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Synthesis of Spirocyclic Pseudoindoxyl Frameworks *via* a Highly Diastereoselective MgI_2-catalysed Ring Expansion Reaction

by

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Science has explained nothing; the more we know the more fantastic the world becomes and the profounder the surrounding darkness.

-Aldous Huxley

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My experience of working in the Dowden group has been thoroughly enjoyable and a great learning experience. Without the assistance of others, I would never have been able to undertake this work or progress to PhD study. I would therefore like to extend my greatest thanks to the following people:

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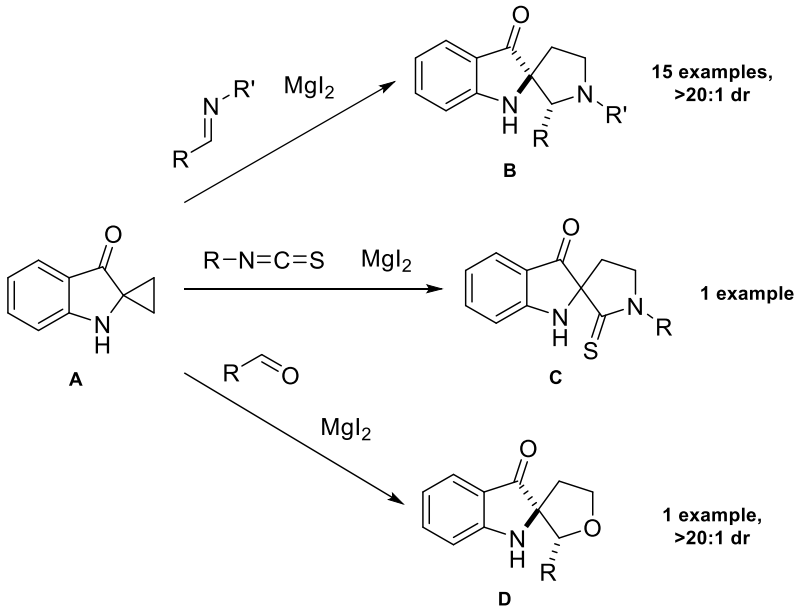
Abstract

The synthesis of a variety of substituted 2-spiropseudoindoxyl structures has been effected through the use of a highly diastereoselective ring expansion reaction between a spirocyclopropane molecule **A** (Scheme A) with aldimines, isothiocyanates and aldehydes. From this method, it has been possible to construct spiropyrrolidine **B**, spirothioamide **C** and spirotetrahydrofuran **D** pseudoindoxyl structures.



Scheme A. This work – construction of substituted spiropseudoindoxyl frameworks *via* an MgI_2 catalysed ring expansion to afford spiropyrrolidine (**B**), spirothioamide (**C**) and spirotetrahydrofuran (**D**) derivatives.

The relative stereochemistry between the stereocentres in structure **A** was elucidated by NOESY experiments to reveal the relative stereochemical configuration shown in Scheme A and a putative transition state model was constructed in order to explain the

observed diastereoselectivity. In addition, the use of various chiral catalysts was explored in an attempt to induce enantioselectivity into this reaction, however these attempts proved ineffectual.

The novel compounds produced in this work represent the exploration of new chemical space for structures of potential medicinal value. With further development, this method could be used in the synthesis of a variety of spirocyclic natural products of medicinal interest.

Abbreviation List

Å	Angstrom
App	Apparent
Aq	Aqueous
Boc	*tert*-Butyl carbamate
°C	Degrees Celsius
Calcd	Calculated
Cat.	Catalytic
Cbz	Carbobenzyloxycarbonyl
COSY	Correlation Spectroscopy
δ	Chemical shift
d	Doublet
DMSO	Dimethyl sulfoxide
Equiv	Equivalents
FTIR	Fourier-transform infrared
g	Gram
h	Hour
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
Hz	Hertz
J	NMR coupling constant
m	Multiplet
mg	Milligram
mL	Millilitre
mol	mole
MMFF	Merck Molecular Force Field
mmol	millimole
MS	Mass Spectrometry
ν	Infrared absorption

NOESY	Nuclear Overhauser Effect Spectroscopy
ppm	Parts per million
q	Quartet
R	Substituent
rt	Room temperature
s	Singlet
Sat.	Saturated
t	Triplet
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Ts	Tosyl

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1. Introduction

1.1 Background

Spirocycles are defined as ring systems fused through a single atom, known as the spirocentre.[1] Chemical structures incorporating spirocycles represent interesting targets for novel drug discovery on account of their unique three-dimensional architectures and conformational rigidity, offering the ability to project functional groups in three dimensions. This potentially affords enhanced binding site specificity over more planar ring systems which typically dominate the modern pharmacopeia.[2,3] Given that biological receptors themselves possess unique spatial landscapes, there is a significant interest in the development of spiro compounds as drug candidates. Consequently, molecules bearing spirocentres are being increasingly reported in the recent medicinal chemistry primary literature.[4] Spirocycles are also commonly occurring structural motifs within many natural products of potential medicinal value.[5,6] Considering that approximately one third of all commercial pharmaceuticals are to some extent based on structures derived from natural products,[7] there is a substantial justification for investigating the synthesis and reactivity of alkaloid-like structures incorporating spirocyclic motifs.

The spiro[indoline-2,3'-pyrrolidin]-3-one (spiropseudoindoxyl) framework (Figure 1, B) is a significantly underrepresented motif in modern drug discovery with only 254 known structures incorporating this framework according to a recent Chemical Abstracts Services search. The spiro[indoline-3,3'-pyrrolidin]-2-one core (Figure 1 A) is

represented in over 8000 known structures and has been widely studied and employed in the synthesis of natural products encompassing a myriad of potential therapeutic applications, most notably as anti-cancer agents.[8,9] Despite this, their spiropseudoindoxyl counterparts remain less thoroughly investigated.

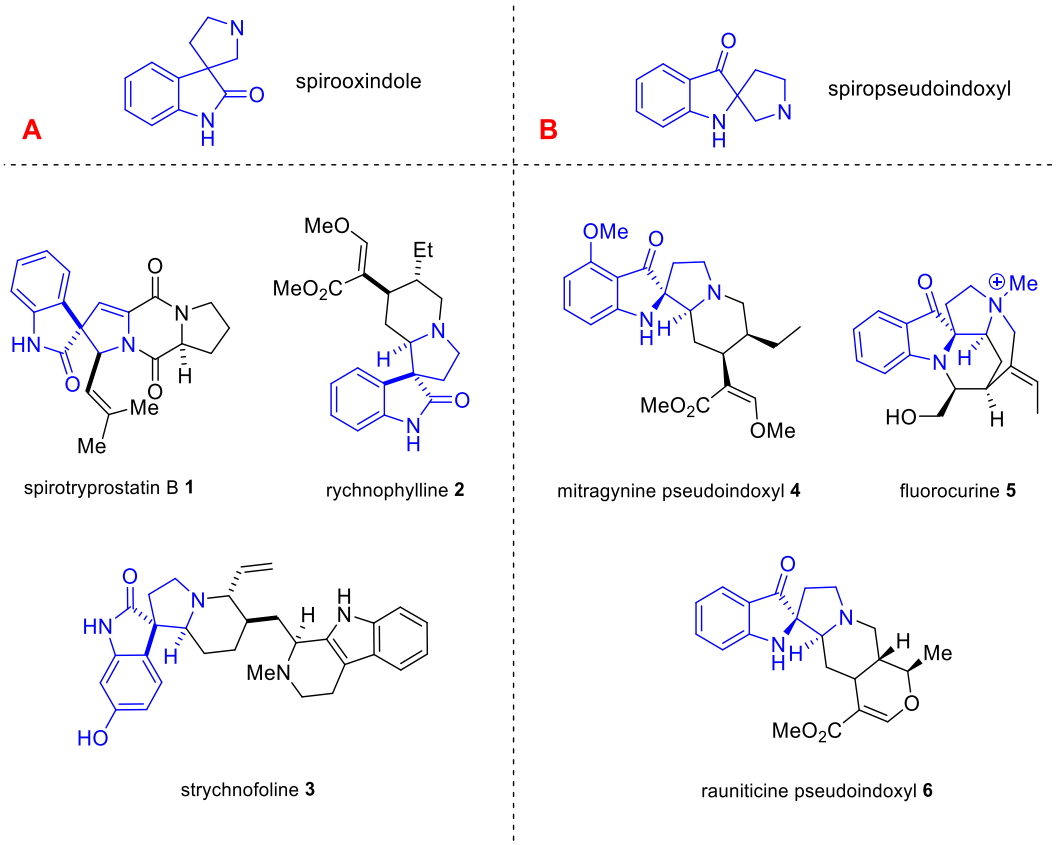


Figure 1. Selected examples of alkaloids incorporating [A] spiro[indoline-3,3'-pyrrolidin]-2-one (oxindole) and [B] spiro[indoline-2,3'-pyrrolidin]-3-one (pseudoindoxyl) structures.

Despite the limited available synthetic strategies for the assembly of spiro[indoline-2,3'-pyrrolidin]-3-one alkaloids, there exist various alkaloids of potential medicinal utility incorporating this structural motif. Perhaps most noteworthy is mitragynine pseudoindoxyl **4**, an oxidative rearrangement product of the alkaloid mitragynine

(Figure 2), originating from the leaves of *Mitragyna speciosa,*[10] a psychoactive plant indigenous to south-east Asia commonly known as Kratom. Mitragynine **7** is known to be a potent μ–opioid agonist,[11] however is differentiated from traditional opioid analgesics, such as morphine, in that it exhibits G-protein biased μ–agonism due to its unique binding pose in the μ–opioid receptor.[12] This denotes that it elicits the anti-nociceptive qualities of morphine type opiates, however due to its specific binding modality it does not activate undesirable downstream signalling pathways such as β–arrestin recruitment. Ultimately, this signifies that *Mitragyna* alkaloids and derivatives thereof have the potential to activate the μ–opioid receptor without incurring the debilitating side effects with which conventional opiates are closely associated, these include; respiratory depression, physical dependence and psychological addiction.[13] Mitragynine pseudoindoxyl is formed *in vivo* through the semi-pinacol rearrangement of mitragynine **7** upon oxidative metabolism, and exhibits μ–opioid binding affinity approximately 10 times higher than that of mitragynine in *in vitro* studies, displaying the same biased agonism as mitragynine.[14] Additionally, conversion of the indole ring system to the spiropseudoindoxyl type structure in other *Mitragyna* alkaloids significantly improved their μ–opioid receptor binding activities.[14] Given this understanding of the pharmacology of the *Mitragyna* alkaloids, highly substituted pseudoindoxyl frameworks present themselves as attractive targets to synthetic chemists.

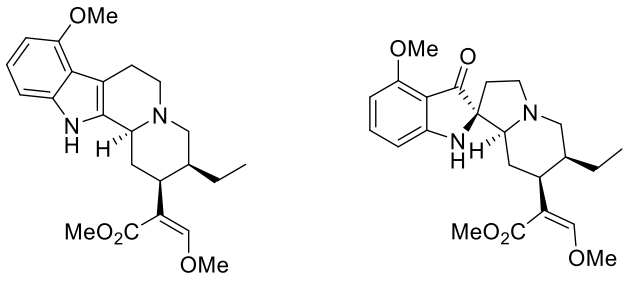
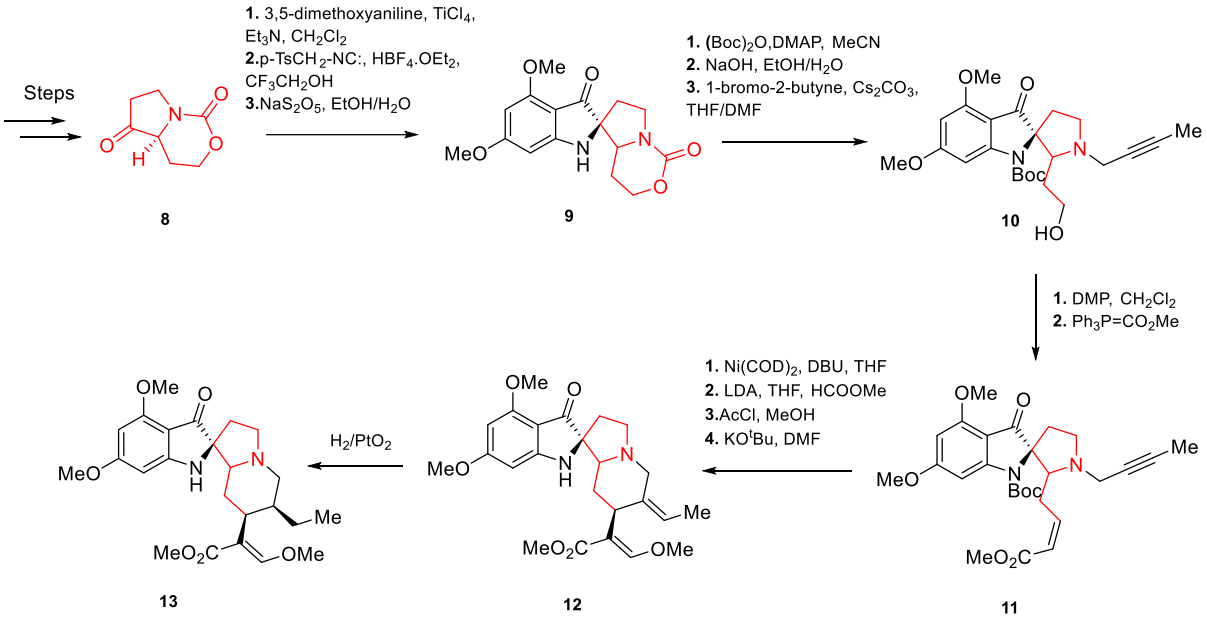


Figure 2. Structural comparison of mitragynine **7** and mitragynine pseudoindoxyl **4**.

Several syntheses of mitragynine **7** have been reported in the literature[12,15,16] however no total synthesis of mitragynine pseudoindoxyl **4** exists. Mitragynine pseudoindoxyl **4** has been prepared by the oxidative rearrangement of mitragynine under basic conditions,[17,18] however these methods often suffer from low yield and inefficient synthetic pathways. These syntheses will be elaborated in Section 1.3.

Sorensen *et al*. reported a synthesis of 11-methoxy mitragynine pseudoindoxyl involving an interrupted Ugi reaction as the key spirocyclisation step between **8** and 3,5-dimethoxyaniline (Scheme 1), (Figure 3). Following decarboxylation of **9** with NaOH and alkylation of the pyrrolidine nitrogen, the amino alcohol **10** is afforded. **10** is oxidised with DMP and an alkene is installed *via* a Wittig reaction to give **11**. The core spiroindolizidine structure is then constructed *via* an $Ni(cod)_2$ catalysed olefin cross-coupling reaction. Further transformations then give **12** and catalytic hydrogenation of the yields 11-methoxy mitragynine pseudoindoxyl **13**.



Scheme 1. Sorensen's synthesis of 11-methoxy mitragynine pseudoindoxyl.[19]

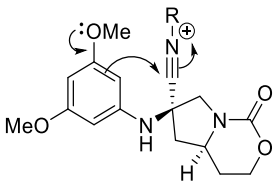
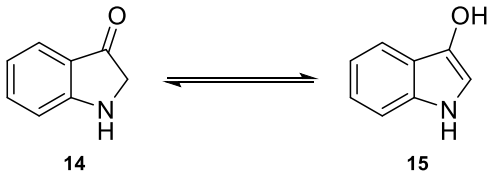


Figure 3. Construction of spiropseudoindoxyl core in Sorenson's synthesis of 11-methoxy mitragynine pseudoindoxyl *via* an internal nitrilium ion.[19]

Whilst the work of Sorensen *et al.* details a novel and innovative strategy towards the construction of the spiro[indoline-2,3'-pyrrolidin]-3-one, it uses a large number of steps and necessitates the use of 3,5-dimethoxyaniline to avoid the generation of different regioisomers in the interrupted Ugi step (Figure 3), this in itself prohibits a total synthesis of mitragynine pseudoindoxyl from this method.

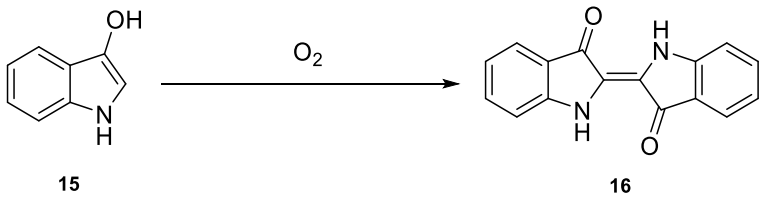
Pseudoindoxyls are defined as molecules incorporating an indolin-3-one **14** structure (Figure 1 B). The ketone functionality in pseudoindoxyl **14** exhibits a strong tendency to tautomerise to form indoxyl **15**, enabling the ring systems to gain full aromaticity[20] (Scheme 2).



14 15

Scheme 2. Tautomerism between indolin-3-one **14** and indoxyl **15**.[20]

The construction of functionalised pseudoindoxyls therefore presents an intrinsic challenge in that unsubstituted pseudoindoxyls **14** readily convert to indoxyls **15** which are relatively unstable due to their strong tendency to dimerise under aerobic conditions, forming indigo dyes[21] (Scheme 3).

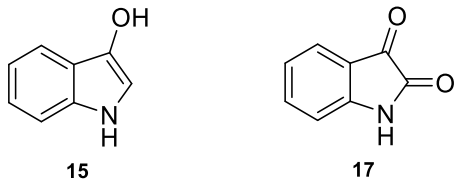


15 16

Scheme 3. Dimerisation of indoxyl **15** to form indigo **16**.[21]

For this reason, there is no generic template for the construction of substituted pseudoindoxyls. Isomeric oxindoles (Figure 1 A) however, possess an inherent stability

owing to the presence of the inbuilt amide functionality. This stability of oxindole derivatives enables compounds such as isatin **17** (Figure 4) to be utilised in syntheses of oxindole derivatives.



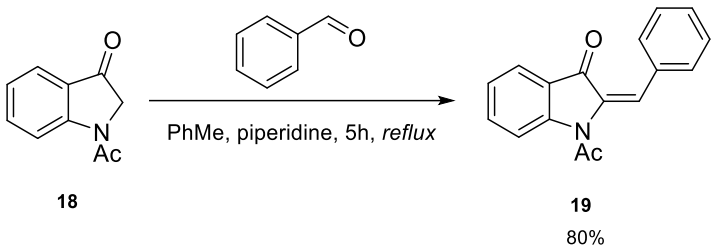
15 **17**

Figure 4. Structures of indoxyl **15** and isatin **17**.

The presence of the reactive ketone functionality in isatin **17** allows for direct functionalisation of the 3-position *via.* nucleophilic additions, dipolar cycloadditions, aldol condensations and Friedel-Crafts alkylations, amongst others.[22] Unfortunately, no directly analogous route to 2-substituted pseudoindoxyls exists, this often necessitates a *de novo* synthesis of the pseudoindoxyl core as a plausible synthetic route to functionalised pseudoindoxyl frameworks. Current literature methods often attempt to bypass these fundamental difficulties associated with the synthesis of 2-substituted pseudoindoxyls and as such they will be discussed herein.

1.2 Synthesis and Reactivity of 2-Unsaturated Pseudoindoxyls

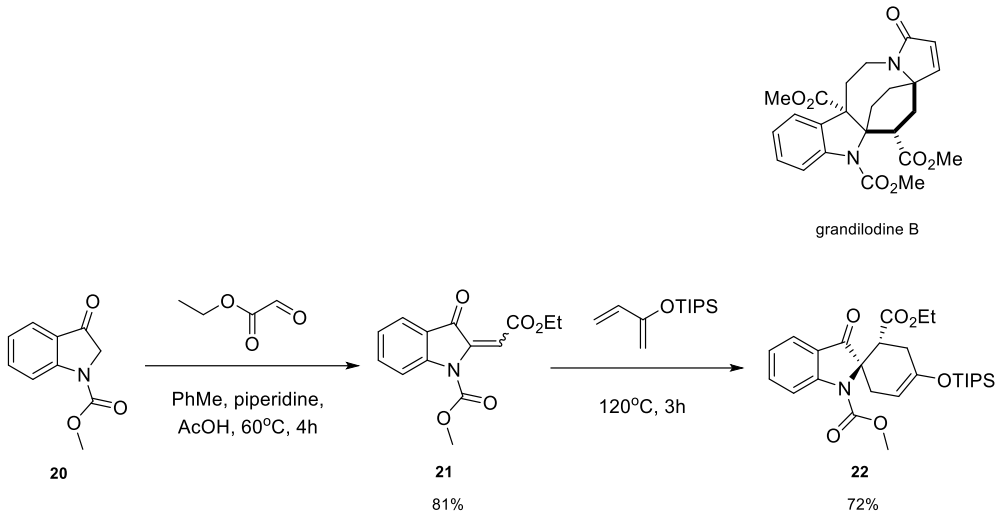
Efforts to construct 2-substituted pseudoindoxyl scaffolds from indoxyl **9** derivatives have been undertaken in the literature, however these methods are often difficult to carry out due to the tendency of indoxyl to dimerise and participate in other side reactions. As an example, Buzas and Merour have reported the synthesis of 2-substituted unsaturated aryl pseudoindoxyl derivatives[23] *via* an aldol condensation (Scheme 4).



18 **19** 80%

Scheme 4. Synthesis of 2-unsaturated pseudoindoxyls by Buzas and Merour.[23]

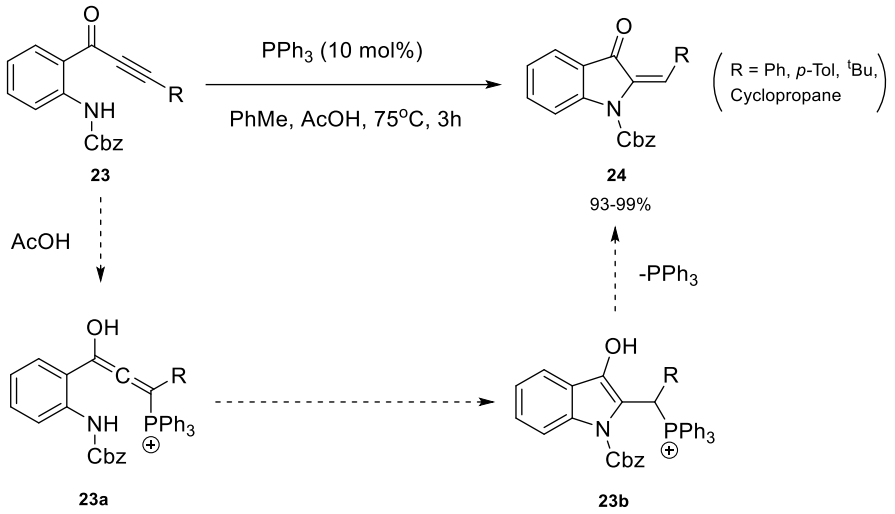
Zu *et al.* utilise this methodology to form an intermediate in the total synthesis of grandilodine B[24] by carrying out a Diels-Alder cycloaddition on the alkene group of dienophile **21,** facilitated by the neighbouring electron withdrawing carbamate group. The result is the construction of a functionalised spirocycle **22** which was carried through to the synthesis of grandilodine B **23** (Scheme 5).



Scheme 5. Initial steps towards the total synthesis of grandilodine B **23** featuring a [4+2] cycloaddition of a pseudoindoxyl derivative **21**.[24]

While these unsaturated pseudoindoxyls, such as **21**, display reasonable synthetic utility, the functionality around the alkene group is almost entirely limited to aryls and electron withdrawing groups, which restricts the scope for the synthesis of diversely substituted spirocycles. Furthermore, it is not possible to access the terminal alkene analogue of these compounds, thus potentially resulting in the installation of unwanted or difficult to remove functional groups.

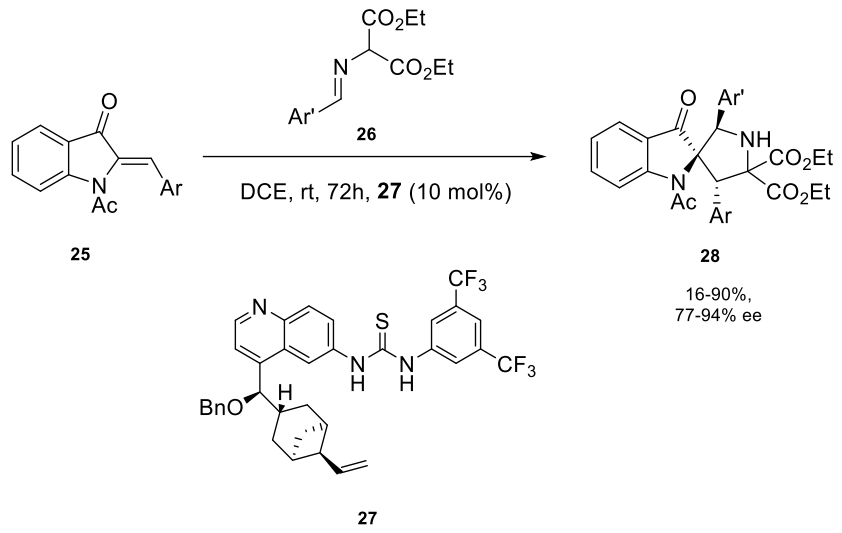
Trost and co-workers recently reported an efficient *de novo* synthetic method for the construction of similar unsaturated pseudoindoxyl derivatives by the catalytic cycloisomerisation of alkynyl aryl ketones proceeding *via* an allenyl phosphonium intermediate **23a** (Scheme 6).[25]



Scheme 6. Trost's synthesis of alkenyl pseudoindoxyls by phosphine catalysed cycloisomerisation.[25]

The work of Trost *et al.* (scheme 6) presents a highly efficient, high yielding method for the construction of substituted 2-unsaturated pseudoindoxyls **24** whilst also expanding the scope of the functional group diversity about the alkene bond. Slight drawbacks include the steps involved in order to access the starting material and the lack of diversity in terms of the substituents that can be incorporated about the alkene bond.

Xu and co-workers describe an efficient process for the asymmetric construction of spiro[indoline-2,3'-pyrrolidin]-3-ones **28** by way of a hydrogen-bonding network promoted (3+2) cycloaddition[26]. This system employs a bifunctional catalytic approach in order to simultaneously achieve substrate activation and asymmetric induction. (Scheme 7)



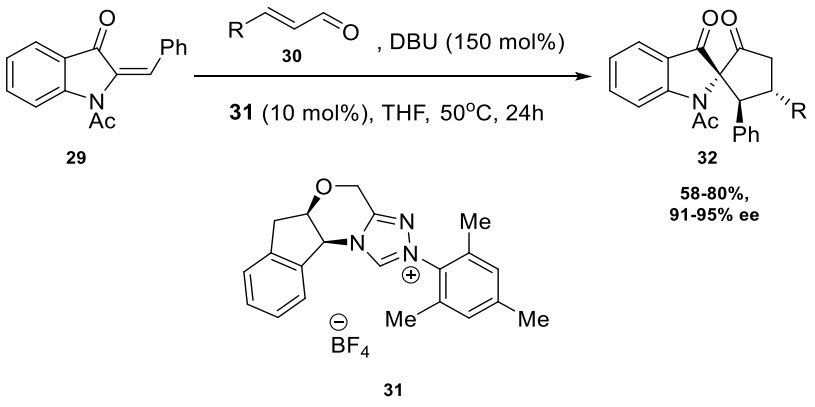
Scheme 7. Asymmetric, catalytic construction of spiro[indoline-2,3'-pyrrolidin]-3-one scaffold by Xu *et al.*[26]

The thiourea group of catalyst **27** acts as a hydrogen bond donor towards the ester carbonyls, activating imine **26** whilst simultaneously introducing an asymmetric environment into the system. This imine activation is required due to the relatively low reactivity of 2-unsaturated pseudoindoxyls as the alkenyl π-system is strongly resonance stabilised by the nitrogen lone pair. It is for this reason that the nitrogen substituent must always incorporate a malonate functionality as a requisite for this system to work. Additionally, long reaction times (72h) are required due to the poorly reactive nature of 2-unsaturated pseudoindoxyls.

Whilst promising, this approach has significant drawbacks. Foremost is the lack of varied functionality around the pyrrolidine ring system; the presence of geminal ethyl ester groups is mandatory in order for this reaction to occur, furthermore, only aryl substituents are able to be incorporated at the 2 and 4 positions. These disadvantages

highly limit the ability to progress to more complex, medicinally valuable scaffolds from this method.

Further synthetic explorations into the synthesis of spiropseudoindoxyls from 2-unsaturated pseudoindoxyls have been carried out by Glorius *et al.* Specifically, N-heterocyclic carbene (NHC) catalysed annulation reactions have been investigated as a means for the asymmetric synthesis of spiropseudoindoxyl derivatives[27] (Scheme 8). This method relies on the formation of a conjugate between an enal **30** and an NHC catalyst **31**. The resulting adduct then undergoes an umpolung 1-4 addition, affording an acyl azolium intermediate (Figure 5 (iii)) which subsequently cyclises and dissociates from the NHC catalyst to return a functionalised 2-spiropseudoindoxyl in a stereoselective manner.



Scheme 8. Chiral NHC-catalysed spiropseudoindoxyl formation by Glorius *et al.*

The specific mode of action of the system developed by Glorius *et al.* hinges on the activation of the enal substrate by NHC catalyst **31** leading to the formation of an NHC homoenolate **(i)** (figure 5), which is subsequently able to undergo a (3+2) annulation

with azaaurone **21** (Figure 5, **ii**), leading to the release of spiropseudoindoxyl compound **32** *via* an acyl azolium intermediate (Figure 5, **iii**).

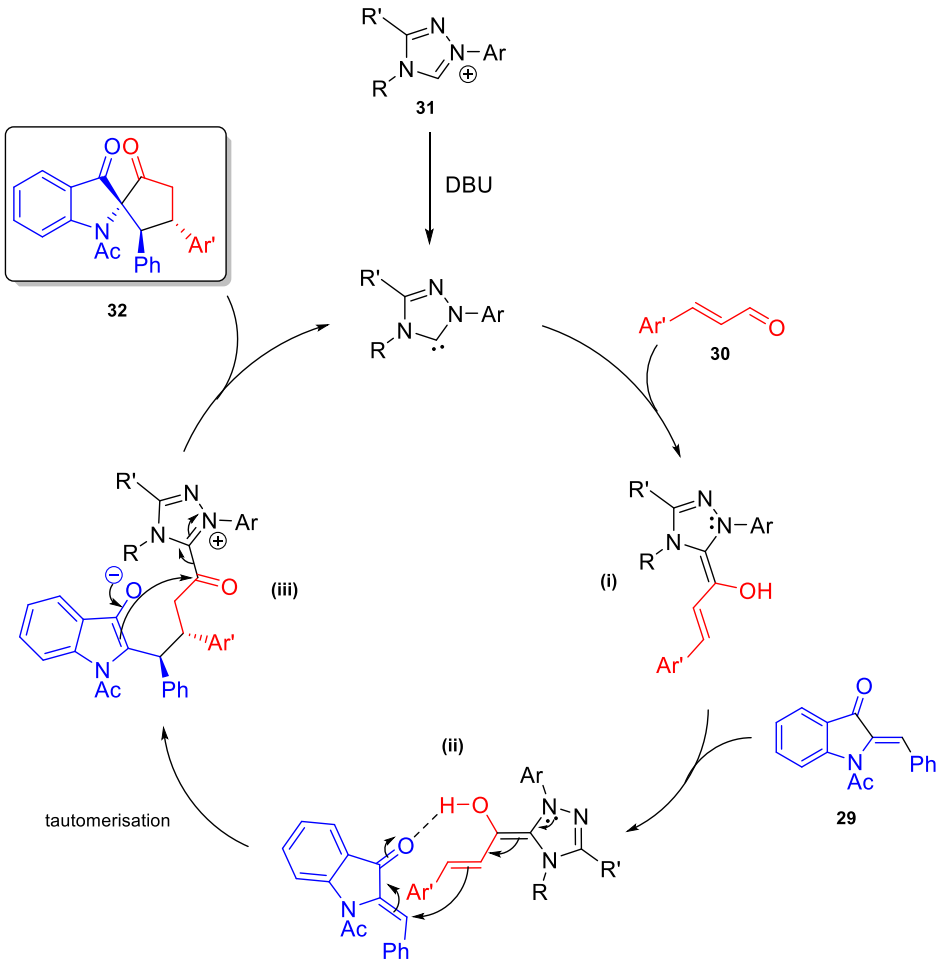


Figure 5. Proposed catalytic cycle for chiral NHC-mediated [3+2] cycloadditon by Glorius *et al.*[27]

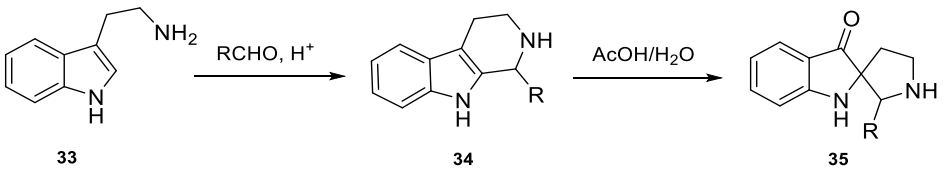
Glorius proposes an excellent method for the construction of spirocyclic that proceeds with good yields and excellent enantiomeric excess. This work is also reflective of the strategy required to circumvent the issue of 2-unsaturated pseudoindoxyls being poorly reactive. However, this method does not allow for the incorporation of heteroatoms into the newly constructed 5-membered ring and its substrate scope is purely limited

to aryl enals. Furthermore, the use of *N*-deacetylated unsaturated pseudoindoxyls leads to no reaction at all. These negatives could potentially limit its efficacy in the synthesis of alkaloid-like structures.

On the whole, the use of 2-unsaturated pseudoindoxyls as a strategy towards the synthesis of substituted pseudoindoxyls has produced some interesting literature examples, but at present is rather limited in terms of scope due to the limited functional group tolerance of these systems.

