University of HUDDERSFIELD

Novel Cascade Aryne-Capture/Rearrangement Reactions

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ABSTRACT

Arynes are reactive intermediates that have been an academic curiosity for over a century. A recent renaissance of interest in the chemistry of these intermediates can be traced back to the development of *ortho*-(silyl)aryl triflates as aryne precursors. The application of aryne chemistry outside academia has been precluded by the expense and laborious preparation of these precursors.

Diphenyliodonium-2-carboxylate has been shown to be a stable and inexpensive benzyne precursor, however application has been limited due to the high temperature (>160 ºC) and long reaction times required to generate benzyne by this protocol. Described within is an investigation whereby diphenyliodonium-2-carboxylate is successfully decomposed using microwave irradiation to generate benzyne. This proof of concept investigation shows diphenyliodonium-2-carboxylate can be applied as an off-the-shelf benzyne precursor; by using microwave radiation, significantly reduced reaction times and lower b.p. solvents can facilitate a more universal application of this protocol than previously described.

The investigation into the reactions of allylamino malonates with arynes is also described. Simple allylamino malonates are shown to perform a novel cascade aryne capture/ring-closure/[2,3]-rearrangement to generate indolin-3-one products. The influence of substitution of the indolin-3-one products on the photophysical properties is probed. Tetrahydropyridine derived aminomalonates result in a ring contraction by [2,3]-rearrangement to *N*-phenyl pyrrolidine products.

Further investigations show *N*-allyl proline methyl esters also generate indolin-3-one products by this novel cascade mechanism. The photophysical properties of these products are also probed. *N*-diallylalanine methyl ester is shown to generate indolin-3-one with benzyne however *N*-allyl sarcosine ethyl ester generates the *N*-phenyl α-allylated amino esters product by aryne capture/[2,3]-rearrangement.

CONTENTS

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Finally, I would like to thank my family for their continued patience and approval.

ABBREVIATIONS

Abbreviation	Meaning
18-c-6	1,4,7,10,13,16-hexaoxacyclooctadecane
Ac	acetyl
bp	boiling point
d	doublet
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	dichlorobenzenes
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DPEphos	bis-[2-(diphenylphosphino)phenyl]ether
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDG	electron donating group
ESI	electrospray ionisation
EWG	electron withdrawing group
HDDA	hexadehydro-Diels-Alder
HMDS	bis(trimethylsilyl)amine
HMPA	*N,N,N',N',N'',N''*-hexamethylphosphoric triamide
IR	infrared
LD	lipid droplets
LDA	lithium diisopropylamide
m	multiplet
***m*CPBA**	*meta*-chloroperoxybenzoic acid

mp	melting point
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nf	1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl
Ph	phenyl
pin	pinacolyl
ppm	parts per million
Py	pyridine
rt	room temperature
s	singlet
SDI	imidazolyl sulfonate
t	triplet
TBAB	tetra-*n*-butylammonium bromide
TBAC	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBDPSCl	*tert*-butyl(chloro)diphenylsilane
TEA	triethylamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
Tol	toluene
Ts	4-toluenesulfonyl
UV	ultraviolet

CHAPTER 1: INTRODUCTION

1.1 Introduction

Arynes are reactive species formally derived by the removal of two *ortho*-hydrogens from an aromatic ring system. For example, when the aromatic system is benzene, the resulting aryne is 1,2-didehydrobenzene or benzyne (**1a**).[1] Although two isomeric forms are possible, *meta*-benzyne (**1b**) and *para*-benzyne (**1c**), they are not synthetically useful and will not be discussed herein (Figure 1).

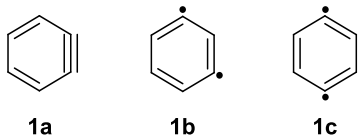
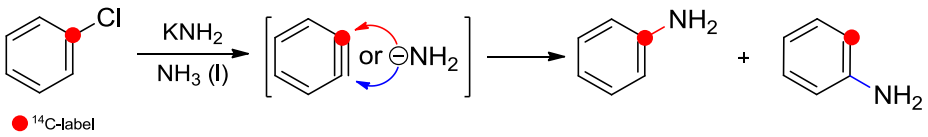


Figure 1

The strained nature of the carbon-carbon triple bond within the small ring system leads to exceptionally high reactivity. Arynes are short lived *in situ* leading to dimer- or trimerisation if no trapping reagent is present.[2] The exploitation of these reactive species has been extensively studied since they were first synthesised in the early 20th century. As the most studied aryne, the conclusions drawn from examining **1a** can equally be inferred for other arynes. Before considering the nature and types of reactions these intermediates undergo it is important to consider the structure itself to help understand their reactivity.

1.2 Structure

The modern synthetic interpretation of the structure of **1a** as a triple-bonded species is derived from the work of Roberts in 1953.[3] Roberts proposed **1a** as an electronically neutral cycloalkyne which he elucidated following a classic ^{14}C labelling experiment. ^{14}C-labeled chlorobenzene was reacted with potassium amide in liquid ammonia resulting in a 1:1 mixture of the two resulting anilines; this lead Roberts to propose an elimination/addition mechanism *via* a strained “benzyne” intermediate (Scheme 1).[4]



Scheme 1

Previous proposed structures to account for the unique reactivity of this species include a diradical (**1d**) and zwitterionic (**1e**) species as proposed by Bachmann and Clarke[5] and Wittig[6] respectively (Figure 2).

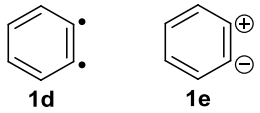
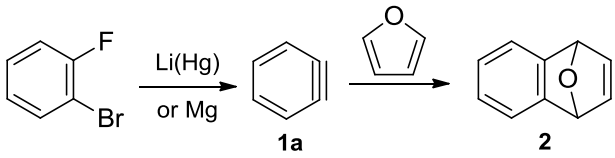


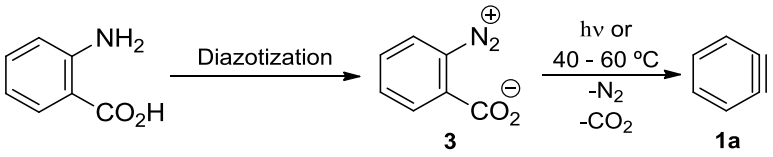
Figure 2

Roberts' proposed structure was subsequently supported following Wittig's later work showing benzyne's reactivity as a dienophile by trapping the intermediate with furan as a Diels-Alder adduct **2** (Scheme 2).[4]



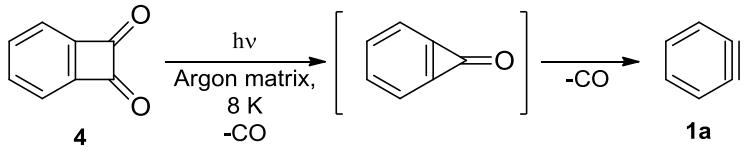
Scheme 2

An important discovery by Stiles and Miller allowed the generation of **1a** from benzenediazonium-2-carboxylate (**3**) by thermal or photolytic means.[7] This promoted a surge of interest in the field due to the ability to generate this intermediate from easily obtained materials without the need for strong organometallic reagents.[8] This paved the way for spectroscopic investigations into the unique structure; a UV spectrum was obtained of gaseous benzyne by photolysis of **3**[9] and mass spectroscopy identified a possible benzyne fragment ($C_6H_4^{\bullet+}$) by an analogous process (Scheme 3).[10]



Scheme 3

An IR spectrum obtained by photolytic decomposition of benzocyclobutenedione (**4**) to **1a** in an argon matrix at low temperature (8 K) allowed for the assignment of the C≡C bond stretch for the first time therefore supporting Roberts' proposed structure (Scheme 4).[11]



Scheme 4

In addition, measurement of the ^{13}C dipolar NMR spectrum of benzyne-1,2-$^{13}C_2$ in an argon matrix at ~20 K allowed for the determination of the acetylenic C≡C bond length (124±2 pm) which was in agreement with the value obtained by microwave spectroscopy (125.5 pm).[12-13] These bond lengths lie between those for ethyne (120.3 pm) and ethene (133.2 pm), while the remaining carbon-carbon bond lengths in the ring are slightly shorter than that of benzene, at 138.3 pm and 139.1 pm respectively. With this data in-hand it could be considered that the structure of benzyne is defined as an aromatic system with an acetylenic bond, however recent NMR studies suggest otherwise.[14] ^{1}H and ^{13}C spectra of benzyne in solution obtained by generation within a hemi-carcerand molecular container (**5**) suggest a less clear-cut view of benzyne's structure (Figure 3).

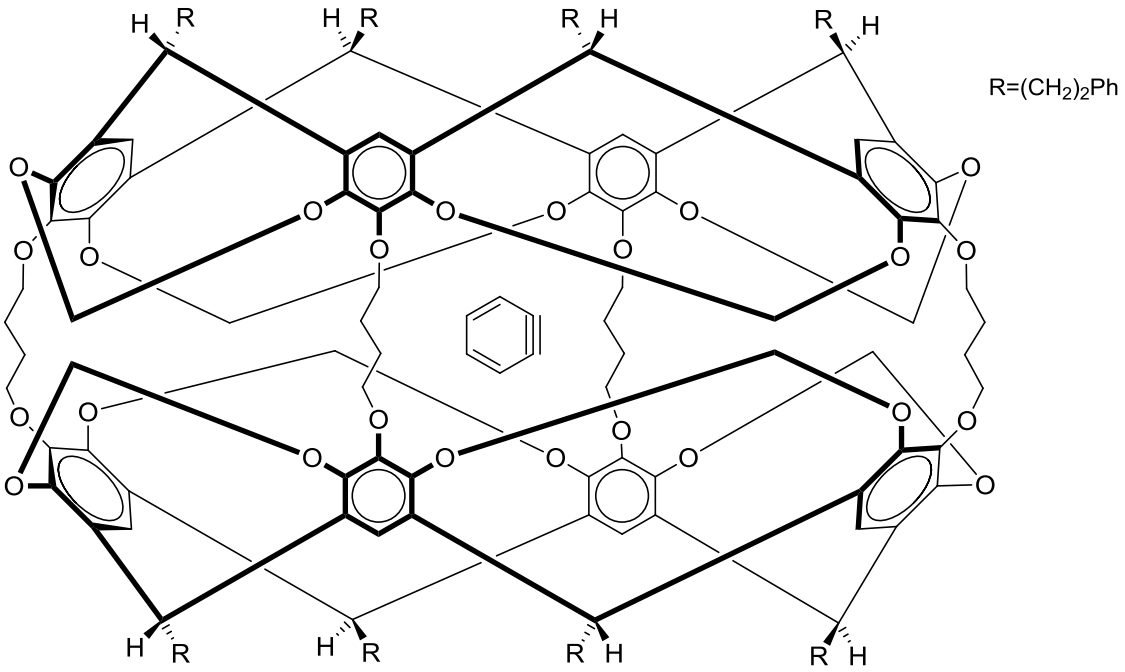


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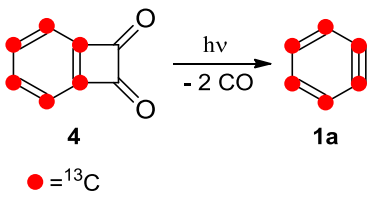
Figure 3

By generating benzyne photolytically from ^{13}C-enriched benzocyclobutenedione (**4**) within molecular container (**5**)**,** benzyne is stable at 175 K for several hours allowing for extensive ^{13}C NMR studies to be performed (Scheme 5).



Scheme 5

These studies revealed: C^1-$C^{1'}$ bond shows triple bond character, C^3-$C^{3'}$ bond shows olefinic character and C^2-C^3 and $C^{2'}$-$C^{3'}$ bonds shows character more akin to two adjacent sp^2 hybridised carbon centres connected by a single bond. These results would suggest that benzyne exists as a resonance hybrid between the acetylenic (**1a**) and the cumulene (**1f**) structure, however the in-plane π-bond induces a proportion of bond localisation resulting in a greater expression of acetylenic character (**1a**) (Figure 4).[14]

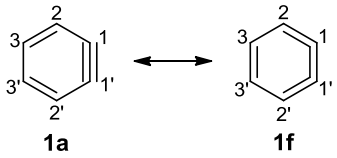
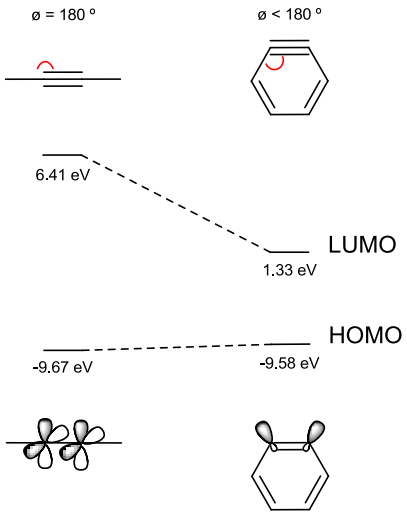


Figure 4

1.3 Reactivity

When comparing the reactivity of the aryne acetylenic bond with a linear alkyne analogue the differing reactivities become apparent. Linear alkynes exhibit both nucleophilic and electrophilic character; however by constraining the alkyne in a small cyclic system, such as benzyne, the alkyne bond exhibit only electrophilic character. *Ab initio* studies attribute this to the decrease in energy of the LUMO when distorting a linear alkyne bond: 6.41 eV for 2-butyne to 1.33 eV for benzyne. The HOMO remains at approximately the same energy (Scheme 6).[15]

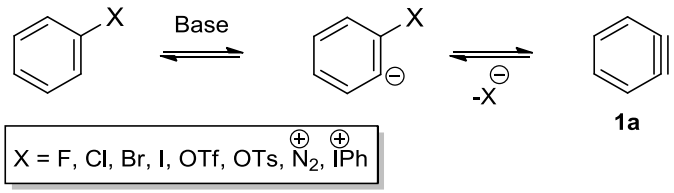


Scheme 6

The low energy of the LUMO is due to the mixing of the p* and s* orbitals. This low-lying LUMO will be closer in energy to the HOMO of the approaching nucleophile, resulting in arynes exhibiting electrophilic character. In addition to this, the low-lying LUMO allows arynes to act as excellent 2π-electron components in pericyclic reactions. This helps define the two major classes of reactions that arynes exhibit as addition of nucleophiles and pericyclic reactions.

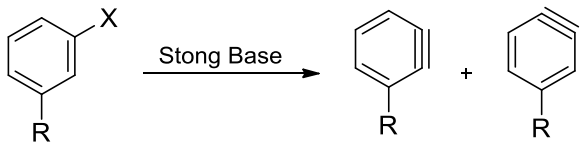
1.4 Aryne generation

Numerous methods for the generation of arynes have been reported in the literature and can broadly be divided into four categories: β-elimination of aryl anions, thermolysis, oxidative and desilylative. Early studies into the chemistry of arynes exploited the reaction of mono-haloarenes with strong bases.[16] This methodology has since been extended to include a variety of leaving groups including: N_2,[17] IPh,[18] $^-$OTs[19] and $^-$OTf,[20] in place of the classic halide (Scheme 7).[21a]



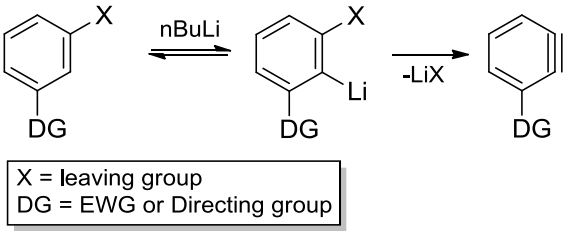
Scheme 7

Although this methodology proved popular, the use of strong bases such as alkali metal amides and alkyllithiums often resulted in problems. When using alkali metal amides such as LDA the competing reaction of the diisopropylamide or diisopropylamine with the aryne was a common side product. In addition to this, the use of strong bases often limited the application of this methodology due to incompatibility with more complex substrates. Furthermore, consideration of the substitution patterns on the aryl ring is important with possible generation of two arynes from a single precursor (Scheme 8).



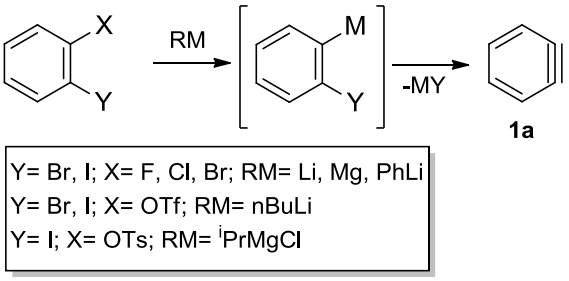
Scheme 8

By placing an electron-withdrawing group or functionality capable of directing *ortho*-lithiation in the position *meta* to the leaving group (X), only a single aryne is generated (Scheme 9).[21g]



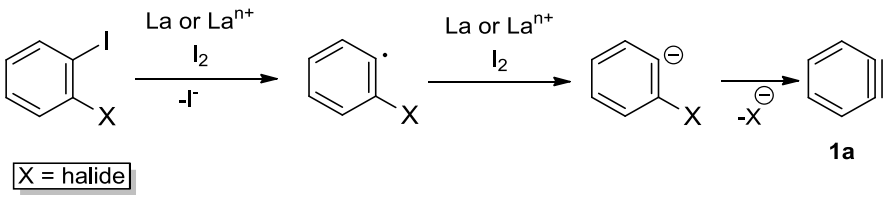
Scheme 9

By using *ortho*-dihalides the problem of regioselectivity in aryne formation is resolved. Initial metal-halogen exchange occurs followed by β-elimination to generate the desired aryne.[22] Other pseudo-halides can be applied to this methodology as the leaving group (Scheme 10).[23,24,25]



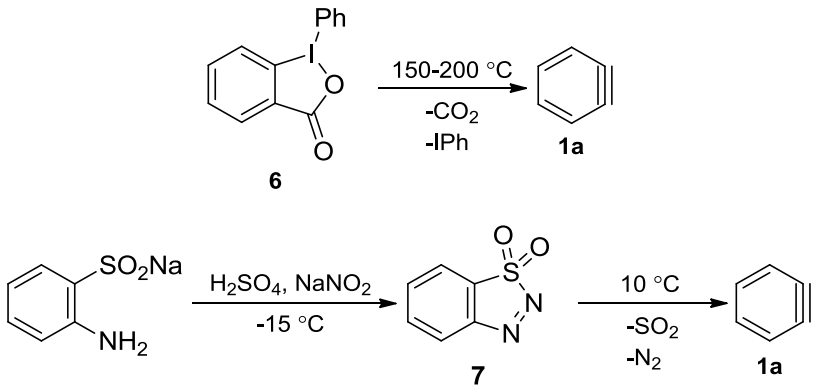
Scheme 10

Sonoda has shown that exposing *ortho*-iodohaloarenes to stoichiometric lanthanum metal and 4 mol% iodine results in aryne generation. The reaction proceeds by two sequential single-electron transfer steps from the lanthanum metal or a low valence lanthanum species generated *in situ* from a reaction between the lanthanum and iodine. The phenyl anion generated subsequently eliminates in the same manner as previously described (Scheme 11).[26]



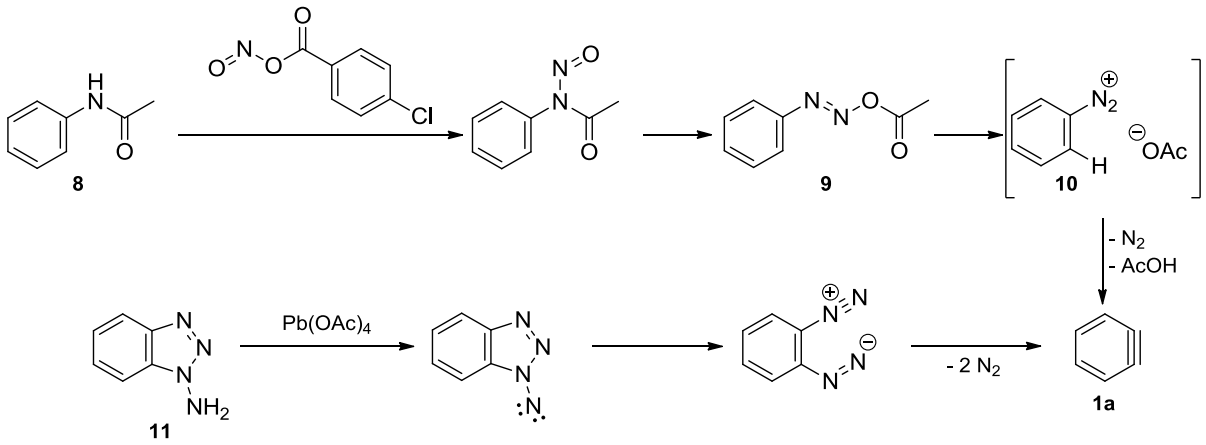
Scheme 11

As previously mentioned, initial applications of aryne methodology were limited due to the use of the strong bases or organometallic components used in the generation of arynes. It wasn't until Stiles and Miller reported that benzenediazonium-2-carboxylate (**3**) derivatives could be used as simple aryne precursors under relatively mild conditions that the popularity of aryne chemistry increased (Scheme 3).[7] The entropic gain in liberating stoichiometric nitrogen and carbon dioxide upon heating of **3** led to energetically favourable generation of **1a**. Similar methodologies exploiting entropic favourability have led to a series of aryne precursors; examples of which include: diphenyliodonium-2-carboxylate (**6**) [27] and 1,2,3-benzothiadiazole 1,1-dioxide (**7**) [28] (Scheme 12).



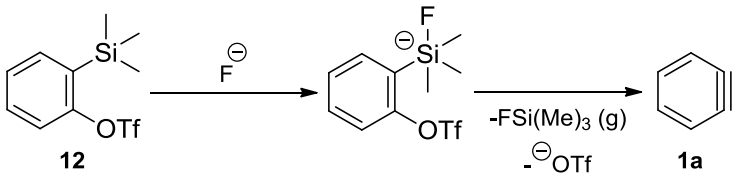
Scheme 12

Although these methodologies avoid the use of organometallic reagents and strong bases, there are still drawbacks. The innate entropic gain in aryne formation results from the instability of the precursors, meaning that storage is often unfeasible and use on a large scale is often dangerous due to possible explosive decomposition. Where the precursor is a stable species such as diphenyliodonium-2-carboxylate (**6**) the method for aryne generation requires high temperatures and long reaction times to achieve yields comparable with other methods.[27] Rees[29] and Cadogan[30] reported methodologies which exploit the entropic gain but overcome the instability of precursors. Cadogan showed that *in situ* oxidation and rearrangement of acetanilide (**8**) to the azoacetate (**9**) followed by decomposition and *ortho*-deprotonation by the acetate anion of diazonium (**10**) affords **1a**. Rees showed that 1-aminoaryltriazoles (**11**) would, following oxidation with lead tetraacetate, lead to aryne generation. The reaction is proposed to proceed *via* an aminonitrene which fragments resulting in generation of two equivalents of nitrogen (Scheme 13). This process has also been shown to occur with *N*-iodosuccinimide (NIS), however iodine incorporation into the final molecule has been shown to occur.[31]



Scheme 13

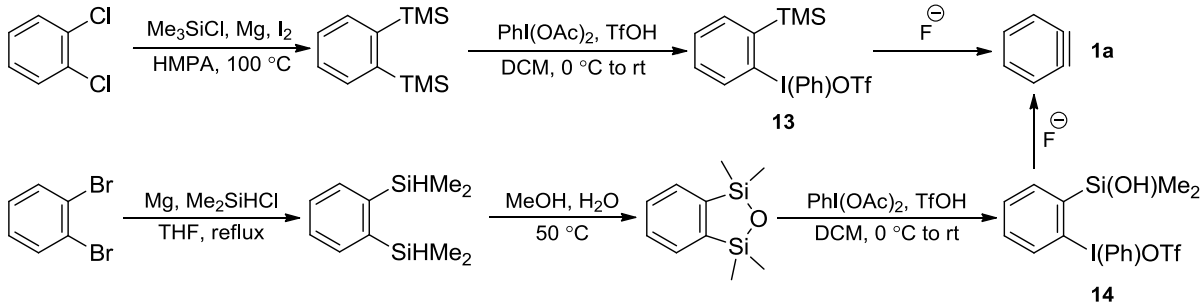
Although these methods have been reported as viable routes to arynes, the use of oxidative conditions may prove problematic with sensitive substrates. In addition, the stoichiometric use of toxic reagents like lead tetraacetate should be discouraged. In 1983 Kobayashi demonstrated that 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**12**) would successfully desilylate to generate arynes under mild room temperature conditions when treated with a suitable fluoride source (Scheme 14).[32]



Scheme 14

This methodology takes advantage of the large enthalpic gain in forming the Si-F bond, the stability in generating a triflate anion upon elimination and the entropic gain in generating fluorotrimethylsilane which is gaseous at ambient temperature. By using fluoride to initiate aryne generation, this methodology tolerates several motifs which may be incompatible with previously described conditions. The mild conditions for generating arynes using this methodology has also allowed for considerable expansion in TM-mediated reactions of arynes; an area of research which has traditionally been under-explored.[23] The mild generation and tolerance of numerous motifs has resulted in Kobayashi's methodology becoming the most prevalent protocol for aryne generation, with a variety of analogous aryne and hetero-aryne precursors now being commercially available. Kitamura has reported (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate (**13**) as an analogous precursor to **12**.[33] Elimination of the *ortho*-substituents occurs by the same desilylative method, however a hypervalent iodine species acts as the leaving group. Kitamura's precursor **13** is advantageously a solid as well as

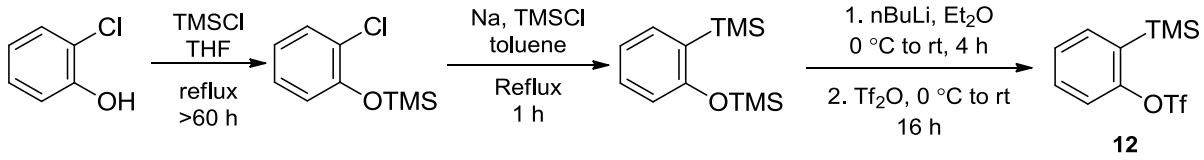
hydrolytically more stable than **12**, however uptake of **13** has been minimal due to the use of HMPA in its synthesis; furthermore, no analogues are commercially available. In an attempt to avoid the use of HMPA Kitamura has reported another analogous precursor, [2-(hydroxydimethylsilyl)-phenyl](phenyl)iodonium triflate (**14**) which is generated in three steps from 1,2-dibromobenzene (Scheme 15).[34]



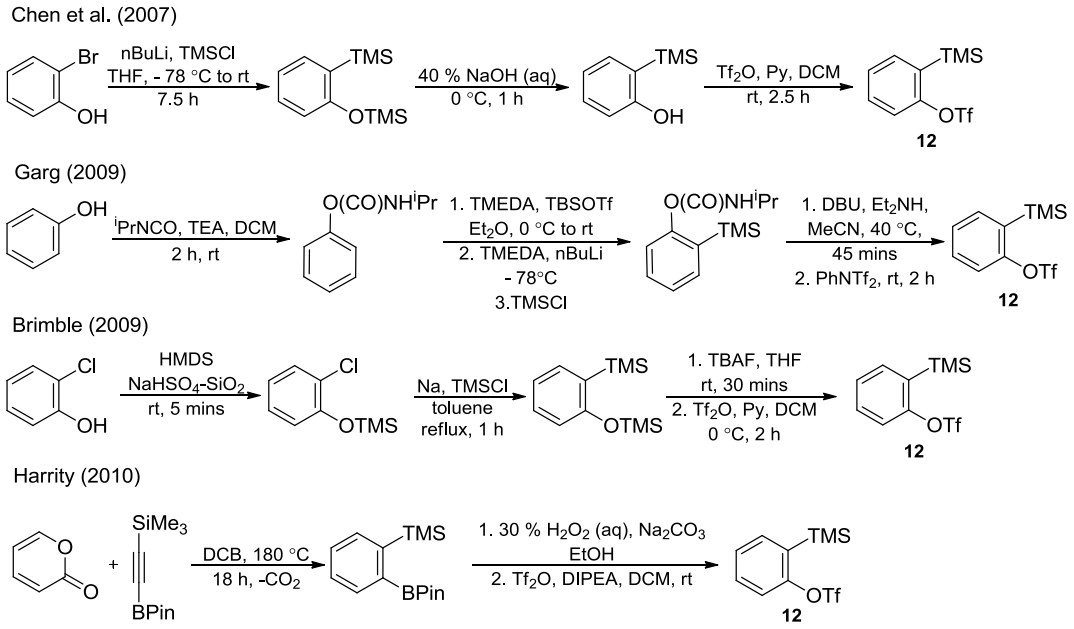
Scheme 15

Although the use of **12** is the most popular protocol for aryne generation with numerous commercially available analogues, the synthesis of the precursor itself is not trivial. Following Kobayashi's published synthesis (Scheme 16), a number of research groups have attempted to improve the synthetic route to **12** (Scheme 17).[35]

Kobayashi (1983)

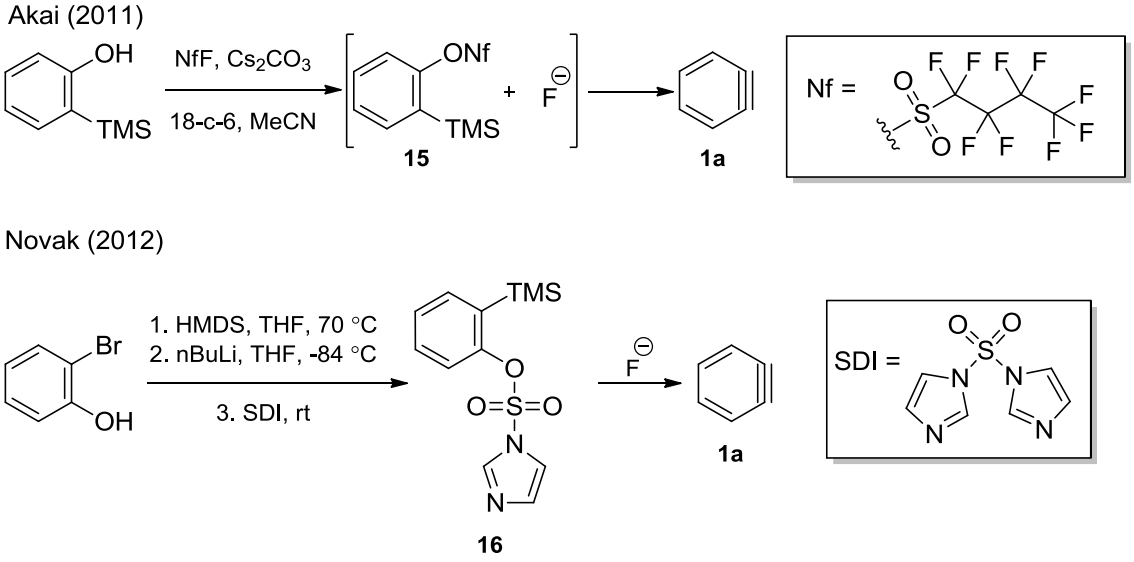


Scheme 16



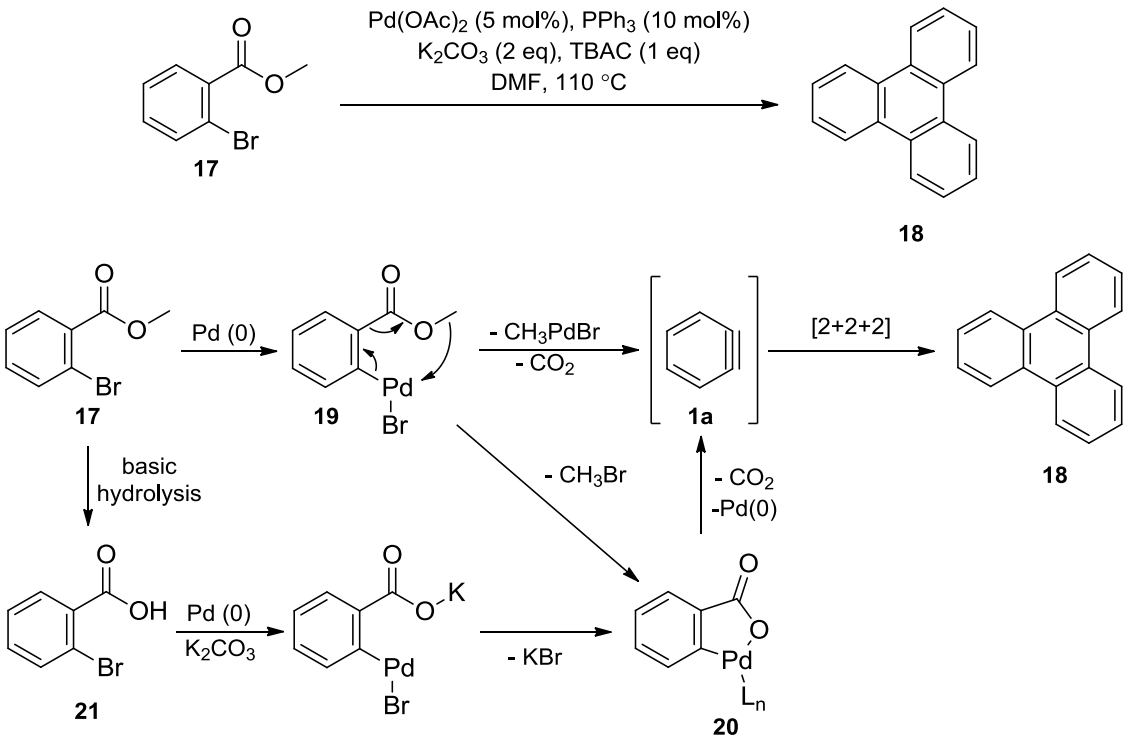
Scheme 17

The use of **12** as an aryne precursor has been criticised due to its poor atom efficiency and need for expensive triflating agents in its synthesis. In addition, aryl triflates can be hydrolysed to generate triflic acid, which is genotoxic. In an attempt to overcome these drawbacks, Akai[36] and Novak[37] have devised alternative protocols that avoid the use of triflates (Scheme 18).



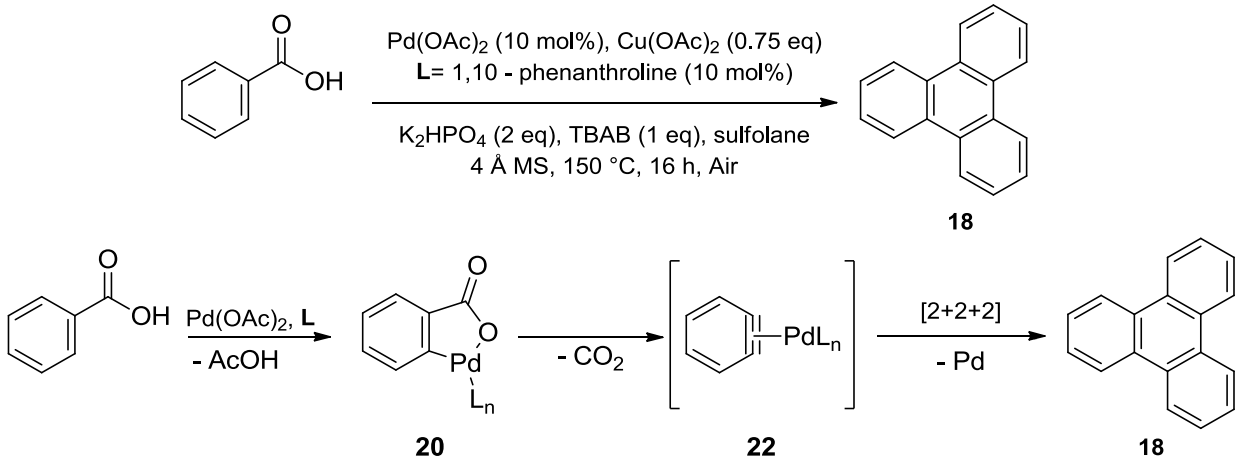
Scheme 18

Akai has demonstrated that nonafluorobutane sulfonyl fluoride (NfF) can act as an *in situ* activating group (generating 2-(trimethylsilyl)phenyl nonaflate (**15**)) and fluoride source to generate arynes from *ortho*-silyl phenols. Novak has shown that replacing the triflate component with an imidazolylsulfonate (**16**), aryne generation occurs successfully upon treatment with fluoride, with the by-product imidazolylsulfonate being hydrolysed to imidazole and sulfonic acid upon aqueous work-up. Greaney has demonstrated the utility of producing **12** using continuous-flow synthesis allowing for scalable production between 2-20 mmol h^{-1}.[38] Furthermore, Greaney showed that by adapting Akai's procedure, **15** could be isolated exploiting the cheaper and hydrolytically stable nonaflate group. Increased interest in TM-mediated reactions of arynes has resulted in a number of examples of aryne generations using palladium mediated methods. Kim has shown that by treating methyl 2-bromobenzoates (**17**) with sub-stoichiometric palladium results in successful triphenylene (**18**) formation.[39] The reaction is proposed to occur by one of two mechanism; the first involves oxidative addition into the aryl bromide bond generating (**19**) followed by δ-carbon elimination and concomitant decarboxylation to generate benzyne (**1a**), which undergoes a palladium mediated [2+2+2]-cycloaddition by known mechanism.[40] Alternatively, bromomethane may be eliminated from (**19**) to generate carboxypalladacycle (**20**) which decarboxylates generating benzyne (**1a**). The second mechanism proceeds by basic hydrolysis of (**17**) to generate (**21**), oxidative addition of palladium into aryl-bromide bond of (**21**) and KBr elimination generates palladacycle (**20**) which generates **18** by the mechanism previous described (Scheme 19).



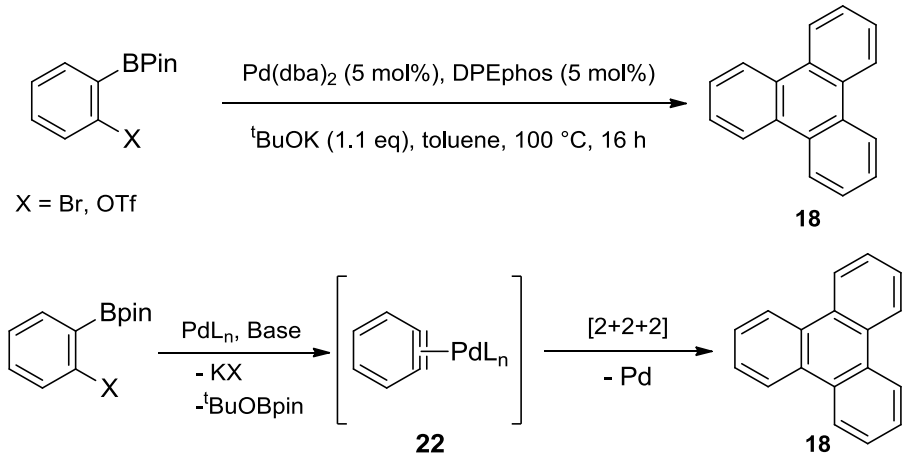
Scheme 19

Greaney reported an analogous process that exploits C-H activation in place of requiring the *ortho*-bromide as described by Kim. The carboxypalladacyle (**20**) is proposed to decarboxylate to Pd-bound aryne (**22**) that in turn cyclotrimerises to **18** (Scheme 20).[41]



Scheme 20

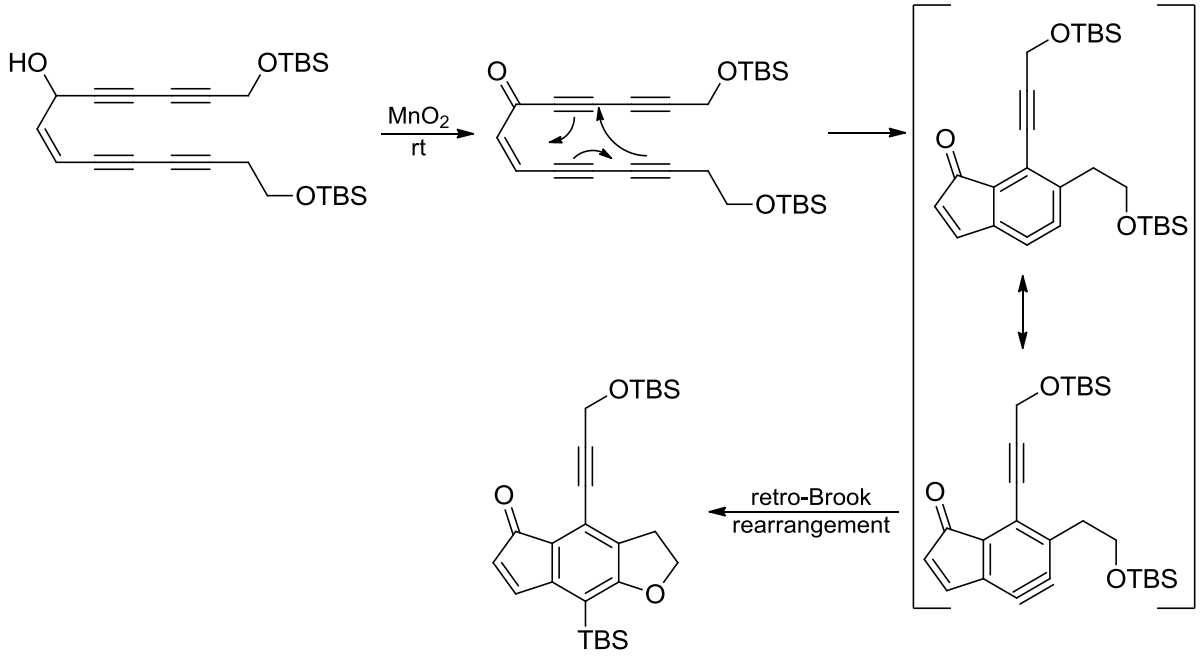
Greaney has also reported the generation of Pd-bound aryne species from *ortho*-bromo and triflatopinacolboranes.[42] The mechanism is proposed to occur *via* initial oxidative addition into the aryl halo/pseudohalo bond followed by base-activated aryne formation to (**22**) which subsequently cyclotrimerises to **18** (Scheme 21).



Scheme 21

The final miscellaneous area of aryne generation is the hexadehydro-Diels-Alder (HDDA) reaction discovered serendipitously by Hoye.[43] In performing an allylic oxidation, an unexpected tricyclic

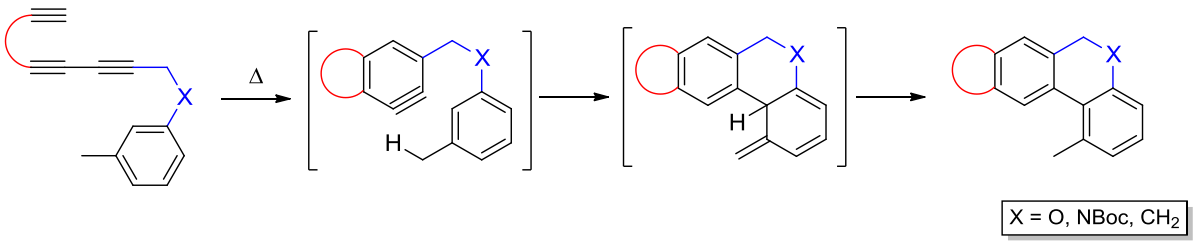
system was isolated from the reaction in 53 %. The proposed reaction mechanism occurs *via* a [4+2]-cycloaddition of the tetra-yne tether followed by subsequent trapping by a retro-Brook rearrangement (Scheme 22).



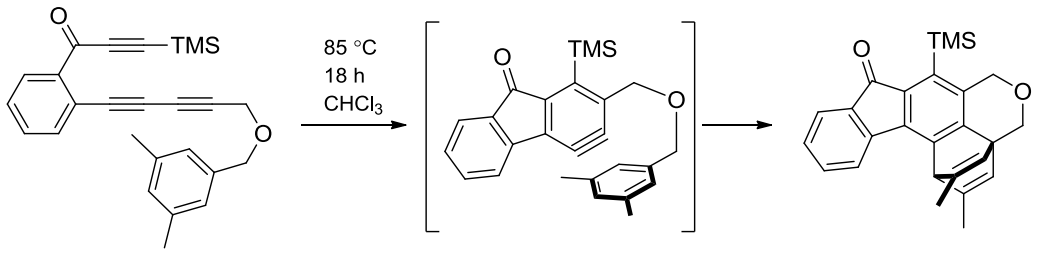
Scheme 22

The most intriguing component of this reaction is the insertion into the Si-O bond as this does not readily occur *via* alternative aryne methodologies. Calculation of the energy of formation of the aryne intermediate is shown to be exothermic by ~50 kcal mol^{-1}. This suggests that the formation of the aryne, which is already a very reactive intermediate, is significantly increased by possessing this additional energy and as such can perform reactions that are rarely seen through alternative aryne protocols.[44] Examples of this, in addition to the insertion of the Si-O bond, include the aromatic ene-reaction[45] as well as the Diels-Alder reaction with benzene to generate benzobarrelene products (Scheme 23).[46]

Aromatic ene-reaction

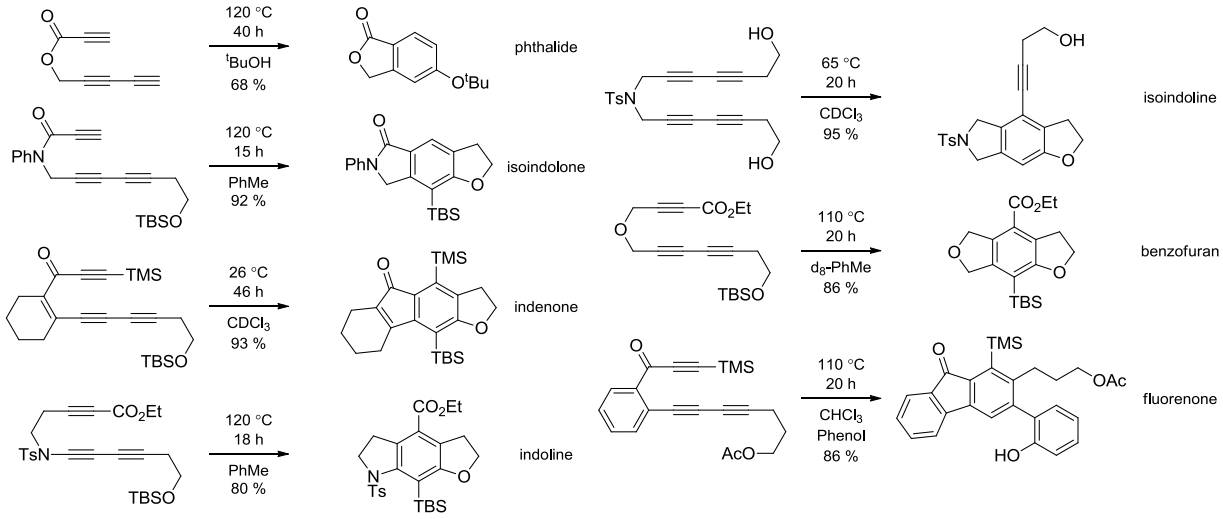


Benzobarrelene generation by Diels-Alder



Scheme 23

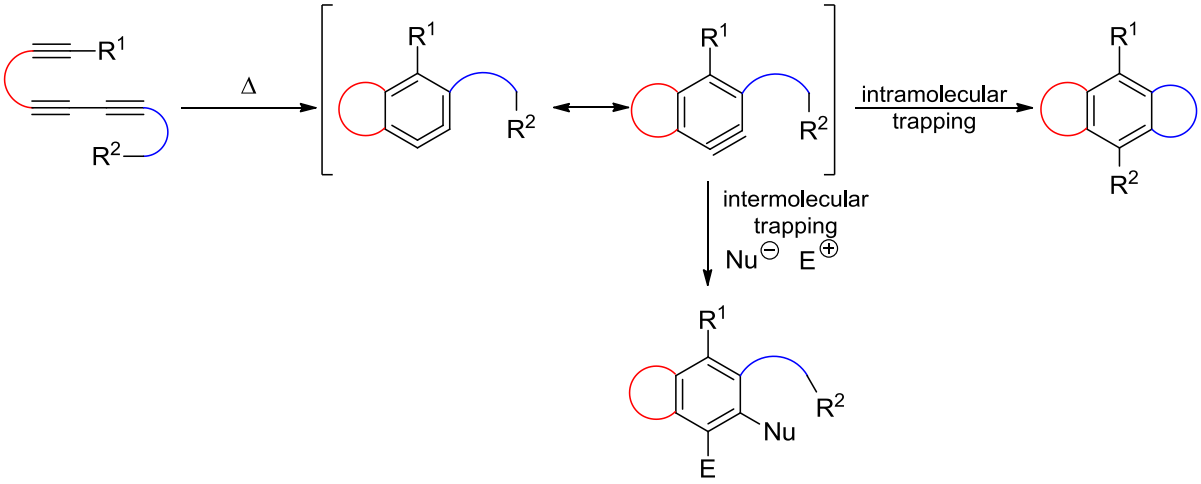
Further investigations by Hoye have shown that by altering the tri-yne tether, a large number of heterocyclic systems can be generated including phthalides, isoindolones, indenones, indolines, isoindolines, benzofurans and fluorenones (Scheme 24).



Scheme 24

In addition to this, intra and intermolecular trapping of the generated aryne can give rise to highly functionalised polycyclic aromatic compounds under relatively benign conditions without the need for

in situ aryne generation by *ortho*-functionalised starting materials. This greatly improves atom efficiency as all components of the starting material are present in the product (Scheme 25).

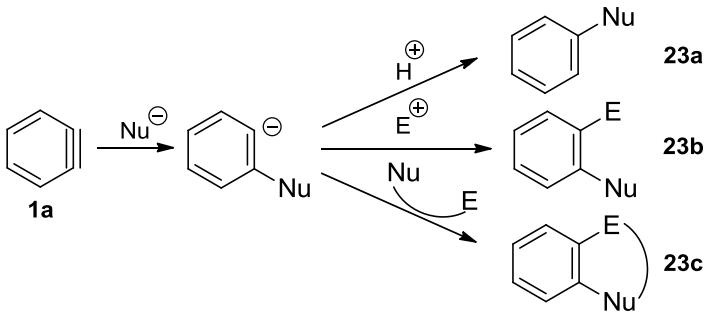


Scheme 25

1.5 Reactions

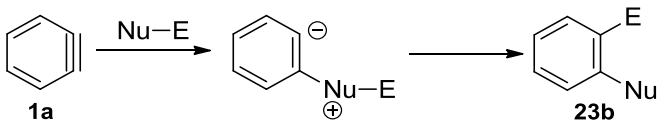
1.5.1 Reactions of nucleophiles with arynes

The low-lying LUMO of aryne species allows for facile nucleophilic addition by a wide range of anionic and uncharged nucleophiles. The resulting carbanion can subsequently be trapped with: a proton, resulting in a mono-substituted arene (**23a**); an external electrophile, resulting in an *ortho*-disubstituted arenes (**23b**) by a three component reaction; or an internal electrophile resulting in a ring system being formed (**23c**) (Scheme 26).[23]



Scheme 26

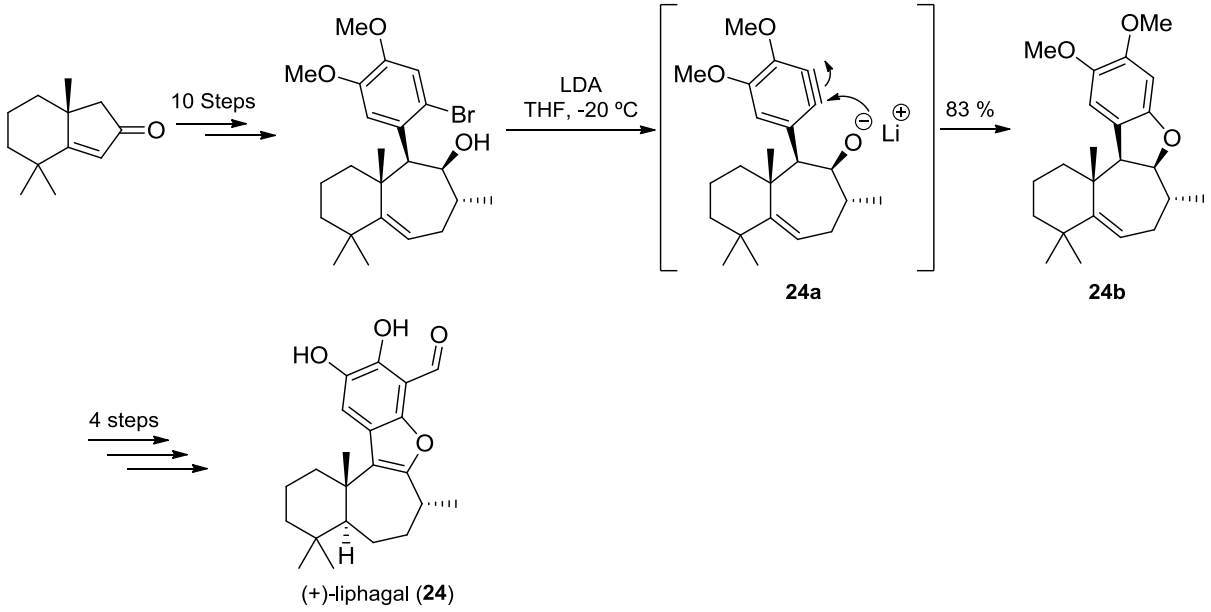
In addition, arynes can insert into σ-bonds of reagents where a nucleophilic and electrophilic component are bound by a facile σ-bond. In the course of the reaction initial nucleophilic addition to the aryne generates a carbanion which adds to the electrophilic component and subsequent bond fission leads to **23b** (Scheme 27).[47]



Scheme 27

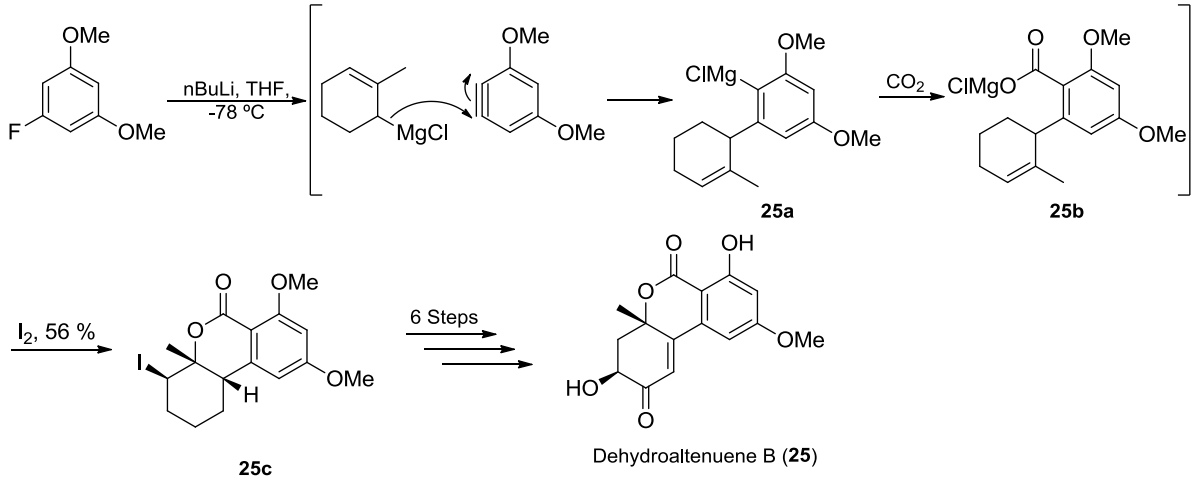
Due to the extensive study of aryne over the past century, numerous examples of each of these processes have been reported.[21] The knowledge garnered from these studies have successfully been applied to numerous total syntheses as the key aryl-bond-forming step.[48]

During Stoltz's synthesis of the tetracyclic meroterpenoid (+)-liphagal (**24**) the construction of the final ring was achieved by addition of an alkoxide to aryne (**24a**) forming the desired dehydrobenzofuran (**24b**) in 83 %.[49] Previous attempts to form this ring by palladium-catalysed etherification had proved unsuccessful. By using aryne methodology at this stage the successful cyclisation left only hydrogenation to form the *trans*-ring junction, followed by an oxidation to benzofuran, formylation and methoxy demethylation to give **24** (Scheme 28).



