Exploring the ring-forming chemistry of yndiamides

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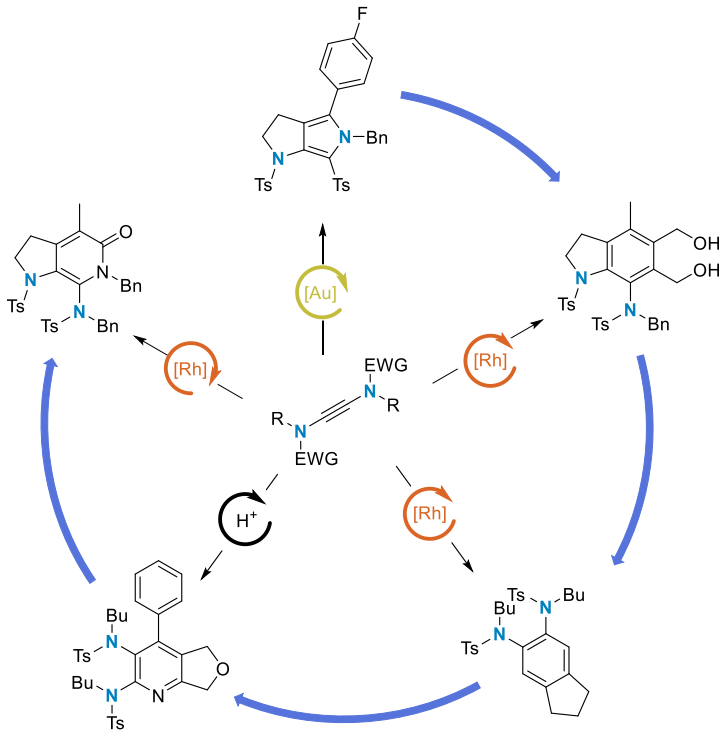
Summary of contents

Yndiamides are a uniquely capable class of doubly heteroatom-substituted alkynes which provide access to many diverse nitrogen-rich structures. This thesis describes the development of new ring-forming reactions of yndiamides. In the course of this work three project areas have been explored:

1. A cycloisomerisation transformation to form fused pyrroles, using either gold-catalysis or by heating in the absence of a catalyst (**Chapter 2**).
2. Two rhodium-catalysed [2+2+2] cyclotrimerisation reactions which form 1,2-diaminobenzene derivatives (**Chapter 3**). Mechanistic studies on this reaction were also carried out using computational methods (**Chapter 4**).
3. Catalytic methods to synthesise diaminopyridine and diaminopyridone derivatives from yndiamides. (**Chapter 5**).

Yndiamides in ring forming reactions



Aspects of this work have been included in two publications:

1. P. J. Smith, Y. Jiang, Z. Tong, H. D. Pickford, K. E. Christensen, J. Nugent, E. A. Anderson, *Org. Lett.* **2021**, 23, 6547–6552.
2. P. J. Smith, Z. Tong, J. Ragus, P. Solon, K. W. Shimkin, E. A. Anderson, *Manuscript submitted*, **2022**.

Contributions have also been made to the following publications:

1. Y. Jiang, R. E. McNamee, P. J. Smith, A. Sozanschi, Z. Tong, E. A. Anderson, *Chem. Soc. Rev.* **2021**, 50, 58–71.
2. Z. Tong, O. L. Garry, P. J. Smith, Y. Jiang, S. J. Mansfield, E. A. Anderson, *Org. Lett.* **2021**, 23, 4888–4892.

Structure of this thesis

This thesis includes a general introduction to ynamides and yndiamides (**Chapter 1**), followed by four chapters (**Chapter**s **2**–**5**) which each include an review of the literature covering the relevant area followed by discussion of the results of this work. Finally, in **Chapter 6**, the findings of this work are summarised and concluding remarks are provided on the future prospects for using yndiamides in ring-forming reactions.

Declaration

The work presented in this thesis was conducted in the Department of Chemistry at the University of Oxford. This thesis is the result of my own work and contains no results obtained by others or through collaboration except where explicitly stated in the text. The work presented has not been submitted, either partially or in full, for any qualification at this or any other institution.

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Glossary of abbreviations

Å	Ångstrom
app.	Apparent
Ar	Aryl
aq.	Aqueous
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BIPHEP	2,2'-Bis(diphenylphosphino)biphenyl
Bn	Benzyl
b.p.	Boiling point
Bpin	Pinacol boronic ester
br	Broad
Bu	Butyl
C	Celsius
$CDCl_3$	Deuterated chloroform
cm^{-1}	Wavenumbers
cod	1,5-Cyclooctadiene
conc.	Concentration
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl ligand
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DMSO-d_6	Deuterated dimethylsulfoxide
ee	Enantiomeric excess
equiv.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron-withdrawing group
g	Gram(s)
h	Hour(s)
HMBC	Heteronuclear Multiple Bond Correlation Spectroscopy
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Correlation Spectroscopy
Hz	Hertz
IR	Infra-red Spectroscopy
i-Pr	Isopropyl
J	Coupling constant
kcal	Kilocalories
LUMO	Lowest Unoccupied Molecular Orbital
m	Meta
Me	Methyl
MeOD-d_4	Deuterated methanol
mg	Milligram(s)
mL	Millilitre(s)
mmol	Millimole(s)

mol	Mole(s)
mol%	Molar percentage
M.P.	Melting Point
ms	Millisecond(s)
Ms	Methanesulfonyl
NHC	*N*-Heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ns	4-Nitrobenzenesulfonyl
o	Ortho
p	Para
Pd/C	Palladium on carbon
Ph	Phenyl
ppm	Parts Per Million
q	Quartet
R	Generic carbon group
R_f	Retention factor
r.t.	Room temperature
s	Second(s)
satd.	Saturated
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	4-Toluenesulfonyl
Tf	Trifluoromethanesulfonate
w/w%	Weight for weight percentage
XRD	X-Ray Diffraction

Acknowledgements

Firstly, I would like to thank Ed for having me in his group for the past three years and for giving me the freedom to explore many strange and remarkable things that yndiamides do, without worrying too much about how immediately applicable the results are! It's been a great time and I've really benefited from Ed's great gift for teaching and I've learned much that I hope I will take forward into the rest of my career.

I'm also really thankful for the whole of the EAA group, F9 and F10 have been a fun place to work and we've been through some rather strange times as a group during it all! Special thanks must go to Zixuan and Julia for making up Team Yndiamide, Ryan for being a great neighbour in the lab, even when trying to blow me up by accidentally drying $CDCl_3$ with *n*-BuLi, Beth, Helena and Jeremy for continual peer pressure to go to Tea even though I don't drink tea or coffee, and Nils and Ben for many trips to ATS. I'd also like to thank those people who never called me 'PJ', it's not a long list: Jieyan, Guaduan, Kenny, Priansh, I appreciate your respect for my name. Of course I'd like to thank the whole group for being such a great group of people to work with – I will miss working with you all!

Returning to more specific chemistry-related acknowledgements, I wouldn't have got anywhere in computational chemistry (**Chapter 4**) without Nils and Zixuan, both of whom have incredible patience for my amateurish questions. I'm thankful to Kirk for providing useful insight into what a medicinal chemist thinks of the weird structures resulting from yndiamide cyclisomerisations and cyclisations. I appreciate the time that many people took to teach me new techniques in the lab, especially Jeremy and Eddie. I'm grateful for all the people who have helped with proofreading this thesis – Zixuan, Ryan, Julia, Beth, Ayan, Ana, Pavle, Kenny, and Nils.

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I'm really grateful to have parents who have supported and cared for me throughout my education: Dad – thank you for inspiring me to follow you into chemistry, and Mum thank you for never complaining about listening to me talk/moan about chemistry.

I'm thankful that after 8 wonderful years in Oxford I get to leave to do something even more exciting: Jenny - I look forward to spending our lives together! Thank you for the joy you have brought into my life and for listening to me and knowing when to laugh at my pointless worrying or tell me that things will be OK when my worrying isn't so pointless!

Finally, and most importantly, I am thankful to God for the opportunities He has given me and for continually leading and guiding through every twist and turn of this DPhil process. It truly is a privilege to be able to explore creation in the lab, to see the intricacies of the world that we live in and to marvel at His handiwork.

‘*The fear of the LORD is the beginning of wisdom; a good understanding have all those who do His commandments. His praise endures forever’ ~ Psalm 111 v 10*

Chapter 1: Introduction to yndiamides

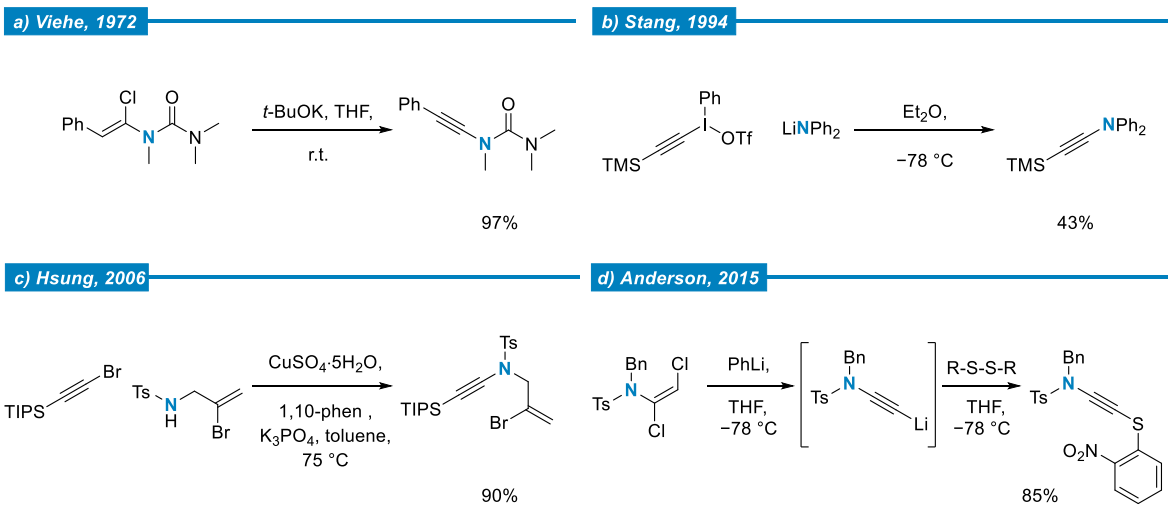
Yndiamides are a class of doubly-nitrogenated alkynes, developed in our group and shown to undergo diverse transformations to form azacycles and structures containing 1,2-diamido motifs.[1] At the time of writing, yndiamides have not been used by other research groups but their unique combination of atom connectivity and reactivity provides many remarkable possibilities for employing them in synthesis. This introduction will summarise our group's previous work on yndiamides and highlight some areas of interest which are currently being explored by our group which fall outside of the content of this thesis.

1.1 Introduction to ynamides and yndiamides

Ynamides are mono-aza substituted alkynes in which the nitrogen atom is stabilised by an electron-withdrawing group, typically a sulfonyl or carbonyl group. Viehe's 1972 work is generally regarded as the first practical synthesis of ynamides (**Scheme 1.1a**),[2] and widely used syntheses of ynamines and ynamides have since been developed by Stang (1994, **Scheme 1.1b**)[3] and Hsung (2006, **Scheme 1.1c**).[4]

Since these pioneering works, the chemistry of ynamides has expanded to encompass a vast range of reactivity, including transition metal-catalysed processes, radical reactions, addition of electrophiles, and cycloaddition processes, much of which has been covered in several review articles.[5–12] The vast array of ring forming reactions of ynamides are of particular interest in the context of this work, providing inspiration for analogous reactions of yndiamides to form doubly nitrogenated ring structures.

Syntheses of ynamides with a second heteroatom appended to the carbon-carbon triple bond were unknown until 2015, when our group reported a method to form thioynamides (**Scheme 1.1d**).[13] In 2016 Davies and co-workers employed a similar synthesis of thioynamides in their cyclisation reactions to form functionalised 4-aminooxazoles.[14]

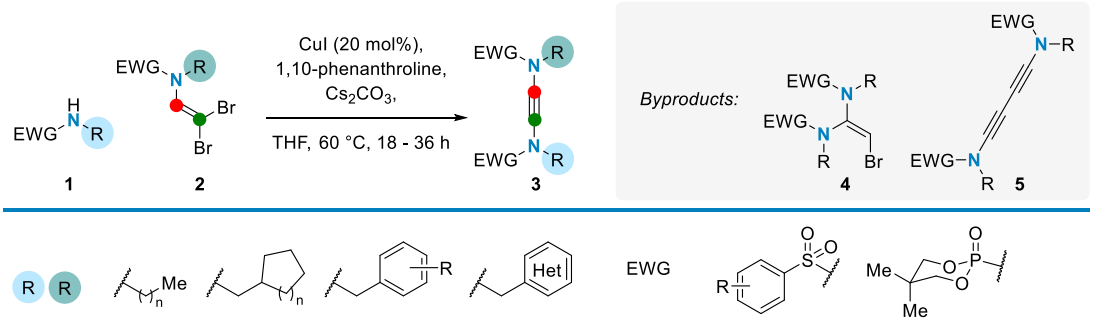


Scheme 1.1: Examples of previously reported syntheses of ynamides.

These reports were followed in 2017 by our group's pioneering synthesis of yndiamides as developed by DPhil student Steven Mansfield,[1,15] who explored a range of yndiamide reactivity and found these motifs to be broadly comparable to ynamides, but with numerous key differences observed. Through an extensive study of their reactivity and physical properties, the field of yndiamide chemistry was established and our group has continued to develop it since.

1.2 Synthesis of yndiamides

The methodology developed in our group uses copper (I) catalysis to promote the coupling of a sulfonamide or phosphoramidite (**1**) with a 1,1-dibromoenamide (**2**) under basic conditions in the presence of a ligand (1,10-phenanthroline) to synthesise yndiamides (**3**) (**Scheme 1.2**).



Scheme 1.2: Synthesis of yndiamides by copper-catalysed cross coupling of sulfonamides and 1,1-dibromoenamides.

This approach is generally applicable to the synthesis of yndiamides with a range of aliphatic and benzylic side chains. Extensive optimisation of the electrophilic coupling partner, catalyst, ligand, base and solvent resulted in conditions which are selective for formation of the desired yndiamides over other byproducts such as bromoketene-aminals (**4**) and diynes (**5**), nevertheless the synthesis of yndiamides still requires particular care to exclude oxygen and water.

Probably the greatest limitation of yndiamide chemistry developed thus far is the reliance on a relatively limited range of 1,1-dibromoenamides as coupling partners – and even those which are suitable can be challenging to prepare. The development of new methods to enhance the variety of electron-withdrawing groups possible in yndiamides, although outside the scope of this work, would doubtless open up further opportunities for applications of yndiamides in synthesis.

1.3 Overview of previously reported reactions of yndiamides

As part of our group's initial report of the synthesis of yndiamides, transformations of yndiamides were also reported (**Figure 1.1**).[1] These transformations provided valuable points of comparison between the reactivity of yndiamides and their ynamide analogues. A selection of previously developed yndiamide ring-forming reactions are described here, and some mechanistic aspects are discussed to introduce the characteristic reactivity of yndiamides.

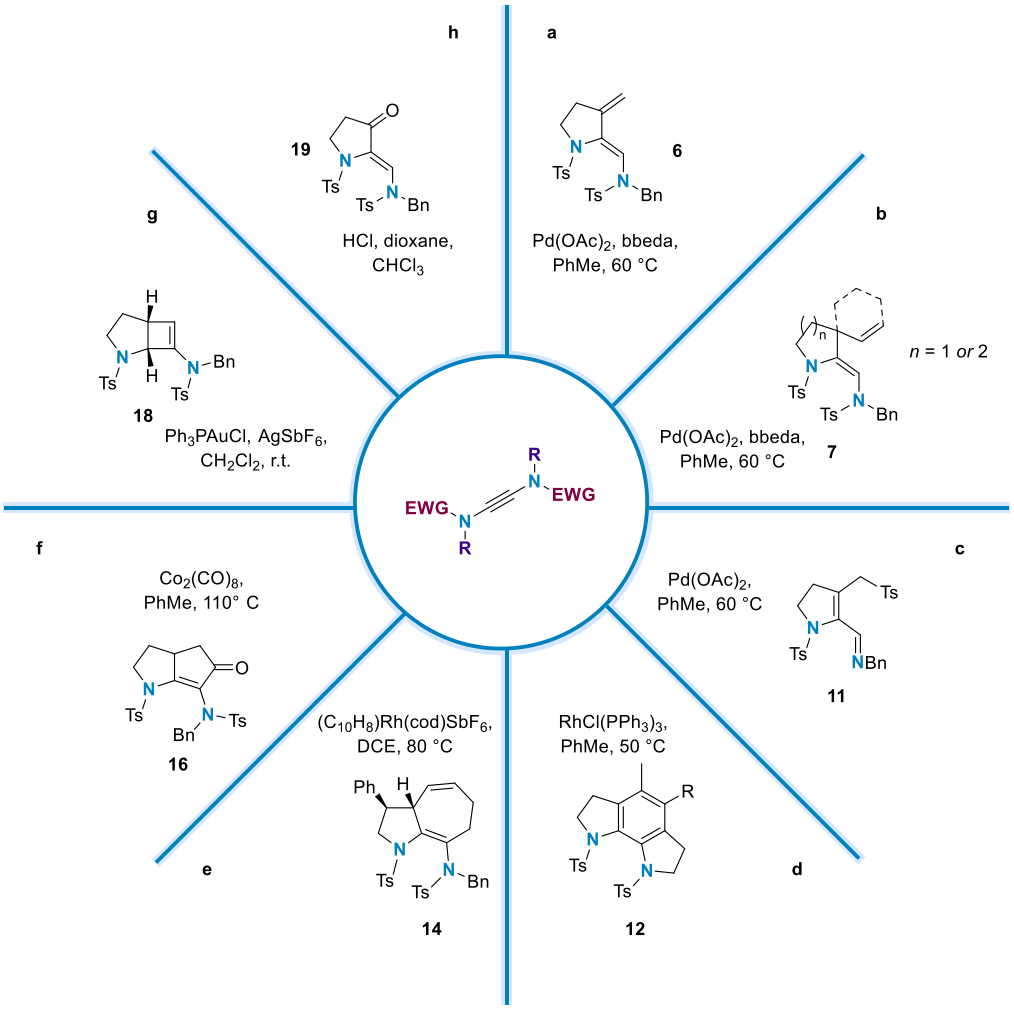
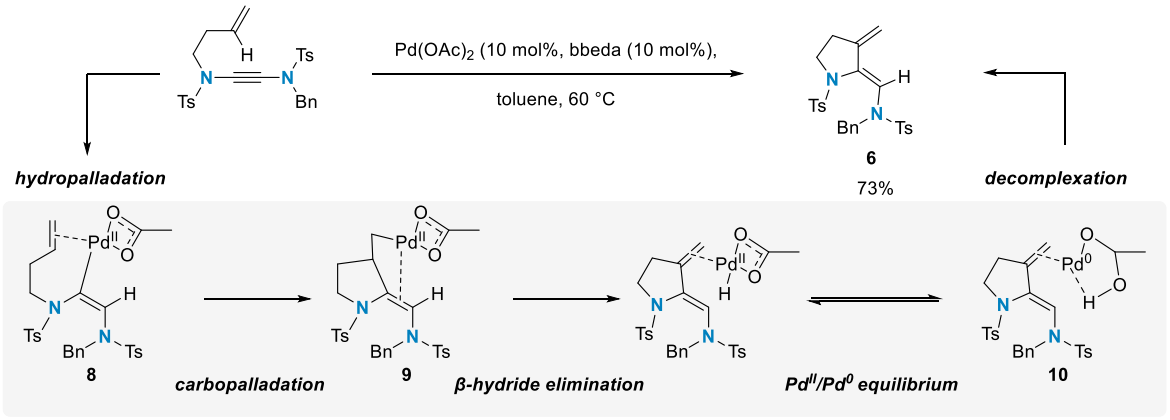


Figure 1.1: Ring-forming reactions of yndiamides developed in our group.[1]

Palladium-catalysed cycloisomerisation reactions of ene-yndiamides led to the formation of 1,3- (**6**) and 1,4- dienes (**7**) (including spirocyclic examples) dependent on the alkene substitution pattern (**Figure 1.1a–c**).[16] The reaction commences with irreversible hydropalladation of the yndiamide (to form **8**) followed by intramolecular (and also irreversible) carbopalladation to form **9**. Following this, rate determining β-hydride elimination and Pd^{0}/Pd^{II} equilibration gives the product with the coordinated catalyst (**10**) (**Scheme 1.3**). The details of the diene decomplexation from the palladium catalyst to give the product **6** are unknown. These reactions were slower than comparable transformations for ynamides; this may be due to the product dienes formed from yndiamides being more electron rich and thus coordinating the catalyst more effectively, thus hindering catalyst

turnover; additionally the increased steric bulk of the products due to the second sulfonamide substituent may disrupt the involvement of a second molecule of substrate or bbeda in the turnover step. Unsaturated imines (**11**) were formed by a similar reaction in the absence of bbeda.

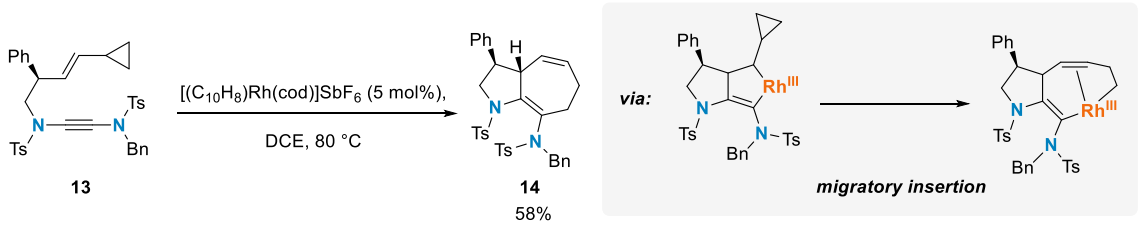


Scheme 1.3: Palladium-catalysed cycloisomerisation of ene-yndiamides.

Rhodium-catalysed cyclotrimerisation reactions were also explored (**Figure 1.1d**) – a fully intramolecular [2+2+2] cyclotrimerisation reactions of diyne-yndiamides formed pyrroloindolines (**12**) more rapidly than for comparable ynamides. This reactivity will be further discussed in **Chapter 3**.

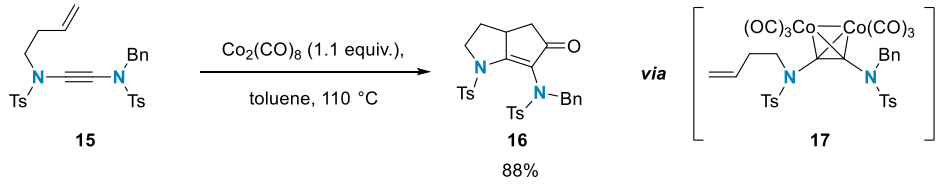
Under rhodium-catalysis a vinylcyclopropane yndiamide (**13**) was cycloisomerised to a single diastereoisomer of a 5,7-fused ring system (**14**), albeit more slowly and at a higher temperature than for similar ynamides (**Figure 1.1e**). Our group had previously explored [5+2] reactivity of vinylcyclopropane ynamides[17] and extensive computational investigations suggest that the reaction proceeds through an oxidative coupling of the alkene-yn(di)amide to form a metallocycle (**Scheme 1.4**). For yndiamides, the additional steric bulk of the second sulfonamide substituent may hinder this process, thus slowing the reaction, and perhaps favouring the alternative pathway that initiates with oxidative addition into the

vinyl cyclopropane. The formation of the metallocycle is followed by migratory insertion of the cyclopropane and reductive elimination to give the product (**14**).



Scheme 1.4: Rhodium-catalysed [5+2] cycloisomerisation of vinyl-cyclopropyl yndiamide **13**. *Ligands on rhodium are not shown for clarity.*

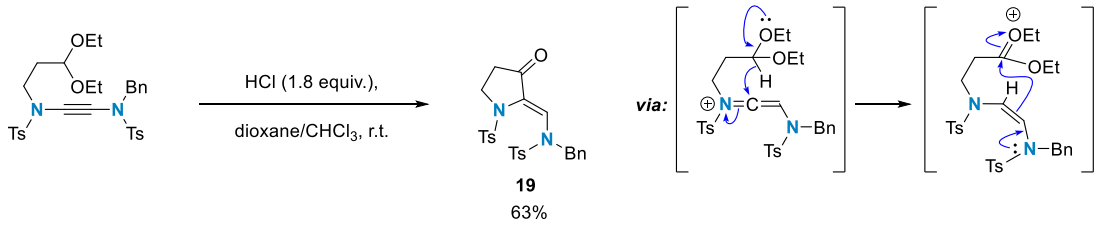
A Pauson-Khand reaction of ene-yndiamide **15** formed amidocyclopentenone **16** (**Figure 1.1f**). Once again this reaction required prolonged reaction times at high temperatures to achieve the cyclisation, although a colour change consistent with the formation of the initial complex **17** was observed to be relatively fast (**Scheme 1.5**).



Scheme 1.5: Pauson-Khand reaction of ene-yndiamide **15**.

As will be discussed in **Chapter 2**, numerous cyclisation reactions of ynamides have been developed using gold catalysts and our group applied some of these transformations to yndiamides (**Figure 1.1g**). Fused cyclobutenes (**18**) could be formed from ene-yndiamides, although a relatively high catalyst loading (30 mol%) was required to achieve full conversion. Notably, other conditions previously reported for analogous reactions of ynamides[18,19] were not applicable to yndiamides, giving negligible starting material conversion – no clear reason was established for this but it may be a consequence of catalyst poisoning by the nitrogen-rich heterocyclic products and intermediates.

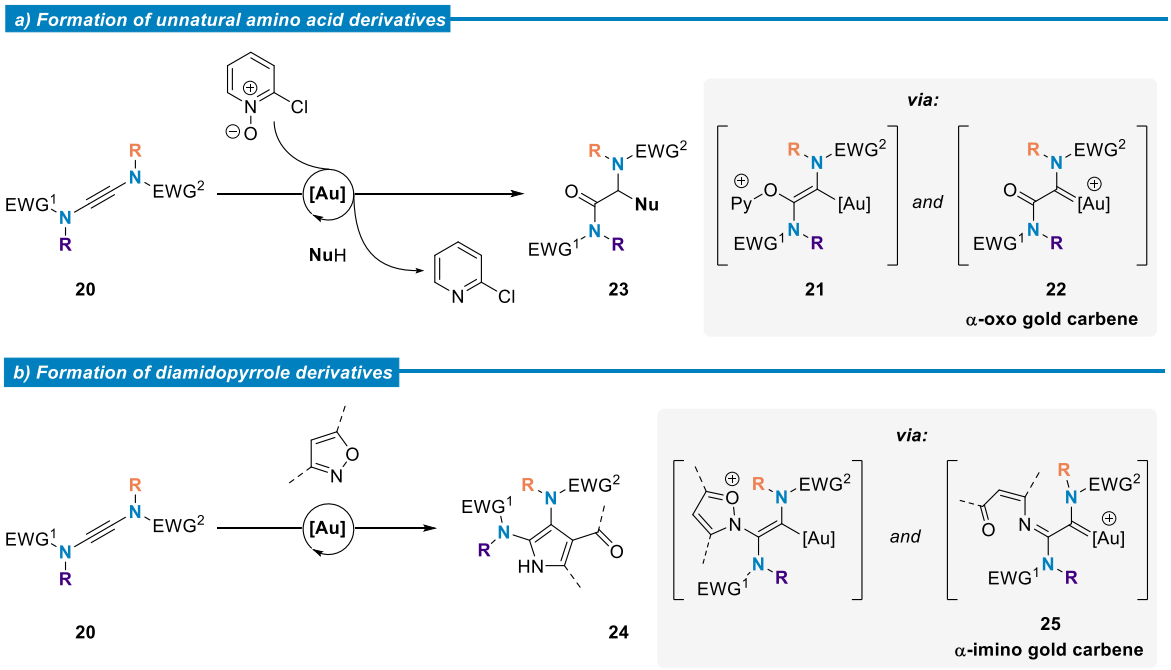
Treatment of an acetal-yndiamide with HCl led to formation of a cyclic enone (**19**, **Figure 1.1h**); this transformation probably occurs by 1,5-hydride transfer from the acetal moiety to a keteniminium ion followed by hydrolysis (**Scheme 1.6**). Subsequent work in our group has revealed that yndiamides are generally sensitive to strong acids, although treatment of some yndiamides with anhydrous HCl does form isolable hydrochlorinated products. An additional Brønsted acid-promoted cyclisation is discussed below.



Scheme 1.6: Acid-promoted cyclisation-hydrolysis of to form cyclic enone **19**.

Building on the gold-catalysed oxidation of ynamides reported by Davies and co-workers in 2011,[20] gold-catalysed oxidative addition to yndiamides (**20**) was developed in our group and was reported in 2021 (**Scheme 1.7a**).[21] A pyridine *N*-oxide (acting as a source of nucleophilic oxygen with a leaving group attached) attacks the keteniminium ion formed from the yndiamide (**21**) and the gold catalyst to form an α-oxo gold Fischer carbene (**22**). This is then attacked by a nucleophile to access unnatural amino acid derivatives (**23**). The regioselectivity of this transformation depends heavily on the steric properties of the nitrogen substituents, with the bulky gold(I) catalyst preferentially forming the keteniminium ion intermediate which places it closer to the smaller nitrogen substituent. Numerous electron-rich heterocycles were used as nucleophiles in this transformation, including indoles, pyrroles, furans, and benzothiophenes. Arenes with strong electron-donating groups (anilines and anisoles) and a silyl enol ether were also able to undergo the transformation. Several of these reactions were also shown to proceed under Brønsted acid catalysis, using $HNTf_2$ as the catalyst.

At the time of writing, gold-catalysed oxidative functionalisation of yndiamides is still being developed in our group (**Scheme 1.7b**), to form pyrroles (**24**) via α-imino gold Fischer carbenes **25**, with isoxazoles shown to undergo addition by nucleophilic attack through nitrogen, in an analogous transformation to those developed by Ye and co-workers using ynamides.[22] The regioselectivity of this transformation again depends strongly on the steric properties of the yndiamide substituents, and computational studies are underway in our group to probe the mechanistic factors controlling the regiochemical outcome.

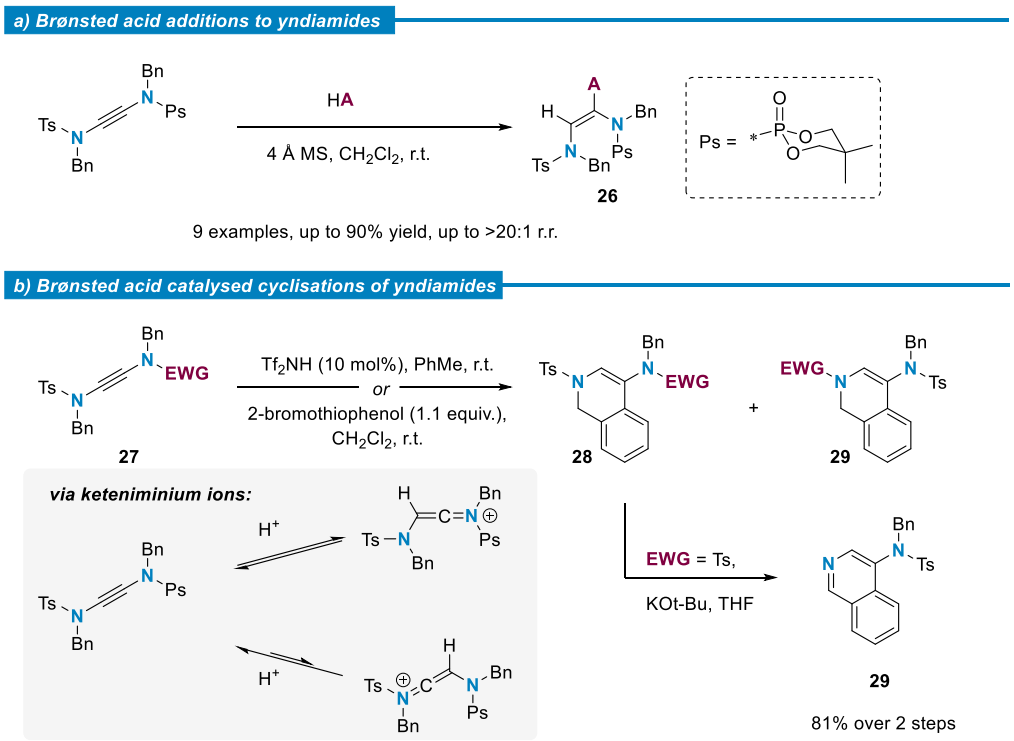


Scheme 1.7: Gold-catalysed oxidative functionalisations of yndiamides to form *a)* unnatural amino acid derivatives,[21] and *b)* diamidopyrrole derivatives.

Brønsted acid additions to yndiamides were developed in our group to form *N,O,N*- and *N,S,N*- trisubstituted ketene acetals **26** (**Scheme 1.8a**).[23,24] Acids with pK_a values in the approximate range 3 to ~ 6.5–7.5 were found to successfully add across the yndiamide to give the products as the *E* isomer. Carboxylic acids, electron-deficient phenols and thiols were added across the yndiamide triple bond, but attempts to add carbon-centred acids (e.g. Meldrum's acid) and HCl were unsuccessful, typically resulting in either no reaction or decomposition. The regioselectivity of these transformations is controlled by the different

electronic properties of the tosyl and phosphonate diester (Ps) electron-withdrawing groups; the dominant protonation at the position distal to the -NPsBn group implies that the Ps group is a weaker electron-withdrawing group than the Ts group. This *electronic* regioselectivity control is in contrast to the *steric* regioselectivity control observed for gold-catalysed reactions of yndiamides.[21]

Cyclisation of the *N*-benzyl group to form dihydroisoquinoline **28** (*via* a keteniminium ion intermediate) was observed when a symmetrical yndiamide (**27**, EWG = Ts) was treated with a catalytic quantity of Tf_2NH **(Scheme 1.8b)**. The same transformation was applied to unsymmetrical yndiamides and excellent regioselectivity was achieved using 2-bromothiophenol to promote the cyclisation. Treatment of **28** with base led to formation of isoquinoline derivative **29**.