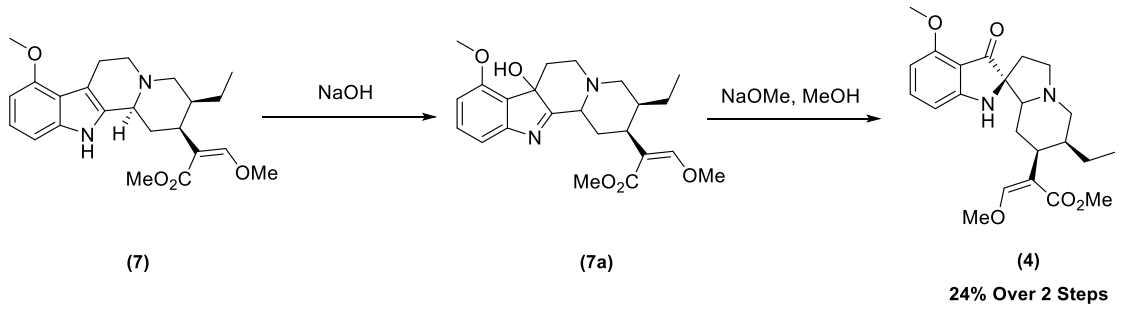
1.3 Oxidative Rearrangements

Biosynthetically, spiropseudoindoxyl alkaloids such as mitragynine pseudoindoxyl **4** are generated through the oxidative rearrangement of chemical systems containing a tryptamine derived fused indole ring system, such as mitragynine **7**.[28] It is therefore unsurprising that possibly the most frequently reported general strategy employed in the synthesis of spiropseudoindoxyls such as **35** (Scheme 7) is the oxidative rearrangement of fused indole derivatives such as **34**, themselves usually prepared from tryptamines **33** *via* Pictet-Spengler reactions.



Scheme 9. Representative scheme for the preparation of spiropseudoindoxyl derivatives from products of Pictet-Spengler reactions.

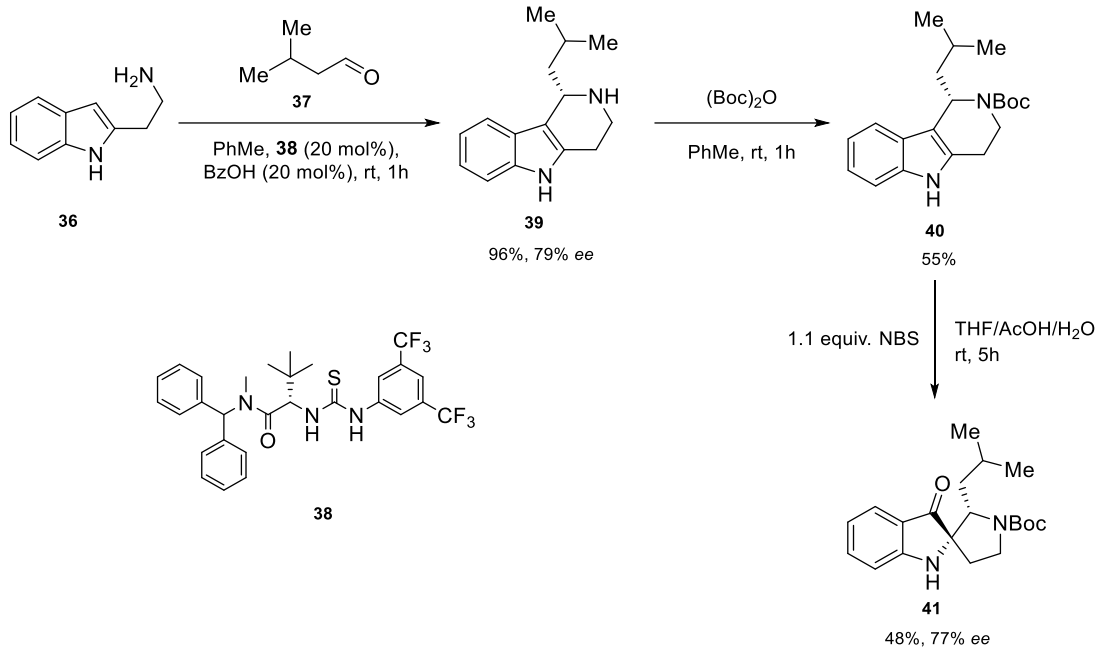
It is through this same general methodology that Takayama *et al.* prepared mitragynine pseudoindoxyl **4** from mitragynine **7**[18] utilising a semi-pinacol rearrangement (Scheme 10).



Scheme 10. Preparation of Mitragynine Pseudoindoxyl **4** from Mitragynine **7** *via*. 7-hydroxy Mitragynine **7a**.[18]

The clear limitation of the method reported by Takayama *et al.* is the low overall yield moving through to the final product.

Jacobsen reported the synthesis of pseudoindoxyl derivatives from isotryptamines, generated from an asymmetric thiourea-catalysed iso-Pictet-Spengler reaction followed by a semi-pinacol rearrangement.[29] The result was the enantioselective generation of spiro[indoline-2,3'-pyrrolidin]-3-ones **41** in moderate yield (Scheme 11).



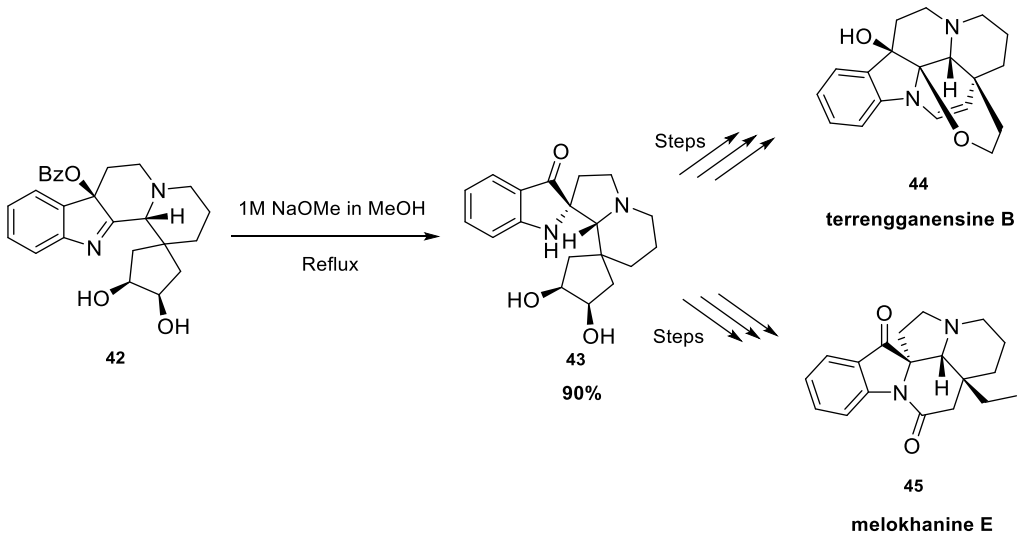
Scheme 11. Jacobsen's synthesis of spiroindoxyl derivatives from isotryptamine.[29]

The method of Jacobsen and co-workers shows the ability to synthesise substituted spiro[indoline-2,3'-pyrrolidin]-3-one derivatives under mild conditions with reasonable control over the stereochemistry of the system and in fair yields. This method features an asymmetric iso-Pictet-Spengler reaction, catalysed by thiourea **38**. The asymmetry that is induced in **39** preserves the enantiomeric excess in the oxidative rearrangement of **40**, enabling this step to be stereospecific.

A key downside to the work of Jacobsen *et al.* is the lack of examples of this chemistry. Only one example is reported with none featuring more functionalised side chains. Theoretically, it may be possible to access structures with more functionalised side chains, facilitating the construction of the spiroindolizidine motif found in numerous alkaloids. Unfortunately, no further work into this area has been reported. Moreover, isotryptamines are considerably more expensive than their tryptamine counterparts on

account of them being difficult to synthesise. This limits the exploration of pseudoindoxyl derivatives using this method. Furthermore, the oxidative rearrangement step (Scheme 11) suffers from the issue of low yields, as observed with the method of Takayama (Scheme 10).

Zhu and co-workers reported the use of spiro[indoline-2,3'-pyrrolidin]-3-ones as intermediates in the synthesis of Eburnane-type alkaloids[30] (Scheme 12).



Scheme 12. Representative example of the use of spiropseudoindoxyl intermediates in the synthesis of Eburnane-type alkaloids.[30]

42 undergoes an oxidative rearrangement to provide pseudoindoxyl intermediate **43**. **43** is then divergently transformed into a series of alkaloid targets, one of which contains a spiropseudoindoxyl motif **45**. Others are converted back to the fused indole form to access indole alkaloids of the same structural family such as **44**. This method is employed in order to introduce the desired conformational behaviour into the

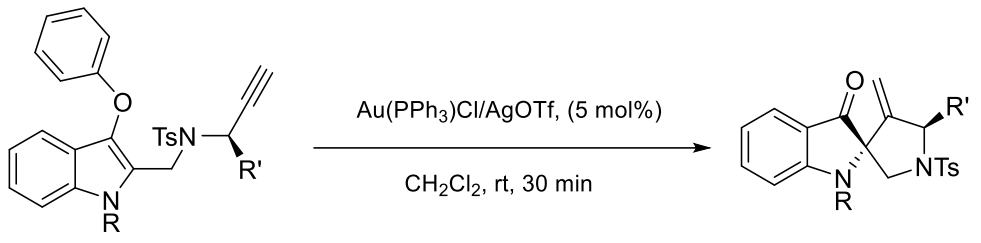
indolizidine ring system, facilitating generation of the correct enantiomers in successive steps. Additionally, intermediate **43** (Scheme 12) was used to synthesise the spiropseudoindoxyl alkaloid melokhanine E **45** and the indole alkaloid terrengganensine B **44**, amongst a series of other alkaloids.

The α–iminol rearrangement to the spiropseudoindoxyl intermediate (**42** to **43**) is promoted under basic conditions and is driven by the deprotection of the benzoyl group, in this case producing a high yield. Due to the stereochemistry of the benzoyl group, the α–iminol rearrangement proceeds with enantioselectivity, enabling the spiro[indoline-2,3'-pyrrolidin]-3-one **43** to be formed asymmetrically. **43** is then is carried through several steps in the synthesis. This method represents a highly elegant solution to the issue of enantioselectivity in natural product synthesis. Furthermore, the versatility of this chemistry is demonstrated by the use a divergent synthesis towards multiple structurally diverse natural products.

Whilst the use of oxidative rearrangements in the synthesis of spiropseudoindoxyls is well investigated and has been utilised in the synthesis of many complex pseudoindoxyl structures, including natural products, this method is often limited by low yields and the necessity to proceed *via* fused indole derivatives which is limiting in terms of synthetic route.

1.4 Transition Metal-catalysed Annulations

Another well investigated general strategy for the construction of spiropseudoindoxyls is *via* gold catalysed annulations. One such method has been reported in the literature by Tu *et al.*, featuring the gold catalysed annulation of alkynyl indoles[31] (Scheme 13).



46 **47**

51-98%

R=CO_2Me, Boc, Ac, Alloc

R'=H, Pr, ^{i}Pr, Cy

Scheme 13. Gold catalysed annulation of alkynyl indoles to form asymmetric spiro[indoline-2,3'-pyrrolidin]-3-ones.[31]

The mechanism for this transformation was elucidated by ^{18}O labelling studies[31] that confirmed the catalytic cycle in Figure 6. The reaction proceeds by the π-coordination of the gold catalyst to the alkyne functionality in **34** as seen in intermediate **(i)**. Subsequently, the enol ether undergoes a nucleophilic attack on the electron deficient alkyne, which ensues the construction of the spirocyclic phenyl oxonium intermediate **(ii)**. Lastly the highly reactive oxonium intermediate is hydrolysed and the alkene is protonated, returning the spiropyrrolidinyl pseudoindoxyl **35**.

The stereoselectivity observed for this reaction relies upon the steric repulsion between the R' substituent on the pyrrolidine ring and the R substituent on the nitrogen. For this reason, the most favourable conformation of **34** exists with both the R and R' groups pointing in opposite directions. Therefore, following the intramolecular nucleophilic addition by the enol ether, only one stereochemical outcome is observed.

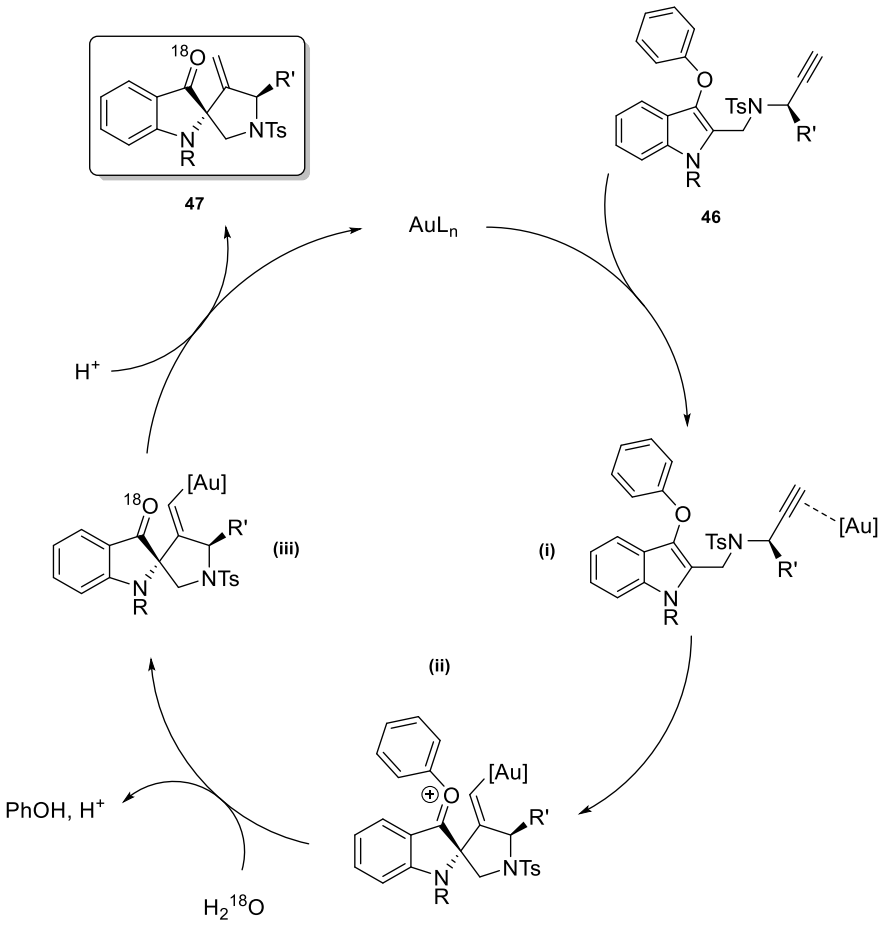
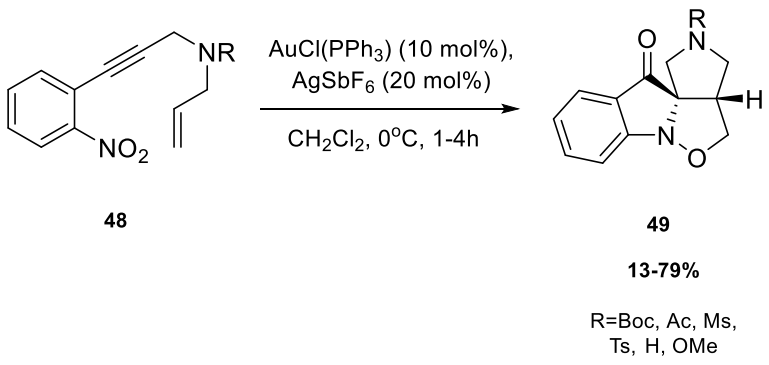


Figure 6. Proposed mechanism for the gold catalysed annulation of alkynyl indoles as studied by ^{18}O labelling by Tu *et al.*[31]

This reaction produces highly functionalised spiro[indoline-2,3'-pyrrolidin]-3-ones in excellent yields. Potential limitations this reaction include the difficulty of accessing the

starting material as this requires numerous steps, lack of varied substitution on the pyrrolidine nitrogen and the limited variation of the pyrrolidine *N*-methylene substituent, given that highly electron rich or electron deficient environments would interfere with the alkynyl-gold system. Therefore, only alkyl substituents are permitted at this position. Additionally, the only nitrogen protecting group used in this work is a tosyl group. These groups are difficult to remove, potentially hindering further transformations of **47**.

Further gold catalysed syntheses of spiropseudoindoxyl frameworks have been reported by Ramana and Kumar[32]. This particular method hinges on a gold catalysed cyclo-isomerisation and subsequent (3 + 2) cycloaddition cascade to afford highly strained spiropseudoindoxyl derivatives (Scheme 14).

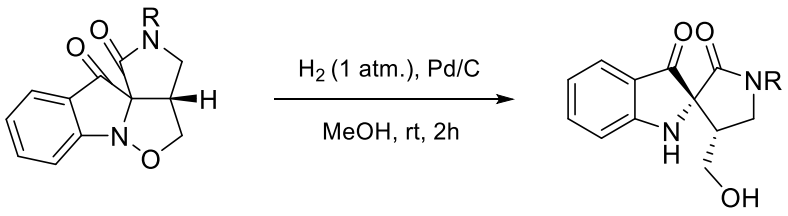


Scheme 14. Gold catalysed Synthesis of fused spiro[indoline-2,3'-pyrrolidin]-3-one isoxazolines[32].

The molecules produced in this work show a great deal of structural novelty and stereospecificity. However, the authors claim that they have produced pseudoindoxyl frameworks akin to those found in natural products such as mitragynine pseudoindoxyl,

yet no attempt is made to cleave the N-O bond to afford the corresponding amino alcohol. Additionally, several steps are required to access the precursor compound **48** (scheme 14).

Following on from this work, Verniest *et al.* developed a mild, catalytic method for the cleavage of the N-O bond to access a series of functionalised spiropseudoindoxyl structures,[33] (Scheme 15). The introduction of an amide functionality into the precursor led to the formation of spirolactam **50**. The electron withdrawing lactam then facilitates the catalytic cleavage of the N-O bond.



50 **51**

91-99%

R=CH_2CONH^tBu

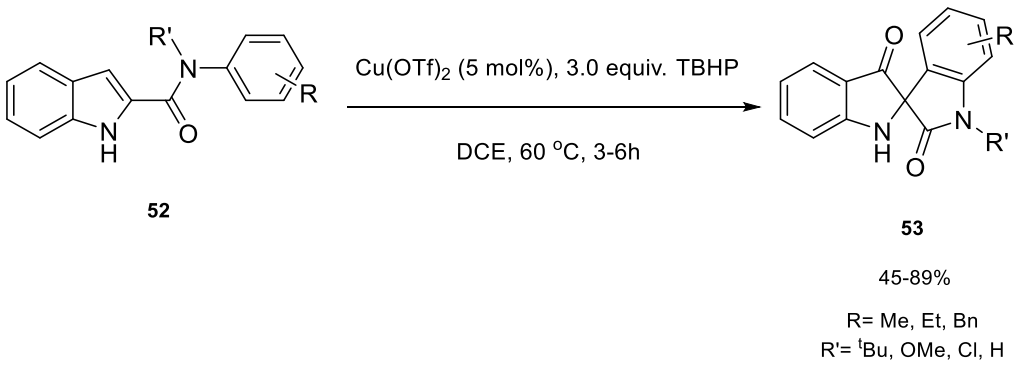
Scheme 15. N-O bond cleavage of strained spiropseudoindoxyls to yield corresponding amino alcohol.[33]

Whilst this method successfully generates the functionalised amino alcohol derivative in an asymmetrical fashion, there is no clear pathway from this structural motif to the highly desirable spiroindolizidine ring system. This is due to the relatively inert amide functionality being present and the inconvenient situation of the alcohol group.

These examples of gold-catalysed intramolecular annulations deliver an efficient construction of the pseudoindoxyl framework with good yields and short reaction

times. However, these methods are hindered by the functional group diversity around the pyrrolidine ring system being highly limited. Additionally, the substitution patterns around the pyrrolidine ring produced by these methods do not seem conducive to the synthesis of pseudoindoxyl alkaloids.

In addition to gold catalysis, copper catalysis has also been used to effect the construction of spiropseudoindoxyls. Li *et al.* report the copper-catalysed oxidative spirocyclisation of indole-2-carboxamides[34] (Scheme 16).



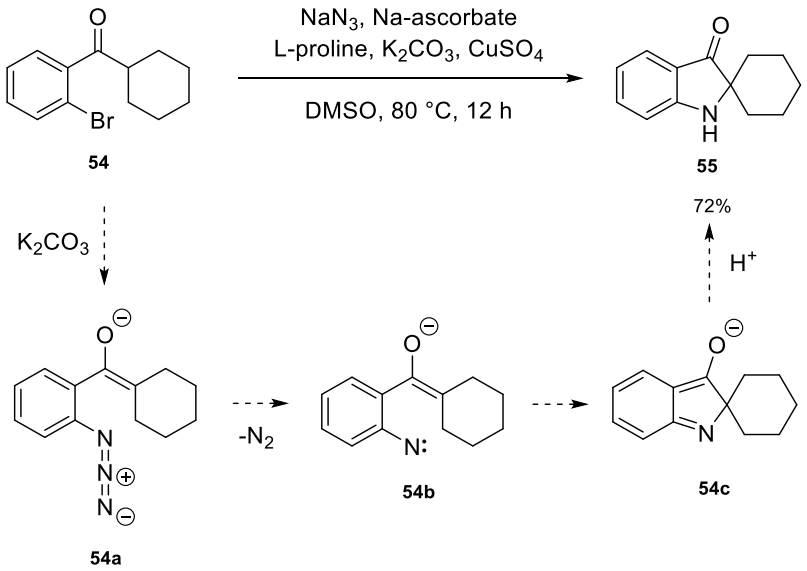
Scheme 16. Copper-catalysed annulation of indole-2-carboxamides by Li *et al*.[34]

The work of Li *et al.* (Scheme 16) shows the construction of spirolactams bearing structural similarity to those of Verniest *et al.* (Scheme 15). In this case the spirocyclisation occurs *via* a copper-catalysed dearomative annulation using *tert*-butyl hydrogen peroxide (TBHP) as an oxidant. Whilst showing a novel route to substituted spiropseudoindoxyls, this method still requires numerous steps to access precursor **52** and no enantioselectivity is observed in this case.

These examples of metal-catalysed intramolecular annulations deliver an efficient construction of the pseudoindoxyl framework in good yields. However, these methods are often hindered by the highly limited functional group diversity around the pyrrolidine ring system. Additionally, the substitution patterns around the pyrrolidine ring produced by these methods do not seem conducive to the synthesis of pseudoindoxyl alkaloids.

1.5 Smalley Cyclisation

Another interesting example achieving *de novo* synthesis of pseudoindoxyls is reported by Goriya and Ramana. The method involves the synthesis of various 2,2-disubstituted pseudoindoxyls *via* a sequential copper catalysed S_NAr and Smalley cyclization (Scheme 17).[35]



Scheme 17. Preparation of spiro[cyclo-1,2'-indolin]-3'-ones by Goriya and Ramana.[35]

This system functions through an initial S_NAr reaction in which azide displaces the bromine from **54** under basic conditions to afford the azido enolate **54a**. Following this, the release of nitrogen to afford the nitrene **54b** is highly entropically favoured. Upon formation of the nitrene, a Smalley cyclisation reaction is initiated by nucleophilic attack on the enolate olefin by the highly reactive nitrene. Finally, a tautomerization occurs to yield the spiropseudoindoxyl product **55** in reasonable yield.

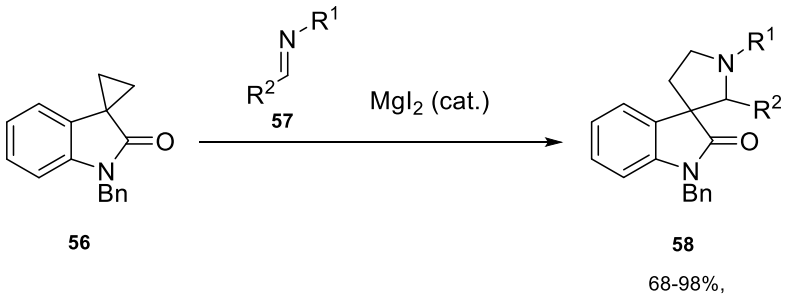
Whilst a novel synthetic route showing good functional group tolerance towards substitution of the aromatic ring, no examples in which a heteroatom is incorporated into the spirocycle are reported. In addition, no examples include a functionalised spirocycle – possibly owing to the reactivity of the nitrene that forms upon the release of N_2 **54b**, potentially resulting in side reactions. For these reasons it seems unlikely that this method may be applied to synthetic methods towards the synthesis of spiropyrrolidinyl, alkaloid-inspired structures.

Thus far, the main compounds that have been discussed as precursors to spiropseudoindoxyl structures consist of azaaurones and fused indole derivatives. Spirocyclopropanes are regularly encountered in the synthesis of spirooxindole structures and have been employed in multiple syntheses of oxindole based natural products, primarily by the Carreira group.[36–38] Despite this, spirocyclopropanes have not been reported as reagents for the construction of complex spiropseudoindoxyl derivatives.

1.6 Synthesis and Dipolar Cycloadditions of Spirocyclopropanes

Cyclopropane derivatives are considered to be highly useful reagents in organic synthesis due to the uniquely reactive character of the three membered ring and likeness of its chemistry to that of a carbon-carbon double bond.[39] The reactivity of cyclopropanes can be explained, in part, in terms of the ring strain that these compounds experience, enabling their participation in ring opening reactions in the presence of a nucleophile in order to alleviate ring strain.

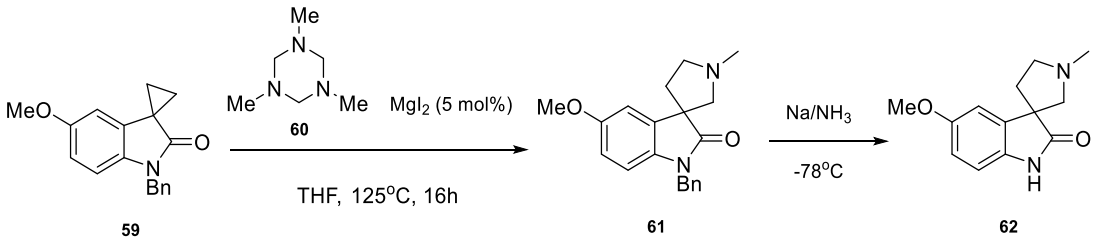
As previously mentioned, cyclopropane derivatives have been employed in the synthesis of various oxindole natural products and related structures. In particular, the ring expansion of 3-spirocyclopropyl oxindoles to produce 3-spiropyrrolidinyl oxindoles has been extensively studied (Scheme 18).



Scheme 18. Dipolar cycloaddition of 1'-benzylspiro[cyclopropane-1,3'-indolin]-2'-one **42** with an aldimine **43** to yield spiro[pyrrolidin-3,3'-oxindoles] **44** by Carreira *et al.*[36]

The reaction shown in Scheme 18 is promoted by MgI_2 mediated ring opening of cyclopropane **56**, effecting the formation of an enolate which is able to act as a nucleophile and an iodoethane group, able to act as an electrophile. Using this

chemistry, numerous alkaloid targets have been accessed. For example, an efficient route to the alkaloid horsfiline was reported using this method (Scheme 19).[40]



Scheme 19. Synthesis of horsfiline *via* an MgI_2 catalysed ring expansion reaction.[40]

The *in-situ* formation of *N*-methyl methanimine from the thermal decomposition of triazine **60** allows for the efficient construction of spiropyrrolidine **61** from cyclopropane **59**. Subsequent removal of the *N*-benzyl protecting group yields the alkaloid horsfiline **62**. This facile synthesis reflects the efficiency of this method.

Mechanistically, there are two possible permutations for the transformation taking place in Scheme 18. These putative mechanistic pathways are elucidated in Figure 7.

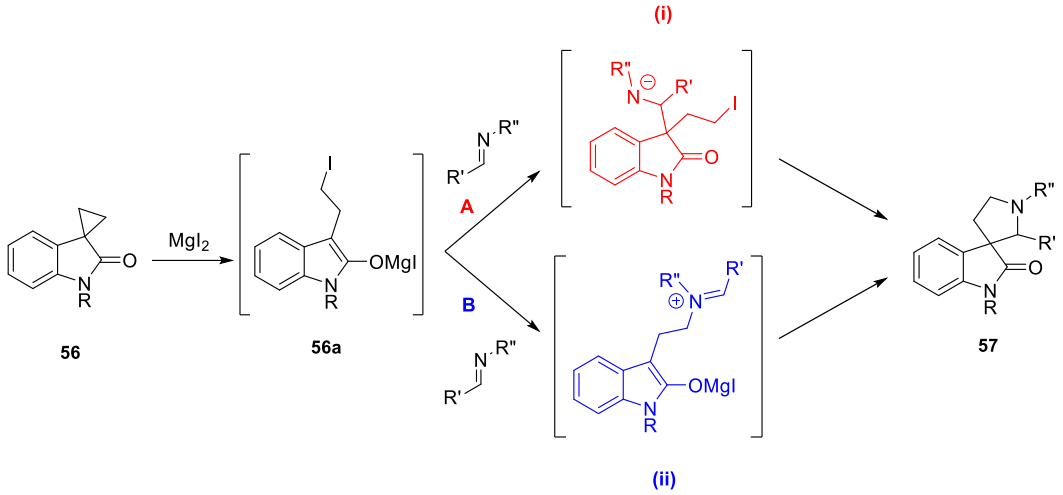
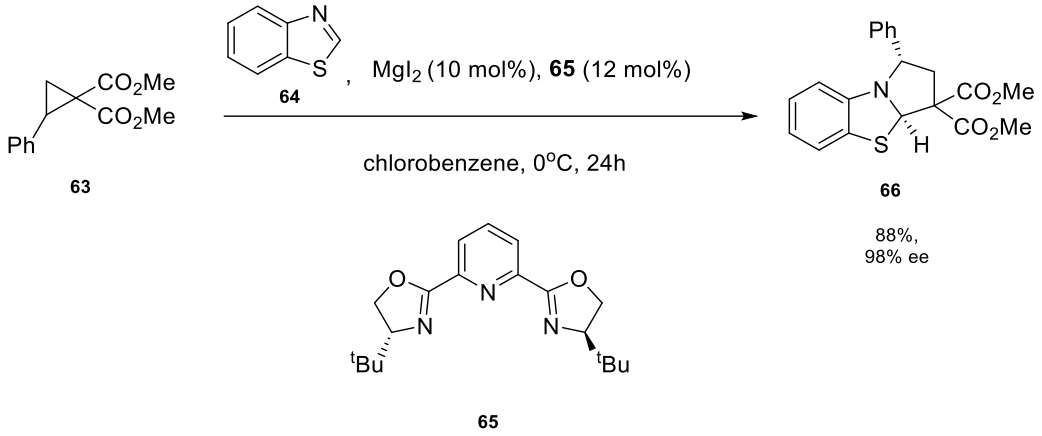


Figure 7. Possible mechanistic routes for the conversion of 1'-benzylspiro[cyclopropane-1,3'-indolin]-2'-one **42** to spiro[pyrrolidin-3,3'-oxindoles] **44**.[36]

The two plausible mechanisms shown in Figure 7 include path A: a Mannich-like reaction of the iodide intermediate **56a** with the imine, promoted by the Lewis acid MgI_2, followed by an S_N2 reaction between the amide and iodine substituted carbon, releasing iodide (intermediate **(i)**). Path B: nucleophilic substitution of iodide by the imine nitrogen followed by Mannich cyclisation (intermediate **(ii)**). It may be the case that both of these mechanisms are in competition and the electronics of the imine substituents may influence which mechanism predominates.

Another instance of MgI_2 promoted (3+2) cycloadditions of cyclopropanes is described in the work of You and co-workers.[41] This work investigates the construction of hydrothiazole frameworks from the coupling of cyclopropanes and benzothiazole in the presence of an asymmetric organocatalyst (Scheme 20).

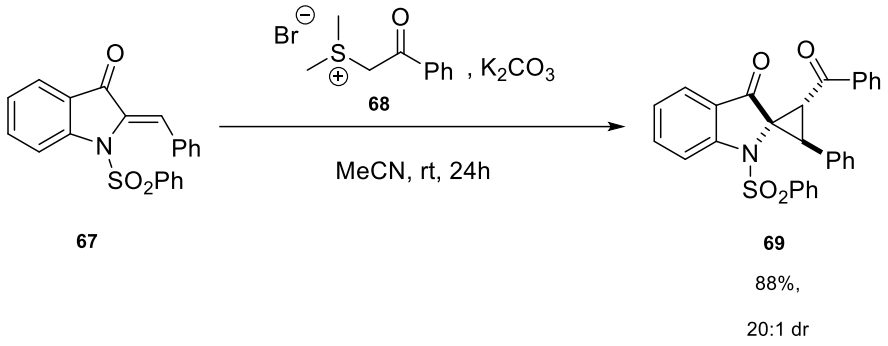


Scheme 20. Asymmetric, dearomative (3+2) cycloadditions of cyclopropanes **45** with benzothiazole **46** to produce hydrothiazole frameworks.[41]

Similarly to the example of Carreira, this reaction is initiated by the magnesium iodide-led ring opening of cyclopropane **63**, enabled by the formation of an enolate. Subsequently, the enolate undergoes a dearomative coupling step with benzothiazole **64** to form hydrothiazole **66**. The high enantiomeric excess of product **66** is enabled by the participation of chiral pyridine bis(oxazoline) (BOX) catalyst in the coupling step.

Evidently, spirocyclopropanes display great utility as substrates in cycloaddition reactions. By this reasoning, accessing 2-spirocyclopropyl pseudoindoxyls would present a good strategy for the synthesis of substituted spiro[indoline-2,3'-pyrrolidin]-3-one frameworks, by analogy of the work of Carreira *et al*.[36]

Huang *et al*. report the highly diastereoselective synthesis of cyclopropane-fused spiropseudoindoxyl derivatives using a (2+1) annulation of azaaurones and sulfonium ylides[42] (Scheme 21).