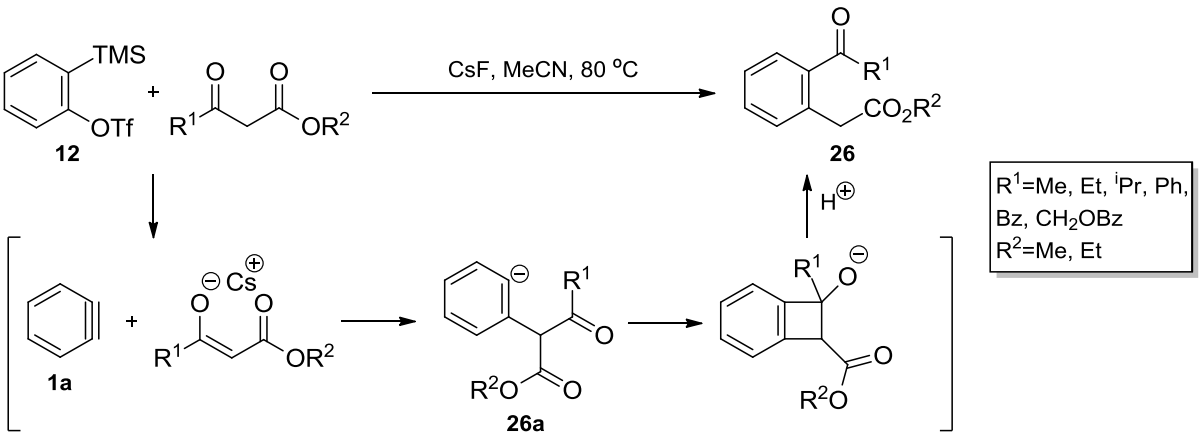
Scheme 28

Barrett's synthesis of dehydroaltenuene B (**25**) provides an excellent example of the use of aryne intermediates in a sequential four-component reaction to achieve a high degree of complexity in a relatively simple series of steps.[50] Following aryne generation, addition of an allylic Grignard reagent results in aryl Grignard (**25a**) which is quenched with CO_2 forming benzoate anion (**25b**). Following addition of iodine to **25b**, the benzoate anion closes the ring to generate the iodolactone (**25c**) in 56 % yield. Substrate controlled cyclisation resulted in a single diasteromer being formed which was beneficially the desired iodolactone **25c**. Following a further 6 steps **25** was successfully synthesised (Scheme 29).



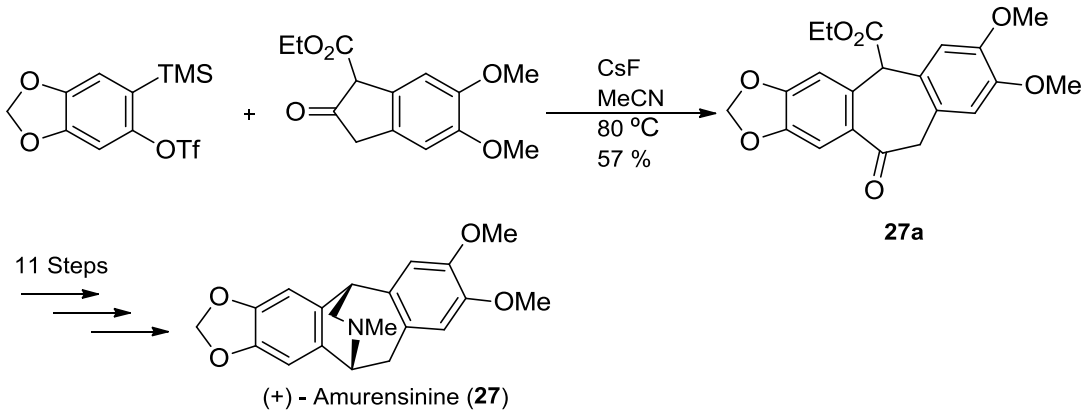
Scheme 29

Stoltz showed β-ketoesters with arynes perform σ-bond insertion reactions generating *ortho* acyl-alkylated arenes (**26**) (Scheme 30).[51] The reaction proceeds by deprotonation of the β-ketoester by fluoride, the resulting enolate attacks the aryne generating carbanion (**26a**). The phenyl anion of **26a** adds into the ketone and following fragmentation and protonation generates **26**.



Scheme 30

Stoltz's synthesis of (+)-Amurensinine (**27**) showed the utility of this procedure where reaction with a cyclic β-ketoester is successfully applied to emplace all but one of the carbons in the final product (**27a**) (Scheme 31).[52]

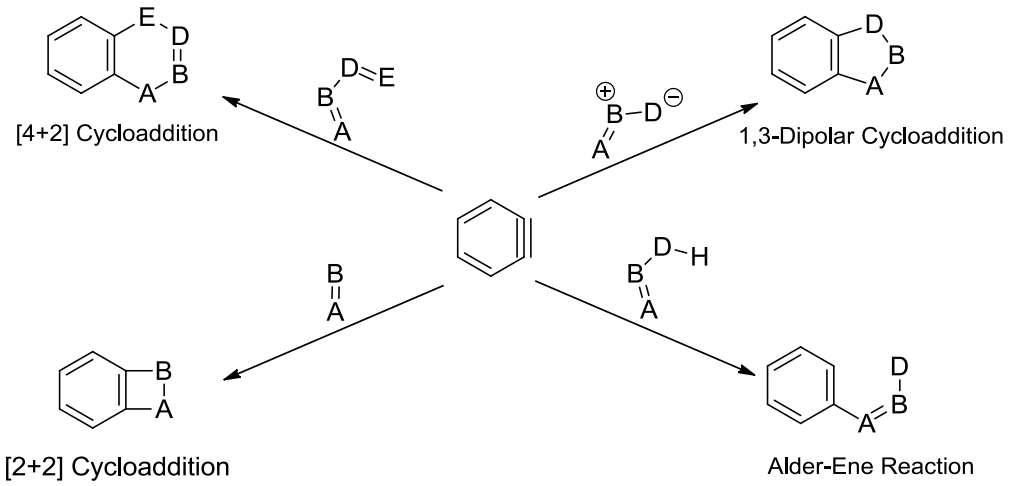


Scheme 31

From **27a**, diasteroselective reduction of the ester and ketone to alcohols followed by selective protection of the primary alcohol and palladium catalysed oxidative kinetic resolution of the secondary alcohol provided the starting point for the final seven steps to generate **27**.

1.5.2 Pericyclic reactions of arynes

Arynes act as 2π-electron components in a number of pericyclic processes (Scheme 32).

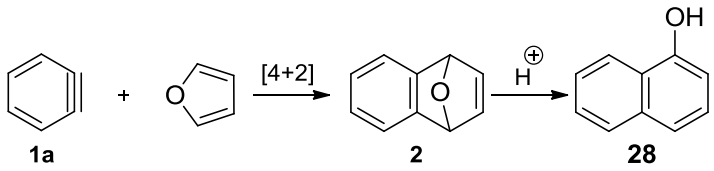


Scheme 32

The nature of the acetylenic LUMO allows for facile pericyclic reactions to be performed, π-electron rich coupling partners react preferentially due to the reduced HOMO-LUMO energy gap.[21a]

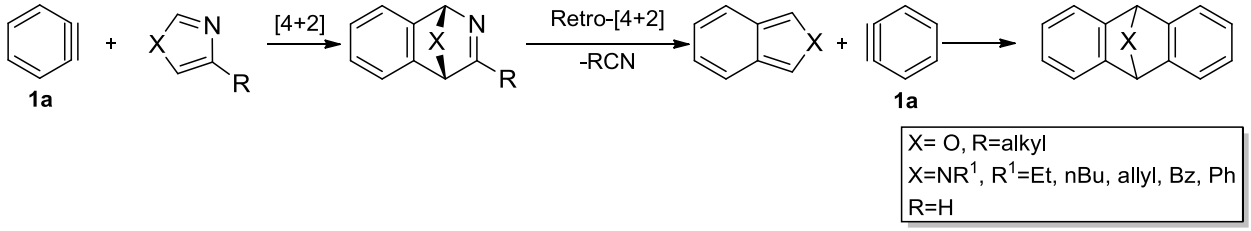
1.5.2.1 – [4+2] - Cycloaddition

Arynes are powerful electrophilic dienophiles and will undergo [4+2]-cycloadditions with a diverse selection of dienes, including aromatic compounds such as thiophenes which are not generally considered viable substrates in this process.[53] 5-Membered carbo- and heterocyclic dienes are common substrate for this reaction. Reactions of arynes with furan and its derivatives have traditionally been used to verify aryne formation; moreover, acidic cleavage of the oxo-bridge of **2** allows for a convenient route into functionalised hydroxynapthalenes (**28**) (Scheme 33).[4]



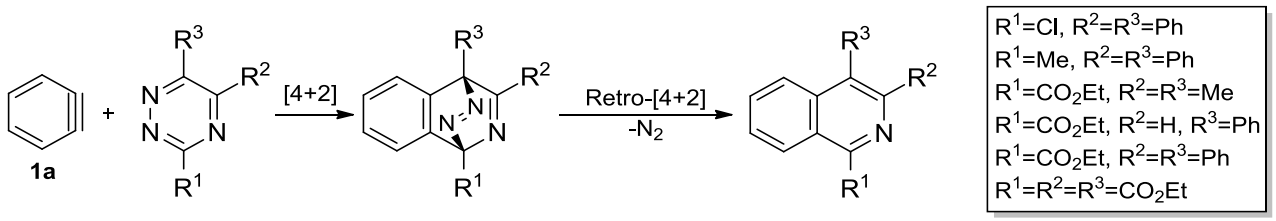
Scheme 33

Other 5-membered heterodienes such as pyrrole[54] follow this reactivity trend; however *N*-substituted imidazoles[55] and oxazoles[56] undergo a retro-[4+2] generating a heterodiene which can undergo a second [4+2]-cycloaddition with another aryne equivalent (Scheme 34).



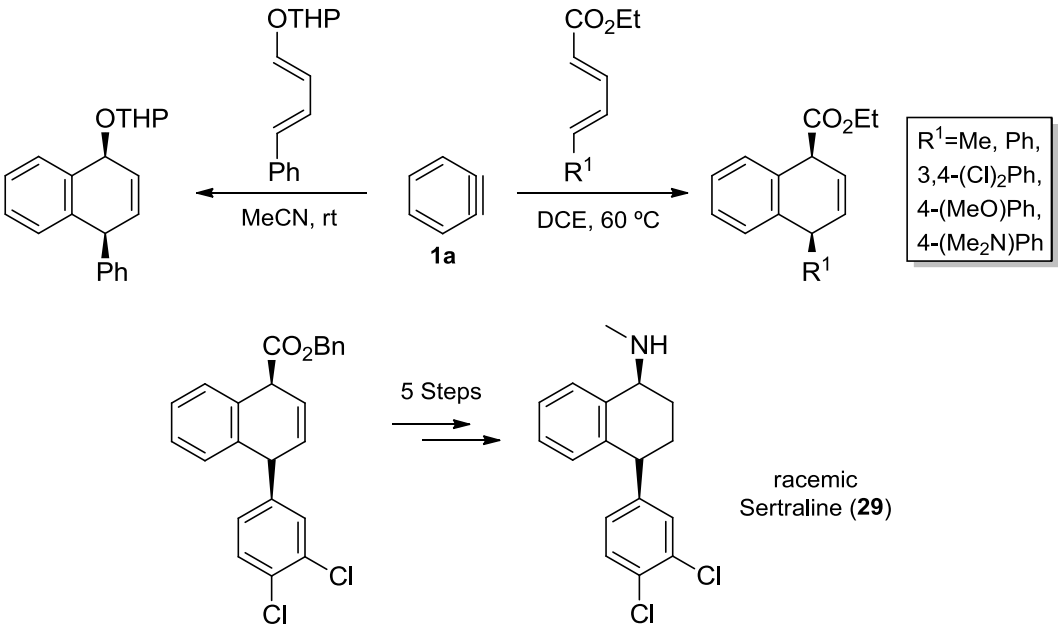
Scheme 34

1,2,4-triazines provide a route to substituted isoquinolines: following initial [4+2], a retro-[4+2] generates diatomic nitrogen and the desired isoquinoline (Scheme 35).[57]



Scheme 35

Acyclic dienes have also been shown to react with arynes in high diastereoselectivity. Lautens' construction of 1,4-dihydronapthalene derivatives was shown to tolerate electron-rich and electron-poor dienes. Lautens went on to apply the chemistry to the synthesis of racemic Sertraline (**29**) (Scheme 36).[58]

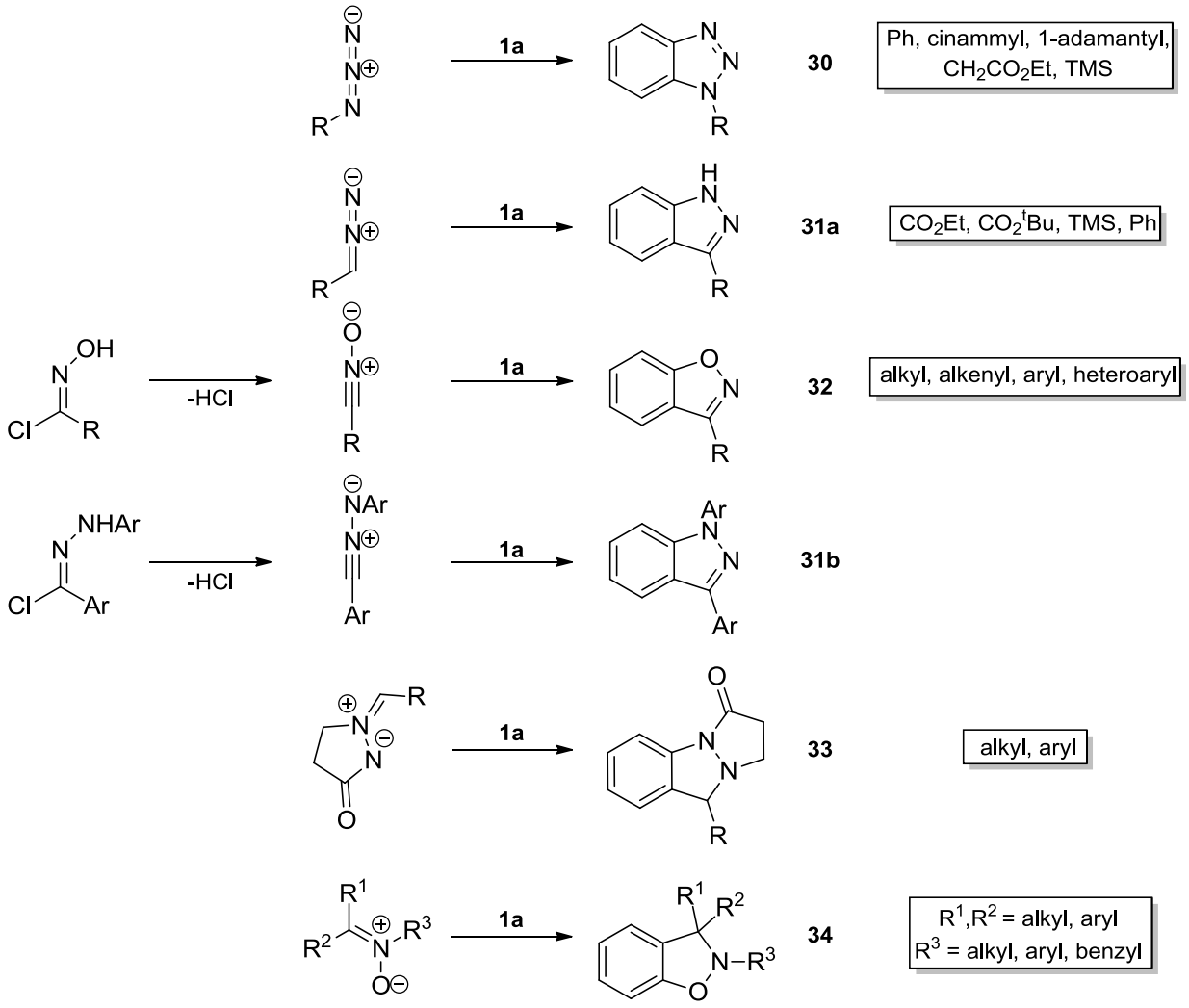


Scheme 36

1.5.2.2 1,3-Dipolar Cycloadditions

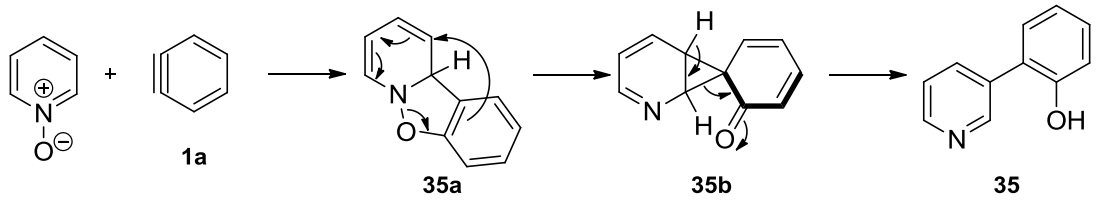
Arynes have been shown to react with a number of 1,3-dipoles providing an advantageous route into a series of heterocycles. Azides[59] and diazo[60] compounds have successfully been used to synthesise triazoles (**30**) and indazoles (**31a**) respectively. Nitrile oxides[61] and nitrile imines[62] have been used to

generate benzisoxazoles (**32**) and indazoles (**31b**); while azomethine imines[63] generate indazolines (**33**) (Scheme 37).



Scheme 37

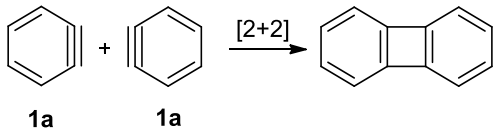
Azomethine ylides[64] have also been shown to react with arynes; nitrones[65] generate benzisoxalones (**34**). Pyridine *N*-oxides with arynes initially forms intermediate (**35a**) which following a rearrangement to cyclopropane (**35b**) fragments generating 3-(2-hydroxyaryl)-pyridine (**35**) (Scheme 38).[66]



Scheme 38

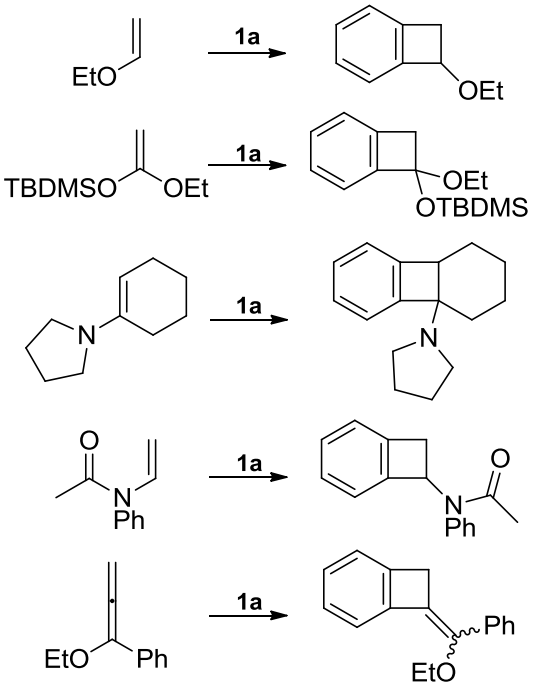
1.5.2.3 [2+2] – cycloaddition

[2+2]-Cycloadditions of arynes are of interest due to their ability to generate strained 4-membered rings. The most common example of the aryne [2+2]-cycloaddition is dimerisation when a suitable trapping agent is not present *in situ* (Scheme 39).[67]



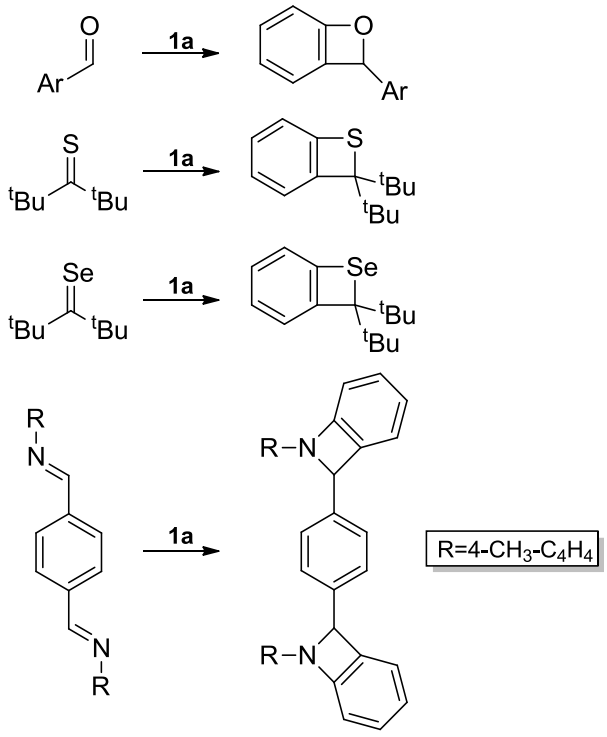
Scheme 39

Electron-rich olefins are favoured partners for these processes with numerous reported examples including enol ethers,[68] ketene silyl acetal,[69] enamines,[70] enamides[71] and allene ethers[72] (Scheme 40).



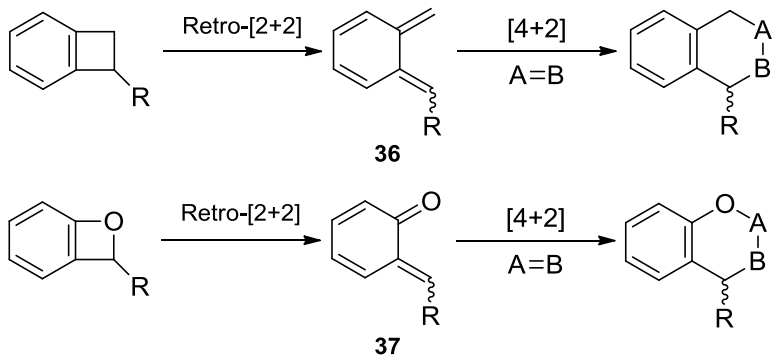
Scheme 40

In addition to this, hetero π-systems in the form of aldehydes,[73] thiones,[74] selenoketones,[75] and imines[76] are also suitable substrates (Scheme 41).



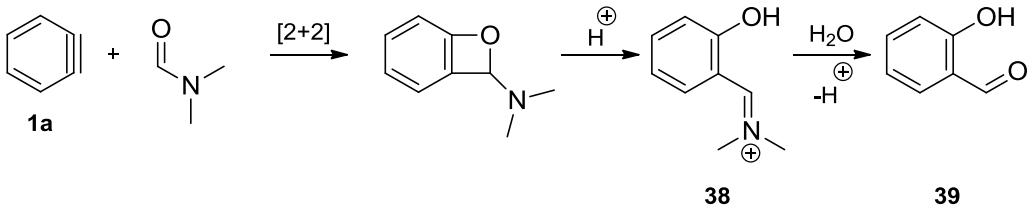
Scheme 41

Of further interest is the possible generation of *ortho*-quinodimethanes (**36**) and *ortho*-quinone methides (**37**) as the result of a retro-[2+2] of the strained 4-membered ring. These intriguing intermediates are suitable dienes for building the carbon skeleton of a number of organic molecules (Scheme 42).[21h]



Scheme 42

Finally, the [2+2]–cycloaddition of DMF with arynes forms the initial oxetane which ring-opens to relieve strain. This generates *ortho*-iminium phenol (**38**) which hydrolyses to *ortho*-formylphenol (**39**) upon aqueous work-up (Scheme 43).[77]



Scheme 43

1.5.2.4 Ene Reaction

The aryne ene reaction competes with the [2+2]-cycloaddition in cases where there is an allylic C-H. The ene reaction is a concerted process that requires an optimum geometry, where the allylic C-H is parallel to the π-system of the olefin (Figure 5).[78]

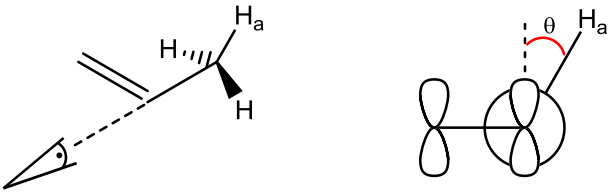


Figure 5

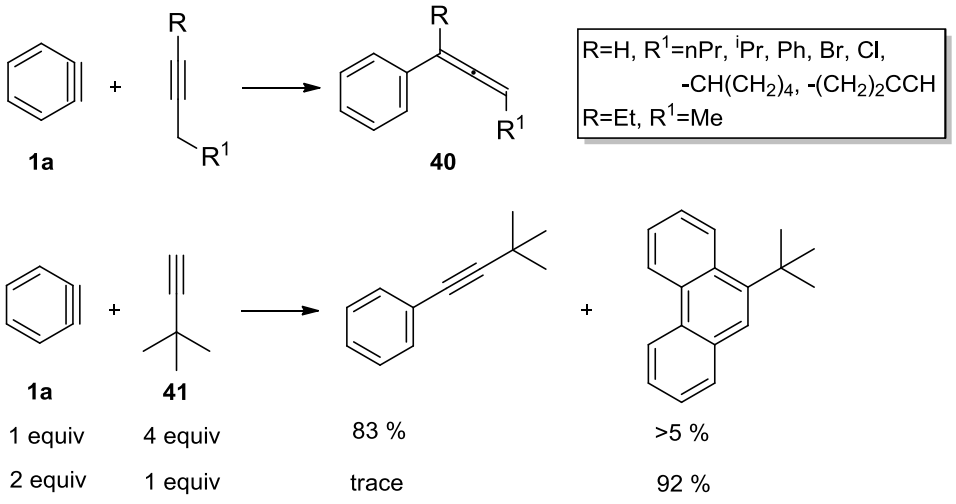
The [2+2] is comparatively insensitive to conformational effects. As such, the ratio of [2+2]:ene products often arises from the ability of the olefin to adopt the desired conformation. This is most prominently observed when considering the product distribution following the reaction of **1a** with cyclic olefins (

Table *1*).[21a]

Table 1

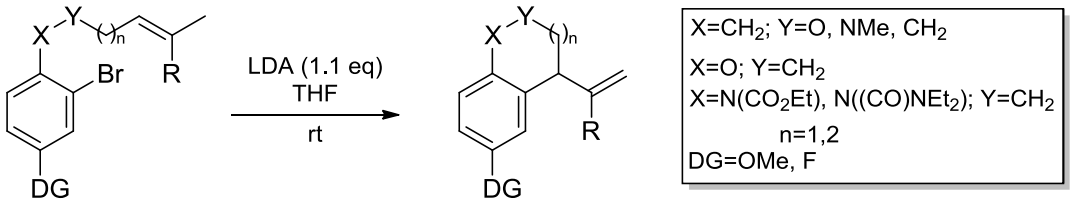
Olefin	Dihedral Angle θ (approx.) (deg.)	Ratio of products, ene:[2+2]
Cyclohexene	4	100:0
Cyclohexa-1,3-diene	5	75:25
Cycloheptane	32	75:25
Cyclohepta-1,3-diene	33	44:56
cycloheptatriene	37	7:97

In addition, the aryne ene reaction is seen to show poor regioselectivity and low yields. Therefore, there are only a limited number of cases in the literature describing successful applications of the ene reaction with arynes until recently.[21a] Cheng showed that intermolecular ene reactions of arynes with alkynes possessing a propargylic hydrogen successfully generate phenylallenes (**40**).[79] It is also interesting to note that when the alkyne did not posess a propargylic hydrogen the products obtained were a mixture of dehydro-Diels-Alder and acetylenic C-H insertion products. The distribution of products depended on the ratio of aryne (**1a**) and alkyne (**41**) (Scheme 44).



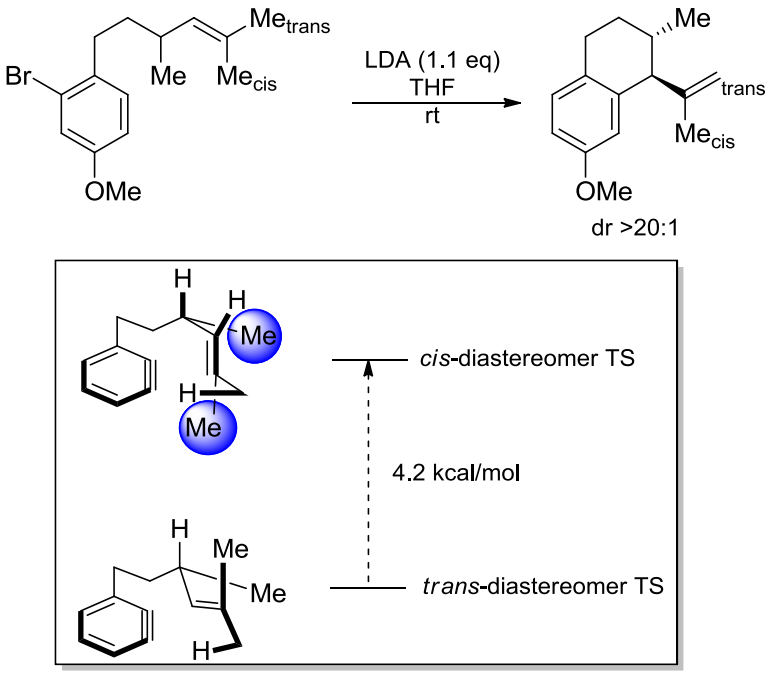
Scheme 44

In an attempt to overcome the problems of the competing [2+2] and subsequent low yields, Lautens demonstrated that by tethering the olefin to the aryne, ene reactions could be successfully performed with high yield and selectivity (Scheme 45).[80a]



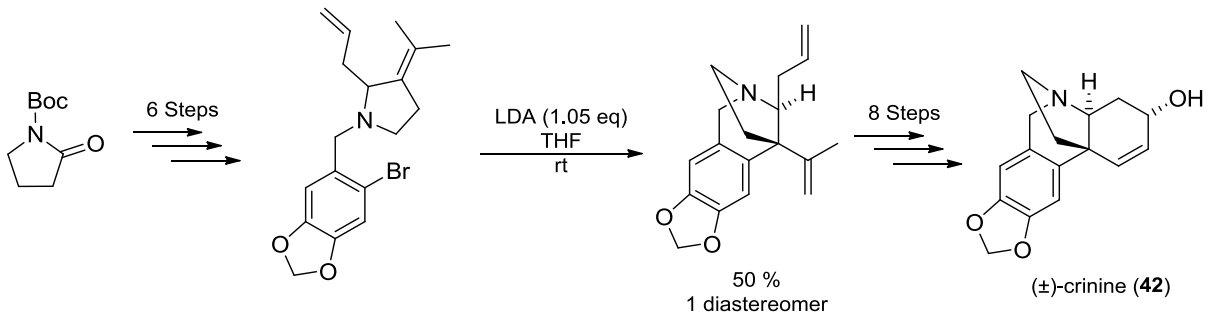
Scheme 45

Density functional theory (DFT) studies conducted in conjunction with this work were useful when considering the course of the reaction. These studies suggested that the ene reaction proceeds in a concerted but asynchronous manner, with the C-C bond forming step being more advanced. Thus, the reaction can be considered as an initial nucleophilic addition from the pendant olefin to the acetylenic aryne bond first. Furthermore, elucidating that the *trans*-allylic C-H migrates was supported by deuterium labelling studies. The DFT studies supported experimental studies in showing that the *trans*-diastereomer would be formed due to a 4.2 kcal/mol difference in the calculated transition states (Scheme 46).



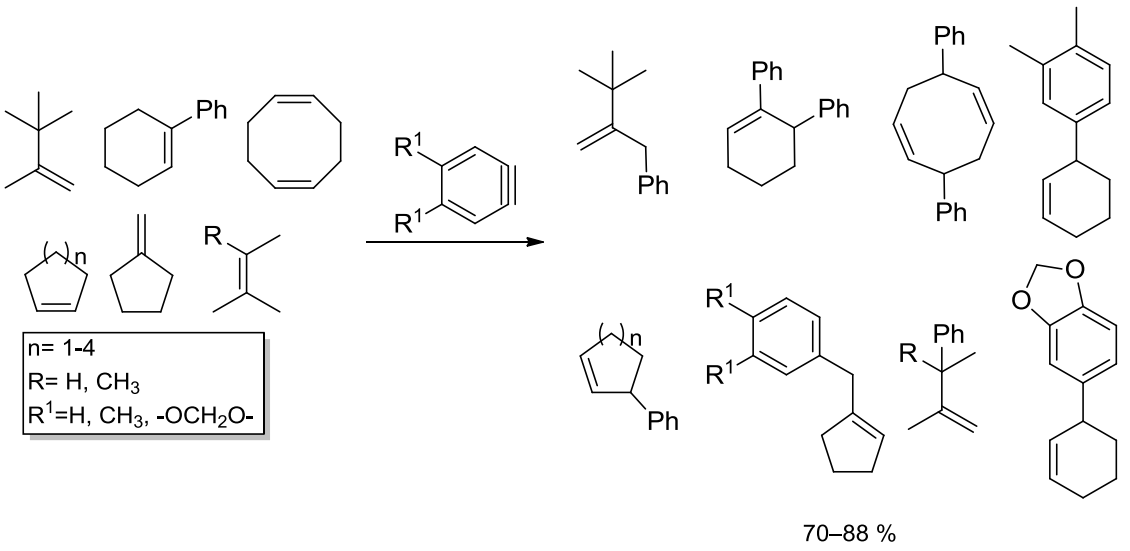
Scheme 46

This work was used in the synthesis of (±)-crinine (**42**) as a key C-C bond forming step (Scheme 47).[80b]



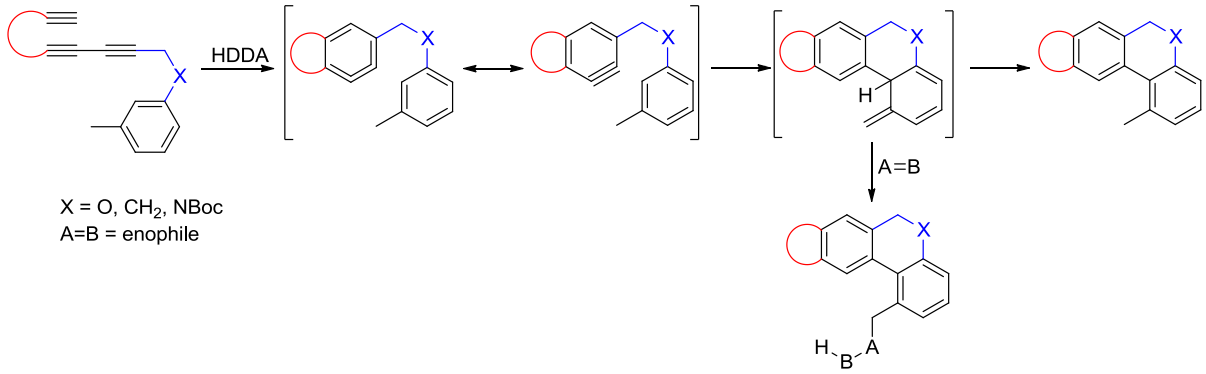
Scheme 47

Yin and Liu *et al.* have investigated the intermolecular aryne ene reaction of olefins showing yields in the range of 70–88 % when conducted with simple cyclic olefins, *exo*-cyclic olefins and substituted butenes. The reaction was shown to be strongly related to the relative proportion of aryne and olefin *in situ* as well as being temperature dependent (Scheme 48).[81]



Scheme 48

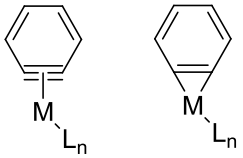
Hoye has also demonstrated using the hexadehydro-Diels-Alder (HDDA) method of aryne generation that pendant tolyl substituents can act as ene donors, which following re-aromatising, results in aryl-aryl bond formation. Furthermore, it was shown that addition of an external enophile could be used to capture the *in situ exo*-methylene cyclohexadiene resulting in functionalisation at the tolyl position (Scheme 49).[45]



Scheme 49

1.5.3 Transition-metal mediated reactions of arynes

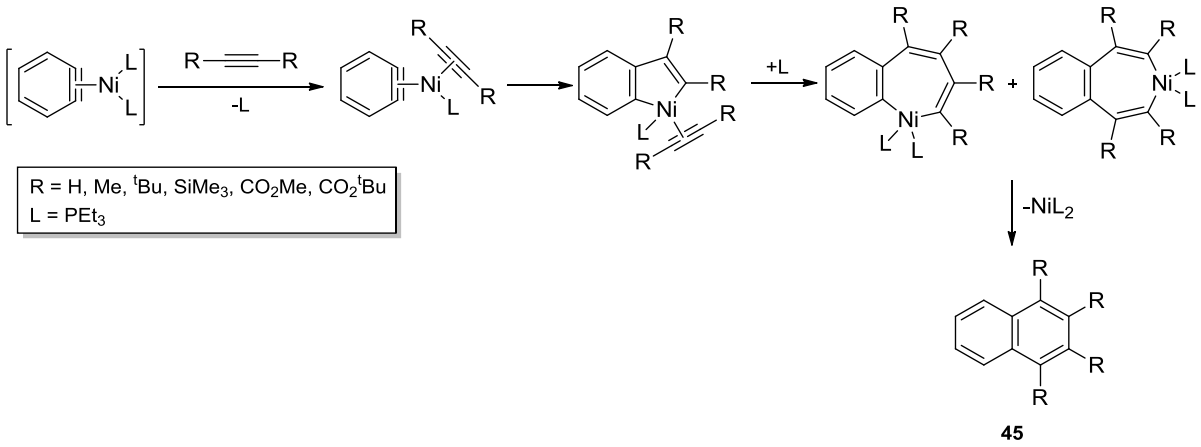
Whilst the generation of transition-metal (TM) coordinated arynes have been known since the mid-1980s, synthetic applications have been slow to follow.[21e,82] The interaction of the aryne acetylenic bond with the metal centre can be envisioned as either a π-complexation (**43**) or bis σ-complexation (**44**) (Figure 6).



43 **44**

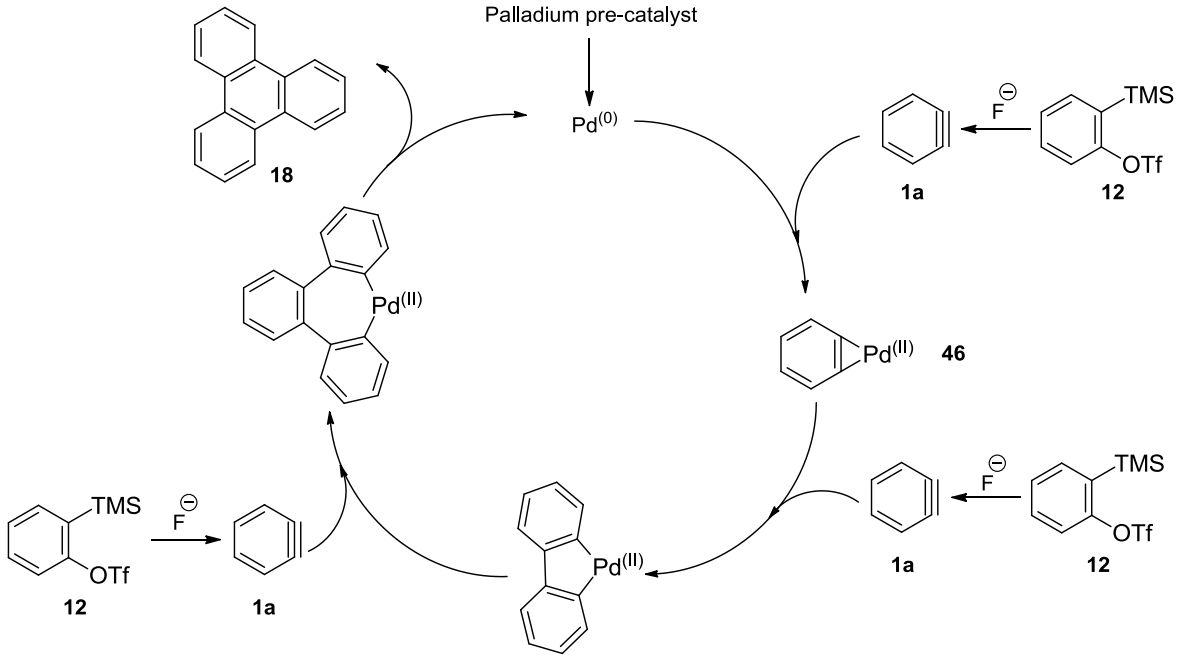
Figure 6

It is important to consider that distinguishing between **43** and **44** is difficult and that TM-mediated reactions of arynes in the literature use both representations almost interchangeably. Mononuclear complexed arynes generally behave as two-electron donor ligands. Bennett showed that a pre-prepared Ni-coordinated aryne complex could be reacted with two equivalents of an alkyne to generate functionalised naphthalenes (**45**) in a proposed [2+2+2]-cyclisation (Scheme 50).[83]



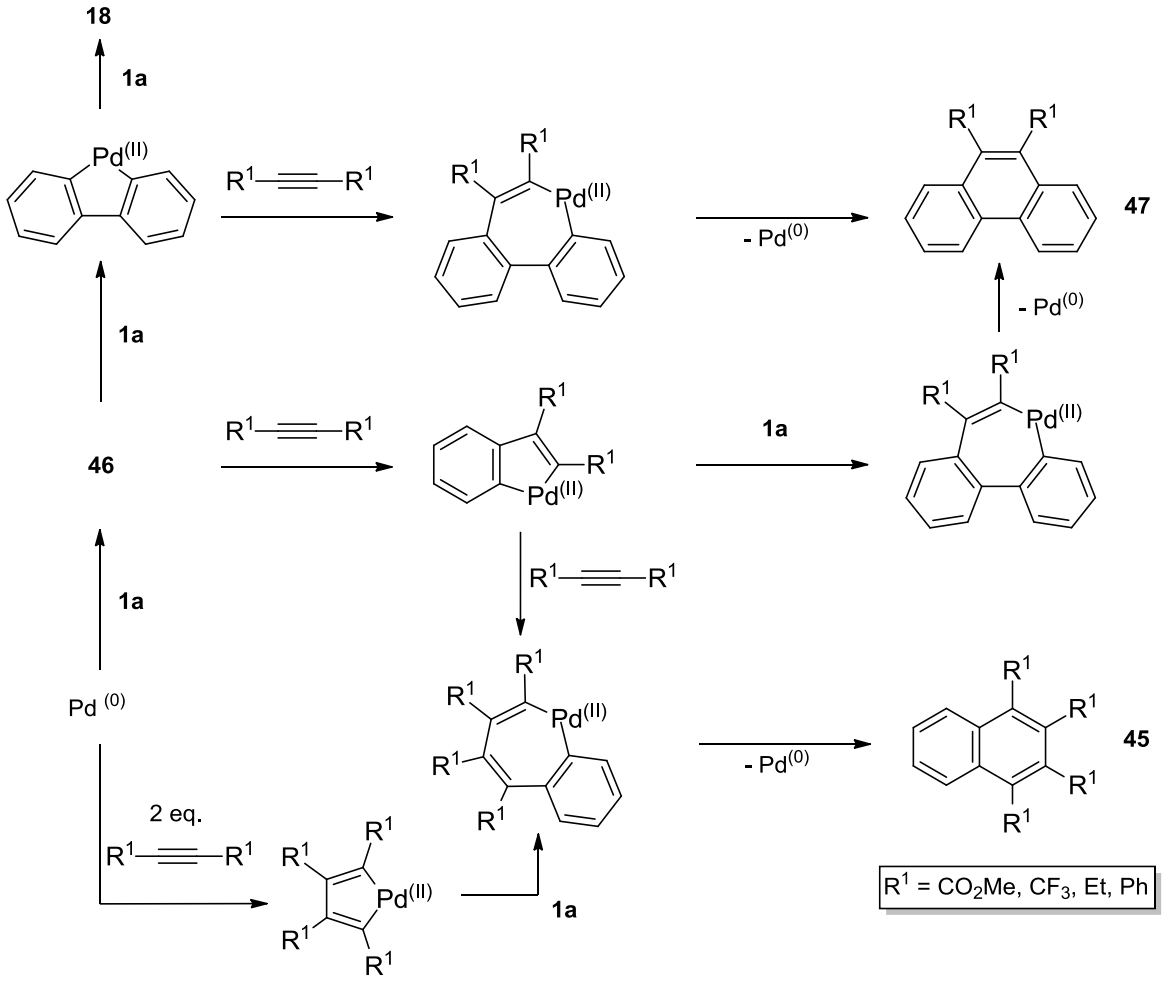
Scheme 50

Guitián was first to describe the cyclotrimerisation of arynes using sub-stoichiometric palladium species following *in situ* aryne generation from **12** to form triphenylenes (**18**) (Scheme 51).[40] This discovery was of great importance as it demonstrated that arynes could be complexed in the reaction and subsequently participate in traditional TM catalytic cycles. The mechanism is proposed to progress through an oxidative addition of free aryne to the $Pd^{(0)}$ species to generate palladacycle (**46**) which following two sequential migratory insertions followed by reductive elimination generates **18** and regenerates the catalytic $Pd^{(0)}$ species.



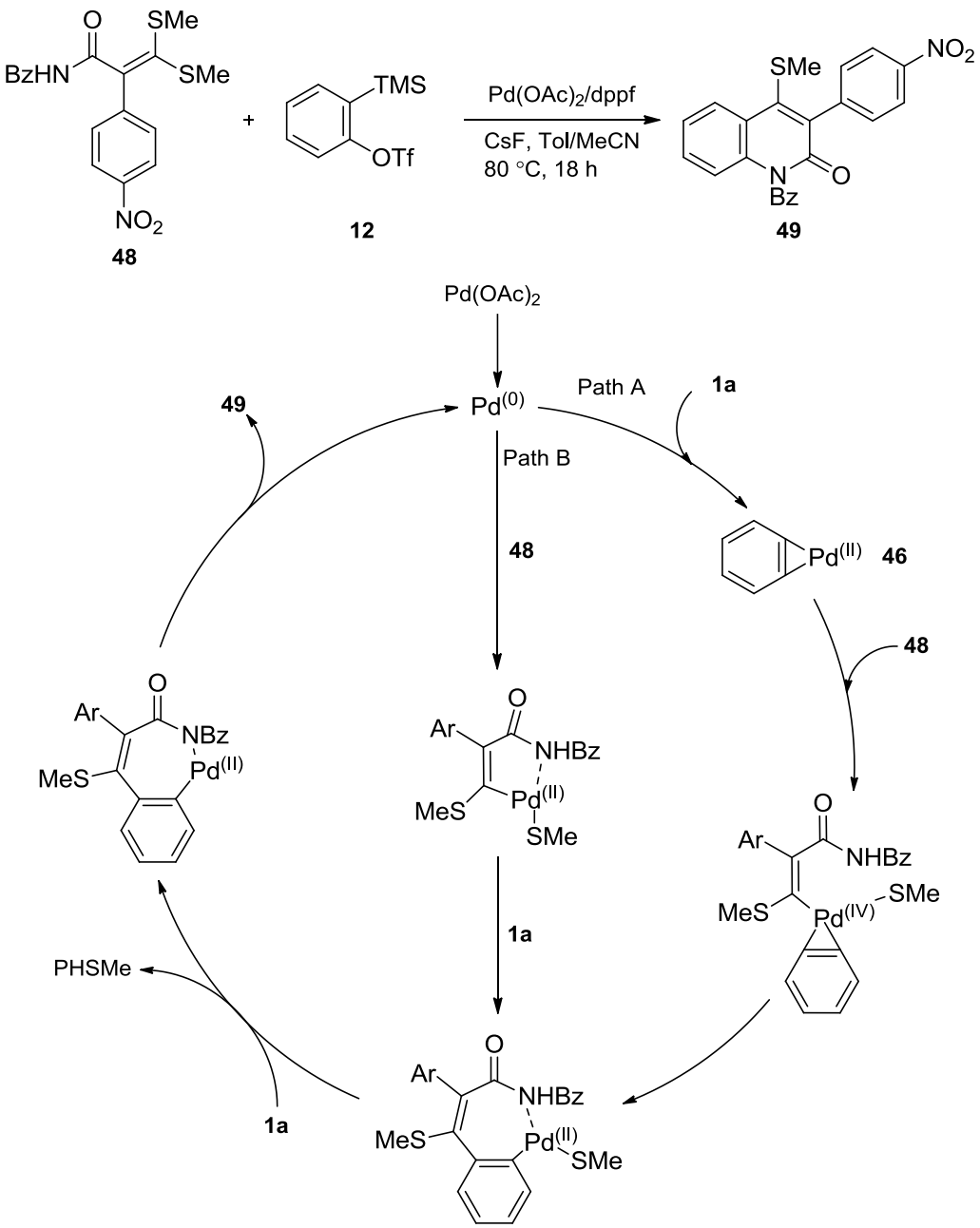
Scheme 51

Further investigations showed that by careful choice of palladium catalyst, co-cyclotrimerisation of arynes with alkynes could be used for the synthesis of **45** (one aryne and two alkynes) and phenanthrene (**47**) (two arynes and one alkyne) derivatives (Scheme 52).[84] Analogous processes have also been reported using alkenes[85] and allenes[86] in the generation of **47** derivatives.



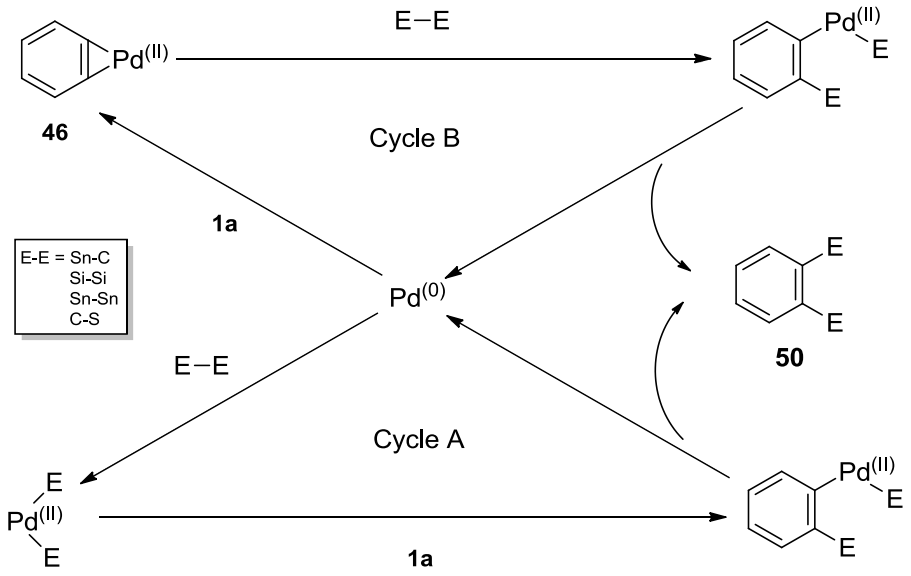
Scheme 52

Insertion reactions have also been shown to be powerful bond-forming steps in transition-metal catalysed reactions of arynes. Examples exploiting palladium catalysis include insertion into Sn-C,[87] Si-Si[88] and Sn-Sn[89] bonds. Carbon-sulfur[90] bond insertion has also been demonstrated however the sulfur component is lost in the course of the reaction (Scheme 53).



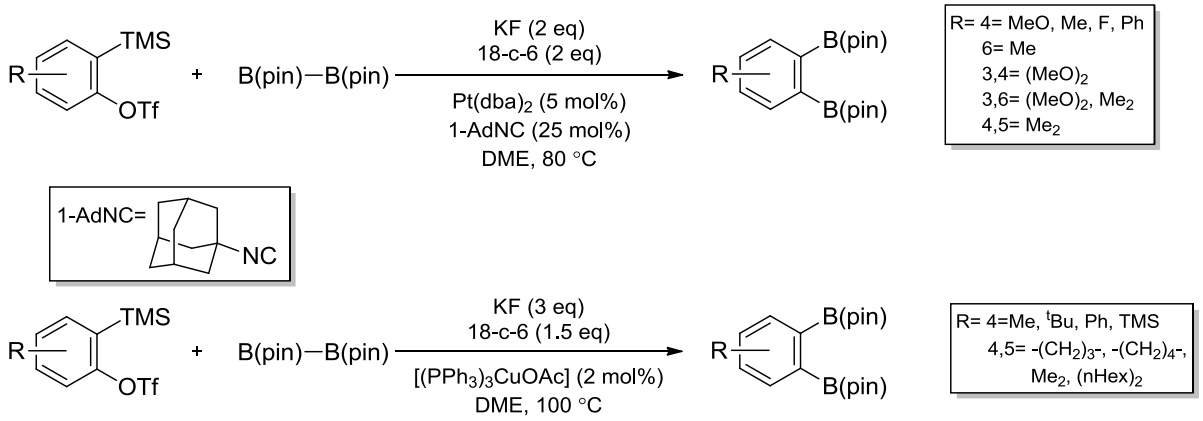
Scheme 53

Mechanistically, two plausible catalytic cycles have been suggested for the former processes (Scheme 54).[21h] Cycle A involves oxidative addition of E-E followed by migratory insertion of **1a** and reductive elimination to give **50**. Cycle B occurs by oxidative addition of **1a** followed by migratory insertion of E-E and reductive elimation to give **50**. Although each of these insertion reactions is not fully understood, there is evidence to suggest that Sn-Sn bond insertion follows cycle A.[89a]



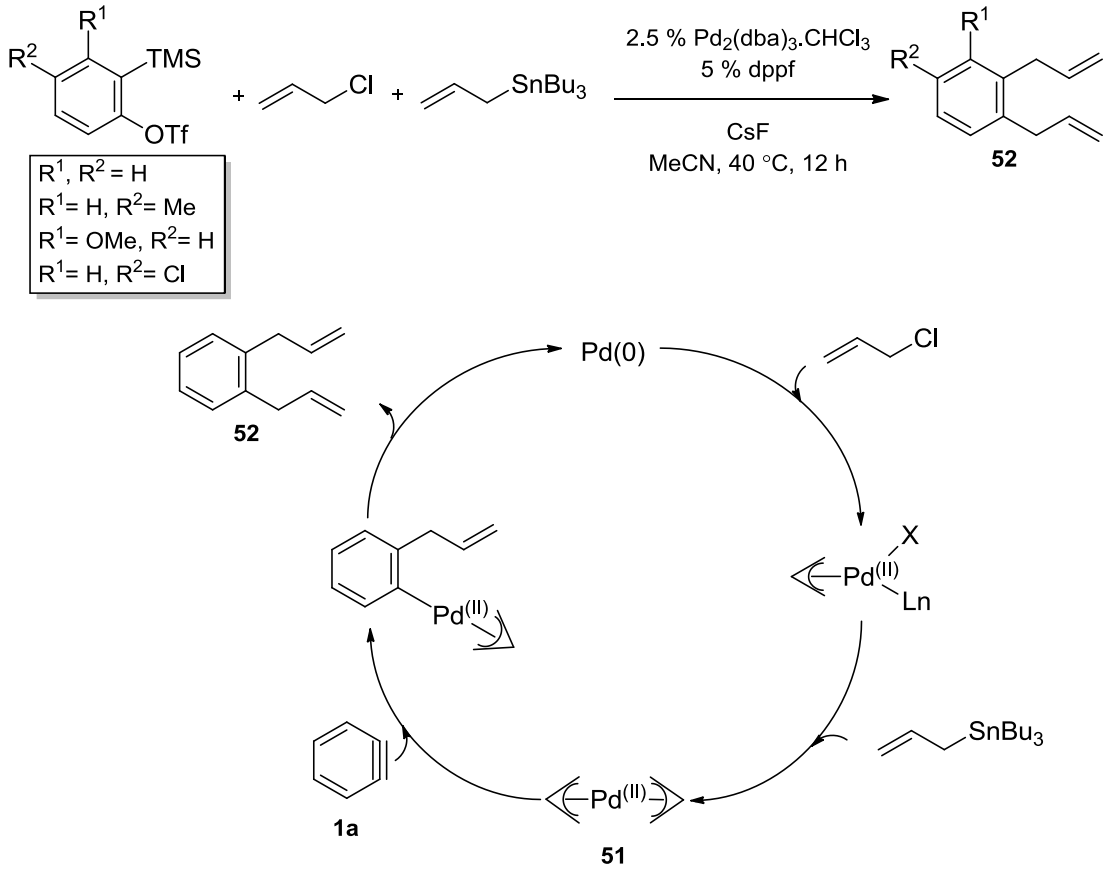
Scheme 54

B-B bond insertion reactions have successfully been performed using platinum[91] and copper[92] as catalysts (Scheme 55).



