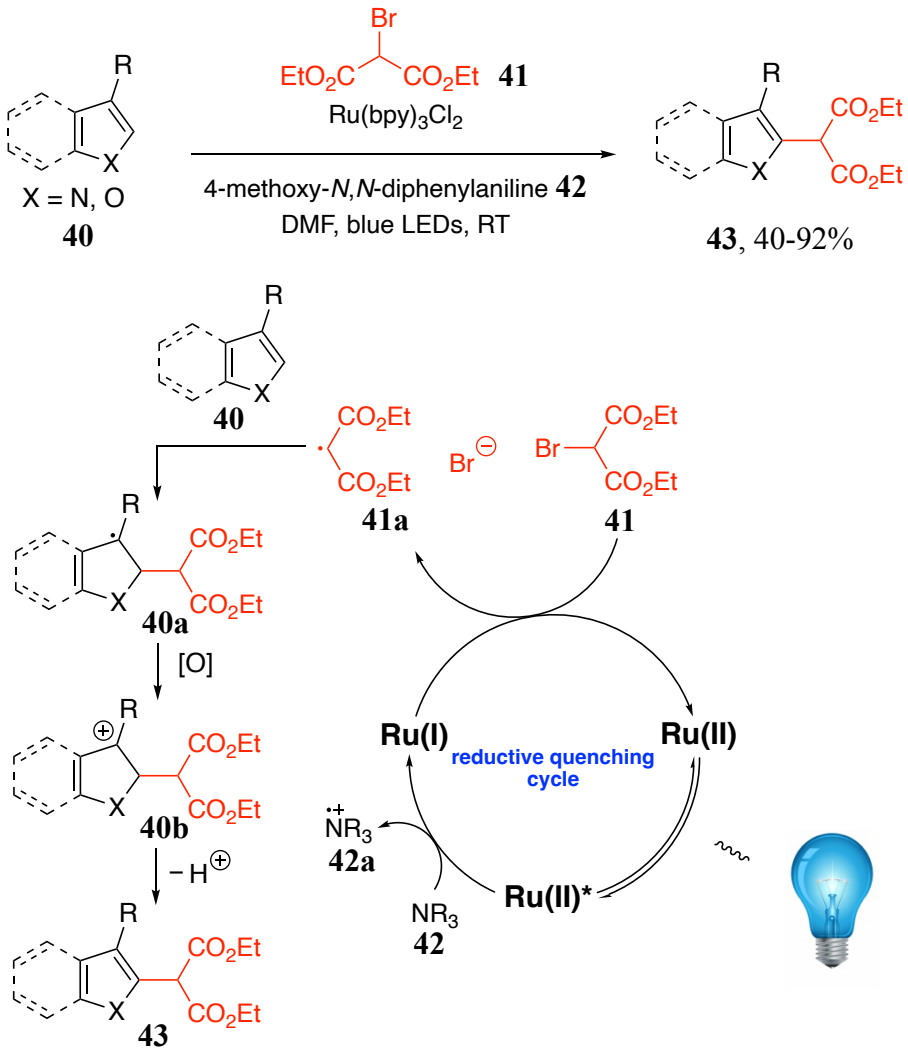
Scheme 6. Intramolecular cyclisation to prepare oxindoles

A method for α-amino C-H arylation between amine **37** and arene **38** was developed by MacMillan and co-workers (Scheme 7).[25] The mechanism operates via an oxidative quenching pathway, which was supported by luminescence quenching studies. In this work, the Ir(III) complex was excited by irradiation with a 26 W fluorescence bulb to form an excited Ir(III)* complex which is a strong reductant ($E_{1/2(IV/III^*)}$ = −1.73 V vs SCE).[19] SET from the excited photocatalyst to 1,4-dicyanobenzene **38** produced an arene radical anion **38a** and Ir(IV) complex, a strong oxidant ($E_{1/2(IV/III)}$ = +0.77 V vs SCE). Ir(IV) complex was then reduced by amine **37** to regenerate the ground state of photocatalyst and the amine radical cation **37a** which was subsequently deprotonated by NaOAc to give α-amino radical **37b**. As a result, the reaction between arene radical **38a** and α-amino radical **37b** generated a bond between two radical species, which finally dearomatised and eliminated cyanide ion to afford the corresponding product **39**.



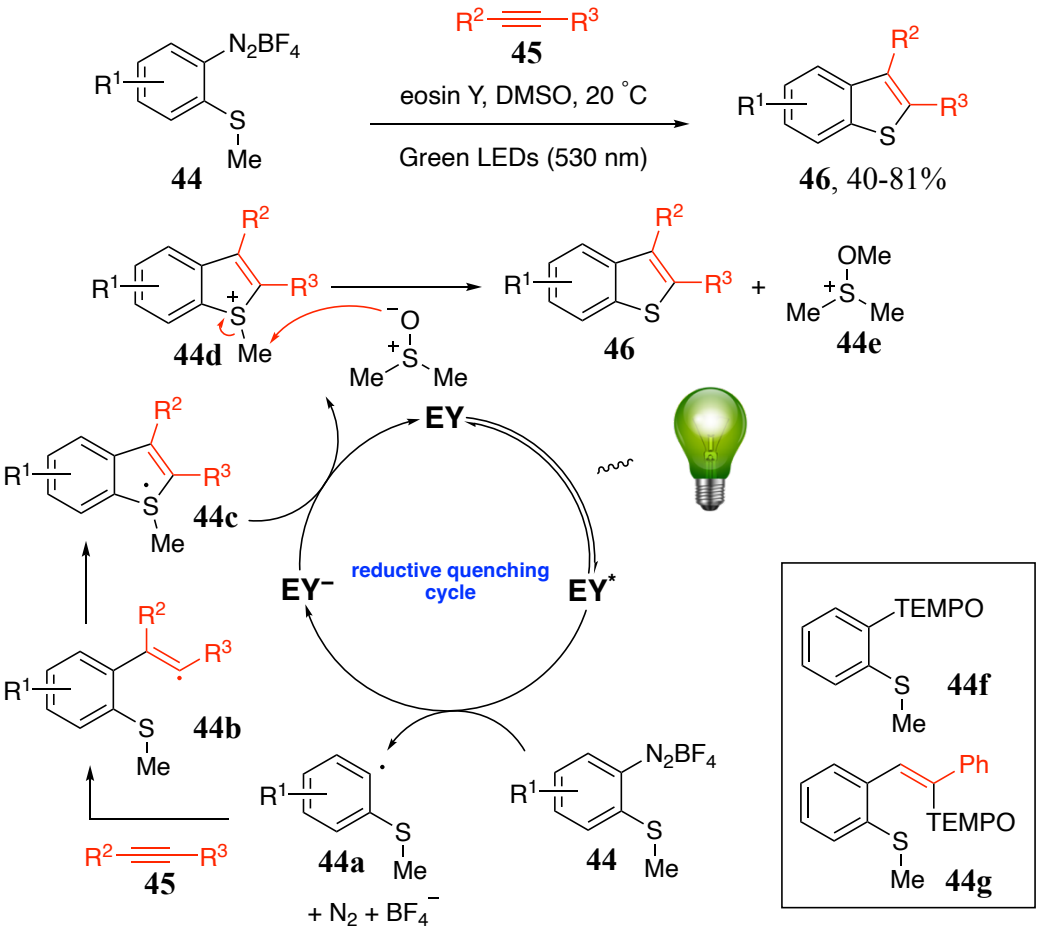
Scheme 7. α-Amino C-H arylation

The C–H functionalisation of electron-rich heterocycle **40** with bromomalonate **41**, was reported by Stephenson and co-workers (Scheme 8).[26] In this case, visible light excitation of the photoredox catalyst generated a strong oxidant Ru(II)* complex ($E_{1/2(II^*/I)}$ = +0.77 V vs SCE) which was then quenched by 4-methoxy-*N*,*N*-diphenylaniline **42** ($E_{1/2}$ = +0.74 V vs SCE) to give the ammonium radical cation **42a** and Ru(I) complex ($E_{1/2(II/I)}$ = −1.33 V vs SCE). Evidence for this quenching process was indicated by a Stern – Volmer study.[27, 28] The Ru(I) complex then reduced bromomalonate **41** to form malonate radical **41a** and regenerate the ground state photocatalyst Ru(II) complex. The coupling reaction between radical species **41a** and electron rich arene **40** at C-2 position led to the formation of benzylic radical **40a** followed by oxidation to generate cation intermediate **40a**. Finally, deprotonation of intermediate **40b** afforded the corresponding product **43**.



Scheme 8. Visible light-mediated Intermolecular C-H functionalisation

Fully organic molecules are also becoming increasingly popular as photocatalysts in photoredox reactions due to their powerful reactivity and environmentally friendly credentials. A wide range of organic photoredox catalysts has also been key to the discovery of new reaction processes. For example, the synthesis of benzothiophenes proceeding through a radical annulation photocatalytic process employing Eosin Y was reported by König and co-workers (Scheme 9).[29] Under irradiation of green LED at 530 nm, Eosin Y (**EY**) absorbed a photon to form an excited state **EY***, which was immediately quenched by aryldiazonium salt **44** giving **EY**$^{-}$ and aryl radical **44a**. The addition of aryl radical **44a** to alkyne **45** formed a vinyl radical intermediate **44b** followed by homolytic annulation at sulfur affording sulphuranyl radical **44c**. The reduction of **EY**$^{-}$ by radical **44c** generated cation **44d**, which then underwent successive demethylation by DMSO in the reaction mixture to yield the corresponding benzothiophene **46**. Radical trapping experiments using TEMPO gave adducts **44f** and **44g**, supporting the reductive quenching cycle.



Scheme 9. Visible light induced synthesis of benzothiophenes

On the contrary, some photocatalysis does not require an added photocatalyst at all to proceed to enable electron-transfer and subsequent radical chemistry. For example, the formation of reactive open-shell species can be promoted via photoexcitation of a complex formed by the combination of a donor **D**, an electron rich compound, and an acceptor **A**, an electron-deficient compound, also known as an electron donor-acceptor (EDA) or charge-transfer complex (CTC, Figure 5).[30-32] After absorbing a photon, the EDA complex forms an excited state species which can go on to promote electron-transfer events and generate radical species able to react further in productive chemistry.

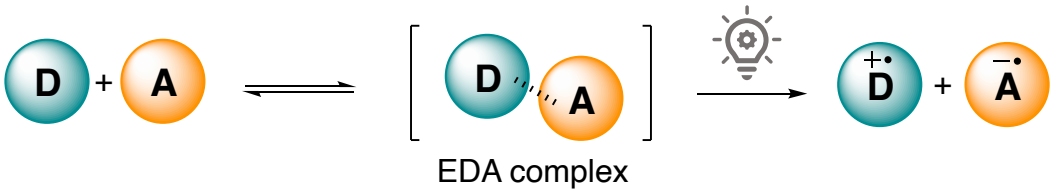
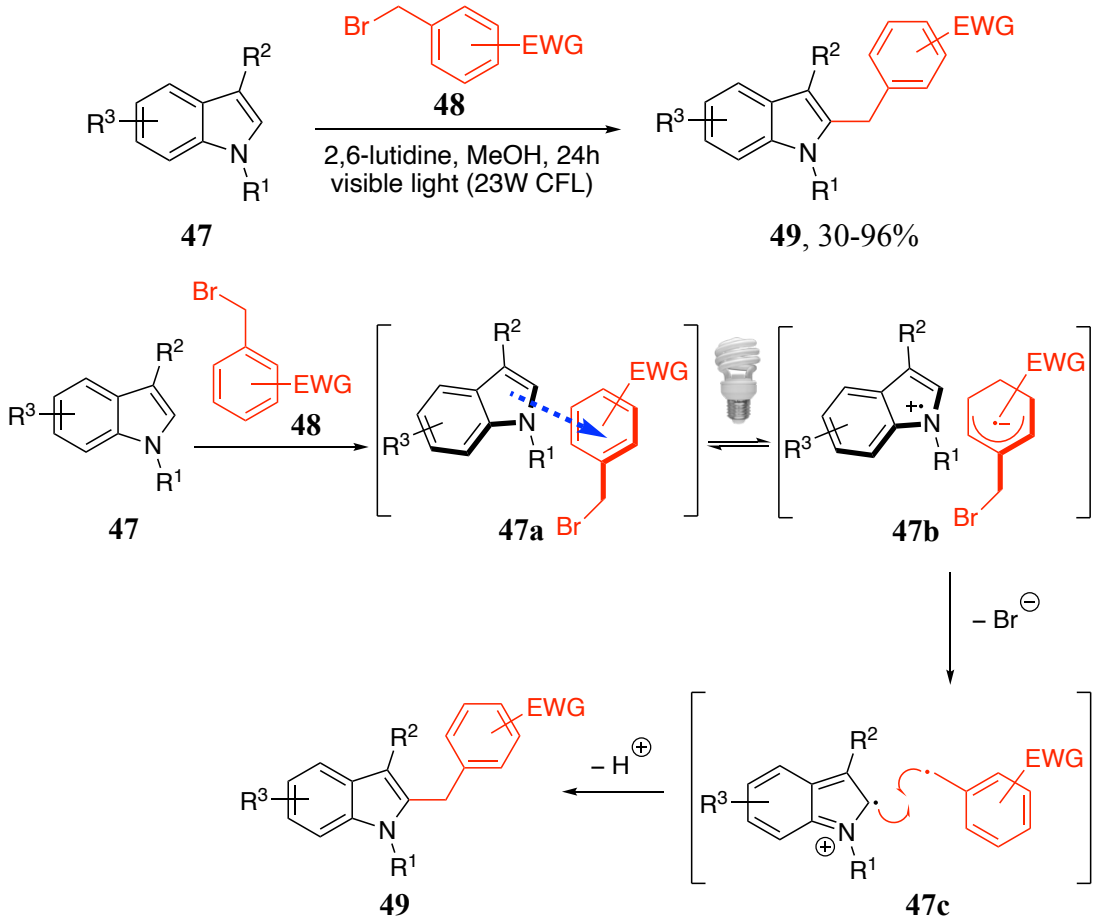


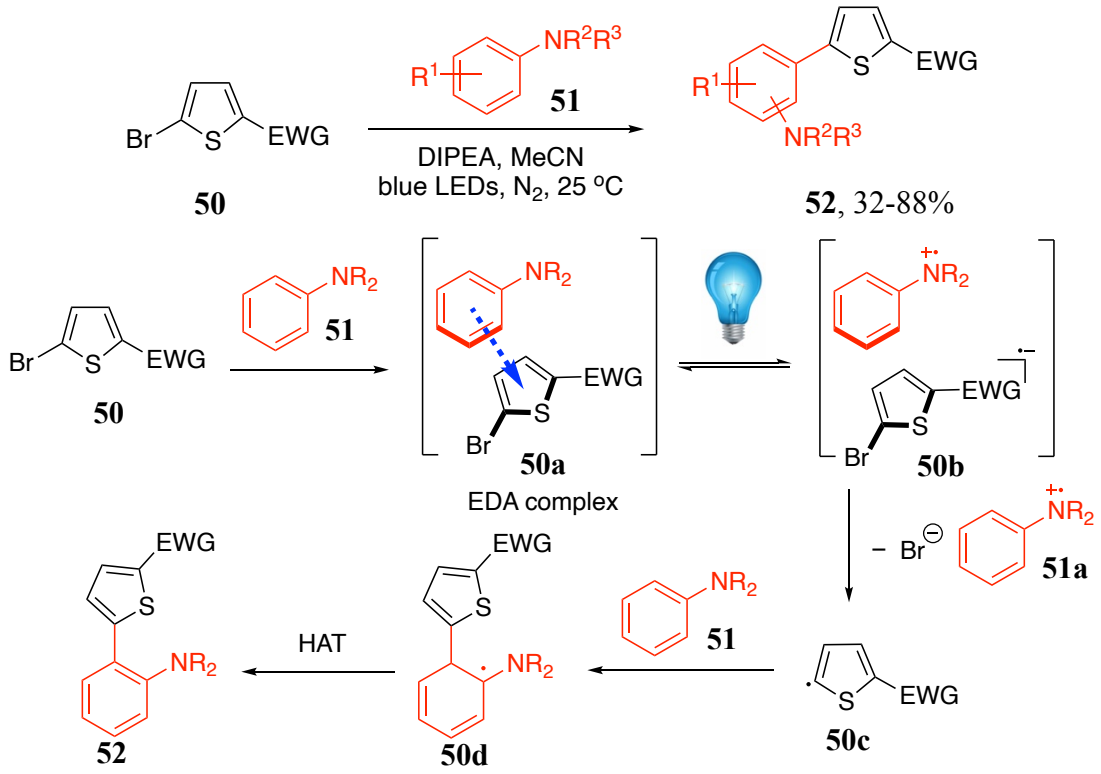
Figure 5. Photocatalysis of EDA complex

Some examples are demonstrated below to illustrate the way EDA complexes have been used in synthesis. The alkylation of indoles driven by the photochemical activity of an EDA complex was reported by Melchiorre and co-workers (Scheme 10).[33] The combination of the donor indole **47** and the acceptor bromide **48** was proposed to lead to the formation of EDA complex **47a**. This was supported by UV–vis spectroscopy studies. Also, X-ray analysis of the proposed EDA complex showed that the distance between 3-methylindole and 2,4-dinitrobenzyl bromide is 3.33 Å, which is lower than the van der Waals separation for aromatic molecules (3.40 Å). Visible light irradiation of the transient EDA complex **47a** induced an electron transfer generating a radical pair complex **47b** which underwent fragmentation to afford bromide anion along with intermediates **47c**. Coupling of these two radical species inside of a solvent cage led to C–C bond formation at the indole C-2 position, and in the final step, rearomatisation assisted by base afforded the corresponding alkylated indole **49**.



Scheme 10. Photochemical C-2 alkylation of indoles

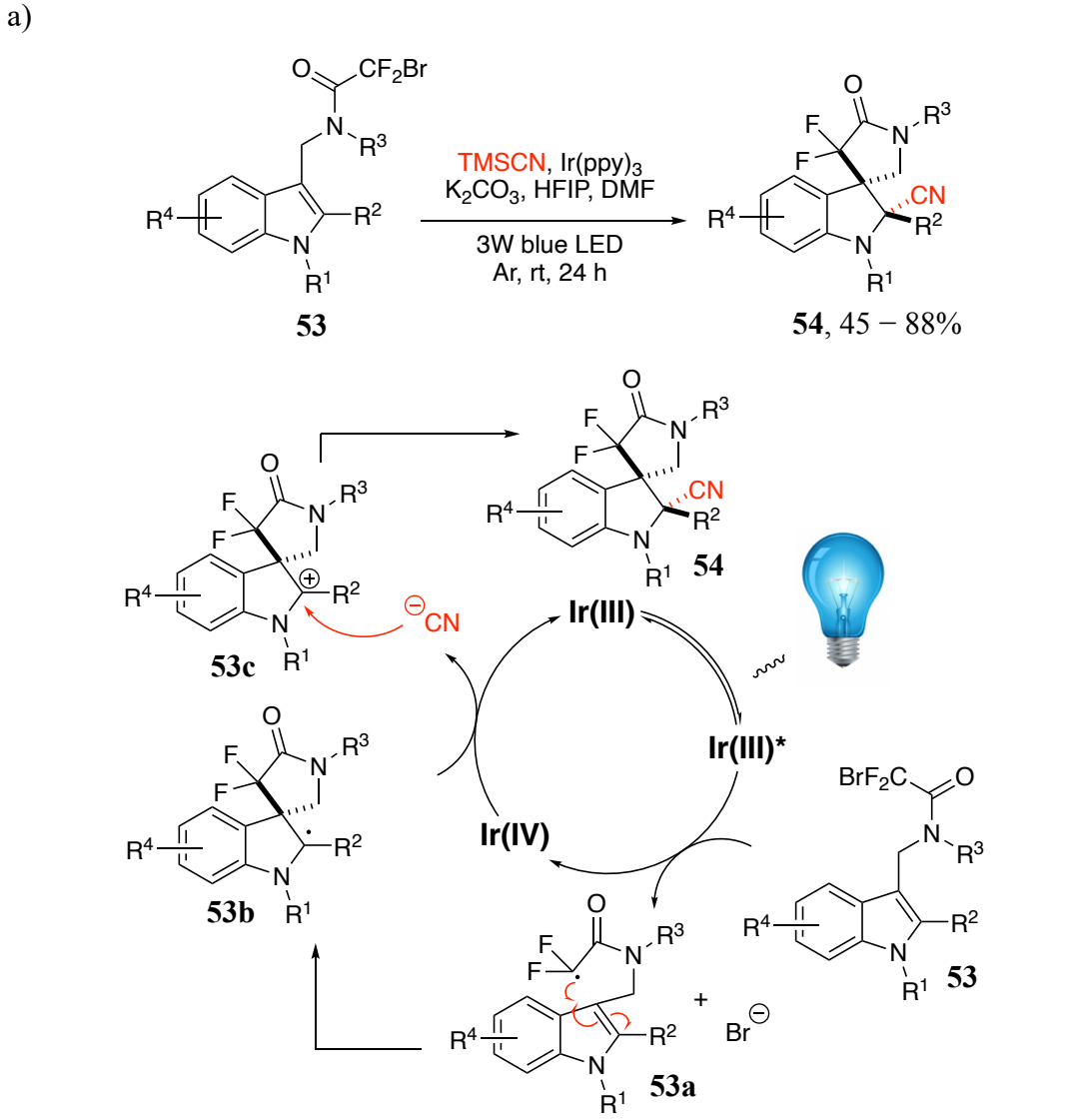
Similarly, visible-light-mediated direct arylation of aniline was developed by König and co-workers (Scheme 11).[34] Initially, the reaction was investigated using rhodamine 6G (Rh-6G) as a photoredox catalyst, but it was ultimately found that the photocatalyst was unnecessary. Instead, the reaction proceeded via the formation of an EDA complex between aryl halide **50** and aniline **51**. Under blue LED irradiation, EDA complex **50a** induced SET between the donor aniline **51** and the acceptor aryl halide **50** to form a radical pair intermediate **50b** followed by cleavage of the C–Br bond to generate aryl radical intermediate **50c**. Next, the coupling between radical species **50c** and aniline **51** allowed C–C bond formation and generated the radical intermediate **50d**. Eventually, rearomatisation by HAT afforded the coupled product **52**.



Scheme 11. Direct arylation of anilines

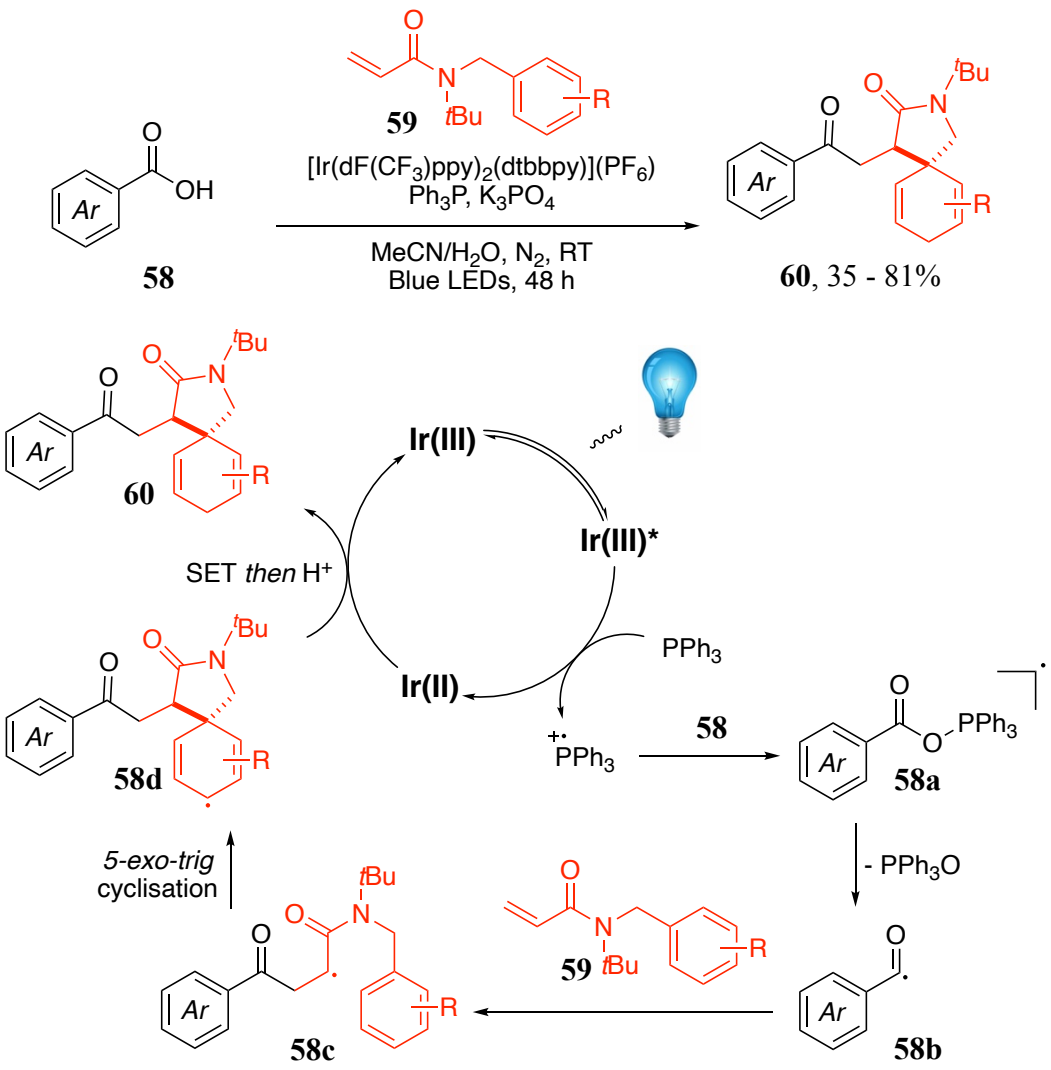
1.3 Photoredox catalysis spirocyclisation cascade reactions

In the past few years, there have been some reports on the application of photocatalytic methods to synthesise spirocyclic frameworks. For example, Wang and co-workers initially reported a photoredox-mediated spirocyclisation/cyanation cascade reaction with indoles (Scheme 12a).[35] The reaction between bromo-difluoroacetamide **53** and trimethylsilyl cyanide (TMSCN) in the presence of $Ir(ppy)_3$ under irradiation of blue LED light provided cyanated spirocyclic indoline **54** in 45 – 88% yields. The process began with single electron transfer (SET) between photoexcited Ir(III) complex and bromo-difluoroacetamide **53**, generating electron-deficient radical **53a**. Then, intermediate **53a** underwent dearomatising spirocyclisation to provide spirocycle radical **53b**, which then donated a single electron to the Ir(IV) complex and formed carbocation intermediate **53c**. Finally, the nucleophilic addition of cyanide ion afforded cyanated spiroindoline **54**. Moreover, Wang and co-workers also used this photoredox catalysis spirocyclisation cascade reaction with indole scaffold **55** to synthesise spiroindolines **57** with various types of nucleophiles, such as phosphine oxide, indole, pyrrole, and cyano groups through intermediate **56** (Scheme 12b).[36]



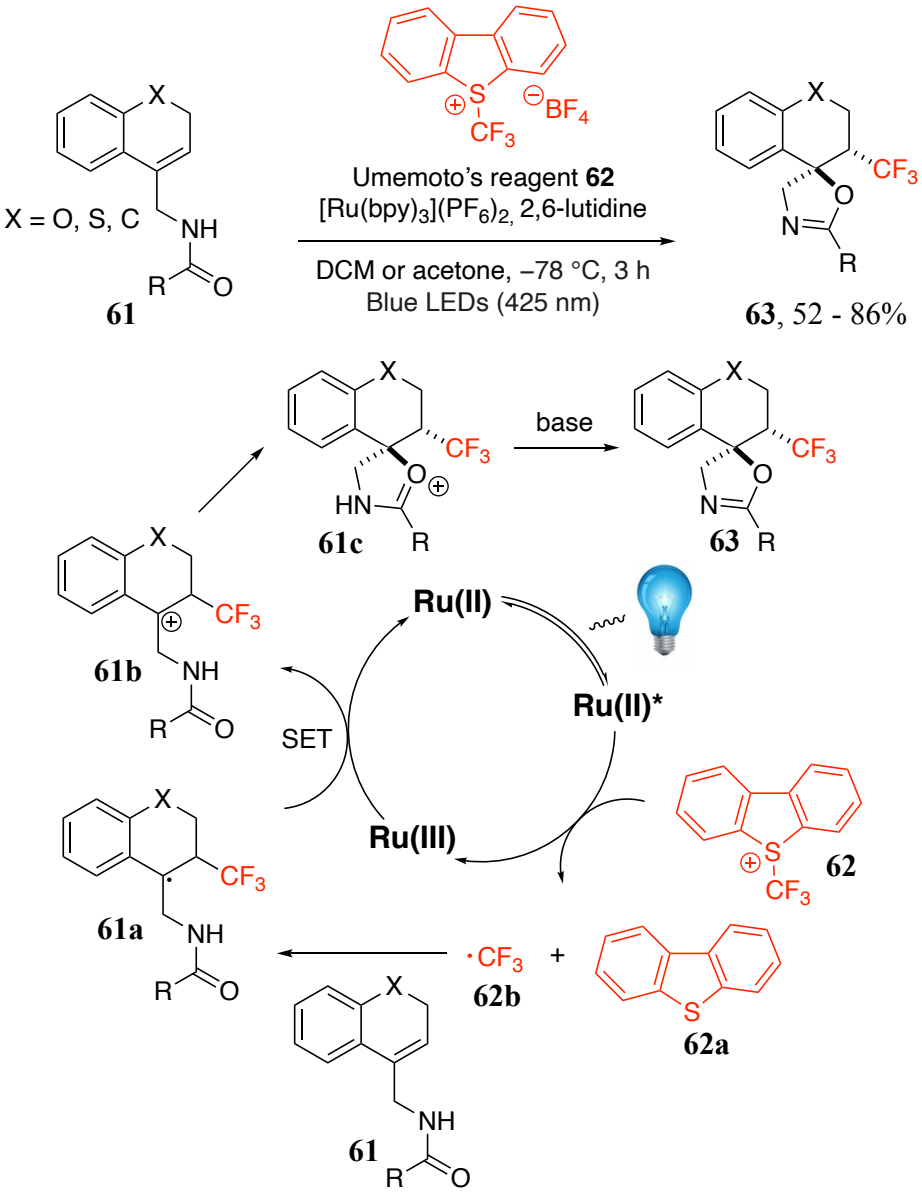
Scheme 12. Spirocyclisation by Wang and co-workers

Next, Diner and co-workers demonstrated a photoredox-mediated dearomatising annulation cascade reaction to produce spirocyclic lactam frameworks (Scheme 13).[37] The photocatalytic conditions were able to convert benzoic acids **58** and acrylamides **59** into spirocyclic lactams **60** in 35 – 81% yields. The process was proposed to begin with the oxidation of triphenylphosphine by the photoexcited Ir(III) complex to form triphenylphosphine radical cation, which then reacted with the carboxylate of carboxylic acid **58** to form intermediate **58a**. Following this, C–O bond cleavage afforded triphenylphosphine oxide and acyl radical **58b**. Then, acyl radical **58b** reacted with acrylamide **59**, forming intermediate **58c**, which subsequently underwent *5-exo-trig* cyclisation to afford spirocyclic radical intermediate **58d**. Finally, SET followed by protonation afforded spirocyclic lactam product **60**.



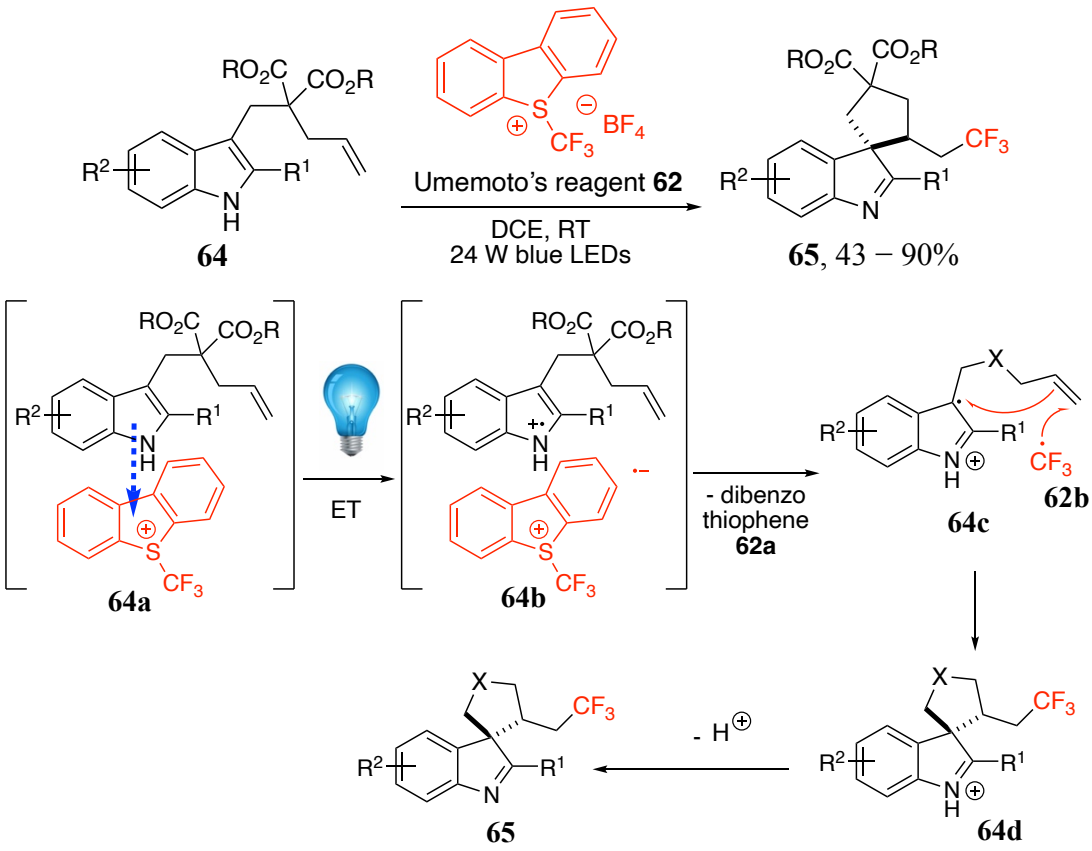
Scheme 13. Photoredox-mediated dearomative annulation cascade

Akita and co-workers reported a trifluoromethylative spirocyclisation cascade reaction to form spirooxazoline scaffolds (Scheme 14).[38] In this work, Umemoto's reagent **62** was able to convert benzamide **61** into CF_3-containing spirooxazolines **63** in 52 – 82% yields. The cascade reaction began with the reduction of Umemoto's reagent **62** by the photoexcited Ru(II) complex to generate trifluoromethyl radical **62b**. Trifluoromethyl radical **62b** was reacted with allylic amide **61**, providing intermediate **61a**. Next, oxidation of **61a** via SET to the Ru(III) complex gave carbocation intermediate **61b**, which was trapped by the tethered amide group, and deprotonated to afford the corresponding trifluoro substituted spirooxazoline **63**.



Scheme 14. Trifluoromethylative spirocyclisation cascade reaction

In addition, a photocatalytic spirocyclisation was also achieved under catalyst-free conditions. In this work, a visible-light-promoted spirocyclisation mediated by an EDA complex was reported by You and co-workers (Scheme 15). [39] The study showed that EDA complex **64a** was formed by a combination of a donor indole derivative **64** and Umemoto's reagent **62** as the acceptor. Irradiation with blue light promoted SET from donor to acceptor, forming intermediate complex **64b**. Then, S–C bond cleavage resulted in the formation of dibenzothiophene **62a**, radical intermediate **64c** and trifluoromethyl radical **62b**. Finally, the combination of two radical intermediates **64c** and **62b** afforded spirocyclic intermediate **64d**, which was subsequently deprotonated to provide the desired product **65**.



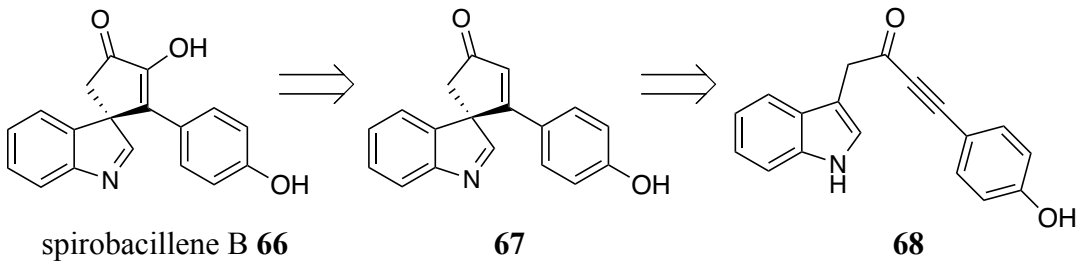
Scheme 15. EDA complex promoted spirocyclisation

All of the aforementioned works clearly demonstrate a trend of using photocatalytic processes to promote spirocyclisation cascade reactions. The reactions also facilitate several new bond formations and ring construction, and the conditions used are mild and mostly run at room temperature, which makes it easier to set up the experiments.

1.4 Unsworth and Taylor groups synthetic methodology

1.4.1 Spirobacillene B

The Unsworth and Taylor groups work in this area started with studies towards the total synthesis of spirobacillene B **66**. This natural product was isolated from an extremophile bacteria strain, *Lysinibacillus fusiformis* KMC003, collected from acidic coal-mine drainage.[40] A unique core structure of spirobacillene B **66** consists of an indolenine ring connected with cyclopentenone at the C-3 position. Therefore, it was envisaged that spirobacillene B **66** could be obtained by oxidation of spirocycle **67** (Scheme 16). Then, spiroindolenine **67** would be formed by *5-endo-dig* dearomatising spirocyclisation from indole-tethered ynone **68**.

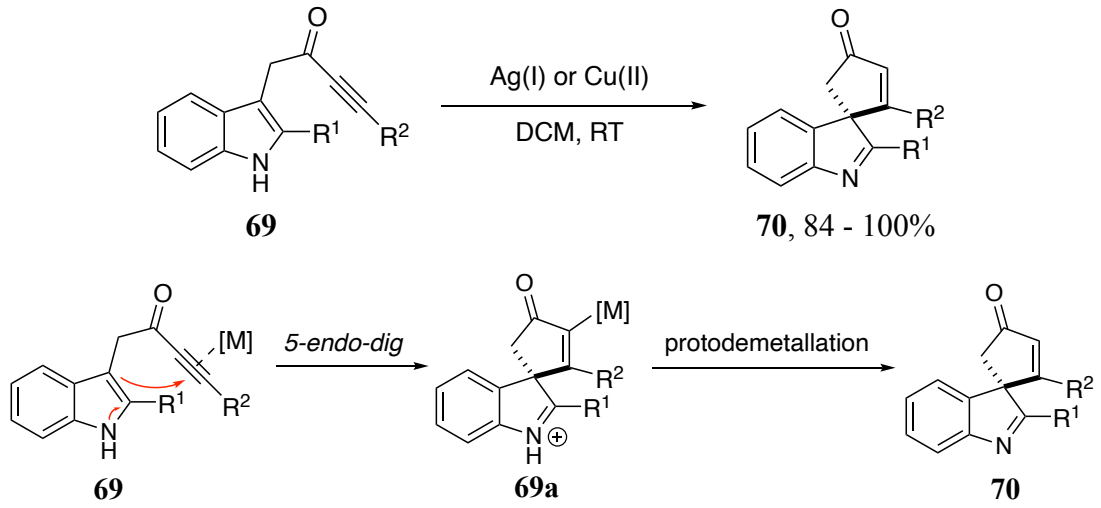


spirobacillene B **66** **67** **68**

Scheme 16. Retrosynthetic analysis of spirobacillene B

1.4.2 Metal catalysed dearomatising spirocyclisation

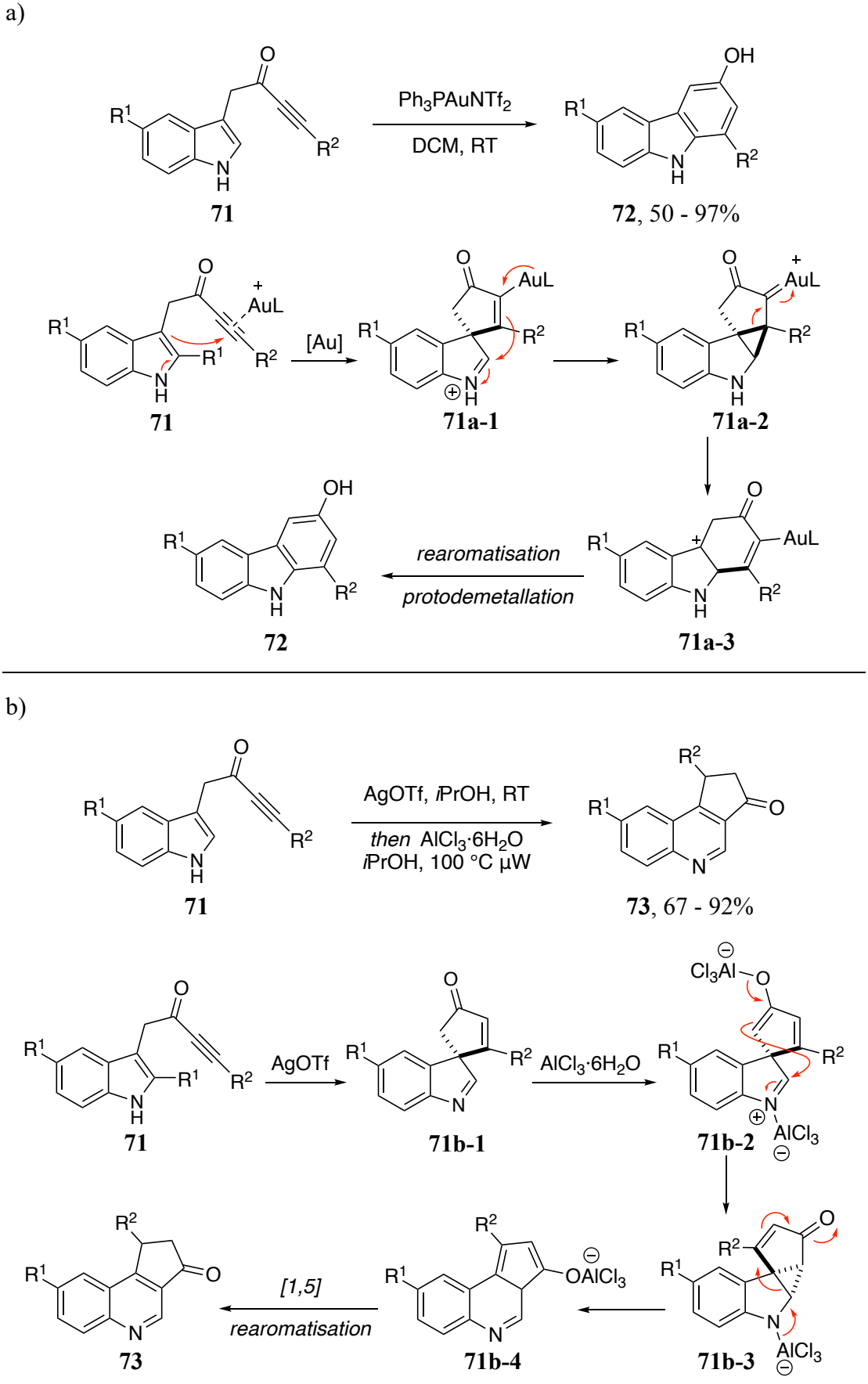
According to the above plan, methodologies to construct spirocycles from indole-tethered ynones were explored. First, metal-catalysed dearomatising spirocyclisation reactions of indolyl ynone scaffolds were developed using π-acidic catalysts (Scheme 17).[41] This strategy worked well, with the efficient transformation of indole-tethered ynone precursor **69** into spiroindolenine frameworks **70** using Ag(I) or Cu(II) catalysis. The reaction mechanism was proposed to proceed by π-acid coordination between the metal catalyst and indolyl ynone **69**, which increases the electrophilicity of the alkyne. Then, dearomatising spirocyclisation was achieved by nucleophilic attack of indole ring through its nucleophilic C-3 position, affording metal-spirocyclic complex **69a**, which subsequently underwent protodemetallation to furnish spirocyclic indolenine **70**.



Scheme 17. Metal-catalysed spirocyclisation

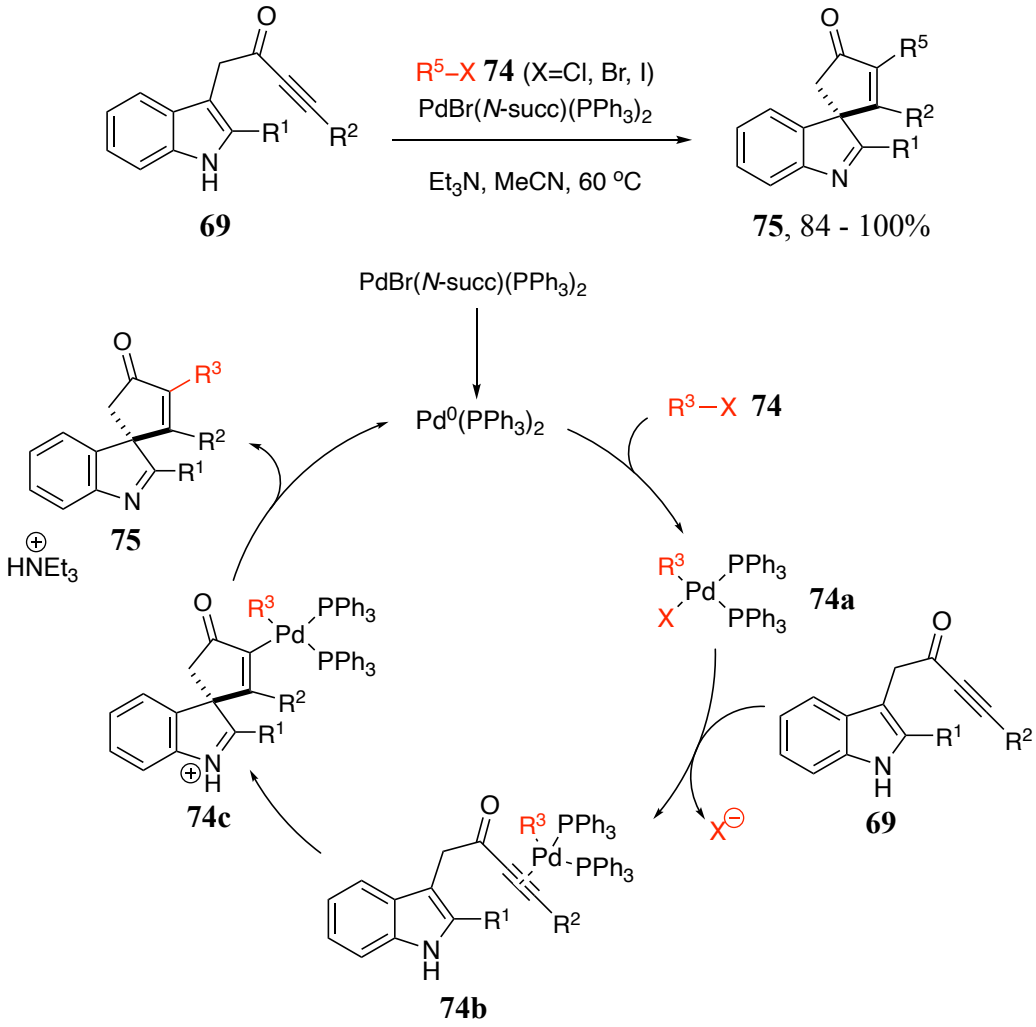
Moreover, indole-tethered ynone **71** was also converted into other classes of heterocyclic compounds when reacted with various other catalysts.[42] The use of $Ph_3PAuNTf_2$ in DCM converted indolyl ynones **71** into carbazoles **72** in 50 – 97% yields (Scheme 18a). The coordination between Au(I) catalyst and indolyl ynone **71** promoted dearomatising spirocyclisation to form spirocyclic gold complex **71a-1**. Then, intermediate **71a-1** underwent ring enlargement, initially proposed to procced via cyclopropane intermediate **71a-2** to provide six-membered ring **71a-3**. Direct cyclisation via the indole C-2 position (not shown) is also possible. Finally, rearomatisation and subsequent protodemetallation furnished carbazole **72**.

Furthermore, the reaction of indole-tethered ynone **71** with AgOTf in *i*PrOH followed by the addition of $AlCl_3 \cdot 6H_2O$ and heating in the microwave provided quinolines **73** in 67 – 92% yields (Scheme 18b). The reaction began with the formation of spiroindolenine intermediate **71b-1** via Ag(I) catalysed dearomatising spirocyclisation. Microwave assisted synthesis using Al(III) catalysis promoted the formation of enolate **71b-2**. Then, ring expansion via cyclopropane intermediate **71b-3** provided intermediate **71b-4**. Lastly, 1,5-sigmatropic H-transfer followed by rearomatisation afforded the corresponding quinoline **73**.



Scheme 18. Other reactivities of indole-tethered ynones

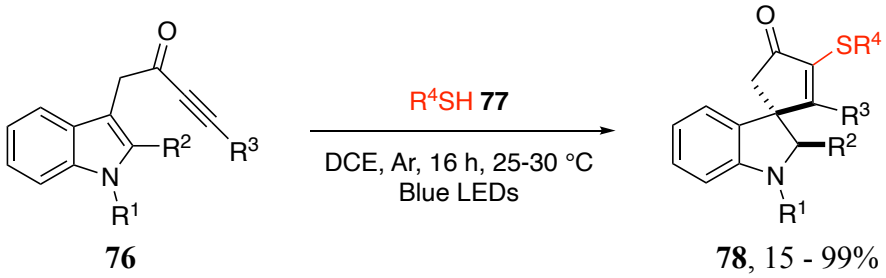
The Unsworth and Taylor groups also explored the spirocyclisation of indole-tethered ynones with catalyst classes other than π-acids. Thus, the palladium-catalysed dearomatising spirocyclisation/cross coupling cascade reaction of indole-tethered ynone **69** was developed (Scheme 19).[43] This reaction protocol enabled indole-tethered ynone **69** to be converted into functionalised tetra-substituted alkene spiroindolenines **75** in 84 – 100 % yields. Mechanistic studies indicated that oxidative addition between Pd(0) complex and aryl halide **74** generated Pd(II) complex **74a**. Ligand dissociation and subsequent coordination with the alkyne of indolyl ynone **69** formed Pd(II) complex **74b**. Then, the nucleophilic attack of the indole through its C-3 position on to the activated alkyne generated Pd(II) spirocycle complex **74c**. Finally, reductive elimination followed by deprotonation afforded spiroindolenine **75**.



Scheme 19. Proposed mechanism of spirocyclisation/cross coupling cascade reaction

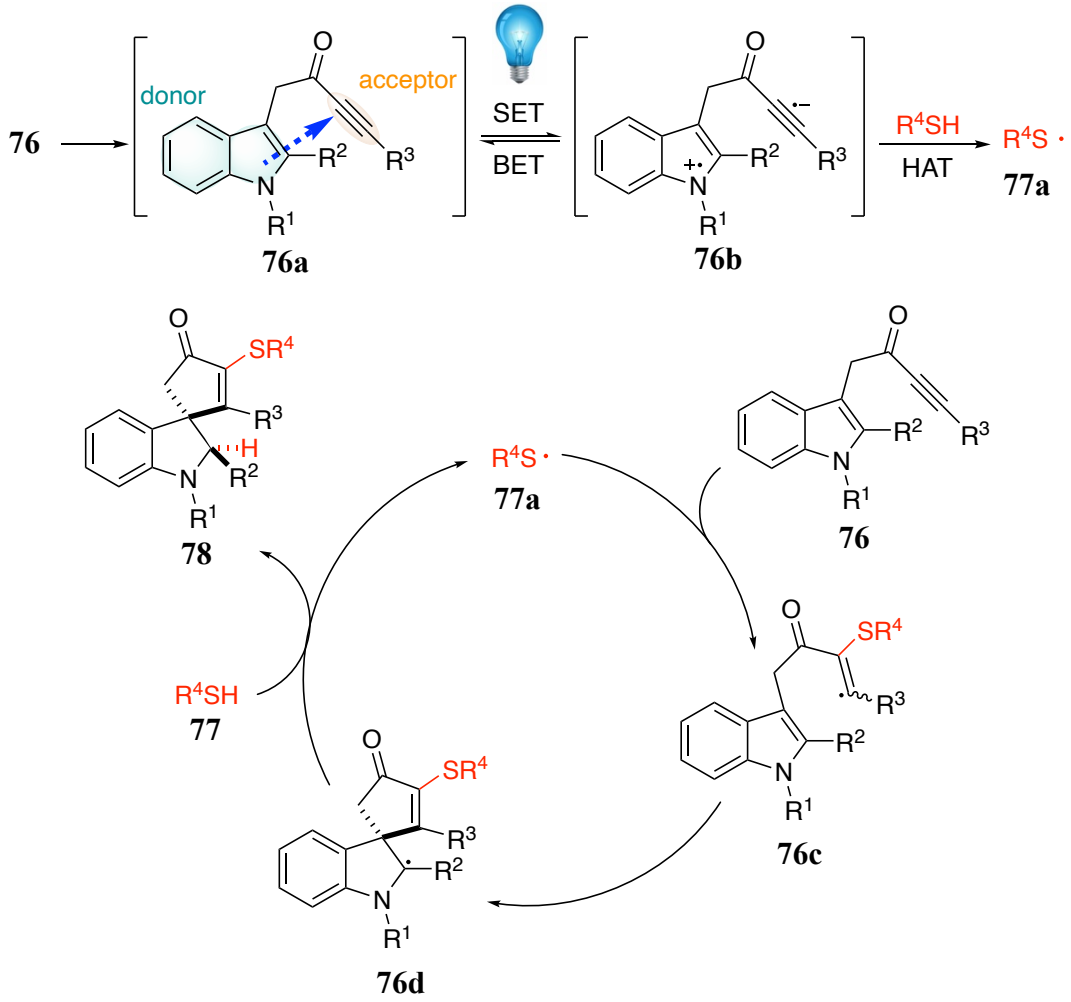
1.4.3 Photocatalytic spirocyclisation cascade reaction

The synthetic methodologies from the Unsworth and Taylor groups discussed above are all based on metal-catalysed and two-electron reaction systems. However, a visible-light-mediated spirocyclisation cascade reaction was later developed using metal-free conditions (Scheme 20).[44] The reaction between indolyl ynones **76** and thiol compounds **77** under irradiation with blue LEDs furnished spiroindolines **78** in 15 – 99% yields. It was proposed that indolyl ynone **76** forms an intramolecular EDA complex **76a** (Scheme 21), in which the indole ring acts as an electron donor and the ynone behaves as an electron acceptor. This EDA complex **76a** is proposed to absorb visible light and forms a photoexcited complex **76b** via SET, which may relax back to EDA complex **76q** via back electron transfer (BET). In the productive pathway, HAT between intermediate **76b** and a thiol compound **77** was proposed to lead to the formation of thiyl radical **77a**. The thiyl radical **77a** then reacted with indolyl ynone **76** to form a new C–S bonded vinyl radical **76c**, which subsequently underwent dearomatising spirocyclisation to form intermediate **76d**. Finally, HAT from the thiol compound **77** formed spiroindoline **78** and regenerated thiyl radical **77a** to propagate a radical chain.



76 **78**, 15 - 99%

Scheme 20. Visible-light mediated spirocyclisation

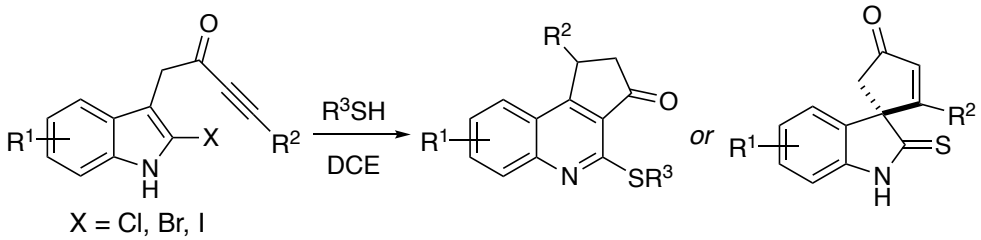


Scheme 21. Proposed mechanism via an EDA complex

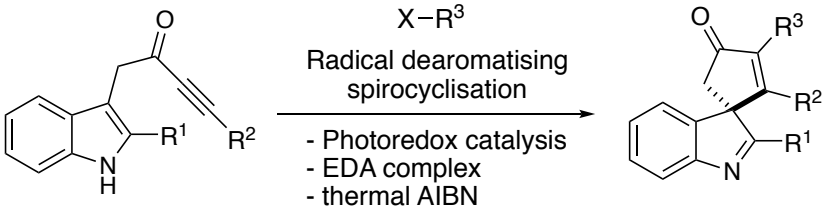
1.5 Project aims

We have seen from the above examples that indole-tethered ynones are useful for silver-catalysed dearomatising spirocyclisation, palladium-catalysed spirocyclisation/ cross-coupling cascade reactions, and also photocatalytic radical spirocyclisations. Therefore, the initial aim of this project was to develop new radical-based cascade reactions with indole-tethered ynones using photocatalysis. We were also keen to explore the reactivity of new heterocycle-tethered ynone substrates. A summary of the main themes of the three Results and Discussion Chapters is given below.

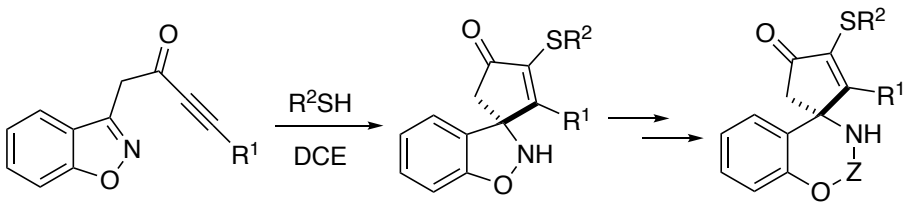
Chapter 2: describes studies of C-2 halo indolyl ynones and thiol compounds. The selective synthesis of heterocycles by using thiol reagents is reported and a reaction mechanism is also investigated and proposed.



Chapter 3: explores the use of indolyl ynones for radical-based dearomatising spirocyclisation cascade reactions using different types of radical species. A general mechanism supported by luminescence studies is proposed.



Chapter 4: focuses on exploring reactions of a novel heterocycle-tethered ynone. The spirocyclisation cascade reaction of benzisoxazole-tethered ynones and thiyl radicals is described. Moreover, a method to modify and ring expand the spirocyclic products is also reported.

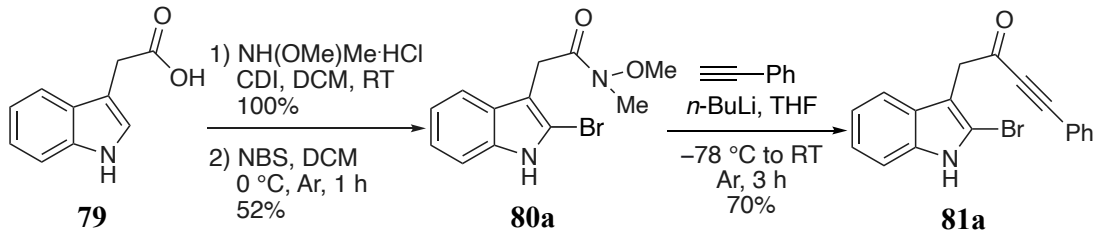


Chapter 2: Thiol-Mediated Cascade Reactions for the Conversion of 2-Halo Indole-tethered Ynones into Quinolines

The new reactivity described in this Chapter was originally found by serendipity. The initially planned project involved the observation of the reactivity between C2-halo indolyl ynones and thiyl radicals.

2.1 Reaction observation and optimisation

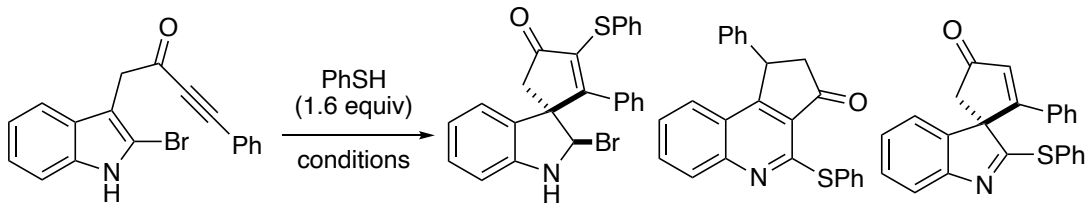
These studies started with the synthesis of suitable test compound, C2-bromo model substrate **81a**, which was prepared in three steps from a commercially available chemical (Scheme 22). First, 3-indole acetic acid **79** was converted into Weinreb amide **80a** in two-step synthesis via amide formation using *N*,*O*-dimethylhydroxyl amine hydrochloride and CDI,[45] followed by bromination using NBS. Then, ynone formation was achieved following the addition of lithiated phenylacetylide to furnish ynone **81a** in 70% yield.



Scheme 22. Three step synthesis of C2-bromo indolyl-ynone **81a**

Then, C2-bromo ynone **81a** was reacted under conditions expected to generate thiyl radicals and promote a radical cascade reaction with the idea being to make spirocycle **82a**. First, we used the conditions reported to promote spirocyclisation on related ynones by our group (Table 1, entry 1).[44] In this reaction, ynone **81a** was reacted with thiophenol in DCE under irradiation with blue LEDs (60 W) at RT for 20 hours. The reaction was performed using 0.2 mmol of ynone **81a** and analysed by ^{1}H NMR spectroscopy. ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture revealed that the expected spirocycle **82a** was not formed. Instead, the reaction

unexpectedly afforded thiol-substituted quinoline **83a** in 52% yield, with the spectroscopic data matching those in the previous report by our research group.[42] To explore whether this reaction was light-mediated, ynone **81a** was then reacted under the same conditions, but without blue LEDs, and this resulted in a dramatic increase in the yield of quinoline **83a** to 93% (entry 2). With this remarkable yield and simple reaction conditions, the aim of this study switched to focus on exploring this interesting method to make quinolines.[46, 47] Three alternative solvents were tested next. Quinoline **83a** was obtained in a slightly lower 84% yield when using DCM (entry 3). However, the use of nonchlorinated solvents, such as THF and MeCN (entries 4 and 5), significantly lowered the efficiency of this reaction as only spirocycle **84a** could be isolated in 20% yield when using MeCN.



81a **82a** **83a** **84a**

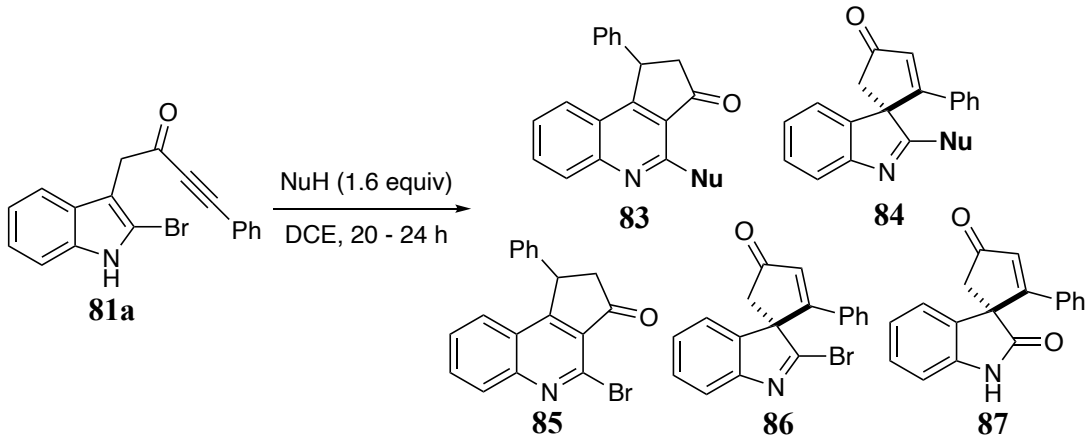
Entry	Conditions	82a	83a	84a
1	PhSH, DCE (0.1 M), RT, Ar, 20 h Blue LEDs (60W)	0%	52%	0%
2	PhSH, DCE (0.1 M), RT, Ar, 20 h	0%	93%	0%
3	PhSH, DCM (0.1 M), RT, Ar, 20 h	0%	84%	0%
4	PhSH, THF (0.1 M), RT, Ar, 20 h	0%	0%	0%
5	PhSH, MeCN (0.1 M), RT, Ar, 20 h	0%	0%	20%

[a] *All reactions were performed with 0.20 mmol of ynone **81a**.*

[b] *Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.*

Table 1. Reactions of C2-bromo ynone **81a**

With good conditions for the formation of quinoline **83a** in hand, the method was next tested with other nucleophilic reagents in place of thiophenol. Phenols were chosen, as our theory at the time was that Bronsted acidity may have been required for the reaction to occur. First, phenol was added into the solution of ynone **81a** in DCE at RT but there was no consumption of ynone **81a** after 24 hours (Table 2, entry 1). Moreover, the same reaction performed at 60 °C also showed no conversion of the starting material **81a** (entry 2). To probe the effects of acidity on the reaction, one equivalent of TFA was added, (entry 3); this reaction resulted in the formation of spiro-oxindole **87** in 62% yield, which was likely promoted by acid-mediated spirocyclisation followed by hydrolysis of spirocycle **86** (see Scheme 23 below for a mechanism). Additionally, these conditions gave quinoline **85** in 21% yield. Next, ynone **81a** was tested with an acidic nucleophile (4-nitrophenol). The reaction performed at RT showed that the expected quinoline **83** was not observed (entry 4). However, the use of 4-nitrophenol performed at 60 °C provided the same products (**85** and **87**) as those observed using phenol and TFA (entry 5). None of these attempts to use phenol-type nucleophiles afforded quinoline **83** or spirocycle **84**. Therefore, a nucleophile with more similar characteristics and pK_a to thiophenol (pK_a 6.6), selenophenol, was investigated (entry 7). Pleasingly, this reagent was able to facilitate the formation of quinoline **83o**, which was formed in 62% yield.

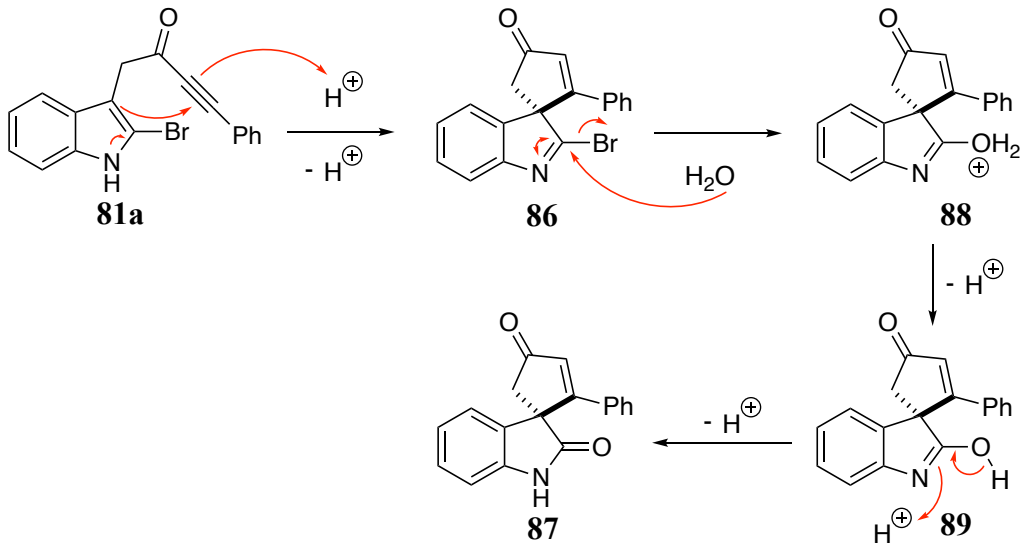


Entry	Nucleophile (NuH)	NuH pK_a	Temperature	Results
1	Phenol	10.0	RT	no reaction
2	Phenol	10.0	60 °C	no reaction
3	Phenol, 1 equiv. TFA	10.0	RT	**85** (21%), **87** (62%)
4	4-Nitrophenol	7.2	RT	no reaction
5	4-Nitrophenol	7.2	60 °C	**85** (45%), **87** (35%)
6	Selenophenol	5.9	RT	**83o** (62%)[c]

[a] *Reactions performed with 0.20 mmol of ynone **81a**.*

[b] *Yield determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.* [c] *Structure of **83o** shown in Scheme 26.*

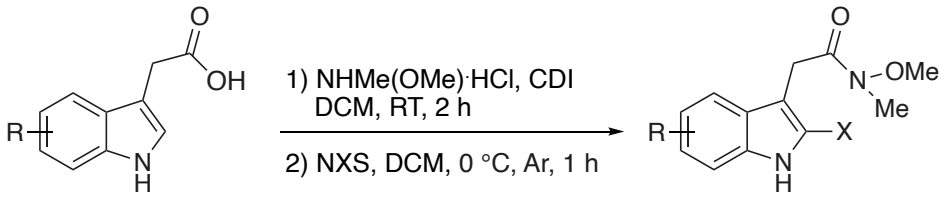
Table 2. Study of alternative nucleophilic reagents



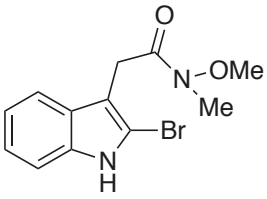
Scheme 23. Formation of spiro-oxindole **87**

2.2 Substrate synthesis

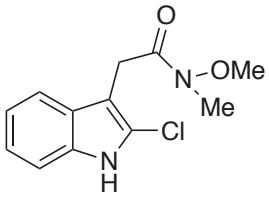
To further explore the scope of this unexpected reactivity, a broad range of substrates bearing different aromatic and aliphatic substituents were prepared using the same conditions introduced in Scheme 22. First, Weinreb amides were prepared from commercially available indole-tethered acetic acids using the previous CDI-promoted conditions (Scheme 24). Then, C2-halo Weinreb amides **80a** – **80d** were successfully synthesised by using halogenating agents (NBS and NCS). Additionally, amide **80c** was prepared by reported conditions with I_2 and AgOTF in THF.[48]



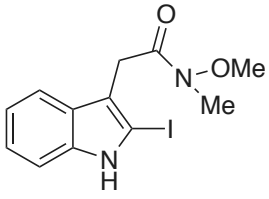
79 **80a - 80d**



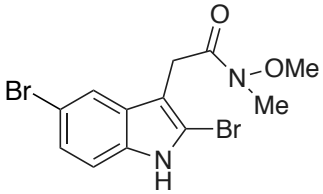
80a, 52%[a]



80b, 61%[b]



80c, 62%[c]

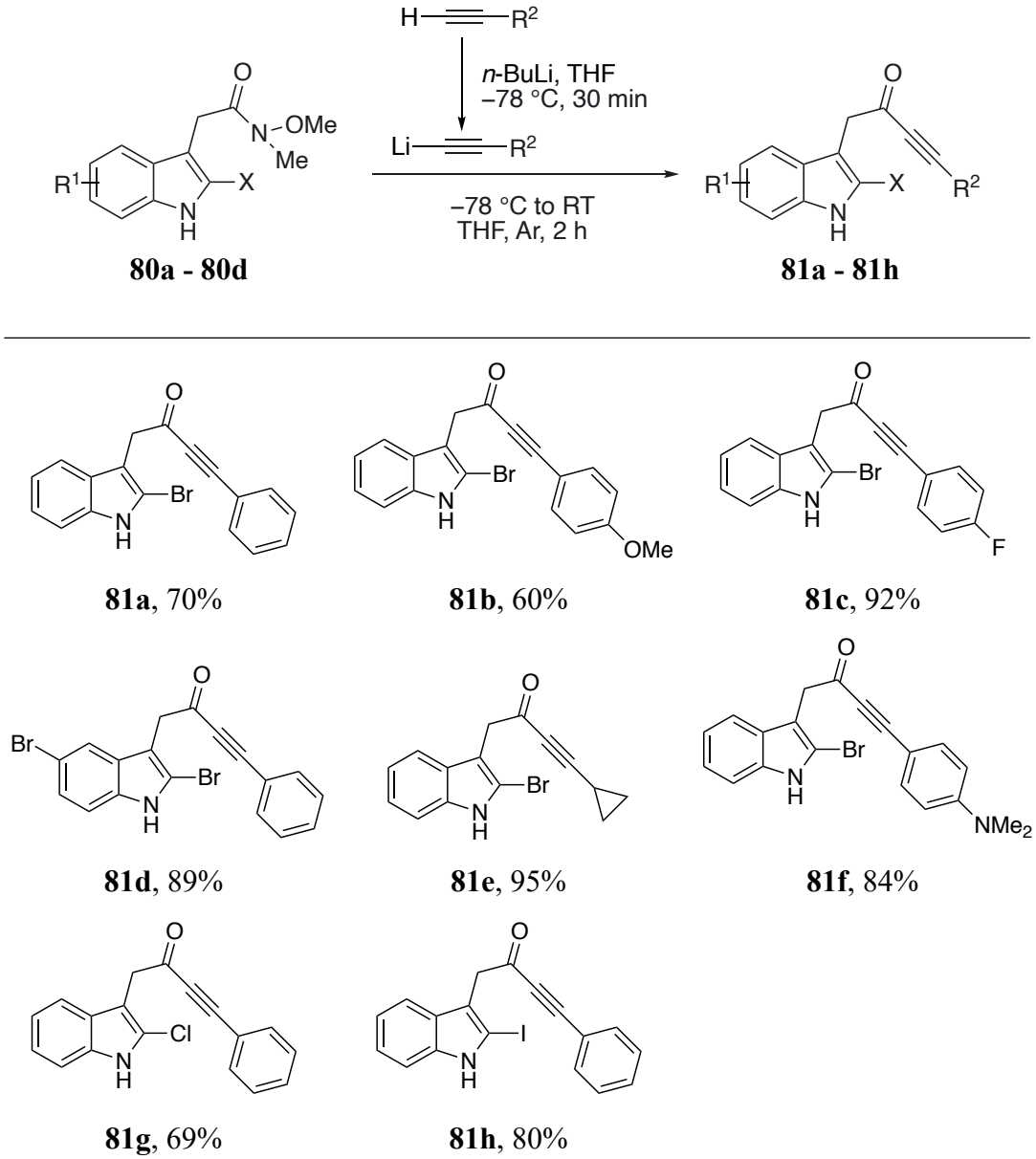


80d, 25%[a]

[a] *Bromination using NBS.* [b] *Chlorination using NCS.* [c] *Iodination using reported conditions; I_2, AgOTf, THF, RT.* [48]

Scheme 24. Synthesis of Weinreb amides

Next, Weinreb amides were reacted with a range of lithium acetylides, which were generated by the reaction of a terminal alkyne and *n*-BuLi at −78 °C, to provide a series of ynones **81a** – **81h** in good yields (Scheme 25).