Scheme 21. Synthesis of cyclopropane-fused spiropseudoindoxyl derivatives by Huang *et al.*[42]

This reaction displays a novel strategy towards the synthesis of spirocyclopropyl pseudoindoxyl derivatives with good diastereoselectivity and yield. The reaction proceeds through the formation of the sulfonium ylide of **68**, following this, a nucleophilic addition is effected by the carbanion onto the olefin of **67** leading to the formation of an enolate. The enolate then participates in an intramolecular nucleophilic substitution, releasing dimethyl sulfide to form **69**. The mechanism for this reaction is outlined in Figure 8.

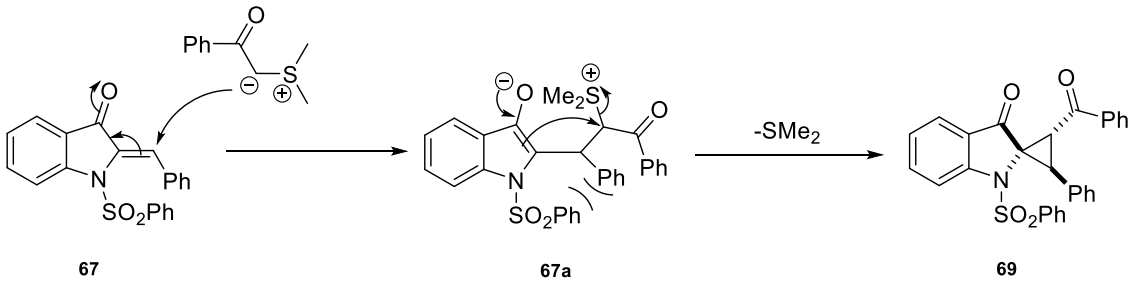
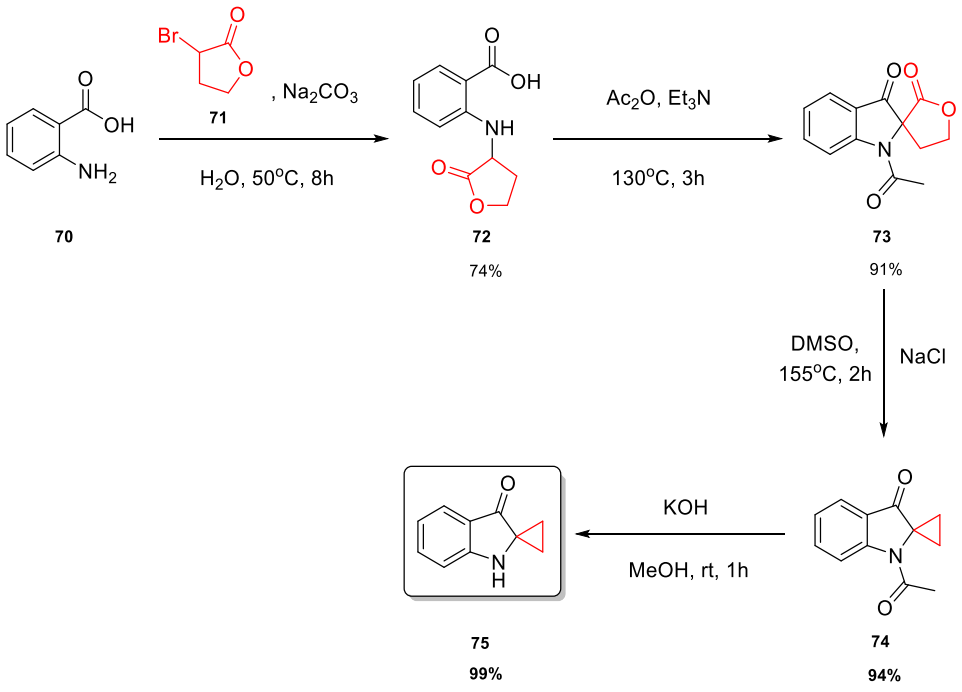


Figure 8. Proposed mechanism for the cyclopropanation of **67** mediated by the sulfonium ylid of **68**.[42]

The origin of the diastereoselectivity for this reaction relies upon the avoidance of unfavourable steric interactions between the bulky nitrogen substituent and the phenyl group of the cyclopropane ring. For this reason, the phenyl substituent projects away from the amine substituent in intermediate **67a**. Overall, this reaction shows promise for the development of spirocyclopropyl pseudoindoxyls however, an ideal case would be the generation of an unsubstituted spirocyclopropane pseudoindoxyl derivative, analogous to the cyclopropyl oxindole species **59** developed by Carreira *et al.*[36]

Kawada and co-workers have reported such a synthesis and have carried out highly detailed evaluations of the reactivity of these compounds.[43–46] The method reported in this case demonstrates a *de novo* synthesis of the spiropseudoindoxyl core from anthranilic acid **70**. The synthetic route leading to the acquisition of this cyclopropyl species **75** (Scheme 22).



Scheme 22. Synthesis of spiro[cyclopropane-1,2'-indolin]-3'-one **75** by Kawada *et al.*[47]

Kawada presents an efficient route to the cyclopropane species **75**, achieving good yields. The α–bromo–γ–butyrolactone **71** serves as a 3-carbon unit for the construction of the spirocyclopropyl moiety. Firstly, a facile S_N2 reaction takes place in order to yield the alkylated anthranilic acid **72**. Secondly, the acid anhydride of **72** is formed in the presence of acetic anhydride and triethylamine, following which, the lactone alpha-proton is removed to afford a carbanion intermediate. This enables the rapid construction of the spirocentre in spirolactone **73**. The cyclopropyl motif is then assembled following a Krapcho-type decarboxylation in the presence of sodium chloride to afford the *N*-acetylated cyclopropane species **74**. Lastly, deacetylation of this cyclopropane species is achieved under basic conditions in methanol leading to the formation of the desired cyclopropane species **75**.

With the ability to access this cyclopropane species **75**, the construction of spiro[indoline-2,3'-pyrrolidin]-3-one frameworks is theoretically enabled by close analogy to the work of Carreira. Accordingly, this methodology for the synthesis of substituted spiropseudoindoxyls *via* the union of **75** with various aldimines in the presence of a Lewis acid catalyst shall be explored in this work.

2. Results and Discussion

2.1 Aims and Objectives

Prior to this work, colleagues from the Dowden group had undertaken research on ring expansion reactions predominantly between *N*-acetylated spirocyclopropane **74** and aldimines. Additionally, predecessors have extensively attempted to form a route from spirolactone **73** directly to spiropseudoindoxyls. Reactions between the *N*-deacetylated spirocyclopropane and aldimines had been carried out and this reaction was known to be diastereoselective however no extensive investigation into the substrate scope had been carried out. Key prior contributors to this work from the Dowden group include previous MSci Final Year Project students; Daniel Matthieu-Raven Nicholas Atkinson, James Harnedy and Ben Allot. Matthieu-Raven pioneered the reaction of the *N*-deacetylated spirocyclopropane **75** with imines. This work was recently continued by Allot, however limited examples of this chemistry exist. Harnedy and Atkinson worked exclusively on the reaction of spirolactone **73** with imines which was not a subject dealt with in this work. Limited examples have been duplicated in this work and have been acknowledged in the experimental.

The novel developments arising from this project include; synthesis of a series of novel spiropseudoindoxyl compounds from cyclopropane **75** and verification of the relative stereochemistry arising from this reaction. Additionally, for the first time, electrophiles other than imines have been explored in the context of this reaction to yield highly novel structures such as spirofurans and spirothioamides.

The experimental aims of this work were to synthesise a series of substituted spiro[indoline-3,3'-pyrrolidin]-2-ones by means of the ring expansion cyclisation of 2-spirocyclopropyl pseudoindoxyls with various aldimines, whilst characterising the relative reactivities of differently substituted aldimines in this reaction. Following this, the objective progressed to expanding the substrate scope of the reaction by investigating the reactivities of different electrophilic species aside from aldimines. Furthermore, the relative stereochemistry of the spiropyrrolidinyl pseudoindoxyl products of these reactions was elucidated by NOESY studies. Subsequently, a method for the asymmetric synthesis of spiro[indoline-3,3'-pyrrolidin]-2-ones from this method was explored through the use of chiral catalysts and variation of the reaction conditions.

2.2 Introduction

The above described reaction between 2-spirocyclopropyl pseudoindoxyls and aldimines was developed by analogy of the work of Carreira *et al.,* as discussed in 1.6.[36] The ring opening of the cyclopropane is promoted by the presence of magnesium iodide which acts as a bifunctional catalyst. The magnesium cation acts as a Lewis acid, activating the carbonyl of **76**. Furthermore, iodide is released which behaves as a Lewis base, enabling the opening of the cyclopropane ring. Following this, the ring expansion of the spirocyclopropane is allowed to take place (Figure 9).

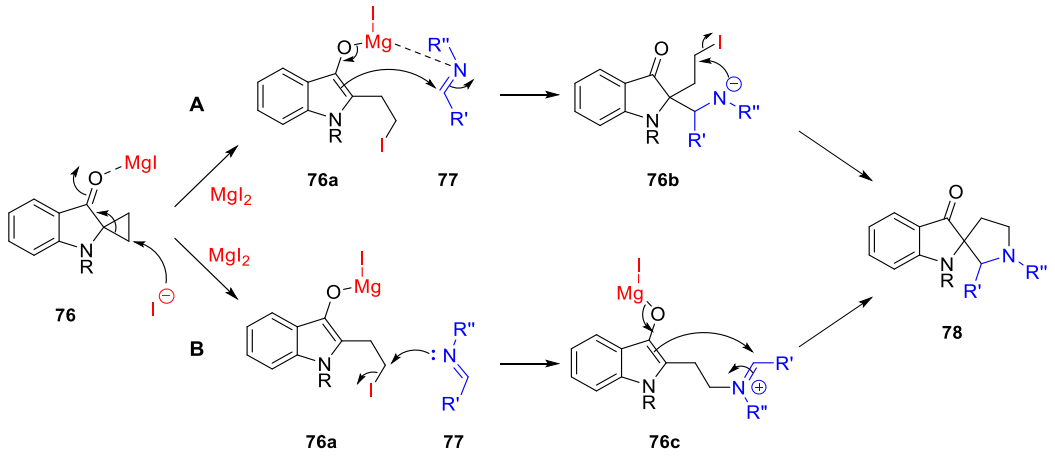
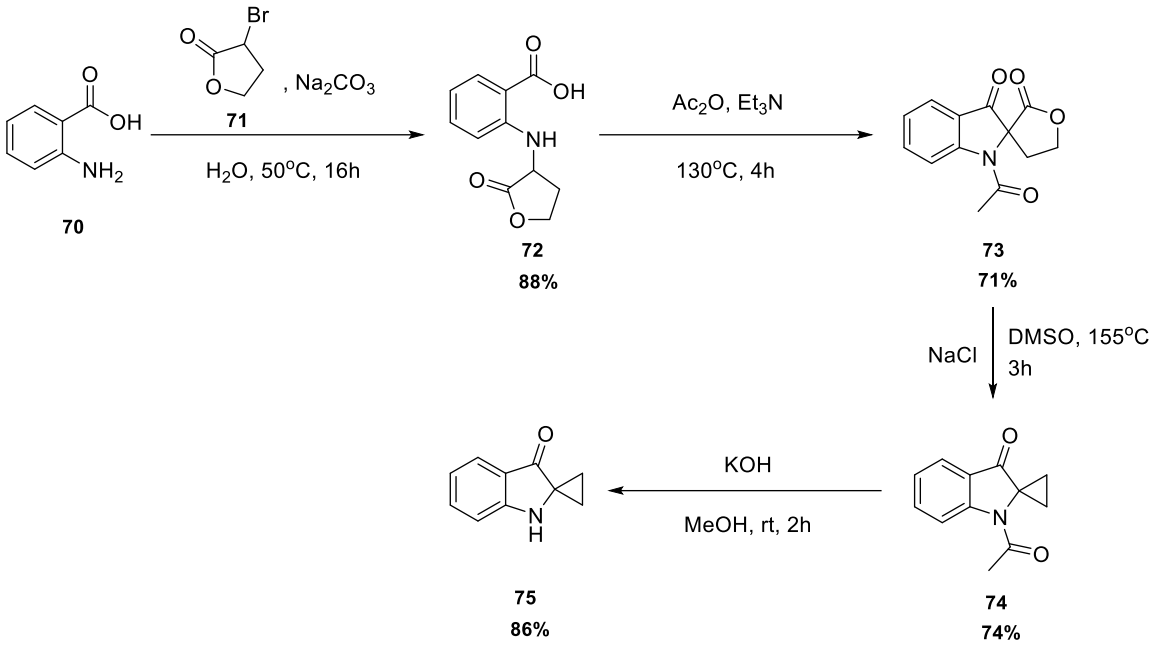


Figure 9. Putative mechanistic pathways for the MgI_2 promoted ring expansion of **76** and **77** to form spiropyrrolidine **78**.

Similarly to Figure 7, there are two possible mechanistic pathways through which this reaction may proceed. **A**: *via* a Mannich-type reaction of **76a** and **77** or **B:** *via* an S_N2 reaction of **76a** and **77**. Following these initial steps, ring closure occurs to give spiropyrrolidine **78**. Mechanism **A** seems to be the more likely pathway to predominate seeing as imines are poorly nucleophilic, therefore it is unlikely that they may participate in an S_N2 reaction.

In order to carry out the reaction shown in Figure 9, 2-spirocyclopropyl pseudoindoxyls **74** and **75** were prepared along with a series of substituted aryl aldimines (Table 1). Spiro[cyclopropane-1,2'-indolin]-3'-one **75** was prepared according to the following procedure, first described by Kawada *et al.*[47] (Scheme 23).

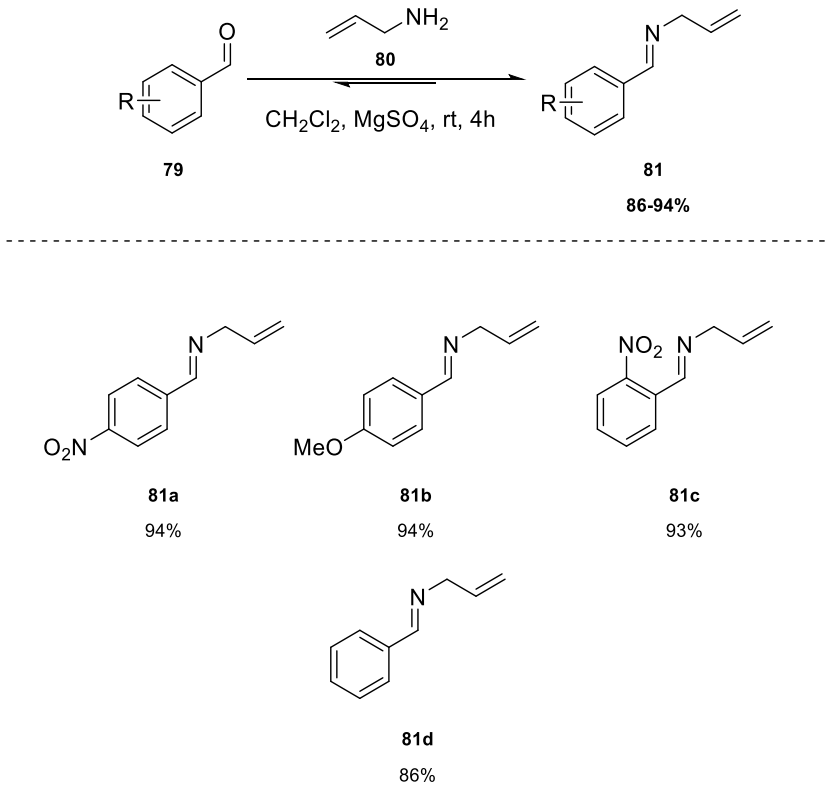


Scheme 23. Preparation of spirocyclopropane **75** from anthranilic acid **70** over 4 steps.

Firstly, an *N*-alkylation of anthranilic acid **70** was carried out using α-bromo-γ-butyrolactone to afford the anthranilic acid derivative **72** in high yield upon precipitation with concentrated HCl. Secondly, spirolactone **73** was formed by refluxing of **72** in acetic anhydride and triethylamine. This occurs via the simultaneous formation of the anhydride and enolate derivatives of **72**, following which, intramolecular concomitant acylation occurs leading to the construction of a spirocentre and acylation of the aniline nitrogen. Following this step, the cyclopropane moiety is produced *via* the Krapcho-type decarboxylation of spirolactone **73** to afford the *N*-acetylated spirocyclopropane **74** The acetyl group is subsequently removed under basic conditions with potassium hydroxide in methanol to produce spirocyclopropane **75** in good yield.

2.3 MgI_2-catalysed Ring Expansions of *N*-Allyl Imines

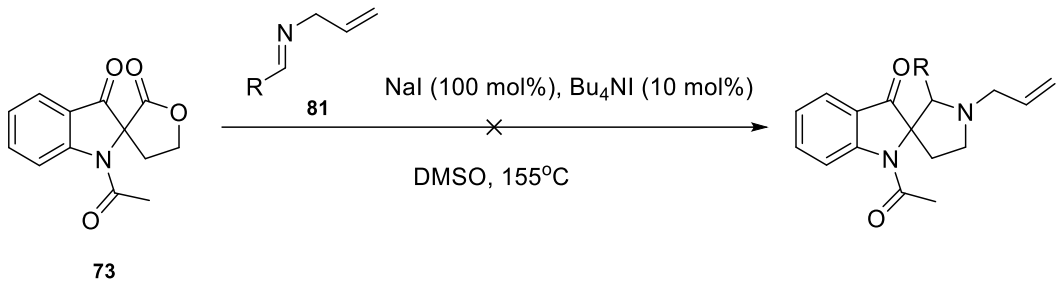
Following a known procedure, aldimines **81** were initially prepared using a commonly employed literature strategy; the condensation of substituted aryl aldehydes **79** with allylamine **80** in the presence of anhydrous magnesium sulfate to exclude water from the equilibrium system (Scheme 24) (Table 1).[48–51]



Scheme 24. Preparation of aryl *N*-allyl aldimines **60** *via* condensation of aryl aldehydes **79** and allylamine **80**.[48–51]

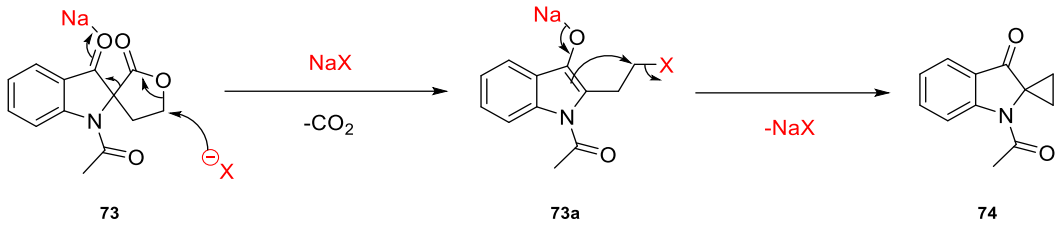
Upon obtaining the imines listed in Scheme 24, one-pot decarboxylative cycloadditions were initially attempted starting from spirolactone **73** (Scheme 25). This reaction was examined in the presence of sodium iodide and tetrabutylammonium iodide as a

solubilising agent in DMSO at 155°C. The motivation for attempting this transformation was the notion that the Krapcho-type decarboxylation step may be omitted by performing the decarboxylation *in situ.*



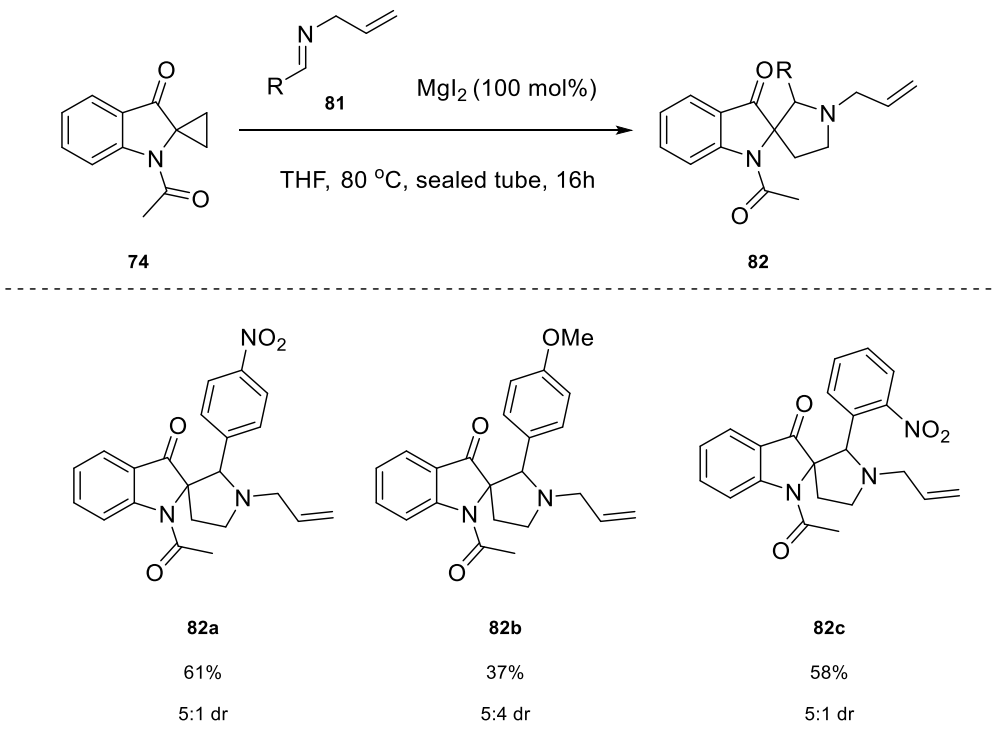
Scheme 25. Attempted decarboxylative cycloaddition of spirolactone **73**.

Unfortunately, attempts to effect this transformation only returned the *N*-acetylated spirocyclopropane **74** with no further reaction being observed. It was considered that this may have been due to the weaker Lewis acid character of sodium iodide in comparison to magnesium iodide. For this reason, activation of the pseudoindoxyl carbonyl or the imine may not have been occurring. Additionally, attempts to decarboxylate **73** with sodium iodide in place of sodium chloride did not return the intended product, neither did it return the starting material. This suggests that iodide participates in side reactions during this step due to its higher relative nucleophilicity. The mechanism of this decarboxylation step is shown in Scheme 26.



Scheme 26. Krapcho-type decarboxylation of spirolactone **73**. X = Cl (74%), X = I (N/A).

As a result, ring expansion reactions were subsequently conducted upon the *N*-acetylated spirocyclopropyl pseudoindoxyl **74** (Scheme 27). The reaction conditions in this case were selected by close analogy to those used by Carreira.[36] MgI_2 was however loaded stoichiometrically in order to increase the probability of the desired reaction occurring.

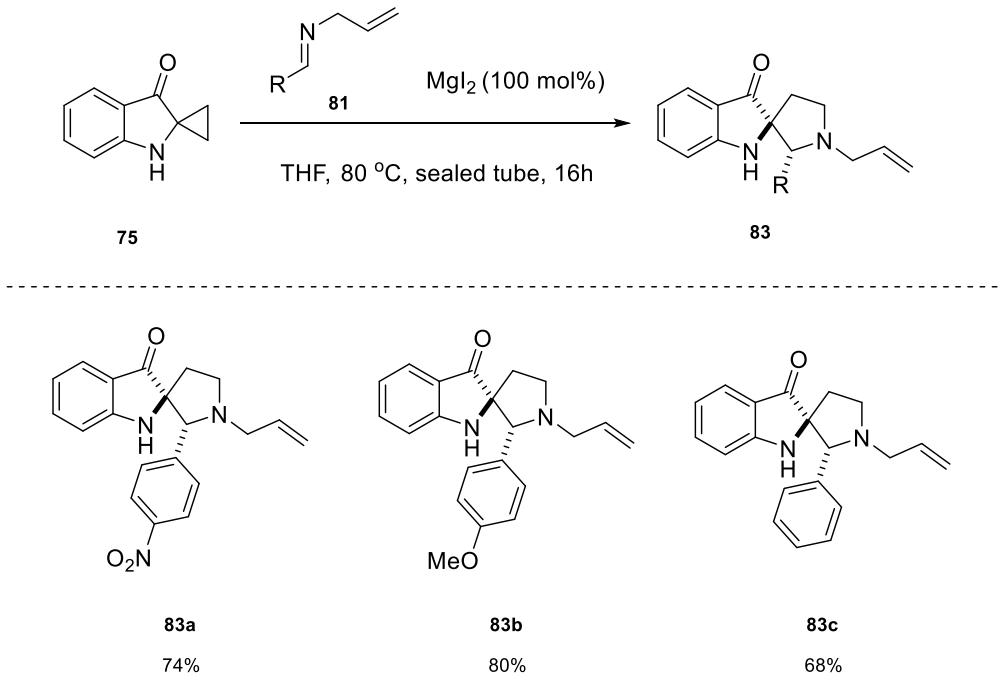


Scheme 27. Ring expansion of *N*-acetyl spirocyclopropane **74**.

The reaction was carried out using the aldimine substrates displayed in Scheme 24. The reaction shown in Scheme 27 showed no distinct diastereoselectivity, evidenced by the detection of two separate diastereomers visible by proton and carbon 13 NMR spectroscopy although the relative stereochemical configurations of these diastereomers was not known at this time.

These reactions proceeded with modest yields with higher yields being recorded for imines bearing an electron withdrawing substituent given that **81a** and **81c** recorded higher yields than **81b**. This may have been due to the electron withdrawing substituent increasing the electrophilicity of the imine, thus better facilitating nucleophilic attack by the enolate. These results also may suggest that the mechanism proceeds *via* mechanism A (Figure 9) as the more electron poor substrates record higher yields.

Consequently, the reactivity of spirocyclopropane **75** was explored next using the same method as was used in the preparation of the acetylated spiropyrrolidines **83** (Scheme 28).



Scheme 28. Preparation of spiropyrrolidine derivatives from **75**.

Upon completion of the reactions upon the deacetylated spirocyclopropane **75**, only a single diastereomer was observed by NMR. Furthermore, it was noted that the yields for this reaction were significantly greater than those reported in Table 2. The results of these experiments are displayed in Scheme 28.

The reasoning behind the higher yields observed for the deacetylated substrate **75** may be due to the removal of the electron withdrawing amide functionality from **74.** As a result, the enolate formed upon the cyclopropane ring opening is better stabilised by the nitrogen lone pair for the *N*-deacetylated system, enhancing its nucleophilicity. Furthermore, the electronics of the imine has less influence upon yield for the reactions of the deacetylated cyclopropane **75**, supporting the idea that the nucleophilicity of the enolate is greater for **75** than for **74**.

2.4. Elucidation of Relative Stereochemistry by NOESY

The relative stereochemistry of product **83** was elucidated through NOESY studies. This was achieved by the observation of nOe correlations between the pseudoindoxyl N-H with the methyne and methylene protons of the pyrrolidine ring for compounds **83a**, **83b** and **83c** (Figure 10).

Shown in Figure 10 is the NOESY spectrum obtained for compound **83b**, nOe correlations from **83b** are labelled A-F. Also labelled are the N-H and methyne (C-H) ^{1}H NMR peaks.

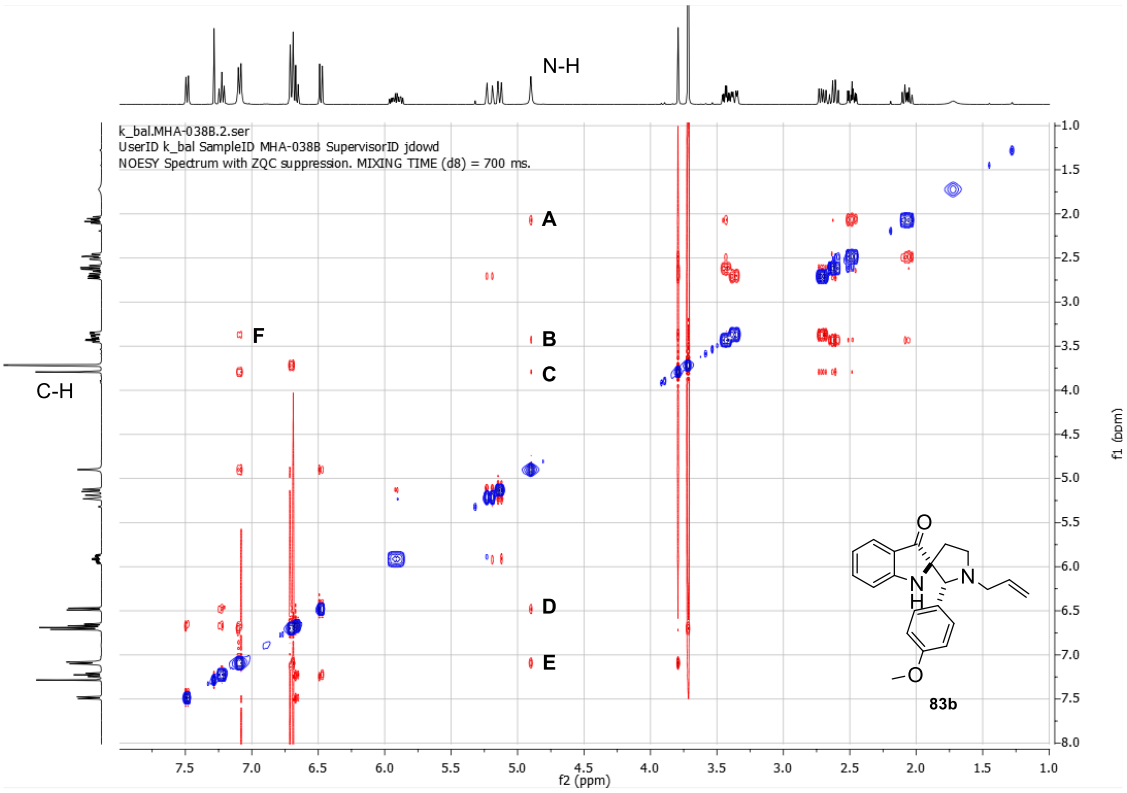


Figure 10. NOESY spectrum of **83b** showing observed NOE correlations.

Correlations **A** and **B** are observed between the N-H proton and methylene protons of the pyrrolidine ring. Correlation **C** is observed between the N-H proton and the methyne proton. Correlations **D** and **E** are observed between the N-H proton and aryl protons. Also shown is correlation **F** observed between a methylene proton and an aryl proton

The key correlation that was particularly revealing of the relative configuration of the two stereocentres was the correlation of the N-H proton and the methyne proton of the pyrrolidine ring, shown as correlation **C** (Figure 11). This is because of the proximity of the methyne and N-H proton is only permitted in the relative stereochemical configuration shown in Scheme 28. In the opposing configuration, the methyne proton would be pointing away from the N-H proton.

In addition, NOE correlations are observed between the upward-facing methylene protons and the aryl group of the pyrrolidine ring (correlation F, Figure 11). This further justifies the relative stereochemical assignment from Scheme 28.

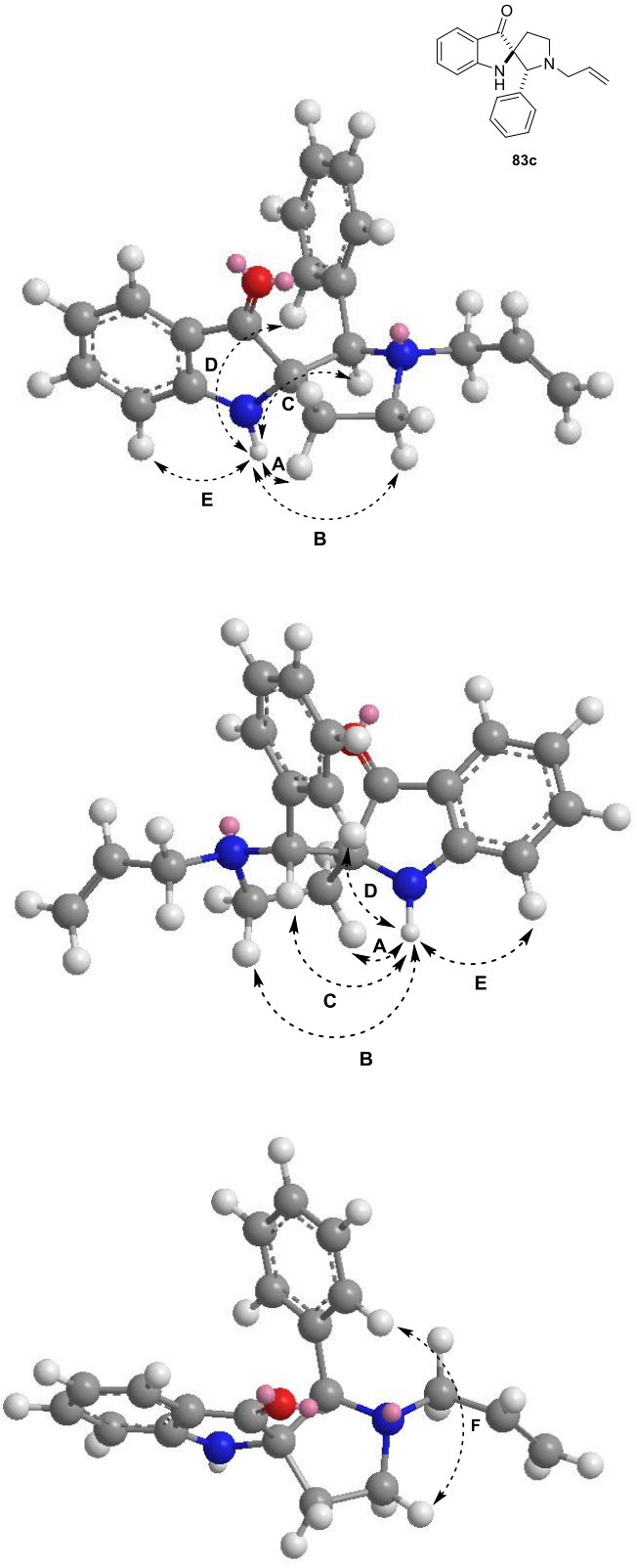


Figure 11. MMFF94 energy-minimised model of **83c** built in Chem3D showing NOE correlations observed between the pseudoindoxyl N-H proton and surrounding protons from different angles. Each correlation is labelled A-F.