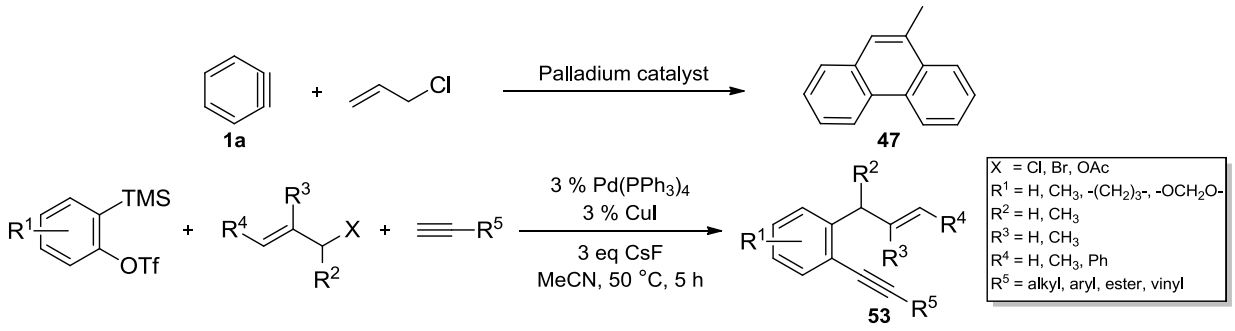
Scheme 55

Finally, transition-metal three-component couplings of arynes are increasingly becoming applicable in generating *ortho*-functionalised C-C bonds. By combining traditional TM-coupling substrates, increasingly complex *ortho*-difunctionalised arenes can be generated. Bis-π-allylpalladium complexes (**51**) generated from allyl chloride and allyltributylstannane generate *ortho*-diallylarenes (**52**) (Scheme 56).[93]

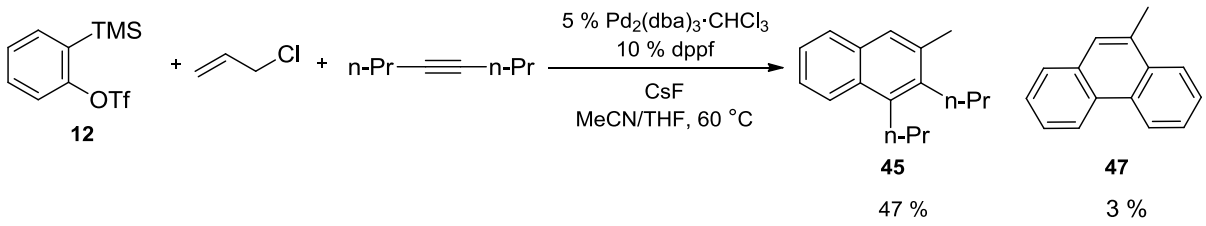


Scheme 56

π-Allylpalladium complexes with arynes generate phenanthrene derivatives (**47**).[94] In combination with copper acetylides generated from cuprous halide and terminal alkyne, *ortho*-allylalkynyl arenes (**53**) are generated (Scheme 57).[95] Using a disubstituted alkyne with π-allylpalladium complex generates a majority functionalised naphthalene (**45**) derived products with a small component **47** derived products (Scheme 58).[96]

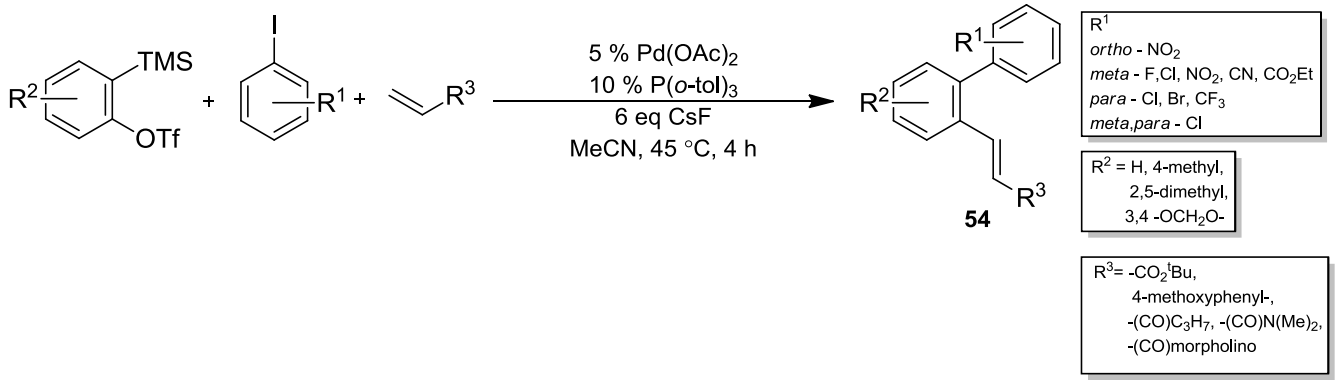


Scheme 57

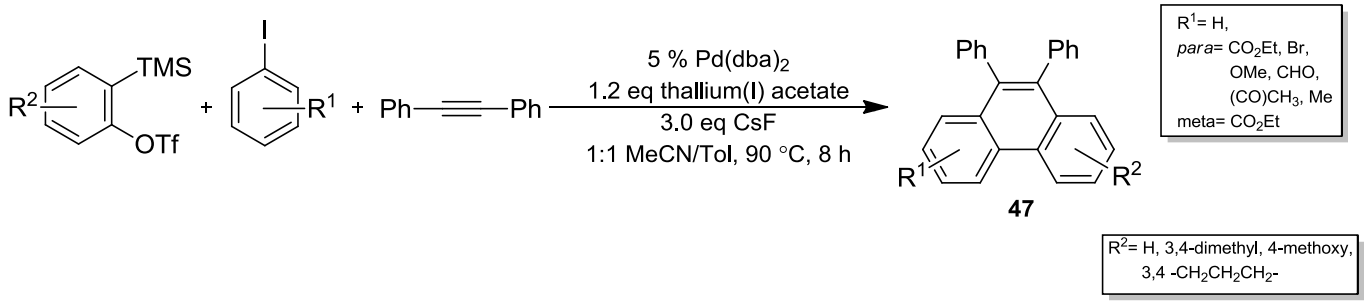


Scheme 58

Coupling of aryl halides with alkenes or internal alkynes results in the formation of *ortho*-arylstyrene (**54**)[97] (Scheme 59) and **47** derivatives respectively (Scheme 60).[98]



Scheme 59



Scheme 60

1.6 Regioselectivity

Due to the symmetrical nature of the aryne triple bond, addition of a nucleophile can occur at either end; when considering reactions with un-substituted or symmetrically substituted benzynes and arynes (e.g. 2,3-napthyne) only one regiochemical outcome is possible. However, in the case of

unsymmetrical benzynes or arynes (e.g. 1,2-napthyne (**55**), pyridynes, indolynes) two regioisomers can be formed. Observed regioselectivities have traditionally been attributed to a combination of steric and/or electronic effects. For example, in the case of 3-methoxybenzyne (**56**), addition occurs with high regioselectivity at C1. This can be summarised as a combination of the steric repulsion by the methoxy-substituent and the inductive electron withdrawing nature of the methoxy- substituent. 4-Fluorobenzyne (**57**) shows high regioselectivity to addition at C1 due to the strong electron-withdrawing nature of the fluorine polarising the aryne triple bond. This generates a partial negative charge at the C2 and a partial positive charge at C1. Bulky 3-substituted benzynes, such as ^{t}Bu or phenyl and **55**, favour addition at the least hindered position; this is C1 for the benzynes due to repulsion from the substituent at C3 and C2 for **55** due to repulsion from the *peri*-hydrogen (Figure 7).[21g,h]

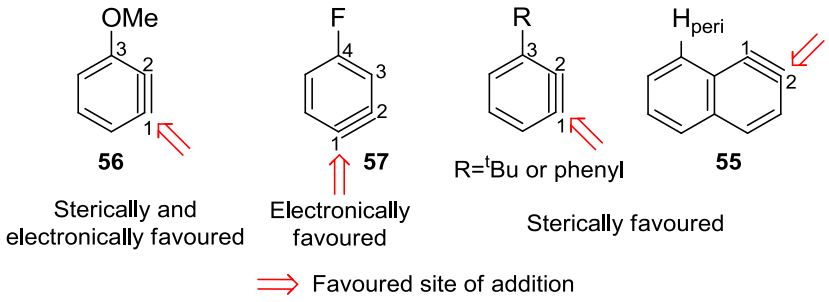


Figure 7

Alternatively, regioselective mixtures can be encountered when applying this is model. For instance 3-methylbenzyne (**58**) sterically favours addition at C1 but the electron donating nature of the methyl substituent makes C1 more electronegative thus favouring addition at C2. This often results in no overall regioselectivity (Figure 8).

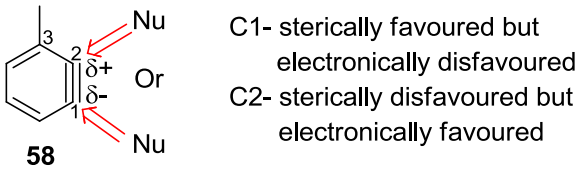


Figure 8

Furthermore, 4-substituted benzynes inherently show a mix of regioisomers, with the previously discussed fluoro-substituent being an exception, as neither the possible steric or electronic nature of

the substituent has a strong enough effect on the regioisomeric outcome due to the remote nature of the substituent (Figure 9).

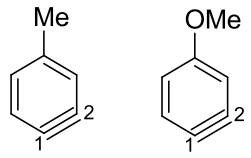


Figure 9

It is also important to consider that using this model to aid the prediction of regioselectivity can be inherently flawed by its simplicity in viewing the substituents. For example, Suzuki showed 3,4-cyclic substituted benzynes exhibit a change in regioselectivity with increasing size of the substituent ring. Fused cyclobutanes (**59**) exhibited regioselectivity for addition at C1, whereas fused cyclopentanes (**60**) showed no selectivity and fused cyclohexanes (**61**) showed reasonable selectivity for C2 (Figure 10).[99]

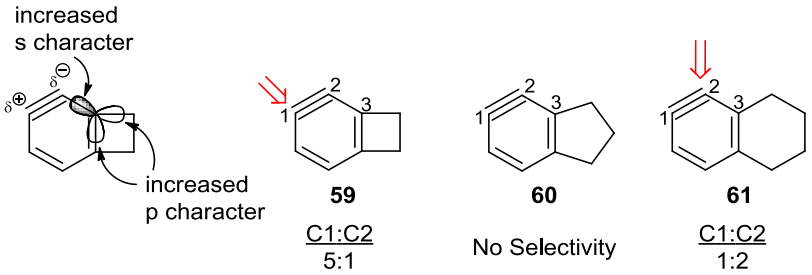
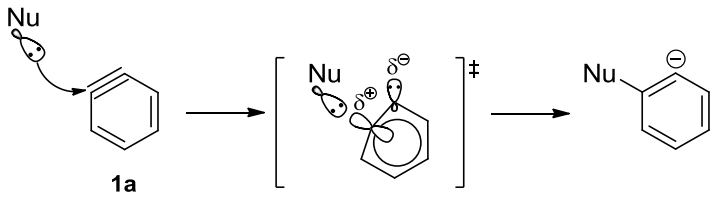


Figure 10

Suzuki reasoned that the regioselectivity originated from the ring strain caused by the substituent ring. In the case of **59**, C3 re-hybridised to use orbitals of higher p-character in bonding the strained ring, leaving the remaining orbital with higher s-character. By exhibiting a greater s-character, an increased electronegativity is observed in the C3-C2 bond rendering C1 comparatively electron-deficient. As **60** and **61** have significantly less ring-strain this rehybridisation doesn't occur, thus the same regioselectivity is not exhibited. However, by using the previous model no overall regioselectivity would be predicted to be observed.

Garg and Houk *et al.* have shown that regioselectivity can be predicted by application of a DFT model to reactions of arynes.[100] By modelling nucleophilic addition to benzyne (**1a**) it was observed that the site of addition was significantly flattened in the transition state, thus exhibiting an increased p-

character. As such, the internal bond angle at the adjacent position was compressed, therefore exhibiting increased s-character to stabilise the developing carbanion (Scheme 61).



Scheme 61

Upon examining the ground state of asymmetrical arynes it was observed that there is geometric distortion around the arynes triple bond. It can therefore be predicted that nucleophilic addition occurs at the carbon of the aryne that requires the least geometric and energetic change from aryne to transition-state, or simply, addition occurs at the position with the larger internal angle. Using this DFT model it is possible to display how the arynes that have previously been discussed exhibit their regioselectivity (Figure 11). As shown for the cyclic substituted benzynes there is a clear trend highlighted by addition to the aryne terminus with the DFT calculated larger bond angle. This is also reflected in the case of 3-methoxybenzyne (**56**). In addition, computed Mulliken charges show that nucleophilic attack is favoured at the flatter, more electropositive terminus of **56**. As displayed in the case of **60** there is little distortion of the internal bond angle, resulting in poor regioselectivity.

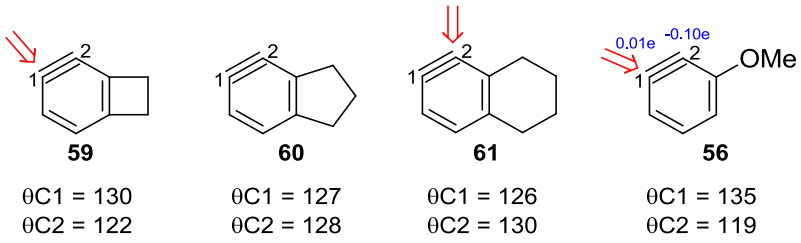


Figure 11

This DFT model has also been used to predict and manipulate regioselectivities in indolyne and pyridyne models. Indolyne has three possible aryne regioisomers: 4,5-indolyne (**62**), 5,6-indolyne (**63**) and 6,7-indolyne (**64**), with the calculated difference between the internal bond angles of each being 4º, 2º and 19º respectively. Experimental studies, following DFT predictions, have shown that the difference in internal bond angle between the two aryne termini must differ by ≥4º to display a synthetically useful level of regioselectivity, although variations are seen depending on the trapping agent.[101] To obtain greater regioselectivity for **62**, bromination at C3 (**65**) resulted in increased

regioselectivity in favour of addition at C5. In contrast, bromination at the 6-position (**66**) resulted in the favoured attack switching to C4 (Figure 12).[102]

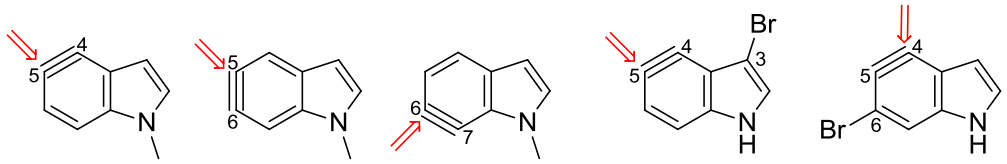
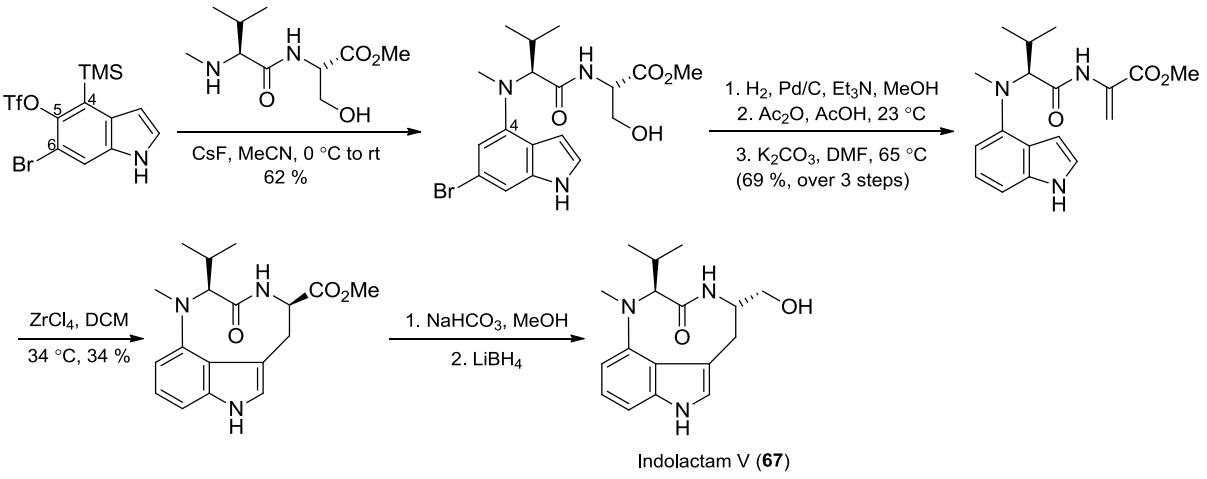


Figure 12

In the case of **66**, it was reasoned that the bromine atom switches regioselectivitiy to C4 due to a combination of indolyne distortion and bromine steric effects. This methodology was exploited in the key bond-forming step in the synthesis of indolactam V (**67**), showing addition of the dipeptide to **66** occurs with <5 % addition at C5 (Scheme 62).[103]



Scheme 62

In the case of pyridyne two aryne regioisomers are possible: 2,3-pyridyne (**68**) and 3,4-pyridyne (**69**). 2,3-Pyridyne is shown to favour regioselective addition at C2 (calculated difference in internal bond angles of 47º) whereas regioselectivity of 3,4-pyridine is very poor (calculated difference in internal bond angles of <1º). Applying DFT predictions shows bromination at C5 (**70**) would favour attack at C3. Sulfamoylation at C2 (**71**) would favours attack at C4 (Figure 13).[104]

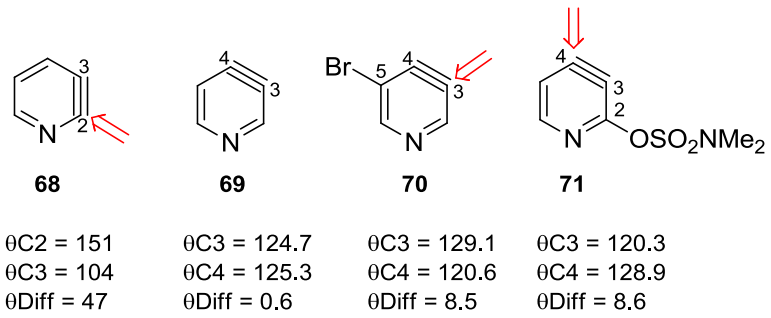
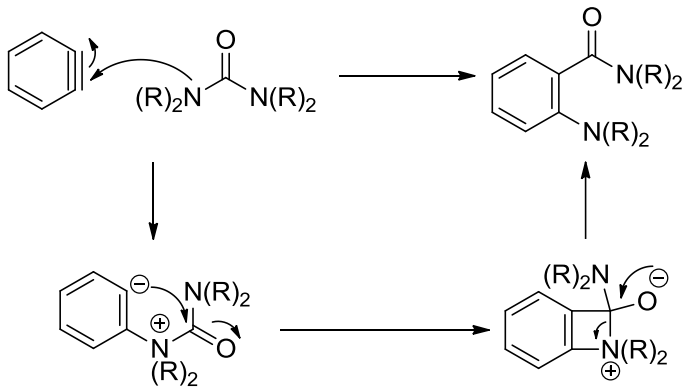


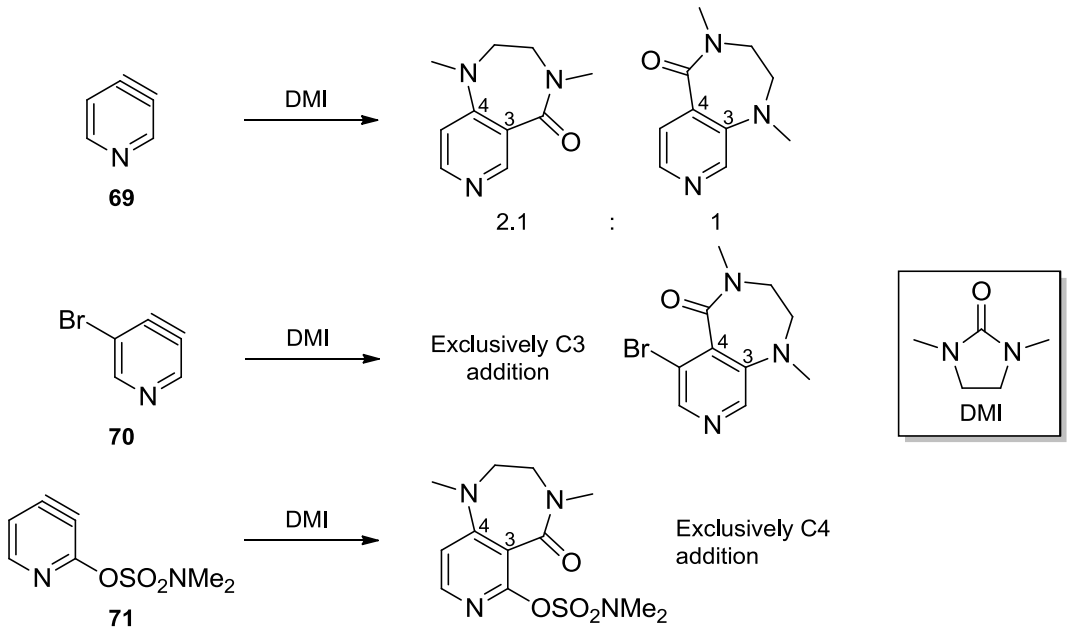
Figure 13

The increased selectivity in these functionalised 3,4-pyridynes is best demonstrated when considering the reaction of **69**, **70** and **71** with 1,3-dimethyl-2-imidazolidinone (DMI). The reaction of arynes with ureas result in a formal C-N bond insertion following a stepwise addition/fragmentation process (Scheme 63).[105]



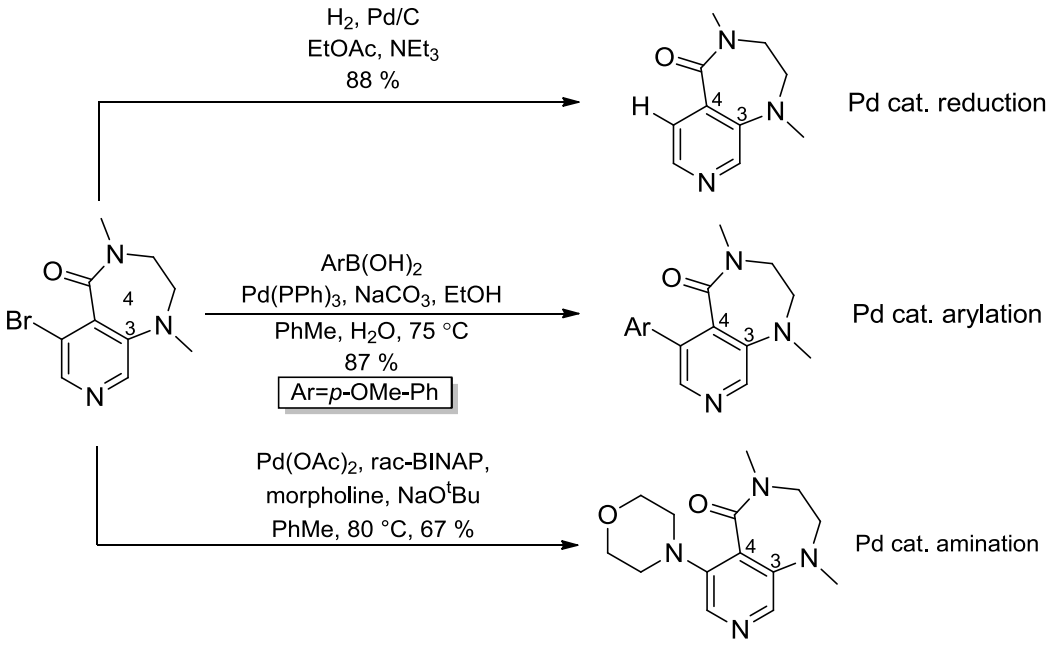
Scheme 63

The unfunctionalised 3,4-pyridyne **69** when reacted with DMI results in a 2.1:1 mixture of benzodiazepines favouring addition at C4 while C5 brominated analogue **70** shows exclusive selectivity for C3 addition and C2 sulfamoylated analogue **71** shows exclusive selectivity for C4 addition (Scheme 64).[104]

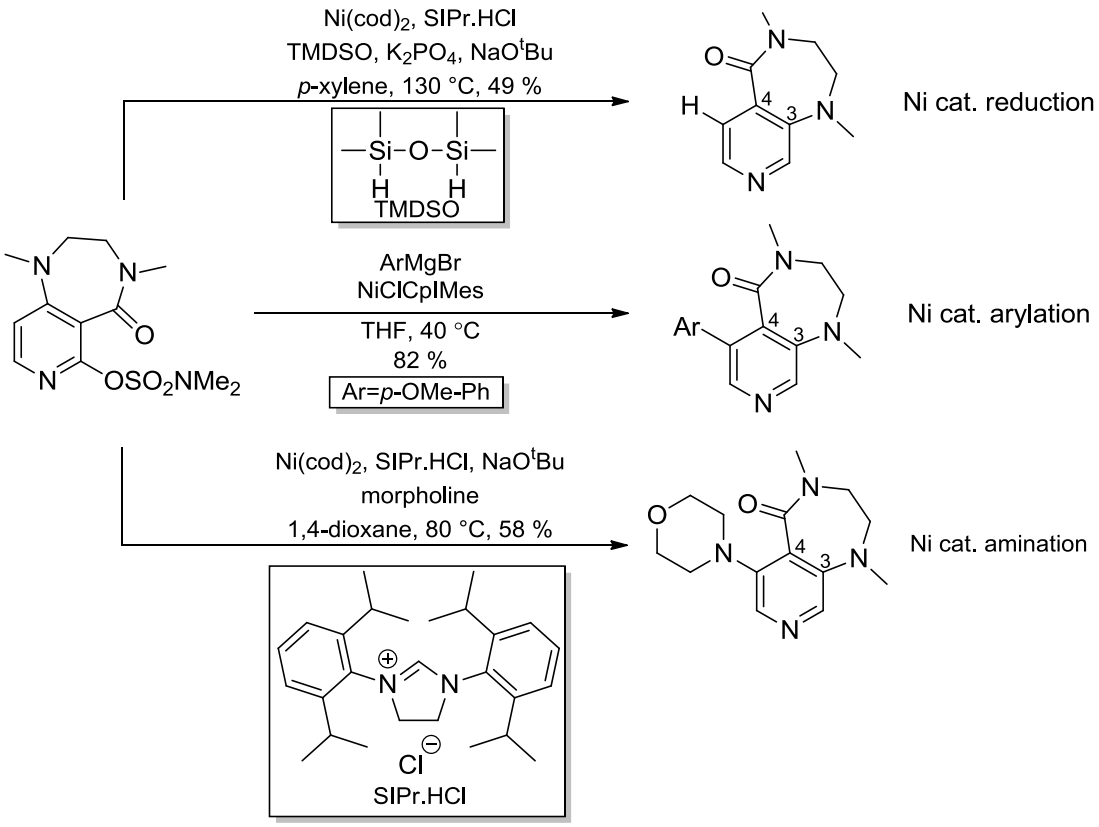


Scheme 64

These benzodiazepines were subsequently used as model systems to demonstrate the utility of functionalising at the pyridyl bromide and pyridyl sulfamate positions following aryne trapping using palladium catalysis (Scheme 65) and nickel catalysis (Scheme 66) respectively.



Scheme 65


Ni(cod)2, SIPr.HCl
TMDSO, K2PO4, NaOtBu
p-xylene, 130 °C, 49 %
TMDSO
Ni cat. reduction
ArMgBr
NiClCpIMes
THF, 40 °C
82 %
Ar=p-OMe-Ph
Ni cat. arylation
Ni(cod)2, SIPr.HCl, NaOtBu
morpholine
1,4-dioxane, 80 °C, 58 %
Ni cat. amination
SIPr.HCl

Scheme 66

CHAPTER 2: RESULTS AND DISCUSSION

2.1 Diphenyliodonium-2-carboxylate as a readily-accessible benzyne precursor

2.1.1 Introduction

Despite over a century of research, arynes remain predominantly of academic interest with few applications in industry.[106] As shown, arynes can play a powerful role as a unique *synthon* in synthetic methodology leading to bond-forming reactions orthogonal to those of traditional aromatic chemistry.[21] The reason for this poor industrial up-take, in addition to the previous poor understanding of aryne regioselectivity,[104] can be attributed to the method of aryne generation and specifically to the development of Kobayashi's *ortho*-silyltriflate (**12**) aryne precursor.[32] The application of this methodology is greatly precluded due to the expensive and laborious preparation of the starting material.[37] In addition, the hydrolytic instability of phenyl-triflates, leading to the potential formation of genotoxic triflic acid and use of stoichiometric fluoride (a Lewis and Brϕnsted base) have been further contributing factors.[21o] Other potential methodologies have also shown poor up-take due to either: generation using stoichiometric organometallic base or toxic oxidant, or poor stability of the starting material.

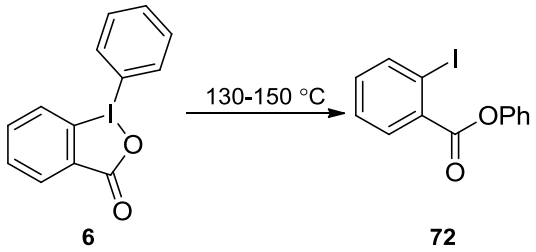
Diphenyliodonium-2-carboxylate (**6**) has been shown to decompose to benzyne at temperatures greater than 160 ºC. The problems associated, however, with high-temperature methodologies such as the use of high b.p. solvents and poor substrate compatibility has impeded its widespread use as a benzyne precursor among academic and industrial communities.[27] Despite this, **6** has a number of favourable qualities as a benzyne precursor; it is thermally and hydrolytically stable, the synthesis is inexpensive and is also suitable for multi-gram scale production. Furthermore, benzyne generation neither requires nor produces toxic compounds.[107] For these reasons we have examined **6** as a potential benzyne precursor and aim to apply contemporary synthetic methods to the generation of benzyne from **6**.

Since the first publications in the mid-1980s, microwave reactors have become increasingly ubiquitous in academic and industrial fields.[108] By using microwave heating, energy is applied directly to the reaction components allowing for an even and reproducible transfer of energy when compared to conventional conductive heating which applies thermal energy to the reaction vessel.[109] Microwave heating is achieved by one of two mechanisms; dielectric heating or conductive heating. Dielectric heating requires the reaction components, either solvent or solute, to possess a dipole moment. When microwave energy is applied, the dipole of the molecules will align with the electric field by rotation; as the field oscillates the individual dipoles try to realign with the field. This leads to energy loss by molecular friction and collisions, resulting in heating. Alternatively, ions will traverse through a solution when microwaves are applied, following the electric field, resulting in an increased number of collisions converting their kinetic energy into heat; this is the conductive mechanism of microwave

heating and it is more significant than dipolar polarisation with regards to the overall heating effect.[110] The necessity for ions or polar molecules in the reaction mixture for microwave heating to occur makes the solvent choice an important one. Solvents can be compared by their relative loss angles δ, which takes into account their ability to couple with microwave radiation, dielectric constant ε', and their efficiency in converting microwave energy to heat, loss factor ε''. This relationship is expressed by the equation $\tan \delta = \varepsilon''/\varepsilon'$. A higher loss tangent, $\tan \delta$, implies the solvent is better at coupling microwave radiation and generating heat.[111]

During dielectric heating of a pure solvent, the suppression of boiling nuclei can result in solvents surpassing their standard boiling point. This phenomenon of solvent superheating can be sustained as long as microwave radiation is applied and can result in the boiling point being raised by up to 26 ºC.[110] The presence of substrates and ions can act as seeds for boiling nuclei formation, subsequently returning the boiling point to normal and suppressing this superheating effect. The increased rate of heating by using microwaves combined with sealed microwave vessels can result in the superheating of solvents as a product of the ideal gas law, PV = nRT. This ability to superheat reactions solvents has been considered responsible for the observed rate increases in solution phase microwave reactions.

By applying microwave methodology to the decomposition of **6** we expected to alleviate the problems traditionally associated with the generation of benzyne using this protocol. In addition to the already highlighted advantages of using microwave heating over conventional heating we hope to limit a comparatively slow but competing side reaction observed when generating benzyne from **6**. Between 130-150 ºC **6** is known to decompose slowly to phenyl *ortho*-iodobenzoate (**72**), while benzyne formation is achieved at temperatures greater than 160 ºC (Scheme 67).[107a]



6 **72**

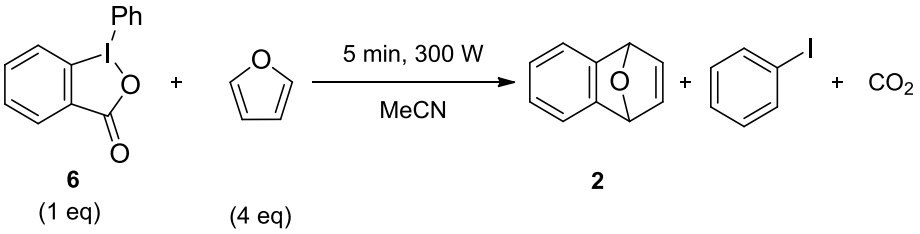
Scheme 67

By applying microwave methodology to this reaction the rate of heating will be faster than conventional heating during the initial temperature ramping on commencing the reaction. This will minimise the time during which the temperature is within the range for this competing side reaction to occur, thus alleviating this as a problem.

2.1.2 Investigation

We began by initially testing the decomposition of **6** under microwave heating conditions using acetonitrile as a solvent and furan as our benzyne trap. Acetonitrile is known to be an ideal microwave solvent, due to its large loss tangent (0.659),[110] as well as being previously applied in aryne methodologies using other aryne generation protocols.[21n] We chose furan as a trap for two reasons; firstly furan is the standard reagent used in assessing the generation of arynes as the subsequent Diels-Alder reaction with aryne intermediates is well documented and facile. Secondly, due to the high temperatures required to decompose **6** to benzyne and the relatively low b.p. of furan (31.3 ºC) this reaction has not been performed using conventional heating and analogous higher bp furan traps have been used instead.[107a] Subsequently, we felt that if this reaction could be performed it would prove the efficacy of using **6** under these conditions to generate benzyne despite the perceived drawback of requiring a high decomposition temperature. To test our hypothesis a screen of reaction temperatures was performed (Table 2).

Table 2



6 (1 eq) (4 eq) **2**

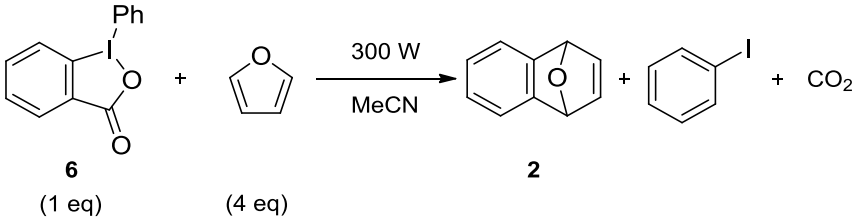
Entry	Temperature (ºC)	Yield of Isolated product 2 (%)[a]
1	150	0
2	160	9
3	170	15
4	180	18
5	190	28
6	200	58

a) Isolated yield based on molar conversion of **6** to **2**.

Successful generation of **2** by this protocol was encouraging. Direct analysis of the results shows a clear trend in the isolated yields with increasing temperature once above the reaction temperature

threshold (entry 2). Attempts to analyse further the extent of this trend by increasing the reaction temperature to 210 ºC highlighted a limitation in the chosen microwave reactor; at the operational limit of 300 W this temperature could not be achieved. It is important to note that entries 2 and 3 did not reach full conversion after 5 minutes and **6** was still present. Furthermore, the analogous process using non-microwave methodology would take up to two hours to reach completion.[27] With this in mind a screening of reaction run-times was performed to achieve a full decomposition of **5** at an ideally lower reaction temperature. In addition, we increased the run-time of the highest yielding reaction temperature (entry 6) to see if this would increase the isolated yield.

Table 3

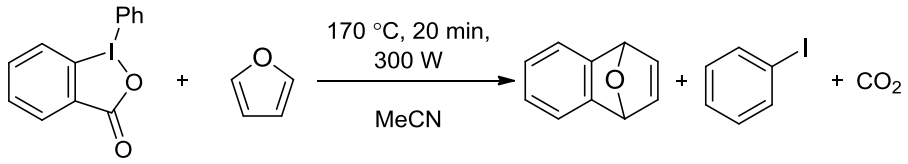


Entry	Temperature (ºC)	Run-time (min)	Yield of Isolated Product 2 (%)[a]
1	200	10	43
2	170	10	29
3	170	15	45
4	170	20	45
5	170	25	47
6	160	10	44
7	160	25	43

a) Isolated yield based on molar conversion of **6** to **2**.

Table 3 shows that increasing the run-time for reactions performed at 200 ºC (entry 1) has no beneficial effect on the isolated yield. This is expected as after 5 min full conversion of **6** was previously observed. In the case of entries 2-7 the increased run-time leads to an increase and subsequent plateau in the isolated yields. We believed this plateau to be a result of the ratio of furan trapping agent to free generated benzyne; we therefore performed a screen whereby the ratio of **6**:furan was explored. The conditions performed in entry 4 were chosen for this screen.

Table 4



6 **2**

Entry	5 (eq)	Furan (eq)	Yield of Isolated Product 2 (%)[a]
1	1	3	48
2	1	10	57
3	1.5	1	14
4	2.0	1	16

a) Isolated yield based on molar conversion of **6** to **2**.

The results observed in Table 4, entry 2 show furan to be the limiting reagent when benzyne generation is performed using this protocol. It is also important to observe that despite the increased run-time and furan equivalences that the isolated yield obtained is still comparable to Table 2, entry 6, therefore suggesting that generation of benzyne from **6** may occur faster and subsequently result in higher yields if performed for a shorter reaction time at a higher temperature. It was therefore decided to halt this project due to the limitations of the available microwave reactor.

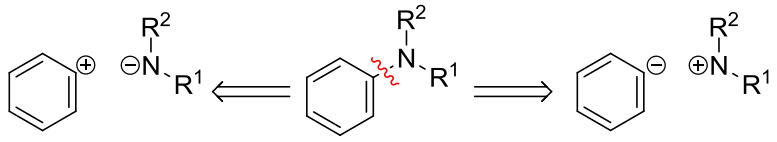
2.1.3 Conclusion

It has been shown by proof of concept microwave reactions that diphenyliodonium-2-carboxylate (**6)** can be a readily-accessible benzyne precursor, with the inherent advantages being its thermal and hydrolytic stability as well as being inexpensive to produce. By using a microwave protocol the trapping of benzyne generated from **6** with furan has been performed for the first time as a suitable example of the benefit of using this method over conventional heating. The results obtained are encouraging, however the power limitations of the available microwave reactor highlight the potential limitations of this protocol.

2.2 Novel cascade aryne-capture/rearrangement reactions

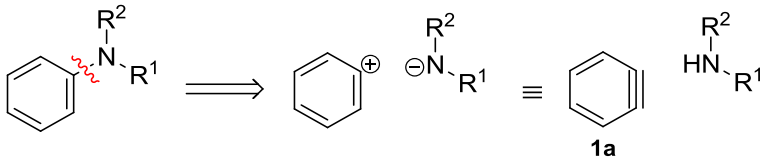
2.2.1 Introduction

Direct amination of arenes still proves a problematic protocol in contemporary organic synthesis due to the inherent requirement for an *umpolung* interaction of either the arene or amine *synthon* (Scheme 68).



Scheme 68

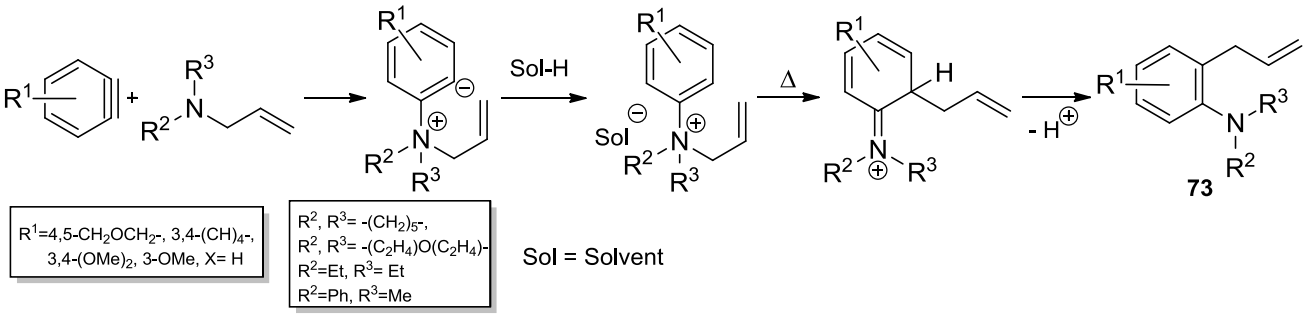
This retrosynthetic disconnection using aryne methodology, however, results in the generation of *synthons* whereby in the forward sense addition of a nucleophilic amine to an electrophilic aryne bond is favoured (Scheme 69).



1a

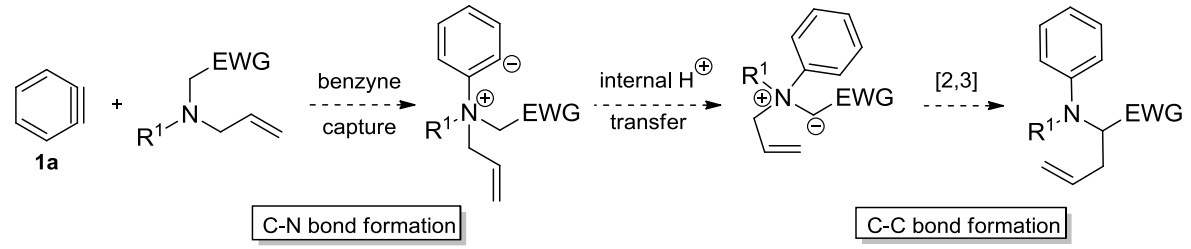
Scheme 69

An example of amination by aryne capture is the benzyne aza-Claisen reaction described by Greaney.[112] This reaction proceeds by nucleophilic addition of a tertiary allylamine to an aryne; the resulting zwitterion is subsequently quenched by the solvent to generate an allylammonium salt, which undergoes a charge-accelerated aza-Claisen rearrangement at elevated temperatures to generate an *ortho*-allylaniline (**73**) (Scheme 70).



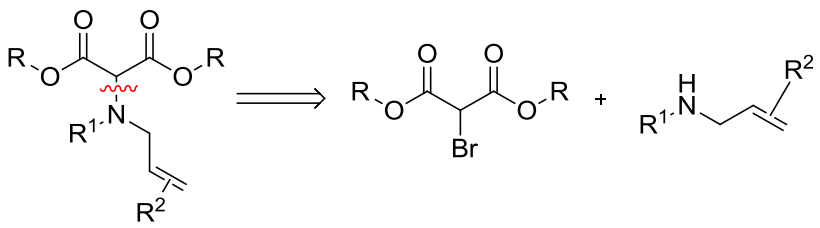
Scheme 70

We proposed that by functionalising the tertiary allylamine with a suitable electron-withdrawing group (EWG) the aza-Claisen reaction could be circumvented in favour of a [2,3]-rearrangement *via* a stabilised ammonium ylide, generated by intramolecular proton transfer (Scheme 71).



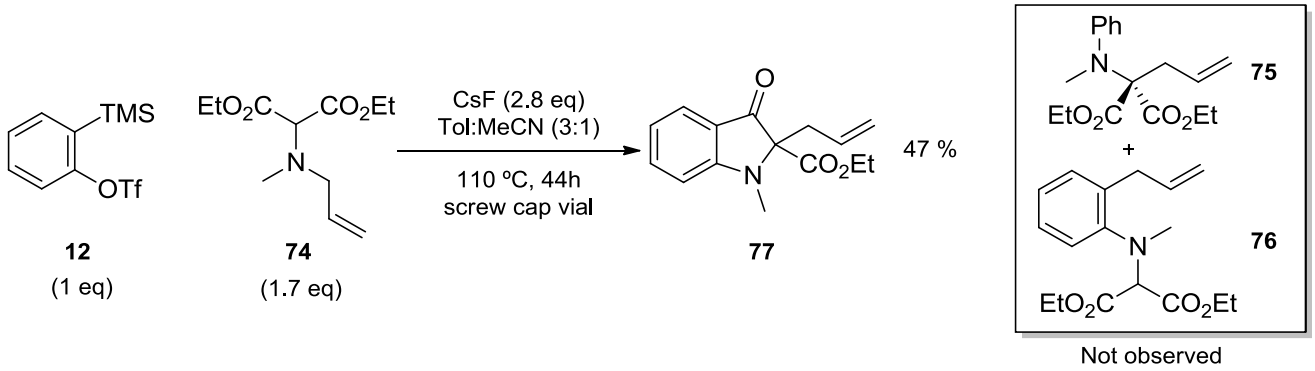
Scheme 71

To facilitate the proton transfer as desired, malonic esters were employed as the EWG. The pKa of the adjacent proton of the intermediate ammonium species would be ~11.8 (DMSO), strongly favouring proton transfer from this position.[113] In addition, synthesis of the tertiary aminomalonate can be easily achieved by the reaction of secondary allylamines with dialkyl bromomalonate (Scheme 72).



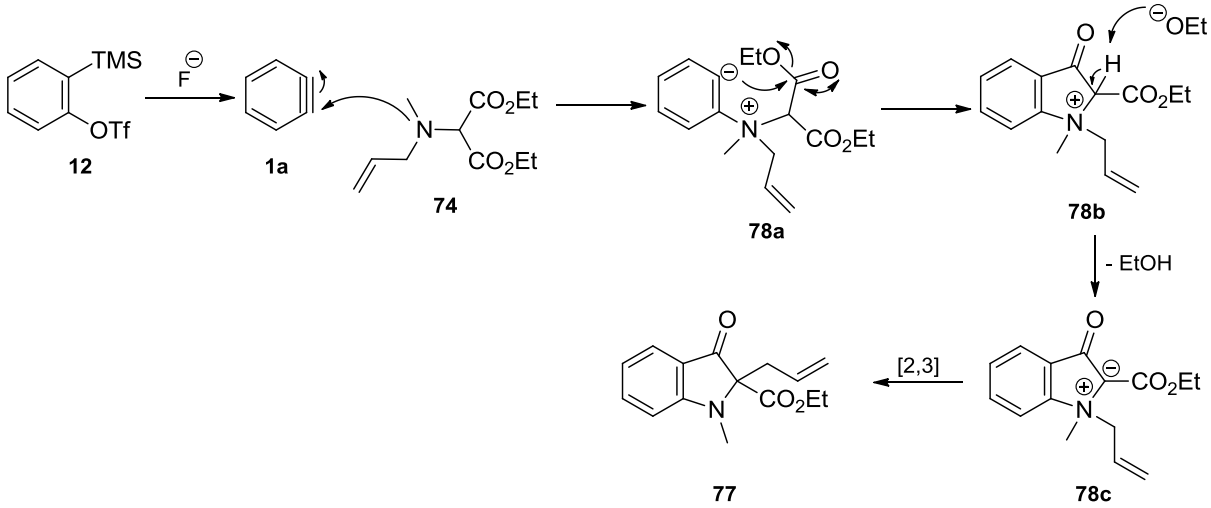
Scheme 72

To test the validity of the proposed reaction, diethyl 2-(allyl(methyl)amino)malonate (**74**) was reacted under the conditions described by Greaney (Scheme 73). The isolated product of the reaction was not as expected. Instead of the proposed α-allylated product (**75**) or that of a benzyne aza-Claisen rearrangement (**76**), ethyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate (**77**) was isolated (Scheme 73).



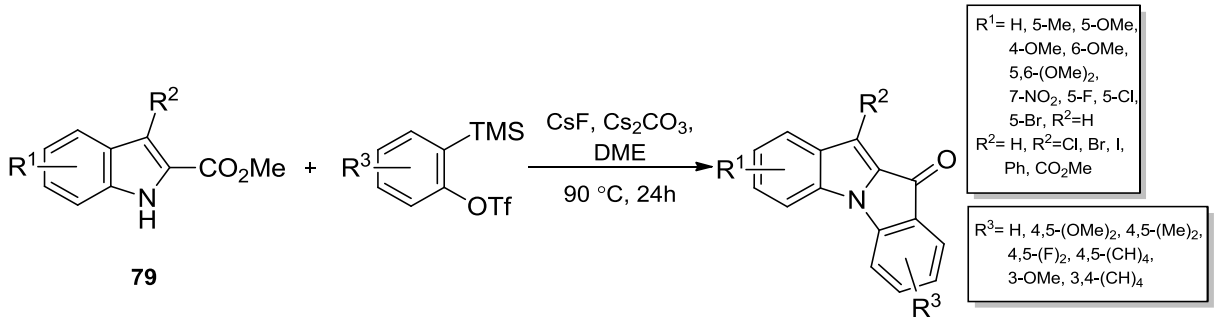
Scheme 73

Presumably nucleophilic attack of **74** at benzyne (**1a**) occurs, resulting in a zwitterion (**78a**) being formed. The phenyl anion subsequently cyclizes, liberating an equivalent of ethoxide. The latter abstracts the α-proton of (**78b**) to generate a stabilised allylammonium ylide (**78c**) which undergoes a [2,3]-rearrangement to generate **77** (Scheme 74).

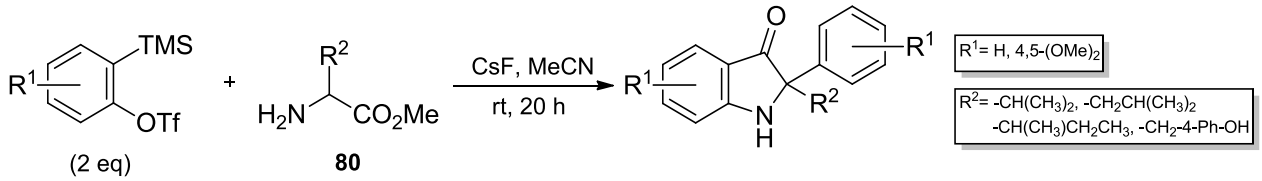


Scheme 74

The generation of indolin-3-ones by aryne methodology have been previously described by Larock from methyl indol-2-carboxylates (**79**) (Scheme 75)[114] and Okuma from amino esters (**80**) (Scheme 76), however the functionalisation of the 2-position is precluded by these methodologies.[115]



Scheme 75



Scheme 76

The 2,2-disubstituted indolin-3-one scaffold is an important structural motif in a number of natural products and compounds of pharmaceutical interest (Figure 14).[116] Efficient methods for the construction of indolin-3-one building blocks would provide new routes into biologically active molecules with the opportunity for increased skeletal diversity.

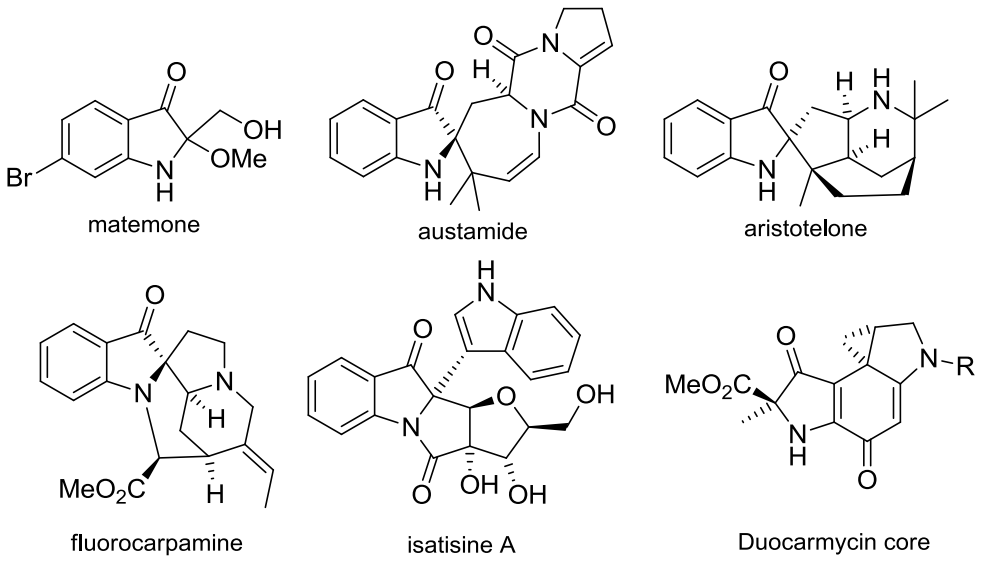
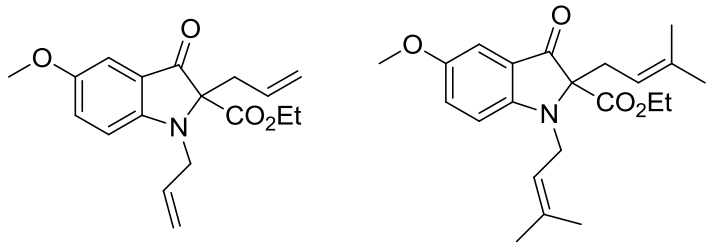


Figure 14

This method could also be of value for preparation of indolin-3-one systems as fluorescent probes; the so-called LipidGreen series of *in vivo* small molecule fluorescent probes have been exemplified in whole organism studies (Figure 15).[117]



LipidGreen (**81a**)
(λ_{ex}= 485 nm, λ_{em}= 515 nm)

LipidGreen2 (**81b**)
(λ_{ex}= 456 nm, λ_{em}= 534 nm)

Figure 15

LipidGreen (**81a**) has been developed for use as a tool for lipid imaging, focusing on research devoted to the investigation of lipid droplets (LD) within adipocytes. LD have long been considered inactive cellular components; however increasing interest is being shown in them due to their role in a number of metabolic processes as well as their potential role in disease states relating to obesity.[118] The use of zebrafish models to study these disease states has in-turn led to the application of fluorescence imaging in determining the concentration and locality of LD *in vivo*.[119] Alternative applications of fluorescent probes including biomolecular labels and environmental indicators as well as their application in cellular staining has resulted in considerable efforts being directed towards the

development and discovery of new probes.[120] The process of fluorescence undergoes three steps as shown in the Jabłoński Diagram (Figure 16).[121]

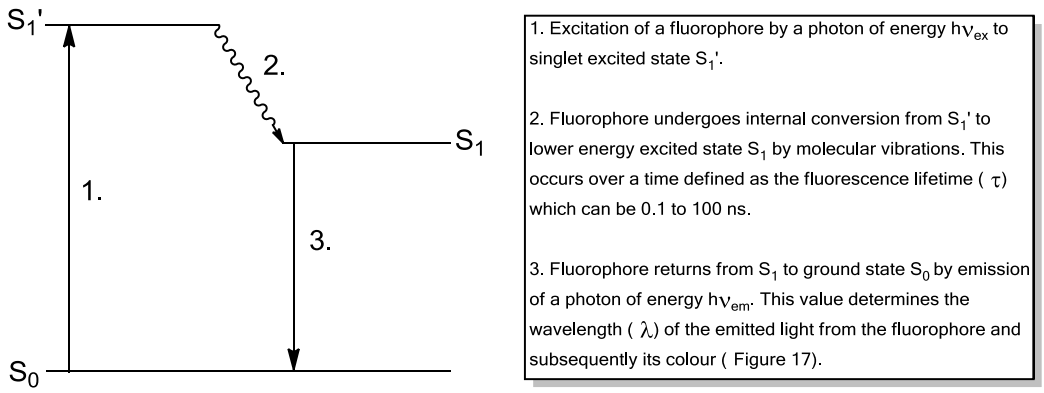


Figure 16

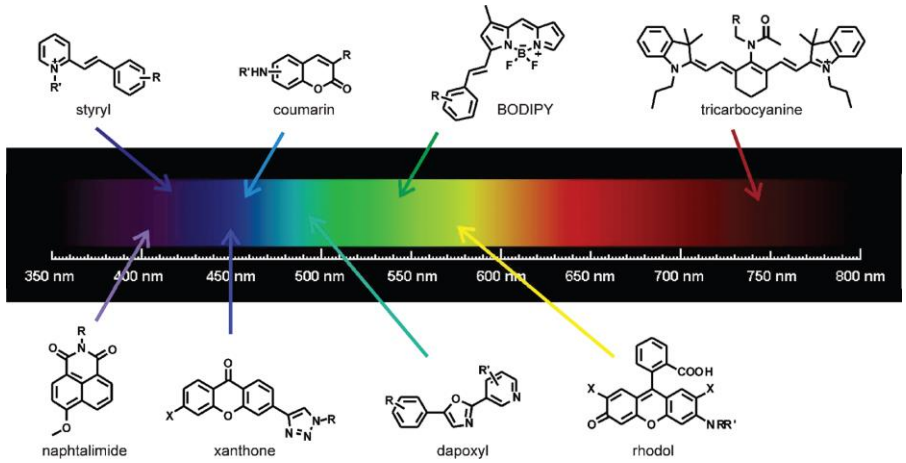


Figure 17: *Image taken from reference 120a without permission.*

The photon emitted ($h\nu_{em}$) by the fluorophore is of a longer wavelength (therefore a lower energy) than that of the excitation photon ($h\nu_{ex}$). The difference in wavelengths (λ_{ex} - λ_{em}) is defined as the Stokes shift. The Stokes shift is an important parameter in the application of fluorescent probes for a number of reasons. The polarity of the environment the fluorescent probe is in influences the size of the Stokes shift. Excited fluorophores typically have a larger dipole than those in their ground state; a more polar environment increases the Stokes shift by stabilising the excited state of the fluorophore. The detection of the fluorescent species is easier when the Stokes shift is large (20 – 50 nm). This is because with a larger Stokes shift, a clear distinction can be observed between $h\nu_{ex}$ and $h\nu_{em}$, while a smaller Stokes shift will exhibit a greater background signal due to the small difference between λ_{ex} and λ_{em} (Figure 18).