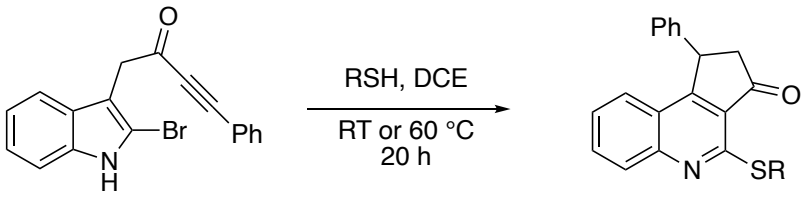


Scheme 25. Synthesis of C2-halo indole-tethered ynones

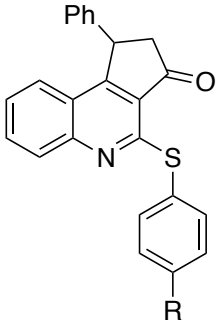
2.3 Substrate study

Having a range of C2-halo indolyl ynones in hand, their reactivity with a variety of thiols was studied. First, ynone **81a** was reacted with various aromatic thiols under the optimised reaction conditions, which used 1.6 equivalents of thiol in DCE (0.1 M) at RT or 60 °C under an argon atmosphere for 20 hours (Scheme 26). Pleasingly, reaction with the aromatic thiols furnished the corresponding quinolines **83a** – **83j** in excellent yields in most cases. Ynone **81a** was then reacted with a range of aliphatic thiols. These reactions also worked well, forming quinolines **83k** – **83n** in excellent yields (53% – 95% yields). However, it should be noted that aliphatic thiols reacted more slowly, and generally required heating to 60 °C. Interestingly, under these conditions the use of benzyl mercaptan formed the desired quinoline **83n** in only 53% yield alongside an unexpected side product, thiol-oxindole **90a**, which was isolated in 27% yield. This result will be discussed in more detail later, including work to optimise formation of the interesting thiol-oxindole product **90a**. Finally, thiophenol was replaced by selenophenol, which led to the formation of the corresponding quinoline **83o** in 62% isolated yield.

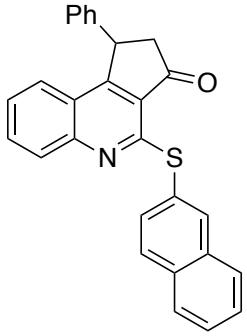
Then, four different types of substituted-ynones were examined with *p*-toluenethiol and *n*-propanethiol representing aromatic and aliphatic thiol respectively (Scheme 27). The reactions were performed at 60 °C and in most cases successfully provided the corresponding quinolines **83p** – **83w** in 40 – 89% yields. The structure of quinoline **83w** was definitively confirmed by X-ray crystallography (Figure 6).[49] The reaction between 4-NMe_2-substituted ynone **81d** and *p*-toluenethiol failed to deliver the expected quinoline. However, in this case, spiroindolenine bromide **86x** was isolated in 89% yield instead; it is thought that NMe_2 group in this example affected the solubility and pH balance of the reaction leading to this alternative product formation, although further studies would be needed to more definitively explain the reason for this anomalous result.



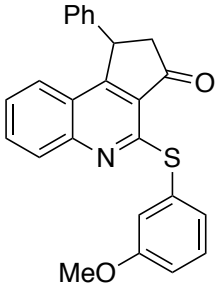
81a **83a - 83n**



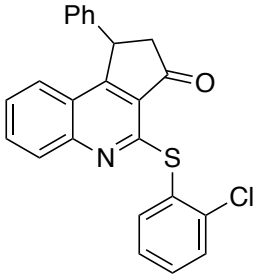
83a (R = H), 93%
83b (R = Me), 95%
83c (R = *t*-Bu), 89%
83d (R = Ph), 93%
83e (R = Br), 92%
83f (R = NO_2), 78%



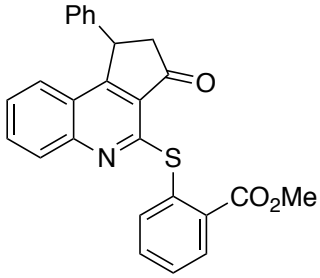
83g, 95%



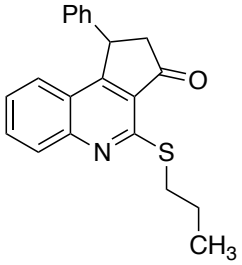
83h, 75%



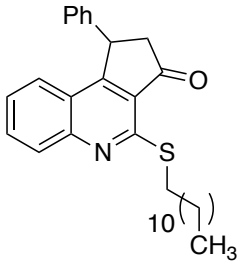
83i, 76%



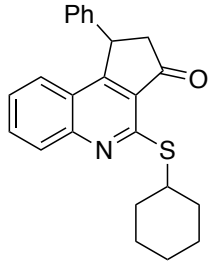
83j, 45%



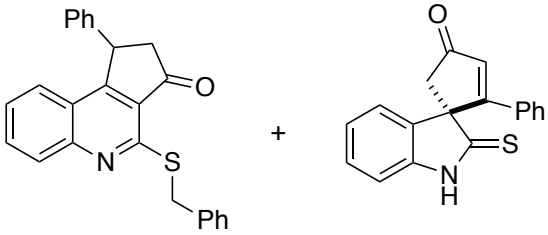
83k, 95%[b]



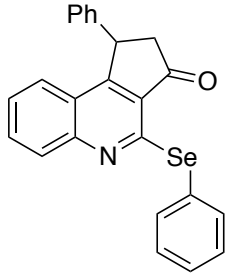
83l, 93%[b]



83m, 88%[b]



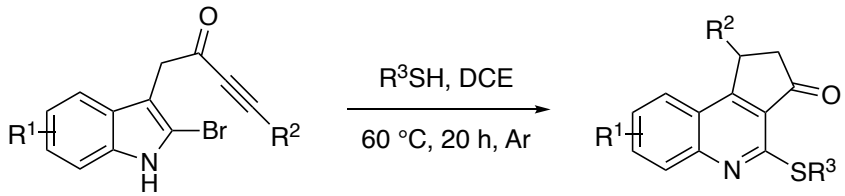
83n, 53%[b] + **90a**, 27%[b]



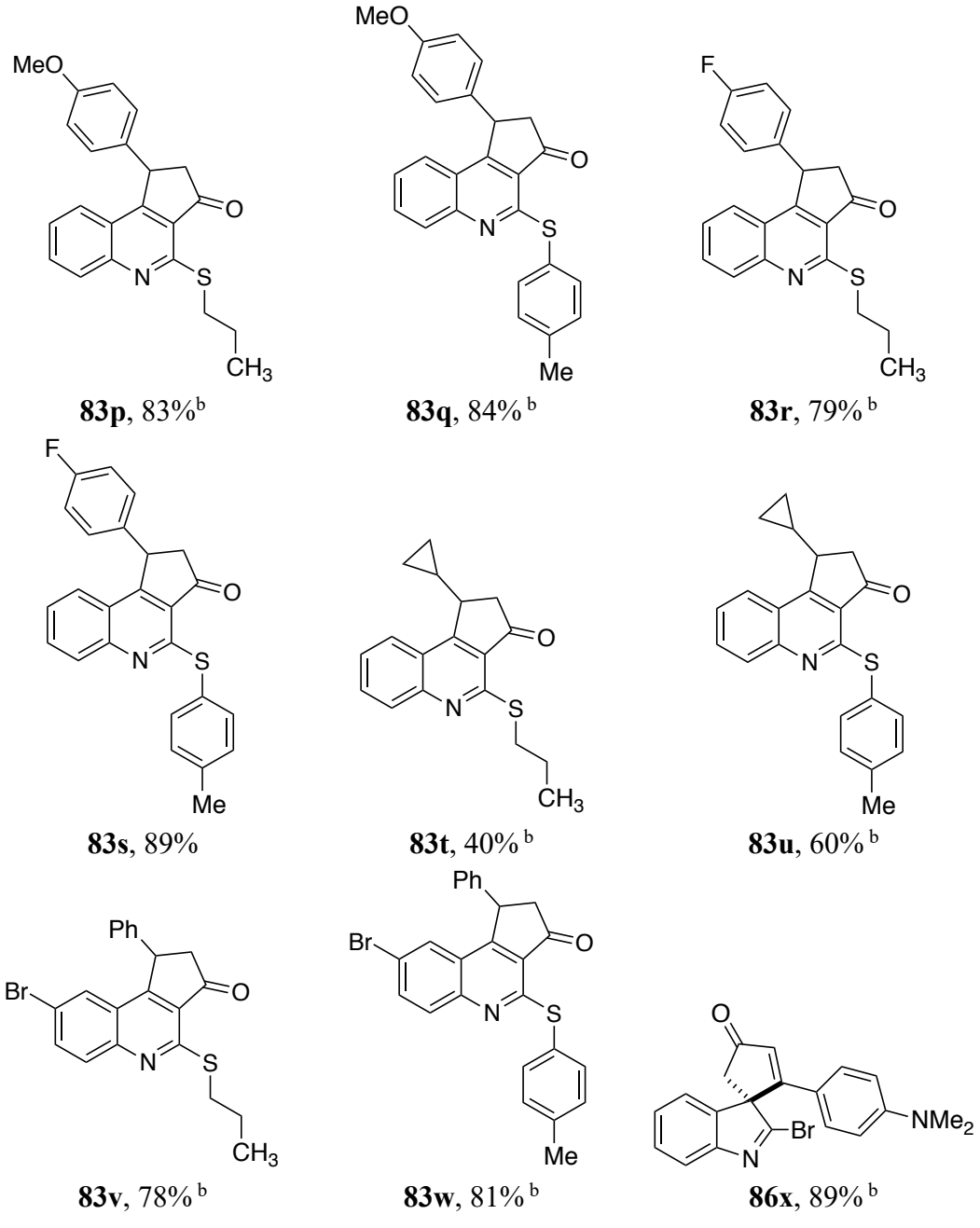
83o, 62%

[a] Reaction performed at RT unless specified [b] Reaction performed at 60 °C

Scheme 26. Variation of the thiol study



81b - 81f **83p - 83w**



83p, 83%[b] **83q**, 84%[b] **83r**, 79%[b]

83s, 89% **83t**, 40%[b] **83u**, 60%[b]

83v, 78%[b] **83w**, 81%[b] **86x**, 89%[b]

[a] Reaction performed at RT unless specified [b] Reaction performed at 60 °C

Scheme 27. Variation of ynone study

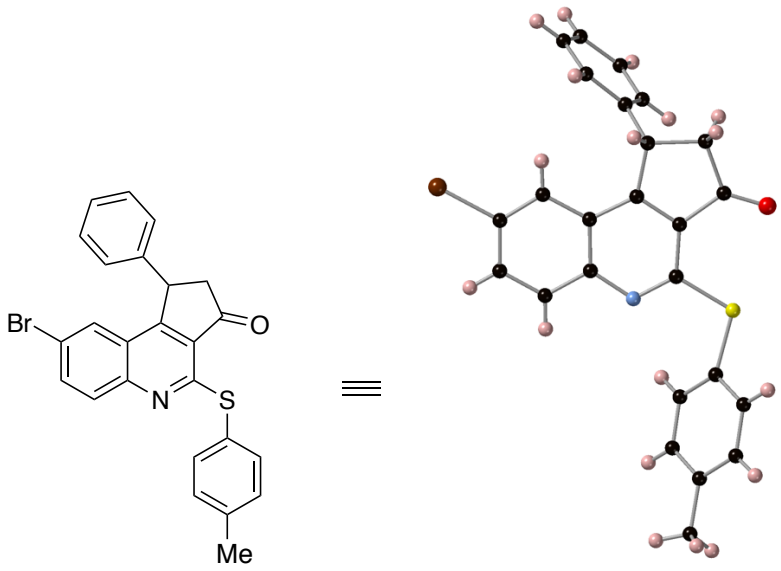
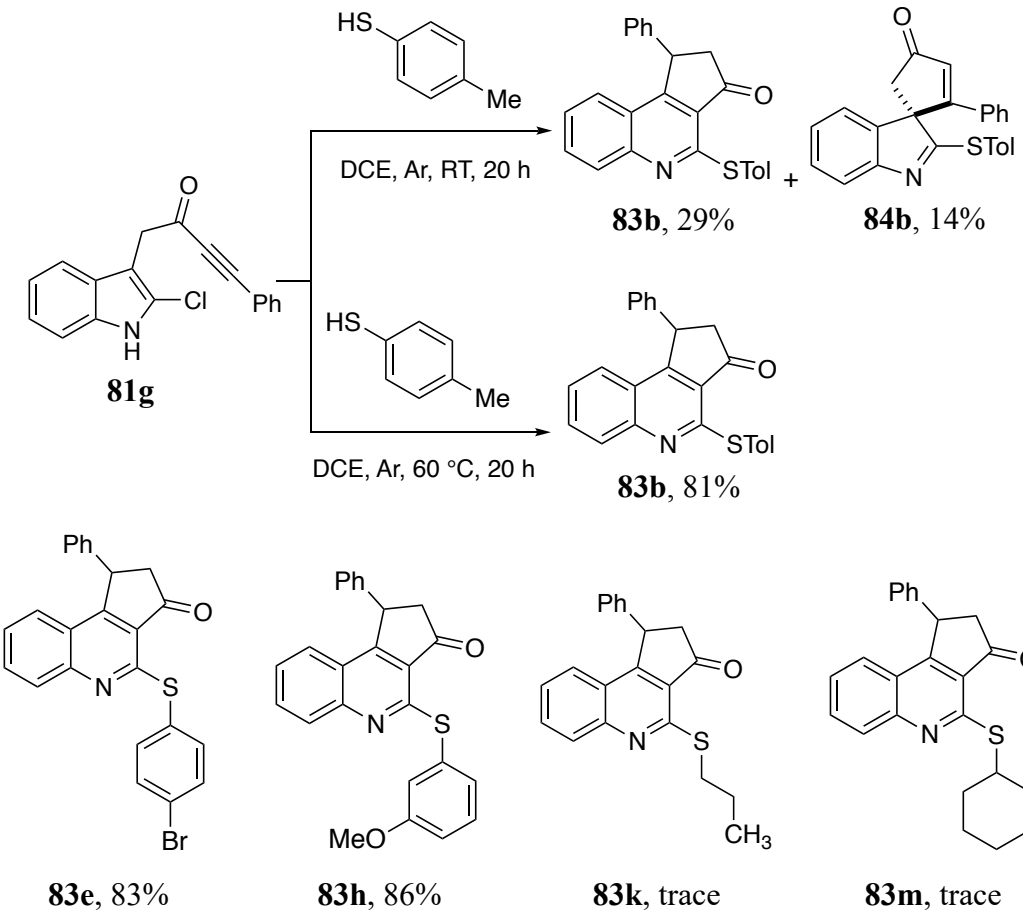


Figure 6. X-ray structure of quinoline **83w** with the thermal ellipsoids 50% (CCDC 2054407)

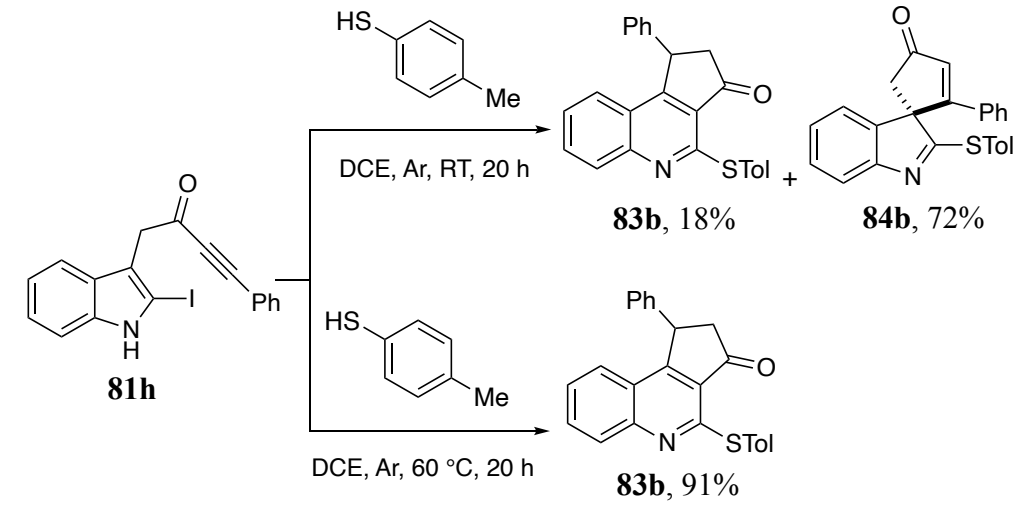
Next, the reactivity of other C2-halo indolyl ynones were examined. First, C2-chloro indolyl ynone **81g** was reacted with *p*-toluenethiol at RT, which afforded the desired quinoline **83b** in only 29% yield and spiroindolenine sulfide **84b** in 14% yield after 20 hours (Scheme 28a). However, this reaction was repeated and heated to 60 °C, which improved the yield to 81%. Chloro ynone **81g** reacted similarly with 4-bromobenzenethiol and 3-methoxybenzenethiol at 60 °C, affording the corresponding quinolines **83e** and **83h** in 83% and 86% yields, respectively. However, a limited reactivity of chloro ynone **81g** was observed when it was reacted with aliphatic thiols, such as propanethiol and cyclohexanethiol, which afforded only traces of quinolines **83k** and **83m**.

Then, C2-iodo indolyl ynone **81h** was reacted with *p*-toluenethiol at RT (Scheme 28b), which provided quinoline **83b** as a minor product (18% yield) and spirocycle **84b** as a major product (72% yield). As with chloro ynone **81g**, the reaction between iodo ynone **81h** and *p*-toluenethiol was examined at 60 °C, which led to the formation of the corresponding quinoline **83b** in an improved 91% yield, which suggested that spiroindolenine sulfide **84b** was consumed and converted into quinoline **83b**.

a)



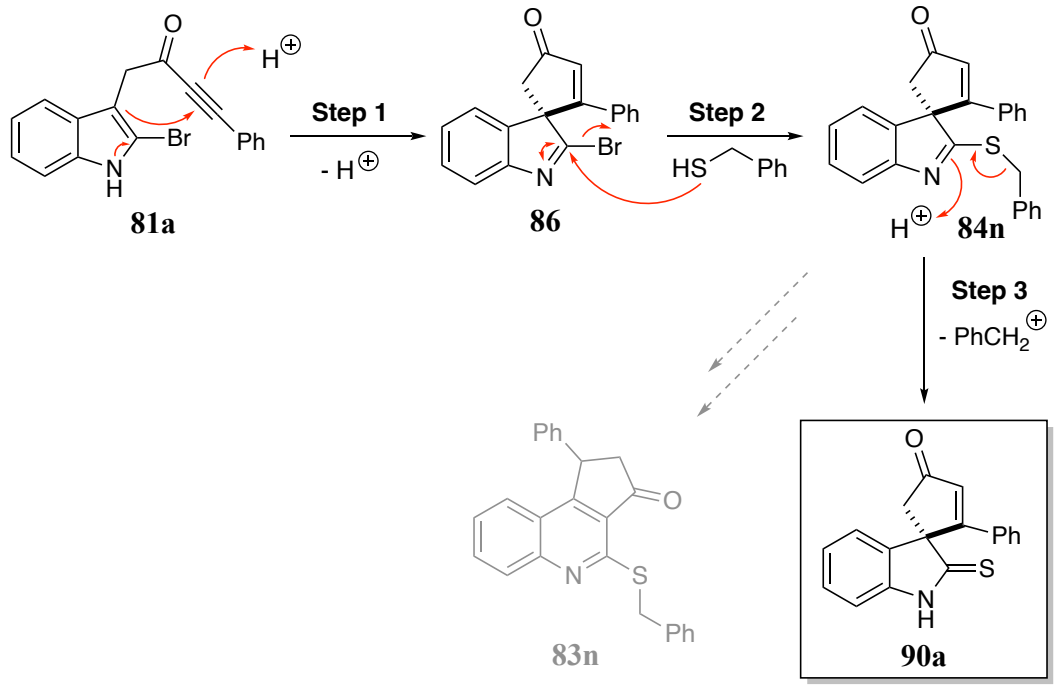
b)



Scheme 28. Variation of C2-halo ynone study

2.4 Formation of thio-oxindoles

As noted above, the use of the thiol benzyl mercaptan (Scheme 26), at 60 °C provided quinoline **83n** in 53% yield, alongside the formation of an unexpected thio-oxindole side product **90a** in 27% yield. This side-product **90a** was assumed to have formed during the process of forming quinoline **83n**. A plausible proposed mechanism for the formation of thio-oxindole **90a** is summarised in Scheme 29. It begins with the acid-mediated dearomatising spirocyclisation (step 1) of ynone **81a** forming spiro-indolenine bromide **86**. Then, spirocycle **86** undergoes nucleophilic substitution (step 2) with benzyl mercaptan providing thiol-substituted spirocycle intermediate **84n**, which may be converted into quinoline **83n** (via a rearrangement discussed later), or alternatively, the benzyl group may be cleavable (*e.g.* under acidic conditions) resulting in loss of the benzyl group and the formation of thio-oxindole **90a** (see step 3).

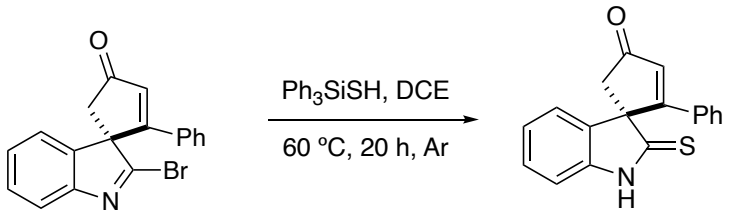


Scheme 29. The formation of thio-oxindole using benzyl mercaptan

To support this hypothesis, and to try establishing a more synthetically useful method to form the thio-oxindole products,[50-52] triphenylsilanethiol was used instead of benzyl mercaptan, which was chosen as the S–Si bond was predicted to be easier to break

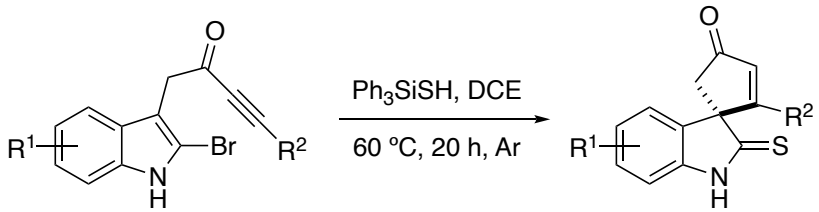
than the benzyl C–S bond. Therefore, spirocyclic intermediate **86** was prepared and reacted with triphenylsilanethiol (Scheme 30a). Pleasingly, the reaction worked smoothly and provided thio-oxindole **90a** in quantitative yield. The efficiency of a one-pot transformation was then explored. Pleasingly, the reaction of ynone **81a** with triphenylsilanethiol under the standard conditions at 60 °C formed thio-oxindole **90a** in 82% yield (Scheme 30b). Then, other indole-tethered ynones **81b** – **81d** were reacted with triphenylsilanethiol, which were all successfully converted into thio-oxindoles **90b** – **90d** in 47 to 85% yields (Scheme 30b). A plausible proposed mechanism for the formation of thio-oxindole **90a** using triphenylsilanethiol is summarised in Scheme 31, which follows a similar mechanism to that proposed for benzyl mercaptan.

a)

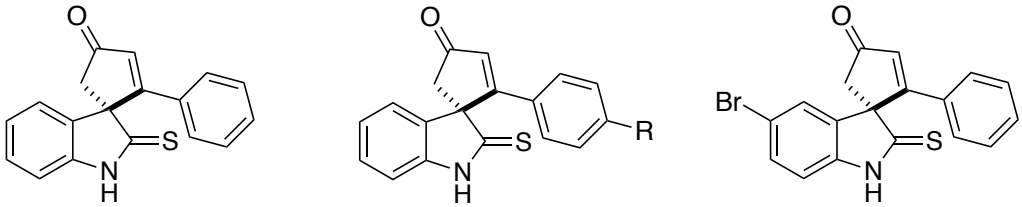


86 **90a**, 100%

b)



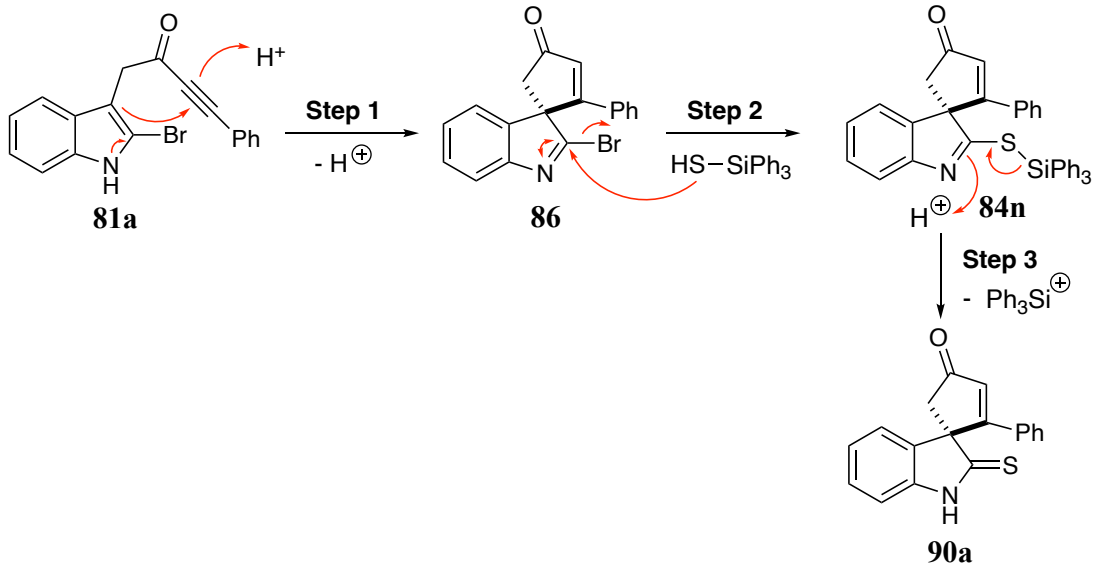
81a - 81d **90a - 90d**



90a, 82% **90b** (R = OMe), 85% **90d**, 71%

90c (R = F), 47%

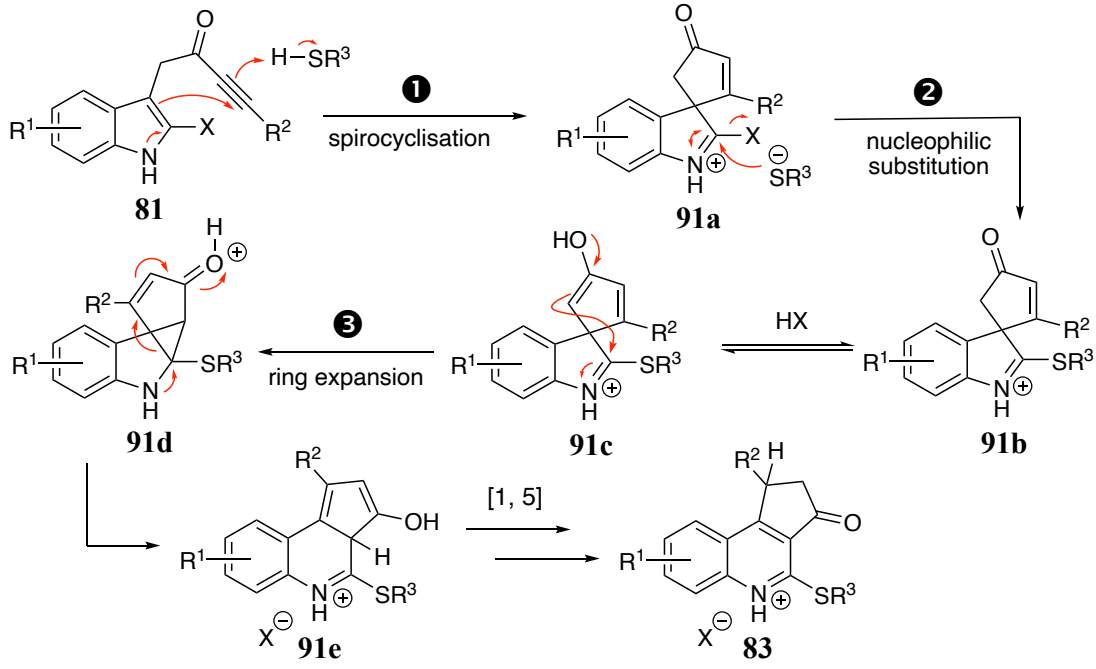
Scheme 30. Formation of thio-oxindoles using Ph_3SiSH



Scheme 31. The formation of thio-oxindole by using triphenylsilanethiol

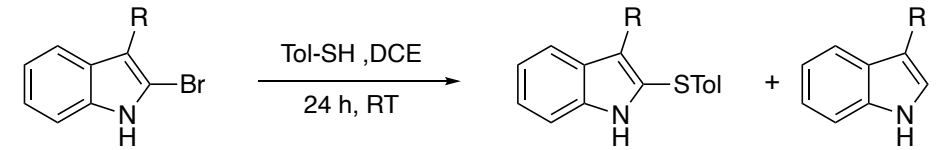
2.5 Mechanistic study of quinoline formation

After exploring the substrate scope, the reaction mechanism was investigated. A three-step cascade reaction was proposed to operate (Scheme 32), involving: 1) acid-mediated dearomatising spirocyclisation, 2) nucleophilic substitution and 3) ring expansion.



Scheme 32. Proposed mechanism for thiol-mediated cascade reaction

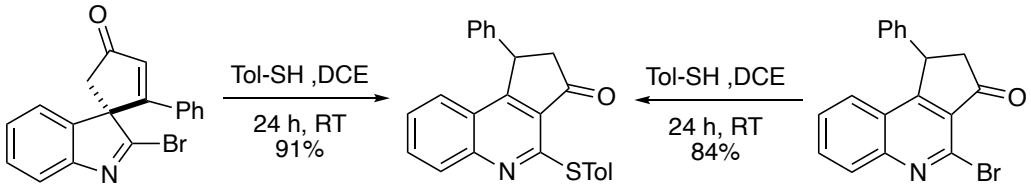
To verify the proposed mechanism, some control experiments were carried out in order to probe the order of steps. First, it was questioned whether the nucleophilic substitution step can proceed before spirocyclisation. To test this, simple C2-bromo indole analogues **80a** and **94** were made and reacted with *p*-toluenethiol under the standard reaction conditions (Scheme 33). Interestingly, indole **80a** was converted into substituted product **92** in 31% yield and hydrodehalogenated indole **93** in 51% yield. This result suggests that thiols may be able to directly substitute the bromo group on the indole C2-position. However, 2-bromo-3-methylindole **94** was also reacted with *p*-toluenethiol, which formed only traces of substitution product **95**, and hydrodehalogenated product **96** could not be observed. Thus, it appears that the reaction is more likely to undergo acid-mediated dearomatising spirocyclisation before nucleophilic substitution. Furthermore, the formation of spiroindolenine bromide **86x** in Scheme 27 also supports this pathway.



80a, R = $CH_2CON(OMe)Me$ — **92**, 31% — **93**, 51%
94, R = Me — **95**, trace — **96**, 0%

Scheme 33. Nucleophilic substitution of C2-position study

Then, it was questioned whether, after the spirocyclisation step the reaction might undergo ring expansion before nucleophilic substitution. To probe this question, spiroindolenine bromide **86** and 2-bromoquinoline **85** were reacted with *p*-toluenethiol under the standard reaction conditions (Scheme 34). Interestingly, both reactions proceeded smoothly and generated quinoline **83b** in excellent yields (91% and 84%). Therefore, these results suggest that the order of nucleophilic substitution and ring expansion may be interchangeable, with both pathways being viable.

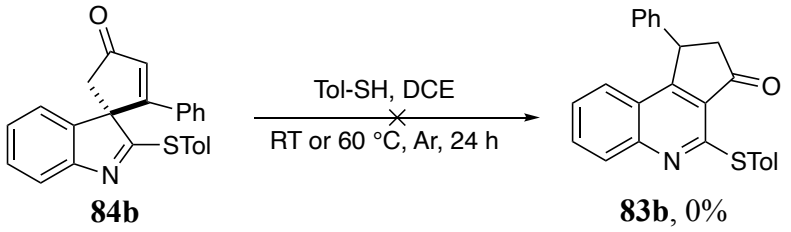


86 — **83b** — **85**

Scheme 34. Ring expansion and nucleophilic substitution step investigation

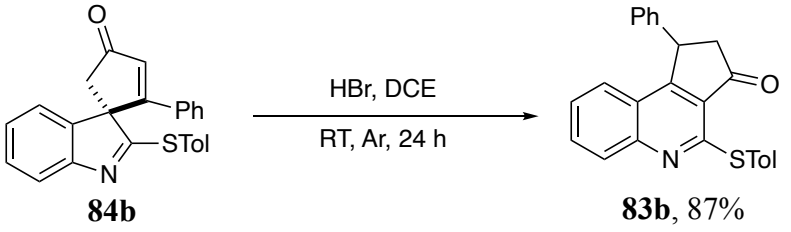
Finally, to gain insight into the ring expansion reaction, spiroindolenine sulfide **84b** was prepared and reacted with *p*-toluenethiol, both at RT and 60 °C (Scheme 35a). The results showed no conversion in both cases, with only the starting material **83b** recovered. In contrast, the reaction of **84b** with 1.1 equiv of 48% HBr aqueous solution afforded quinoline **83b** in 87% yield (Scheme 35b), implying a strong Bronsted acid (HBr) is required to promote the ring expansion. Therefore, it is proposed that the strong acid (HBr) generated *in situ* during the reaction is important in promoting the ring expansion step.

a)



84b **83b**, 0%

b)

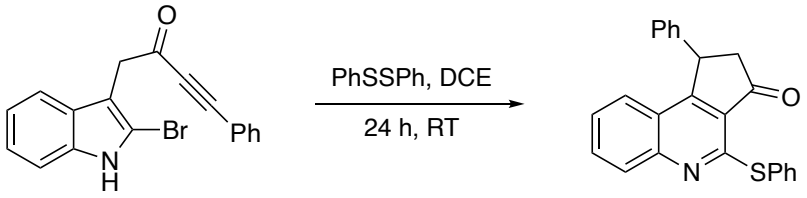


84b **83b**, 87%

Scheme 35. Ring expansion study

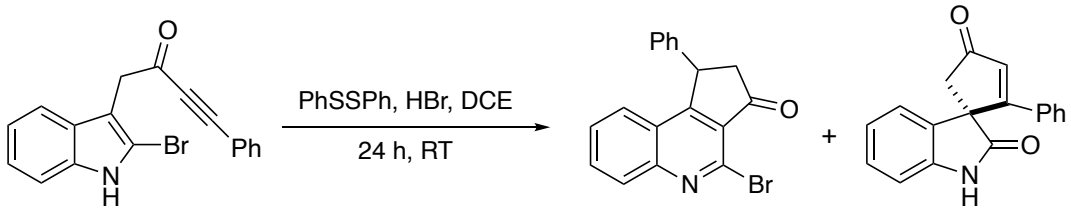
To explore alternative radical mechanisms, ynone **81a** was reacted with diphenyl disulfide (PhSSPh) instead of thiophenol under the standard conditions (Scheme 36a), as homolytic S–S bond cleavage to form thiyl radicals is a relatively facile process; the idea was that if thiyl radicals are involved in the cascade reaction quinoline **83a** should have formed. However, the quinoline product **83a** was not observed in the reaction. It is therefore unlikely that the reaction proceeds via a radical intermediate. This reaction was also repeated with the addition of 1.1 equiv. of HBr, which afforded quinoline **85** in 72% yield and spiro-oxindole **87** in 18% yield, with no thiol substitution observed in either product (Scheme 36b).

a)



81a **83a**, 0%

b)

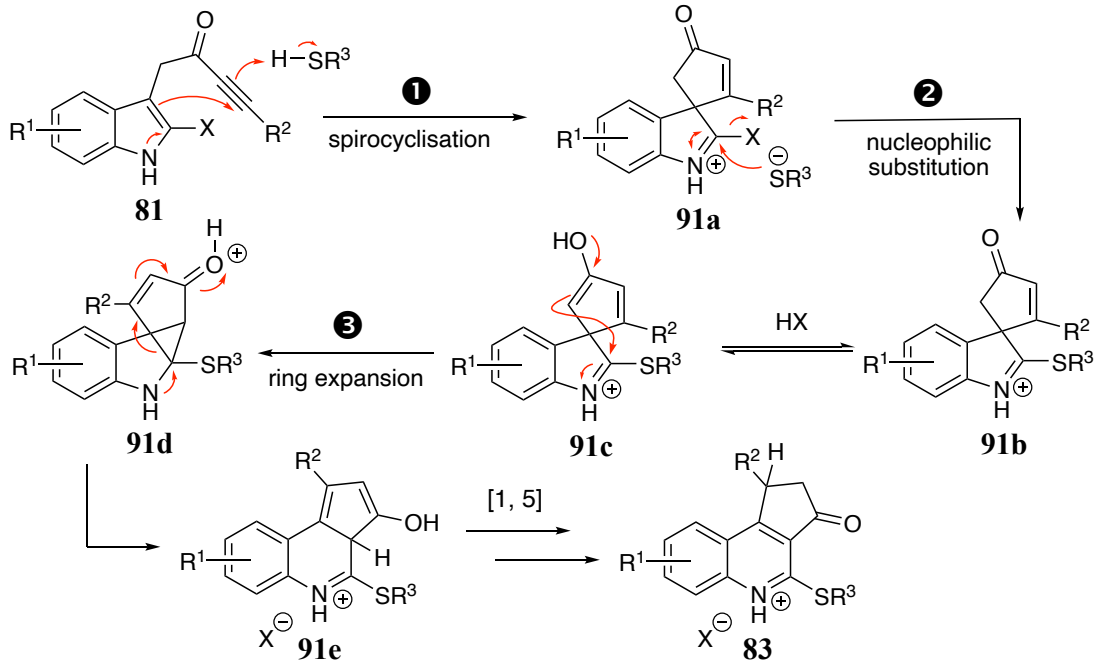


81a **85**, 72% **87**, 18%

Scheme 36. Radical investigation

2.6 Proposed mechanism

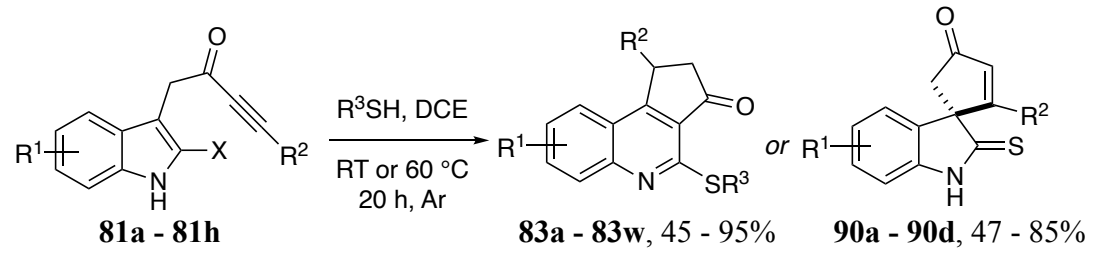
Thus, based on all of the results, substrate studies, control experiments and previous reports, we can propose a mechanism for this cascade reaction which proceeds via 3 steps (Scheme 37).[42, 53, 54] First, the dearomatising spirocyclisation (step 1) of C2-halide ynone **81** is catalysed by the moderately acidic thiol reagent, to form C2-halide spirocyclic indolenine **91a**. Then, nucleophilic substitution by thiolate ion to the resulting spirocyclic iminium ion gives spiroindolenine sulfide intermediate **91b** and generates a strong Bronsted acid (*e.g*. HBr, HCl and HI) *in situ* (step 2). This acid promotes keto – enol tautomerisation to give enol adduct **91c**, which then subsequently promotes ring expansion (step 3) via cyclopropane intermediate **91d** to furnish a six-membered ring intermediate **91e**. Finally, 1,5-sigmatropic H-transfer and rearomatisation results in the formation of quinoline **83**. In addition, it should be noted that once a suitable concentration of strong acid has accumulated, this may stimulate the ring expansion before the nucleophilic substitution, and thus interchange the order of steps 2 and 3.



Scheme 37. Proposed mechanism for thiol-mediated cascade reaction

2.7 Chapter summary

In summary, the reactivity of C2-halo indole-tethered ynones was investigated with thiol compounds. The studies showed that thiol reagents could convert reactive ynones **81a** – **81h** via a three-step cascade reaction into functionalised quinolines **83a** – **83w** in high yields under operationally simple and mild conditions. Additionally, a novel synthetic methodology to synthesise spiro thio-oxindoles **90a** – **90d** was discovered by serendipity.

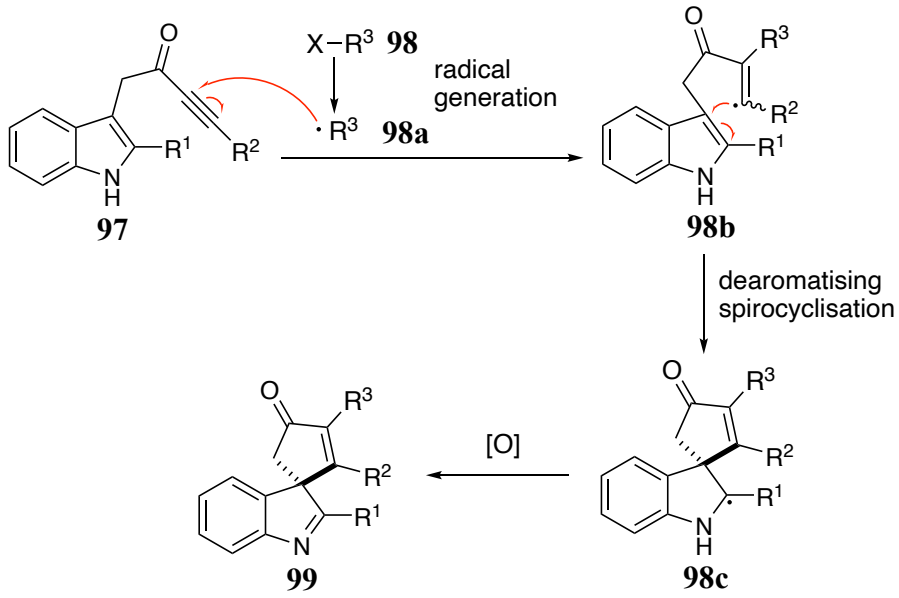


Scheme 38. Chapter 2 summary

Chapter 3: Radical Dearomatising Spirocyclisation Cascades with Indole-tethered Ynones

3.1 Introduction

In the previous Chapter, we found that C-2 halo indole-tethered ynones were converted into quinolines a through thiol-mediated cascade reaction, with this cascade initially discovered by serendipity. In this Chapter, we return to the original aim of exploring indole-tethered ynones as substrates for spirocyclisation cascade reactions using photocatalysis, as introduced in Chapter 1. We envisaged that a photocatalytic approach could be used to initiate the formation of different radical species, which then could react with indole-tethered ynones to deliver functionalised spiroindolenines. In addition to the use of photocatalysis, we also aimed to investigate whether similar reactivity could be promoted using other radical generation methods.

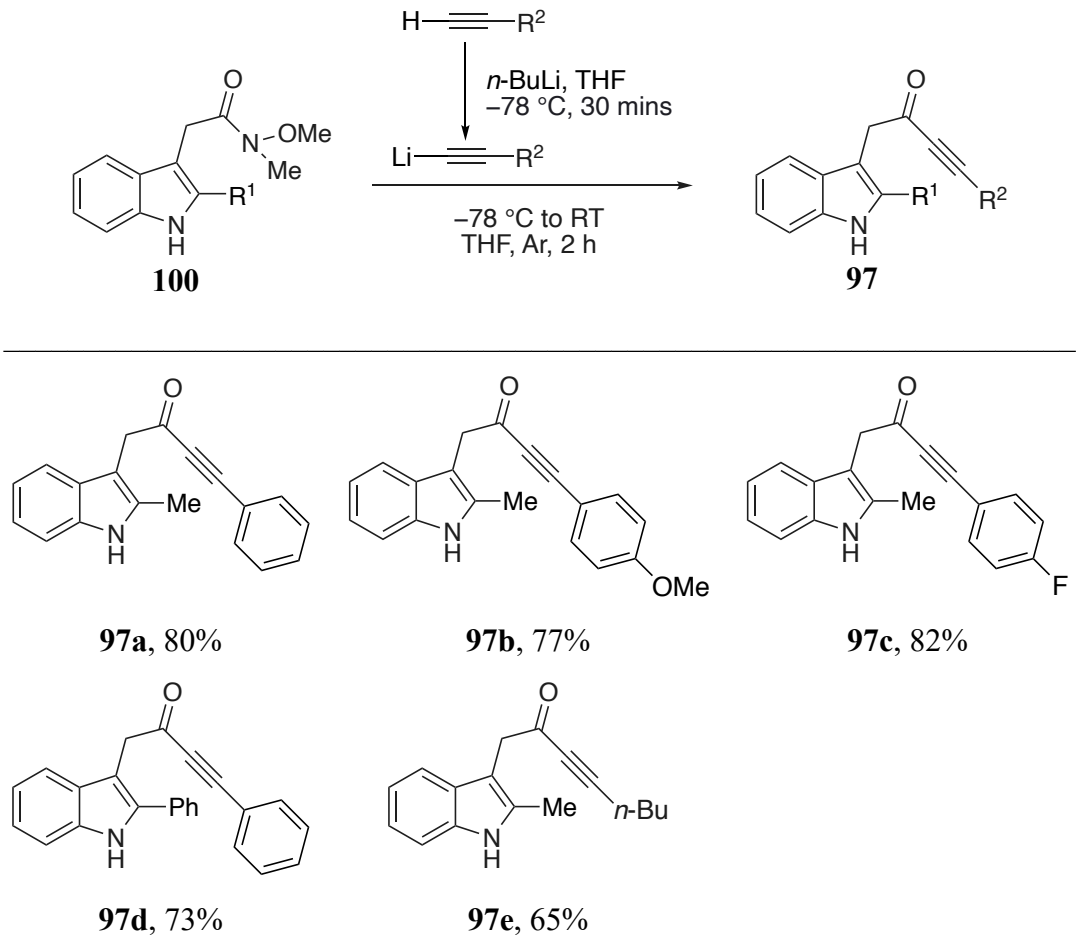


Scheme 39. Radical-based dearomatising spirocyclisation cascade reactions

3.2 Substrate synthesis

To study a radical-based spirocyclisation cascade with ynones, a suitable test substrate was needed. Thus, ynone **97a** was prepared by reacting Weinreb amide **100** (R^1 = Me)

with lithium phenylacetylide, furnishing ynone **97a** in 80% yield, which was subsequently used as the main model substrate for this study (Scheme 40). A range of other lithium acetylides were also reacted with Weinreb amide (R^1 = Me, Ph), providing the corresponding ynones **97b** – **97e**, generally in good yields.

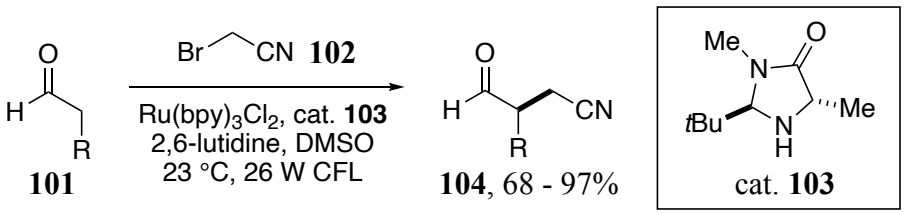


Scheme 40. Substrate synthesis

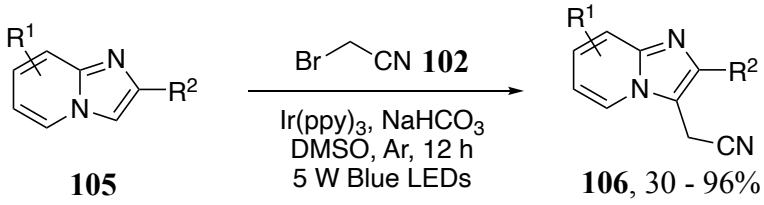
3.3 Cyanomethylation

We began by trying to develop a new method for cyanomethylation, as there have been some literature reports of direct cyanomethylation by using photoredox catalysis. For example, the enantioselective cyanomethylation of aldehydes by MacMillan and co-workers (Scheme 41a).[55] Here, a photocatalyst cooperating with an organocatalyst **103** was used to convert aldehydes **101** into cyanomethylated products **103**. Sun and co-workers also reported a regioselective cyanomethylation of imidazopyridine scaffold **105** (Scheme 41b).[56] Likewise, direct cyanomethylation of indole derivatives **107** was demonstrated by Conrad and co-workers (Scheme 41c).[57] These examples clearly showed that the use of photoredox catalysis to generate cyanomethyl radicals from bromoacetonitrile **102** is viable, and this provided good encouragement for this study.

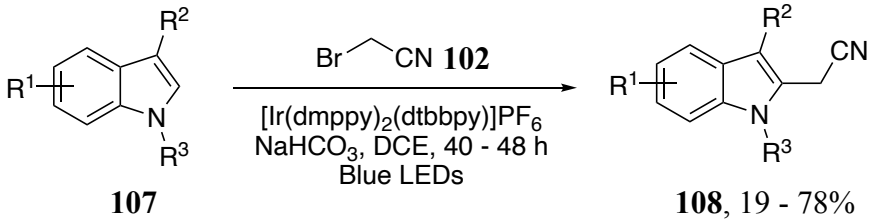
a)



b)



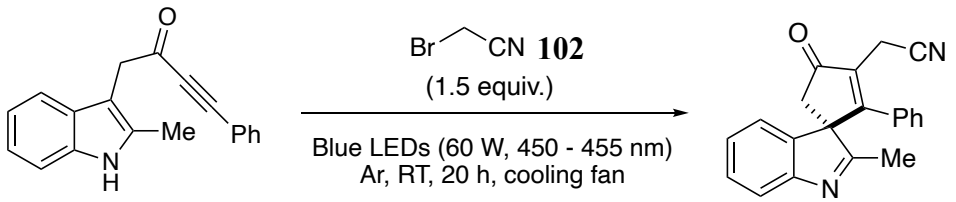
c)



Scheme 41. Direct cyanomethylation reactions in the literature

3.3.1 Reaction optimisation

To start, ynone **97a** was reacted with bromoacetonitrile **102**, 2,6-lutidine and $Ir(ppy)_3$ (1 mol%) in DCE under irradiation of blue LEDs for 20 hours, which formed spiroindolenine **109a** in 60% yield (Table 3, entry 1). These initial conditions were adapted from those used by Conrad and co-workers in their previous study.[57] Then, photocatalyst screening was carried out (entries 2 – 5), which showed that Ir(*p*-F-ppy)$_3$ was more effective and could be used to furnish spirocycle **109a** in 76% isolated yield. However, $Ru(bpy)_3(PF_6)_2$ and Eosin Y were unable to form spirocycle **109a**. Other bases, such as 2,4,6-collidine and K_2CO_3, only gave moderate yields of the desired product **109a** (entries 6 – 7). Next, the solvent was varied (entries 8 – 9), which led to solubility problems and again reduced the yield of spirocycle **109a**. Finally, some control reactions were conducted (entries 10 – 13). There was no conversion of ynone **97a** in the absence of light and the addition of TEMPO also turned off all reactivity, with no products formed. These results provide evidence to suggest that the reaction likely operates via a light-promoted radical spirocyclisation. Interestingly, performing the reaction without a photocatalyst also furnished spirocycle **109a** in 31% yield, implying that EDA complexes may initiate dearomatising spirocyclisation, as observed in Unsworth and Taylor's published thiyl radical process.[44] However, as the yield was lower than for the Ir(III)-catalysed version, it was decided to focus on the metal-catalysed reaction in this study.



97a **109a**

Entry	Reaction conditions			Yield of 109a (%)[b]
	Photocatalyst (1 mol%)	**Solvent** (0.1M)	**Base** (2.0 equiv.)	
1	$Ir(ppy)_3$	DCE	2,6-lutidine	60
2	$Ru(bpy)_3(PF_6)_2$	DCE	2,6-lutidine	0
3	Ir(*p*-F-ppy)$_3$	DCE	2,6-lutidine	(76)
4	Eosin Y	DCE	2,6-lutidine	0
5	10-phenyl phenothiazine	DCE	2,6-lutidine	7
6	Ir(*p*-F-ppy)$_3$	DCE	2,4,6-collidine	60
7	Ir(*p*-F-ppy)$_3$	DCE	K_2CO_3	40
8	Ir(*p*-F-ppy)$_3$	MeCN	2,6-lutidine	28
9	Ir(*p*-F-ppy)$_3$	DMSO	2,6-lutidine	33
10	Ir(*p*-F-ppy)$_3$	DCE	-	13
11[c]	Ir(*p*-F-ppy)$_3$	DCE	2,6-lutidine	0
12[d]	Ir(*p*-F-ppy)$_3$	DCE	2,6-lutidine	0
13	-	DCE	2,6-lutidine	31

*[a] All reactions were performed with 0.20 mmol of ynone **97a**.*

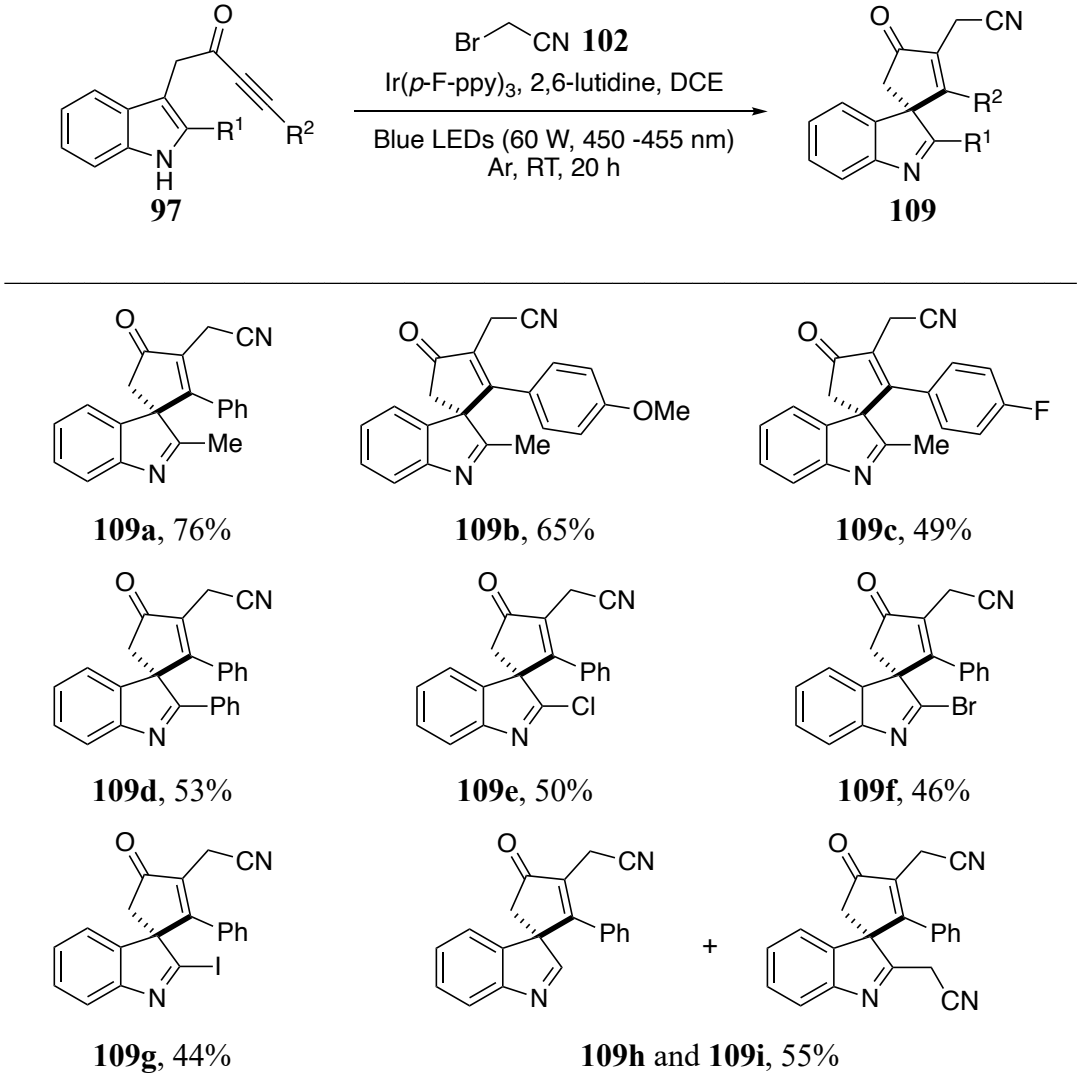
[b] Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard; in one case, an isolated yield is shown in parentheses. [c]In the dark. [d] TEMPO (2.0 equiv) was added.

Table 3. Reaction optimisation of photoredox promoted cyanomethylation

3.3.2 Substrate study

After establishing the optimised reaction conditions using bromoacetonitrile **102**, Ir(*p*-F-ppy)$_3$ and 2,6-lutidine in DCE under irradiation with blue LEDs, these conditions were then tested with the prepared indole-tethered ynones (Scheme 42). The substrate

investigation started by comparing ynones with different substituents on the aromatic ring, which afforded the corresponding spiroindolenines **109b** and **109c** in 65 and 49% yields, respectively. Next, C-2 substituted phenyl indolyl ynone **97d** was tested, which provided the desired cyanomethylated spirocycle **109d** in 53% yield. Having C2-halo indolyl ynones **81a**, **81g** and **81h** from Chapter 2 in hand, they were also reacted under the cyanomethylation cascade reaction conditions and successfully converted into spiroindolenines **109e** – **109g** in 44 – 50% yields. However, the reaction between indolyl-ynone without a C2-substituent (R^1 = H) and bromoacetonitrile provided an inseparable mixture of desired spirocycle **109h** and unwanted product **109i**, which was presumably formed by competing cyanomethyl radical addition to the C-2 position of indole ring.

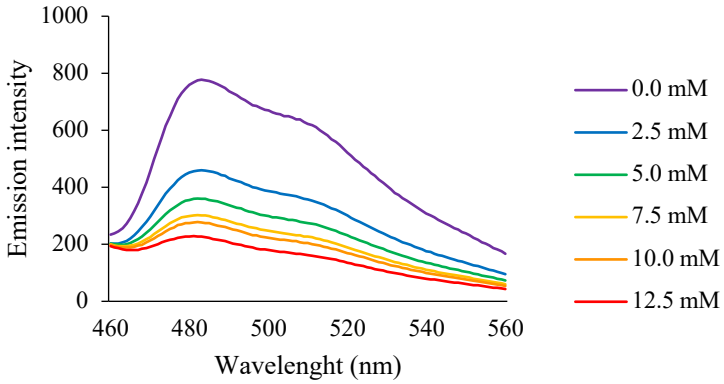


Scheme 42. Substrate study of cyanomethylations

3.3.3 Mechanistic studies

To better understand the reaction mechanism, a Stern-Volmer luminescence quenching study was used to help elucidate the photocatalytic reaction mechanism. A solution of Ir(*p*-F-ppy)$_3$ with various concentrations of bromoacetonitrile was irradiated at 380 nm, whilst the emission was measured at 483 nm (Figure 7a). The results showed that the emission intensity of the excited Ir(*p*-F-ppy)$_3$ was significantly decreased by increasing the concentration of bromoacetonitrile. Then, these data were plotted, from the Stern-Volmer equation in Figure 7b, comparing fluorescence intensity in the absence of bromoacetonitrile with the intensity in the presence of bromoacetonitrile (y axis) and concentration of bromoacetonitrile (x axis). The result showed a linear trend in Figure 7c. These results provide strong evidence that the excited Ir(*p*-F-ppy)$_3$ likely participates in SET with bromoacetonitrile.

a)



b)

$$\frac{I_o}{I} = 1 + K_q \tau_0 [Q]$$

I_o = Intensity in the absence of a quencher

I = Intensity in the presence of a quencher

K_q = Quencher rate coefficient

τ_0 = Lifetime of the excited state

$[Q]$ = Concentration of the quencher

c)

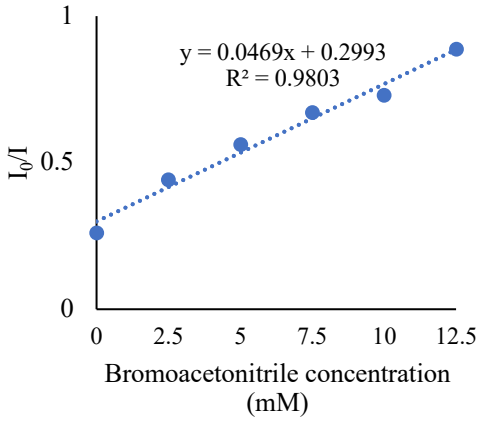
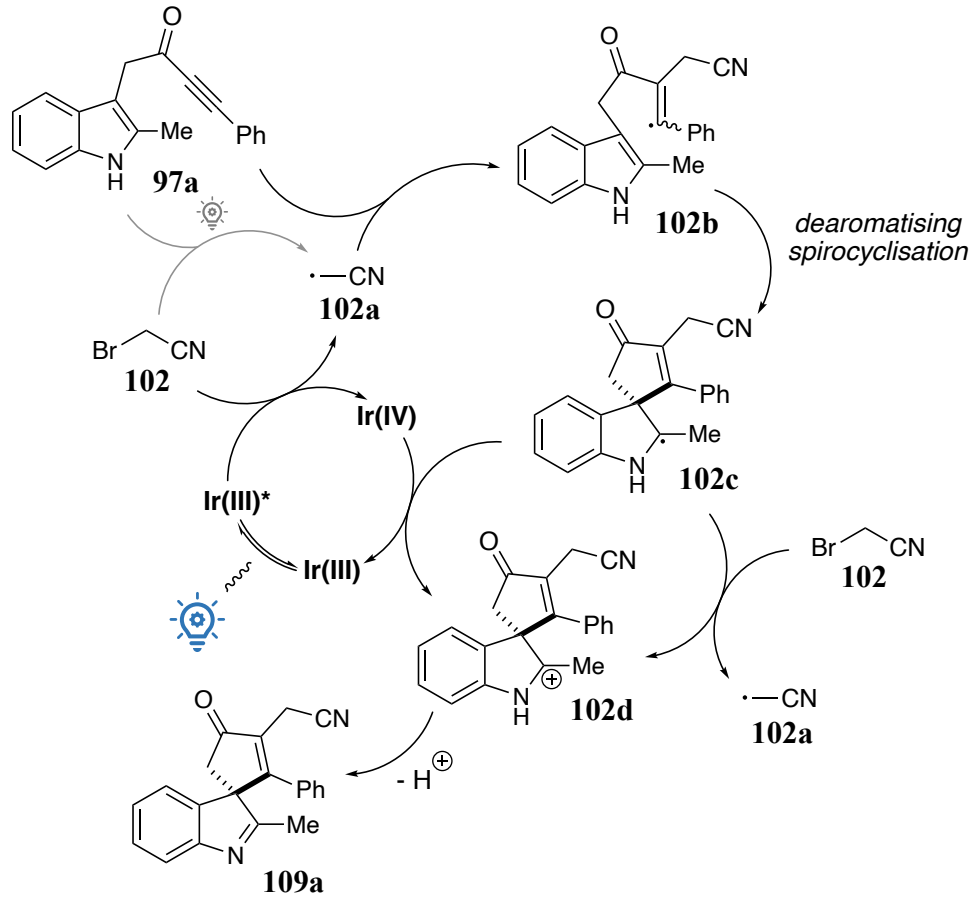


Figure 7. Quenching of Ir(*p*-F-ppy)$_3$ emission in the presence of bromoacetonitrile

3.3.4 Proposed mechanism

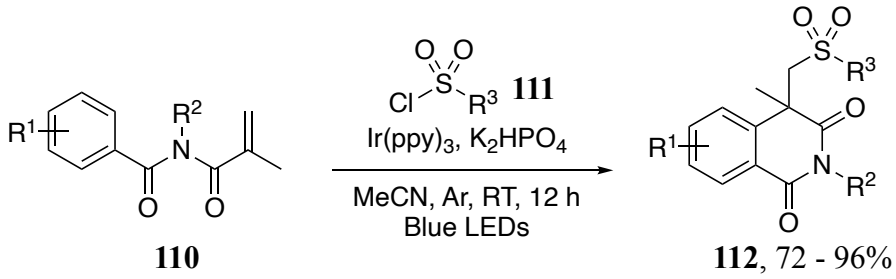
Based on the above results and previous reports, a reaction mechanism is likely to operate, under photocatalysis via an oxidative quenching pathway (Scheme 43). In our proposed mechanism, the Ir(III) complex is first excited under irradiation with blue LEDs to generate photoexcited Ir(III)* complex ($E_{1/2\ (IV/III)^*} = -1.91$ V vs SCE),[19] which then reduces bromoacetonitrile **102** ($E_{1/2} = -0.69$ V vs SCE)[58] to form cyanomethyl radical **102a** and Ir(IV) complex.[19] Next, the cyanomethyl radical **102a** reacts with ynone **97a**, resulting in the formation of vinyl radical **102b**, followed by dearomatising spirocyclisation to afford spirocyclic radical **102c**. Finally, this intermediate **102c** donates a single electron via SET to the Ir(IV) complex to regenerate the Ir(III) complex and carbocation intermediate **102d**, which then undergoes deprotonation to afford spiroindolenine **109a**. Alternatively, a chain reaction via SET between intermediate **102c** and bromoacetonitrile **102** initiates the formation of cyanomethyl radical **102a** and carbocation intermediate **102d**.



Scheme 43. Proposed mechanism via an oxidative quenching cycle

3.4 Sulfonylation

Having successfully developed a photocatalysed spirocyclisation protocol with cyanomethyl radicals, attention then turned to sulfonyl radicals. This type of radical can be easily generated under photocatalytic conditions.[59] For example, the synthesis of isoquinolinediones via a sulfonylation/cyclisation cascade reaction was reported by Sun and co-workers (Scheme 44).[60] This approach converted the sulfonyl chloride into a sulfonyl radical, which reacted well with benzamide **110**. Therefore, we envisaged that sulfonyl chlorides may also be used with indole-tethered ynones to afford functionalised spirocycles.

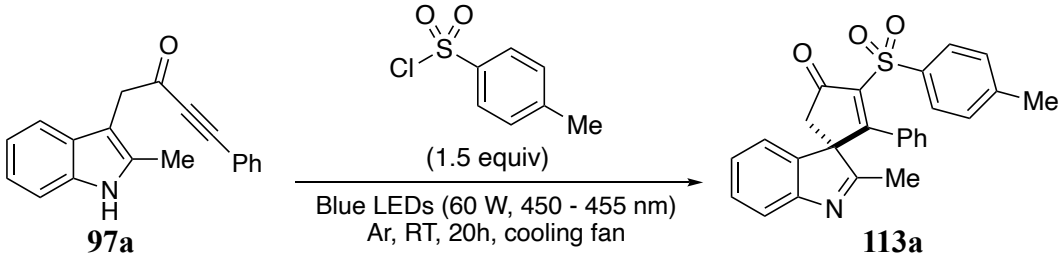


Scheme 44. Sulfonylation/cyclisation cascade reaction[60]

3.4.1 Reaction optimisation studies

The reaction optimisation began by reacting ynone **97a** with *p*-toluenesulfonyl chloride under the previous optimised conditions for cyanomethylation, using Ir(*p*-F-ppy)$_3$ (1 mol%) and 2,6-lutidine in DCE under irradiation with blue LEDs (Table 4, entry 1). These conditions provided the corresponding spirocycle **113a** in 61% yield. Ynone **97a** was then tested with other photocatalysts, Ir(ppy)$_3$ and Ru(bpy)$_3$(PF$_6$)$_2$, which led to decreased yields of spirocycle **113a** (entries 2 – 3). Next, solvent screening was carried out and revealed that the yield was improved dramatically (89% yield after purification) by performing the reaction in 1,4-dioxane (entries 4 – 7), while the use of MeOH gave only a 9 % yield. Switching the base to morpholine and pyridine decreased the yield of spirocycle **113a** (entries 8 – 9). Next, replacing the light source by using a CFL 23W bulb instead of blue LEDs gave the desired product **113a** in only 26% yield, which implied that this system was more effective when using blue light (entry 10). A reaction performed in the dark confirmed that light was essential to this

transformation (entry 11). The formation of **113a** was also completely inhibited by the addition of TEMPO (entry 12). Interestingly, the base was also shown to be essential for the transformation (entry 13). Finally, the reaction in the absence of the photocatalyst furnished the corresponding spiroindolenine **113a** in 77% yield, implying that productive EDA complexes may also be formed in solution (entry 14).[44]



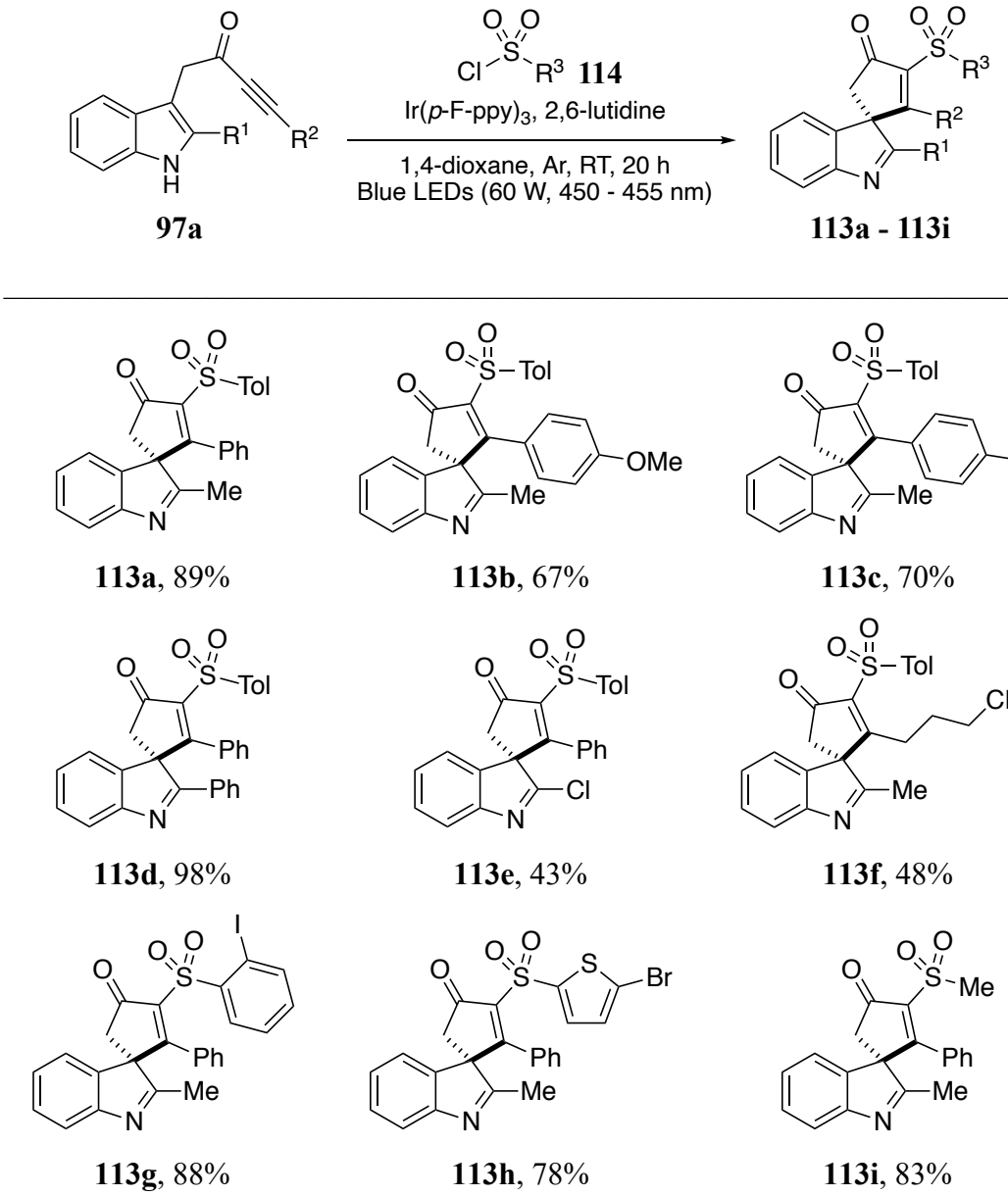
Entry	Reaction conditions			Yield of 113a (%)[b]
	Photocatalyst (1 mol%)	**Solvent** (0.1M)	**Base** (2.0 equiv)	
1	Ir(*p*-F-ppy)$_3$	DCE	2,6-lutidine	61
2	Ir(ppy)$_3$	DCE	2,6-lutidine	56
3	Ru(bpy)$_3$(PF$_6$)$_2$	DCE	2,6-lutidine	37
4	Ir(*p*-F-ppy)$_3$	MeCN	2,6-lutidine	47
5	Ir(*p*-F-ppy)$_3$	MeOH	2,6-lutidine	9
6	Ir(*p*-F-ppy)$_3$	acetone	2,6-lutidine	54
7	Ir(*p*-F-ppy)$_3$	1,4-dioxane	2,6-lutidine	(89)
8	Ir(*p*-F-ppy)$_3$	1,4-dioxane	morpholine	18
9	Ir(*p*-F-ppy)$_3$	1,4-dioxane	pyridine	39
10[c]	Ir(*p*-F-ppy)$_3$	1,4-dioxane	2,6-lutidine	26
11[d]	Ir(*p*-F-ppy)$_3$	1,4-dioxane	2,6-lutidine	0
12[e]	Ir(*p*-F-ppy)$_3$	1,4-dioxane	2,6-lutidine	0
13	Ir(*p*-F-ppy)$_3$	1,4-dioxane	-	0
14	-	1,4-dioxane	2,6-lutidine	77

*[a] Reactions performed with 0.20 mmol of ynone **97a**. [b] Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard: isolated yield is shown in parentheses. [c] CFL 23W instead of Blue LEDs. [d] In the dark. [e] TEMPO (2.0 equiv.) was added.*

Table 4. Reaction optimisation of photoredox promoted sulfonylation

3.4.3 Substrate study

With a number of prepared ynones already in hand, the scope of this sulfonylation reaction was explored (Scheme 45). Indole-tethered ynone derivatives with different aromatic and C2 substituents were reacted with *p*-toluenesulfonyl chloride, which were all converted into the corresponding spirocycles **113a** – **113e** in moderate to excellent yields (43 – 98%). The structure of sulfonylated spirocycle **113a** was confirmed by X-ray crystallography (Figure 8).[61] Aliphatic substituted ynone **97e** could also be converted into spirocycle **113f** in 48% yield. Next, ynone **97a** was reacted with other aromatic sulfonyl chlorides, leading to the formation of the corresponding spirocycles **113g** – **113h** in 88 and 78% yields. Notably, a scaled-up reaction between ynone **97a** (1.0 mmol) and 5-bromothiophene-2-sulfonyl chloride (1.5 mmol) was performed under identical reaction conditions, affording the desired product **113h** in 72% yield. Finally, the reaction between ynone **97a** and methanesulfonyl chloride worked smoothly and provided the corresponding spirocycle **113i** in 83% yield.