The key correlation that was particularly revealing of the relative configuration of the two stereocentres was the correlation of the N-H proton and the methyne proton of the pyrrolidine ring, shown as correlation **C** (Figure 11). This is because of the proximity of the methyne and N-H proton is only permitted in the relative stereochemical configuration shown in Scheme 28. In the opposing configuration, the methyne proton would be pointing away from the N-H proton.

In addition, NOE correlations are observed between the upward-facing methylene protons and the aryl group of the pyrrolidine ring (correlation F, Figure 11). This further justifies the relative stereochemical assignment from Scheme 28.

The cause of the observed diastereoselectivity for the reactions carried out on **75** is somewhat ambiguous. One idea is that the major diastereomer forms in order to minimise steric repulsion between the R group of the imine and the aromatic ring of the pseudoindoxyl in the transition state. The proposed selectivity model for the observed diastereoselectivity is displayed in Figure 12.

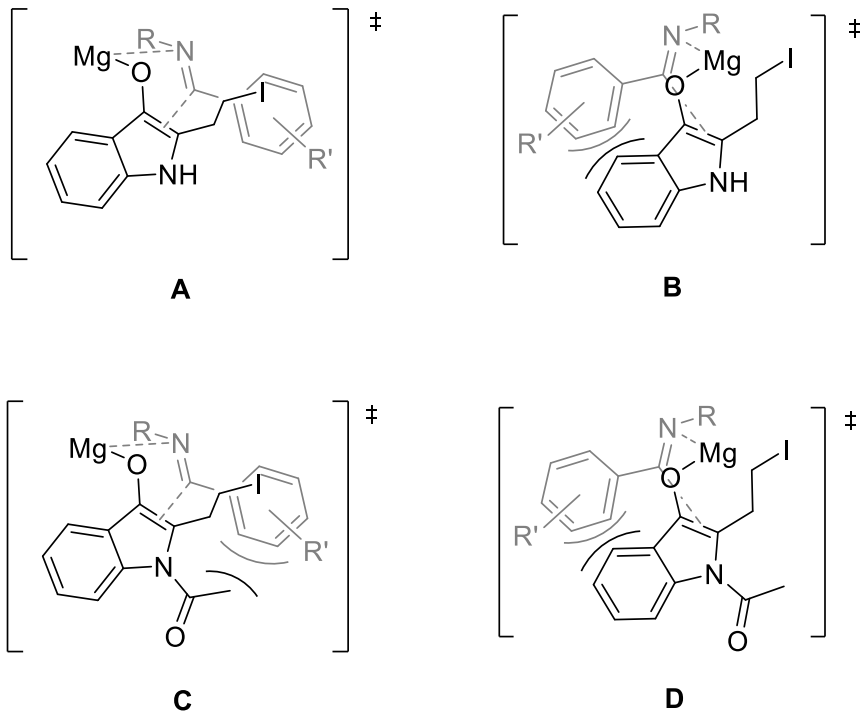


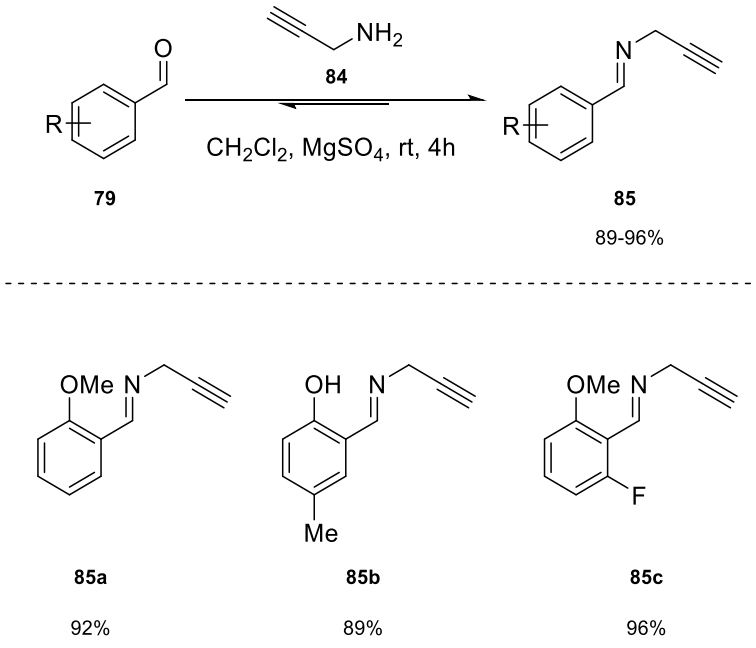
Figure 12. Proposed transition state model for the observed diastereoselectivity in product **83**. **A** depicts the sterically preferred transition state orientation of the imine (background) in relation to the indoxyl (foreground). **B** depicts the sterically disfavoured transition state orientation. Images **C** and **D** show the proposed transition state geometries for the *N-acetylated* analogues **82**.

The energetically favoured transition state model **A** (Figure 12) serves to minimise steric repulsion between the aryl systems of the imine and pseudoindoxyl as the enolate approaches the imine carbon from the Bürgi-Dunitz angle. Transition state **B** (Figure 12) is energetically disfavoured due to steric clashing of the aryl systems. In the case of the acetylated spiropyrrolidines **82**, the acetyl group may create some steric demand against the imine aryl group in transition state **C** (Figure 12). Whereas, in transition state **D** there is steric clashing between the aryl systems but not between the acetyl and aryl groups. It may be as a result of these competing steric interactions that there is a lack of absolute diastereoselectivity for the reaction of the acetylated substrate **74**.

2.5 MgI_2-catalysed Ring Expansions of *N*-Propargyl Imines

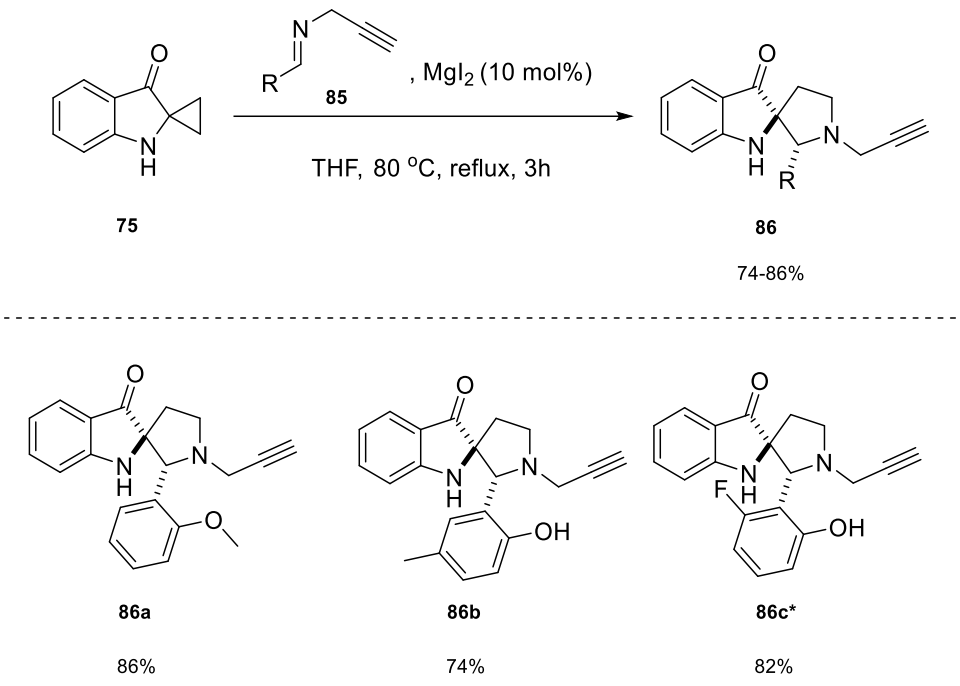
N-Propargyl spiropyrrolidines have been used by Sorensen *et al.* in the synthesis of 11-methoxy mitragynine pseudoindoxyl[19] (Scheme 1) in order to effect the olefin cross-coupling to access the spiroindolizidine core of mitragynine pseudoindoxyl. Incorporation of *N*-propargylic imines into this reaction begins to assess the compatibility of this method with that of Sorensen for the construction of mitragynine pseudoindoxyl **4**.

Various *N*-propargyl imines were prepared from propargylamine and substituted aryl aldehydes in the same fashion as first described in Scheme 24. The results of these reactions are displayed in Scheme 29.



Scheme 29. Preparation of *N*-propargyl aryl imines **85**.

Upon preparation of the imines from Scheme 29, ring expansion reactions were conducted upon **75** (Scheme 30). The catalytic loading of MgI_2 (10 mol %) as opposed to stoichiometric loading was attempted for this series of reactions. The result of lowering the catalyst load seemed to have no impact upon the efficiency of the reaction, as evidenced by the good yield shown in Scheme 30.



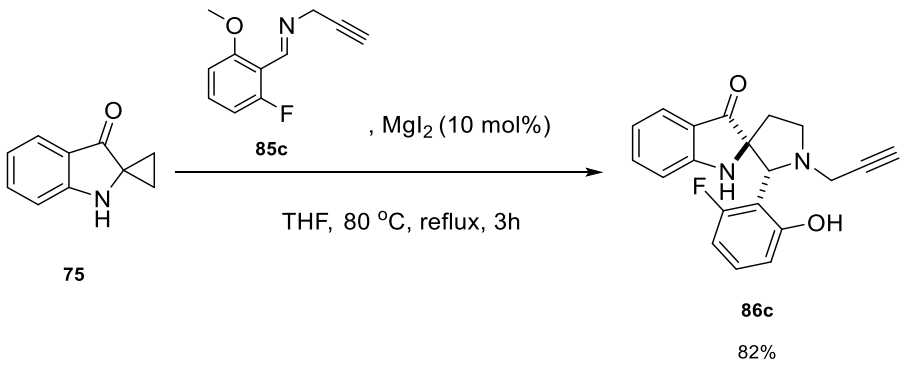
Scheme 30. Preparation of *N*-propargyl spiropyrrolidines from **75** and **85**.

*Did not form intended product

Products **86a** and **86b** formed successfully in good yield, NOESY studies revealed that the relative stereochemistry of these products was in accordance with that of their allylic counterparts (see appendix 5.1). Additionally, these reactions were attempted for the first time under reflux as opposed to using a sealed tube setup. The result was the

successful formation of the product with relatively short reaction times of around 3 hours in comparison to those of the previous method which lasted 16h.

Interestingly, imine **85c** did not form the expected product. The 6-methoxy group was surprisingly converted into a phenol group in the reaction vessel. This transformation was confirmed by both ^{1}H NMR spectroscopy and mass spectrometry (Scheme 31, Figure 13).



Scheme 31. Formation of *N*-propargyl spiropyrrolidine derivative **86c** featuring an unexpected demethylation.

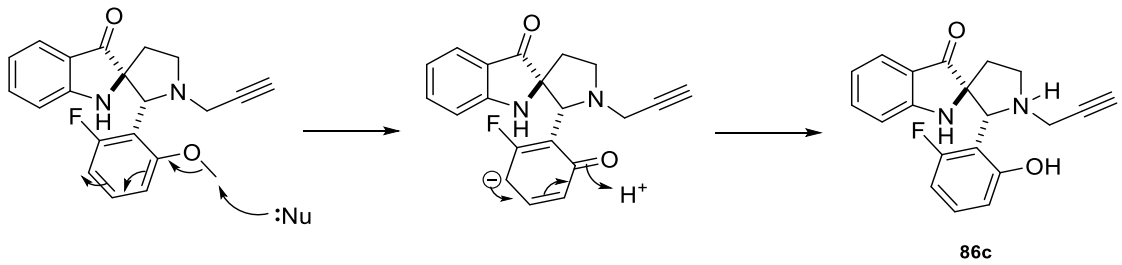
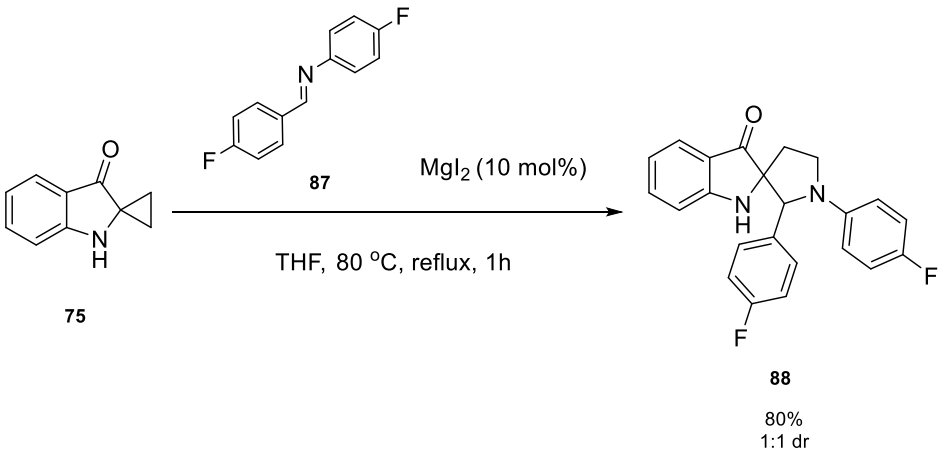


Figure 13. Potential mechanism for the demethylation of the aryl methoxy group to form **86c**.

The fluorine substituent on the aryl ring renders the methoxy group electrophilic due to the electron poor nature of the system. As a result, the methyl is attacked by a nucleophile, likely to be iodide or water, leading to removal of the methyl group to form a phenol.

2.6 MgI_2-catalysed Ring Expansions of *N*-Phenyl Imines

Following the exploration of *N*-propargyl spiropyrrolidine systems, *N*-phenyl spiropyrrolidine systems were investigated. This line of investigation came about due to the loss of diastereoselectivity observed for the reaction in Scheme 32.

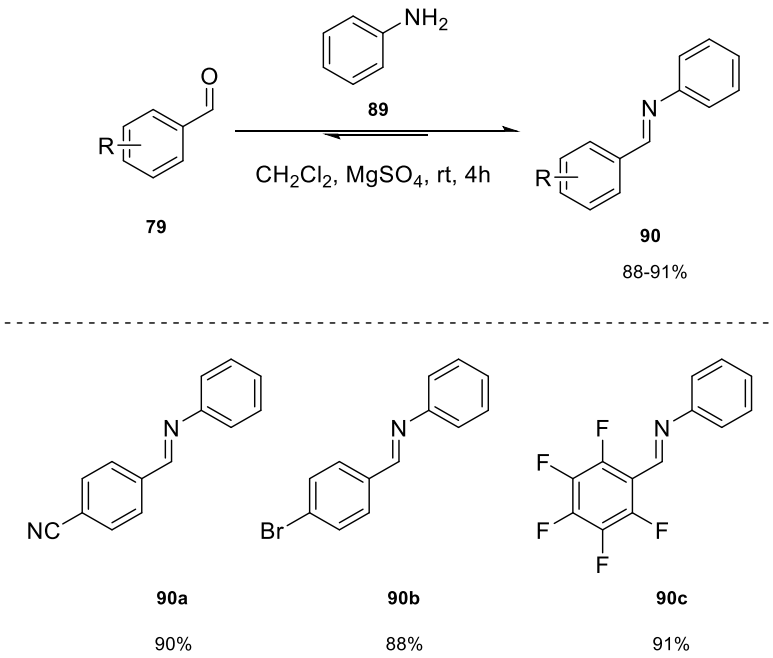


Scheme 32. Formation of an *N*-fluoroaniline spiropyrrolidine derivative **88** in 1:1 dr.

The reaction of fluorinated *N*-aryl imine **87** with **75** led to the formation of **88** with no control over the relative stereochemistry of the system. The product formed in 1:1 dr as visible by relative integration of ^{1}H NMR peaks. For example, two N-H proton signals of equal integral appear in the ^{1}H NMR spectrum. The origin of this lack of

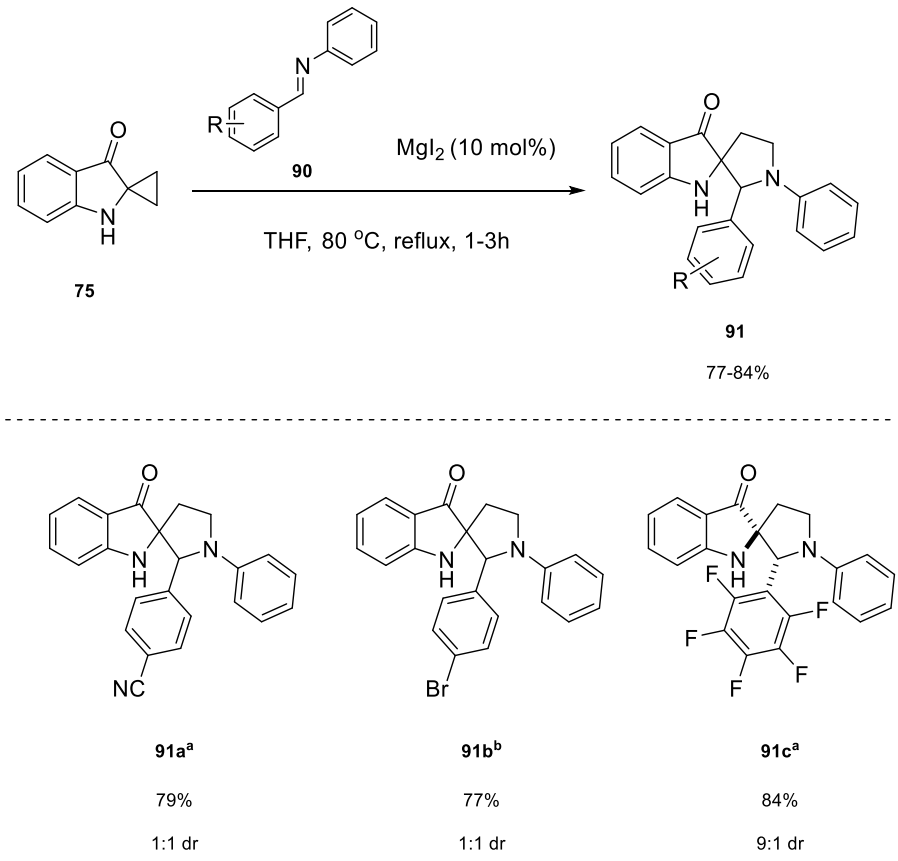
diastereoselectivity was explored intensively through the incorporation of various *N*-phenyl and *N*-benzyl imines into the spiropyrrolidine system.

N-Phenyl imines were prepared according to the same method outlined in Scheme 20. The fact that product **88** formed as an equal mixture of diastereomers potentially suggested that the system was epimerising following the cycloaddition. For this reason, electron withdrawing aryl substituents were incorporated adjacent to the *N*-phenyl system in an attempt to provoke this behaviour. The imines that were prepared are listed in Scheme 33 and Table 6.



Scheme 33. Preparation of *N*-phenyl imines **90** from substituted aryl aldehydes **79** and aniline **89**.

Upon obtaining the imines listed in Table 6, they were subjected to cycloaddition reactions with spirocyclopropane **75**. The results of these reactions are listed in Scheme 34.



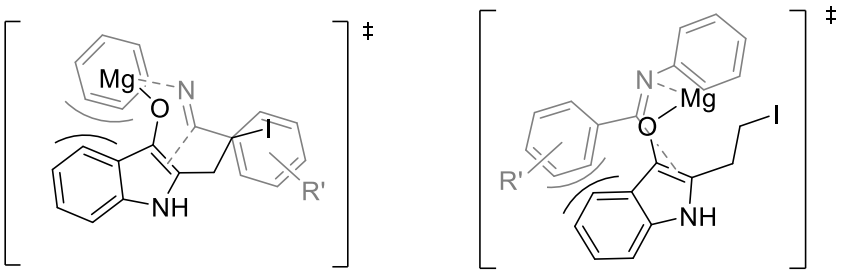
Scheme 34. Preparation of *N*-phenyl spiropyrrolidines **91** from **75** and *N*-aryl imines **90**.

Conditions were as follows; (a) THF, 80°C, reflux, 1h (b) THF, 80°C, reflux, 3h.

‡ dr calculated by relative integration of ^{1}H NMR peaks.

Interestingly, imines **90a** and **90b** led to the formation of a 1:1 mixture of diastereomers, whereas imine **90c** unexpectedly led to the formation of a single diastereomer observable by ^{1}H and ^{13}C NMR spectroscopy. It was initially considered that this may be an electronic effect involving the opening of the pyrrolidine ring, resulting in the epimerisation of the spirocentre. This effect was thought to be encouraged by the presence of an electron withdrawing group on the aldehyde component of the imine. However, the observation of a single diastereomer of product **91c** discounted this

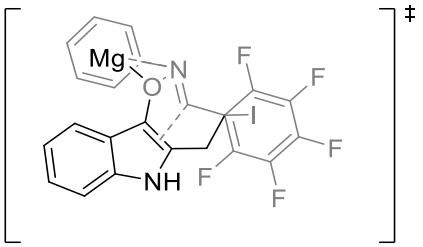
hypothesis. It was then considered that this is might be a steric effect based upon the transition state geometries of imines **90** and **75a** (Figure 14).



A **B**

Figure 14. Proposed transition state model for the reaction between **75** and *N*-aryl imines **90**.

The model shown in Figure 14 provides an explanation for the loss of diastereoselectivity observed in products **88**, **91a** and **91b**. The presence of the *N*-aryl group leads to the absence of a clearly energetically favourable transition state geometry. Transition state **A** (Figure 14) shows unfavourable steric interactions between the *N*-aryl group of **90** and the pseudoindoxyl aryl system of **75**. Transition state **B** shows the unfavourable steric interactions of the aryl group belonging to the aldehyde component of imine **90** with the aryl system of pseudoindoxyl **75**. This absence of an energetically favourable transition state means that there is no preferred orientation in which for the imine to align with **75**, as a result a 1:1 mixture of diastereomers is observed. Separation of these diastereomers was attempted by flash chromatography for individual characterisation of each diastereomer, however no separation could be achieved.



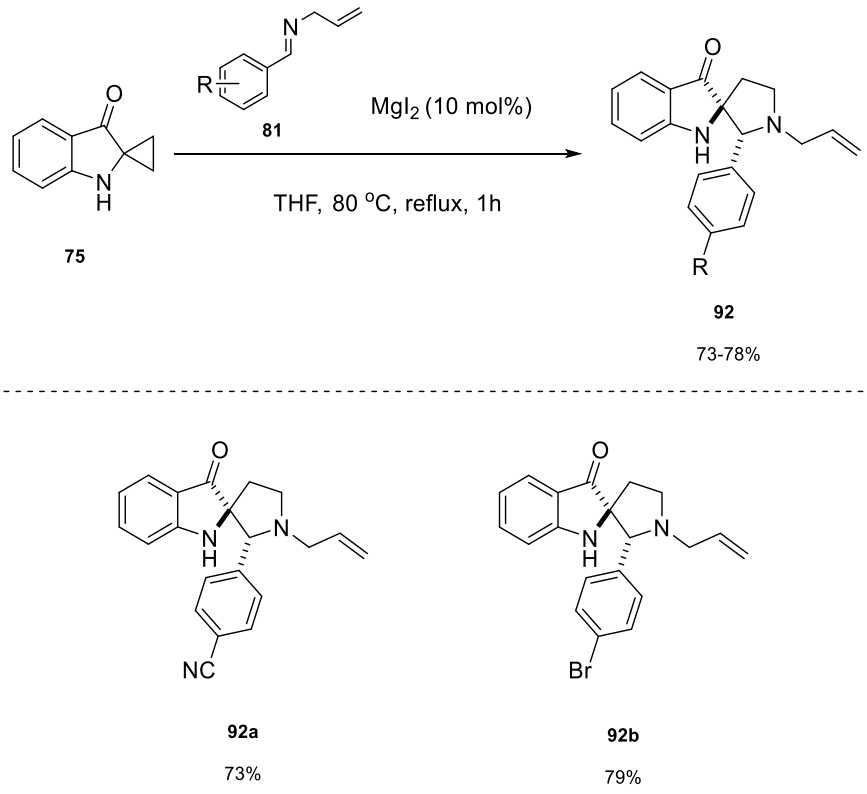
C

Figure 15. Proposed optimum transition state geometry between **75a** and imine **90c**.

This hypothesis holds true for the result observed for product **91c** (Figure 15). The polyfluorinated aryl system is considerably more sterically demanding than the *N*-phenyl aryl system. As a result, the preferred transition state orientation is that with the perfluorinated aryl system of **90c** pointing away from the pseudoindoxyl aryl system of **75a** (Figure 15, transition state **C**). These observations support the hypothesis of the diastereoselectivity being under steric control, initially presented in Figure 12.

These models present an iterative hypothesis to explain the origin of the diastereoselectivity of the ring expansion reaction based on observed outcomes. No definitive evidential backing exists for these models.

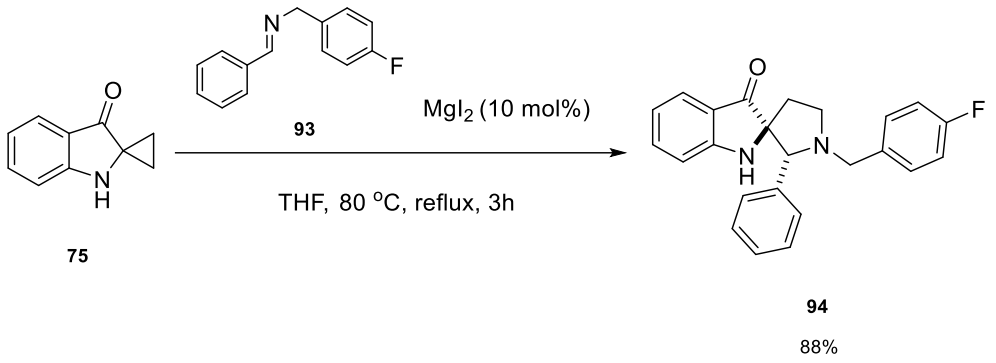
In order to demonstrate that this interconversion behaviour was a result of the *N*-phenyl substituent being present, allylic analogues of the 4-cyano **91a** and 4-bromo **91b** *N*-phenyl spiropyrrolidines were synthesised as per Scheme 35.



Scheme 35. Synthesis of *N*-allyl analogues of **91a** and **91b**.

As shown in Scheme 35, products **92a** and **92b** proceeded to form with complete diastereoselectivity, indicating that the presence of the *N*-phenyl group in products **91a** and **91b** is the cause behind the loss of diastereoselectivity. As previously alluded to, this may be a steric effect, prohibiting the existence of a highly favourable transition state orientation between the imine and the pseudoindoxyl.

Following on from these findings, the use of an *N*-benzyl substituent was probed in order to examine whether or not this would lead to a single diastereomer. This reaction is displayed in Scheme 36.



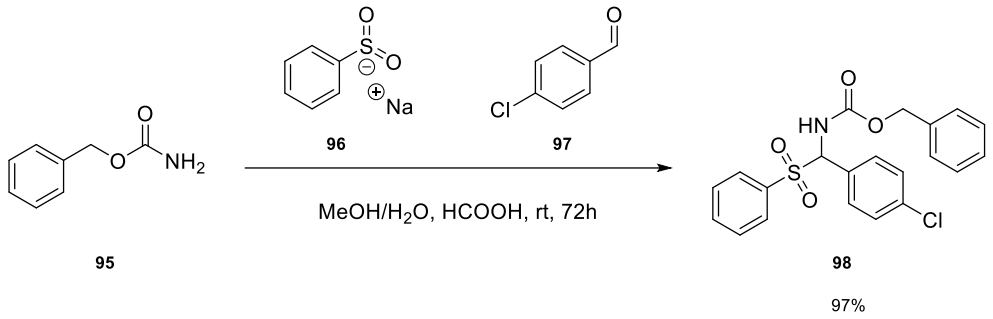
Scheme 36. Synthesis of an *N*-4-Fluorobenzyl spiropyrrolidine derivative **94**.

The ring expansion reaction between **75** and **93** proceeded to the formation of a single diastereomer in excellent yield.

2.7 Incorporation of New Substrate-types

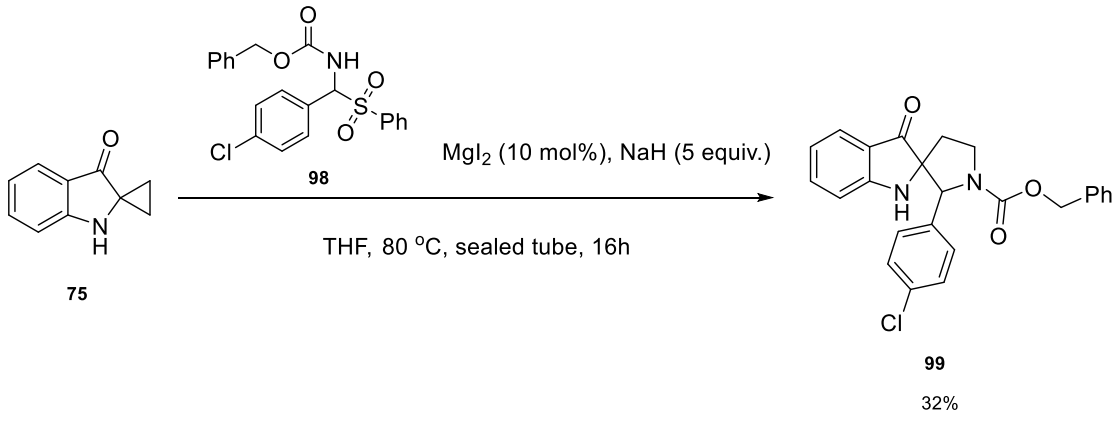
The substrate scope of the ring expansion reaction of spirocyclopropane **75** was explored and expanded through the use of electrophiles other than aldimines and the use of more sterically and electronically demanding nitrogen environments.

Firstly, the *in-situ* generation of imines was explored as a method for incorporating difficult to access imines into the spiropyrrolidine framework. The Cbz functional group is a useful protecting group in organic synthesis, however due to the poorly nucleophilic nature of carbamates, *N*-Cbz aldimines are more challenging to access using the method previously delineated in this work. Using sulfonate **98**, the *in-situ* generation of an aldimine is possible under basic conditions. This is a commonly employed literature strategy for the generation of aldimines.[52]



Scheme 37. Synthesis of sulfinate-protected carbamate **105**.[53]

This method (Scheme 37) benefits from the addition of phenylsulfinate upon formation of the imine, prohibiting the reversibility of the reaction. As a result, higher yields are achievable for poorly nucleophilic amines than for the method in Scheme 24. Adduct **98** was synthesised by DTP rotation student James Kapp, it was then used in this work for the preparation of *N*-Cbz spiropyrrolidine **99** (Scheme 38).

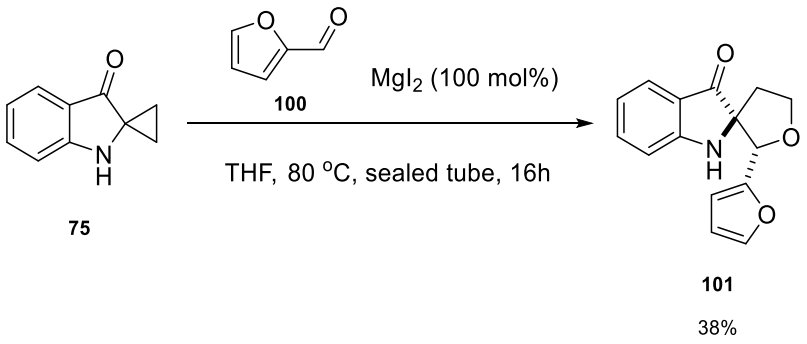


Scheme 38. One-pot formation of an *N*-Cbz spiropyrrolidine derivative **106** through *in situ* imine formation from **105** and NaH.

The imine appears to form *in-situ* due to the deprotonation of the amine nitrogen by NaH and subsequent elimination of the sulfonate. This reaction proceeded to from the intended product however did so in poor yield (32%). Nonetheless, this experiment demonstrated that this type of one-pot cycloaddition was possible in the presence of sodium hydride. This highlights the robustness of this reaction due to its tolerance towards strongly basic conditions.

Product **99** appeared to form as a single diastereomer however no clear assertions relating to the relative stereochemical assignment could be made from its NOESY spectrum.

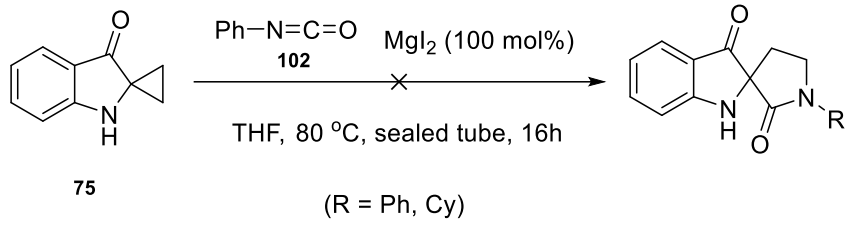
Secondly, aldehydes were utilised in order to create spirotetrahydrofuran frameworks. The results of this reaction are displayed in Scheme 39.



Scheme 39. Ring expansion of **75** with furfural **100** to yield spirotetrahydrofuran **101**.

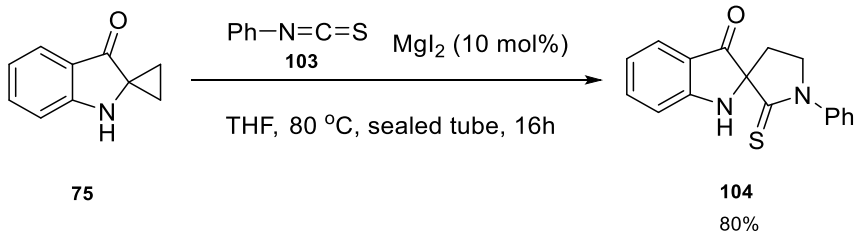
The reaction shown in Scheme 39 proceeded to the formation of **101** as a single diastereomer in modest yield. The relatively low yield may be a result of the increased electrophilicity of aldehydes in relation to imines, leading to side reactions.