Scheme 1.8: *a)* Brønsted acid additions to yndiamides and *b)* Brønsted acid promoted cyclisation of *N*-benzyl yndiamides to form dihydroisoquinoline derivatives.[23,24]

1.4 Conclusions and project aims

The reactions of yndiamides surveyed in this section lay the foundation for the work which will be discussed in later chapters. Specifically, the suitability of yndiamides for functionalisation by gold-catalysis provided inspiration for the gold-catalysed cycloisomerisation described in **Chapter 2**, and intramolecular rhodium-catalysed cyclotrimerisations of yndiamides are developed in **Chapter 3**. Although yndiamides are (to the best of our knowledge) yet to be employed by other researchers, it is hoped that by showcasing their application in the synthesis of doubly nitrogenated (hetero)cycles, yndiamides will become a part of the 'toolkit' of organic chemistry in a similar manner to the widespread use of ynamides in synthesis over the past two decades. Furthermore, by probing the differing reactivity of yndiamides and ynamides, interesting mechanistic details will be uncovered which improve our understanding of these remarkable compounds. Perhaps most significantly, yndiamides will herein be shown to be a remarkable source of new, and often surprising, reactivity – and due to the potential medicinal relevance of the scaffolds being prepared it is hoped that this reactivity will go beyond academic curiosity.

Chapter 2: Cycloisomerisation reactions of yndiamides to form fused pyrroles

The development of novel syntheses of nitrogen heterocycles is often heralded as one of the most important challenges in organic chemistry, with publications describing such procedures frequently referencing the fact that the majority of US Food and Drug Administration-approved small molecule drugs contain at least one nitrogen heterocycle.[25] The importance of these structural motifs leads to a great interest in the synthesis of such rings, including pyrroles,[26] and yndiamides have a potential application in this area. Building on our group's previous syntheses of a diverse range of yndiamides, we investigated a cycloisomerisation approach to synthesise pyrroles from yndiamides.

This chapter details the serendipitous discovery and development of a novel tandem cycloisomerisation/1,2-sulfonyl migration reaction of yndiamides to form highly substituted fused pyrroles. Before starting this work, this cycloisomerisation reaction was also unknown for ynamide analogues, however after completion of the experimental work (but prior to publication) Gagosz and co-workers reported a comparable transformation of *ynamides* using thermal conditions, which they described as a formal [3+2] cycloaddition.[27] Although their work somewhat detracted from the novelty of our yndiamide cycloisomerisation reaction, it provided opportunities to compare the reactivity of yndiamides and ynamides.

2.1 Introduction to ynamide cycloisomerisation

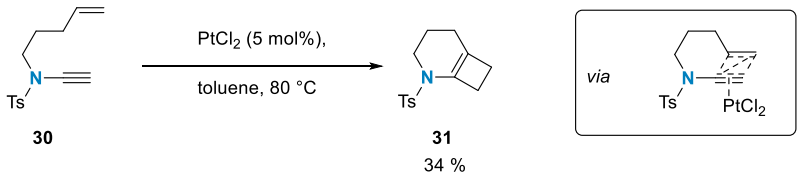
Cycloisomerisation reactions are a powerful method for synthesising complex polycyclic structures from linear precursors.[28–30] Ynamides have been widely employed in cycloisomerisation reactions to form various nitrogen heterocycles, and a well-known review by Hsung and co-workers describes many of these reactions dating from before 2010.[5] More recently other authors have also reviewed the field of ynamide cycloisomerisations.[9,31] There are also numerous examples of ynamides undergoing *intermolecular* cycloadditions/annulations, including with isoxazoles,[22] azirines,[32] anthranils,[33] and many other nucleophiles – these are outside the scope of this section but several excellent reviews cover the area in detail.[12,34,35]

As this section will show, ynamide cycloisomerisation chemistry is dominated by gold-catalysed transformations, which were reviewed by Ye and co-workers in 2016[31], and by Sahoo and co-workers in 2021.[12] The examples discussed in this section were selected to showcase the diversity of ynamide cycloisomerisation chemistry forming nitrogen heterocycles; there will be a focus (but not exclusively) on gold-catalysed catalysed reactions, which will demonstrate the versatility of this mode of ynamide activation, and will provide inspiration for similar transformations of yndiamides.

Cycloisomerisation reactions of ynamides typically require the presence of at least one other unsaturated moiety or heteroatom in the molecule. Hence, the development of such reactivity was rapidly accelerated by the advent of facile methods to synthesise ynamides with diverse side chains; syntheses using alkynyliodonium salts[3] and bromoalkynes[4] are the most widely encountered.

2.2 Review of ynamide cycloisomerisation reactions

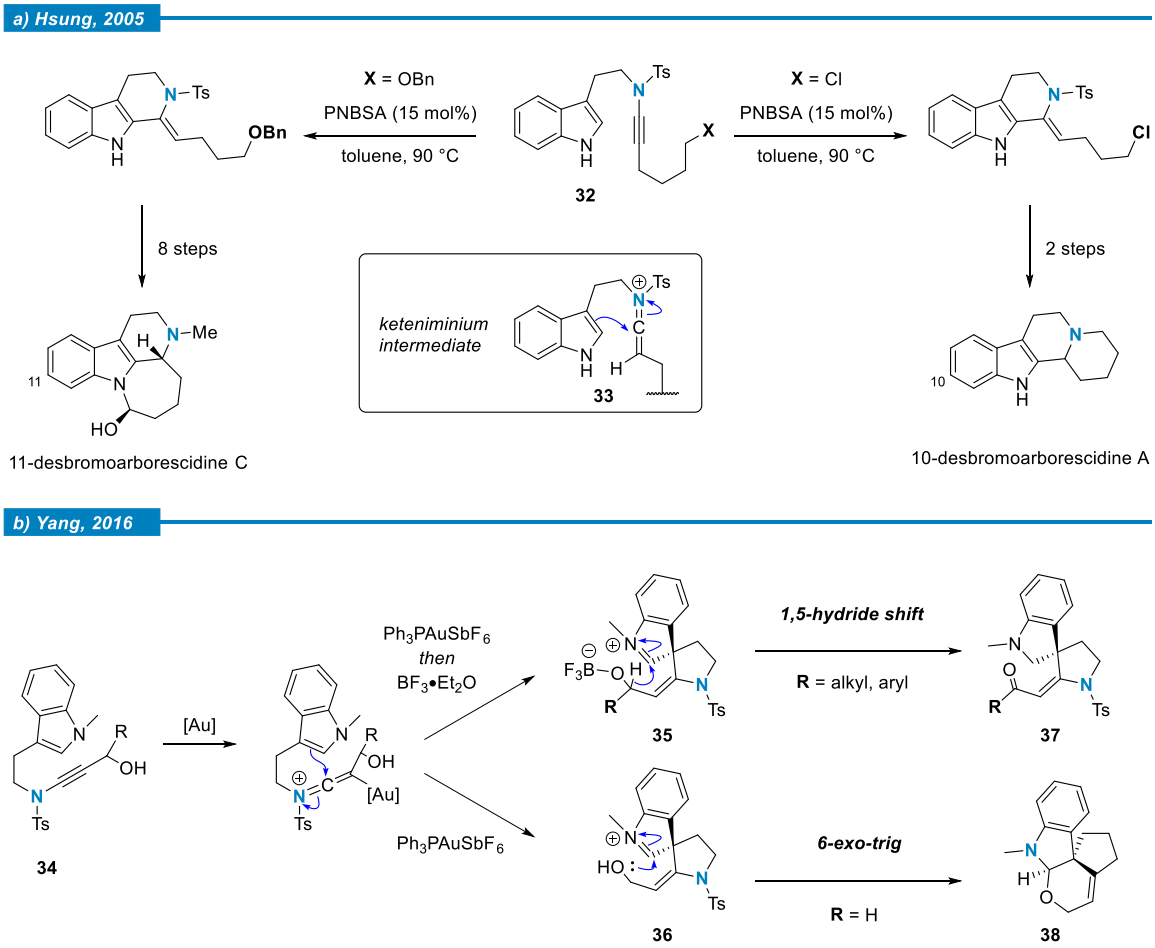
The first cycloisomerisation of ene-ynamides (**30**) was reported by Malacria and Fensterbank in 2004, using a platinum catalyst to form aza-bicycles (**31**) (**Scheme 2.1**) in a formal [2+2] reaction.[18] This set a precedent for utilising π-acidic metal-catalysts to activate ynamides in cycloisomerisation reactions, which other researchers have since exploited to form nitrogen heterocycles.



Scheme 2.1: First report of the cycloisomerisation of ene-ynamides under Pt-catalysis.[18]

Shortly after Malacria and Fensterbank's initial report of ene-ynamide cycloisomerisations, Hsung and co-workers pioneered the use of indol-ynamides (**32**) in alkaloid natural product synthesis with their syntheses of desbromoarborescidines A and C (**Scheme 2.2a**).[36] The key step in these syntheses was a Brønsted acid-catalysed Pictet-Spengler cyclisation of the indole C2 position onto keteniminium ion **33**. The authors did not comment on the absolute configuration of the final products, so the stereochemistry (or absence thereof) shown in **Scheme 2.2a** is as reported in the publication. The reaction of the indole at C2 occurs by initial reaction at C3 followed by migration of the spirocyclic intermediate onto the iminium ion. Contrasting reactivity is seen in the gold-catalysed cyclisation of similar indole-ynamides **34** reported by Yang and co-workers in 2016 (**Scheme 2.2b**).[37] In this case more typical C3 reactivity of the indole moiety occurs to form spirocyclic intermediates **35** and **36**; the absence of migration is presumably because the alcohol substituent allows alternative pathways for trapping of the iminium ion intermediate. The overall reaction outcome was controlled by the substitution in the propargylic position – having a secondary alcohol in the propargylic position promoted a 1,5-hydride shift (in the presence of a Lewis acid) to form

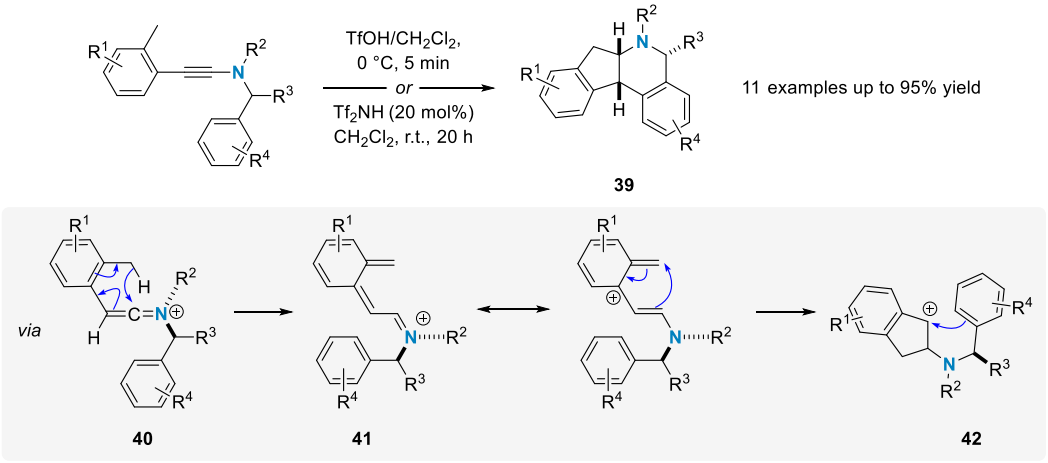
an exocyclic α,β-unsaturated ketone (**37**), whereas primary alcohols underwent a further cyclisation to form a third (dihydropyran) ring (**38**). The transformations shown in **Scheme 2.2** illustrate the divergent cyclisation reactivity arising from these two modes of keteniminium ion formation.



Scheme 2.2: *a)* Synthesis of desbromoarborescidines A and C from tryptamine-derived ynamide **32**.[36] *b)* Synthesis of spirocyclic pyrrolidinoindolines from tryptamine-derived ynamide **34**.[37]

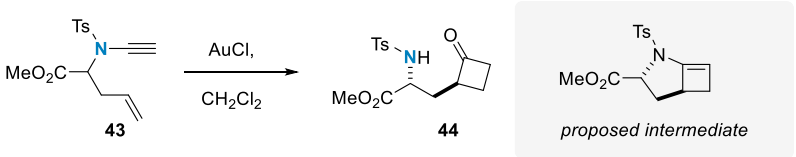
Brønsted-acid-promoted *poly*cyclisation initiated by keteniminium ion formation remained an unexplored field until 2014, when Evano and co-workers reported a synthesis of polycyclic nitrogen heterocycles containing up to three contiguous stereocentres (**39**) from ynamides (**Scheme 2.3**).[38] This reaction proceeds via a 1,5-sigmatropic hydrogen shift of keteniminium ion **40** to form conjugated iminium **41**, which undergoes 4π conrotatory electrocyclisation to form **42**. They found that π-acids were not suitable catalysts for this

transformation, instead TfOH or Tf_2NH were required. It is surprising that neither gold or copper complexes were effective catalysts (instead giving hydrolysis or decomposition), given that the formation of keteniminium ions from ynamides is well precedented using π-acidic catalysts and is applicable in numerous other ynamide cycloisomerisation reactions (see below).



Scheme 2.3: Bronsted-acid mediated cyclisation of ynamides.[38]

The advent of gold-catalysis in ynamide cycloisomerisation chemistry came in 2006 with Cossy and co-workers' report of diastereoselective gold-catalysed cycloisomerisation reactions of ene-ynamides **43** (**Scheme 2.4**), with exposure to atmospheric moisture upon workup being sufficient to hydrolyse the expected cyclobutene intermediate to a cyclobutanone **44.**[19]

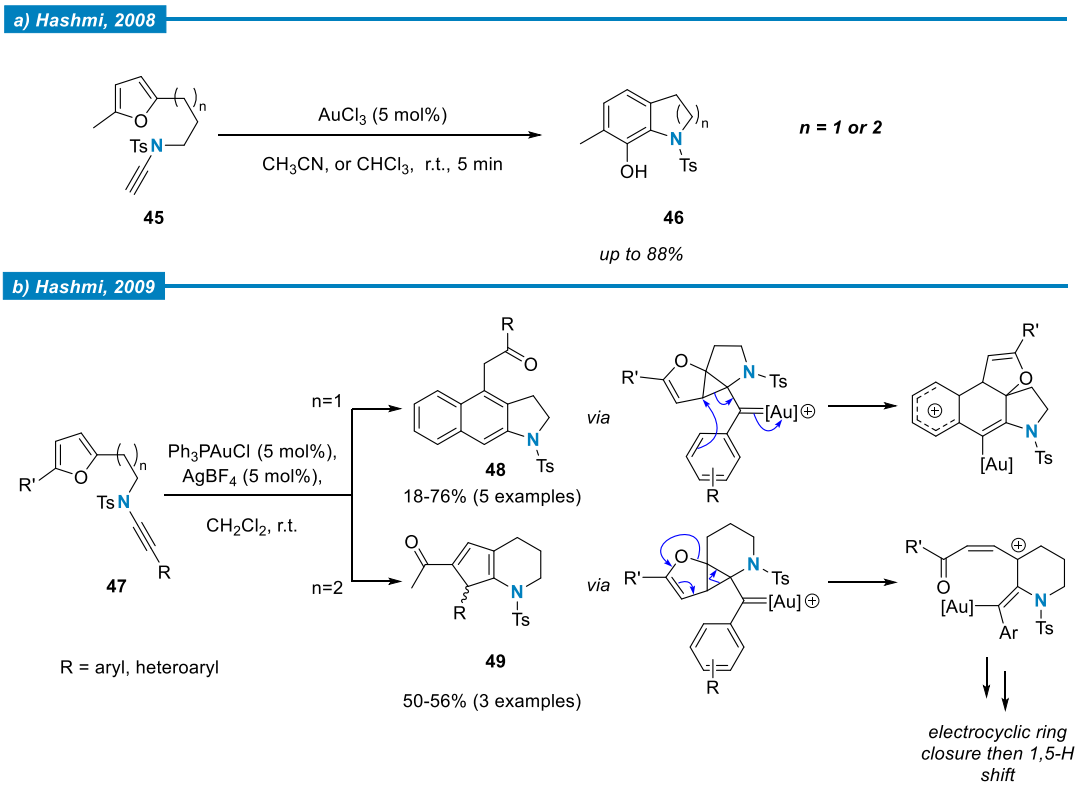


Scheme 2.4: First reported gold-catalysed cycloisomerisation reaction of ynamides.[19]

This development set the stage for many gold-catalysed cycloisomerisation reactions of ynamides to follow, and is of special importance because of the affinity of gold(I) for carbon-carbon triple bonds, which enables greater chemoselectivity by avoiding acid-promoted

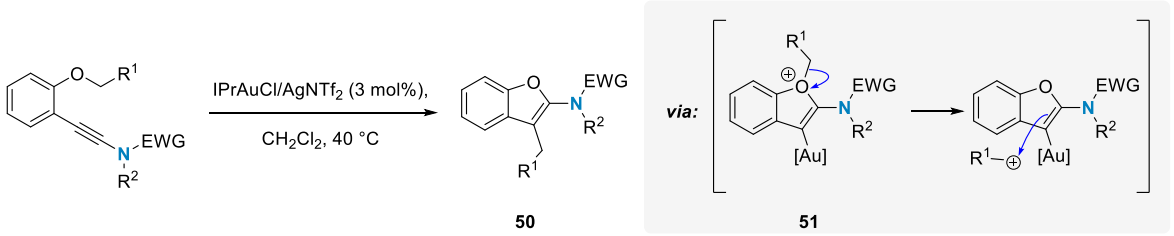
degradation of other functionalities in the molecule (such as carbamate protecting groups). Since this development, gold activation of ynamides *via* keteniminium ion formation has been widely adopted as the 'gold standard' for achieving a broad scope of ynamide transformations.[11,12,31,34] However, it is worth noting that many of these transformations involve oxidation of the ynamide, using an activating agent such as pyridine-*N*-oxide to form α-imido gold carbenes, and are therefore not strictly applicable to the transformations which form the objective of this project. Oxidative functionalisation of yndiamides is being explored by our group, and we recently reported the transformation of yndiamides to unnatural amino acid derivatives (as discussed in **Chapter 1**).[21]

In 2008 Hashmi and co-workers utilised gold-catalysis to achieve cycloisomerisation reactions of ynamides with a tethered furan (**45**) to form dihydroindole and tetrahydroquinoline derivatives **46** (**Scheme 2.5a**).[39] They followed this work in 2009 with an exploration of the effect of tether length on the outcome of these reactions using ynamides **47** to form azacycles (**48** and **49)** (**Scheme 2.5b**).[28] Their work demonstrates the remarkable possibilities for formation of poly(aza)cyclic structures by cycloisomerisation of ynamides with tethered unsaturated groups and showcases the elegant mechanistic complexity often observed in cycloisomerisations of ynamides. The same group further developed this reactivity to form novel fused tetracyclic azacycles rather than phenols by using ether-linked substrates.[40] These reactions are believed to proceed *via* activation of the ynamide by gold followed by nucleophilic attack by the electron-rich furan moiety to form a gold carbene, which undergoes one of two modes of ring expansion depending on the tether length. Similar reactivity is also known for other electron-rich alkynes (such as ynol ethers) with tethered furans.



Scheme 2.5: Gold-catalysed cyclisomerisation reactions of furan-tethered ynamides to form *a)* hydroxyindolines and *b)* polyaromatic ring systems with outcomes controlled by tether length.[28,39]

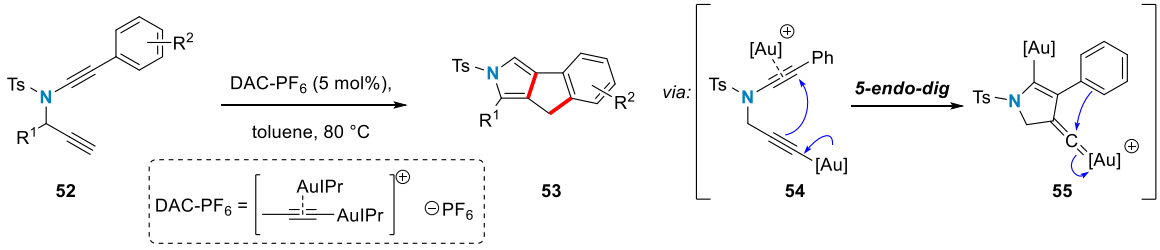
A synthesis of highly substituted benzofurans (**50**) from ynamide-aryl ethers was reported by Hashmi and co-workers in 2013 (**Scheme 2.6**).[41] This proceeded by attack of the aryl ether on the gold keteniminium ion, followed by migration from the oxonium intermediate (**51**). A well-stabilised carbocation migrating group was required and crossover experiments showed that the process was intermolecular, explaining the need for a stabilised carbocation.



Scheme 2.6: Synthesis of benzofurans by gold-catalysed cyclisation of ynamide-aryl ethers.[41]

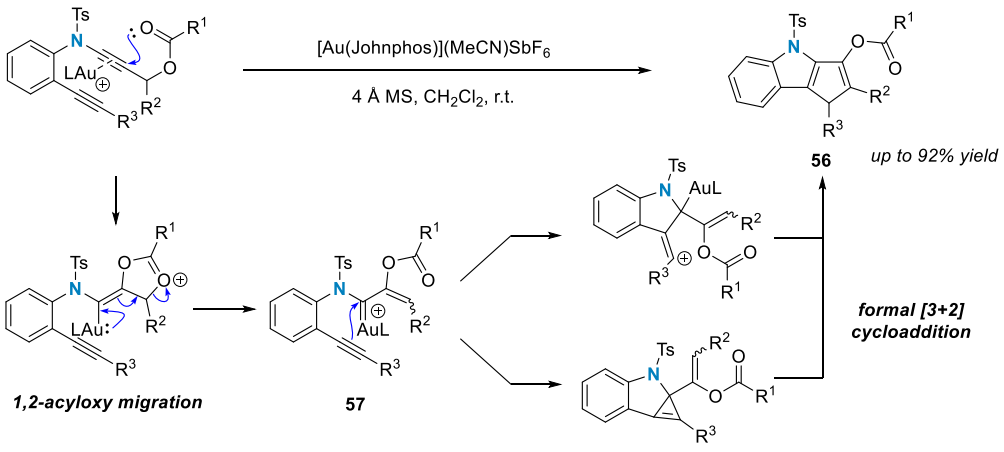
The use of a gold Dual Activation Catalyst (DAC) with ynamides was pioneered by Hashmi and Ohno and co-workers in 2015 to cycloisomerise propargylic ynamides **52** into various

fused pyrroles **53** (**Scheme 2.7**).[42] This reactivity involves C–H activation and attack of the gold acetylide **54** thus formed onto the gold-activated ynamide in a 5-*endo-dig* cyclisation step. The second cyclisation event is attack of the aryl group onto the gold carbene **55** (a tethered alkene can also perform this step); protodeauration and tautomerisation forms **53**.



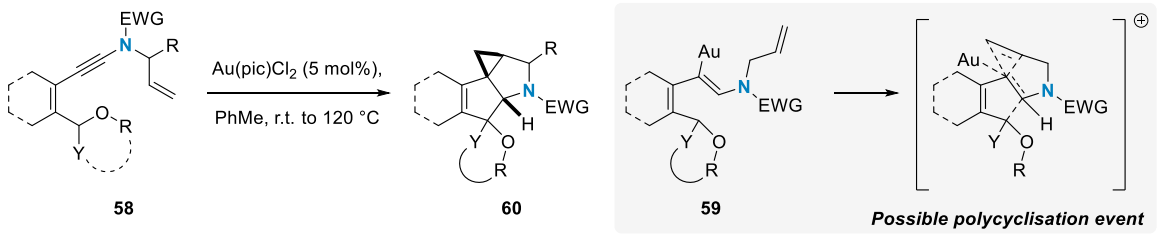
Scheme 2.7: Dual-activation catalysis in the synthesis of fused pyrroles.[42]

Gold-catalysis was applied to ynamides bearing heteroatom tethered propargyl carboxylates by Liu and co-workers in 2015 (**Scheme 2.8**) in their synthesis of cyclopenta[*b*]indoles (**56**) formed by a tandem 1,2-acyloxy migration/[3+2] cycloaddition process, with a key intermediate being gold carbene **57**.[43] The outcome of this transformation was dependent on the nature of the gold(I) catalyst, with the authors selecting [Au(Johnphos)](MeCN)SbF_6 as the optimal catalyst; other less bulky ligands promoted a competing tandem 3,3-rearrangement/oxocarbenium ion formation/acyl migration process which is presumably hindered by the bulkier ligand.



Scheme 2.8: Gold-catalysed cyclisomerisation reactions of ynamides with tethered propargyl carboxylates.[43]

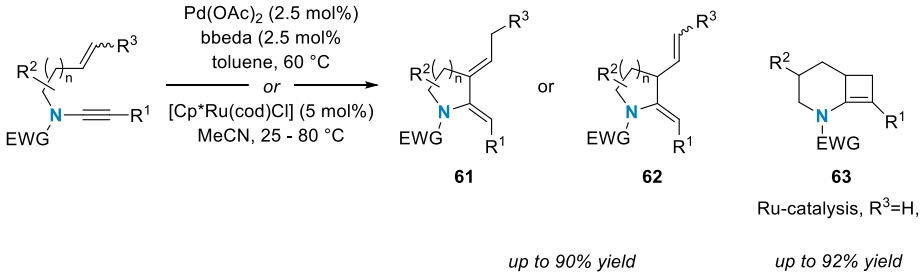
Davies and co-workers reported a series of divergent C–H insertion-cyclisation cascades of *N*-allyl ynamides **58** in 2015 (**Scheme 2.9**).[44] The *N*-allyl moiety was incorporated to serve as a trap for the gold carbenoid intermediate **59** to form the cyclopropanated product **60**. However, other gold(III) catalysts ($AuCl_3$ and $AuBr_3$) promoted formation of a 1,4-disubstituted isoquinoline by elimination of water. At lower temperatures (or in more polar solvents) indenyl amides were formed by a C–H insertion event from the gold carbenoid. Despite the competing pathways the authors controlled the reaction outcome by adjusting the catalyst and temperature, with by-products arising from failure of the final cyclopropanation event becoming more prevalent at lower temperatures and in more polar solvents.



Scheme 2.9: Gold-catalysed ynamide C–H inserition-cyclopropanation cascade.[44]

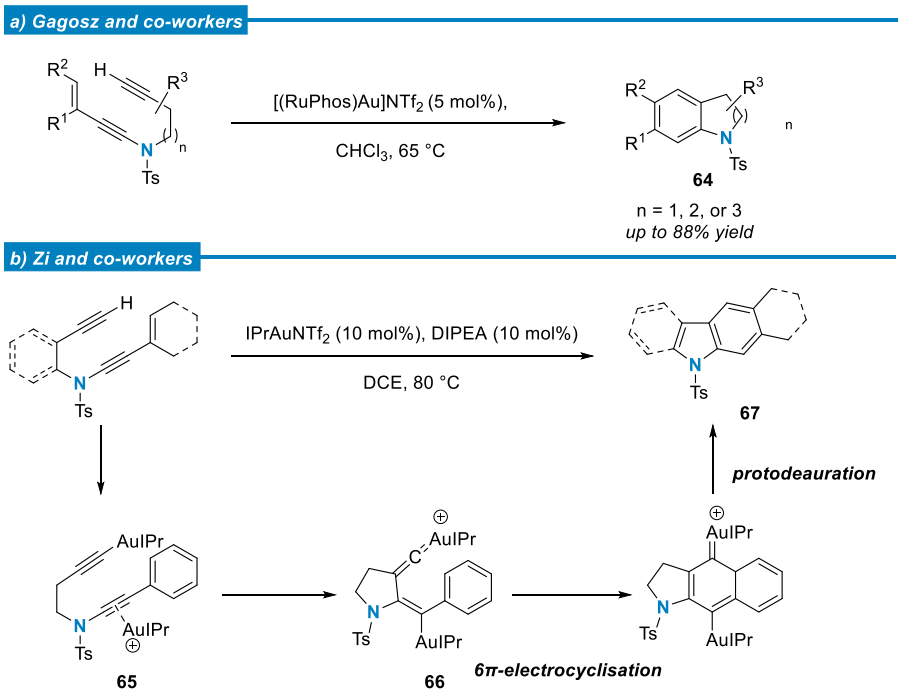
Our group developed Pd or Ru-catalysed cycloisomerisation of ene-ynamides to form azacycles stereoselectively (**Scheme 2.10**).[45] 1,6-Ene-ynamides were found to undergo cycloisomerisation under Pd catalysis with high efficiency to give pyrrolidine enamides **61** and **62**, with 1,7-ene-ynamides also being competent substrates under the same conditions, forming analogous piperidine enamides. The same transformation could also be achieved under Ru-catalysis, although a change in the reaction outcome occurred for 1,7-ene-ynamides under these conditions: 6,4-fused cyclobutenes **63** were formed in excellent yields. This is an unusual example of a formal [2+2] reaction between an ynamide and an alkene which is not activated by either strain or electron-deficiency. When disubstituted alkenes were used, the selectivity for the 1,3- or 1,4- dienes likely arose from the different barriers

to β-hydride elimination from the alkyl palladium intermediates. This reactivity was also applied to yndiamides (see **Chapter 1**).[15]



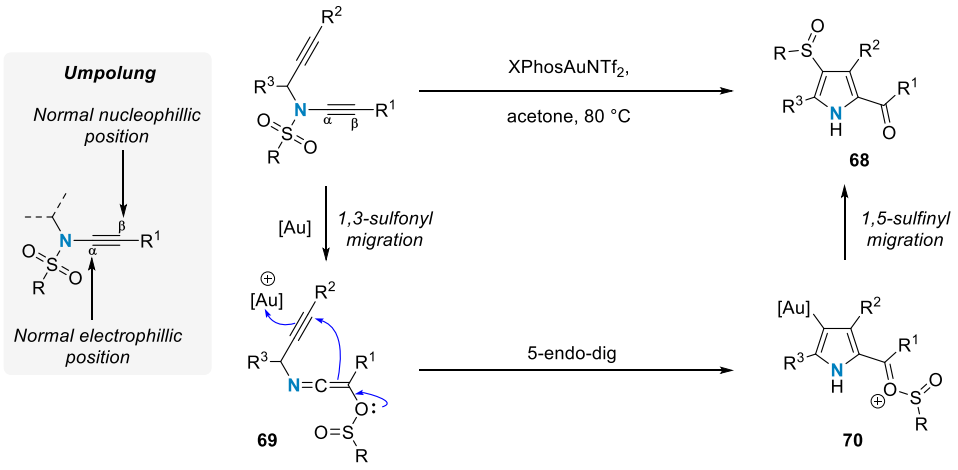
Scheme 2.10: Pd- or Ru-catalysed cyclisomerisation of ynamides to form azacycles.[45]

In 2018 Gagosz and co-workers reported a dual gold-catalysed formal tetradehydro-Diels-Alder (TDDA) reaction of ynamides to form indoline derivatives **64** (**Scheme 2.11a**),[46] followed shortly after by a similar report by Zi and co-workers (**Scheme 2.11b**).[47] In these transformations gold(I) is involved in both the formation of a gold(I) acetylide and activation of the ynamide triple bond. By using gold(I) in this dual-catalytic mode, both transformations avoid undesirable reaction conditions (high temperatures, low concentration, and radical inhibitors) commonly associated with intramolecular TDDA reactions, enabling them to synthesise various *N*-containing aromatic heterocycles. Deuterium labelling experiments conducted by Zi and co-workers suggested that the attack of the gold-acetylide (**65**) on the gold π-complex is followed by 6π-electrocyclisation of the diaurated intermediate **66**, then a 1,2-H shift and protodeauration to give the polycyclic product **67**. A more detailed mechanistic investigation was published in 2021 by Gagosz and co-workers;[48] in this work they provided further evidence for the formation of an intermediate diaurated (σ,π-) complex.