Scheme 45. Sulfonylation substrate scoping study

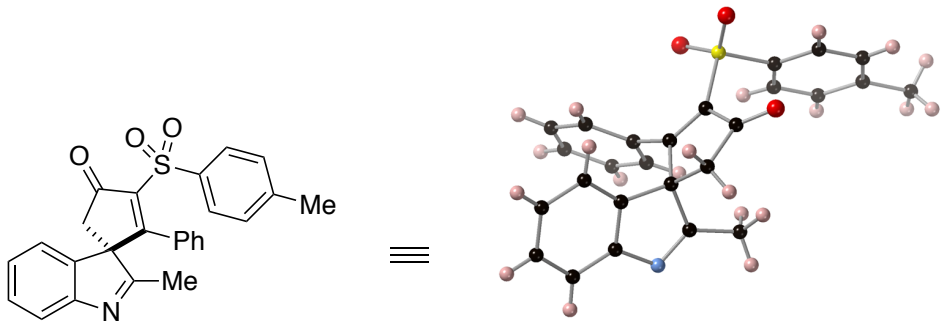
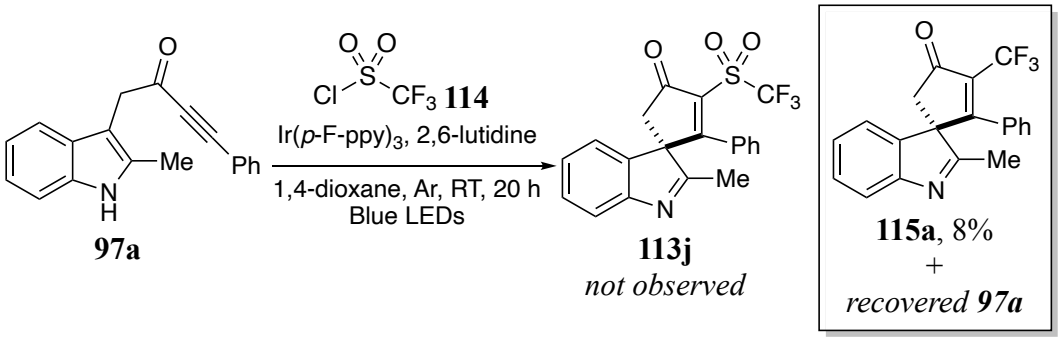
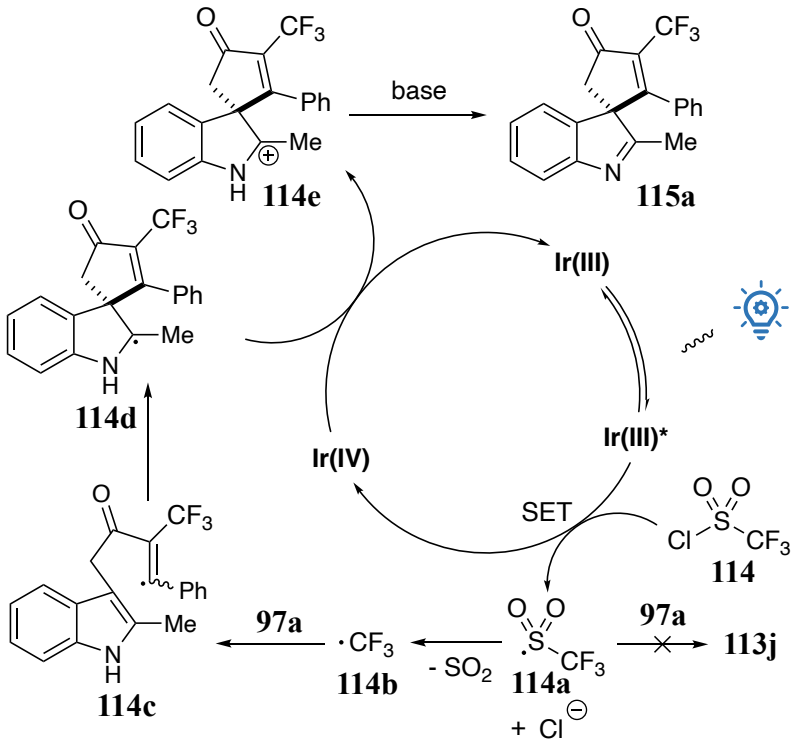


Figure 8. X-ray structure of sulfonylated spirocycle **113a** with the thermal ellipsoids 50% (CCDC 2087802)

Not all of the substrates tested were successful; the reaction between ynone **97a** and trifluoromethanesulfonyl chloride **114** under the optimised reaction conditions failed to form sulfonylated spirocycle **113j**; instead ynone **97a** was recovered as well as trifluoromethylated spirocycle **115a** in 8% yield (Scheme 46). The formation of trifluoromethylated spirocycle **115a** was interesting nonetheless, despite the low yield, suggesting the trifluoromethyl radical may have been formed *in situ*. In the literature, it is known that trifluoromethanesulfonyl chloride **114** can facilitate the generation of trifluoromethyl radicals using photoredox catalysis, as shown in a study by MacMillan and co-workers.[62] It was reported that SET between the photoexcited Ir(III)* complex and trifluoromethanesulfonyl chloride **114a** generated the Ir(IV) complex and sulfonyl radical **114a**, which rapidly released sulfur dioxide and formed trifluoromethyl radical **114b** (Scheme 47). It is therefore proposed that the electron deficient trifluoromethyl radical **114b** reacted with electron-rich ynone **97a** and induced dearomatising spirocyclisation to from spirocyclic intermediate **114d**. A SET followed by deprotonation afforded spirocycle **115a**. The formation of trifluoromethyl radical and its successful incorporation into a spirocyclic product piqued our attention towards trifluoromethylation, with this discussed more in the next section.



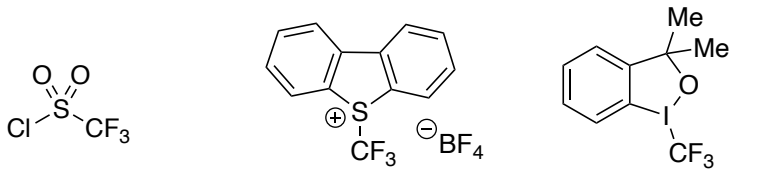
Scheme 46. Study of trifluoromethanesulfonyl chloride



Scheme 47. Proposed mechanism for the trifluoromethyl radical spirocyclisation

3.5 Trifluoromethylation

The trifluoromethyl group has become very attractive in the organic synthesis community due to its utilisation in the agrochemical and pharmaceutical industries. There are a broad range of versatile trifluoromethylating reagents, which are commonly used in organic synthesis such as trifluoromethanesulfonyl chloride **114**, Umemoto's reagent I **116** and Togni's reagent I **117** (Figure 9).[63] As the trifluoromethyl radical showed an ability to participate in a radical cascade reaction in the previous section, we therefore aimed to continue the development of reaction conditions for a radical-based trifluoromethylation spirocyclisation.

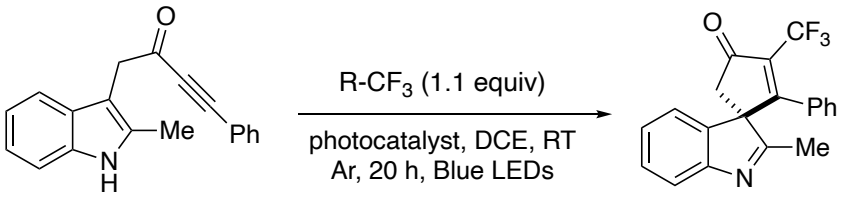


trifluoromethanesulfonyl chloride **114** | Umemoto's reagent I **116** | Togni's reagent I **117**

Figure 9. Trifluoromethyl sources

3.5.1 Reaction optimisation

Reaction optimisation began with the reaction between ynone **97a** and Umemoto's reagent I **116** in the presence of 2,6-lutidine and $Ru(bpy)_3(PF_6)_2$ under irradiation with blue LEDs (Table 5, entry 1). These conditions led to the desired product **115a** being formed in 36% yield. Ynone **97a** was reacted with Togni's reagent I **117** under the same reaction conditions, providing spirocycle **115a** in 35% yield (entry 2). Conditions were then tested without the addition of 2,6-lutidine, resulting in an improvement in the yield of spirocycle **115a** (entry 3). A small photocatalyst screen was carried out (entries 4 – 5), in which Eosin Y gave a slightly higher yield of isolated spirocycle **115a** in 45% yield. However, the reaction in the dark showed that spirocycle **115a** could still be obtained in 38% yield (entry 6). This result implied that there might be a competitive thermal reaction pathway operative in this system. Finally, Eosin Y, which has a strong absorption band at 520 nm, was tested with green light (entry 7), but this system gave slightly lower yield than with blue light.



97a **115a**

Entry	Conditions	Yield of 115a (%)[b]
1	Umemoto's **116**, 2,6-lutidine, $Ru(bpy)_3(PF_6)_2$ (1 mol%)	36
2	Togni's **117**, 2,6-lutidine, $Ru(bpy)_3(PF_6)_2$ (1 mol%)	35
3	Togni's **117**, $Ru(bpy)_3(PF_6)_2$ (1 mol%)	44
4	Togni's **117**, Ir(*p*-F-ppy)$_3$ (1 mol%)	44
5	Togni's **117**, Eosin Y (1 mol%)	48(45)
6[c]	Togni's **117**, Eosin Y (1 mol%)	38
7[d]	Togni's **117**, Eosin Y (1 mol%)	43

*[a] All reactions were performed with 0.20 mmol of ynone **97a**.*

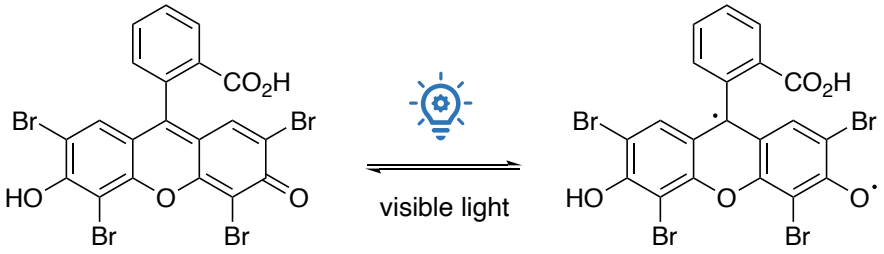
[b] Yield determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard; isolated yield is shown in parentheses.

[c] reaction performed in the dark. [d] using green LEDs.

Table 5. Reaction optimisation of photoredox promoted trifluoromethylation

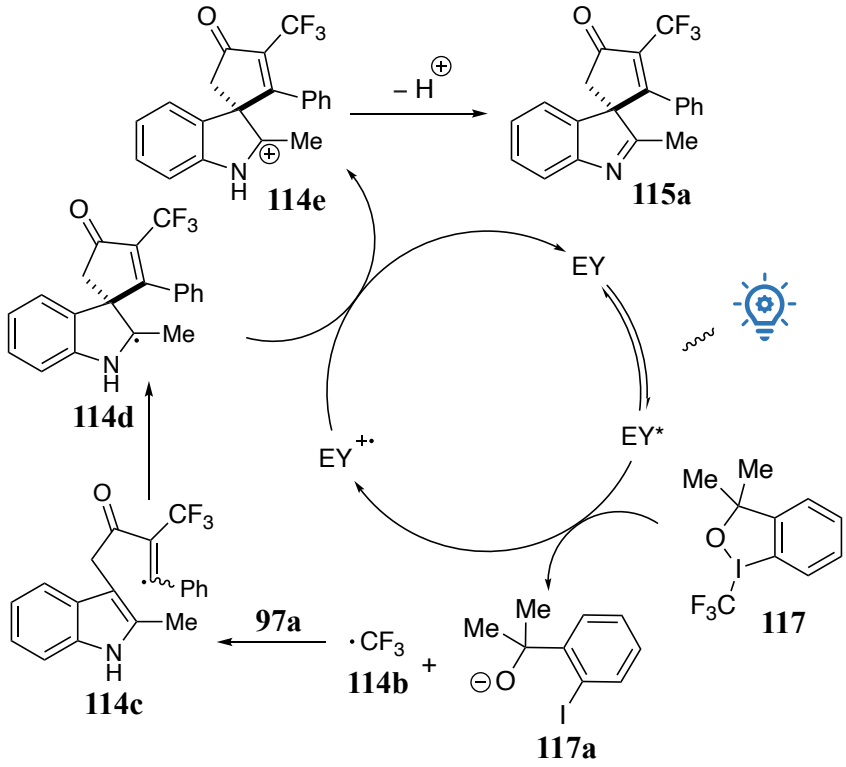
To understand the operation of Eosin Y (EY), the structure is demonstrated in Scheme 48a. This metal-free photoredox catalyst contains organic chromophores, which can be photoexcited to form excited state EY*. In this stage, EY* serves as a reactive species for photocatalytic processes. Therefore, the observed trifluoromethylation cascade reaction presumably began with the reaction between EY* and Togni's reagent I **117** via SET to form $EY^{+\cdot}$, alkoxide **117a** and trifluoromethyl radical **114b** (Scheme 48b). Then, radical **114b** added to ynone **97a** to form spirocyclic radical **114d** via vinyl radical **114c**. Eventually, SET followed by deprotonation afforded the corresponding spirocycle **115a**.

a)



Eosin Y, **EY** Eosin Y*, **EY***

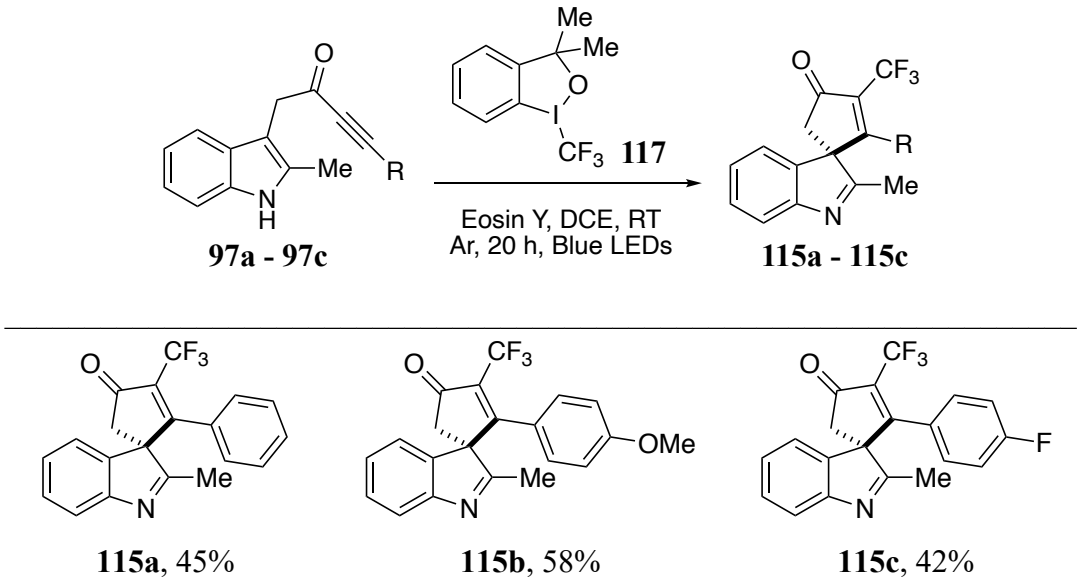
b)



Scheme 48. Trifluoromethylation cascade reaction using Eosin Y

3.5.2 Substrate studies

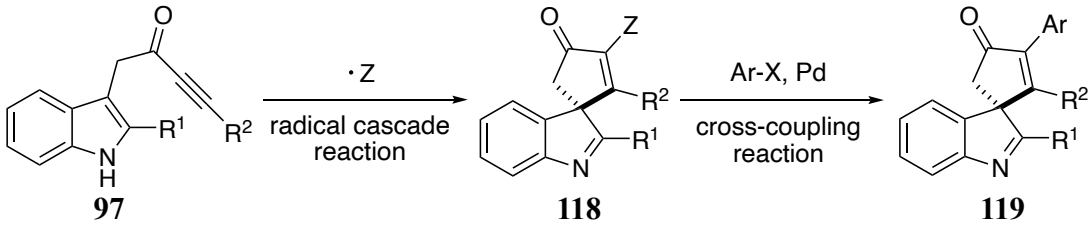
The developed conditions for trifluoromethylation were then applied to a selection of three ynone substrates (Scheme 49). The reaction between indole-tethered ynones and Togni's reagent I **117** afforded the corresponding trifluoromethylated spirocycles **115b** and **115c** in moderate yields.



Scheme 49. Substrate study for trifluoromethylation reactions

3.6 Stannylation

Next, radical species which could be used for cross-coupling reactions post spirocyclisation were explored (Scheme 50). Therefore, attention was turned towards stannylation reactions via a radical process, as it was envisaged that the stannylated product could then be readily used in a Stille cross-coupling reactions.[64]

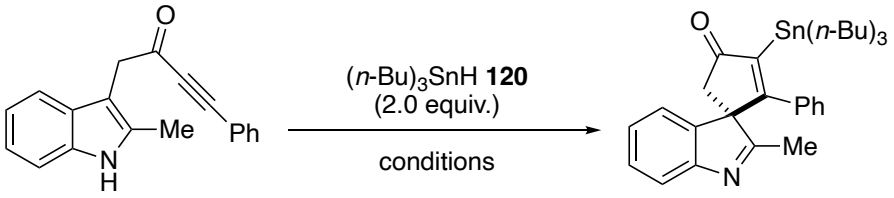


Scheme 50. Proposed cross-coupling sequence

3.6.1 Reaction optimisation

First, ynone **97a** was reacted with tributyltin hydride **120** with a more traditional radical generation method, using AIBN in refluxing benzene. This reaction worked well, furnishing the corresponding spirocycle **121a** in 67% yield (Table 6, entry 1). Thermolysis of AIBN, which is driven by nitrogen gas formation, leads to the

formation of 2-cyano-propyl radicals **122**, which react with tributyltin hydride **120** to form tributyltin radicals **120a** (Scheme 51a). It was therefore assumed that tributyltin radical **120a** would react with ynone **97a** in the usual way to form stannylated spirocycle **121a**. We also explored whether ynone **97a** could react with tributyltin hydride in the absence of AIBN; this was considered possible, due to the formation of photoactive EDA complexes discussed in section 3.3.1. Therefore, ynone **97a** was reacted with tributyltin hydride in benzene under irradiation with blue LEDs (entry 2), and pleasingly, this resulted in formation of the corresponding spirocycle **121a** in 50% yield. Our proposed explanation for this reactivity is that intramolecular EDA complex **97a** absorbed a visible light to form photoexcited complex **97a*** (Scheme 51b). Then, HAT from tributyltin hydride **120** to photoexcited complex **97a*** formed tributyltin radical **120a**. A brief solvent screening for this photochemical reaction was then carried out, which revealed that DCE could be used to provide spirocycle **121a** in a slightly better yield before purification (entry 4).



97a **121a**

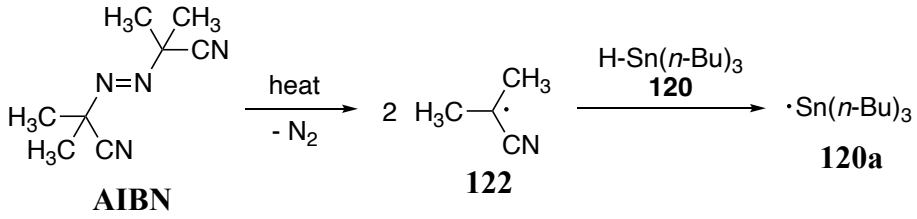
Entry	Conditions	Yield of 121a (%)[b]
1	AIBN (1.0 equiv), benzene (0.1 M), 80 °C, Ar, 2 h	67
2	benzene (0.1 M), RT, Ar, 20 h, Blue LEDs	50
3	toluene (0.1 M), RT, Ar, 20 h, Blue LEDs	38
4	DCE (0.1 M), RT, Ar, 20 h, Blue LEDs	52 (45)

*[a] All reactions were performed with 0.20 mmol of ynone **97a**.*

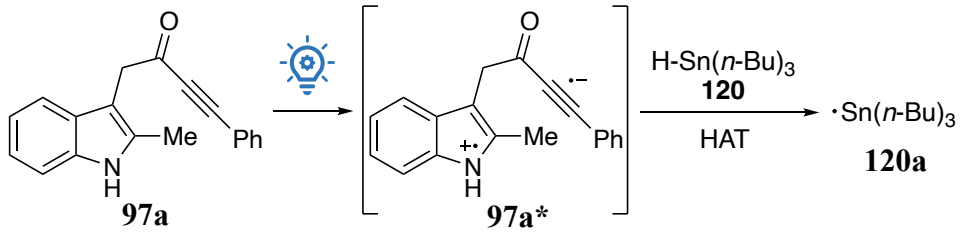
[b] Yield determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard; isolated yield is shown in parentheses.

Table 6. Reaction optimisation of stannylation via two modes of radical generation

a)



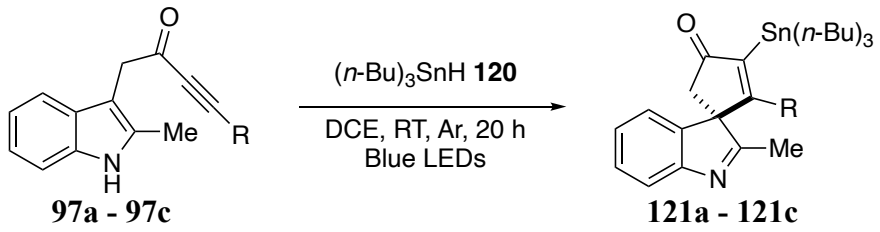
b)

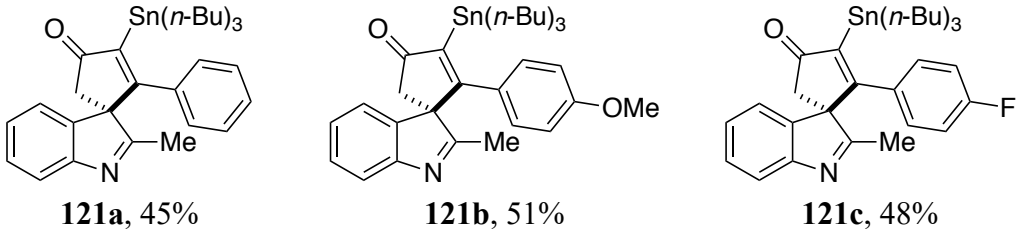


Scheme 51. Proposed mechanisms for tributyltin radical generation

3.6.1 Substrate study for stannylation reactions

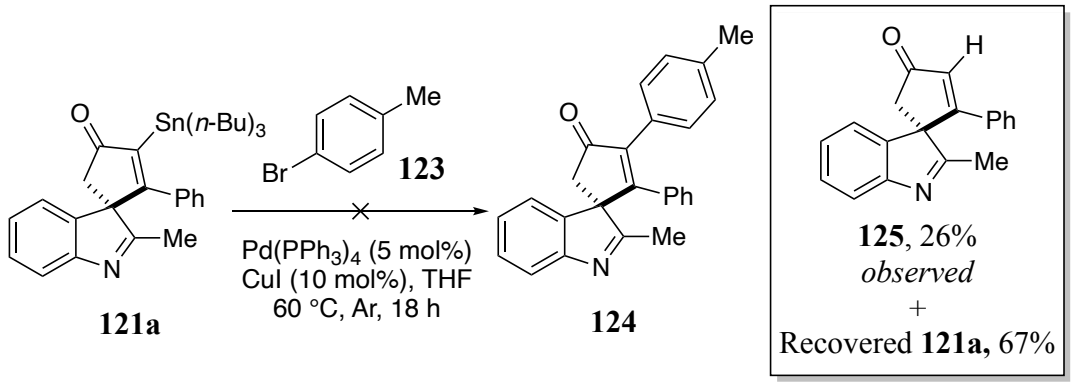
After developing two different modes of tributyltin radical generation, a small substrate study was carried out using the visible-light-mediated conditions, as they are milder, and avoid the use of toxic benzene and explosive AIBN (Scheme 52; note the organic reagent and products are highly toxic so special care was taken when performing these reactions). The three reactions performed led to formation of the corresponding spirocycles **121a** – **121c** in moderate yields.





Scheme 52. Substrate study

The stannylated product **121a** was then tested as a substrate for a Stille cross-coupling reaction. Stannylated spirocycle **121a** was reacted with *p*-bromotoluene **123** in the presence of $Pd(PPh_3)_4$ and CuI in THF at 60 °C (Scheme 53). However, the reaction failed to form the desired product **124** and instead gave only recovered spirocycle **121a** and destannylated product **125**.

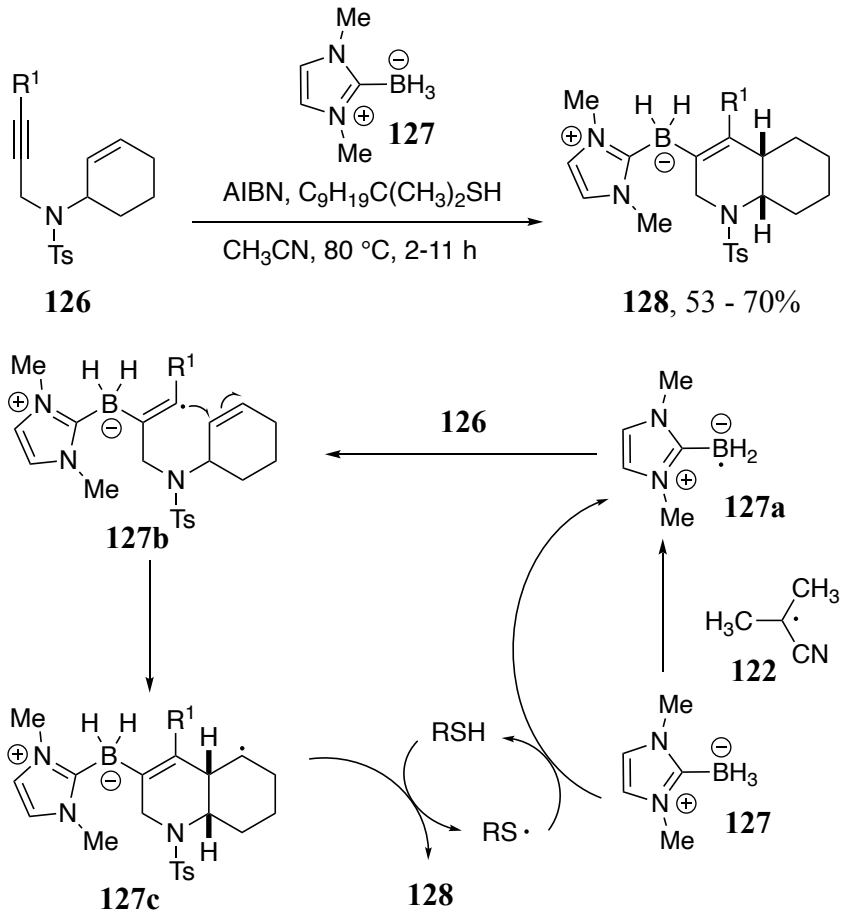


Scheme 53. Stille cross coupling reaction

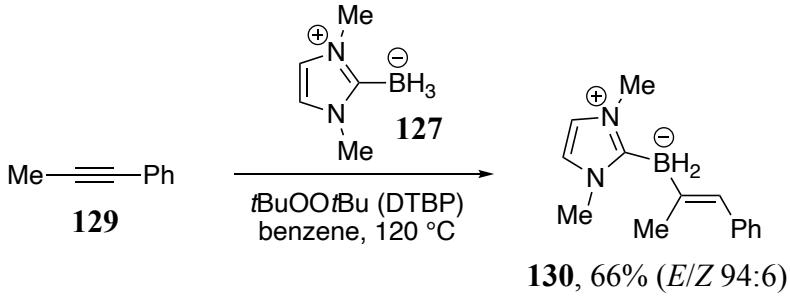
3.7 Borylation

In pursuit of another functionality that could be used in a cross-coupling reaction post spirocyclisation, we turned our attention towards the use of boron compounds as the radical partner for the cascade reaction. Following a literature review, *N*-heterocyclic carbene (NHC) borane was introduced as a reactive borane, which could be used to generate boryl radicals.[65] For example, Ren and co-workers reported the borylation cyclisation cascade of 1,6-enyne **126** to afford heterocycle **128** in moderate yields (Scheme 54a).[66] This work introduced NHC borane **127**, which could be used to access NHC-boryl radical **127a**. Next, NHC-boryl radical **127a** reacted with alkyne **126** to form vinyl radical **127b**, followed by *6-exo-dig* ring closure to afford intermediate **127c**. Then, hydrogen atom transfer between intermediate **127c** and the thiol compound provided bicyclic product **128**. In addition, Shimoi and co-workers also reported borylation of alkyne **129** via a radical process using NHC-borane **127** to form borylated product **130** (Scheme 54b).[67] With the reactivity of NHC-borane **127** well-documented in the literature, this borane species was chosen to be tested with our indole-tethered ynone system.

a)



b)

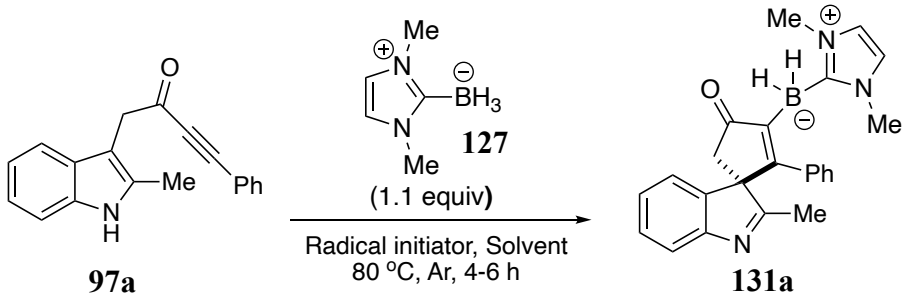


Scheme 54. Borylation using NHC borane **127** via radical processes

3.7.1 Reaction optimisation

Reaction optimisation for the borylation cascade began by examining the reaction between ynone **97a** and NHC-borane **127** based on literature precedent. First, AIBN (0.2 equiv.) was examined as an initiator in the presence of *tert*-dodecanethiol (0.5 equiv.), which formed borylated spirocycle **131a** in 33% yield (Table 7, entry 1). The

addition of tris(trimethylsilyl)silane (TTMSS) into the solution of ynone **97a** instead of *tert*-dodecanethiol resulted in an increased yield of spirocycle **97a** to 51% yield (entry 2). However, such additives were deemed unnecessary as the yield of spirocycle could be increased to 80% by increasing the equivalents of AIBN (1.1 equiv., entry 3). Next, ynone **97a** and NHC-borane **127** were also tested with 1,1-azodi(hexahydro-benzonitrile) (ACCN) as an initiator instead of AIBN (entries 5 – 7). The results showed that the addition of ACCN also provided spirocycle **131a** in good yields (65 – 85%), but they were slightly less than using AIBN.



Entry	radical initiator (equiv.)	Additive (equiv.)	Solvent (M)	yield of 131a (%)[a]
1	AIBN (0.2)	*tert*-dodecanethiol (0.5)	toluene (0.10)	33
2	AIBN (0.5)	TTMSS (1.0)	benzene (0.10)	51
3	AIBN (1.1)	-	benzene (0.13)	88 (80)[d]
4	AIBN (1.1)	-	MeCN (0.13)	70
5	ACCN (1.1)	-	benzene (0.13)	85
6[c]	ACCN (1.3)	-	benzene (0.13)	74
7[d]	ACCN (1.5)	-	benzene (0.13)	65

*[a] All reactions were performed with 0.30 mmol of ynone **97a**.*

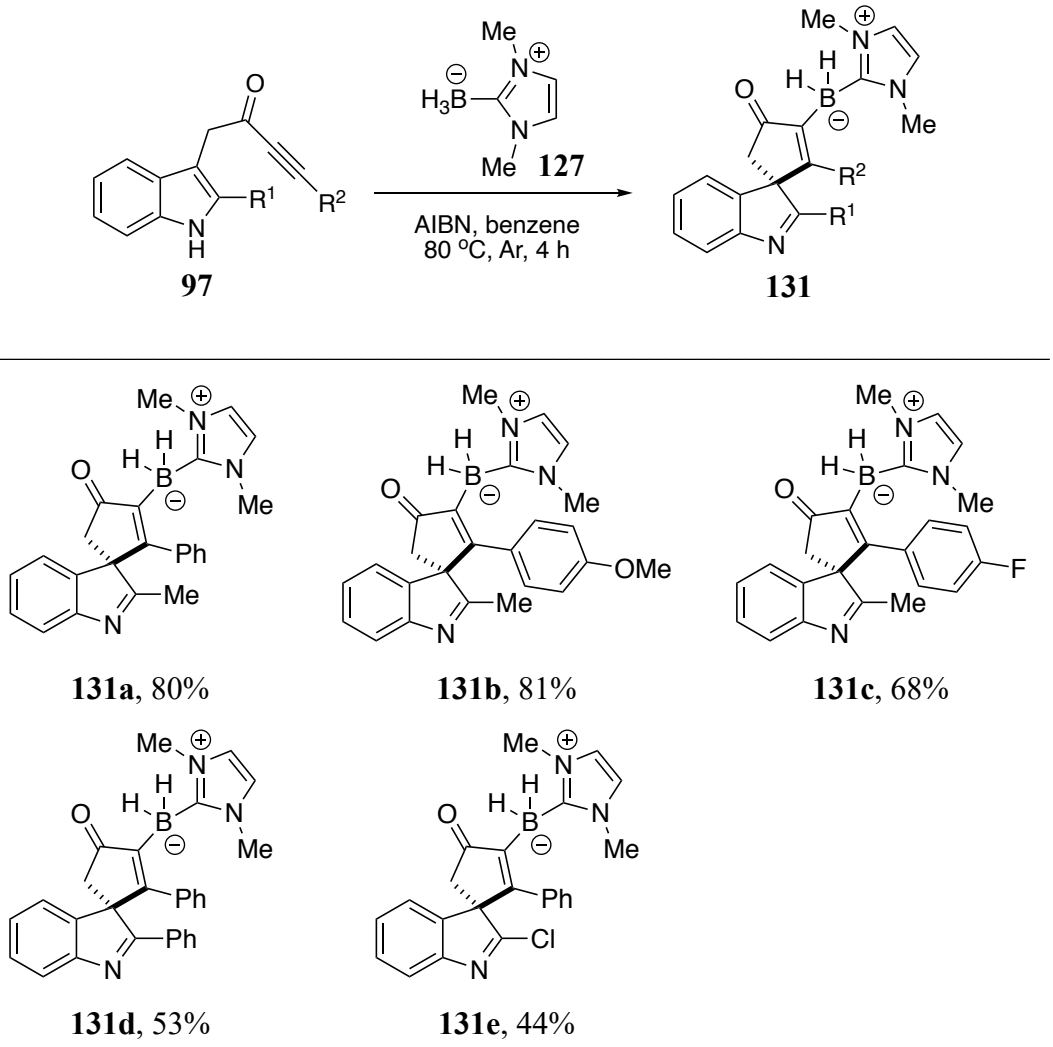
[b] Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard; isolated yield is shown in parentheses.

*[c] 1.3 equiv. of NHC-borane **127**. [d] 1.5 equiv. of NHC-borane **127**.*

Table 7. Reaction optimisation of borylation with NHC-borane **127**

3.7.2 Substrate study

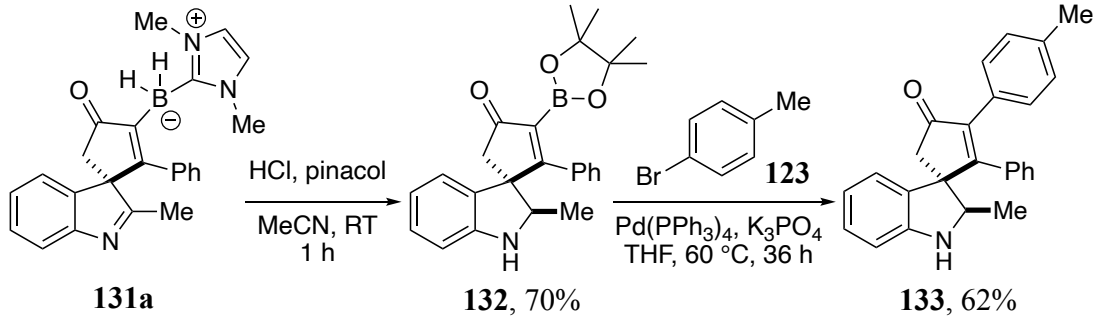
As before, other indolyl ynones **97** were then reacted under the developed conditions (Scheme 55). The results revealed that indole-tethered ynones could be successfully converted into the corresponding borylated ynones **131a** – **131e** in 44% to 81% yields. Pleasingly, C2-chloro spirocyclic indolenine **131e** was also compatible with this method.



Scheme 55. Substrate study of radical borylation process

To utilise the borylated product, spirocycle **131a** was reacted with pinacol under acidic conditions, leading to its conversion into pinacol ester **132** in 70% yield. Interestingly, BPin formation was accompanied by the reduction of the indolenine C=N bond to form indoline **132** (Scheme 56). The relative configuration of spirocycle **132** was confirmed

by a NOESY experiment (Figure 10). Finally, Suzuki cross-coupling between pinacol ester **132** and 4-bromotoluene **123** was performed using $Pd(PPh_3)_4$ and K_3PO_4 in THF to form the arylated product **133** in 62% yield.



Scheme 56. Transformation of borylated product **131a**

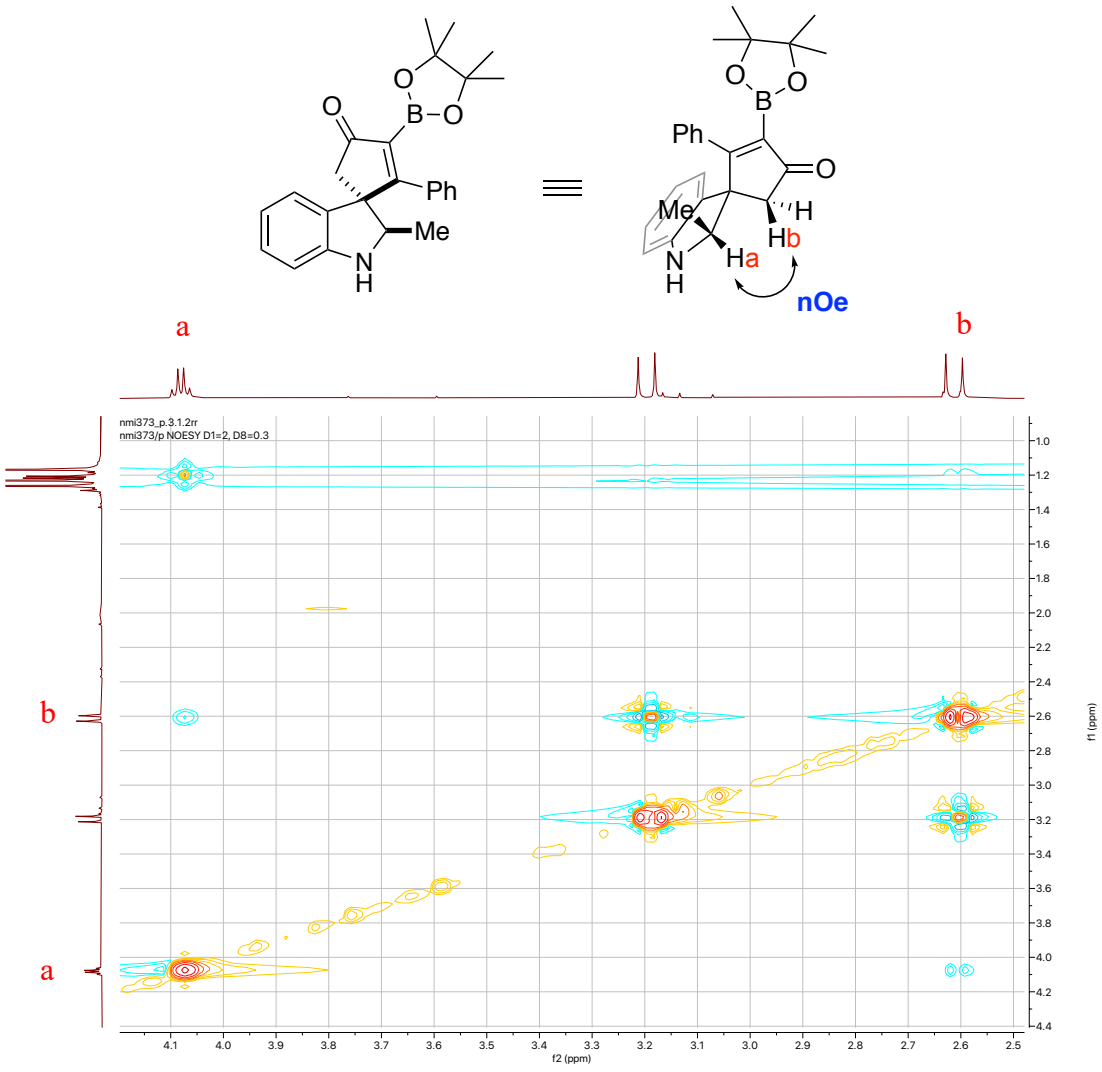
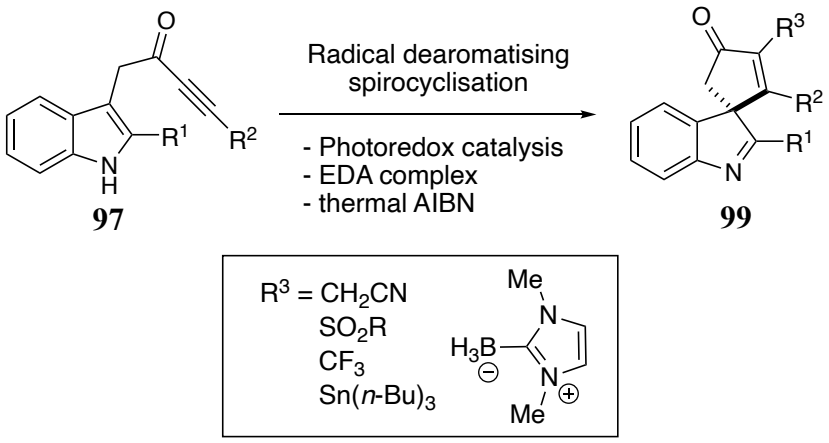


Figure 10. Stereochemistry determination of spirocycle **132**

3.8 Chapter summary

In this Chapter, indole-tethered ynones were successfully explored as substrates for radical-based dearomatising spirocyclisation cascade reactions. The synthetic protocols for cyanomethylation, sulfonylation and trifluoromethylation were developed using photoredox catalysis. These approaches were carried out under mild conditions and were simple to perform. Indole-tethered ynones also showed initiate photochemical reactivity, leading to the development of photocatlyst-free conditions for stannylation. Finally, borylation between indole-tethered ynones and NHC-borane was initiated by the classical thermolysis of AIBN.



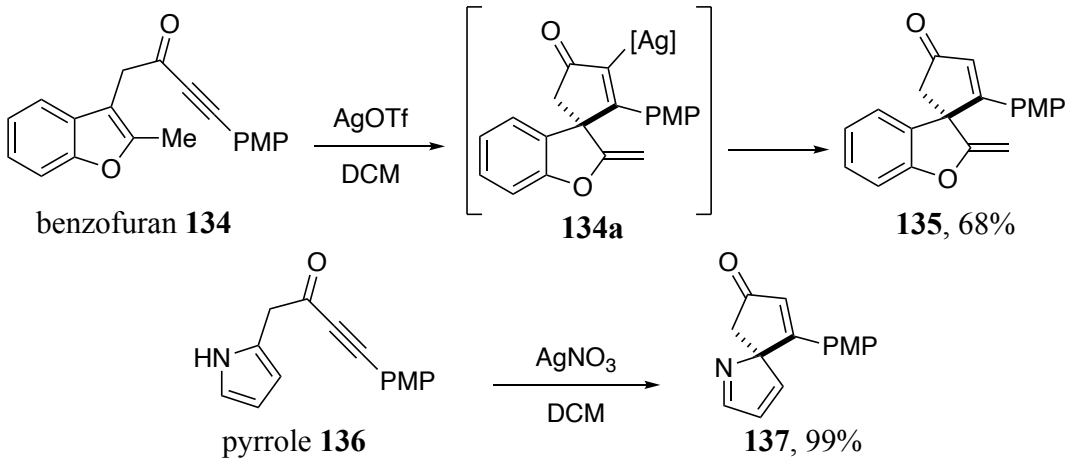
Scheme 57. Chapter 3 summary

Chapter 4: Radical Dearomatising Spirocyclisation Cascade with Benzisoxazole-tethered Ynones

4.1 Introduction

In the previous Chapters, research focused on the reaction of indole-tethered ynones. In this Chapter, the aim was to explore radical-based spirocyclisation reactions of other classes of heterocycle-tethered ynones. There are a few examples of non-radical reactions with different heterocycle-tethered ynones in two-electron spirocyclisation and annulation reactions.[68] For example, Unsworth and co-workers reported the silver-catalysed spirocyclisation of benzofuran/pyrrole-tethered ynones **134** and **136** (Scheme 58a).[41] These Ag(I)-catalysed reactions allowed spirocycles **135** and **137** to be prepared in good and excellent yields. After that, Mehta and co-workers demonstrated that furan/thiophene-tethered ynones **138** and **140** could be converted into benzofuran **139** and benzothiophene **141** via a Michael addition and 6π electrocyclisation benzannulation cascade (Scheme 58b).[69]

a)

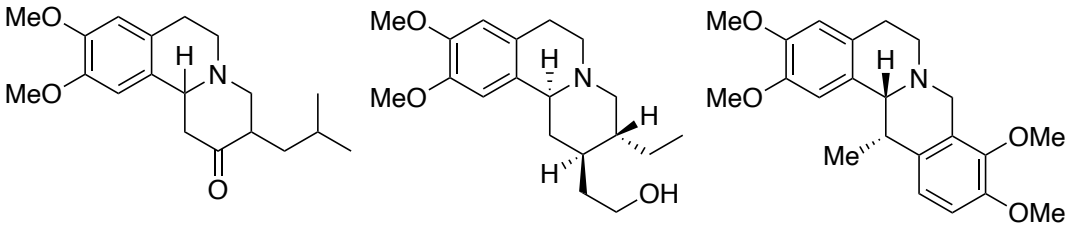


b)

Scheme 58. Previous reactions of heterocycle-tethered ynones

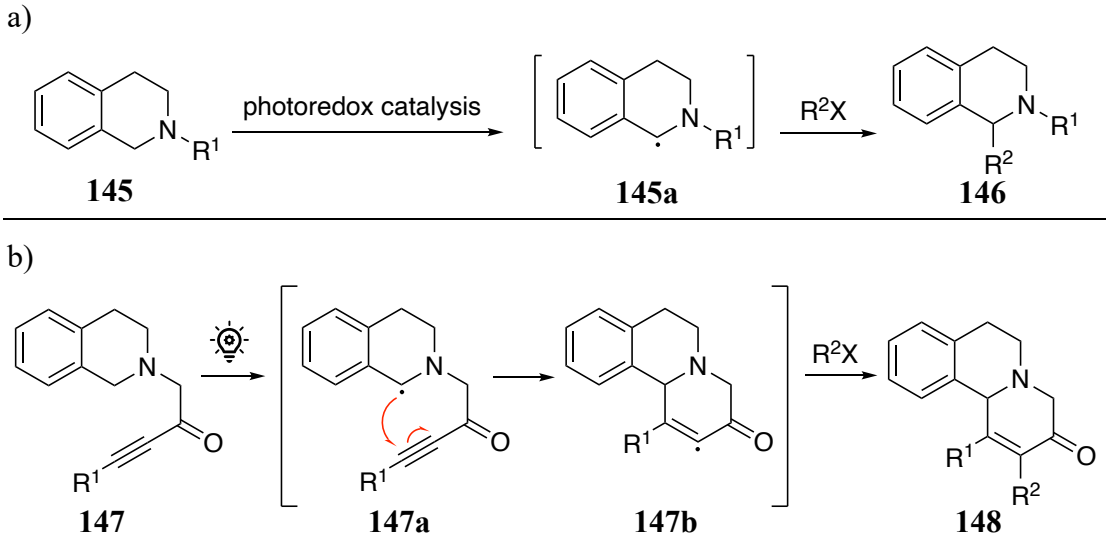
4.2 Heterocycle ynone screening

The first substrate class targeted was based on tetrahydroisoquinoline.[70, 71] The tetrahydroisoquinoline core is an essential part of drugs and natural product compounds such as tetrabenazine **142**, protoemitinol **143** and corydaline **144** (Figure 11). It has been reported that by using photoredox catalysis, α-amino radicals **145a** can be generated from isoquinoline substrates **145** (Scheme 59a).[23, 72-75] These α-amino radicals can be used to form functionalised tetrahydroisoquinoline analogues **146**. With this work in mind, it was planned to use tetrahydroisoquinoline ynone **147** as a substrate for a novel cascade reaction (Scheme 59b). It was envisaged that ynone **147** could be converted into α-amino radical **147a** and afford a tricyclic fused ring **147b** via a *6-endo-dig* cyclisation, which would afford tetrahydroisoquinoline analogue **148** following further functionalisation.



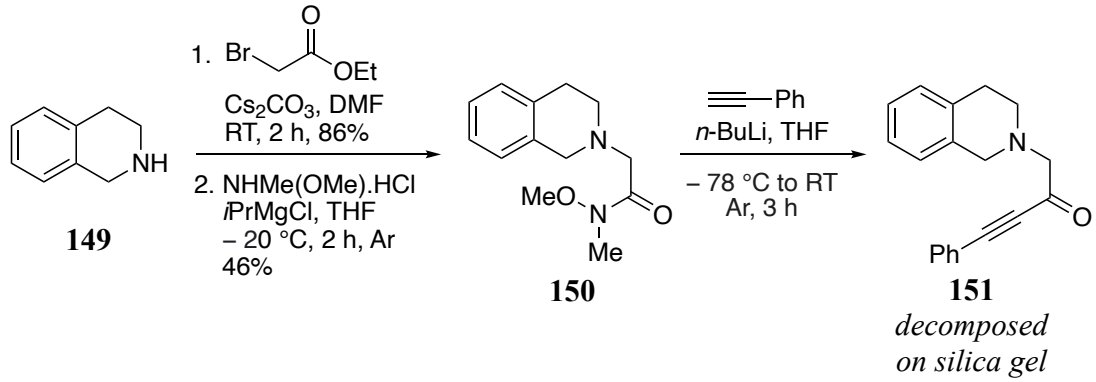
tetrabenazine **142** protoemetinol **143** corydaline **144**

Figure 11. Bioactive tetrahydroisoquinolines



Scheme 59. Project aim of *6-endo-dig* cyclisation via an α-amino radical intermediate

The preparation of tetrahydroisoquinoline-tethered ynone **151** started with *N*-alkylation between commercially available 1,2,3,4-tetrahydroisoquinoline **149** and ethylbromo acetate in the presence of Cs_2CO_3, followed by amide formation by using *N*,*O*-dimethylhydroxylamine hydrochloride and *i*PrMgCl to afford Weinreb amide **150** in 46% yield (Scheme 60). Weinreb amide **150** was then reacted with lithium phenylacetylide to form an unstable material presumed to be tetrahydroisoquinoline-tethered ynone **151**. However, this material rapidly decomposed during purification on silica gel and could not be isolated. Therefore, further studies with ynone **151** were discontinued due to its poor stability.



Scheme 60. Synthesis of tetrahydroisoquinoline-tethered ynone

The project was then switched to focus on another class of heterocycle. It was postulated that benzisoxazoles could be viable substrates as they share closer structural similarity to indoles. In addition, benzisoxazoles are an important class of compounds in medicinal chemistry. Some benzisoxazole analogues possess interesting biological activities such as antibiotic, anti-HIV, anticonvulsant, antipsychotic, anti-Alzheimer and anticancer.[76-78] Figure 12 shows examples of commercially available drugs in this class. Through this study, it was hoped to create a new synthetic methodology that could generate a library of spirocycles beneficial for organic and medicinal chemistry. We envisioned using benzisoxazole-tethered ynone **155** in radical cascade reactions, via dearomatising spirocyclisation, to access unusual spirocyclic products like compound **156** (Scheme 61).

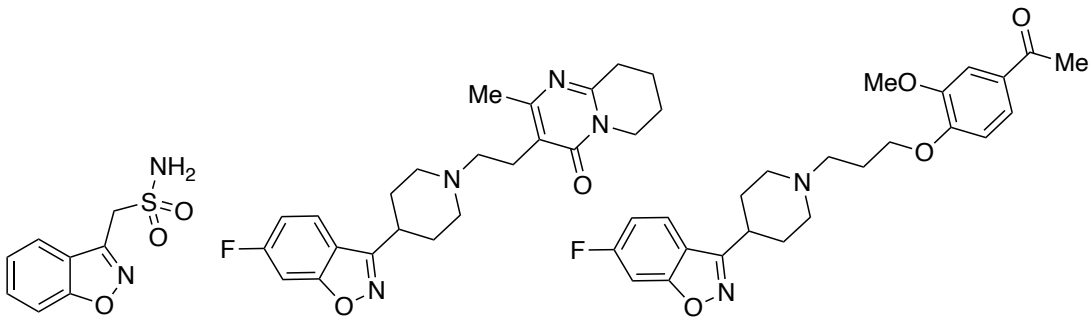
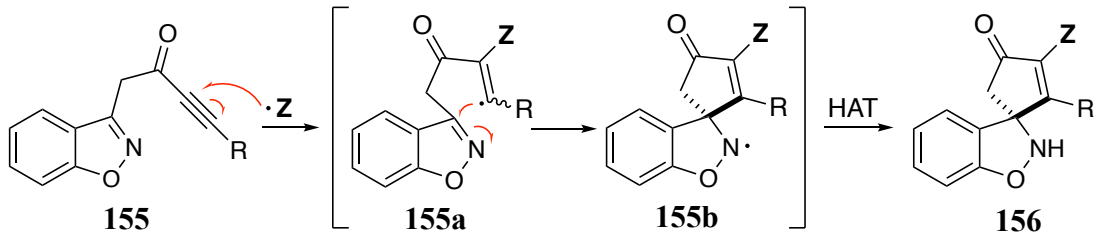
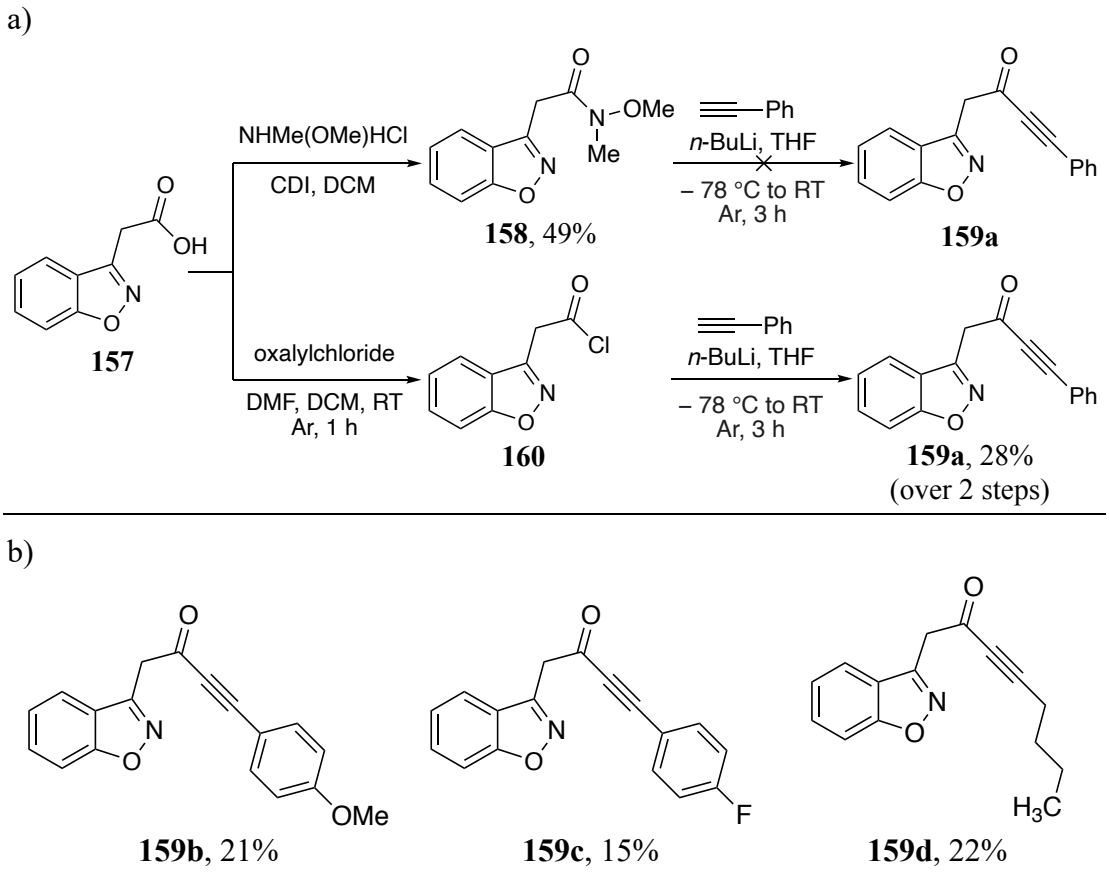


Figure 12. Benzisoxazole drugs



Scheme 61. Proposed two-step synthesis of spirobenzisoxazoles via a radical chain reaction

Synthesis of the required starting material for this project started from the conversion of commercially available benzoisoxazole **157** into Weinreb amide **158** in 49% yield (Scheme 62a). Weinreb amide **158** was then reacted with lithium phenylacetylide, but no conversion of the starting material was observed. Therefore, in an attempt to increase the reactivity of the carboxylic acid derivative, benzisoxazole **157** was reacted with oxalyl chloride in the presence of DMF in catalytic amount to form acid chloride **160** (Scheme 62b). Acid chloride **160** was then reacted with lithium phenylacetylide to form the desired benzoisoxazole-tethered ynone **159a** in 28% yield over 2 steps. By varying the lithium arylacetylide, products **159b** and **159c** were also obtained in 21% and 15% yields, respectively. Moreover, acid chloride **160** was also reacted with the lithium alkylacetylide, which afforded the corresponding ynone **159d** in 22% yield. None of these yields were as high as hoped for, but they were sufficient to provide enough material to progress the project and study the subsequent radical spirocyclisation reactions.

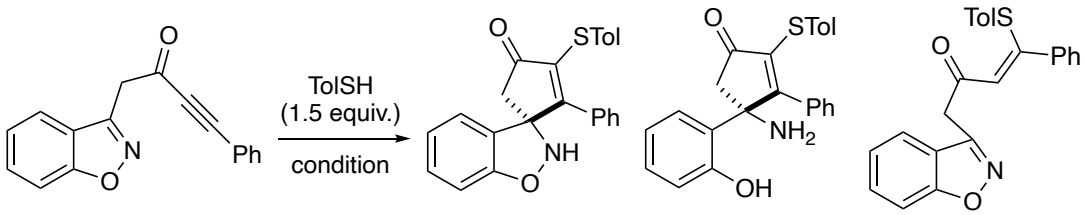


Scheme 62. Substrate synthesis: benzoisozaxole-tethered ynones

4.3 Reaction observation and optimisation

Studies into the reactivity of benzoisozaxole-tethered ynone **159a** as a substrate for radical-based spirocyclisation began using a thiol reagent. First, applying the conditions developed in Chapter 2, ynone **159a** was reacted with *p*-toluenethiol (TolSH) in DCE at RT for 21 hours under irradiation with blue LEDs (Table 8, entry 1).[44] This led to the conversion of ynone **159a** into spirocycle **161a** in 36% yield and amino alcohol **162a** in 34% yield, with the alcohol presumed to derive from reductive N–O bond cleavage.[79-82] Switching DCE to MeCN, the reaction gave spirocycle **161a** in a trace amount, amino alcohol **162a** in 8% yield and thiol conjugated addition product **163a** in 53% yield (entry 2). However, when reacted at 60 °C in the absence of blue light, these conditions promoted full conversion of the ynone into spirocycle **161a**, which demonstrated that blue LEDs were unnecessary for the transformation (entry 3). A small solvent screen under thermal conditions was carried out (entries 4 – 6), which revealed that DCE worked best. To further investigate the reactivity of ynone **159a** with *p*-toluenethiol, the reaction was tested with the addition of 1 equiv. of Et_3N

(entry 7), which switched the selectivity, with the unwanted conjugate addition product **163a** formed in 95% yield (see Scheme 63 below for a mechanism).[83] Then, a radical trapping experiment was tested by adding 1 equiv. of TEMPO into the reaction (entry 8). Interestingly, the spirocyclic product **161a** was not observed, but the conjugate addition product **163a** was isolated in 83% yield instead. Moreover, a TEMPO-sulfinamide adduct was detected by HRMS;[84] both of these observations suggest that the reaction operates via a radical process. The addition of 9,10-dihydroanthracene (DHA), which is a strong hydrogen donor, inhibited the formation of spirocycle **161a** (entry 9).[85] Finally, the reaction performed under air afforded spirocycle **161a** in quantitative yield; this shows that the reaction is not sentitive to oxygen, and indeed based on the proposed mechanism (see later, Scheme 71) oxygen is thought to be beneficial in the reaction by facilitating thiyl radical formation (entry 10).



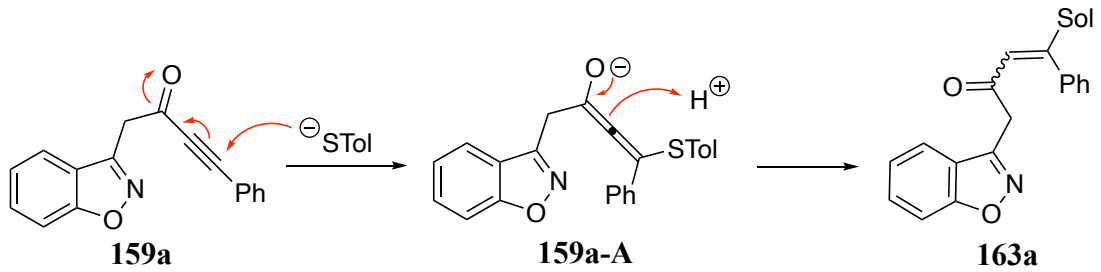
159a **161a** **162a** **163a**

Entry	Reaction condition	161a	162a	163a
1	DCE (0.1 M), Ar, RT, 21 h, Blue LEDs	36%	34%	-
2	MeCN (0.1 M), Ar, RT, 24 h, Blue LEDs	trace	8%	53%
3	DCE (0.1 M), Ar, 60 °C, 20 h	100%	-	-
4	MeCN (0.1 M), Ar, 60 °C, 20 h	4%	11%	65%
5	THF (0.1 M), Ar, 60 °C, 20 h	42%	18%	-
6	Toluene (0.1 M), Ar, 60 °C, 20 h	85%	4%	-
7	DCE (0.1 M), Et_3N (1.0 equiv), Ar, 60 °C, 20 h	-	-	95%
8	DCE (0.1 M), TEMPO (1.0 equiv), Ar, 60 °C, 20 h	-	-	83%
9	DCE (0.1 M), DHA (1.0 equiv), Ar, 60 °C, 20 h	trace	-	35%
10	DCE (0.1 M), air, 60 °C, 20 h	100%	-	-

*[a] All reactions were performed with 0.20 mmol of ynone **159a**.*

[b] Yield determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.

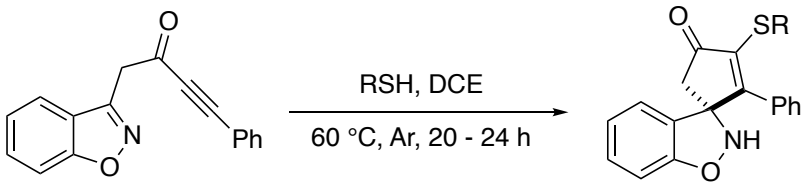
Table 8. Reaction optimisation of thiyl radical mediated spirocyclisation



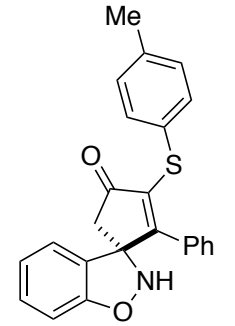
Scheme 63. Formation of conjugate addition product **163a**

4.4 Substrate study

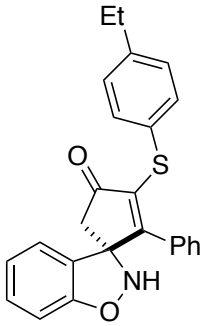
Following optimisation, an exploration of the reaction scope began by testing a range of aromatic thiols (Scheme 64). Alkylated thiophenols reacted smoothly with ynone **159a**, furnishing spirocycles **161a** – **161f** in excellent yields ranging from 97% to 100%. The electron-rich thiophenols were then tested, which also provided spirocycles **161g** – **161i** in very good yields in most cases. The yield of spirocycle **161i** was comparatively low compared to the others, likely caused by the higher polarity of this compound and associated loss of material during the purification process. Then, halogenated thiophenols were reacted with ynone **159a** and used to form the desired products **161j** – **161l** in 80 – 97% yield. Pleasingly, the structure of spirocycle **161l** was also definitively confirmed by X-ray crystallography (Figure 13).[86]



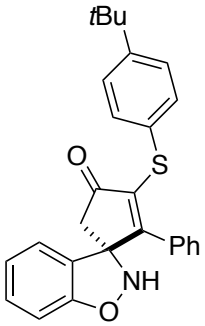
159a **161a - 161l**



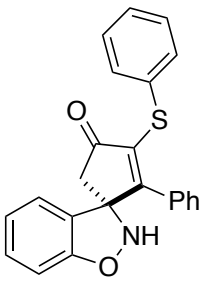
161a, 100%



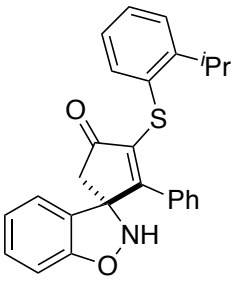
161b, 98%



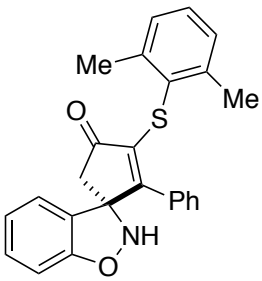
161c, 99%



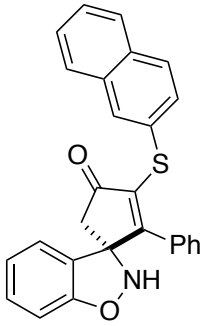
161d, 100%



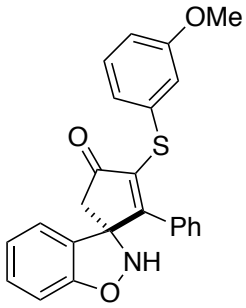
161e, 98%



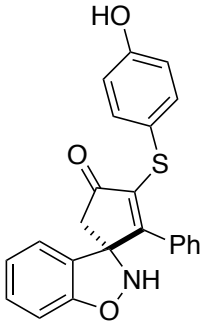
161f, 97%



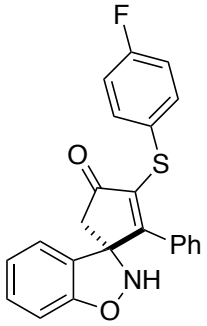
161g, 100%



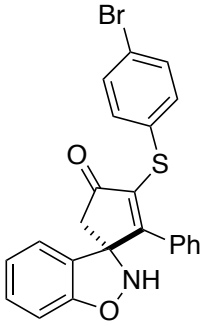
161h, 90%



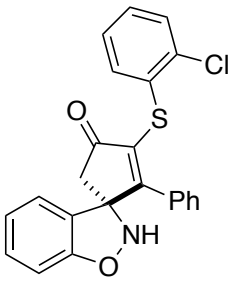
161i, 71%



161j, 87%



161k, 80%



161l, 97%

Scheme 64. Thiol substrate scope

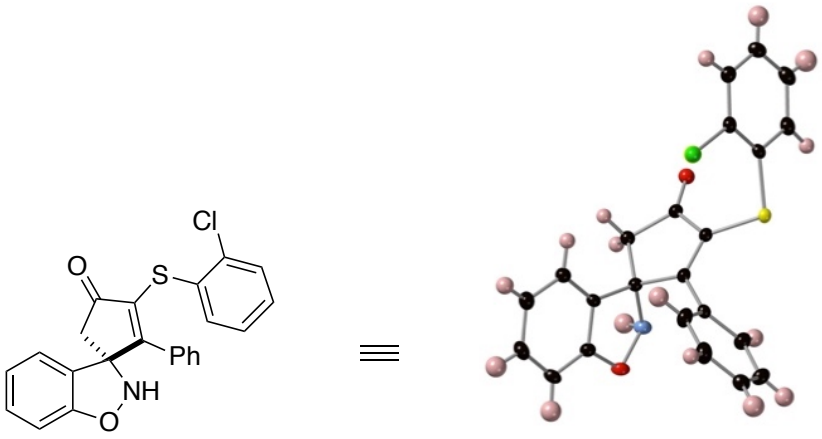
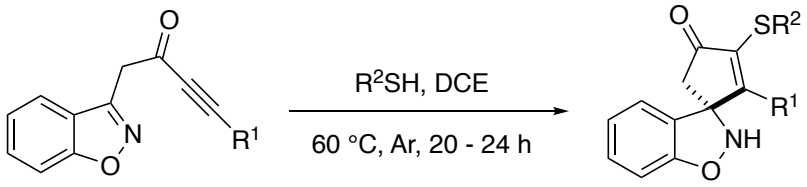
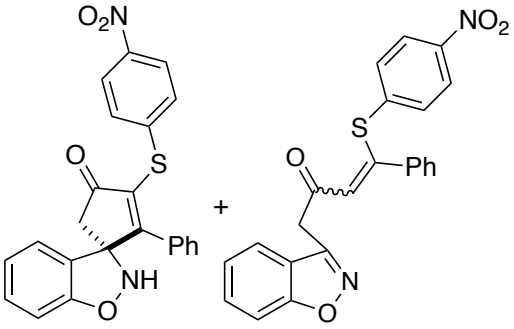


Figure 13. X-ray structure of spirocycle **161l** with the thermal ellipsoids 50% (CCDC 2257467)

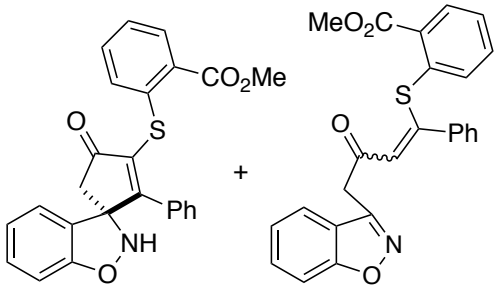
Continuing the substrate scope study, ynone **159a** was tested with more acidic thiols (Scheme 65). First, the treatment of 4-nitrothiophenol gave a desire product **161m** in only 28% yield, along with an unwanted conjugate addition product **163m** in 59% yield. In the same fashion, methyl thiosalicylate also provided a desired product **161n** in 22% yield together with the conjugate addition product **163n** in 75% yield. This problem was not encountered with 1,4-benzenedithiol which delivered spirocycle **161o** in 88% yield (*dr* = 1:1) via reaction through both thiol groups. Next, other aryl ynones with different electronic properties (*e.g.* 4-methoxy and 4-fluoro groups) were reacted with thiophenol, which formed the corresponding spirocycles **161p** and **161q** in 100% and 87% yields, respectively. An aliphatic substituted ynone **159d** was also reacted with thiophenol, providing spirocycle **161r** in 38% yield. Finally, a range of aliphatic thiols (*e.g.* propanethiol, cyclohexylthiol and benzylmercaptan) were reacted with ynone **159a**. However, only traces or very low yields of the desired product spirocycles **161s** – **161u** were detected. These results indicate a limitation of the reaction, which currently is only compatible with aromatic thiols.