Modest yield notwithstanding, the experiment shown in Scheme 39 showed great promise that the substrate scope of this reaction could extend beyond imines, as such, the use of further electrophiles was explored. Isocyanates are common electrophilic building blocks in organic synthesis, notably in the synthesis of ureas. The cycloaddition of **75** was attempted with phenyl isocyanate **102** in order to attempt the synthesis of spirolactams as shown in Scheme 40.



Scheme 40. Attempted formation of spirolactams from isocyanates.

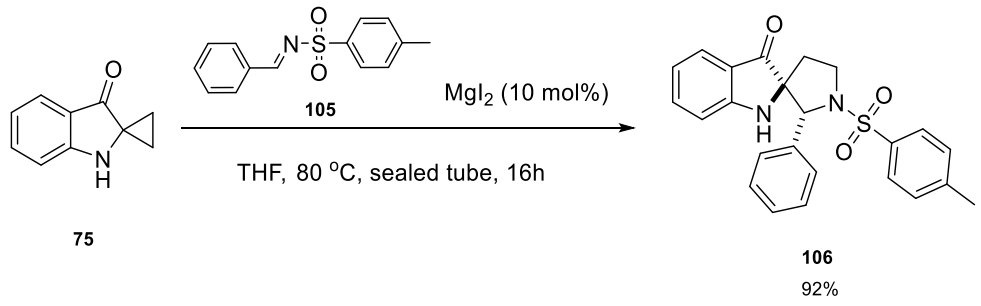
Unfortunately, no reaction was observed for these experiments. As a result, the use of isothiocyanates was explored with the hope of eliciting a reaction due their higher relative electrophilicity (Scheme 41).



Scheme 41. Formation of spirothioamide **104** *via* cycloaddition of **75** and phenyl isothiocyanate **103**.

The reaction between **75** and phenyl isothiocyanate **103** showed great success, achieving 80% yield and forming the highly structurally novel spirothioamide **104**. Thioamides have previously been employed in the synthesis of indolizidine alkaloids as the carbon-sulfur double bond may be converted to an olefin *via* an Eschenmoser coupling, enabling the construction of the indolizidine ring system in subsequent steps.[54]

The installation of *N*-tosyl environments on the pyrrolidine ring system was explored in order to challenge the electronics of the system. This was achieved through the use of *N*-tosyl methanimine **105** in the ring expansion reaction of **75** (Scheme 42).



Scheme 42. Formation of *N*-tosyl spiropyrrolidine structure **106** from *N*-tosyl methanimine **105** and **75**.

The reaction in Scheme 42 proceeded with excellent yield, this may have been an effect of the electron deficiency of the tosyl system, rendering imine **104** a good electrophile.

2.8 Screen for Asymmetric Catalysts

Hitherto, the diastereoselectivity resulting from the ring expansion reaction present throughout this work has been extensively characterised and discussed, however enantioselectivity has yet to be probed. The development of a catalytic method for the asymmetric construction of the spiropyrrolidine framework was explored through the screening of various asymmetric catalysts as shown in Figure 16.

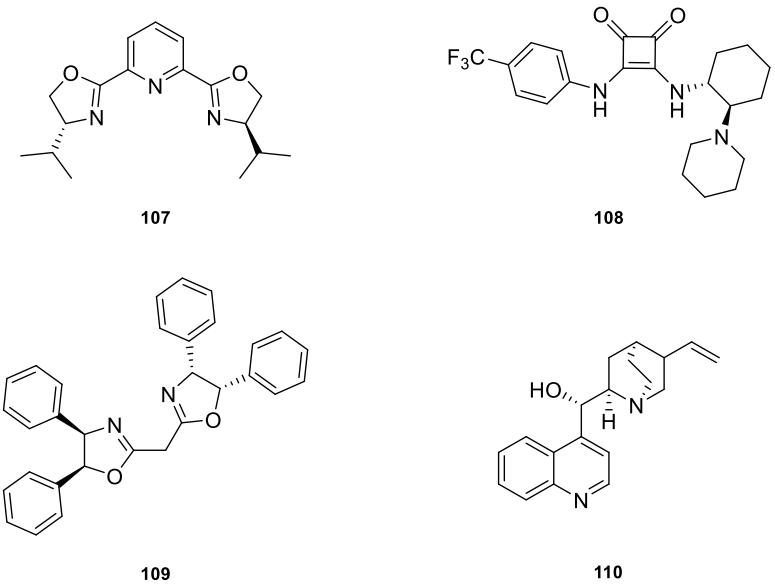
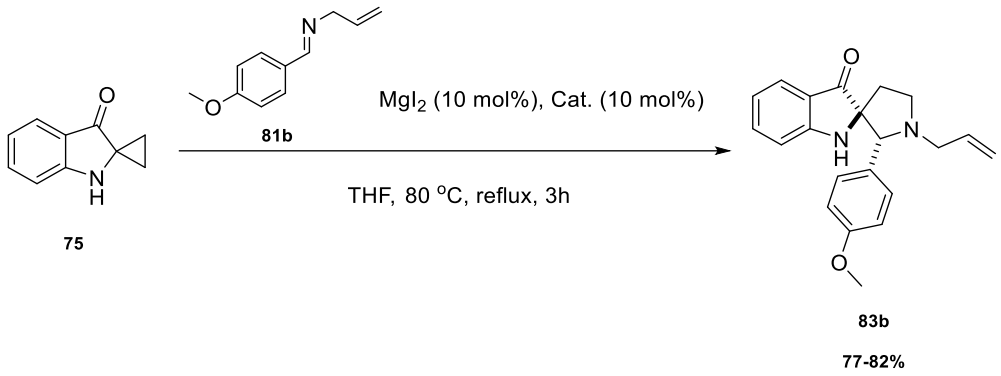


Figure 16. Selected asymmetric catalysts that were screened for the asymmetric synthesis of spiropyrrolidine **83b**.

Each catalyst shown in Figure 16 was initially screened under the standard reaction conditions as first depicted in Scheme 23. A particular imine, **81b**, was selected to take part in a model reaction which would be used to assess the efficacy of the selected catalysts (Scheme 43).



Scheme 43. Reagents and conditions used for the asymmetric catalyst screen (Figure 12).

Upon completion of the reactions involving the catalysts from Figure 17, the enantiomeric excess (*ee*) of the products was determined by chiral HPLC with UV detection. The relative integrals of the peaks from the chiral HPLC trace allowed to ascertain as to whether any asymmetric induction had been achieved by any of the selected catalysts. The results obtained from these HPLC experiments are shown in Figure 17.

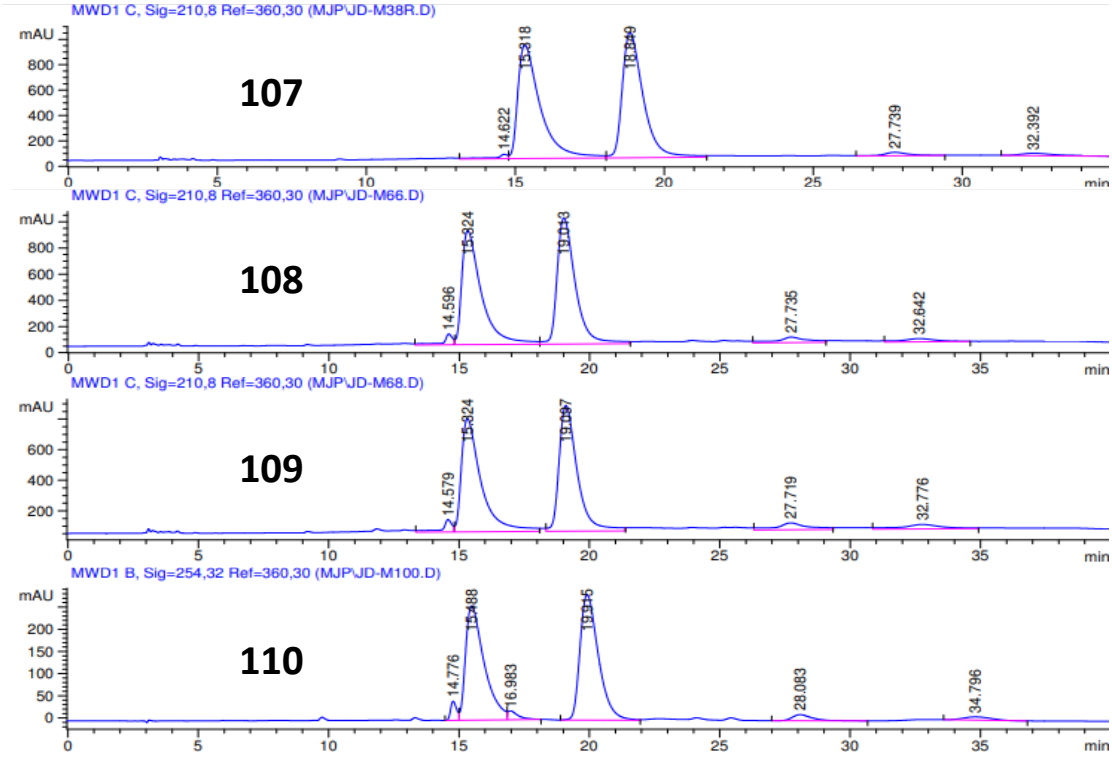
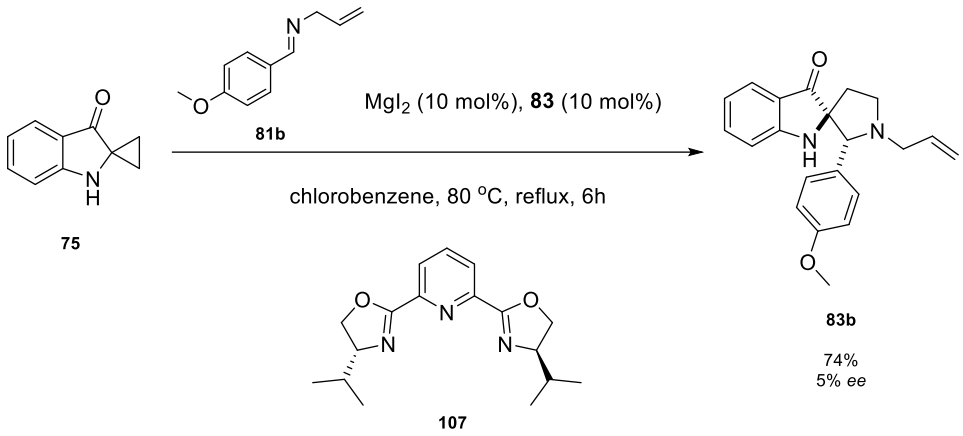


Figure 17. HPLC traces of product **38b** from each asymmetric catalysis attempt. The number of the catalyst used is overlaid over the corresponding trace.

Whilst a method for enantiomeric separation by HPLC was successfully devised (see appendix 5.2), no significant asymmetric induction was observed by any of the catalysts in Figure 16. Of the catalysts that were used, **107** seemed to show the most promise as a potential candidate for asymmetric catalysis. As a result, the reaction conditions were varied in the presence of catalyst **107**. It was considered that the use of a coordinating solvent (THF) may have been inhibiting the ability of the Lewis base catalyst **107** to bind to the magnesium enolate **75a**, thereby inducing an asymmetric environment. Consequently, a non-coordinating solvent was selected for the second round of the catalyst screen. Chlorobenzene was used by analogy of the asymmetric synthesis

achieved by You *et al*.[41] The reagents and conditions for this second round of screening are displayed in Scheme 44.



Scheme 44. Variation of solvent for screening of **107** as a candidate for asymmetric catalysis.

Unfortunately, no significant asymmetric induction was observed for this change in reaction conditions (Figure 19). Attempts were also made to slow down the reaction by allowing it to run at room temperature over 48 hours. In this case no reaction was observed. This may have been due to the activation barrier for the opening of the cyclopropane ring not having been surpassed on account of the mild conditions that were used.

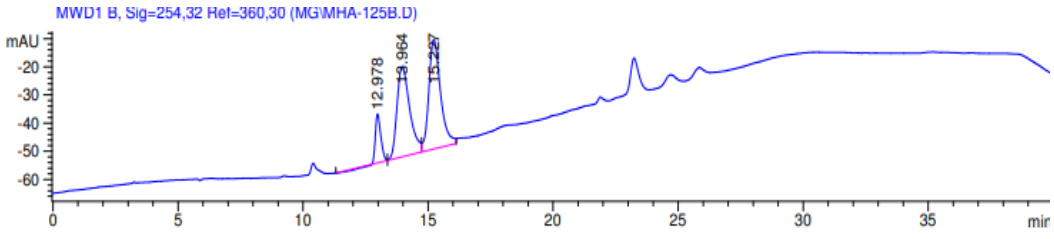


Figure 19. HPLC trace of product **38b** formed in the presence of **107** in chlorobenzene.

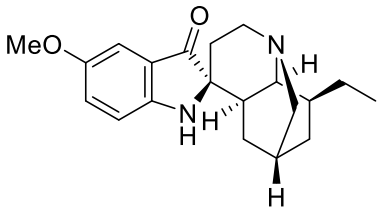
More work is required towards the generation of an enantioselective method for this reaction. This would include the variation of reaction temperature and solvent in order to enable effective complexation of the asymmetric ligand to the Lewis acid. Additionally, variation of the Lewis acid catalyst should be explored.

3. Conclusion and Further Work

A novel strategy for the construction of substituted 2-spiropseudoindoxyl frameworks has been developed and the substrate scope has been explored extensively. Additionally, the diastereoselectivity arising from this method has been characterised and explained through the use of transition state models. For the first time, this work has seen the characterisation of the diastereoselectivity of the ring expansion products of **75**. Also for the first time, this work has seen incorporation of new electrophiles into the ring expansion of **75** including, isothiocyanates, aldehydes and sulfonate-protected carbamates. Additionally, in this work an explanation is presented for the previously observed loss of diastereoselectivity with the use of certain imine substrates.

Further work would include the development of an enantioselective method, compatible with the ring expansion of **75**. The use of chiral ligands **107-110** proved ineffectual and attempts to run the reaction at low temperatures did not return the intended product. Enantioselectivity may be achieved through the use of other Lewis acid catalysts such as palladium (II) iodide. The empty d-orbitals of the palladium may allow for better coordination by the chiral catalyst, thus ensuring that the complex remains stable under the reaction conditions.

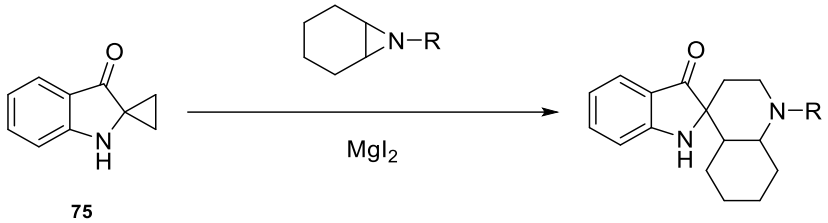
In addition to 2-spiropyrrolidinyl pseudoindoxyls, 2-spiropiperidinyl pseudoindoxyl frameworks exist as core structures of many natural products of possible medicinal utility. This is perhaps exemplified by pseudoindoxyl alkaloids of the *Ervatamia* family such as iboluteine **111** (Figure 20) which incorporates a spirodecahydroquinoline motif.[55]



111

Figure 20. Structure of iboluteine **111**.[55]

Alkaloids from the genus *Ervatamia* are showing good promise as anti-tumour agents and potent acetylcholinesterase (AChE) inhibitors.[56,57] Theoretically, the core motif from many of these alkaloids may be constructed using the same strategy as used in this work through the utilisation of aziridines (Scheme 45).

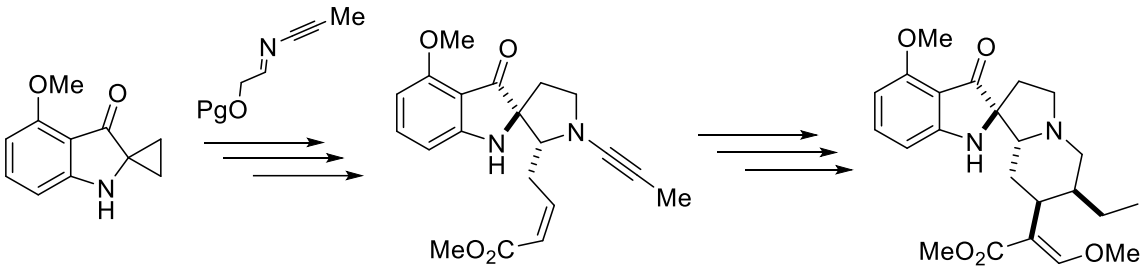


75

Scheme 45. Proposed synthesis of the iboluteine core structure using the method from this work.

In addition, the total synthesis of mitragynine pseudoindoxyl **4** could be explored from the method in this work. In this work, only aryl imines were used in the ring expansion reaction as non-aryl imines only returned trace yields. A system that optimises the reaction between spirocyclopropane **75** and aliphatic imines could therefore be explored, perhaps through Brønsted acid catalysis. This would enable the method

applied by Sorensen[19] (Scheme 1) to be utilised in the total synthesis of mitragynine pseudoindoxyl **4**. An iterative scheme for this proposed route is shown in Scheme 46.



Scheme 46. Proposed synthetic route to mitragynine pseudoindoxyl, combining methods from this work and from the work of Sorensen *et al.*[19]

4. Experimental Part

4.1 General Experimental

All solvents and reagents were purchased from Sigma-Aldrich or Fischer Scientific and were used without further purification, other than THF which was purified by distillation. All reactions were carried out under a positive pressure of argon.

All reactions were magnetically stirred and monitored by Thin Layer Chromatography (TLC) on silica gel TLC plates and visualised under UV light. Flash column chromatography was performed using 60Å, 200-500 micron silica gel procured from Fluorochem. Rotary evaporation was performed at 40^{o}C under the appropriate pressure. Compounds were further dried under high vacuum to remove solvent traces. Yields refer to mass of product recovered after chromatography (If chromatography was required).

All NMR spectra were recorded on a Brüker 400 MHz spectrometer. Chemical shifts are reported in ppm relative to the residual solvent and the internal standard. NMR integrals and coupling constants were calculated in MestReNova 9.1.0.

Mass spectrometry data was acquired through the University of Nottingham open access mass spectrometry service, recorded on a Brüker TOF spectrometer using electrospray ionisation (ESI) as the ionisation method.

Infrared spectra were collected on a Brüker Alpha attenuated total reflectance (ATR) FTIR spectrophotometer and absorptions are given in wavenumbers (cm^{-1}).

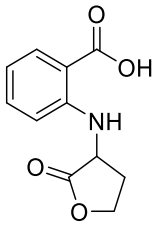
HPLC traces were obtained using an Agilent 1100 series HPLC equipped with an Agilent InfinityLab Poroshell 120 chiral column. A 9:1 isohexane : isopropanol solvent system was used with gradient elution.

Melting points were obtained after recrystallization using a Gallenkamp melting point apparatus.

4.2 Experimental Data

4.2.1 Preparation of Spirocyclopropane 75

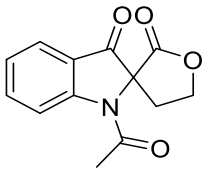
2-[(Tetrahydro-2-oxo-3-furanyl)amino] benzoic acid **72**[47]



Anthranilic acid **70** (10.0 g, 72.8 mmol, 1.0 equiv.), was dissolved in H_2O (50 mL). Na_2CO_3 (19.3 g, 91.1 mmol, 2.50 equiv.) in H_2O (75 mL), was subsequently added to the solution over a period of 10 minutes. The solution was stirred for 1h, then heated to 50°C. Subsequently, α-bromo-γ-butyrolactone **71** (6.50 mL, 91.1 mmol, 1.25 equiv.), was added. The heated reaction mixture was allowed to stir for 16 hours. Once cooled, the reaction mixture was acidified with conc. HCl to pH 0.5 and stirred for 3 hours at room temperature to afford the title compound as a beige precipitate which was filtered, washed with H_2O and dried under vacuum, (14.0 g, 87%), m.p. (EtOH) = 196-199°C (lit. 197-199°C)[47] ^{1}H NMR (CD_3OD, 400MHz); δ = 7.95 (1H, app d, *J* = 8.4 Hz, Ar*H*), 7.41 (1H, app t, *J* = 8.4 Hz, Ar*H*), 6.87 (1H, app d, *J* = 8.4 Hz, Ar*H*), 6.70 (1H, app t, *J* = 8.4 Hz, Ar*H*), 4.55 (1H, dd, *J* = 11.1, 9.1 Hz, COOCH_aH$_b$), 4.55 (1H, t, *J* = 9.1 Hz, NCC*H*CO), 4.39 (1H, ddd, *J* = 11.1, 9.1, 5.8 Hz, COOCH$_a$$H_b$), 2.90 (1H, ddd, *J* = 11.1, 9.1, 5.8 Hz, COOCH$_2$CH_aH$_b$), 2.18 (1H, qd, *J* = 11.1, 9.1 Hz, COOCH$_2$CH$_a$$H_b$) ^{13}C NMR ($CD_3OD$, 100MHz); δ = 177.0, 170.4, 150.0, 134.3, 131.8, 115.6, 111.8, 111.2, 65.8, 51.6, 30.8 HRMS (ESI+); m/z calcd for $C_{11}H_{12}NO_4$ = 222.0766, found = 222.0766 [M+H], m/z calcd for $C_{11}H_{11}NaNO_4$ = 244.0586, found = 244.0586 [M+Na]. ν (cm^{-1}) (neat); 3304 (OH), 1767 (C=O), 1659 (C=O)

Spectroscopic data match literature[47]

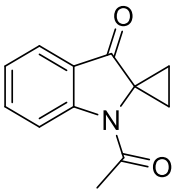
1-Acetyl-4,5-dihydrospiro[furan-3(2H),2'-[2H]indole]-2,3'(1'H)dione **73**[47]



2-[(Tetrahydro-2-oxo-3-furanyl)amino] benzoic acid **72** (5.00 g, 22.6 mmol, 1.0 equiv) was dissolved in Ac_2O (135 mL, 974 mmol, 43 equiv.) under argon, to which was added triethylamine (67.5 mL, 715 mmol, 32 equiv). The reaction mixture was then heated to 130°C and allowed to stir under reflux for 3 hours. Once cooled, the reaction mixture was concentrated *in vacuo,* affording a dark brown residue which was subsequently triturated with H_2O to afford a light brown solid. The resulting solid was filtered, washed with Et_2O and dried to yield the title compound as a brown solid. (3.95 g, 71%) m.p. (EtOH) = 157-158°C (lit. 159-160°C)[47], ^{1}H NMR ($CDCl_3$, 400MHz); δ = 7.84 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.76 (1H, app t, *J* = 7.7 Hz, Ar*H*), 7.58 – 7.51 (1H, m, Ar*H*), 7.34 (1H, t, *J* = 7.7 Hz, Ar-*H*), 4.8 – 4.7 (2H, m, OCH_2), 3.0 – 2.9 (1H, m, $OCH_2CH_aH_b$), 2.74 – 2.55 (4H, m, $OCH_2CH_aH_b$, $COCH_3$) ^{13}C NMR ($CDCl_3$, 100 MHz); 194.4, 170.0, 167.6, 152.0, 138.1, 125.9, 124.6, 123.0, 115.0, 72.2, 66.1, 30.6, 25.8 HRMS (ESI+); m/z calcd for $C_{13}H_{12}NO_4$ = 246.0761, found 246.0763 [M+H], m/z calcd for $C_{13}H_{15}N_2O_4$ = 263.1026, found = 263.1019 [M+NH_4], m/z calcd for $C_{13}H_{11}NNaO_4$: 268.0580, found 268.0578 [M+Na]. ν (cm^{-1}) (neat); 1771.84 (C=O), 1710.82 (C=O), 1666.86 (C=O)

Spectroscopic data match literature[47]

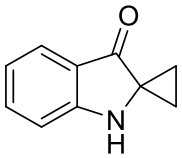
1'-Acetylspiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-one **74**[47]



1-Acetyl-4,5-dihydrospiro[furan-3(2H),2'-[2H]indole]-2,3'(1'H)dione **73** (1.00 g, 4.08 mmol, 1.0 equiv) and NaCl (0.26 g, 4.48 mmol, 1.1 equiv) were dissolved in dry DMSO (5 mL) under argon. The reaction mixture was heated to 155°C and allowed to stir for 2 hours. Upon cooling, the reaction mixture was poured into ice H_2O, affording a grey precipitate which was extracted with EtOAc. The organic extracts were washed with water and brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford a grey solid which was dissolved in dichloromethane, decolourised with activated charcoal and filtered through diatomaceous earth. The resulting filtrate was evaporated to dryness *in vacuo* to afford the title compound as a pale yellow solid. (623 mg, 76%) m.p. (EtOH) = 155-157°C (lit. = 156-157°C)[47], ^{1}H NMR ($CDCl_3$, 400MHz); δ = 7.8 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.7 – 7.6 (2H, m, Ar*H*), 7.3 – 7.2 (1H, m, Ar*H*), 2.5 (3H, s, COC*H*$_3$), 2.5 – 2.4 (2H, m, C*H*$_2$), 1.5 – 1.4 (2H, m, C*H*$_2$) ^{13}C NMR ($CDCl_3$, 100MHz); δ = 197.0, 167.9, 151.5, 135.7, 124.0, 123.7, 116.1, 67.4, 54.7, 27.1, 16.9 HRMS (ESI+); m/z calcd for $C_{12}H_{12}NO_2$ = 202.0868, found = 202.0888 [M+H], m/z calcd for $C_{12}H_{11}NNaO_2$ = 224.0687, found = 224.0680 [M+Na] ν (cm^{-1}) (neat); 1705.48 (C=O), 1664.65 (C=O)

Spectroscopic data match literature[47]

Spiro[cyclopropane-1,2'-indolin]-3'-one **75**[47]

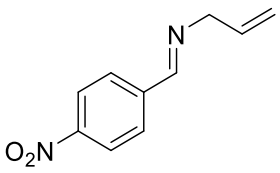


1'-Acetylspiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-one **74** (500 mg, 2.48 mmol, 1.0 equiv) was dissolved in methanol (2.5 mL) to which was added potassium hydroxide (167 mg, 2.98 mmol, 1.2 equiv) in methanol (1 mL). The reaction mixture was stirred at room temperature for 3 hours, after which, the reaction mixture was evaporated to dryness *in vacuo.* The resulting residue was diluted with ice-water and chloroform, the organic extracts were collected and the aqueous washings extracted with chloroform. The combined organic washings were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford the title compound as a bright yellow solid. (337 mg, 85%), m.p. (^{i}PrOH) = 108-110°C (lit. = 110-111°C)[47] ^{1}H NMR ($CDCl_3$, 400MHz); δ = 7.7 (1H, app d, *J* = 8.0 Hz, Ar*H*), 7.5 (1H, app t, *J* = 8.0 Hz, Ar*H*), 7.0 (1H, app d, *J* = 8.0 Hz, Ar*H*), 6.9 (1H, app t, *J* = 8.0 Hz, Ar*H*), 5.25 (1H, s, N*H*), 1.58 – 1.50 (m, 2H, CCH_2), 1.50 – 1.43 (m, 2H, CCH_2) ^{13}C NMR ($CDCl_3$, 100MHz); δ = 200.5, 159.9, 135.8, 123.7, 121.8, 119.3, 113.3, 49.2, 17.2 HRMS (ESI+); m/z calcd for $C_{10}H_{10}NO$ = 160.0757, found = 160.0762 [M+H], m/z calcd for $C_{10}H_9NNaO$ = 182.0576, found = 182.0580 [M+Na] ν (cm^{-1}) (neat); 3356.21 (NH), 1656.30 (C=O)

Spectroscopic data match literature[47]

4.2.2 Preparation of Aldimines

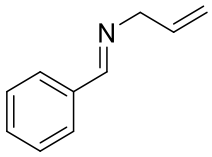
N-allyl-1-(4-methoxyphenyl)methanimine **81a**[51]



4-Anisaldehyde (5.00 g, 4.50 mL, 36.7 mmol, 1.0 equiv.) and allylamine (2.00 g, 2.75 mL, 36.7 mmol, 1.0 equiv.) were dissolved in dichloromethane 25 mL. To the solution was added anhydrous $MgSO_4$ and the reaction mixture was allowed to stir at room temperature for 4 hours. Upon completion, the reaction mixture was filtered and the resulting filtrate was evaporated to dryness *in vacuo* to afford a pale yellow solid. (6.07 g, 94%), m.p. (EtOH) = 60-63°C (lit. 62-63°C)[51], ^{1}H NMR ($CDCl_3$, 400MHz); δ = 8.4 (1H, s, C*H*N), 8.3 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.9 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.1 (1H, ddt, *J* = 17.3, 10.3, 5.7 Hz, CH_2CHCH_2), 5.3 (1H, d, *J* = 17.3 Hz, CH=CH_aH$_b$), 5.2 (1H, d, *J* = 10.3 Hz, CH=CH$_a$$H_b$), 4.3 (2H, d, *J* = 5.7 Hz, NCH_2CH) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 161.7, 161.3, 129.7, 129.2, 115.8, 114.0, 63.4, 55.3 HRMS (ESI+); m/z calcd for $C_{10}H_{11}N_2O_2$ = 191.0815, found = 191.0826 [M+H] ν (cm^{-1}) (neat); 1650 (C=C), 1650 (C=N), 1512 (N-O)

Spectroscopic data match literature[50]

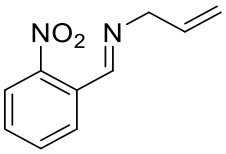
N-allyl-1-phenylmethanimine **81d**[50]



Benzaldehyde (2.00 g, 1.92 mL, 19.0 mmol, 1.0 equiv.) and allylamine (1.08 g, 1.49 mL, 19.0 mmol, 1.0 equiv.) were dissolved in dichloromethane (4 mL) and anhydrous $MgSO_4$ (1.5 g) was added to the solution. The reaction mixture was allowed to stir at room temperature for 4h. After 4h the reaction mixture was filtered and the $MgSO_4$ washed with dichloromethane. The resulting filtrate was evaporated to dryness *in vacuo* to afford a pale green oil. (2.40 g, 86%). ^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.3 (s, 1H, C*H*N), 7.8 – 7.7 (2H, m, Ar*H*), 7.5 – 7.4 (3H, m, Ar*H*), 6.1 (1H, ddt, *J* = 17.2, 10.3, 5.7 Hz, CH_2CHCH_2), 5.3 (d, *J* = 17.2 Hz, 1H, CH=CH_aH_b), 5.2 (d, *J* = 10.3 Hz, 1H, CH=CH_aH_b), 4.3 (2H, d, *J* = 5.7 Hz, NCH_2CH) ^{13}C NMR ($CDCl_3$, 100MHz) δ = 161.9, 136.2, 135.9, 130.7, 128.6, 116.1, 63.6, 53.5 HRMS (ESI+); m/z calcd for $C_{10}H_{12}N$ = 146.0964, found = 146.0977 [M+H] ν (cm^{-1}) (neat); 1650 (C=N), 1519 (C=C)

The spectroscopic data match those in the literature.[49]

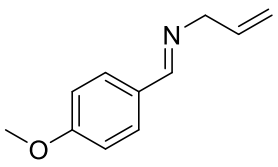
N-allyl-1-(2-nitrophenyl)methanimine **81c**[50]



2-Nitrobenzaldehyde (1.00 g, 6.62 mmol, 1.0 equiv) was dissolved in dichloromethane (4 mL) to which was added allylamine (0.50 mL, 6.62 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (0.2 g). The reaction mixture was stirred at room temperature for 4 hours, after which, it was filtered and evaporated to dryness *in vacuo* to afford the title compound as an orange oil (1.17 g, 93 %). ^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.7 (1H, s, C*H*N), 8.1 (1H, app d, *J* = 8.0 Hz, Ar*H*), 8.0 (1H, app d, *J* = 8.0 Hz, Ar*H*), 7.7 (1H, app t, *J* = 8.0 Hz, Ar*H*), 7.6 (1H, app t, *J* = 8.0 Hz, Ar*H*), 6.07 (1H, ddt, *J* = 17.2, 10.2, 5.6 Hz, NCH_2CHCH_2), 5.26 (1H, d, *J* = 17.2 Hz, $NCH_2CHCH_aH_b$), 5.19 (1H, d, *J* = 10.2 Hz, $NCH_2CHCH_aH_b$), 4.32 (2H, d, *J* = 5.6 Hz, NCH_2CHCH_2) ^{13}C NMR ($CDCl_3$, 100MHz); 157.7, 148.9, 135.2, 133.5, 131.2, 130.7, 129.7, 124.3, 116.7, 63.5 HRMS (ESI+); m/z calcd for $C_{10}H_{11}N_2O_2$ = 191.0815, found = 191.0835 [M+H], m/z calcd for $C_{10}H_{10}N_2NaO_2$ = 213.0634, found = 213.0609 [M+Na] ν (cm^{-1}) (neat); 1628 (C=N), 1520 (N-O) 1507 (C=C)

Spectroscopic data match literature[50]

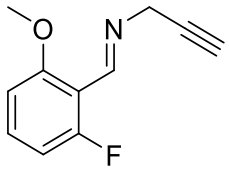
N-allyl-1-(4-methoxyphenyl)methanimine **81b**[50]