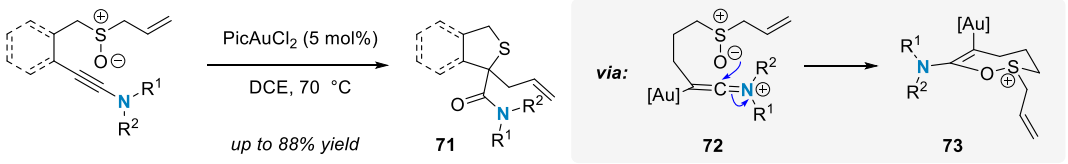
Scheme 2.11: Gold-catalysed TDDA reactions of ynamides featuring dual gold-catalysis.[46,47]

In the reactivity discussed thus far, the sulfonyl groups typically present in ynamides have generally been spectators in the cycloisomerisation processes, remaining attached to the nitrogen atom and requiring (reductive) removal post cycloisomerisation. This *status quo* changed with Sahoo and co-workers' 2019 work reporting a sulfonyl/sulfinyl migration cycloisomerisation cascade of yne-ynamides, to form sulfinylated pyrroles **68** (**Scheme 2.12**).[49] Their experimental work was accompanied by computational studies of the mechanism, which they propose consists of a gold-promoted 1,3-sulfonyl migration to form **69**, followed by an umpolung 5-*endo*-*dig* ring closure to form **70**, then a 1,5-sulfinyl migration. The 5-*endo*-*dig* cyclisation is an umpolung transformation because it involves the (former) ynamide α-carbon acting as a nucleophile to attack the tethered alkyne. Overall, a carbonyl moiety is installed at what had been the *β-position* of the ynamide – such functionality would normally be introduced at the *α-position* by nucleophilic attack on a keteniminium ion intermediate.[20]



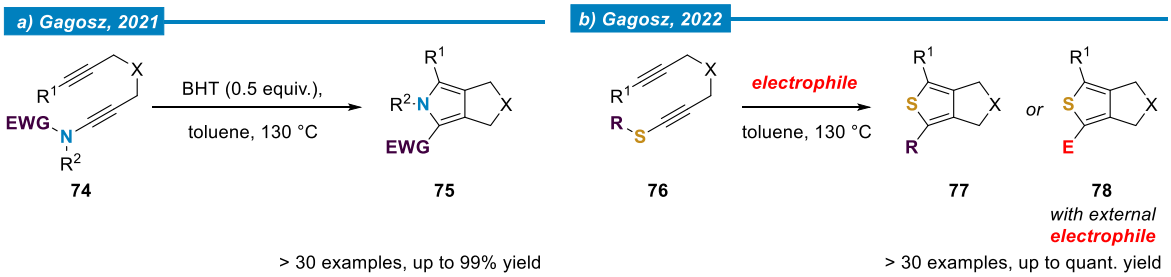
Scheme 2.12: Umpolung reactivity of ynamides with a tandem sulfonyl/sulfinyl migration under gold-catalysis.[49]

While syntheses of oxygen and nitrogen heterocycles by cycloisomerisation reactions are common, similar syntheses of sulfur heterocycles are less frequently encountered. In 2021 Davies and co-workers reported an unusual synthesis of tetrahydrothiophenes **71** by gold-catalysed cycloisomerisation of ynamides (also formally an intramolecular redox process) with a tethered allyl sulfoxide (**Scheme 2.13**).[50] In common with many of the reactions discussed previously, this transformation is proposed to proceed *via* a gold keteniminium ion (**72**). In a departure from the previously seen intramolecular attack by nucleophilic carbon atoms, the sulfoxide oxygen atom attacks the keteniminium ion, forming cyclic intermediate **73**, resulting in a formal intramolecular redox step. The regiochemical outcome was controlled by formation of one specific keteniminium ion from the ynamide – giving an overall *endo*- mode of reactivity in contrast to the same authors' previous work on alkyne-tethered allyl sulfoxides which gave predominantly *exo*- reactivity (as alkyne-gold complexes do not necessarily give inherent regioselectivity).[51]



Scheme 2.13 Cycloisomerisation of ynamides bearing a tethered allyl sulfoxide.[50]

Finally, in 2021, following the completion of the experimental work described below, Gagosz and co-workers reported an almost identical transformation of ynamides **74** to form fused pyrroles **75**, which proceeded with heating in the absence of a catalyst (**Scheme 2.14a**).[27] The mechanism of this transformation, and its relevance to the work described in this chapter, will be discussed in **Section 2.11**. In 2022, the authors extended this reactivity to alkynyl sulfides (**76**) to form thiophenes (**77** and **78**); they conducted extensive mechanistic experiments which supported the proposed existence of thiophenium ylide intermediates and were able to trap these species with various electrophiles (**Scheme 2.14b**).[52]



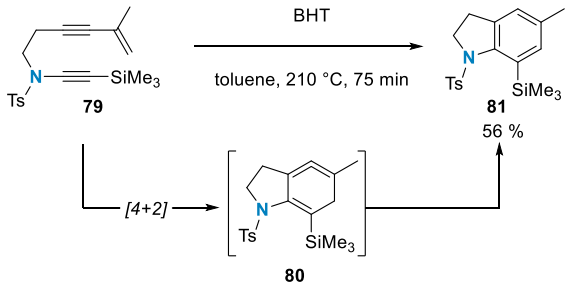
Scheme 2.14: *a)* Yne-yndiamides[27] and *b)* yne-alkynyl sulfides in [3+2] cycloisomerisation reactions.[52]

The reactivity reviewed in this section illustrates the broad range of known ynamide cycloisomerisation reactions, and forms the basis for the gold-catalysed reactions of yndiamides described below. Some of the reactivity discussed in this introduction is not directly applicable to yndiamides (for example reactions of terminal ynamides which do not have yndiamide analogues) but the general principles of how gold-keteniminium ions are trapped are useful when designing gold-catalysed cycloisomerisation reactions of yndiamdes. Furthermore, the frequency with which keteniminium ions are proposed as intermediates in these reactions poses both an opportunity and a challenge for yndiamide chemistry: yndiamides can form two isomeric keteniminium ions (potentially allowing access to two products), but forming these intermediates selectively is not a simple

proposition. As this chapter will describe, this has a profound impact on the reaction outcome.

2.3 Initial investigations and reaction discovery

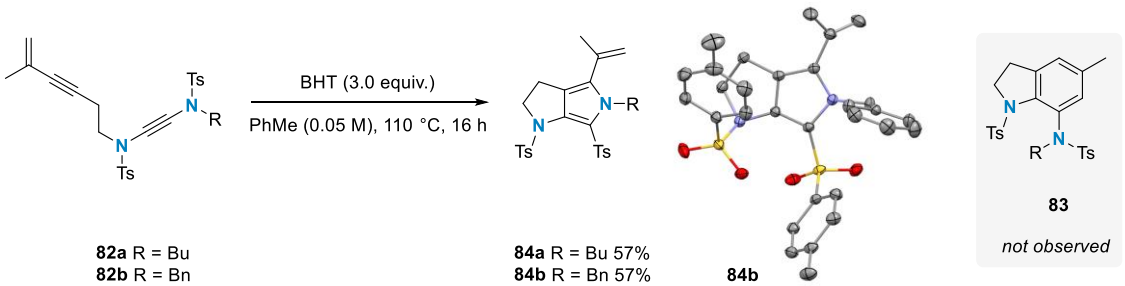
An initial interest in the synthesis of 1,2-diaminobenzene derivatives from yndiamides drew us to the formal [4+2] cycloaddition reactions of ynamides reported by Danheiser in 2005 (**Scheme 2.15**).[53] In this transformation, the ynamide in **79** undergoes a [4+2] cycloaddition reaction with the tethered ene-yne to initially form an isoaromatic cyclic allene (**80**) which rearranges to form the aromatised product **81**. This transformation was performed on various ynamides to form substituted indolines, some of which were then deprotected and oxidised to indoles. A similar [4+2] reaction of yne-yndiamides would provide access to 7-aminoindolines, and it was intended that exploring this transformation would stimulate further investigation of [4+2] reactivity of yndiamides.



Scheme 2.15: Formal [4+2] cycloaddition of ynamide with tethered ene-yne.[53]

Yndiamide **82a** was prepared using the standard yndiamide synthesis conditions and subjected to comparable conditions to those described by Danheiser and co-workers (**Scheme 2.16**). Complete consumption of **82a** was observed under the reaction conditions, however this was not accompanied by formation of the intended product **83**, as evidenced by the retention of the distinctive methylene proton signals in the ^{1}H NMR spectrum of the observed product **84a**. The analogous *N*-benzyl yndiamide **82b** was prepared and was subjected to the same reaction conditions to form the product **84b** which was easily

recrystallised, and single crystal XRD enabled the identification of **84b** as a fused pyrrole, remarkably featuring a new C–Ts bond (*crystallography and analysis performed by Dr Kirsten Christensen*). Consideration of how **84a** and **84b** might be formed suggested a formal [3+2] cycloaddition between the yndiamide and the alkyne followed by 1,2-sulfonyl migration. Although not the expected products, **84a** and **84b** are significant as members of an almost entirely unexplored class of nitrogen heterocycles, so this transformation was investigated further.



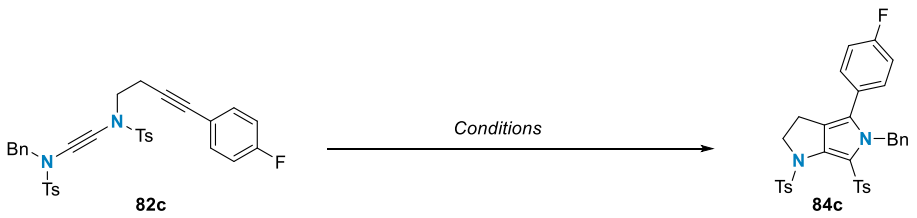
Scheme 2.16: Initial observations of a tandem cyclisomerisation-sulfonyl migration of ene-yne-yndiamides and single-crystal XRD structure of **84b**. Displacement plot for **84b** is displayed at 50% probability with hydrogen atoms hidden for clarity.

As the alkenyl moiety in **82a/b** did not directly participate in the cycloisomerisation reaction, aryl-substituted analogue **82c** was selected for further investigation of the transformation. Whilst the thermal cycloisomerisation conditions were appealing on the basis of operational simplicity, the cycloisomerisation reaction also presented the possibility of using transition metal-catalysis to achieve the transformation under milder conditions (**Section 2.5**).

2.4 Optimisation of thermally-promoted reaction conditions

Before searching for catalytic conditions to achieve the transformation, the thermal conditions were first optimised (**Table 2.1**). A radical inhibitor such as BHT (butylated hydroxytoluene) was required to avoid decomposition pathways (entries 2 and 3), although its loading could be reduced to 1.0 equivalent without detriment to the yield (entries 4 and 5). A further reduction in BHT loading to 0.10 equivalents was possible in the case of **82c**

(entry 6), but when this reduced loading was applied to other substrates increased decomposition was observed so a stoichiometric quantity of BHT was used to explore the scope of the reaction.



Entry	Additive	Time	Solvent	Temperature	Yield of 84c
1	-	18 h	DCE	r.t.	n.r.
2	-	18 h	DCE	80 °C	38%
3	-	18 h	PhMe	110 °C	41%
4	3.0 equiv. of BHT	18 h	PhMe	110 °C	76%
5	1.0 equiv. of BHT	18 h	PhMe	110 °C	78% (76%)
6	0.10 equiv. of BHT	18 h	PhMe	110 °C	74%

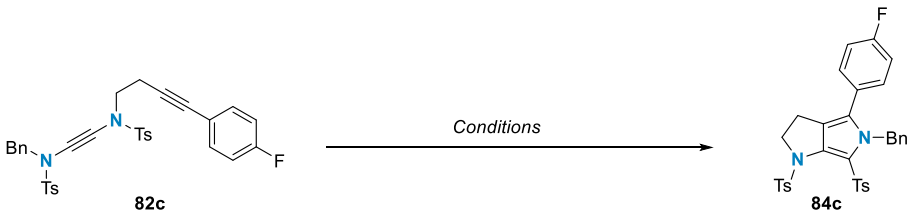
Table 2.1: Optimisation of thermal cycloisomerisation conditions for the transformation of **82c** to **84c**. All concentrations 0.050 M. Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. n.r. = No reaction.

2.5 Optimisation of transition metal-catalysed reaction conditions

In recent years the use of gold in the formation of heterocycles from ynamides has been widely explored (**Section 2.2**), and our group has also shown that yndiamides can be activated by formation of gold-keteniminium species.[21] Building on this, we anticipated that this cycloisomerisation reaction might also be promoted by transition metal-catalysis, so various silver(I) and gold(I) catalysts were screened to attempt to promote the reaction of yne-yndiamide **82c** (**Table 2.2**).

Silver(I) salts were ineffective catalysts for the transformation, leading to low conversion of **82c** to **84c**, accompanied by extensive decomposition of **82c** (entries 1–3); other groups have previously observed silver(I) catalysts to be poor promoters of ynamide cycloisomerisations.[54] Gold(I) chloride pre-catalysts alone were (unsurprisingly) poorly

effective (entries 4 and 5) but an NHC-Au catalyst and gold(I) pre-catalyst in conjunction with silver(I) salts (to activate the linear gold(I) complexes) gave vastly improved yields (entries 6–10). Using pre-formed $Ph_3PAuNTf_2$ (entry 11) gave a significant improvement in yield, probably related to the absence of silver(I), which appears to cause substrate decomposition (*see above*). The use of a more electron deficient phosphine ligand reduced the yield (entry 12), and a solvent screen identified 1,2-dichloroethane (DCE) as a suitable solvent (entries 13–17). In order to probe the possibility of a Brønsted acid-catalysed pathway operating, $HNTf_2$ was investigated as a catalyst, but this led to very low conversion to **84c**. The conditions in entry 11 were therefore selected to be used for the cycloisomerisation transformation.



Entry	Catalyst	Time	Solvent	Yield of 84c
1	$AgSbF_6$ [a]	18 h	DCE	8%
2	$AgNTf_2$ [a]	18 h	DCE	8%
3	$AgBF_4$ [a]	18 h	DCE	9%
4	Me_2SAuCl [a]	18 h	DCE	19%
5	PPh_3AuCl [a]	18 h	DCE	0%
6	$IPrAuNTf_2$ [a]	18 h	DCE	55%
7	Me_2SAuCl [a] + $AgNTf_2$ [a]	18 h	DCE	50%
8	PPh_3AuCl [a] + $AgNTf_2$ [a]	18 h	DCE	54%
9	PPh_3AuCl [a] + $AgNTf_2$ [a]	3 h	DCE	50%
10	XPhosAuCl [a] + $AgNTf_2$ [a]	3 h	DCE	41%
11	**PPh_3AuNTf_2 [a]**	**3 h**	**DCE**	**75%**
12	$(4\text{-}C_6H_4F)_3PAuNTf_2$ [a]	3 h	DCE	52%
13	PPh_3AuNTf_2 [a]	3 h	Acetone	< 5%
14	PPh_3AuNTf_2 [a]	3 h	$CHCl_3$	67%
15	PPh_3AuNTf_2 [a]	3 h	CH_2Cl_2	50%
16	PPh_3AuNTf_2 [a]	3 h	EtOAc	12%
17	PPh_3AuNTf_2 [a]	3 h	Benzene	27%
17	$HNTf_2$ [a]	3h	DCE	6%

Table 2.2: Optimisation of transition-metal catalysed cycloisomerisation conditions for the transformation of **82c** to **84c**. All reactions at room temperature. All reactions on 0.050 mmol scale. All concentrations 0.17 M. Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [a]10 mol%.

2.5.1 Gold(I) catalyst synthesis

For entries 10–16 the gold(I) catalysts were prepared from commercially available precursors. See the Supporting Information (**Section 7.3.1**) for details.

2.6 Yne-yndiamide synthesis

A range of yne-yndiamides (**82a-y**) were prepared next in order to explore the scope of the transformation (**Scheme 2.17**). A convergent route was used in which but-3-yn-1-ol underwent Sonagashira coupling reactions with a range of aryl iodides/bromides to form

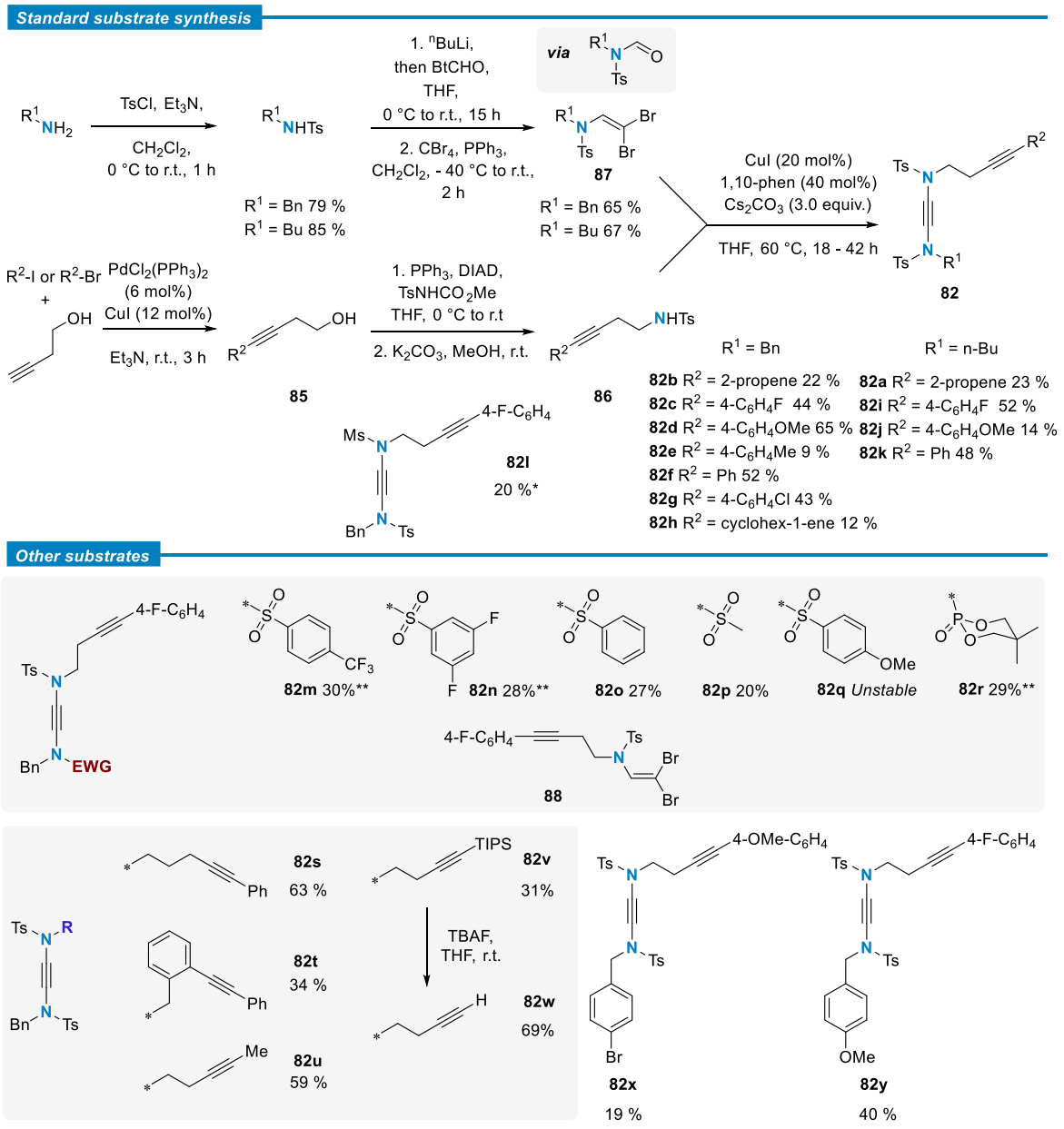
arylated alkynols (**85**), which were then converted to alkynyl sulfonamides (**86**) by a Mitsunobu reaction and subsequent base-promoted carbamate deprotection. Although reversing the order of the Sonagashira and Mitsunobu steps would have given a more divergent synthesis, this approach was not chosen as the presence of a sulfonamide was proved to be detrimental to the success of the Sonagashira reaction.

The 1,1-dibromoenamide coupling partners (**87**) required for the yndiamide synthesis were prepared in three steps from commercially available amines, with representative routes shown starting from benzylamine and butylamine. The synthesis of 1,1-dibromoenamides was found to be capricious in both the formylation and olefination steps, being sensitive to water content and rates of addition of reagents; nevertheless the required compounds were synthesised, albeit often in low yields.

The standard yndiamide synthesis procedure, developed in our group by Steven Mansfield,[1] was used without further modification for the preparation of all substrates, with yields ranging from low to moderate. In general, the formation of yndiamides **82a-y** was not problematic and they were routinely purified by chromatography without difficulty.

The alkynyl sulfonamides **86** were typically used as the nucleophilic component in the yndiamide coupling, however the olefination step using CBr_4/PPh_3 was unsuccessful using formamides protected with strongly electron-withdrawing groups (**82m–n** and **82r**). In these cases the coupling reaction was reversed, and the 1,1-dibromoenamide moiety was instead installed on the alkynyl sulfonamide precursor (**88**).

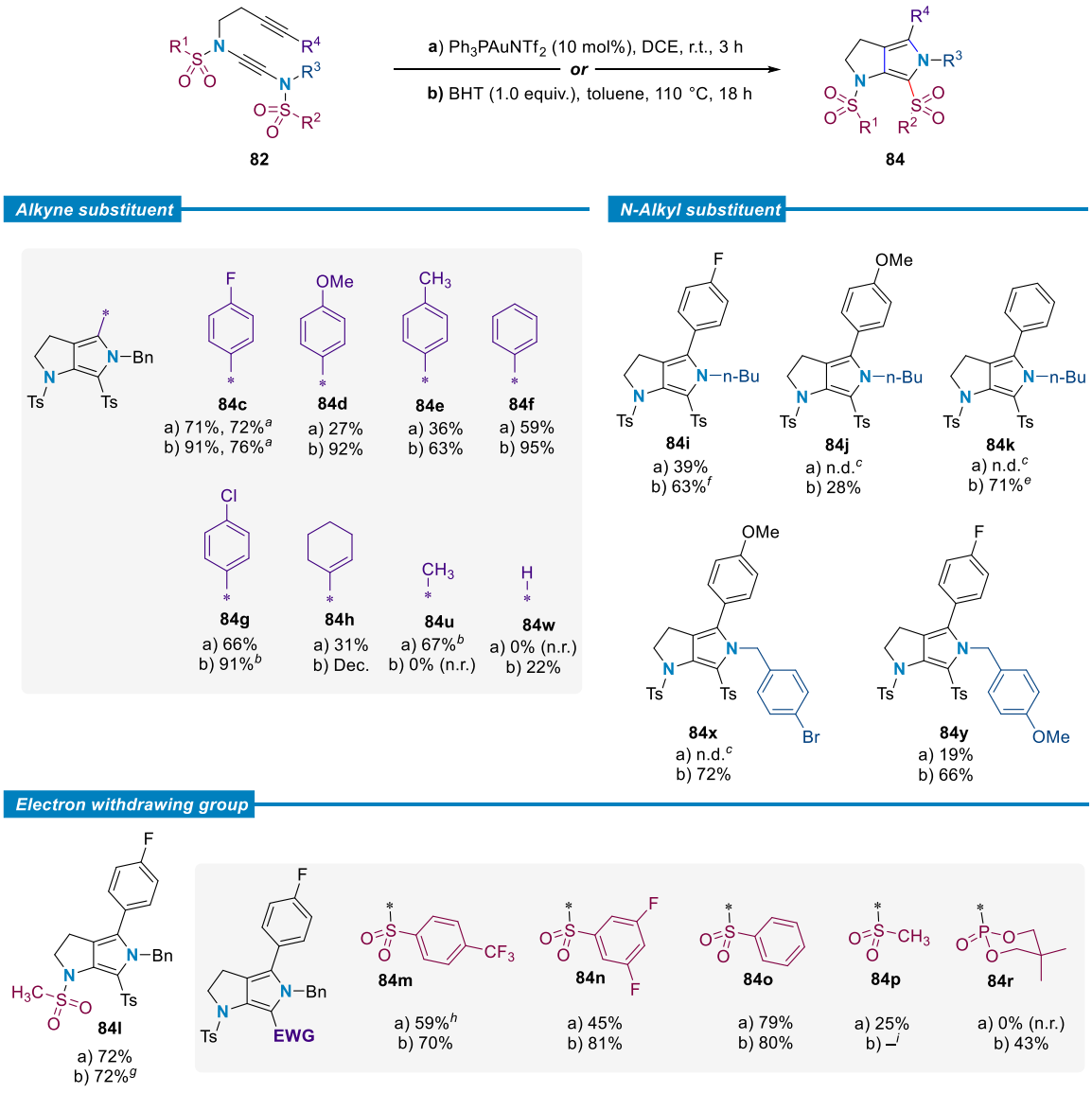
Attempts to prepare yne-yndiamide **82w** directly from the corresponding sulfonamide were unsuccessful, so the triisopropylsilyl protected yne-yndiamide (**82v**) was prepared and deprotected by treatment with TBAF to give **82w**.



Scheme 2.17: Synthesis of yndiamides **82a**–**y**. * Substrate prepared by Prof. Yubo Jiang. ** Substrates prepared using **88** as the 1,1-dibromoenamide partner.

2.7 Reaction scope of yne-yndiamide cycloisomerisation

The scope of the cycloisomerisation transformation was then investigated. Both sets of optimised conditions were applied to each substrate to demonstrate the complementarity of the approaches, and to gain mechanistic understanding by comparison of the reaction outcomes (**Scheme 2.18**).



Scheme 2.18: Scope of the cycloisomerisation of yne-yndiamides to fused pyrroles by gold-catalysis or under thermal conditions in the absence of a catalyst. All reactions on 0.10 mmol scale except where stated. [a] Reaction on 1.0 mmol scale. [b] Reaction on 0.050 mmol scale. [c] Yield of reaction not determined (n.d.) due to extensive decomposition. [e] 3.0 Equiv. BHT used. [f] 0.10 Equiv. BHT used. [g] Reaction on 0.060 mmol scale. [h] Reaction time 24 h. [i] Reaction not conducted due to starting material instability.

The cycloisomerisation reaction was found to be broadly applicable to aryl-substituted alkynes **82c**–**g**, forming the corresponding pyrroles **84c**–**g**, although for electron rich aromatic rings (**84d**–**e**) the thermal process was more effective than the gold-catalysed conditions because electron-donating aryl groups promoted the formation of piperidin-3-imines **93d**–**e** and **93x** (**Scheme 2.22**) as the major products. The formation of these products is discussed in **Section 2.9**.

The complementary nature of the two reaction conditions was demonstrated in the case of yne-yndiamide **82u** containing a methyl-substituted alkyne; under thermal conditions no reaction was observed, implying a beneficial effect of an unsaturated moiety at the alkyne terminus. In contrast, when **82u** was subjected to the Au-catalysed conditions, pyrrole **84u** was formed in good yield. The converse situation was encountered for **82w**; no reaction was observed under gold-catalysis, which may be due to the formation of a σ-complex between the terminal alkyne and the gold(I) catalyst.[42,48,55,56] Formation of a σ-complex would prevent the gold catalyst activating the yndiamide, so no cyclisation could occur. However, when **82w** was heated it underwent the cycloisomerisation to form **84w** in low yield, with the remaining material being insoluble decomposition products. With hindsight, the thermal reaction of **82w** may have benefited from more rigorous measures to avoid decomposition of the terminal alkyne, such as solvent degassing or investigation of alternative radical inhibitors. The mechanistic implications of these observations are discussed in **Section 2.12**.

Ene-yne-yndiamides (**82b** and **82h**) were of special interest because of their selectivity for the observed cycloisomerisation/1,2-sulfonyl migration process over the initially expected intramolecular [4+2] process.[53] Both **82b** and **82h** reacted under gold-catalysis to give the corresponding pyrroles **84b** and **84h**, but whereas **82b** was successfully isomerised to **82h** under thermal conditions, **82h** was not, instead completely decomposing. It is conceivable that steric clash of the bulky sulfonamide moieties of the yndiamide with the cyclohexene ring prevented the concerted approach required for the thermal cycloisomerisation (**Section 2.12**). In contrast, the stepwise mechanism proposed for the gold-catalysed approach (**Section 2.13**) does not require a concerted approach of the yndiamide and alkyne. The lack of expected [4+2] reactivity under the thermal conditions further demonstrates the differing reactivity of yndiamides and ynamides, as well as emphasising that the carbon-carbon triple bond of an yndiamide or ynamide must be viewed as distinct from non-

heteroatom substituted alkynes. The absence of [4+2] reactivity is also consistent with the observations of Gagosz and co-workers in their 2021 report of ynamide [3+2] cycloadditions.[27]

Varying the non-migrating group on the terminal sulfonamide formed pyrroles with different *N*-substitution (**82i**–**k**, **82x**–**y**), and while the reactivity was generally reliable for the thermal conditions, application of the gold-catalysed conditions to electron-rich *N*-*p*-methoxybenzyl substituted yndiamide **82y** resulted in a low yield of the product **84y** as part of a complex mixture of products.

Finally, the scope of the electron-withdrawing groups on nitrogen was investigated. The *non-migrating* sulfonyl group (on the internal nitrogen atom of the yne-yndiamide) was changed to a methanesulfonyl group without detriment to the yield under both sets of conditions (**84l**). Other sulfonyl protecting groups may also suitable for the 'internal' nitrogen atom of the yndiamide but this was not further investigated as derivatisation of the products showed that selective removal of the *N*-Ts group was facile (**Section 2.11**). This would allow functionalisation of the nitrogen atom *post-cycloisomerisation.*

The electronic properties of the migrating sulfonyl group were investigated (**82m–r**) and a positive correlation was found between increasing electron-withdrawing strength and reaction time (**84m–o**), with remaining starting material being observed after the standard reaction time. Migration of a methanesulfonyl group was more problematic; while **84p** was formed under gold-catalysis, under thermal conditions **82p** decomposed. Migrations of methanesulfonyl groups have previously been reported as challenging and this is proposed to be due to competing deprotonation of the methanesulfonyl group to form a sulfene – a decomposition pathway which cannot occur for arylsulfonamides as they lack the necessary α-protons.[57] It may be that a similar decomposition pathway is in operation in the case of

82p. An attempt to investigate the migration of a less electron-withdrawing *p*-methoxybenzenesulfonyl group was not possible because yndiamide **82q** was unstable as a result of the reduced electron-withdrawing stabilisation offered by this group.

As discussed in **Section 1.2**, yndiamides can incorporate phosphonate diesters as electron-withdrawing groups, although the synthesis of these compounds is more challenging. Although subjecting phosphoramidate yndiamide **82r** to the gold-catalysed conditions was not successful, the desired product **84r** was formed by heating **82r**, involving a remarkable 1,2-migration of a phosphonate diester. The success of the tandem cycloisomerisation-migration process was initially indicated by observation of splitting of aromatic ^{13}C NMR peaks due to $^{13}C–^{31}P$ coupling, and was confirmed by single crystal XRD of **84r** (**Figure 2.1**). To the best of our knowledge such a migration of a phosphonate diester has not been observed before in ynamide chemistry. This is in contrast to the proliferation of sulfonyl migrations reported in recent years[58] – indeed there is good precedent for *N*-phosphoryl ynamides undergoing a variety of transformations *without* migration of a phosphonate diester.[59,60]The formation of **84r** is significant as it provides access to an α-aminophosphonate derivative; these compounds are often biologically active and some are of potential medicinal interest.[61,62]

Fused pyrroles **84c** and **84r** were recrystallised to prepare crystals suitable for analysis by single-crystal XRD (**Figure 2.1**). *The data collection and processing for this aspect of the work were carried out by Dr Kirsten Christensen and Helena Pickford.*

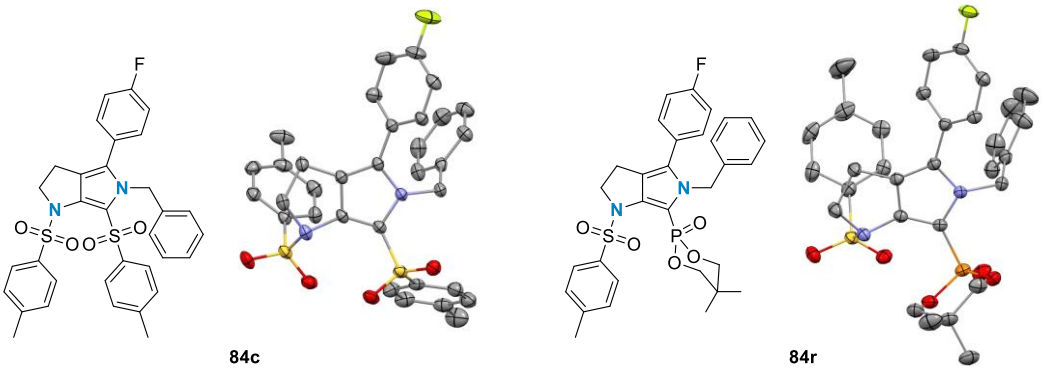
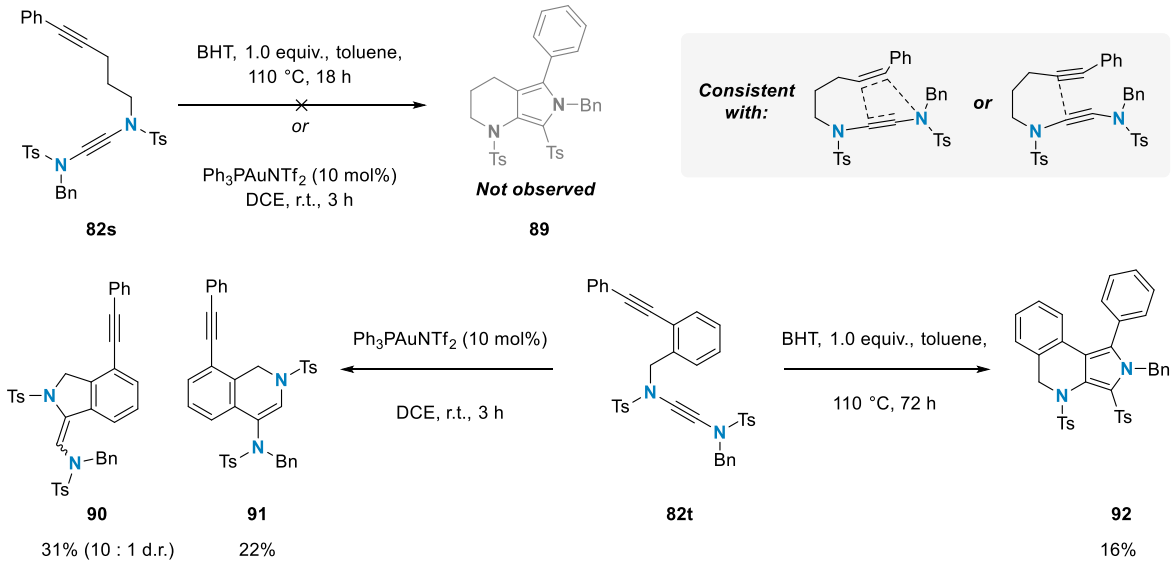


Figure 2.1: Single crystal XRD structures for fused pyrroles **84c** and **84r**. Displacement plots are displayed at 50% probability with hydrogen atoms hidden for clarity. *Note: **84r** crystallised with methanol, which has been hidden for clarity.*

2.8 Unsuccessful yne-yndiamide substrates

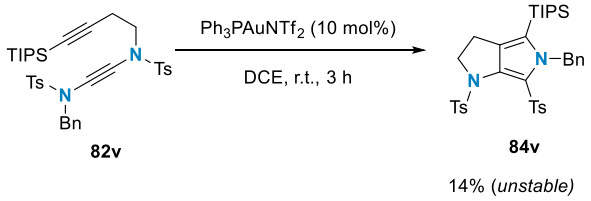
The substrates which *did not* undergo the cycloisomerisation reaction will now be discussed and the limitations of the reactivity will be analysed.