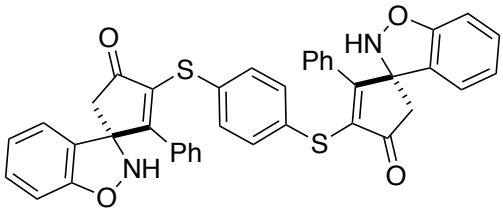
159a - 159d **161m - 161t**



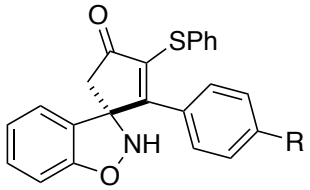
161m, 28% + **163m**, 59%



161n, 22% + **163n**, 75%

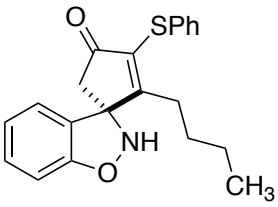


161o, 88% (*dr* = 1:1)

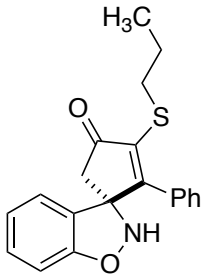


161p (R = OMe), 100%

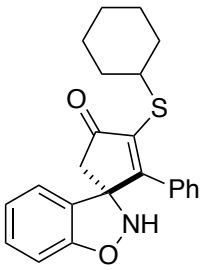
161q (R = F), 87%



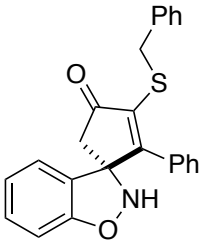
161r, 38%



161s, trace



161t, trace

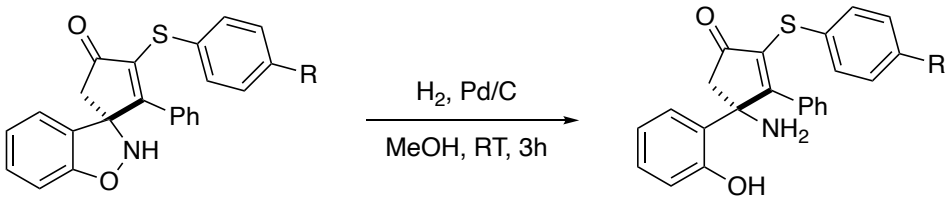


161u, trace

Scheme 65. Thiol substrate scope

4.5 Ring modification

As observed during the reaction optimisation (Table 8), amino alcohol spirocycle **162a** was formed and was considered likely to arise from the cleavage of the weak N–O bond. To turn this drawback into an advantage, spirocycle **161a** was reacted under hydrogenation condition. Hydrogenation worked smoothly and provided the desired amino alcohol product **162a** in quantitative yield (Scheme 66).[87] Additionally, hydrogenation of spirocycle **161k** also provided the corresponding amino alcohol **162k** in 95% yield. The structure of alcohol amino **162k** was confirmed by X-ray crystallography (Figure 14).[88]



161a (R = Me)
161k (R = Br)

162a (R = Me), 100%
162k (R = Br), 95%

Scheme 66. N–O bond cleavage by hydrogenation

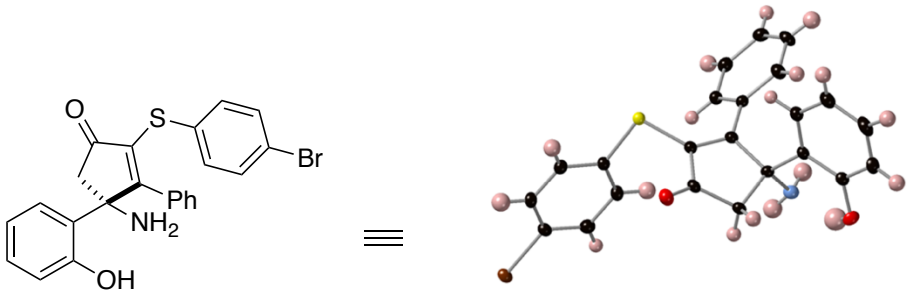
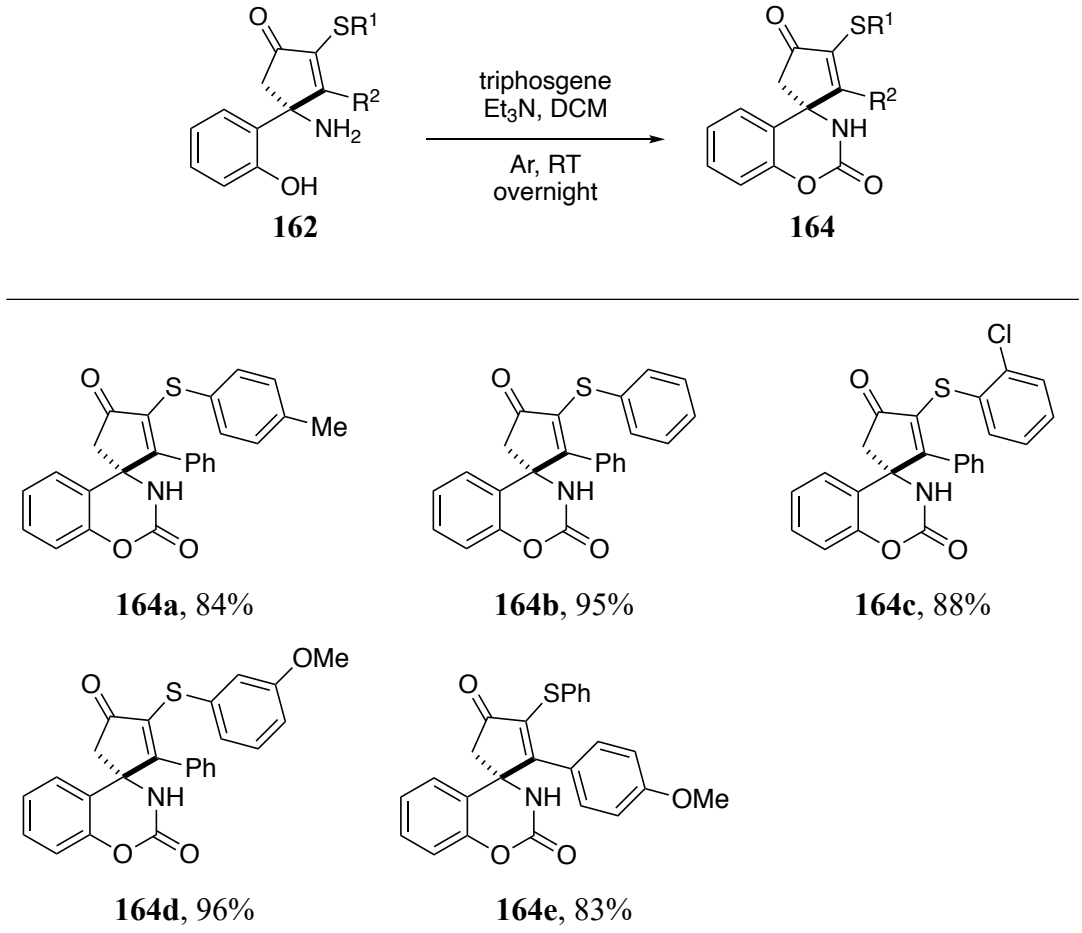


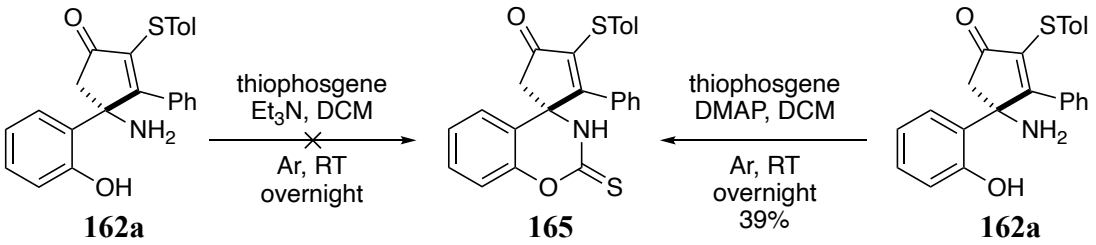
Figure 14. X-ray structure of alcohol amino **162k** with the thermal ellipsoids 50% (CCDC 2257468)

It was anticipated that amino alcohol **162a** would readily form new six-membered ring products following cyclisation with electrophilic reagents. First, amino alcohol **162a** was reacted with triphosgene and triethylamine (Et_3N) in DCM at RT;[89] these conditions afforded the corresponding cyclic carbamate **164a** in 84% yield (Scheme 67). Other amino alcohol products were also converted into cyclic carbamates **164b** – **164e** in excellent yields (83 – 96%) using these reaction conditions.



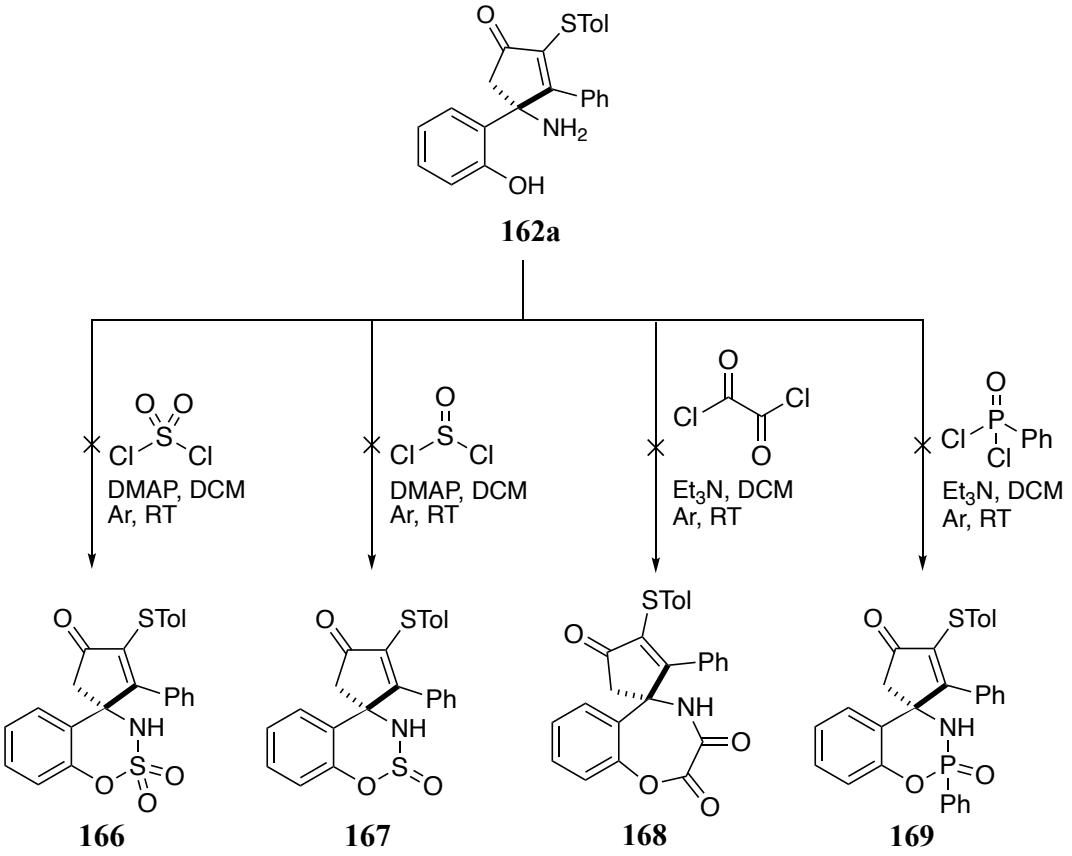
Scheme 67. Construction of cyclic carbamates

The reactivity of amino alcohol **162a** with other electrophilic reagents was then investigated in order to construct other six-membered ring adducts. Amino alcohol **162a** was therefore reacted with thiophosgene and triethylamine in DCM, but no cyclised product **165** was observed (Scheme 68). However, the desired product could be obtained by using DMAP instead of Et_3N,[90] which enabled amino alcohol **162a** to be converted into thiocarbamate **165** in 39% yield.



Scheme 68. Construction of cyclic thiocarbamate

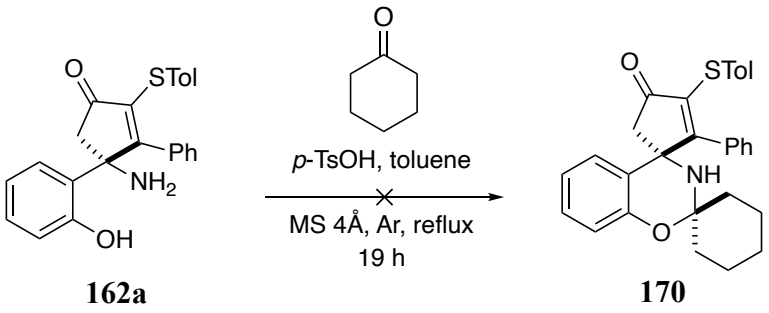
Amino alcohol **162a** was further reacted with other electrophilic species such as sulfuryl chloride, thionyl chloride, oxalyl chloride and phenylphosphonic dichloride under similar conditions (Scheme 69). However, formation of the desired products **166** – **169** was not observed.



Scheme 69. Expanding ring construction scope study

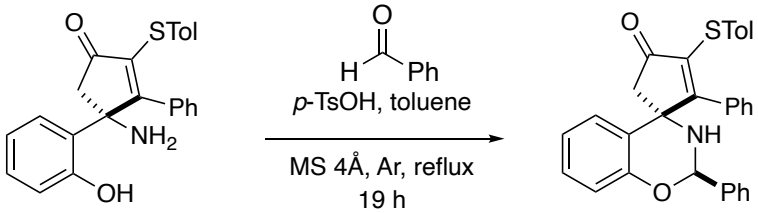
Finally, amino alcohol **162a** was envisioned to form other ring systems through condensation reactions. Amino alcohol **162a** was reacted with cyclohexanone in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene (Scheme 70a). However, the reaction failed to form spirocycle **170** after 19 hours. Therefore, to increase the reactivity of the condensation reaction, amino alcohol **162a** was then reacted with benzaldehyde (Scheme 70b),[91] leading to the formation of a desired product **171** in 65% yield (*dr* = 78:22). The major diastereoisomer was assigned by a NOESY experiment (Scheme 70c).

a)



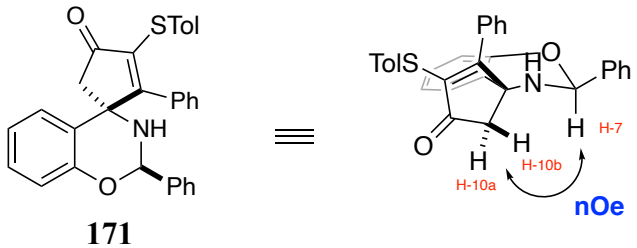
162a **170**

b)



162a **171**, 65%
dr = 78 : 22

c)

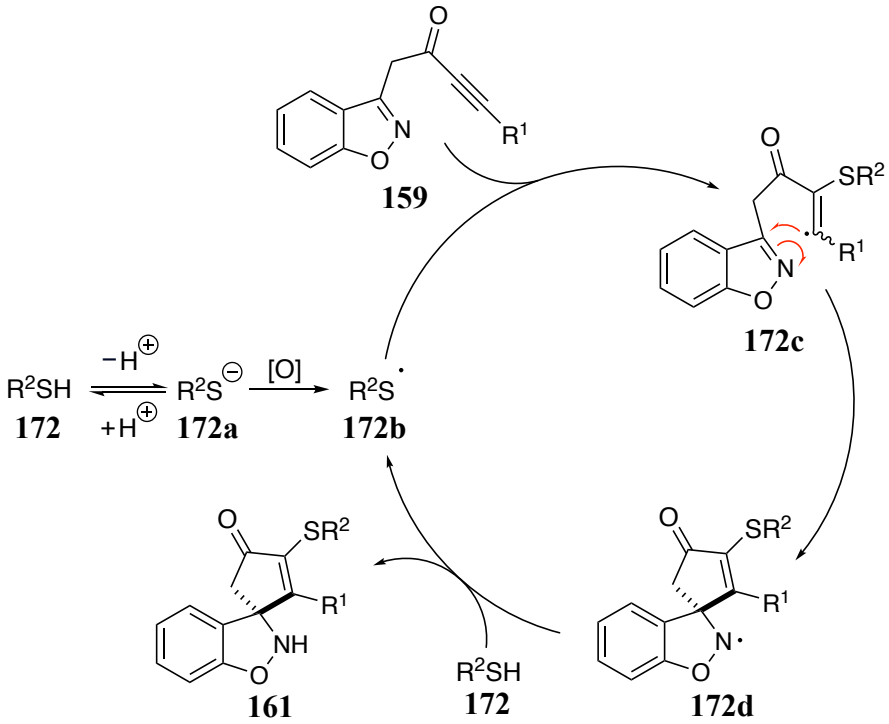


171

Scheme 70. Condensation reactions of amino alcohol **162a**

4.6 Proposed mechanism

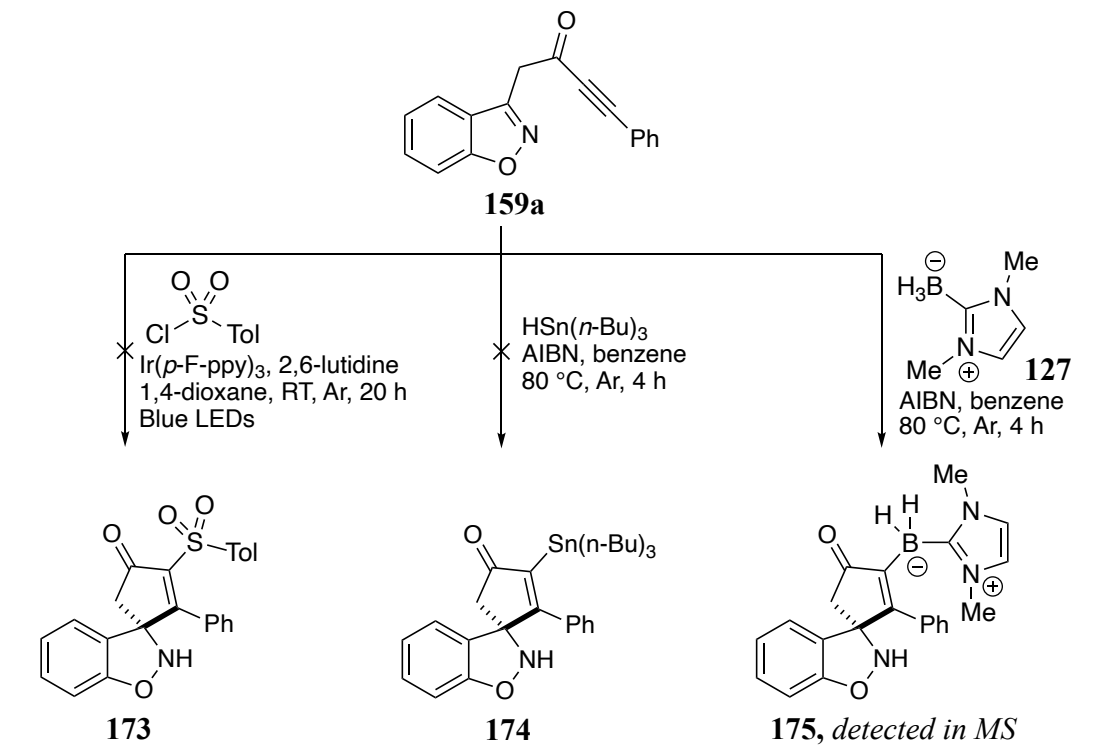
A plausible reaction mechanism for the radical dearomatising spirocyclisation cascade is proposed in Scheme 71.[92-94] First, thiyl radical **172b** is likely to be generated by the oxidation of a thiolate ion with adventitious oxygen.[95] Thiyl radical **172b** reacts with ynone **159** to furnish vinyl radical **172c**, which then undergoes dearomatising spirocyclisation and generates nitrogen-centred radical **172d**. Finally, HAT from the thiol reagent to intermediate **172d** forms the corresponding spirocycle **161**, whilst also generating a new thiyl radical **172b** to propagate a radical chain.

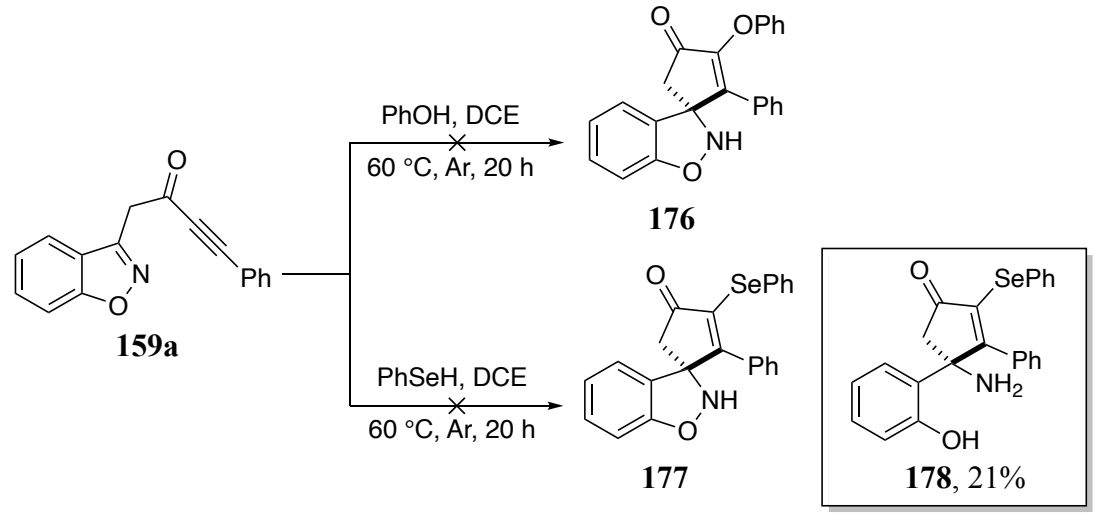


Scheme 71. Proposed mechanism via radical chain reaction

4.7 Other reactivities of benzisoxazole-tethered ynones

As indole-tethered ynones were shown to react with a number of different radical species in Chapter 3, the reactivity of benzisoxazole-tethered ynones with other radicals was then explored. Ynone **159a** was reacted under the various reaction conditions developed in Chapter 3, ranging from sulfonylation under photocatalysis, stannylation and borylation under thermal radical generation (Scheme 72a). However, none of the desired products **173**, **174** and **175** could be isolated. Then, phenol and selenophenol, which were expected to easily form oxyl and selenyl radicals like thiols, were reacted with ynone **159a**, but spirocycles **176** and **177** could again not be isolated (Scheme 72b). However, amino alcohol **178** was isolated in 21% yield suggesting that selenyl radicals may be compatible with benzisoxazole-tethered ynones. Finally, a brief investigation into the reactivity of ynone **159a** under silver-catalysed conditions was carried out (Scheme 72c).[41] Pleasingly, ynone **159a** performed very well forming the six-membered ring product **179** in 96% yield.



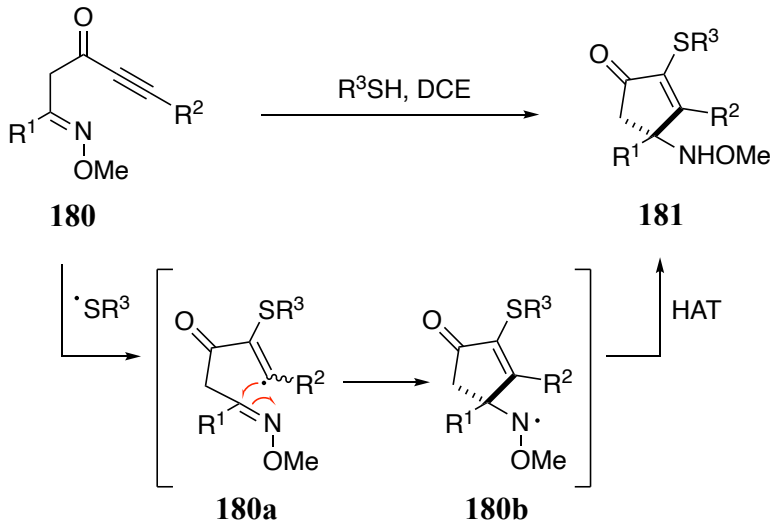


Scheme 72. Other reactivity observations of benzisoxazole-tethered ynones

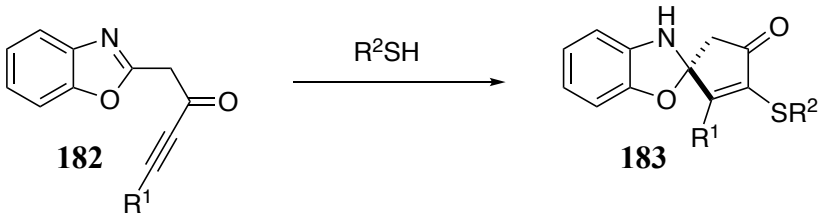
4.8 Future work

Inspired by the reactivity observed with benzisoxazole ynones, future studies could explore the use of oxime **180** as a substrate for the construction of cyclopentenone **181**, via radical cascade reaction (Scheme 73a). Further research could also be conducted to identify new heterocycle-tethered ynones such as benzoxazole-tethered ynone **182** and investigate the formation and utility of spirocycle products **183** (Scheme 73b).

a)



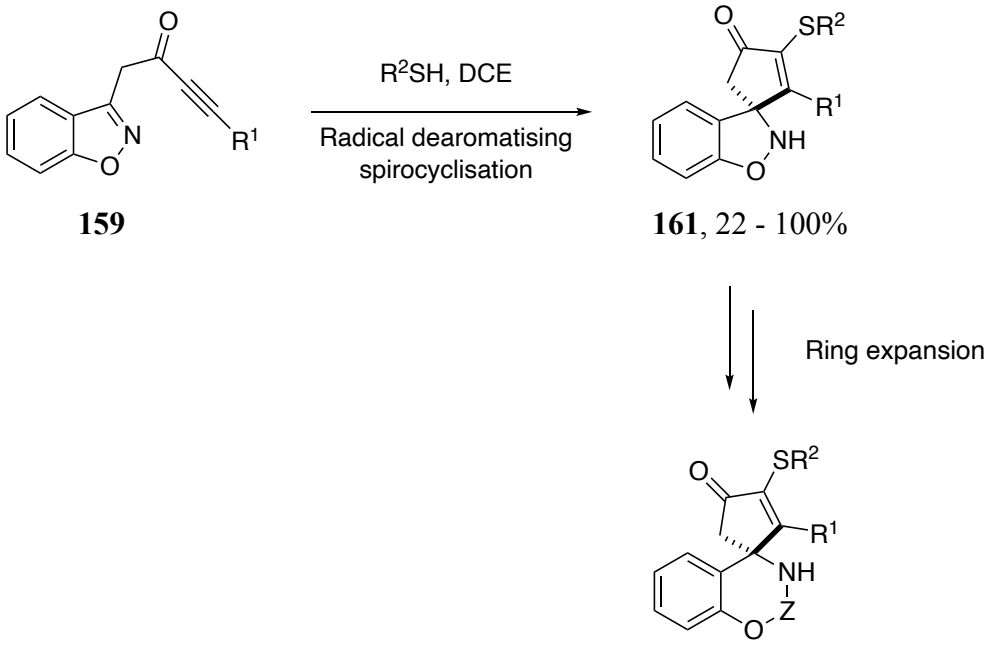
b)



Scheme 73. Future work suggestions

4.9 Chapter summary

In this chapter, a novel class of heterocycle-tethered ynones was introduced. Benzisoxazole-tethered ynones were used to form spirocycles via a thiyl radical-based chain reaction. The reaction conditions were notable for their simplicity and provided spirocycles in excellent yields in most cases. Moreover, the isoxazolidine ring could be modified via a two-step sequence, allowing access to new spirocyclic frameworks.



159 **161**, 22 - 100%

Scheme 74. Chapter 4 summary

4.10 Thesis summary

In conclusion, this thesis discussed cascade reactions of heterocycle-tethered ynones in three main chapters. In Chapter 2, the studies showed the reactivity between C-2 halo indole-tethered ynones and thiol reagents for thiol-mediated cascade reaction. The reaction could provide functionalised quinolines in excellent yields in most cases under simple and mild reaction conditions. A reaction mechanism was investigated and proposed based on substrate studies, control experiments and previous reports. Moreover, an unexpected product, thio-oxindole, was discovered by serendipity leading to a novel method for the synthesis of thio-oxindole frameworks. This work was published in *Organic Letter* and shown in Appendix I.

In Chapter 3, the studies continuously investigated the reactivity of indole-tethered ynones. The radical-based dearomatising spirocyclisation cascade reactions were developed for different synthetic protocols; cyanomethylation, sulfonylation, trifluoromethylation, stannylation and borylation; by using photoredox catalysis, EDA complex and thermolysis of AIBN. A reaction mechanism was investigated based on Stern-Volemer luminescence study. This work was published in *Organic Letter* and shown in Appendix II.

In Chapter 4, a new class of heterocycle-tethered ynone was introduced. Benzisoxazole-tethered ynones were initially examined with arylthiols, which led to the development of radical spirocyclisation cascade reaction. The optimised condition provided functionalised spirocycles in notable yields in most cases. In addition, the spirocyclic products were also converted into other classes of spirocyclic frameworks via a two-step synthesis. This work was published in *European Journal of Organic Chemistry* and shown in Appendix III.

Chapter 5: Experimental data

5.1 General Information

All reagents were purchased from commercial sources and purification. Anhydrous DCM, THF, MeCN, DMF and toluene were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Anhydrous DCE, 1,4-dioxane, benzene and MeOH were obtained from Sigma Aldrich. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR and ^{11}B{^{1}H} spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz, 100 MHz, 376 MHz and 128 MHz respectively. Additionally, ^{19}F NMR spectra were also recorded on a Bruker AVIII300NB or Bruker AVIIIHD500 spectrometer, operating at 282 MHz and 471 MHz respectively.

All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.16 for $CDCl_3$, δ_H 2.50 and δ_C 39.52 for DMSO-*d6* was 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, p pentet, sx sextet, br s broad singlet, br d broad doublet, br q broad quartet, dd doublet of doublets, ddd doublet of doublet of doublets, dt doublet of triplets, td triplet of doublets and m multiplet. Signal assignment was achieved by analysis of DEPT-135, COSY, HSQC and HMBC experiments where required.

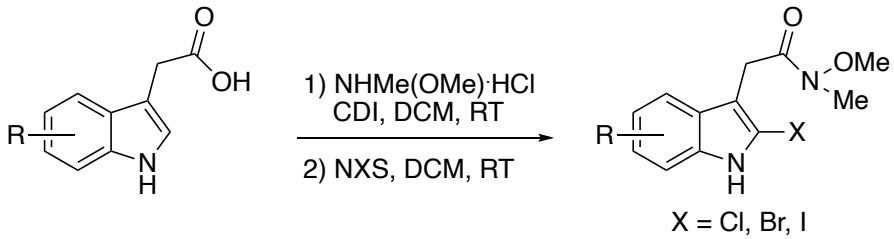
Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either DCM or $CDCl_3$. Mass spectra (high-resolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus.

Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Merck silica gel (SiO_2), 35 – 75 μm, 60 Å or Fuji Silysia

Chromatorex Silica gel (SiO_2), neutral MB100, 75- 200 μm, 100 Å, under a light positive pressure, eluting with the specified solvent system.

5.2 Experimental for Chapter 2

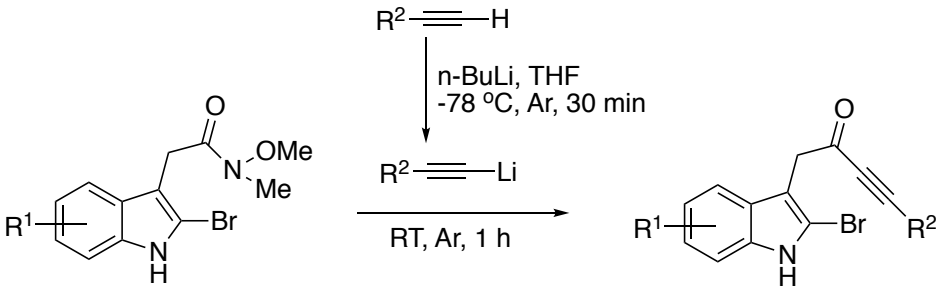
General Procedure A



To a suspension of carboxylic acid (1.00 mmol) in DCM (10 mL) at room temperature was added 1,1'-carbonyldiimidazole (1.20 mmol). A homogeneous solution quickly formed, and was stirred at RT for 30 mins, after which time *N*,*O*-dimethylhydroxylamine hydrochloride (1.20 mmol) was added and stirred for a further 2 h. The reaction mixture was then poured into water (10 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 then dried over anhydrous $MgSO_4$ and concentrated *in vacuo,* affording the Weinreb amide which was used without further purification.

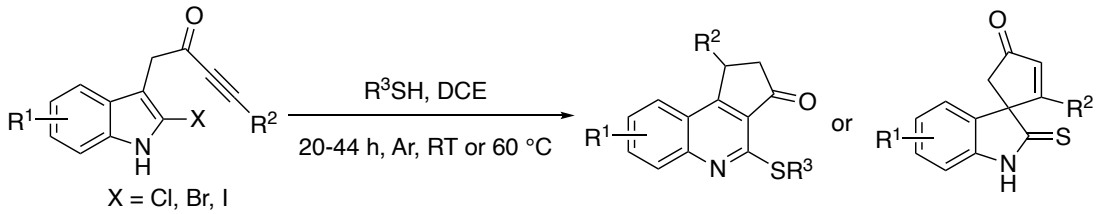
Then, to a stirred solution of Weinreb amide (1.00 mmol) in anhydrous DCM (10 mL) under argon atmosphere was added NXS (1.00 mmol) at 0 °C for 30 minutes. Then the mixture was filtered and concentrated by *vacuo*. The crude product was purified by flash column chromatography.

General Procedure B



To a stirred solution of alkyne (2.50 mmol) in THF (3 mL) in an oven-dried round-bottom flask at −78 °C under argon was added *n*-BuLi (1.00 mL, 2.5 mmol, 2.5 M in hexanes) dropwise. The resulting solution was stirred for 30 min at −78 °C. Next, the solution was transferred via cannula into another round-bottom flask containing a solution of Weinreb amide (1.00 mmol) in dry THF (10 mL) at −78 °C. Then, the mixture was warmed to room temperature and stirred for 1 hour. After the reaction was completed, it was quenched with sat. aq. NH_4Cl (20 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography.

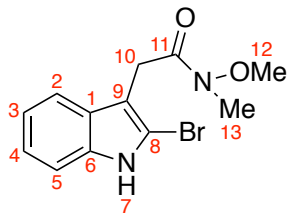
General Procedure C



To a solution of indolyl-ynone (0.20 mmol) in DCE (2 mL, 0.1 M) in a sealed vial was added thiol (0.32 mmol). Then, the vial was degassed with argon for 5 minutes. The solution mixture was stirred for 20 – 44 hours at room temperature or 60 °C in a heating block. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography.

Characterisation Data and Procedures

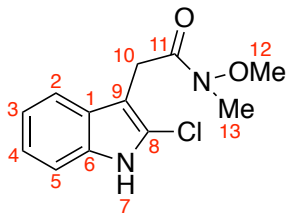
2-(2-Bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (80a)



Synthesized using **General Procedure A** with 2-(1*H*-indol-3-yl)acetic acid **79** (2.48 g, 14.1 mmol), 1,1'-carbonyldiimidazole (2.76 g, 17.0 mmol), *N*,*O*-dimethylhydroxyl amine hydrochloride (1.65 g, 1.70 mmol) and DCM (20 mL). Then, 2-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (0.50 g, 2.29 mmol), NBS (0.41 g, 2.29 mmol) and DCM (20 mL). Purification by flash column chromatography (hexane:EtOAc, 2:1 v/v) afforded the title product (0.35 g, 52%) as a yellow solid.

mp: 84 – 87 °C; $\mathbf{R_f}$ 0.35 (hexane: EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (1H, s, H-7), 7.63 – 7.56 (1H, m, H-2), 7.19 – 7.06 (3H, m, H-3,4,5), 3.88 (2H, s, H-10), 3.67 (3H, s, H-12), 3.22 (3H, s, H- 13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8 (C, C-11), 136.2 (C, C-6), 127.8 (C, C-1), 122.4 (CH, C-4), 120.3 (CH, C-3), 118.7 (CH, C-2), 110.6 (CH, C-5), 109.8 (C, C-8/9), 108.9 (C, C-8/9), 61.4 (CH_3, C-12), 32.5 (CH_3, C-13), 29.4 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{12}H_{13}{}^{79}BrN_2NaO_2$ 319.0053; Found 319.0047, $[M + H]^+$ Calcd for $C_{12}H_{14}{}^{79}BrN_2O_2$ 297.0233; Found 297.0227 ; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3244, 1640, 1450, 1425, 1338, 1176, 1001, 742.

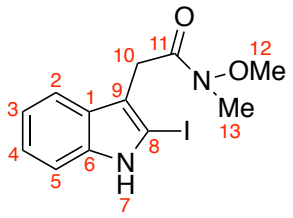
2-(2-Chloro-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (80b)



Synthesized using **General Procedure A** with 2-(1*H*-indol-3-yl)acetic acid **79** (2.48 g, 14.1 mmol), 1,1'-carbonyldiimidazole (2.76 g, 17.0 mmol), *N*,*O*-dimethylhydroxyl amine hydrochloride (1.65 g, 1.70 mmol) and DCM (20 mL). Then, 2-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (0.60 g, 2.75 mmol), NCS (0.37 g, 2.75 mmol) and DCM (20 mL). Purification by flash column chromatography (hexane:EtOAc, 1:1 v/v) afforded the title product (0.42 g, 61%) as a yellow solid.

R_f 0.40 (1:1 hexane: EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (1H, br s, H-7), 7.62 – 7.54 (1H, m, H-2), 7.16 – 7.05 (3H, m, H-3,4,5), 3.88 (2H, s, H-10), 3.67 (3H, s, H-12), 3.22 (3H, s, H-13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0 (C, C-11), 134.6 (C, C-6), 127.7 (C, C-1), 122.4 (CH, C-4), 122.3 (C, C-8), 120.4 (CH, C-3), 118.8 (CH, C-2), 110.7 (CH, C-5), 105.5 (C, C-9), 61.4 (CH_3, C-12), 32.5 (CH_3, C-13), 28.7 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{12}H_{13}{}^{35}ClN_2NaO_2$ 275.0558; Found 275.0556, $[M + H]^+$ Calcd for $C_{12}H_{14}{}^{35}ClN_2O_2$ 253.0738; Found 253.0737; **ν_{max}** (thin film)/cm^{-1} 3239, 2936, 1723, 1642, 1452, 1430, 1387, 1340, 1178, 1003.

2-(2-Iodo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (80c)

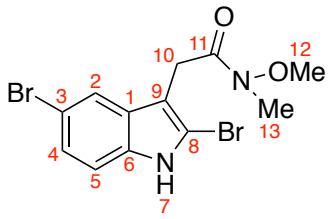


Synthesized using **General Procedure A** with 2-(1*H*-indol-3-yl)acetic acid **79** (2.48 g, 14.1 mmol), 1,1'-carbonyldiimidazole (2.76 g, 17.0 mmol), *N*,*O*-dimethylhydroxyl amine hydrochloride (1.65 g, 1.70 mmol) and DCM (20 mL). Procedure followed from

Ekebergh *et al.*[48] To a stirred solution of 2-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (0.60 , 2.75 mmol) and I_2 (0.68 g, 2.67 mmol) in anhydrous THF (10 mL) under argon atmosphere was added dropwise AgOTf (0.79 g, 3.07 mmol) in anhydrous THF under vigorous stirring. The mixture solution was stirred for 10 minutes and added $Na_2S_2O_3$ (20 mL). Then, it was extracted with EtOAc (20 mL × 3). The organic layer was combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated by *vacuo*. The crude product was purified by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title product (0.59 g, 62%) as a yellow solid.

mp: 126 – 128 °C; **R_f** 0.65 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (1H, br s, H-7), 7.64 – 7.58 (1H, m, H-2), 7.09 – 7.02 (3H, m, H-3,4,5), 3.89 (2H, s, H-10), 3.65 (3H, s, H-12), 3.22 (3H, s, H-13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.0 (C, C-11), 138.9 (C, C-6), 127.5 (C, C-1), 122.1 (C, C-9), 119.8 (CH, C-4), 118.3 (CH, C-3), 114.9 (CH, C-2), 110.7 (CH, C-5), 80.6 (C, C-8), 61.4 (CH_3, C-12), 32.5(CH_3, C-13), 31.9 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{12}H_{13}IN_2NaO_2$ 366.9914; Found 366.9905, $[M + H]^+$ Calcd for $C_{12}H_{14}IN_2O_2$ 345.0095; Found 345.0084; **ν_{max}** (thin film)/cm^{-1} 3250, 2935, 2245, 1639, 1447, 1420, 1386, 1338, 1243, 1000.

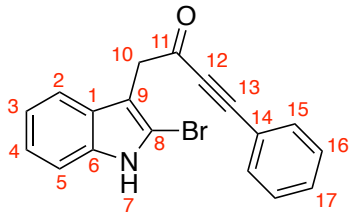
2-(2,5-dibromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (80d)



Synthesized using **General Procedure A** with 2-(5-bromo-1*H*-indol-3-yl)acetic acid (1.00 g, 3.94 mmol), 1,1'-carbonyldiimidazole (0.77 g, 4.72 mmol), *N*,*O*-dimethyl hydroxylamine hydrochloride (0.46 g, 4.72 mmol) and DCM (40 mL). Then, 2-(5-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide (1.17 g, 3.93 mmol), NBS (0.70 g, 3.93 mmol) and DCM (40 mL). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title product (0.37 g, 25%) as a yellow solid.

R_f 0.48 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (1H, br s, H-7), 7.64 (1H, d, *J* = 1.9 Hz, H-2), 7.14 (1H, dd, *J* = 8.6, 1.9 Hz, H-4), 6.94 (1H, dd, *J* = 8.6, 0.6 Hz, H-5), 3.82 (2H, s, H-10), 3.74 (3H, s, H-12), 3.25 (s, 3H, H-13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5 (C, C-11), 134.8 (C, C-6), 129.4 (C, C-1), 125.2 (CH, C-Ar), 121.1 (CH, C-Ar), 113.7 (C, C-3), 112.2 (CH, C-Ar), 111.4 (C, C-8/9), 108.6 (C, C-8/9), 61.5 (CH_3, C-12), 32.6 (CH_3, C-13), 29.2 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{12}H_{12}{}^{79}Br_2N_2NaO_2$ 396.9158; Found 396.9164, $[M + H]^+$ Calcd for $C_{12}H_{13}{}^{79}Br_2N_2O_2$ 374.9338; Found 374.9340.

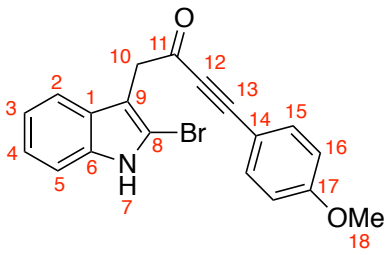
1-(2-Bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (81a)



Synthesized using **General Procedure B** with 2-(2-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80a** (0.68 g, 2.30 mmol), phenyl-acetylene (0.63 mL, 5.75 mmol), *n*-BuLi (2.30 mL, 5.75 mmol, 2.5 M in THF) and THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (0.54 g, 70%) as a yellow solid.

mp: 107 – 112 °C; **R_f** = 0.53 (hexane:EtOAc, 2:1 v/v). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (1H, br s, H-7), 7.57 (1H, d, *J* = 7.8 Hz, H-2), 7.46 – 7.28 (6H, m, H-5,15,16,17), 7.23 – 7.12 (2H, m, H-3,4), 4.03 (1H, s, H-10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.4 (C, C-11), 136.2 (C, C-6), 133.4 (2CH, C-15), 130.9 (CH, C-17), 128.6 (2CH, C-16), 127.9 (C, C-1), 122.8 (CH, C-Ar), 120.8 (CH, C-Ar), 120.0 (C, C-14), 118.6 (CH, C-Ar), 110.7 (C, C-5), 110.5 (C, C-8), 108.0 (C, C-9), 92.5 (C, C-13), 87.9 (C, C-12), 41.9 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{18}H_{12}{}^{79}BrNNaO$ 359.9994; Found 359.9991, $[M + H]^+$ Calcd for $C_{18}H_{13}{}^{79}BrNO$ 338.0175; Found 338.0170; **ν_{max}** (thin film)/cm^{-1} 3335, 2202, 1658, 1489, 1450, 1417, 1338, 1287, 1241, 1097.

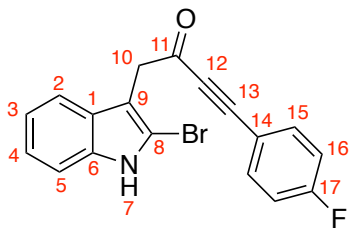
1-(2-Bromo-1*H*-indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one (81b)



Synthesized using **General Procedure B** with 2-(2-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80a** (1.35 g, 4.55 mmol), 1-ethynyl-4-methoxybenzene (1.45 mL, 11.4 mmol) and *n*-BuLi (4.55 mL, 2.5 M in hexanes) in dry THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title product (1.00 g, 60%) as a yellow solid.

mp: 76 – 80 °C; **R_f** 0.45 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (1H, br s, H-7), 7.56 – 7.52 (1H, m, H-Ar), 7.31 – 7.22 (m, 3H, H-Ar), 7.19 – 7.14 (1H, m, H-Ar), 7.14 – 7.09 (1H, m, H-Ar), 6.80 – 6.75 (m, 2H, H-16), 3.98 (s, 2H, H-10), 3.77 (s, 3H, H-18); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.4 (C, C-11), 161.8 (C, C-17), 136.2 (C, C-6), 135.4 (2CH, C-15), 128.0 (C, C-1), 122.8 (CH, C-Ar), 120.7 (CH, C-Ar), 118.7 (CH, C-Ar), 114.4 (2CH, C-16), 111.8 (C, C-14), 110.7 (CH, C-Ar), 110.4 (C, C-8), 108.3 (C, C-9), 93.7 (C, C-13), 87.9 (C, C-12), 55.5 (CH_3, C-18), 41.8 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{19}H_{14}{}^{79}BrNNaO_2$ 390.0100; Found 390.0093, $[M + H]^+$ Calcd for $C_{19}H_{15}{}^{79}BrNO_2$ 368.0281; Found 368.0277; **ν_{max}** (thin film)/cm^{-1} 3302, 2924, 2194, 1651, 1600, 1508, 1250, 1171, 1026, 831, 735.

1-(2-Bromo-1*H*-indol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one (81c)

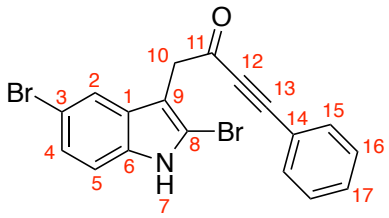


Synthesized using **General Procedure B** with 2-(2-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80a** (0.90 g, 3.03 mmol), 1-ethynyl-4-fluorobenzene

(0.91 g, 7.57 mmol) and *n*-BuLi (3.03 mL, 2.5 M in hexanes) in dry THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 5:1 v/v) afforded the title product (1.00 g, 93%) as a yellow solid.

mp: 137 – 140 °C; **R_f** 0.51 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (1H, br s, H-7), 7.57 – 7.54 (1H, m, H-Ar), 7.34 – 7.27 (3H, m, H-Ar), 7.23 – 7.18 (1H, m, H-Ar), 7.18 – 7.12 (1H, m, H-Ar), 7.03 – 6.95 (2H, m, H-16), 4.02 (2H, s, H-10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.3 (C, C-11), 164.1 (C, d, C–F, $^1J_{C–F}$ = 254.0 Hz, C-17), 136.2 (C, C-6), 135.6 (2CH, d, C–F, $^3J_{C–F}$ = 9.0 Hz, C-15), 127.9 (C, C-1), 122.9 (CH, C-Ar), 120.8 (CH, C-Ar), 118.5 (CH, C-Ar), 116.2 (2CH, d, C–F, $^2J_{C–F}$ = 22.3 Hz, C-16), 116.1 (C, d, C–F, $^4J_{C–F}$ = 3.3 Hz, C-14), 110.8 (CH, C-Ar), 110.5 (C, C-8), 107.9 (C, C-9), 91.5 (C, C-13), 87.8 (C, C-12), 41.8 (CH_2, C-10); **^{19}F NMR** (376 MHz, $CDCl_3$) −105.85 – −105.97 (1F, m); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{11}{}^{79}BrFNNaO$ 377.9900; Found 377.9900, $[M + H]^+$ Calcd for $C_{18}H_{12}{}^{79}BrFNO$ 356.0081; Found 356.0079; **ν_{max}** (thin film)/cm^{-1} 3383, 3313, 2203, 1657, 1599, 1505, 1234, 837, 743.

1-(2,5-Dibromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (81d)

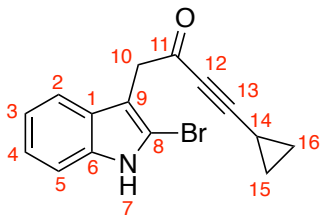


Synthesized using **General Procedure B** with 2-(2,5-dibromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80d** (0.7702 g, 2.05 mmol), ethynylbenzene (0.56 mL, 5.12 mmol) and *n*-BuLi (2.05 mL, 2.5 M in hexanes) in dry THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title product (0.76 g, 89%) as a yellow solid.

mp: 121 – 124 °C; **R_f** 0.55 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (1H, br s, H-7), 7.71 (1H, d, *J* = 1.8 Hz, H-2), 7.46 – 7.39 (3H, m, H-15,17), 7.37 – 7.31 (2H, m, H-16), 7.28 (1H, dd, *J* = 8.6, 1.8 Hz, H-4), 7.17 (1H, d, *J* = 8.6 Hz, H-5), 3.99 (2H, s, H-10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.7 (C, C-11), 134.8 (C, C-6), 133.4 (2CH, C-15), 131.0 (CH, C-17), 129.5 (C, C-1), 128.7 (2CH, C-16), 125.8

(CH, C-4), 121.2 (CH, C-3), 119.8 (C, C-14), 114.2 (C, C-3), 112.2 (CH, C-5), 111.8 (C, C-8), 107.7 (C, C-9), 92.7 (C, C-13), 87.8 (C, C-12), 41.7 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{11}{}^{79}Br_2NNaO$ 437.9100; Found 437.9093; ν_{max} (thin film)/cm^{-1} 3405, 3302, 2201, 1656, 1442, 1081, 757, 687.

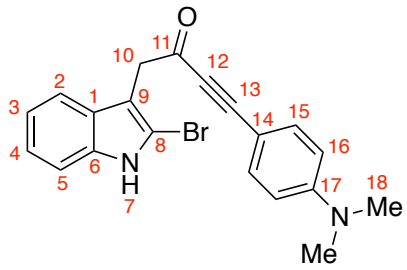
1-(2-Bromo-1*H*-indol-3-yl)-4-cyclopropylbut-3-yn-2-one (81e)



Synthesized using **General Procedure B** with 2-(2-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80a** (0.90 g, 3.03 mmol), ethynylcyclopropane (0.64 mL, 7.57 mmol) and *n*-BuLi (3.03 mL, 2.5 M in hexanes) in dry THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 4:1 v/v) afforded the title product (0.87 g, 95%) as a pale yellow oil.

R_f 0.53 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (1H, br s, H-7), 7.48 (1H, br d, *J* = 7.8 Hz, H-Ar), 7.29 – 7.25 (m, 1H, H-Ar), 7.20 – 7.15 (1H, m, H-Ar), 7.14 – 7.09 (1H, m, H-Ar), 3.87 (2H, s, H-10), 1.31 – 1.20 (1H, m, H-14), 0.91 – 0.82 (2H, m, H-15), 0.71 – 0.65 (2H, m, H-16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.4 (C, C-11), 136.1 (C, C-6), 127.8 (C, C-1), 122.7 (CH, C-Ar), 120.5 (CH, C-Ar), 118.5 (CH, C-Ar), 110.7 (CH, C-Ar), 110.3 (C, C-8), 108.2 (C, C-9), 101.1 (C, C-12), 76.6 (C, C-13), 41.7 (CH_2, C-10), 9.9 ($2CH_2$, C-15,16), −0.2 (CH, C-14); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}{}^{79}BrNNaO$ 323.9994; Found 323.9992, $[M + H]^+$ Calcd for $C_{15}H_{13}{}^{79}BrNO$ 302.0175; Found 302.0175; ν_{max} (thin film)/cm^{-1} 3309, 2197, 1651, 1450, 1420, 1337, 1238, 946, 742.

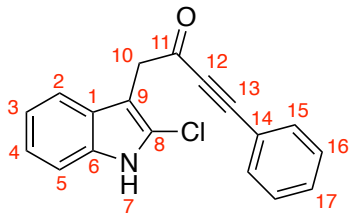
1-(2-Bromo-1*H*-indol-3-yl)-4-(4-(dimethylamino)phenyl)but-3-yn-2-one (81f)



Synthesized using **General Procedure B** with 2-(2-bromo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide 8**0a** (0.7934 g, 2.67 mmol), 4-ethynyl-*N*,*N*-dimethyl aniline (0.97 g, 6.68 mmol) and *n*-BuLi (2.67 mL, 2.5 M in hexanes) in dry THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (0.72 g, 84%) as a yellow solid.

mp: 125 – 128 °C; R_f 0.33 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (1H, br s, H-7), 7.60 – 7.56 (1H, m, H-Ar), 7.32 – 7.27 (1H, m, H-Ar), 7.23 – 7.16 (3H, m, H-Ar), 7.16 – 7.11 (1H, m, H-Ar), 6.56 – 6.51 (2H, m, H-16), 3.99 (2H, s, H-10), 2.98 (6H, s, H-18); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.5 (C, C-11), 151.8 (C, C-17), 136.2 (C, C-6), 135.3 (2CH, C-15), 128.0 (C, C-1), 122.6 (CH, C-Ar), 120.6 (CH, C-Ar), 118.7 (CH, C-Ar), 111.5 (CH, C-16), 110.7 (CH, C-Ar), 110.3 (C, C-8), 108.7 (C, C-9), 105.5 (C, C-14), 97.1 (C, C-13), 88.8 (C, C-12), 41.6 (CH_2, C-10), 40.1 ($2CH_3$, C-18); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}{}^{79}BrN_2NaO$ 403.0416; Found 403.0407, $[M + H]^+$ Calcd for $C_{20}H_{18}{}^{79}BrN_2O$ 381.0597; Found 381.0585; ν_{max} (thin film)/cm^{-1} 3276, 2187, 2149, 1595, 1526, 1372, 1098, 817, 742.

1-(2-Chloro-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (81g)

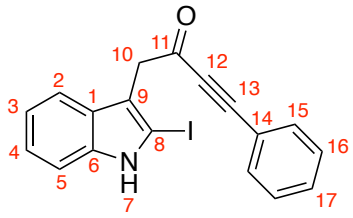


Synthesized using **General Procedure B** with 2-(2-chloro-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80b** (0.66 g, 2.59 mmol), phenyl-acetylene (0.71 mL,

6.48 mmol), *n*-BuLi (2.59 mL, 6.48 mmol, 2.5 M in THF) and THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (0.52 g, 69%) as a yellow solid.

mp: 109 – 113 °C; $\mathbf{R_f}$ = 0.55 (hexane:EtOAc , 2:1 v/v). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (1H, brs, H-7), 7.57 – 7.54 (1H, m, H-2), 7.44 – 7.27 (6H, m, 5,15,16,17), 7.24 – 7.14 (2H, m, H-3,4), 4.05 (2H, s, H-10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.6 (C, C-11), 134.5 (C, C-6), 133.3 (2CH, C-15), 130.9 (CH, C-17), 128.6 (2CH, C-16), 127.7 (C, C-1), 123.0 (C, C-8), 122.8 (CH, C-2/3/4), 120.8 (CH, C-2/3/4), 119.9 (C, C-14), 118.6 (CH, C-2/3/4), 110.8 (CH, C-5), 104.4 (C, C-9), 92.6 (C, C-13), 87.9 (C, C-12), 40.8 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{12}{}^{35}ClNNaO$ 316.0500; Found 316.0502, $[M + H]^+$ Calcd for $C_{18}H_{13}{}^{35}ClNO$ 294.0680; Found 294.0682; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3337, 3060, 2201, 1658, 1489, 1452, 1423, 1339, 1289, 1104.

1-(2-Iodo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (81h)

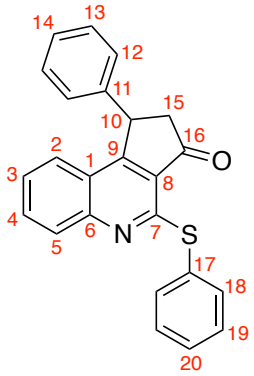


Synthesized using **General Procedure B** with 2-(2-iodo-1*H*-indol-3-yl)-*N*-methoxy-*N*-methylacetamide **80c** (0.57 g, 1.64 mmol), phenylacetylene (0.45 mL, 4.11 mmol), *n*-BuLi (1.64 mL, 4.11 mmol, 2.5 M in THF) and THF (15 mL). Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (0.51 g, 80%) as a pale orange solid.

mp: 138 – 140 °C; $\mathbf{R_f}$ = 0.55 (hexane:EtOAc , 2:1 v/v). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (1H, br s, H-7), 7.60 – 7.56 (1H, m, H-2), 7.44 – 7.27 (6H, m, H-5,15,16,17), 7.19 – 7.10 (2H, m, H-3,4), 4.02 (2H, s, H-10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.6 (C, C-11), 138.9 (C, C-6), 133.4 (2CH, C-15), 130.9 (CH, C-17), 128.6 (2CH, C-16), 127.8 (C, C-1), 122.8 (CH, C-Ar), 120.5 (CH, C-Ar), 120.0 (C, C-14), 118.4 (CH, C-Ar), 114.4 (C, C-9), 110.7 (CH,C-Ar), 92.5 (C, C-13), 88.0 (C, C-12), 80.8 (C, C-8), 43.8 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{12}INNaO$ 407.9856;

Found 407.9845, $[M + H]^+$ Calcd for $C_{18}H_{13}INO$ 386.0036; Found 386.0024; ν_{max} (thin film)/cm^{-1} 3346, 3058, 2201, 1655, 1489, 1446, 1412, 1338, 1285, 1097.

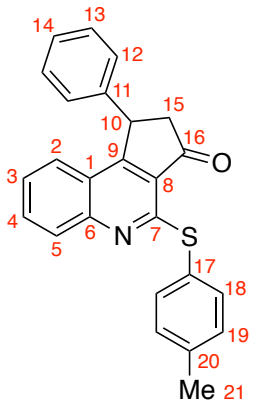
1-Phenyl-4-(phenylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83a)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), thiophenol (32.6 μL, 0.32 mmol), and DCE (2 mL, 0.1M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (68.0 mg, 93%) as a yellow solid. **mp**: 152 – 156 °C; **R_f** 0.60 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.66 (3H, m, H-2,18), 7.63 – 7.54 (2H, m, H-3,5), 7.50 – 7.45 (3H, m, H-19,20), 7.33 – 7.22 (4H, m, H-4,13,14), 7.15 – 7.09 (2H, m, H-12), 4.97 (1H, dd, J = 8.1, 2.7 Hz, H-10), 3.41 (1H, dd, J = 19.2, 8.1 Hz, H-15a), 2.77 (1H, dd, J = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 166.9 (C, C-9), 156.9 (C, C-7), 150.6 (C, C-6), 142.7 (C, C-11), 135.9 (2CH, C-18), 132.6 (CH, C-3), 129.4 (3CH, C-13,20), 129.1 (CH, C-2), 129.0 (2CH, C-19), 128.7 (C, C-17), 128.0 (C, C-8), 127.5 (CH, C-14), 127.4 (2CH, C-12), 126.1 (CH, C-4), 125.5 (CH, C-5), 123.5 (C, C-1), 47.5 (CH_2, C-15), 43.8 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{17}NNaOS$ 390.0923; Found 390.0924, $[M + H]^+$ Calcd for $C_{24}H_{18}NOS$ 368.1104; Found 368.1105; ν_{max} (thin film)/cm^{-1} 1706, 1612, 1577, 1548, 1495, 1404, 1302, 1160, 1098, 954.

Spectroscopic data matched those previously reported in the literature.[42, 53]

1-Phenyl-4-(*p*-tolylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83b)

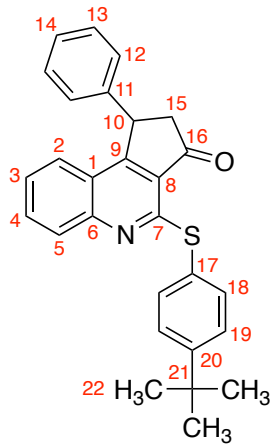


Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 4-methylbenzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (72.7 mg, 95%) as a pale yellow solid.

mp: 172 – 175 °C; **R_f** 0.40 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (1H, br d, *J* = 8.4 Hz, H-2), 7.63 – 7.53 (4H, m, H-3,5,18), 7.35 – 7.21 (6H, m, H-4,13,14,19), 7.16 – 7.09 (2H, m, H-12), 4.96 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.40 (1H, dd, *J* = 19.2, 8.1 Hz, H-15a), 2.76 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b), 2.44 (3H, s, H-21); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.6 (C, C-16), 166.8 (C, C-9), 157.3 (C, C-7), 150.6 (C, C-6), 142.8 (C, C-11), 139.2 (C, C-20), 135.8 (2CH, C-18), 132.5 (CH, C-3), 129.9 (2CH, C-19), 129.44 (CH, C-2), 129.39 (2CH, C-13), 128.1 (C, C-8), 127.5 (3CH, C-12,14), 126.0 (CH, C-4), 125.5 (CH, C-5), 125.0 (C, C-17), 123.4 (C, C-1), 47.6 (CH_2, C-15), 43.8 (CH, C-10), 21.6 (CH_3, C-20); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaOS$ 404.1080; Found 404.1084, $[M + H]^+$ Calcd for $C_{25}H_{20}NOS$ 382.1260; Found 382.1261; **ν_{max}** (thin film)/cm^{-1} 3060, 3025, 1709, 1615, 1579, 1549, 1493, 1404, 1305, 952, 761.

The same compound was also prepared on 1 mmol scale.

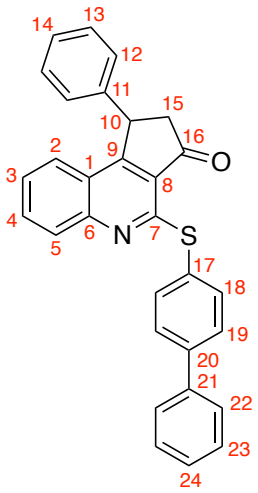
4-((4-(*tert*-Butyl)phenyl)thio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83c)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 4-(*tert*-butyl)benzenethiol (55.2 μL, 0.32 mmol), and DCE (2 mL, 0.1M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (75.0 mg, 89%) as a pale yellow oil.

R_f 0.40 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (1H, br d, J = 8.2 Hz, H-2), 7.67 – 7.62 (2H, m, H-18), 7.63 – 7.59 (1H, m, H-3), 7.58 – 7.54 (1H, m, H-5), 7.53 – 7.47 (2H, m, H-19), 7.33 – 7.21 (4H, m, H-4,13,14), 7.15 – 7.10 (2H, m, H-12), 4.96 (1H, dd, J = 8.0, 2.7 Hz, H-10), 3.40 (1H, dd, J = 19.2, 8.0 Hz, H-15a), 2.77 (1H, dd, J = 19.2, 2.7 Hz, H-15b), 1.40 (9H, s, H-22); **^{13}C NMR** (100 MHz, $CDCl_3$) 203.6 (C, C-16), 166.9 (C, C-9), 157.3 (C, C-7), 152.3 (C, C-20), 150.6 (C, C-6), 142.8 (C, C-11), 135.4 (2CH, C-18), 132.5 (CH, C-3), 129.5 (CH, C-2), 129.4 (2CH, C-13), 128.1 (C, C-8), 127.5 (3CH, C-12,14), 126.13 (2CH, C-19), 126.06 (CH, C-4), 125.5 (CH, C-5), 125.1 (C, C-17), 123.5 (C, C-1), 47.6 (CH_2, C-15), 43.8 (CH, C-10), 34.9 (C, C-21), 31.5 ($3CH_3$, C-22); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{28}H_{25}NNaOS$ 446.1549; Found 446.1555, $[M + H]^+$ Calcd for $C_{28}H_{26}NOS$ 424.1730; Found 424.1737; **ν_{max}** (thin film)/cm^{-1} 2962, 1706, 1613, 1578, 1548, 1494, 1403, 1302, 1235, 954, 909. 761.

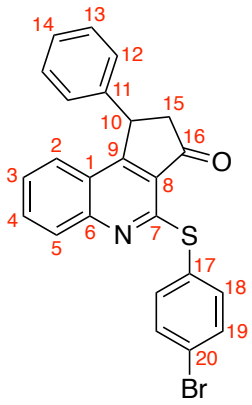
4-([1,1'-Biphenyl]-4-ylthio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83d)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), [1,1'-biphenyl]-4-thiol (59.6 mg, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (82.3 mg, 93%) as a pale yellow solid.

mp: 105 – 107 °C; **R_f** 0.33 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (2H, m, H-Ar), 7.76 (1H, ddd, *J* = 8.5, 1.2, 0.6 Hz, H-2), 7.73 – 7.67 (4H, m, H-Ar), 7.63 – 7.56 (2H, m, H-3,5), 7.52 – 7.46 (2H, m, H-Ar), 7.42 – 7.37 (1H, m, H-Ar), 7.34 – 7.23 (m, 4H, H-Ar), 7.16 – 7.11 (2H, m, H-Ar), 4.98 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.41 (1H, dd, *J* = 19.2, 8.1 Hz, H-15a), 2.78 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 166.9 (C, C-9), 156.9 (C, C-7), 150.6 (C, C-6), 142.7 (C, C-11), 141.9 (C, C-Ar), 140.6 (C, C-Ar), 136.1 (2CH, C-Ar), 132.6 (CH, C-3), 129.4 (3CH, C-2,13), 129.0 (2CH, C-Ar), 128.1 (C, C-8), 127.8 (CH, C-Ar), 127.7 (2CH, C-Ar), 127.6 (C, C-17), 127.50 (CH, C-14), 127.46 (2CH, C-12), 127.3 (2CH, C-Ar), 126.2 (CH, C-4), 125.6 (CH, C-5), 123.5 (C, C-1), 47.6 (CH_2, C-15), 43.8 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{21}NNaOS$ 466.1236; Found 466.1243, $[M + H]^+$ Calcd for $C_{30}H_{22}NOS$ 444.1417; Found 444.1420; **ν_{max}** (thin film)/cm^{-1} 3068, 3033, 1708, 1578, 1548, 1479, 1404, 1308, 1161, 954, 760, 700.

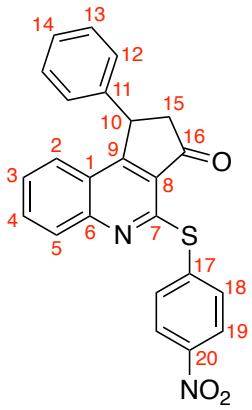
4-((4-Bromophenyl)thio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83e)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 4-bromobenzene thiol (60.5 mg, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (82.1 mg, 92%) as a pale yellow solid.

mp: 222 – 224 °C; $\mathbf{R_f}$ 0.38 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (1H, br d, *J* = 8.4 Hz, H-2), 7.67 – 7.50 (6H, m, H-Ar), 7.35 – 7.22 (4H, m, H-Ar), 7.16 – 7.08 (2H, m, H-12), 4.98 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.40 (1H, dd, *J* = 19.2, 8.1 Hz, H-15a), 2.77 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 167.0 (C, C-9), 156.1 (C, C-7), 150.5 (C, C-6), 142.6 (C, C-11), 137.4 (2CH, C-Ar), 132.7 (CH, C-3), 132.2 (2CH, C-Ar), 129.45 (2CH, C-13), 129.38 (CH, C-2), 128.0 (C, C-Ar), 127.9 (C, C-Ar), 127.6 (CH, C-14), 127.5 (2CH, C-12), 126.4 (CH,C-4), 125.6 (CH, C-5), 123.7 (C, C-Ar), 123.6 (C, C-Ar), 47.5 (CH_2, C-15), 43.9 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{16}{}^{79}BrNNaOS$ 468.0028; Found 468.0024, $[M + H]^+$ Calcd for $C_{24}H_{17}{}^{79}BrNOS$ 446.0209; Found 446.0199; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3064, 1708, 1611, 1578, 1548, 1473, 1404, 1160, 1098, 1010, 954, 762.

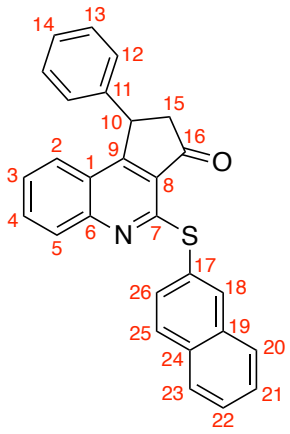
4-((4-Nitrophenyl)thio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83f)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 4-nitrobenzenethiol (49.7 mg, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (64.2 mg, 78%) as a pale yellow solid.

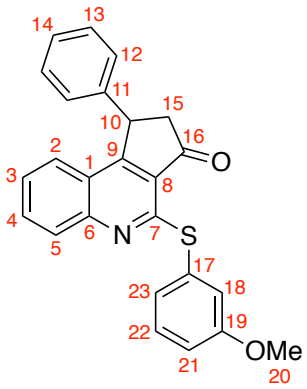
mp: 213 – 215 °C; **R_f** 0.56 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 – 8.27 (2H, m, H-19), 7.93 – 7.87 (2H, m, H-18), 7.75 (1H, ddd, *J* = 8.5, 1.3, 0.6 Hz, H-2), 7.69 – 7.63 (1H, m, H-3), 7.61 (1H, ddd, *J* = 8.3, 1.5, 0.6 Hz, H-5), 7.36 – 7.23 (4H, m, H-4,13,14), 7.16 – 7.09 (2H, m, H-12), 5.01 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.43 (1H, dd, *J* = 19.3, 8.0 Hz, H-15a), 2.79 (1H, dd, *J* = 19.3, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.4 (C, C-16), 167.3 (C, C-9), 154.5 (C, C-7), 150.4 (C, C-6), 148.0 (C, C-20), 142.4 (C, C-11), 138.2 (C, C-17), 135.8 (2CH, C-18), 133.0 (CH, C-3), 129.5 (2CH, C-13), 129.3 (CH, C-2), 128.0 (C, C-8), 127.6 (CH, C-14), 127.4 (2CH, C-12), 126.8 (CH, C-4), 125.7 (CH, C-5), 123.8 (C, C-1), 123.7 (2CH, C-19), 47.5 (CH_2, C-15), 43.9 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{16}N_2NaO_3S$ 435.0774; Found 435.0775, $[M + H]^+$ Calcd for $C_{24}H_{17}N_2O_3S$ 413.0954; Found 413.0956; **ν_{max}** (thin film)/cm^{-1} 3064, 3029, 1705, 1574, 1549, 1515, 1340, 1306, 953, 909, 852, 762, 729.

4-(Naphthalen-2-ylthio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83g)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 2-naphthalenethiol (51.3 mg, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (79.6 mg, 95%) as a yellow solid. **mp**: 161 – 165 °C; **R_f** 0.34 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (1H, br s, H-Ar), 7.94 – 7.85 (3H, m, H-Ar), 7.75 (1H, dd, *J* = 8.6, 1.7 Hz, H-Ar), 7.67 – 7.63 (1H, m, H-Ar), 7.59 – 7.49 (4H, m, H-Ar), 7.34 – 7.22 (4H, m, H-Ar), 7.16 – 7.10 (2H, m, H-Ar), 4.98 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.42 (1H, dd, *J* = 19.2, 8.1 Hz, H-15a), 2.79 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 166.9 (C, C-9), 157.0 (C, C-7), 150.6 (C, C-6), 142.7 (C, C-11), 134.9 (CH, C-Ar), 133.9 (C, C-Ar), 133.4 (C, C-Ar), 132.8 (CH, C-Ar), 132.6 (CH, C-Ar), 129.39 (2CH, C-13), 129.37 (CH, C-Ar), 128.13 (CH, C-Ar), 128.11 (CH, C-Ar), 128.06 (C, C-8), 127.9 (CH, C-Ar), 127.5 (CH, C-Ar), 127.5 (2CH, C-12), 127.0 (CH, C-Ar), 126.4 (C, C-17), 126.3 (CH, C-Ar), 126.1 (CH, C-Ar), 125.5 (CH, C-Ar), 123.5 (C, C-1), 47.6 (CH_2, C-15), 43.8 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{19}NNaOS$ 440.1080; Found 440.1081, $[M + H]^+$ Calcd for $C_{28}H_{20}NOS$ 418.1260; Found 418.1260; **ν_{max}** (thin film)/cm^{-1} 3060, 1705, 1578, 1549, 1404, 1303, 1160, 954, 761, 730.

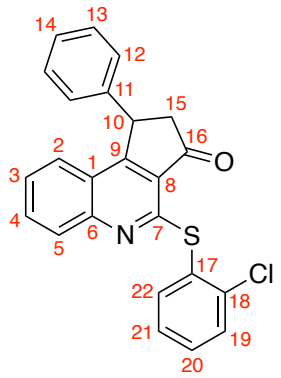
4-((3-Methoxyphenyl)thio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83h)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 3-methoxybenzenethiol (39.7 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (60.0 mg, 75%) as a yellow solid.

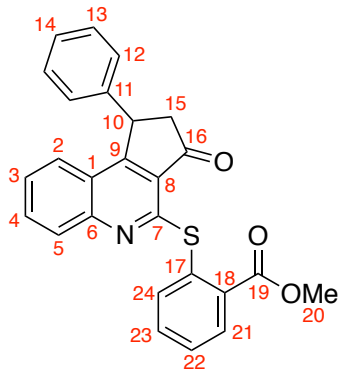
mp: 78 – 80 °C; **R$_f$** 0.28 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (1H, ddd, *J* = 8.5, 1.2, 0.6 Hz, H-2), 7.63 – 7.58 (1H, m, H-3), 7.56 (1H, ddd, *J* = 8.3, 1.5, 0.6 Hz, H-5), 7.38 (1H, t, *J* = 8.2 Hz, H-Ar), 7.33 – 7.21 (6H, m, H-Ar), 7.14 – 7.09 (2H, m, H-12), 7.01 (1H, ddd, *J* = 8.2, 2.5, 1.2 Hz, H-Ar), 4.96 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.84 (3H, s, H-20), 3.39 (1H, dd, *J* = 19.2, 8.0 Hz, H-15a), 2.76 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 166.9 (C, C-9), 159.8 (C, C-19), 156.8 (C, C-7), 150.6 (C, C-6), 142.7 (C, C-11), 132.6 (CH, C-3), 129.70 (C, C-17), 129.69 (CH, C-Ar), 129.42 (CH, C-2), 129.39 (2CH, C-13), 128.0 (C, C-8), 127.9 (CH, C-Ar), 127.5 (CH, C-14), 127.4 (2CH, C-12), 126.2 (CH, C-4), 125.5 (CH, C-5), 123.5 (C, C-1), 120.6 (CH, C-Ar), 115.4 (CH, C-Ar), 55.5 (CH_3, C-20), 47.5 (CH_2, C-15), 43.8 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_2S$ 420.1029; Found 420.1033, $[M + H]^+$ Calcd for $C_{25}H_{20}NO_2S$ 398.1209; Found 398.1214; **ν_{max}** (thin film)/cm^{-1} 3064, 1707, 1613, 1577, 1549, 1478, 1404, 1304, 1283, 1233, 1041, 762.