4-Methoxybenzaldehyde (4.5 mL, 36.7 mmol, 1.0 equiv) was dissolved in dichloromethane (25 mL) to which was added allylamine (2.75 mL, 36.7 mmol, 1.0 equiv), and anhydrous $MgSO_4$ (2.25 g). The reaction mixture was allowed to stir at room temperature for 4 hours, following which, the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as an orange oil (6.07 g, 94%). ^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.2 (1H, s, C*H*N), 7.7 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.9 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.07 (1H, ddt, *J* = 17.2, 10.1, 5.7 Hz, C*H*=CH_2), 5.2 (1H, d, *J* = 17.2 Hz, CH=CH_aH$_b$), 5.1 (1H, d, *J* = 10.1 Hz, CH=CH$_a$$H_b$), 4.2 (2H, d, *J* = 5.7 Hz, NCH_2CH), 3.8 (3H, s, OCH_3) ^{13}C NMR ($CDCl_3$, 100MHz); δ = 161.7, 161.3, 136.2, 129.7, 129.2, 115.9, 114.0, 63.4, 55.3 HRMS (ESI+); m/z calcd for $C_{11}H_{14}NO$ = 176.1070, found = 176.1082 [M+H], m/z calcd for $C_{11}H_{13}NNaO$ = 198.0889, found = 198.0892 [M+Na] ν (cm^{-1}) (neat); 1648 (C=N), 1577 (C=C), 1105 (C-O)

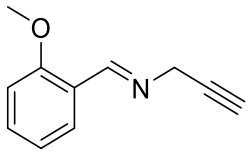
Spectroscopic data match literature[58]

1-(2-fluoro-6-methoxyphenyl)-N-(prop-2-yn-1-yl)methanimine **85c**[50]



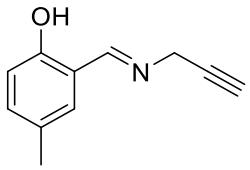
To a 50 mL round bottom flask was added; 2-fluoro-6-methoxybenzaldehyde (500 mg, 3.24 mmol, 1 equiv.), propargylamine (0.21 mL, 3.24 mmol, 1 equiv.) and anhydrous $MgSO_4$ (80 mg, 0.67 mmol, 0.2 equiv.). Dichloromethane (2mL) was then added and the reaction mixture was stirred under argon for 3 hours. Upon completion, the reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo* to afford the title compound as an orange oil (608 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.9 (1H, s, C*H*N), 7.4 – 7.3 (1H, m, Ar*H*), 6.8 – 6.7 (2H, m, Ar*H*), 4.6 (2H, s, NCH_2), 3.9 (3H, s, OCH_3), 2.6 (1H, s, CC*H*) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 163.1, 160.6, 160.0, 159.9, 156.1, 131.8, 106.6, 78.8, 76.0, 56.2, 48.4 HRMS (ESI+); m/z calcd for $C_{11}H_{11}FNO$ = 192.0830, found = 192.0822 [M+H] ν (cm^{-1}) (neat); 1640 (C=N), 1076 (C-O)

1-(2-methoxyphenyl)-N-(prop-2-yn-1-yl)methanimine **85a**[50]



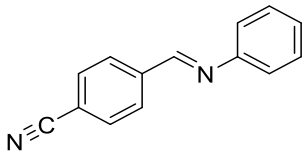
2-Methoxybenzaldehyde (500 mg, 3.67 mmol, 1.0 equiv) was dissolved in dichloromethane (5 mL) to which was added propargylamine (0.24 mL, 3.67 mmol, 1.0 equiv), and anhydrous $MgSO_4$ (80 mg). The reaction mixture was allowed to stir at room temperature for 4 hours, following which, the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as an orange oil (633 mg, 92%). ^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.6 (1H, s, CC*H*N), 7.4 – 7.3 (3H, m, Ar*H*), 7.0 (1H, d, *J* = 7.8 Hz, Ar*H*), 4.5 (2H, s, NCH_2), 3.8 (3H, s, OCH_3), 2.6 (1H, s, CH_2CC*H*) ^{13}C NMR ($CDCl_3$) (100 MHz); 162.4, 137.2, 129.6, 123.6, 121.7, 117.9, 111.6, 79.0, 75.7, 55.4, 47.1 δ = HRMS (ESI+); m/z calcd for $C_{11}H_{12}NO$ = 174.0924, found = 174.0927 [M+H] ν (cm^{-1}) (neat); 1681 (C=N), 1081 (C-O)

4-methyl-2-((prop-2-yn-1-ylimino)methyl)phenol **85b**[50]



2-Hydroxy-5-methylbenzaldehyde (200 mg, 1.47 mmol, 1.0 equiv.) was dissolved in dichloromethane (2 mL). Propargylamine (0.10 mL, 1.47 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (32 mg) were subsequently added and the reaction mixture was allowed to stir at room temperature for 4 hours. Upon completion, the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as an orange oil (227 mg, 89%) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 12.7 (1H, s, O*H*), 8.6 (1H, s, CC*H*N), 7.2 – 7.1 (2H, m, Ar*H*), 6.9 (1H, m, Ar*H*), 4.5 (2H, s, NCH_2), 2.6 (1H, s, CH_2CC*H*), 2.3 (3H, s, CH_3) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 165.8, 158.4, 138.0, 133.4, 131.8, 127.8, 118.4, 117.3, 76.5, 45.5, 20.3 HRMS (ESI+) m/z calcd for $C_{11}H_{12}NO$ = 174.0924, found = 174.0933 [M+H], m/z calcd for $C_{11}H_{11}NNaO$ = 196.0743, found = 196.0739 [M+Na] ν (cm^{-1}) (neat); 1683 (C=N), 1365 (O-H)

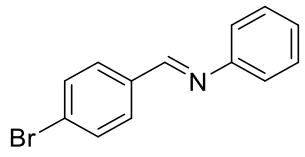
4-((phenylimino)methyl)benzonitrile **90a**[50]



4-Formylbenzonitrile (359 mg, 2.74 mmol, 1.0 equiv) was dissolved in dichloromethane (2 mL). Aniline (0.25 mL, 2.74 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (66 mg) were added to the reaction mixture which was allowed to stir at room temperature for 4 hours. Upon completion the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as a yellow oil (509 mg, 90%) ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.5 (1H, s, CC*H*N), 8.0 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.8 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.4 (2H, app t, *J* = 7.7 Hz, Ar*H*), 7.4 – 7.2 (3H, m, Ar*H*) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 157.9, 151.0, 140.0, 132.6, 129.3, 129.1, 127.0, 121.0, 118.5, 114.4 HRMS (ESI+); m/z calcd for $C_{14}H_{11}N_2$ = 207.0922, found = 207.0923 [M+H] ν (cm^{-1}) (neat); 2227 (C≡N), 1643 (C=N)

Spectroscopic data match literature[59]

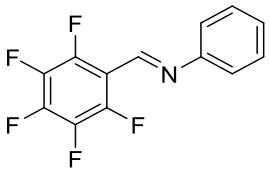
1-(4-bromophenyl)-N-phenylmethanimine **90b**[50]



4-Bromobenzaldehyde (507 mg, 2.74 mmol, 1.0 equiv) was dissolved in dichloromethane (2 mL). Aniline (0.25 mL, 2.74 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (66 mg) were added to the reaction mixture which was allowed to stir at room temperature for 4 hours. Upon completion the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as a colourless oil (627 mg, 88%) ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.4 (1H, s, C*H*N), 7.8 (1H, app d, *J* = 8.5 Hz, Ar*H*), 7.6 (1H, app d, *J* = 8.5 Hz, Ar*H*), 7.4 (1H, app t, *J* = 8.5 Hz, Ar*H*), 7.3 – 7.2 (1H, m, Ar*H*) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 158.9, 151.7, 135.2, 132.1, 130.2, 129.2, 126.3, 125.9, 120.9 HRMS (ESI+); m/z calcd for $C_{13}H_{11}{}^{81}BrN$ = 262.0054, found = 262.0069 [M+H] m/z calcd for $C_{13}H_{11}{}^{79}BrN$ = 260.0075, found = 260.0066 [M+H] ν (cm^{-1}) (neat); 1681 (C=N), 536 (C-Br)

Spectroscopic data match literature[60]

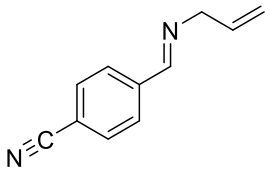
1-(perfluorophenyl)-N-phenylmethanimine **90c**[50]



2,3,4,5,6-Pentafluorobenzaldehyde (536 mg, 2.74 mmol, 1.0 equiv) was dissolved in dichloromethane (2 mL). Aniline (0.25 mL, 2.74 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (66 mg) were added to the reaction mixture which was allowed to stir at room temperature for 4 hours. Upon completion the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as a pale yellow solid (676 mg, 91%) m.p. (EtOH) = 115-117°C, (lit. = 117°C)[61], ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.6 (1H, s, CC*H*N), 7.5 – 7.4 (2H, m, Ar*H*), 7.4 – 7.3 (1H, m, Ar*H*), 7.3 – 7.2 (2H, m, Ar*H*) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 151.3, 148.4, 148.4, 148.4, 148.4, 147.5, 129.3, 127.3, 120.8 HRMS (ESI+) m/z calcd for $C_{13}H_7F_5N$ = 272.0499, found = 272.0500 [M+H] ν (cm^{-1}) (neat); 1683 (C=N)

Spectroscopic data match literature[60]

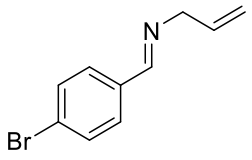
4-((allylimino)methyl)benzonitrile **81e**[50]



4-formylbenzonitrile (250 mg, 1.91 mmol, 1.0 equiv) was dissolved in dichloromethane (2 mL). Allylamine (0.14 mL, 1.91 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (66 mg) were added to the reaction mixture which was allowed to stir at room temperature for 4 hours. Upon completion the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as a yellow oil (283 mg, 87%) ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.3 (1H, s, C*H*N), 7.9 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.7 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.1 (1H, ddt, *J* = 17.2, 10.3, 5.8 Hz, C*H*=CH_2), 5.2 (1H, d, *J* = 17.2, CH=C$H_a$$H_b$), 5.2 (1H, d, *J* = 10.3 Hz, CH=$CH_a$$H_b$), 4.3 (2H, d, *J* = 5.8 Hz, NCH_2) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 160.0, 140.0, 135.2, 132.4, 128.5, 118.5, 116.6, 113.9, 63.5 HRMS (ESI+) m/z calcd for $C_{11}H_{11}N_2$ = 171.0922, found = 171.0917 [M+H] ν (cm^{-1}) (neat); 2222 (C≡N), 1643 (C=N), 1580 (C=C)

Spectroscopic data match literature[62]

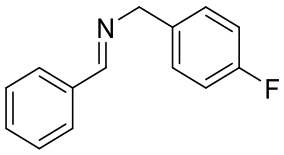
N-allyl-1-(4-bromophenyl)methanimine **81f**[50]



4-bromobenzaldehyde (200 mg, 1.08 mmol, 1.0 equiv) was dissolved in dichloromethane (2 mL). Allylamine (0.08 mL, 1.08 mmol, 1.0 equiv) and anhydrous $MgSO_4$ (66 mg) were added to the reaction mixture which was allowed to stir at room temperature for 4 hours. Upon completion the reaction mixture was filtered and evaporated to dryness *in vacuo* to afford the title compound as a colourless oil (218 mg, 90%) ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.2 (1H, s, CC*H*N), 7.7 – 7.6 (2H, m, Ar*H*), 7.6 – 7.5 (2H, m, Ar*H*), 6.1 (1H, dddd, J=17.1, 10.2, 5.7, 1.6 Hz), 5.2 (2H, d, *J* = 17.1 Hz, CHCH_aH$_b$), 5.2 (2H, d, *J* = 10.2 Hz, CHCH$_a$$H_b$), 4.3 (2H, m, NC$H_2$) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 160.7, 135.6, 135.1, 131.8, 129.6, 125.1, 116.3, 63.5 HRMS (ESI+); m/z calcd for $C_{10}H_{11}{}^{79}BrN$ = 224.0075, found = 224.0078 [M+H] ν (cm^{-1}) (neat); 1647 (C=N), 560 (C-Br)

Spectroscopic data match literature[63]

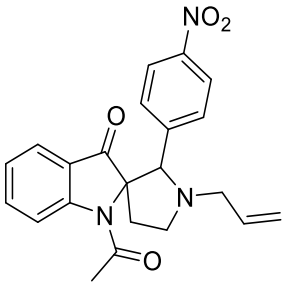
N-(4-fluorobenzyl)-1-phenylmethanimine **93**[50]



4-Fluorobenzylamine (0.27 mL, 2.45 mmol, 1.0 equiv.) was dissolved in dichloromethane (2 mL), to which was added benzaldehyde (0.25 mL, 2.45 mmol, 1.0 equiv.) and anhydrous $MgSO_4$ (66 mg). The reaction mixture was allowed to stir at room temperature for 4h, after which it was filtered and evaporated to dryness *in vacuo* to yield the title compound as a colourless oil (465 mg, 89%) ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 8.4 (1H, s, C*H*N), 7.9 – 7.8 (2H, m, Ar*H*), 7.5 – 7.4 (3H, m, Ar*H*), 7.4 – 7.3 (2H, m, Ar*H*), 7.2 – 7.0 (2H, m, Ar*H*), 4.8 (2H, s, NCH_2) ^{13}C NMR ($CDCl_3$, 100 MHz); 162.1, 136.2, 131.0, 129.6, 129.5, 128.7, 128.4, 115.5, 115.2, 64.3 HRMS (ESI+); m/z calcd for $C_{14}H_{13}FN$ = 214.1032, found = 214.1037 [M+H] ν (cm^{-1}) (neat); 1643 (C=N)

4.2.3 MgI_2-catalysed Ring Expansions of Spirocyclopropane 75

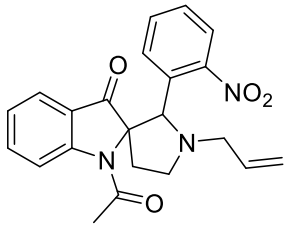
1-acetyl-1'-allyl-2'-(4-nitrophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **82a**[36]



1'-acetylspiro[cyclopropane-1,2'-indolin]-3'-one **74** (200 mg, 0.99 mmol, 1.0 equiv.), *N*-allyl-1-(4-nitrophenyl)methanimine **81a** (210 mg, 1.09 mmol, 1.1 equiv.) and MgI_2 (276 mg, 0.994 mmol, 1.0 equiv.) were charged into a pressure tube which was sealed and purged with argon. Dry THF (1.5 mL) was added and the tube was placed into a pre heated oil bath at 80°C where it was allowed to stir for 16 hours. Upon cooling, the reaction mixture was diluted with diethyl ether and saturated aqueous $NaHCO_3$. The organic washings were collected and washed with water and brine. The resulting organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The product was purified by flash column chromatography (silica gel, 5:1 pentane:EtOAc). This yielded the title compound as a crystalline yellow solid (237 mg, 61%, 5:1 dr[†]) m.p. (EtOH) = 149°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.9 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.6 – 7.4 (2H, m, Ar*H*), 7.3 – 7.2 (3H, m, Ar*H*), 7.0 (1H, app t, *J* = 8.3 Hz, Ar*H*), 6.0 (1H, dddd, *J* = 17.1, 10.1, 8.5, 4.8 Hz, C*H*=CH_2), 5.21 – 5.10 (2H, m, CH=CH_2), 4.54 (1H, s, CC*H*N), 3.6 – 3.4 (1H, m, $CCH_2CH_aH_bN$), 3.27 (1H, dd, *J* = 13.8, 4.8 Hz, $NCH_aH_bCH=CH_2$), 3.2 – 3.1 (1H, m, $CCH_2CH_aH_bN$), 2.79 (1H, dd, *J* = 13.8, 8.5 Hz, $NCH_aH_bCH=CH_2$), 2.69 (3H, s, NCOCH_3), 2.54 – 2.43 (2H, m, CCH_2CH_2N) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 199.1, 168.0, 151.1, 147.4, 144.7, 136.8, 134.4, 129.0, 124.5, 124.0, 123.0, 117.7, 114.9, 79.9, 72.3, 55.7, 52.4, 32.2, 27.4 HRMS (ESI+): m/z calcd for $C_{22}H_{22}N_3O_4$ = 392.1605, found = 392.1599 [M+H] ν (cm^{-1}) (neat); 1712 (C=O), 1676 (C=O), 1589 (C=C)

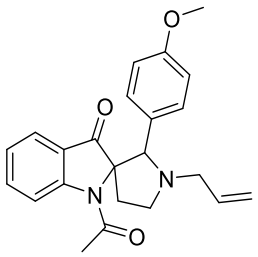
[†]Reported are the peaks of the major diastereomer, dr was established by relative integration of ^{1}H NMR peaks.

1-acetyl-1'-allyl-2'-(2-nitrophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **82c**[36]



1'-acetylspiro[cyclopropane-1,2'-indolin]-3'-one **74** (200 mg, 0.99 mmol, 1.0 equiv.), *N*-allyl-1-(2-nitrophenyl)methanimine **81c** (210 mg, 1.09 mmol, 1.1 equiv.) and MgI_2 (276 mg, 0.994 mmol, 1.0 equiv.) were charged into a pressure tube which was sealed and purged with argon. Dry THF (1.5 mL) was added and the tube was placed into a pre heated oil bath at 80˚C where it was allowed to stir for 16 hours. Upon cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic washings were collected and washed with water (2 x 10 mL) and brine (10 mL). The resulting organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The product was purified by flash column chromatography (silica gel, 5:1 pentane:EtOAc). This yielded the title compound as a pale yellow oil (225 mg, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 8.0 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.6 – 7.4 (3H, m, Ar*H*), 7.34 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.32 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.2 (1H, app t, *J* = 8.0 Hz, Ar*H*), 7.0 (1H, app t, *J* = 8.0 Hz, Ar*H*), 5.9 (1H, dddd, *J* = 17.1, 10.1, 8.0, 4.9 Hz, C*H*=CH_2), 5.2 (1H, d, *J* = 17.1 Hz, CH=C$H_a$$H_b$), 5.1 (1H, d, *J* = 10.1 Hz, CH=C$H_a$$H_b$), 5.07 (1H, s, CC*H*N), 3.5 (1H, app t, *J* = 8.0 Hz, $CCH_2CH_aH_bN$), 3.3 (dt, *J* = 10.1, 8.0 Hz, $CCH_2CH_aH_bN$), 3.2 – 3.1 (1H, dd, *J* = 13.4, 4.9 Hz, $NCH_aH_bCHCH_2$), 2.8 (1H, dd, *J* = 13.4, 8.0 Hz, $NCH_aH_bCHCH_2$), 2.7 (3H, s, NCOCH_3), 2.5 (1H, dt, *J* = 13.4, 10.1 Hz, $CCH_aH_bCH_2N$), 2.4 (1H, dt, *J* = 13.4, 8.0 Hz, $CCH_aH_bCH_2N$) ^{13}C NMR ($CDCl_3$, 100 MHz); 199.4, 168.3, 151.5, 150.7, 136.8, 134.2, 132.23, 132.20, 130.9, 128.3, 126.0, 124.2, 123.5, 121.7, 117.9, 115.6, 79.8, 65.7, 55.7, 52.4, 33.2, 27.5 HRMS (ESI+): m/z calcd for $C_{22}H_{22}N_3O_4$ = 392.1605, found = 392.1625 [M+H]. m/z calcd for $C_{22}H_{21}N_3NaO_4$ = 414.1424, found = 414.1431 [M+Na] ν (cm^{-1}) (neat); 1710 (C=O), 1670 (C=O), 1588 (C=C), 1518 (N-O)

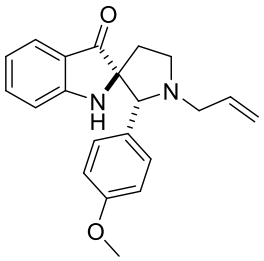
1-acetyl-2'-(4-methoxyphenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **82b**[36]



1'-acetylspiro[cyclopropane-1,2'-indolin]-3'-one **74** (200 mg, 0.99 mmol, 1.0 equiv.), N-allyl-1-(4-methoxyphenyl)methanimine **81b** (192 mg, 1.09 mmol, 1.1 equiv.) and MgI_2 (276 mg, 0.994 mmol, 1.0 equiv.) were charged into a pressure tube which was sealed and purged with argon. Dry THF (1.5 mL) was added and the tube was placed into a pre heated oil bath at 80°C where it was allowed to stir for 16 hours. Upon cooling, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$. The organic washings were collected and washed with water (2 x 10 mL) and brine (10 mL). The resulting organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The product was purified by flash column chromatography (silica gel, 5:1 pentane:EtOAc). This yielded the title compound as an orange oil (128 mg, 37%, 5:4 dr). ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.8 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.5 – 7.5 (2H, m, Ar*H*), 7.3 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.2 – 7.1 (1H, app t, *J* = 7.8 Hz, Ar*H*), 7.1 – 6.9 (2H, m, Ar*H*), 6.7 – 6.5 (2H, m, Ar*H*), 6.0 – 5.9 (1H, m, NCH_2CHCH_2), 5.3 – 5.1 (2H, m, NCH_2CHCH_2), 4.3 (1H, s, NC*H*C)*, 3.9 (1H, s, NC*H*C), 3.7 (3H, s, OCH_3), 3.7 (3H, s, OCH_3)*, 3.6 – 3.4 (2H, m, NCH_2CH), 3.4 – 3.3 (1H, m, $NCH_aH_bCH_2$), 3.1 – 3.0 (1H, m, $NCH_aH_bCH_2$), 2.8 – 2.7 (5H, m, NCH_2CH_2, $COCH_3$)*, 2.7 (3H, s, $COCH_3$), 2.6 – 2.3 (2H, m, NCH_2CH_2) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 200.0*, 190.8, 170.4*, 167.1, 159.2*, 159.0*, 154.2, 137.4*, 136.2, 134.7, 129.3*, 128.2, 124.4*, 124.0, 123.6*, 123.5, 122.8*, 118.9*, 117.5, 114.3*, 113.5*, 113.3, 78.7*, 57.0*, 55.5, 55.16*, 55.11, 52.7*, 52.1, 33.2*, 31.4, 29.7*, 26.1, 22.7 HRMS (ESI+); m/z calcd for $C_{23}H_{25}N_2O_3$ = 377.1865, found = 377.1885 [M+H] ν (cm^{-1}) (neat); 1772 (C=O), 1711 (C=O), 1604 (C=C), 1102 (C-O)

*Signals of minor diastereomer, dr determined by relative integration of ^{1}H NMR peaks.

1'-allyl-2'-(4-methoxyphenyl)spiro[indoline-2,3'-pyrrolidin]-3-one* **83b**[36]

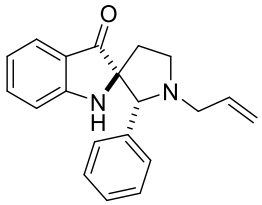


Spiro[cyclopropane-1,2'-indolin]-3'-one **75** (85 mg, 0.53 mmol, 1.0 equiv), *N*-allyl-1-(4-methoxyphenyl) methanimine **81b** (103 mg, 0.59 mmol, 1.1 equiv) and MgI_2 (147 mg, 0.53 mmol, 1.0 equiv) were charged into a pressure tube which was then purged with argon. Dry THF (1 mL) was added and the reaction mixture was heated to 80°C and stirred for 16h. Upon cooling, the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL) saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to give a light brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc) to afford the title compound as a pale yellow solid. (142 mg, 80%) m.p. (EtOH) = 124 - 125°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.5 (1H, app d, *J* = 7.9 Hz, Ar*H*), 7.2 (1H, app d, *J* = 7.9 Hz, Ar*H*), 7.1 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.7 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.6 (1H, app t, *J* = 7.9 Hz, Ar*H*), 6.5 (1H, app d, *J* = 7.9 Hz, Ar*H*), 5.9 (1H, dddd, *J* = 17.5, 10.1, 7.6, 5.0 Hz, NCH_2CHCH_2), 5.2 (1H, d, *J* = 17.5 Hz, CH=CH_aH$_b$), 5.1 (1H, d, *J* = 10.1 Hz, CH=CH$_a$*H$_b$*), 5.0 (1H, s, N*H*), 3.8 (1H, s, NC*H*C), 3.7 (3H, s, OC*H$_3$*), 3.4 (1H, td, *J* = 10.1, 3.5 Hz, NC*H$_a$*H$_b$CH$_2$), 3.4 (1H, dd, *J* = 13.8, 5.0 Hz, NC*H$_a$*H$_b$CH=CH$_2$), 2.7 (1H, dd, *J* = 13.8, 7.6 Hz, NCH$_a$*H$_b$*CH=CH$_2$), 2.6 (1H, dt, *J* = 10.1, 8.0 Hz, NCH$_a$*H$_b$*CH$_2$), 2.5 (1H, ddd *J* = 13.8, 10.1, 3.5 Hz, NCH$_2$C*H$_a$*H$_b$), 2.1 (1H, dt, *J* = 13.8, 7.6 Hz, NCH$_2$CH$_a$*H$_b$*) ^{13}C NMR ($CDCl_3$, 100 MHz); 202.9, 160.5, 159.0, 136.9, 135.3, 128.8, 127.8, 124.1, 120.9, 118.4, 117.0, 113.4, 111.7, 76.5, 75.5, 56.5, 55.1, 51.4, 34.5 HRMS (ESI+); m/z calcd for $C_{21}H_{23}N_2O_2$ = 335.1765, found = 335.1776 [M+H], m/z calcd for $C_{21}H_{22}N_2NaO_2$ = 357.1573, found = 357.1558 [M+Na] ν (cm^{-1}) (neat); 3509 (N-H), 1643 (C=O), 1582 (C=C), 1095 (C-O)

Originally synthesised by Daniel Matthieu-Raven

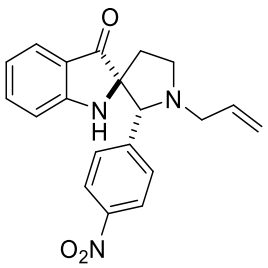
*Relative stereochemistry assigned by NOESY

1'-allyl-2'-phenylspiro[indoline-2,3'-pyrrolidin]-3-one **83c**[36]



Spiro[cyclopropane-1,2'-indolin]-3'-one **75** (85 mg, 0.53 mmol, 1.0 equiv), N-allyl-1-phenylmethanimine **81d** (87 mg, 0.59 mmol, 1.1 equiv) and MgI_2 (147 mg, 0.53 mmol, 1.0 equiv) were charged into a pressure tube which was then purged with argon. Dry THF (1 mL) was added and the reaction mixture was heated to 80°C and stirred for 16h. Upon cooling, the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL) saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to give a green solid. The crude product was purified by flash column chromatography, (silica gel, 4:1 pentane:EtOAc) to afford the title compound as a pale green solid. (109 mg, 63%) m.p. (EtOH) = 150°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.5 (1H, app d, *J* = 7.9 Hz, Ar*H*), 7.2 – 7.1 (6H, m, Ar*H*), 6.6 (1H, app t, *J* = 7.9 Hz, Ar*H*), 6.4 (1H, app d, *J* = 7.9 Hz, Ar*H*), 5.9 (1H, dddd, *J* = 17.3, 10.2, 7.7, 4.9 Hz, C*H*=CH_2), 5.2 (1H, d, *J* = 17.3 Hz, CH=CH_aH$_b$), 5.1 (1H, d, *J* = 10.2 Hz, CH=CH_a*H$_b$*), 5.0 (1H, s, N*H*), 3.9 (1H, s, CC*H*N), 3.5 (1H, td, *J* = 9.5, 3.6 Hz, $CCH_2CH_aH_b$N), 3.4 (1H, dd, *J* = 13.8, 4.9 Hz, NCH_aH$_b$CH=CH_2) 2.7 (1H, dd, *J* = 13.8, 7.7 Hz, NCH_a*H$_b$*CH=CH_2), 2.6 (1H, td, *J* = 9.5, 7.7 Hz, CCH_2CH_a*H$_b$*N), 2.5 (1H, ddd, *J* = 13.8, 9.5, 4.9 Hz, CCH_aH$_b$$CH_2$N), 2.1 – 2.0 (1H, m, CCH_a*H$_b$*CH_2N) ^{13}C NMR ($CDCl_3$, 100 MHz); 202.7, 160.5, 136.9, 135.9, 135.3, 128.0, 127.7, 124.1, 120.9, 118.4, 117.0, 111.6, 77.0, 75.5, 56.6, 51.5, 34.5 HRMS (ESI+); m/z calcd for $C_{20}H_{21}N_2O$ = 305.1659, found = 305.1667 [M+H], m/z calcd for $C_{20}H_{20}N_2NaO$ = 327.1468, found = 327.1475 [M+Na] ν (cm^{-1}) (neat); 3367 (N-H), 1710 (C=O), 1582 (C=C)

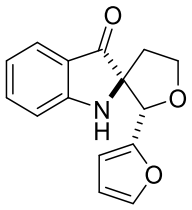
1'-allyl-2'-(4-nitrophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **83a**[36]



Spiro[cyclopropane-1,2'-indolin]-3'-one **75** (85 mg, 0.53 mmol, 1.0 equiv), N-allyl-1-(4-nitrophenyl)methanimine **81a** (112 mg, 0.59 mmol, 1.1 equiv) and MgI_2 (147 mg, 0.53 mmol, 1.0 equiv) were charged into a pressure tube which was then purged with argon. Dry THF (1 mL) was added and the reaction mixture was heated to 80°C and stirred for 16h. Upon cooling, the reaction mixture was diluted with EtOAc and washed with water saturated aqueous $NaHCO_3$ and brine. The organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to give a brown oil. The crude product was purified by flash column chromatography, (silica gel, 4:1 pentane:EtOAc) to afford the title compound as a light brown oil. (139 mg, 74%) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 8.0 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.5 (1H, app d, *J* = 7.4 Hz, Ar*H*), 7.4 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.2 (1H, app t, *J* = 8.3 Hz, Ar*H*), 6.7 (1H, app t, *J* = 7.4 Hz, 1H, Ar*H*), 6.5 (1H, app d, *J* = 7.4 Hz, Ar*H*), 5.9 (1H, dddd, *J* = 17.2, 10.0, 7.4, 4.5 Hz, C*H*=CH_2), 5.2 (1H, d, *J* = 17.2 Hz, CH=C$H_a$$H_b$), 5.1 (1H, d, *J* = 10.0 Hz, CH=$CH_a$$H_b$) 5.0 (1H s, N*H*), 4.0 (1H, s, CC*H*N), 3.5 (1H, td, *J* = 10.0, 4.5 Hz, CCH_2C$H_a$$H_b$N), 3.3 (1H, dd, *J* = 13.8, 4.5 Hz, NC$H_a$$H_b$CH=$CH_2$), 2.8 (1H, dd, *J* = 13.8, 7.4 Hz, $NCH_a$$H_b$CH=$CH_2$), 2.7 (1H, td, *J* = 10.0, 7.4 Hz, $CCH_2CH_a$$H_b$N), 2.5 (1H, ddd, *J* = 13.8, 10.0, 4.5 Hz, CC$H_a$$H_b$$CH_2$N), 2.1 (1H, dt, *J* = 13.8, 7.4 Hz, $CCH_a$$H_b$$CH_2$N) ^{13}C NMR ($CDCl_3$, 100 MHz); 201.7, 160.0, 147.3, 144.3, 137.5, 134.6, 128.7, 124.3, 120.2, 118.8, 117.6, 114.0, 111.5, 75.9, 75.5, 56.5, 51.3, 34.9 HRMS (ESI+); m/z calcd for $C_{20}H_{20}N_3O_3$ = 350.1499, found = 350.1513 [M+H] m/z calcd for $C_{20}H_{19}N_3NaO_3$ = 372.1319, found = 372.1313 [M+Na] ν (cm^{-1}) (neat); 3369 (N-H), 1673 (C=O), 1613 (C=C), 1516 (N-O)

Originally synthesised by Daniel Matthieu-Raven

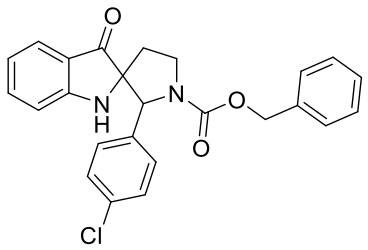
2-(Furan-2-yl)-4,5-dihydro-2*H*-spiro[furan-3,2'-indolin]-3'-one **101**



Spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), 2-furfural **100** (0.05 mL, 0.55 mmol, 1.1 equiv.) and MgI_2 were charged into a pressure tube which was purged with argon. Dry THF 1 mL was added and the reaction mixture was allowed to stir for 16 hours at 80°C. Upon completion, the reaction mixture was diluted with ethyl acetate and washed with water, sat. aq. $NaHCO_3$ and brine. The organic washings were then dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (Silica gel, 3:1 pentane:EtOAc). The product-containing fractions were collected, combined and evaporated to dryness *in vacuo* to afford the title compound as an orange oil (49 mg, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.6 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.38 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.30 – 7.28 (1H, m, CHC*H*O), 6.8 (1H, app t, *J* = 7.6 Hz, Ar*H*), 6.7 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.3 – 6.2 (2H, m, C*H*CHO, C*H*CHCHO), 5.1 (1H, s, N*H*), 5.0 (1H, s, CH_2OCH), 4.4 – 4.20 (2H, m, CH_2CH_2O), 2.7 – 2.6 (1H, m, $CH_aH_bCH_2O$), 2.4 – 2.3 (1H, m, $CH_aH_bCH_2O$). ^{13}C NMR ($CDCl_3$, 100MHz); δ = 200.5, 160.6, 149.5, 142.9, 137.8, 124.5, 120.5, 119.2, 112.2, 110.1, 109.0, 81.3, 75.3, 67.3, 37.9. HRMS (ESI+); m/z calcd for $C_{15}H_{13}NNaO_3$ = 278.0788, found = 278.0784 [M+Na]

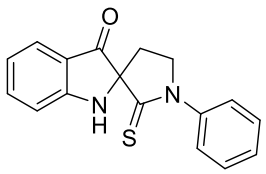
ν (cm^{-1}) (neat); 3328 (N-H), 1679 (C=O)

Benzyl 2'-(4-chlorophenyl)-3-oxospiro[indoline-2,3'-pyrrolidine]-1'-carboxylate **99**[52]