Attempts to utilise a longer linker between the yndiamide and alkyne moieties in the cycloisomerisation reaction were unsuccessful – yne-yndiamide **82s** was completely unreactive under both sets of conditions and the desired product **89** was not observed (**Scheme 2.19**). Even when the linker was substituted with a benzene ring (**82t**), no desired product was observed under gold-catalysis, instead a Pictet-Spengler type cyclisation occurred to give a mixture of products **90** and **91**. Heating **82t** for an extended period of time was required to achieve the cyclisation in very low yield (**92**). This reduced reactivity with the extended tether is consistent with a mechanism involving an asynchronous cyclisation event which would be promoted by close proximity of the triple bonds, as is the case in a 1,6-yne-yndiamide. Furthermore, these observations are consistent with other cycloisomerisation reactions; diyne cycloisomerisations, while prolific for 1,5- and 1,6-diynes, are less common for higher 1,n-diynes. It is important to note the additional substitution typically present in the linkers of the substrates for reactions of higher 1,n-diynes, which are consequently promoted by a Thorpe-Ingold effect.[63,64]



Scheme 2.19: Reactivity of yndiamides **82s** and **82t** under gold-catalysis or thermal conditions.

Triisopropylsilyl-substituted yndiamide **82v** reacted under the gold(I)-catalysed conditions to give a complex mixture of products (**Scheme 2.20**). The desired product **84v** was isolated in low yield but it proved to be unstable in both $CDCl_3$ and C_6D_6, preventing full characterisation (however, preliminary data was indicative of its successful formation). Silylated pyrroles readily undergo acid-promoted rearrangement/decomposition processes,[65] and it is possible that this explains both the low yield and instability of **84v**.

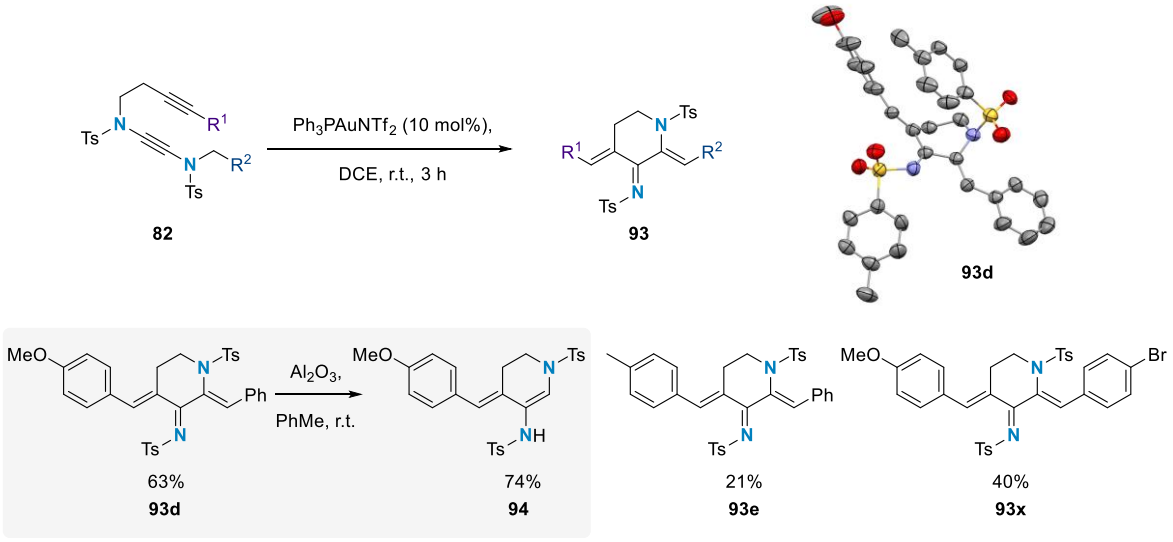


Scheme 2.20: Cycloisomerisation of TIPS-protected yne-yndiamide **82v** under gold-catalysis.

2.9 Piperidine-3-imine synthesis

The major products of gold-catalysed cycloisomerisations of yndiamides bearing electron-rich aryl alkynes (**82d–e** and **82x**) initially eluded identification as the NMR spectra of the products (**93d–e** and **93x**) exhibited extreme broadening in the aliphatic region of the ^{1}H NMR spectrum, which made normal methods of analysis by means of 2D spectra (COSY,

HSQC and HMBC) extremely challenging. Eventually, single crystal XRD of **93d** allowed identification of the structure as a piperidine-3-imine derivative (**Scheme 2.21**) (*data collection and analysis carried out by Dr Kirsten Christensen)*. An attempt to hydrolyse the tosylimine in **93d** with basic alumina[66] instead resulted in a hydration / retro-aldol type reaction to form **94** in good yield.

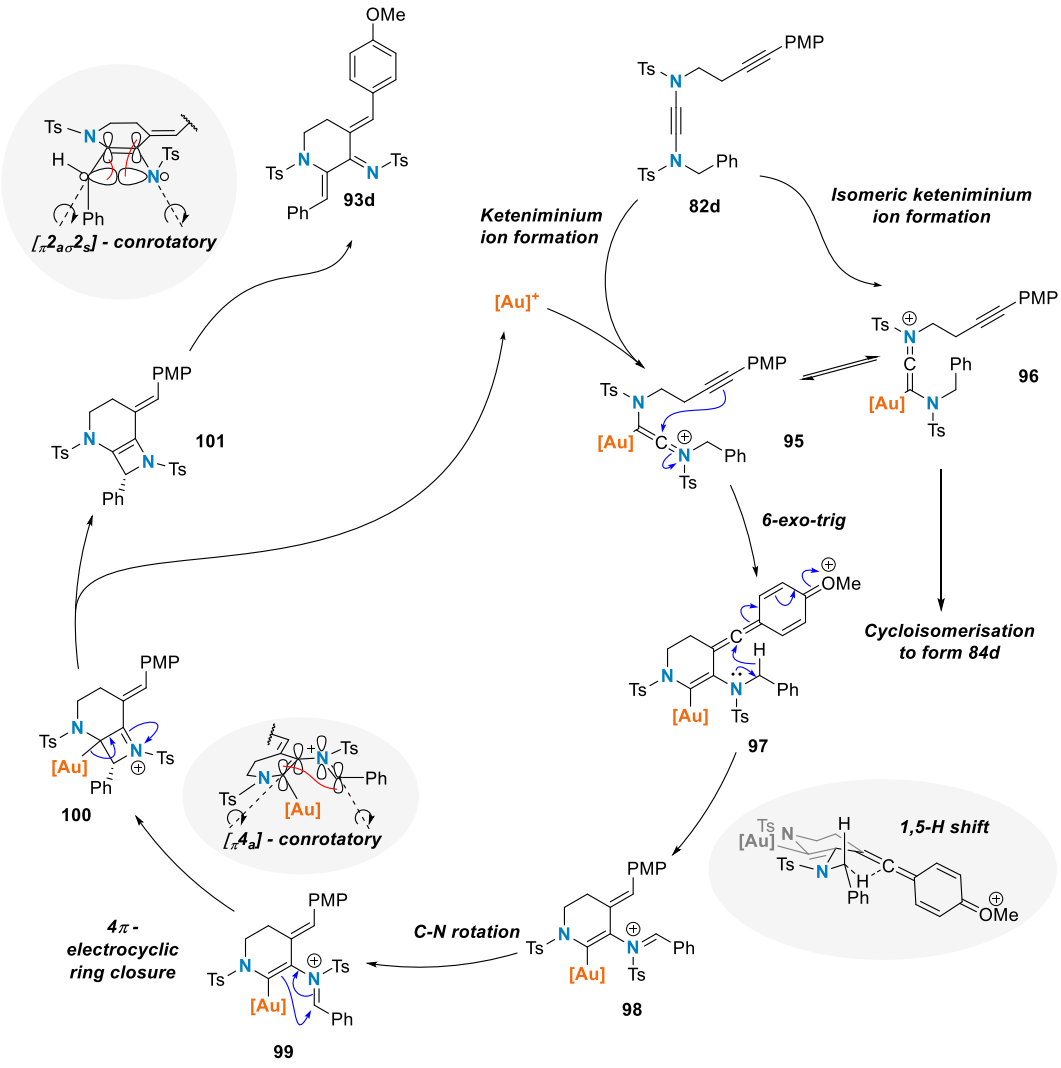


Scheme 2.21: Cycloisomerisation of yne-yndiamides featuring electron-donating aryl groups to form piperidine-3-imines **93d–e** and **93x** and single crystal XRD structure of piperidine-3-imine **93d**. Displacement plot for **93d** is displayed at 50% probability with hydrogen atoms hidden for clarity.

The formation of **93d–e** and **93x** poses an interesting mechanistic question. First, the formation of these products is only observed when R^1 is an electron-rich aryl group, suggesting that the mechanism might involve stabilisation of an intermediate containing a benzylic cation. The observed regioisomer of **93d–e** and **93x** implies formation of the opposite keteniminium ion to that required for formation of the typically observed cycloisomerisation products **84**. A related computational mechanistic investigation of gold-catalysed oxidative functionalisations of yndiamides currently being carried out in our group by Zixuan Tong revealed that the two possible keteniminium ions formed from an unsymmetrical yndiamide can interchange through a transition state that strongly resembles

a classical alkyne-metal π-complex. This exchange could account for the existence of the required keteniminium ion in the formation of **93d–e** and **93x**.

A mechanism for the formation of **93d** is proposed in **Scheme 2.22**. First, π-coordination of the yndiamide to gold forms keteniminium ion **95** (or its isomer **96**, which can isomerise to **95**); the tethered electron-rich alkyne then attacks the keteniminium ion in a *6-exo-trig* process forms the piperidine ring (**97**). Rearomatisation of the PMP ring could then occur by a 1,5-hydride donation from the α-benzylamine group to form **98**; similar hydride shifts have been reported with both stabilisation by an α-heteroatom and attack onto an allene[67–69]. Rotation about the exocyclic C–N bond would then position the newly-formed iminium ion **99** to take part in a 4π conrotatory electrocyclic ring closure, forming **100**, which would be followed by a deauration step to form a dihydroazete (**101**). A 4π conrotatory electrocyclic ring opening would give the product (**93d**) with the observed alkene and imine geometries.



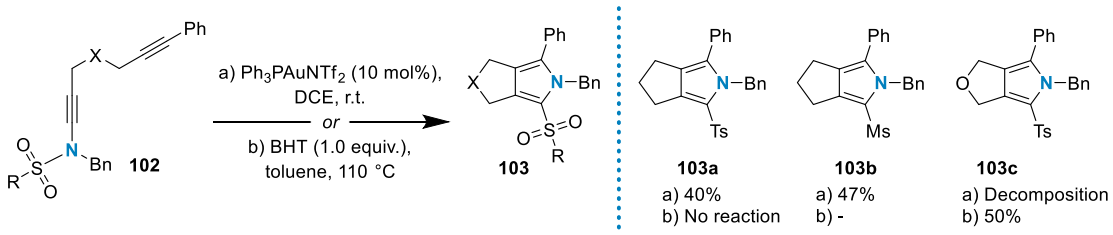
Scheme 2.22: Proposed mechanism for the cycloisomerisation of **82d** to form **93d** under gold-catalysis.

This divergent reactivity of electron-rich yne-yndiamides under gold-catalysis provided useful insight into the behaviour of yndiamides under these conditions and demonstrates the significance of keteniminium ion interconversion in determining reaction outcome. Notably, the products **93d–e** and **93x** are a structurally interesting class of aza-dendraline derivatives, which might offer potential for future development.

2.10 Investigation of yne-ynamide reactivity

A brief investigation of the thermal and gold-catalysed cycloisomerisation of ynamides was carried out in order to explore how their reactivity differs to yndiamides. This work was carried out prior to Gagosz and co-workers's report of this reactivity for a much larger range

of ynamides; their method was broadly similar but employed higher temperatures (**Section 2.2**).[27] Ynamides **102a**–**c** were prepared by Professor Yubo Jiang according to the procedure developed by Hsung and co-workers[4] and were subjected to the previously optimised conditions for the cycloisomerisation transformation, forming pyrroles **103a**–**c** (**Scheme 2.23**). Under gold-catalysis the reaction was slower, and less selective, than for the analogous yndiamides. Reduced (slower) reactivity was also observed for the thermal process – this is unsurprising when considering the higher temperatures employed by Gagosz and co-workers to achieve the same transformation. The mechanistic implications of the poorer performance of gold-catalysis for ynamides will be discussed in **Section 2.13**.



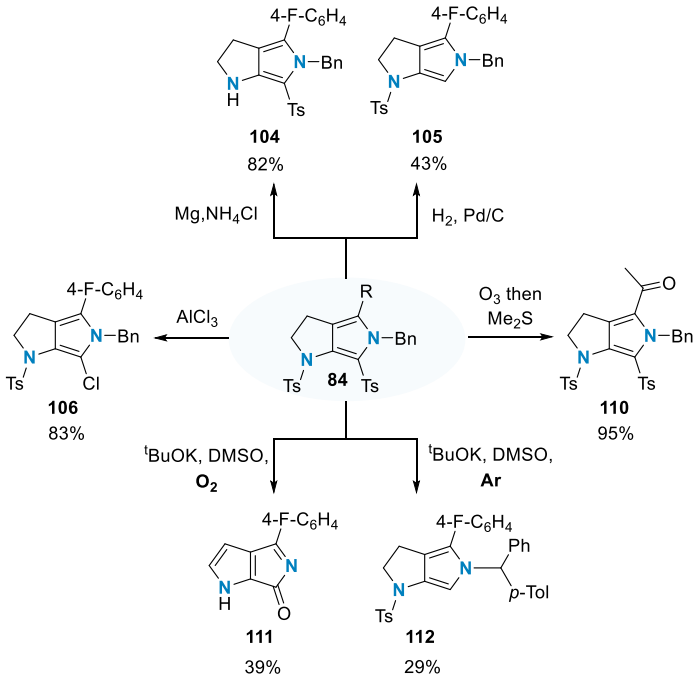
Scheme 2.23: Reactivity of ynamides **99a–c** under gold-catalysis or thermal conditions. All reaction times 18 h.

2.11 Derivatisation reactions of fused pyrrole products

To demonstrate the applicability of these novel fused pyrrole scaffolds in the synthesis of biologically and medicinally relevant molecules, we explored various modes of derivatisation of pyrroles **84b** and **84c** (**Scheme 2.24**). As a result of the 1,2-sulfonyl migration which occurs in tandem with the cycloisomerisation process, this class of fused pyrroles contains three protecting groups which we envisaged would be removable under orthogonal conditions: *i)* C–Ts, *ii)* N–Ts, and *iii)* N–Bn. We set out to achieve individual deprotections of each of these groups.

Treatment of **84c** with magnesium turnings in MeOH under sonication selectively removed the N–Ts group to form **104**. Further functionalisation of the unprotected nitrogen atom could be envisaged from this product.

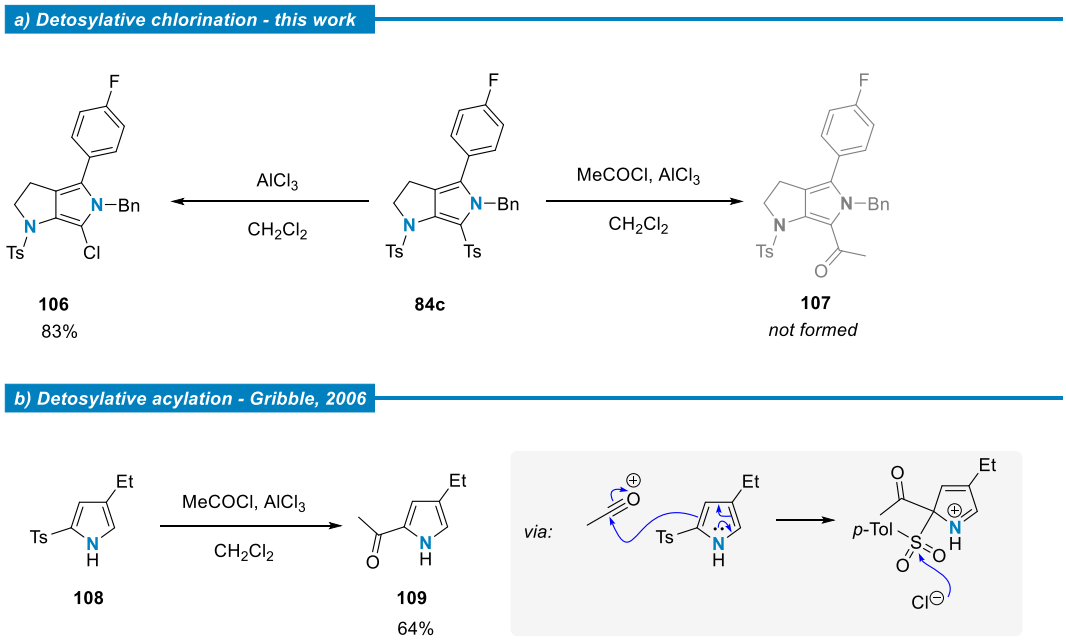
The C–Ts group was removed by hydrogenation to form **105**, and although this process was slow (requiring 4 days reaction time and additional catalyst after 2 days to maximise the conversion), it was completely selective for the C–Ts group over the N–Ts group. Somewhat surprisingly, no (N–Bn) debenzylation was observed under these conditions.



Scheme 2.24: Derivatisation reactions of fused pyrroles **84b** and **84c**.

An attempt to achieve a detosylative Friedel-Crafts acylation of **84c** led to the serendipitous discovery of a detosylative chlorination at the 2-position of the pyrrole ring (**106**). This was inspired by Gribble and co-workers' electrophilic *ipso* acylation-detosylation of pyrroles,[70] but application of their conditions to **84c** led to only formation of the chlorinated product (**106**) and no formation of the acylated product (**107**), using either acetyl chloride or isovaleryl chloride as the acylating agent (**Scheme 2.25a**). In their exploration of similar transformations, Gribble and co-workers observed detosylation of pyrrole **108** and formation of a 2-acylated pyrrole (**109**), proposing a mechanism involving *ipso*-electrophillic attack to form the new acyl bond followed by chloride attack on the sulfonyl group to liberate tosyl

chloride and form the product **109** (**Scheme 2.25b**). The authors do not comment on whether the chlorinated product was also formed in this transformation.



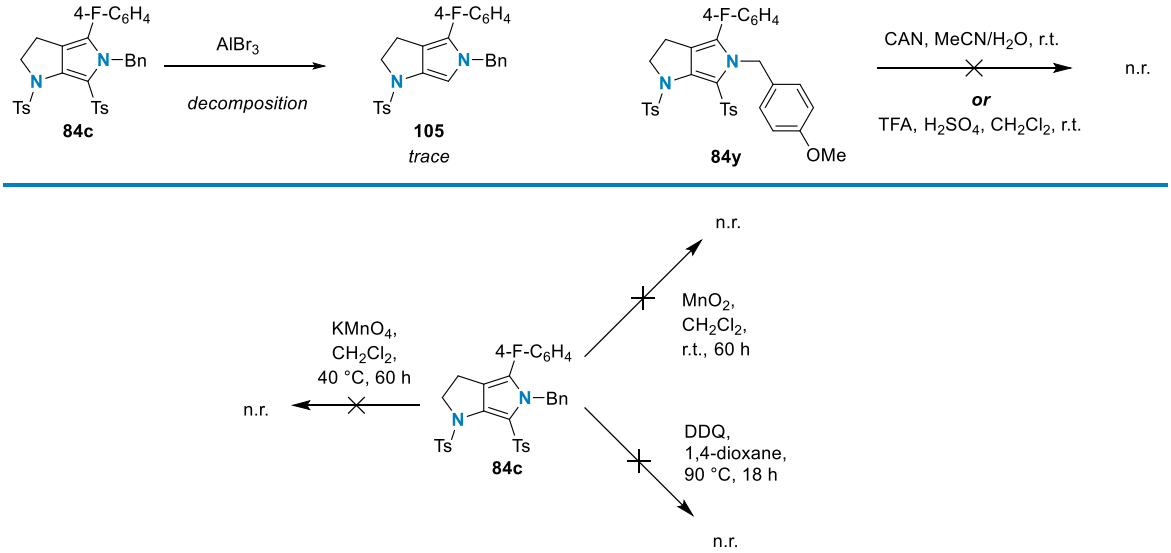
Scheme 2.25: *a)* Detosylative chlorination observed for pyrrole **84c** and *b)* proposed mechanism for the detosylative acylation of 2-tosylpyrroles reported by Gribble and co-workers.[70]

Similar reactivity was *not* observed using $AlBr_3$; instead, formation of the detosylated (but not brominated) product **105** was observed (**Scheme 2.26**) in low yield as part of a complex mixture of decomposition products. The decomposition may be due to the greater Lewis acidity of $AlBr_3$ not being compatible with the pyrrole moiety.

A carbonyl group was introduced into the 5-position of the pyrrole ring by ozonolysis of **84b** to give methyl ketone **110** in excellent yield, thus demonstrating the potential for post-cycloisomerisation introduction of functionality onto the pyrrole ring.

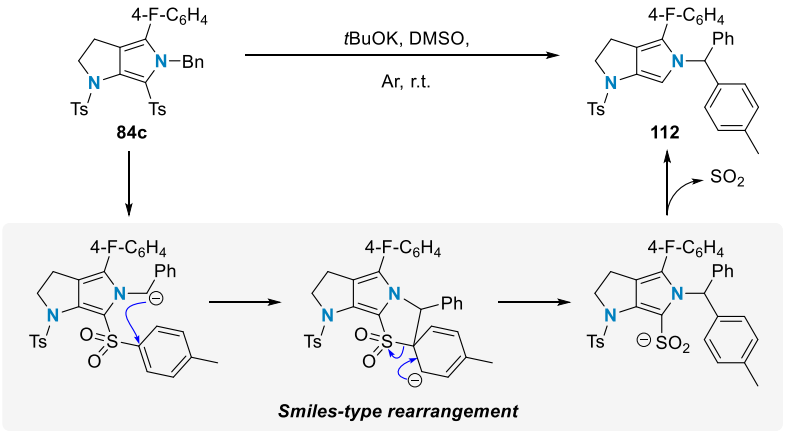
The investigation then turned to subjecting **84c** to oxidative conditions which might enable selective removal of the N-Bn group, possibly with concomitant oxidation of the pyrrolidine ring, however none of the three approaches resulted in any reaction, and **84c** was returned unchanged in all cases (**Scheme 2.26**). PMB-protected pyrrole **84y** was also synthesised (see

Scheme 2.17) and was subjected to oxidative cleavage conditions to attempt to form the unprotected pyrrole, but once again this was not successful. Although the lack of reactivity under any of the oxidative conditions investigated appears disappointing, it does suggest that other oxidative transformations might be feasible without affecting the core of the structure.



Scheme 2.26: Unsuccessful functionalisation attempts of fused pyrroles **84c** and **84y**.

As a final attempt to achieve the *N*-benzyl deprotection, **84c** was treated with potassium *tert*-butoxide in DMSO under an atmosphere of O_2. Oxidation/deprotection occurred at *four* sites, forming **111** in low yield. Intriguingly, when the same reagents were employed under an atmosphere of argon, a Smiles-type rearrangement occurred, forming **112** (**Scheme 2.27**). This reactivity is appealing from a mechanistic perspective and it is possible that it might also be applicable to a broader range of pyrroles or heterocycles.

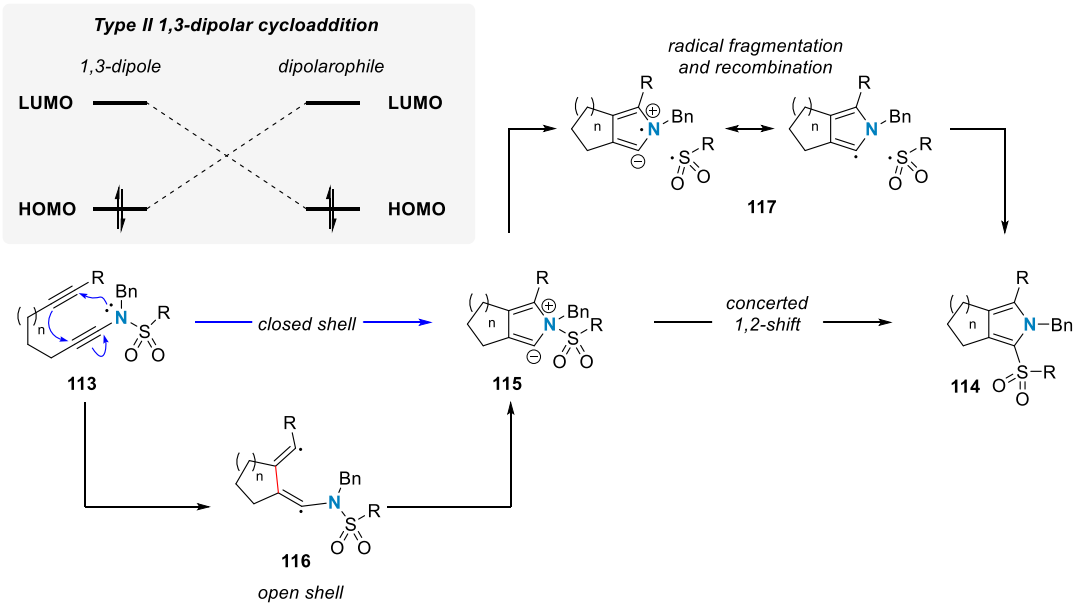


Scheme 2.27: Proposed mechanism for Smiles-type rearrangement of **84c** under basic conditions.

2.12 Mechanism of the thermal cycloisomerisation reaction

The mechanism by which pyrroles **84** are formed in this cycloisomerisation process is of interest as it gives further insight into the reactivity of yndiamides compared to ynamides.

The mechanistic discussion of the thermal cycloisomerisation reaction of yne-yndiamides will build upon the analogous report for yne-ynamides (**113**) from Gagosz and co-workers to form pyrroles (**114**) (**Scheme 2.28**).[27]



Scheme 2.28: Mechanistic proposal provided by Gagosz and-coworkers for formal [3+2] cycloaddition of yne-yndiamides.[27]

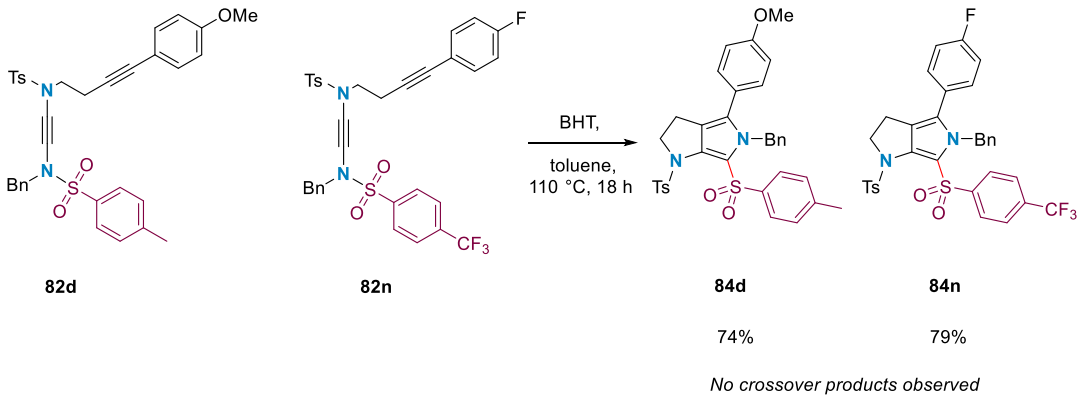
The first step of the mechanism – the thermal [3+2] cycloaddition/1,2-sulfonyl migration of ynamides – was investigated in detail by Gagosz and co-workers, using experimental and computational methods. Based on a U-shaped Hammett plot of experimentally determined rate constants, they suggested that the cyclisation could occur by one of three mechanisms: *i)* a type II cycloaddition process (**113**→**115**) (controlled by the HOMO and LUMO energies of the 1,3-diople[71]), *ii)* a diradical process (*via* **116**), or *iii)* by divergent mechanisms. The authors demonstrated the plausibility of a closed shell type II cycloaddition process by locating the pyrrolium ylide intermediate (**115**) and the concerted transition state by DFT, and they were also able to locate singlet diradical intermediates (**116**) and transition states which were consistent with the diradical mechanism.

Gagosz and co-workers were unable to trap any radical intermediates with TEMPO or molecular oxygen, although the possibility that short-lived radicals may not interact with other molecules present prompted them to use an intramolecular probe – a cyclopropyl alkyne – which showed significant isomerisation and supported a possible radical mechanism. Based on their experimental and computational findings, the authors could not rule out either pathway, but they proposed that whichever mechanism operates (pericyclic or diradical) the bond forming is asynchronous and goes through short-lived intermediates. Additionally, their finding that alkyl-substituted alkynes had a significantly higher energy barrier in this process is consistent with our observation that **82u** (bearing a methyl-substituted alkyne) was unreactive under the standard thermal conditions and required application of the gold-catalysed conditions to produce fused pyrrole **84u**.

Considering the cycloisomerisation of yndiamides, when a sample of **82a** was stored in d_8-toluene for 2 months, approximately 15% conversion to the cycloisomerised product **84a** was observed (in comparison with Gagosz and co-workers's observation of the rearrangement process occurring at room temperature over 1.5 weeks in 99% yield). It is

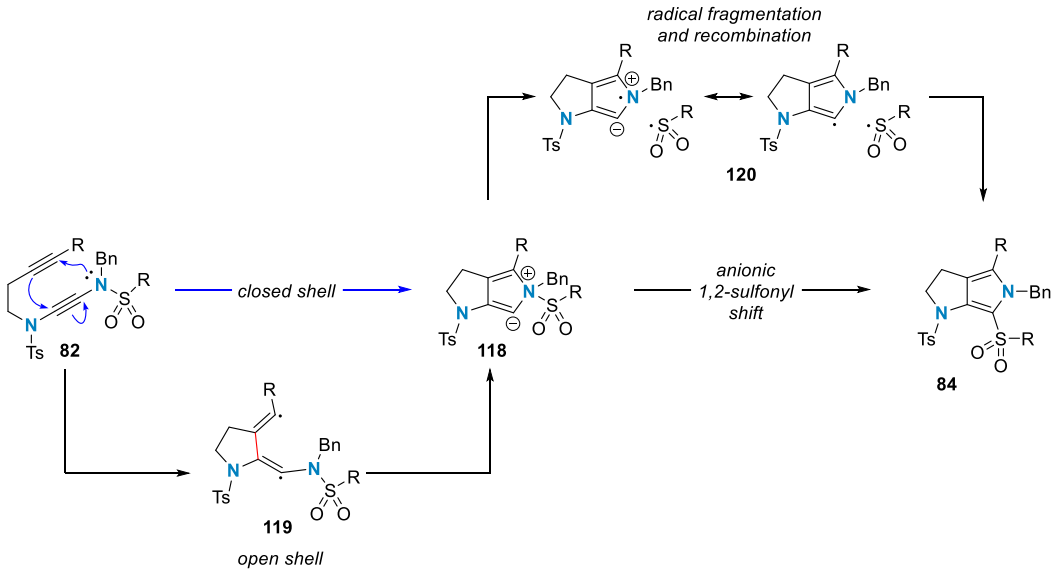
important to note that this is not necessarily proof of a spontaneous room temperature cycloisomerisation process as trace metal contamination (palladium and copper, which might conceivably catalyse the reaction) from the synthesis of **82a** cannot be ruled out. When the same sample of **82a** was subjected to Variable Temperature (VT) ^{1}H NMR spectroscopy at 100 °C, rapid isomerisation to **84a** occurred, but no intermediates were observed, implying that they do not accumulate to an observable quantity.

For yndiamides, the proposed 1,2-sulfonyl migration was investigated by a crossover experiment (**Scheme 2.29**). No crossover products were observed, which is consistent with an intramolecular 1,2-sulfonyl migration process with transient intermediates (**117**/**120**) which do not interact outside of the solvent cage, and agrees with the findings of Gagosz and co-workers, who performed a similar experiment.[27] The success of this step in the presence of excess BHT (a radical inhibitor, which would trap any radical intermediates which did escape the solvent cage) is also consistent with a closed-shell pathway. This also agrees with the computational results obtained by Gagosz and co-workers, who calculated a very low barrier (6.1 kcal/mol) for a [1,5]-sigmatropic rearrangement taking place through the π-system of the pyrrolium intermediate (**118**).



Scheme 2.29: Thermal crossover experiment between **82d** and **82n**. *Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.*

Following consideration of our experimental observations alongside the experimental and computational findings of Gagosz and co-workers, a mechanistic proposal is given in **Scheme 2.30**. The initial cyclisation event may happen by either a closed (**82**→**118**) or open (**119**) shell pathway, followed by a radical (**120**) or anionic sulfonyl migration. The available data is insufficient to allow the mechanism to be elucidated with more certainty.