4-((2-Chlorophenyl)thio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83i)



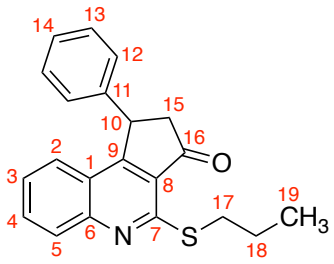
Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 2-chlorobenzenethiol (36.3 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (61.0 mg, 76%) as a white solid. **mp**: 94 – 97 °C; **R_f** 0.36 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 7.6, 1.7 Hz, H-19), 7.68 (1H, ddd, *J* = 8.5, 1.3, 0.6 Hz, H-2), 7.63 – 7.54 (3H, m, H-3,5,22), 7.46 – 7.40 (1H, m, H-21), 7.38 – 7.33 (1H, m, H-20), 7.33 – 7.22 (4H, m, H-4,13,14), 7.15 – 7.10 (2H, m, H-12), 4.98 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.41 (1H, dd, *J* = 19.2, 8.0 Hz, H-15a), 2.78 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 166.9 (C, C-9), 155.3 (C, C-7), 150.6 (C, C-6), 142.7 (C, C-11), 140.5 (C, C-18), 138.1 (CH, C-19), 132.6 (CH, C-3), 130.9 (CH, C-21), 130.1 (CH, C-22), 129.5 (CH, C-2), 129.4 (2CH, C-13), 128.4 (C, C-17), 128.1 (C, C-8), 127.50 (CH, C-14), 127.48 (2CH, C-12), 127.2 (CH, C-20), 126.2 (CH, C-4), 125.6 (CH, C-5), 123.5 (C, C-1), 47.5 (CH_2, C-15), 43.9 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{16}{}^{35}ClNNaOS$ 424.0533; Found 424.0544, $[M + H]^+$ Calcd for $C_{24}H_{17}{}^{35}ClNOS$ 402.0714; Found 402.0723; **ν_{max}** (thin film)/cm^{-1} 3063, 1707, 1613, 1579, 1550, 1453, 1405, 1161, 1096, 954, 759, 732.

Methyl 2-((3-oxo-1-phenyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolin-4-yl)thio)benzoate (83j)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), methyl thiolsalicylate (44.0 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 5:1 v/v) afforded the title product (36.6 mg, 43%) as a yellow solid. **mp**: 85 – 88 °C; **R$_f$** 0.20 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (1H, m, H-Ar), 7.80 – 7.73 (2H, m, H-Ar), 7.62 – 7.56 (1H, m, H-Ar), 7.58 – 7.49 (3H, m, H-Ar), 7.33 – 7.22 (4H, m, H-Ar), 7.14 – 7.09 (2H, m, H-12), 4.96 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.60 (3H, s, H-20), 3.40 (1H, dd, *J* = 19.2, 8.1 Hz, H-15a), 2.76 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.2 (C, C-16), 167.7 (C, C-19), 166.9 (C, C-9), 155.7 (C, C-7), 150.3 (C, C-6), 142.7 (C, C-11), 136.4 (CH, C-Ar), 136.2 (C, C-17), 132.6 (CH, C-Ar), 131.7 (CH, C-Ar), 130.5 (CH, C-Ar), 129.4 (2CH, C-13 and C, C-18), 129.2 (CH, C-Ar), 129.0 (CH, C-Ar), 128.1 (C, C-8), 127.50 (CH, C-Ar), 127.47 (2CH, C-12), 126.2 (CH, C-Ar), 125.5 (CH, C-Ar), 123.5 (C, C-1), 52.1 (CH_3, C-20), 47.5 (CH_2, C-15), 43.9 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{19}NNaO_3S$ 448.0978; Found 448.0976, $[M + H]^+$ Calcd for $C_{26}H_{20}NO_3S$ 426.1158; Found 426.1158; **ν_{max}** (thin film)/cm^{-1} 3068, 2950, 1710, 1612, 1578, 1550, 1294, 1256, 1114, 1056, 955, 760.

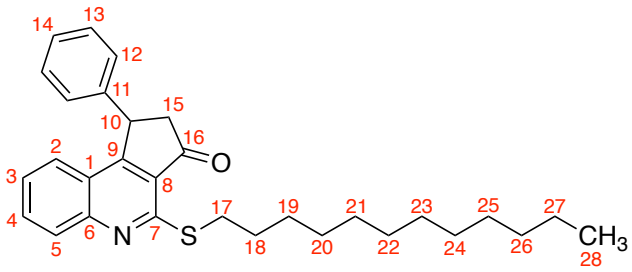
1-Phenyl-4-(propylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83k)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 1-propanethiol (29.0 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 8:1 v/v) afforded the title product (63.4 mg, 95%) as a pale yellow solid.

mp: 146 – 148 °C; **R_f** 0.48 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (1H, br d, *J* = 8.4 Hz, H-2), 7.71 – 7.63 (1H, m, H-3), 7.58 (1H, dd, *J* = 8.4, 1.4 Hz, H-5), 7.34 – 7.21 (4H, m, H-4,13,14), 7.14 – 7.09 (2H, m, H-12), 4.93 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.41 (2H, t, *J* = 7.4 Hz, H-17), 3.35 (1H, dd, *J* = 19.2, 8.0 Hz, H-15a), 2.72 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b), 1.89 (2H, sx, *J* = 7.4 Hz, H-18), 1.15 (3H, t, *J* = 7.4 Hz, H-19); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.6 (C, C-16), 166.6 (C, C-9), 157.7 (C, C-7), 150.7 (C, C-6), 142.9 (C, C-11), 132.6 (CH, C-3), 129.4 (2CH, C-13), 128.9 (CH, C-2), 128.5 (C, C-8), 127.5 (2CH, C-12), 127.4 (CH, C-14), 125.74 (CH, C-4), 125.70 (CH, C-5), 123.0 (C, C-1), 47.6 (CH_2, C-15), 43.6 (CH, C-10), 30.7 (CH_2, C-17), 22.5 (CH_2, C-18), 13.9 (CH_3, C-19); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{19}NNaOS$ 356.1080; Found 356.1072, $[M + H]^+$ Calcd for $C_{21}H_{20}NOS$ 334.1260; Found 334.1253; **ν_{max}** (thin film)/cm^{-1} 2963, 2929, 1707, 1613, 1580, 1548, 1495, 1404, 1161, 1099, 762, 701.

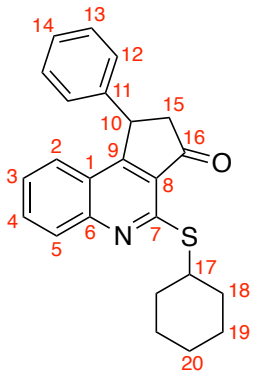
4-(Dodecylthio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83l)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), 1-dodecanethiol (76.6 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 8:1 v/v) afforded the title product (85.1 mg, 93%) as a pale yellow solid.

mp: 102 – 104 °C; **R_f** 0.64 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (1H, ddd, *J* = 8.5, 1.1, 0.5 Hz, H-2), 7.72 – 7.65 (1H, m, H-3), 7.57 (1H, ddd, *J* = 8.3, 1.5, 0.5 Hz, H-5), 7.33 – 7.19 (4H, m, H-4,13,14), 7.14 – 7.07 (2H, m, H-12), 4.92 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.41 (2H, t, *J* = 7.4 Hz, H-17), 3.34 (1H, dd, *J* = 19.1, 8.0 Hz, H-15a), 2.71 (1H, dd, *J* = 19.1, 2.7 Hz, H-15b), 1.83 (2H, p, *J* = 7.4 Hz, H-18), 1.54 (2H, p, *J* = 7.4 Hz, H-19), 1.37 – 1.21 (16H, m, H-20,21,22,23,24,25,26,27), 0.88 (3H, t, *J* = 6.9 Hz, H-28); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.6 (C, C-16), 166.6 (C, C-9), 157.7 (C, C-7), 150.7 (C, C-6), 142.9 (C, C-11), 132.6 (CH, C-3), 129.4 (2CH, C-13), 128.9 (CH, C-2), 128.5 (C, C-8), 127.5 (2CH, C-12), 127.4 (CH, C-14), 125.7 (CH, C-4), 125.7 (CH, C-5), 123.1 (C, C-1), 47.6 (CH_2, C-15), 43.6 (CH, C-10), 32.1 (CH_2, C-Al), 29.83 (CH_2, C-Al), 29.79 ($2CH_2$, C-Al), 29.7 (CH_2, C-Al), 29.5 (CH_2, C-Al), 29.4 (CH_2, C-Al), 29.3 (CH_2, C-Al), 29.1 (CH_2, C-Al), 28.7 (CH_2, C-Al), 22.8 (CH_2, C-Al), 14.3 (CH_3, C-28); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{37}NNaOS$ 482.2488; Found 482.2488, $[M + H]^+$ Calcd for $C_{30}H_{38}NOS$ 460.2669; Found 460.2680; **ν_{max}** (thin film)/cm^{-1} 2922, 2852, 1709, 1613, 1580, 1547, 1404, 1300, 1098, 957, 761, 701.

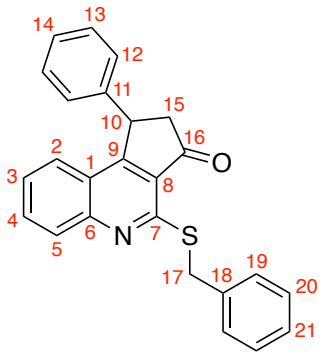
4-(Cyclohexylthio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83m)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), cyclohexanethiol (39.1 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 7:1 v/v) afforded the title product (65.8 mg, 88%) as a pale yellow solid.

mp: 172 – 175 °C; **R_f** 0.46 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (1H, br d, *J* = 8.4 Hz, H-2), 7.72 – 7.65 (1H, m, H-3), 7.56 (1H, dd, *J* = 8.2, 1.4 Hz, H-5), 7.32 – 7.20 (4H, m, H-4,13,14), 7.13 – 7.06 (2H, m, H-12), 4.91 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 4.35 – 4.26 (1H, m, H-17), 3.33 (1H, dd, *J* = 19.1, 8.0 Hz, H-15a), 2.70 (1H, dd, *J* = 19.1, 2.7 Hz, H-15b), 2.29 – 2.15 (2H, m, H-18), 1.91 – 1.79 (2H, m, H-19), 1.74 – 1.49 (4H, m, H-18,19), 1.29 – 1.21 (2H, m, H-20); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-16), 166.6 (C, C-9), 157.6 (C, C-7), 150.7 (C, C-6), 142.9 (C, C-11), 132.6 (CH, C-3), 129.4 (2CH, C-13), 128.9 (CH, C-2), 128.5 (C, C-8), 127.5 (2CH, C-12), 127.4 (CH, C-14), 125.70 (CH, C-4), 125.68 (CH, C-5), 123.0 (C, C-1), 47.6 (CH_2, C-15), 43.6 (CH, C-10), 41.2 (CH, C-17), 33.1 (CH_2, C-18), 33.0 (CH_2, C-18), 29.8 (CH_2, C-20), 26.4 (CH_2, C-19), 26.06 (CH_2, C-19); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaOS$ 396.1393; Found 396.1396, $[M + H]^+$ Calcd for $C_{24}H_{24}NOS$ 374.1573; Found 374.1578; **ν_{max}** (thin film)/cm^{-1} 2927, 2851, 1707, 1613, 1579, 1548, 1404, 1299, 1161, 957, 761, 730.

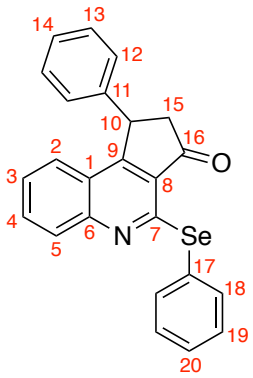
4-(Benzylthio)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83n)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), benzylmercaptan (37.5 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (40.8 mg, 53%) as a pale yellow solid.

mp: 188 – 190 °C; **R_f** 0.38 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (1H, ddd, *J* = 8.5, 1.2, 0.6 Hz, H-2), 7.75 – 7.69 (1H, m, H-3), 7.60 – 7.53 (3H, m, H-5,19), 7.35 – 7.21 (7H, m, H-4,13,14,20,21), 7.13 – 7.08 (2H, m, H-12), 4.92 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 4.68 (2H, s, H-17), 3.33 (1H, dd, *J* = 19.1, 8.0 Hz, H-15a), 2.70 (1H, dd, *J* = 19.1, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.4 (C, C-16), 166.7 (C, C-9), 156.8 (C, C-7), 150.6 (C, C-6), 142.7 (C, C-11), 138.2 (C, C-18), 132.7 (CH, C-3), 129.7 (2CH, C-19), 129.4 (2CH, C-13), 128.9 (CH, C-2), 128.5 (2CH, C-20), 128.4 (C, C-8), 127.5 (3CH, C-12,14), 127.2 (CH, C-21), 125.9 (CH, C-4), 125.8 (CH, C-5), 123.3 (C, C-1), 47.5 (CH_2, C-15), 43.8 (CH, C-10), 33.0 (CH_2, C-17); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaOS$ 404.1080; Found 404.1080, $[M + H]^+$ Calcd for $C_{25}H_{20}NOS$ 382.1260; Found 382.1260; **ν_{max}** (thin film)/cm^{-1} 3060, 3028, 1707, 1612, 1579, 1548, 1495, 1404, 1161, 1098, 762.

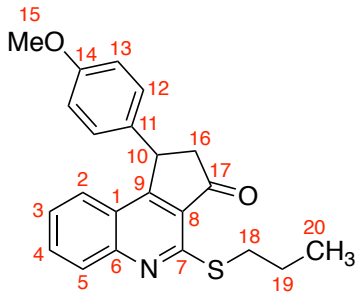
1-Phenyl-4-(phenylselanyl)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83o)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), selenophenol (34.0 μL, 0.32 mmol), and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (51.1 mg, 62%) as a yellow solid.

mp: 161 – 163 °C; **R_f** 0.36 (hexane:EtOAc, 4:1 then 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (2H, m, H-18), 7.74 (1H, ddd, *J* = 8.5, 1.3, 0.7 Hz, H-2), 7.63 – 7.58 (1H, m, H-3), 7.56 (1H, ddd, *J* = 8.3, 1.6, 0.7 Hz, H-5), 7.48 – 7.42 (3H, m, H-19,20), 7.34 – 7.23 (4H, m, H-4,13,14), 7.14 – 7.09 (2H, m, H-12), 4.98 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.40 (1H, dd, *J* = 19.2, 8.0 Hz, H-15a), 2.76 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.2 (C, C-16), 166.2 (C, C-9), 155.4 (C, C-7), 151.3 (C, C-6), 142.6 (C, C-11), 137.0 (2CH, C-18), 132.5 (CH, C-3), 129.9 (C, C-8), 129.6 (CH, C-2), 129.4 (2CH, C-13), 129.0 (2CH, C-19), 128.75 (CH, C-20), 127.49 (CH, C-14), 127.45 (2CH, C-12), 126.4 (C, C-17), 126.3 (CH, C-4), 125.6 (CH, C-5), 123.7 (C, C-1), 47.4 (CH_2, C-15), 43.9 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{17}NNaOSe$ 438.0368; Found 438.0372, $[M + H]^+$ Calcd for $C_{24}H_{18}NOSe$ 416.0548; Found 416.0551; **ν_{max}** (thin film)/cm^{-1} 3061, 1704, 1613, 1574, 1548, 1404, 1303, 1157, 1092, 944, 760, 739.

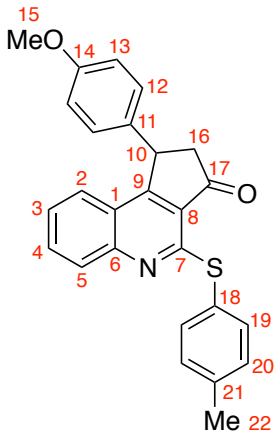
1-(4-Methoxyphenyl)-4-(propylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83p)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-methoxyphenyl) but-3-yn-2-one **81b** (73.6 mg, 0.20 mmol), propanethiol (29.0 µL, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 5:1 v/v) afforded the title product (60.4 mg, 83%) as a yellow solid.

mp: 128 – 130 °C; **R_f** 0.36 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (2H, br d, *J* = 8.5 Hz, H-2), 7.72 – 7.66 (1H, m, H-3), 7.59 (1H, ddd, *J* = 8.2, 1.5, 0.6 Hz, H-5), 7.30 – 7.26 (1H, m, H-4), 7.04 – 6.97 (2H, m, H-12), 6.84 – 6.78 (2H, m, H-13), 4.88 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.76 (3H, s, H-15), 3.40 (2H, t, *J* = 7.3 Hz, H-18), 3.32 (1H, dd, *J* = 19.1, 8.0 Hz, H-16a), 2.67 (1H, dd, *J* = 19.1, 2.7 Hz, H-16b), 1.87 (2H, sx, *J* = 7.3 Hz, H-19), 1.13 (3H, t, *J* = 7.3 Hz, H-20); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.7 (C, C-17), 166.9 (C, C-9), 158.8 (C, C-14), 157.7 (C, C-7), 150.5 (C, C-6), 134.9 (C, C-11), 132.6 (CH, C-3), 128.8 (CH, C-2), 128.5 (2CH, C-12), 128.4 (C, C-8), 125.79 (CH, C-4), 125.76 (CH, C-5), 123.1 (C, C-1), 114.7 (2CH, C-13), 55.4 (CH_3, C-15), 47.7 (CH_2, C-16), 42.9 (CH, C-10), 30.7 (CH_2, C-18), 22.5 (CH_2, C-19), 13.9 (CH_3, C-20); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{21}NNaO_2S$ 386.1185; Found 386.1181, $[M + H]^+$ Calcd for $C_{22}H_{22}NO_2S$ 364.1366; Found 364.1365; **ν_{max}** (thin film)/cm^{-1} 2961, 2931, 1707, 1612, 1549, 1511, 1247, 1034, 957, 765.

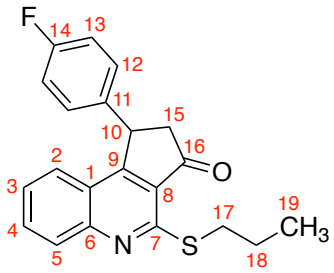
1-(4-Methoxyphenyl)-4-(*p*-tolylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83q)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one **81b** (73.6 mg, 0.20 mmol), 4-methylbenzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (69.5 mg, 84%) as a pale yellow solid.

mp: 144 – 146 °C; $\mathbf{R_f}$ 0.46 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (1H, br d, *J* = 8.4 Hz, H-2), 7.62 – 7.54 (4H, m, H-3,5,19), 7.33 – 7.21 (3H, m, H-4,20), 7.07 – 6.98 (2H, m, H-12), 6.85 – 6.78 (2H, m, H-13), 4.92 (1H, dd, *J* = 8.0, 2.7 Hz, H-10), 3.77 (3H, s, H-15), 3.37 (1H, dd, *J* = 19.2, 8.0 Hz, H-16a), 2.73 (1H, dd, *J* = 19.2, 2.7 Hz, H-16b), 2.45 (3H, s, H-22); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.8 (C, C-17), 167.1 (C, C-9), 158.8 (C, C-14), 157.3 (C, C-7), 150.6 (C, C-6), 139.2 (C, C-21), 135.8 (2CH, C-19), 134.8 (C, C-11), 132.5 (CH, C-3), 129.9 (2CH, C-20), 129.4 (CH, C-2), 128.5 (2CH, C-12), 128.0 (C, C-8), 126.0 (CH, C-4), 125.6 (CH, C-5), 125.0 (C, C-18), 123.5 (C, C-11), 114.7 (2CH, C-13), 55.4 (CH_3, C-15), 47.7 (CH_2, C-16), 43.0 (CH, C-10), 21.6 (CH_3, C-22); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{21}NNaO_2S$ 434.1185; Found 434.1198, $[M + H]^+$ Calcd for $C_{26}H_{22}NO_2S$ 412.1366; Found 412.1381; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 2955, 2836, 1706, 1612, 1578, 1550, 1511, 1404, 1303, 1247, 1179, 954, 731.

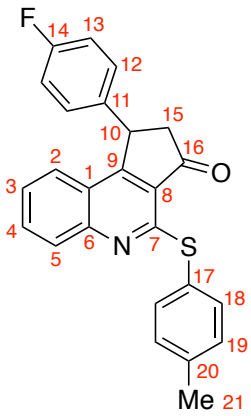
1-(4-Fluorophenyl)-4-(propylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83r)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one **81c** (71.2 mg, 0.20 mmol), propanethiol (29.0 µL, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (55.8 mg, 79%) as a pale yellow solid.

mp: 180 – 182 °C; **R_f** 0.45 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (1H, br d, *J* = 8.5 Hz, H-2), 7.73 – 7.67 (1H, m, H-3), 7.53 (1H, ddd, *J* = 8.2, 1.5, 0.6 Hz, H-5), 7.32 – 7.26 (1H, m, H-4), 7.11 – 7.03 (2H, m, H-12), 7.01 – 6.95 (2H, m, H-13), 4.92 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.40 (2H, t, *J* = 7.4 Hz, H-17), 3.34 (1H, dd, *J* = 19.1, 8.1 Hz, H-15a), 2.66 (1H, dd, *J* = 19.1, 2.7 Hz, H-15b), 1.87 (2H, sx, *J* = 7.4 Hz, H-18), 1.13 (3H, t, *J* = 7.4 Hz, H-19); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.2 (C, C-16), 166.3 (C, C-9), 162.0 (C, d, C–F, $^1J_{C–F}$ = 246.4 Hz, C-14), 157.8 (C, C-7), 150.6 (C, C-6), 138.6 (C, d, C–F, $^4J_{C–F}$ = 3.4 Hz, C-11), 132.8 (CH, C-3), 129.0 (2CH, d, C–F , $^3J_{C–F}$ = 7.7 Hz, C-12), 128.9 (CH, C-2), 128.5 (C, C-8), 125.9 (CH, C-4), 125.6 (CH, C-5), 122.9 (C, C-1), 116.3 (2CH, d, C–F, $^2J_{C–F}$ = 21.6 Hz, C-13), 47.5 (CH_2, C-15), 42.8 (CH, C-10), 30.7 (CH_2, C-17), 22.5 (CH_2, C-18), 13.9 (CH_3, C-19); **^{19}F NMR** (376 MHz, $CDCl_3$) δ −114.62 – −114.74 (1F, m, F-14); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{18}FNNaOS$ 374.0985; Found 374.0975, $[M + H]^+$ Calcd for $C_{21}H_{19}FNOS$ 352.1166; Found 352.1155; **ν_{max}** (thin film)/cm^{-1} 2963, 2926, 1708, 1580, 1548, 1508, 1403, 1225, 1160, 957, 837, 766.

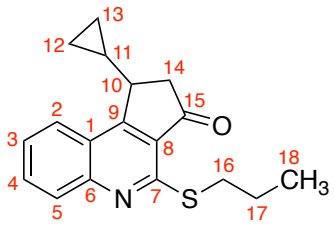
1-(4-Fluorophenyl)-4-(*p*-tolylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83s)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one **81c** (71.2 mg, 0.20 mmol), 4-methylbenzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title product (71.0 mg, 89%) as a pale yellow solid.

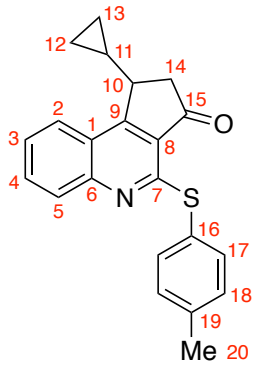
mp: 200 – 202 °C; $\mathbf{R_f}$ 0.38 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (1H, br d, *J* = 8.5 Hz, H-2), 7.63 – 7.55 (3H, m, H-3,18), 7.51 (1H, dd, *J* = 8.2, 1.4 Hz, H-5), 7.32 – 7.24 (3H, m, H-4,19), 7.12 – 7.05 (2H, m, H-12), 7.03 – 6.95 (2H, m, H-13), 4.96 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.39 (1H, dd, *J* = 19.1, 8.1 Hz, H-15a), 2.71 (1H, dd, *J* = 19.1, 2.7 Hz, H-15b), 2.44 (3H, s, H-21); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.3 (C, C-16), 166.5 (C, C-9), 162.0 (C, d, C–F, $^2J_{C–F}$ = 246.6 Hz, C-14), 157.4 (C, C-7), 150.7 (C, C-6), 139.3 (C, C-20), 138.5 (C, d, C–F, $^4J_{C–F}$ = 3.3 Hz, C-11), 135.8 (2CH, C-18), 132.6 (CH, C-3), 129.9 (2CH, C-19), 129.5 (CH, C-2), 129.0 (2CH, d, C–F, $^3J_{C–F}$ = 8.1 Hz, C-12), 128.0 (C, C-8), 126.1 (CH, C-4), 125.4 (CH, C-5), 124.9 (C, C-17), 123.3 (C, C-1), 116.4 (2CH, d, C–F, $^2J_{C–F}$ = 21.6 Hz, C-13), 47.5 (CH_2, C-15), 43.0 (CH, C-10), 21.6 (CH_3, C-21); **^{19}F NMR** (376 MHz, $CDCl_3$) δ −114.55 – −114.67 (1F, m, F-14); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{18}FNNaOS$ 422.0985; Found 422.0998, $[M + H]^+$ Calcd for $C_{25}H_{19}FNOS$ 400.1166; Found 400.1174; $\boldsymbol{\nu_{max}}$ (thin film)/cm^{-1} 3073, 2918, 1708, 1580, 1550, 1509, 1404, 1160, 954, 838.

1-Cyclopropyl-4-(propylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83t)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-cyclopropylbut-3-yn-2-one **81e** (60.4 mg, 0.20 mmol), propanethiol (29.0 µL, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 8:1 v/v) afforded the title product (23.6 mg, 40%) as a yellow solid. **mp**: 99 – 102 °C; **R_f** 0.53 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (1H, ddd, *J* = 8.2, 1.5, 0.6 Hz, H-2), 8.01 (1H, ddd, *J* = 8.5, 1.3, 0.6 Hz, H-5), 7.81 – 7.75 (1H, m, H-4), 7.54 – 7.48 (1H, m, H-3), 3.46 – 3.40 (1H, m, H-10), 3.36 (2H, t, *J* = 7.3 Hz, H-16), 2.93 (1H, dd, *J* = 18.8, 7.5 Hz, H-14a), 2.63 (1H, dd, *J* = 18.8, 2.0 Hz, H-14b), 1.83 (2H, sx, *J* = 7.3 Hz, H-17), 1.16 – 1.01 (4H, m, H-11,18), 0.82 – 0.74 (1H, m, H-12a), 0.68 – 0.61 (1H, m, H-12b), 0.61 – 0.53 (1H, m, H-13a), 0.37 – 0.30 (m, 1H, H-13b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.9 (C, C-14), 168.2 (C, C-9), 157.8 (C, C-7), 150.4 (C, C-6), 132.6 (CH, C-4), 129.0 (CH, C-5), 127.5 (C, C-8), 126.0 (CH, C-2), 125.6 (CH, C-3), 123.5 (C, C-1), 43.5 (CH_2, C-14), 41.0 (CH, C-10), 30.6 (CH_2, C-16), 22.5 (CH_2, C-17), 17.3 (CH, C-11), 13.9 (CH_3, C-18), 7.5 (CH_2, C-12), 4.1 (CH_2, C-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{19}NNaOS$ 320.1080; Found 320.1078, $[M + H]^+$ Calcd for $C_{18}H_{20}NOS$ 298.1260 ; Found 298.1260; **ν_{max}** (thin film)/cm^{-1} 2963, 1706, 1612, 1578, 1548, 1405, 1160, 1100, 762.

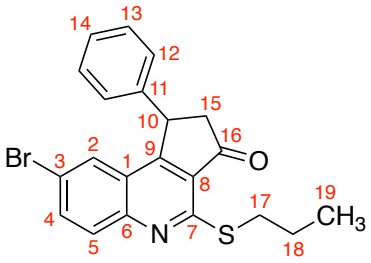
1-Cyclopropyl-4-(*p*-tolylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83u)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-cyclopropylbut-3-yn-2-one **81e** (60.4 mg, 0.20 mmol), 4-methylbenzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (41.8 mg, 60%) as a yellow solid.

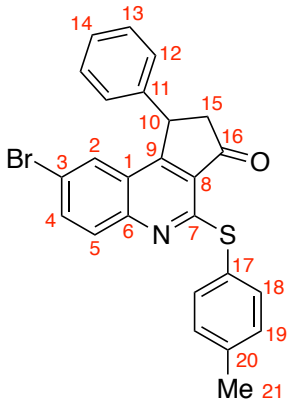
mp: 99 – 101 °C; **R_f** 0.39 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (1H, ddd, *J* = 8.2, 1.5, 0.6 Hz, H-2), 7.76 (1H, ddd, *J* = 8.5, 1.4, 0.6 Hz, H-5), 7.72 – 7.65 (1H, m, H-4), 7.57 – 7.53 (2H, m, H-17), 7.52 – 7.46 (1H, m, H-3), 7.31 – 7.21 (m, 2H, H-18), 3.51 – 3.45 (1H, m, H-10), 2.99 (1H, dd, *J* = 18.8, 7.6 Hz, H-14a), 2.69 (1H, dd, *J* = 18.8, 2.0 Hz, H-14b), 2.43 (3H, s, H-20), 1.14 – 1.03 (1H, m, H-11), 0.84 – 0.75 (1H, m, H-12a), 0.72 – 0.54 (m, 2H,H-12b,13a), 0.39 – 0.31 (1H, m, H-13a); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.9 (C, C-15), 168.5 (C, C-9), 157.5 (C, C-7), 150.5 (C, C-6), 139.1 (C, C-19), 135.7 (2CH, C-17), 132.5 (CH, C-4), 129.8 (2CH, C-18), 129.5 (CH, C-5), 127.1 (C, C-8), 125.9 (CH, C-3), 125.8 (CH, C-2), 125.2 (C, C-6, 123.9 (C, C-1), 43.6 (CH_2, C-14), 41.2 (CH, C-10), 21.6 (CH_3, C-20), 17.3 (CH, C-11), 7.5 (CH_2, C-12), 4.1 (CH_2, C-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{19}NNaOS$ 368.1080; Found 368.1080, $[M + H]^+$ Calcd for $C_{22}H_{20}NOS$ 346.1260; Found 346.1257; **ν_{max}** (thin film)/cm^{-1} 1706, 1612, 1576, 1550, 1493, 1406, 1302, 1159, 1091, 765.

8-Bromo-1-phenyl-4-(propylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83v)



Synthesized using **General Procedure C** with 1-(2,5-dibromo-1H-indol-3-yl)-4-phenylbut-3-yn-2-one **81d** (83.4 mg, 0.20 mmol), propanethiol (29.0 μL, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (64.7 mg, 78%) as a yellow solid. **mp**: 165 – 169 °C; **R_f** 0.54 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 8.9 Hz, H-2), 7.73 (1H, dd, *J* = 8.9, 2.2 Hz, H-4), 7.67 (1H, d, *J* = 2.2 Hz, H-5), 7.34 – 7.23 (3H, m, H-13,14), 7.12 – 7.06 (2H, m, H-12), 4.86 (1H, dd, *J* = 8.0, 2.6 Hz, H-10), 3.39 – 3.30 (3H, m, H-17), 3.35 (1H, dd, *J* = 19.2, 8.0 Hz, H-15a), 2.72 (dd, *J* = 19.2, 2.6 Hz, 1H, H-15b), 1.85 (2H, sx, *J* = 7.4 Hz, H-18), 1.12 (3H, t, *J* = 7.4 Hz, H-19); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.3 (C, C-16), 165.4 (C, C-9), 158.4 (C, C-7), 149.2 (C, C-6), 142.1 (C, C-11), 135.8 (CH, C-4), 130.5 (CH, C-2), 129.5 (2CH, C-13), 128.9 (C, C-8), 127.8 (CH, C-5), 127.7 (CH, C-4), 127.4 (2CH, C-12), 124.3 (C, C-1), 119.3 (C, C-3), 47.5 (CH_2, C-15), 43.5 (CH, C-10), 30.8 (CH_2, C-17), 22.4 (CH_2, C-18), 13.9 (CH_3, C-19); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{18}{}^{79}BrNNaOS$ 434.0185; Found 434.0194; **ν_{max}** (thin film)/cm^{-1} 2964, 2927, 1709, 1577, 1542, 1386, 1066, 936, 830, 701.

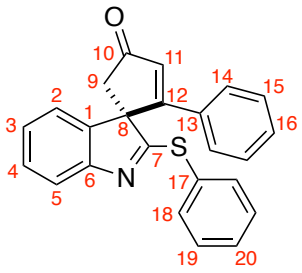
8-Bromo-1-phenyl-4-(*p*-tolylthio)-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (83w)



Synthesized using **General Procedure C** with 1-(2,5-dibromo-1H-indol-3-yl)-4-phenylbut-3-yn-2-one **81d** (83.4 mg, 0.20 mmol), 4-methylbenzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (74.2 mg, 81%) as a yellow solid.

mp: 170 – 172 °C; **R_f** 0.45 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, *J* = 2.2, 0.6 Hz, H-2), 7.63 (1H, dd, *J* = 8.9, 2.2 Hz, H-4), 7.59 – 7.54 (3H, m, H-5,18), 7.36 – 7.24 (5H, m, H-13,14,19), 7.14 – 7.09 (2H, m, H-12), 4.90 (1H, dd, *J* = 8.1, 2.7 Hz, H-10), 3.40 (1H, dd, *J* = 19.2, 8.1 Hz, H-15a), 2.77 (1H, dd, *J* = 19.2, 2.7 Hz, H-15b), 2.44 (3H, s, H-21); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.3 (C, C-16), 165.6 (C, C-9), 158.1 (C, C-7), 149.2 (C, C-6), 142.1 (C, C-11), 139.4 (C, C-20), 135.8 (2CH, C-18), 135.6 (CH, C-4), 131.0 (CH, C-2), 129.9 (2CH, C-19), 129.6 (2CH, C-13), 128.5 (C, C-8), 127.8 (CH, C-5), 127.6 (CH, C-14), 127.4 (2CH, C-12), 124.7 (C, C-1), 124.6 (C, C-17), 119.7 (C, C-3), 47.5 (CH_2, C-15), 43.7 (CH, C-10), 21.6 (CH_3, C-21); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{18}{}^{79}BrNNaOS$ 482.0185; Found 482.0186, $[M + H]^+$ Calcd for $C_{25}H_{19}{}^{79}BrNOS$ 460.0365; Found 460.0368; **ν_{max}** (thin film)/cm^{-1} 3027, 2916, 1711, 1575, 1544, 1490, 1387, 1066, 962, 829, 702.

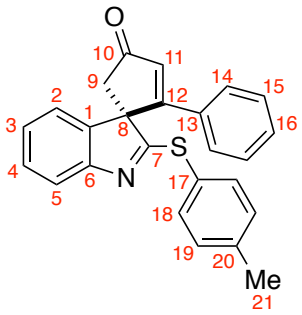
2-Phenyl-2'-(phenylthio)spiro[cyclopentane-1,3'-indol]-2-en-4-one (84a)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), thiolphenol (32.6 μL, 0.32 mmol), and MeCN (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (14.4 mg, 20%) as a yellow solid. **mp**: 169 – 173 °C; $\mathbf{R_f}$ 0.50 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 –7.47 (3H, m, H-2,18), 7.43 – 7.37 (3H, m, H-3,19), 7.37 – 7.31 (2H, m, H-5,16), 7.27 – 7.20 (2H, m, H-15), 7.18 – 7.12 (2H, m, H-4,20), 7.11 – 7.05 (2H, m, H-14), 6.84 (1H, s, H-11), 3.18 (1H, d, J = 18.6 Hz, H-9a), 2.83 (1H, d, J = 18.6 Hz, H-9b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.8 (C, C-10), 183.2 (C, C-7), 172.1 (C, C-12), 154.7 (C, C-6), 141.7. (C, C-17), 134.5 (2CH, C-18), 132.3 (C, C-13), 131.4 (CH, C-16), 131.1 (CH, C-11) 129.7 (CH, C-3), 129.6 (2CH, C-19), 129.2 (CH, C-5), 129.1 (2CH, C-15), 127.4 (2CH, C-14), 127.2 (C, C-1), 125.9 (CH, C-20), 121.4 (CH, C-4), 120.3 (CH, C-2), 67.5 (C, C-8), 48.2 (CH_2, C-9); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{17}NNaOS$ 390.0923; Found 390.0927, $[M + H]^+$ Calcd for $C_{24}H_{18}NOS$ 368.1104; Found 368.1106; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3059, 2923, 1722, 1697, 1511, 1448, 1261, 953, 762, 747, 687.

Spectroscopic data matched those previously reported in the literature.[42, 53]

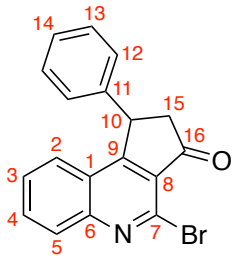
2-Phenyl-2'-(*p*-tolylthio)spiro[cyclopentane-1,3'-indol]-2-en-4-one (84b)



Synthesized using **General Procedure C** with 1-(2-iodo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81h** (77.0 mg, 0.20 mmol), 4-methylbenzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (55.0 mg, 72%) as a yellow solid.

mp: 164 – 166 °C; $\mathbf{R_f}$ 0.48 (hexane:EtOAc, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (1H, br d, *J* = 7.8 Hz, H-2), 7.40 – 7.29 (4H, m, H-3,16,18), 7.25 – 7.18 (4H, m, H-15,19), 7.16 – 7.05 (4H, m, H-4,5,14), 6.83 (1H, s, H-11), 3.17 (1H, d, *J* = 18.6 Hz, H-9a), 2.82 (1H, d, *J* = 18.6 Hz, H-9b), 2.38 (3H, s, H-21); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.8 (C, C-10), 183.7 (C, C-7), 172.2 (C, C-12), 154.8 (C, C-6), 141.8 (C, C-17), 140.1 (C, C-20), 134.6 (2CH, C-18), 132.4 (C, C-13), 131.4 (CH, C-16), 131.1 (CH, C-11), 130.4 (2CH, C-19), 129.1 (CH, C-3), 129.0 (2CH, C-15), 127.4 (2CH, C-14), 125.8 (CH, C-5), 123.5 (C, C-1), 121.4 (CH, C-4), 120.3 (CH, C-2), 67.4 (C, C-8), 48.3 (CH_2, C-9), 21.5 (CH_3, C-21); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaOS$ 404.1080; Found 404.1074, $[M + H]^+$ Calcd for $C_{25}H_{20}NOS$ 382.1260; Found 382.1258; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3060, 1721, 1696, 1510, 1493, 1448, 953, 762.

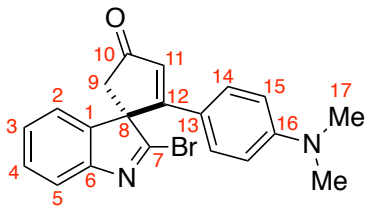
4-Bromo-1-phenyl-1,2-dihydro-3*H*-cyclopenta[*c*]quinolin-3-one (85)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), phenol (30.1 mg, 0.32 mmol), trifluoroacetic acid (15.3 μL, 0.20 mmol) and DCE (2 mL, 0.1 M) at RT. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (14.2 mg, 21%) as a yellow solid.

mp: 146 – 149 °C; $\mathbf{R_f}$ 0.48 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (1H, br d, *J* = 8.4 Hz, H-2), 7.83 – 7.78 (1H, m, H-3), 7.70 (1H, ddd, *J* = 8.4, 1.4, 0.6 Hz, H-5), 7.51 – 7.44 (1H, m, H-4), 7.34 – 7.23 (3H, m, H-13,14), 7.14 – 7.07 (2H, m, H-12), 4.96 (1H, dd, *J* = 8.2, 2.8 Hz, H-10), 3.42 (1H, dd, *J* = 19.2, 8.2 Hz, H-15a), 2.80 (1H, dd, *J* = 19.2, 2.8 Hz, H-15b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.7 (C, C-16), 168.8 (C, C-9), 150.8 (C, C-6), 142.3 (C, C-11), 136.6 (C, C-7), 133.5 (CH, C-13), 129.7 (2CH, C-13), 129.6 (CH, C-2), 129.0 (C, C-8), 128.0 (C, C-4), 127.7 (CH, C-14), 127.5 (2CH, C-12), 125.8 (CH, C-5), 124.8 (C, C-1), 48.0 (CH_2, C-15), 42.7 (CH, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{12}{}^{79}BrNNaO$ 359.9994; Found 359.9997, $[M + H]^+$ Calcd for $C_{18}H_{13}{}^{79}BrNO$ 338.0175; Found 338.0176; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3063, 2924, 1721, 1613, 1568, 1559, 1498, 1404, 1089, 762.

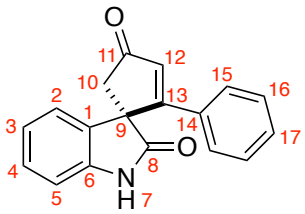
2'-Bromo-2-(4-(dimethylamino)phenyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (86x)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-(dimethylamino)phenyl)but-3-yn-2-one **81f** (76.3 mg, 0.20 mmol), 4-methyl benzenethiol (39.7 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (68.0 mg, 89%) as a yellow solid.

mp: 195 – 197 °C; **R_f** 0.48 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.67 (1H, m, H-2), 7.41 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H, H-3), 7.27 – 7.22 (1H, m, H-5), 7.21 (ddd, *J* = 7.4, 1.6, 0.7 Hz, 1H, H-4), 6.95 – 6.87 (2H, m, H-14), 6.75 (1H, s, H-11), 6.45 (2H, br d, *J* = 8.8 Hz, H-15), 2.95 (1H, d, *J* = 18.3 Hz, H-9a), 2.94 (6H, s, H-17), 2.62 (1H, d, *J* = 18.3 Hz, H-9b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.3 (C, C-10), 170.2 (C, C-12), 167.2 (C, C-7), 153.5 (C, C-1), 152.3 (C, C-13), 142.7 (C, C-6), 129.2 (CH. C-3), 129.0 (2CH, C-14), 127.6 (CH, C-4), 126.5 (CH, C-11), 122.0 (CH, C-5), 121.3 (CH, C-2), 118.8 (C, C-16), 111.7 (2CH, C-15), 69.5 (C, C-8), 45.4 (CH_2, C-9), 40.0 ($2CH_3$, C-17); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}BrN_2NaO$ 403.0416; Found 403.0424, $[M + H]^+$ Calcd for $C_{20}H_{18}BrN_2O$ 381.0597; Found 381.0601; **ν_{max}** (thin film)/cm^{-1} 2909, 1687, 1606, 1570, 1522, 1202, 1171, 946, 819, 731.

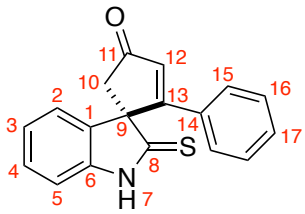
2-Phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2',4-dione (87)



Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), phenol (30.1 mg, 0.32 mmol), trifluoroacetic acid (15.3 μL, 0.20 mmol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (33.9 mg, 62%) as a brown oil.

R_f 0.14 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.24 (1H, br s, H-7), 7.34 – 7.17 (6H, m, H-Ar), 7.09 – 6.98 (3H, m, H-Ar), 6.82 (1H, s, H-12), 3.14 (1H, d, J = 18.2 Hz, H-10a), 2.74 (1H, d, J = 18.2 Hz, H-10b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.3 (C, C-11), 179.5 (C, C-8), 172.0 (C, C-13), 140.5 (C, C-6), 132.5 (C, C-14), 131.7 (CH, C-12), 131.6 (C, C-1), 131.2 (CH, C-Ar), 129.4 (CH, C-Ar), 129.1 (2CH, C-16), 127.4 (2CH, C-15), 123.9 (CH, C-Ar), 123.3 (CH, C-Ar), 111.0 (CH, C-Ar), 58.3 (C, C-9), 49.0 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}NNaO_2$ 298.0838; Found 298.0838, $[M + H]^+$ Calcd for $C_{18}H_{14}NO_2$ 276.1019; Found 276.1019; **ν_{max}** (thin film)/cm^{-1} 3229, 1712, 1696, 1619, 1592, 1570, 1324, 1204, 750, 731.

2-Phenyl-2'-thioxospiro[cyclopentane-1,3'-indolin]-2-en-4-one (90a)



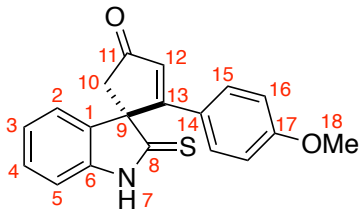
Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.20 mmol), triphenylsilanethiol (93.6 mg, 0.32 mmol), and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography

(hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (47.9 mg, 82%) as a yellow solid.

mp: 200 – 202 °C ; **R_f** 0.31 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (1H, br s, H-7), 7.34 (1H, ddd, *J* = 7.8, 6.3, 2.5 Hz, H-Ar), 7.31 – 7.25 (1H, m, H-Ar), 7.22 – 7.13 (4H, m, H-Ar), 7.11 – 7.04 (3H, m, H-Ar), 6.82 (1H, s, H-12), 3.18 (1H, d, *J* = 18.0 Hz, H-10a), 2.81 (1H, d, *J* = 18.0 Hz, H-10b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.8 (C, C-8), 205.6 (C, C-11), 172.7 (C, C-13), 142.4 (C, C-6), 136.1 (C, C-1), 132.6 (C, C-14), 131.6 (CH, C-12), 131.0 (CH, C-Ar), 129.5 (CH, C-Ar), 128.9 (2CH, C-16), 127.6 (2CH, C-15), 125.2 (CH, C-Ar), 123.7 (CH, C-Ar), 110.8 (CH, C-Ar), 68.1 (C, C-9), 53.1 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}NNaOS$ 314.0610 ; Found 314.0615, $[M + H]^+$ Calcd for $C_{18}H_{14}NOS$ 292.0791; Found 292.0796; **ν_{max}** (thin film)/cm^{-1} 3173, 3056, 1685, 1465, 1439, 1345, 1270, 1227, 1206, 965, 753, 728.

Spiro thio-oxindole **9a** was also synthesized using **General Procedure C** with 1-(2-bromo-1H-indol-3-yl)-4-phenylbut-3-yn-2-one (67.6 mg, 0.20 mmol), benzylmercaptan (37.5 μL, 0.32 mmol) and DCE (2 mL, 0.1M) at 60 °C for 24 hours. The crude product was purified by column chromatography (hexane:EtOAc, 6:1 then 2:1 v/v) to afford the title product as a yellow solid (15.7 mg, 27%).

2-(4-Methoxyphenyl)-2'-thioxospiro[cyclopentane-1,3'-indolin]-2-en-4-one (90b)

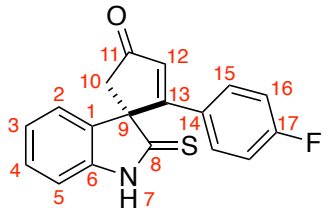


Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one **81b** (73.6 mg, 0.20 mmol), triphenylsilanethiol (93.6 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 3:1 then 2:1 v/v) afforded the title product (30.0 mg, 47%) as a brown oil.

R_f 0.25 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.89 (1H, br s, H-7), 7.33 (1H, ddd, *J* = 7.7, 5.8, 3.1 Hz, H-Ar), 7.16 – 7.09 (3H, m, H-Ar), 7.08 – 7.02

(2H, m, H-15), 6.82 (1H, s, H-12), 6.72 – 6.67 (2H, m, H-16), 3.69 (3H, s, H-18), 3.15 (1H, d, J = 18.0 Hz, H-10a), 2.79 (1H, d, J = 18.0 Hz, H-10b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.2 (C, C-8), 205.6 (C, C-11), 172.1 (C, C-13), 161.9 (C, C-17), 142.3 (C, C-6), 136.6 (C, C-1), 129.5 (2CH, C-15), 129.4 (2CH, C-Ar), 125.2 (CH, C-Ar), 124.8 (C, C-14), 123.6 (CH, C-Ar), 114.4 (2CH, C-16), 111.0 (CH, C-Ar), 67.9 (C, C-9), 55.4 (CH_3, C-18), 53.3 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{15}NNaO_2S$ 344.0716; Found 344.0716, $[M + H]^+$ Calcd for $C_{19}H_{16}NO_2S$ 322.0896; Found 322.0898; **ν_{max}** (thin film)/cm^{-1} 3163, 1678, 1603, 1583, 1510, 1467, 1436, 1259, 1180, 834, 728.

2-(4-Fluorophenyl)-2'-thioxospiro[cyclopentane-1,3'-indolin]-2-en-4-one (90c)

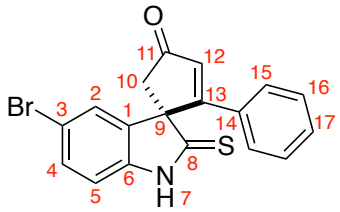


Synthesized using **General Procedure C** with 1-(2-bromo-1*H*-indol-3-yl)-4-(4-fluorophenyl) but-3-yn-2-one **81c** (71.2 mg, 0.20 mmol), triphenylsilanethiol (93.6 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (52.3 mg, 85%) as an orange oil.

R_f 0.39 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.78 (1H, br s, H-7), 7.38 – 7.31 (1H, m, H-Ar), 7.17 – 7.10 (3H, m, H-Ar), 7.09 – 7.01 (2H, m, H-15), 6.91 – 6.83 (2H, m, H-16), 6.80 (1H, s, H-12), 3.17 (1H, d, J = 18.1 Hz, H-8a), 2.82 (1H, d, J = 18.1 Hz, H-8b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.5 (C, C-8), 205.6 (C, C-11), 171.5 (C, C-13), 164.1 (C, d, C–F, $^2J_{C-F}$ = 253.2 Hz, C-17), 142.4 (C, C-6), 135.8 (C, C-1), 131.4 (CH, C-12), 129.8 (2CH, d, C–F, $^3J_{C-F}$ = 8.7 Hz, C-15), 129.7 (CH, C-Ar), 128.7 (C, d, C–F, $^4J_{C-F}$ = 3.4 Hz, C-14), 125.3 (CH, C-Ar), 123.7 (CH, C-Ar), 116.2 (2CH, d, C–F, $^2J_{C-F}$ = 22.4 Hz, C-16), 111.0 (CH, C-Ar), 68.1 (C, C-9), 53.0 (CH_2, C-10); **^{19}F NMR** (376 MHz, $CDCl_3$) δ −107.85 – −108.03 (1F, m, F-17); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{12}FNNaOS$ 332.0516; Found 332.0516,

[M + H]$^+$ Calcd for $C_{18}H_{13}FNOS$ 310.0696; Found 310.0693; ν_{max} (thin film)/cm^{-1} 3177, 1685, 1601, 1507, 1467, 1437, 1236, 1162, 837, 753, 729.

5'-Bromo-2-phenyl-2'-thioxospiro[cyclopentane-1,3'-indolin]-2-en-4-one (90d)



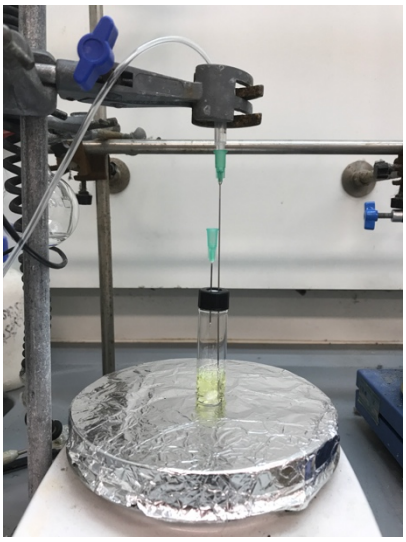
Synthesized using **General Procedure C** with 1-(2,5-dibromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81d** (83.4 mg, 0.20 mmol), triphenylsilanethiol (93.6 mg, 0.32 mmol) and DCE (2 mL, 0.1 M) at 60 °C. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (52.4 mg, 71%) as a pink solid.

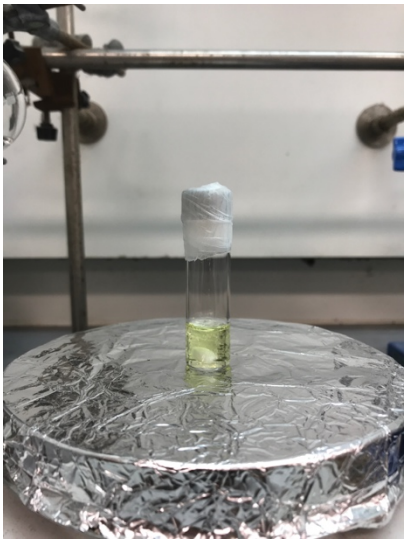
mp: 247 – 249 °C; **R$_f$** 0.44 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.20 (1H, br s, H-7), 7.53 – 7.47 (2H, m, H-4,5), 7.36 – 7.24 (3H, m, H-16,17), 7.13 – 7.05 (3H, m, H-2,15), 7.04 (1H, s, H-12), 2.84 (1H, d, J = 17.9 Hz, H-10a), 2.72 (1H, d, J = 17.9 Hz, H-10b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 207.2 (C, C-8), 204.5 (C, C-11), 170.1 (C, C-13), 142.7 (C, C-6), 138.4 (C, C-1), 132.3 (C, C-14), 132.1 (CH, C-5), 131.8 (CH, C-12), 130.9 (CH, C-17), 128.9 (2CH, C-16), 127.2 (2CH, C-15), 126.9 (CH, C-4), 116.8 (C, C-3), 112.8 (CH, C-2), 67.6 (C, C-9), 52.1 (CH_2, C-10); **HRMS** (ESI) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{12}{}^{79}BrNNaOS$ 391.9715; Found 391.9718; ν_{max} (thin film)/cm^{-1} 3187, 1689, 1457, 1403, 1331, 766.

5.3 Experimental for Chapter 3

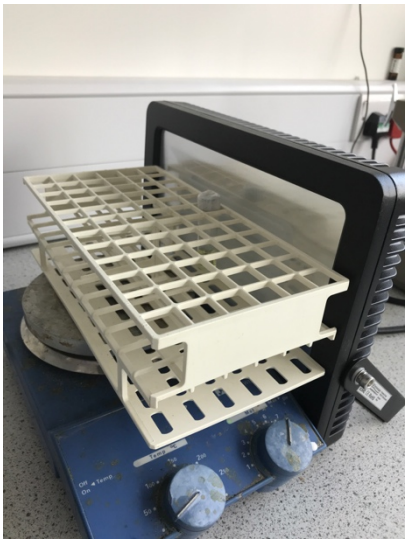
General method: images of photochemistry experimental setup

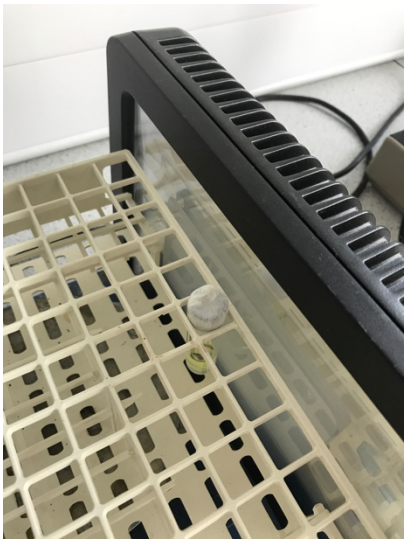
1. The reaction vial was degassed with argon and sealed with parafilm.[a]





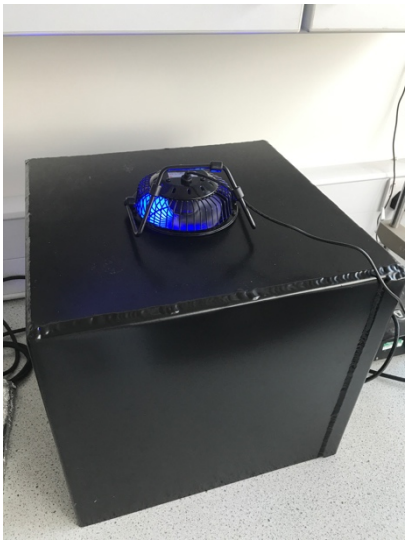
2. The reaction vial was arranged in a rack alongside the LED lamp which was far away from light source about 1 cm.[b]

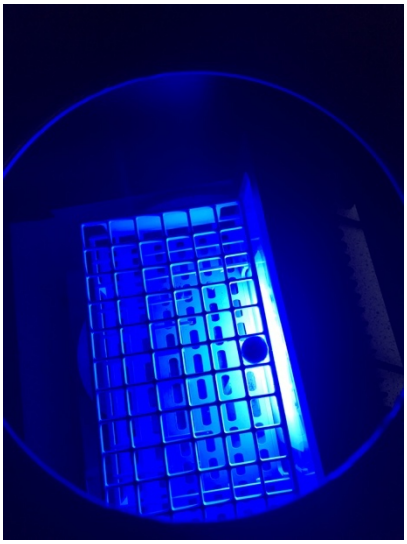




3. When the reaction was in progress, it was placed under a black box with a cooling fan as shown. Internal reaction temperatures were not monitored as standard in all

experiments, but when measured, we found that this set-up enables a consistent internal temperature of 25–30 °C to be maintained for prolonged reaction periods.

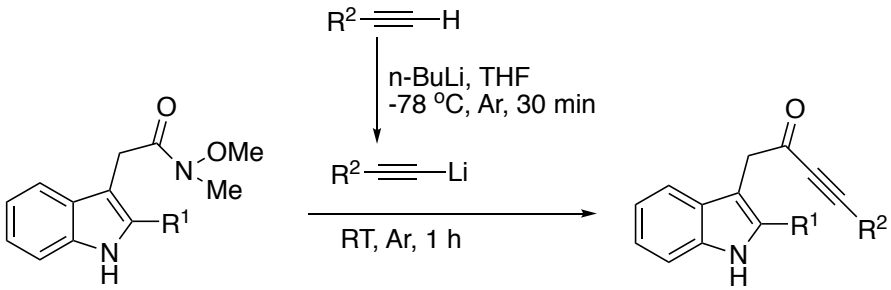




[a]The vials were purchased from VWR, Cat. No. 548-0821. For further information: www.vwr.com

[b]A benchmark 60 W blue LED was purchased from LED Technologies, model name: HH-T025-60W, product code: 100.334. For further information: www.ledtechnologies.co.uk

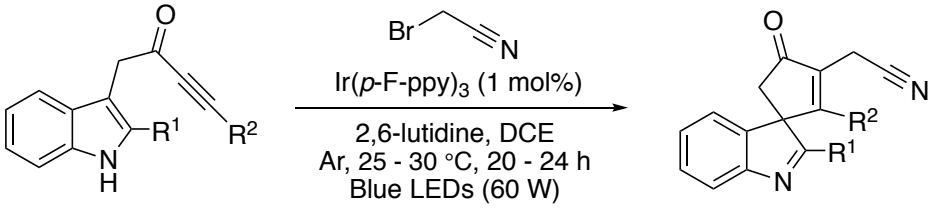
General Procedure D



To a stirred solution of alkyne (2.50 mmol) in THF (3 mL) in an dried-oven round-bottom flask at −78 °C under argon was added *n*-BuLi (1.00 mL, 2.5 mmol, 2.5 M in hexanes) dropwise. The resulting solution was stirred for 30 min at −78 °C. Next, the solution was transferred via cannula into another round-bottom flask containing a solution of Weinreb amide (1.00 mmol) in dry THF (10 mL) at −78 °C. Then, the

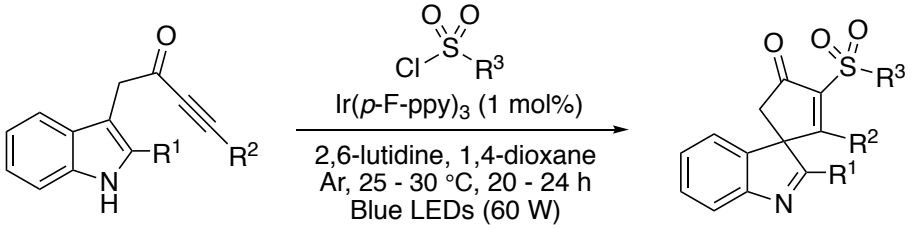
mixture was warmed to room temperature and stirred for 1 hour. After the reaction was completed, it was quenched with sat. aq. NH_4Cl (20 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure E



To a solution of indole-ynone (0.20 mmol) and Ir(*p*-F-ppy)$_3$ (0.002 mmol, 1 mol%) in DCE (2.0 mL) in a sealed vial was added bromoacetonitrile (0.40 mmol) and 2,6-lutidine (0.40 mmol). Then, the vial was degassed with argon for 5 minutes. The reaction mixture was stirred under irradiation (60 W blue LEDs) and fan cooling for 20–24 hours (25–30 °C). The reaction mixture was concentrated in *vacuo* and then the crude product was purified by flash column chromatography using Merck silica gel (SiO_2), 35–70 μm, 60 Å.

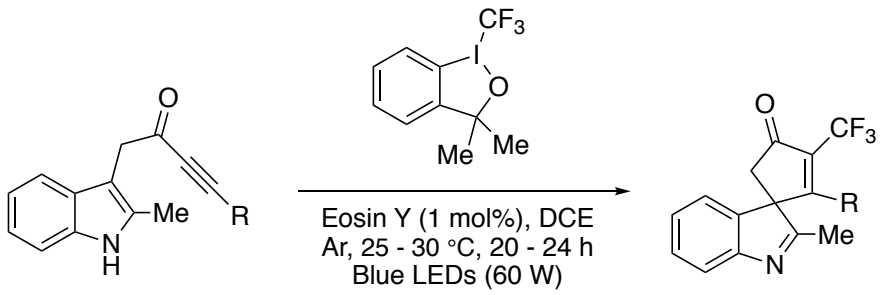
General Procedure F



To a solution of indolyl-ynone (0.20 mmol) and Ir(*p*-F-ppy)$_3$ (0.002 mmol, 1 mol%) in 1,4-dioxane (2.0 mL) in a sealed vial was added sulfonyl chloride (0.30 mmol) and 2,6-lutidine (0.40 mmol). Then, the vial was degassed with argon for 5 minutes. The reaction mixture was stirred under irradiation (60 W blue LEDs) and fan cooling for 20–24 hours (25–30 °C). The reaction mixture was concentrated in *vacuo* and then the

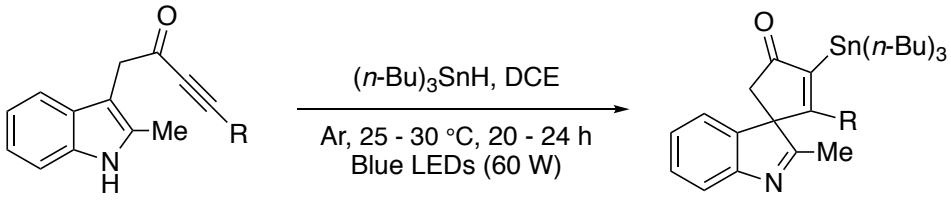
crude product was purified by flash column chromatography using Merck silica gel (SiO_2), 35–70 μm, 60 Å.

General Procedure G



To a solution of indolyl-ynone (0.20 mmol) and Eosin Y (0.002 mmol, 1 mol%) in DCE (2.0 mL) in a sealed vial was added Togni reagent I (0.22 mmol). Then, the vial was degassed with argon for 5 minutes. The reaction mixture was stirred under irradiation (60 W blue LEDs) and fan cooling for 20–24 hours (25–30 °C). The reaction mixture was then filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography using Merck silica gel (SiO_2), 35–70 μm, 60 Å.

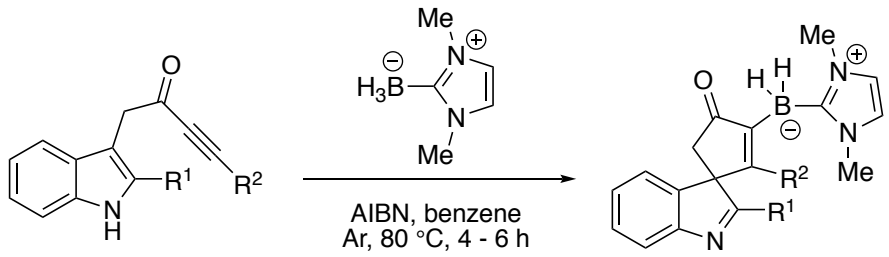
General Procedure H



To a solution of indolyl-ynone (0.20 mmol) in DCE (2.0 mL, 0.1 M) in a sealed vial was added tributyltin hydride (0.4 mmol). Then, the vial was degassed with argon for 5 minutes. The reaction mixture was stirred under irradiation (60 W blue LEDs) and fan cooling for 20–24 hours (25–30 °C). The reaction mixture was then filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography using Fuji Silysia Chromatorex Silica gel (SiO_2), neutral MB100, 75-

200 µm, 100 Å. The use of Fuji Silysia Chromatorex Silica gel improved the isolation yields for stannylated compounds.

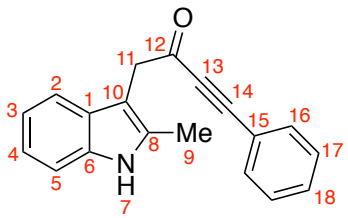
General Procedure I



To a solution of indolyl-ynone (0.30 mmol) in benzene (2.3 mL, 0.13 M) in a sealed vial was added AIBN (0.33 mmol) and NHC-borane (0.33 mmol). Then, the vial was degassed with argon for 5 minutes. The reaction mixture was stirred for 4–6 hours at 80 °C in a metal heating block. The reaction mixture was then filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography using Fuji Silysia Chromatorex Silica gel (SiO_2), neutral MB100, 75-200 µm, 100 Å. The use of Fuji Silysia Chromatorex Silica gel improved the isolation yields for borylated compounds.

Characterisation Data and Procedures

1-(2-Methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (97a)

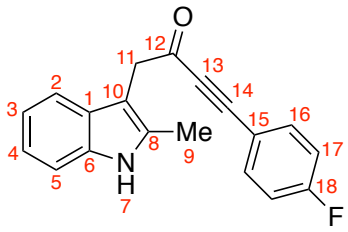


Synthesized using **General Procedure D** with *N*-methoxy-*N*-methyl-2-(2-methyl-1*H*-indol-3-yl)acetamide **100** (1.60 g, 6.89 mmol), phenylacetylene (1.89 mL, 11.2 mmol), *n*-BuLi (6.89 mL, 11.2 mmol, 2.5 M in hexanes). Purification by flash column

chromatography (hexane: EtOAc, 6:1 then 4:1 v/v) afforded the title product (1.50 g, 80%) as a yellow solid.

R_f 0.50 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (1H, br s, H-7), 7.63 – 7.56 (1H, m, H-Ar), 7.43 – 7.35 (1H, m, H-Ar), 7.35 – 7.27 (5H, m, H-Ar), 7.20 – 7.08 (2H, m, H-Ar), 3.99 (2H, s, H-11), 2.45 (3H, s, H-9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.4 (C, C-12), 135.4 (C, C-Ar), 133.6 (C, C-Ar), 133.2 (2CH, C-Ar), 130.7 (CH, C-Ar), 128.8 (C, C-Ar), 128.6 (2CH, C-Ar), 121.6 (CH, C-Ar), 120.1 (C, C-Ar), 119. 9 (CH, C-Ar), 118.3 (CH, C-Ar), 110.5 (CH, C-Ar), 103.7 (C, C-Ar), 91.8 (C, C-14), 88.2 (C, C-13), 41.3 (CH_2, C-11), 12.0 (CH_3, C-9).

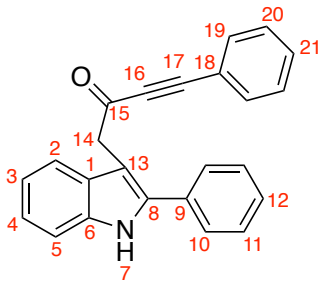
4-(4-Fluorophenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one (97c)



Synthesized using **General Procedure D** with *N*-methoxy-*N*-methyl-2-(2-methyl-1*H*-indol-3-yl)acetamide **100** (0.70 g, 3.01 mmol), 1-ethynyl-4-fluorobenzene (0.90 g, 7.53 mmol), *n*-BuLi (3.01 mL, 7.53 mmol, 2.5 M in hexanes). Purification by flash column chromatography (hexane: EtOAc, 6:1 then 4:1 v/v) afforded the title product (0.72 g, 82%) as a yellow solid.

R_f 0.50 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (1H, br s, H-7), 7.65 – 7.55 (1H, m, H-Ar), 7.34 – 7.11 (5H, m, H-Ar), 6.97 (2H, t, J = 8.5 Hz, H-Ar), 3.99 (2H, s, H-11), 2.40 (3H, s, H-9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.5 (C, C-12), 163.9 (C, d, $^1J_{C\text{-}F}$ = 253.8 Hz, C-18), 135.4 (2CH, d, $^3J_{C\text{-}F}$ = 9.1 Hz, C-16), 135.4 (C, C-Ar) 133.7 (C, C-Ar), 128.7 (C, C-Ar), 121.4 (CH, C-Ar), 119.7 (CH, C-Ar), 118.1 (CH, C-Ar), 116.1 (2CH, d, $^2J_{C\text{-}F}$ = 22.3 Hz, C-17), 116.0 (C, d, $^4J_{C\text{-}F}$ = 3.4 Hz, C-15), 110.6 (CH, C-Ar), 103.3 (C, C-Ar), 90.9 (C, C-14), 88.0 (C, C-13), 41.2 (CH_2, C-11), 11.8 (CH_3, C-9); **^{19}F NMR** (282 MHz, $CDCl_3$) δ – 106.12 – – 106.37 (F, m) ; **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{14}FNNaO$ 314.0952; Found 314.0951, $[M + H]^+$ Calcd for $C_{19}H_{15}FNO$ 292.1132; Found 292.1132.

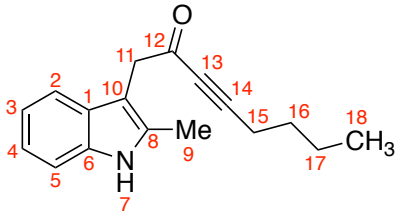
4-Phenyl-1-(2-phenyl-1*H*-indol-3-yl)but-3-yn-2-one (97d)



Synthesized using **General Procedure D** with *N*-methoxy-*N*-methyl-2-(2-phenyl-1*H*-indol-3-yl)acetamide **100** (0.54 g, 1.82 mmol), phenylacetylene (0.50 mL, 4.54 mmol), *n*-BuLi (1.82 mL, 4.54 mmol, 2.5 M in hexanes). Purification by flash column chromatography (hexane: EtOAc, 6:1 then 4:1 v/v) afforded the title product (0.44 g, 73%) as a yellow oil.

R_f 0.58 (hexane:EtOAc , 2:1 v/v);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (1H, br s, H-7), 7.73 (1H, d, *J* = 7.7 Hz, H-2), 7.68 – 7.57 (2H, m, H-19), 7.49 – 7.43 (2H, m, H-20), 7.42 – 7.33 (3H, m, H-Ar), 7.29 – 7.17 (6H, m, H-Ar), 4.19 (2H, s, H-10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.4 (C, C-11) , 136.8 (C, C-6), 135.9 (C, C-1), 133.2 (2CH, C-Ar), 132.3 (C, C-8), 130.8 (CH, C-Ar), 129.2 (C, C-18), 129.0 (2CH, C-Ar), 128.5 (3CH, C-Ar), 128.1 (2CH, C-Ar), 122.6 (CH, C-Ar), 120.2 (CH, C-Ar), 119.7 (C, C-14), 119.3 (CH, C-2), 111.2 (C, C-5), 104.4 (C, C-9), 92.7 (C, C-13), 88.4 (C, C-12), 41.8 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{17}NNaO$ 358.1202; Found 358.1201, $[M + H]^+$ Calcd for $C_{24}H_{18}NO$ 336.1383; Found 336.1381; **ν_{max}** (thin film)/cm^{-1} 3364, 3059, 2200, 1655, 1602, 1489, 1454, 1287, 1084, 908.

1-(2-Methyl-1*H*-indol-3-yl)oct-3-yn-2-one (97e)

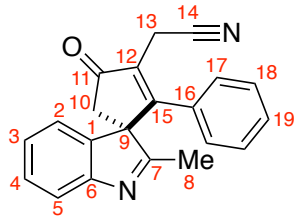


Synthesized using **General Procedure D** with *N*-methoxy-*N*-methyl-2-(2-methyl-1*H*-indol-3-yl)acetamide **100** (0.65 g, 2.80 mmol), hex-1-yne (0.80 mL, 6.70 mmol),

n-BuLi (2.80 mL, 6.70 mmol, 2.5 M in hexanes). Purification by flash column chromatography (hexane: EtOAc, 7:1 then 6:1 v/v) afforded the title product (0.46 g, 65%) as a pale orange oil.

R_f 0.54 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (1H, br s, H-7), 7.58 – 7.49 (1H, m, H-Ar), 7.27 – 7.20 (1H, m, H-Ar), 7.18 – 7.08 (2H, m, H-Ar), 3.90 (2H, s, H-11), 2.34 (3H, s, H-9), 2.25 (2H, t, *J* = 7.0 Hz, H-15), 1.47 – 1.38 (2H, m, H-16), 1.35 – 1.24 (2H, m, H-17), 0.87 (3H, t, *J* = 7.3 Hz, H-18); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.9 (C, C-12), 135.3 (C, C-Ar), 133.5 (C, C-Ar), 128.6 (C, C-Ar), 121.2 (CH, C-Ar), 119.5 (CH, C-Ar), 118.0 (CH, C-Ar), 110.5 (CH, C-Ar), 103.4 (C, C-Ar), 95.6 (C, C-14), 81.1 (CH_2, C-13), 41.3 (CH_2, C-11), 29.6 (CH_2, C-16), 21.8 (CH_2, C-17), 18.7 (CH_2, C-15), 13.5 (CH_3, C-18), 11.7 (CH_3, C-9); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{19}NNaO$ 276.1359; Found 276.1357, $[M + H]^+$ Calcd for $C_{17}H_{20}NO$ 254.1539; Found 254.1543.