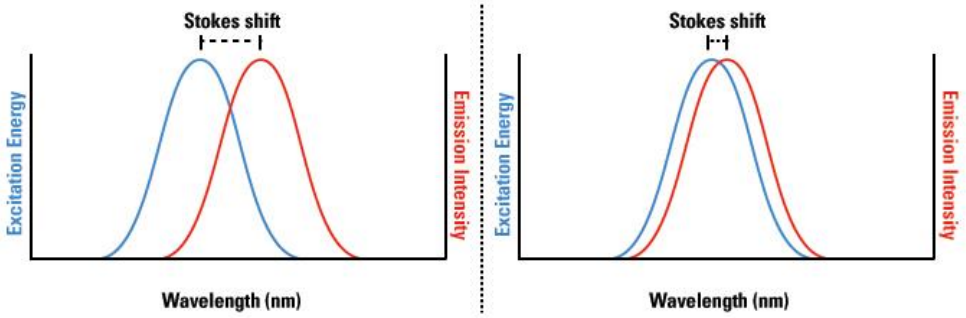
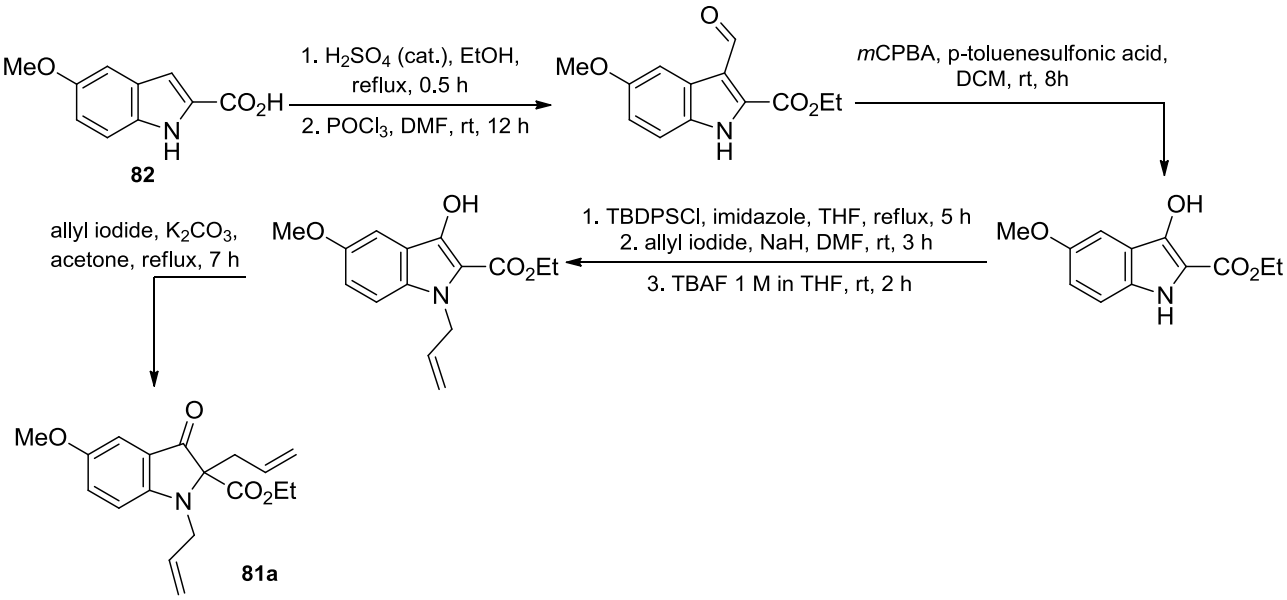


Figure 18: *Image taken from reference 122 without permission.*

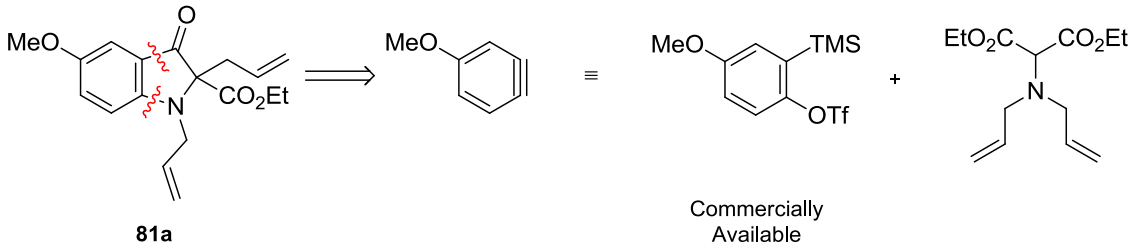
The luminosity of a fluorophore can be determined as the product of the quantum yield (Φ), which is the ratio of photons fluoresced to those absorbed, and the extinction coefficient (ε / $M^{-1}cm^{-1}$), the absorptivity of a molecule at a given wavelength (as determined by the Beer-Lambert-Bouguer Law).[120b]

With the importance of developing new fluorophores in mind, a potential modular approach to LipidGreen (**81a**) analogues can be envisioned using the reaction of allylamino malonates with arynes. The published route to these compounds from 5-methoxyindole-2-carboxylic acid (**82**) requires a four step synthesis; applying this new method to these indolin-3-one systems would potentially allow for a single-step synthesis from easily obtained materials (Scheme 77).

Literature route to LipidGreen (**81a**)



Benzyne capture route to LipidGreen (**81a**)

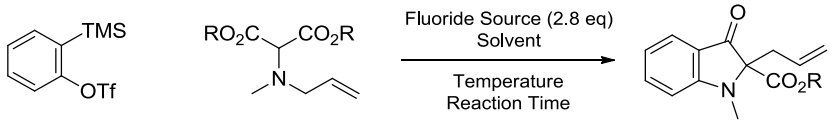


Scheme 77[117]

2.2.2 Allylamino malonates

Following the discovery of the reaction of benzyne with allylamino malonates to generate indolin-3-ones (Scheme 73), it was important to optimise the conditions which could then be applied in the generation of a series of analogous compounds (Table 5).

Table 5



12 (1 eq)

74 R=Et
83a R=Me

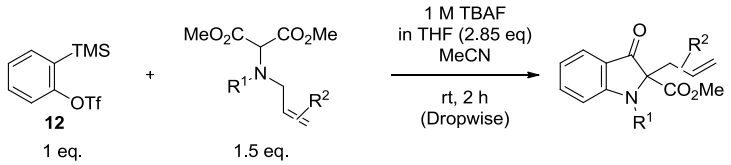
77 R=Et
84a R=Me

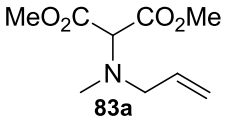
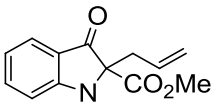
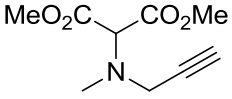
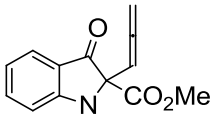
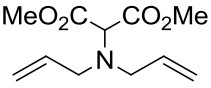
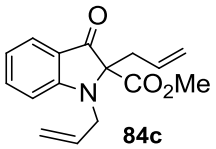
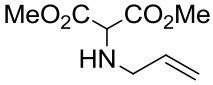
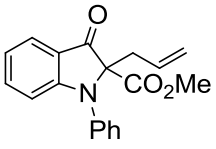
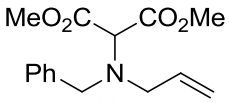
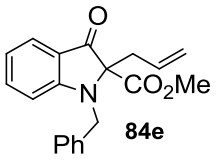
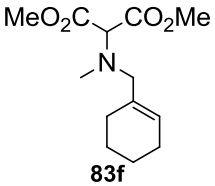
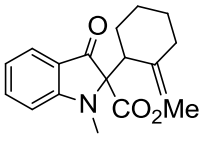
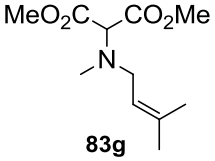
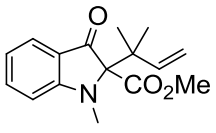
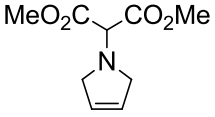
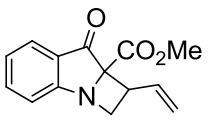
Entry	Aminomalonate [eq]	Fluoride Source	Solvent	Temperature (ºC)	Reaction Time (h)	Isolated Yield (%) [Product]
1	**74** [1.7]	CsF	Tol:MeCN (3:1)	110	44	47 [**77**]
2	**74** [1.4]	CsF	Tol:MeCN (3:1)	rt	65	49 [**77**]
3	**74** [1.4]	TBAF[a]	MeCN	rt	1	43 [**77**]
4	**83a** [1.5]	TBAF[a]	MeCN	rt	24	81 [**84a**]
5	**83a** [1.5]	TBAF[a]	MeCN	rt	2	95 [**84a**]

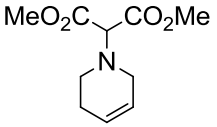
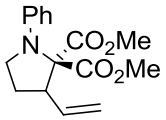
a) THF solution, 1 M

It was first important to establish if the reaction could be performed at ambient temperatures (entry 2). It was found that this was the case and although a longer reaction time was allowed, there was no significant increase in isolated yield. Knowing that the reaction could occur successfully at room temperature, toluene was removed from the solvent system in favour of just MeCN. From this point an alternative fluoride source was applied to the reaction in the form of tetrabutylammonium fluoride (TBAF) (entry 3). This choice was made knowing that by using an ammonium fluoride source rather than an alkali metal fluoride, the weakened ionic bond would increase the solubility in organic solvents which in turn would increase the rate of benzyne generation.[123] Although the yield did not increase, the reaction time was significantly reduced. NMR analysis showed that the reaction had not reached completion after 1 h. From this point it was decided that further screening reactions would be performed with dimethyl 2-(allyl(methyl)amino)malonate (**83a**) due in part to the availability of starting materials, but also with the aim that by using the dimethyl malonate instead of diethyl malonate, the initial nucleophilic addition at benzyne would be more efficient due to a reduced steric encumbrance. Increasing the reaction time to 24 h gave an increased yield (entry 4), however a small proportion of side products resulting from benzyne dimerization was isolated. This suggested that adding the TBAF in one portion may be rapidly generating large quantities of benzyne which was subsequently dimerising rather than reacting with **83a** as desired. To minimise this drop-wise addition of TBAF was performed over 2 h, followed by eluting the reaction mixture through a silica plug to remove the excess TBAF from the reaction. By doing this it was proposed that the concentration of the reactive benzyne species would be reduced, resulting in a reduction in side reactions (entry 5). This was found to be the case and **84a** was isolated in 95 %. This optimised procedure was subsequently used to perform a screen with a range of allylamino malonates (Table 6).

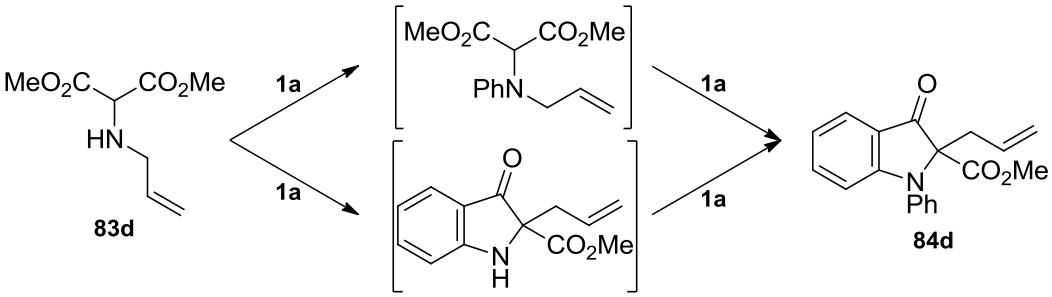
Table 6



Entry	Amino Malonate 83	Product 84	Isolated Yield (%)
1	 **83a**	 **84a**	95
2	 **83b**	 **84b**	92
3	 **83c**	 **84c**	52
4	 **83d**	 **84d**	76
5	 **83e**	 **84e**	61
6	 **83f**	 **84f**	27
7	 **83g**	 **84g**	48
8	 **83h**	 **84h**	No Product or Starting Material Recovered

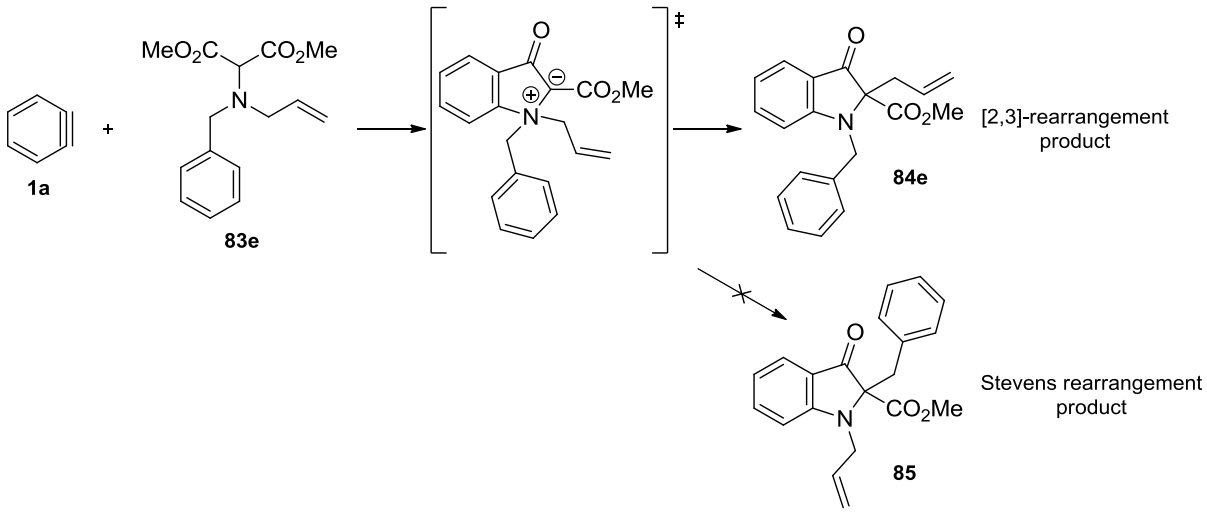
9	 **83i**	 **84i**	69

Successful application of the optimised procedure to propargyl analogue **83b** resulted in formation of the expected allene **84b** in 92 % (entry 2). The reaction of secondary amine **83d** leads to product **84d** which is the result of two sequential reactions with benzyne (entry 4). Two pathways can be proposed the transformation of **83d** to **84d** (Scheme 78).



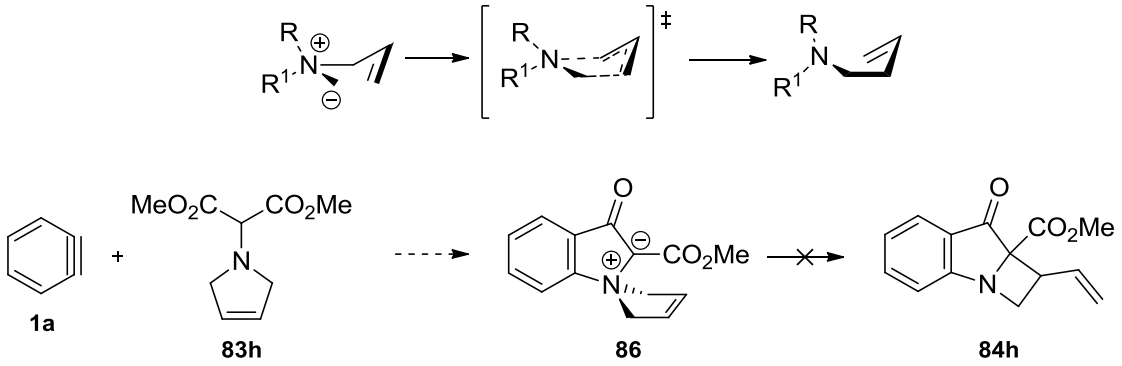
Scheme 78

Reaction of **83e** showed only evidence of the [2,3]-rearrangement product with no Stevens product (**85**) being isolated (Scheme 79).



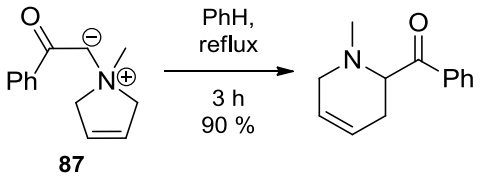
Scheme 79

This would be expected as [2,3]-rearrangements are symmetry allowed reactions occurring *via* a concerted mechanism with a lower activation energy than the Stevens rearrangement.[124] The reaction with **83h** (entry 8) proved unsuccessful; **84h** could not be detected in the complex crude ^{1}H NMR following the reaction. Revaluation of the reaction shows that to achieve the 5-membered "envelope" transition state prior to the [2,3]-rearrangement, the 3-pyrroline ring would have to adopt a highly strained conformation (**86**) subsequently precluding **84h** formation (Scheme 80).



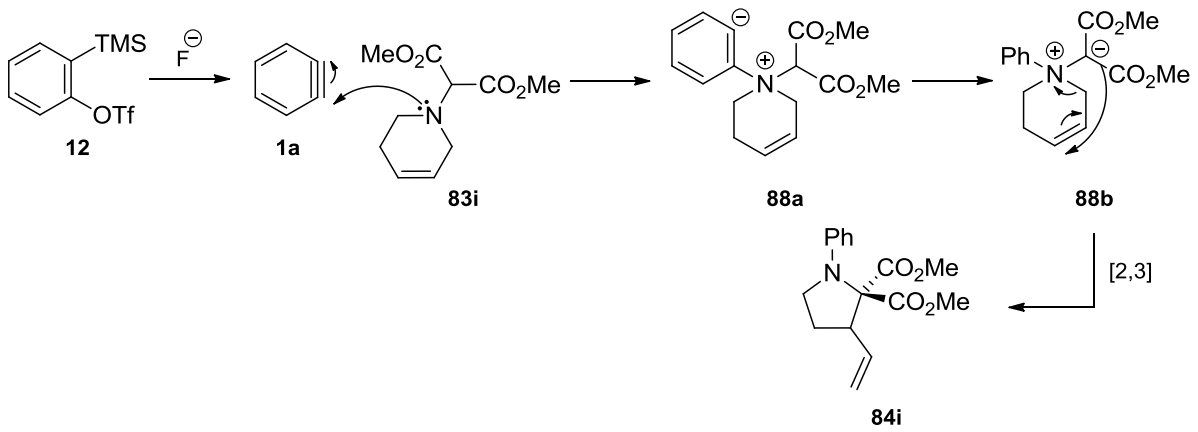
Scheme 80

Literature precedent supports this as demonstrated by Ollis, whereby a similarly constrained 3-pyrroline derived ylide (**87**) gave only the [1,2]-rearrangement product upon heating (Scheme 81).[124a]



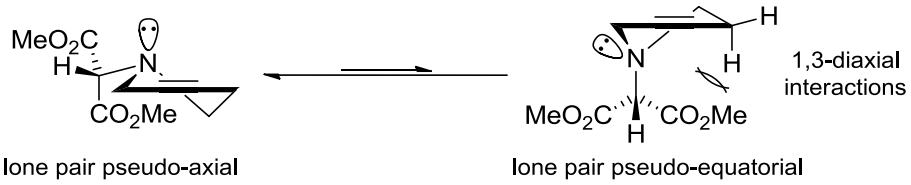
Scheme 81

Application of the new methodology to a tetrahydropyridinyl derived amino malonate resulted in an unexpected product (entry 9). The generation of **84i** is proposed to occur by initial nucleophilic attack of **83i** at benzyne to generate zwitterion (**88a**). Internal proton transfer leads to stabilised ammonium ylide (**88b**). Ammonium ylide (**88b**) performs a [2,3]-rearrangement resulting in a ring contraction and the generation of **84i** (Scheme 82).



Scheme 82

Although this is an unexpected transformation, analogous [2,3]-rearrangements of tetrahydropyridine derived ammonium ylides have previously been published by Ollis[125] and Sweeney.[126] In this instance, the nitrogen loan pair would lie preferentially pseudo-axial, with the malonate component lying pseudo-equatorial to minimise 1,3-diaxial interactions (Scheme 83).



Scheme 83

To achieve the least hindered nucleophile approach to benzyne, the malonate ester would lie between the ring methylene positions of the tetrahydropyridine ring, resulting in a *gauche* conformation between the malonate hydrogen and the nitrogen lone pair (**89a**). Eclipsing the malonate esters with the ring methylenes would be a higher energy conformation and placing the malonates above the plane of the ring (**89b**) would hinder the approach of the electrophile (Figure 19).

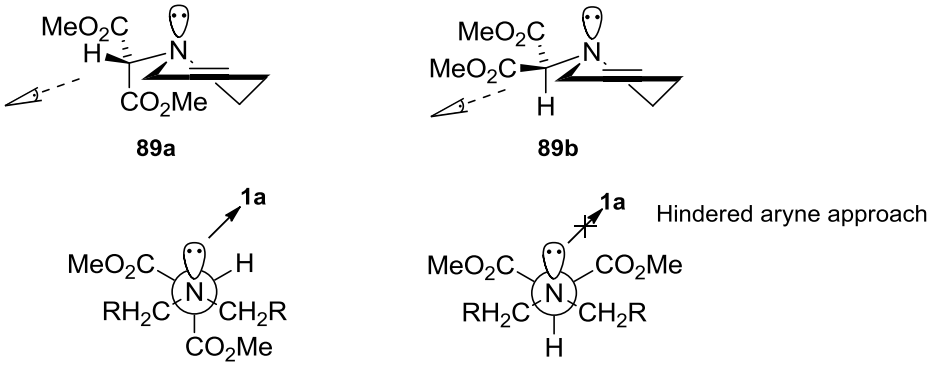
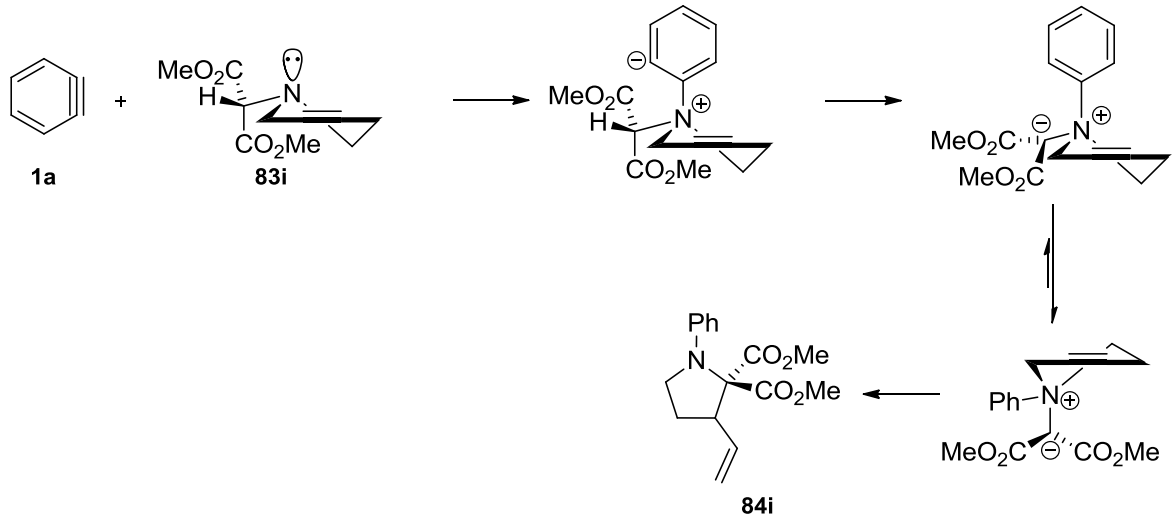


Figure 19

Following addition to benzyne the hydrogen is preferentially placed to be abstracted. Due to the steric encumbrance, the phenyl component will occupy the pseuo-equatorial position following a ring inversion. The malonate, bearing the ylide anion, now sits pseudo-axial in the required envelope conformation for the [2,3]-rearrangement to occur (Scheme 84).

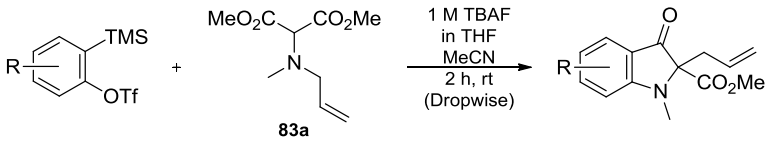


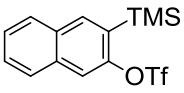
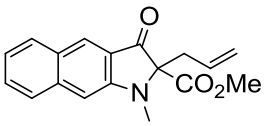
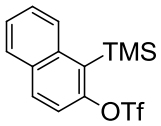
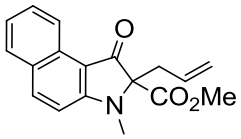
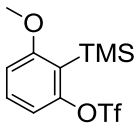
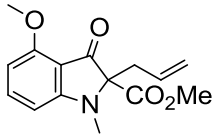
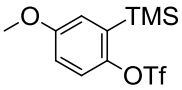
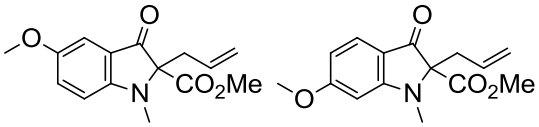
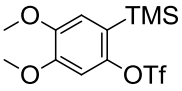
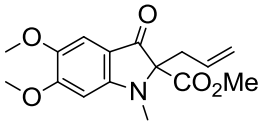
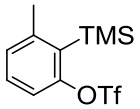
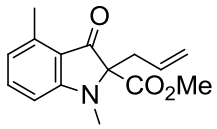
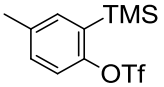
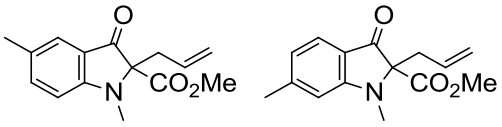
Scheme 84

2.2.3 Screen of napthynes and functionalised-benzynes

Following the screening of a number of allylated aminomalonate derivatives, a screen of functionalised-benzynes and napthynes using the optimised conditions was performed. Dimethyl 2-(allyl(methyl)amino)malonate (**83a**) was used as the standard aryne trap (Table 7).

Table 7



Entry	Aryne Precursor	Product	Isolated Yield (%)
1		 **90a**	61
2		 **90b**	73
3		 **90c**	97
4		 **90d** **90e**	**90d**: 54 **90e**: 39
5		 **90f**	81
6		 **90g**	86
7		 **90h** **90i**	**90h**: 40 **90i**: 51

We were delighted that further optimisation of the protocol was not required when applied to the functionalised-benzynes and napthynes. High regioselectivity was observed, as predicted, in the cases of 1,2-napthyne (**55**) (entry 2) and 3-methoxybenzyne (**56**) (entry 3), generating single regioisomers **90b** and **90c** respectively. In addition, only a single regioisomer (**90g**) was formed in the reaction of 3-methylbenzyne (**58**) (entry 6). Examination of the crude NMR showed only the product from addition at the C1; we attribute the regioselectivity to the crowded steric nature of the nucleophile.

The reaction of 4-methoxybenzyne (entry 4) and 4-methylbenzyne (entry 7) both gave regioisomeric mixtures. The distribution of the product mixtures can be attributed to the electronic nature of the substituent. In the case of 4-methoxybenzyne (entry 4), the regioselectivity is due to a combination of steric effects and electronic effects, whereby C1 is marginally more electron deficient than C2 due to the electron-withdrawing nature of the -OMe favouring **90d** over **90e**. This slight preference for addition at C1 has been highlighted previously in the literature.[127] The slight regioselectivity for C2 of 4-methylbenzyne (entry 7), however, is due to the electron-donating nature of the methyl substituent making C1 comparatively electron-rich, thus favouring **90i** over **90h**.

2.2.4 Photophysical properties

Following the synthesis of a variety of analogous indolin-3-ones, we examined the photophysical properties as a means of comparing their potential utility as fluorophores. Methyl 2-allyl-1-methyl-3-oxo-2,3-dihydro-1H-benzo[f]indole-2-carboxylate (**90a**) shows no fluorescence and is red/orange in colour.

Table 8

Compound	λ_{ex} (nm) [ε_{max} (X10^3) / M^{-1}cm^{-1}][a]	λ_{em} (nm)[b]	Stokes Shift (λ_{em}-λ_{ex}) (nm)
81a[117a]	485[c]	515[c]	30
81b[117c]	456[c]	534[c]	78
77	421 [6,400]	491	70
84a	422 [2,000]	492	70
84b	420 [1,800]	497	77
84c	412 [3,100]	484	72
84d	411 [1,100]	496	85
84e	412 [1,800]	483	71
84f	421 [2,100]	491	70
84g	412 [740]	494	82
90b	446 [3,500]	472	26
90c	407 [1,800]	487	80
90d	446 [5,100]	549	103
90e	394 [2,400]	469	75
90f	420 [4,200]	496	76
90g	418 [510]	495	76
90h	431 [1,800]	511	80
90i	416 [3,800]	486	70

a) EtOH (3.0 X10^{-5} M) b) λ_{ex} measured at λ_{em} c) stained cell line 3T3-L1

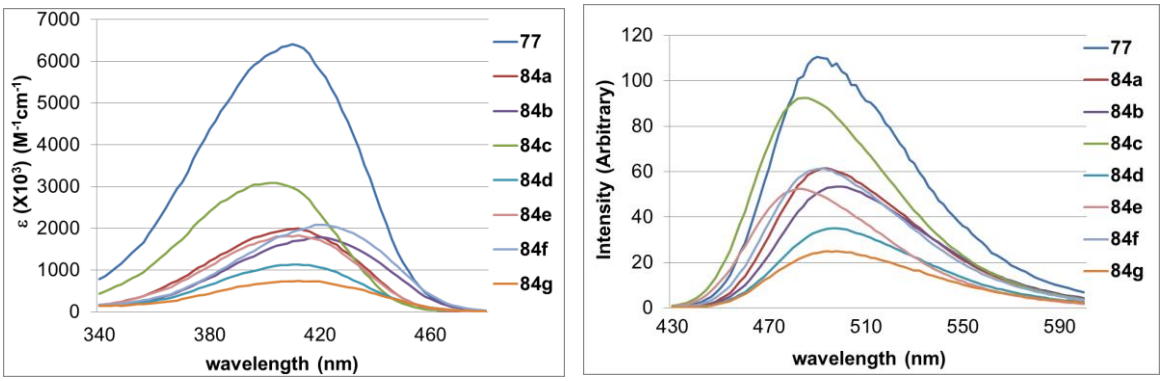


Figure 20: left – excitation spectra; right – emission spectra

Figure 21: (left to right) **77**, **84a**, **84c**, **84b**, **84d**, **84g**, **84f**, **84e** in DCM illuminated at 365 nm.

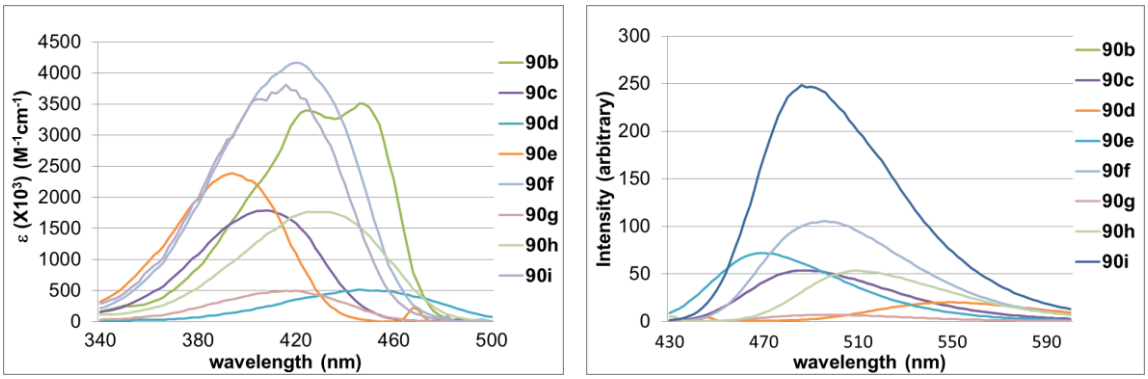
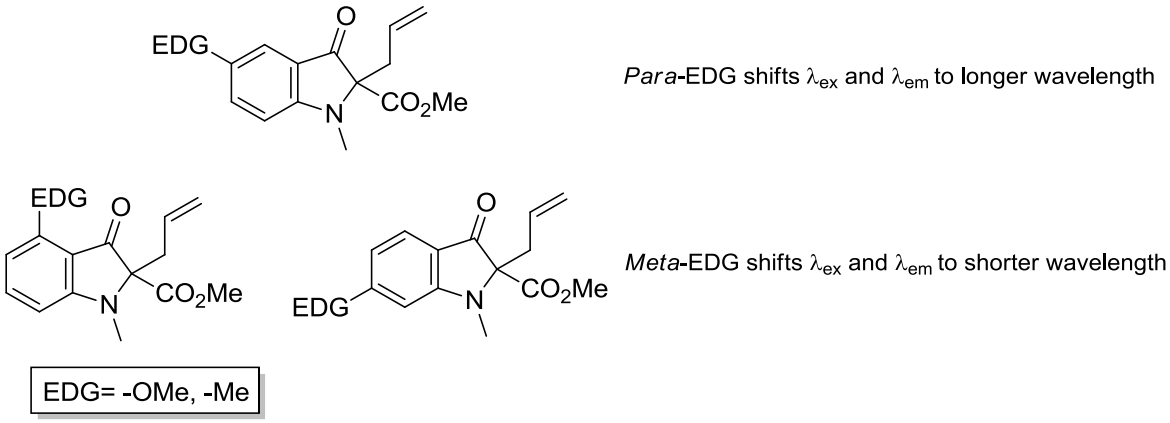


Figure 22: left – excitation spectra; right – emission spectra

Figure 23: (left to right) **90b**, **90c**, **90d**, **90e**, **90f**, **90g**, **90h**, **90i** in DCM illuminated at 365 nm.

The fluorescence exhibited by indolin-3-one systems originates from a donor/acceptor relationship between the amine (donor) and the ketone (acceptor) components which are connected *via* a π-system (arene). Previous work analysing the fluorescence of indolin-3-ones have identified that alterations to the donor, acceptor or π-system affect a change in the photophysical characteristics.[128] Alterations at the 2-position are unlikely to affect a large change in the photophysical properties

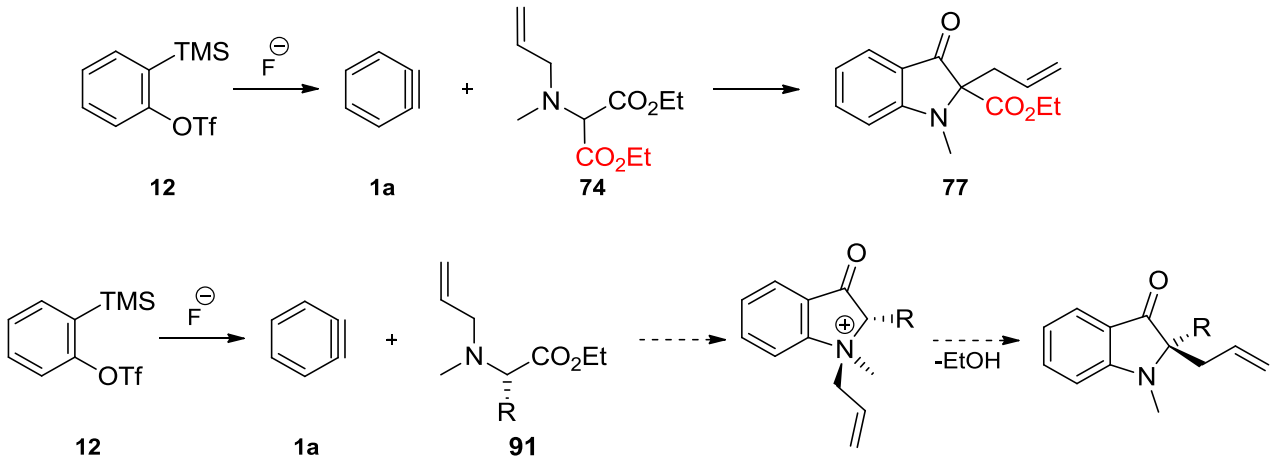
unless they increase molecular rigidity; this in turn will reduce non-radiative relaxation by collisions thus increase fluorescence. When analysing the effect of arene substituents an interesting trend is seen. Substituents *para* to the amine component (**90d** and **90h**) exhibit a distinct shift, in λ_{ex} and λ_{em}, to longer wavelength and larger Stokes shifts. In the case of the *para*-methoxy- this has been identified previously and attributed to enhancing the donor character of the amine.[128b] As this effect has been shown in both methoxy- and methyl- substituents it would suggest the *ortho*/*para* activating nature of these substituents increases the electron density in the ring in a complimentary fashion with the amine, subsequently reducing the energy required to fluoresce. The relative difference in Stokes shift between **90d** and **90h**, a difference of 20 nm, is due to the relative activating strengths of the -OMe vs -Me groups; the increased activation strength results in an increased Stokes shift. Substituents placed *meta* to the amine however act in a non-complementary manner with the amine, resulting in a shift to shorter wavelengths, displaying an increased energy requirement to fluoresce (Scheme 85). The observed change in Stokes shift is smaller than that observed for EDG *para* to the amine.



Scheme 85

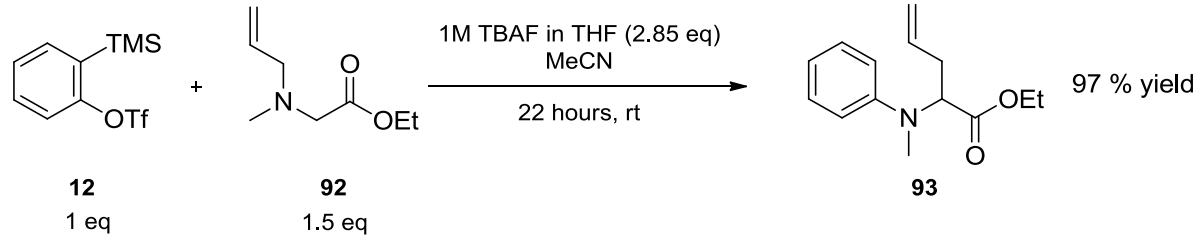
2.2.5 Allylamino acetates

Following working with allylamino malonates, we chose to investigate 2-(allyl)amino acetates (**91**). Investigating the reaction of arynes with **91** should allow us to generate enantioenriched products by exploiting the amino acid motif. The stereochemistry of the product originates from the chiral ammonium intermediate which should be influenced by the orientation of the R group substituent of **91** (Scheme 86).



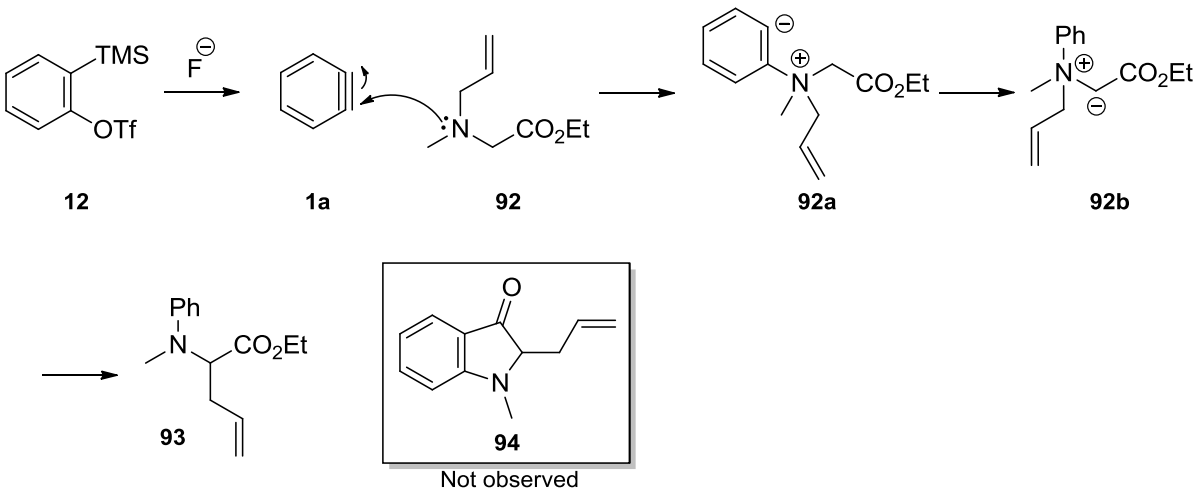
Scheme 86

To begin our investigation we reacted the achiral ethyl 2-(allyl(methyl)amino)acetate (**92**) with benzyne resulting in the generation of ethyl 2-(methyl(phenyl)amino)pent-4-enoate (**93**) in 97 % yield (Scheme 87).



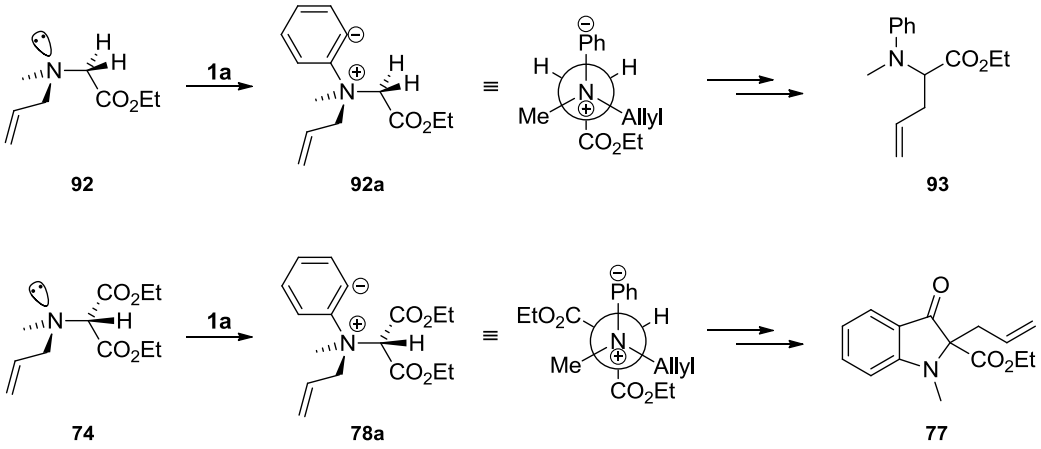
Scheme 87

A proposed mechanism for this transformation involves nucleophilic addition of **92** to benzyne (**1a**), generating a zwitterion (**92a**) which subsequently performs an intramolecular proton transfer to generate an ammonium ylide (**92b**) which undergoes a [2,3]-rearrangement generating **93** (Scheme 88).



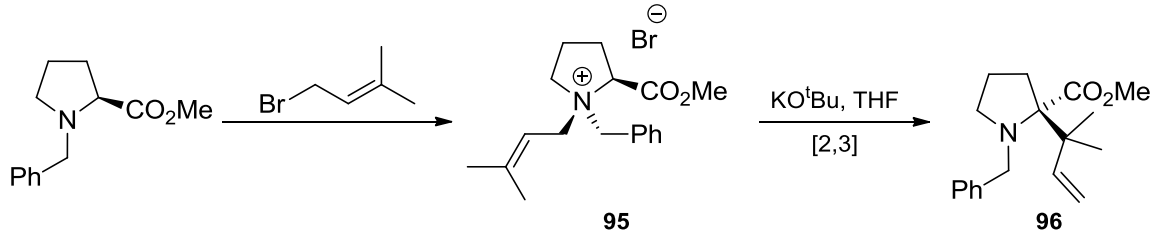
Scheme 88

We reasoned that the generation of **93** instead of indolin-3-one derived **94** could be attributed to the conformation of the zwitterion intermediate (**92a**). The least hindered approach of allylamino acetate **92** to benzyne (**1a**) would generate zwitterion **92a** which when viewed as a Newman projection has an *anti*-periplanar relationship between the phenyl group and the ester. This would subsequently require a 180º bond rotation to achieve the desired *syn*-periplanar conformation between the ester and phenyl group for ring-closure and **94** formation. During this bond rotation one of the two hydrogens on the α–carbon would achieve a *syn*-periplanar relationship with the phenyl group facilitating the observed proton transfer which ultimately leads to **93**. This isn't observed when reacting allylamino malonate (**74**) with **1a** because the least hindered approach of **74** to benzyne generates zwitterion **78a** which when observed as a Newman projection has a *gauche* relationship between the phenyl group and one of the two esters. The bond rotation to achieve the *syn*-periplanar conformation between the phenyl group and the ester can occur without placing the hydrogen on the α-carbon in a *syn*-periplanar relationship to the phenyl group ultimately resulting in **77** formation (Scheme 89).



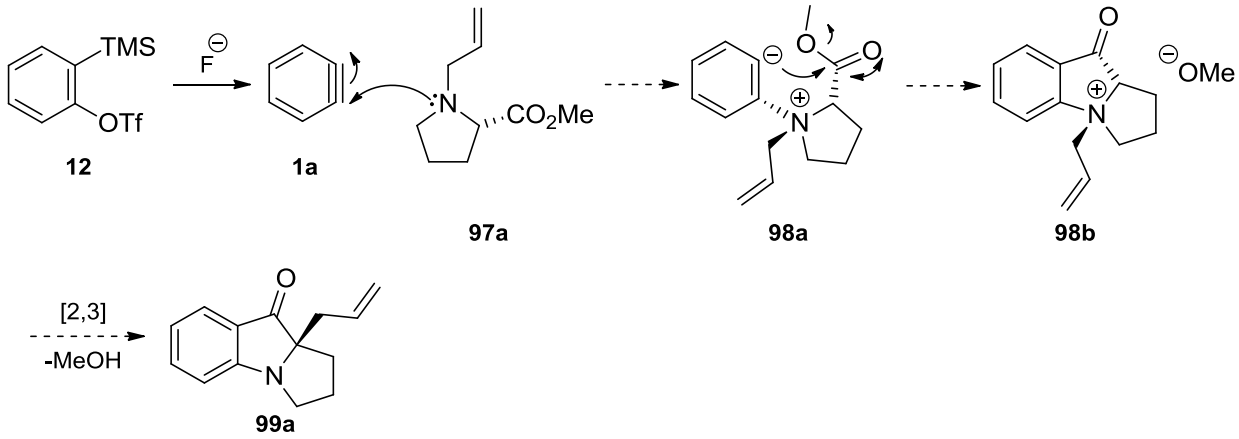
Scheme 89

Okuma showed that when reacting **1a** with amino esters the glycine derivative resulted in *N*-phenylation rather than indolin-3-one formation.[115] West has shown that *N*-benzylproline methyl ester undergoes *cis*-selective alkylation with prenyl bromide to generate ammonium salt (**95**) where the benzyl and carbomethoxy groups are *trans*.[129] The stereochemistry of **95** is controlled by the adjacent stereocentre at C2. This ammonium salt **95** under basic conditions undergoes a [2,3]-rearrangement to generate a single enantiomer **96** (Scheme 90).



Scheme 90

By reacting *N*-allylproline methyl ester (**97a**) with benzyne (**1a**) we would expect to generate zwitterion (**98a**). With the arene *cis* to the methyl ester we envisioned the phenyl carbanion would react at the ester to generate an intermediary ammonium salt (**98b**) which would perform a [2,3]-rearrangement to generate indolin-3-one (**99a**) with the described enantioenrichment at C2 (Scheme 91).

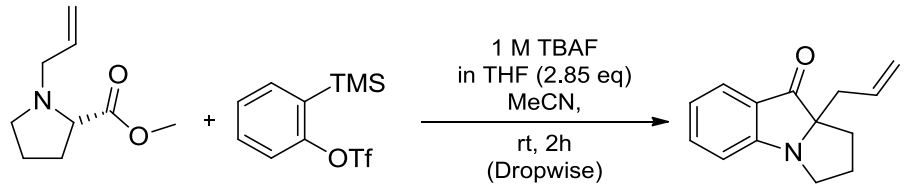


Scheme 91

The reaction was performed using the previously described protocol (Table 6) to successfully generate 9a-allyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (**99a**) in 37 % yield. Interestingly, it should be noted that Okuma only achieved *N*-phenylation when reacting proline methyl ester with

benzyne.[115] By increasing the equivalents of **97a** an increased isolated yield of 61 % was achieved (Table 9, entry 4).

Table 9



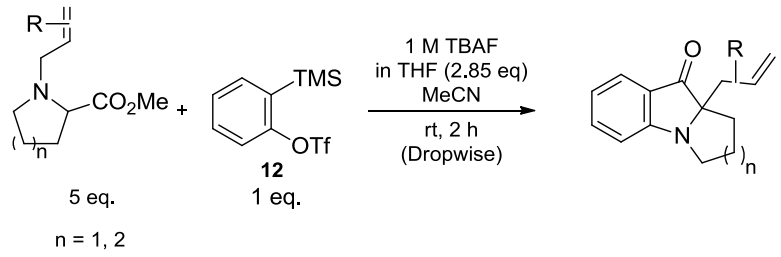
97a **12** 1 eq **99a**

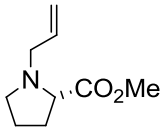
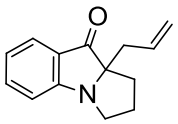
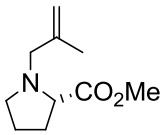
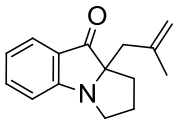
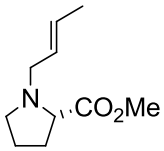
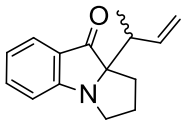
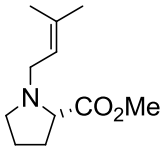
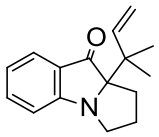
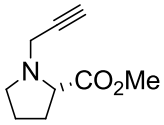
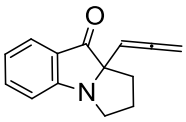
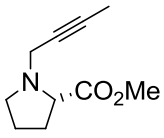
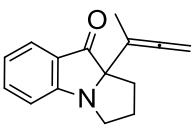
Entry	97a (equiv)	Isolated Yield 99a (%)[a]
1	1.5	37
2	2	51
3	2.5	54
4	5	61
5	10	54

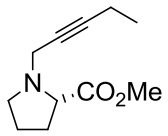
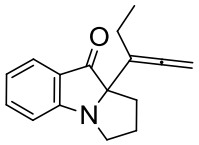
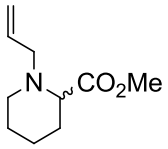
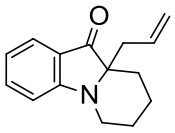
a) Isolated yields based on molar conversion of **12** to **99a**.

With an optimised protocol in place, a screen of allylated proline methyl esters was performed (Table 10).

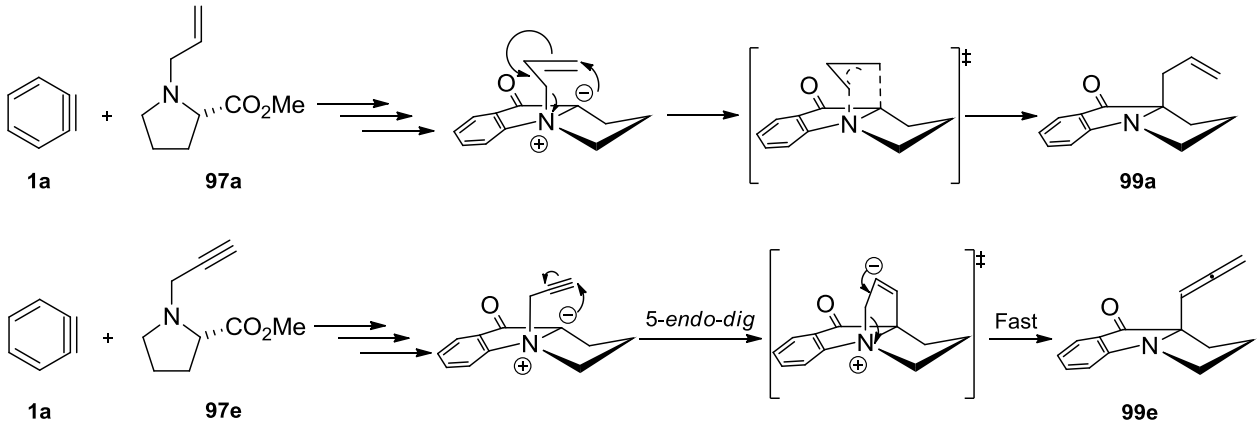
Table 10



Entry	Allyl proline methyl ester 97	Product 99	Isolated yield (%)
1	 **97a**	 **99a**	61
2	 **97b**	 **99b**	47
3	 **97c**	 **99c**	65 (d.r. 1:0.2)
4	 **97d**	 **99d**	70
5	 **97e**	 **99e**	95
6	 **97f**	 **99f**	98

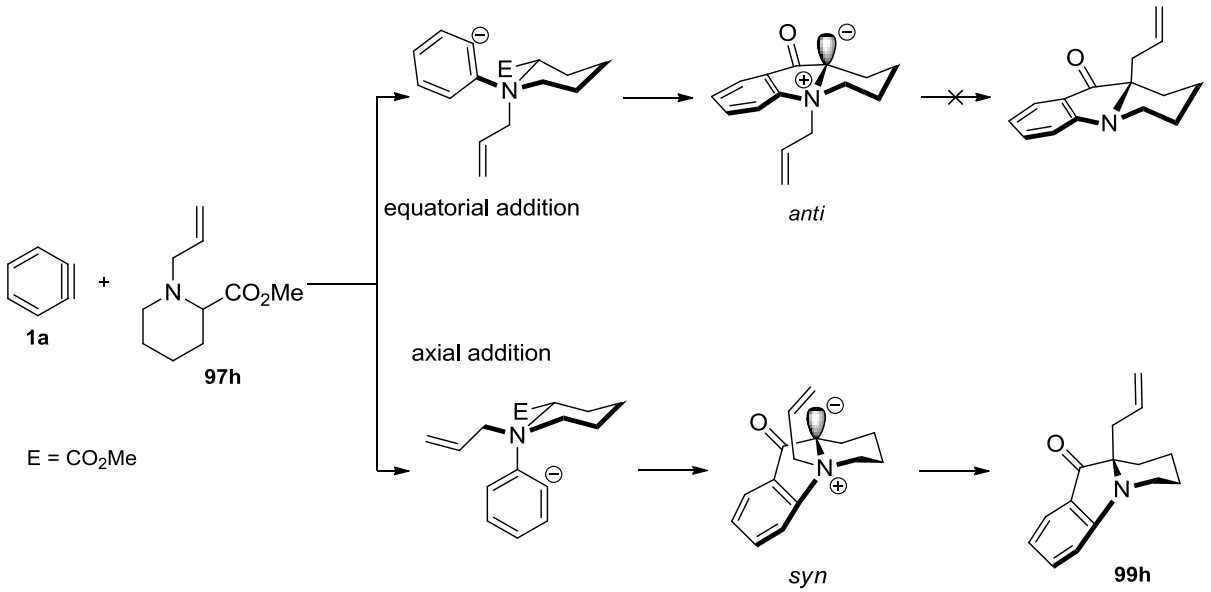
7	 **97g**	 **99g**	97
8	 **97h**	 **99h**	6

In examining these results, an interesting trend is highlighted when considering the yields of the allylic vs propargylic [2,3]-rearrangement products. There is a clear trend whereby propargylic substituents rearrange more efficiently to their products. Ollis has shown that propargylic [2,3]-rearrangements do not occur *via* a concerted process but *via* a stepwise mechanism (Scheme 92).[130]



Scheme 92

This proceeds first *via* a favoured 5-*endo*-*dig* cyclisation followed by a fast *anti*-elimination of the vinyl anion to generate the allene product. This stepwise process subsequently does not have the rigorous steric requirements of the concerted allylic [2,3]-rearrangement resulting in a faster and ultimately higher yielding reaction. Application of this stepwise mechanism to that of the allylic [2,3]-rearrangement would be strongly disfavoured as the initial cyclisation would have to occur *via* a disfavoured 5-*endo*-*trig* cyclisation. Only the sterically demanding concerted mechanism can be inferred for this process. Of additional interest is the significant drop in yield when the core pyrrolidine ring is exchanged for piperidine (**99a** vs **99h**). This can be explained when considering the two lowest energy pathways (Scheme 93).