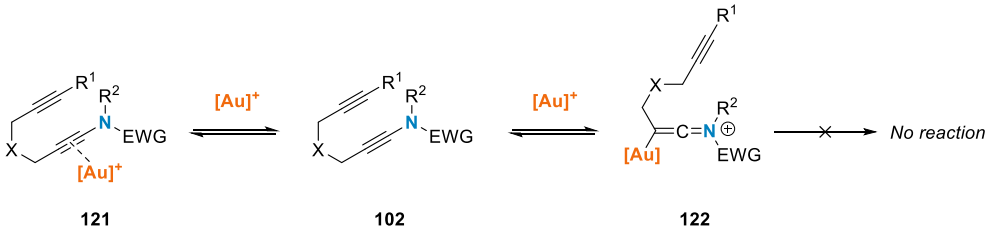


Scheme 2.30: Possible mechanistic pathways for the thermal cycliosomerisation reaction, adapted from the mechanisms proposed by Gagosz and co-workers.[27]

2.13 Mechanism of the gold-catalysed cycloisomerisation reaction

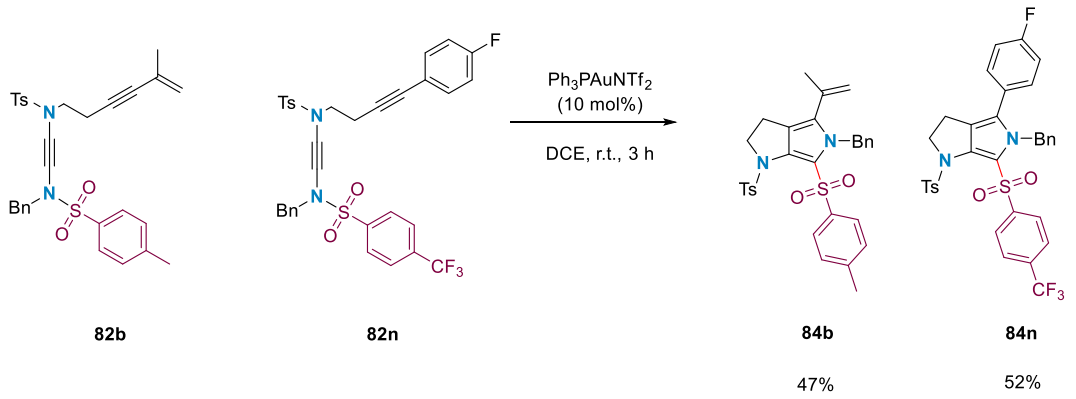
Turning to the gold-catalysed cycloisomerisation process, comparison of the behaviour of yndiamides and ynamides under the same catalytic conditions is useful for probing the mechanism of the transformation. Ynamides readily form reactive keteniminium ion intermediates with a variety of electrophiles,[72] and recently our group reported a gold-catalysed transformation of yndiamides, which also proceeds *via* a gold keteniminium ion intermediate.[21] It is therefore probable that this gold-catalysed cycloisomerisation also occurs *via* formation of a keteniminium ion. The pseudosymmetric nature of yndiamides means that two keteniminium ions could be formed by coordination to gold(I), but only one of these leads to the observed product. As noted above, an ongoing computational study

being undertaken in our group by Zixuan Tong (as yet unpublished) has shown that there is a low barrier (~ 5 kcalmol^{-1}) to interconversion of the two isomers of yndiamide keteniminium ions. Importantly, for ynamides **102a**–**c**, formation of the required gold keteniminium ions is not possible due to the absence of the internal nitrogen atom, so the activation by gold(I) is instead proposed to occur by π-acidic coordination to the carbon-carbon triple bond (**121**) with direct attack by the tethered alkyne (**Scheme 2.31**). Keteniminium ion **122** could be formed but would not lead to the formation of the product (**103**). The absence of the specific, required, keteniminium ion likely leads to the reduced reactivity of ynamides compared to yndiamides under these conditions, as the ynamide is not as strongly activated towards attack by the tethered alkyne.



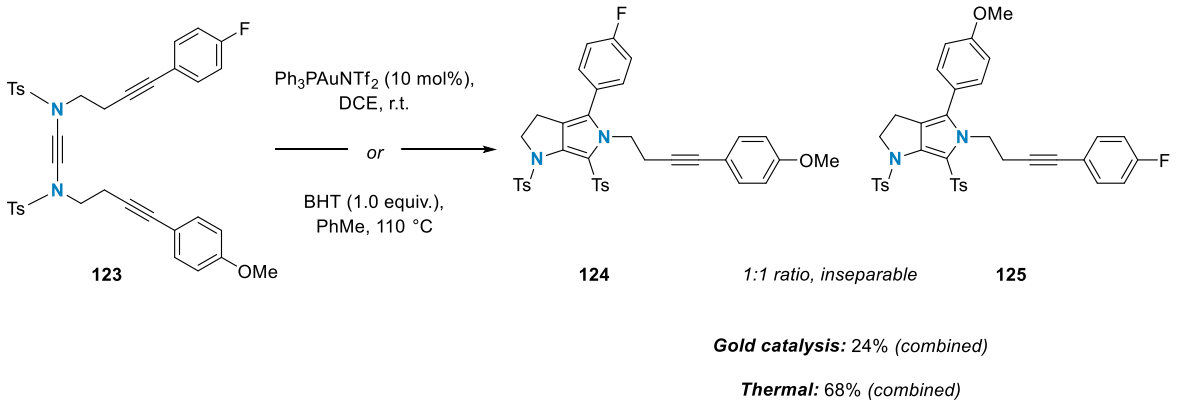
Scheme 2.31: Formation of a single keteniminium ion from ynamides **102**.

The Au-catalysed crossover experiment could not be carried out with substrate **82d** used for the thermal process in **Scheme 2.29** due to the poor selectivity and low yield of the Au-catalysed reaction of **82d**, hence **82b** and **82n** were used in this crossover experiment (**Scheme 2.32**). Once again no crossover products were observed, suggesting that the sulfonyl migration process also occurs intramolecularly under gold-catalysis.



Scheme 2.32: Gold-catalysed crossover experiments. *Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.*

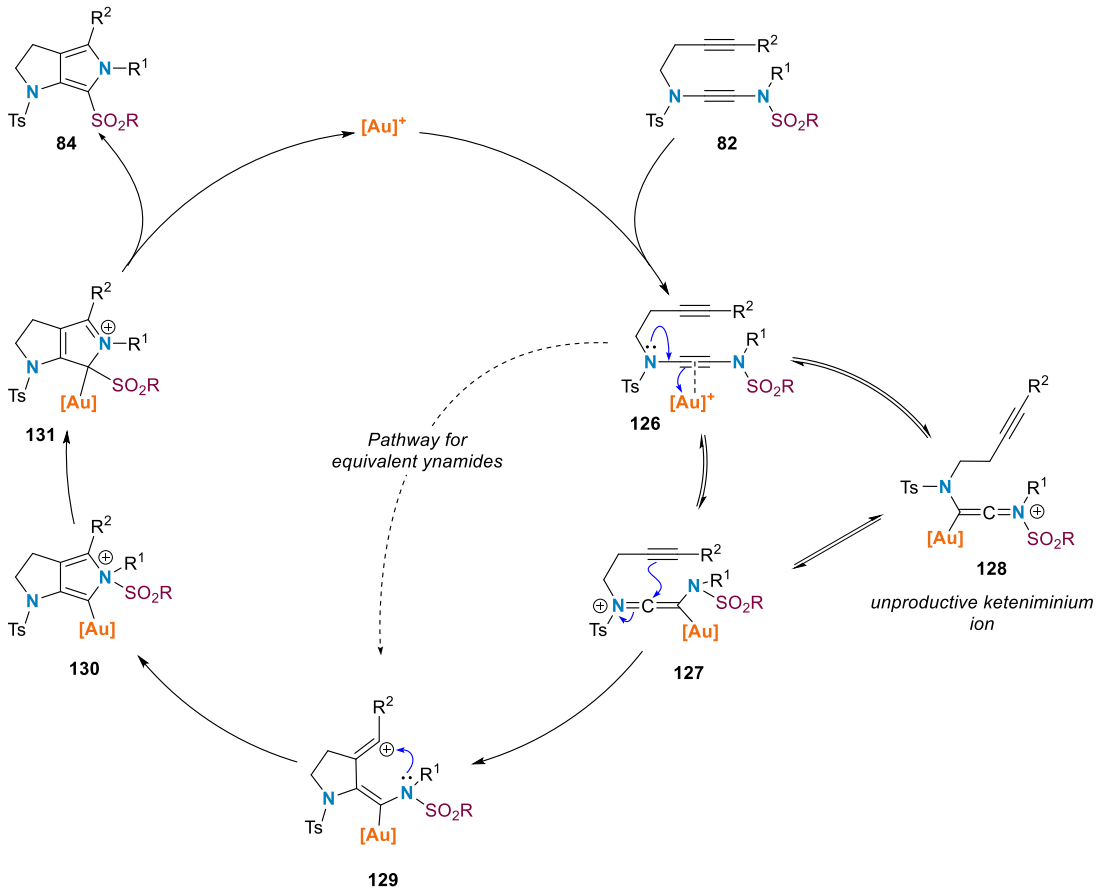
A second attempt to probe the mechanism of the transformation used yndiamide **123**. This allowed a comparison between alkynes bearing an electron-donating group (C_6H_4OMe) and an approximately electron-neutral group (C_6H_4F) (**Scheme 2.33**). Under both sets of conditions the products **124** and **125** were formed in equimolar quantities; unsurprisingly these compounds were inseparable by chromatography but the characterisation data of the mixture was consistent with the proposed structures. While detailed mechanistic conclusions cannot be drawn from these findings, they are consistent with a rapid and unselective cyclisation in both cases.



Scheme 2.33: Intramolecular competition experiments. Full consumption of **123** was observed under both sets of conditions.

The proposed mechanism for formation of the pyrrole product is as follows (**Scheme 2.34**): coordination of Au(I) by the yndiamide (**82**) in complex **126** to form the productive

keteniminium ion **127** (the alternative, unproductive keteniminium ion **128** is probably also formed at this stage) is followed by attack by the tethered alkyne to form the pyrrolidine ring and a vinyl cation (**129**). Nucleophilic attack by the 'external' nitrogen atom of the yndiamide closes the second (pyrrole) ring (**130**). An intramolecular 1,2-sulfonyl migration (which may be better viewed as a 1,5-sigmatropic rearrangement) completes the final atom connectivity of the product (**131**), and deaurative aromatisation followed by de-coordination from the pyrrole gives the product **84** and returns Au(I) (as Ph_3PAu^+) into the catalytic cycle.



Scheme 2.34: Proposed mechanism of the cyclisomerisation of yne-yndiamides (**82**) under gold-catalysis. Ligands on gold are not shown for clarity, but the complex is assumed to be linear about the gold centre.

2.14 Concluding remarks on yndiamide cycloisomerisation

The cycloisomerisation reactions of yndiamides described in this chapter demonstrate the unique opportunities they provide for the synthesis of novel nitrogen-heterocyclic structures. The tandem cycloisomerisation/1,2-sulfonyl migration process can be carried out using

gold-catalysis at ambient temperature or under catalyst-free thermal conditions; these two complementary sets of conditions allow the transformation to be applied to a diverse scope of yne-yndiamides. The importance of the two-carbon tether for the success of the reaction was also explored, and the mechanism of the thermal process was probed and was consistent with the mechanism proposed for analogous reactions of ynamides. Comparison of the behaviour of analogous ene-yne-ynamides and ene-yne-yndiamides under thermal conditions, specifically the observed absence of intramolecular [4+2] reactivity for yndiamides, reveals further divergence of the reactivity of these two closely related functional groups. The Au-catalysed mechanism was explored by comparison of the reaction outcomes for ynamides and yndiamides; this underlined the importance of the formation of a keteniminium ion as an intermediate in the cycloisomerisation process. Divergent reactivity was observed under gold-catalysis for certain substrates, and this was used to demonstrate the significance of the proposed interconversion of yndiamide gold-keteniminium ions. Furthermore, in the gold-catalysed transformation both nitrogen atoms are directly involved in the proposed mechanism, demonstrating that yndiamides are more than just derivatives of ynamides – they exhibit modes of reactivity which are not possible for their mono-aza analogues. In other words, the second nitrogen atom is more than a spectator in some transformations of yndiamides.

Finally, the findings reported herein raise further questions which, if explored, may lead to the discovery of other novel ring-forming reactions of yndiamides:

1. *Can yndiamides act as neutral three-atom components in other formal [3+2] cycloaddition processes (for example with alkenes)?*
2. *Can keteniminium ions formed from yndiamides with a gold(I) catalyst be employed in other formal cycloaddition processes (such as tetra-dehydro Diels Alder reactions)?*

Chapter 3: [2+2+2] Cyclotrimerisation reactions of yndiamides with alkynes

Yndiamides have untapped potential for use in the synthesis of compounds containing 1,2-diamino motifs. Specifically, there is an opportunity for involving the carbon-carbon triple bond in a [2+2+2] cyclotrimerisation reaction with two other alkyne units, thus forming a benzene ring bearing two nitrogen substituents in a 1,2-arrangement. Cyclotrimerisation reactions catalysed by rhodium, cobalt, nickel and ruthenium are frequently encountered, alongside other metals such as molybdenum and iridium,[73,74] including using ynamides as substrates, and such reactions inspired the content of this chapter. Cyclotrimerisation reactions of ynamides have been widely studied,[5] and in our group's initial report of yndiamides, two examples of fully intramolecular [2+2+2] cyclotrimerisation reactions of yndiamides were reported.[1] Inspired by these examples, we set out to expand the cyclotrimerisation chemistry of yndiamides, setting two targets for the project at the outset:

1. *Achieve a [2+2+2] cyclotrimerisation reaction of a tethered yne-yndiamide with a monoalkyne.*
2. *Achieve a [2+2+2] cyclotrimerisation reaction of an yndiamide with a diyne.*

This chapter will review the literature covering [2+2+2] cyclotrimerisation reactions of ynamides and will describe the development of transformations achieving these targets.

3.1 Introduction

1,2-Diaminobenzene derivatives are a pharmaceutically relevant motif, being found in numerous drug molecules[75–78] (**Figure 3.1a**) and natural products, including psychotrimine (northern fragment), staurosporine, demarcozine I and dichotomocej F (**Figure 3.1b**).[79–82] While routes to many diaminobenzene derivatives are known, the development of new methods to synthesise such structures in a regioselective manner from yndiamides may open up investigations of underexplored diaminobenzene motifs.

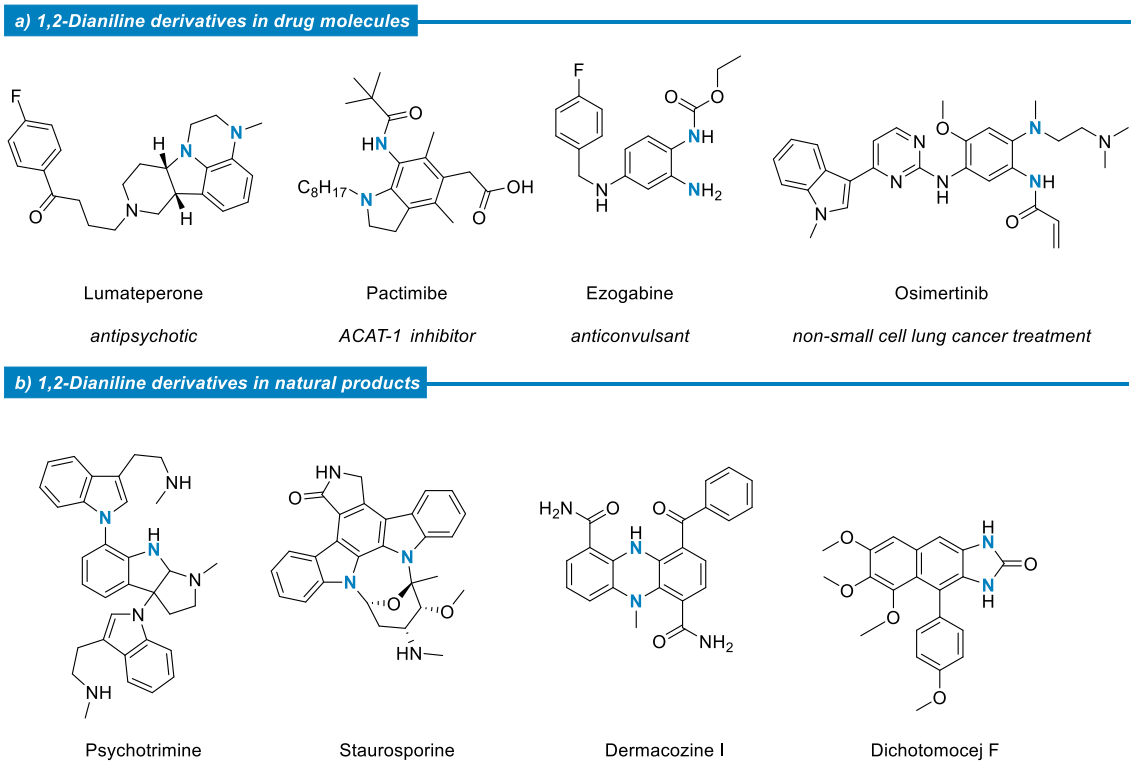


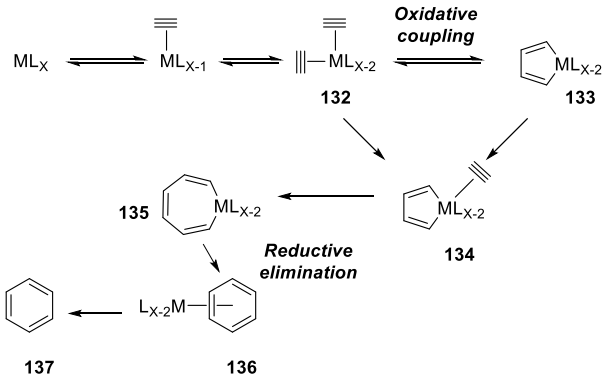
Figure 3.1: *a)* Selected drug molecules containing 1,2-diaminobenzene derivatives and *b)*selected natural products containing 1,2-diaminobenzene derivatives.

As explained in **Chapter 2**, [4+2] cycloaddition reactions of yne-yndiamides have thus far not been found to be an appropriate method to synthesise 1,2-diaminobenzene derivatives due to the dominant tandem cycloisomerisation/1,2-sulfonyl migration

process. A transition metal-catalysed cyclotrimerisation reaction was therefore considered as an alternative approach.

Since the first report of transition metal-catalysed [2+2+2] cyclotrimerisation reactions by Reppe in 1948,[83] many alkynes have been employed in such processes to form polysubstituted benzene rings, with several reports from Vollhardt and co-workers being of particular importance.[84–88] Reports of such reactivity often have a particular focus on achieving regioselectivity.[89] Applying [2+2+2] reactivity to yndiamides was appealing for several reasons: firstly it would provide access to highly substituted diaminobenzene derivatives, secondly it would enable further comparison of the reactivity of yndiamides to ynamides and alkynes, and thirdly it would provide a unique regioselectivity challenge.

A general mechanistic outline of transition metal-catalysed [2+2+2] reactivity is shown in **Scheme 3.1**: first, two alkyne moieties displace two ligands on the metal, forming a complex **132** which undergoes oxidative coupling to form metallocyclopentadiene **133**. This is coordinatively unsaturated and can therefore coordinate another alkyne, forming a complex **134**. From **134**, alkyne insertion forms a metallocycloheptatriene (**135**) followed by reductive elimination to form **136**. Finally, decomplexation of the metal forms the arene product **137**.

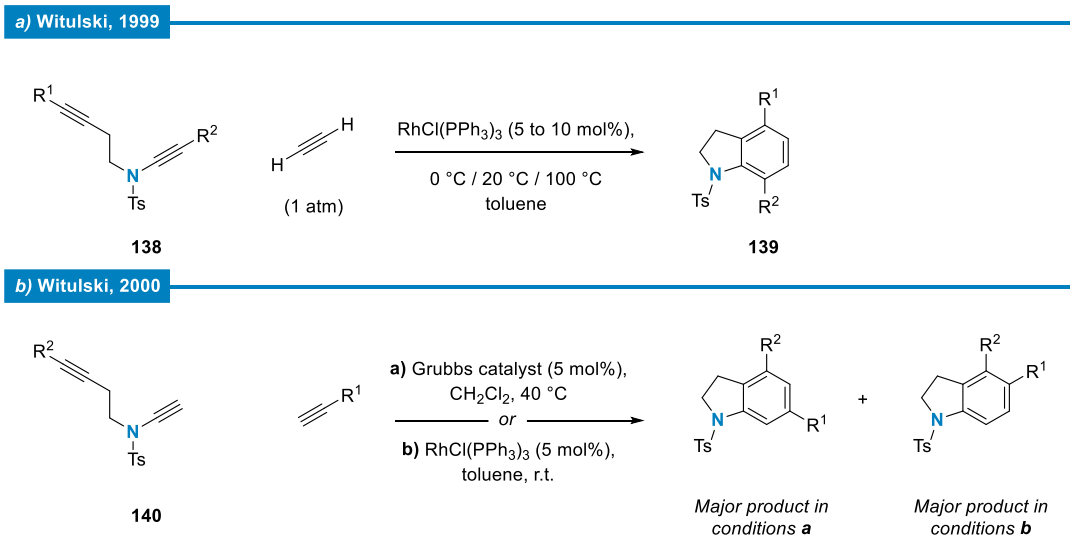


Scheme 3.1: Mechanistic outline of transition metal-catalysed [2+2+2] reactivity.

3.2 Review of ynamide [2+2+2] cyclotrimerisation reactions

This section will explore the precedent for the participation of ynamides in [2+2+2] cyclotrimerisation reactions with alkynes.

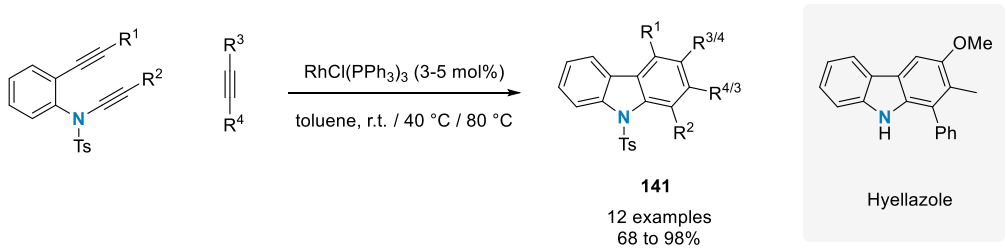
The first example of ynamides undergoing a [2+2+2] cyclotrimerisation was reported by Witulski and co-workers in 1999;[90] they reacted various yne-ynamides (**138**) with acetylene and other monoalkynes using Wilkinson's catalyst to prepare multifunctionalised indolines **139** (**Scheme 3.2a**). The same group reported control over the regiochemical outcome of similar transformations in 2000[91] by using Grubbs' 1st Generation catalyst or Wilkinson's catalyst using terminal ynamides **140** (**Scheme 3.2b**). The reaction catalysed by Grubbs' 1st Generation catalyst is proposed to occur by addition of the ylidine-ruthenium complex to the less substituted alkyne in the diyne, although beyond this the authors give little justification for the observed regioselectivity.



Scheme 3.2: *a)* Cyclotrimerisation of yne-ynamides with acetylene[90] and *b)* Regioselective approaches to cyclotrimerisation of yne-ynamides with monoalkynes.

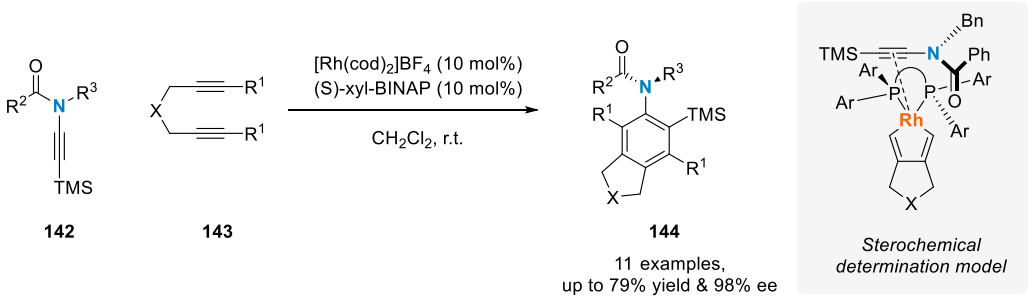
In 2002, Witulski and co-workers further enhanced the field of ynamide [2+2+2] cyclotrimerisation reactions with their report of a synthesis of carbazoles (**141**) from

similar yne-ynamides; in this case the alkyne component was not limited to acetylene and significant regioselectivity was observed dependent on steric factors and solvent effects. The authors suggested that there is an electronic component to the regiochemical outcome of the reaction, although the data was not sufficient to decouple the reaction outcome from potentially important steric factors. The methodology was also successfully applied to the synthesis of the marine carbazole alkaloid hyellazole (**Scheme 3.3**). This cyclotrimerisation approach to 3-oxygenated carbazole natural products has since been used by the same group in the total syntheses of antiostatin A_1[92] and 6-chlorohyellazole, 4-deoxycarbazomycin B, carazostatin, and carbazomycins A and B.[93]



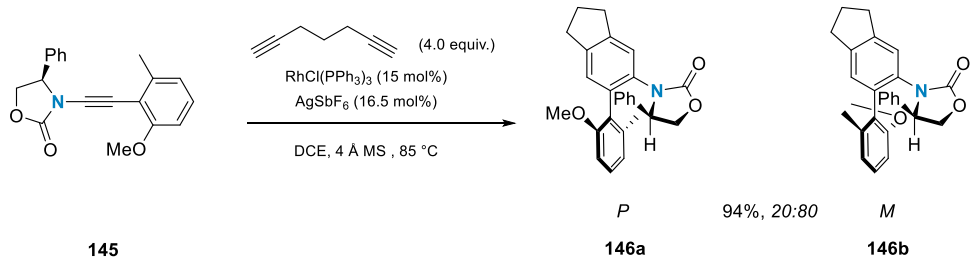
Scheme 3.3: Synthesis of carbazoles by rhodium-catalysed [2+2+2] cyclotrimerisation of yne-ynamides and alkynes.[94]

A major contribution was made to the field in 2006 by Tanaka and co-workers, who reported the first enantioselective Rh catalysed [2+2+2] reaction of trimethylsilylynamides (**142**) with 1,6-diynes (**143**) to form anilides with restricted rotation about the C–N axis (**144**) (**Scheme 3.4**).[95] Using a single enantiomer of a bidentate phosphine catalyst ((*S*)-xyl-BINAP) the anilide products were formed in excellent *ee*. The reaction was applied to a range of 1,6-diynes but was unsuccessful for terminal ynamides. Homodimerisation of the diyne component was the major side reaction; similar issues were encountered in this work and the approach taken to overcome it is discussed in **Section 3.7**.



Scheme 3.4: Enantioselective synthesis of axially chiral anilides by rhodium-catalysed [2+2+2] cyclotrimerisation.[95]

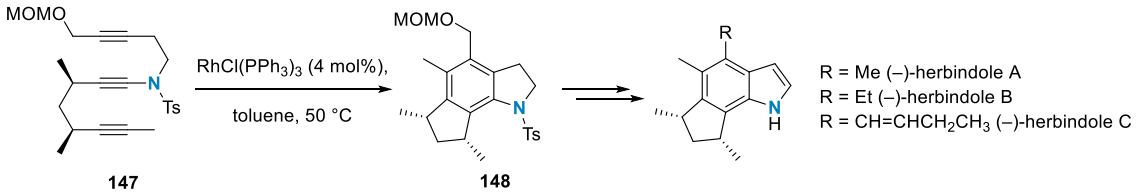
Shortly after Tanaka and co-workers' report, also in 2006, Hsung and co-workers reported a Rh catalysed [2+2+2] cyclotrimerisation of sterically crowded aryl ynamides (**144**) with diynes to form chiral anilides as a mixture of *P* and *M* isomers **146a** and **146b** (which were readily separable), with the key concept in this work being the transfer of chiral information from a stereogenic centre to an axis of chirality (**Scheme 3.5**).[96] The authors reported modest selectivity for the *M* isomer using an Evans' auxiliary on the ynamide.



Scheme 3.5: Synthesis of amide-substituted biaryls from sterically encumbered ynamides.[96]

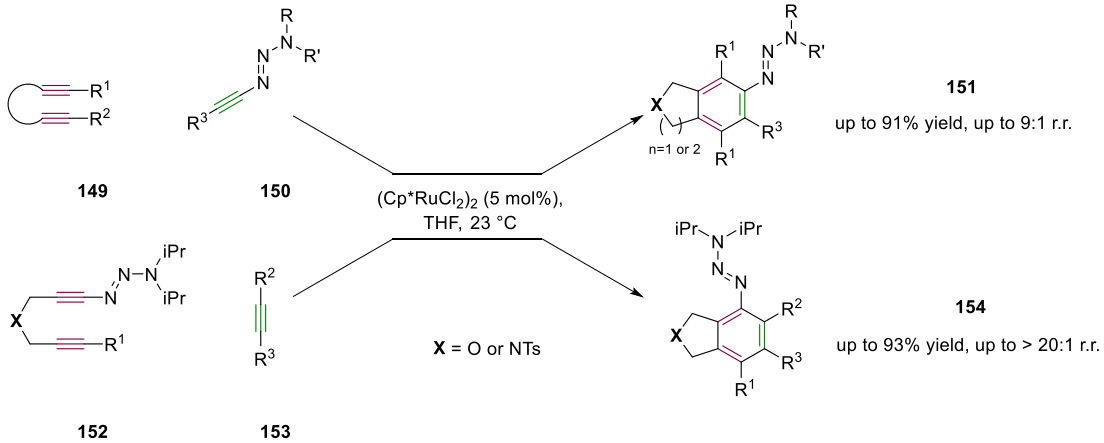
In 2012, Sato and co-workers used an intramolecular [2+2+2] cyclotrimerisation between an ynamide and two diynes catalysed by Wilkinson's catalyst to assemble the core (**148**) of (–)-herbindoles A, B, and C (**Scheme 3.6**) from triyne **147**. Ruthenium and nickel catalysts were also effective in achieving the transformation, but Pd_2dba_3•$CHCl_3$ returned the starting material unchanged. Subsequent transformations delivered the three natural products in remarkably high overall yields, demonstrating the synthetic power of the rapid

formation of the tricyclic nitrogen-containing core (for example (–)-herbindole A was formed in 49% yield over 15 steps).



Scheme 3.6: Synthesis of herbindoles by [2+2+2] cyclotrimerisation.[97]

Although it does not use ynamides, Cramer and co-workers' 2019 report of the cyclotrimerisation of alkynyl triazenes highlighted the utility of nitrogen-substituted alkynes in achieving regioselective [2+2+2] reactions (**Scheme 3.7**).[98] Alkynyl triazenes (**150**) underwent ruthenium-catalysed [2+2+2] reactions with 1,6- and 1,7-diynes (**149**) to form arenes (**151**) in good yields. Regioselectivity was observed with heteroatom-linked 1,7-diynes, the products of which (**151**) positioned the triazene moiety *meta* to the benzylic nitrogen or oxygen atom. The transformation was also applicable to 1,6-diynyl triazenes (**152**) and simple alkynes (**153**), forming products (**154**) in which the triazene is proximal to the fused ring in moderate to excellent yields.

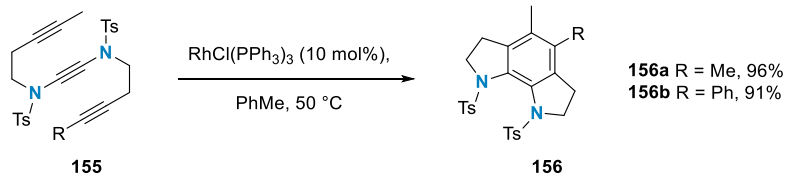


Scheme 3.7: [2+2+2] Cyclotrimerisation reactions of alkynyl triazenes.[98]

The reactions of ynamides discussed in this section lay the foundation for analogous reactivity of yndiamides. They also provide useful indications of some challenges likely to be involved in employing yndiamides in [2+2+2] reactions – specifically chemoselectivity (overcoming the inherent tendency of alkynes to dimerise and trimerise with transition metal catalysis) and the impact of steric congestion on the reactivity of metallocycle intermediates. More generally, as with most [2+2+2] cyclotrimerisation reactions, achieving regioselectivity will be a goal of this work. Overcoming these challenges forms a key part of the work described in this chapter.

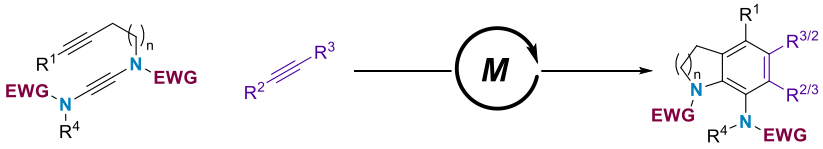
3.3 Introduction to [2+2+2] Cyclotrimerisation reactions of yndiamides

Previous work in our group has demonstrated that a fully intramolecular Rh catalysed [2+2+2] cyclotrimerisation reaction is possible when an yndiamide (**155**) contains two tethered alkynes (**Scheme 3.8**).[1] The excellent yields of **156a** and **156b** suggested that these conditions would be a good starting point to expand this reactivity into an intramolecular context.



Scheme 3.8: Yndiamide [2+2+2] cyclotrimerisation reactions previously developed in our group.[1]

By tethering an alkyne to the yndiamide and reacting this with a monoalkyne component, the formation of the initial metallocyclopentadiene from the yne-yndiamide should be favourable, and monoalkyne insertion would form 7-aminoindoline derivatives (**Scheme 3.9**). This intermolecular reaction facilitates different regiochemical outcomes which might conceivably be influenced by steric or electronic properties of the yndiamide or alkyne.