2-(2'-Methyl-4-oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109a)

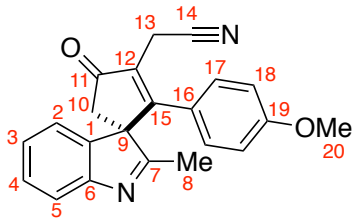


Synthesized using **General Procedure E** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), bromoacetonitrile (28 µL, 0.4 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane: EtOAc, 2:1 then 1:1 v/v) afforded the title compound (46.9 mg, 75%) as a brown oil.

R_f 0.23 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (1H, br d, *J* = 7.7 Hz, H-2), 7.41 – 7.35 (1H, m, H-3), 7.34 – 7.29 (1H, m, H-19), 7.28 – 7.18 (4H, m, H-4,5,18), 6.79 – 6.71 (2H, m, H-17), 3.46 (1H, d, *J* = 17.1 Hz, H-13a), 3.40 (1H, d, *J* = 17.1 Hz, H-13b), 2.94 (1H, d, *J* = 19.0 Hz, H-10a), 2.86 (1H, d, *J* = 19.0 Hz, H-10b), 2.22 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.0 (C, C-11), 180.7 (C, C-7), 172.3 (C, C-15), 155.4 (C, C-6), 139.8 (C, C-1), 133.3 (C, C-12), 131.5 (C, C-16),

130.9 (CH, C-19), 129.5 (CH, C-3), 129.3 (2CH, C-18), 126.7 (CH, C-5), 126.5 (2CH, C-17), 122.0 (CH, C-4), 120.9 (CH, C-2), 116.1 (C, C-14), 67.2 (C, C-9), 43.0 (CH_2, C-10), 16.0 (CH_3, C-8), 13.7 (CH_2, C-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{16}N_2NaO$ 335.1155; Found 335.1152, $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O$ 313.1335; Found 313.1333; ν_{max} (thin film)/cm^{-1} 2258 (C≡N), 1711 (C=O), 1579 (C=C).

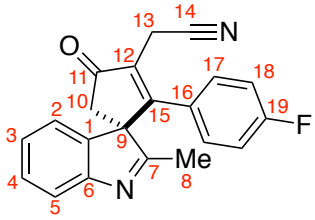
2-(2-(4-Methoxyphenyl)-2'-methyl-4-oxospiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109b)



Synthesized using **General Procedure E** with 4-(4-methoxyphenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97b** (60.7 mg, 0.2 mmol), bromoacetonitrile (28 μL, 0.4 mmol), 2,6-lutidine (47 μL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol %) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (44.2 mg, 65%) as a brown oil.

R_f 0.18 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (1H, br d, *J* = 7.7 Hz, H-2), 7.40 (1H, ddd, *J* = 7.7, 7.1, 1.6 Hz, H-3), 7.25 – 7.21 (1H, m, H-4), 7.20 (1H, ddd, *J* = 7.4, 7.2, 1.1 Hz, H-5), 6.74 (4H, s, H-17,18), 3.74 (3H, s, H-20), 3.51 (1H, d, *J* = 17.0 Hz, H-13a), 3.45 (1H, d, *J* = 17.0 Hz, H-13b), 2.90 (1H, d, *J* = 18.9 Hz, H-10a), 2.81 (1H, d, *J* = 18.9 Hz, H-10b), 2.18 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.0 (C, C-11), 181.5 (C, C-7), 171.5 (C, C-15), 161.7 (C, C-19), 155.3 (C, C-6), 140.5 (C, C-1), 131.8 (C, C-12), 129.4 (CH, C-3), 128.6 (2CH, C-17), 126.8 (CH, C-5), 123.8 (C, C-16), 121.9 (CH, C-4), 120.9 (CH, C-2), 116.4 (C, C-14), 114.8 (2CH, C-18), 67.1 (C, C-9), 55.4 (CH_3, C-20), 43.3 (CH_2, C-10), 16.0 (CH_3, C-8), 14.0 (CH_2, C-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}N_2NaO_2$ 365.1260; Found 365.1264, $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2$ 343.1441; Found 343.1444; ν_{max} (thin film)/cm^{-1} 2251 (C≡N), 1707 (C=O).

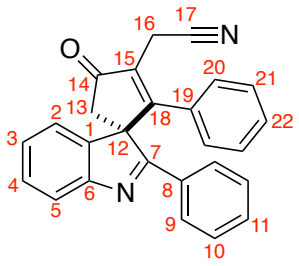
2-(2-(4-Fluorophenyl)-2'-methyl-4-oxospiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109c)



Synthesized using **General Procedure E** with 4-(4-fluorophenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97c** (58.3 mg, 0.2 mmol), bromoacetonitrile (28 µL, 0.4 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol %) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (32.5 mg, 49%) as a yellow oil.

R$_f$ 0.21 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, br d, *J* = 7.7 Hz, H-2), 7.40 (1H, ddd, *J* = 7.7, 7.0, 1.7 Hz, H-3), 7.28 – 7.24 (1H, m, H-4), 7.22 (1H, ddd, 7.4, 1.7, 0.7 Hz, H-5), 6.98 – 6.88 (2H, m, H-18), 6.80 – 6.73 (2H, m, H-17), 3.46 (1H, d, *J* = 17.2 Hz, H-13a), 3.40 (1H, d, *J* = 17.2 Hz, H-13b), 2.94 (1H, d, *J* = 19.1 Hz, H-10a), 2.86 (1H, d, *J* = 19.1 Hz, H-10b), 2.21 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.8 (C, C-11), 180.6 (C, C-7), 171.1 (C, C-15), 163.7 (C, d, $^1J_{C\text{-}F}$ = 253.2 Hz, C-19), 155.4 (C, C-6), 139.7 (C, C-1), 133.4 (C, C-12), 129.7 (CH, C-3), 128.8 (2CH, d, $^3J_{C\text{-}F}$ = 8.7 Hz, C-17), 127.5 (C, d, $^4J_{C\text{-}F}$ = 3.4 Hz, C-16), 126.9 (CH, C-5), 122.0 (CH, C-4), 121.0 (CH, C-2), 116.7 (2CH, d, $^2J_{C\text{-}F}$ = 21.8 Hz, C-18), 116.0 (C, C-14), 67.2 (C, C-9), 42.8 (CH_2, C-10), 16.0 (CH_3, C-8), 13.7 (CH_2, C-13); **^{19}F NMR** (282 MHz, $CDCl_3$) δ –107.85 – –108.14 (1F, m, F-19); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{15}FN_2NaO$ 353.1061; Found 353.1060, $[M + H]^+$ Calcd for $C_{21}H_{16}FN_2O$ 331.1241; Found 331.1239; **ν_{max}** (thin film)/cm^{-1} 2253 (C≡N), 1711 (C=O).

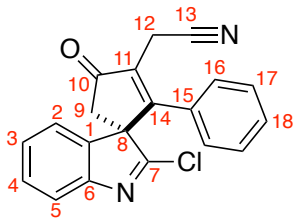
2-(4-Oxo-2,2'-diphenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109d)



Synthesized using **General Procedure E** with 4-phenyl-1-(2-phenyl-1*H*-indol-3-yl)but-3-yn-2-one **97d** (67.1 mg, 0.2 mmol), bromoacetonitrile (28 µL, 0.4 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol %) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title compound (39.8 mg, 53%) as a yellow oil.

R$_f$ = 0.55 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.90 (2H, m, H-9), 7.68 (1H ,br d, *J* = 7.7 Hz, H-2), 7.52 – 7.41 (4H, m, H-Ar), 7.31 (1H, td, *J* = 7.4, 1.2 Hz, H-Ar), 7.27 – 7.19 (2H, m, H-Ar), 7.18 – 7.11 (2H, m, H-21), 6.77 – 6.62 (2H, m, H-20), 3.53 (1H, d, *J* = 16.9 Hz, H-16a), 3.47 (1H, d, *J* = 16.9 Hz, H-16b), 3.27 (1H, d, *J* = 19.2 Hz, H-13a), 2.91 (1H, d, *J* = 19.2 Hz, H-13b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.5 (C, C-14), 176.3 (C, C-7), 174.4 (C, C-18), 154.7 (C, C-6), 141.2 (C, C-1), 132.2 (C, C-Ar), 132.1 (C, C-Ar), 131.9 (CH, C-Ar), 131.5 (C, C-19), 130.8 (CH, C-22), 129.7 (CH, C-Ar), 129.4 (2CH, C-10), 129.1 (2CH, C-21), 127.7 (2CH, C-9), 127.3 (CH, C-Ar), 126.7 (2CH, C-20), 121.8 (CH, C-2), 121.2 (CH, C-Ar), 116.0 (C, C-17), 65.9 (C, C-12), 45.1 (CH_2, C-13), 13.7 (CH_2, C-16); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{18}N_2NaO$ 397.1311; Found 397.1319, $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O$ 375.1492; Found 375.1498; **ν_{max}** (thin film)/cm^{-1} 2252 (C≡N), 1711 (C=O).

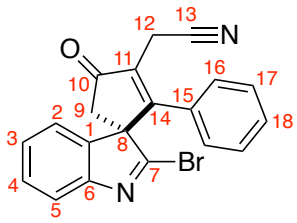
2-(2'-Chloro-4-oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109e)



Synthesized using **General Procedure E** with 1-(2-chloro-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81g** (58.8 mg, 0.2 mmol), bromoacetonitrile (28 μL, 0.4 mmol), 2,6-lutidine (47 μL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title compound (33.4 mg, 50%) as a yellow oil.

R$_f$ 0.43 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (1H, br d, *J* = 7.7 Hz, H-2), 7.44 – 7.38 (1H, m, H-3), 7.36 – 7.22 (5H, m, H-4,5,17,18), 6.86 – 6.76 (2H, m, H-16), 3.42 (1H, d, *J* = 17.2 Hz, H-12a), 3.67 (1H, d, *J* = 17.2 Hz, H-12b), 3.13 (1H, d, *J* = 18.8 Hz, H-9a), 2.90 (1H, d, *J* = 18.8 Hz, H-9b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.8 (C, C-11), 170.2 (C, C-14), 169.9 (C, C-7), 153.2 (C, C-6), 138.9 (C, C-1), 134.6 (C, C-11), 130.9 (CH, C-18), 130.7 (C, C-15), 130.0 (CH, C-3), 129.2 (2CH, C-17), 127.6 (CH, C-5), 126.6 (2CH, C-16), 122.2 (CH, C-4), 121.5 (CH, C-2), 115.7 (C, C-13), 68.1 (C, C-8), 42.6 (CH_2, C-9), 13.6 (CH_2, C-12); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{13}{}^{35}ClN_2NaO$ 355.0609; Found 355.0608, $[M + H]^+$ Calcd for $C_{20}H_{14}{}^{35}ClN_2O$ 333.0789; Found 333.0787; **ν_{max}** (thin film)/cm^{-1} 2258 (C≡N), 1718 (C=O).

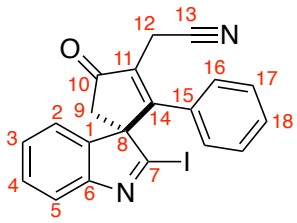
2-(2'-Bromo-4-oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109f)



Synthesized using **General Procedure E** with 1-(2-bromo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81a** (67.6 mg, 0.2 mmol), bromoacetonitrile (28 μL, 0.4 mmol), 2,6-lutidine (47 μL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and anhydrous DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title compound (34.5 mg, 46%) as a yellow oil.

R_f 0.40 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (1H, br d, *J* = 7.7 Hz, H-2), 7.44 – 7.38 (1H, m, H-3), 7.37 – 7.31 (3H, m, H-Ar), 7.29 – 7.23 (2H, m, H-Ar), 6.85 – 6.81 (2H, m, H-16), 3.41 (1H, d, *J* = 17.1 Hz, H-12a), 3.40 (1H, d, *J* = 17.1 Hz, H-12b), 3.11 (1H, d, *J* = 18.8 Hz, H-12a), 2.87 (1H, d, *J* = 18.8 Hz, H-12b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.7 (C, C-11), 170.0 (C, C-14), 164.0 (C, C-7), 154.1 (C, C-6), 139.1 (C, C-1), 134.7 (C, C-11), 130.9 (CH, C-18), 130.7 (C, C-15), 129.9 (CH, C-3), 129.1 (2CH, C-17), 127.7 (CH, C-5), 126.7 (2CH, C-16), 122.3 (CH, C-4), 121.2 (CH, C-2), 115.7 (C, C-13), 70.2 (C, C-8), 42.8 (CH_2, C-9), 13.6 (CH_2, C-12); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{13}{}^{79}BrN_2NaO$ 399.0103; Found 399.0107, $[M + H]^+$ Calcd for $C_{20}H_{14}{}^{79}BrN_2O$ 377.0284; Found 377.0289; $\boldsymbol{\nu}_{max}$ (thin film)/cm^{-1} 2254 (C≡N), 1718 (C=O).

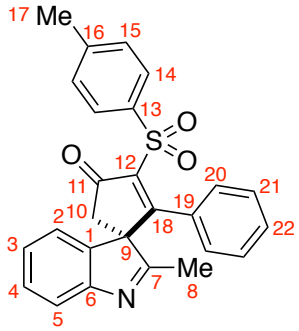
2-(2'-Iodo-4-oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)acetonitrile (109g)



Synthesized using **General Procedure E** with 1-(2-iodo-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81h** (77.0 mg, 0.2 mmol), bromoacetonitrile (28 μL, 0.4 mmol), 2,6-lutidine (47 μL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title compound (37.7 mg, 44%) as a yellow oil.

R$_f$ 0.43 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 7.7 Hz, H-2), 7.42 – 7.16 (6H, m, H-3,4,5,17,18), 6.84 – 6.77 (2H, m, H-16), 3.41 (2H, s, H-12), 2.97 (1H, d, *J* = 18.9 Hz, H-9a), 2.77 (1H, d, *J* = 18.9 Hz, H-9b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.9 (C, C-10), 170.4 (C, C-14), 156.6 (C, C-6), 146.5 (C, C-7), 139.5 (C, C-1), 134.9 (C, C-11), 130.9 (CH, C-18), 130.8 (C, C-15), 129.7 (CH, C-3), 129.1 (2CH, C-17), 127.6 (CH, C-5), 126.9 (2CH, C-16), 122.4 (CH, C-4), 121.2 (CH, C-2), 115.6 (C, C-13), 73.0 (C, C-8), 43.3 (CH_2, C-9), 13.7 (CH_2, C-12); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{13}IN_2NaO$ 446.9965; Found 446.9969, $[M + H]^+$ Calcd for $C_{20}H_{14}IN_2O$ 425.0145; Found 425.0147; **ν_{max}** (thin film)/cm^{-1} 2257 (C≡N), 1715 (C=O).

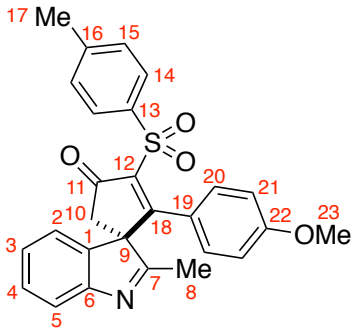
2'-Methyl-2-phenyl-3-tosylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113a)



Synthesized using **General Procedure F** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), *p*-toluene sulfonyl chloride (57.2 mg, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (76.4 mg, 89%) as a brown solid.

Mp. 181 – 184 °C; **R$_f$** 0.56 (hexane: EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (2H, m, H-14), 7.47 (1H, br d, *J* = 7.7 Hz, H-2), 7.40 – 7.28 (4H, m, H-3,15,22), 7.23 (1H, td, *J* = 7.6, 0.8 Hz, H-4), 7.20 – 7.14 (2H, m, H-21), 7.11 (1H, d, *J* = 7.4 Hz, H-5), 6.78 – 6.74 (2H, m, H-20), 2.89 (1H, d, *J* = 18.9 Hz, H-10a), 2.80 (1H, d, *J* = 18.9 Hz, H-10b), 2.46 (3H, s, H-17), 2.16 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.0 (C, C-11), 180.0 (C, C-18), 179.1 (C, C-7), 155.7 (C, C-6), 145.4 (C, C-16), 141.7 (C, C-12), 138.9 (C, C-1), 137.0 (C, C-13), 131.1 (CH, C-22), 130.6 (C, C-19), 129.9 (CH, C-3), 129.8 (2CH, C-15), 129.0 (2CH, C-14), 128.0 (2CH, C-21), 126.8 (CH, C-4), 126.7 (2CH, C-20), 122.1 (CH, C-5), 121.0 (CH, C-2), 67.7 (C, C-9), 43.2 (CH_2, C-10), 21.9 (CH_3, C-17), 16.3 (CH_3, C-8); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{21}NNaO_3S$ 450.1134; Found 450.1138, $[M + H]^+$ Calcd for $C_{26}H_{22}NO_3S$ 428.1315; Found 428.1319; **ν_{max}** (thin film)/cm^{-1} 1724 (C=O), 1326 (S=O).

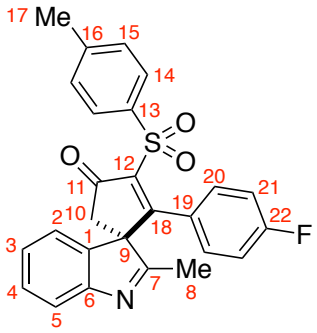
2-(4-Methoxyphenyl)-2'-methyl-3-tosylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113b)



Synthesized using **General Procedure F** with 4-(4-methoxyphenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97b** (60.7 mg, 0.2 mmol), *p*-toluene sulfonyl chloride (57.2 mg, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (61.5 mg, 67%) as a yellow oil.

R$_f$ 0.30 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (100 MHz, $CDCl_3$) δ 7.91 – 7.85 (2H, m, H-14), 7.53 (1H, br d, *J* = 7.7 Hz, H-2), 7.39 (1H, td, *J* = 7.7, 1.2 Hz, H-3), 7.36 – 7.32 (2H, m, H-15), 7.23 – 7.18 (1H, m, H-4), 7.04 (1H, ddd, *J* = 7.6, 1.2, 0.6 Hz, H-5), 6.86 – 6.79 (2H, m, H-20), 6.72 – 6.67 (2H, m, H-21), 3.75 (3H, s, H-23), 2.83 (1H, d, *J* = 18.7 Hz, H-10a), 2.70 (1H, d, *J* = 18.7 Hz, H-10b), 2.45 (3H, s, H-17), 2.10 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.8 (C, C-11), 180.2 (C, C-7), 178.9 (C, C-18), 162.5 (C, C-22), 155.5 (C, C-6), 145.3 (C, C-16), 139.9 (C,C-1), 139.8 (C, C-12), 137.1 (C, C-13), 129.9 (2CH, C-20), 129.8 (CH, C-3), 129.7 (2CH, C-15), 129.0 (2CH, C-14), 126.9 (CH, C-4), 123.0 (C, C-19), 121.9 (CH, C-5), 121.0 (CH, C-2), 113.6 (2CH, C-21), 67.5 (C, C-9), 55.4 (CH_3, C-23), 43.7 (CH_2, C-10), 21.9 (CH_3, C-17), 16.1 (CH_3, C-8); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{23}NNaO_4S$ 480.1240; Found 480.1242, $[M + H]^+$ Calcd for $C_{27}H_{24}NO_4S$ 458.1421; Found 458.1424; **ν_{max}** (thin film)/cm^{-1} 2938, 2843, 1719 (C=O), 1323 (S=O).

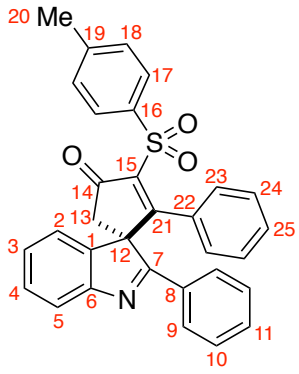
2-(4-Fluorophenyl)-2'-methyl-3-tosylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113c)



Synthesized using **General Procedure F** with 4-(4-fluorophenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97c** (58.3 mg, 0.2 mmol), *p*-toluene sulfonyl chloride (57.2 mg, 0.3 mmol), 2,6-lutidine (47 μL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (62.5 mg, 70%) as a yellow oil.

R$_f$ 0.30 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.81 (2H, m, H-14), 7.49 (1H, br d, J = 7.7 Hz, H-2), 7.41 – 7.36 (1H, m, H-3), 7.36 – 7.32 (2H, m, H-15), 7.26 – 7.20 (1H, m, H-4), 7.09 (1H, ddd, J = 7.5, 1.2, 0.6 Hz, H-5), 6.91 – 6.83 (2H, m, H-21), 6.81 – 6.74 (2H, m, H-20), 2.88 (1H, d, J = 18.9 Hz, H-10a), 2.79 (1H, d, J = 18.9 Hz, H-10b), 2.45 (1H, s, H-17), 2.15 (1H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.8 (C, C-11), 179.1 (C, C-7), 178.3 (C, C-18), 164.3 (C, d, $^1J_{C\text{-}F}$ = 253.0 Hz, C-22), 155.6 (C, C-6), 145.6 (C, C-16), 141.8 (C, C-12), 138.8 (C, C-1), 136.7 (C, C-13), 130.0 (CH, C-3), 129.8 (2CH, C-15), 129.3 (2CH, d, $^3J_{C\text{-}F}$ = 8.7 Hz, C-20), 129.0 (2CH, C-14), 126.9 (CH, C-4), 126.5 (C, d, $^4J_{C\text{-}F}$ = 3.5 Hz, C-19), 122.0 (CH, C-5), 121.1 (CH, C-2), 115.4 (2CH, d, $^2J_{C\text{-}F}$ = 22.0 Hz, C-21), 67.6 (C, C-9), 43.1 (CH_2, C-10), 21.9 (CH_3, C-17), 16.2 (CH_3, C-8); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −107.86 – −107.99 (1F, m, F-22); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}FNNaO_3S$ 468.1040; Found 468.1042, $[M + H]^+$ Calcd for $C_{26}H_{21}FNO_3S$ 446.1221; Found 446.1226; ν_{max} (thin film)/cm^{-1} 1724 (C=O), 1325 (S=O).

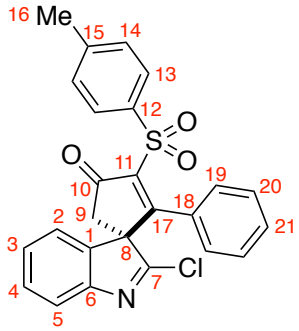
2,2'-Diphenyl-3-tosylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113d)



Synthesized using **General Procedure F** with 4-phenyl-1-(2-phenyl-1*H*-indol-3-yl)but-3-yn-2-one **97d** (67.1 mg, 0.2 mmol), *p*-toluene sulfonyl chloride (57.2 mg, 0.3 mmol), 2,6-lutidine (47 μL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title compound (95.9 mg, 98%) as a white solid.

Mp. 193 – 194°C; **R$_f$** 0.38 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (2H, m, H-17), 7.81 – 7.73 (2H, m, H-9), 7.59 (1H, br d, *J* = 7.8 Hz, H-2), 7.51 – 7.44 (1H, m, H-11), 7.44 – 7.32 (5H, m, H-3,10,18), 7.30 – 7.26 (1H, m, H-4), 7.24 – 7.18 (1H, m, H-25), 7.14 (1H, ddd, *J* = 7.5, 1.2, 0.7 Hz, H-5), 7.09 – 7.02 (2H, m, H-24), 6.74 – 6.65 (2H, m, H-23), 3.19 (1H, d, *J* = 19.3 Hz, H-13a), 2.86 (1H, d, *J* = 19.3 Hz, H-13b), 2.49 (3H, s, H-20); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.5 (C, C-14), 181.7 (C, C-21), 175.0 (C, C-7), 154.9 (C, C-6), 145.4 (C, C-19), 140.9 (C, C-15), 140.1 (C, C-1), 136.9 (C, C-16), 131.9 (CH, C-11), 131.8 (C, C-8), 130.7 (CH, C-25), 130.4 (C, C-22), 130.0 (CH, C-3), 129.8 (2CH, C-18), 129.3 (2CH, C-10), 129.0 (2CH, C-17), 127.8 (2CH, C-9), 127.6 (2CH, C-24), 127.3 (CH, C-4), 126.9 (2CH, C-23), 121.8 (CH, C-2), 121.4 (CH, C-5), 66.3 (C, C-12), 45.1 (CH_2, C-13), 21.9 (CH_3, C-20); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{23}NNaO_3S$ 512.1291; Found 512.1304, $[M + H]^+$ Calcd for $C_{31}H_{24}NO_3S$ 490.1471; Found 490.1485; ν_{max} (thin film)/cm^{-1} 1724 (C=O), 1330 (S=O).

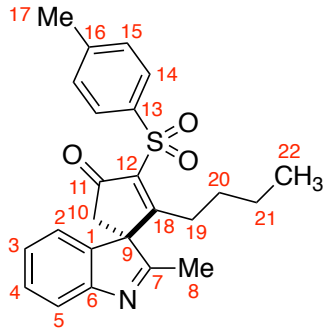
2'-Chloro-2-phenyl-3-tosylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113e)



Synthesized using **General Procedure F** with 1-(2-chloro-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81g** (58.8 mg, 0.2 mmol), *p*-toluene sulfonyl chloride (57.2 mg, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 6:1 then 4:1 v/v) afforded the title compound (38.8 mg, 43%) as a yellow solid.

Mp. 229 – 231 °C; **R$_f$** 0.35 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.82 (2H, m, H-13), 7.46 (1H, ddd, *J* = 7.6, 1.2, 0.6 Hz, H-2), 7.42 – 7.36 (1H, m, H-3), 7.36 – 7.28 (4H, m, H-4,14,21), 7.22 – 7.16 (3H, m, H-5,20), 6.84 – 6.79 (2H, m, H-19), 3.08 (1H, d, *J* = 18.8 Hz, H-9a), 2.85 (1H, d, *J* = 18.8 Hz, H-9b), 2.46 (3H, s, H-16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.9 (C, C-10), 176.9 (C, C-17), 168.4 (C, C-7), 153.4 (C, C-6), 145.6 (C, C-15), 142.9 (C, C-11), 137.9 (C, C-1), 136.7 (C, C-12), 130.8 (CH, C-21), 130.3 (CH, C-3), 129.9 (C, C-18), 129.8 (2CH, C-14), 129.03 (2CH, C-13), 127.9 (2CH, C-20), 127.7 (CH, C-4), 126.6 (2CH, C-19), 122.4 (CH, C-5), 121.5 (CH, C-2), 68.5 (C, C-8), 42.8 (CH_2, C-9), 21.9 (CH_3, C-16); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{18}{}^{35}ClNNaO_3S$ 470.0588; Found 470.0591, $[M + H]^+$ Calcd for $C_{25}H_{19}{}^{35}ClNO_3S$ 448.0769; Found 448.0775; **ν_{max}** (thin film)/ cm^{-1} 1731 (C=O), 1330 (S=O).

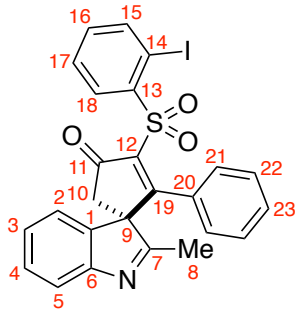
2-Butyl-2'-methyl-3-tosylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113f)



Synthesized using **General Procedure F** with 1-(2-methyl-1*H*-indol-3-yl)oct-3-yn-2-one **97e** (50.7 mg, 0.2 mmol), *p*-toluene sulfonyl chloride (57.2 mg, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 3:1 then 2:1 v/v) afforded the title compound (39.2 mg, 48%) as a yellow oil.

R$_f$ 0.21 (hexane: EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (2H, m, H-14), 7.62 (1H, br d, *J* = 7.7 Hz, H-2), 7.46 – 7.41 (1H, m, H-3), 7.40 – 7.35 (2H, m, H-15), 7.30 – 7.23 (1H, m, H-4), 7.14 – 7.11 (1H, m, H-5), 2.72 (1H, d, *J* = 19.1 Hz, H-10a), 2.64 (1H, d, *J* = 19.1 Hz, H-10b), 2.54 – 2.47 (1H, m, H-Al), 2.46 (3H, s, H-17), 2.43 – 2.31 (1H, m, H-Al), 2.08 (3H, s, H-8), 1.98 – 1.89 (1H, m, H-Al), 1.53 – 1.42 (1H, m, H-Al), 1.30 – 1.03 (2H, m, H-21), 0.68 (3H, t, *J* = 7.1 Hz, H-22); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.4 (C, C-11), 186.2 (C, C-18), 179.8 (C, C-7), 156.0 (C, C-6), 145.5 (C, C-16), 140.9 (C, C-12), 138.6 (C, C-1), 137.2 (C, C-13), 129.9 (CH, C-3), 129.9 (2CH, C-15), 128.8 (2CH, C-14), 126.6 (CH, C-4), 122.6 (CH, C-5), 121.0 (CH, C-2), 67.9 (C, C-9), 42.0 (CH_2, C-10), 32.6 (CH_2, C-Al), 28.6 (CH_2, C-Al), 23.3 (CH_2, C-Al), 21.9 (CH_3, C-17), 16.0 (CH_3, C-8), 13.3 (CH_3, C-22); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{25}NNaO_3S$ 430.1447; Found 430.1456, $[M + H]^+$ Calcd for $C_{24}H_{26}NO_3S$ 408.1628; Found 408.1638; **ν_{max}** (thin film)/cm^{-1} 2960 (C–H), 2931 (C–H), 1721 (C=O), 1320 (S=O).

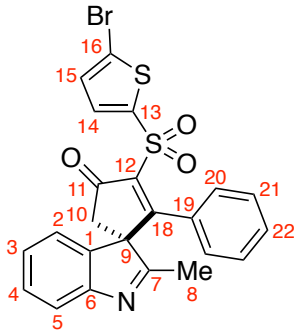
3-((2-Iodophenyl)sulfonyl)-2'-methyl-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113g)



Synthesized using **General Procedure F** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), 2-iodobenzene sulfonyl chloride (90.8 mg, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (95.3 mg, 88%) as a yellow oil.

R$_f$ 0.48 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (1H, dd, *J* = 7.9, 1.6 Hz, H-Ar), 8.00 (1H, dd, *J* = 7.9, 1.2 Hz, H-Ar), 7.57 (1H, ddd, *J* = 7.5, 1.2, 0.6 Hz, H-Ar), 7.51 – 7.39 (3H, m, H-Ar), 7.32 (1H, td, *J* = 7.5, 1.2 Hz, H-Ar), 7.29 – 7.24 (1H, m, H-23), 7.21 (1H, td, *J* = 7.6, 1.6 Hz, H-Ar), 7.12 – 7.07 (2H, m, H-22), 6.80 – 6.73 (2H, m, H-21), 2.99 (1H, d, *J* = 19.1 Hz, H-10a), 2.92 (1H, d, *J* = 19.1 Hz, H-10b), 2.31 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ. 196.4 (C, C-11), 180.3 (C, C-19), 179.7 (C, C-7), 155.2 (C, C-6), 142.1 (CH, C-Ar), 141.4 (C, C-13), 139.7 (C, C-12), 138.6 (C, C-1), 134.7 (CH, C-Ar), 132.7 (CH, C-Ar), 131.3 (CH, C-Ar), 130.2 (C, C-20), 130.1 (CH, C-Ar), 128.6 (CH, C-Ar), 128.0 (2CH, C-22), 127.0 (3CH, C-21,23), 123.1 (CH, C-Ar), 120.9 (CH, C-Ar), 93.1 (C, C-14), 67.5 (C, C-9), 42.8 (CH_2, C-10), 16.6 (CH_3, C-8); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{18}INNaO_3S$ 561.9944; Found 561.9944, $[M + H]^+$ Calcd for $C_{25}H_{19}INO_3S$ 540.0125; Found 540.0125; **ν_{max}** (thin film)/cm^{-1} 1697 (C=O), 1330 (S=O).

3-((5-Bromothiophen-2-yl)sulfonyl)-2'-methyl-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113h)

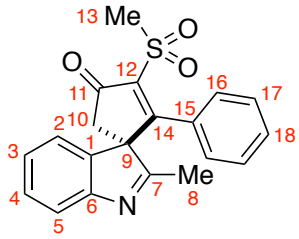


Synthesized using **General Procedure F** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), 5-bromothiophene-2-sulfonyl chloride (78.5 mg, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (78.2 mg, 78%) as a yellow solid.

Mp. 154 – 155 °C; **R$_f$** 0.59 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* = 4.1 Hz, H-15), 7.51 (1H, br d, *J* = 7.7 Hz, H-2), 7.43 – 7.37 (1H, m, H-3), 7.35 – 7.30 (1H, m, H-21), 7.30 – 7.24 (1H, m, H-4), 7.22 – 7.16 (3H, m, H-5,20), 7.13 (1H, d, *J* = 4.1 Hz, H-14), 6.77 – 6.72 (2H, m, H-19), 2.96 (1H, d, *J* = 18.9 Hz, H-10a), 2.87 (1H, d, *J* = 18.9 Hz, H-10b), 2.22 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.6 (C, C-11), 179.9 (C, C-17), 179.2 (C, C-7), 155.2 (C, C-6), 141.2 (C, C-13), 141.0 (C, C-12), 138.6 (C, C-1), 136.5 (CH, C-15), 131.4 (CH, C-21), 131.2 (CH, C-14), 130.3 (C, C-18), 130.1 (CH, C-3), 128.1 (2CH, C-20), 127.1 (CH, C-4), 126.7 (2CH, C-19), 124.0 (C, C-16), 122.2 (CH, C-5), 121.0 (CH, C-2), 67.7 (C, C-9), 43.2 (CH_2, C-10), 16.3 (CH_3, C-8); **HRMS** (ESI) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{16}{}^{79}BrNNaO_3S_2$ 519.9647; Found 519.9647, [M + H]$^+$ Calcd for $C_{23}H_{17}{}^{79}BrNO_3S_2$ 497.9828; Found 497.9826; **ν_{max}** (thin film)/cm^{-1} 1725 (C=O), 1336 (S=O).

The same compound was also prepared on 1.00 mmol scale from indole-ynone **97a** (273.3 mg, 1.00 mmol), 5-bromothiophene-2-sulfonyl chloride (392.3 mg, 1.50 mmol), 2,6-lutidine (0.23 mL, 2.00 mmol), Ir(*p*-F-ppy)$_3$ (7.1 mg, 1 mol%) and 1,4-dioxane (10 mL, 0.1 M) for 25 h, which afforded **113h** in 72% yield (358.5 mg).

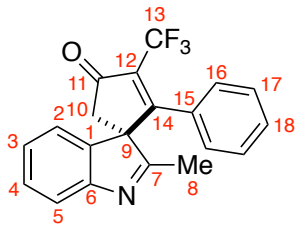
2'-Methyl-3-(methylsulfonyl)-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-4-one (113i)



Synthesized using **General Procedure F** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), methanesulfonyl chloride (23 µL, 0.3 mmol), 2,6-lutidine (47 µL, 0.4 mmol), Ir(*p*-F-ppy)$_3$ (1.4 mg, 1 mol%) and 1,4-dioxane (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:2 v/v) afforded the title compound (58.3 mg, 83%) as a yellow oil.

R$_f$ 0.38 (hexane:EtOAc , 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (1H, br d, *J* = 7.7 Hz, H-2), 7.45 – 7.39 (1H, m, H-3), 7.34 – 7.27 (3H, m, H-4,5,18), 7.19 – 7.14 (2H, m, H-17), 6.83 – 6.78 (2H, m, H-16), 3.29 (3H, s, H-13), 3.04 (1H, d, *J* = 19.0 Hz, H-10a), 2.94 (1H, d, *J* = 19.0 Hz, H-10b), 2.25 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.0 (C, C-11), 180.4 (C, C-14), 179.1 (C, C-7), 155.5 (C, C-6), 141.0 (C, C-12), 138.7 (C, C-1), 131.7 (CH, C-5), 130.2 (C, C-15), 130.1 (CH, C-3), 128.1 (2CH, C-17), 127.0 (3CH, C-16,18), 122.2 (CH, C-4), 121.1 (CH, C-2), 67.6 (C, C-9), 43.6 (CH_2, C-10), 43.1 (CH_3, C-13), 16.2 (CH_3, C-8); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}NNaO_3S$ 372.0821; Found 372.0821, $[M + H]^+$ Calcd for $C_{20}H_{18}NO_3S$ 352.1002; Found 352.1002; **ν_{max}** (thin film)/cm^{-1} 1719 (C=O), 1312 (S=O).

2'-Methyl-2-phenyl-3-(trifluoromethyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (115a)

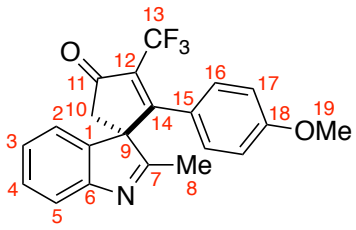


Synthesized using **General Procedure G** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (72.6 mg, 0.22 mmol), Eosin Y (1.3 mg, 1%mol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 3:1 then 2:1 v/v) afforded the title compound (30.7 mg, 45%) as a yellow oil.

R_f 0.30 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (1H, br d, *J* = 7.8 Hz, H-2), 7.40 (1H, ddd, *J* = 7.8, 6.8, 1.9 Hz, H-3), 7.34 – 7.26 (3H, m, H-4,5,-18), 7.19 – 7.13 (2H, m, H-17), 6.84 – 6.45 (2H, m, H-16), 2.98 (1H, d, *J* = 19.1 Hz, H-10a), 2.91 (1H, d, *J* = 19.1 Hz, H-10b), 2.26 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.6 (C, C-11), 179.4 (C, C-7), 177.4 (C, d, $^3J_{C\text{-}F}$ = 3.2 Hz, C-14), 155.4 (C, C-6), 138.8 (C, C-1), 132.1 (C, d, $^2J_{C\text{-}F}$ = 32.1 Hz, C-12), 130.9 (CH, C-18), 130.8 (C, C-15), 129.9 (CH, -3), 128.4 (2CH, C-17), 126.9 (CH, C-4), 126.1 (2CH, C-16), 122.2 (CH, -5), 120.9 (CH, C-2), 120.8 (C, q, $^1J_{C\text{-}F}$ = 273.0 Hz, C-13), 67.4 (C, C-9), 43.1 (CH_2, C-10), 16.1 (CH_3, C-8); **^{19}F NMR** (282 MHz, $CDCl_3$) δ –59.83 (3F, s, F-13). **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{14}F_3NNaO$ 364.0920; Found 364.0920, $[M + H]^+$ Calcd for $C_{20}H_{15}F_3NO$ 342.1100; Found 342.1100; **ν_{max}** (thin film)/cm^{-1} 1728 (C=O).

Spectroscopic data matched those previously reported in the literature.[96]

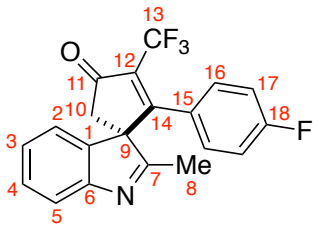
2-(4-Methoxyphenyl)-2'-methyl-3-(trifluoromethyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (115b)



Synthesized using **General Procedure G** with 4-(4-methoxyphenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97b** (60.7 mg, 0.2 mmol), 3,3-dimethyl-1-(trifluoromethyl) -1,2-benziodoxole (72.6 mg, 0.22 mmol), Eosin Y (1.3 mg, 1%mol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 3:1 then 2:1 v/v) afforded the title compound (43.1 mg, 58%) as a yellow oil.

R_f 0.18 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, br d, J = 7.7 Hz, H-2), 7.45 – 7.38 (1H, m, H-3), 7.30 – 7.26 (2H, m, H-4,5), 6.67 (s, 4H, H-16,17), 3.72 (3H, s, H-19), 2.94 (1H, d, J = 19.0 Hz, H-10a), 2.85 (1H, d, J = 19.0 Hz, H-10b), 2.20 (3H, s, H-8). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.7 (C, C-11), 180.3 (C, C-7), 176.8 (C, d, $^3J_{C\text{-}F}$ = 3.0 Hz, C-14), 162.0 (C, C-18), 155.4 (C, C-6), 139.6 (C, C-1), 130.7 (C, d, $^2J_{C\text{-}F}$ = 31.8 Hz, C-12), 129.8 (CH, C-3), 128.5 (2CH, C-16), 126.9 (CH, C-4), 123.2 (C, -15), 122.1 (CH, C-5), 121.1 (C, q, $^1J_{C\text{-}F}$ = 273.7 Hz, C-13), 121.0 (CH, C-2), 114.0 (2CH, C-17), 67.2 (C, C-9), 55.4 (CH_3, C-19), 43.5 (CH_2, C-10), 16.0 (CH_3, C-8); **^{19}F NMR** (282 MHz, $CDCl_3$) δ –59.64 (3F, s, F-13). **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{16}F_3NNaO_2$ 394.1025; Found 394.1038, $[M + H]^+$ Calcd for $C_{21}H_{17}F_3NO_2$ 372.1206; Found 372.1214; **ν_{max}** (thin film)/cm^{-1} 1725 (C=O).

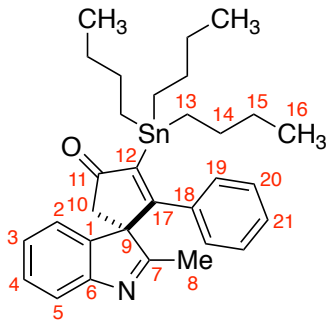
2-(4-Fluorophenyl)-2'-methyl-3-(trifluoromethyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (115c)



Synthesized using **General Procedure G** with 4-(4-fluorophenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97c** (58.3 mg, 0.2 mmol), 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (72.6 mg, 0.22 mmol), Eosin Y (1.3 mg, 1%mol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 v/v) afforded the title compound (30.2 mg, 42%) as a yellow oil.

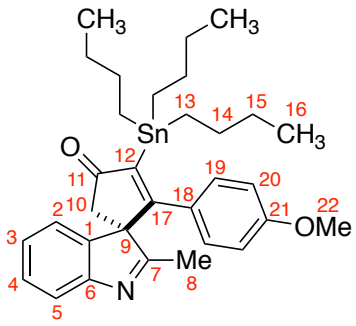
R_f 0.23 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 7.8 Hz, H-2), 7.42 (1H, ddd, *J* = 7.8, 5.3, 3.4 Hz, H-3), 7.33 – 7.27 (2H, m, H-4,5), 6.91 – 6.82 (2H, m, H-17), 6.73 – 6.66 (2H, m, H-16), 2.98 (2H, d, *J* = 19.1 Hz, H-10a), 2.91 (2H, d, *J* = 19.1 Hz, H-10b), 2.25 (3H, s, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.4 (C, C-11), 179.3 (C, C-7), 176.1 (C, d, $^3J_{C\text{-}F}$ = 3.0 Hz, C-14), 164.1 (C, d, $^1J_{C\text{-}F}$ = 252.8 Hz, C-18), 155.5 (C, C-6), 138.7 (C, C-1), 132.3 (C, d, $^2J_{C\text{-}F}$ = 32.2 Hz, C-12), 130.1 (CH, C-3), 128.5 (2CH, d, $^3J_{C\text{-}F}$ = 8.7 Hz, C-16), 127.0 (CH, C-4), 126.8 (C, d, $^4J_{C\text{-}F}$ = 3.5 Hz, C-15), 122.1 (CH, C-5), 121.1 (CH, C-2), 120.7 (C, q, $^1J_{C\text{-}F}$ = 271.7 Hz, C-13), 115.9 (2CH, d, $^2J_{C\text{-}F}$ = 22.0 Hz, C-17), 67.3 (C, C-9), 43.0 (CH_2, C-10), 16.1 (CH_3, C-8); **^{19}F NMR** (471 MHz, $CDCl_3$) δ –59.82 (3F, s, F-13), –108.24 – –128.35 (1F, m, F-18); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{20}H_{13}F_4NNaO$ 382.0825; Found 382.0831, $[M + H]^+$ Calcd for $C_{20}H_{14}F_4NO$ 360.1006; Found 360.1010; **ν_{max}** (thin film)/cm^{-1} 1730 (C=O).

2'-Methyl-2-phenyl-3-(tributylstannyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (121a)



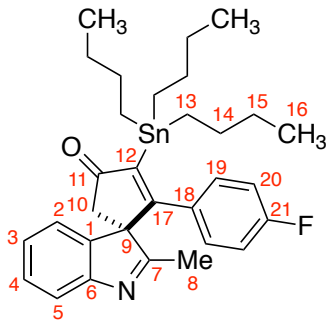
Synthesized using **General Procedure H** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (54.7 mg, 0.2 mmol), tributyltin hydride (108 µL, 0.4 mmol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 4:1 v/v) afforded the title compound (50.6 mg, 45%) as a yellow oil. **R_f** 0.55 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (1H, br d, *J* = 7.7 Hz, H-2), 7.36 – 7.29 (1H, m, H-3), 7.25 – 7.17 (3H, m, H-4,5,21), 7.12 – 7.07 (2H, m, H-20), 6.68 – 6.62 (2H, m, H-19), 2.89 (1H, d, *J* = 18.5 Hz, H-10a), 2.81 (1H, d, *J* = 18.5 Hz, H-10b), 2.22 (3H, s, H-8), 1.41 – 1.31 (6H, m, H-13), 1.27 – 1.13 (6H, m, H-14), 0.86 – 0.80 (15H, m, H-15,16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.2 (C, C-11), 183.4 (C, C-17), 181.8 (C, C-7), 155.4 (C, C-6), 149.5 (C, C-12), 140.9 (C, C-1), 136.0 (C, C-18), 129.6 (CH, C-21), 128.8 (CH, C-3), 128.3 (2CH, C-20), 126.4 (2CH, C-19), 126.2 (CH, C-4), 122.0 (CH, C-5), 120.4 (CH, C-2), 71.7 (C, C-9), 44.1 (CH_2, C-10), 29.2 ($3CH_2$, C-13), 27.3 ($3CH_2$, C-14), 15.9 (CH_3, C-8), 13.8 ($3CH_3$, C-16), 10.5 ($3CH_2$, C-15); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{31}H_{41}NNaOSn$ 586.2102; Found 586.2124, $[M + H]^+$ Calcd for $C_{31}H_{42}NOSn$ 564.2283; Found 564.2297; **ν_{max}** (thin film)/cm^{-1} 2955 (C–H), 2920 (C–H), 2871 (C–H), 2852 (C–H), 1691 (C=O).

2-(4-Methoxyphenyl)-2'-methyl-3-(tributylstannyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (121b)



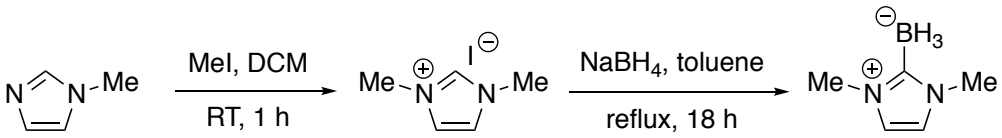
Synthesized using **General Procedure H** with 4-(4-methoxyphenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97b** (60.7 mg, 0.2 mmol), tributyltin hydride (108 µL, 0.4 mmol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 4:1 v/v) afforded the title compound (60.5 mg, 51%) as a yellow oil. **R_f** 0.45 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (1H, br d, *J* = 7.7 Hz, H-2), 7.39 – 7.32 (1H, m, H-3), 7.24 – 7.18 (m, 2H, H-4,5), 6.65 – 6.56 (4H, m, H-19,20), 3.71 (3H, s, H-22), 2.87 (1H, d, *J* = 18.4 Hz, H-10a), 2.78 (1H, d, *J* = 18.4 Hz, H-10b), 2.19 (s, 3H, H-8), 1.45 – 1.31 (6H, m, H-13), 1.30 – 1.12 (6H, m, H-14), 0.92 – 0.80 (15H, m, H-15,16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.1 (C, C-11), 182.8 (C, C-17), 182.6 (C, C-7), 160.8 (C, C-21), 155.1 (C, C-6), 148.3 (C, C-12), 141.4 (C, C-1), 128.8 (CH, C-3), 128.5 (C, C-18), 128.0 (2CH, C-19), 126.3 (CH, C-4), 121.9 (CH, C-5), 120.4 (CH, C-2), 113.8 (2CH, C-20), 71.5 (C, C-9), 55.3 (CH_3, C-22), 44.4 (CH_2, C-10), 29.2 ($3CH_2$, C-13), 27.3 ($3CH_2$, C-14), 15.8 (CH_3, C-8), 13.8 ($3CH_3$, C-16), 10.7 ($3CH_2$, C-15); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{32}H_{43}NNaO_2Sn$ 616.2208; Found 616.2225, $[M + H]^+$ Calcd for $C_{32}H_{44}NO_2Sn$ 594.2389; Found 594.2400; **ν_{max}** (thin film)/cm^{-1} 2955 (C–H), 2921 (C–H), 2871 (C–H), 2852 (C–H), 1689 (C=O).

2-(4-Fluorophenyl)-2'-methyl-3-(tributylstannyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one (121c)



Synthesized using **General Procedure H** with 4-(4-fluorophenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97c** (58.3 mg, 0.2 mmol), tributyltin hydride (108 µL, 0.4 mmol) and DCE (2 mL, 0.1 M). Purification by flash column chromatography (hexane:EtOAc, 4:1 v/v) afforded the title compound (55.8 mg, 48%) as a yellow oil. **R_f** 0.46 (hexane:EtOAc , 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (1H, br d, *J* = 7.7 Hz, H-2), 7.35 (1H, ddd, *J* = 7.7, 5.6, 3.2 Hz, H-3), 7.25 – 7.20 (2H, m, H-4,5), 6.85 – 6.76 (2H, m, H-20), 6.66 – 6.58 (2H, m, H-19), 2.89 (1H, d, *J* = 18.6 Hz, H-10a), 2.81 (1H, d, *J* = 18.6 Hz, H-10b), 2.21 (3H, s, H-8), 1.43 – 1.30 (6H, m, H-13), 1.29 – 1.16 (6H, m, H-14), 0.89 – 0.79 (15H, m, H-15,16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.0 (C, C-11), 182.0 (C, C-17), 181.8 (C, C-7), 163.4 (C, d, $^1J_{C\text{-}F}$ = 250.2 Hz, C-21), 155.3 (C, C-6), 149.9 (C, C-12), 140.7 (C, C-1), 132.1 (C, d, $^4J_{C\text{-}F}$ = 3.4 Hz, C-18), 129.0 (CH, C-3), 128.3 (2CH, d, $^3J_{C\text{-}F}$ = 8.3 Hz, C-19), 126.3 (CH, C-4), 121.9 (CH, C-5), 120.5 (CH, C-2), 115.5 (2CH, d, $^2J_{C\text{-}F}$ = 21.6 Hz, C-20), 71.7 (C, C-9), 44.0 (CH_2, C-10), 29.15 ($3CH_2$, C-13), 27.31 ($3CH_2$, C-14), 15.86 (CH_3, C-8), 13.79 ($3CH_3$, C-16), 10.59 ($3CH_2$, C-15); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −110.89 – −111.21 (1F, m, F-21); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{31}H_{40}FNNaOSn$ 604.2008; Found 604.2028, $[M + H]^+$ Calcd for $C_{31}H_{41}FNOSn$ 582.2189; Found 582.2200; **ν_{max}** (thin film)/cm^{-1} 2956 (C–H), 2921 (C–H), 2871 (C–H), 2853 (C–H), 1692 (C=O).

(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (127)

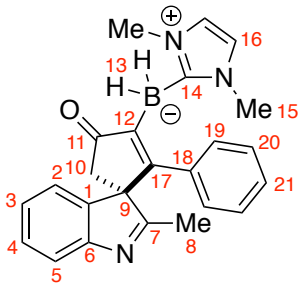


Synthesis following the reported method.[97] To a stirred solution of 1-methylimidazole (2.00 mL, 25.1 mmol) in dry DCM (5.0 mL) was slowly added iodomethane (1.87 mL, 30.1 mmol) under argon atmosphere. The solution mixture was stirred for 1 hour and then concentrated *in vacuo* to afford 1,3-dimethyl-1*H*-imidazol-3-ium iodide as a yellow solid (5.86 g, 100%), which a product will be used without further purification. Then, to a stirred solution of 1,3-dimethyl-1*H*-imidazol-3-ium iodide (3.00 g, 8.93 mmol) in dry toluene (14.0 mL) was added sodium borohydride (0.61 g, 10.71 mmol) under argon atmosphere. The solution mixture was heated to reflux for 18 hours. Then, the remaining hot solvent was poured out from the round bottom flask. Next, the insoluble mixture was washed with hot toluene (3 × 10 mL). The organic layers were combined and concentrated *in vacuo* to afford the title product as a white solid (0.60 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (2H, s), 3.73 (6H, s), 1.01 (3H, q, $J_{B\text{-}H}$ = 86.3 Hz); **^{11}B{^{1}H} NMR** (128 MHz, $CDCl_3$) δ –38.49 (1B, s); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_5H_{11}BN_2Na$ 133.0907; Found 133.0907.

Spectroscopic data matched those previously reported in the literature.[97]

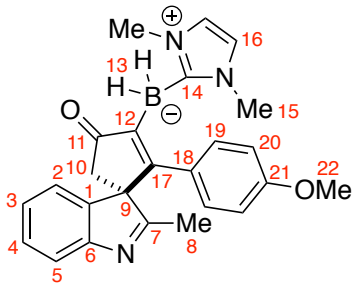
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2'-methyl-4-oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)dihydroborate (131a)



Synthesized using **General Procedure I** with 1-(2-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **97a** (81.9 mg, 0.3 mmol), (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (36.3 mg, 0.33 mmol), AIBN (54.2 mg, 0.33 mmol) and benzene (2.30 mL, 0.13 M). Purification by flash column chromatography (DCM:MeOH, 50:1 v/v) afforded the title compound (92.0 mg, 80%) as a yellow oil.

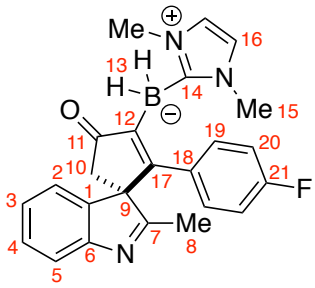
R_f 0.30 (DCM:MeOH, 20:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (1H, br d, *J* = 7.7 Hz, H-2), 7.29 (1H, ddd, *J* = 7.7, 5.8, 3.0 Hz, H-3), 7.18 – 7.11 (2H, m, H-4,5), 7.09 – 6.98 (3H, m, H-20,21), 6.79 – 6.74 (2H, m, H-19), 6.69 (2H, s, H-16), 3.61 (6H, s, H-15), 2.74 (1H, d, *J* = 18.3 Hz, H-10a), 2.62 (1H, d, *J* = 18.3 Hz, H-10b), 2.14 (3H, s, H-8), 2.03 (2H, br q, $J_{B\text{-}H}$ = 83.6 Hz, H-13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.4 (C, C-11), 184.4 (C, C-7), 171.5 (C, C-17), 155.3 (C, C-6), 143.0 (C, C-1), 136.9 (C, C-18), 128.2 (CH, C-21), 128.1 (CH, C-3), 127.4 (2CH, C-20), 127.3 (2CH, C-19), 125.7 (CH, C-4), 121.5 (CH, C-5), 120.2 (3CH, C-2,16), 69.3 (C, C-9), 44.7 (CH_2, C-10), 36.0 ($2CH_3$, C-15), 16.0 (CH_3, C-8) Note: the two ^{13}C NMR C–B (C-12,14) nuclei were not detected due to quadrupolar relaxation. **^{11}B{^{1}H} NMR** (128 MHz, $CDCl_3$) δ –31.94 (1B, br s, B-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{24}H_{24}BN_3NaO$ 404.1905; Found 404.1908, $[M + H]^+$ Calcd for $C_{24}H_{25}BN_3O$ 382.2085; Found 382.2088; **ν_{max}** (thin film)/cm^{-1} 2324 (B–H), 1680 (C=O).

(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-(4-methoxyphenyl)-2'-methyl-4-oxospiro [cyclopentane-1,3'-indol]-2-en-3-yl)dihydroborate (131b)



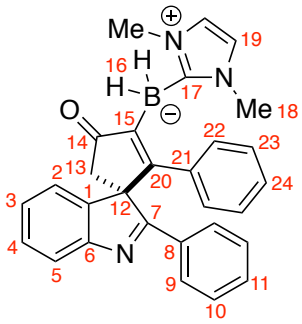
Synthesized using **General Procedure I** with 4-(4-methoxyphenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97b** (91.0 mg, 0.3 mmol), (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydro borate (36.3 mg, 0.33 mmol), AIBN (54.2 mg, 0.33 mmol) and benzene (2.30 mL, 0.13 M). Purification by flash column chromatography (DCM:MeOH, 50:1 v/v) afforded the title compound (100.5 mg, 81%) as a yellow oil. **R_f** 0.34 (DCM:MeOH, 20:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (1H, br d, *J* = 7.7 Hz, H-2), 7.33 – 7.27 (1H, m, H-4), 7.18 – 7.07 (2H, m, H-4,5), 6.86 – 6.80 (2H, m, H-19), 6.75 (2H, s, H-16), 6.63 – 6.56 (2H, m, H-20), 3.68 (3H, s, H-22), 3.65 (6H, s, H-15), 2.70 (1H, d, *J* = 18.2 Hz, H-10a), 2.57 (1H, d, *J* = 18.2 Hz, H-10b), 2.11 (3H, s, H-8), 2.04 (2H, br q, $J_{B\text{-}H}$ = 79.9 Hz, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.3 (C, C-11), 185.1 (C, C-7), 171.1 (C, C-17), 159.5 (C, C-21), 155.2 (C, C-6), 143.6 (C, C-1), 129.4 (C, C-18), 129.2 (2CH, C-19), 128.1 (CH, C-3), 125.8 (CH, C-4), 121.4 (CH, C-5), 120.3 (2CH, C-16), 120.2 (CH, C-2), 112.8 (2CH, C-20), 69.2 (C, C-9), 55.1 (CH_3, C-22), 45.1 (CH_2, C-10), 36.1 ($2CH_3$, C-15), 16.0 (CH_3, C-8). Note: the two ^{13}C NMR C–B (C-12,14) nuclei were not detected due to quadrupolar relaxation. **^{11}B{^{1}H} NMR** (128 MHz, $CDCl_3$) δ –31.63 (1B, br s, B-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{25}H_{26}BN_3NaO_2$ 434.2010; Found 434.2028, $[M + H]^+$ Calcd for $C_{25}H_{27}BN_3O_2$ 412.2191; Found : 412.2207; **ν_{max}** (thin film)/cm^{-1} 2323 (B–H), 1676 (C=O).

(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-(4-fluorophenyl)-2'-methyl-4-oxospiro [cyclopentane-1,3'-indol]-2-en-3-yl)dihydroborate (131c)



Synthesized using **General Procedure I** with 4-(4-fluorophenyl)-1-(2-methyl-1*H*-indol-3-yl)but-3-yn-2-one **97c** (87.4 mg, 0.3 mmol), (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (36.3 mg, 0.33 mmol), AIBN (54.2 mg, 0.33 mmol) and benzene (2.30 mL, 0.13 M). Purification by flash column chromatography (DCM:MeOH, 50:1 v/v) afforded the title compound (81.2 mg, 68%) as a yellow oil. **R_f** 0.50 (DCM:MeOH, 20:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (1H, br d, J = 7.7 Hz, H-2), 7.34 – 7.28 (1H, m, H-3), 7.18 – 7.22 (1H, m, H-4), 7.11 (1H, ddd, J = 7.4, 1.5, 0.7 Hz, H-5), 6.86 – 6.80 (2H, m, H-19), 6.78 – 6.72 (4H, m, H-16,20), 3.65 (6H, s, H-15), 2.72 (1H, d, J = 18.3 Hz, H-10a), 2.61 (1H, d, J = 18.3 Hz, H-10b), 2.13 (3H, s, H-8), 2.01 (2H, br q, $J_{B\text{-}H}$ = 82.3 Hz, H-13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.2 (C, C-11), 184.5 (C, C-7), 170.2 (C, C-17), 162.5 (C, d, $^1J_{C\text{-}F}$ = 248.2 Hz, C-21), 155.2 (C, C-6), 143.0 (C, C-1), 133.0 (C, d, $^4J_{C\text{-}F}$ = 3.3 Hz, C-18), 129.5 (2CH, d, $^3J_{C\text{-}F}$ = 8.1 Hz, C-19), 128.4 (CH, C-3), 125.9 (CH, C-4), 121.5 (CH, C-5), 120.4 (CH, C-2), 120.3 (2CH, C-16), 114.5 (2CH, d, $^2J_{C\text{-}F}$ = 21.3 Hz, C-20), 69.2 (C, C-9), 44.8 (CH_2, C-10), 36.1 ($2CH_3$, C-15), 16.0 (CH_3, C-8). Note: the two ^{13}C NMR C–B (C-12,14) nuclei were not detected due to quadrupolar relaxation; **^{11}B{^{1}H} NMR** (128 MHz, $CDCl_3$) δ –31.84 (1B, br s, B-13); **^{19}F NMR** (282 MHz, $CDCl_3$) δ –113.04 – –113.28 (1F, m, F-21); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{24}H_{23}BFN_3NaO$ 422.1810; Found 422.1822, $[M + H]^+$ Calcd for $C_{24}H_{24}BFN_3O$ 400.1991; Found : 400.2000; **ν_{max}** (thin film)/cm^{-1} 2327 (B–H), 1681 (C=O).

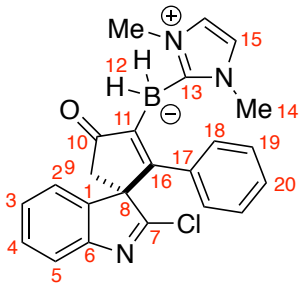
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(4-oxo-2,2'-diphenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)dihydroborate (131d)



Synthesized using **General Procedure I** with 4-phenyl-1-(2-phenyl-1*H*-indol-3-yl)but-3-yn-2-one **97d** (100.6 mg, 0.3 mmol), (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (36.3 mg, 0.33 mmol), AIBN (54.2 mg, 0.33 mmol) and benzene (2.30 mL, 0.13 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (71.1 mg, 53%) as a yellow oil.

R_f 0.15 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.99 (2H, m, H-9), 7.63 (1H, br d, *J* = 7.8 Hz, H-1), 7.45 – 7.31 (4H, m, H-3,10,11), 7.23 – 7.14 (2H, m, H-4,5), 7.01 – 6.89 (3H, m, H-23,24), 6.79 – 6.72 (2H, m, H-22), 6.69 (2H, s, H-19), 3.63 (6H, s, H-18), 3.08 (1H, d, *J* = 18.5 Hz, H-13a), 2.69 (1H, d, *J* = 18.5 Hz, H-13b). 2.08 (2H, br q, $J_{B\text{-}H}$ = 82.4 Hz, H-16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 213.7 (C, C-14), 179.2 (C, C-7), 173.5 (C, C-20), 154.5 (C, C-6), 144.4 (C, C-1), 137.0 (C, C-21), 133.0 (C, C-8), 131.0 (CH, C-11), 128.8 (2CH, C-10), 128.4 (CH, C-3), 128.0 (2CH, C-9), 128.0 (CH, C-24), 127.4 (2CH, C-22), 127.3 (2CH, C-23), 126.3 (CH, C-4), 121.2 (CH, C-2), 121.0 (CH, C-5), 120.3 (2CH, C-19), 68.2 (C, C-12), 46.9 (CH_2, C-13), 36.1 ($2CH_3$, C-18). Note: the two ^{13}C NMR C–B (C-15,17) nuclei were not detected due to quadrupolar relaxation; **^{11}B{^{1}H} NMR** (128 MHz, $CDCl_3$) δ –31.87 (1B, br s, B-16); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{29}H_{26}BN_3NaO$ 466.2061; Found 466.2074, $[M + H]^+$ Calcd for $C_{29}H_{27}BN_3O$ 444.2242; Found 444.2255; **ν_{max}** (thin film)/ cm^{-1} 2328 (B–H), 1682 (C=O).

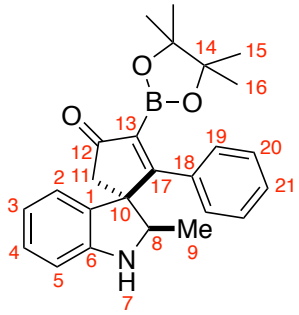
(2'-Chloro-4-oxo-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-3-yl)(1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)dihydroborate (131e)



Synthesized using **General Procedure I** with 1-(2-chloro-1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one **81g** (88.1 mg, 0.3 mmol), (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (36.3 mg, 0.33 mmol), AIBN (54.2 mg, 0.33 mmol) and benzene (2.30 mL, 0.13 M). Purification by flash column chromatography (hexane:EtOAc, 2:1 then 1:1 v/v) afforded the title compound (53.5 mg, 44%) as a yellow oil.

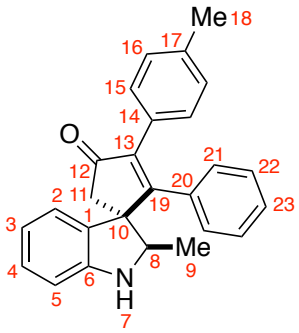
R_f 0.20 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (1H, br d, J = 7.7 Hz, H-2), 7.30 – 7.22 (1H, m, H-3), 7.20 – 7.15 (2H, m, H-4,5), 7.08 – 6.97 (3H, m, H-19,20), 6.87 – 6.79 (2H, m, H-18), 6.66 (2H, s, H-15), 3.59 (6H, s, H-14), 2.93 (1H, d, J = 18.2 Hz, H-9a), 2.71 (1H, d, J = 18.2 Hz, H-9b), 1.95 (2H, br q, $J_{B\text{-}H}$ = 84.7 Hz, H-12); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.1 (C, C-10), 173.3 (C, C-7), 169.1 (C, C-16), 152.9 (C, C-6), 141.8 (C, C-1), 136.5 (C, C-17), 128.5 (CH, C-3), 128.0 (CH, C-20), 127.5 (2CH, C-19), 127.2 (2CH, C-18), 126.7 (CH, C-4), 122.0 (CH, C-5), 120.7 (CH, C-2), 120.3 (2CH, C-15), 70.3 (C,C-8), 44.4 (CH_2, C-9), 36.0 ($2CH_3$, C-14). Note: the two ^{13}C NMR C–B (C-11,13) nuclei were not detected due to quadrupolar relaxation; **^{11}B{^{1}H} NMR** (128 MHz, $CDCl_3$) δ –32.14 (1B, br s, B-12); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{23}H_{21}B^{35}ClN_3NaO$ 424.1358; Found 424.1359; **ν_{max}** (thin film)/cm^{-1} 2332 (B–H), 1689 (C=O).

2'-Methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopentane-1,3'-indolin]-2-en-4-one (132)



To a stirred solution of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)(2'-methyl-4-oxo-2-phenyl spiro[cyclopentane-1,3'-indol]-2-en-3-yl)dihydroborate **131a** (95.0 mg, 0.25 mmol) in MeCN (5.00 mL) was added pinacol (58.9 mg, 0.50 mmol) and 1M HCl (0.65 mL, 0.65 mmol). The solution was stirred at room temperature for 1 hour. After the reaction was completed, it was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 2:1 v/v) afforded the title compound (70.2 mg, 70%) as a yellow oil. **R_f** 0.20 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (1H, br d, *J* = 7.6 Hz, H-Ar), 7.18–7.10 (4H, m, H-Ar), 6.88 – 6.82 (1H, m, H-Ar), 6.77 – 6.71 (2H, m, H-Ar), 6.64 – 6.59 (1H, m, H-Ar), 4.06 (1H, q, *J* = 6.4 Hz, H-8), 3.18 (1H, d, *J* = 19.2 Hz, H-11a), 2.59 (1H, d, *J* = 19.2 Hz, H-11b), 1.21 (6H, s, H-15/16), 1.19 (3H, d, *J* = 6.4 Hz, H-9), 1.15 (6H, s, H-15/16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.0 (C, C-12), 183.9 (C, C-Ar), 151.6 (C, C-Ar), 137.8 (C, C-Ar), 131.9 (C, C-Ar), 129.2 (CH, C-Ar), 129.1 (CH, C-Ar), 127.8 (2CH, C-Ar), 127.7 (2CH, C-Ar), 124.0 (CH, C-Ar), 120.1 (CH, C-Ar), 110.4 (CH, C-Ar), 84.3 (2C, C-14), 66.1 (CH, C-8), 60.2 (C, C-10), 51.0 (CH_2, C-11), 24.8 ($2CH_3$, C-15/16), 24.6 ($2CH_3$, C-15/16), 14.6 (CH_3, C-9); **^{11}B{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 29.05 (1B, br s); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd $C_{25}H_{28}BNNaO_3$ 424.2054; Found 424.2057, $[M + H]^+$ Calcd for $C_{25}H_{29}BNO_3$ 402.2235; Found : 402.2236; **ν_{max}** (thin film)/cm^{-1}: 3356 (N–H), 1688 (C=O).

2'-Methyl-2-phenyl-3-(*p*-tolyl)spiro[cyclopentane-1,3'-indolin]-2-en-4-one (133)

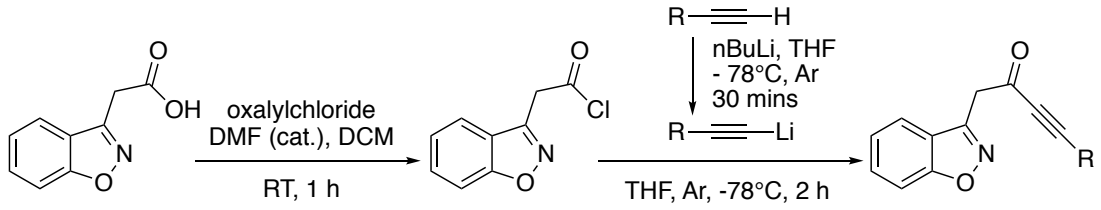


Synthesised according to modified literature procedure.[98] To a stirred solution of 2'-methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopentane-1,3'-indolin]-2-en-4-one **132** (41.5 mg, 0.10 mmol) in THF (2.00 mL, 0.05 M) under argon was added 4-bromotoluene (17.1 mg, 0.10 mmol), $Pd(PPh_3)_4$ (5.78 mg, 5 mol%) and K_3PO_4 (0.2 mL, 0.6 mmol, 6 equiv from 3M aq. solution). The solution was stirred at 60 °C for 36 hours. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 4:1 *v/v*) afforded the title compound (22.6 mg, 62%) as a red solid.

Mp: 161 – 163 °C; $\mathbf{R_f}$ = 0.32 (hexane:EtOAc , 4:1 *v/v*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.14 (3H, m, H-Ar), 7.05 – 6.88 (7H, m, H-Ar), 6.65 (1H, d, *J* = 7.5 Hz, H-Ar), 6.59 – 6.57 (2H, m, H-Ar), 4.12 (1H, q, *J* = 6.7 Hz, H-8), 3.80 (1H, br s, H-7), 3.29 (1H, d, *J* = 18.8 Hz, H-11a), 2.72 (1H, d, *J* = 18.8 Hz, H-11b), 2.26 (3H, s, H-18), 1.27 (3H, d, *J* = 6.7 Hz, H-9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.9 (C, C-12), 171.0 (C, C-Ar), 151.7 (C, C-Ar), 141.3 (C, C-Ar), 137.6 (C, C-Ar), 136.4 (C, C-Ar), 132.2 (C, C-Ar), 129.9 (2CH, C-Ar), 129.2 (CH, C-Ar), 128.8 (2CH, C-Ar), 128.7 (2CH, C-Ar), 128.5 (CH, C-Ar), 128.1 (C, C-Ar), 127.9 (2CH, C-Ar), 123.7 (CH, C-Ar), 120.1 (CH, C-Ar), 110.6 (CH, C-Ar), 66.0 (CH, C-8), 57.6 (C, C-10), 50.1 (CH_2, C-11), 21.4 (CH_3, C-18), 14.5 (CH_3, C-9); **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}NO$ 366.1852; Found : 366.1852; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1}: 3357 (N–H), 1696 (C=O).

5.4 Experimental for Chapter 4

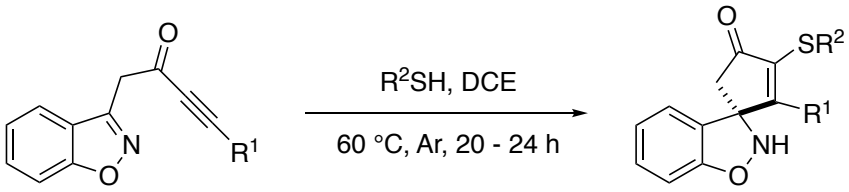
General Procedure J



To a stirred solution of 2-(benzo[*d*]isoxazol-3-yl)acetic acid (10 mmol) in dry DCM (20 mL) in a round bottom flask was added oxalyl chloride (30 mmol) under argon atmosphere. Then, DMF (10 drops) was added. The solution was stirred for 1 hour at ambient temperature. The reaction mixture was concentrated *in vacuo* for 1 hour to remove all solvent and excess oxalyl chloride to give 2-(benzo[*d*]isoxazol-3-yl)acetyl chloride. The crude product was used in the next step without purification.

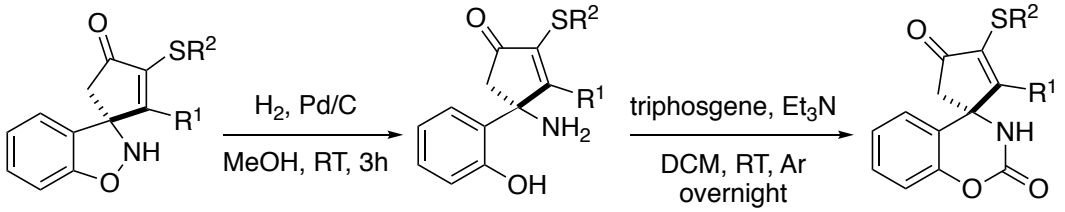
Then, to a stirred solution of alkyne (15 mmol) in THF (10 mL) in a dried-oven round-bottom flask at −78 °C under argon was added *n*-BuLi (15 mmol, 2.5 M in hexanes) dropwise. Next, the solution was transferred via cannula into another round-bottom flask containing a solution of 2-(benzo[*d*]isoxazol-3-yl)acetyl chloride (10 mmol) in dry THF (10 mL) at −78 °C. Then, the mixture was stirred for 2 hours. After the reaction was completed, it was warmed to room temperature for 30 minutes and quenched with sat. aq. NH_4Cl (20 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure K



To a solution of 1,2-benzisoxazole-ynone (0.20 mmol) in DCE (2 mL, 0.1 M) in a sealed vial was added thiol (0.30 mmol). Then, the vial was degassed with argon for 5 minutes. The solution mixture was stirred for 20 – 24 hours at 60 °C in a heating block. Then, a crude mixture was quenched with sat. aq. $NaHCO_3$ (5.0 mL) and extracted with DCM (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure L



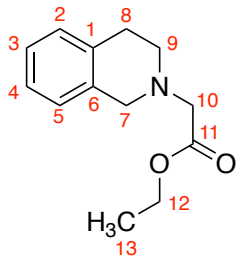
To a stirred solution of spirocycle (0.20 mmol) in MeOH (10.0 mL) in a round bottom flask was added palladium on carbon (10 mol%) under argon atmosphere. A reaction mixture was evacuated and backfilled with hydrogen gas (via balloon) several time. Then, it was stirred at ambient temperature for 3 hours. A crude mixture was purged with argon, filtered through Celite, washed with EtOAc and concentrated *in vacuo*. The crude product was used in the next step without purification.