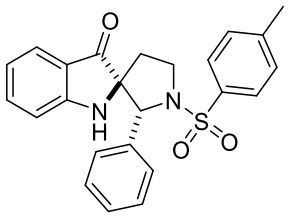
Spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), benzyl ((4-chlorophenyl)(phenylsulfonyl)methyl)carbamate **98** (230 mg, 0.55 mmol, 1.1 equiv.), magnesium iodide (15 mg, 0.05 mmol, 10 mol%) and sodium hydride (60 mg, 2.50 mmol, 5.0 equiv) were charged into a pressure tube, to which was added dry THF (2 mL). The reaction mixture was then allowed to stir at 80°C for 16 hours. Upon cooling the reaction was quenched with glacial acetic acid, then diluted with water and extracted with Et_2O. The combined organic washings were then washed with sat. aq. $NaHCO_3$ and brine, before being dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford a brown solid. The crude product was purified by flash column chromatography (silica gel, 5:1 pentane:EtOAc). The relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a pale brown solid. (53 mg, 32%). ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 7.7 (1H, app d, *J* = 7.9 Hz, Ar*H*), 7.4 – 7.3 (7H, m, Ar*H*), 7.3 (1H, app t, *J* = 7.9 Hz, Ar*H*), 7.3 (1H, app t, *J* = 7.9 Hz, Ar*H*), 6.4 (1H, app d, *J* = 7.9 Hz, Ar*H*), 6.2 – 6.0 (2H, m, Ar*H*), 5.2 – 5.1 (2H, m, CH_2Ph), 5.1 (1H, s, NHCC*H*), 4.8 (1H, s, N*H*), 1.6 – 1.4 (4H, m, NCH_2, NCH$_2$CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz); 198.1, 156.0, 155.7, 136.2, 135.5, 134.6, 129.4, 128.7, 128.6, 128.4, 127.7, 124.4, 122.1, 119.2, 111.8, 71.3, 67.7, 62.2, 52.0, 15.6, 14.5. HRMS (ESI+); m/z calcd for $C_{25}H_{21}ClN_2NaO_3$ = 455.1133, found = 455.1130 [M+Na] ν (cm^{-1}) (neat); 3319 (N-H), 1689 (C=O), 1612 (C=O), 747 (C-Cl)

1'-phenyl-2'-thioxospiro[indoline-2,3'-pyrrolidin]-3-one **104**



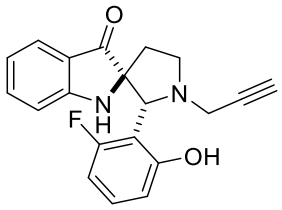
To a pressure tube was added spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), phenyl isothiocyanate **103** (0.065 mL, 0.55 mmol, 1.1 equiv.) and magnesium iodide (15 mg, 0.05 mmol, 10 mol%). After purging with argon, dry THF (1 mL) was added and the reaction mixture was allowed to stir at 80°C for 16 hours. Upon cooling, the contents of the reaction vessel were diluted with water, washed with sat. aq. $NaHCO_3$ and subsequently extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo* to afford a brown solid. The crude product was purified by flash column chromatography (silica gel, 5:1 pentane:EtOAc). The resulting product-containing fractions were combined and evaporated to dryness *in vacuo* to afford a pale yellow solid. (118 mg, 80%) m.p. (EtOH) = 152 - 153°C ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 7.6 (1H, app d, *J* = 7.6 Hz, Ar*H*), 7.5 (1H, t, *J* = 8.4 Hz, Ar*H*), 7.4 – 7.3 (2H, m, Ar*H*), 7.13 (1H, app t, *J* = 7.6 Hz, Ar*H*), 7.0 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.0 – 6.9 (3H, m, Ar*H*), 5.1 (1H, s, N*H*), 3.9 (1H, td, *J* = 10.8, 6.0 Hz, NCH_aH$_b$), 3.2 (1H, ddd, *J* = 10.8, 7.6, 2.2 Hz, NCH$_a$$H_b$), 2.6 (1H, ddd, *J* = 13.0, 6.0, 2.2 Hz, NCH$_2$$H_aH_b$), 2.4 (1H, ddd, *J*=13.0, 10.8, 7.6 Hz, NCH$_2$H$_a$$H_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); $\delta =$ 199.1, 171.0, 162.0, 150.9, 137.5, 129.0, 125.2, 125.0, 120.7, 120.3, 120.0, 114.0, 35.3, 27.3 HRMS (ESI+); m/z calcd for $C_{17}H_{15}N_2OS$ = 295.0905, found = 295.0912 [M+H] ν (cm^{-1}) (neat); 3366 (N-H), 1690 (C=O), 1611 (C=S)

2'-phenyl-1'-tosylspiro[indoline-2,3'-pyrrolidin]-3-one **106**[36]



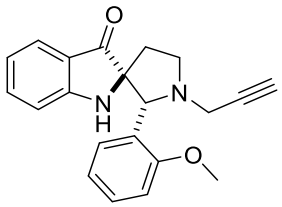
To a pressure tube was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), *N*-benzylidene-4-methylbenzensulfonamide **105** (143 mg, 0.55 mmol, 1.1 equiv.) and magnesium iodide (15 mg, 0.05 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 16 hours. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a thick brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a yellow oil (192 mg, 92%) m.p. (EtOH) = 142 - 143°C ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 7.8 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.8 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.5 (1H, app d, *J* = 7.8 Hz, Ar*H*), 7.4 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.4 – 7.3 (2H, m, Ar*H*), 7.3 – 7.2 (3H, m, Ar*H*), 7.2 – 7.2 (1H, m, Ar*H*), 6.8 (1H, app t, *J* = 7.8 Hz, Ar*H*), 6.5 (1H, d, *J* = 8.3, Ar*H*), 4.9 (1H, s, N*H*), 4.8 (1H, s, CC*H*), 3.9 – 3.8 (2H, m, NCH_2), 2.5 (3H, s, CH_3), 2.0 – 1.9 (2H, m, NCH_2CH_2) ^{13}C NMR ($CDCl_3$, 100 MHz); 200.8, 159.9, 144.0, 137.6, 137.5, 133.9, 129.8, 129.7, 128.4, 128.1, 128.0, 126.7, 126.5, 119.5, 112.1, 74.0, 68.2, 47.3, 34.2, 21.7 HRMS (ESI+); m/z calcd for $C_{24}H_{23}N_2O_3S$ = 419.1429, found = 419.1435 [M+H] ν (cm^{-1}) (neat); 3354 (N-H), 1686 (C=O), 1329 (S=O)

2'-(2-fluoro-6-hydroxyphenyl)-1'-(prop-2-yn-1-yl)spiro[indoline-2,3'-pyrrolidin]-3-one **86c**[36]



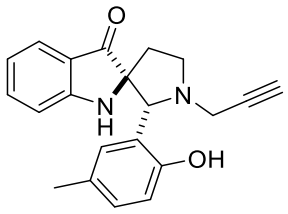
To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), 1-(2-fluoro-6-methoxyphenyl)-N-(prop-2-yn-1-yl)methanimine **85c** (143 mg, 0.55 mmol, 1.1 equiv.) and magnesium iodide (15 mg, 0.05 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a thick brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a yellow solid (138 mg, 82%) m.p. (EtOH) = 141 - 143°C ^{1}H NMR ($CDCl_3$, 400 MHz); $\delta =$ 12.2 – 11.1 (1H, s, O*H*), 7.6 (1H, app d, *J* = 7.6 Hz, Ar*H*), 7.3 – 7.2 (1H, m, Ar*H*), 7.1 – 7.0 (1H, m, Ar*H*), 6.7 (1H, app t, *J* = 7.6 Hz, Ar*H*), 6.6 (1H, app d, *J* = 8.3 Hz, Ar*H*), 6.5 (1H, app d, *J* = 8.3 Hz, Ar*H*), 6.3 (1H, app t, *J* = 8.3 Hz, Ar*H*), 5.0 (1H, s, N*H*), 4.6 (1H, s, NC*H*), 3.6 (1H, dd, *J* = 17.0, 2.5 Hz, NC$H_a$$H_b$CCH), 3.5 (1H, ddd, *J* = 10.3, 8.0, 2.5 Hz, NC$H_a$$H_b$$CH_2$), 3.4 (1H, dd, *J* = 17.0, 2.5 Hz, NC$H_a$$H_b$CCH), 3.1 (1H, ddd, J=10.3, 8.0, 2.5 Hz, NC$H_a$$H_b$$CH_2$), 2.6 (1H, ddd, *J* = 13.5, 8.0, 2.5 Hz, NCH_2C$H_a$$H_b$), 2.4 (1H, s, CC*H*), 2.2 (1H, ddd, *J* = 13.5, 10.3, 8.0 Hz, $NCH_2CH_a$$H_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); 201.8, 160.4, 137.4, 130.3, 130.2, 124.6, 119.2, 119.0, 112.4, 112.4, 111.4, 106.5, 106.3, 76.2, 75.2, 74.5, 68.2, 50.6, 41.3, 35.3 HRMS (ESI+); m/z calcd for $C_{20}H_{18}FN_2O_2$ = 337.1370, found = 337.1359 [M+H] m/z calcd for $C_{20}H_{17}NaFN_2O_2$ = 359.1166, found = 359.1170 [M+Na] ν (cm^{-1}) (neat); 3275 (N-H), 1614 (C=O), 1327 (O-H)

2'-(2-methoxyphenyl)-1'-(prop-2-yn-1-yl)spiro[indoline-2,3'-pyrrolidin]-3-one **86a**[36]



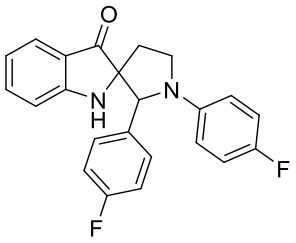
To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), 1-(2-methoxyphenyl)-N-(prop-2-yn-1-yl)methanimine **85a** (96 mg, 0.55 mmol, 1.1 equiv.) and magnesium iodide (15 mg, 0.05 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford an orange oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as an orange solid (143 mg, 86%) m.p. (EtOH) = 138 - 139°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.6 (1H, d, *J* = 7.8 Hz), 7.5 (1H, app d, *J* = 7.8 Hz), 7.2 (1H, app t, *J* = 8.3 Hz Ar*H*), 7.2 (1H, app t, *J* = 7.8 Hz, Ar*H*), 7.0 (1H, app t, *J* = 7.8 Hz, Ar*H*), 6.7 (1H, app t, *J* = 8.3 Hz, Ar*H*), 6.6 (1H, app d, *J* = 8.3 Hz, Ar*H*), 6.4 (1H, app d, *J* = 8.3 Hz, Ar*H*), 4.4 (1H, s, N*H*), 4.3 (1H, s, NC*H*), 3.6 (1H, dd, *J* = 16.9, 2.5 Hz, NCH_aH$_b$CCH), 3.4 (1H, ddd, *J* = 10.3, 9.0, 2.5 Hz, NCH_aH$_b$CH$_2$), 3.3 (2H, dd, *J* = 16.9, 2.5 Hz, NCH$_a$$H_b$CCH), 3.2 (3H, s, OC$H_3$), 3.0 (1H, ddd, *J* = 10.3, 9.0, 8.0 Hz, NCH$_a$$H_bCH_2$), 2.4 (1H, ddd, *J* = 13.1, 9.0, 2.5 Hz), 2.2 – 2.0 (1H, m) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 203.6, 160.1, 157.8, 136.3, 128.4, 127.3, 124.7, 123.9, 120.8, 120.3, 118.3, 111.3, 109.8, 79.0, 74.2, 73.2, 68.8, 54.1, 51.3, 41.6, 35.2 HRMS (ESI+) m/z calcd for $C_{21}H_{19}N_2O_2$ = 333.1598, found = 333.1627 [M+H] ν (cm^{-1}) (neat); 3332 (N-H), 1721 (C=O), 1100 (C-O)

2'-(2-hydroxy-5-methylphenyl)-1'-(prop-2-yn-1-yl)spiro[indoline-2,3'-pyrrolidin]-3-one **86b**[36]



To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), 4-methyl-2-((prop-2-yn-1-ylimino)methyl)phenol **85b** (96 mg, 0.55 mmol, 1.1 equiv.) and magnesium iodide (15 mg, 0.05 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford an orange oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as an orange solid (123 mg, 74%) m.p. (EtOH) = 131 - 133°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 10.8 (1H, s, O*H*), 7.5 (1H, app d, *J* = 7.8 Hz, Ar*H*), 7.3 (1H, app t, *J* = 8.3 Hz, Ar*H*), 6.9 (1H, app d, *J* = 8.3 Hz, Ar*H*), 6.8 – 6.7 (2H, m, Ar*H*), 6.5 (1H, app d, *J* = 8.3 Hz, Ar*H*), 6.5 – 6.4 (1H, m, Ar*H*), 5.4 (1H, s, N*H*), 4.1 (1H, s, NC*H*), 3.6 (1H, dd, *J* = 17.1, 2.5 Hz, NCH_aH$_b$CCH), 3.4 (1H, ddd, *J* = 9.1, 8.2, 2.5 Hz, NCH_aH$_b$CH$_2$), 3.3 (1H, dd, *J* = 17.1, 2.5 Hz, NCH$_a$$H_b$CCH), 3.2 – 3.0 (1H, dt, *J* = 9.1, 8.2 Hz, NCH$_a$$H_bCH_2$), 2.5 (1H, ddd, *J* = 13.5, 9.1, 2.5 Hz, NCH$_2$CH_aH$_b$), 2.4 (1H, s, CH$_2$CC*H*), 2.2 (1H, ddd, *J* = 13.5, 9.1, 8.2 Hz, NCH$_2$CH$_a$$H_b$), 2.0 (3H, s, C$H_3$) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 202.3, 160.9, 154.8, 137.4, 130.2, 129.8, 129.0, 124.3, 119.5, 118.6, 118.0, 116.4, 111.6, 76.5, 75.7, 75.5, 74.9, 50.3, 41.0, 35.2, 20.2 HRMS (ESI+) m/z calcd for $C_{21}H_{21}N_2O_2$ = 333.1614, found = 333.1621, [M+H] m/z calcd for $C_{21}H_{20}NaN_2O_2$ = 355.1417, found = 355.1428 [M+Na] ν (cm^{-1}) (neat); 3288 (N-H), 1683 (C=O), 1323 (O-H)

1',2'-bis(4-fluorophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **88**[36]

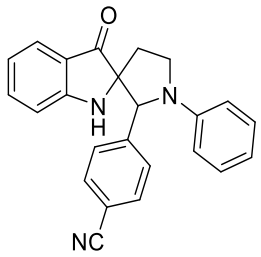


To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (80 mg, 0.50 mmol, 1.0 equiv.), N-(4-Fluorobenzylidene)-4-fluoroaniline **87** (120 mg, 0.55 mmol, 1.1 equiv.) and magnesium iodide (15 mg, 0.05 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford an orange oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a yellow solid (150 mg, 80%, 1:1 dr) m.p. (EtOH) = 130°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.6 (1H, app d, *J* = 8.3 Hz, Ar*H*), 7.5 (1H, app d, *J* = 8.3 Hz, Ar*H*), 7.5 (1H, app t, *J* = 8.3 Hz, Ar*H*), 7.4 (1H, app t, *J* = 8.3 Hz, Ar*H*), 7.2 – 7.1 (2H, m, Ar*H*), 7.0 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.0 – 6.9 (4H, m, Ar*H*), 6.9 – 6.8 (7H, m, Ar*H*), 6.7 – 6.6 (1H, m, Ar*H*), 6.5 – 6.4 (4H, m, Ar*H*), 5.1 (1H, s, N*H*), 4.7 (1H, s, NC*H*), 4.7 (1H, s, NC*H*)*, 4.3 (1H, s, N*H*)*, 4.2 - 4.1 (1H, m, NCH_aH$_b$), 4.0 – 3.9 (1H, m, NCH_aH$_b$)*, 3.9 (1H, dt, *J* = 8.8, 7.5 Hz, $NCH_2CH_aH_b$)*, 3.7 (1H, td, *J* = 8.8, 7.5 Hz, NCH_aH$_b$), 2.6 (1H, dt, *J* = 12.8, 8.8 Hz, $NCH_2H_aH_b$), 2.4 (1H, ddd, *J* = 12.8, 7.5, 5.1 Hz, $NCH_2H_aH_b$)*, 2.2 (1H, dt, *J* = 12.8, 7.5 Hz, $NCH_2CH_aH_b$)*, 2.2 – 2.1 (1H, m, $NCH_2CH_aH_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 201.9*, 197.9, 163.6*, 163.5, 161.1*, 159.9, 159.4*, 157.0, 156.7*, 154.6, 154.3, 143.6*, 142.6, 137.5*, 137.3, 134.2*, 133.0, 128.7*, 128.6, 128.44*, 128.42, 124.8*, 124.7, 121.6*, 120.0, 119.5*, 119.3, 115.8*, 115.7, 115.5*, 115.4, 115.3*, 115.2, 114.4*, 114.3, 113.2*, 112.4*, 111.9, 76.0*,

74.0, 72.3*, 67.6, 48.1*, 47.7, 33.0*, 32.6 ^{19}F NMR ($CDCl_3$, 376 MHz); δ = -113.9 – -114.1 (m), -127.6 – -128.6 (m) HRMS (ESI+); m/z calcd for $C_{23}H_{19}F_2N_2O$ = 377.1460, found = 377.1452 [M+H], m/z calcd for $C_{23}H_{18}NaF_2N_2O$ = 399.1279, found = 399.1278 [M+Na] ν (cm^{-1}) (neat); 3333 (N-H), 1679 (C=O)

*Signals observed for alternate diastereomer, dr was calculated by relative integration of ^{1}H NMR peaks.

4-(3-oxo-1'-phenylspiro[indoline-2,3'-pyrrolidin]-2'-yl)benzonitrile **91a**[36]

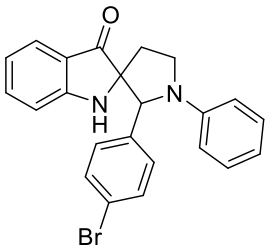


To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (50 mg, 0.31 mmol, 1.0 equiv.), 4-((phenylimino)methyl)benzonitrile **90a** (72 mg, 0.35 mmol, 1.1 equiv.) and magnesium iodide (12 mg, 0.03 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 1 hour under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as an orange oil (89 mg, 79%, 1:1 dr) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.6 – 7.5 (6H, m, Ar*H*), 7.5 – 7.4 (2H, m, Ar*H*), 7.3 – 7.2 (2H, m, Ar*H*), 7.2 – 7.1 (6H, m, Ar*H*), 6.9 – 6.8 (3H, m, Ar*H*), 6.8 – 6.7 (2H, m, Ar*H*), 6.6 (1H, d, *J* = 8.2 Hz, Ar*H*), 6.5 (4H, app t, *J* = 8.2 Hz, Ar*H*), 5.2 (1H, s, N*H*), 4.9 (1H, s, NC*H*), 4.8 (1H, s, NC*H*), 4.4 (1H, s, N*H*), 4.1 (1H, ddd, *J* = 9.5, 8.4, 2.8 Hz, NCH_aH$_b$), 4.0 (1H, ddd, *J* = 9.5, 7.5, 6.2 Hz, NCH_aH$_b$)*, 3.9 (1H, ddd, *J* = 9.5, 7.5, 6.2 Hz, NCH$_a$$H_b$)*, 3.8 (1H, td, *J* = 9.5, 7.5 Hz, NCH$_a$$H_b$), 2.6 (1H, ddd, *J* = 12.6, 9.5, 8.4 Hz, NCH$_2$$H_aH_b$), 2.5 (1H, ddd, *J* = 12.6, 7.5, 6.2 Hz, NCH$_2$CH_aH$_b$)*, 2.2 – 2.2 (1H, m, NCH$_2$CH$_a$$H_b$)*, 2.1 (1H, ddd, *J* = 12.6, 7.5, 2.8 Hz, NCH$_2$CH$_a$$H_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 201.1*, 197.7, 159.7*, 159.4, 157.9*, 146.7, 145.6*, 144.5*, 143.4, 137.7*, 137.6, 132.6*, 132.3, 132.2*, 129.3*, 129.0, 128.0*, 127.7, 124.8*, 124.7, 121.3*, 121.0, 119.7*, 119.5, 118.9*, 118.7, 117.9*, 117.5, 113.9*, 112.7*, 112.5, 112.0, 75.9*, 74.2, 72.1*, 68.0, 48.1*, 47.4, 33.6*, 32.8 HRMS (ESI+) m/z calcd for $C_{24}H_{20}N_3O$ = 366.1601,

found = 366.1602 [M+H] m/z calcd for $C_{24}H_{19}NaN_3O$ = 388.1420, found = 388.1424 [M+Na] ν (cm^{-1}) (neat); 3341.96 (N-H), 2226.82 (C≡N), 1683.45 (C=O)

*Signals observed for alternate diastereomer, dr was calculated by relative integration of ^1H NMR peaks.

2'-(4-bromophenyl)-1'-phenylspiro[indoline-2,3'-pyrrolidin]-3-one **91b**[36]

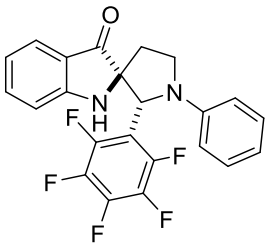


To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (50 mg, 0.31 mmol, 1.0 equiv.), 1-(4-bromophenyl)-N-phenylmethanimine **90b** (91 mg, 0.35 mmol, 1.1 equiv.) and magnesium iodide (12 mg, 0.03 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a light brown oil (100 mg, 77%, 1:1 dr) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.8 – 7.7 (2H, m, Ar*H*), 7.64 – 7.62 (2H, m, Ar*H*), 7.5 (1H, m, Ar*H*), 7.47 – 7.44 (4H, m, Ar*H*), 7.2 – 7.1 (3H, m, Ar*H*), 7.1 – 7.0 (1H, m, Ar*H*), 7.0 – 6.9 (2H, m, Ar*H*), 6.96 – 6.93 (2H, m, Ar*H*), 6.9 – 6.8 (1H, m, Ar*H*), 6.8 – 6.7 (1H, m, Ar*H*), 6.7 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.5 (2H, t, *J* = 8.5 Hz, Ar*H*), 5.0 (1H, s, N*H*) 4.8 (1H, s, NC*H*), 4.7 (1H, s, NC*H*), 4.2 (1H, s, N*H*), 4.2 – 4.1 (1H, m, NCH_aH$_b$), 4.0 – 3.9 (2H, m, NCH_aH$_b$*, NCH$_a$$H_B$*), 3.8 (1H, td, J=9.5, 7.0 Hz, NCH$_a$$H_B$), 2.6 (1H, ddd, J=12.8, 9.5, 8.5 Hz, NCH$_2$CH_aH$_b$), 2.4 (1H, ddd, J=12.8, 7.0, 5.4 Hz, NCH$_2$CH_aH$_b$)*, 2.3 – 2.2 (1H, m, NCH$_2$CH$_a$$H_B$)*, 2.1 – 2.1 (1H, m, NCH$_2$CH$_a$$H_B$) ^{13}C NMR ($CDCl_3$, 100 MHz); 201.6*, 197.5, 159.7*, 159.3, 146.9*, 145.8, 138.0*, 137.4, 137.3*, 136.5, 132.5, 131.8*, 131.5, 131.0*, 129.3, 128.9*, 128.8*, 128.6, 124.84*, 124.81, 121.7, 120.0*, 119.6*, 119.4, 117.4*, 117.2, 113.6, 112.6*, 112.4, 111.9, 77.2*, 76.0, 73.7*, 72.3, 67.1*, 47.5*, 47.2, 33.1*, 32.5 HRMS (ESI+); m/z calcd for $C_{23}H_{20}{}^{79}BrN_2O$ =

419.0759, found = 417.0752 [M+H], m/z calcd for $C_{23}H_{19}Na^{79}BrN_2O$ = 441.0578, found = 441.0582 [M+Na] ν (cm^{-1}) (neat); 3304 (N-H), 1676 (C=O), 691 (C-Br)

*Signals observed for alternate diastereomer, dr was calculated by relative integration of ^1H NMR peaks.

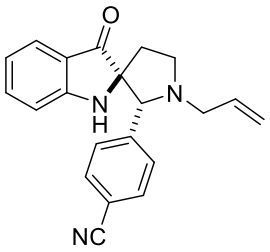
2'-(perfluorophenyl)-1'-phenylspiro[indoline-2,3'-pyrrolidin]-3-one **91c**[36]



To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (50 mg, 0.31 mmol, 1.0 equiv.), 1-(perfluorophenyl)-N-phenylmethanimine **90c** (95 mg, 0.35 mmol, 1.1 equiv.) and magnesium iodide (12 mg, 0.03 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 1 hour under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a light brown oil (112 mg, 84%, 9:1 dr) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.6 (1H, app d, *J* = 8.0 Hz, Ar*H*), 7.5 (1H, app t, *J* = 8.0 Hz, Ar*H*), 7.3 – 7.2 (2H, m, Ar*H*), 6.9 – 6.9 (2H, m, Ar*H*), 6.8 – 6.7 (1H, m, Ar*H*), 6.55 – 6.53 (2H, m, Ar*H*), 5.3 (1H, s, N*H*), 5.1 (1H, s, NC*H*), 4.0 – 3.8 (1H, m, NCH_aH$_b$), 3.7 - 3.6 (1H, m, NCH$_a$$H_b$), 2.7 – 2.6 (1H, m, NCH$_2CH_aH_b$), 2.2 – 2.1 (1H, m, NCH$_2CH_a$$H_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); 197.0, 159.3, 144.8, 137.8, 132.6, 129.6, 129.1, 128.5, 127.4, 127.0, 124.9, 119.8, 117.5, 112.4, 111.8, 75.2, 46.5, 34.3, 14.2 ^{19}F NMR (376 MHz, $CDCl_3$); δ = -141.8 (1F, dd, *J* = 23.2, 7.9 Hz), -146.3 (1F, dd, *J* = 23.2, 7.9 Hz), -154.1 (1F, t, *J* = 23.2 Hz), -161.5 (1F, td, *J* = 23.2, 7.9 Hz), -162.2 (1F, td, *J* = 23.2, 7.9 Hz) HRMS (ESI+); m/z calcd for $C_{23}H_{16}F_5N_2O$ = 431.1183, found = 431.1186 [M+H], m/z calcd for $C_{23}H_{15}F_5N_2NaO$ = 453.1002, found = 453.1019 [M+Na] ν (cm^{-1}) (neat); 3332 (N-H), 1678 (C=O)

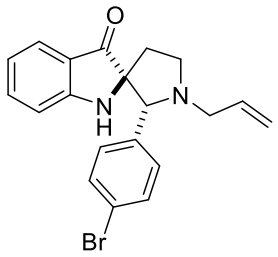
*Major diastereomer signals reported, dr calculated by relative integration of ^{1}H NMR peaks.

1'-allyl-2'-(4-fluorophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **92a**[36]



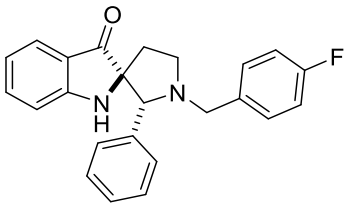
To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (50 mg, 0.31 mmol, 1.0 equiv.), 4-((allylimino)methyl)benzonitrile **81e** (53 mg, 0.35 mmol, 1.1 equiv.) and magnesium iodide (12 mg, 0.03 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a light brown solid (75 mg, 73%) m.p. (EtOH) = 128 - 129°C ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.5 – 7.4 (3H, m, Ar*H*), 7.4 – 7.1 (3H, m, Ar*H*), 6.7 – 6.6 (1H, m, Ar*H*), 6.5 – 6.4 (1H, m, Ar*H*), 5.9 (1H, dddd, J=17.5, 10.2, 7.6, 4.5 Hz, CH_2CH=CH_2), 5.2 (1H, d, *J* = 17.5 Hz, CH=CH_aH$_b$), 5.1 (1H, d, *J* = 10.2 Hz, CH=CH$_a$$H_b$), 4.9 (1H, s, N*H*), 3.9 (1H, s, NC*H*), 3.5 (1H, ddd, *J* = 9.5, 7.6, 4.5 Hz, NCH_aH$_b$CH$_2$), 3.3 (1H, dd, *J* = 13.8, 4.5 Hz, NCH_aH$_b$CH=CH$_2$), 2.8 (1H, dd, *J* = 13.8, 7.6 Hz, NCH$_a$$H_b$CH=CH$_2$), 2.7 (1H, td, *J* = 9.5, 7.6 Hz, NCH$_a$$H_bCH_2$), 2.5 (1H, ddd, *J* = 13.8, 9.5, 4.5 Hz, NCH$_2$CH_aH$_b$), 2.1 (1H, ddd, *J* = 13.8, 8.5, 7.4 Hz, NCH$_2$CH$_a$$H_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 201.7, 159.9, 141.9, 137.5, 134.5, 131.7, 128.5, 124.3, 120.4, 118.8, 117.6, 111.4, 76.3, 75.4, 56.5, 51.3, 34.7 HRMS (ESI+); m/z calcd for $C_{21}H_{20}N_3O$ = 330.1606, found = 330.1630 [M+H] ν (cm^{-1}) (neat); 3324 (N-H), 2231 (C≡N), 1687 (C=O)

1'-allyl-2'-(4-bromophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **92b**[36]



To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (50 mg, 0.31 mmol, 1.0 equiv.), N-allyl-1-(4-bromophenyl)methanimine **81f** (70 mg, 0.35 mmol, 1.1 equiv.) and magnesium iodide (12 mg, 0.03 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a yellow oil (93 mg, 78%) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.5 (1H, app d, *J* = 8.0 Hz, Ar*H*), 7.3 – 7.2 (3H, m, Ar*H*), 7.1 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.7 (1H, app t, *J* = 8.0 Hz, Ar*H*), 6.5 (1H, app d, *J* = 8.0 Hz, Ar*H*), 5.9 (1H, dddd, *J* = 17.6, 10.0, 7.5, 5.0 Hz, NCH_2CH=CH_2), 5.2 (1H, d, *J* = 17.6 Hz, CH_2CH=CH_aH_b), 5.1 (1H, d, *J* = 10.2 Hz, CH_2CH=CH_aH_b), 4.9 (1H, s, N*H*), 3.8 (1H, s, NC*H*), 3.4 (1H, td, *J* = 10.0, 3.8 Hz, NC$H_aH_bCH_2$), 3.3 (1H, dd, *J* = 13.8, 5.0 Hz, NCH_aH_bCH=CH_2), 2.7 (1H, dd, *J* = 13.8, 7.5 Hz, NCH_aH_bCH=CH_2), 2.6 (1H, td, *J* = 10.0, 7.5 Hz, NC$H_aH_bCH_2$), 2.5 (1H, ddd, *J* = 13.8, 10.0, 3.8 Hz, $NCH_2CH_aH_b$), 2.1 (1H, ddd, *J* = 13.6, 10.0, 7.5 Hz, $NCH_2CH_aH_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); 202.3, 160.2, 137.3, 135.2, 134.9, 131.1, 129.5, 124.2, 121.5, 120.6, 118.6, 117.3, 111.6, 76.1, 75.3, 56.4, 51.3, 34.7 HRMS (ESI+); m/z calcd for $C_{20}H_{20}BrN_2O$ = 383.0759, found = 383.0786 [M+H] ν (cm^{-1}) (neat); 3321 (N-H), 1677 (C=O), 688 (C-Br)

1'-(4-fluorobenzyl)-2'-phenylspiro[indoline-2,3'-pyrrolidin]-3-one **94**



To a 10 mL arrowhead flask was added; spiro[cyclopropane-1,2'-indolin]-3'-one **75** (50 mg, 0.31 mmol, 1.0 equiv.), N-allyl-1-(4-bromophenyl)methanimine **93** (70 mg, 0.35 mmol, 1.1 equiv.) and magnesium iodide (12 mg, 0.03 mmol, 10 mol%). The reaction vessel was purged with argon and dry THF (1 mL) was added. The reaction mixture was heated to 80°C and allowed to stir for 3 hours under reflux. Upon completion, the reaction mixture was diluted with water, washed with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford a brown oil. The crude product was purified by flash column chromatography (silica gel, 4:1 pentane:EtOAc), the relevant fractions were combined and evaporated to dryness *in vacuo* to afford the title compound as a yellow oil (102 mg, 88%) ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.53 – 7.51 (1H, m, Ar*H*), 7.4 – 7.3 (4H, m, Ar*H*), 7.2 – 7.1 (4H, m, Ar*H*), 7.1 – 7.0 (2H, m, Ar*H*), 6.7 - 6.6 (1H, m, Ar*H*), 6.5 – 6.4 (1H, m, Ar*H*), 5.0 (1H, s, N*H*), 4.0 – 3.9 (2H, m, NC*H*, NCH_aH$_b$Ar), 3.2 - 3.1 (1H, m, NCH_aH$_b$CH$_2$), 3.2 – 3.1 (1H, m, NCH$_a$$H_b$Ar), 2.6 – 2.5 (1H, m, NCH$_a$$H_bCH_2$), 2.5 – 2.4 (1H, m, NCH$_2CH_aH_b$), 2.1 – 2.0 (1H, m, NCH$_2CH_a$$H_b$) ^{13}C NMR ($CDCl_3$, 100 MHz); δ = 202.7, 160.5, 137.0, 135.8, 134.4, 130.1, 130.0, 128.1, 127.9, 127.8, 124.2, 120.8, 118.5, 115.2, 115.0, 111.6, 75.4, 57.3, 51.4, 34.5 ^{19}F NMR ($CDCl_3$ 376 MHz); δ = -115.8 (t, *J* = 7.4 Hz) HRMS (ESI+); m/z calcd for $C_{24}H_{22}FN_2O$ = 373.1716, found = 373.1731 [M+H] ν (cm^{-1}) (neat); 3320 (N-H), 1674 (C=O)