Scheme 3.9: Proposed [2+2+2] cyclotrimerisation reaction to form 7-aminoindoline derivatives.

3.4 Optimisation of [2+2+2] cyclotrimerisation of yne-yndiamides

Investigation of this reaction commenced with the conditions previously developed in our group for the intramolecular transformation (see **Scheme 3.8**), using yne-yndiamide **82u** (see **Section 2.6),** and 2-butyne-1,4-diol (**157**) as the monoalkyne component (this alkyne was selected as it is an electron-neutral alkyne which has the practical advantage of being a solid at room temperature) (**Table 3.1**).

Commencing the investigation with Wilkinson's catalyst ($(PPh_3)_3RhCl$) in toluene at 50 °C (entry 1), the desired product **158** was formed in 36% yield which increased to 75% by addition of $AgSbF_6$ to form a cationic rhodium species *in situ* (entry 2). Changing the catalyst to $[Rh(cod)Cl]_2$ resulted in a lower yield (entry 3) and adding $AgSbF_6$ and *rac*-BINAP was even more detrimental to the yield (entry 4).

As previously observed (**Section 2.5**), silver(I) salts can promote decomposition of yndiamides bearing tethered alkynes, therefore it was desirable to avoid the presence of silver(I) cations in the reaction mixture. Counter-ion exchange promoted by silver(I) is a useful method for the generation of cationic rhodium(I) species, but this process does not necessarily have to occur *in situ*; bench stable cationic rhodium(I) catalysts can be prepared, typically using bidentate phosphine ligands such as BINAP or BIPHEP.[99] These pre-formed cationic rhodium(I) catalysts have several distinct advantages over the $(PPh_3)_3RhCl)/AgSbF_6$ system (which as entry 2 shows is also effective) – firstly they are not particularly moisture sensitive, and thus avoid regular use of $AgSbF_6$ (which is

extremely hygroscopic); and secondly they have potential for employing single enantiomer ligands in atroposelective processes to exploit restricted rotation about the C–N axis.[95] Furthermore, neutral rhodium complexes (such as $RhCl(PPh_3)_3$) are known to promote undesired dimerisation of terminal alkynes to form butenyne derivatives and higher oligomers.[100] Pleasingly, the yield of **158** was improved by using pre-formed cationic Rh catalysts (entries 5 and 6) and pre-formed (*rac*-BINAP)Rh(cod)SbF_6 was selected as the catalyst for further screening. Reducing the reaction time to 5 hours resulted in a lower yield (entry 7). Reducing the reaction temperature to 40 °C gave a lower yield of **158** (entry 8) and almost no reaction was observed at room temperature (entry 9). In the absence of a catalyst no reaction was observed between **82u** and **157** (entry 10). Other solvents (THF, 1,4-dioxane, and DCE) were screened (entries 11–13) and DCE was selected as optimal. A dramatic reduction in the yield was observed when only 1.5 equivalents of the monoalkyne component were used (entry 14), but returning to 3.0 equivalents of the alkyne and increasing the concentration to 0.100 M gave the highest yield (90%, entry 15). These conditions were then selected to be used to explore the scope of this transformation.

82u **157** **158**

Entry	Catalyst/additives	Solvent/concentration	Time	Temperature	Equivalents 157	Yield
1	$(Ph_3P)_3RhCl$ (5 mol%)	PhMe/0.033 M	16 h	50 °C	3.0	36%
2	$(Ph_3P)_3RhCl$ (5 mol%), $AgSbF_6$ (5 mol%)	PhMe/0.033 M	16 h	50 °C	3.0	75%
3	$[Rh(cod)Cl]_2$ (5 mol%)	PhMe/0.033 M	16 h	50 °C	3.0	21%
4	$[Rh(cod)Cl]_2$ (5 mol%), $AgSbF_6$ (10 mol%) *rac*-BINAP (10 mol%)	PhMe/0.033 M	16 h	50 °C	3.0	9%
5	**Rh-1** (5 mol%)	PhMe/0.033 M	16 h	50 °C	3.0	82%
6	**Rh-2** (5 mol%)	PhMe/0.033 M	16 h	50 °C	3.0	82%
7	**Rh-2** (5 mol%)	PhMe/0.033 M	5 h	50 °C	3.0	47%
8	**Rh-2** (5 mol%)	PhMe/0.033 M	16 h	40 °C	3.0	25%
9	**Rh-2** (5 mol%)	PhMe/0.033 M	16 h	r.t.	3.0	< 5%
10	-	PhMe/0.033 M	16 h	85 °C	3.0	0%
11	**Rh-2** (5 mol%)	THF/0.033 M	16 h	50 °C	3.0	80%
12	**Rh-2** (5 mol%)	1,4-dioxane/0.033 M	16 h	50 °C	3.0	22%
13	**Rh-2** (5 mol%)	DCE/0.033 M	16 h	50 °C	3.0	86%
14	**Rh-2** (5 mol%)	DCE/0.033 M	16 h	50 °C	1.5	20%
15	**Rh-2 (5 mol%)**	**DCE/0.100 M**	**16 h**	**50 °C**	**3.0**	**90%**

Table 3.1: All reactions on 0.050 mmol scale under Ar atmosphere. Yields determined by quantitative ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. **Rh-1** = (*rac*-BIPHEP)Rh(cod)SbF_6. **Rh-2** = (*rac*-BINAP)Rh(cod)SbF_6.

3.4.1 Rhodium(I) catalyst synthesis

The cationic rhodium catalysts **Rh-1** and **Rh-2** were prepared in two steps from commercially available precursors. See the Supporting Information **Section 7.4.1** for details.

3.5 Reaction scope of yne-yndiamide [2+2+2] cyclotrimerisation

The optimised conditions for the cyclotrimerisation of **82u** and **157** were used to explore the scope of the reaction. Four aspects of the scope were explored:

1. *Aliphatic alkynes as the monoalkyne partner.*
2. *Aryl-substituted alkynes as the monoalkyne partner.*
3. *Heteroatom-substituted alkynes as the monoalkyne partner.*
4. *Nature of the yne-yndiamide (diyne) partner.*

By exploring the transformation in this way we aimed to demonstrate this [2+2+2] cyclotrimerisation process as a useful method for the construction of diverse 7-aminoindoline motifs with potential for further derivatisation.

3.5.1 Aliphatic alkynes as the monoalkyne partner

Having shown 2-butyne-1,4-diol to be an excellent monalkyne partner in the [2+2+2] cyclotrimerisation reaction with **82u**, the transformation was carried out on a 1.0 mmol scale, forming **158** in 92% yield (0.56 g).

Double methylation of 2-butyne-1,4-diol gave 1,4-dimethoxybut-2-yne,[101] which was successfully reacted with **82u** to form **159**, albeit in a low yield. Curiously, the analogous monomethylated substrate (4-methoxybut-2-yn-1-ol[102]), did not undergo the cyclotrimerisation reaction at all (as observed by ^{1}H NMR and mass spectrometry), with the starting materials returned unchanged in multiple attempts at this reaction. There is an absence of reported cyclotrimerisation reactions for this substrate in the literature and it is unclear why 4-methoxybut-2-yn-1-ol does not undergo this (or other) cyclotrimerisation reactions.

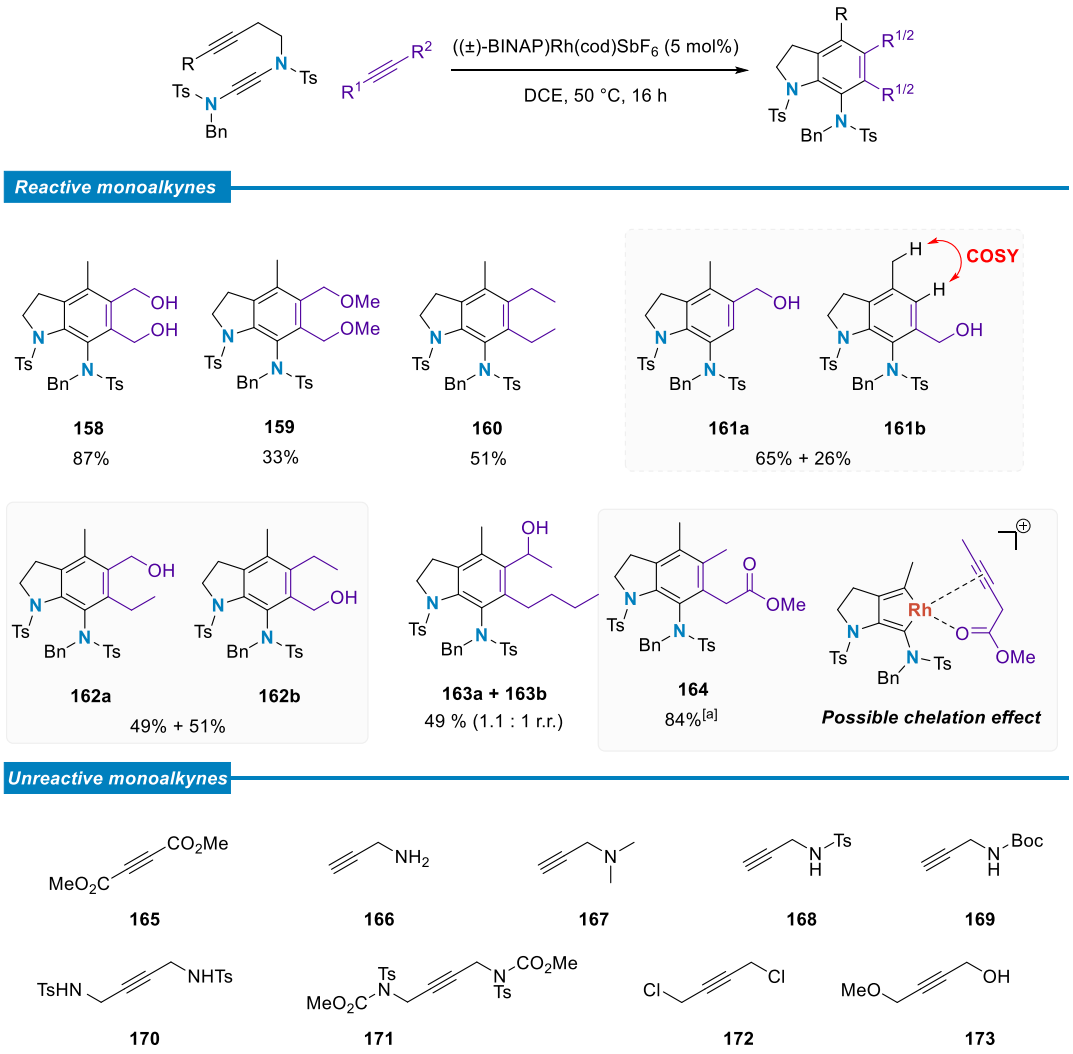
3-Hexyne reacted with **82u** to give **160** in moderate yield; one could envisage longer aliphatic side chains being incorporated in analogous reactions with homologous alkynes, although the data gathered in this study suggests that it is unlikely that any significant regioselectivity would be observed in such reactions.

Other aliphatic alkynes were also explored as potential monoalkyne components. Propargyl alcohol underwent the cyclotrimerisation to form isomeric products **161a** and **161b** in 65% and 26% yields respectively; these were chromatographically separable and the regiochemistry of the two products was confirmed using ^{1}H–^{13}C HMBC and ^{1}H–^{1}H COSY correlations. Other propargylic alcohols were then investigated as monoalkyne partners. 2-Pentyn-1-ol gave **162a** and **162b** in a 1:1 ratio which were again separated by chromatography. Oct-3-yn-2-ol (prepared by addition of 1-hexyne to acetaldehyde[103]) gave **163a** and **163b** as an inseparable mixture of isomers, but 2-methyloct-3-yn-2-ol (prepared by addition of 1-hexyne to acetone[104]) was completely unreactive, returning unreacted starting materials, probably because the additional methyl group hinders its approach to the rhodacycle.

An attempt to synthesise the core of the hypercholesterolemia drug Pactimibe[76] (**Figure 3.1**) by a [2+2+2] cyclotrimerisation of **82u** with methyl pent-3-ynoate was unsuccessful as the undesired isomer (**164**) was formed as the sole product. Such pronounced regioselectivity was unexpected given the mixtures of isomers formed by cyclotrimerisation of other aliphatic alkynes (**161–163**). While a mechanistic justification cannot be elucidated from the available data, it is plausible that the coordination of the 1,3-enyne carboxylic ester to rhodium is significant, as similar 5-membered chelates were proposed as important intermediates in Tanaka and co-workers' 2022 report of an enantioselective [2+2+2] synthesis of axially chiral styrenes.[105]

Dimethyl acetylenedicarboxylate (**165**) has been used as the monoalkyne component in [2+2+2] reactions of alkynes,[106] but it was unreactive with **82u**, possibly because of the steric demand of approach of the congested rhodacycle and the sterically hindered alkyne. Propargylamine and derivatives thereof (**166**–**169**) also did not react with **82u** under Rh

catalysis; it is possible that this is due to catalyst inhibition by competitive binding of the amine moiety to the cationic rhodium species. The same problem probably accounts for the unreactivity of bis-amino analogues **170** and **171**. 1,4-Dichlorobut-2-yne (**172**) was also unreactive under the optimised conditions, which cannot be readily explained on steric grounds (c.f. reaction of 2-butyne-1,4-diol, with similar steric properties), although it is worth noting that previously reported [2+2+2] reactions of **172** were catalysed by molybdenum[107] or ruthenium[108]. This highlights the importance of further developing yndiamide reactivity using different metal catalysts, as it is possible that more cyclotrimerisation partners could be used by changing the metal catalyst.



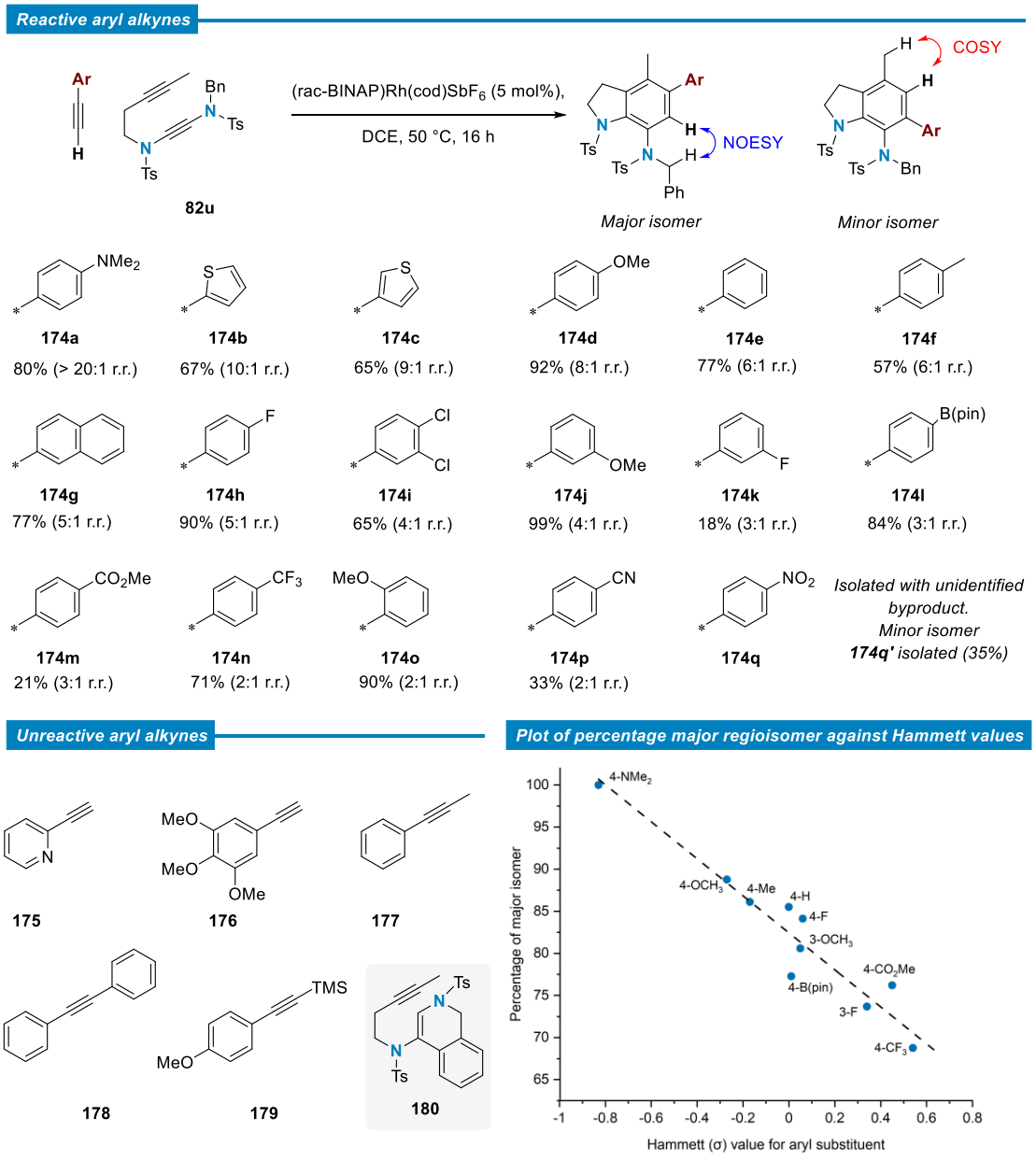
Scheme 3.10: Scope of aliphatic alkynes explored as monoalkyne component in the [2+2+2] cyclotrimerisation reaction with yne-yndiamide **82u**. All reactions on 0.10 mmol scale except where stated. [a] Reaction on 0.50 mmol scale.

Although only a small range of aliphatic alkynes were successfully used in this reaction, some regioselective derivatisation was possible, as will be discussed in **Section 3.6**.

3.5.2 Aryl alkynes as the monoalkyne partner

Aryl alkynes are appealing substrates for [2+2+2] cyclotrimerisation reactions as a method to synthesise biaryl compounds; these structures (and more specifically those exhibiting atropisomerism as a result of restricted C–C rotation) are widely encountered as moieties in ligands,[109] natural products,[110] and increasingly feature in medicinal

chemistry applications.[111] Employing aryl alkynes in this particular [2+2+2] cyclotrimerisation was also appealing as a means to control the regiochemical outcome.



Scheme 3.11: Scope of aryl alkynes used as monoalkyne partners in [2+2+2] cyclotrimerisation reactions with **82u**. *In all cases the major product in the isolated mixture was the isomer with methyl and aryl proximal.* Regioisomeric ratios (r.r.) obtained from crude ^{1}H NMR spectra. All reactions on 0.10 mmol scale under Ar atmosphere using anhydrous solvent. All yields are isolated, except for **174m**, the yield of which was determined by quantitative ^{1}H NMR.

Monoaryl alkynes bearing *para*-, *meta*-, and *ortho*- substituents with varying electronic properties, as well as heteroaryl alkynes, were subjected to the optimised conditions and

the arylated 7-aminoindolines **174a**–**q** were isolated in low to excellent yields, as mixtures of two positional isomers which were typically not separable by chromatography (**Scheme 3.11**). In all cases the major product was the isomer in which the aryl group was positioned *meta*- to the benzyltosylamide substituent; this was identified by a ^{1}H–^{1}H NOESY correlation between the benzylic protons and the single aromatic aminoindoline proton. The minor isomer was identified by a ^{1}H–^{1}H COSY correlation between the aminoindoline methyl protons and the single aromatic aminoindoline proton. The reaction of **82u** with 4-nitrophenylacetylene gave the product **174q** as a ~ 4 :1 mixture with a similar unidentified compound which was *not* the minor isomer (the minor isomer **174q'** was isolated separately). In some cases (**174n** and **174p**) for the minor isomer splitting of the *N*-benzyl CH_2 signals in the ^{1}H NMR spectrum suggested possible restricted rotation about the C–N axis, but as the minor isomer generally could not be isolated cleanly this observation was not investigated further.

A remarkable correlation was observed between the electronic properties of the aryl alkyne partner and the regiochemical outcome of the reaction, with electron rich aryl alkynes giving excellent regioselectivity for the major isomer. The regioselectivity declined significantly for electron-neutral and electron-poor aryl alkynes, as well as for *ortho*-substituted example **174o**, in which steric clash with the aminoindoline substituents is probably important, and may outweigh the electron-donating effect of the methoxy group. The effect of an electron-withdrawing group was maintained in the *meta*- position (**174j** and **174k**). This trend is clearly seen in a plot of the percentage of the major isomer formed against the Hammett substituent constant values for the aryl alkynes (**Scheme 3.11**). These observations raised a clear question: why do the electronic properties of the aryl alkyne have such a dramatic effect on the regiochemical outcome

of the reaction? To rationalise this observation a computational investigation of the reaction mechanism was carried out, which will be discussed in **Chapter 4**.

In addition to the aryl alkynes which were successfully employed to form arylated aminoindolines, several examples were found to be unsuccesful. 2-Ethynylpyridine (**175**) was completely unreactive, returning **82u** completely unchanged, and without the degradation usually observed after exposing an yne-yndiamide to a rhodium catalyst. This is probably due to sequestration of the rhodium catalyst by the pyridine moiety. 3,4,5-Trimethoxyphenylacetylene (**176**) was also unreactive towards **82u** under the standard conditions, and no product formation was observed when the reaction was conducted at 85 °C, although at this temperature **82u** underwent an undesired cyclisation reaction to form dihydroisoquinoline derivative **180**. Such cyclisations have been previously reported by our group in the context of Bronsted acid additions (**Section 1.3**),[24] and have also been observed in gold-catalysed transformations. It is probable that in this case the cationic rhodium catalyst is facilitating this cyclisation in the absence of a productive cyclotrimerisation reaction.

Aryl alkynes bearing multiple substituents (aryl / aryl, aryl / aliphatic, and aryl / heteroatom) (**177**–**179**) were completely unreactive in the cyclotrimerisation reaction; this suggests that the reaction is extremely sensitive to steric congestion in the approach of the alkyne to the rhodacycle, and agrees with later observations of significant steric issues in [2+2+2] cyclotrimerisations of simple yndiamides with diyne-derived rhodacycles (**Section 3.7**).

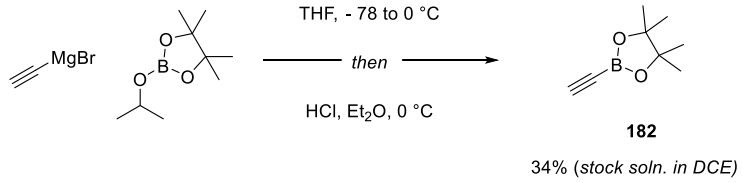
3.5.3 Heteroatom-substituted alkynes as the monoalkyne partner

Using an yndiamide as one of the components in a [2+2+2] cyclotrimerisation reaction forms an aromatic ring bearing two heteroatom (nitrogen) substituents, and we were interested to investigate whether further incorporation of a third heteroatom substituent was possible by using a heteroatom-substituted alkyne as the monoalkyne component (**Scheme 3.12**).

Alkynyl silanes are known to undergo [2+2+2] cyclotrimerisation reactions to form silylated aromatic rings[112] and introduce potential for further transformations, for example by oxidation or cross-coupling. Yne-yndiamide **82u** was subjected to a cyclotrimerisation reaction with trimethylsilylacetylene, which gave **181a** as the major product in a regioisomeric mixture (6:1) in 71% yield, with the regiochemistry of **181a** being determined by COSY correlations. When tri*ethyl*silylacetylene was employed in this transformation a marked improvement in the regioselectivity was observed (>20:1 for **181b**), but tri*isopropyl*silylacetylene (**184**) did not undergo the cyclotrimerisation, probably because the additional bulk of the silyl group prevents approach of the alkyne to the rhodacycle (which itself is sterically encumbered by the bulky phosphine ligand). A similar lack of reactivity of triisopropylsilylacetylene in a rhodium-catalysed [2+2+2] reaction was observed by Tanaka and co-workers.[113]

To open up routes for further functionalisation of the 7-aminoindoline products, a means to introduce a boron-substituent was required – borylated compounds are significant due to their obvious utility in cross coupling reactions.[114] Borylated alkynes have previously been employed in [2+2+2] cyclotrimerisation reactions,[115–120] although they have not been used in such reactions with ynamides. In order to incorporate a boron substituent using this methodology, 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**182**) was

selected as the monoalkyne component. Although there are reported syntheses of **182** in the literature,[121,122] when these methods were attempted no product formation was observed. Instead, **182** was prepared from the reaction of ethynyl magnesium bromide and ethynyl boronic acid pinacol ester, but distillation was not successful for removing the impurities so it was used as a solution of known concentration in DCE (**Scheme 3.13**).



Scheme 3.13: Preparation of 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

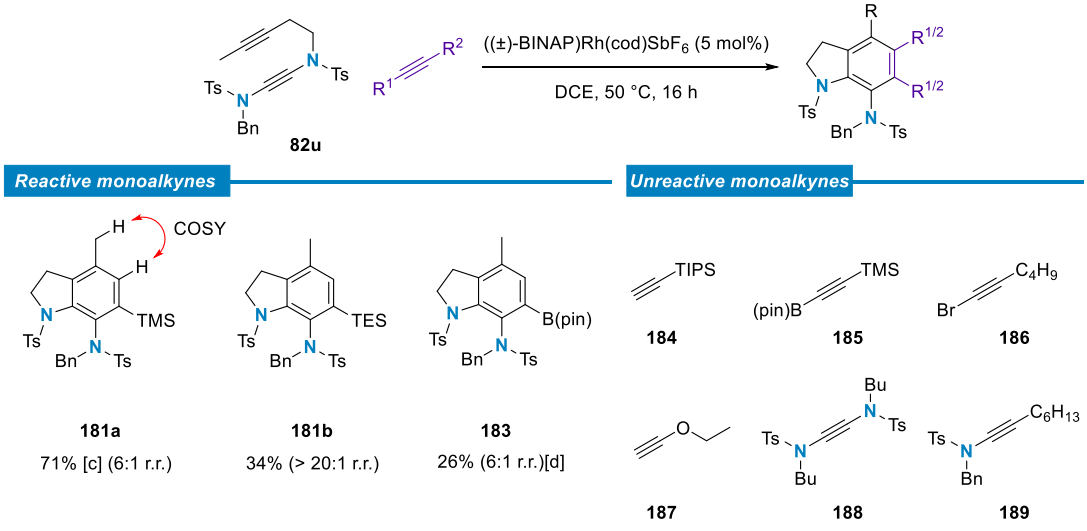
The cyclotrimerisation reaction with **82u** was attempted and the borylated 7-aminoindoline **183** was formed in moderate yield. In common with the silylated examples **181a** and **181b**, the heteroatom (B(pin)) substituent occupied the position proximal to the -*NTsBn* substituent (identified by COSY correlations).

Disappointingly an attempt to incorporate both boron *and* silicon substituents using trimethyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl)silane (**185**) resulted in no reaction, although it is interesting to consider what regioselectivity, if any, would have been observed in such a transformation given the preference of both substituents individually to be positioned proximal to the nitrogen substituent.

Other possible heteroatomic substituents were then considered for introduction to the 7-aminoindoline core by a [2+2+2] cyclotrimerisation. Introduction of a bromine atom, with its potential for further cross-coupling reactions, was appealing, but no reaction was observed between 1-bromo-hex-1-yne (**186**) and **82u**, with the starting materials being returned unchanged.

Ethoxyacetylene was investigated to introduce an oxygen substituent to the aminoindoline core, but no reaction was observed, although the reaction mixture turned black immediately upon addition of ethoxyacetylene (**187**) (as opposed to typical reactions which remained dark orange). It is plausible that the electron-rich alkyne in ethoxyacetylene binds irreversibly to the rhodium catalyst, preventing any reaction occurring. Previous examples of ynol ethers undergoing rhodium-catalysed cyclotrimerisation processes in the literature[123–125] are limited to *aryl* ynol ethers, where the aromatic group on oxygen acts as an electron-withdrawing group and moderates the electron-rich nature of the triple bond.

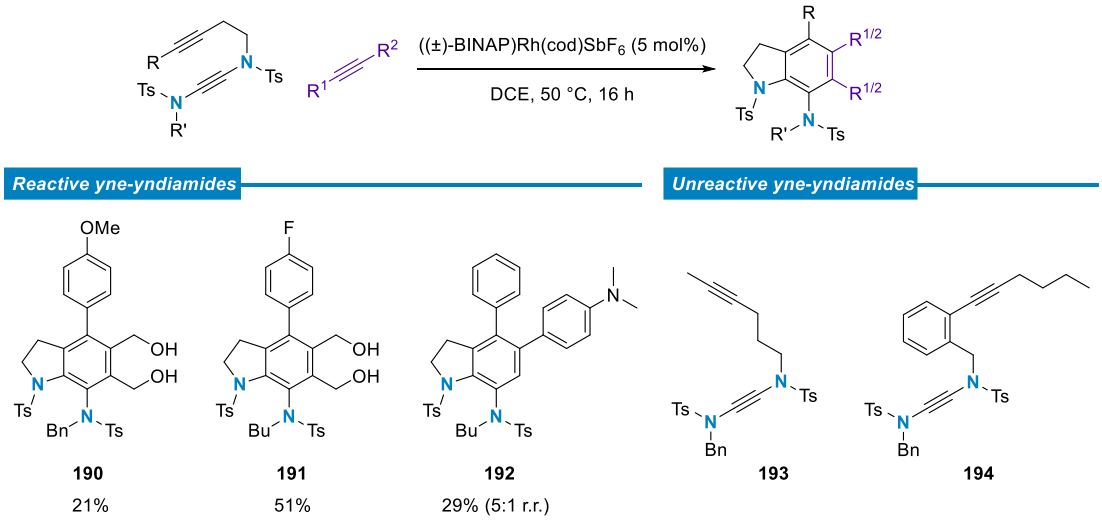
Ynamides and yndiamides were also investigated as the monoalkyne partner in the cyclotrimerisation but perhaps unsurprisingly no product formation was observed when **82u** was treated with either yndiamide **188** or ynamide **189**. The observed lack of reactivity is likely due to the sterically congested nature of the yndiamide and ynamide triple bonds, which, in conjunction with the crowded rhodacycle intermediate, could prevent the reaction.



Scheme 3.12: Scope of heteroatom-substituted alkynes reacted with yne-yndiamide **82u**.

3.5.4 Other yne-yndiamides as cyclotrimerisation partners

Several other yne-yndiamides **82i**–**k** previously used in the cycloisomerisation transformation discussed in **Chapter 2** were then employed in this cyclotrimerisation with different alkynes to form aminoindoline derivatives **190**–**192** (**Scheme 3.13**). In the case of **192**, despite an electron-rich aryl alkyne being used, a mixture of regioisomers were formed because the larger R=Ph group makes formation of the major product more sterically challenging than in the case where R=Me. Extending the carbon chain length connecting the yndiamide and the alkyne completely inhibited the desired reactivity, with no product formation being observed when yne-yndiamides **193** and **194** were subjected to the standard reaction conditions with 2-butyne-1,4-diol.



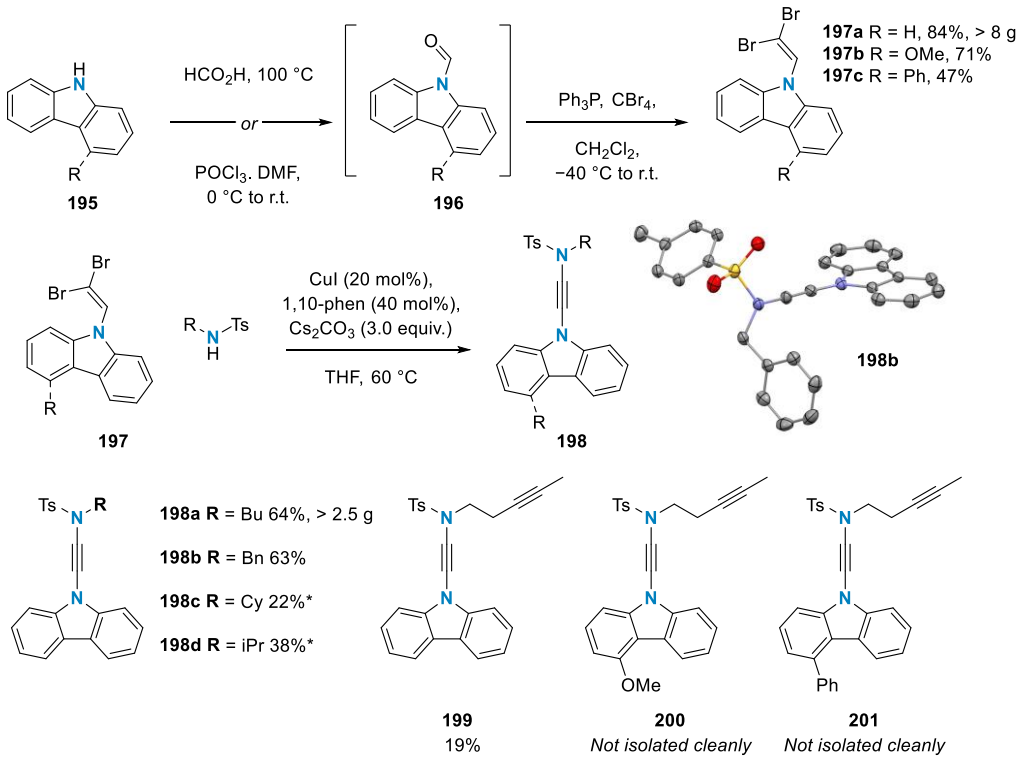
Scheme 3.13: Scope of yndiamide substitution in [2+2+2] cyclotrimerisation reactions with alkynes.