Scheme 93

The favoured equatorial addition, ring closure and deprotonation would result in an *anti*-arranged ylide which subsequently cannot rearrange; whereas, the disfavoured axial addition would lead to the *syn*-arranged ylide which can rearrange to the desired product. We propose the observed yield results from the product of the initial axial addition and rearrangement.

Preliminary chiral analysis for these compounds has been performed (Table 11).

Table 11

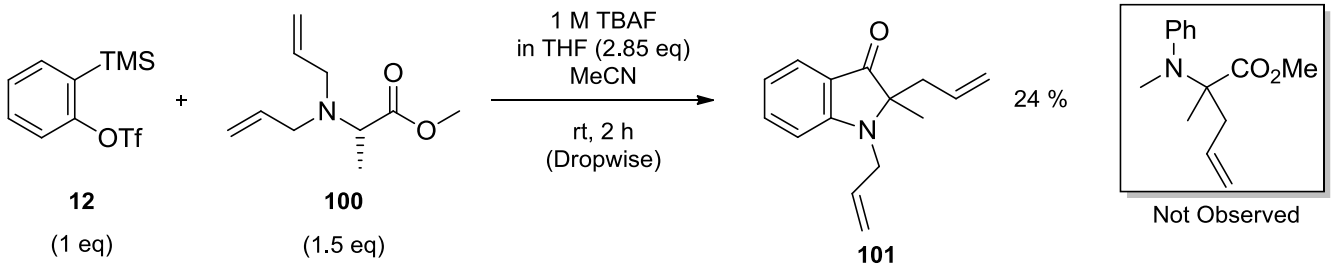
Compounds	Percentage Enantiomeric Excess (%)[a]
99a	24.0
99b	44.8
99c	Diastereomer 1: 69.7
	Diastereomer 2: 69.0
99d	42.2
99e	59.4
99f	88.4
99g	85.6

a) Percentage enantiomeric excess determined by chiral GC-MS

The enantiomeric excess for these compounds would appear to be lower than expected for the proposed mechanism. This may be attributed to one of two possible reasons: Firstly, the starting materials (**97a**-**g**) have not had their enantiopurity confirmed and although synthesised from

enantiopure (*S*)-proline methyl ester hydrochloride the mildly basic allylation/propargylation conditions may lead to some degree of racemisation. Secondly, under the mildly basic reaction conditions to generate indolin-3-ones **99a**-**g** the starting materials **97a**-**g** may undergo racemisation. This work is ongoing to determine the cause of this reduced enantiomeric excess.

Following the screen of proline derived starting materials we reinvestigated the nature of using acyclic amino esters in generating indolin-3-ones. Okuma's work showed that by functionalising at the α-position, indolin-3-one formation became more prevalent. With this in mind we performed the reaction of (*S*)-methyl 2-(diallylamino)propanoate (**100**) with **1a** (Scheme 94).



Scheme 94

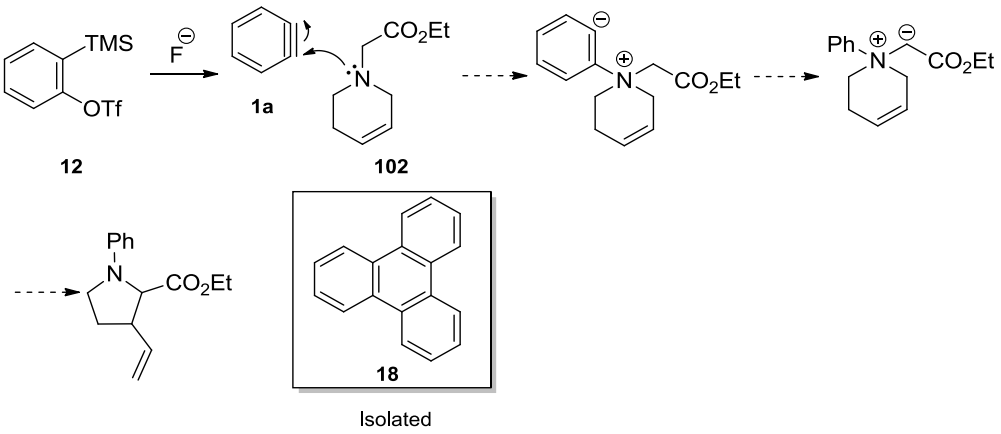
1,2-Diallyl-2-methylindolin-3-one (**101**) was isolated in 24 % yield as the only product. Attempts to increase the isolated yield by increasing the equivalents of **100** resulted in an isolated yield of 36 % (Table 12).

Table 12

Entry	100 (equiv.)	Isolated Yield 101 (%)
1	1.5	24
2	2	25
3	5	30
4	10	36

The inability to significantly increase the yield by increasing the equivalents of **100** would suggest that **100** is the reactions limiting factor. This may be due to the poor nucleophilicity of the substrate due to the two pendent allyl groups as shown previously (Table 6, Entry 3).

Now fully aware of the scope of reacting amino acetates with benzyne, we attempted the reaction of ethyl 2-(5,6-dihydropyridin-1(2H)-yl)acetate (**102**) with **1a** to see if the analogous ring contraction product (observed in Table 6, Entry 9) would be isolated (Scheme 95).



Scheme 95

The reaction was performed and only triphenylene (**18**) was isolated. Attempts to isolate any potential phenyl ammonium salt generated by reaction of **102** with benzyne and subsequent quenching of the zwitterion with adventitious proton were not isolated and there was no sign of consumption of **102** starting material.

2.2.6 Photophysical properties

As previously identified, alteration of the 2-position substituent has a minimal effect on the photophysical properties of the molecule; however it is poignant to identify that allene components result in an increase in the absorption coefficient. Overall, the absorption coefficient of the proline derived indolin-3-ones (Table 13) is lower than those of the amino malonate derived indolin-3-ones (Table 8). In addition, the Stokes shift is larger in the proline derived indolin-3-ones than the aminomalonate derived indolin-3-ones. Interestingly, when the pyrrolidine ring is expanded to a piperidine ring, **99h**, the photophysical properties more closely resemble those of an aminomalonate derived indolin-3-ones (Table 8, **84a**). This is also the case when comparing the photophysical properties of the alanine derived indolin-3-one, **101** vs Table 8, **84c**. This may suggest that the deviation from the 6,5,5-ring system results in an increased number of molecular conformations and subsequently an increased chance of molecular collisions when in the excited state. This in turn will result in an increase in non-radiative relaxation and subsequently a reduction in Stokes Shift.[121]

Table 13

Compound	λ_{ex} (nm) [ε_{max} ($X10^3$) / $M^{-1}cm^{-1}$][a]	λ_{em} (nm)[b]	Stokes Shift (λ_{em}-λ_{ex}) (nm)
99a	390 [620]	505	115
99b	392 [840]	505	113
99c	390 [990]	510	120
99d	393 [400]	507	114
99e	391 [1,400]	509	118
99f	392 [890]	510	118
99g	391 [1,800]	510	119
99h	419 [2,800]	489	70
101	412 [2,900]	481	69

a) EtOH ($3.0 X10^{-5}$ M) b) λ_{ex} measured at λ_{em}

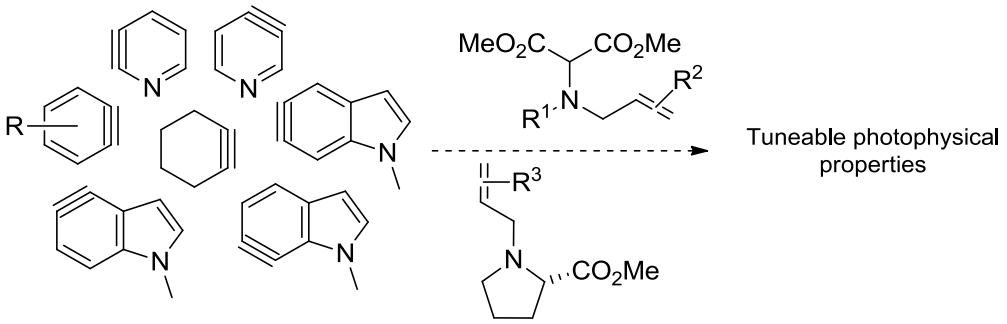
Figure 24: (left to right) **99a**, **99c**, **99**, **99b**, **99e**, **99f**, **99g**, **99h**, **101** in DCM illuminated at 365 nm

2.2.7 Conclusion

The discovery of a novel tandem aryne-capture/cyclisation/[2,3]-rearrangement route to prized indolin-3-one systems from *N*-allylamino malonates and *N*-allyl amino esters is described. This optimised procedure offers a single-step protocol to a series of analogous fluorophores which bear structural similarities to the known LipidGreen series. The photophysical properties of these compounds have been investigated showing beneficial characteristics of potential fluorescent probes as well as highlighting the influence of arene functionality on these characteristics. In addition, the aryne-capture/[2,3]-rearrangements of tetrahydropyridine malonates and *N*-allyl sarcosine esters have been identified as a novel route to *N*-phenyl pyrrolidine and α-allylated *N*-phenyl sarcosine esters.

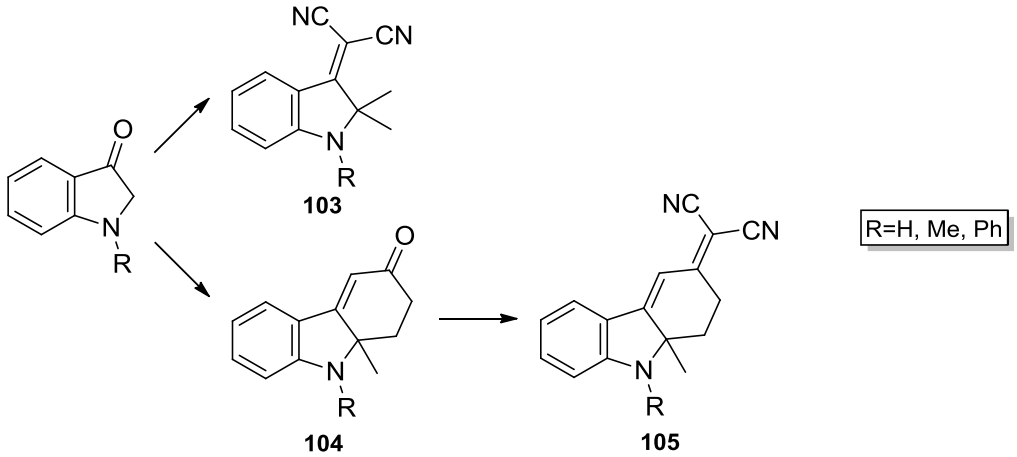
2.2.8 Future work

Investigations into the influence of the arene component on the photophysical properties have still been under explored. The described protocol allows for further expansion by reactions with more complex benzynes and arynes such as indolynes and pyridynes as well as similarly reactive intermediates such as cyclohexynes. The understanding obtained by altering the arene component of the indolin-3-one could be applied to generate a range of tuneable fluorophores (Scheme 96).



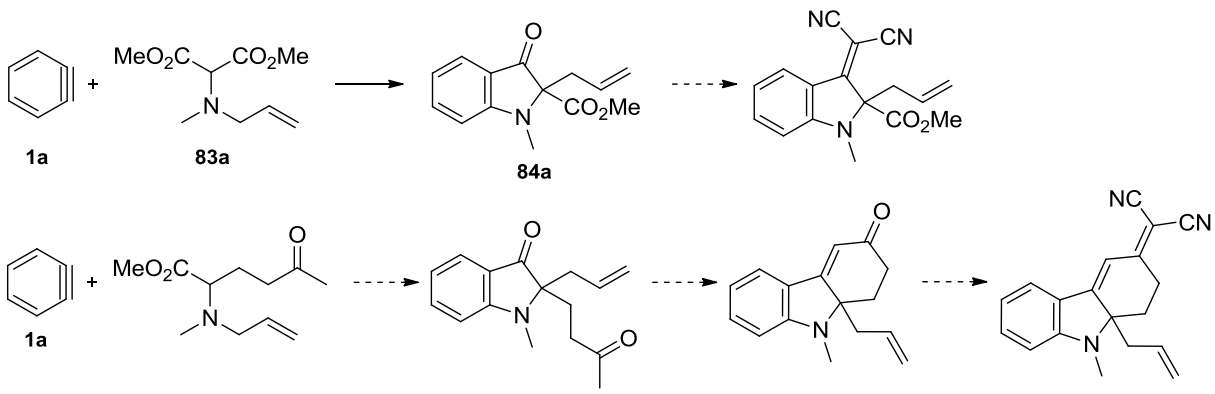
Scheme 96

Matsumoto previously describe how the photophysical properties of indolin-3-one could be altered by converting the ketone to a dicyanomethylene (**103**) as well as by Robinson ring annulation (**104**); this in turn can be further functionalised to the α,β-unsaturated dicyanomethylene (**105**) (Scheme 97).[128a]



Scheme 97

Application of these previously describe protocols could allow for further expansion of this fluorophore library (Scheme 98).



Scheme 98

CHAPTER 3: EXPERIMENTAL

All chemicals were supplied by Sigma Aldrich, Tokyo Chemical Industry, Acros and Fisher Scientific and were used as received. Dimethylformamide (DMF), toluene and benzene were purchased anhydrous. MeCN and MeOH were distilled from calcium hydride. Dichloromethane (DCM) and chloroform were distilled from calcium sulfate. All experiments were performed in oven-dry glassware under a protective atmosphere of nitrogen (dried by passage through anhydrous phosphorus pentoxide) as required.

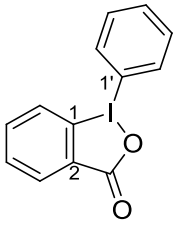
All column chromatography was performed using Fisher silica gel, 60 Å pore size, 230-400 mesh, 40-63 µm. 'Petrol' refers to petroleum ether, boiling range 40-60 ºC. All thin layer chromatography (TLC) analysis was performed using silica gel on Merck aluminium TLC silica gel plates, 60 with 254 nm fluorescent indicator, with visualisation by fluorescence quenching using 254 nm light or staining with potassium permanganate solution.
All melting points (mp) were obtained using a Stuart SMP10 melting point instrument and are uncorrected.

Nuclear magnetic resonance (NMR) data were acquired using a Bruker Avance 400 MHz spectrometer with samples dissolved in an appropriate deuterated solvent. Chemical shifts (δ_H) for hydrogen are expressed in parts per million (ppm) relative to tetramethylsilane (0.0 ppm). Chemical shifts for carbon (δ_C) are reported in parts per million relative to the carbon resonances of the residual solvent peak. Carbon resonances were assigned by correlation with hydrogen resonance using HSQC and HMBC spectra. NMR results are reported as singlet (s), doublet (d), triplet (t), quartet (q) or combinations thereof, or multiplet (m). Coupling constants (J) are expressed in Hz and rounded to the nearest 0.1 Hz.

All Fourier transform infra-red (FTIR) data acquired as thin films using a Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers (ν_{max}) being reported in cm-1.

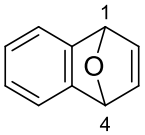
Mass spectrum (MS) data exploiting electron impact ionization in the positive mode (EI+) was acquired using an Agilent Technologies 7890A GC System (Agilent Technologies 30 m × 0.250 mm, 0.25 µm film) with on-line Agilent Technologies 5975B inert XL EI/CI MSD. MS data exploiting electrospray ionisation in the positive mode (ESI+) was acquired using a Bruker MicrOTOF-Q spectrometer or Thermo Scientific LTQ Orbitrap XL spectrometer with direct injection. Photophysical data was obtained using an Agilent Technologies Cary Eclipse Fluorescence Spectrophotometer and an Agilent Technologies Cary 60 UV-Visible Spectrophotometer.
Microwave reaction vessels were oven dried and all experiments were performed under an air atmosphere. All microwave reactions were performed using a CEM Discover LabMate reactor and 10 mL microwave vessel.

Diphenyliodonium-2-carboxylate **6**[107]



Ortho-iodobenzoic acid (5.06 g, 20.4 mmol) was added to sulfuric acid (44 mL, 18 M) at 0 ºC and stirred for 5 minutes. Potassium persulfate (10.54 g, 39.0 mmol) was added portion-wise over 10 minutes maintaining the temperature below 5 ºC before stirring for a further hour at rt. Benzene (19 mL) was added and the reaction mixture stirred at rt for 21 h. The mixture was poured onto ice and made alkaline with sodium hydroxide solution (550 mL, 6 M) retaining the temperature below 40 ºC. The mixture was extracted with chloroform (2 x 250 mL) and the volume reduced *in vacuo* to near dryness before addition of Et_2O (250 mL). The mixture was filtered and the filter cake dried azeotropically with a DCM/MeOH mixture (1:1, 250 mL) *in vacuo* to give diphenyliodonium-2-carboxylate as a colourless solid (5.41 g, 82 %); mp: 215-216 ºC dec. (lit: 220 ºC dec.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.77 (d, *J* 8.3 Hz, 1H, 4'-H), 7.42 (t, *J* 7.7 Hz, 1H, 6-H), 7.61 (t, *J* 7.7 Hz, 3H, 4-H, 3'-H, 5'-H), 7.79 (t, *J* 7.6 Hz, 1H, 5-H), 7.95 (d, *J* 7.4 Hz, 2H, 2'-H, 6'-H), 8.49 (d, *J* 7.5 Hz, 1H, 3-H); ^{13}C NMR (100 MHz) δ_C 115.1 (1'-C), 115.4 (1-C), 125.8 (4'-CH), 130.9 (4-CH), 131.9 (3'-CH, 5'-CH), 132.7 (5-CH), 132.9 (3-CH), 133.2 (2-C), 133.7 (6-CH), 137.1 (2'-CH, 6'-CH), 166.3 (C=O); ν_{max} (solid, cm^{-1}) 1616 (CO_2), 1347 (CO_2), *m/z* (ESI$^+$) calculated for $C_{13}H_9IO_2$ $[M+H]^+$ 324.9720; found 324.9736 (error 5.25 ppm).

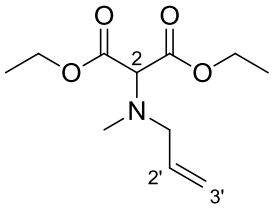
1,4-Dihydro-1,4-epoxynaphthalene **2**[37]



In an oven dried reaction vessel was combined diphenyliodonium-2-carboxylate (150 mg, 462.8 µmol), furan (0.05 mL, 687.5 µmol) and MeCN (3 mL). The reaction mixture was exposed to microwave irradiation (300 W, 200 ºC) for 5 mins and then cooled. The solution was then concentrated *in vacuo* and the residue purified by column chromatography (9:1 v/v petol:Et_2O) to yield 1,4-dihydro-1,4-epoxynaphthalene as a colourless solid (38.4 mg, 58 %); Rf = 0.12 (9:1 v/v petrol:Et_2O); mp: 53 - 55 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.72 (s, 2H, HC(O)CH), 6.97 (dd, *J* 2.9 Hz 5.1 Hz, 2H, 5-H, 8-H), 7.09 (s, 2H, 2-H, 3-H), 7.25 (dd, *J* 3.0 Hz 5.0 Hz, 2H, 6-H, 7-H); ^{13}C NMR (100 MHz) δ_C 82.3 (1-CH, 4-CH), 120.3 (6-CH, 7-CH), 125.0 (5-CH, 8-CH), 143.0 (2-CH, 3-CH), 149.0 (4a-C, 8a-C); νmax (solid, cm-1) 3020 (C-H), 1278 (C-O), 843 (C-H), m/z (ESI+) calculated for $C_{10}H_8O$

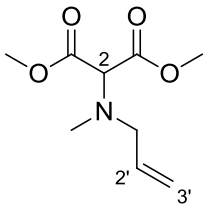
$[M+H]^+$ 145.0648; found 145.0646 (error -0.69 ppm).

Diethyl 2-(allyl(methyl)amino)malonate **74**



N-allylmethylamine (0.84 mL, 8.8 mmol) was added to a stirred solution of diethyl bromomalonate (1.50 mL, 8.8 mmol) and potassium carbonate (1.49 g, 10.8 mmol) in DMF (25 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 21 h at that temperature prior to addition of water (200 mL). The aqueous solution was subsequently extracted with EtOAc (2 x 100 mL) and the combined organic extracts washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield a yellow oil (2.23 g) which was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield diethyl 2-(allyl(methyl)amino)malonate as a colourless oil (1.93 g, 96 %); R_f = 0.41 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.29 (t, *J* 7.1 Hz, 6H, 2x $CO_2CH_2C\underline{H}_3$), 2.47 (s, 3H, $NC\underline{H}_3$), 3.28 (d, *J* 6.6 Hz, 2H, $=CHC\underline{H}_2N$), 4.19 (s, 1H, 2-$\underline{H}$), 4.25 (q, *J* 7.1 Hz, 4H, 2x $CO_2C\underline{H}_2CH_3$), 5.18 (dd, *J* 1.6 Hz 10.1 Hz, 1H, 3'-$\underline{H}_{trans}$), 5.23 (dd, *J* 1.6 Hz 17.0 Hz, 1H, 3'-$\underline{H}_{cis}$), 5.86 (ddt, *J* 6.6 Hz 10.1 Hz 17.0 Hz, 1H, 2'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 14.2 (2x $CO_2CH_2\underline{C}H3$), 39.1 ($N\underline{C}H_3$), 58.1 ($=CH\underline{C}H_2N$), 61.3 (2x $CO_2\underline{C}H_2CH_3$), 68.6 (2-$\underline{C}H$), 118.4 (3'-$\underline{C}H_2$), 135.3 (2'-$\underline{C}H$), 164.7 (1-$\underline{C}O_2Et$, 3-$\underline{C}O_2Et$); ν_{max} (thin film, cm^{-1}) 1730 (C=O ester), 1148 (C-O ester), 1027 (C-N amine); *m/z* (ESI^+) calculated for $C_{11}H_{19}NO_4$ $[M+H]^+$; 230.1387, found 230.1393 (error -2.70 ppm).

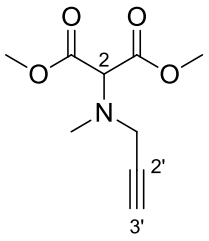
Dimethyl 2-(allyl(methyl)amino)malonate **83a**



N-allylmethylamine (2.20 mL, 22.8 mmol) was added to a stirred solution of dimethyl bromomalonate (3 mL, 22.8 mmol) and potassium carbonate (3.78 g, 28.4 mmol) in DMF (40 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 83 h at that temperature prior to addition of water (250 mL) and extracting with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL) dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give a yellow oil (3.59 g). The crude oil was purified by column chromatography (7:3 v/v petrol:EtOAc) to give dimethyl

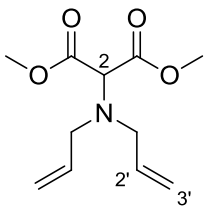
2-(allyl(methyl)amino)malonate as a colourless oil (2.30 g, 50 %); R_f = 0.37 (7:3 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.47 (s, 3H, NC$\underline{H}_3$), 3.27 (d, *J* 6.6 Hz, 2H, =CHC$\underline{H}_2$N), 3.78 (s, 6H, 2x $CO_2C\underline{H}_3$), 4.24 (s, 1H, 2-$\underline{H}$), 5.18 (dd, *J* 1.2 Hz 10.1 Hz, 1H, 3'-$\underline{H}_{trans}$), 5.23 (dd, *J* 1.2 Hz 17.1 Hz, 1H, 3'-$\underline{H}_{cis}$), 5.85 (ddt, *J* 6.6 Hz 10.2 Hz 17.1 Hz, 1H, 2'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 39.1 (N$\underline{C}H_3$), 52.3 (2x $CO_2\underline{C}H_3$), 58.2 (=CH$\underline{C}H_2$N), 68.3 (2-$\underline{C}$H), 118.6 (3'-$\underline{C}H_2$), 135.1 (2'-$\underline{C}$H), 168.1 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1736 (C=O ester), 1155 (C-O ester), 1054 (C-N amine)**;** *m/z* (ESI$^+$) calculated for $C_9H_{15}NO_4$ $[M+H]^+$; 202.1074, found 202.1081 (error -3.54 ppm).

Dimethyl 2-(methyl(prop-2-yn-1-yl)amino)malonate **83b**



N-methylpropargylamine (2.60 mL, 30.8 mmol) was added to a stirred solution of dimethyl bromomalonate (4.06 mL, 30.8 mmol) and potassium carbonate (5.15 g, 37.2 mmol) in DMF (40 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 96 h at that temperature prior to addition of water (250 mL) and extracted with EtOAc (3 x 125 mL). The combined organic layers were washed with water (250 mL) and brine (250 mL) sequentially, dried over Na_2SO_4, filtered and the filtrated evaporated *in vacuo* to yield an orange oil (4.59 g). The crude oil was purified by bulb to bulb distillation (b.p. 110 ºC, 3.75 mmHg) to yield dimethyl 2-(methyl(prop-2-yn-1-yl)amino)malonate as a colourless oil (2.55 g, 42 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.28 (t, *J* 2.5 Hz, 1H, 3'-C$\underline{H}$), 2.56 (s, 3H, NC$\underline{H}_3$), 3.59 (d, *J* 2.4 Hz, 2H, ≡CC$\underline{H}_2$N), 3.79 (s, 6H, 2x $CO_2C\underline{H}_3$), 4.31 (s, 1H, 2-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 39.2 (N$\underline{C}H_3$), 43.9 (≡C$\underline{C}H_2$N), 52.5 (2x $CO_2\underline{C}H_3$), 68.2 (2-$\underline{C}$H), 73.5 (3'-$\underline{C}$H), 78.8 (2'-$\underline{C}$), 167.6 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1735 (C=O ester), 1153 (C-O ester), 1055 (C-N amine)**;** *m/z* (ESI$^+$) calculated for $C_9H_{13}NO_4$ $[M+H]^+$; 200.0917, found 200.0923 (error -2.77 ppm).

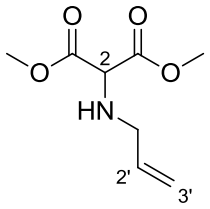
Dimethyl 2-(diallylamino)malonate **83c**



Diallylamine (1.41 mL, 11.4 mmol) was added to a stirred solution of dimethyl bromomalonate (1.50 mL, 11.4 mmol) and potassium carbonate (1.91 g, 13.8 mmol) in DMF (40 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 68 h at that temperature prior to addition of water (275 mL)

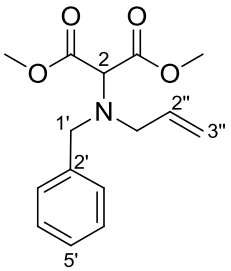
and extracting with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (150 mL) dried over Na_2SO_4, filtered and the filtrated evaporated *in vacuo* to give a crude yellow oil (2.04 g). The crude oil was purified by column chromatography (7:3 v/v petrol:EtOAc) to yield dimethyl 2-(diallylamino)malonate as a colourless oil (505 mg, 20 %); R_f = 0.52 (7:3 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.33 (d, *J* 6.5 Hz, 4H, 2x =CHC<u>H</u>$_2$N), 3.77 (s, 6H, 2x $CO_2C\underline{H}_3$), 4.36 (s, 1H, 2-<u>H</u>), 5.15 (dd, *J* 1.2 Hz 10.1 Hz, 2H, 2x 3'-<u>H</u>$_{trans}$), 5.22 (dd, *J* 1.2 Hz 17.0 Hz, 2H, 2x 3'-<u>H</u>$_{cis}$), 5.82 (ddt, *J* 6.4 Hz 10.1 Hz 17.0 Hz, 2H, 2x 2'-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 52.4 (2x $CO_2\underline{C}H_3$), 54.5 (2x =CH<u>C</u>H$_2$N), 65.6 (2-<u>C</u>H), 118.1 (2x 3'-<u>C</u>H$_2$), 135.6 (2x 2'-<u>C</u>H), 168.7 (1-<u>C</u>O$_2$Me, 3-<u>C</u>O$_2$Me); ν_{max} (thin film, cm^{-1}) 1736 (C=O ester), 1156 (C-O ester), 1025 (C-N amine)**;** *m/z* (ESI$^+$) calculated for $C_{11}H_{17}NO_4$ $[M+H]^+$; 228.1230, found 228.1237 (error -2.21 ppm).

Dimethyl 2-(allylamino)malonate **83d**[131]



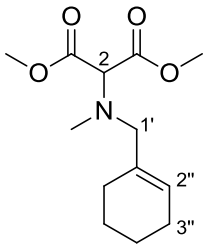
Allylamine (0.86 mL, 11.5 mmol) was added to a stirred solution of dimethyl bromomalonate (1.50 mL, 11.4 mmol) and potassium carbonate (1.90 g, 13.8 mmol) in DMF (40 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 41 h prior to quenching with water (150 mL) and extracting with EtOAc (2 x 125 mL). The combined organic extracts were washed with water (2 x 100 mL) dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield a yellow oil (1.62 g). The oil was purified by bulb to bulb distillation (b.p. 130 ºC, 3.75 mmHg) to yield dimethyl 2-(allylamino)malomate as a colourless oil (632 mg, 30 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.27 (d, *J* 6.1 Hz, 2H, =CHC<u>H</u>$_2$N), 3.79 (s, 6H, 2x $CO_2C\underline{H}_3$), 4.11 (s, 1H, 2-<u>H</u>), 5.14 (dd, *J* 1.1 Hz 10.3 Hz, 1H, 3'-<u>H</u>$_{trans}$), 5.21 (dd, *J* 1.1 Hz 16.8 Hz, 1H, 3'-<u>H</u>$_{cis}$), 5.85 (ddt, *J* 6.1 Hz 10.3 Hz 16.8 Hz, 1H, 2'-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 50.4 (=CH<u>C</u>H$_2$N), 52.9 (2x $CO_2\underline{C}H_3$), 63.6 (2-<u>C</u>H), 117.5 (3'-<u>C</u>H$_2$), 135.2 (2'-<u>C</u>H), 169.0 (1-<u>C</u>O$_2$Me, 3-<u>C</u>O$_2$Me); ν_{max} (thin film, cm^{-1}) 1736 (C=O ester), 1159 (C-O ester)**;** *m/z* (ESI$^+$) calculated for $C_8H_{13}NO_4$ $[M+H]^+$; 188.0917, found 188.0919 (error -1.24 ppm).

Dimethyl 2-(allyl(benzyl)amino)malonate **83e**



Dimethyl bromomalonate (0.85 mL, 6.4 mmol) was added to a stirred solution of *N*-benzylprop-2-en-1-amine (970 mg, 6.6 mmol) and potassium carbonate (1.41 g, 8.3 mmol) in DMF (15 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 72 h at that temperature prior to addition of water (200 mL) and extracting with EtOAc (2 x 125 mL). The combined organic extracts were washed with water (150 mL) and brine (150 mL) sequentially, dried with over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give an orange oil (1.76 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) yield dimethyl 2-(allyl(benzyl)amino)malonate as a colourless oil (421 mg, 24 %); R_f = 0.44 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.30 (d, J 6.4 Hz, 2H, =CHC$\underline{H_2}$N), 3.77 (s, 6H, 2x $CO_2C\underline{H_3}$), 3.87 (s, 2H, 1'-$\underline{H_2}$), 4.33 (s, 1H, 2-$\underline{H}$), 5.16 (dd, *J* 1.5 Hz 10.1 Hz, 1H, 3''-$\underline{H_{trans}}$), 5.21 (dd, *J* 1.5 Hz 17.0 Hz, 1H, 3''-$\underline{H_{cis}}$), 5.81 (ddt, *J* 6.3 Hz 10.1 Hz 17.0 Hz, 1H, 2''-$\underline{H}$), 7.25 (d, *J* 6.0 Hz, 1H, 5'-$\underline{H}$), 7.31 (t, *J* 7.6 Hz, 2H, 4'-$\underline{H}$, 6'-$\underline{H}$), 7.39 (d, *J* 7.2 Hz, 2H, 3'-$\underline{H}$, 7'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 52.2 (2x $CO_2\underline{C}H_3$), 54.5 (=CH$\underline{C}H_2$N), 55.2 (1'-$\underline{C}H_2$), 65.5 (2-$\underline{C}$H), 118.2 (3''-$\underline{C}H_2$), 127.1 (5'-$\underline{C}$H), 128.3 (4'-$\underline{C}$H, 6'-$\underline{C}$H), 128.7 (3'-$\underline{C}$H, 7'-$\underline{C}$H), 135.6 (2''-$\underline{C}$H), 139.1 (2'-$\underline{C}$), 168.7 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1735 (C=O ester), 1154 (C-O ester), 1027 (C-N amine)**;** *m/z* (ESI^+) calculated for $C_{15}H_{19}NO_4$ $[M+H]^+$; 278.1387, found 278.1395 (error -3.10 ppm).

Dimethyl 2-((cyclohex-1-en-1-ylmethyl)(methyl)amino)malonate **83f**[132]

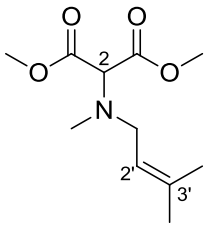


Triethylamine (1.55 mL, 11.1 mmol) was added to a stirred solution of 1-cyclohexene-1-carboxaldehyde (1.06 mL, 9.3 mmol) and methylamine hydrochloride (2.01 g, 29.8 mmol) in MeOH (10 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 3 h before cooling on ice for 10 minutes after which sodium borohydride (0.45 g, 11.9 mmol) was added portion-wise over 10 minutes. Following addition the cooling bath was removed and the mixture stirred for 1 hour before quenching with hydrochloric acid (3 M, 50 mL). The mixture was then extracted with DCM (2 x 75 mL) and the aqueous layer basified to pH 8 with potassium hydroxide. The aqueous layer was extracted with Et_2O (2 x 100 mL) dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield 1-(cyclohex-1-en-1-yl)-*N*-methylmethanamine as a yellow oil (804 mg) which was used without further purification.

Dimethyl bromomalonate (0.85 mL, 6.4 mmol) was added to a stirred solution of 1-(cyclohex-1-en-1-yl)-*N*-methylmethanamine (804 mg, 6.4 mmol) and potassium carbonate (1.07 g, 7.7 mmol) in DMF (15 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 60 h at that temperature prior to addition of water (100 mL) and extracting with EtOAc (2 x 75 mL). The combined organic extracts were then washed with water (150 mL) and brine (50 mL) sequentially, dried over Na_2SO_4,

filtered and the filtrate evaporated in vacuo to give an orange oil (1.53 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield dimethyl 2-((cyclohex-1-en-1-ylmethyl)(methyl)amino)malonate as a colourless oil (863 mg, 36 % over 2 steps); R_f = 0.48 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.54-1.65 (m, 4H, 4''-$\underline{H_2}$, 3''-$\underline{H_2}$), 1.96-2.04 (m, 4H, 5''-$\underline{H_2}$, 6''-$\underline{H_2}$), 2.42 (s, 3H, NC$\underline{H_3}$), 3.10 (s, 2H, 1'-$\underline{H_2}$), 3.77 (s, 6H, 2x $CO_2C\underline{H_3}$), 4.20 (s, 1H, 2-$\underline{H}$), 5.61 (br s, 1H, 2''-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 22.5 (4''-$\underline{C}H_2$), 22.8 (3''-$\underline{C}H_2$), 25.2 (5''-$\underline{C}H_2$), 26.6 (6''-$\underline{C}H_2$), 39.0 (N$\underline{C}H_3$), 52.1 (2x $CO_2\underline{C}H_3$), 62.1 (1'-$\underline{C}H_2$), 67.7 (2-$\underline{C}$H), 126.0 (2''-$\underline{C}$H), 134.9 (1''-$\underline{C}$), 168.4 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1736 (C=O ester), 1149 (C-O ester), 1055 (C-N amine)**;** *m/z* (ESI^+) calculated for $C_{13}H_{21}NO_4$ $[M+H]^+$; 256.1543, found 256.1548 (error -1.59 ppm).

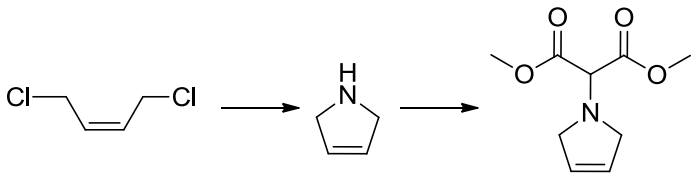
Dimethyl 2-(methyl(3-methylbut-2-en-1-yl)amino)malonate **83g**



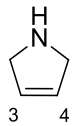
Triethylamine (4.8 mL, 34.5 mmol) was added to a stirred solution of 3-methylcrotonaldehyde (2.78 mL, 28.8 mmol) and methylamine hydrochloride (5.89 g, 87.2 mmol) in MeOH (25 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 3 h before cooling on ice for 10 minutes after which sodium borohydride (1.15 g, 30.3 mmol) was added portion-wise over 10 minutes. Following addition the cooling bath was removed and the mixture stirred for 30 minutes before addition of hydrochloride acid (3 M, 150 mL) and extracting with DCM (2 X 100 mL). The aqueous layer was then basified to pH 8 with potassium hydroxide and extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield *N*-3-dimethylbut-2-en-1-amine (1.26 g) as an orange oil which was used without further purification.

Dimethyl bromomalonate (1.67 mL, 12.7 mmol) was added to a stirred solution of *N*-3-dimethylbut-2-en-1-amine (1.26 g, 12.7 mmol) and potassium carbonate (2.13 g, 15.4 mmol) in DMF (20 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 50 h at that temperature prior to addition of water (175 mL) and extracting with EtOAc (2 x 125 mL). The combined organic extracts were washed with brine (2 x 150 ml) dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield an orange oil (2.14 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield dimethyl 2-(methyl(3-methylbut-2-en-1-yl)amino)malonate as a yellow oil (239 mg, 4 % over 2 steps); R_f = 0.28 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.65 (s, 3H, 3'-$C_{\underline{trans}}\underline{H_3}$), 1.74 (s, 3H, 3'-$C_{\underline{cis}}\underline{H_3}$), 2.47 (s, 3H, NC$\underline{H_3}$), 3.23 (d, *J* 7.1 Hz, 2H, =CHC$\underline{H_2}$N), 3.78 (s, 6H, 2x $CO_2C\underline{H_3}$), 4.26 (s, 1H, 2-$\underline{H}$), 5.23 (t, *J* 7.2 Hz, 1H, 2'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 17.9 (3'-$\underline{C_{trans}}H_3$), 26.0 (3'-$\underline{C_{cis}}H_3$), 39.1 (N$\underline{C}H_3$), 52.2 (2x $CO_2\underline{C}H_3$), 52.6 (=CH$\underline{C}H_2$N), 67.9 (2-$\underline{C}$H), 120.94 (2'-$\underline{C}$H), 136.8 (3'-$\underline{C}$), 168.3 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1735 (C=O ester), 1144 (C-O), 1045 (C-N amine)**;** *m/z* (ESI^+) calculated for $C_{11}H_{19}NO_4$ $[M+H]^+$; 230.1387, found 230.1392 (error -2.19 ppm).

Dimethyl 2-(2,5-dihydro-1H-pyrrol-1-yl)malonate **83h**[133]



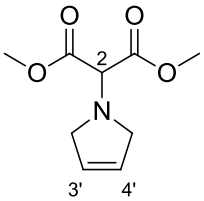
83h



Hexamethylenetetramine (17.21 g, 122.8 mmol) and cis-1,4-dichloro-2-butene (12.92 mL, 122.8 mmol) were combined in chloroform (220 mL) and heated to reflux for 20 h. The mixture was cooled on ice, filtered and the filter cake washed with chloroform (2 x 50 mL) prior to drying under suction to yield (3r,5r,7r)-1-((Z)-4-chlorobut-2-en-1-yl)-1,3,5,7-tetraazaadamantan-1-ium chloride as a colourless solid (31.44 g) which was used without further purification.

Hydrochloric acid (12 M, 33 mL, 379.5 mmol) was added to a stirred solution of (3r,5r,7r)-1-((Z)-4-chlorobut-2-en-1-yl)-1,3,5,7-tetraazaadamantan-1-ium chloride (31.44 g, 118.6 mmol) in aqueous EtOH (95 %, 190 mL) at 25 ºC. The mixture was stirred for 20 h prior to cooling on ice. The mixture was filtered and the filtrate evaporated *in vacuo* to yield an orange semi-solid. This was taken up in a minimum cold EtOH (<50 mL), filtered and the filter cake washed with cold EtOH (2 x 20 mL). The filtrate was evaporated *in vacuo* and the process repeated twice more. The solid was then recrystallized from hot EtOAc to yield (Z)-4-chlorobut-2-en-1-aminium chloride as a pale yellow solid (18.90 g) which was used without further purification.

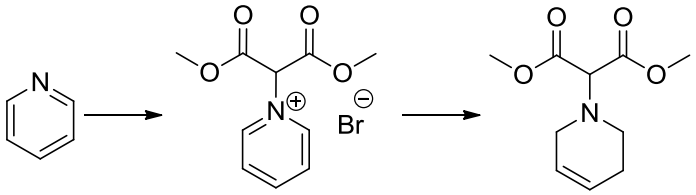
DBU (39.8 mL, 266.2 mmol) was added over 15 mins to (Z)-4-chlorobut-2-en-1-aminium chloride (18.90 g, 133.1 mmol) cooled in an ice-bath. The resulting orange slurry was distilled and the fraction between 80-86 ºC collected to yield 2,5-dihydro-1H-pyrrole as a colourless oil (3.95 g, 46 % over 3 steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.91 (s, 1H, N<u>H</u>), 3.74 (s, 4H, =CHC<u>H</u>$_2$N, =CHC<u>H</u>$_2$N), 5.87 (br s, 2H, =C<u>H</u>, =C<u>H</u>); ^{13}C NMR (100 MHz) δ_C 53.8 (=CH<u>C</u>H$_2$N, =CH<u>C</u>H$_2$N), 128.5 (=<u>C</u>H, =<u>C</u>H); ν_{max} (thin film, cm^{-1}) 1198 (C-N amine)**;** *m/z* (ESI$^+$) calculated for C_4H_7N $[M+H]^+$; 70.0651, found 70.0653 (error -2.50 ppm).



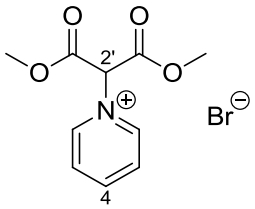
Dimethyl bromomalonate (9.12 mL, 69.2 mmol) was added to a stirred solution of 2,5-dihydro-1H-pyrrole (4.78 g, 69.2 mmol) and potassium carbonate (11.47 g, 83.0 mmol) in DMF (100 mL) under an

atmosphere of N_2 at 25 ºC. The mixture was stirred for 96 h prior to quenching with water (400 mL) and extracting with EtOAc (3 x 250 mL). The combined organic extracts were washed with water (2 x 175 ml) and brine (2 x 100 ml) dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield an orange oil (9.83 g). Excess 2,5-dihydro-1H-pyrrole was removed from the oil *in vacuo* (50 ºC, 5 mbar) and the resulting residue treated with oxalic acid in Et_2O (6.20 g in 450 mL) and washed with water (2 x 250 mL). The aqueous layer was treated with Na_2HCO_3 until ~pH 7 and subsequently extracted with Et_2O (3 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield dimethyl 2-(2,5-dihydro-1H-pyrrol-1-yl)malonate as a yellow oil (5.17 g, 38 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.79 (s, 6H, 2x $CO_2C\underline{H}_3$), 3.83 (s, 4H, =CHC$\underline{H}_2$N, =CHC$\underline{H}_2$N), 4.37 (s, 1H, 2-$\underline{H}$), 5.77 (s, 2H, =C$\underline{H}$, =C$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 52.5 (2x $CO_2\underline{C}H_3$), 57.1 (=CH$\underline{C}H_2$N, =CH$\underline{C}H_2$N), 67.3 (2-$\underline{C}$H), 126.9 (=$\underline{C}$H, =$\underline{C}$H), 168.1 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1732 (C=O ester), 1155 (C-O ester), 1017 (C-N amine)**;** *m/z* (ESI$^+$) calculated for $C_9H_{13}NO_4$ $[M+H]^+$; 200.0917, found 200.0923 (error -2.73 ppm).

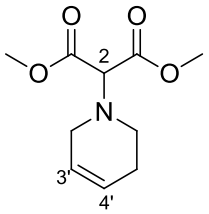
Dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate **83i**[134]



83i

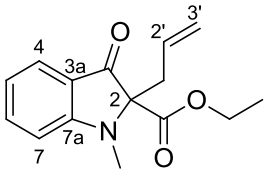


Pyridine (2.02 mL, 25.0 mmol) was added to a stirred solution of dimethyl bromomalonate (3 ml, 22.8 mmol) in acetone (30 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred at this temperature for 42 h and the mixture was then filtered. The filter cake was washed with cold acetone (2 x 10 mL) prior to drying under suction to yield 1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)pyridin-1-ium bromide (4.30 g, 90 %) as a colourless solid that was used without further purification. mp: 126 ºC dec.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.96 (s, 6H, 2x $CO_2C\underline{H}_3$), 8.06 (t, *J* 7.1 Hz, 2H, 3-$\underline{H}$, 5-$\underline{H}$), 8.68 (s, 1H, 2'-$\underline{H}$), 8.68 (t, *J* 7.7 Hz, 1H, 4-$\underline{H}$), 9.88 (d, *J* 6.0 Hz, 2H, 2-$\underline{H}$, 6-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 55.2 (2x $CO_2\underline{C}H_3$), 70.9 (2'-$\underline{C}$H), 127.3 (3-$\underline{C}$H, 5-$\underline{C}$H), 147.0 (2-$\underline{C}$H, 6-$\underline{C}$H), 147.3 (4-$\underline{C}$H), 163.3 (1'-$\underline{C}O_2$Me, 3'-$\underline{C}O_2$Me); ν_{max} (solid, cm^{-1}) 1736 (C=O ester), 1200 (C-O); *m/z* (ESI$^+$) calculated for $C_{10}H_{12}NO_4$ $[M]^+$; 210.0766, found 210.0761 (error -0.23 ppm).



1-(1,3-dimethoxy-1,3-dioxopropan-2-yl)pyridin-1-ium bromide (1.17 g, 4.0 mmol) was added to a stirred solution of ammonium chloride (0.30 g, 5.5 mmol) in MeOH (30 mL) and cooled in an ice-bath. To the mixture sodium borohydride (0.83 g, 22.0 mmol) was added portion-wise over 5 minutes. The mixture was the equilibrated to rt and stirred for 1 h under and atmosphere of N_2. The mixture was quenched with water (150 mL) and extracted with DCM (2 x 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give an orange semi-solid. The semi-solid was dissolved in EtOAc (350 mL) and extracted with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give an orange oil (578 mg) which was purified by bulb to bulb distillation (150 ºC, 5 mbar) to yield dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (445 mg, 52 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.19-2.25 (m, 2H, 5'-$\underline{H_2}$), 2.85 (t, *J* 5.6 Hz, 2H, 2'-$\underline{H_2}$), 3.30 (q, *J* 2.8 Hz, 2H, 6'-$\underline{H_2}$), 3.78 (s, 6H, 2x $CO_2C\underline{H_3}$), 4.20 (s, 1H, 2-$\underline{H}$), 5.62-5.67 (m, 1H, 4'-$\underline{H}$), 5.74-5.79 (m, 1H, 3'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 26.5 (5'-$\underline{C}H_2$), 46.9 (2'-$\underline{C}H_2$), 49.6 (6'-$\underline{C}H_2$), 52.3 (2x $CO_2\underline{C}H_3$), 70.4 (2-$\underline{C}$H), 124.9 (4'-$\underline{C}$H), 125.1 (3'-$\underline{C}$H), 167.7 (1-$\underline{C}O_2$Me, 3-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1732 (C=O ester), 1194 (C-N amine), 1149 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{10}H_{15}NO_4$ $[M+H]^+$; 214.1074, found 214.1080 (error -3.34 ppm).

Ethyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate **77**



To a flame dried round-bottom flask, tetrabutylammonium fluoride solution (1M, 0.94 mL, 940.0 µmol) was added *via* syringe in one portion to a solution of diethyl 2-(allyl(methyl)amino)malonate (95.3 mg, 473.6 µmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 329.5 µmol) in MeCN (10 mL) and stirred under an atmosphere of N_2 at 25 ºC. After one hour the reaction mixture was concentrated in vacuo to give a crude orange oil (938.6 mg). The crude oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield ethyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate (49.5 mg, 43 %) as a fluorescent yellow oil; R_f = 0.29 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.22 (t, *J* 7.1 Hz, 3H, $CO_2CH_2C\underline{H_3}$), 2.88 (dd, *J* 7.6 Hz 14.6 Hz, 1H, 1'-$\underline{H}$), 3.00 (s, 3H, $NC\underline{H_3}$), 3.07 (dd, *J* 6.8 Hz 14.6 Hz, 1H, 1'-$\underline{H}$), 4.12-4.23 (m, 2H, $CO_2C\underline{H_2}CH_3$), 4.97 (dd, *J* 1.6 Hz 10.1 Hz, 1H, 3'-$\underline{H_{\textit{trans}}}$), 5.14 (dd, *J* 1.6 Hz 17.0 Hz, 1H, 3'-$\underline{H_{\textit{cis}}}$), 5.41 (ddt, *J* 7.2 Hz 10.1 Hz 17.0 Hz, 1H, 2'-$\underline{H}$), 6.74 (t, *J* 7.4 Hz, 1H, 5-$\underline{H}$), 6.79 (d, *J* 8.5 Hz, 1H, 7-$\underline{H}$), 7.49 (ddd, *J* 1.3 Hz 7.2 Hz 8.4 Hz, 1H, 6-$\underline{H}$), 7.56 (d,

J 7.7 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 14.1 ($CO_2CH_2\underline{C}H_3$), 29.2 ($N\underline{C}H_3$), 36.5 (1'-$\underline{C}H_2$), 62.2 ($CO_2\underline{C}H_2CH_3$), 77.2 (2-C), 108.3 (7-CH), 117.5 (5-CH), 119.1 (3a-C), 119.6 (3'-$\underline{C}H_2$), 125.1 (4-CH), 130.8 (2'-CH), 137.9 (6-CH), 161.8 (7a-C), 167.1 ($\underline{C}O_2Et$), 195.4 (3-C=O); ν_{max} (thin film, cm^{-1}) 1739 (C=O ester), 1701 (C=O aryl), 1322 (C-N aryl)**;** UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 202 (7836), 237 (6865), 421 (696); *m/z* (ESI^+) calculated for $C_{15}H_{17}NO_3$ $[M+H]^+$; 260.1281, found 260.1285 (error -1.49 ppm).

General Procedure 1

To a flame dried round-bottom flask, amine (1.5 eq) was added to a stirred solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 329.5 µmol) in MeCN (10 mL) under an atmosphere of N_2 at 25 ºC. To the mixture tetrabutylammonium fluoride solution (1 M, 0.94 mL, 940 µmol) was added by syringe pump over 2 h (dropwise). The mixture was run through a silica plug washing with EtOAc until all colour was removed (~125 mL). The filtrate was evaporated *in vacuo* to give the crude material which is purified by column chromatography (solutions of petrol and EtOAc as the eluent).

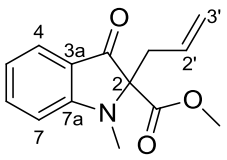
General Procedure 2

To a flame dried round-bottom flask, amine (1.5 eq) was added to a stirred solution of aryne precursor (0.08 mL) in MeCN (10 mL) under an atmosphere of N_2 at 25 ºC. To the mixture tetrabutylammonium fluoride solution (1 M, 2.9 eq) was added over 2 h (dropwise). The mixture was run through a silica plug washing with EtOAc until all colour is removed (~125 mL). The filtrate was evaporated *in vacuo* to give the crude material which is purified by column chromatography (solutions of petrol and EtOAc or Et_2O as the eluent).

General Procedure 3

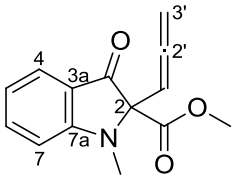
To a flame dried round-bottom flask, amine (5.0 eq) was added to a stirred solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 329.5 µmol) in MeCN (10 mL) under an atmosphere of N_2 at 25 ºC. To the mixture tetrabutylammonium fluoride in THF (1 M, 0.94 mL, 940 µmol) was added over 2 h (dropwise). The mixture was run through a silica plug washing with EtOAc until all colour was removed (~125 mL). The filtrate was evaporated *in vacuo* to give the crude material which is purified by column chromatography (solutions of petrol and EtOAc as the eluent).

Methyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate **84a**



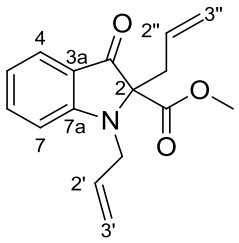
Generated from dimethyl 2-(allyl(methyl)amino)malonate (105 mg, 520.0 µmol) using general procedure 1 to yield after column chromatography (9:1 v/v petrol:EtOAc) methyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate (76.4 mg, 95 %) as a fluorescent yellow solid; R_f = 0.14 (9:1 v/v petrol:EtOAc); mp: 70 - 72 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.82 (dd, *J* 7.5 Hz 14.5 Hz, 1H, 1'-H), 2.93 (s, 3H, NCH_3), 3.00 (dd, *J* 6.8 Hz 14.5 Hz, 1H, 1'-H), 3.65 (s, 3H, CO_2CH_3), 4.91 (dd, *J* 1.6 Hz 10.1 Hz, 1H, 3'-H_{trans}), 5.08 (dd, *J* 1.6 Hz 17.0 Hz, 1H, 3'-H_{cis}), 5.34 (ddt, *J* 7.2 Hz 10.1 Hz 17.0 Hz, 1H, 2'-H), 6.67 (t, *J* 7.6 Hz, 1H, 5-H), 6.72 (d, *J* 8.4 Hz, 1H, 7-H), 7.42 (ddd, *J* 1.3 Hz 7.1 Hz 8.4 Hz, 1H, 6-H), 7.49 (d, *J* 7.7 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 29.2 (NCH_3), 36.5 (1'-CH_2), 53.1 (CO_2CH_3), 76.9 (2-C), 108.3 (7-CH), 117.6 (5-CH), 119.1 (3a-C), 119.7 (3'-CH_2), 125.2 (4-CH), 130.7 (2'-CH), 138.0 (6-CH), 161.7 (7a-C), 167.7 (CO_2Me), 195.3 (3-C=O); ν_{max} (thin film, cm^{-1}) 1740 (C=O ester), 1697 (C=O aryl), 1322 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 231 (8707), 416 (5386); *m/z* (ESI$^+$) calculated for $C_{14}H_{15}NO_3$ $[M+H]^+$; 246.1125, found 246.1131 (error -2.86 ppm)

Methyl 1-methyl-3-oxo-2-(propa-1,2-dien-1-yl)indoline-2-carboxylate **84b**



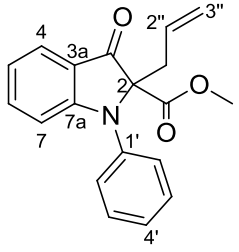
Generated from dimethyl 2-(methyl(prop-2-yn-1-yl)amino)malonate (106 mg, 530 µmol, 1.6 eq) using general procedure 1 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) methyl 1-methyl-3-oxo-2-(propa-1,2-dien-1-yl)indoline-2-carboxylate (73.2 mg, 0.30 mmol, 91 %) as a fluorescent yellow oil; R_f = 0.06 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.01 (s, 3H, NCH_3), 3.77 (s, 3H, CO_2CH_3), 4.88 (dd, *J* 6.6 Hz 11.5 Hz, 1H, 3'-H), 4.98 (dd, *J* 6.7 Hz 11.5 Hz, 1H, 3'-H), 5.78 (t, *J* 6.0 Hz, 1H, 1'-H), 6.76 (t, *J* 7.3 Hz, 1H, 5-H), 6.79 (d, *J* 8.4 Hz, 1H, 7-H), 7.50 (ddd, *J* 1.3 Hz 7.2 Hz 8.4 Hz, 1H, 6-H), 7.57 (d, *J* 7.7 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 30.1 (NCH_3), 53.4 (CO_2CH_3), 77.2 (C2-quat. C), 79.3 (C3'-CH_2), 87.9 (C1'-CH), 108.4 (C7-CH), 117.8 (C3a-quat. C), 117.9 (C5-CH), 125.8 (C4-CH), 138.2 (C6-CH), 161.4 (C7a-quat. C), 166.7 (C-quat. CO_2Me), 193.5 (C-quat. C=O), 207.4 (2'-C); ν_{max} (thin film, cm^{-1}) 1742 (C=O ester), 1702 (C=O aryl), 1324 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 200 (14811), 236 (12320), 417 (1546); *m/z* (ESI$^+$) calculated for $C_{14}H_{13}NO_3$ $[M+H]^+$; 244.0968, found 244.0974 (error -2.39 ppm).

Methyl 1,2-allyl-3-oxoindoline-2-carboxylate **84c**



Generated from dimethyl 2-(diallylamino)malonate (117 mg, 520.0 µmol) using general procedure 1 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) methyl 1,2-allyl-3-oxoindoline-2-carboxylate (46.1 mg, 52 %) as a fluorescent yellow oil; R_f = 0.10 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.94 (dd, *J* 7.5 Hz 14.7 Hz, 1H, 1''-H), 3.02 (dd, *J* 7.0 Hz 14.7 Hz, 1H, 1''-H), 3.68 (s, 3H, CO_2CH_3), 3.94 (dd, *J* 5.2 Hz 17.0 Hz, 1H, 1'-H), 4.03 (dd, *J* 5.7 Hz 17.0 Hz, 1H, 1'-H), 4.99 (dd, *J* 1.4 Hz 10.1 Hz, 1H, 3''-H_{trans}), 5.16 (dd, *J* 1.4 Hz 17.0 Hz, 1H, 3''-H_{cis}), 5.23 (dd, *J* 1.3 Hz 10.2 Hz, 1H, 3'-H_{trans}), 5.30 (dd, *J* 1.3 Hz 17.2 Hz, 1H, 3'-H_{cis}), 5.45 (ddt, *J* 7.2 Hz 10.1 Hz 17.0 Hz, 1H, 2''-H), 5.83-5.93 (m, 1H, 2'-H), 6.77 (t, *J* 7.4 Hz, 1H, 5-H), 6.83 (d, *J* 8.4 Hz, 1H, 7-H), 7.46 (ddd, *J* 1.2 Hz 7.1 Hz, 8.3 Hz, 1H, 6-H), 7.58 (d, *J* 7.7 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 36.9 (C1''-CH_2), 47.1 (1'-CH_2), 52.9 (CO_2CH_3), 76.9 (2-C), 109.5 (7-CH), 117.5 (3'-CH_2), 118.1 (5-CH), 119.5 (3a-C), 120.0 (3''-CH_2), 125.1 (4-CH), 130.6 (2''-CH), 133.3 (2'-CH), 137.8 (6-CH), 161.4 (7a-C), 168.1 (CO_2Me), 195.6 (3-C=O); ν_{max} (thin film, cm^{-1}) 1740 (C=O ester), 1699 (C=O aryl), 1322 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 201 (18339), 237 (16767), 411 (2117); *m/z* (ESI^+) calculated for $C_{16}H_{17}NO_3$ $[M+H]^+$; 272.1281, found 272.1282 (error -0.61 ppm).

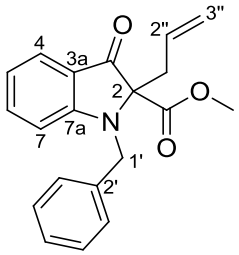
Methyl 2-allyl-3-oxo-1-phenylindoline-2-carboxylate **84d**



Generated from dimethyl 2-(allylamino)malonate (94.3 mg, 504 µmmol) using general procedure 1 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) methyl 2-allyl-3-oxo-1-phenylindoline-2-carboxylate (38.5 mg, 76 %) as a fluorescent yellow oil; R_f = 0.06 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.77 (s, 3H, CO_2CH_3), 4.02 (dd, *J* 5.5 Hz 17.2 Hz, 1H, 1''-H), 4.13 (dd, *J* 4.9 Hz 17.2 Hz, 1H, 1''-H), 5.14 (dd, *J* 1.3 Hz 3.8 Hz, 1H, 3''-H_{trans}), 5.17 (dd, *J* 1.3 Hz 11.0 Hz, 1H, 3''-H_{cis}), 5.70-5.79 (m, 1H, 2''-H), 6.82 (t, *J* 7.4 Hz, 1H, 5-H), 6.89 (d, *J* 8.3 Hz, 1H, 7-H), 7.29-7.32 (m, 2H, 2'-H, 6'-H), 7.35-7.37 (m, 3H, 3'-H, 4'-H, 5'-H), 7.51 (t, *J* 7.5 Hz, 1H, 6-H), 7.60 (d, *J* 7.6 Hz, 1H, 4-H);

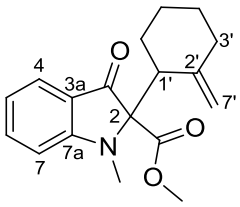
^{13}C NMR (100 MHz) δ_C 47.1 (1''-$\underline{C}H_2$), 53.1 ($CO_2\underline{C}H_3$), 79.5 (2-$\underline{C}$), 109.4 (7-$\underline{C}$H), 117.0 (3''-$\underline{C}H_2$), 118.5 (5-$\underline{C}$H), 118.5 (3a-$\underline{C}$), 125.9 (4-$\underline{C}$H), 127.4 (2'-$\underline{C}$H, 6'-$\underline{C}$H), 128.7 (3'-$\underline{C}$H, 5'-$\underline{C}$H), 128.8 (4'-$\underline{C}$H), 132.8 (2''-$\underline{C}$H), 134.0 (1'-$\underline{C}$), 137.9 (6-$\underline{C}$H), 160.6 (7a-$\underline{C}$), 168.3 ($\underline{C}O_2$Me), 194.5 (3-$\underline{C}$=O); ν_{max} (thin film, cm^{-1}) 1743 (C=O ester), 1710 (C=O aryl), 1320 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 204 (36835), 234 (28565), 412 (2998); *m/z* (ESI^+) calculated for $C_{19}H_{17}NO_3$ $[M+H]^+$; 308.1281, found 308.1283 (error -0.46 ppm).

Methyl 2-allyl-1-benzyl-3-oxoindoline-2-carboxylate **84e**



Generated from dimethyl 2-(allyl(benzyl)amino)malonate (143.5 mg, 517.5 µmol) using general procedure 1 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) methyl 2-allyl-1-benzyl-3-oxoindoline-2-carboxylate (64.6 mg, 61 %) as a fluorescent yellow oil; R_f = 0.09 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.97 (dd, *J* 7.3 Hz 14.7 Hz, 1H, 1''-$\underline{H}$), 3.03 (dd, *J* 6.8 Hz 14.7 Hz, 1H, 1''-$\underline{H}$), 3.56 (s, 3H, $CO_2C\underline{H}_3$), 4.58 (d, *J* 6.5 Hz, 2H, 1'-$\underline{H}_2$), 4.97 (dd, *J* 1.3 Hz 10.2 Hz, 1H, 3''-$\underline{H}_{trans}$), 5.11 (dd, *J* 1.3 Hz 17.1 Hz, 1H, 3''-$\underline{H}_{cis}$), 5.46 (ddt, *J* 7.2 Hz 10.2 Hz 17.1 Hz, 1H, 2''-$\underline{H}$), 6.66 (d, *J* 8.4 Hz, 1H, 5-$\underline{H}$), 6.80 (d, *J* 7.4 Hz, 1H, 7-$\underline{H}$), 7.29-7.33 (m, 5H, 5x Ar-$\underline{H}$), 7.40 (dd, *J* 1.3 Hz 7.2 Hz 8.4 Hz, 1H, 6-$\underline{H}$), 7.62 (d, *J* 7.7 Hz, 1H, 4-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 36.8 (1''-$\underline{C}H_2$), 48.4 (1'-$\underline{C}H_2$), 52.8 ($CO_2\underline{C}H_3$), 76.9 (2-$\underline{C}$), 109.8 (5-$\underline{C}$H), 118.4 (7-$\underline{C}$H), 119.8 (3a-$\underline{C}$), 120.1 (3''-$\underline{C}H_2$), 125.1 (4-$\underline{C}$H), 127.1 (3'-$\underline{C}$H, 7'-$\underline{C}$H), 127.5 (4'-$\underline{C}$H, 6'-$\underline{C}$H), 128.7 (5'-$\underline{C}$H), 130.5 (2''-$\underline{C}$H), 136.9 (2'-$\underline{C}$), 137.8 (6-$\underline{C}$H), 161.8 (7a-$\underline{C}$), 168.1 ($\underline{C}O_2$Me), 195.8 (3-$\underline{C}$=O); ν_{max} (thin film, cm^{-1}) 1742 (C=O ester), 1704 (C=O aryl), 1322 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 202 (9523), 205 (8574), 236 (5885), 410 (756); *m/z* (ESI^+) calculated for $C_{20}H_{19}NO_3$ $[M+Na]^+$; 344.1257, found 344.1255 (error -0.93 ppm).

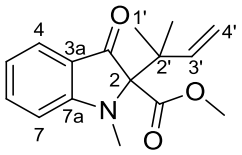
Methyl 1-methyl-2-(2-methylenecyclohexyl)-3-oxoindoline-2-carboxylate **84f**



Generated from dimethyl 2-((cyclohex-1-en-1-ylmethyl)(methyl)amino)malonate (129.8 mg 508 µmol) using general procedure 1 to yield after column chromatograph (9:1 petrol:EtOAc) methyl 1-methyl-2-

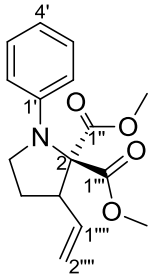
(2-methylenecyclohexyl)-3-oxoindoline-2-carboxylate (26.7 mg, 27 %) as a fluorescent yellow oil; R_f = 0.23 (9:1 petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.32-1.44 (m, 4H, 5'-H$_2$, 4'-H, 6'-H), 1.68-1.71 (m, 1H, 6'-H), 1.75-1.78 (m, 1H, 4'-H), 2.13 (td, *J* 4.0 Hz 12.4 Hz, 1H, 3'-H), 2.32 (d, *J* 13.4 Hz, 1H, 3'-H), 3.20 (s, 3H, NCH$_3$), 3.34 (d, *J* 10.4 Hz, 1H, 1'-H), 3.70 (s, 3H, CO_2CH_3), 4.51 (s, 1H, 7'-H), 4.79 (s, 1H, 7'-H), 6.72 (t, *J* 7.4 Hz, 1H, 5-H), 6.75 (d, *J* 8.3 Hz, 1H, 7-H), 7.48 (t, *J* 7.8 Hz, 1H, 6-H), 7.56 (d, *J* 7.7 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 25.8 (6'-CH$_2$), 27.95 (4'-CH$_2$), 27.99 (5'-CH$_2$), 31.0 (NCH$_3$), 37.8 (3'-CH$_2$), 48.7 (1'-CH), 53.0 (CO_2CH_3), 79.4 (2-C), 107.4 (7'-CH$_2$), 108.5 (7-CH), 117.4 (5-CH), 118.5 (3a-C), 125.0 (4-CH), 138.0 (6-CH), 148.1 (2'-C), 161.8 (7a-C), 168.0 (CO_2Me), 195.3 (3-C=O); ν_{max} (thin film, cm^{-1}) 1733 (C=O ester), 1705 (C=O aryl), 1321 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 202 (17770), 236 (19870), 419 (2189); *m/z* (ESI$^+$) calculated for $C_{18}H_{21}NO_3$ [M+H]$^+$; 300.1594, found 300.1600 (error -2.19 ppm).

Methyl 1-methyl-2-(2-methylbut-3-en-2-yl)-3-oxoindoline-2-carboxylate **84g**



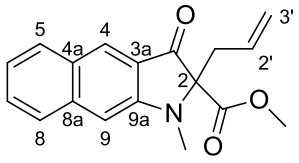
Generated from dimethyl 2-(methyl(3-methylbut-2-en-1-yl)amino)malonate (116.8 mg, 509 µmol) using general procedure 1 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) methyl 1-methyl-2-(2-methylbut-3-en-2-yl)-3-oxoindoline-2-carboxylate (42.8 mg, 48 %) as a fluorescent yellow oil; R_f = 0.15 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.18 (s, 3H, 1'-H$_3$), 1.38 (s, 3H, 2'-CH$_3$), 3.02 (s, 3H, NCH$_3$), 3.66 (s, 3H, CO_2CH_3), 5.05 (dd, *J* 0.9 Hz 9.6 Hz, 1H, 4'-H$_{trans}$), 5.09 (dd, *J* 0.9 Hz 16.3 Hz, 1H, 4'-H$_{cis}$), 6.29 (dd, *J* 9.6 Hz 16.3 Hz, 1H, 3'-H), 6.79 (t, *J* 7.4 Hz, 1H, 5-H), 6.80 (d, *J* 8.4 Hz, 1H, 7-H), 7.49 (ddd, *J* 1.1 Hz 7.1 Hz 8.3 Hz, 1H, 6-H), 7.55 (d, *J* 7.6 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 21.7 (1'-CH$_3$), 22.7 (2'-CH$_3$), 33.8 (NCH$_3$), 44.2 (2'-C), 52.3 (CO_2CH_3), 80.5 (2-C), 109.3 (7-CH), 113.6 (4'-CH$_2$), 118.2 (5-CH), 120.9 (3a-C), 124.7 (4-CH), 137.4 (6-CH), 143.6 (3'-CH), 162.2 (7a-C), 167.2 (CO_2Me), 196.6 (3-C=O); ν_{max} (thin film, cm^{-1}) 1742 (C=O ester), 1702 (C=O aryl), 1321 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 202 (15494), 237 (15727), 409 (1597); *m/z* (ESI$^+$) calculated for $C_{16}H_{19}NO_3$ [M+H]$^+$; 274.1438, found 274.1441 (error 0.77 ppm).

Dimethyl 1-phenyl-3-vinylpyrrolidine-2,2-dicarboxylate **84i**



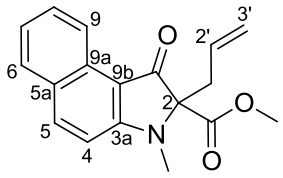
Generated from dimethyl 2-(5,6-dihydropyridin-1(2H)-yl)malonate (111.6 mg, 523.3 µmol) using general procedure 1 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) dimethyl 1-phenyl-3-vinylpyrrolidine-2,2-dicarboxylate (65.3 mg, 69 %) as a colourless oil; R_f = 0.07 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.16-2.22 (m, 2H, 4-$\underline{H}_2$), 3.39 (dd, *J* 7.8 Hz 16.8 Hz, 1H, 3-$\underline{H}$), 3.67 (s, 3H, 1''O_2-C$\underline{H}_3$), 3.68 (dd, *J* 5.8 Hz 7.8 Hz, 2H, 5-$\underline{H}_2$), 3.72 (s, 3H, 1'''O_2-C$\underline{H}_3$), 5.16 (d, *J* 1.3 Hz, 1H, 2''''-$\underline{H}_{trans}$), 5.20 (dt, *J* 1.3 Hz 8.6 Hz, 1H, 2''''-$\underline{H}_{cis}$), 5.88 (ddd, *J* 7.7 Hz 10.4 Hz 17.0 Hz, 1H, 1''''-$\underline{H}$), 6.55 (d, *J* 8.0 Hz, 2H, 2'-$\underline{H}$, 6'-$\underline{H}$), 6.73 (t, *J* 7.3 Hz, 1H, 4'-$\underline{H}$), 7.17 (dd, *J* 7.4 Hz 8.7 Hz, 2H, 3'-$\underline{H}$, 5'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 28.6 (4-$\underline{C}H_2$), 49.2 (5-$\underline{C}H_2$), 52.4 (1''O_2-$\underline{C}H_3$), 52.8 (1'''O_2-$\underline{C}H_3$), 54.0 (3-$\underline{C}$H), 75.8 (2-$\underline{C}$), 113.3 (2'-$\underline{C}$H, 6'-$\underline{C}$H), 117.4 (4'-$\underline{C}$H), 118.1 (2''''-$\underline{C}H_2$), 128.7 (3'-$\underline{C}$H, 5'-$\underline{C}$H), 134.5 (1''''-$\underline{C}$H), 145.5 (1'-$\underline{C}$), 169.1 (1''-$\underline{C}O_2$Me), 170.1 (1'''-$\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1734 (C=O ester), 1336 (C-N aryl), 1193 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{16}H_{19}NO_4$ $[M+H]^+$; 290.1387, found 290.1390 (error -1.30 ppm).

Methyl 2-allyl-1-methyl-3-oxo-2,3-dihydro-1H-benzo[f]indole-2-carboxylate **90a**



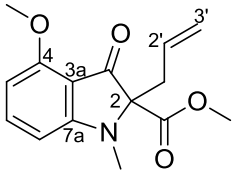
Generated from dimethyl 2-(allyl(methyl)amino)malonate (143.5 mg, 517.5 µmol) and 3-(trimethylsilyl)-2-naphthyl trifluoromethanesulfonate (0.08 mL, 289.3 µmol) using general procedure 2 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) methyl 2-allyl-1-methyl-3-oxo-2,3-dihydro-1H-benzo[f]indole-2-carboxylate (64.6 mg, 61 %) as a red solid; R_f = 0.24 (9.5:0.5 v/v petrol:EtOAc); mp: 94 - 96 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.98 (dd, *J* 7.3 Hz 14.7 Hz, 1H, 1'-$\underline{H}$), 3.07 (s, 3H, NC$\underline{H}_3$), 3.12 (dd, *J* 7.0 Hz 14.7 Hz, 1H, 1'-$\underline{H}$), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 4.98 (dd, *J* 1.1 Hz 10.1 Hz, 1H, 3'-$\underline{H}_{trans}$), 5.18 (dd, *J* 1.1 Hz 17.0 Hz, 1H, 3'-$\underline{H}_{cis}$), 5.44 (ddt, *J* 7.1 Hz 10.1 Hz 17.0 Hz, 1H, 2'-$\underline{H}$), 6.92 (s, 1H, 9-$\underline{H}$), 7.23 (t, *J* 7.5 Hz, 1H, 6-$\underline{H}$), 7.47 (t, *J* 7.6 Hz, 1H, 7-$\underline{H}$), 7.66 (d, *J* 8.4 Hz, 1H, 8-$\underline{H}$), 7.79 (d, *J* 8.2 Hz, 1H, 5-$\underline{H}$), 8.16 (s, 1H, 4-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 29.3 (N$\underline{C}H_3$), 36.3 (1'-$\underline{C}H_2$), 53.0 ($CO_2\underline{C}H_3$), 76.8 (2-$\underline{C}$), 101.2 (9-$\underline{C}$H), 119.9 (3'-$\underline{C}H_2$), 121.9 (3a-$\underline{C}$), 122.9 (6-$\underline{C}$H), 126.4 (8-$\underline{C}$H), 126.7 (4-$\underline{C}$H), 127.1 (4a-$\underline{C}$), 129.7 (7-$\underline{C}$H), 130.6 (2'-$\underline{C}$H), 130.9 (5-$\underline{C}$H), 140.2 (8a-$\underline{C}$), 155.1 (9a-$\underline{C}$), 168.2 ($\underline{C}O_2$Me), 196.6 (3-$\underline{C}$=O); ν_{max} (solid, cm^{-1}) 1744 (C=O ester), 1714 (C=O aryl), 1327 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 251 (58250), 258 (58250), 325 (5016), 484 (1298); *m/z* (ESI$^+$) calculated for $C_{18}H_{17}NO_3$ $[M+Na]^+$; 318.1101, found 318.1100 (error 0 ppm).

Methyl 2-allyl-3-methyl-1-oxo-2,3-dihydro-1H-benzo[e]indole-2-carboxylate **90b**



Generated from dimethyl 2-(allyl(methyl)amino)malonate (91.4 mg, 454.2 µmol) and 1-(trimethylsilyl)-2-naphthyl trifluoromethanesulfonate (0.08 mL, 293.9 µmol) using general procedure 2 to yield after column chromatography (9:1 v/v petrol:EtOAc) methyl 2-allyl-3-methyl-1-oxo-2,3-dihydro-1H-benzo[e]indole-2-carboxylate (63.6 mg, 73 %) as a fluorescent yellow solid; R_f = 0.06 (9:1 v/v petrol:EtOAc); mp: 136 - 138 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.93 (dd, *J* 8.0 Hz 14.6 Hz, 1H, 1'-H), 3.13 (s, 3H, NCH_3), 3.20 (dd, *J* 6.4 Hz 14.6 Hz, 1H, 1'-H), 3.74 (s, 3H, CO_2CH_3), 4.95 (dd, *J* 1.3 Hz 10.1 Hz, 1H, 3'-H_{trans}), 5.17 (dd, *J* 1.3 Hz 16.9 Hz, 1H, 3'-H_{cis}), 5.44 (ddt, *J* 7.1 Hz 10.1 Hz 16.9 Hz, 1H, 2'-H), 7.06 (d, *J* 9.1 Hz, 1H, 9-H), 7.31 (ddd, *J* 0.9 Hz 7.1 Hz 8.0 Hz, 1H, 8-H), 7.58 (ddd, *J* 1.1 Hz 7.1 Hz 8.2 Hz, 1H, 7-H), 7.71 (d, *J* 8.1 Hz, 1H, 5-H), 7.94 (d, *J* 9.0 Hz, 1H, 4-H), 8.70 (d, *J* 8.3 Hz, 1H, 6-H); ^{13}C NMR (100 MHz) δ_C 29.4 (NCH_3), 36.8 (1'-CH_2), 53.2 (CO_2CH_3), 77.6 (2-C), 109.4 (9b-C), 110.1 (9-CH), 119.6 (3'-CH_2), 122.7 (6-CH), 123.6 (8-CH), 127.1 (9a-C), 128.5 (5-CH), 130.1 (7-CH), 130.5 (5a-C), 130.8 (2'-CH), 140.0 (4-CH), 164.1 (3a-C), 167.6 (CO_2Me), 193.1 (1-C=O); ν_{max} (solid, cm^{-1}) 1736 (C=O ester), 1654 (C=O aryl), 1377 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 204 (20551), 256 (20603), 269 (19628), 320 (4138), 426 (3434), 447 (3371); *m/z* (ESI$^+$) calculated for $C_{18}H_{17}NO_3$ $[M+H]^+$; 296.1281, found 296.1286 (error 2.37 ppm).

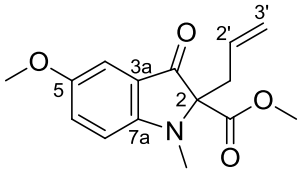
Methyl 2-allyl-4-methoxy-1-methyl-3-oxoindoline-2-carboxylate **90c**



Generated from dimethyl 2-(allyl(methyl)amino)malonate (91.9 mg, 456.7 µmol) and 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 304.5 µmol) using general procedure 2 to yield after column chromatography (8:2 v/v petrol:EtOAc) methyl 2-allyl-4-methoxy-1-methyl-3-oxoindoline-2-carboxylate (76.2 mg, 97 %) as a fluorescent yellow solid; R_f = 0.08 (8:2 v/v petrol:EtOAc); mp: 120 - 121 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.86 (dd, *J* 7.6 Hz 14.6 Hz, 1H, 1'-H), 2.97 (s, 3H, NCH_3), 3.08 (dd, *J* 6.7 Hz 14.6 Hz, 1H, 1'-H), 3.70 (s, 3H, CO_2CH_3), 3.91 (s, 3H, 4-OCH_3), 4.99 (dd, *J* 1.5 Hz 10.0 Hz, 1H, 3'-H_{trans}), 5.16 (dd, *J* 1.5 Hz 17.1 Hz, 1H, 3'-H_{cis}), 5.45 (ddt, *J* 7.2 Hz 10.0 Hz 17.1 Hz, 1H, 2'-H), 6.15 (d, *J* 8.1 Hz, 1H, 5-H), 6.34 (d, *J* 8.1 Hz, 1H, 7-H), 7.40 (t, *J* 8.2 Hz, 1H, 6-H); ^{13}C NMR (100 MHz) δ_C 29.4 (NCH_3), 36.6 (1'-CH_2), 53.0 (CO_2CH_3), 55.8 (4-OCH_3), 76.9 (2-C), 98.9 (5-CH), 100.5 (7-CH), 108.2 (3a-C), 119.6 (3'-CH_2), 130.8 (2'-CH_2), 139.6 (6-CH), 159.3 (4-

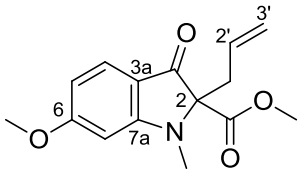
C), 163.1 (7a-C), 167.8 (CO_2Me), 192.4 (3-C=O); ν_{max} (solid, cm^{-1}) 1739 (C=O ester), 1687 (C=O aryl), 1332 (C-N aryl), 1218 (C-O aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 233 (13711), 236 (13938), 296 (5875), 407 (4138); *m/z* (ESI^+) calculated for $C_{15}H_{17}NO_4$ $[M+Na]^+$ 298.105, found 298.1054 (error 1.82 ppm).

Methyl 2-allyl-5-methoxy-1-methyl-3-oxoindoline-2-carboxylate **90d**



Generated from dimethyl 2-(allyl(methyl)amino)malonate (93.1 mg, 462.7 µmol) and 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 304.5 µmol) using general procedure 2 to yield after column chromatography (9:1 to 8:2 v/v petrol:EtOAc) methyl 2-allyl-5-methoxy-1-methyl-3-oxoindoline-2-carboxylate (42.9 mg, 54 %) and methyl 2-allyl-6-methoxy-1-methyl-3-oxoindoline-2-carboxylate (31.0 mg, 39 %) both as fluorescent yellow solids; R_f = 0.19 (8:2 v/v petrol:EtOAc); mp: 62 - 64 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.88 (dd, *J* 7.4 Hz 14.5 Hz, 1H, 1'-H), 2.98 (s, 3H, NCH_3), 3.05 (dd, *J* 6.9 Hz 14.5 Hz, 1H, 1'-H), 3.71 (s, 3H, CO_2CH_3), 3.76 (s, 3H, 5-OCH_3), 4.98 (dd, *J* 1.3 Hz 10.1 Hz, 1H, 3'-H_{trans}), 5.15 (dd, *J* 1.3 Hz 17.1 Hz, 1H, 3'-H_{cis}), 5.41 (ddt, *J* 7.1 Hz 10.1 Hz 17.1 Hz, 1H, 2'-H), 6.76 (d, *J* 9.0 Hz, 1H, 7-H), 7.01 (d, *J* 2.7 Hz, 1H, 4-H), 7.18 (dd, *J* 2.7 Hz 8.9 Hz, 1H, 6-H); ^{13}C NMR (100 MHz) δ_C 29.4 (NCH_3), 36.5 (1'-CH_2), 53.0 (CO_2CH_3), 55.8 (5-OCH_3), 77.5 (2-C), 105.0 (4-CH), 109.7 (7-CH), 118.9 (3a-C), 119.6 (3'-CH_2), 128.7 (6-CH), 130.8 (2'-CH), 152.4 (5-C), 158.1 (7a-C), 167.8 (CO_2CH_3), 195.2 (3-C=O); ν_{max} (solid, cm^{-1}) 1735 (C=O ester), 1678 (C=O aryl), 1338 (C-N aryl), 1221 (C-O aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 201 (24758), 235 (30087), 448 (4641); *m/z* (ESI^+) calculated for $C_{15}H_{17}NO_4$ $[M+H]^+$ 276.1230, found 276.1225 (error -1.82 ppm).

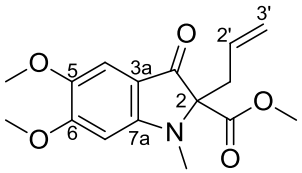
Methyl 2-allyl-6-methoxy-1-methyl-3-oxoindoline-2-carboxylate **90e**



R_f = 0.12 (8:2 v/v petrol:EtOAc); mp: 94 - 96 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.86 (dd, *J* 7.6 Hz 14.6 Hz, 1H, 1'-H), 2.98 (s, 3H, NCH_3), 3.08 (dd, *J* 6.8 Hz 14.6 Hz, 1H, 1'-H), 3.72 (s, 3H, CO_2CH_3), 3.88 (s, 3H, 6-OCH_3), 4.98 (dd, *J* 1.4 Hz 9.8 Hz, 1H, 3'-H_{trans}), 5.15 (dd, *J* 1.4 Hz 17.0 Hz, 1H, 3'-H_{cis}), 5.42 (ddt, *J* 7.2 Hz 9.8 Hz 17.0 Hz, 1H, 2'-H), 6.15 (d, *J* 2.0 Hz, 1H, 7-H), 6.33 (dd, *J* 2.0 Hz 8.7 Hz, 1H, 5-H), 7.49 (d, *J* 8.6 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 29.2 (NCH_3), 36.6 (1'-CH_2), 53.1 (CO_2CH_3),

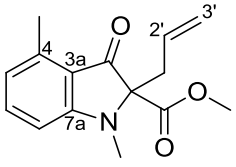
55.6 (6-O<u>C</u>H$_3$), 77.5 (2-<u>C</u>), 91.1 (7-<u>C</u>H), 107.2 (5-<u>C</u>H), 112.7 (3a-<u>C</u>), 119.5 (3'-<u>C</u>H$_2$), 126.8 (4-<u>C</u>H), 130.9 (2'-<u>C</u>H), 163.8 (7a-<u>C</u>), 167.9 (<u>C</u>O$_2$Me), 168.5 (6-<u>C</u>), 192.5 (3-<u>C</u>=O); ν_{max} (solid, cm^{-1}) 1734 (C=O ester), 1670 (C=O aryl), 1342 (C-N aryl), 1219 (C-O aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 222 (16946), 251 (23989), 286 (13446), 395 (6632); *m/z* (ESI$^+$) calculated for $C_{15}H_{17}NO_4$ $[M+H]^+$ 276.1230, found 276.1230 (error -0.36 ppm).

Methyl 2-allyl-5,6-dimethoxy-1-methyl-3-oxoindoline-2-carboxylate **90f**



Generated from dimethyl 2-(allyl(methyl)amino)malonate (90.0 mg, 447.3 µmol) and 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 289.1 µmol) using general procedure 2 to yield after column chromatography (6:4 v/v petrol:EtOAc) methyl 2-allyl-5,6-dimethoxy-1-methyl-3-oxoindoline-2-carboxylate (71.8 mg, 81 %) as a fluorescent yellow solid; R_f = 0.17 (6:4 v/v petrol:EtOAc); mp: 100 - 101 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.86 (dd, *J* 7.5 Hz 14.5 Hz, 1H, 1'-<u>H</u>), 3.00 (s, 3H, NC<u>H</u>$_3$), 3.07 (dd, *J* 6.6 Hz 14.5 Hz, 1H, 1'-<u>H</u>), 3.73 (s, 3H, CO$_2$C<u>H</u>$_3$), 3.82 (s, 3H, 5-OC<u>H</u>$_3$), 3.99 (s, 3H, 6-OC<u>H</u>$_3$), 4.99 (dd, *J* 1.5 Hz 10.0 Hz, 1H, 3'-<u>H</u>$_{trans}$), 5.15 (dd, *J* 1.5 Hz 17.1 Hz, 1H, 3'-<u>H</u>$_{cis}$), 5.42 (ddt, *J* 7.1 Hz 10.0 Hz 17.1 Hz, 1H, 2'-<u>H</u>), 6.23 (s, 1H, 7-<u>H</u>), 6.99 (s, 1H, 4-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 29.5 (N<u>C</u>H$_3$), 36.5 (1'-<u>C</u>H$_2$), 53.1 (CO$_2$<u>C</u>H$_3$), 56.2 (5-O<u>C</u>H$_3$), 56.3 (6-O<u>C</u>H$_3$), 77.2 (2-<u>C</u>), 90.6 (7-<u>C</u>H), 104.8 (4-<u>C</u>H), 110.2 (3a-<u>C</u>), 119.4 (3'-<u>C</u>H$_2$), 131.0 (2'-<u>C</u>H), 143.2 (5-<u>C</u>), 159.2 (6-<u>C</u>), 159.8 (7a-<u>C</u>), 168.0 (<u>C</u>O$_2$Me), 192.5 (3-<u>C</u>=O); ν_{max} (solid, cm^{-1}) 1732 (C=O ester), 1661 (C=O aryl), 1347 (C-N aryl), 1218 (C-O aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 224 (13364), 251 (15354), 283 (11763), 418 (6938); *m/z* (ESI$^+$) calculated for $C_{16}H_{19}NO_5$ $[M+H]^+$ 306.1336, found 306.1335 (error -0.66 ppm).

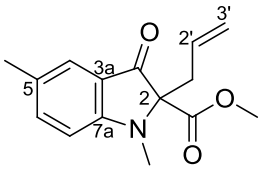
Methyl 2-allyl-1,4-dimethyl-3-oxoindoline-2-carboxylate **90g**



Generated from dimethyl 2-(allyl(methyl)amino)malonate (99.7 mg, 495.5 µmol) and 2-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 315.0 µmol) using general procedure 2 to yield after column chromatography (9:1 v/v petrol:Et$_2$O) methyl 2-allyl-1,4-dimethyl-3-oxoindoline-2-carboxylate (69.9 mg, 86 %) as a fluorescent yellow solid; R_f = 0.14 (8:2 v/v petrol:Et$_2$O); mp: 91 - 92 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.53 (s, 3H, 4-C<u>H</u>$_3$), 2.87 (dd, *J* 7.6 Hz 14.7 Hz, 1H, 1'-<u>H</u>), 2.97 (s,

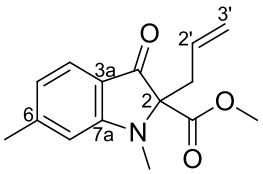
3H, NC$\underline{H}_3$), 3.05 (dd, *J* 6.7 Hz 14.7 Hz, 1H, 1'-$\underline{H}$), 3.72 (s, 3H, $CO_2C\underline{H}_3$), 4.98 (dd, *J* 1.6, 9.9 Hz, 1H, 3'-$\underline{H}_{\underline{trans}}$), 5.14 (dd, *J* 1.6 Hz 17.1 Hz, 1H, 3'-$\underline{H}_{\underline{cis}}$), 5.42 (ddt, *J* 7.1 Hz 9.9 Hz 17.1 Hz, 1H, 2'-$\underline{H}$), 6.49 (d, *J* 7.4 Hz, 1H, 5-$\underline{H}$), 6.59 (d, *J* 8.3 Hz, 1H, 7-$\underline{H}$), 7.33 (t, *J* 7.8 Hz, 1H, 6-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 18.4 (4-$\underline{C}H_3$), 29.3 (N$\underline{C}H_3$), 36.8 (1'-$\underline{C}H_2$), 53.0 ($CO_2\underline{C}H_3$), 76.8 (2-$\underline{C}$), 105.4 (7-$\underline{C}$H), 117.3 (3a-$\underline{C}$), 119.3 (5-$\underline{C}$H), 119.5 (3'-$\underline{C}H_2$), 131.0 (2'-$\underline{C}$H), 137.3 (6-$\underline{C}$H), 140.6 (4-$\underline{C}$), 162.3 (7a-$\underline{C}$), 167.9 ($\underline{C}O_2CH_3$), 195.5 (3-$\underline{C}$=O); ν_{max} (solid, cm^{-1}) 1732 (C=O ester), 1677 (C=O aryl), 1315 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 201 (6284), 239 (10482), 417 (1662); *m/z* (ESI^+) calculated for $C_{15}H_{17}NO_3$ $[M+H]^+$ 260.1281, found 260.1289 (error 2.32 ppm).

Methyl 2-allyl-1,5-dimethyl-3-oxoindoline-2-carboxylate **90h**



Generated from dimethyl 2-(allyl(methyl)amino)malonate (101.3 mg, 503.4 µmol) and 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 312.4 µmol) using general procedure 2 to yield after column chromatography (8:2 v/v petrol:Et_2O) methyl 2-allyl-1,5-dimethyl-3-oxoindoline-2-carboxylate (32.6 mg, 40 %) and methyl 2-allyl-1,6-dimethyl-3-oxoindoline-2-carboxylate (41.5 mg, 51 %) both as fluorescent yellow solids; R_f = 0.10 (8:2 v/v petrol:Et_2O); mp: 72 - 74 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.27 (s, 3H, 5-C$\underline{H}_3$), 2.88 (dd, *J* 7.5 Hz 14.6 Hz, 1H, 1'-$\underline{H}$), 2.98 (s, 3H, NC$\underline{H}_3$), 3.05 (dd, *J* 6.8 Hz 14.6 Hz, 1H, 1'-$\underline{H}$), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 4.97 (dd, *J* 1.5 Hz 10.0 Hz, 1H, 3'-$\underline{H}_{\underline{trans}}$), 5.14 (dd, *J* 1.5 Hz 17.0 Hz, 1H, 3'-$\underline{H}_{\underline{cis}}$), 5.40 (ddt, *J* 7.1 Hz 10.0 Hz 17.0 Hz, 1H, 2'-$\underline{H}$), 6.72 (d, *J* 8.3 Hz, 1H, 7-$\underline{H}$), 7.33 (dd, *J* 1.5 Hz 8.4 Hz, 1H, 6-$\underline{H}$), 7.36 (s, 1H, 4-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 20.4 (5-$\underline{C}H_3$), 29.3 (N$\underline{C}H_3$), 36.5 (1'-$\underline{C}H_2$), 53.0 ($CO_2\underline{C}H_3$), 77.1 (2-$\underline{C}$), 108.2 (7-$\underline{C}$H), 119.2 (3a-$\underline{C}$), 119.6 (3'-$\underline{C}H_2$), 124.5 (4-$\underline{C}$H), 127.1 (5-$\underline{C}$), 130.8 (2'-$\underline{C}$H), 139.5 (6-$\underline{C}$H), 160.4 (7a-$\underline{C}$), 167.8 ($\underline{C}O_2Me$), 195.3 (3-$\underline{C}$=O); ν_{max} (solid, cm^{-1}) 1741 (C=O ester), 1697 (C=O aryl), 1317 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 200 (7667), 240 (17292), 428 (2283); *m/z* (ESI^+) calculated for $C_{15}H_{17}NO_3$ $[M+Na]^+$ 282.1101, found 282.1112 (error 4.63 ppm).

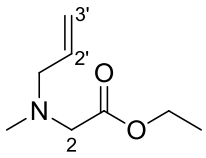
Methyl 2-allyl-1,6-dimethyl-3-oxoindoline-2-carboxylate **90i**



R_f = 0.10 (8:2 v/v petrol:Et_2O); mp: 89 - 91 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 2.38 (s, 3H, 6-C$\underline{H}_3$), 2.87 (dd, *J* 7.5 Hz 14.6 Hz, 1H, 1'-$\underline{H}$), 2.98 (s, 3H, NC$\underline{H}_3$), 3.07 (dd, *J* 6.7 Hz 14.6 Hz, 1H, 1'-$\underline{H}$), 3.71 (s,

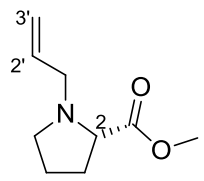
3H, $CO_2C\underline{H}_3$), 4.97 (dd, *J* 1.1 Hz 10.0 Hz, 1H, 3'-$\underline{H}_{trans}$), 5.14 (dd, *J* 1.1 Hz 17.1 Hz, 1H, 3'-$\underline{H}_{cis}$), 5.40 (ddt, *J* 7.1 Hz 10.0 Hz 17.1 Hz, 1H, 2'-H), 6.58 (d, *J* 9.7 Hz, 1H, 5-H), 6.59 (s, 1H, 7-H), 7.46 (d, *J* 7.8 Hz, 1H, 4-H); ^{13}C NMR (100 MHz) δ_C 22.8 (6-$\underline{C}H_3$), 29.1 (N$\underline{C}H_3$), 36.5 (1'-$\underline{C}H_2$), 53.1 ($CO_2\underline{C}H_3$), 77.2 (2-C), 108.5 (7-CH), 117.0 (3a-C), 119.5 (5-CH), 119.6 (3'-$\underline{C}H_2$), 124.9 (4-CH), 130.8 (2'-CH), 149.9 (6-C), 162.2 (7a-C), 167.9 ($\underline{C}O_2Me$), 194.4 (3-C=O); ν_{max} (solid, cm^{-1}) 1741 (C=O ester), 1697 (C=O aryl), 1326 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 202 (22938), 243 (40562), 415 (5957); *m/z* (ESI$^+$) calculated for $C_{15}H_{17}NO_3$ $[M+Na]^+$ 282.1101, found 282.1112 (error 4.63 ppm).

Ethyl *N*-allylsarcosinate **92**[135]



Triethylamine (11.3 mL, 81.0 mmol) was added to a stirred solution of sarcosine ethyl ester hydrochloride (3.39 g, 22.1 mmol) in DCM (50 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 15 minutes followed by the addition of toluene (110 mL) and allyl bromide (2.33 mL, 27.0 mmol). The mixture was heated to reflux for 4 h before washing with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to yield ethyl *N*-allylsarcosinate (2.13 g, 62 %) as an orange oil which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.28 (t, *J* 7.1, 3H, $CO_2CH_2C\underline{H}_3$), 3.11 (s, 3H, NC$\underline{H}_3$), 3.14 (d, *J* 6.6, 2H, =CHC$\underline{H}_2$N), 3.23 (s, 2H, 2-$\underline{H}_2$), 4.19 (q, *J* 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.19 (dd, *J* 1.3 Hz 10.3 Hz, 1H, 3'-$\underline{H}_{trans}$), 5.20 (dd, *J* 1.3 Hz 17.0 Hz, 1H 3'-H_{cis}), 5.88 (ddt, *J* 6.7 Hz 10.3 Hz 17.0 Hz, 1H, 2'-H); ^{13}C NMR (100 MHz) δ_C 14.3 ($CO_2CH_2\underline{C}H_3$), 42.5 (N$\underline{C}H_3$), 57.7 (2-$\underline{C}H_2$), 60.4 (=CH$\underline{C}H_2$N), 60.5 ($CO_2\underline{C}H_2CH_3$) 118.3 (3'-$\underline{C}H_2$), 135.1 (2'-CH), 171.0 ($\underline{C}O_2Et$); ν_{max} (thin film, cm^{-1}) 1733 (C=O ester), 1182 (C-O ester), 1030 (C-N amine); *m/z* (ESI$^+$) calculated for $C_8H_{15}NO_2$ $[M+H]^+$; 158.1176, found 158.1180 (error -2.76 ppm).

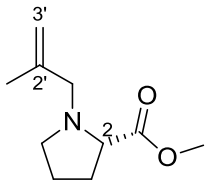
(*S*)-Methyl 1-allylpyrrolidine-2-carboxylate **97a**[136]



Allyl bromide (0.79 mL, 9.1 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.47 g, 8.9 mmol) and triethylamine (2.6 mL, 18.7 mmol) in DMF (15 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 69 h at that temperature before addition of water (100 mL) and extracting with EtOAc (2 x 75 mL). The combine organic extracts were washed

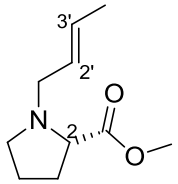
with water (2 x 75 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give an orange oil (1.56 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-methyl 1-allylpyrrolidine-2-carboxylate (1.15 g, 77 %) as an orange oil. R_f= 0.21 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.75-1.82 (m, 1H, 4-H), 1.87-1.97 (m, 2H, 3-H, 4-H), 2.10-2.16 (m, 1H, 3-H), 2.37 (dd, *J* 8.3 Hz 16.6 Hz, 1H, 5-H), 3.12 (dd, *J* 7.3 Hz 14.2 Hz, 1H =CHCH_2N), 3.15 (dd, *J* 6.1 Hz 9.0 Hz, 2H, 5-H, 2-H), 3.30 (dd, *J* 6.5 Hz 13.1 Hz 1H =CHCH_2N), 3.71 (s, 3H, CO_2CH_3), 5.08 (dd, *J* 1.5 Hz 10.1 Hz, 1H, 3'-H_{trans}), 5.13 (dd, *J* 1.5 Hz 17.0 Hz, 1H, 3'-H_{cis}), 5.91 (ddt, *J* 6.8 Hz 10.1 Hz 17.0 Hz, 1H, 2'-H); ^{13}C NMR (100 MHz) δ_C 23.1 (4-CH_2), 29.6 (3-CH_2), 51.9 (CO_2CH_3), 53.6 (5-CH_2), 57.9 (=CHCH_2N), 65.3 (2-CH), 117.6 (3'-CH_2), 135.3 (2'-CH), 174.7 (CO_2Me); ν_{max} (thin film, cm^{-1}) 1734 (C=O ester), 1199 (C-O ester); *m/z* (ESI$^+$) calculated for $C_9H_{15}NO_2$ $[M+H]^+$; 170.1176, found 170.1178 (error -1.40 ppm).

(*S*)-Methyl 1-(2-methylallyl)pyrrolidine-2-carboxylate **97b**



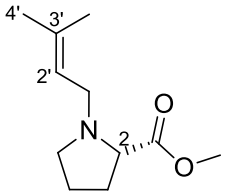
3-Bromo-2-methylpropene (0.91 mL, 9.0 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.5 g, 9.1 mmol) and triethylamine (2.6 mL, 18.7 mmol) in DMF (35 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 25 h at that temperature before addition of water (100 mL) and extracting with EtOAc (2 x 75 mL). The combine organic extracts were washed with water (2 x 100 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give a red brown oil (1.45 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-methyl 1-(2-methylallyl)pyrrolidine-2-carboxylate (1.30 g, 78 %) as an colourless oil. Rf= 0.74 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.78 (s, 3H, 2'-CH_3), 1.80-1.88 (m, 1H, 4-H), 1.89-1.98 (m, 2H, 3-H, 4-H), 2.10-2.18 (m, 1H, 3-H), 2.36 (dd, *J* 7.8 Hz 16.7 Hz, 1H, 5-H), 2.97 (d, *J* 12.6 Hz, 1H, =CHCH_2N), 3.05-3.10 (m, 1H, 5-H), 3.18 (dd, *J* 5.8 Hz 9.0 Hz, 1H, 2-H), 3.23 (d, *J* 12.9 Hz, 1H, =CHCH_2N), 3.70 (s, 3H, CO_2CH_3), 4.80 (br s, 1H, 3'-H), 4.83 (br s, 1H, 3'-H); ^{13}C NMR (100 MHz) δ_C 20.9 (2'-CH_3), 23.1 (4-CH_2), 29.4 (3-CH_2), 51.7 (CO_2CH_3), 53.5 (5-CH_2), 61.7 (=CHCH_2N), 65.6 (2-CH), 112.8 (3'-CH_2), 143.6 (2'-C), 174.8 (CO_2Me); ν_{max} (thin film, cm^{-1}) 1734 (C=O ester), 1200 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$; 184.1332, found 184.1336 (error -2.25 ppm).

(*S*)-(*E*)-Methyl 1-(but-2-en-1-yl)pyrrolidine-2-carboxylate **97c**



Crotyl bromide (0.93 mL, 9.0 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.5 g, 9.1 mmol) and triethylamine (2.6 mL, 18.7 mmol) in DMF (35 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 101 h at that temperature before addition of water (100 mL) and extracting with EtOAc (2 x 75 mL). The combine organic extracts were washed with water (2 x 100 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give an orange oil (1.45 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-(*E*)-methyl 1-(but-2-en-1-yl)pyrrolidine-2-carboxylate (0.64 g, 39 %) as an colourless oil. R_f = 0.13 (8:2 v/v petrol:EtOAc) ^{1}H NMR (C_6D_6, 400 MHz) δ_H 1.41-1.52 (m, 1H, 4-H), 1.53 (d, *J* 5.9 Hz, 3H, 4'-H_3), 1.70-1.85 (m, 2H, 3-H, 4-H), 1.87-1.96 (m, 1H, 3-H), 2.25 (dd, *J* 7.9 Hz 15.9 Hz, 1H, 5-H), 2.99-3.04 (m, 1H, 5-H), 3.06 (dd, *J* 7.1 Hz 12.7 Hz, 1H, =CHCH_2N), 3.20 (dd, *J* 5.6 Hz 8.0 Hz, 1H, 2-H), 3.35 (s, 3H, CO_2CH_3), 3.38 (dd, *J* 5.9 Hz 13.2 Hz, 1H, =CHCH_2N), 5.52 (dq, J 6.3 Hz 15.1 Hz, 1H 3'-H), 5.62 (dt, J 6.6 Hz 15.1 Hz, 1H, 2'-H); ^{13}C NMR (100 MHz) δ_C 17.5 (4'-CH_3), 23.3 (4-CH_2), 29.2 (3-CH_2), 50.6 (CO_2CH_3), 52.7 (5-CH_2), 56.1 (=CHCH_2N), 64.6 (2-CH), 127.2 (3'-CH), 129.1 (2'-CH), 173.8 (CO_2Me); ν_{max} (thin film, cm^{-1}) 1732 (C=O ester), 1195 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$; 184.1332, found 184.1325 (error -3.82 ppm).

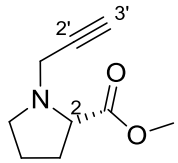
(*S*)-Methyl 1-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxylate **97d**[137]



3,3-Dimethylallyl bromide (1.05 mL, 9.1 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.5 g, 9.1 mmol) and triethylamine (2.6 mL, 18.7 mmol) in DMF (35 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 96 h at that temperature before addition of water (100 mL) and extracting with EtOAc (2 x 75 mL). The combine organic extracts were washed with water (2 x 100 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate evaporated *in vacuo* to give a yellow oil (1.46 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-methyl 1-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxylate (1.09 g, 61 %) as an colourless oil. R_f = 0.03 (8:2 v/v petrol:EtOAc) ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.65 (s, 3H, 4'-H_3),

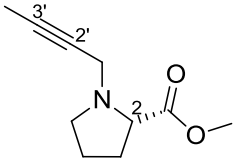
1.71 (s, 3H, 3'-C$\underline{H}_3$), 1.74-1.82 (m, 1H, 4-C$\underline{H}$), 1.86-1.98 (m, 2H, 3-$\underline{H}$, 4-$\underline{H}$), 2.09-2.17 (m, 1H, 3-$\underline{H}$), 2.35 (dd, *J* 8.6 Hz 16.8 Hz, 1H, 5-$\underline{H}$), 3.12 (dd, *J* 6.2 Hz, 8.9 Hz, 1H, 2-$\underline{H}$), 3.17 (ddd, *J* 7.3 Hz 13.2 Hz 72.0 Hz, 2H, =CHC$\underline{H}_2$N), 3.18 (m, 1H, 5-$\underline{H}$), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 5.29 (t, *J* 7.2 Hz, 1H, 2'-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 17.9 (4'-$\underline{C}H_3$), 23.1 (4-$\underline{C}H_2$), 25.9 (3'-$\underline{C}H_3$), 29.5 (3-$\underline{C}H_2$), 51.8 ($CO_2\underline{C}H_3$), 51.9 (=CH$\underline{C}H_2$N), 53.6 (5-$\underline{C}H_2$), 65.5 (2-$\underline{C}$H), 121.0 (2'-$\underline{C}$H), 135.2 (3'-$\underline{C}$), 174.9 ($\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1733 (C=O ester), 1194 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{11}H_{19}NO_2$ [M+H]$^+$; 198.1489, found 198.1479 (error -4.57 ppm).

(*S*)-Methyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **97e**[138]



Propargyl bromide (80 % wt. in toluene, 1.16 mL, 10.4 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.5 g, 9.1 mmol) and triethylamine (2.8 mL, 20.1 mmol) in toluene (35 mL) under an atmosphere of N_2. The mixture was bought to reflux for 17 h. The mixture was cooled and treated with saturated sodium hydrogen carbonate (75 mL). The organic extract was washed with water (150 mL) and brine (100 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate evaporated in vacuo to give a red/brown oil (0.84 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-methyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (0.63 g, 42 %) as a colourless oil. R_f = 0.11 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.81-1.86 (m, 1H, 4-$\underline{H}$), 1.88-2.04 (m, 2H, 3-$\underline{H}$, 4-$\underline{H}$), 2.14-2.19 (m, 1H, 3-$\underline{H}$), 2.21 (t, *J* 2.2 Hz, 1H, 3'-$\underline{H}$), 2.73 (dd, *J* 8.6 Hz 16.8 Hz, 1H, 5-$\underline{H}$), 3.07 (ddd, *J* 2.4 Hz 6.8 Hz 9.3 Hz, 1H, 5-$\underline{H}$), 3.45 (dd, *J* 6.8 Hz 9.2 Hz, 1H, 2-$\underline{H}$), 3.61 (t, *J* 2.1 Hz, 2H, ≡CC$\underline{H}_2$N), 3.74 (s, 3H, $CO_2C\underline{H}_3$); ^{13}C NMR (100 MHz) δ_C 23.3 (4-$\underline{C}H_2$), 29.6 (3-$\underline{C}H_2$), 41.2 (≡C$\underline{C}H_2$N), 52.0 ($CO_2\underline{C}H_3$), 52.2 (5-$\underline{C}H_2$), 62.5 (2-$\underline{C}$H), 73.2 (3'-$\underline{C}$H), 78.3 (2'-$\underline{C}$), 174.1 ($\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1743 (C=O ester), 1201 (C-O ester), *m/z* (ESI$^+$) calculated for $C_9H_{13}NO_2$ [M+H]+; 168.1019, found 168.1009 (error -5.39 ppm).