Then, to a stirred solution of amino-alcohol spirocycle (0.20 mmol) in DCM was added Et_3N (1.0 mmol) under argon atmosphere. The solution mixture was added triphosgene (0.08 mmol) and stirred at ambient temperature overnight. A crude mixture was quenched with sat. aq. $NaHCO_3$ (5.0 mL) and extracted with DCM (3 × 5 mL). The

organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography.

Characterisation Data and Procedures

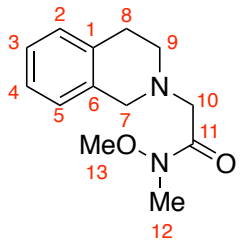
Ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (149a)



To a stirred solution of 1,2,3,4-tetrahydroisoquinoline **149** (2.00 mL, 15.8 mmol) in DMF (20.0 mL) was added ethyl bromoacetate (2.09 mL, 18.9 mmol) and Cs_2CO_3 (6.16 g, 18.9 mmol) under argon atmosphere. The solution mixture was stirred at ambient temperature for 2 hours. Then, a crude mixture was quenched with water (20 mL) and extracted with EtOAc (20 × 3 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 4:1 → 2:1 v/v) afforded the title product (2.96 g, 86%) as a yellow oil.

Rf 0.55 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 – 7.07 (3H, m, H-Ar), 7.03 – 6.98 (1H, m, H-Ar), 4.22 (2H, q, J = 7.1 Hz, H-12), 3.81 (2H, s, H-7), 3.42 (2H, s, H-10), 2.96 – 2.92 (2H, m, H-8/9), 2.92 – 2.87 (2H, m, H-8/9), 1.29 (3H, t, J = 7.1 Hz, H-13); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6 (C, C-11), 134.3 (C, C-Ar), 133.9 (C, C-Ar), 128.8 (CH, C-Ar), 126.6 (CH, C-Ar), 126.3 (CH, C-Ar), 125.8 (CH, C-Ar), 60.8 (CH_2, C-12), 59.2 (CH_2, C-10), 55.4 (CH_2, C-7), 50.8 (CH_2, C-8/9), 29.0 (CH_2, C-8/9), 14.4 (CH_3, C-13); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{17}NNaO_2$ 242.1151; Found 242.1152, $[M + H]^+$ Calcd for $C_{13}H_{18}NO_2$ 220.1332; Found 220.1332.

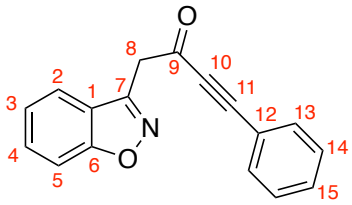
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-methoxy-*N*-methylacetamide (150)



To a stirred solution of ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **149a** (2.61 g, 11.9 mmol) in THF (20.0 mL) was added *N*,*O*-dimethylhedroxylamine hydrochloride (1.74 g, 17.9 mmol) under argon atmosphere at – 20 °C. The solution mixture was added *i*PrMgCl (14.9 mL, 29.8 mmol, 2 M in THF) and stirred – 20 °C for 1 hour. Then, a crude mixture was warmed to room temperature, quenched with NH_4Cl (20 mL) and extracted with EtOAc (20 × 3 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (EtOAc, 100%) afforded the title product (1.43 g, 51%) as a yellow solid.

Rf 0.30 (EtOAc, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 – 7.05 (3H, m, H-Ar), 7.04 – 6.96 (1H, m, H-Ar), 3.81 (2H, s, H-7), 3.72 (3H, s, H-13), 3.51 (2H, s, H-10), 3.21 (3H, s, H-12), 2.98 – 2.85 (4H, m, H-8,9); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5 (C, C-11), 134.6 (C, C-Ar), 134.1 (C, C-Ar), 128.7 (CH, C-Ar), 126.6 (CH, C-Ar), 126.2 (CH, C-Ar), 125.7 (CH, C-Ar), 61.6 (CH_3, C-13), 58.0 (CH_2, C-10), 55.9 (CH_2, C-7), 51.1 (CH_2, C-8/9), 32.3 (CH_3, C-12), 29.1 (CH_2, C-8/9); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{18}N_2NaO_2$ 257.1260; Found 257.1261, $[M + H]^+$ Calcd for $C_{13}H_{19}N_2O_2$ 235.1441; Found 235.1438.

1-(Benzo[d]isoxazol-3-yl)-4-phenylbut-3-yn-2-one (159a)

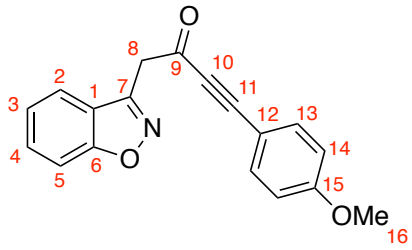


Synthesized using **General Procedure J** with 2-(benzo[*d*]isoxazol-3-yl)acetic acid **157** (1.77 g, 10 mmol), oxalylchloride (2.57 mL, 30 mmol), DMF (10 drops), DCM

(20.00 mL) phenylacetylene (1.65 mL, 15 mmol), *n*-BuLi (6.00 mL, 15 mmol) and THF (20.00 mL). Purification by flash column chromatography (hexane:EtOAc, 8:1 then 6:1 v/v) afforded the title product (0.73 g, 28 %) as a yellow solid.

mp: 35 – 37 °C; Rf 0.68 (hexane:EtOAc, 2:1 v/v); 1H NMR (400 MHz, CDCl3) δ 7.69 (1H, dt, J = 8.0, 1.0 Hz, H-2), 7.63 – 7.51 (2H, m, H-3,4), 7.48 – 7.39 (3H, m, H-,14), 7.36 – 7.30 (3H, m, H-15,16), 4.36 (2H, s, H-8). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.9 (C, C-9), 163.5 (C, C-6), 152.1 (C, C-7), 133.4 (2CH, C-14), 131.4 (CH, C-5), 130.2 (CH, C-3), 128.7 (2CH, C-15), 123.9 (CH, C-16), 121.8 (CH, C-2), 121.6 (C, C-1), 119.3 (C, C-13), 110.1 (CH, C-4), 94.3 (C, C-12), 87.4 (C, C-10), 41.8 (CH_2, C-8); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{17}H_{11}NNaO_2$ 284.0682; Found 284.0686, $[M + H]^+$ Calcd for $C_{17}H_{12}NO_2$ 262.0863; Found 262.0865; **ν_{max}** (thin film)/cm^{-1} 2199, 1668, 1488, 1380, 1076.

1-(Benzo[*d*]isoxazol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one (159b)

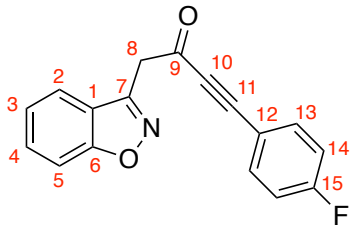


Synthesized using **General Procedure J** with 2-(benzo[*d*]isoxazol-3-yl)acetic acid **157** (1.77 g, 10 mmol), oxalylchloride (2.57 mL, 30 mmol), DMF (10 drops), DCM (20.00 mL), 4-ethynylanisole (1.95 mL, 15 mmol), *n*-BuLi (6.00 mL, 15 mmol) and THF (20.00 mL). Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (0.60 g, 21 %) as a yellow solid.

mp: 75 – 77 °C; **Rf** 0.45 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (1H, dt, *J* = 7.9, 1.0 Hz, H-2), 7.62 – 7.53 (2H, m, H-2,3), 7.38 – 7.30 (3, m, H-5,13), 6.87 – 6.80 (2H, m, H-14), 4.33 (2H, s, H-8), 3.81 (3H, s, H-16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.9 (C, C-9), 163.5 (C, C-6), 162.2 (C, C-15), 152.3 (C, C-7), 135.5 (2CH, C-13), 130.1 (CH, C-3), 123.9 (CH, C-5), 121.8 (CH, C-2), 121.6 (C, C-1), 114.5 (2CH, C-14), 111.0 (C, C-12), 110.1 (CH, C-4), 95.8 (C, C-11), 87.6 (C, C-10), 55.5 (CH_3, C-16), 41.6 (CH_2, C-8); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{18}H_{13}NNaO_3$

314.0788; Found 314.0792, [M + H]$^+$ Calcd for $C_{18}H_{14}NO_3$ 292.0968; Found 292.0973; ν_{max} (thin film)/cm^{-1} 2190, 1665, 1600, 1508, 1253, 1075.

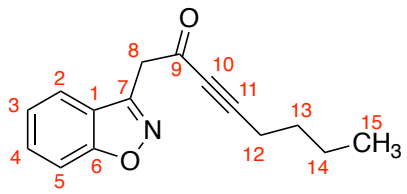
1-(Benzo[*d*]isoxazol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one (159c)



Synthesized using **General Procedure J** with 2-(benzo[*d*]isoxazol-3-yl)acetic acid **157** (1.77 g, 10 mmol), oxalylchloride (2.57 mL, 30 mmol), DMF (10 drops), DCM (20.00 mL), 4-ethynylanisole (1.80 g, 15 mmol), *n*-BuLi (6.00 mL, 15 mmol) and THF (20.00 mL). Purification by flash column chromatography (hexane:EtOAc, 8:1 then 6:1 v/v) afforded the title product (0.4120 g, 15 %) as a yellow solid.

mp: 68 – 71 °C; **Rf** 0.63 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (1H, dt, *J* = 8.0, 1.0 Hz, H-2), 7.63 – 7.54 (2H, m, H-3,4), 7.45 – 7.38 (2H, m, H-13), 7.33 (1H, ddd, *J* = 7.9, 6.6, 1.3 Hz, H-5), 7.07 – 7.00 (2H, m, H-14), 4.35 (2H, s, H-8); **^{13}C NMR** (100 MHz, , $CDCl_3$) δ 180.8 (C, C-9), 164.4 (C, d, $^1J_{C\text{-}F}$ = 254.8 Hz, C-15), 163.5 (C, C-6), 152.1 (C, C-7), 135.8 (2CH, d, $^3J_{C\text{-}F}$ = 8.9 Hz, C-13), 130.2 (CH, C-3), 123.9 (CH, C-5), 121.7 (CH, C-2), 121.6 (C, C-1), 116.4 (2CH, d, $^2J_{C\text{-}F}$ = 22.4 Hz, C-14), 115.4 (C, d, $^4J_{C\text{-}F}$ = 3.4 Hz, C-12), 110.2 (CH, C-4), 93.3 (C, C-11), 87.3 (C, C-10), 41.8 (CH_2, C-8); **^{19}F NMR** (376 MHz, $CDCl_3$) δ (−104.86) – (−104.96) (m, 1F, F-15); **HRMS** (ESI) m/z : [M + Na]$^+$ Calcd for $C_{17}H_{10}FNNaO_2$ 302.0588; Found 302.0594, [M + H]$^+$ Calcd for $C_{17}H_{11}FNO_2$ 280.0768; Found 280.0773; ν_{max} (thin film)/cm^{-1} 2203, 1674, 1599, 1505, 1233, 1075.

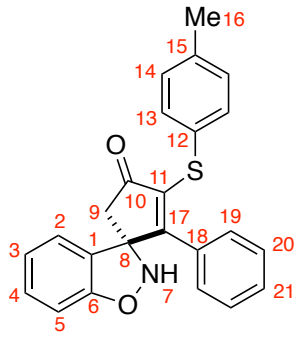
1-(Benzo[*d*]isoxazol-3-yl)oct-3-yn-2-one (159d)



Synthesized using **General Procedure J** with 2-(benzo[*d*]isoxazol-3-yl)acetic acid **157** (1.77 g, 10 mmol), oxalylchloride (2.57 mL, 30 mmol), DMF (10 drops), DCM (20 mL) 1-hexyne (1.71 mL, 15 mmol), *n*-BuLi (6.00 mL, 15 mmol) and THF (20 mL). Purification by flash column chromatography (hexane:EtOAc, 8:1 v/v) afforded the title product (0.54 g, 22%) as a yellow oil.

Rf 0.70 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (1H, dt, *J* = 8.0, 1.0 Hz, H-2), 7.59 – 7.52 (2H, m, H-3,4), 7.31 (1H, ddd, *J* = 8.0, 6.3, 1.6 Hz, H-5), 4.22 (2H, s, H-8), 2.29 (2H, t, *J* = 7.0 Hz, H-12), 1.48 – 1.37 (2H, m, H-13), 1.35 – 1.21 (2H, m, H-14), 0.84 (3H, t, *J* = 7.3 Hz, H-15); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.2 (C, C-9), 163.4 (C, C-6), 152.2 (C, C-7), 130.1 (CH, C-3), 123.8 (CH, C-5), 121.8 (CH, C-2), 121.6 (C, C-1), 110.1 (CH, C-4), 98.3 (C, C-11), 80.4 (C, C-10), 41.8 (CH_2, C-8), 29.4 (CH_2, C-13), 21.9 (CH_2, C-14), 18.8 (CH_2, C-12), 13.5 (CH_3, C-15); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{15}H_{15}NNaO_2$ 264.0995; Found 264.0994, $[M + H]^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1176; Found 242.1171; **ν_{max}** (thin film)/cm^{-1} 2959, 2938, 2874, 2212, 1676, 1612,1438, 1381, 1234.

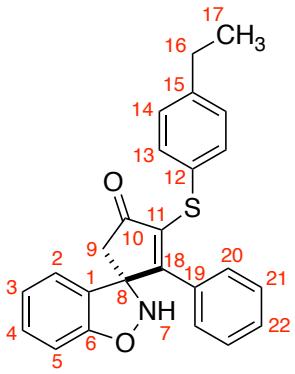
2'-Phenyl-3'-(*p*-tolylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161a)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-methylbenzenethiol (37.3 mg, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 → 4:1 v/v) afforded the title product (77.1 mg, 100%) as a yellow solid.

mp: 120 – 124 °C; **Rf** 0.54 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.78 (1H, s, H-7), 7.35 – 7.31 (1H, m, H-Ar), 7.30 – 7.15 (4H, m, H-Ar), 7.13 – 7.03 (6H, m, H-Ar), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.76 (1H, d, J = 8.0 Hz, H-Ar), 3.23 (1H, d, J = 18.7 Hz, H-9a), 3.09 (1H, d, J = 18.7 Hz, H-9b), 2.24 (3H, s, H-16); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.8 (C, C-10), 174.0 (C, C-17), 158.8 (C, C-6), 136.0 (C, C-15), 133.5 (C, C-Ar), 133.0 (C, C-Ar), 129.7 (2CH, C-Ar), 129.4 (CH, C-Ar), 129.3 (C, C-Ar), 129.2 (CH, C-Ar), 128.9 (2CH, C-Ar), 128.8 (C, C-Ar), 127.7 (2CH, C-Ar), 127.7 (2CH, C-Ar), 122.8 (CH, C-Ar), 121.9 (CH, C-Ar), 107.4 (CH, C-Ar), 73.2 (C, C-8), 46.9 (CH_2, C-9), 20.5 (CH_3, C-16); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{24}H_{19}NNaO_2S$ 408.1029; Found 408.1032; **ν_{max}** (thin film)/cm^{-1} 3223, 3056, 2921, 2853, 1717, 1594, 1491, 1210.

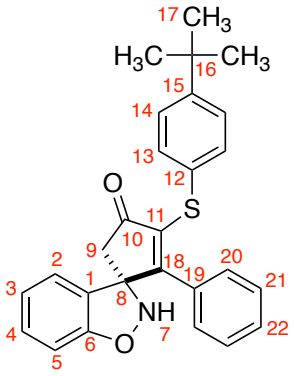
3'-((4-Ethylphenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161b)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-ethylbenzenethiol (40.7 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 → 4:1 v/v) afforded the title product (78.5 mg, 98%) as a yellow solid.

mp: 170 – 173 °C; **Rf** 0.58 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.76 (1H, s, H-7), 7.33 (1H, dd, J = 7.4, 1.3 Hz, H-Ar), 7.29 – 7.15 (4H, m, H-Ar), 7.10 (4H, s, H-Ar), 7.07 – 7.02 (2H, m, H-Ar), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.75 (1H, d, J = 8.0 Hz, H-Ar), 3.23 (1H, d, J = 18.7 Hz, H-9a), 3.08 (1H, d, J = 18.7 Hz, H-9b), 2.53 (2H, q, J = 7.6 Hz, H-16), 1.13 (3H, t, J = 7.6 Hz, H-17); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.8 (C, C-10), 174.1 (C, C-18), 158.8 (C, C-6), 142.3 (C, C-15), 133.5 (C, C-Ar), 133.0 (C, C-Ar), 129.6 (C, C-Ar), 129.5 (CH, C-Ar), 129.2 (CH, C-Ar), 128.8 (2CH, C-Ar), 128.8 (C, C-Ar), 128.6 (2CH, C-Ar), 127.7 (4CH, C-Ar), 122.8 (CH, C-Ar), 121.9 (CH, C-Ar), 107.4 (CH, C-Ar), 73.2 (C, C-8), 46.8 (CH_2, C-9), 27.7 (CH_2, C-16), 15.5 (CH_3, C-17); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{25}H_{21}NNaO_2S$ 422.1185; Found 422.1200, $[M + H]^+$ Calcd for $C_{25}H_{22}NO_2S$ 400.1366; Found 400.1375; **ν_{max}** (thin film)/cm^{-1} 3065, 3057, 2964, 2924, 1720, 1585, 1562, 1493.

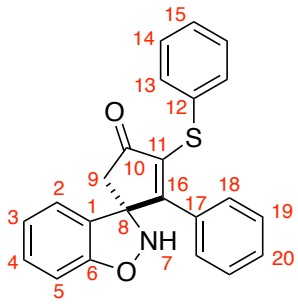
3'-((4-(*tert*-Butyl)phenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161c)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-(*tert*-butyl)benzenethiol (51.7 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (84.3 mg, 99%) as a yellow solid.

mp: 127 – 130 °C; **Rf** 0.56 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.78 (1H, s, H-7), 7.35 (1H, dd, J = 7.5, 1.3 Hz, H-Ar), 7.29 – 7.15 (6H, m, H-Ar), 7.13 – 7.07 (2H, m, H-Ar), 7.07 – 7.02 (2H, m, H-Ar), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.75 (1H, d, J = 8.0 Hz, H-Ar), 3.26 (1H, d, J = 18.7 Hz, H-9a), 3.09 (1H, d, J = 18.7 Hz, H-9b), 1.23 (9H, s, H-17); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.9 (C, C-10), 174.4 (C, C-18), 158.8 (C, C-6), 149.0 (C, C-15), 133.3 (C, C-Ar), 133.0 (C, C-Ar), 129.5 (CH, C-Ar), 129.4 (C, C-Ar), 129.2 (CH, C-Ar), 128.7 (C, C-Ar), 128.3 (2CH, C-Ar), 127.7 (4CH, C-Ar), 126.0 (2CH, C-Ar), 122.8 (CH, C-Ar), 121.9 (CH, C-Ar), 107.4 (CH, C-Ar), 73.3 (C, C-8), 46.8 (CH_2, C-9), 34.2 (C, C-16), 31.0 ($3CH_3$, C-17); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{27}H_{25}NNaO_2S$ 450.1498; Found 450.1508, $[M + H]^+$ Calcd for $C_{27}H_{26}NO_2S$ 428.1679; Found 428.1680; **ν_{max}** (thin film)/cm^{-1} 3057, 2962, 1719, 1489, 1475, 1495, 1212, 1011.

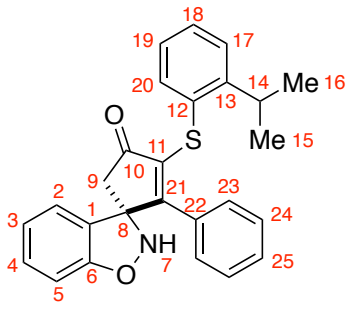
2'-Phenyl-3'-(phenylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161d)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), thiophenol (30.6 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 $\rightarrow$ 4:1 v/v) afforded the title product (74.5 mg, 100%) as a yellow solid.

mp: 105 – 109 °C; **Rf** 0.54 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.80 (1H, s, H-7), 7.36 (1H, dd, J = 7.6, 1.3 Hz, H-Ar), 7.30 – 7.16 (9H, m, H-Ar), 7.10 – 7.05 (2H, m, H-Ar), 6.98 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.76 (1H, d, J = 7.8 Hz, H-Ar), 3.27 (1H, d, J = 18.7 Hz, H-9a), 3.12 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.8 (C, C-10), 174.9 (C, C-16), 158.8 (C, C-6), 133.2 (C, C-Ar), 132.98 (C, C-Ar), 132.95 (C, C-Ar), 129.5 (CH, C-Ar), 129.3 (CH, C-Ar), 129.1 (2CH, C-Ar), 128.7 (C, C-Ar), 128.2 (2CH, C-Ar), 127.7 (2CH, C-Ar), 127.7 (2CH, C-Ar), 126.3 (CH, C-Ar), 122.9 (CH, C-Ar), 121.9 (CH, C-Ar), 107.4 (CH, C-Ar), 73.3 (C, C-8), 46.8 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{17}NNaO_2S$ 394.0872; Found 394.0873, $[M + H]^+$ Calcd for $C_{23}H_{18}NO_2S$ 372.1053; Found 372.1053; **ν_{max}** (thin film)/cm^{-1} 3224, 3057, 1719, 1583, 1474, 1439, 1211.

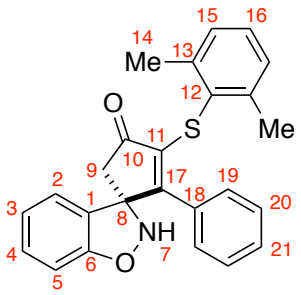
3'-((2-Isopropylphenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161e)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 2-isopropylbenzenethiol (45.5 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 $\rightarrow$ 4:1 v/v) afforded the title product (80.9 mg, 98%) as a yellow oil.

Rf 0.59 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.77 (1H, s, H-7), 7.33 (1H, dd, J = 7.5, 1.3 Hz, H-Ar), 7.28 – 7.13 (6H, m, H-Ar), 7.12 – 7.02 (4H, m, H-Ar), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.75 (1H, d, J = 8.1 Hz, H-Ar), 3.31 – 3.20 (2H, m, H-9a,14), 3.07 (1H, d, J = 18.7 Hz, H-9b), 1.14 (3H, d, J = 4.5 Hz, H-15/16), 1.12 (3H, d, J = 4.5 Hz, H-15/16); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.9 (C, C-10), 174.3 (C, C-21), 158.8 (C, C-6), 147.3 (C, C-13), 134.1 (C, C-Ar), 133.0 (C, C-Ar), 131.1 (C, C-Ar), 129.8 (CH, C-Ar), 129.5 (CH, C-Ar), 129.2 (CH, C-Ar), 128.8 (C, C-Ar), 127.7 (2CH, C-Ar), 127.6 (2CH, C-Ar), 127.2 (CH, C-Ar), 126.4 (CH, C-Ar), 125.6 (CH, C-Ar), 122.8 (CH, C-Ar), 121.9 (CH, C-Ar), 107.4 (CH, C-Ar), 73.2 (C, C-8), 46.7 (CH_2, C-9), 30.1 (CH, C-14), 23.0 (CH_3, C-15/16), 22.9 (CH_3, C-15/16); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{26}H_{23}NNaO_2S$ 436.1342; Found 436.1346; **ν_{max}** (thin film)/cm^{-1} 3058, 2961, 2928, 1721, 1585, 1471, 1440.

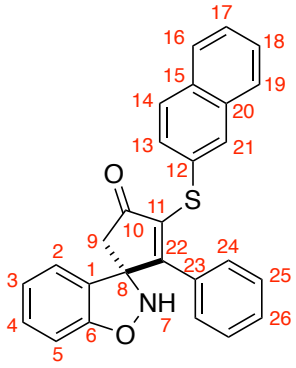
3'-((2,6-dimethylphenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161f)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 2,6-dimethylthiophenol (40.0 μL, 0.30 mmol), and DCE (2 mL, 0.1 M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 $\rightarrow$ 4:1 v/v) afforded the title product (72.3 mg, 97%) as a yellow solid.

mp: 122 – 126 °C; **Rf** 0.55 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.64 (1H, s, H-7), 7.28 (1H, dd, J = 7.5, 1.2 Hz, H-Ar), 7.19 – 7.12 (2H, m, H-Ar), 7.12 – 7.06 (2H, m, H-Ar), 7.03 – 6.91 (4H, m, H-Ar), 6.90 – 6.86 (2H, m, H-Ar), 6.70 (1H, d, J = 8.0 Hz, H-Ar), 3.19 (1H, d, J = 18.8 Hz, H-9a), 2.97 (1H, d, J = 18.8 Hz, H-9b), 2.28 (6H, s, H-14); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 200.0 (C, C-10), 168.4 (C, C-17), 158.9 (C, C-6), 141.7 (2C, C-13), 134.7 (C, C-Ar), 132.8 (C, C-Ar), 129.3 (CH, C-Ar), 128.9 (C, C-Ar), 128.6 (CH, C-Ar), 128.5 (C, C-Ar), 128.4 (CH, C-Ar), 127.9 (2CH, C-Ar), 127.3 (2CH, C-Ar), 127.1 (2CH, C-Ar), 122.7 (CH, C-Ar), 121.7 (CH, C-Ar), 107.4 (CH, C-Ar), 73.2 (C, C-8), 46.3 (CH_2, C-9), 21.7 ($2CH_3$, C-14); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{25}H_{21}NNaO_2S$ 422.1185; Found 422.1188, $[M + H]^+$ Calcd for $C_{25}H_{22}NO_2S$ 400.1366; Found 400.1377; **ν_{max}** (thin film)/cm^{-1} 3224, 3056, 2922, 1716, 1473, 1459, 1212.

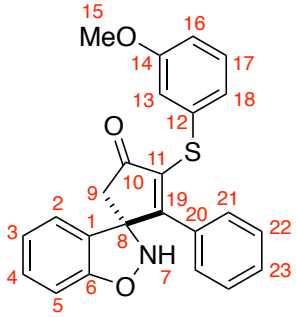
3'-(Naphthalen-2-ylthio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161g)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 2-naphthalenethiol (48.1 mg, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 → 4:1 v/v) afforded the title product (85.0 mg, 100%) as a pale yellow solid.

mp: 136 – 140 °C; **Rf** 0.45 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.84 (1H, s, H-7), 7.90 – 7.78 (3H, m, H-Ar), 7.73 (1H, s, H-Ar), 7.54 – 7.45 (2H, m, H-Ar), 7.44 – 7.39 (1H, m, H-Ar), 7.31 (1H, dt, J = 8.5, 1.7 Hz, H-Ar), 7.25 – 7.17 (4H, m, H-Ar), 7.14 – 7.08 (2H, m, H-Ar), 7.01 (1H, td, J = 7.5, 0.9 Hz, H-Ar), 6.78 (1H, d, J = 8.0 Hz, H-Ar), 3.30 (1H, d, J = 18.6 Hz, H-9a), 3.16 (1H, d, J = 18.6 Hz, H-9b). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.8 (C, C-10), 174.7 (C, C-22), 158.8 (C, C-6), 133.2 (C, C-Ar), 133.0 (2C, C-Ar), 131.4 (C, C-Ar), 130.6 (C, C-Ar), 129.5 (CH, C-Ar), 129.3 (CH, C-Ar), 128.7 (C, C-Ar), 128.6 (CH, C-Ar), 127.7 (2CH, C-Ar), 127.7 (2CH, C-Ar), 127.6 (CH, C-Ar), 127.1 (CH, C-Ar), 126.8 (CH, C-Ar), 126.6 (CH, C-Ar), 126.4 (CH, C-Ar), 126.0 (CH, C-Ar), 122.9 (CH, C-Ar), 121.9 (CH, C-Ar), 107.5 (CH, C-Ar), 73.3 (C, C-8), 46.9 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{27}H_{19}NNaO_2S$ 444.1029; Found 444.1032, $[M + H]^+$ Calcd for $C_{27}H_{20}NO_2S$ 422.1209; Found 422.1221; **ν_{max}** (thin film)/cm^{-1} 3228, 3054, 2924, 1716, 1589, 1473, 1211.

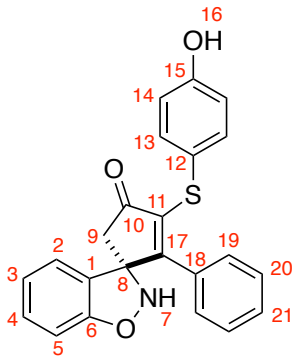
3'-((3-Methoxyphenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161h)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 3-methoxythiophenol (37.2 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 4:1 v/v) afforded the title product (72.1 mg, 90%) as a yellow oil.

Rf 0.43 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.80 (1H, s, H-7), 7.35 (1H, dd, J = 7.6, 1.3 Hz, H-Ar), 7.29 – 7.14 (5H, m, H-Ar), 7.10 – 7.04 (2H, m, H-Ar), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.79 – 6.67 (4H, m, H-Ar), 3.71 (3H, s, H-15), 3.28 (1H, d, J = 18.7 Hz, H-9a), 3.12 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.9 (C, C-10), 175.3 (C, C-19), 159.5 (C, C-14), 158.9 (C, C-6), 134.5 (C, C-Ar), 133.0 (C, C-Ar), 132.9 (C, C-Ar), 130.1 (CH, C-Ar), 129.6 (CH, C-Ar), 129.3 (CH, C-Ar), 128.7 (C, C-Ar), 127.7 (2CH, C-Ar), 127.6 (2CH, C-Ar), 122.8 (CH, C-Ar), 121.9 (CH, C-Ar), 120.3 (CH, C-Ar), 113.4 (CH, C-Ar), 112.2 (CH, C-Ar), 107.5 (CH, C-Ar), 73.3 (C, C-8), 55.1 (CH_3, C-15), 46.8 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{24}H_{19}NNaO_3S$ 424.0978; Found 424.0992, $[M + H]^+$ Calcd for $C_{24}H_{20}NO_3S$ 402.1158; Found 402.1170; **ν_{max}** (thin film)/cm^{-1} 3220, 3060, 2935, 1719, 1590, 1476, 1246, 1037.

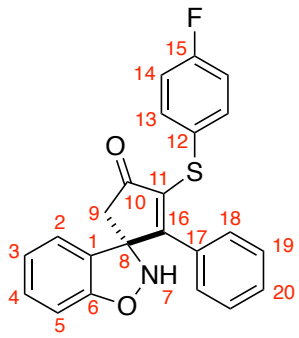
3'-((4-Hydroxyphenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161i)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-mercaptophenol (37.8 mg, 0.30 mmol), and DCE (2 mL, 0.1 M) at 60 °C for 20 hours. Purification by flash column chromatography (DCM:MeOH, 100:1 v/v) afforded the title product (55.5 mg, 71%) as a yellow solid.

mp: 156 – 160 °C; **Rf** 0.25 (DCM:MeOH, 25:1 v/v);**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.59 (1H, s, H-16), 8.70 (1H, s, H-7), 7.30 – 7.11 (5H, m, H-Ar), 7.08 – 6.99 (4H, m, H-Ar), 6.95 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.73 (1H, d, J = 8.1 Hz, H-Ar), 6.68 – 6.59 (2H, m, H-14), 3.16 (1H, d, J = 18.7 Hz, H-9a), 3.02 (1H, d, J = 18.7 Hz, H-9b).**^{13}C NMR** (100 MHz, DMSO-d_6) δ 200.1 (C, C-10), 172.0 (C, C-17), 158.9 (C, C-6), 157.1 (C, C-15), 135.0 (C, C-Ar), 133.2 (C, C-Ar), 132.5 (2CH, C-13), 129.5 (CH, C-Ar), 129.1 (CH, C-Ar), 129.0 (C, C-Ar), 127.9 (2CH, C-Ar), 127.7 (2CH, C-Ar), 122.8 (CH, C-Ar), 122.0 (CH, C-Ar), 120.3 (C, C-12), 116.2 (2CH, C-14), 107.5 (CH, C-Ar), 73.1 (C, C-8), 47.0 (CH_2, C-9); **HRMS** (ESI) m/z : $[M - H]^-$ Calcd for $C_{23}H_{16}NO_3S$ 386.0856; Found 386.0863; **ν_{max}** (thin film)/cm^{-1} 3340, 3063, 2927, 1710, 1599, 1583, 1494, 1267, 1217.

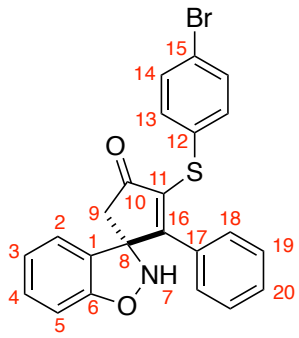
3'-((4-Fluorophenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161j)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-fluorothiophenol (32.0 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 → 4:1 v/v) afforded the title product (68.1 mg, 87%) as a yellow solid.

mp: 118 – 123 °C; **Rf** 0.51 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.76 (1H, s, H-7), 7.35 (1H, dd, J = 7.6, 1.3 Hz, H-Ar), 7.29 – 7.15 (6H, m, H-Ar), 7.13 – 7.06 (4H, m, H-Ar), 7.06 – 7.01 (2H, m, H-Ar), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.75 (1H, d, J = 8.1 Hz, H-Ar), 3.23 (1H, d, J = 18.7 Hz, H-9a), 3.09 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.8 (C, C-10), 173.6 (C, C-16), 161.2 (C, d, $^1J_{C\text{-}F}$ = 244.1 Hz, C-15), 158.8 (C, C-6), 133.6 (C, C-Ar), 132.9 (C, C-Ar), 131.5 (2CH, d, $^3J_{C\text{-}F}$ = 8.2 Hz, C-13), 129.5 (CH, C-Ar), 129.2 (CH, C-Ar), 128.7 (C, C-Ar), 128.1 (C, d, $^4J_{C\text{-}F}$ = 3.0 Hz, C-12), 127.7 (2CH, C-Ar), 127.7 (2CH, C-Ar), 122.9 (CH, C-Ar), 121.9 (CH, C-Ar), 116.1 (2CH, d, $^2J_{C\text{-}F}$ = 22.2 Hz, C-14), 107.4 (CH, C-Ar), 73.2 (C, C-8), 46.8 (CH_2, C-9); **^{19}F NMR** (376 MHz, DMSO-d_6) δ (−115.23) – (−115.34) (m, 1F); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{16}FNNaO_2S$ 412.0778; Found 412.0787, $[M + H]^+$ Calcd for $C_{23}H_{17}FNO_2S$ 390.0959; Found 390.0955; **ν_{max}** (thin film)/cm^{-1} 3228, 3062, 2921, 1718, 1588, 1489, 1225.

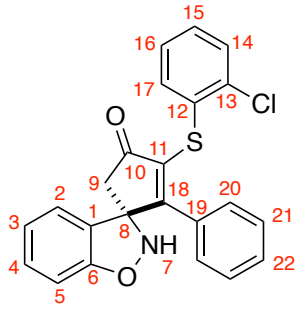
3'-((4-Bromophenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161k)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-bromobenzenethiol (56.7 mg, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 8:1 → 6:1 v/v) afforded the title product (72.3 mg, 80%) as a yellow solid.

mp: 127 – 131 °C; **Rf** 0.65 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.80 (1H, s, H-7), 7.49 – 7.41 (2H, m, H-14), 7.39 – 7.33 (1H, m, H-Ar), 7.30 – 7.12 (6H, m, H-Ar), 7.09 – 7.04 (2H, m, H-Ar), 7.02 – 6.94 (1H, m, H-Ar), 6.76 (1H, d, J = 8.0 Hz, H-Ar), 3.26 (1H, d, J = 18.7 Hz, H-9a), 3.12 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.6 (C, C-10), 174.8 (C, C-16), 158.8 (C, C-6), 132.9 (C, C-Ar), 132.7 (2C, C-Ar), 131.9 (2CH, C-14), 130.5 (2CH, C-13), 129.5 (CH, C-Ar), 129.4 (CH, C-Ar), 128.6 (C, C-Ar), 127.8 (2CH, C-Ar), 127.6 (2CH, C-Ar), 122.9 (CH, C-Ar), 121.9 (CH, C-Ar), 119.5 (C, C-15), 107.4 (CH, C-Ar), 73.3 (C, C-8), 46.8 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{16}{}^{79}BrNNaO_2$ 471.9977; Found 471.9984, $[M + H]^+$ Calcd for $C_{23}H_{17}{}^{79}BrNO_2$ 450.0158; Found 450.0168; **ν_{max}** (thin film)/cm^{-1} 3227, 3057, 2921, 1717, 1472, 1212, 1007.

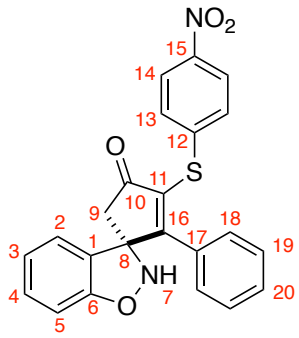
3'-((2-Chlorophenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161l)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 2-chlorothiophenol (34.0 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 $\rightarrow$ 4:1 v/v) afforded the title product (78.7 mg, 97%) as a yellow solid.

mp: 140 – 142 °C; **Rf** 0.46 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.82 (1H, s, H-7), 7.44 – 7.38 (2H, m, H-Ar), 7.29 – 7.15 (7H, m, H-Ar), 7.08 – 7.03 (2H, m, H-Ar), 6.99 (1H, t, J = 7.4 Hz, H-Ar), 6.76 (1H, d, J = 8.1 Hz, H-Ar), 3.31 (1H, d, J = 18.7 Hz, H-9a), 3.16 (1H, d, J = 18.7 Hz, 9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.6 (C, C-10), 175.8 (C, C-18), 158.9 (C, C-6), 132.8 (C, C-Ar), 132.2 (C, C-Ar), 131.8 (C, C-Ar), 131.6 (C, C-Ar), 129.7 (CH, C-Ar), 129.6 (CH, C-Ar), 129.4 (2CH, C-Ar), 128.5 (C, C-Ar), 127.80 (2CH, C-Ar), 127.77 (2CH, C-Ar), 127.5 (2CH, C-Ar), 123.0 (CH, C-Ar), 121.9 (CH, C-Ar), 107.5 (CH, C-Ar), 73.4 (C, C-8), 46.7 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{16}{}^{35}ClNNaO_2S$ 428.0482; Found 428.0493, $[M + H]^+$ Calcd for $C_{23}H_{17}{}^{35}ClNO_2S$ 406.0663; Found 406.0670; **ν_{max}** (thin film)/cm^{-1} 3226, 3058, 1716, 1451, 1211, 1032.

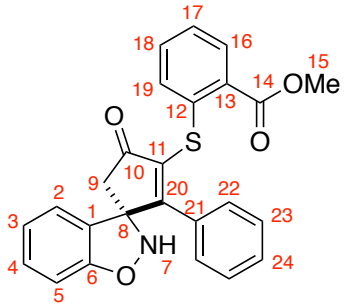
3'-((4-Nitrophenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161m)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-nitrobenzenethiol (46.6 mg, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 45 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product (23.4 mg, 28%) as a yellow solid.

mp: 153 – 156 °C; **Rf** 0.41 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.87 (1H, br s, H-7), 8.17 – 8.05 (2H, m, H-14), 7.46 (1H, dd, J = 7.6, 1.2 Hz, H-Ar), 7.44 – 7.40 (2H, m, H-13), 7.34 – 7.13 (4H, m, H-Ar), 7.12 – 7.04 (2H, m, H-18), 7.00 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.77 (1H, d, J = 8.1 Hz, H-Ar), 3.33 (1H, d, J = 18.7 Hz, H-9a), 3.20 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.4 (C, C-10), 177.4 (C, C-16), 158.9 (C, C-6), 145.3 (C, C-12), 143.6 (C, C-15), 132.6 (C, C-Ar), 130.9 (C, C-Ar), 129.69 (CH, C-Ar), 129.67 (CH, C-Ar), 128.4 (C, C-Ar), 127.9 (2CH, C-19), 127.5 (4CH, C-13,18), 124.1 (2CH, C-14), 123.1 (CH, C-Ar), 122.0 (CH, C-Ar), 107.5 (CH, C-Ar), 73.5 (C, C-8), 46.6 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{16}N_2NaO_4S$ 439.0723; Found 439.0744; **ν_{max}** (thin film)/cm^{-1} 3230, 3062, 2921, 1718, 1512, 1337, 1212.

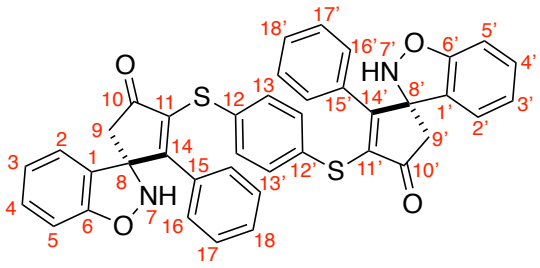
Methyl 2-((4'-oxo-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-3'-yl)thio)benzoate (161n)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), methyl thiosalicylate (41.3 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 45 hours. Purification by flash column chromatography (hexane:EtOAc, 4:1 → 2:1 v/v) afforded the title product (19.3 mg, 22%) as a yellow oil.

Rf 0.35 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.84 (1H, s, H-7), 7.90 (1H, dd, J = 7.8, 1.5 Hz, H-Ar), 7.53 (1H, ddd, J = 8.1, 7.3, 1.6 Hz, H-Ar), 7.42 (1H, dd, J = 7.5, 0.7 Hz, H-Ar), 7.31 – 7.16 (6H, m, H-Ar), 7.11 – 7.05 (2H, m, H-Ar), 6.99 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.77 (1H, d, J = 8.0 Hz, H-Ar), 3.82 (3H, s, H-15), 3.31 (1H, d, J = 18.7 Hz, H-9a), 3.16 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 200.1 (C, C-10), 177.4 (C, C-20), 166.0 (C, C-14), 158.9 (C, C-6), 137.6 (C, C-Ar), 133.02 (CH, C-Ar), 132.97 (2C, C-Ar), 131.0 (CH, C-Ar), 129.6 (CH, C-Ar), 129.5 (CH, C-Ar), 128.6 (C, C-Ar), 127.8 (2CH, C-Ar), 127.6 (CH, C-Ar), 127.5 (2CH, C-Ar), 127.0 (C, C-Ar), 125.4 (CH, C-Ar), 123.0 (CH, C-Ar), 121.9 (CH, C-Ar), 107.5 (CH, C-Ar), 73.4 (C, C-8), 52.4 (CH_3, C-15), 46.7 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_4S$ 452.0927; Found 452.0936, $[M + H]^+$ Calcd for $C_{25}H_{20}NO_4S$ 430.1108; Found 430.1113; **ν_{max}** (thin film)/cm^{-1} 3239, 3065, 2954, 1718, 1436, 1273, 1255.

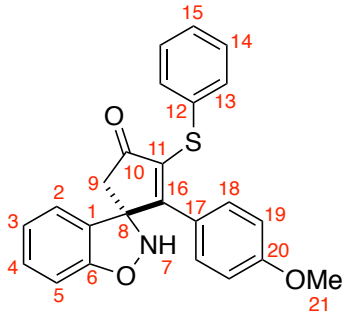
3',3'''-(1,4-Phenylenebis(sulfanediyl))bis(2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one) (161o)



Synthesized using **General Procedure K** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), benzene-1,4-dithiol (14.2 mg, 0.10 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 2:1 → 1:1 → 0:1 v/v) afforded the title product (58.3 mg, 88%) as a yellow solid.

mp: 185 – 189 °C; **Rf** 0.26 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.79 (2H, s, H-7,7'), 7.36 (2H, dd, J = 7.6, 1.3 Hz, H-Ar), 7.29 – 7.15 (8H, m, H-Ar), 7.10 – 7.01 (8H, m, H-Ar), 6.98 (2H, t, J = 7.4, H-Ar), 6.76 (2H, d, J = 8.1 Hz, H-Ar), 3.26 (2H, dd, J = 18.7, 2.1 Hz, H-9a,9a'), 3.10 (2H, d, J = 18.7 Hz, H-9b,9b'); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.7 (2C, C-10,10'), 175.2 (2C, C-14,14'), 158.8 (2C, C-6,6'), 132.9 (2C, C-Ar), 132.72 (C, C-Ar), 132.69 (C, C-Ar), 131.3 (2C, C-Ar), 129.6 (2CH, C-Ar), 129.4 (2CH, C-Ar), 128.9 (4CH, C-Ar), 128.7 (2C, C-Ar), 127.8 (4CH, C-Ar), 127.7 (4CH, C-Ar), 122.9 (2CH, C-Ar), 121.9 (2CH, C-Ar), 107.5 (2CH, C-Ar), 73.3 (2C, C-8,8'), 46.8 ($2CH_2$, C-9,9'); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{40}H_{28}N_2NaO_4S_2$ 687.1383; Found 687.1402; **ν_{max}** (thin film)/cm^{-1} 3245, 3060, 2924, 1718, 1698, 1474, 1216.

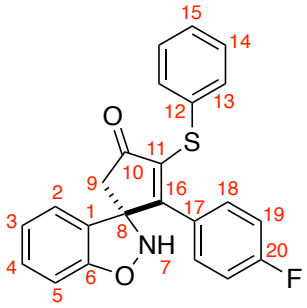
2'-(4-Methoxyphenyl)-3'-(phenylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161p)



Synthesized using **General Procedure K** with 1-(Benzo[*d*]isoxazol-3-yl)-4-(4-methoxyphenyl)but-3-yn-2-one **159b** (58.3 mg, 0.20 mmol), thiophenol (30.6 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 4:1 then 2:1 v/v) afforded the title product (83.4 mg, 100%) as a yellow oil.

Rf 0.33 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.81 (1H, s, H-7), 7.32 – 7.23 (3H, m, H-Ar), 7.23 – 7.12 (6H, m, H-Ar), 6.96 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.84 – 6.75 (3H, m, H-Ar), 3.69 (3H, s, H-21), 3.20 (1H, d, J = 18.6 Hz, H-9a), 3.11 (1H, d, J = 18.6 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.7 (C, C-10), 174.7 (C, C-16), 160.3 (C, C-20), 158.6 (C, C-6), 133.6 (C, C-Ar), 131.7 (C, C-Ar), 129.7 (2CH, C-Ar), 129.5 (CH, C-Ar), 129.2 (C, C-17), 129.1 (2CH, C-Ar), 127.8 (2CH, C-Ar), 126.2 (CH, C-Ar), 125.0 (C, C-Ar), 122.8 (CH, C-Ar), 121.9 (CH, C-Ar), 113.3 (2CH, C-19), 107.5 (CH, C-Ar), 73.3 (C, C-8), 55.1 (CH_3, C-21), 47.6 (CH_2, C-9); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{24}H_{19}NNaO_3S$ 424.0978; Found 424.0991, $[M + H]^+$ Calcd for $C_{24}H_{20}NO_3S$ 402.1158; Found 402.1165; **ν_{max}** (thin film)/cm^{-1} 3223, 2927, 1716, 1604, 1505, 1252, 1178, 1024.

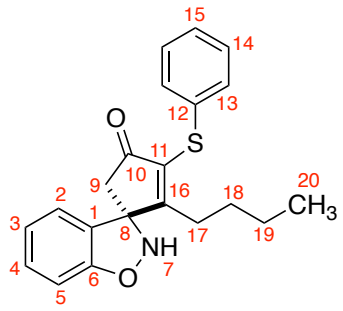
2'-(4-Fluorophenyl)-3'-(phenylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161q)



Synthesized using **General Procedure K** with 1-(Benzo[*d*]isoxazol-3-yl)-4-(4-fluorophenyl)but-3-yn-2-one **159c** (83.8 mg, 0.30 mmol), thiophenol (45.9 μL, 0.45 mmol), and DCE (3 mL, 0.1M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 4:1 v/v) afforded the title product (102.2 mg, 87%) as a yellow solid.

mp: 87 – 91 °C; **Rf** 0.55 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.83 (1H, s, H-7), 7.35 (1H, dd, J = 7.5, 1.3 Hz, H-Ar), 7.29 – 7.22 (2H, m, H-Ar), 7.21 – 7.16 (4H, m, H-Ar), 7.16 – 7.10 (2H, m, H-18), 7.09 – 7.03 (2H, m, H-19), 6.97 (1H, td, J = 7.4, 0.9 Hz, H-Ar), 6.77 (1H, d, J = 8.1 Hz, H-Ar), 3.26 (1H, d, J = 18.7 Hz, H-9a), 3.11 (1H, d, J = 18.7 Hz, H-9b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.8 (C, C-10), 173.3 (C, C-16), 162.5 (C, d, $^{1}J_{C\text{-}F}$ = 247.1 Hz, C-20), 158.7 (C, C-6), 133.4 (C, C-Ar), 132.8 (C, C-Ar), 130.1 (2CH, d, $^{3}J_{C\text{-}F}$ = 8.7 Hz, C-18), 129.6 (CH, C-Ar), 129.3 (C, d, $^{4}J_{C\text{-}F}$ = 3.3 Hz, C-17), 129.1 (2CH, C-13/14), 128.6 (C, C-Ar), 128.5 (2CH, C-13/14), 126.5 (CH, C-Ar), 122.9 (CH, C-Ar), 121.9 (CH, C-Ar), 114.9 (2CH, d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, C-19), 107.5 (CH, C-Ar), 73.2 (C, C-8), 46.7 (CH_2, C-9); **^{19}F NMR** (376 MHz, DMSO-d_6) δ (−111.35) – (−111.53) (m, 1F); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{16}FNNaO_2S$ 412.0778; Found 412.0780 ; **ν_{max}** (thin film)/cm^{-1} 3225, 3061, 2928, 1718, 1601, 1503, 1475, 1234, 1214, 1159.

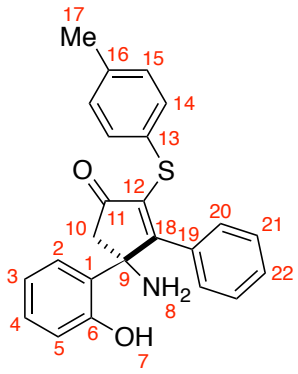
2'-Butyl-3'-(phenylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one (161r)



Synthesized using **General Procedure K** with 1-(Benzo[*d*]isoxazol-3-yl)oct-3-yn-2-one **159d** (48.3 mg, 0.20 mmol), thiophenol (30.6 μL, 0.30 mmol), and DCE (2 mL) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 8:1 $\rightarrow$ 6:1 v/v) afforded the title product (26.7 mg, 38%) as a yellow oil.

Rf 0.51 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (6H, m, H-Ar), 7.05 – 6.96 (2H, m, H-Ar), 6.93 (1H, dt, *J* = 8.0, 0.7 Hz, H-Ar), 3.01 (1H, d, *J* = 18.2 Hz, H-9a), 2.80 (1H, d, *J* = 18.2 Hz, H-9b), 2.55 (1H, ddd, *J* = 12.5, 10.7, 5.2 Hz, H-17a), 2.38 (1H, ddd, *J* = 12.5, 10.7, 5.7 Hz, H-17b), 1.44 – 1.30 (1H, m, H-18a), 1.20 (2H, sx, *J* = 7.2 Hz, H-19), 1.13 – 1.00 (1H, m, H-18b), 0.75 (3H, t, *J* = 7.2 Hz, H-20); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.7 (C, C-10), 179.9 (C, C-16), 159.5 (C, C-6), 134.8 (C, C-11), 133.2 (C, C-1), 129.9 (CH, C-Ar), 129.7 (2CH, C-Ar), 129.2 (2CH, C-Ar), 128.6 (C, C-12), 127.0 (CH, C-Ar), 122.7 (CH, C-Ar), 122.2 (CH, C-Ar), 108.4 (CH, C-Ar), 73.5 (C, C-8), 47.6 (CH_2, C-9), 30.9 (CH_2, C-18), 28.6 (CH_2, C-17), 23.2 (CH_2, C-19), 13.6 (CH_3, C-20) ; **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{21}H_{21}NNaO_2S$ 374.1185; Found 374.1186, $[M + H]^+$ Calcd for $C_{21}H_{22}NO_2S$ 352.1366; Found 352.1364; **ν_{max}** (thin film)/cm^{-1} 3225, 2958, 2930, 2871, 1716, 1595, 1474, 1458, 1213.

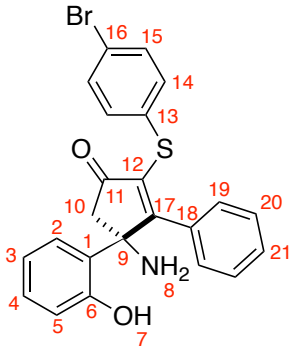
4-Amino-4-(2-hydroxyphenyl)-3-phenyl-2-(*p*-tolylthio)cyclopent-2-en-1-one (162a)



To a stirred solution of 2'-phenyl-3'-(*p*-tolylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclo pentan]-2'-en-4'-one **161a** (93.3 mg, 0.24 mmol) in MeOH (10.0 mL) in a round bottom flask was added palladium on carbon (25.8 mg, 10 mol%) under argon atmosphere. A reaction mixture was evacuated and backfilled with hydrogen gas (via balloon) several time. Then, it was stirred at ambient temperature for 3 hours. A crude mixture was purged with argon, filtered through Celite, washed with EtOAc and concentrated *in vacuo* afforded the title product (93.8 mg, 100%) as a yellow solid.

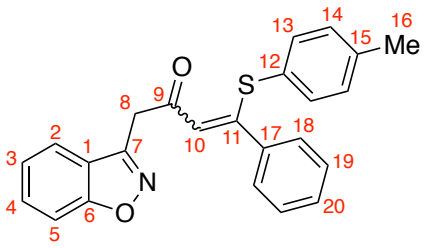
mp: 115 – 118 °C; **Rf** 0.23 (Et_2O:hexane, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (2H, m, H-Ar), 7.40 – 7.31 (3H, m, H-Ar), 7.25 – 7.20 (3H, m, H-Ar), 7.06 – 7.00 (2H, m, H-Ar), 6.97 (1H, dd, *J* = 7.8, 1.6 Hz, H-Ar), 6.92 (1H, dd, *J* = 8.2, 1.3 Hz, H-Ar), 6.76 (1H, td, *J* = 7.5, 1.3 Hz, H-Ar), 3.04 (1H, d, *J* = 18.0 Hz, H-10a), 2.86 (1H, d, *J* = 18.0 Hz, H-10b), 2.28 (3H, s, H-17); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.7 (C, C-11), 171.1 (C, C-18), 157.7 (C, C-6), 137.7 (C, C-14), 136.6 (C, C-Ar), 131.9 (C, C-Ar), 131.3 (2CH, C-Ar), 130.5 (CH, C-Ar), 130.0 (CH, C-Ar), 129.9 (2CH, C-Ar), 129.8 (2CH, C-Ar), 128.9 (2CH, C-Ar), 128.7 (C, C-Ar), 127.6 (C, C-Ar), 126.7 (CH, C-Ar), 119.5 (CH, C-Ar), 118.4 (CH, C-Ar), 65.9 (C, C-9), 54.0 (CH_2, C-10), 21.2 (CH_3, C-17); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{24}H_{21}NNaO_2S$ 410.1185; Found 410.1192; ν_{max} (thin film)/cm^{-1} 3358, 3292, 2921, 1710, 1584, 1490, 1465, 1211.

4-Amino-2-((4-bromophenyl)thio)-4-(2-hydroxyphenyl)-3-phenylcyclopent-2-en-1-one (162k)



To a stirred solution of 3'-((4-bromophenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*] isoxazole-3,1'-cyclopentan]-2'-en-4'-one **161k** (82.8 mg, 0.18 mmol) in MeOH (10.0 mL) in a round bottom flask was added palladium on carbon (19.6 mg, 10 mol%) under argon atmosphere. A reaction mixture was evacuated and backfilled with hydrogen gas (via balloon) several time. Then, it was stirred at ambient temperature for 3 hours. A crude mixture was purged with argon, filtered through Celite, washed with EtOAc and concentrated *in vacuo* afforded the title product (77.6 mg, 95%) as a yellow solid. **mp**: 120 – 124 °C; **Rf** 0.28 (Et_2O:hexane, 4:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (2H, m, H-Ar), 7.43 – 7.31 (5H, m, H-Ar), 7.27 – 7.21 (1H, m, H-Ar), 7.21 – 7.15 (2H, m, H-Ar), 6.99 – 6.91 (2H, m, H-Ar), 6.78 (1H, td, *J* = 7.5, 1.3 Hz, H-Ar), 3.08 (1H, d, *J* = 18.1 Hz, H-10a), 2.88 (1H, d, *J* = 18.1 Hz, H-10b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4 (C, C-11), 172.3 (C, C-17), 157.7 (C, C-6), 135.4 (C, C-Ar), 132.3 (2CH, C-Ar), 132.2 (2CH, C-Ar), 131.69 (C, C-Ar), 131.66 (C, C-Ar), 130.9 (CH, C-Ar), 130.2 (CH, C-Ar), 129.8 (2CH, C-Ar), 129.1 (2CH, C-Ar), 127.4 (C, C-Ar), 126.6 (CH, C-Ar), 121.6 (C, C-Ar), 119.5 (CH, C-Ar), 118.5 (CH, C-Ar), 66.0 (C, C-9), 54.0 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{18}{}^{79}BrNNaO_2S$ 474.0134; Found 474.0139; **ν_{max}** (thin film)/cm^{-1} 3354, 3287, 2925, 1710, 1584, 1471, 1252, 1211.

1-(Benzo[*d*]isoxazol-3-yl)-4-phenyl-4-(*p*-tolylthio)but-3-en-2-one (163a)

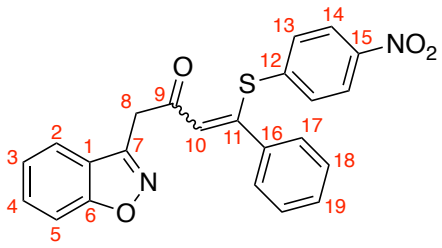


To a stirred solution of 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol) in DCE (2 mL, 0.1 M) in a sealed vial was added 4-methylbenzenethiol (37.3 mg, 0.30 mmol) and Et_3N (27.9 μL, 0.3 mmol). Then, the vial was degassed with argon for 5 minutes. The solution mixture was stirred for 21 hours at 60 °C in a heating block. Then, a crude mixture was quenched with sat. aq. $NaHCO_3$ (5.0 mL) and extracted with DCM (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product as an inseparable mixture of *E*/*Z* isomers (73.0 mg, 95%, *E*/*Z* = 35:65) as a yellow oil.

Rf 0.61 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (2H, dt, *J* = 8.0, 1.0 Hz, H-Ar), 7.60 – 7.53 (4H, m, H-Ar), 7.52 – 7.49 (2H, m, H-Ar), 7.46 (1H, dt, *J* = 8.0, 1.1 Hz, H-Ar), 7.43 – 7.30 (9H, m, H-Ar), 7.26 – 7.18 (4H, m, H-Ar), 7.15 – 7.02 (10H, m, H-Ar), 7.01 – 6.97 (4H, m, H-Ar), 6.87 – 6.81 (4H, m, H-Ar), 6.57 (1H, s, H-10, major), 5.72 (1H, s, H-10, minor), 4.27 (2H, s, H-8, major), 3.75 (2H, s, H-8, minor), 2.41 (3H, s, H-16, minor), 2.17 (3H, s, H-16, major); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.5 (C, C-9, major), 190.6 (C, C-9, minor), 164.0 (C, C-11, major), 163.7 (C, C-11, minor), 163.4 (C, C-6, major), 163.2 (C, C-6, minor), 153.6 (C, C-7, major), 153.5 (C, C-7, minor), 140.8 (C, C-Ar), 138.3 (C, C-Ar), 138.1 (C, C-Ar), 136.6 (C, C-Ar), 135.3 (CH, C-Ar), 134.3 (CH, C-Ar), 130.9 (CH, C-Ar), 130.1 (CH, C-Ar), 129.9 (CH, C-Ar), 129.8 (CH, C-Ar), 129.3 (CH, C-Ar), 128.9 (CH, C-Ar), 128.7 (CH, C-Ar), 128.61 (CH, C-Ar), 128.59 (CH, C-Ar), 128.5 (C, C-Ar), 127.9 (CH, C-Ar), 126.1 (C, C-Ar), 123.8 (CH, C-Ar), 123.5 (CH, C-Ar), 122.4 (CH, C-Ar), 122.1 (CH, C-Ar), 121.8 (C, C-Ar), 121.7 (C, C-Ar), 120.9 (CH, C-10, major), 118.9 (CH, C-10, minor), 110.0 (CH, C-Ar), 109.8 (CH, C-Ar), 40.2 (CH_2, C-8, major), 39.7 (CH_2, C-8, minor), 21.5 (CH_3, C-16, minor), 21.2 (CH_3, C-16, major); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}NNaO_2S$ 408.1029; Found 408.1033, $[M + H]^+$ Calcd for

$C_{24}H_{20}NO_2S$ 386.1209; Found 386.1217; ν_{max} (thin film)/cm^{-1} 3057, 2921, 1668, 1537, 1489, 1439, 1380, 1234, 1096.

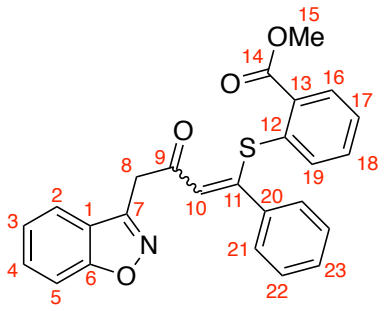
1-(Benzo[*d*]isoxazol-3-yl)-4-((4-nitrophenyl)thio)-4-phenylbut-3-en-2-one (163m)



Synthesized using **General Procedure B** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), 4-nitrobenzenethiol (46.6 mg, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 45 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product as an inseparable mixture of *E*/*Z* isomers (49.5 mg, 59%, *E*/*Z* = 11:89) as a yellow oil.

Rf 0.51 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.01 (2H, m, H-Ar), 7.90 – 7.81 (16H, m, H-Ar), 7.75 (8H, dt, *J* = 8.0, 1.0 Hz, H-Ar), 7.63 – 7.48 (20H, m, H-Ar), 7.48 – 7.43 (1H, m, H-Ar), 7.40 – 7.30 (13H, m, H-Ar), 7.29 – 7.24 (2H, m, H-Ar), 7.23 – 7.19 (16H, m, H-Ar), 7.19 – 7.15 (9H, m, H-Ar), 7.15 – 7.12 (30H, m, H-Ar), 6.76 (1H, s, H-10, major), 6.05 (1H, s, H-10H, minor), 4.30 (2H, s, H-8, major), 3.84 (2H, s, H-8, minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.8 (C, C-9, major), 191.0 (C, C-9, minor), 163.5 (C, C-6, major), 163.2 (C, C-6, minor), 158.8 (C, C-11, minor), 158.6 (C, C-11, major), 153.2 (C, C-7), 146.9 (C, C-Ar), 141.9 (C, C-Ar), 138.9 (C, C-Ar), 137.3 (C, C-Ar), 135.5 (C, C-Ar), 134.7 (CH, C-Ar), 133.5 (CH, C-Ar), 130.4 (CH, C-Ar), 130.2 (CH, C-Ar), 130.2 (CH, C-Ar), 129.7 (CH, C-Ar), 129.0 (CH, C-Ar), 128.7 (CH, C-Ar), 128.5 (CH, C-Ar), 124.5 (CH, C-Ar), 123.9 (CH, C-Ar), 123.7 (CH, C-Ar), 123.6 (CH, C-Ar), 123.4 (CH, C-Ar), 122.1 (CH, C-Ar), 121.7 (CH, C-Ar), 121.6 (C, C-Ar), 110.1 (CH, C-Ar), 110.0 (CH, C-Ar), 40.3 (CH_2, C-8, major), 39.9 (CH_2, C-8, minor); **HRMS** (ESI) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{16}N_2NaO_4S$ 439.0723; Found 439.0726, [M + H]$^+$ Calcd for $C_{23}H_{17}N_2O_4S$ 417.0904; Found 417.0896; ν_{max} (thin film)/cm^{-1} 3098, 3065, 1671, 1598, 1576, 1542, 1515, 1340.

Methyl 2-((4-(benzo[*d*]isoxazol-3-yl)-3-oxo-1-phenylbut-1-en-1-yl)thio)benzoate (163n)

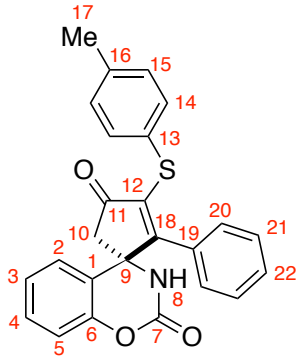


Synthesized using **General Procedure B** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), methyl thiosalicylate (41.3 μL, 0.30 mmol), and DCE (2 mL, 0.1M) at 60 °C for 45 hours. Purification by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product as an inseparable mixture of *E*/*Z* isomers (64.3 mg, 75%, *E*/*Z* = 24:76) as a yellow oil.

Rf 0.48 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (1H, dd, *J* = 5.9, 3.4 Hz, H-Ar), 7.79 (1H, dt, *J* = 7.9, 1.0 Hz, H-Ar), 7.65 – 7.60 (3H, m, H-Ar), 7.59 – 7.54 (6H, m, H-Ar), 7.54 – 7.45 (5H, m, H-Ar), 7.45 – 7.39 (4H, m, H-Ar), 7.37 – 7.29 (7H, m, H-Ar), 7.25 – 7.20 (1H, m, H-Ar), 7.17 – 7.04 (26H, m, H-Ar), 6.67 (1H, s, H-10, major), 5.96 (1H, s, H-10, minor), 4.31 (2H, s, H-8, major), 3.88 (3H, s, H-15, minor), 3.87 (3H, s, H-15, major), 3.79 (2H, s, H-8, minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.7 (C, C-9, major), 191.1 (C, C-9, minor), 166.9 (C, C-14, major), 166.7 (C, C-14, minor), 163.4 (C, C-6, major), 163.2 (C, C-6, minor), 161.1 (C, C-11), 153.5 (C, C-7, major), 153.3 (C, C-7, minor), 138.3 (C, C-Ar), 136.6 (CH, C-Ar), 136.3 (C, C-Ar), 136.0 (CH, C-Ar), 134.7 (C, C-Ar), 134.0 (C, C-Ar), 133.4 (C, C-Ar), 132.4 (CH, C-Ar), 131.3 (CH, C-Ar), 131.2 (CH, C-Ar), 130.9 (C, C-Ar), 130.5 (CH, C-Ar), 130.1 (CH, C-Ar), 130.0 (CH, C-Ar), 129.9 (CH, C-Ar), 129.6 (CH, C-Ar), 129.1 (C, C-Ar), 129.1 (CH, C-Ar), 128.9 (CH, C-Ar), 128.5 (CH, C-Ar), 128.0 (CH, C-Ar), 127.9 (CH, C-Ar), 123.8 (CH, C-Ar), 123.6 (CH, C-Ar), 123.1 (CH, C-Ar), 122.4 (CH, C-Ar), 122.0 (CH, C-Ar), 121.8 (C, C-Ar), 121.7 (C, C-Ar), 121.2 (CH, C-Ar), 109.93 (CH, C-Ar), 109.88 (CH, C-Ar), 52.6 (CH_3, C-15, minor), 52.4 (CH_3, C-15, major), 40.2 (CH_2, C-8, major), 39.8 (CH_2, C-8, minor); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_4S$ 452.0927; Found 452.0942, $[M + H]^+$ Calcd

for $C_{25}H_{20}NO_4S$ 430.1108; Found 430.1119; ν_{max} (thin film)/cm^{-1} 3063, 2951, 2924, 1722, 1537, 1437, 1291, 1255.

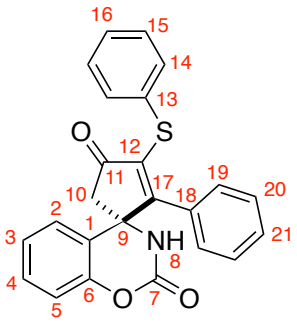
2'-Phenyl-3'-(*p*-tolylthio)spiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-ene-2,4'(3*H*)-dione (164a)



To a stirred solution of 4-amino-4-(2-hydroxyphenyl)-3-phenyl-2-(*p*-tolylthio) cyclopent-2-en-1-one **162a** (69.7 mg,0.18 mmol) in DCM (5.0 mL) was added Et_3N (0.12 mL, 0.89 mmol) under argon atmosphere. The solution mixture was added triphosgene (21.1 mg, 0.071 mmol) and stirred at ambient temperature overnight. A crude mixture was quenched with sat. aq. $NaHCO_3$ (5.0 mL) and extracted with DCM (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 3:1 → 1:1 v/v) afforded the title product (62.0 mg, 84%) as a yellow solid.

mp: 240 – 244 °C; **Rf** 0.59 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.83 (1H, s, H-8), 7.39 – 7.20 (6H, m, H-Ar), 7.18 – 7.13 (2H, m, H-Ar), 7.09 – 7.04 (2H, m, H-15), 6.98 – 6.93 (1H, m, H-Ar), 6.88 – 6.80 (2H, m, H-Ar), 3.26 (1H, d, J = 18.6 Hz, H-10a), 3.11 (1H, d, J = 18.6 Hz, H-10b), 2.24 (3H, s, H-17); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.5 (C, C-11), 173.0 (C, C-18), 149.0 (C, C-6), 148.0 (C, C-7), 136.3 (C, C-16), 134.8 (C, C-Ar), 132.3 (C, C-Ar), 130.2 (CH, C-Ar), 129.7 (2CH, C-15), 129.39 (CH, C-Ar), 129.36 (2CH, C-Ar), 128.8 (C, C-Ar), 128.2 (2CH, C-Ar), 127.4 (2CH, C-Ar), 125.4 (CH, C-Ar), 125.2 (CH, C-Ar), 119.9 (C, C-Ar), 116.3 (CH, C-Ar), 63.9 (C, C-9), 52.6 (CH_2, C-10), 20.6 (CH_3, C-17); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_3S$ 436.0978; Found 436.0978, $[M + H]^+$ Calcd for $C_{25}H_{20}NO_3S$ 414.1158; Found 414.1150 ; ν_{max} (thin film)/cm^{-1} 2923, 1730, 1711, 1493, 1451, 1367, 1220.

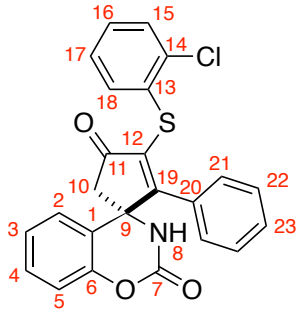
2'-Phenyl-3'-(phenylthio)spiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-ene-2,4'(3*H*)-dione (164b)



Synthesized using **General Procedure L** with 2'-phenyl-3'-(phenylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one **161d** (86.7 mg, 0.23 mmol), Pd/C (24.8 mg, 10 mol%) and MeOH (10.0 mL). Then, triphosgene (27.7 mg, 0.093 mmol), Et_3N (0.16 mL, 1.15 mmol) and DCM (5.0 mL). Purification by flash column chromatography (DCM:MeOH, 50:1 v/v) afforded the title product (90.5 mg, 97%) as a yellow solid.

mp: 214 – 218 °C; **Rf** 0.25 (DCM:MeOH, 50:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.88 (1H, s, H-8), 7.35 (1H, ddd, J = 8.5, 7.1, 1.8 Hz, H-Ar), 7.32 – 7.22 (9H, m, H-Ar), 7.21 – 7.16 (1H, m, H-Ar), 6.97 (1H, dd, J = 8.1, 1.2 Hz, H-Ar), 6.92 – 6.82 (2H, m, H-Ar), 3.29 (1H, d, J = 18.7 Hz, H-10a), 3.15 (1H, d, J = 18.7 Hz, H-10b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.5 (C, C-11), 173.8 (C, C-17), 149.0 (C, C-6), 148.0 (C, C-7), 134.3 (C, C-Ar), 132.7 (C, C-Ar), 132.3 (C, C-Ar), 130.3 (CH, C-Ar), 129.5 (CH, C-Ar), 129.1 (2CH, C-Ar), 128.7 (2CH, C-Ar), 128.2 (2CH, C-Ar), 127.4 (2CH, C-Ar), 126.6 (CH, C-Ar), 125.5 (CH, C-Ar), 125.2 (CH, C-Ar), 119.8 (C, C-Ar), 116.3 (CH, C-Ar), 63.9 (C, C-9), 52.6 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{24}H_{17}NNaO_3S$ 422.0821; Found 422.0820, $[M + H]^+$ Calcd for $C_{24}H_{18}NO_3S$ 400.1002; Found 400.1001; ν_{max} (thin film)/cm^{-1} 2956, 2923, 2853, 1716, 1451, 1361, 1221.