3.5.5 Carbazole-yndiamides as cyclotrimerisation partners

Having explored the scope of cyclotrimerisation of yndiamides bearing two sulfonamide groups the methodology was next applied to the synthesis of *N*–arylated heterocycles, using *N*–aryl 'yndiamides' as substrates. These substrates constitute a new class of doubly-aza substituted alkyne as they lack one of the two electron-withdrawing groups

that occur in yndiamides. In this discussion these substrates will be referred to as *carbazole-yndiamides*.

The synthesis of these novel carbazole-yndiamides commenced with the formylation of carbazole (**195→196**),[126,127] followed by formation of the corresponding dibromoolefin **197**, which reacted with sulfonamides using the standard yndiamide synthesis conditions[1] to form yndiamides **198**–**199** in low to excellent yields, including **199** which contains an alkynyl side chain suitable for involvement in a [2+2+2] cyclotrimerisation reaction (**198c** and **198d** were prepared by a Part II student, Julia Ragus[128]). Dibromoenamides **197b** and **197c** were also synthesised in which the carbazole ring was substituted in the 4-position with an -OMe or -Ph group, and while coupling of these with an appropriate sulfonamide formed the desired yndiamides **200** and **201**, they were both formed as inseparable mixtures with a similar unidentified product.

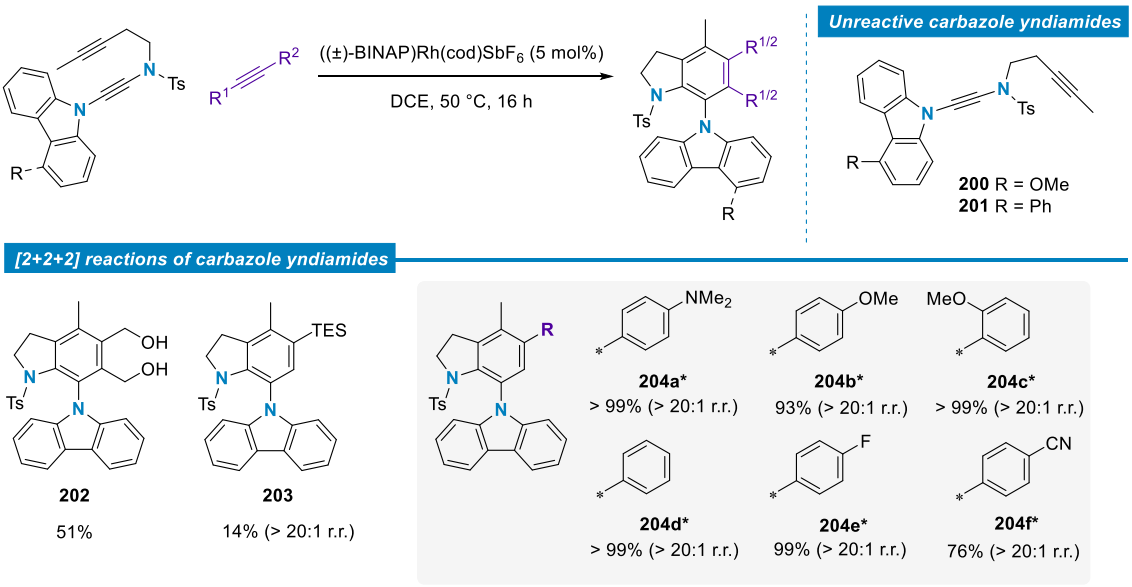


Scheme 3.14: Synthesis of carbazole-yndiamides and single-crystal XRD structure of **198b**. Displacement plot for **198b** is displayed at 50% probability with hydrogen atoms hidden for clarity. *Substrates prepared by Julia Ragus.[128]

The scope of cyclotrimerisation reactions of carbazole-yndiamides was then investigated (**Scheme 3.15**), starting with the cyclotrimerisation reaction of **199** with 2-butyne-1,4-diol which formed **202** in good yield. When **199** was reacted with triethylsilylacetylene, **203** was formed as a single regioisomer – with opposite regiochemistry to that observed for the reaction of **82u** with triethylsilylacetylene (**181b, Scheme 3.12**). Attempts to use the crude material of both **200** and **201** (neither of which could be purified, see above) in [2+2+2] cyclotrimerisation reactions with 2-butyne-1,4-diol returned only unreacted starting material in both cases; it is not possible to be certain whether this is as a result of the carbazole substitution, or because of the contamination of the crude material.

The reactivity of **199** with aryl alkynes was investigated by Julia Ragus (a Part II student); the results of this investigation are included here as a point of interest.[128] Remarkably, the desired products **204a**–**f** were formed as single regioisomers in good to excellent

yields, without the correlation with the electronic properties of the aryl group observed for analogous reactions of **82u** (**Scheme 3.11**). The reasons for this dramatic shift in regioselectivity are not clear, but both steric and electronic factors may be important. One explanation may be that the aromatic rings of the carbazole block the aryl alkyne from approaching in the orientation to form the previously observed minor isomer.



Scheme 3.15: Scope of [2+2+2] cyclotrimerisations of carbazole-yndiamides. Reactions marked with * conducted by Julia Ragus.

3.5.6 Restricted rotation in products

Analysis of the ^{1}H NMR spectrum of aminoindoline product **158** revealed diastereotopic character of the *N*–benzyl protons (**H^{C}**), which was indicative of restricted rotation about the C–N axis (**Figure 3.2**). In recent years the development of C–N atropisomeric compounds has become a lively area of research,[111,129–131] and we recognised the potential for the synthesis of atropisomeric 7-aminoindolines by this [2+2+2] cyclotrimerisation reaction. The restricted rotation in **158** was confirmed by variable temperature ^{1}H NMR spectroscopy in DMSO-d$_6$, increasing the temperature to a maximum of 102 °C. Significant coalescence occurred at the higher temperatures, and in

order to accurately determine the rotational energy barrier of **158**, a dynamic (variable temperature) HPLC study was carried out in collaboration with DPhil student Pearse Solon (see Supporting Information **Section 7.4.9**). This identified two species with identical UV/visible spectroscopic properties (consistent with atropisomers) which underwent exchange on the HPLC timescale. From this data an inversion barrier of 21.9 $kcalmol^{-1}$ was calculated, equating to a half-life of 1260 s. According to the widely recognised, but arbitrary, definition of atropisomers as species exhibiting restricted rotation with a half-life of greater than 1000 s,[132] **158** is an atropisomeric compound. However, in practice, attempts to isolate the atropisomers of **158** were thwarted as they racemised rapidly following separation by HPLC. It is important to note that the half-life calculated by dynamic HPLC is only truly applicable in that particular (chiral) environment. *The data for the dynamic HPLC study was collected and processed by DPhil student Pearse Solon.*

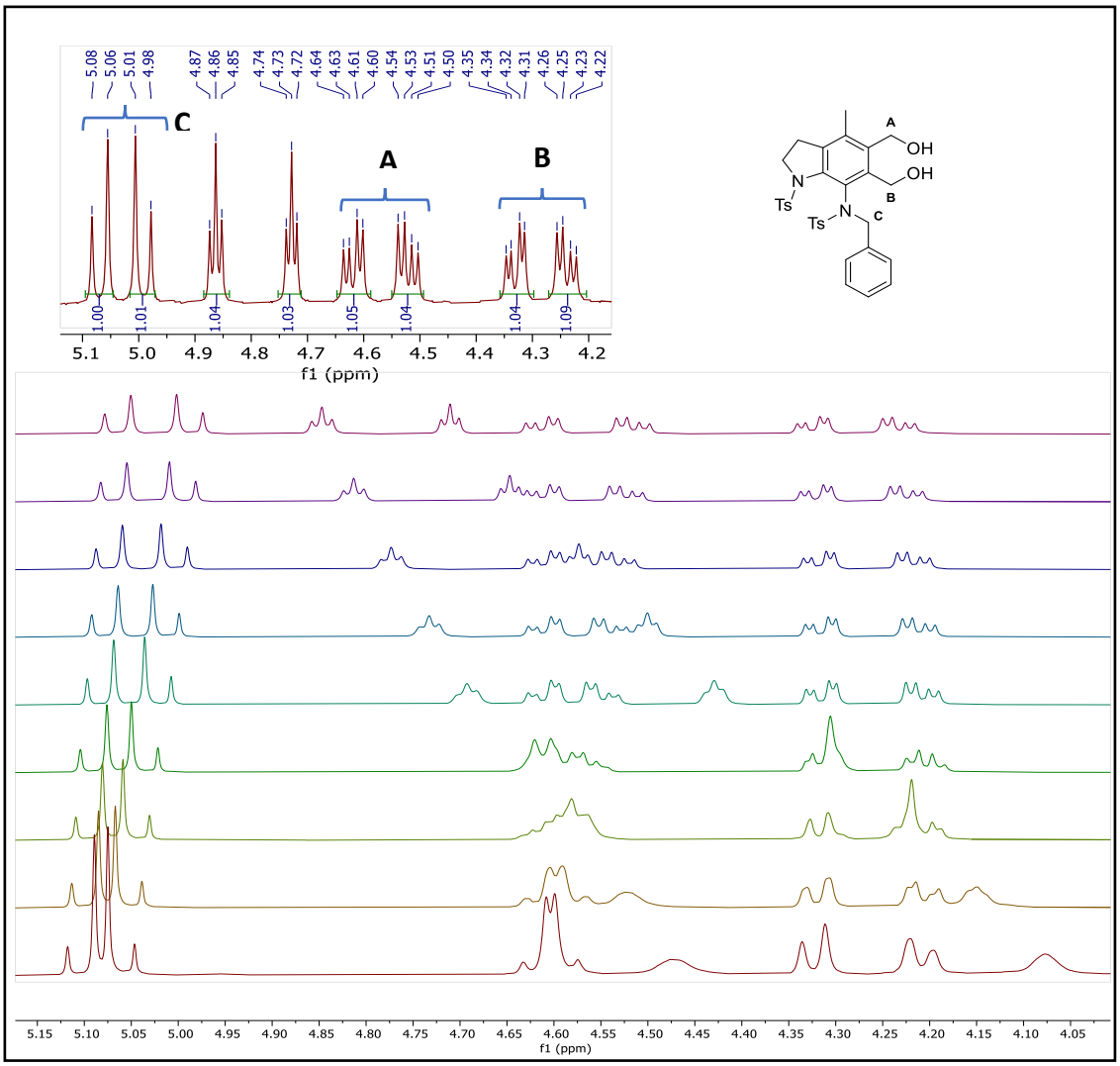


Figure 3.2: Variable temperature ^{1}H NMR spectroscopy of **158**. Spectra recorded in DMSO-d_6, temperatures from 22 °C (top), to 102 °C (bottom) in intervals of 10 °C.

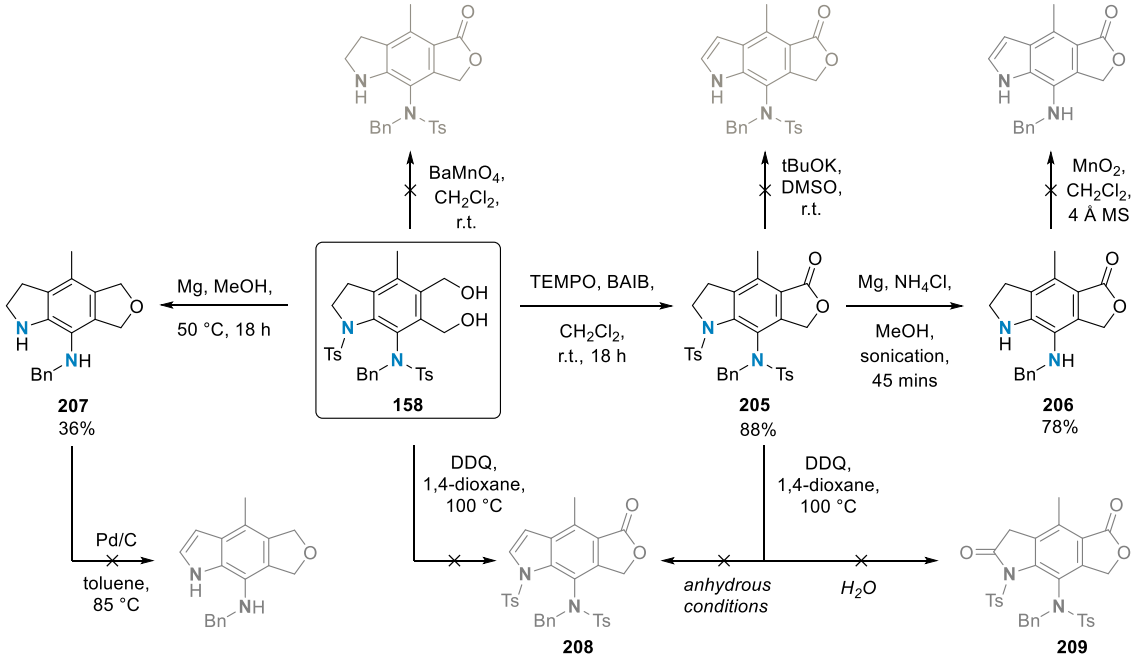
3.6 Derivatisation of 7-aminoindoline products

In addition to the interesting mechanistic observations to emerge from this project, the cyclotrimerisation of **82u** with 2-butyne-1,4-diol also enabled the preparation of a significant quantity of 7-aminoindoline **158**, which is an attractive substrate for further functionalisation to access more diverse indoline and indole structures.

The derivatisation of **158** is explored in **Scheme 3.16**, commencing with a selective oxidative cyclisation using a TEMPO/BAIB system (selective for the more electron rich

hydroxymethyl group) to form lactone **205** in good yield. The oxidation of similar diols has been previously reported with $BaMnO_4$[133] but no formation of **205** was observed when these conditions were used. Removal of the N–Ts groups in **205** proceeded smoothly by sonication with magnesium turnings to form **206**; in contrast, the deprotection of the parent diol **158** required heating and occurred concomitantly with cyclisation of the diol moiety to form **207**.

Attempts to oxidise the 7-aminoindoline core either directly from **158** or (after oxidation of the diol) from **205** using DDQ (under both anhydrous conditions – to form **208** – and in the presence of water to form **209**) were unsuccessful, as was an attempt to eliminate the N–Ts group using potassium *tert*-butoxide to achieve the oxidation of **205** (*this approach was previously shown to be effective in the oxidation of **84→111** in **Section 2.11**)*. Manganese dioxide was not effective in oxidising **206**,[134] nor was an attempt to dehydrogenate **207** using Pd/C.[135]



Scheme 3.16: Derivatisation reactions of **158**.

Although only limited functionalisation of the 7-aminoindoline core was achieved, the pseudo-desymmetrising oxidation of the diol moiety in **158** could be a powerful tool for accessing a substituted aminoindoline **205** with potential for further derviatisation. Combined with the range of aliphatic, aryl, heteroaryl, and heteroatomic substituents which can be incorporated in the [2+2+2] reaction, the reactivity described above gives access to many 7-aminoindolines.

3.7 Application to reactions of yndiamides with diynes

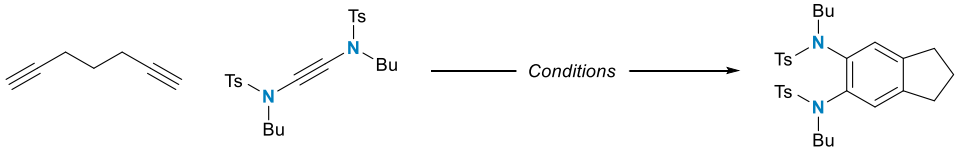
The reactivity described thus far in this chapter constitutes a synthesis of 7-aminoindolines, which are a sub-class of 1,2-diaminobenzene derivatives. A more general synthesis of 1,2-diaminobenzene derivatives might be of greater synthetic value and would demonstrate yndiamides as building blocks for the synthesis of 1,2-diaza-substituted structures.

In order to meet this challenge using [2+2+2] reactivity, a simple yndiamide would be required to undergo a cyclotrimerisation reaction with a diyne. Analogous reactivity is well precedented for ynamides, with the field being pioneered in 2006 by the groups of Tanaka[95] and Hsung[96], both of which employed rhodium catalysts to form aniline derivatives, again introducing restricted rotation about a C–N axis (S**ection 3.2**).

3.8 Opimisation of [2+2+2] cyclotrimerisation of yndiamides with diynes

The investigation of this aspect of the reactivity commenced with similar conditions to those employed by Hsung, using yndiamide **188** and 1,6-heptadiyne (**210**) (**Table 3.2**, entry 1), but disappointingly no product formation was observed, with the only reactivity being dimerisation and cyclotrimerisation of **210**. Use of an excess of **188** was unsuccessful, again resulting no product formation (entry 2). From these results it

appeared that **188** was significantly less reactive towards a rhodacycle than the ynamides reported in the literature. Several ruthenium catalysts were tried unsuccessfully (entry 3), but returning to the pre-formed rhodium(I) catalyst discussed in **Section 3.4** gave a low yield of the desired product **211** (entry 4). Building on this promising result, the issue of diyne dimerisation was tackled by slow addition of **210** to a solution of **188** and the catalyst (entry 5), which formed **211** in 45% yield. The success of the reaction was dramatically affected by the rate of the addition and the initial and final concentrations also had an effect (entries 6–12), with product formation out-competing dimer formation when slow addition was employed. Although Rh-catalysed cyclotrimerisation reactions are commonly carried out in alcohol solvents[90,136] no reaction was observed when *iso*-butanol was used as the solvent (entry 13). 1,4-Dioxane was found to be a suitable solvent (entry 14) – being more polar it might be of use when using reagents which are not soluble in toluene. Varying the rate of addition and concentration (entries 15–19) led to the optimised conditions for the cyclotrimerisation of **188** and **210** (entry 19).



210 **188** **211**

Entry	Catalyst	Solvent	Equiv. 188	Equiv. 210	Temp.	Time	Conc.	Yield
1	$(PPh_3)_3RhCl$ (20 mol%), $AgSbF_6$ (20 mol%)	DCE	1.0	10.0	85 °C	16 h	0.25 M (w.r.t. **188**)	0%
2	$(PPh_3)_3RhCl$ (20 mol%), $AgSbF_6$ (20 mol%)	DCE	2.0	1.0	85 °C	16 h	0.050 M (w.r.t. **188**)	0%
3	[Ru][b] (10 mol%)	PhMe	1.0	10.0	100 °C	1.5 h [c]	[a]	0%
4	**Rh-2** (5 mol%)	PhMe	2.0	1.0	85 °C	1.5 h	0.050 M (w.r.t **188**)	14%
5	**Rh-2** (5 mol%)	PhMe	1.0	10.0	85 °C	16 h[h]	[d]	45%
6	**Rh-2** (5 mol%)	PhMe	1.0	10.0	100 °C	1.5 h	[a]	51%
7	**Rh-2** (10 mol%)	PhMe	1.0	10.0	100 °C	1.5 h	[a]	54%
8	**Rh-2** (10 mol%)	PhMe	1.0	10.0	100 °C	16 h	[d]	50%
9	**Rh-2** (10 mol%)	PhMe	1.0	10.0	100 °C	16 h	[a]	27%
10	**Rh-2** (10 mol%)	PhMe	1.0	10.0	100 °C	16 h [c]	[a]	57%
11	**Rh-2** (10 mol%)	PhMe	1.0	10.0	100 °C	4 h [e]	[a]	67%
12	**Rh-2** (10 mol%)	PhMe	1.0	10.0	100 °C	6 h [f]	[a]	59%
13	**Rh-2** (10 mol%)	i-BuOH	1.0	10.0	100 °C	4 h [e]	[a]	0%
14	**Rh-2** (10 mol%)	1,4-dioxane	1.0	10.0	100 °C	4 h [e]	[a]	63%
15	**Rh-2** (10 mol%)	PhMe	1.0	5.0	100 °C	4 h [g]	[a]	77%
16	**Rh-2** (10 mol%)	PhMe	1.0	5.0	100 °C	16 h [h]	[a]	73%
17	**Rh-2** (10 mol%)	PhMe	1.0	2.5	100 °C	4 h [i]	[a]	72% (14% **188**)
18	**Rh-2** (5 mol%)	PhMe	1.0	5.0	100 °C	4 h [g]	[a]	62% (21% **188**)
19	**Rh-2 (5 mol%)**	**PhMe**	**1.0**	**5.0**	**100 °C**	**4 h [g]**	**0.50 M [j]**	**78%**

Table 3.2: All reactions on 0.050 mmol scale under Ar atmosphere. Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. **Rh-2** = (*rac*-BINAP)Rh(cod)SbF_6. [a] 0.25 M (w.r.t **188**) to 0.050 M after addition; [b] [Ru(*p*-cymene)Cl_2]$_2$ *or* Cp*RuCl(cod) *or* Grubbs I *or* $Ru_3(CO)_{12}$ (3.3 mol%) + PPh_3 (5 mol%); [c] Addition of **210** over 1 h; [d] 0.25 M (w.r.t **188**) to 0.010 M after addition; [e] Addition of **210** over 3 h; [f] Addition of **210** over 5 h; [g] Addition of **210** over 1.5 h; [h] Addition of **210** over 10 h; [i] Addition of **210** over 0.75 h; [j] 0.5 M (w.r.t **188**) to 0.10 M after addition.

3.9 Reaction scope of yndiamide [2+2+2] cyclotrimerisation with diynes

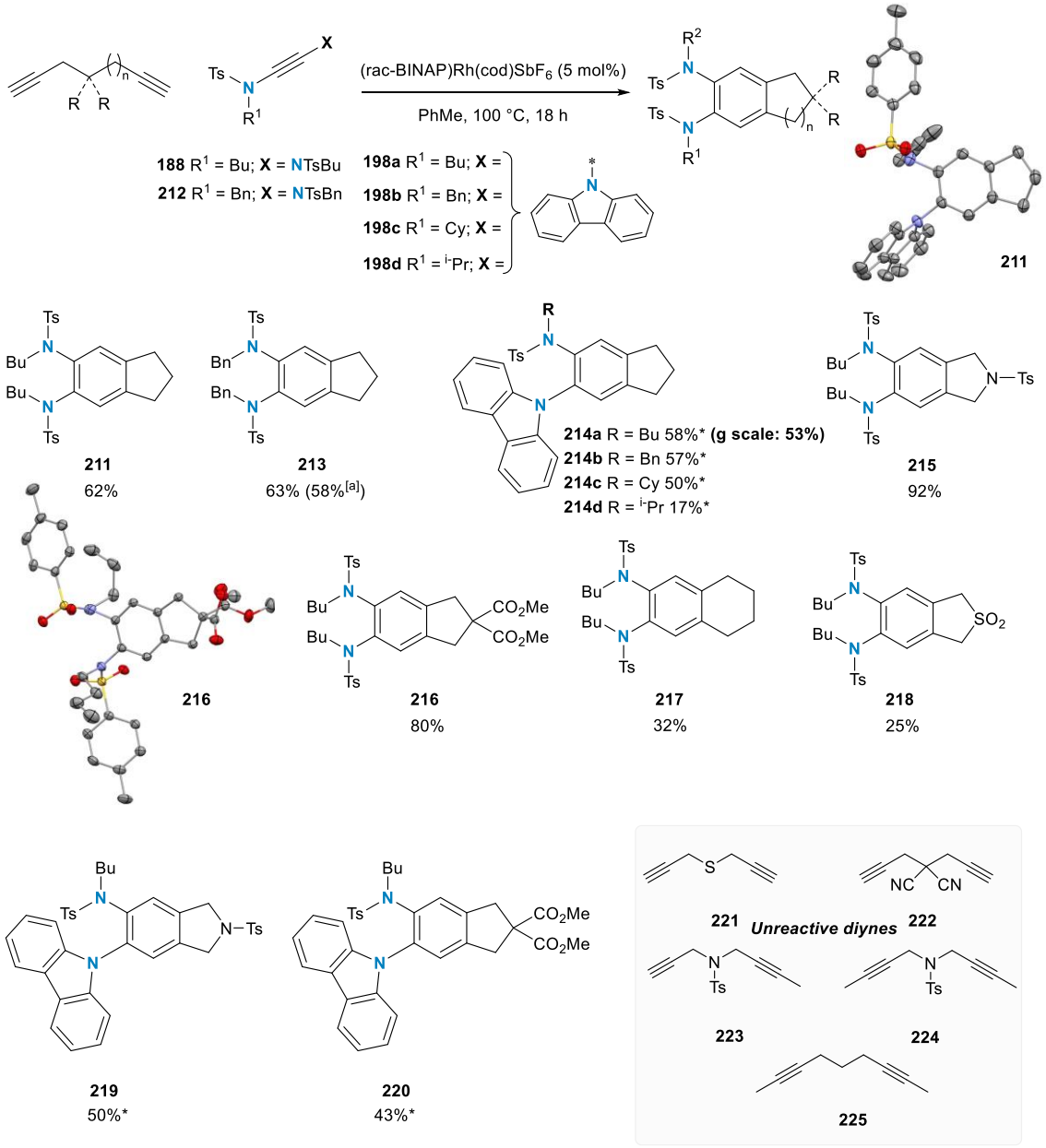
The scope of the cyclotrimerisation was then explored, focussing in turn on varying the yndiamide and the diyne partner (**Scheme 3.17**).

Symmetrical yndiamides **188** and **212** reacted with 1,6-heptadiyne to give **211** and **213** respectively in good yield. The ^{1}H NMR spectrum of **213** showed significant broadening of the benzylic protons; upon heating with variable temperature ^{1}H NMR spectroscopy these signals were resolved to a singlet and triplet respectively, which is consistent with slow C–N bond rotation on the NMR timescale at room temperature. *N*-Arylated carbazoles **214a**–**d** were formed successfully in good yields by cyclotrimerisation of carbazole-yndiamide **198a**–**d** with 1,6-heptadiyne (*compounds **214a**–**d** were prepared by Julia Ragus, with the exception of the gram-scale example for **214**, which was performed by the author*[128]). The diyne linker was then varied, with a sulfonamide (**215**) and dimethyl ester (**216**) being well tolerated. The use of 1,7-octadiyne formed tetrahydronaphthalene derivative **217**, although the yield was lower due to formation of the required rhodacycle being less favourable with a four-carbon linker than with a three-carbon linker; this is likely an entropic effect. Finally, a sulfone linker was employed in the form of 3-(prop-2-yn-1-ylsulfonyl)prop-1-yne, which required a solvent change to 1,4-dioxane because 3-(prop-2-yn-1-ylsulfonyl)prop-1-yne is insoluble in toluene, and was carried out at a lower temperature due to the lower boiling point of 1,4-dioxane. The desired product **218** was formed in low yield accompanied by extensive decomposition potentially due to SO_2 extrusion. Carbazole-yndiamides were also successfully reacted with diynes containing substituted linkers to form the products **219** and **220** (*compounds **219** and **220** were prepared by Julia Ragus).*

The cyclotrimerisations of yndiamide **188** with terminal 1,6-diynes were not all successful; a reaction was observed between **188** and di(prop-2-yn-1-yl)sulfane (**221**) but the product could not be isolated, and 2,2-di(prop-2-yn-1-yl)malononitrile (**222**) was

completely unreactive, probably as a result of the nitrile groups coordinating to the rhodium catalyst.

Moving from terminal 1,6-diynes to their substituted analogues, a disappointing reduction in reactivity occurred. No product formation was observed from the reaction between yndiamide **188** and **223** by either crude ^{1}H NMR spectroscopy or mass spectrometry, with only dimerisation of the diyne being observed. This lack of reactivity of yndiamide **188** towards a substituted diyne that is known to be capable of undergoing numerous transition metal-catalysed [2+2+2] cyclotrimerisations[98,137–141] is suggestive of significant steric effects on the outcome of the reaction (in comparison to the excellent reactivity observed with its non-substituted analogue). Unsurprisingly, the bis-methyl substituted analogue **224** also failed to react with yndiamide **188**. In order to provide a better comparison with known ynamide reactivity, nona-2,7-diyne (**225**) (shown by Hsung and co-workers to successfully react with ynamides[96]) was also subjected to the cyclotrimerisation conditions with yndiamide **188** but again no product formation was observed.



Scheme 3.17: Scope of [2+2+2] cyclotrimerisation reactions between yndiamides and diynes and single crystal XRD structures of **211** and **216**. All reactions under Ar atmosphere on 0.10 mmol scale except where stated. Displacement plots for **211** and **216** are displayed at 50% probability with hydrogen atoms hidden for clarity. [a] Reaction on 1.0 mmol scale. * Reactions done by Julia Ragus.[128]

Returning to the unsymmetrical diyne **223**, attempts were made to achieve reactivity with yndiamides by using an alternative rhodium catalytic system – $Rh(cod)_2BF_4$/ *rac*-BINAP with a H_2 pre-purge[142] – but this was also unable to promote the desired reactivity. Using a cobalt (I) catalyst (CpCo(CO)(dmfu) – see **Chapter 5**) was also unsuccessful.

Carbazole-yndiamides **198a** and **198b** also failed to react with **223**, and were returned unchanged.

With even the smallest carbon substituent – a methyl group – not tolerated on the diyne reactant, the options for investigating regiochemical control of this [2+2+2] reaction were clearly limited and this avenue of investigation was left in favour of exploring the formation of di-aza substituted 6-membered heterocycles (see **Chapter 5**). Nevertheless, the results of this investigation are significant in that they demonstrate the reduced reactivity of yndiamides towards intramolecular [2+2+2] reactions compared to previously reported (oxazolidone) ynamides. It is plausible that this reduced reactivity is due to the steric bulk of the sulfonamide substituents on the yndiamide – this is consistent with the observation by Hsung and co-workers that *N*-tosyl ynamides were unreactive under Rh catalysed cyclotrimerisation conditions.[143]

3.10 Derivatisation of 1,2-diaminobenzene products

Having developed and demonstrated a method for the synthesis of 1,2-diaminobenzene derivatives from yndiamides, the focus turned to investigating derivatisation of these compounds. The removal of *N*-tosyl groups from the products of yndiamide reactions has been a challenge throughout our group's exploration of yndiamide chemistry, and this again posed a major obstacle to derivatisation of these 1,2-dianilide products.

A variety of reductive conditions were explored to achieve the removal of the *N*-tosyl protecting groups in **213** (**Table 3.3**). Although consumption of the starting material was observed in several cases (entries **1**,**2**,**4**,**5**), only in the case of Li-naphthalenide was a product observed by crude ^{1}H NMR which might correspond to the elusive

diaminobenzene derivative **226**, however attempts to isolate this compound were unsuccessful.

213 **226**

Entry	Conditions	Outcome
1	Mg (20.0 equiv.), NH_4Cl (2.0 equiv.), MeOH, sonicate, r.t.	85% consumption of SM, no product observed
2	Mg (20.0 equiv.), NH_4Cl (2.0 equiv.), MeOH, 6 0 °C	71% consumption of SM, no product observed
3	$TiCl_3$, Li, THF, 80 °C[144]	< 10% consumption of SM, no product observed
4	LiDBB (4.0 equiv.), THF, - 78 °C to r.t.[145]	65% consumption of SM, no product observed
5	Li-naphthalenide (4.0 equiv.), THF, r.t.	100% consumption of SM, possible product observed by ^1H NMR but no product isolated
6	SmI_2, pyrrolidine, water, THF, r.t.[146]	0% consumption of SM

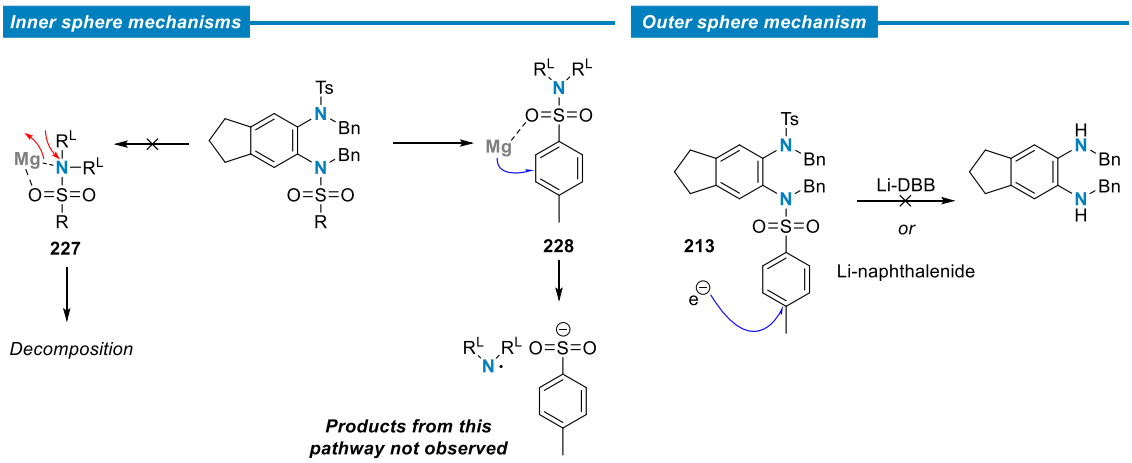
Table 3.3: All reactions under Ar atmosphere on 0.050 mmol scale. Consumption of starting materials measured by quantitative ^1H NMR spectroscopy, using 1,3,5-trimethoxybenzene as an internal standard.

The difficulties encountered when attempting the double detosylation of **213** are consistent with the observations of Keller and co-workers in their work on deprotection of chiral 1,2-bis(tosylamides),[147] and although their work focussed on *aliphatic* tosylamides, the mechanistic discussion contained therein is useful when considering the lack of reactivity of **213** towards typical detosylation conditions.

Detosylation under reductive conditions can occur by either Inner Sphere Single Electron Transfer (SET) or Outer Sphere SET pathways (**Scheme 3.18**), with reduction by magnesium in methanol proposed to occur by an Inner Sphere pathway.[147] Considering this mechanistic proposal may shed some light on why **213** was not deprotected using these conditions, and why even the successful detosylation (**Scheme 3.19**) was slow and low yielding.