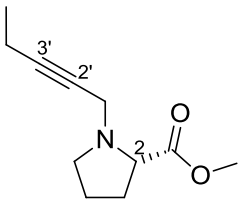
(*S*)-Methyl 1-(but-2-yn-1-yl)pyrrolidine-2-carboxylate **97f**



1-bromo-2-butyne (0.79 mL, 9.0 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.5 g, 9.1 mmol) and triethylamine (2.6 mL, 18.7 mmol) in DMF (35 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 96 h at that temperature before addition of

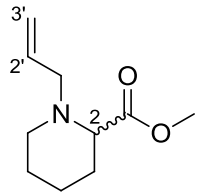
water (100 mL) and extracting with EtOAc (2 x 75 mL). The combine organic extracts were washed with water (2 x 100 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate evaporated in vacuo to give an orange oil (1.19 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-methyl 1-(but-2-yn-1-yl)pyrrolidine-2-carboxylate (1.05 g, 64 %) as a colourless oil. R_f = 0.26 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.82 (t, *J* 2.1 Hz, 3H, 4'-$\underline{H}_3$), 1.85-2.02 (m, 3H, 3-$\underline{H}$, 4-$\underline{H}_2$), 2.13-2.18 (m, 1H, 3-$\underline{H}$), 2.68 (dd, *J* 8.9 Hz 16.7 Hz, 1H, 5-$\underline{H}$), 3.06 (ddd, *J* 2.5 Hz 6.7 Hz 9.1 Hz, 1H, 5-$\underline{H}$), 3.40 (dd, *J* 6.7 Hz, 9.0 Hz, 1H, 2-$\underline{H}$), 3.52 (d, *J* 2.3 Hz, 2H, ≡CC$\underline{H}_2$N), 3.74 (s, 3H, $CO_2C\underline{H}_3$); ^{13}C NMR (100 MHz) δ_C 3.5 (4'-$\underline{C}H_3$), 23.3 (4-$\underline{C}H_2$), 29.7 (3-$\underline{C}H_2$), 41.7 (≡C$\underline{C}H_2$N), 52.0 ($CO_2\underline{C}H_3$), 52.4 (5-$\underline{C}H_2$), 62.8 (2-$\underline{C}$H), 73.5 (3'-$\underline{C}$), 80.9 (2'-$\underline{C}$), 174.3 ($\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1732 (C=O ester), 1198 (C-O ester), 1038 (C-N amine); *m/z* (ESI$^+$) calculated for $C_{10}H_{15}NO_2$ $[M+H]^+$; 182.1176, found 182.1167 (error -4.42 ppm).

(*S*)-Methyl 1-(pent-2-yn-1-yl)pyrrolidine-2-carboxylate **97g**[139]



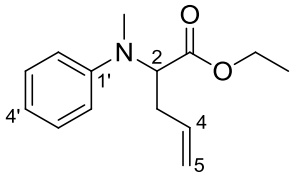
1-Bromo-2-pentyne (0.93 mL, 9.1 mmol) was added to a stirred solution of (*S*)-proline methyl ester hydrochloride (1.5 g, 9.1 mmol) and triethylamine (2.6 mL, 18.7 mmol) in DMF (35 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 73 h at that temperature before addition of water (100 mL) and extracting with EtOAc (2 x 75 mL). The combine organic extracts were washed with water (2 x 100 mL) and brine (50 mL) sequentially, dried over Na2SO4, filtered and the filtrate evaporated in vacuo to give an orange oil (1.27 g). The oil was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (*S*)-methyl 1-(pent-2-yn-1-yl)pyrrolidine-2-carboxylate (1.01 g, 57 %) as a colourless oil. R_f = 0.13 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.13 (t, *J* 7.5 Hz, 3H, 5'-$\underline{H}_3$), 1.79-1.84 (m, 1H, 4-$\underline{H}$), 1.88-2.01 (m, 2H, 3-$\underline{H}$, 4-$\underline{H}$), 2.11-2.23 (m, 3H, 3-$\underline{H}$, 4'-$\underline{H}_2$), 2.68 (dd, *J* 8.8 Hz 16.7 Hz, 1H, 5-$\underline{H}$), 3.07 (ddd, *J* 2.4 Hz 6.7 Hz 9.1 Hz, 1H, 5-$\underline{H}$), 3.41 (dd, *J* 6.7 Hz 9.0 Hz, 1H, 2-$\underline{H}$), 3.54 (br s, 2H, ≡CC$\underline{H}_2$N), 3.74 (s, 3H, $CO_2C\underline{H}_3$); ^{13}C NMR (100 MHz) δ_C 12.4 (4'-$\underline{C}H_2$), 14.2 (5'-$\underline{C}H_3$), 23.3 (4-$\underline{C}H_2$), 29.7 (3-$\underline{C}H_2$), 41.8 (≡C$\underline{C}H_2$N), 52.0 ($CO_2\underline{C}H_3$), 52.4 (5-$\underline{C}H_2$), 62.8 (2-$\underline{C}$H), 73.6 (2'-$\underline{C}$), 87.0 (3'-$\underline{C}$), 174.4 ($\underline{C}O_2$Me); ν_{max} (thin film, cm^{-1}) 1733 (C=O ester), 1197 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{11}H_{17}NO_2$ $[M+H]^+$; 196.1332, found 196.1323 (error -4.10 ppm).

(±)-Methyl 1-allylpiperidine-2-carboxylate **97h**[140]



Allyl bromide (1.2 mL, 13.9 mmol) was added to a stirred solution of (±)-methyl pipecolinate hydrochloride (2.50 g, 13.9 mmol) and triethylamine (3.9 mL, 28.0 mmol) in DMF (50 mL) under an atmosphere of N_2 at 25 ºC. The mixture was stirred for 91 h at that temperature before addition of water (100 mL) and extracting with EtOAc (2 x 125 mL). The combined organic extracts were washed with water (200 mL) and brine (50 mL) sequentially before drying over Na_2SO_4, filtered and evaporated *in vacuo* to give an orange oil (2.29 g) that was purified by column chromatography (8:2 v/v petrol:EtOAc) to yield (±)-methyl 1-allylpiperidine-2-carboxylate (2.02 g, 79 %) as a colourless oil; R_f = 0.23 (8:2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.29-1.39 (m, 1H, 5-C<u>H</u>), 1.59-1.71 (m, 3H, 5-C<u>H</u>, 4-C<u>H$_2$</u>), 1.72-1.79 (m, 1H, 3-C<u>H</u>), 1.81-1.88 (m, 1H, 3-C<u>H</u>), 2.12-2.18 (m, 1H, 6-<u>H</u>), 2.92 (dd, *J* 7.9 Hz 13.5 Hz, 1H, =CHC<u>H$_2$</u>N), 3.01-3.08 (m, 2H, 2-<u>H</u>, 6-<u>H</u>), 3.24 (ddt, J 1.4 Hz 5.6 Hz 13.5 Hz, 1H, =CHC<u>H$_2$</u>N), 3.72 (s, 3H, $CO_2C\underline{H_3}$), 5.12-5.14 (m, 1H, 3'-<u>H$_{trans}$</u>), 5.15-5.18 (m, 1H, 3'-<u>H$_{cis}$</u>), 5.83-5.93 (m, 1H, 2'-<u>H</u>); ^{13}C NMR (100 MHz) δ_C 22.8 (5-<u>C</u>H$_2$), 25.2 (4-<u>C</u>H$_2$), 29.7 (3-<u>C</u>H$_2$), 50.9 (6-<u>C</u>H$_2$), 51.6 ($CO_2\underline{C}H_3$), 59.7 (=CH<u>C</u>H$_2$N), 65.0 (2-CH), 118.1 (3'-<u>C</u>H$_2$), 134.7 (2'-<u>C</u>H), 174.2 (<u>C</u>O$_2$Me); ν_{max} (thin film, cm^{-1}) 1736 (C=O), 1192 (C-N), 1163 (C-O); *m/z* (ESI$^+$) calculated for $C_{10}H_{17}NO_2$ $[M+H]^+$; 184.1332, found 184.1335 (error -1.79 ppm).

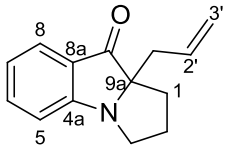
Ethyl 2-(methyl(phenyl)amino)pent-4-enoate **93**[141]



TBAF solution (1M in THF, 0.94 mL, 0.94 mmol) was added to a stirred solution of 2-trimethylsilyl(phenyl) trifluoromethanesulfonate (0.08 mL, 329.5 µmol) and ethyl 2-(allyl(methyl)amino)acetate (77.8 mg, 494.9 µmol) in MeCN (10 mL) under an atmosphere of N_2 at 25 °C. The solution was stirred for 22 h at that temperature before evaporating *in vacuo* to yield a crude orange oil (212 mg) that was purified by column chromatography (8:2 v/v petrol:Et_2O) to yield ethyl 2-(methyl(phenyl)amino)pent-4-enoate (74.6 mg, 97 %) as an orange oil; R_f = 0.50 (8:2 v/v petrol:Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.22 (t, *J* 7.1 Hz, 3H, $CO_2CH_2C\underline{H_3}$), 2.56-2.64 (m, 1H, 3-<u>H</u>), 2.69-2.76 (m, 1H, 3-<u>H</u>), 2.91 (s, 3H, $NC\underline{H_3}$), 4.15 (m, 2H, $CO_2C\underline{H_2}CH_3$), 4.43 (dd, *J* 6.4 Hz 8.9 Hz, 1H, 2-<u>H</u>), 5.05 (dd, *J* 1.4 Hz 10.2 Hz, 1H, 5-<u>H$_{trans}$</u>), 5.15 (ddd, *J* 1.4 Hz 17.1 Hz, 1H, 5-<u>H$_{cis}$</u>), 5.77 (ddt, *J* 6.9 Hz 10.2

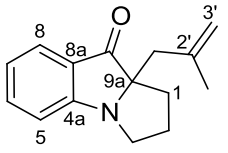
Hz 17.1 Hz, 1H, 4-H), 6.75 (t, *J* 7.3 Hz, 1H, 4'-H), 6.81 (d, *J* 8.1 Hz, 2H, 2'-H, 6'-H), 7.23 (dd, *J* 7.2 Hz 8.9 Hz, 2H, 3'-H, 5'-H); ^{13}C NMR (100 MHz) δ_C 14.3 ($CO_2CH_2CH_3$), 32.9 (NCH_3), 34.1 (3-CH_2), 60.8 ($CO_2CH_2CH_3$), 61.6 (2-CH), 113.5 (2'-CH, 6'-CH), 117.6 (5-CH_2, 4'-CH), 129.1 (3'-CH, 5'-CH), 134.3 (4-CH), 150.0 (1'-C), 172.2 (CO_2Et); ν_{max} (thin film, cm^{-1}) 1730 (C=O ester), 1312 (C-N aryl), 1183 (C-O ester); *m/z* (ESI$^+$) calculated for $C_{14}H_{19}NO_2$ $[M+H]^+$; 234.1489, found 234.1495 (error -2.54 ppm).

9a-Allyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99a**



Generated from (*S*)-methyl 1-allylpyrrolidine-2-carboxylate (279.4 mg, 1.7 mmol) using general procedure 3 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) 9a-allyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (42.8 mg, 61 %) as fluorescent yellow oil; R_f = 0.13 (9.5:0.5 v/v petrol:EtOAc); $[\alpha]^{25}_D$ +138.6 (c 1.9, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.78-1.94 (m, 3H, 1-H_2, 2-H), 2.01-2.09 (m, 1H, 2-H), 2.48 (dd, *J* 7.1 Hz 13.9 Hz, 1H, 1'-H), 2.58 (dd, *J* 7.2 Hz 13.9 Hz, 1H, 1'-H), 3.32-3.37 (m, 1H, 3-H), 3.48-3.54 (m, 1H, 3-H), 5.02 (dd, *J* 1.2 Hz 10.2 Hz, H, 3'-H_{trans}), 5.13 (dd, *J* 1.2 Hz 17.1 Hz, H, 3'-H_{cis}), 5.72 (ddt, *J* 7.1 Hz 10.2 Hz 17.1 Hz, 1H, 2'-H), 6.92 (t, *J* 7.2 Hz, 1H, 7-H), 6.94 (d, *J* 8.2 Hz, 1H, 5-H), 7.51 (t, *J* 7.7 Hz, 1H, 6-H), 7.55 (d, *J* 7.7 Hz, 1H, 8-H); ^{13}C NMR (100 MHz) δ_C 27.0 (2-CH_2), 31.8 (1-CH_2), 40.7 (1'-CH_2), 51.3 (3-CH_2), 78.2 (9a-C), 114.3 (5-CH), 118.6 (3'-CH_2), 120.5 (7-CH), 123.8 (8a-C), 124.4 (8-CH), 133.0 (2'-CH), 137.1 (6-CH), 165.2 (4a-C), 206.2 (9-C=O); ν_{max} (thin film, cm^{-1}) 1699 (C=O aryl), 1315 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 213 (5729), 230 (6388), 327 (1103), 388 (2462); *m/z* (ESI$^+$) calculated for $C_{14}H_{15}NO$ $[M+H]^+$; 214.1226, found 214.1228 (error -0.87 ppm).

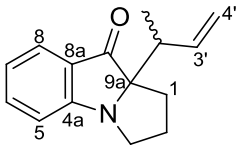
9a-(2-Methylallyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99b**



Generated from (*S*)-methyl 1-(2-methylallyl)pyrrolidine-2-carboxylate (305.9 mg, 1.7 mmol) using general procedure 3 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) 9a-allyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (35.1 mg, 47 %) as fluorescent yellow oil; R_f =0.25 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.68 (s, 3H, 2'-CH_3), 1.72-1.77 (m, 1H, 1-H), 1.84-1.90 (m, 1H, 1-H), 1.92-1.97 (m, 1H, 2-H), 2.05-2.12 (m, 1H, 2-H), 2.42 (d, *J* 13.7 Hz, 1H, 1'-H), 2.66 (d, *J* 13.7 Hz, 1H, 1'-H), 3.34 (dd, J 6.6 Hz 17.9 Hz, 1H, 3-H), 3.51 (dd, J 7.0 Hz 17.9 Hz, 1H, 3-H), 4.73 (d, *J* 1.4 Hz, 2H, 3'-H_2), 6.90 (t, *J* 7.8 Hz, 1H, 7-H), 6.91 (d, *J* 8.5 Hz, 1H, 5-H), 7.50 (td, *J* 1.3 Hz

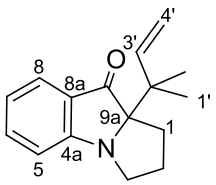
7.0 Hz, 1H, 6-H), 7.55 (d, *J* 7.6 Hz, 1H, 8-H); ^{13}C NMR (100 MHz) δ_C 24.0 (2'-CH$_3$), 27.0 (2-CH$_2$), 32.7 (1-CH$_2$), 43.5 (1'-CH$_2$), 50.7 (3-CH$_2$), 78.6 (9a-C), 114.0 (5-CH), 120.3 (7-CH), 123.6 (8a-C), 124.5 (8-CH), 137.0 (6-CH), 141.6 (2'-C), 165.1 (4a-C), 206.0 (9-C=O); ν_{max} (thin film, cm^{-1}) 1702 (C=O aryl), 1316 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 200 (10588), 203 (9989), 236 (10856), 322 (513), 389 (999); *m/z* (ESI$^+$) calculated for $C_{15}H_{17}NO$ [M+H]$^+$; 228.1383, found 228.1386 (error -0.92 ppm).

9a-(But-3-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99c**



Generated from (*S*)-(*E*)-methyl 1-(but-2-en-1-yl)pyrrolidine-2-carboxylate (307.7 mg, 1.7 mmol) using general procedure 3 after column chromatography (9.8:0.2 v/v petrol:EtOAc) to yield 9a-(but-3-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (d.r. 1:0.2) (48.5 mg, 65 %) as fluorescent yellow oil; R_f =0.07 (9.8:0.2 v/v petrol:EtOAc); ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H 0.93 (d, *J* 6.8 Hz, 3H, 1'-H$_3$ major diastereomer), 1.05 (d, *J* 6.9 Hz, 3H, 1'-H$_3$ minor diastereomer), 1.65-1.73 (m, 1H, 2-H), 1.84-1.91 (m, 2H, 1-H, 2-H), 2.01-2.06 (m, 1H, 1-H), 2.64 (dq, *J* 6.7 Hz 9.0 Hz, 1H, 2'-H), 3.31-3.41 (m, 2H, 3-H$_2$), 5.10 (dd, *J* 1.8 Hz 10.2 Hz, 1H, 4'-H$_{trans}$), 5.16 (dd, *J* 1.8 Hz 17.2 Hz, 1H, 4'-H$_{cis}$), 5.83 (ddd, *J* 9.2 Hz 10.2 Hz 17.2 Hz, 1H, 3'-H), 6.92 (t, *J* 7.4 Hz, 1H, 7-H), 6.98 (d, *J* 8.2 Hz, 1H, 5-H), 7.51 (td, *J* 1.3 Hz 7.6 Hz, 1H, 6-H), 7.54 (d, *J* 7.7 Hz, 1H, 8-H); ^{13}C NMR (100 MHz) δ_C 15.1 (1'-CH$_3$ major diastereomer), 15.3 (1'-CH$_3$ minor diastereomer), 26.2 (2-CH$_2$), 31.0 (1-CH$_2$), 45.3 (2'-CH), 52.7 (3-CH$_2$), 80.8 (9a-C), 114.7 (5-CH), 116.5 (4'-CH$_2$), 120.6 (7-CH), 124.0 (8-CH), 125.0 (8a-C), 137.0 (6-CH), 140.0 (3'-CH), 166.3 (4a-C), 207.8 (9-C=O); ν_{max} (neat oil, cm^{-1}) 1697 (C=O aryl), 1310 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε (M^{-1}cm^{-1}) 202 (8636), 206 (8610), 235 (14460), 327 (799), 389 (1295); *m/z* (ESI$^+$) calculated for $C_{15}H_{17}NO$ [M+H]$^+$; 228.1383, found 228.1385 (error 0.88 ppm).

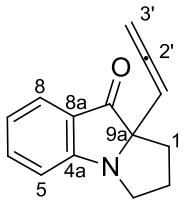
9a-(2-Methylbut-3-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99d**



Generated from (*S*)-methyl 1-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxylate (331.0 mg, 1.7 mmol) using general procedure 3. The crude residue was dissolved in Et$_2$O (50 mL) and treated with oxalic acid in Et$_2$O (0.5 g in 20 mL). The organic mixture was extracted with water (2 x 35 mL) and brine (50 mL) sequentially prior to drying over Na_2SO_4, filtering and the filtrate evaporated *in vacuo*. The

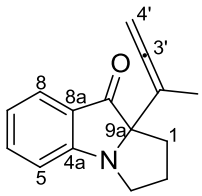
residue was purified by column chromatography (9.8:0.2 v/v petrol:EtOAc) to yield 9a-(2-methylbut-3-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (55.6 mg, 70 %) as fluorescent yellow oil; R_f =0.08 (9.8:0.2 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.05 (s, 3H, 1'-$\underline{H}_3$), 1.14 (s, 3H, 2'-C$\underline{H}_3$), 1.74 (d, *J* 15.9 Hz, 2H, 2-$\underline{H}_2$), 1.94-1.99 (m, 2H, 1-$\underline{H}_2$), 3.23 (td, *J* 5.4 Hz 14.0 Hz, 1H, 3-$\underline{H}$), 3.42 (td, *J* 7.2 Hz 14.0 Hz, 1H, 3-$\underline{H}$), 5.03 (br s, 1H, 4'-$\underline{H}_{trans}$), 5.07 (dd, *J* 1.4 Hz 7.4 Hz, 1H, 4'-$\underline{H}_{cis}$), 6.11 (dd, *J* 11.1 Hz 17.2 Hz, 1H, C3'-C$\underline{H}$), 6.91 (t, *J* 7.4 Hz, 1H, 7-$\underline{H}$), 6.98 (d, *J* 8.4 Hz, 1H, 5-$\underline{H}$), 7.49 (t, *J* 7.1 Hz, 1H, 8-$\underline{H}$), 7.49 (dd, *J* 1.3 Hz 7.6 Hz, 1H, 6-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 21.1 (2'-$\underline{C}H_3$), 22.5 (1'-$\underline{C}H_3$), 25.7 (2-$\underline{C}H_2$), 29.6 (1-$\underline{C}H_2$), 43.6 (2'-$\underline{C}$), 53.7 (3-$\underline{C}H_2$), 82.5 (9a-$\underline{C}$), 113.2 (4'-$\underline{C}H_2$), 115.0 (5-$\underline{C}$H), 120.8 (7-$\underline{C}$H), 123.6 (8-$\underline{C}$H), 126.4 (8a-$\underline{C}$), 136.7 (6-$\underline{C}$H), 144.5 (3'-$\underline{C}$H), 165.9 (4a-$\underline{C}$), 208.5 (9-$\underline{C}$=O); ν_{max} (neat oil, cm^{-1}) 1699 (C=O aryl), 1311 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 203 (6629), 236 (6705), 320 (496), 386 (483); *m/z* (ESI^+) calculated for $C_{16}H_{19}NO$ $[M+H]^+$; 242.1539, found 242.1545 (error 2.07 ppm).

9a-(Propa-1,2-dien-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99e**



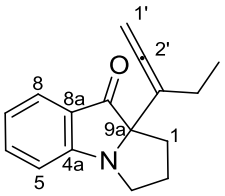
Generated from (*S*)-methyl 1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (279.7 mg, 1.7 mmol) using general procedure 3 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) 9a-(propa-1,2-dien-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (66.0 mg, 95 %) as fluorescent yellow oil; R_f = 0.22 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.70 (dd, *J* 7.5 Hz 12.2 Hz, 1H, 1-$\underline{H}$), 2.04-2.17 (m, 2H, 1-$\underline{H}$, 2-$\underline{H}$), 2.19-2.28 (m, 1H, 2-$\underline{H}$), 3.24 (dt, *J* 7.5 Hz 10.4 Hz, 1H, 3-$\underline{H}$), 3.61 (ddd, *J* 4.1 Hz 7.9 Hz 10.2 Hz, 1H, 3-$\underline{H}$), 4.92 (dd, *J* 6.5 Hz 11.0 Hz, 1H, 3'-$\underline{H}$), 4.98 (dd, J 6.6 Hz 11.0 Hz, 1H, 3'-H), 5.33 (t, *J* 6.6 Hz, 1H, 1'-$\underline{H}$), 6.89 (d, *J* 8.2 Hz, 1H, 5-$\underline{H}$), 6.91 (t, *J* 7.5 Hz, 1H, 7-$\underline{H}$), 7.52 (t, *J* 7.7 Hz, 1H, 6-$\underline{H}$), 7.58 (d, *J* 7.7 Hz, 1H, 8-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 27.7 (2-$\underline{C}H_2$), 32.0 (1-$\underline{C}H_2$), 50.5 (3-$\underline{C}H_2$), 77.2 (9a-$\underline{C}$), 78.5 (3'-$\underline{C}H_2$), 92.1 (1'-$\underline{C}$H), 113.8 (5-$\underline{C}$H), 120.4 (7-$\underline{C}$H), 122.4 (8a-$\underline{C}$), 125.0 (8-$\underline{C}$H), 137.4 (6-$\underline{C}$H), 164.6 (4a-$\underline{C}$), 202.9 (9-$\underline{C}$=O), 207.8 (2'-$\underline{C}$); ν_{max} (thin film, cm^{-1}) 1701 (C=O aryl), 1316 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 234 (13006), 335 (1068), 391 (2404); *m/z* (ESI^+) calculated for $C_{14}H_{13}NO$ $[M+H]^+$; 212.1070, found 212.1081 (error 5.68 ppm).

9a-(Buta-2,3-dien-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99f**



Generated from (*S*)-methyl 1-(but-2-yn-1-yl)pyrrolidine-2-carboxylate (302.3 mg, 1.7 mmol) using general procedure 3 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) 9a-(buta-2,3-dien-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (72.9 mg, 98 %) as fluorescent yellow oil which solidified on standing to a waxy fluorescent yellow solid; R_f = 0.28 (9.5:0.5 v/v petrol:EtOAc); mp: 73 - 74 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.59-1.64 (m, 1H, 1-H), 1.62 (t, *J* 3.1 Hz, 3H, 1'-H_3), 1.99-2.06 (m, 1H, 2-H), 2.11-2.18 (m, 1H, 2-H), 2.28-2.34 (m, 1H, 1-H), 3.26 (dt, *J* 7.5 Hz 10.5 Hz, 1H, 3-H), 3.54 (ddd, *J* 4.9 Hz 7.9 Hz 10.6 Hz, 1H, 3-H), 4.85 (dq, *J* 3.1 Hz 10.1 Hz, 1H, 4'-H), 4.95 (dq, *J* 3.1 Hz, 10.2 Hz, 1H, 4'-H), 6.90 (t, *J* 7.2 Hz, 1H, 7-H), 6.91 (d, *J* 8.5 Hz, 1H, 5-H), 7.52 (ddd, *J* 1.0 Hz 7.2 Hz 8.2 Hz, 1H, 6-H), 7.57 (d, *J* 7.7 Hz, 1H, 8-H); ^{13}C NMR (100 MHz) δ_C 14.5 (1'-CH_3), 27.9 (2-CH_2), 30.5 (1-CH_2), 50.1 (3-CH_2), 77.5 (4'-CH_2), 79.3 (9a-C), 99.2 (2'-C), 113.7 (5-CH), 120.2 (7-CH), 123.0 (8-C), 124.7 (8-CH), 137.3 (6-CH), 165.3 (4a-C), 204.0 (9-C=O), 206.5 (3'-C); ν_{max} (solid, cm^{-1}) 1704 (C=O aryl), 1320 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 233 (12934), 337 (1092), 392 (2350); *m/z* (ESI^+) calculated for $C_{15}H_{15}NO$ $[M+H]^+$; 226.1226, found 226.1225 (error -0.89 ppm).

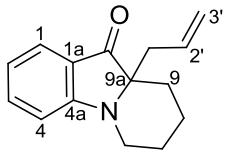
9a-(Penta-1,2-dien-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99g**



Generated from (*S*)-methyl 1-(pent-2-yn-1-yl)pyrrolidine-2-carboxylate (326.3 mg, 1.7 mmol) using general procedure 3 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) 9a-(penta-1,2-dien-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (76.2 mg, 97 %) as fluorescent yellow oil; R_f = 0.35 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.95 (t, *J* 7.3 Hz, 3H, 5'-H_3), 1.55-1.63 (m, 1H, 1-H), 1.71-1.82 (m, 1H, 4'-H), 1.93-2.09 (m, 2H, 4'-H 2-H), 2.11-2.20 (m, 1H, 2-H), 2.35 (ddd, *J* 3.9 Hz 6.7 Hz 12.5 Hz, 1H, 1-H), 3.26 (dt, *J* 7.6 Hz 10.5 Hz, 1H, 3-H), 3.54 (ddd, *J* 4.7 Hz 8.0 Hz 10.6 Hz, 1H, 3-H), 4.97 (dt, *J* 3.8 Hz 9.9 Hz, 1H, 1'-H), 5.08 (dt, *J* 3.8 Hz 9.9 Hz, 1H, 1'-H), 6.90 (d, *J* 8.2 Hz, 1H, 5-H), 6.90 (t, *J* 7.3 Hz, 1H, 7-H), 7.51 (t, *J* 7.6 Hz, 1H, 6-H), 7.56 (d, *J* 7.7 Hz, 1H, 8-H); ^{13}C NMR (100 MHz) δ_C 12.2 (5'-CH_3), 20.1 (4'-CH_2), 28.0 (2-CH_2), 30.8 (1-CH_2), 50.1 (3-CH_2), 79.4 (9a-C), 80.0 (1'-CH_2), 106.3 (3'-C), 113.6 (5-CH), 120.2 (7-CH), 123.0 (8a-C), 124.8 (8-CH), 137.2 (6-CH), 165.3 (4a-C), 204.2 (9-C=O), 205.8 (2'-C); ν_{max} (thin film, cm^{-1}) 1705 (C=O aryl), 1319 (C-N aryl);

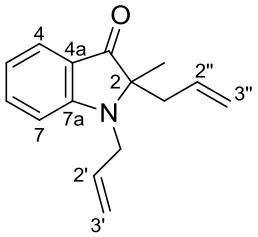
UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 228 (13711), 232 (33376), 236 (33376), 337 (3189), 391 (6833); *m/z* (ESI^+) calculated for $C_{16}H_{17}NO$ $[M+H]^+$; 240.1383, found 240.1381 (error -4.18 ppm).

9a-Allyl-7,8,9,9a-tetrahydropyrido[1,2-a]indol-10(6H)-one **99h**



Generated from methyl 1-allylpiperidine-2-carboxylate (304.7 mg, 1.7 mmol) using general procedure 3 to yield after column chromatography (9.5:0.5 v/v petrol:EtOAc) 9a-allyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one (4.4 mg, 6 %) as fluorescent yellow oil; R_f =0.07 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.34-1.42 (m, 2H, 8-H, 9-H), 1.66-1.83 (m, 4H, 7-H_2, 8-H, 9-H), 2.56 (dd, *J* 6.7 Hz 14.3 Hz, 1H, 1'-H), 2.77 (dd J 7.3 Hz 14.3 Hz, 1H, 1'-H), 3.19 (td, *J* 3.1 Hz 13.6 Hz, 1H, 6-H), 3.88 (dd, *J* 4.2 Hz 14.2 Hz, 1H, 6-H), 4.91 (dd, *J* 1.3 Hz 10.1 Hz, 1H, 3'-H_{trans}), 5.06 (dd, *J* 1.3 Hz, 17.1 Hz, 1H, 3'-H_{cis}), 5.43 (ddt, J 7.2 Hz 10.1 Hz 17.1 Hz, 1H, 2'-H), 6.66 (t, *J* 7.3 Hz, 1H, 2-H), 6.78 (d, *J* 8.4 Hz, 1H, 4-H), 7.43 (t, *J* 7.2 Hz, 1H, 3-H), 7.59 (d, *J* 7.7 Hz, 1H, 1-H); ^{13}C NMR (100 MHz) δ_C 20.4 (7-CH_2), 25.5 (8-CH_2), 31.3 (9-CH_2), 35.6 (1'-CH_2), 40.5 (6-CH_2), 68.4 (9a-C), 108.4 (4-CH), 116.5 (2-CH), 118.0 (3'-CH_2), 119.4 (1a-C), 125.2 (1-CH), 132.1 (2'-CH), 137.1 (3-CH), 159.5 (4a-C), 204.6 (10-C=O); ν_{max} (thin film, cm^{-1}) 1693 (C=O aryl), 1321 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 201 (11053), 236 (16369), 261 (5534), 414 (2407); *m/z* (ESI+) calculated for $C_{15}H_{17}NO$ [M+H]+; 228.1383, found 228.1380 (error -1.76 ppm).

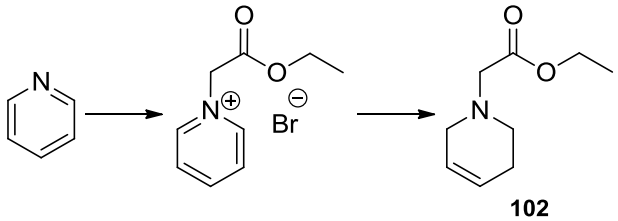
1,2-Diallyl-2-methylindolin-3-one **101**



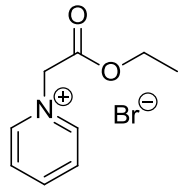
To flame dried glassware (*S*)-methyl 2-(diallylamino)propanoate (609.0 mg, 3.32 mmol) was added to a stirred solution of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.08 mL, 329.5 µmol) in MeCN (10 mL) under an atmosphere of N_2 at 25 ºC. To the mixture tetrabutylammonium fluoride solution (1 M, 0.94 mL, 940 µmol) was added over 2 h (dropwise). The reaction mixture was run through a silica plug washing with EtOAc (125 mL) and conc. *in vacuo.* The residue was dissolved in Et_2O (40 mL) and treated with oxalic acid in Et_2O (415.4 mg in 20 mL). The mixture was washed with water (150 mL) and brine (50 mL) sequentially, dried over Na_2SO_4, filtered and the filtrate conc. in vacuo to yield the crude product (191.1 mg). The crude was purified by column chromatography (9.5:0.5 v/v

petrol:EtOAc) to yield 1,2-diallyl-2-methylindolin-3-one (27.3 mg, 36 %) as a fluorescent yellow oil; R_f =0.17 (9.5:0.5 v/v petrol:EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.27 (s, 3H, 2-C$\underline{H}_3$), 2.45 (dd, J 7.6 Hz 14.3 Hz, 1H, 1''-$\underline{H}$), 2.58 (dd, J 6.7 Hz 14.3 Hz, 1H, 1''-$\underline{H}$), 3.95 (dd, J 5.5 Hz 17.1 Hz, 1H, 1'-$\underline{H}$), 4.01 (dd, J 5.4 Hz 17.1 Hz, 1H, 1'-$\underline{H}$), 4.92 (dd, J 1.5 Hz 10.1 Hz, 1H, 3''-$\underline{H}_{trans}$), 5.05 (dd, J 1.5 Hz 17.1, 1H, 3''-$\underline{H}_{cis}$), 5.22 (dd, J 1.5 Hz 10.3 Hz, 1H, 3'-$\underline{H}_{trans}$), 5.27 (dd, J 1.5 Hz 17.2 Hz, 1H, 3'-$\underline{H}_{cis}$), 5.42 (ddd, J 7.2 Hz 10.1 Hz 17.1 Hz, 1H, 2''-$\underline{H}$), 5.82-5.92 (m, 1H, 2'-$\underline{H}$), 6.70 (t, J 7.4 Hz, 1H, 5-$\underline{H}$), 6.73 (d, J 8.1 Hz, 1H, 7-$\underline{H}$), 7.42 (td, J 0.8 Hz 7.8 Hz, 1H, 6-$\underline{H}$), 7.59 (d, J 7.7 Hz, 1H, 4-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 21.5 (2-$\underline{C}H_3$), 40.9 (1''-$\underline{C}H_2$), 44.9 (1'-$\underline{C}H_2$), 70.4 (2-$\underline{C}$), 109.0 (7-$\underline{C}$H), 116.9 (5-$\underline{C}$H), 117.0 (3''-$\underline{C}H_2$), 118.7 (3'-$\underline{C}H_2$), 119.3 (4a-$\underline{C}$), 124.7 (4-$\underline{C}$H), 128.5 (2''-$\underline{C}$H), 134.2 (2'-$\underline{C}$H), 137.4 (6-$\underline{C}$H), 159.6 (7a-$\underline{C}$), 203.4 (3-$\underline{C}$=O); ν_{max} (neat oil, cm^{-1}) 1691 (C=O aryl), 1318 (C-N aryl); UV-Vis (EtOH) λ_{max} (nm), ε ($M^{-1}cm^{-1}$) 201 (13864), 235 (20601), 260 (6447), 317 (1029), 409 (3287); *m/z* (ESI^+) calculated for $C_{15}H_{17}NO$ $[M+H]^+$; 228.1383, found 228.1380 (error -1.32 ppm).

Ethyl 2-(5,6-dihydropyridin-1(2H)-yl)acetate **102**[142,143]

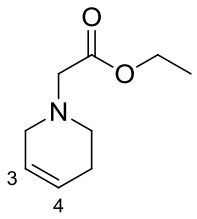


102



4

Pyridine (2.5 mL, 30.9 mmol) was added to a stirred solution of ethyl bromoacetate (3.43 mL, 30.9 mmol) in THF (40 mL). The solution was stirred for 19 h at 25 °C prior to cooling on ice followed by filtering. The filter cake was washed with cold Et_2O (150 mL) and dried under suction to yield 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (4.83 g, 64 %) as a colourless solid that was used without further purification. mp: 133 ºC (lit: 135 - 136 ºC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.33 (t, *J* 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.30 (q, *J* 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 6.38 (s, 2H, $NC\underline{H}_2CO_2Et$), 8.09 (t, *J* 7.2 Hz, 2H, 3-$\underline{H}$, 5-$\underline{H}$), 8.54 (t, *J* 7.8 Hz, 1H, 4-$\underline{H}$), 9.50 (d, *J* 5.7 Hz, 2H, 2-$\underline{H}$, 6-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 14.1 ($CO_2CH_2\underline{C}H_3$), 61.1 ($N\underline{C}H_2CO_2Et$), 63.5 ($CO_2\underline{C}H_2CH_3$), 127.6 (3-$\underline{C}$H, 5-$\underline{C}$H), 145.9 (4-$\underline{C}$H), 146.8 (2-$\underline{C}$H, 6-$\underline{C}$H), 165.8 ($\underline{C}O_2Et$) ν_{max} (solid, cm^{-1}) 1737 (C=O ester), 1198 (C-O), m/z (ESI+) calculated for $C_9H_{12}NO_2$ $[M]^+$; 166.0868, found 166.0868 (error 0 ppm).



Sodium borohydride (1.55 g, 40.94 mmol) was added portion-wise to a stirred solution of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (2.50 g, 10.2 mmol) in MeOH (30 mL) on ice after which the solution was equilibrated to rt and stirred for 2.5 h. The solution was subsequently reduced by half by evaporation *in vacuo* followed by quenching with water (100 mL) and extracting with EtOAc (2 X 75 mL). The combined organic extracts were dried with Na_2SO_4, filtered and evaporated *in vacuo* to yield ethyl 2-(5,6-dihydropyridin-1(2H)-yl)acetate (1.46 g, 85 %) as an orange oil that was used without further purification; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.28 (t, *J* 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 2.18-2.24 (m, 2H, 5-$\underline{H}_2$), 2.71 (t, *J* 5.7 Hz, 2H, 2-$\underline{H}_2$), 3.13 (quin, *J* 2.7 Hz, 2H, 6-$\underline{H}_2$), 3.31 (s, 2H, $NC\underline{H}_2CO_2Et$), 4.20 (dd, *J* 7.1 Hz 14.3 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.71 (ddt, *J* 1.9 Hz 10.0 Hz 42.2 Hz, 2H, 3-$\underline{H}$. 4-$\underline{H}$); ^{13}C NMR (100 MHz) δ_C 14.3 ($CO_2CH_2\underline{C}H_3$), 25.9 (5-$\underline{C}H_2$), 49.7 (2-$\underline{C}H_2$), 51.9 (6-$\underline{C}H_2$), 59.2 ($N\underline{C}H_2CO_2Et$), 60.5 ($CO_2\underline{C}H_2CH_3$), 124.9 (4-$\underline{C}$H), 125.0 (3-$\underline{C}$H), 170.6 ($\underline{C}O_2Et$); ν_{max} (thin film, cm^{-1}) 1732 (C=O ester), 1177 (C-N amine), 1154 (C-O ester), *m/z* (ESI$^+$) calculated for $C_9H_{15}NO_2$ $[M+H]^+$; 170.1176, found 170.1169 (error -4.14 ppm).

CHAPTER 4: REFERENCES

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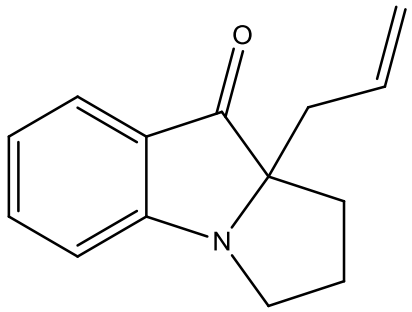
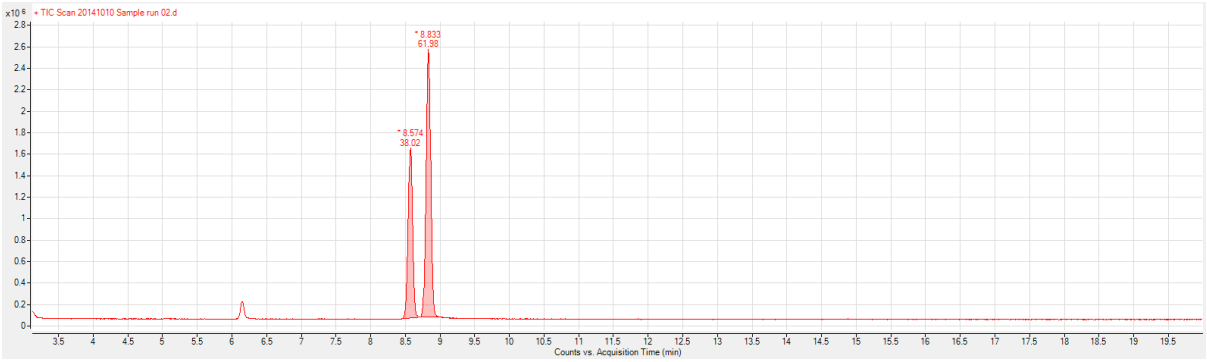
APPENDIX A

Structure 1:

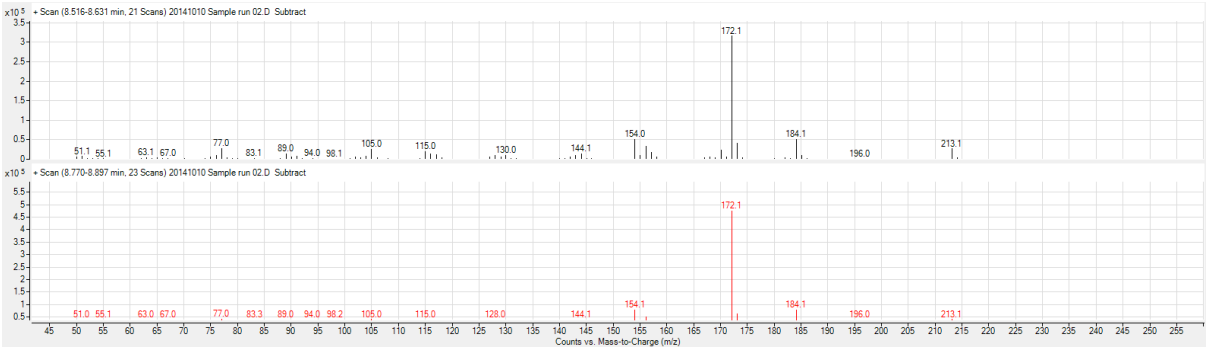


M.W. 213

TIC:

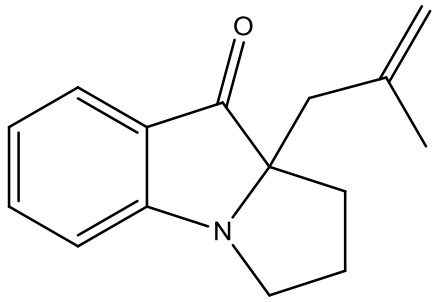


Mass Spectra of Highlighted Peaks:



%ee = 24.0% ee

Structure 2:



M.W. 227

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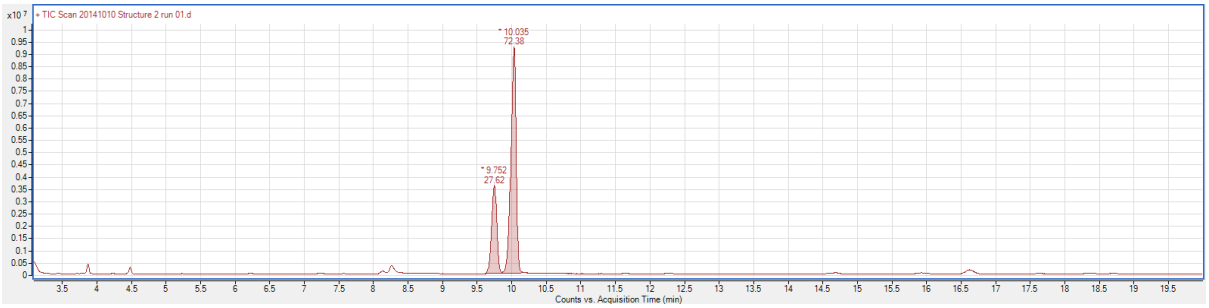

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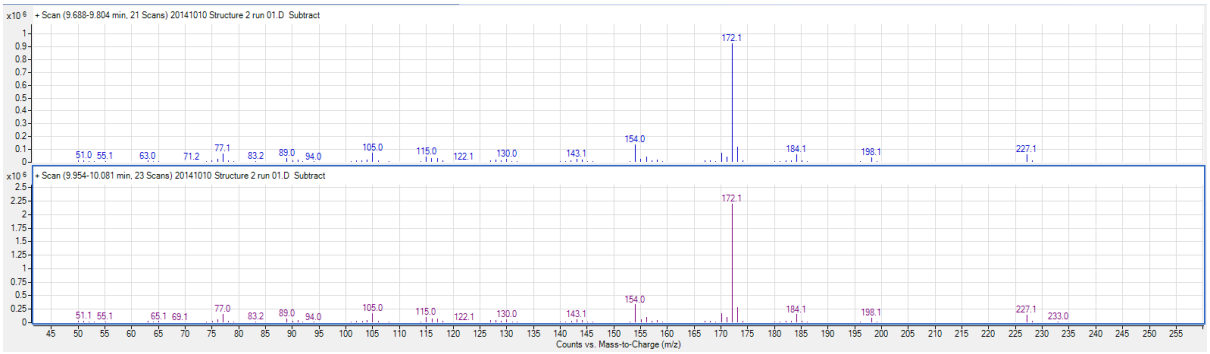
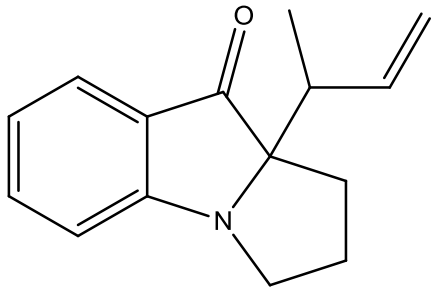


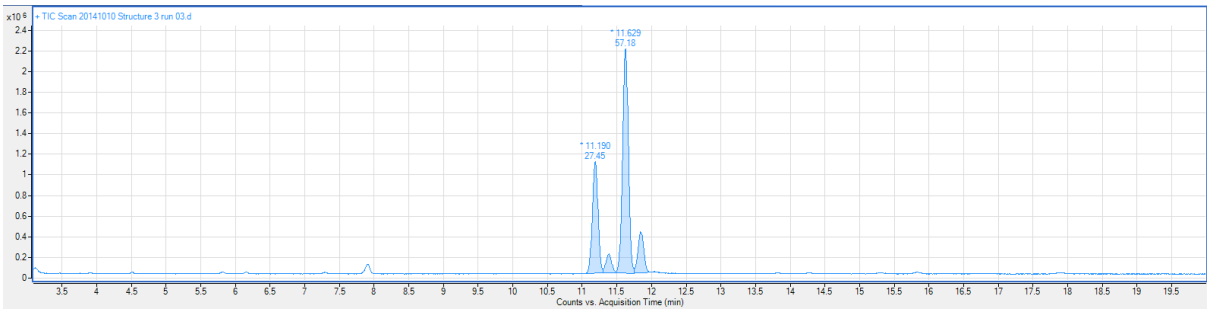
%ee = 44.8% ee

Structure 3:



M.W. 227

TIC:



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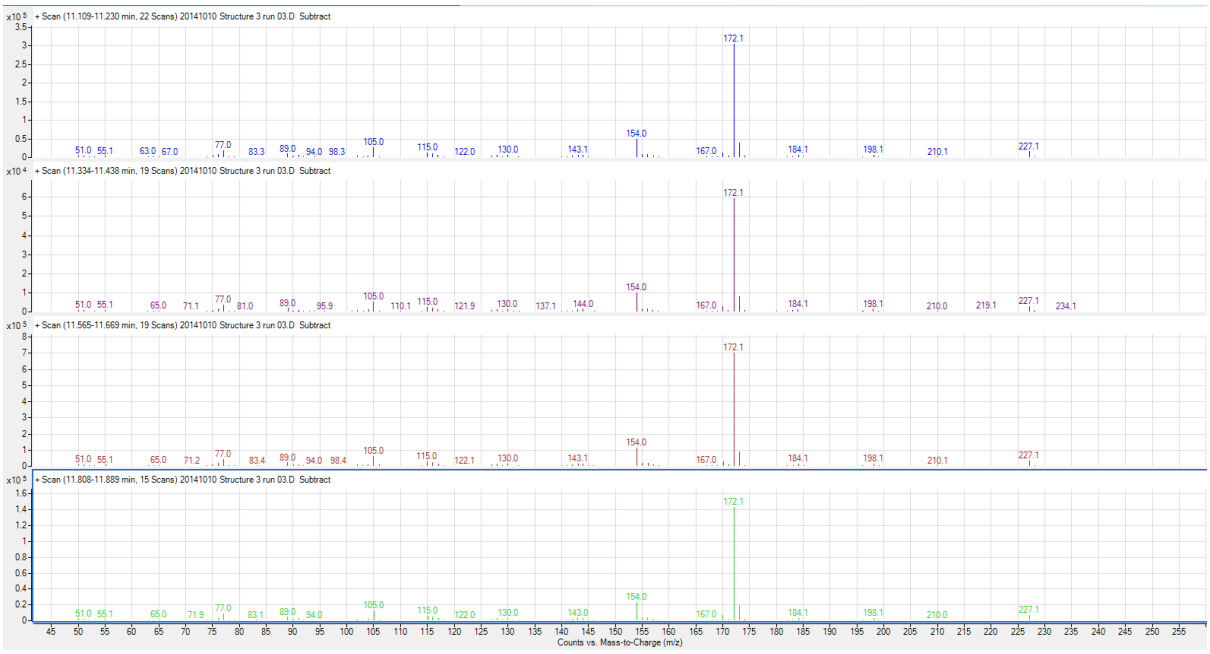


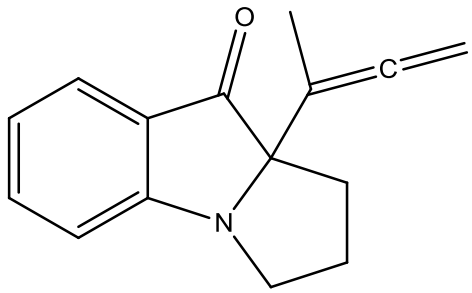
It was assumed the first two peaks were the enantiomers of diastereoisomer 1 and the last two peaks were the enantiomers of diastereoisomer 2.