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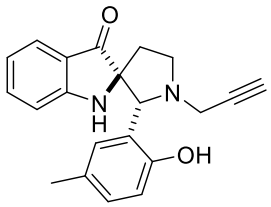
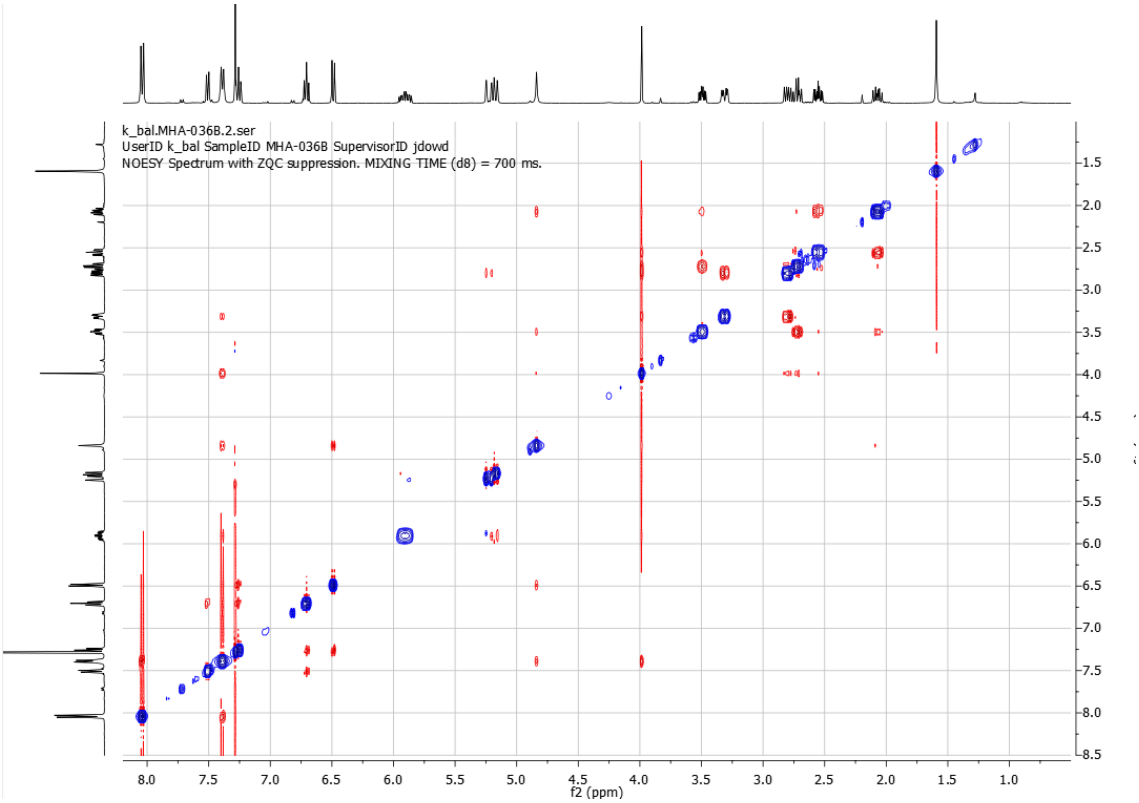
5. Appendix

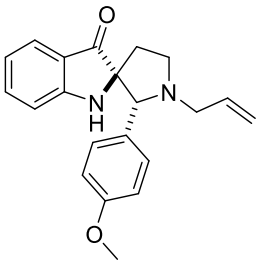
5.1 NOESY NMR Spectra

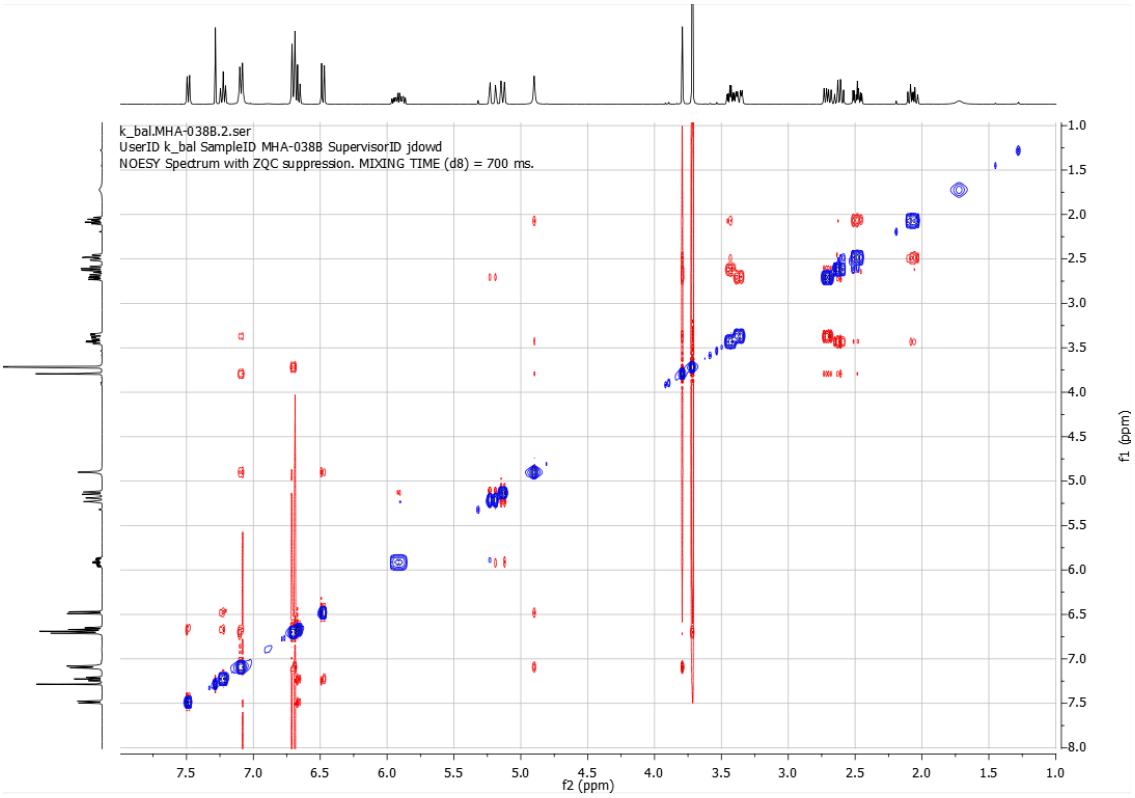
1'-allyl-2'-(4-nitrophenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **83a**



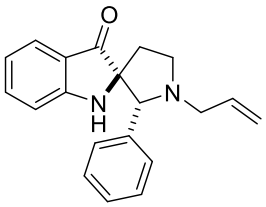


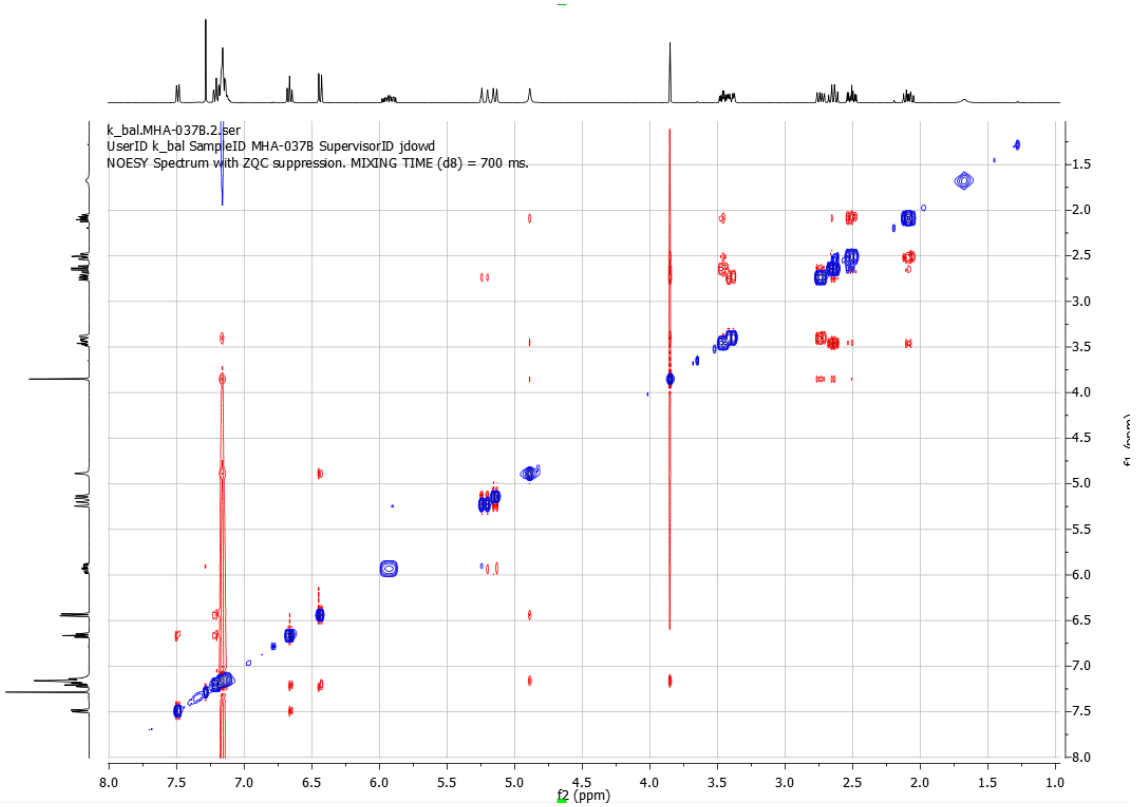
1'-allyl-2'-(4-methoxyphenyl)spiro[indoline-2,3'-pyrrolidin]-3-one **83b**



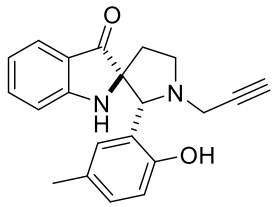


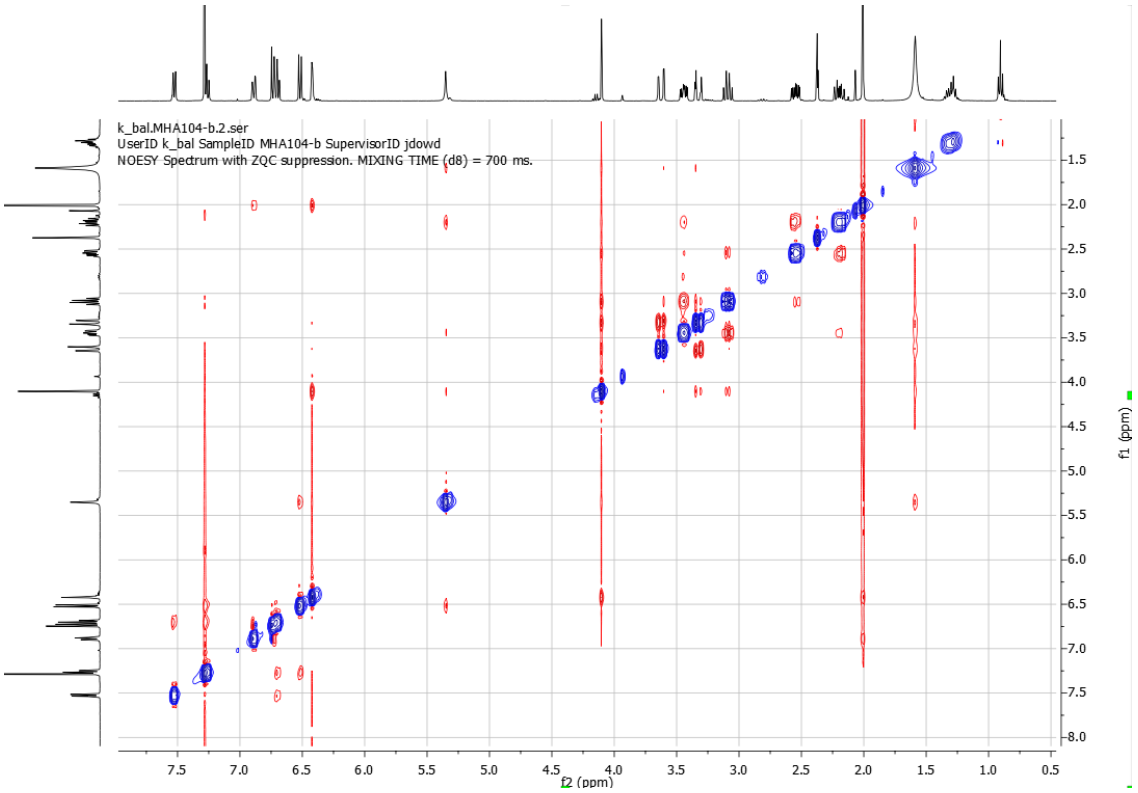
1'-allyl-2'-phenylspiro[indoline-2,3'-pyrrolidin]-3-one **83c**



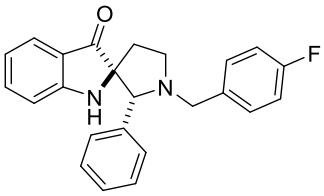


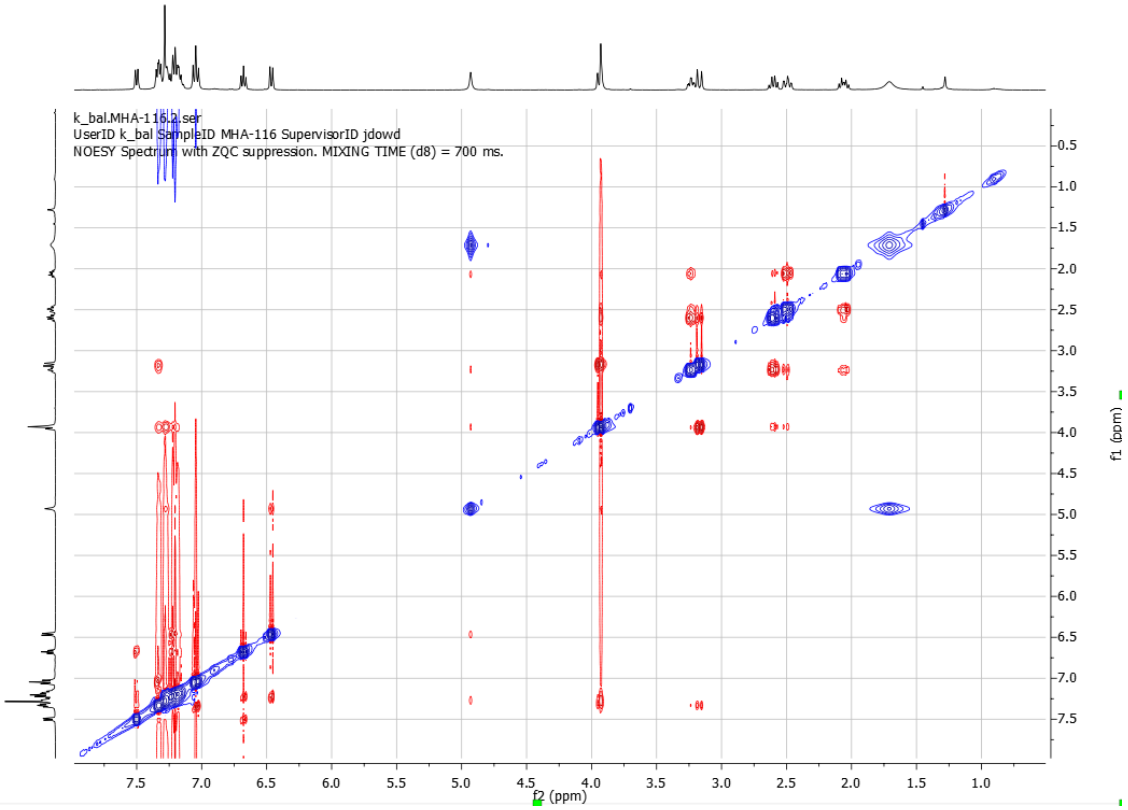
2'-(2-hydroxy-5-methylphenyl)-1'-(prop-2-yn-1-yl)spiro[indoline-2,3'-pyrrolidin]-3-one **86b**





1'-(4-fluorobenzyl)-2'-phenylspiro[indoline-2,3'-pyrrolidin]-3-one **94**





5.2 HPLC Traces

The elution conditions used for all HPLC runs were as follows:

Solvents (A - iso-hexane; B - IPA)

Gradient,

Time = 0 min, 4% B

Time = 5 min, 4% B

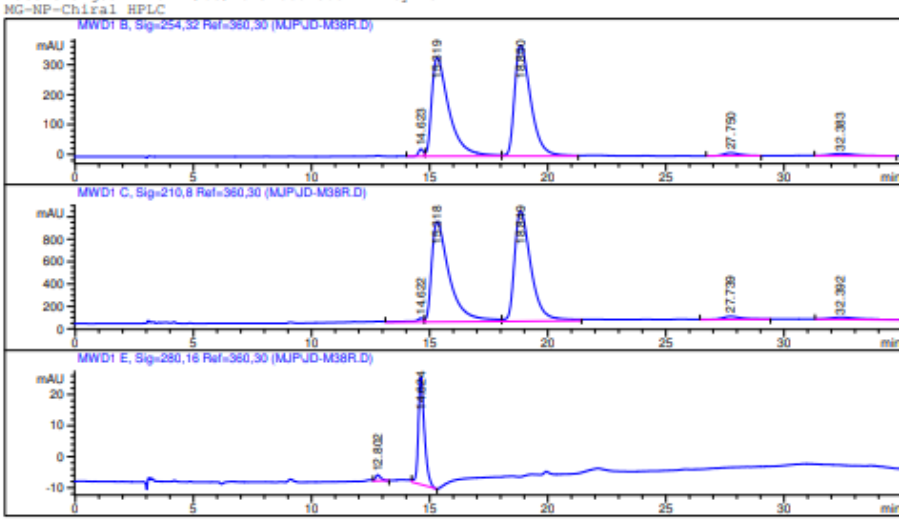
Time = 25 min, 16% B

Time = 35 min, 16% B

Time = 40 min, 4% B

Catalyst **107** (THF)

```
Injection Date  : 14/08/2019 07:28:48 PM
Sample Name     : JD-M38R                          Location : Vial 1
Acq. Operator   : MJP
Acq. Method     : C:\HPCHEM\2\METHODS\MJD-NP-C.M
Last changed    : 14/08/2019 07:28:14 PM by MJP
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MG-NP-C.M
Last changed    : 14/08/2019 06:48:37 PM by MJP
MG-NP-Chiral HPLC
```

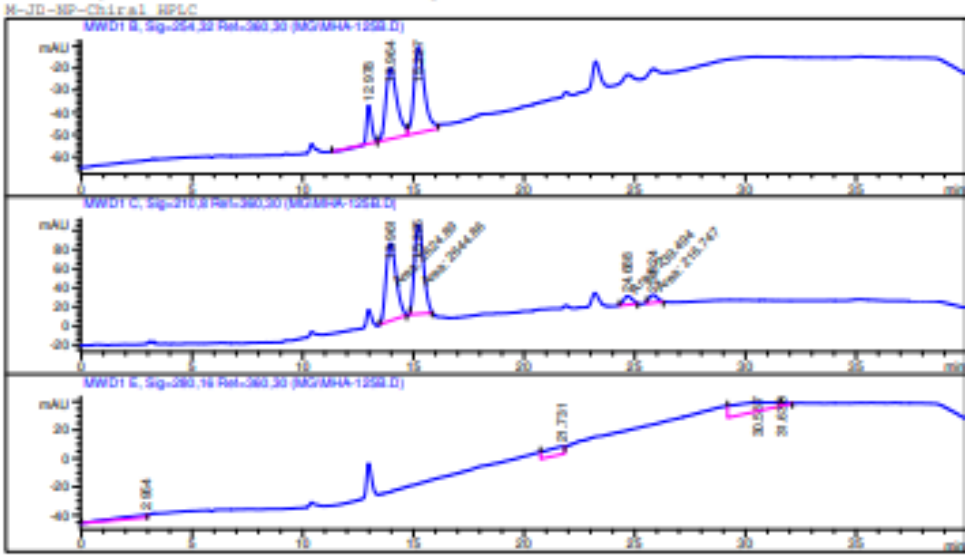



```
                          Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: MWD1 B, Sig=254,32 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
---|-------|----|-------|----------|----------|--------|
   1  14.623 BV    0.2302  363.99792   24.10399   1.0104
   2  15.319 VV    0.7585 1.68970e4   330.48550  46.9048
   3  18.850 VB    0.7250 1.76740e4   371.53317  49.0616
   4  27.750 BB    0.6466  475.83374    9.90312   1.3209
   5  32.383 BB    0.9788  613.24384    7.44671   1.7023

Totals :                  3.60241e4   743.47250

 Results obtained with enhanced integrator!

Signal 2: MWD1 C, Sig=210,8 Ref=360,30
```

```
HPLC 15/08/2019 15:10:18 PM MJP                                  Page 1 of 2
Data File C:\HPCHEM\2\DATA\MJP\JD-M38R.D                    Sample Name: JD-M38R

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
---|-------|----|-------|----------|----------|--------|
   1  14.622 VV    0.4432 1196.39392   35.67542   1.2001
   2  15.318 VV    0.7740 4.69952e4   895.90826  47.1401
   3  18.849 VB    0.7401 4.81612e4   985.58331  48.3097
   4  27.739 VV    0.8304 1617.92249   27.02742   1.6229
   5  32.392 BBA   1.0637 1721.82483   19.35818   1.7271

Totals :                  9.96925e4  1963.55260

 Results obtained with enhanced integrator!

Signal 3: MWD1 E, Sig=280,16 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
---|-------|----|-------|----------|----------|--------|
   1  12.802 VB    0.2236   28.86892    1.91759   4.4368
   2  14.624 BP    0.2631  621.80231   34.69189  95.5632

Totals :                   650.67122   36.60948

 Results obtained with enhanced integrator!

                          *** End of Report ***
```

Catalyst **107** (Chlorobenzene)

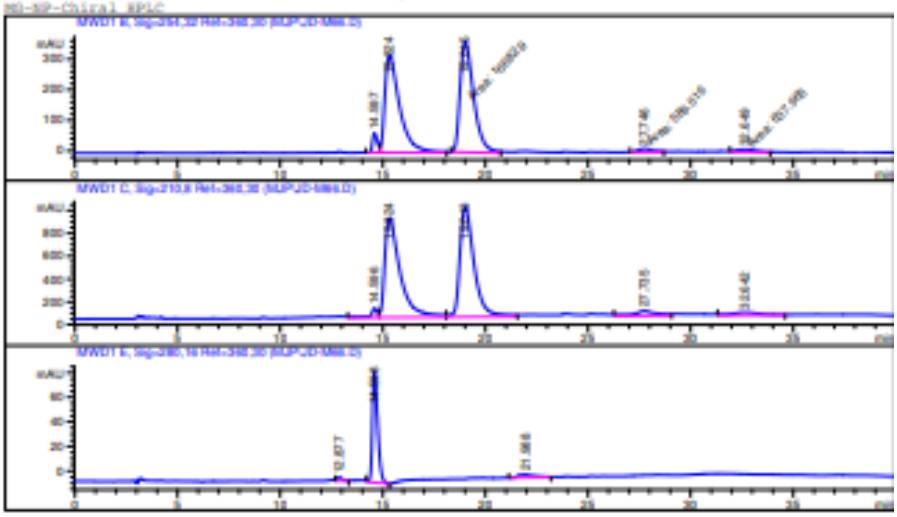
```
Injection Date  : 21/08/2019 11:49:12 PM
Sample Name     : MHA-1258                          Location : Vial 1
Acq. Operator   : MG
Method          : C:\HPCHEM\2\METHODS\MJD-NP-C.M
Last changed    : 14/08/2019 10:48:28 PM by MJP
M-JD-NP-Chiral HPLC
```




```
                          Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: MWD1 R, Sig=254,32 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.978 PV    0.2145  240.80467   17.28360   9.1076
   2  13.964 VV    0.5396 1130.49475   32.04563  42.7573
   3  15.227 VV    0.4962 1272.68396   38.84839  48.1351

Totals :                  2643.98338   88.17762

 Results obtained with enhanced integrator!

Signal 2: MWD1 C, Sig=210,8 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.961 MM    0.5365 2624.88965   81.54771  45.8416
   2  15.225 MM    0.4705 2644.86450   93.68436  46.1905
   3  24.688 MM    0.4451  239.49384    8.96738   4.1826
   4  25.824 MM    0.4244  216.74709    8.51234   3.7853

Totals :                  5725.99507  192.71180

HPLC 21/08/2019 13:38:32 PM MG                                  Page 1 of 2
Data File C:\HPCHEM\2\DATA\MG\MHA-1258.D                        Sample Name: MHA-1258

 Results obtained with enhanced integrator!

Signal 3: MWD1 E, Sig=280,16 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   2.954 BV    1.1990  203.63614    2.00153  13.9146
   2  21.731 BV    0.7449  340.92984    5.38300  23.2960
   3  30.587 BV    1.7084  874.26611    5.99830  59.7393
   4  31.638 VB    0.2380   44.63606    2.30407   3.0500

Totals :                  1463.46815   15.68691

 Results obtained with enhanced integrator!

                          *** End of Report ***
```

Catalyst **108**

```
Injection Date  : 14/08/2019 08:12:07 PM
Sample Name     : JD-M66                          Location : Vial 1
Acq. Operator   : MJP
Acq. Method     : C:\HPCHEM\2\METHODS\MJD-NP-C.M
Last changed    : 14/08/2019 08:10:20 PM by MJP
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MG-NP-C.M
Last changed    : 14/08/2019 06:48:27 PM by MJP
MG-NP-Chiral HPLC
```



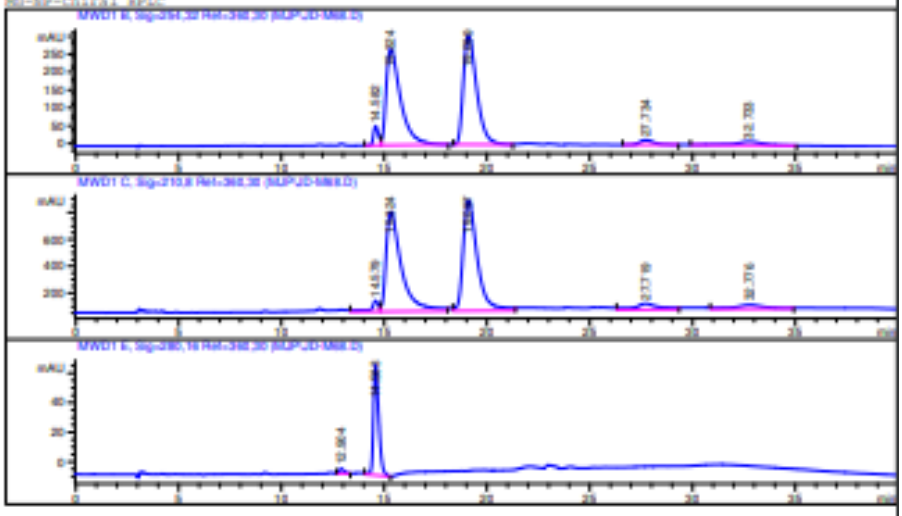
```
                        Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: MWD1 B, Sig=254,32 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.597 BV    0.2491 1052.41638   64.25351   3.0042
   2  15.224 VB    0.7492 1.60697e4   319.26477  45.8716
   3  19.015 BB    0.7703 1.66829e4   360.95129  47.6218
   4  27.746 BB    0.8429  589.01599   11.64612   1.6814
   5  22.649 BB    1.2280  627.96472    8.65847   1.8211

Totals :                  3.50225e4   764.77417

 Results obtained with enhanced integrator!

Signal 2: MWD1 C, Sig=210,8 Ref=360,30
```



```
Data File C:\HPCHEM\2\DATA\MJP\JD-M66.D                    Sample Name: JD-M66

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.596 VV    0.3577 2144.35547   82.93581   2.1412
   2  15.224 VV    0.7728 4.54262e4   870.46631  45.3592
   3  19.013 VV    0.7335 4.68969e4   964.82362  46.8277
   4  27.725 VV    1.8634 3418.04199   42.52854   3.4130
   5  22.642 VV    1.1405 2262.21021   24.51726   2.2589

Totals :                  1.00148e5  1984.48074

 Results obtained with enhanced integrator!

Signal 3: MWD1 E, Sig=280,16 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.877 VP    0.3201   41.37814    2.65068   2.3238
   2  14.598 BP    0.2659 1609.28056   98.31027  90.3745
   3  21.988 PV    0.6723  130.01207    2.30398   7.3016

Totals :                  1780.59077   95.26493

 Results obtained with enhanced integrator!

                        *** End of Report ***
```

Catalyst **109**

Injection Date : 14/08/2019 09:11:17 PM
Sample Name : JD-M69 Location : Vial 1
Acq. Operator : MJP
Acq. Method : C:\EPCHEM\2\METHODS\MJD-NP-C.M
Last changed : 14/08/2019 08:10:20 PM by MJP
(modified after loading)
Analysis Method : C:\EPCHEM\2\METHODS\MD-NP-C.M
Last changed : 14/08/2019 06:48:27 PM by MJP
MD-NP-Chiral EPLC



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: MWD1 B, Sig=254,32 Ref=360,30

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.582	PV	0.2508	895.73730	54.42727	3.0208
2	15.224	VB	0.7326	1.32426e4	269.81128	44.6601
3	19.099	BB	0.6993	1.38948e4	306.25684	46.8597
4	27.734	BV	0.6270	646.93219	13.45430	2.1818
5	32.733	VV	1.1389	971.98155	10.89769	3.2777

Totals : 2.96519e4 654.84658

Results obtained with enhanced integrator!

Signal 2: MWD1 C, Sig=210,8 Ref=360,30

LC 15/08/2019 15:16:00 PM MJP Page 1 of 2

Data File C:\EPCHEM\2\DATA\MJP\JD-M69.D Sample Name: JD-M69

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.579	VV	0.3692	2163.52490	91.62535	2.4633
2	15.224	VV	0.7707	3.87565e4	748.40710	44.1273
3	19.097	VV	0.7348	3.97664e4	822.55768	45.2772
4	27.719	VV	1.1538	3848.55493	44.91058	4.3819
5	32.776	VV	1.3771	3293.84473	28.36527	3.7503

Totals : 8.78288e4 1718.76599

Results obtained with enhanced integrator!

Signal 3: MWD1 E, Sig=280,16 Ref=360,30

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.904	VB	0.2326	53.02590	3.38789	3.8211
2	14.583	VP	0.3696	1334.68286	74.28120	96.1789

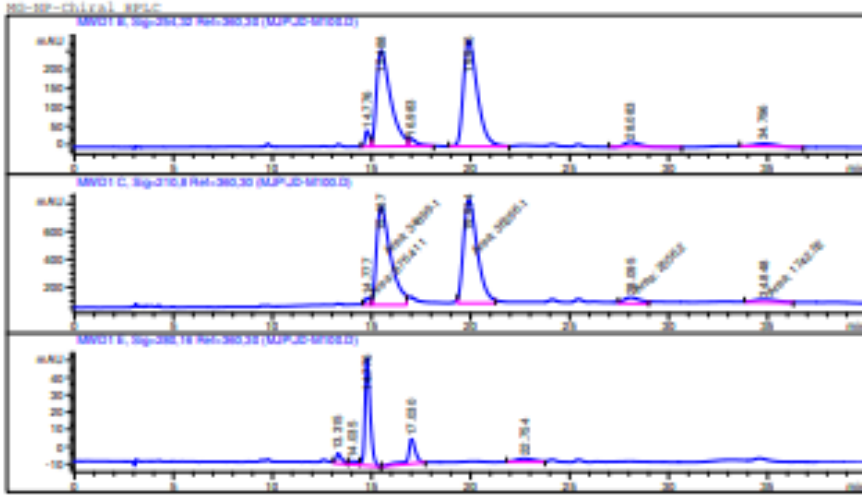
Totals : 1387.70876 77.66909

Results obtained with enhanced integrator!

*** End of Report ***

Catalyst **110**

```
Injection Date  : 14/06/2019 10:30:37 PM
Sample Name     : JD-M103                          Location : Vial 1
Acq. Operator   : MJP
Acq. Method     : C:\HPCHEM\2\METHODS\MJD-NP-C.M
Last changed    : 14/06/2019 08:10:20 PM by MJP
                  (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\MD-NP-C.M
Last changed    : 14/06/2019 06:48:37 PM by MJP
MD-NP-Chiral HPLC
```



```
                          Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: MWD1 B, Sig=254,32 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|--------|----|-------|----------|----------|--------|
   1  14.776 VV     0.2413  685.83417   43.17825   2.3680
   2  15.488 VV     0.7403 1.27747e4   257.73865  43.7252
   3  16.982 VB     0.3922   558.80066   19.74298   1.9131
   4  19.915 PB     0.7467 1.39041e4   283.23911  47.6017
   5  28.882 VV     0.7502   736.22821   13.76022   2.5205
   6  34.796 BP     0.8774   549.55505    7.37496   1.8814

Totals :                  2.92092e4   625.03417

 Results obtained with enhanced integrator!
```

```
:C 15/06/2019 15:13:28 PM MJP                                  Page 1 of 2
:A File C:\HPCHEM\2\DATA\MJP\JD-M103.D                         Sample Name: JD-M103
```

```
Signal 2: MWD1 C, Sig=210,8 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|--------|----|-------|----------|----------|--------|
   1  14.777 MM     0.2632  476.41064   51.58188   1.1480
   2  15.487 MM     0.8287 3.48991e4   701.98320  45.7154
   3  19.914 MM     0.8105 3.62661e4   745.73047  47.5062
   4  28.895 MM     0.9769 2556.19946   43.61219   3.3484
   5  34.848 MM     1.3866 1742.81929   20.93798   2.2819

Totals :                  7.63398e4  1563.76572

 Results obtained with enhanced integrator!

Signal 3: MWD1 E, Sig=298,16 Ref=360,30

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|--------|----|-------|----------|----------|--------|
   1  13.315 BB     0.2928  121.63718    5.81505   6.6839
   2  14.035 BV     0.3971   62.96313    1.92753   3.4598
   3  14.776 VP     0.2705 1127.73328   61.92855  61.9683
   4  17.830 PB     0.3866  381.96960   14.16529  20.9890
   5  22.754 BV     0.7646  125.55252    1.94635   6.8990

Totals :                  1819.85571   85.78277

 Results obtained with enhanced integrator!

                          *** End of Report ***
```