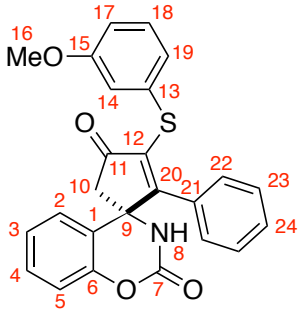
3'-((2-Chlorophenyl)thio)-2'-phenylspiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-ene-2,4'(3*H*)-dione (164c)



Synthesized using **General Procedure L** with 3'-((2-chlorophenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one **161l** (85.1 mg, 0.21 mmol), Pd/C (22.3 mg, 10 mol%) and MeOH (10.0 mL). Then, triphosgene (24.9 mg, 0.084 mmol), Et_3N (0.15 mL, 1.05 mmol) and DCM (5.0 mL). Purification by flash column chromatography (hexane:EtOAc, 2:1 v/v) afforded the title product (79.8 mg, 88%) as a yellow solid.

mp: 170 – 174 °C; **Rf** 0.45 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.90 (1H, s, H-8), 7.41 (1H, dd, J = 7.4, 1.9 Hz, H-Ar), 7.39 – 7.28 (5H, m, H-Ar), 7.28 – 7.17 (4H, m, H-Ar), 7.01 – 6.94 (1H, m, H-Ar), 6.90 – 6.80 (2H, m, H-21), 3.35 (1H, d, J = 18.8 Hz, H-10a), 3.19 (1H, d, J = 18.8 Hz, H-10b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.2 (C, C-11), 174.8 (C, C-19), 149.0 (C, C-6), 148.0 (C, C-7), 133.1 (C, C-Ar), 132.0 (C, C-Ar), 131.8 (C, C-Ar), 131.8 (C, C-Ar), 130.3 (CH, C-Ar), 130.0 (CH, C-Ar), 129.64 (CH, C-Ar), 129.61 (CH, C-Ar), 128.3 (2CH, C-22), 128.0 (CH, C-Ar), 127.7 (CH, C-Ar), 127.2 (2CH, C-21), 125.6 (CH, C-Ar), 125.2 (CH, C-Ar), 119.6 (C, C-Ar), 116.3 (CH, C-Ar), 64.1 (C, C-9), 52.4 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{24}H_{16}{}^{35}ClNNaO_3S$ 456.0432; Found 456.0433; **ν_{max}** (thin film)/cm^{-1} 3267, 3142, 2926, 1713, 1451, 1361, 1220.

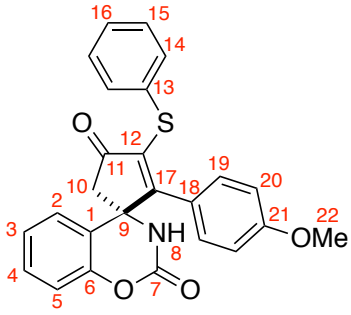
3'-((3-Methoxyphenyl)thio)-2'-phenylspiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-ene-2,4'(3*H*)-dione (164d)



Synthesized using **General Procedure L** with 3'-((3-methoxyphenyl)thio)-2'-phenyl-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one **161h** (72.5 mg, 0.18 mmol), Pd/C (19.2 mg, 10 mol%) and MeOH (10.0 mL). Then, triphosgene (21.4 mg, 0.072 mmol), Et_3N (0.13 mL, 0.90 mmol) and DCM (5.0 mL). Purification by flash column chromatography (hexane:EtOAc, 2:1 v/v) afforded the title product (74.4 mg, 96%) as a yellow solid.

mp: 155 – 159 °C; **Rf** 0.43 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.89 (1H, s, H-8), 7.35 (1H, ddd, J = 8.5, 7.0, 1.9 Hz, H-Ar), 7.32 – 7.20 (5H, m, H-Ar), 7.17 (1H, t, J = 7.9 Hz, H-Ar), 6.98 (1H, dd, J = 8.2, 1.1 Hz, H-Ar), 6.89 – 6.81 (3H, m, H-Ar), 6.80 – 6.72 (2H, m, H-Ar), 3.71 (3H, s, H-16), 3.30 (1H, d, J = 18.7 Hz, H-10a), 3.15 (1H, d, J = 18.7 Hz, H-10b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 199.5 (C, C-11), 173.8 (C, C-20), 159.5 (C, C-15), 149.0 (C, C-6), 148.0 (C, C-7), 134.2 (C, C-Ar), 133.8 (C, C-Ar), 132.2 (C, C-Ar), 130.3 (CH, C-Ar), 130.0 (CH, C-Ar), 129.5 (CH, C-Ar), 128.2 (2CH, C-Ar), 127.3 (2CH, C-Ar), 125.4 (CH, C-Ar), 125.2 (CH, C-Ar), 120.9 (CH, C-Ar), 119.8 (C, C-Ar), 116.3 (CH, C-Ar), 114.1 (CH, C-Ar), 112.3 (CH, C-Ar), 64.0 (C, C-9), 55.2 (CH_3, C-16), 52.6 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_4S$ 452.0927; Found 452.0940, $[M + H]^+$ Calcd for $C_{25}H_{20}NNaO_4S$ 430.1108; Found 430.1121; ν_{max} (thin film)/cm^{-1} 2927, 1745, 1717, 1590, 1479, 1452, 1222.

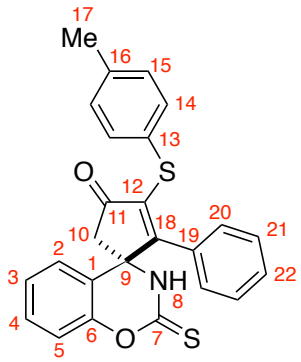
2'-(4-Methoxyphenyl)-3'-(phenylthio)spiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-ene-2,4'(3*H*)-dione (164e)



Synthesized using **General Procedure L** with 2'-(4-methoxyphenyl)-3'-(phenylthio)-2*H*-spiro[benzo[*d*]isoxazole-3,1'-cyclopentan]-2'-en-4'-one **161p** (107.8 mg, 0.25 mmol), Pd/C (26.7 mg, 10 mol%) and MeOH (10.0 mL). Then, triphosgene (29.7 mg, 0.10 mmol), Et_3N (0.17 mL, 1.25 mmol) and DCM (5.0 mL). Purification by flash column chromatography (hexane:EtOAc, 2:1 → 1:1 v/v) afforded the title product (88.9 mg, 83%) as a yellow oil.

Rf 0.35 (hexane:EtOAc, 1:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (1H, s, H-8), 7.33 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz, H-Ar), 7.27 – 7.22 (2H, m, H-14), 7.20 – 7.11 (4H, m, H-Ar), 7.06 – 7.01 (2H, m, H-Ar), 6.99 – 6.93 (2H, m, H-19), 6.67 – 6.60 (2H, m, H-20), 3.65 (3H, s, H-22), 3.11 (1H, d, *J* = 18.5 Hz, H-10a), 2.99 (1H, d, *J* = 18.5 Hz, H-10b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.5 (C, C-11), 170.9 (C, C-17), 160.9 (C, C-21), 150.2 (C, C-6), 148.9 (C, C-7), 135.7 (C, C-Ar), 132.2 (C, C-Ar), 130.5 (2CH, C-14), 130.4 (CH, C-Ar), 129.9 (2CH, C-19), 129.1 (2CH, C-15), 127.2 (CH, C-Ar), 125.8 (CH, C-Ar), 124.6 (CH, C-Ar), 124.0 (C, C-18), 120.8 (C, C-Ar), 117.3 (CH, C-Ar), 114.0 (2CH, C-20), 64.4 (C, C-9), 55.3 (CH_3, C-22), 54.5 (CH_2, C-10); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_4S$ 452.0927; Found 452.0930, $[M + H]^+$ Calcd for $C_{25}H_{20}NO_4S$ 430.1108; Found 430.1123; **ν_{max}** (thin film)/cm^{-1} 3272, 3146, 2939, 1714, 1604, 1505, 1251, 1219.

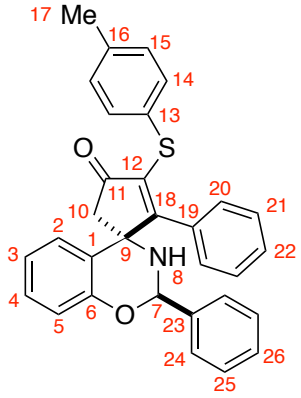
2'-Phenyl-2-thioxo-3'-(*p*-tolylthio)-2,3-dihydrospiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-en-4'-one (165)



To a stirred solution of 4-amino-4-(2-hydroxyphenyl)-3-phenyl-2-(*p*-tolylthio) cyclopent-2-en-1-one **162a** (89.1 mg, 0.23 mmol) in DCM (5.0 mL) was added DMAP (141.7 mg, 1.16 mmol) under argon atmosphere. The solution mixture was added thiophosgene (21.4 μL, 0.28 mmol) and stirred at ambient temperature overnight. A crude mixture was quenched with sat. aq. $NaHCO_3$ (5.0 mL) and extracted with DCM (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 6:1 → 4:1 v/v) afforded the title product (39.0 mg, 39%) as a yellow solid.

mp: 217 – 221 °C; **Rf** 0.48 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.49 (1H, s, H-8), 7.39 – 7.33 (1H, m, H-Ar), 7.28 – 7.20 (2H, m, H-Ar), 7.20 – 7.11 (4H, m, H-Ar), 7.09 (2H, dd, *J* = 8.2, 1.2 Hz, H-Ar), 7.06 (2H, dd, *J* = 7.8, 1.5 Hz, H-Ar), 7.01 – 6.96 (2H, m, H-15), 6.95 – 6.90 (2H, m, H-Ar), 3.13 (1H, d, *J* = 18.5 Hz, H-10a), 3.07 (1H, d, *J* = 18.5 Hz, H-10b), 2.25 (3H, s, H-17); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.7 (C, C-11), 181.6 (C, C-18), 168.0 (C, C-7), 148.0 (C, C-6), 138.8 (C, C-Ar), 138.0 (C, C-16), 131.9 (2CH, C-Ar), 131.5 (C, C-Ar), 130.7 (CH, C-Ar), 129.9 (2CH, C-15), 129.9 (CH, C-Ar), 128.6 (2CH, C-Ar), 128.1 (2CH, C-Ar), 127.1 (C, C-Ar), 126.7 (CH, C-Ar), 124.5 (CH, C-Ar), 119.8 (C, C-Ar), 117.1 (CH, C-Ar), 64.4 (C, C-9), 53.7 (CH_2, C-10), 21.2 (CH_3, C-17); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NNaO_2S_2$ 452.0749; Found 452.0778; **ν_{max}** (thin film)/cm^{-1} 3061, 2922, 1714, 1595, 1491, 1451, 1220.

2,2'-Diphenyl-3'-(*p*-tolylthio)-2,3-dihydrospiro[benzo[*e*][1,3]oxazine-4,1'-cyclopentan]-2'-en-4'-one (171)

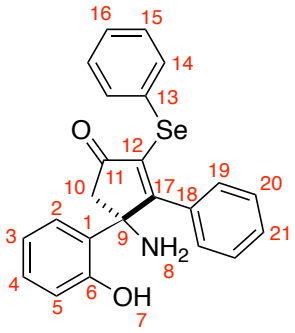


To a stirred solution of 4-amino-4-(2-hydroxyphenyl)-3-phenyl-2-(*p*-tolylthio) cyclopent-2-en-1-one **162a** (96.2 mg, 0.25 mmol) in toluene (5.0 mL) in a round bottom flask was added *p*-toluenesulfonic acid (9.4 mg, 20 mol%) and benzaldehyde (38.0 μL, 0.37 mmol) in the presence of molecular sieve 4Å. The mixture solution was stirred and refluxed under argon atmosphere for 19 hours. Then, it was quenched with sat. aq. $NaHCO_3$ (5.0 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc, 6:1 v/v) afforded the title product as an inseparable mixture of diastereomers (77.0 mg, 65%, *dr* = 78:22) as a yellow oil.

Rf 0.58 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (4H, m, H-Ar), 7.41 – 7.17 (73H, m, H-Ar), 7.12 – 7.08 (8H, m, H-Ar), 7.05 – 6.96 (45H, m, H-Ar), 5.77 (1H, d, *J* = 13.2 Hz, H-7, major), 5.02 (1H, s, H-7, minor), 3.23 (1H, d, *J* = 17.9 Hz, H-10, major), 3.11 (1H, d, *J* = 17.9 Hz, H-10, major), 3.01 (1H, d, *J* = 18.0 Hz, H-10, minor), 2.80 (1H, d, *J* = 18.0 Hz, H-10, minor), 2.45 (1H, d, *J* = 13.2 Hz, 8, major), 2.28 (3H, s, H-17, major); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.4 (C, C-11, major), 201.3 (C, C-11, minor), 171.3 (C, C-18), 155.1 (C, C-6, minor), 154.6 (C, C-6, major), 138.27 (C, C-Ar), 138.25 (C, C-Ar), 137.4 (C, C-20, major), 137.3 (C, C-20, minor), 132.0 (C, C-Ar), 131.3 (CH, C-Ar), 131.2 (CH, C-Ar), 130.2 (CH, C-Ar), 129.8 (CH, C-Ar), 129.8 (CH, C-Ar), 129.2 (CH, C-Ar), 129.2 (CH, C-Ar), 128.9 (CH, C-Ar), 128.9 (CH, C-Ar), 128.8 (C, C-Ar), 128.7 (CH, C-Ar), 128.6 (CH, C-Ar), 128.6 (CH, C-Ar), 128.4 (CH, C-Ar), 127.9 (CH, C-Ar), 126.1 (CH, C-Ar), 126.09 (CH, C-Ar), 126.05 (CH, C-Ar), 125.9 (CH, C-Ar), 125.2 (C, C-Ar), 122.2 (CH, C-Ar), 122.0

(CH, C-Ar), 118.5 (CH, C-Ar), 118.5 (CH, C-Ar), 84.7 (CH, C-7, major), 84.6 (CH, C-7, minor), 63.6 (C, C-9, major), 62.3 (C, C-9, minor), 56.1 (CH_2, C-10, major), 53.9 (CH_2, C-10, minor), 21.2 (CH_3, C-17); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{25}NNaO_2S$ 498.1498; Found 498.1504, $[M + H]^+$ Calcd for $C_{31}H_{26}NO_2S$ 476.1679; Found 476.1684; ν_{max} (thin film)/cm^{-1} 3309, 3061, 3033, 1718, 1483, 1454, 1281, 1232.

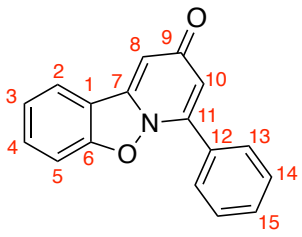
4-Amino-4-(2-hydroxyphenyl)-3-phenyl-2-(phenylselanyl)cyclopent-2-en-1-one (178)



Synthesized using **General Procedure B** with 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (52.3 mg, 0.20 mmol), benzeneselenol (31.9 μL, 0.30 mmol), and DCE (2 mL, 0.1 M) at 60 °C for 20 hours. Purification by flash column chromatography (hexane:EtOAc, 2:1 → 1:1 v/v) afforded the title product (17.7 mg, 21%) as a yellow oil.

Rf 0.23 (hexane:EtOAc, 2:1 v/v); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.37 – 7.31 (2H, m, H-Ar), 7.30 – 7.15 (7H, m, H-Ar), 7.14 – 7.05 (3H, m, H-Ar), 6.80 – 6.70 (2H, m, H-Ar), 3.03 (1H, d, J = 17.8 Hz, H-10a), 2.80 (1H, d, J = 17.8 Hz, H-10b); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 202.3 (C, C-11), 180.6 (C, C-17), 155.7 (C, C-6), 134.1 (C, C-Ar), 130.3 (2CH, C-Ar), 130.2 (C, C-Ar), 129.6 (C, C-Ar), 129.1 (2CH, C-Ar), 128.9 (CH, C-Ar), 128.7 (CH, C-Ar), 128.4 (C, C-Ar), 128.1 (2CH, C-Ar), 127.7 (2CH, C-Ar), 127.2 (CH, C-Ar), 126.3 (CH, C-Ar), 118.6 CH, C-Ar), 116.0 (CH, C-Ar), 64.7 (C, C-9), 51.9 (CH_2, C-10); **HRMS** (ESI) m/z : $[M + Na]^+$ Calcd for $C_{23}H_{19}NNaO_2{}^{80}Se$ 444.0473; Found 444.0476 ; ν_{max} (thin film)/cm^{-1} 3357, 3291, 2924, 2854, 1706, 1582, 1464, 1253, 1211.

7-Phenyl-9*H*-benzo[4,5]isoxazolo[2,3-*a*]pyridin-9-one (179)



To a stirred solution of 1-(benzo[*d*]isoxazol-3-yl)-4-phenylbut-3-yn-2-one **159a** (50.1 mg, 0.19 mmol) in DCM (2.0 mL) was added $AgNO_3$ (3.3 mg, 10 mol%) under argon atmosphere. The solution mixture was stirred at ambient temperature for 18 hours. A crude mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (DCM:MeOH, 20:1 → 10:1 v/v) afforded the title product (47.9 mg, 96%) as a yellow solid.

mp: 104 – 107 °C; **Rf** 0.49 (DCM:MeOH, 10:1 v/v); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (1H, m), 7.73 – 7.65 (2H, m), 7.65 – 7.58 (1H, m), 7.57 – 7.49 (3H, m), 7.45 – 7.37 (1H, m), 7.35 – 7.30 (1H, m), 6.82 (1H, d, J = 2.8 Hz), 6.57 (1H, d, J = 2.9 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.5 (C), 154.9 (C), 142.5 (C), 140.8 (C), 132.6 (CH), 130.8 (CH), 129.8 (C), 129.0 (2CH), 128.7 (2CH), 125.3 (CH), 122.4 (CH), 117.9 (C), 117.6 (CH), 108.9 (CH), 105.1 (CH); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{11}NNaO_2$ 284.0682; Found 284.0690, $[M + H]^+$ Calcd for $C_{17}H_{12}NO_2$ 262.0863; Found 262.0865; **ν_{max}** (thin film)/cm^{-1}; **ν_{max}** (thin film)/cm^{-1} 3380, 3061, 1625, 1612, 1527, 1493, 1467.

Appendices

Appendix I. A Thiol-Mediated Three-Step Ring Expansion Cascade for the Conversion of Indoles into Functionalized Quinolines

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A Thiol-Mediated Three-Step Ring Expansion Cascade for the Conversion of Indoles into Functionalized Quinolines

Nantachai Inprung, Michael J. James,* Richard J. K. Taylor,* and William P. Unsworth*

Cite This: *Org. Lett.* 2021, 23, 2063−2068 Read Online

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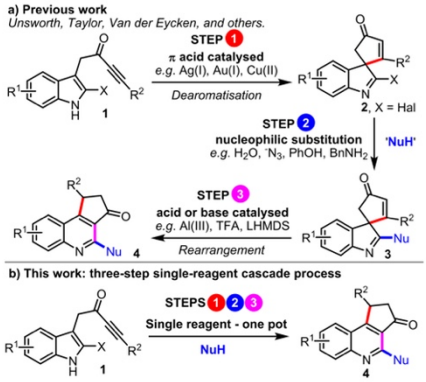
ABSTRACT: An operationally simple, high yielding three-step cascade process is described for the direct conversion of indole-tethered ynones into functionalized quinolines. A single "multi-tasking" thiol reagent is used to promote a three-step dearomatizing spirocyclization, nucleophilic substitution, and one-atom ring expansion reaction cascade under remarkably mild conditions. In addition, a novel route to thio-oxindoles is described, which was discovered by serendipity.

Cascade reactions (chemical processes by which two or more consecutive reactions take place in a single pot-process, also known as "tandem" or "domino" reactions) have wide utility in synthetic chemistry.[1,2] Incorporating cascade reaction sequences into synthetic routes can significantly improve the speed and ease with which complex target molecules can be prepared and often means that the direct handling of reactive, unstable and/or toxic species can be avoided by forming these intermediates in situ.

This manuscript concerns a three-step cascade reaction sequence, starting from indole-tethered ynones **1** (Scheme 1). In recent years, ynones of this type have emerged as valuable precursors for the preparation of a diverse array of molecular scaffolds.[3−6] For example, our groups and others have shown that the activation of the alkyne moiety of **1** promotes efficient dearomatizing spirocyclization[7,8] to form medicinally important spirocyclic indolenines **2**;[9,10] this is most commonly done using π-acidic catalysts (especially Ag(I) species), although Brønsted acids, palladium(II) complexes, and electrophilic halogenation reagents can also be used (**1** → **2**, Scheme 1a, step 1).[3,11,12] Our groups have also shown that dearomatization works well on 2-halogenated indoles (i.e., **1** where X = Cl, Br or I) and that the resulting indoleninyl halide products (i.e., **2** where X = Cl, Br or I) can be transformed further via reaction with nucleophiles, or via Pd-catalyzed cross-coupling, to substitute the halide for various other groups (**2** → **3**, Scheme 1a, step 2).[5] Finally, our groups and others have demonstrated that spirocyclic indolenines of the form **3** will rearrange via a one-atom ring expansion reaction[13] to form annulated quinolines, with both acidic and basic reagents able to promote this transformation (**3** → **4**, Scheme 1a, step 3).[6]

Efficient protocols for each of the individual steps represented in Scheme 1a are therefore established, but three steps are still required to generate functionalized quinolines **4** from ynones **1**. Quinolines are found in many marketed drugs, as well as in various other applications.[14] On the basis of a growing understanding of each of the three individual processes discussed above,[3,5,6] we recognized that certain reagents may be able to promote all three steps and enable the transformation of **1** into **4** via a single-cascade process (Scheme 1b); such a reagent would need to act as an acid

Scheme 1. Transformations of Indole-Tethered Ynones



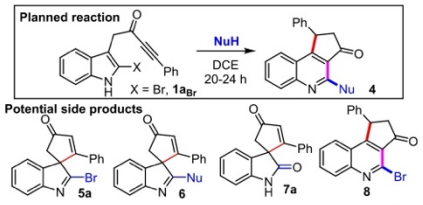
Received: January 21, 2021
Published: March 1, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00205
Org. Lett. 2021, 23, 2063−2068

to promote step 1, a nucleophile in step 2, and a Brønsted acid to promote step 3. The successful realization of this strategy is reported herein, with thiols emerging as the optimum "multitasking" reagent class capable of promoting the envisaged cascade, under remarkably mild and operationally simple conditions.

We started by exploring the reactivity of model 2-bromo ynone $\mathbf{1a_{Br}}$ with various reagents (**NuH**) that we thought might have the required acidity and nucleophilicity to promote its conversion into a quinoline of the form **4**. Phenol was tested first, and added to a solution of $\mathbf{1a_{Br}}$ in DCE,[15] but no reaction was observed after stirring at RT or 60 °C (entries 1 and 2, Table 1). Next, TFA was included as an additive in the reaction, which led to the consumption of the starting material, but the only tractable products observed were oxindole **7a** (presumably formed via acid-mediated dearomatizing spirocyclization and hydrolysis of the resulting spirocycle **5a**),[5] and bromoquinoline **8**, which likely formed via a Bronsted acid-mediated rearrangement of **5a** (*cf.* step 3).[6b] A more acidic **NuH** reagent, 4-nitrophenol, was tested but no reaction was observed at RT (entry 4), while at 60 °C the same side products **7a** and **8** were formed (entry 5). We then decided to move on to species of similarly acidity to phenol, but also more nucleophilic, and pleasingly, thiols[16] were found to possess this attractive combination of properties; using *n*-propanethiol, no conversion was observed at RT (entry 6), but excellent conversion into the desired quinoline **4a** was observed upon heating to 60 °C (entry 7). Furthermore, the more acidic thiophenol was able to promote the conversion of $\mathbf{1a_{Br}}$ into quinoline **4b** smoothly at RT (entry 8).

Table 1. Initial Optimization[a]



entry	nucleophile (NuH)	temp	outcome[b]
1	phenol (Nu = PhO)	RT	no reaction
2	phenol (Nu = PhO)	60 °C	no reaction
3	phenol (Nu = PhO) with 1 equiv of TFA	RT	**7a** (62%) **8** (21%)
4	4-nitrophenol (Nu = 4-$NO_2C_6H_4O$)	RT	no reaction
5	4-nitrophenol (Nu = 4-$NO_2C_6H_4O$)	60 °C	**7a** (35%) **8** (45%)
6	*n*-propanethiol (Nu = n-PrS)	RT	no reaction
7	*n*-propanethiol (Nu = n-PrS)	60 °C	**4a** (95%)
8	thiophenol (Nu = PhS)	RT	**4b** (93%)

[a]$\mathbf{1a_{Br}}$ (1 equiv) and **NuH** (1.6 equiv) were stirred in DCE (0.1 M, degassed) for 20−24 h at the specified temperature. [b]Yields are isolated material after column chromatography.

With conditions for the cascade established, attention turned to examining the reaction scope. A range of aromatic thiols were tested (Scheme 2A), and all reacted well with ynone $\mathbf{1a_{Br}}$; quinolines **4b**−**k** were all prepared in this manner, generally in high yield, under the standard RT conditions using a range of electronically diverse substituted thiophenols. Other aliphatic thiols were also explored, with quinolines **4a** and **4l**−**n** prepared, although in this series heating to 60 °C was required. The yield for quinoline **4n** was comparatively low (53%), with thio-oxindole **9a** also formed in 27% yield; this unexpected side reaction is discussed later in the manuscript (see Scheme 3).[17]

Next, the 2-halide substituent was varied (Scheme 2B). Thus, 2-chloro ($\mathbf{1a_{Cl}}$) and 2-iodo ($\mathbf{1a_{I}}$) analogues of ynone $\mathbf{1a_{Br}}$ were prepared,[5] and both reacted smoothly with 4-methylbenzenethiol to form quinoline **4d** in high yield, albeit at a higher reaction temperature (60 °C). Finally, we explored variation of the indole-tethered ynone component **1**. Four different additional 2-bromo-indole-tethered ynones were successfully tested, with variations to the ynone and the indole motifs explored. For each ynone, a representative aliphatic (*n*-propanethiol) and aromatic thiol (4-methylbenzenethiol) were tested, with the expected quinoline products **4o**−**v** to be isolated successfully in all cases.[18] The only substrate tested that did not deliver the expected quinoline was 4-NMe_2-substituted ynone $\mathbf{1f_{Br}}$; in this case, spirocyclic indoleninyl bromide **5b** was isolated in 89% yield.[19] Despite not delivering the expected quinoline, the isolation of spirocycle **5b** does provide indirect mechanistic evidence for the intermediacy of indoleninyl halides in the reaction cascade (see later for discussion). Finally, by replacing the thiol with benzeneselenol, the analogous selenide product $\mathbf{4b_{Se}}$ was obtained in 62% yield.

The unexpected isolation of thio-oxindole **9a** during the synthesis of **4n** prompted additional studies, in part to better understand this side reaction, but also to try and harness it productively, as a new way to make thio-oxindoles.[20] Our theory for how thio-oxindole **9a** formed is summarized in Scheme 3a. The reaction is likely to have started as expected, and thus it proceeded through the normal dearomatizing spirocyclization and nucleophilic substitution steps (i.e., steps 1 and 2). This would generate spirocycle **10**, and at this point, it appears that the route diverges, with some of the material going on to form quinoline **4n** in the usual way, and the rest undergoing debenzylation, either via an S_N1-type pathway as drawn, or the analogous S_N2-type cleavage (not shown). To test this idea and improve the yield of thio-oxindole **9a**, the reaction was repeated using the silylated thiol Ph_3SiSH **11**; the idea was that the weak Si−S would cleave more easily than the S−Bn bond in **10**, and facilitate thio-oxindole formation via a desilylative mechanism. This idea worked well; the reaction of ynone $\mathbf{1a_{Br}}$ with Ph_3SiSH **11** using the standard 60 °C procedure led to the formation of thio-oxindole **9a** in 82% isolated yield (Scheme 3b). The same procedure was applied to other 2-halo-indole-tethered ynones, with thio-oxindoles **9b**−**9d** (47−85%) prepared in the same way.

A proposed mechanism for the three-step cascade is outlined in Scheme 4a. The cascade likely initiates with dearomatizing spirocyclization, promoted by the relatively acidic thiol (**A** → **B**, step 1, Scheme 4a); protic acids have been shown to promote spirocyclization of related ynones,[3b,6b] and the isolation of spirocyclic indoleninyl bromide **5b** discussed earlier lends further support to this notion. The resulting iminium−thiolate ion pair **2** may then undergo facile nucleophilic substitution to afford substituted spirocycle **12** (step 2).[5] The rearrangement of **12** into **17** is then thought to proceed via a previously studied acid-catalyzed one-atom ring-expansion.[6c]

https://dx.doi.org/10.1021/acs.orglett.1c00205
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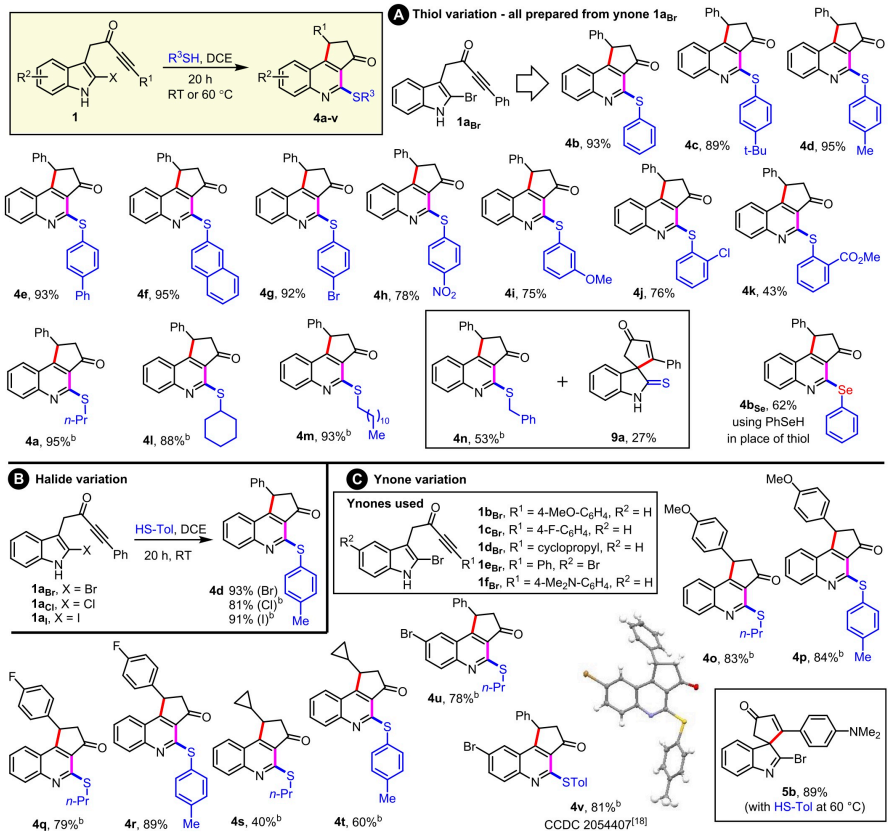
Scheme 2. Scope of the Three-Step Thiol-Mediated Cascade for the Conversion of Ynones 1 into Quinolines 4[a]



[a]**1** (1 equiv) and RSH (1.6 equiv) were stirred in DCE (0.1 M) for 20 h at RT unless specified. [b]Reaction performed at 60 °C. HS-Tol = 4-methylbenzenethiol.

Several control experiments were conducted to investigate this mechanism and the ordering of the steps. First, to probe whether the nucleophilic substitution step may proceed *before* spirocyclization, 2-bromo-indole substrates lacking an ynone substituent (**18** and **21**) were each reacted under the standard conditions with 4-methylbenzenethiol (Scheme 4b, eq 1). In the case of indole **18**, some bromide substitution was indeed observed, with sulfide **19** formed in 31% yield. This confirms that nucleophilic substitution directly on the indole is possible, although the yield was low, and the major product was in fact the reduced product **20**. Treating the analogous 3-methyl-indole **21** in the same way resulted in trace formation of **22** only. In view of these results, and given that no reduction products were observed in any of the synthetic reactions, it seems unlikely that nucleophilic substitution precedes dearomatizing spirocyclization.

We then questioned whether the iminium−thiolate ion pair **B** might first undergo ring expansion to form a quinoline and that nucleophilic substitution follows this step. To probe this idea, both indoleninyl bromide **5a** and 2-bromoquinoline **8** were reacted with 4-methylbenzenethiol under the standard reaction conditions. Interestingly, both reactions afforded the expected quinoline product **4d** in high yields (Scheme 4b, eqs 2 and 3), suggesting that the order of steps 2 and 3 could be interchanged.

To investigate this idea further, a discrete sample of the substituted spirocyclic sulfide **6a** was reacted with 4-methylbenzenethiol under the standard reaction conditions (eq 4). No conversion into quinoline **4d** was observed and

https://dx.doi.org/10.1021/acs.orglett.1c00205
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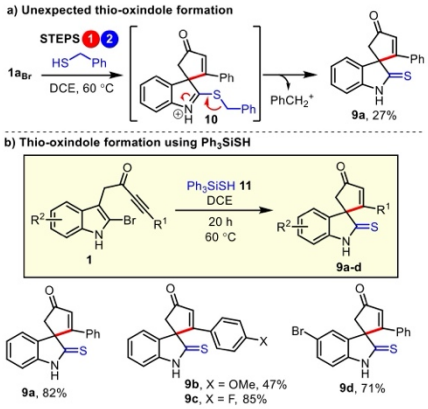
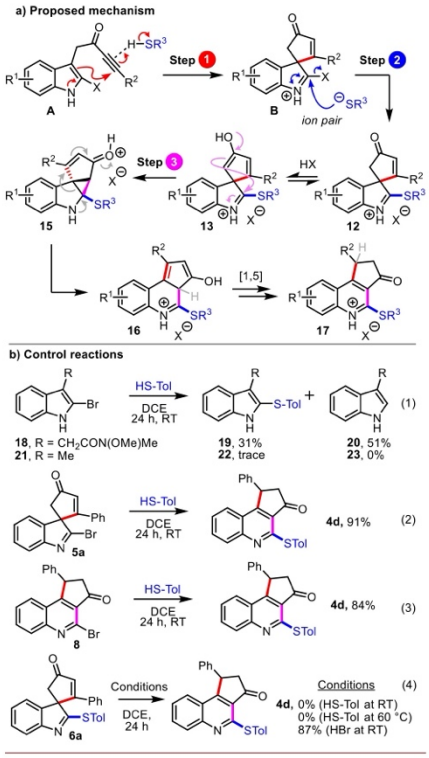
Scheme 3. Conversion of Ynones 1 into Thio-Oxindoles 9 via a Desilylative Cascade Process[a]



[a]**1** (1 equiv) and thiol **11** (1.6 equiv) were stirred in DCE (0.1 M) for 20 h at 60 °C.

Scheme 4. Proposed Mechanism and Control Reactions



only **6a** was recovered after stirring for 24 h at both RT and 60 °C. However, the quinoline product **4d** could be formed in high yield at RT upon the addition of 1.1 equiv of 48% aq. HBr to spirocyclic sulfide **6a**. This result suggests that a strong Brønsted acid is required to promote the ring expansion, and such an acid would only be present in the reaction following the nucleophilic substitution step (which generates HX), thus supporting the originally proposed order of steps. Furthermore, the success of the series of thio-oxindole forming reactions described in Scheme 3 also supports the same pathway, because in these reactions the successful formation of spirocyclic products **9a**–**d** means that nucleophilic substitution must have out-competed ring expansion in these cases.

Considering all these observations, we can be confident that the first step of the cascade is a thiol-promoted dearomatizing spirocyclization (step 1). The next step is most likely to be nucleophilic substitution (step 2) of the resultant iminium–thiolate ion pair, which generates a strong Brønsted acid (HBr) in situ. This acid then promotes a one-atom ring expansion (step 3) to form a stable aromatic quinoline product **4**. Some interchange in the ordering of steps 2 and 3 cannot be ruled out once a reasonable concentration of HBr has built up in the reaction, however.

In summary, a three-step cascade process has been developed that allows for the direct conversion of 2-halo-indole-tethered ynones into substituted quinolines. The key to the process is the use of thiols as "multitasking" reagents able to promote dearomatizing spirocyclization and nucleophilic substitution directly, as well promoting a one-atom ring expansion indirectly, via the formation of a strong Brønsted acid (HBr) in situ. The reactions are very simple to perform[21] and are typically high yielding, enabling the facile synthesis of a diverse array of functionalized quinolines. They are also easily scalable; for example, quinoline **4d** was formed in 97% yield on a 1 mmol scale (see Supporting Information). In addition, a related route to thio-oxindoles was also developed following a serendipitous discovery of an unexpected side reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00205.

Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Accession Codes

CCDC 2054407 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://dx.doi.org/10.1021/acs.orglett.1c00205
Org. Lett. 2021, 23, 2063−2068

AUTHOR INFORMATION

Corresponding Authors

Michael J. James − *Department of Chemistry, University of York, Heslington, U.K. YO10 5DD*; Email: michael.james@york.ac.uk

Richard J. K. Taylor − *Department of Chemistry, University of York, Heslington, U.K. YO10 5DD*; Email: richard.taylor@york.ac.uk

William P. Unsworth − *Department of Chemistry, University of York, Heslington, U.K. YO10 5DD*; orcid.org/0000-0002-9169-5156; Email: william.unsworth@york.ac.uk

Author

Nantachai Inprung − *Department of Chemistry, University of York, Heslington, U.K. YO10 5DD*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00205

Author Contributions

The manuscript was written through contributions of all authors

Funding

The Leverhulme Trust (ECF-2019-135)

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the Development and Promotion of Science and Technology Talents Project (DPST), Royal Thai Government (N.I. EP/N035119/1), and the University of York and the Leverhulme Trust (for an Early Career Fellowship, ECF-2019-135, M.J.J.) for financial support. We are also grateful for the provision of an Eleanor Dodson Fellowship (to W.P.U.). We also thank Dr. Victor Chechik (University of York) for helpful discussions concerning the mechanism and Theo Tanner (X-ray crystallography service, University of York) for collecting and processing the X-ray data.

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(18) CCDC 2054407 contains the crystallographic data for compound **4v**, see www.ccdc.cam.ac.uk/data_request/cif.

(19) The reason for this difference is not fully clear. Solubility differences and/or changes to the electronic properties of the ynone may both have had an influence, while the relatively basic aniline group may also have altered the pH balance and affected proton transfer in the reaction. Notably, in previous studies we have found that other 4-NMe2-substituted ynones have also reacted differently to other seemingly similar substrates in the series (see ref 6).

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(21) Although degassed solvent was typically used in this study to help ensure consistent results, this level of precaution is generally not needed; for example, the conversion of $\mathbf{1a}_{\mathbf{Br}}$ into **4d** worked in 98% yield when done without degassing. The insensitivity of the reaction to oxygen also suggests that alternative radical pathways (*cf.* ref 4a) are unlikely to operate. In addition, it was found that ynone $\mathbf{1a}_{\mathbf{Br}}$ does not react when treated with PhSSPh in place of PhSH under the standard RT conditions, which further reduces the likelihood that the cascade reaction involves thiyl radical intermediates. The analogous reaction with PhSSPh and 1 equiv of HBr led only to the formation of products in which sulfur had not been incorporated: **7a** (18%) and **8** (72%).

https://dx.doi.org/10.1021/acs.orglett.1c00205
Org. Lett. 2021, 23, 2063−2068

Appendix II. Indole-ynones as Privileged Substrates for Radical Dearomatizing Spirocyclization Cascades

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Indole-ynones as Privileged Substrates for Radical Dearomatizing Spirocyclization Cascades

Nantachai Inprung, Hon Eong Ho, James A. Rossi-Ashton, Ryan G. Epton, Adrian C. Whitwood, Jason M. Lynam, Richard J. K. Taylor, Michael J. James,* and William P. Unsworth*

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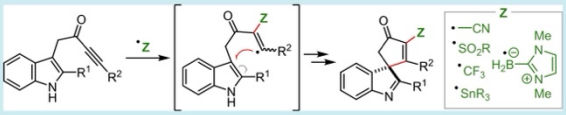


ABSTRACT: Indole-ynones have been established as general substrates for radical dearomatizing spirocyclization cascade reactions. Five distinct and varied synthetic protocols have been developed—cyanomethylation, sulfonylation, trifluoromethylation, stannylation and borylation—using a variety of radical generation modes, ranging from photoredox catalysis to traditional AIBN methods. The simple and easily prepared indole-ynones can be used to rapidly generate diverse, densely functionalized spirocycles and have the potential to become routinely used to explore radical reactivity. Experimental and computational investigations support the proposed radical cascade mechanism and suggest that other new methods are now primed for development.

Compound classes that expedite access to privileged biologically active scaffolds are highly prized in synthetic chemistry.[1] For example, *N*-arylacrylamides **1** are prominent precursors for the synthesis of biologically important 3,3-disubstituted oxindoles,[2] with a number of elegant (and asymmetric) metal-catalyzed strategies known (**1** → **2** → **3**, Scheme 1A).[3] Complementary radical-based strategies (**1** → **4** → **5**, Z = various, Scheme 1A) have also been developed.[4] Indeed, these methods are so well established that *N*-arylacrylamide-based radical addition−cyclization cascades have become a "go-to" system with which to probe radical mechanisms and benchmark new (and old) methods for the reactions of radicals.[5]

The identification of new scaffolds with the utility of *N*-arylacrylamides therefore has great potential in synthetic and medicinal chemistry—both for their ability to facilitate the exploration of novel biologically relevant chemical space and as testing grounds for new methodologies. Indole-ynones (**6**) are an emerging class of compounds that rival the versatile reactivity of *N*-arylacrylamides, most notably for the synthesis of spirocyclic indolenines.[6,7] A number of synthetic methods have been reported, by our groups and others, based on the reaction of the electron-rich indole moieties with a tethered ynone group, promoted by alkyne activation with various reagent classes, including π-acids,[8] Brønsted acids,[9] palladium-(II) complexes,[10] electrophilic halogenation reagents,[11] and others[12,13] (**6** → **7** → **8**, Scheme 1B).

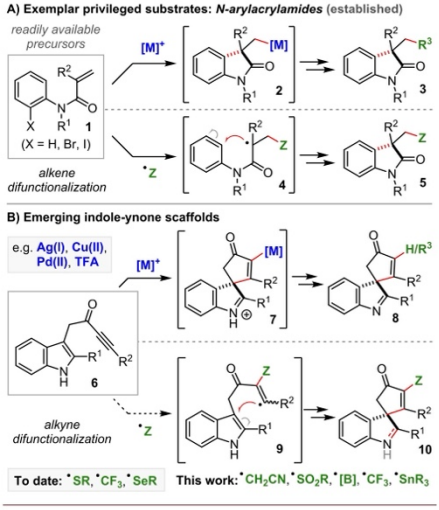
These previous studies focused on two-electron processes, but in 2020, our group published the first radical-based spirocyclization of an indole-ynone. In this work, thiyl radicals generated *in situ* were shown to promote dearomatizing spirocyclization with concomitant C−S bond formation (**6** → **9** → **10**, Scheme 1B) via a hydrogen atom transfer based radical chain process.[14,15] Interestingly, the thiyl radical formation that initiates this process was shown to be promoted by visible-light-mediated photoexcitation of an intramolecular electron donor−acceptor (EDA) complex, formed between the indole and alkyne moieties in the indole-ynone **6**.[16,17] Soon afterward, related radical spirocyclization methods began to emerge from other groups. For example, Liu, Han and co-workers reported an efficient Cu(I)-catalyzed trifluoromethylation protocol, which proceeds via the formation of trifluoromethyl radicals from Togni's reagent (Z = CF_3).[18a] A similar cascade was also reported by Xu, Pan, Ma and co-workers; in this case, dearomatizing spirocyclization was promoted by selenyl radicals, formed via the homolysis of diselenides (Z = SeR).[18b]

We postulated that in addition to being versatile precursors for two-electron processes,[8,13,19] indole-ynones **6** may be similarly privileged substrates for radical cascade reactions.[20] Thus, herein we describe efforts to fully establish indole-ynones as general precursors for radical dearomatizing spirocyclization reactions. In total, five efficient, novel synthetic protocols have been established for dearomative cyanomethy-

Received: December 6, 2021
Published: January 5, 2022

https://doi.org/10.1021/acs.orglett.1c04098
Org. Lett. 2022, 24, 668−674

Scheme 1. Privileged Substrates in Synthetic Chemistry

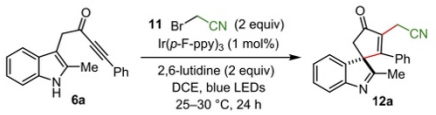


lation, sulfonylation, trifluoromethylation, stannylation, and borylation. Demonstrating that spirocyclization can be achieved using a range of radical generation methods was also an important goal, and the new methods developed rely on various radical reaction modes ranging from traditional AIBN homolysis to more modern photoredox catalysis and EDA complex activation.

The first radical class utilized were cyanomethyl radicals.[21] Cyanomethyl radicals can be generated from bromoacetonitrile **11** via known photoredox catalysis methods.[22,23] Optimization results for the conversion of indole-ynone **6a** into spirocyclic indolenine **12a** are included in Table 1. Optimal conditions (entry 1) were identified based on the use of catalytic Ir(*p*-F-ppy)$_3$ (1 mol %) and 2,6-lutidine in DCE with blue light irradiation (25−30 °C, fan cooling). Light is essential for reactivity (entry 2), and the reaction is shut down by the addition of TEMPO (entry 3), which taken together strongly indicates that a light-promoted radical process operates. Changes to the quantity and identity of base led to inferior conversion (entries 4−7). Other photocatalysts were trialed (entries 8−11), but only Ir(III) catalysts resulted in satisfactory conversion into **12a**, with the relatively reducing catalyst Ir(*p*-F-ppy)$_3$ being the most effective. Interestingly, modest conversion into **12a** was also observed in the absence of an added photocatalyst (entry 12), indicating that electron-donor−acceptor (EDA) complexes may also be photoexcited to initiate dearomative spirocyclization,[14] albeit with lower efficiency than the reaction with Ir(*p*-F-ppy)$_3$.

Next, the generality of the cyanomethylation reaction was explored (Scheme 2A).[24] A selection of indole-tethered ynones **6a−g** were prepared and tested using the optimized conditions, and all were converted into spirocyclic indolenines **12a−g** in 44−75% yield; this series includes 2-halo substituted systems, which furnished synthetically useful spirocyclic indoleninyl halides **12e−g**.[8d] Attempts to perform the reaction

Table 1. Cyanomethylation Optimization[a]



entry	deviation from standard conditions[a]	**12a** (%)[b]	**6a** (%)[b]
1	none	75[c]	12[c]
2	without light	0	99
3	with TEMPO (2 equiv)	0	99
4	without 2,6-lutidine	13	52
5	2,6-lutidine (1 equiv)	40	42
6	2,4,6-collidine (2 equiv)	60	15
7	K_2CO_3 (2 equiv)	40	42
8	Ir(ppy)$_3$ (1 mol %)	60	6
9	Ru(bpy)$_3$(PF$_6$)$_2$ (1 mol %)	0	74
10	Eosin Y (1 mol %)	0	80
11	10-phenyl phenothiazine (1 mol %)	7	93
12	without photocatalyst	31	56

[a]Standard conditions: Ir(*p*-F-ppy)$_3$ (1 mol %), 2,6-lutidine (2 equiv), DCE (0.1 M), rt, blue LED, on 0.2 mmol scale. [b]Yields based on ^{1}H NMR analysis of the unpurified reaction mixture using CH_2Br_2 as an internal standard unless stated. [c]Isolated yield following column chromatography.

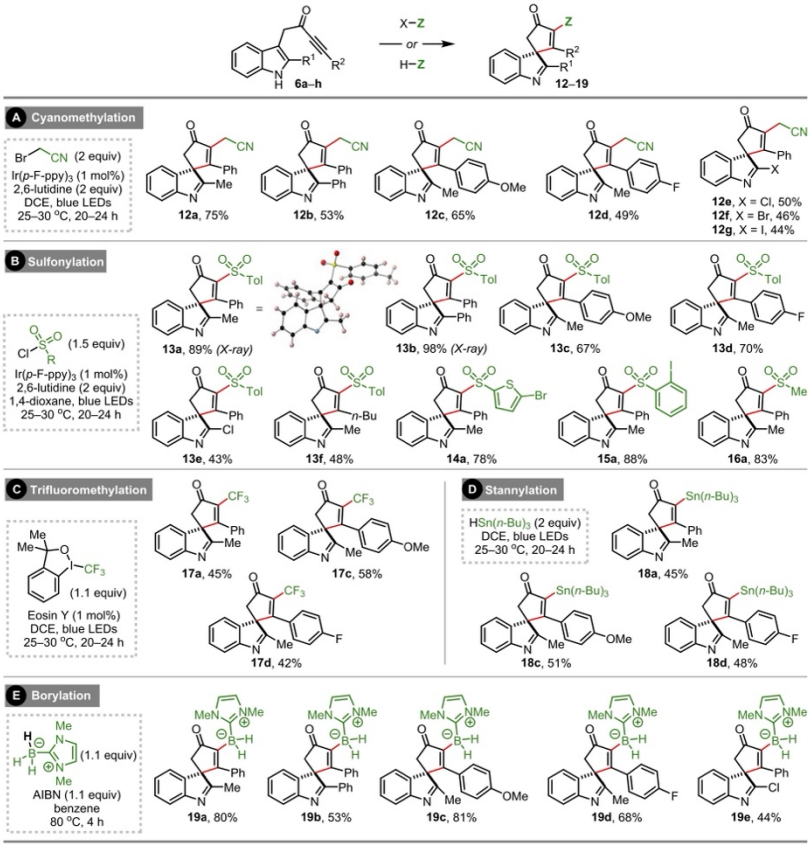
on indole-ynones without a 2-substitutent (i.e., R^1 = H in the general scheme) were not successful however, with these reactions complicated by competing radical addition to the indole ring.

Attention then turned toward the development of reactions based on other radical types. In total, four additional distinct reaction classes have been developed (Scheme 2B−E), with additional synthetic and optimization details included in the Supporting Information. First, known photoredox-catalyzed methods for the generation of sulfonyl radicals using sulfonyl chlorides[25] were adapted and used to prepare sulfonylated spirocycles **13−16** in good to excellent yields (9 examples, 43−98%, Scheme 2B).[26] This series confirms that switching to other reactive radical species can be achieved remarkably easily, with high yields obtained.[27] A transition-metal-free method for the synthesis of trifluoromethylated spirocycles was also developed that complements the copper-catalyzed reaction reported by Liu, Han and co-workers featured in Scheme 1B.[18a] Here, Togni's reagent was used with the photoredox catalyst Eosin Y to form trifluoromethylated spirocycles **17a,c−d** in 42−65% yield (Scheme 2C). Note that, in this system, control reactions show that product **17a** could be obtained in reduced yield in the absence of an added photocatalyst, or in the dark, indicating that EDA complex activation[14,28] may also enable trifluoromethyl radical formation alongside the Eosin Y catalyzed pathway.

In addition, a remarkable additive-free stannylative dearomatizing spirocyclization reaction was developed, which can be performed simply by irradiating a mixture of the indole-ynone and tributyltin hydride in DCE with blue LEDs (Scheme 2D). Using these mild conditions, stannylated spirocyclic indolenines **18a,c−d** were formed in 45−51% yield. In line with our previous work with thiols,[14] we propose that these reactions were initiated either via a hydrogen atom transfer or an electron transfer event between the photoexcited indole-ynone and tributyltin hydride to generate a tributyltin

https://doi.org/10.1021/acs.orglett.1c04098
Org. Lett. 2022, 24, 668−674

Scheme 2. Radical Spirocyclization Cascades with Diverse Radicals Generated via a Range of Methods



radical. The potential to develop other unconventional additive-free dearomatizing spirocyclization reactions of this type highlights the still relatively untapped synthetic utility of this substrate class. Finally, we have also shown that similar reactivity can be promoted using classical thermal radical generation conditions. AIBN in refluxing benzene was used to generate *N*-heterocyclic carbene (NHC) boryl radicals[29] that go on to form borylated spirocycles **19a–e** in 44–81% yield (Scheme 2E). Diversification of these products was also briefly explored, in which we confirmed that borylated spirocycle **19a** could be converted into a pinacol ester and undergo subsequent Suzuki–Miyaura cross-coupling (see Supporting Information).

A proposed mechanism, exemplified on the initial cyanomethylation system, is presented in Scheme 3A. First, it is known that photoexcited Ir(III) complexes such as Ir(*p*-F-ppy)$_3$ are able to reduce bromoacetonitrile **11** to form cyanomethyl radical **A**,[23] which we presume initiates the radical cascade.[30] This is supported by Stern–Volmer luminescence quenching studies, which show that the photocatalyst Ir(*p*-F-ppy)$_3$ excited state is quenched by bromoacetonitrile (see Supporting Information). Next, we propose that cyanomethyl radical **A** reacts with the ynone moiety of **6a** to form vinylic radical **B**, which cyclizes quickly to form α-amino alkyl radical **C**. Intermediate **C** may then either (i) be oxidized by an Ir(IV) species to regenerate the Ir(III) photoredox catalyst and form the spirocyclic product **D** (which is deprotonated in the presence of 2,6-lutidine) or (ii) propagate a radical chain by reacting with **11** via halogen-atom transfer[31] or electron transfer[32] to form cyanomethyl radical **A** and spirocyclic product **D**.

To gauge whether steps subsequent to radical formation could be limiting the reaction, DFT calculations of the individual steps were undertaken (Scheme 3B). Of these steps, the addition of the cyanomethyl radical is the slowest step (**TS$_1$**) and the calculated $\Delta G^{\ddagger}$ of 57 kJ/mol is accessible for a

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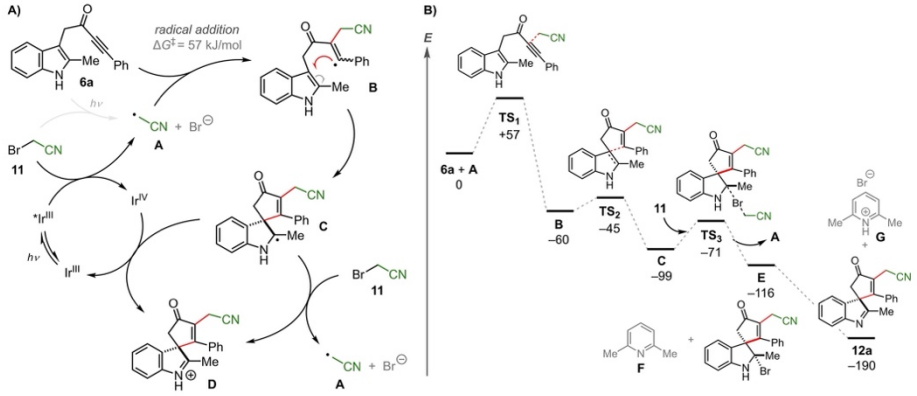
Org. Lett. 2022, 24, 668–674

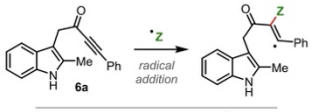
Scheme 3. Proposed Radical Spirocyclization Mechanism with Cyanomethyl Radical[a]



[a]Energies are Gibbs energies in kJ/mol and were calculated using the D3-B3LYP/def2-TZVPP//B3LYP/def2-SVP level of theory at 298 K with COSMO solvent correction in DCE.

room temperature reaction. The analogous energy barrier was also calculated for each of the other four radical classes featured in this manuscript (i.e., sulfonyl, trifluoromethyl, stannyl, and boryl radical addition to indole-ynone **6a**), as well as for the previously reported thiyl[14] and selenyl[18b] radical systems (Table 2; see the Supporting Information for further details). In all cases, this barrier was calculated to be lower in energy than that of the cyanomethyl system, strongly indicating that the radical addition step is not only viable, but likely to be facile across a range of radical species. For cyanomethylation, the subsequent radical spirocyclization through $\mathbf{TS_2}$ and bromine abstraction leading to chain propagation via $\mathbf{TS_3}$ have low free energies of activation and are therefore probably not rate controlling.

Table 2. Calculated Activation Barriers[a] for the Addition of Radicals (·Z) to Indole-ynone 6a



·Z	ΔG‡
·—CN	57 kJ/mol
·Ts	42 kJ/mol
·CF_3	44 kJ/mol
·$SnMe_3$	34 kJ/mol
·H_2B–NHC	35 kJ/mol
·SPh	15 kJ/mol
·SePh	17 kJ/mol

[a]Gibbs energies calculated using the D3-B3LYP/def2-TZVPP//B3LYP/def2-SVP level of theory at 298 K with appropriate COSMO solvent corrections.

Based on the above, we consider it likely that all reaction series developed herein operate via the same general mechanism; the exact nature of the oxidative step (**C** → **D** in Scheme 3A) will vary depending on the reagents used and reaction conditions on a case-by-case basis, and of course the radical initiation modes differ in each series. For clarity, full proposed mechanisms for each of the reactions in Scheme 2B–E are included in the Supporting Information. Having demonstrated the feasibility of the radical cascades using diverse reagents and conditions, both experimentally and computationally, it is likely that variants based on various other radical intermediates will also be feasible, and new methods will emerge in time. The development of any new radical spriocyclization of these types could be facilitated by virtual screening of the radical addition step for proposed radical species, using the DFT method established in this study. Of course, the ability of indole-ynones to undergo facile two-electron cyclization reactions means that it will be important to test for this possibility when developing new methods. Further, the opportunity to develop novel catalyst-free activation modes should also be possible based on photoexcitation of the indole-ynone itself.

In closing, we have demonstrated that indole-ynones are general precursors for radical dearomatizing spirocyclization cascades through the development of five different synthetic protocols. These easily prepared reagents can be used to provide expedient access to libraries of densely functionalized spirocycles with rich biological potential. Our mechanistic studies indicate that many other cascade protocols of comparable/higher efficiency should be feasible using other radical classes and/or initiation modes. Moreover, we anticipate that these findings will facilitate the development and identification of other privileged substrate systems based on other heterocycle-ynone frameworks.

https://doi.org/10.1021/acs.orglett.1c04098
Org. Lett. 2022, 24, 668−674

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c04098.

Experimental procedures, characterization data, computational details, and copies of ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR spectra for all compounds featured in this manuscript. (PDF)

Accession Codes

CCDC 2087802 and 2087806 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Michael J. James − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0003-2591-0046; Email: michael.james@york.ac.uk

William P. Unsworth − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0002-9169-5156; Email: william.unsworth@york.ac.uk

Authors

Nantachai Inprung − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.*

Hon Eong Ho − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0003-1037-2505

James A. Rossi-Ashton − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0002-0989-2506

Ryan G. Epton − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0001-7717-7339

Adrian C. Whitwood − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0002-5132-5468

Jason M. Lynam − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.;* orcid.org/0000-0003-0103-9479

Richard J. K. Taylor − *Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c04098

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank the Development and Promotion of Science and Technology Talents Project (DPST), Royal Thai Government. (N.I. EP/N035119/1), the University of York, and the Leverhulme Trust (for an Early Career Fellowship, ECF-2019-135, M.J.J.) for financial support. We are also grateful to the University of York for the provision of an Eleanor Dodson Fellowship (to W.P.U.).[30]

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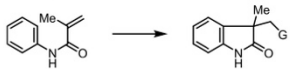

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Appendix III. Radical Dearomatising Spirocyclisation of Benzisoxazole-Tethered Ynones

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Radical Dearomatising Spirocyclisation of Benzisoxazole-Tethered Ynones

Nantachai Inprung,[a] Adrian C. Whitwood,[a] Richard J. K. Taylor,[a] Michael J. James,*[b] and William P. Unsworth*[a]

Dedicated to Prof. Dennis P. Curran on the occasion of his 70th birthday.

The dearomative spirocyclisation of benzisoxazoles through a radical chain mechanism is described. Densely functionalised spirocycles were prepared in high yields by reacting benzisoxazole-tethered ynones with aryl thiols in 1,2-dichloroethane (DCE) at 60 °C. The identification of stabilising three-electron interactions was key to the development of this new radical cascade reaction. The obtained spirocyclic products were converted into other spirocyclic scaffolds through a two-step hydrogenolysis-cyclisation sequence.

Introduction

Radical dearomatising spirocyclisation cascade reactions enable simple aromatic substrates to be converted into densely functionalised and highly prized molecular scaffolds in a single step.[1] The effectiveness of this reaction strategy to quickly access complex 3-dimensional chemical space has inspired significant progress and a number of substrate systems have been developed to explore this approach.[2] However, a significant proportion of systems developed to date are based on a simple design principle: tether an electron-rich (hetero)arene to a reactive radical acceptor or precursor.

In addition to polarity effects lowering the barrier to spirocyclisation,[3] we hypothesised that one reason electron-rich (hetero)arenes have proven so effective is their ability to form partially stabilised radical intermediates upon spirocyclisation. For example, indole-tethered ynones **2** were proposed to rapidly react with a variety of different radical species to form spirocyclic α-amino radicals **2**,[4,5] which are stabilised by two-centre three-electron (2c,3e) bonding interactions (Scheme 1a).[6] Based on this rationale, we reasoned that the elusive radical dearomative spirocyclisation of comparatively electron-deficient heteroarenes might be realised if similar interactions could be incorporated into the substrate. Thus, we identified benzisoxazole-tethered ynones **3** as promising candidates for study (Scheme 1b). Here, the addition of a transient vinyl radical to the C=N bond of the adjacent benzisoxazole ring would form nitrogen-centred radical **4**,[7] which would be stabilised by 2c,3e bonding with the lone-pair on the adjacent oxygen atom.

Herein, we describe validation of this design rationale and, to the best of our knowledge, the first dearomative spirocyclisation of benzisoxazoles. The straightforward conversion of the products into other spirocyclic scaffolds through a divergent, two-step ring expansion sequence is also reported.

[a] N. Inprung, Dr. A. C. Whitwood, Prof. R. J. K. Taylor, Dr. W. P. Unsworth
Department of Chemistry
University of York
Heslington, York, YO10 5DD (UK)
E-mail: william.unsworth@york.ac.uk

[b] Dr. M. J. James
Department of Chemistry
The University of Manchester
Oxford Road
Manchester, M13 9PL (UK)
E-mail: michael.james@manchester.ac.uk

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202300603

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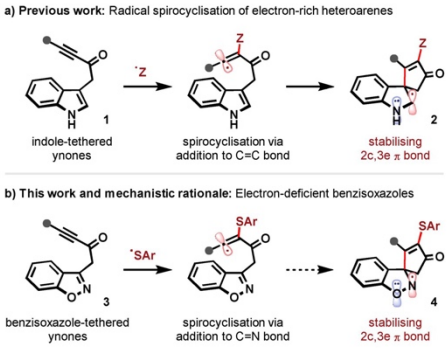

Scheme 1. Radical dearomatising spirocyclisation cascades.

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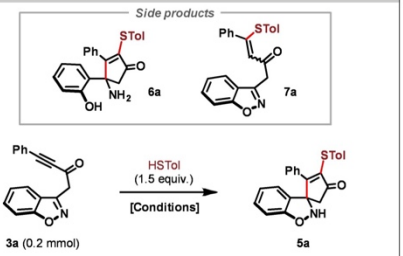
Results and Discussion

Our studies began by reacting ynone **3a** with *p*-toluenethiol (HSTol) in MeCN at 60 °C for 20 h (Table 1, entry 1), which led to the formation of a complex mixture of: i) the desired spirocycle **5a** in 4% yield; ii) amino alcohol **6a** in 11% yield, which was presumed to form via the cleavage of the weak N–O bond of spirocycle **5a**; and iii) a ~3:7 mixture *E*/*Z* alkenes **7a** in 65% yield, which presumably formed via conjugate addition of the thiol to the electrophilic ynone. Fortunately, a solvent screen (entries 2–4) revealed that the formation of both side-products **6a** and **7a** could be completely supressed by using DCE, which produced the desired spirocycle **5a** as the sole product in quantitative yield (entry 4).[8] Attempts to accelerate this reaction under photochemical conditions led to the unwanted formation of amino alcohol **6a** (entry 5). Interestingly, the addition of basic additives, such as triethylamine, completely switched the selectivity to favour formation of conjugate addition product **7a** (entry 6). The addition of TEMPO completely inhibited the formation of spirocycle **5a** and only conjugate addition products **7a** were observed (entry 7). Moreover, a thiyl radical TEMPO adduct was observed by HRMS (see the supporting information). Finally, the formation of spirocycle **5a** was also strongly inhibited by the addition of 9,10-dihydroanthracene (DHA), which is an excellent hydrogen atom donor (entry 8).[9]

Table 1. Reaction optimisation studies.

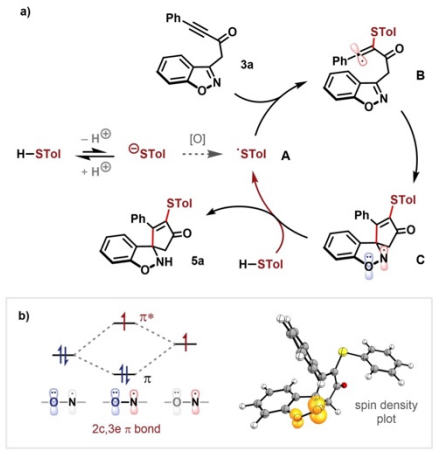


Entry[a]	Reaction conditions	Yield[b] 5a/%	Yield[b] 6a/%	Yield[b] 7a/%
1	MeCN, 60 °C, 20 h	4	11	65
2	THF, 60 °C, 20 h	42	18	–
3	PhMe, 60 °C, 20 h	85	4	–
4	DCE, 60 °C, 20 h	100	–	–
5	DCE, blue LEDs, rt, 21 h	36	34	–
6	Et_3N (1 equiv.), DCE, 60 °C, 20 h	–	–	95
7	TEMPO (1 equiv.), DCE, 60 °C, 20 h	–	–	83
8	DHA (1 equiv.), DCE, 60 °C, 20 h	trace	–	35

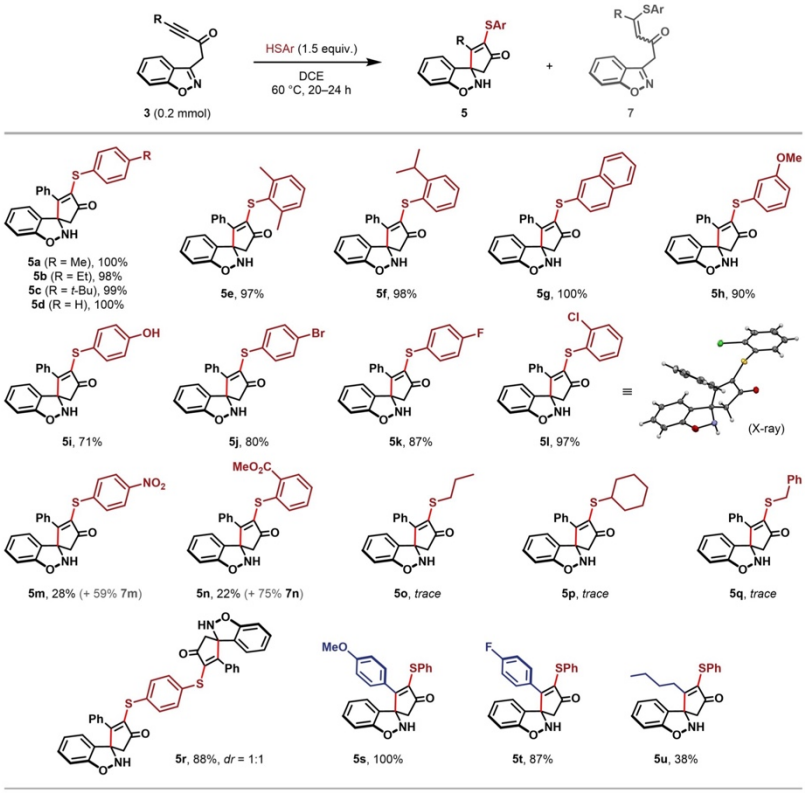
[a] All reactions were performed with 0.2 mmol of ynone **3a** and 0.3 mmol of HSTol in the stated solvent (2 mL) under argon. [b] Determined by ^{1}H NMR spectroscopy against an internal standard (dibromomethane).

Based on these observations and previous work in this area, we propose that a radical chain mechanism is likely operative and is initiated by the generation of thiyl radical **A** (Scheme 2a).[10] We propose that thiyl radical **A** is likely formed by the facile single electron oxidation of the corresponding thiolate anion present in solution; the oxidant may simply be adventitious oxygen, and/or a cationic organic oxidant formed in situ.[11] The regioselective addition of radical **A** to ynone **3a** forms vinyl radical **B**, which undergoes rapid spirocyclisation to form nitrogen-centred radical **C**. Intermediate **C** may then abstract a hydrogen atom from HSTol to regenerate thiyl radical **A** and afford spirocycle **5a**. Computational studies support the viability of this radical chain, and the idea that intermediate **C** is stabilised by 2c,3e bonding interactions (Scheme 2b, see the Supporting Information for details).[12]

The scope of this dearomative spirocyclisation cascade was next explored using the optimised reaction conditions (Scheme 3). First, different thiols were examined and pleasingly a wide variety of alkylated benzenethiols could be used to afford spirocycles **5a–f** in near quantitative yields. It should be noted that these reactions were easily scalable as spirocycle **5a** could be isolated in 93% yield when the reaction was performed with 1.0 mmol of ynone **3a**. More electron-rich aryl thiols, including unprotected 4-hydroxybenzenethiol, were similarly compatible and used to obtain spirocycles **5g–i** in excellent yields. Halogenated benzenethiols were also readily incorporated into spirocycles **5j–l** and the structure of **5l** was unambiguously confirmed by X-ray crystallography.[13] More acidic electron-deficient aryl thiols primarily afforded conjugate addition products **7m,n**, with spirocycles **5m,n** only obtained in low yield, presumably due to there being a higher concentration of thiolate anions in solution. Unfortunately, very



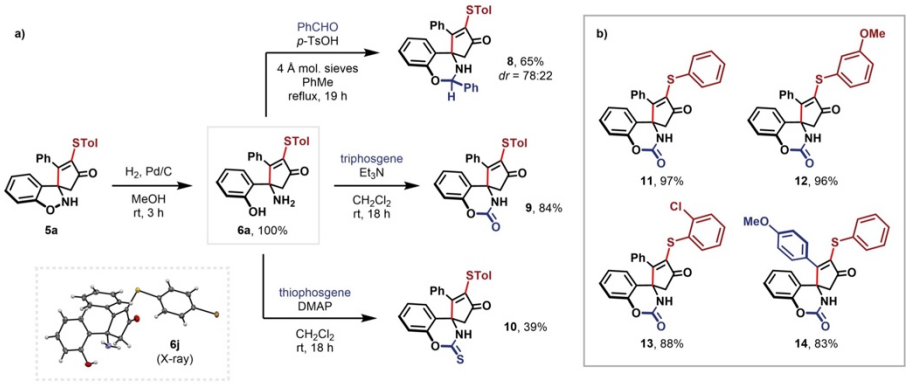
Scheme 2. a) Proposed radical chain mechanism; b) Orbital illustration and calculated spin density plot to support the proposed 2c,3e π bonding interaction.



Scheme 3. Scope of the radical dearomative spirocyclisation cascade. Reactions performed on a 0.2 mmol scale in 2 mL of DCE.

limited reactivity was observed when alkyl thiols were used (spirocycles **5o**–**q** were only formed in trace amounts or low yields), which is likely due to the higher bond-dissociation energy (BDE) of the alkyl thiol S–H bonds.[14] However, dithiols such as 1,4-benznedithiol were compatible and could be used to form spirocycle **5r** in excellent yield, as a ~1 : 1 mixture of diastereoisomers. Other methoxy- and fluoro- substituted aromatic ynones were prepared and converted into spirocycles **5s**,**t** in excellent yields. Finally, an alkyl ynone substrate was also prepared and converted into spirocycle **5u** in 38% yield. The reduced reactivity of this alkyl ynone may be due to the lack of resonance stabilisation of the intermediate vinyl radical,[15] which could change the geometry of the vinyl radical (from linear to bent) and make thiyl radical addition to the ynone less thermodynamically favourable.

The synthetic utility of this novel spirocyclic framework was next explored, by testing a series of divergent reactions to convert spirocycle **5a** into other spirocyclic products. Guided by our previous observation that the N–O bond could be readily cleaved, hydrogenolysis was performed to selectively obtain amino alcohol **6a** in quantitative yield (Scheme 4a). This procedure was also compatible with other spirocycles and the structure of amino alcohol **6j** was unambiguously confirmed by confirmed by X-ray crystallography.[13] Amino alcohol **6a** was then readily cyclised under simple reaction conditions to access a variety of novel spirocycle frameworks **8**–**10** in 39–84% yield. To confirm that other spirocycles could be derivatised similarly, spirocyclic carbamates **11**–**14** were also prepared in the same way, in excellent yields (Scheme 4b).



Scheme 4. Diversification of the spirocycle products through a two-step ring expansion sequence.

Conclusions

In conclusion, the first radical dearomative spirocyclisation cascade with benzisoxazoles has been developed. The reactions are proposed to proceed via a thiyl radical-based chain mechanism, which is initiated under operationally simple thermal conditions. Thanks to the synthetic versatility of the weak N–O bond, the densely functionalised spirocyclic products obtained with this method could be used to access other novel spirocyclic scaffolds, via divergent, two-step ring expansion reaction sequences. Considering the prominence of both benzisoxazoles and spirocycles in medicinal chemistry,[16,17] this work will enable diverse libraries of medicinally relevant spirocyclic molecules to be rapidly generated. The discovery that ynones tethered to electron deficient arenes undergo dearomative spirocyclisation should also encourage the exploration of analogous reactions with other arenes in future studies.

Experimental Section

General procedure for the synthesis of spirocycles 5: To a solution of benzioxazole-tethered ynone (0.2 mmol) in DCE (2 mL) in a sealed vial was added thiol (0.3 mmol). The reaction mixture was degassed with argon for 5 minutes, before being stirred at 60 °C for 20–24 h in a preheated metal heating block. The crude mixture was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography to afford the spirocycle product.

Acknowledgements

The authors would like to thank the Development and Promotion of Science and Technology Talents Project (DPST), Royal Thai Government. (N.I. EP/N035119/1), the University of York, and the University of Manchester for financial support. We would also like to thank Prof. Victor Chechik for helpful discussions.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cascade · dearomatisation · radical · ring expansion · spirocyclisation

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Manuscript received: June 20, 2023
Revised manuscript received: August 9, 2023
Accepted manuscript online: August 15, 2023
Version of record online: September 27, 2023

Abbreviations

ACCN	1,1-azodi(hexahydrobenzonitrile)
AIBN	azobisisobutyronitrile
BET	back electron transfer
br	broad
CCDC	Cambridge crystallographic data centre
CDI	1,1'-carbonyldiimidazole
CFL	compact fluorescent lamp
COSY	correlation spectroscopy
CTC	charge transfer complex
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	disortionless enchancement by polarisation transfer
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDA	electron donor/accepter
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
HAT	hydrogen atom transfer
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear single quantum coherence
ISC	intersystem crossing
LED	light emitting diode
Me	methyl
MLCT	metal-to-ligand charge transfer
NBS	*N*-bromosuccinamide
NCS	*N*-chlorosuccinamide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect

p	pentet
PC	photocatalyst
q	quartet
RT	room temperature
s	singlet
SCE	saturated calomel electrode
SET	single electron transfer
sx	sextet
t	triplet
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCN	trimethylsilyl cyanide
UV	ultraviolet

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