%ee diastereoisomer 1 = 69.7% ee

%ee diastereoisomer 2 = 69.0% ee

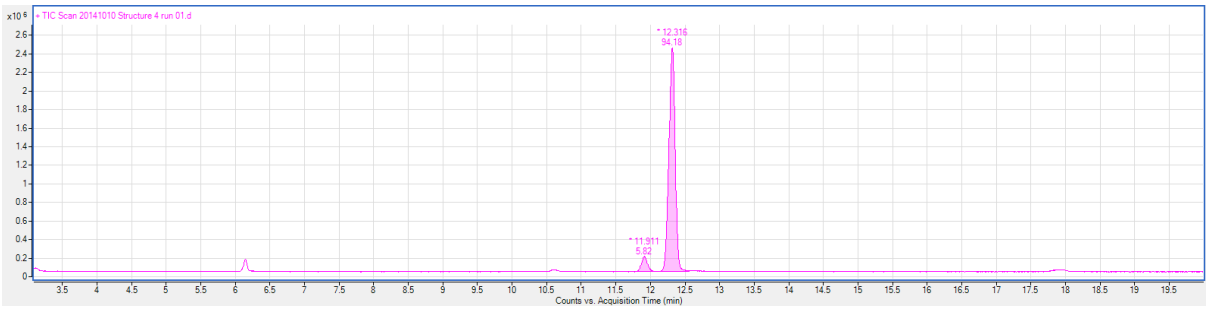
%de = 35.3% de

Structure 4:

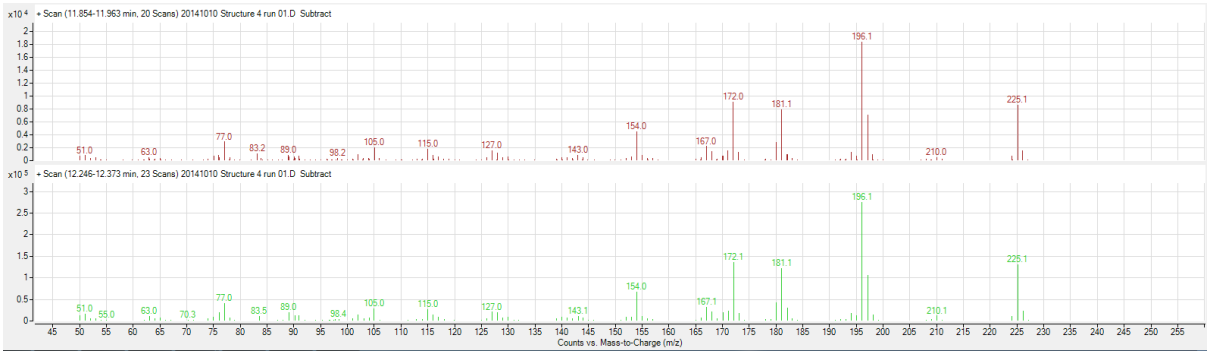


M.W. 225

TIC:

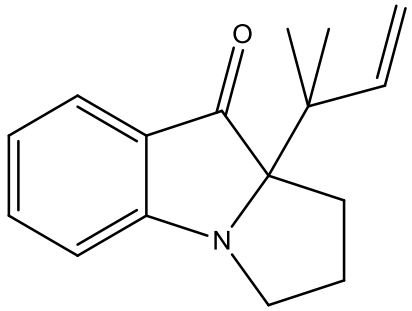


Mass Spectra of Highlighted Peaks:



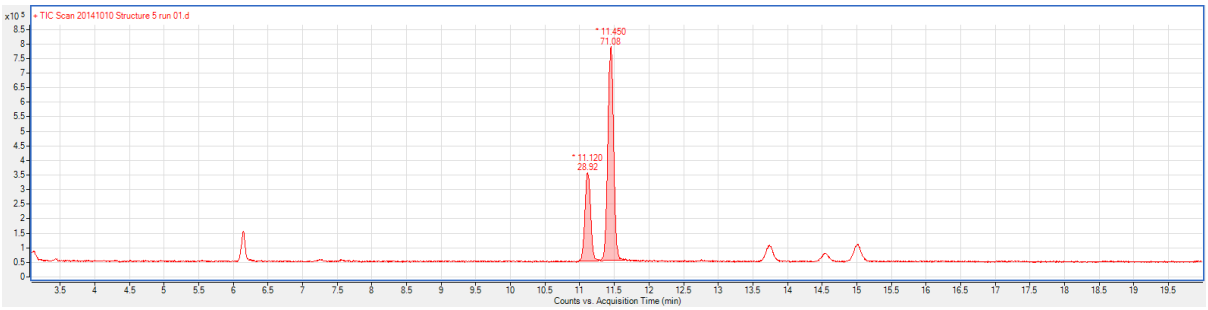
%ee = 88.4% ee

Structure 5:

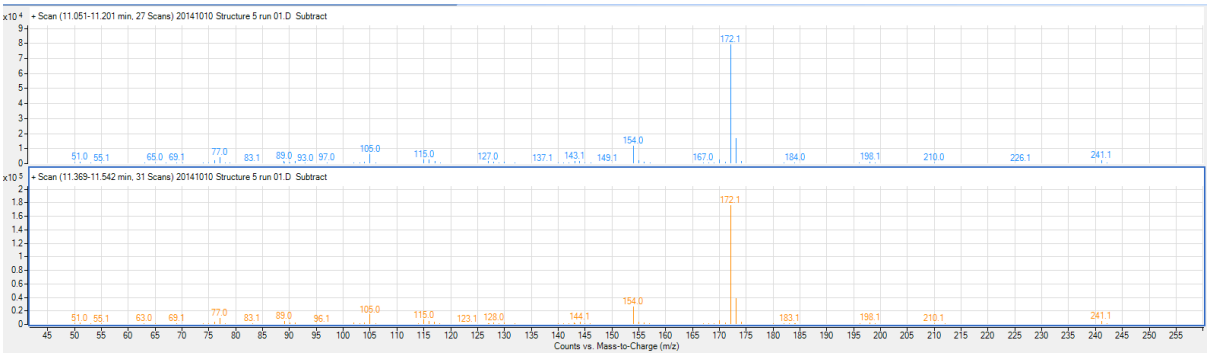


M.W. 241

TIC:

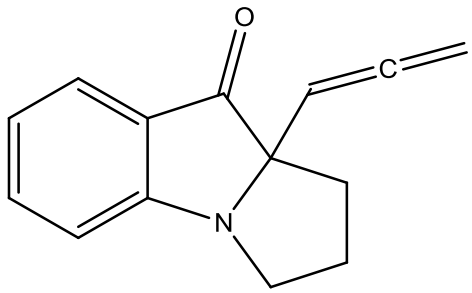


Mass Spectra of Highlighted Peaks:



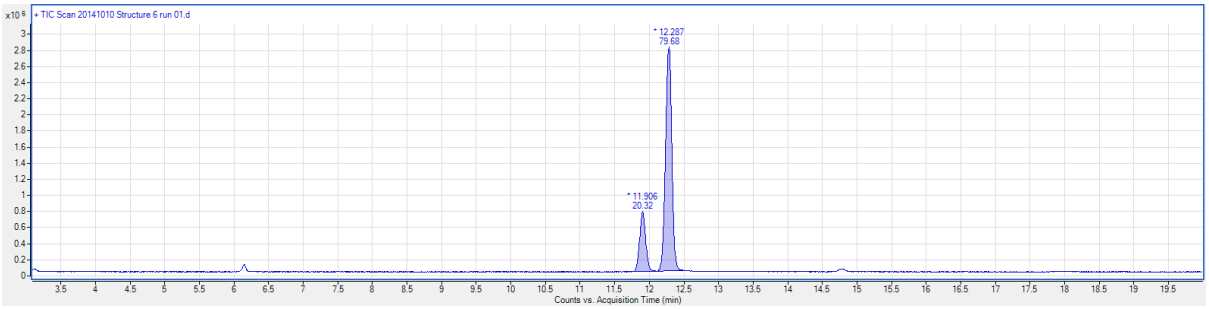
%ee = 42.2% ee

Structure 6:

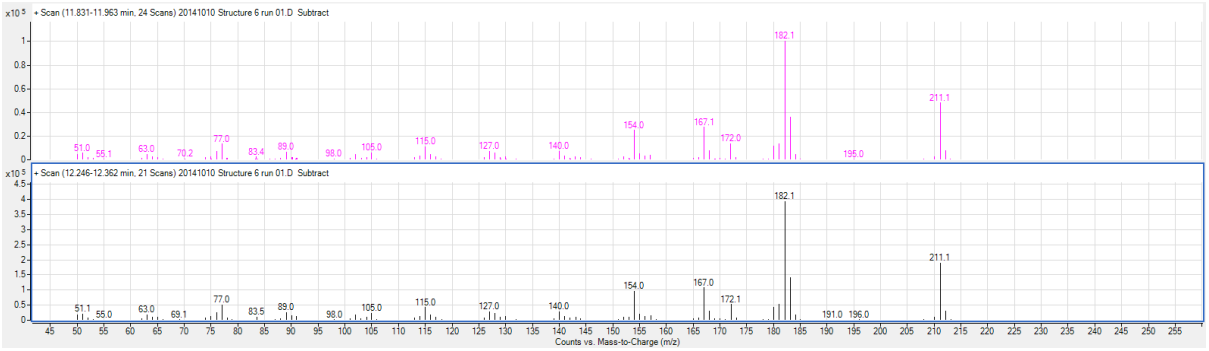


M.W. 211

TIC:

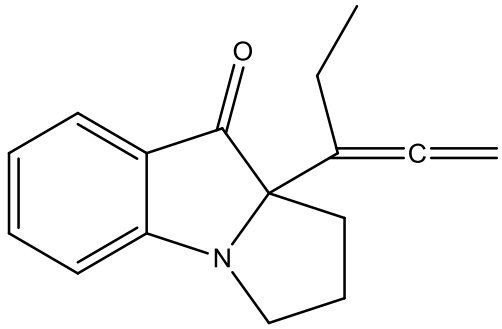


Mass Spectra of Highlighted Peaks:



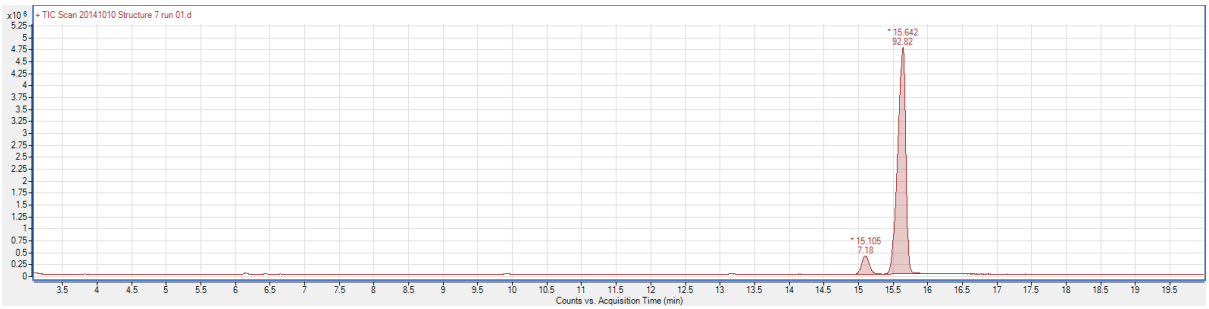
%ee = 59.4% ee

Structure 7:

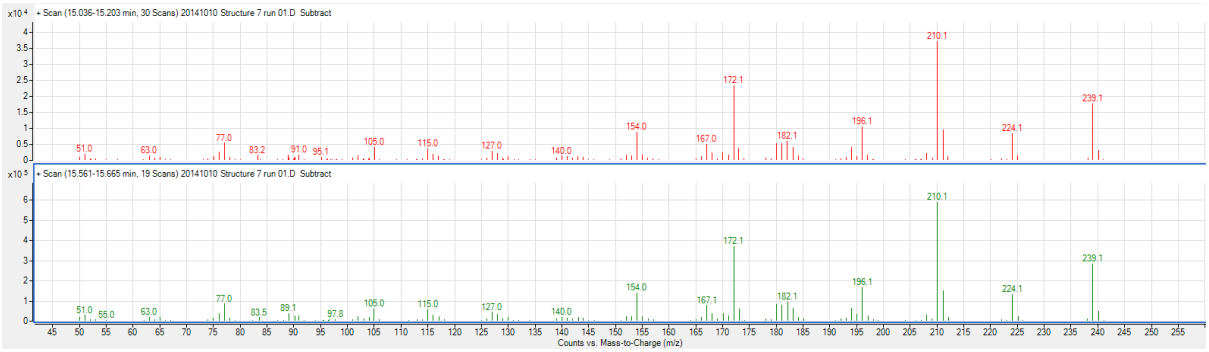


M.W. 239

TIC:



Mass Spectra of Highlighted Peaks:



%ee = 85.6% ee

GC-MS Method Details

Compounds 1, 2, 4, 5, 6 and 7

GC -MS		
Instrument	Agilent 7890 + 5975C	
Oven	Oven Profile	170°C isothermal
	Run time mins	20 mins
	Equilibration time mins	1
Inlet	Injector type/temp°C	Split/250
	Injection volume µl	1
	Split ratio	25:1
	Column head pressure psi	11.65
Column	Type	CP-Chirasil Dex CB (25m x 0.25mm x 0.25µm)
	Carrier Gas / Flow mls/min	He/1 ml/min (constant flow)
MS	Transfer line temp °C Mode Source temp °C Quadrupole temp°C Mass range m/z	320°C Scan 230°C 150°C 45 - 550

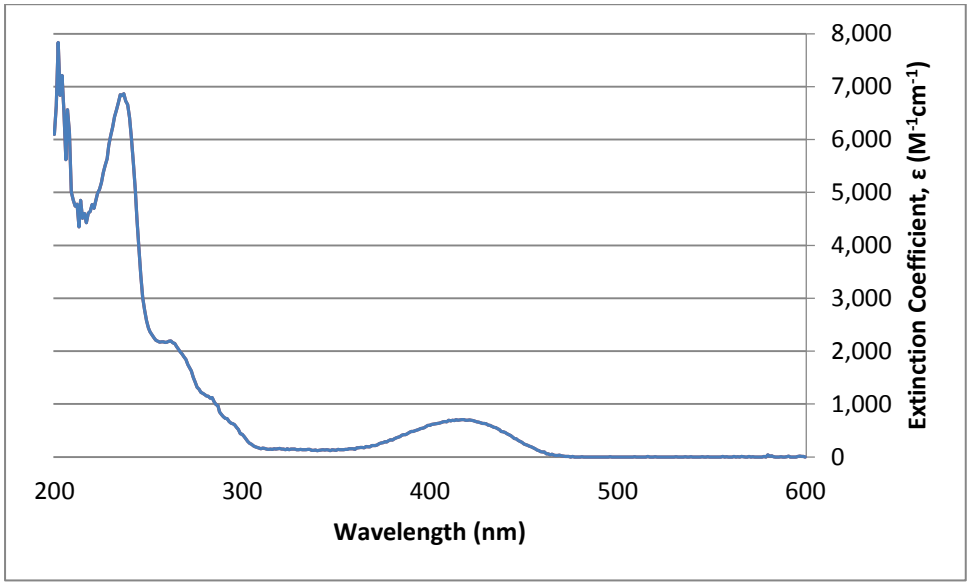
Compound 3

GC -MS		
Instrument	Agilent 7890 + 5975C	
Oven	Oven Profile	165°C isothermal
	Run time mins	20 mins
	Equilibration time mins	1
Inlet	Injector type/temp°C	Split/250
	Injection volume µl	1
	Split ratio	25:1
	Column head pressure psi	11.65
Column	Type	CP-Chirasil Dex CB (25m x 0.25mm x 0.25µm)
	Carrier Gas / Flow mls/min	He/1 ml/min (constant flow)
MS	Transfer line temp °C Mode Source temp °C Quadrupole temp°C Mass range m/z	320°C Scan 230°C 150°C 45 - 550

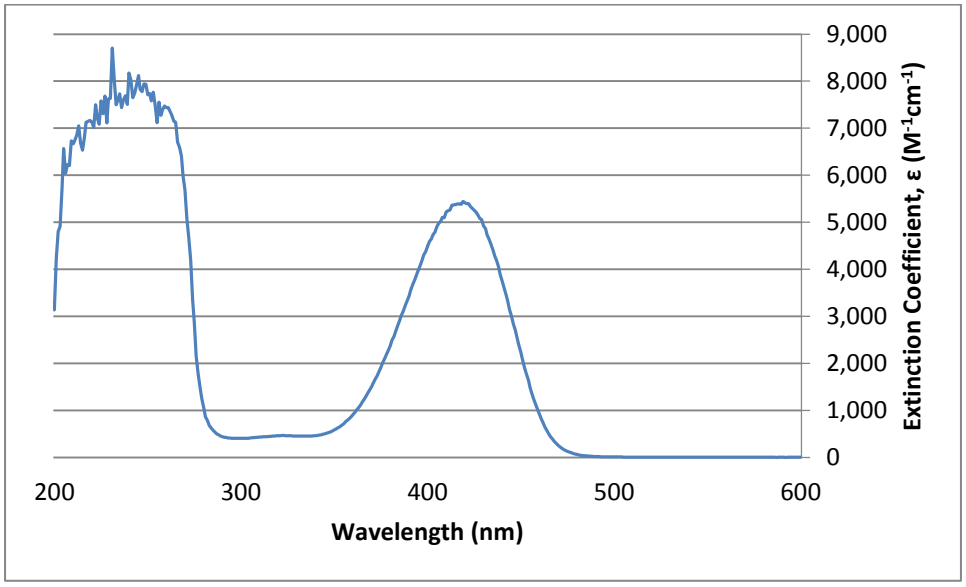
APPENDIX B

UV-VISUAL SPECTROSCOPY DATA

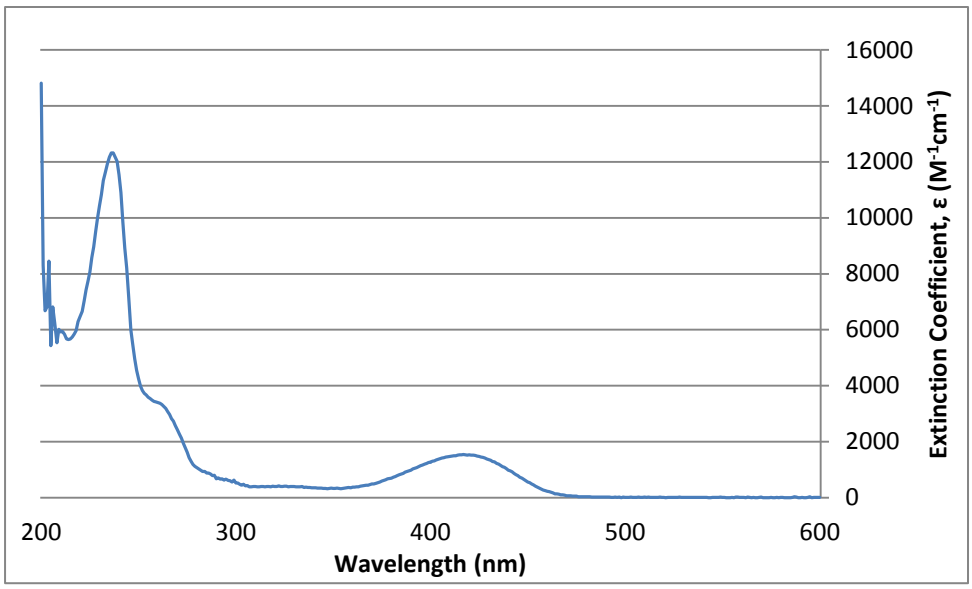
Ethyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate **77**



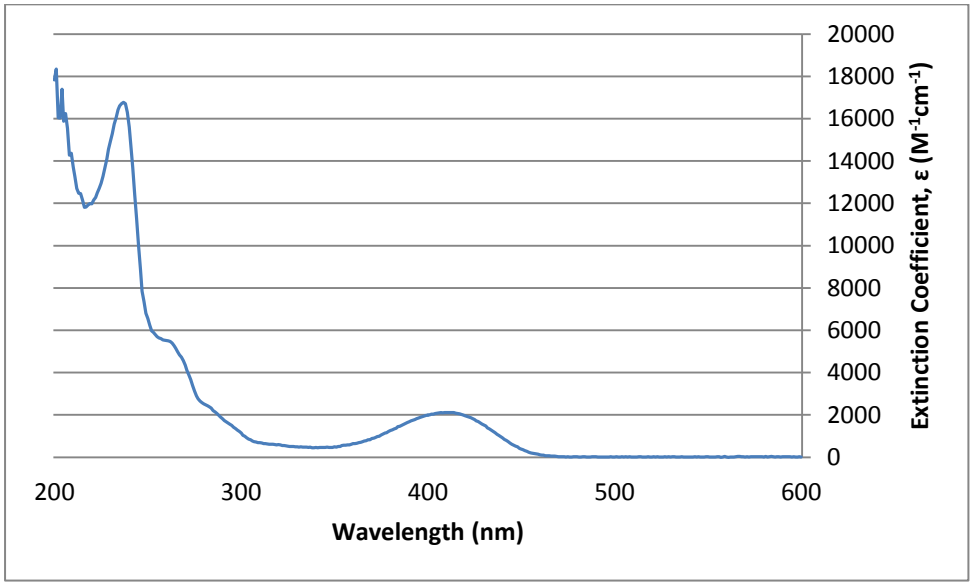
Methyl 2-allyl-1-methyl-3-oxoindoline-2-carboxylate **84a**



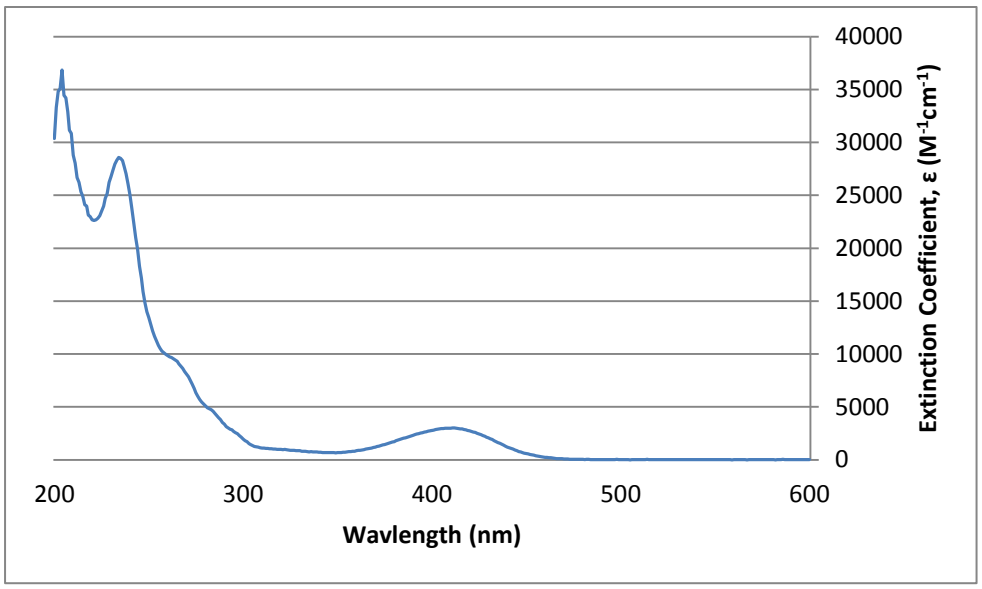
Methyl 1-methyl-3-oxo-2-(propa-1,2-dien-1-yl)indoline-2-carboxylate **84b**



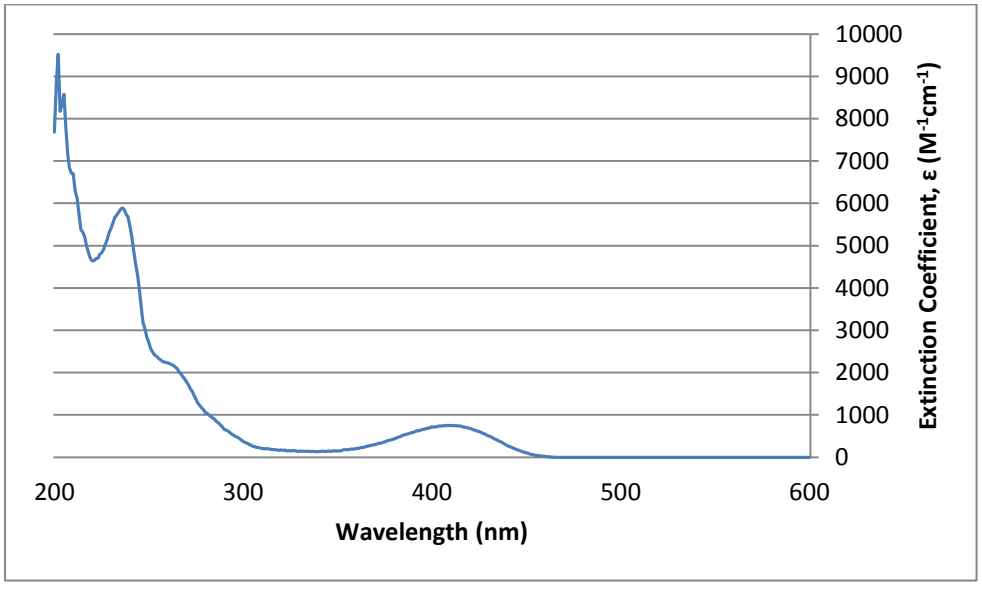
Methyl 1,2-allyl-3-oxoindoline-2-carboxylate **84c**



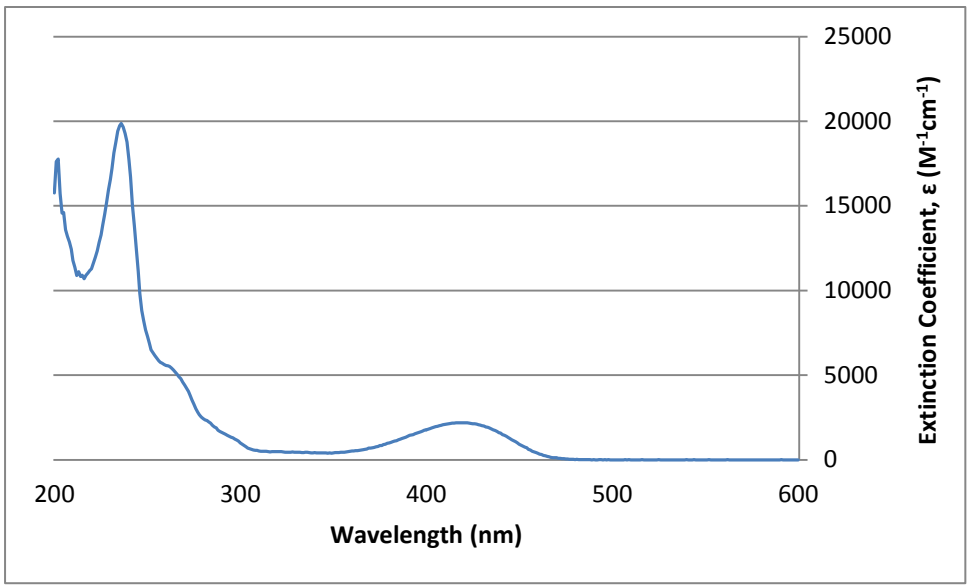
Methyl 2-allyl-3-oxo-1-phenylindoline-2-carboxylate **84d**



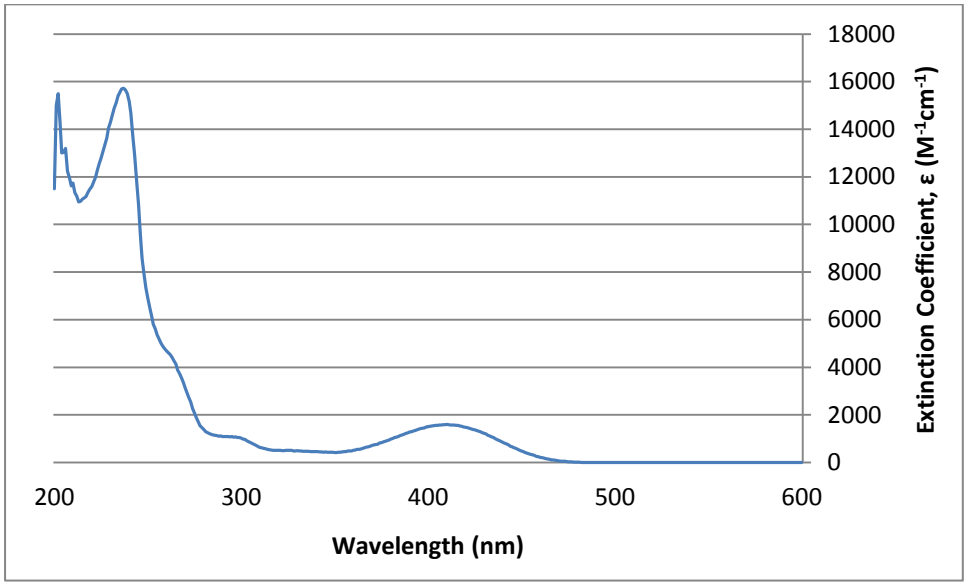
Methyl 2-allyl-1-benzyl-3-oxoindoline-2-carboxylate **84e**



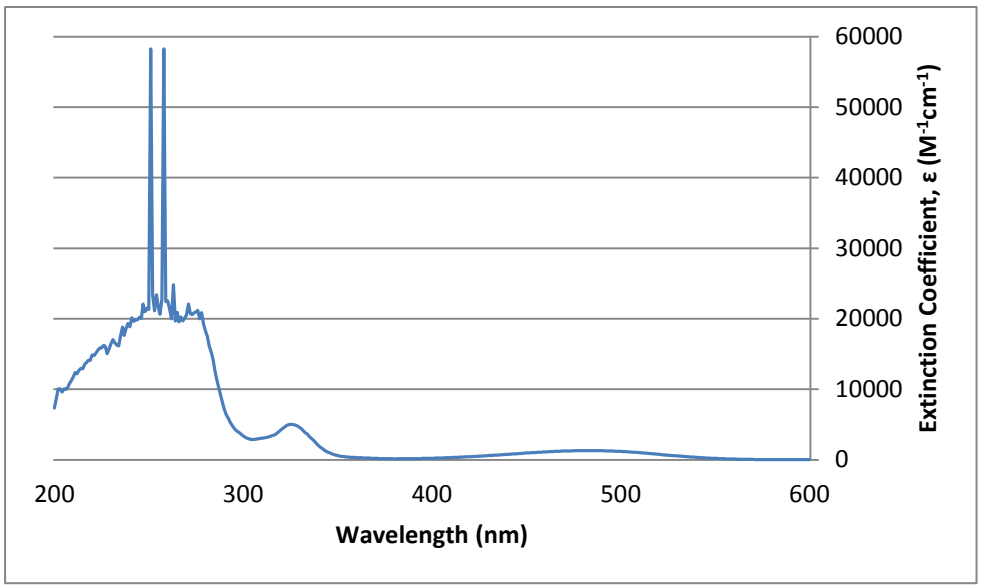
Methyl 1-methyl-2-(2-methylenecyclohexyl)-3-oxoindoline-2-carboxylate **84f**



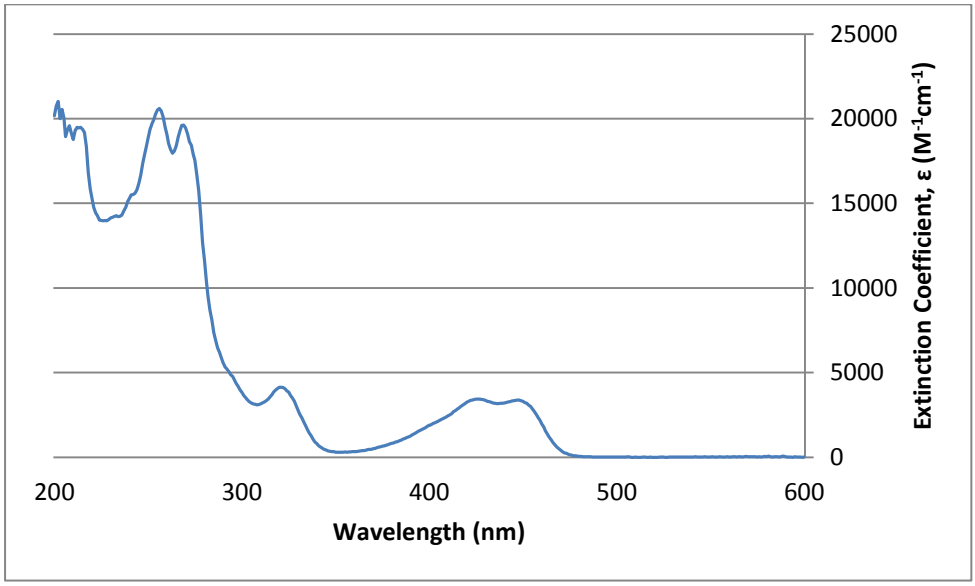
Methyl 1-methyl-2-(2-methylbut-3-en-2-yl)-3-oxoindoline-2-carboxylate **84g**



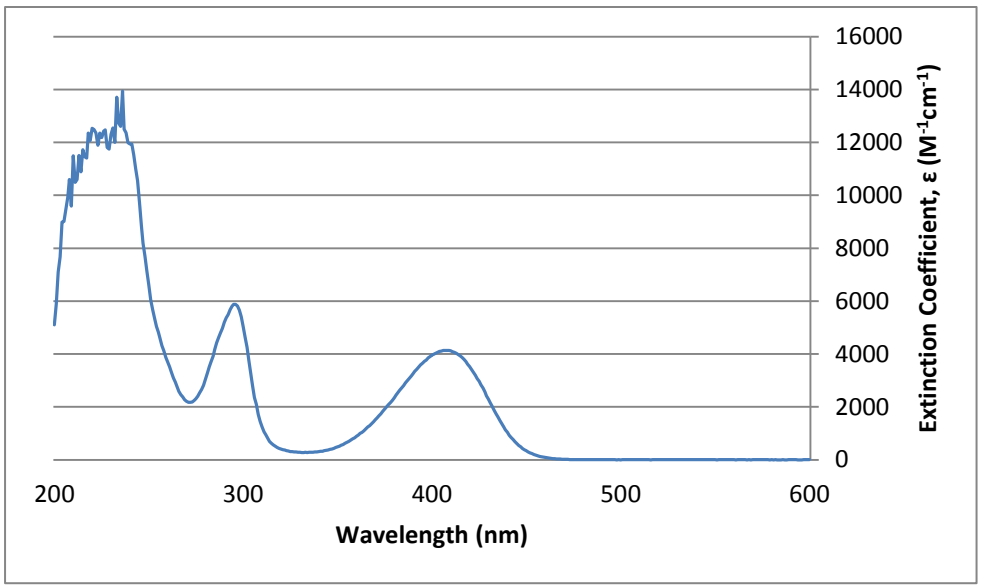
Methyl 2-allyl-1-methyl-3-oxo-2,3-dihydro-1H-benzo[f]indole-2-carboxylate **90a**



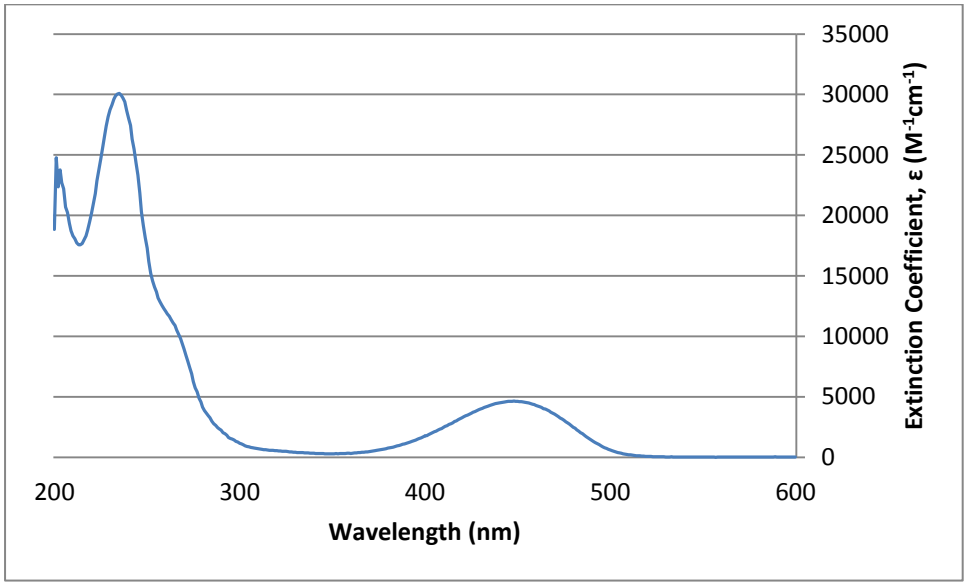
Methyl 2-allyl-3-methyl-1-oxo-2,3-dihydro-1H-benzo[e]indole-2-carboxylate **90b**



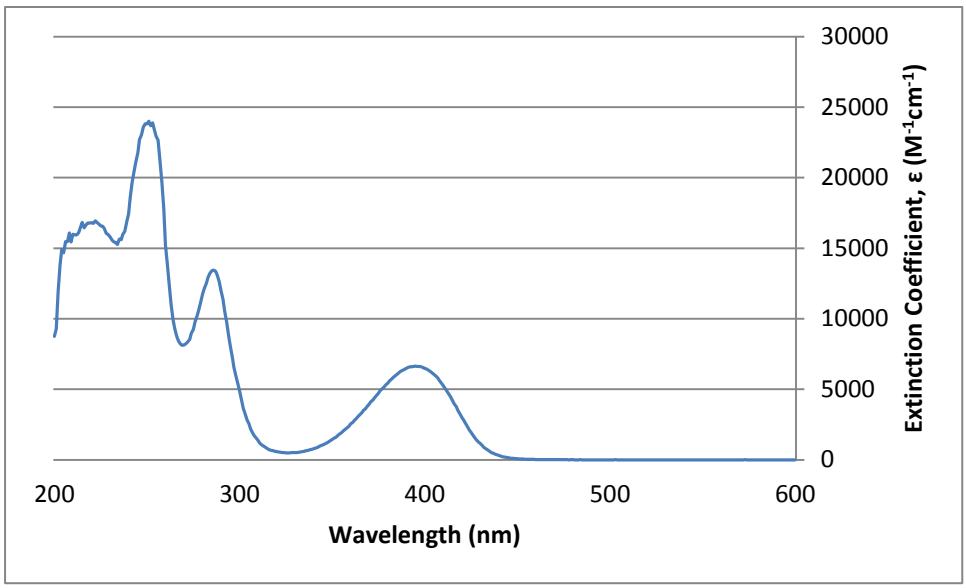
Methyl 2-allyl-4-methoxy-1-methyl-3-oxoindoline-2-carboxylate **90c**



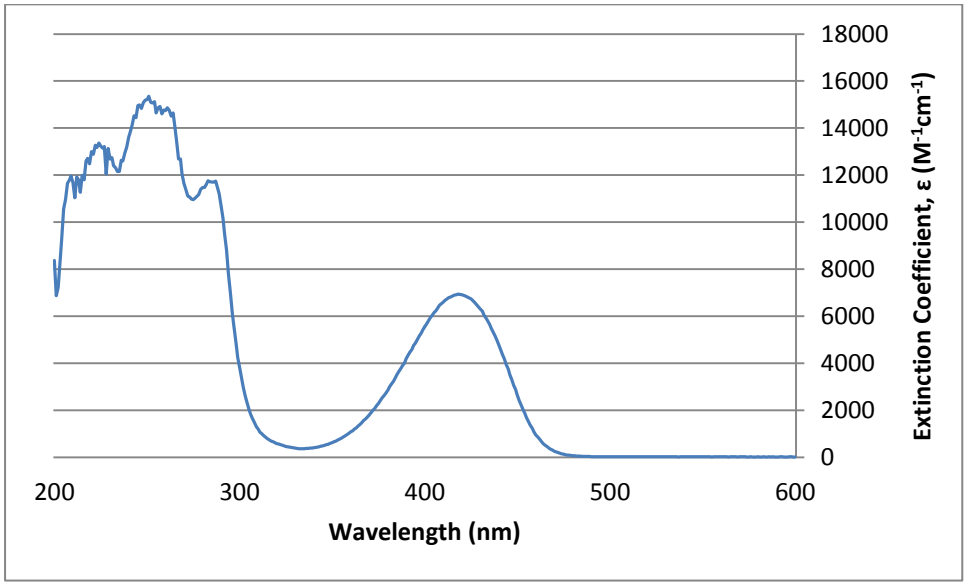
Methyl 2-allyl-5-methoxy-1-methyl-3-oxoindoline-2-carboxylate **90d**



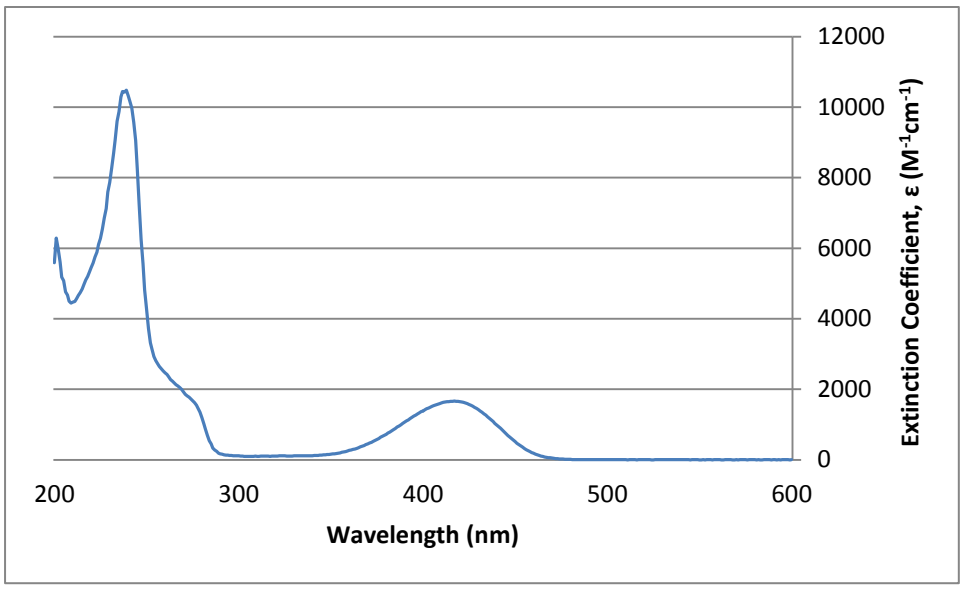
Methyl 2-allyl-6-methoxy-1-methyl-3-oxoindoline-2-carboxylate **90e**



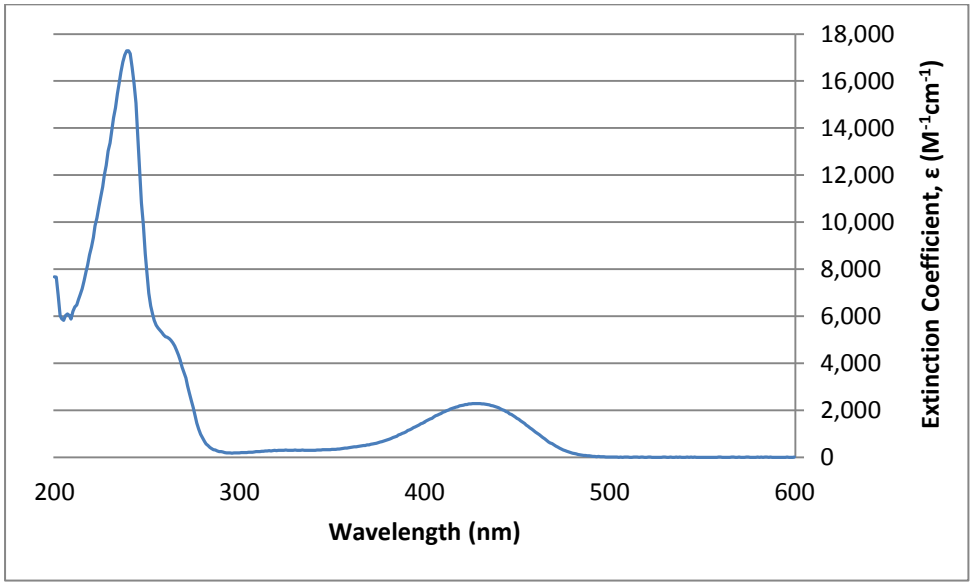
Methyl 2-allyl-5,6-dimethoxy-1-methyl-3-oxoindoline-2-carboxylate **90f**



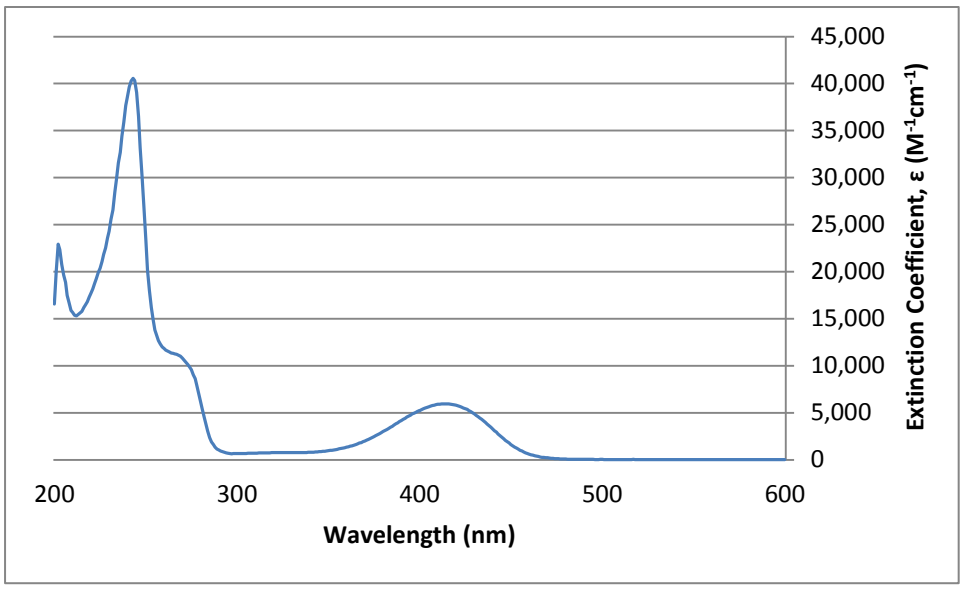
Methyl 2-allyl-1,4-dimethyl-3-oxoindoline-2-carboxylate **90g**



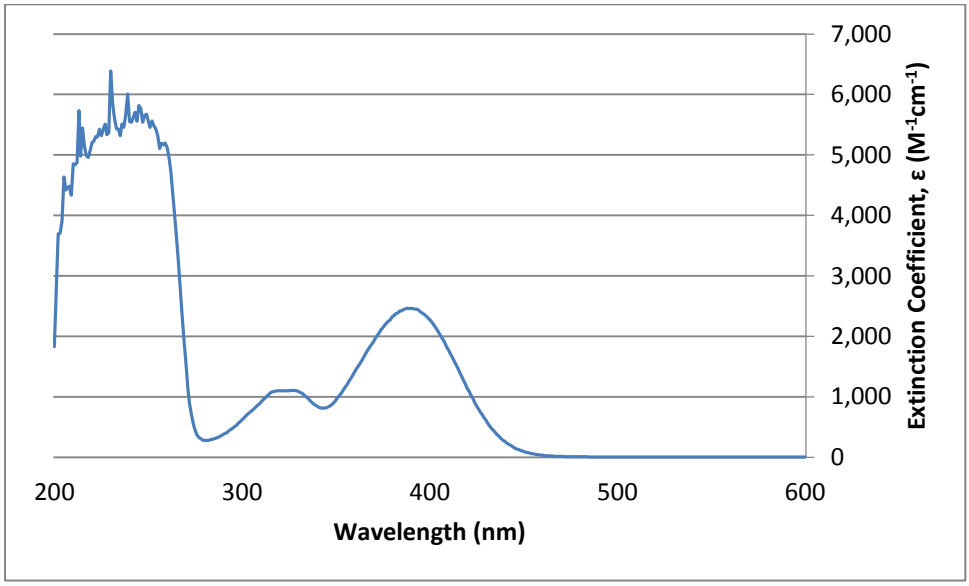
Methyl 2-allyl-1,5-dimethyl-3-oxoindoline-2-carboxylate **90h**



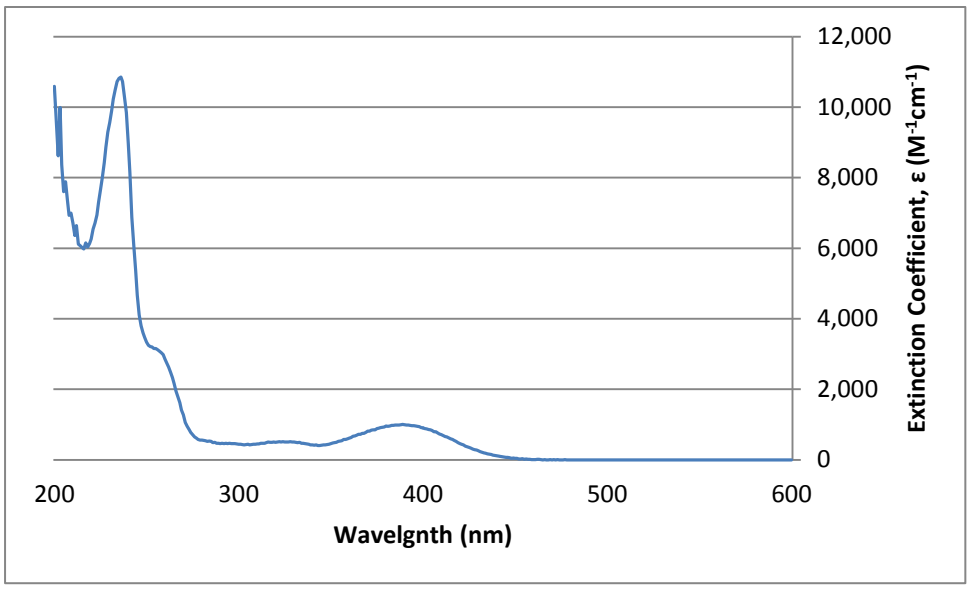
Methyl 2-allyl-1,6-dimethyl-3-oxoindoline-2-carboxylate **90i**



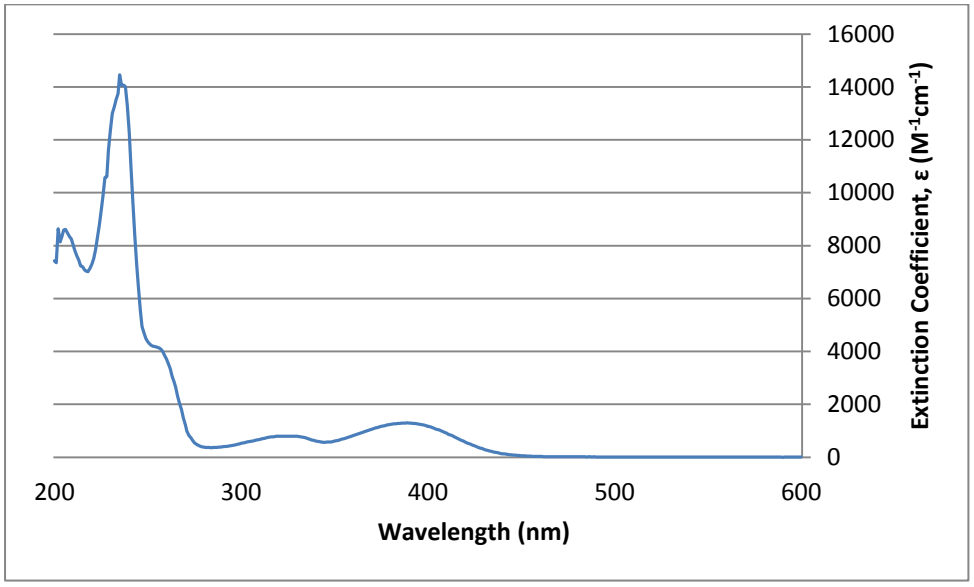
9a-Allyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99a**



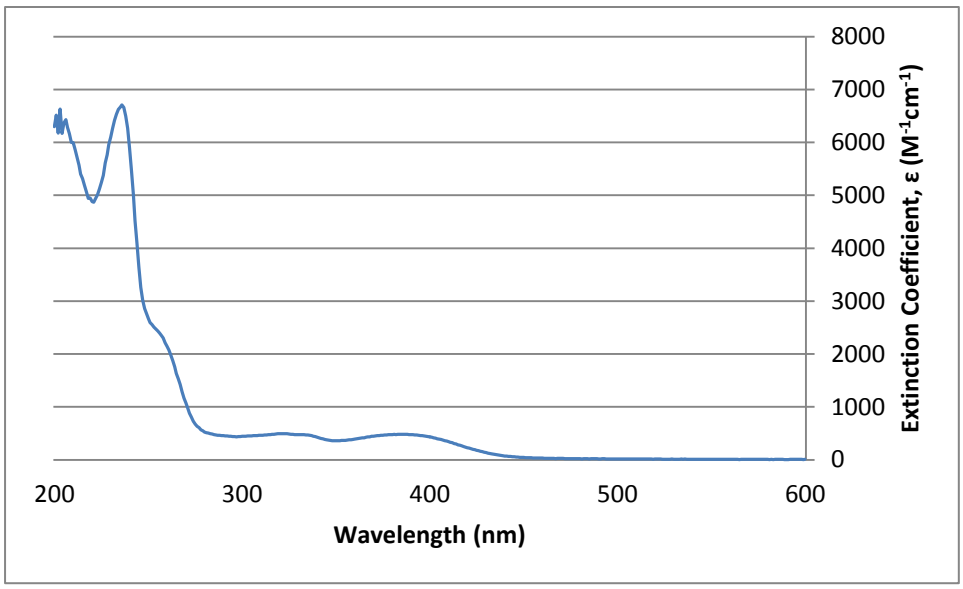
9a-(2-Methylallyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99b**



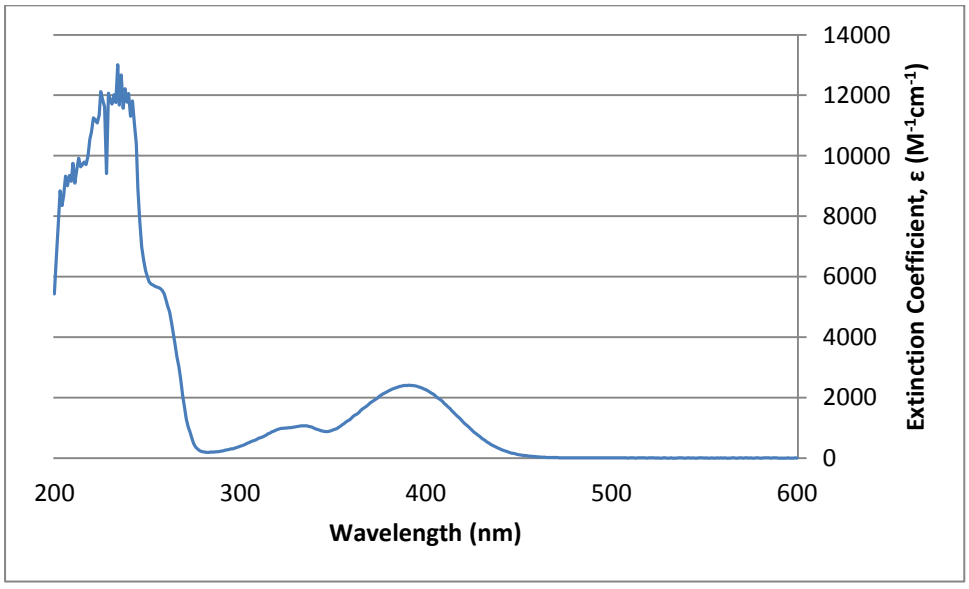
9a-(But-3-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99c**



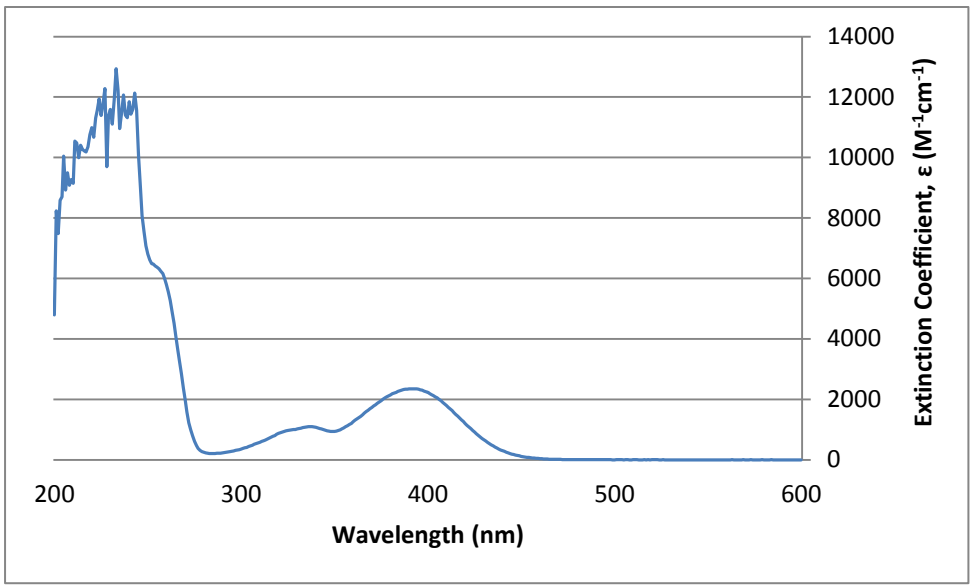
9a-(2-Methylbut-3-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99d**



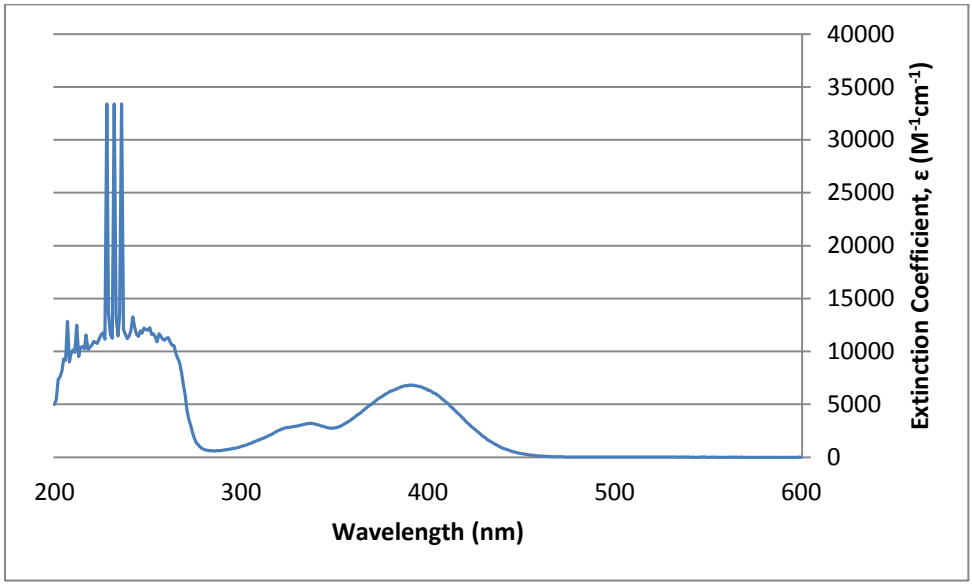
9a-(Propa-1,2-dien-1-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99e**



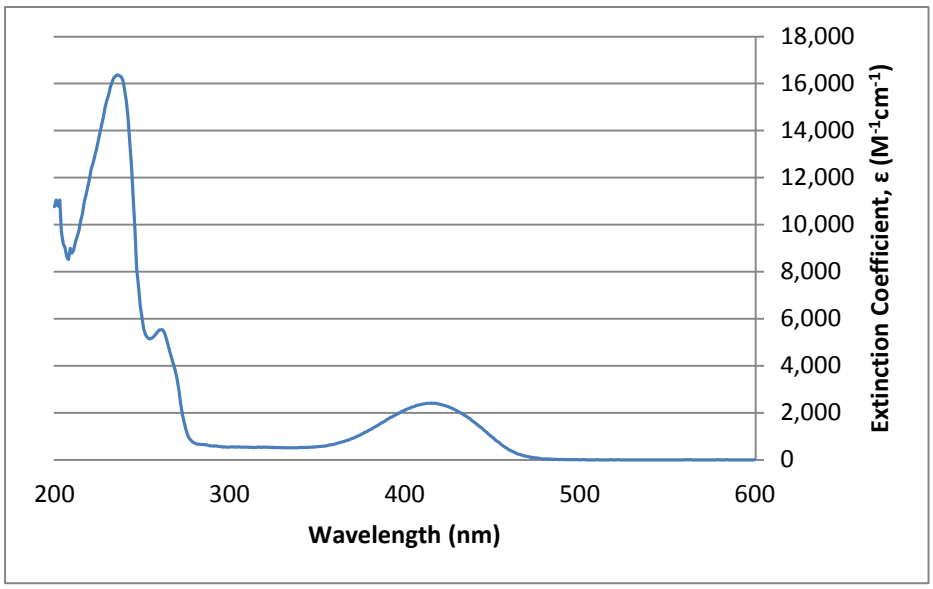
9a-(Buta-2,3-dien-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99f**



9a-(Penta-1,2-dien-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9(9aH)-one **99g**



9a-Allyl-7,8,9,9a-tetrahydropyrido[1,2-a]indol-10(6H)-one **99h**



1,2-Diallyl-2-methylindolin-3-one **101**