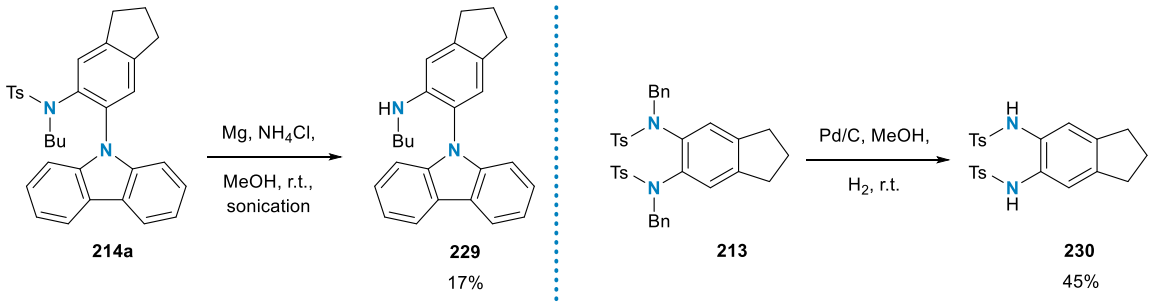
Two possible pathways for the Inner Sphere reaction are to be considered – firstly the formation of a complex **227** involving coordination of the sulfonamide nitrogen and one of the oxygen atoms to the magnesium atom. This pathway is considered unlikely for two reasons – firstly the steric bulk of the diaminobenzene moiety would make it unfavourable, and secondly the nitrogen lone pair may not be available due to delocalisation into the aromatic ring. The steric issues with this pathway for the substrates under consideration here are actually of little consequence because this is not a productive pathway, leading to undesired decomposition reactions.

The second Inner Sphere pathway, which is believed to be favoured for sulfonamides with large nitrogen substituents, involves coordination of the magnesium by the oxygen atoms of the sulfonamide (**228**) followed by electron transfer to the aromatic ring, resulting in cleavage of the N–S bond. As the substituents on nitrogen in **213** are large, it is plausible that this second ISET pathway is operating, and although the reasons for the lack of product formation are not clear it is likely that it relates to the two adjacent sulfonyl groups, as replacing one of these with a carbazole group did allow detosylation (albeit in low yield) (**Scheme 3.19**).



Scheme 3.18: Proposed ISET and OSET mechanisms for deprotection of *N*-Ts compounds using reducing conditions.

Despite the difficulties encountered with deprotection of **213**, two successful derivatisation reactions of the dianilide products were carried out (**Scheme 3.19**). Treatment of **213** with Mg in MeOH while sonicating gave **229** in low yield. When **213** was subjected to mild hydrogenation conditions, a facile double debenzylation occurred to form **230** in moderate yield. Further functionalisation of sulfonamide-protected diaminobenzene **230** may be possible, for example to introduce functionality not tolerated in the synthesis of yndiamides (such as *N*-aryl groups).



Scheme 3.19: Deprotection reactions of 1,2-diaminobenzene derivatives **214a** and **213**.

3.11 Concluding remarks on yndiamide [2+2+2] cyclotrimerisation

Two [2+2+2] cyclotrimerisation reactions of yndiamides have been developed, the first involving yne-yndiamides and monoalkynes, and the second involving yndiamides and diynes, forming 7-aminoindoline and 1,2-diaminobenzene derivatives respectively. The first transformation is of interest primarily for its remarkable dependence of the regiochemical outcome on the electronic properties of the monoalkyne partner, the mechanistic rationale for which will be explored in **Chapter 4**. The second transformation is significant as it overcomes the poor reactivity of sulfonamide yndiamides with rhodacycle intermediates. Unfortunately both transformations are limited by the scope for derivatisation of the products, which limits their utility in the synthesis of 1,2-diaza aromatic compounds. Nevertheless, as a demonstration of the

potential for employing yndiamides in arene ring forming reactions, they are significant and complement the already extensive ynamide literature in this field.

Future work in this area might focus on demonstrating the utility of yndiamide [2+2+2] cyclotrimerisation reactions in the synthesis of biologically relevant scaffolds in drug molecules and natural products containing 1,2-diaza substitution on aromatic rings. This is likely to require development of new synthetic methods to prepare yndiamides with a more diverse range of nitrogen substituents.

Chapter 4: Computational study on [2+2+2] cyclotrimerisation reactions of yne-yndiamides with alkynes

The [2+2+2] cyclotrimerisation reaction of yne-yndiamides with aryl alkynes discussed in **Chapter 3** featured a remarkable dependency of the regiochemical outcome on the electronic properties of the aryl alkyne. This observation prompted a computational investigation into the mechanism of this particular cyclotrimerisation reaction, which will be discussed in this chapter. The mechanistic proposal for the cyclotrimerisation of an yne-yndiamide with an alkyne was validated computationally, and the regiochemical outcome was probed. This work was carried out with advice from Zixuan Tong and Nils Frank.

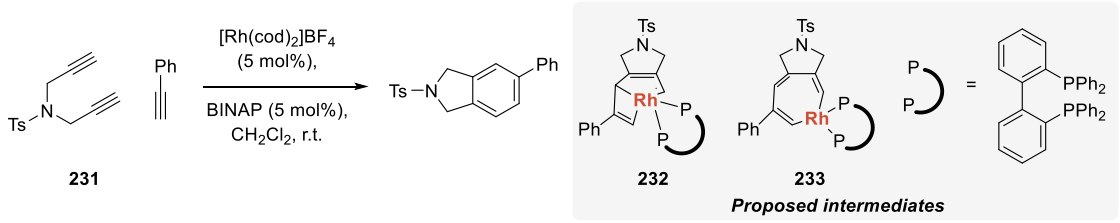
4.1 Introduction to DFT studies of [2+2+2] cyclotrimerisation

DFT (Density Functional Theory) is a computational quantum mechanical method which strikes a balance between accuracy and computational time requirements and as a result has become a key part of the toolkit for investigating organic reactions, alongside synthesis and spectroscopy.[148] The method is based on the Hohenberg-Kohn theorems, which allow the energy of a chemical system to be calculated from the electron density using an appropriate functional.[149] DFT is generally reliable and can be applied to complex systems, generally with a small risk of generating entirely incorrect results as the methods are extensively benchmarked, making it a useable tool for non-specialists to apply in a 'black-box' fashion to solve mechanistic problems.[148] In this investigation, DFT will be used in this 'black-box' manner to investigate the regiochemical outcome of [2+2+2] cyclotrimerisation reactions of yndiamides.

The mechanistic aspects of [2+2+2] cyclotrimerisation reactions of alkynes have been studied extensively using computational methods, specifically DFT, over the past two decades and these studies were covered in a comprehensive review by Solà and co-workers in 2021.[150] An informative example of such work will now be summarised.

In 2012, Roglans and co-workers used ESI-MS methods to observe intermediates in the catalytic cycle of the rhodium-catalysed [2+2+2] reaction between diyne **231** and monoalkynes and they supported their proposed intermediates (**232** and **233**) for the monoalkyne insertion step with DFT calculations (**Scheme 4.1**).[151] Although the reported reactions did not include a regioselectivity aspect (as they used symmetrical diynes), this work provides useful precedence for DFT studies of [2+2+2] cyclotrimerisation reactions. In their work, the reaction between diyne **231** and phenylacetylene was studied at the B3LYP/cc-pVDZ-PP level of theory, with some

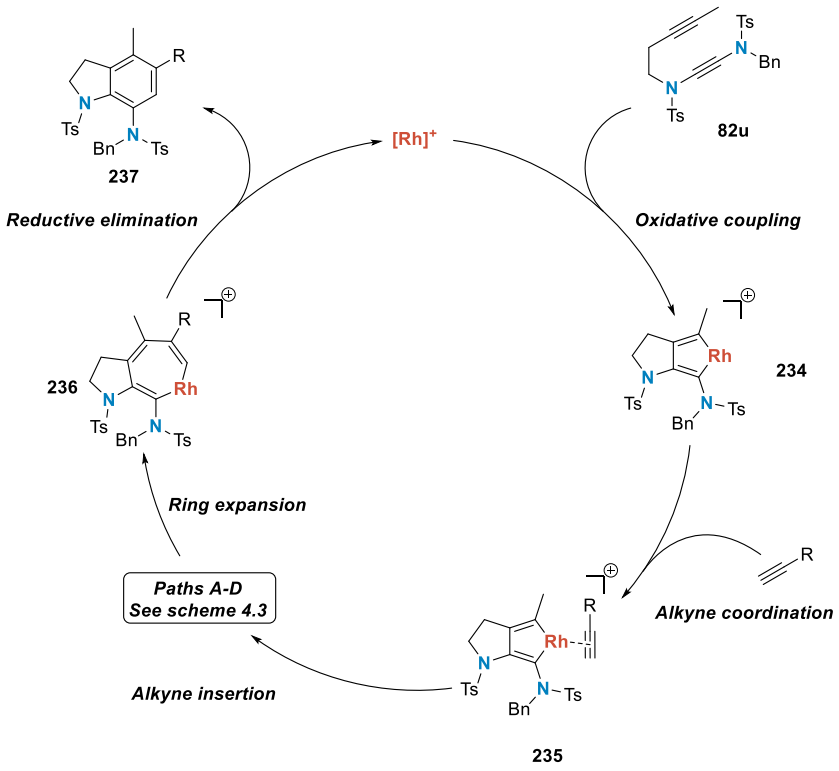
simplifications to the structure (replacing Ts- groups with Ms- groups and using BIPHEP in place of BINAP) to reduce the computational cost. These simplifications and the proposed intermediates were useful in designing the models to be used in our investigation.



Scheme 4.1: [2+2+2] Cyclotrimerisation reaction investigated by Roglans and co-workers using DFT at B3LYP/cc-pVDZ-PP level of theory.[151]

4.2 General [2+2+2] cyclotrimerisation mechanism

A generally accepted [2+2+2] cyclotrimerisation mechanism was initially proposed for the cyclotrimerisation of **82u** with aryl alkynes, to be used as the basis for the computational investigation (**Scheme 4.2**). The mechanism is proposed to be as follows: an oxidative coupling of the yne-yndiamide (**82u)** with the rhodium active catalytic species forms the metallocyclopentadiene **(234)**, which is coordinated by the alkyne followed by a formal [5+2]/alkyne insertion step to form **235**. A 'ring expansion' step then occurs to form a metallocycloheptatriene (**236**), which undergoes reductive elimination and decomplexation from the catalyst to form the product (**237**). In **Scheme 4.2**, the details of the alkyne insertion (**235→236**) are not shown, as four different pathways (each leading to one of two product isomers) can be considered, which are analysed in **Scheme 4.3**.

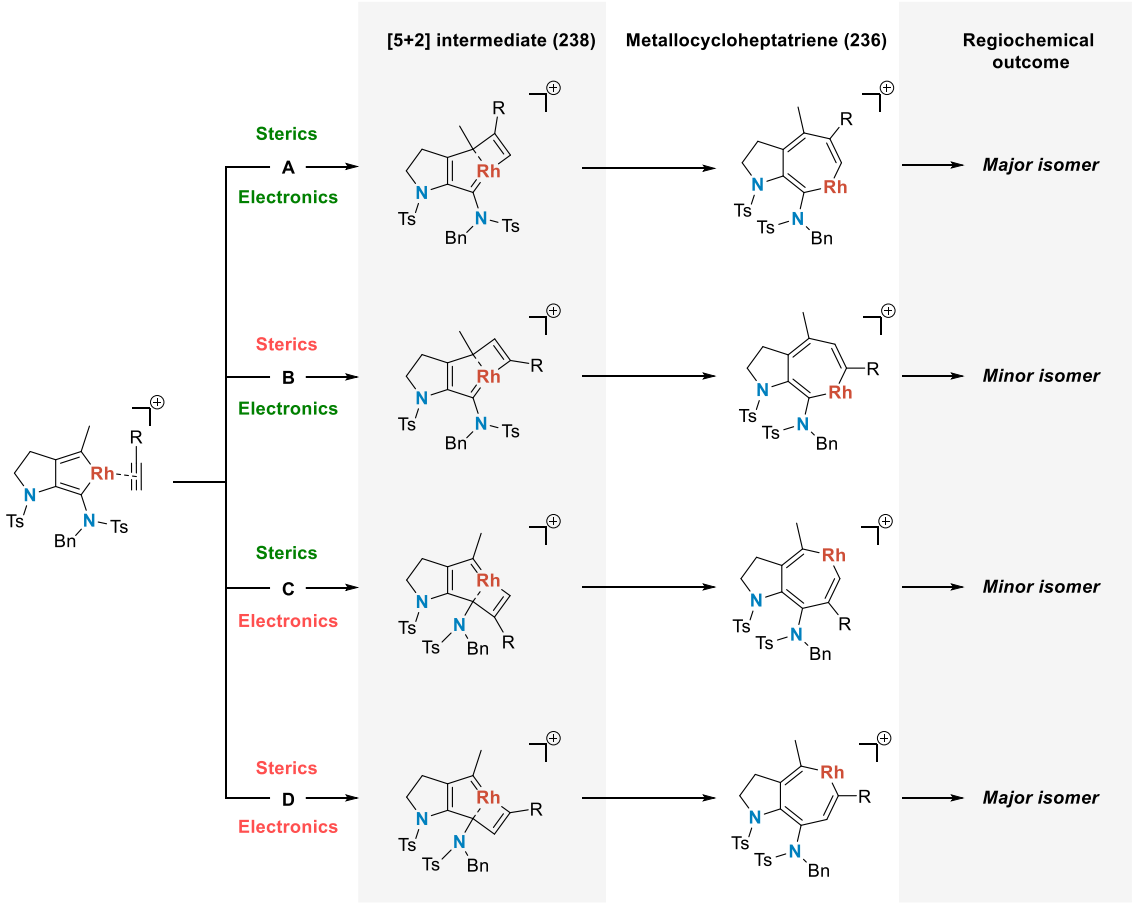


Scheme 4.2: Initially proposed mechanism for the [2+2+2] cyclotrimerisation of yne-yndiamide **82u** with alkynes. *Note: only one regiochemical outcome, occurring by one of the four possible paths **A**–**D** (**Scheme 4.3**), is shown for clarity.* Ligands on rhodium not shown for clarity.

Although the overall rate-determining step of this mechanism is likely the oxidative coupling of the yne-yndiamide with the rhodium catalyst,[152,153] it is important to note that in some cases the alkyne insertion has been calculated to be the rate-determining step.[154] The oxidative coupling step does not affect the regiochemical outcome of the reaction as the alkyne partner is not involved at this stage. Therefore, for the investigations contained within this chapter, the reaction was considered to start from the metallocyclopentadiene **236**, thus making the next largest Gibbs free activation energy *after* this intermediate the effective rate determining step, and thus regiochemistry determining step, for the purposes of these calculations.

In their 2021 report of rhodium-catalysed [2+2+2] cyclotrimerisation of ynamides,[93] Witulski and Alayrac provided a helpful analysis of the regiochemistry of the alkyne

insertion step; a similar analysis will be performed for the yndiamides under consideration here (**Scheme 4.3**). Insertion of the alkyne by a formal [5+2] cycloaddition can occur into either of the C–Rh bonds, forming intermediates **238**, and in each case two alkyne orientations are possible, leading to four possible pathways (**A**, **B**, **C** and **D**).



Scheme 4.3: Analysis of possible alkyne insertion pathways with expected regiochemical outcomes *if they were followed to completion.* Ligands on rhodium not shown for clarity.

Application of Bent's rule ("*atomic s character concentrates in orbitals directed toward electropositive substituents*"[155], or alternatively "*the energetically lower lying valence orbital concentrates in bonds directed toward electropositive substituents*"[156]) suggests that pathways **A** and **B** should be electronically favoured, as they position the $C_{carbene}$ *s*-character orbitals towards rhodium (electropositive) and the $C_{carbene}$ *p*-character orbitals towards nitrogen (electronegative). Additionally, the exocyclic nitrogen atom in

pathways **A** and **B** might donate π-electron density to give the $C_{carbene}$–Rh bond Fischer carbene character and thus stabilise the intermediates and transition states on these pathways. Furthermore, pathway **A** should allow an electron-rich aryl group to participate in mesomeric stabilisation of the charge on rhodium by electron-donation through the rhodacyclobutene π-system. Such stabilisation is not possible in pathway **B**.

On steric grounds, pathways **A** and **C** are predicted to be favoured, as they position the incoming aryl alkyne group far from the bulky ligands on rhodium. Pathway **D** should be disfavoured on both steric and electronic grounds. Therefore, although pathway **D** would form the experimentally observed major isomer, it is not thought to be a feasible pathway for the reaction.

Consideration of electronic and steric factors leads to the hypothesis that pathway **A** should be the most favourable of the four pathways considered here, leading to the formation of the experimentally observed major regioisomer, followed by pathway **B** which would form the experimentally observed minor isomer. This hypothesis was tested computationally by comparison of pathways **A** and **B** (**Section 4.3**).

4.3 DFT study of [2+2+2] cyclotrimerisation reactions of yne-yndiamides with aryl alkynes

The cyclotrimerisation reaction between a simplified yne-yndiamide and phenylacetylene was investigated using Gaussian16[157] at the PCM(Dichloroethane)-B3LYP-GD3/cc-pVDZ level of theory[158,159] with the LANL2DZ(Rh) pseudopotential for rhodium[160–162] and the GD3 dispersion correction.[163] This level of theory closely resembles that previously reported for investigating the cyclotrimerisation of alkynes.[151,164] When planning the study, pathways **A** and **B** (**Scheme 4.3**) were selected as the most probable

routes to form the major and minor products respectively – pathways **C** and **D** were not investigated due to the excessive computational cost of investigating all pathways.

4.3.1 Modelling the [2+2+2] reaction using model PH_3 ligands

The ligand on rhodium was initially simplified by using two PH_3 ligands to replace the BINAP ligand present in the real system to minimise the computational cost of the calculations. A similar simplification has been previously reported for PPh_3 ligands,[152] but the extension of this simplification to a bidentate phosphine ligand was later found to be an oversimplification.

The geometries of five intermediates were optimised, for each of the major and minor products:

SM: rhodacycle and phenylacetylene,

Int1: complex formed between the rhodacycle and phenylacetylene,

Int2: initial [5+2] adduct,

Int3: rhodacycloheptatriene**,**

Int4: reductive elimination product complex.

Intermediates **Int1** and **Int2**, and the transition state(s) connecting them were recognised to be of particular relevance to the regiochemical outcome of the reaction.The calculated Gibbs free energy profiles for the formation of the major and minor products of the reaction between the simplified yne-yndiamide and phenylacetylene is shown in **Figure 4.1**. It is apparent from examination of the respective Gibbs free activation energies for alkyne insertion into the rhodacycle to form the major (27.1 kcal mol^{-1}) and minor (25.3 kcal mol^{-1}) isomers that this model is unable to correctly predict/justify the

regiochemical outcome of the reaction. Furthermore, the PH_3 ligands were observed to be a poor mimic of the true (bidentate) ligand as the P–Rh–P bond angles fluctuated significantly throughout the cycle (from ~ 90 to 180°), which is not possible with the true ligand. A more sophisticated model of the ligand system was therefore required.

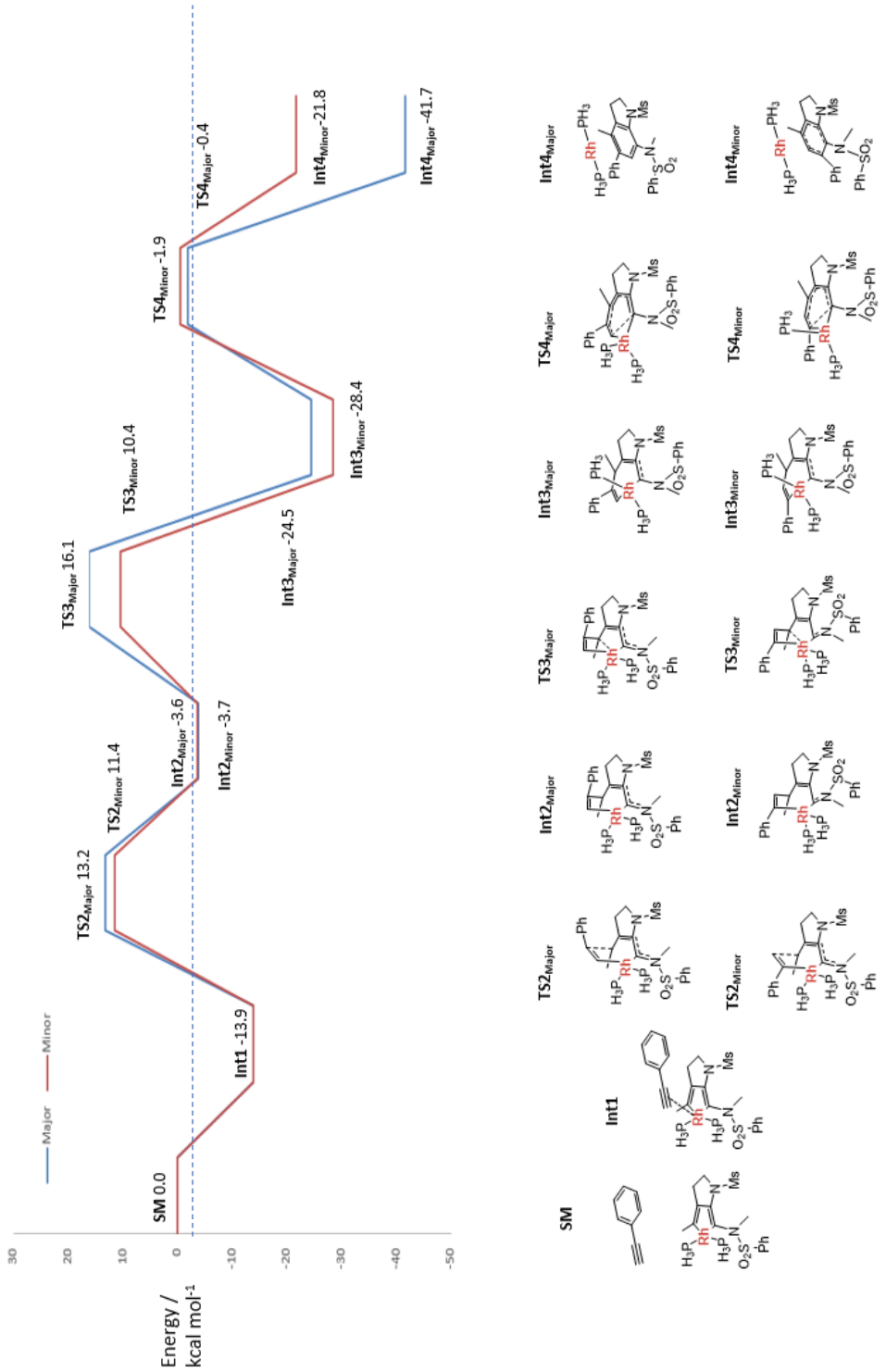


Figure 4.1: Gibbs free energy profile for [2+2+2] cyclotrimerisation computed with PH_3 ligands. Computed at the CPCM(Dichloroethane)-DLPNO-CCSD(T)/def2-TZVPP//PCM(Dichloroethane)-B3LYP-GD3/cc-pVDZ+LANL2DZ(Rh) level of theory.

4.3.2 Modelling the [2+2+2] reaction using a model bidentate ligand

In an attempt to more accurately model the ligand system surrounding rhodium, while involving a minimal increase in computational cost, a simplified bidentate ligand (derived from BIPHEP with the four phenyl groups replaced by hydrogen atoms) was chosen for the next stage of the investigation (**Figure 4.2**).

The formation of the major and minor products was once again modelled but was in this case found to proceed through only four intermediates:

***SM**: rhodacycle and phenylacetylene,

***Int1**: complex formed between the rhodacycle and phenylacetylene,

***Int2**: formal [5+2] adduct,

***Int3**: the reductive elimination product complex.

***Int2** was observed to exist in at least two similar low-energy conformations but no transition state could be located for their interconversion so ***Int2** was used as a single intermediate in place of **Int2** and **Int3** from the first cycle.

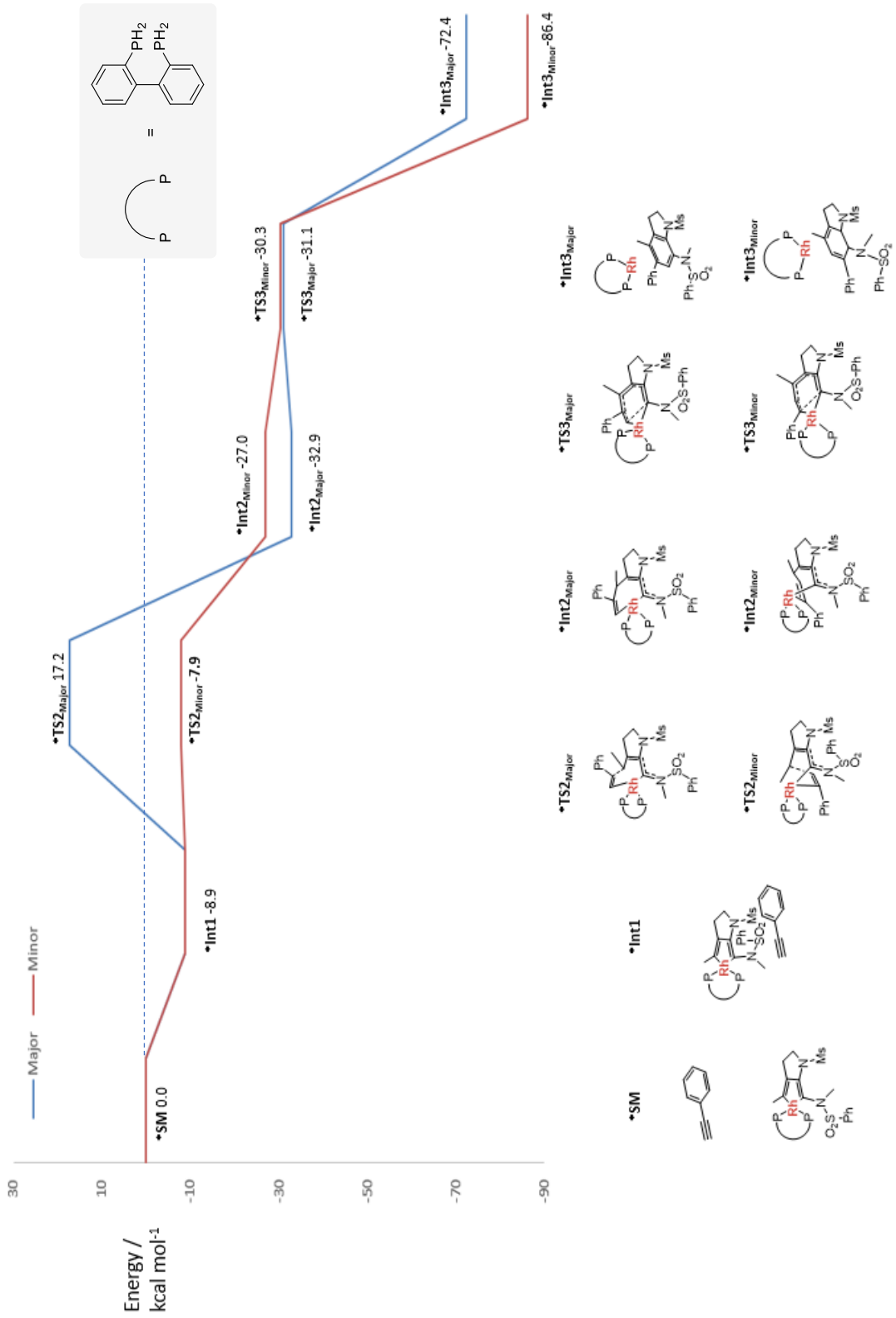


Figure 4.2: Gibbs free energy profile for [2+2+2] cyclotrimerisation computed with simplified bidentate ligand. Computed at the CPCM(Dichloroethane)-DLPNO-CCSD(T)/def2-TZVPP//PCM(Dichloroethane)-B3LYP-GD3/cc-pVDZ+LANL2DZ(Rh) level of theory.

Analysis of the computed Gibbs free activation energies for the key alkyne insertion step in this more sophisticated model once again shows that the energy barriers for the alkyne insertion to form the major (26.1 kcal mol^{-1}) and minor (1.0 kcal mol^{-1}) isomers fail to predict the experimentally observed regiochemical outcome. The extremely low Gibbs free activation energy calculated for insertion of the monoalkyne to form the minor isomer is clearly unrealistically small, suggesting that the simplified bidentate ligand is not an appropriate model. This model likely suffers from the problem that the methyl-aryl steric interaction is more significant than the ligand-aryl group steric interaction, which is hypothesised to control the regiochemical outcome in the real system. The ligand-aryl group steric interaction is probably artificially reduced in the simplified model used herein because the ligand can adopt a conformation in which the biaryl backbone is on the opposite face of the rhodacycle to the incoming aryl alkyne (**Figure 4.3**).

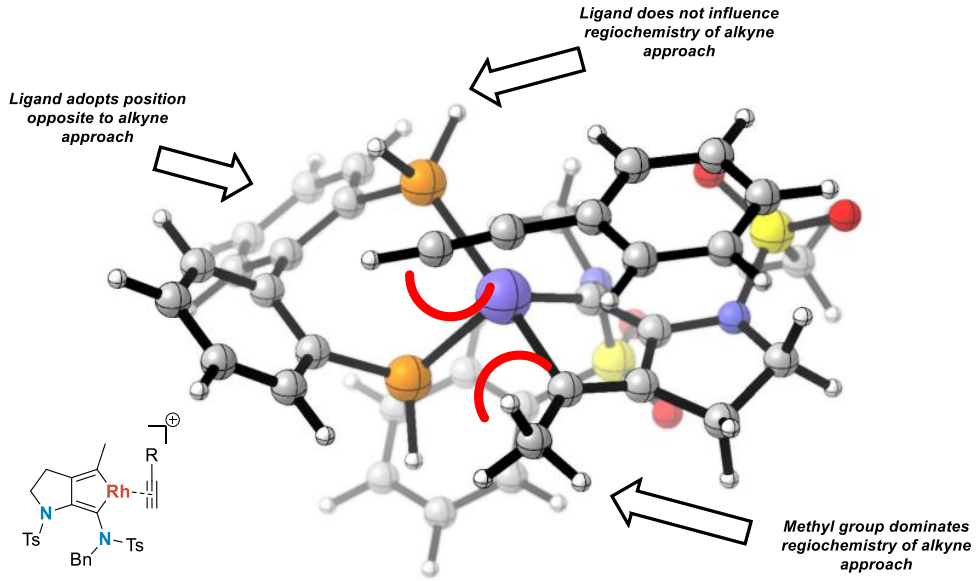


Figure 4.3: Optimised structure of ***Int1** showing lack of regiochemical control conferred by the model bidentate ligand.

Despite the failure of this model to match the experimentally observed regiochemical outcome, initial indications of the Natural Bond Orbital (NBO) character of ***TS2**$_{\mathbf{Major}}$

were obtained (**Figure 4.4**). The HOMO in ***TS2$_{Major}$** can be interpreted as a linear combination of one of the alkyne π orbitals with a Rh 4d orbital, and the LUMO consists primarily of the π* orbital of the rhodacycle. This appears to be indicative of an asymmetric transition state in which the terminal alkyne carbon is strongly coordinated to the rhodium atom (2.07 Å Rh–C_{alkyne} bond length).

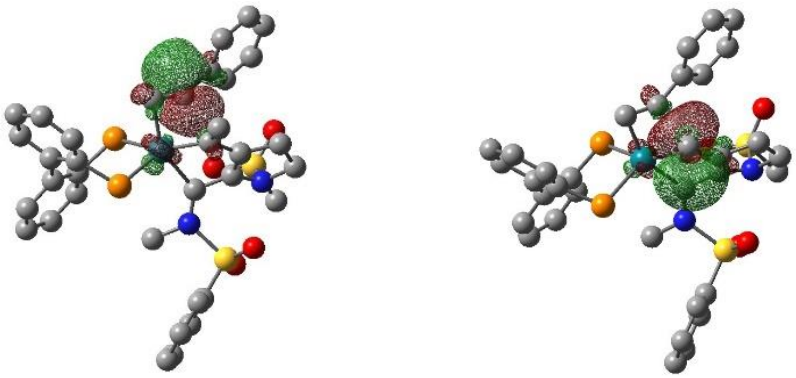


Figure 4.4: Calculated HOMO (left) and LUMO (right) for ***TS2$_{Major}$**. Iso value 0.02. Hydrogen atoms are omitted for clarity.

Analysis of the NBO (Natural Bond Orbital) character of ***TS2$_{Minor}$** showed that the relevant orbitals for the interaction of the alkyne with the rhodacycle were the HOMO-9 and HOMO-8 (appearing to correspond to the HOMO and LUMO respectively in ***TS2$_{Major}$**) (**Figure 4.5**). The HOMO-9 consists primarily of the interaction between one of the alkyne π-orbitals and the rhodacycle π-system and the HOMO-8 consists primarily of the rhodacycle π-system. The bond formation between the alkyne and the rhodacycle in ***TS2$_{Minor}$** appears to be more concerted than in ***TS2$_{Major}$** (***TS2$_{Minor}$** has a Rh–C_{alkyne} bond length of 2.16 Å as opposed to 2.07 Å for ***TS2$_{Major}$**); this suggests that two different reaction pathways have in fact been calculated: a stepwise pathway for the major isomer and a more concerted pathway for the minor isomer. This may account for the surprisingly low Gibbs free activation energy calculated for ***Int1**→***TS2$_{Minor}$**.

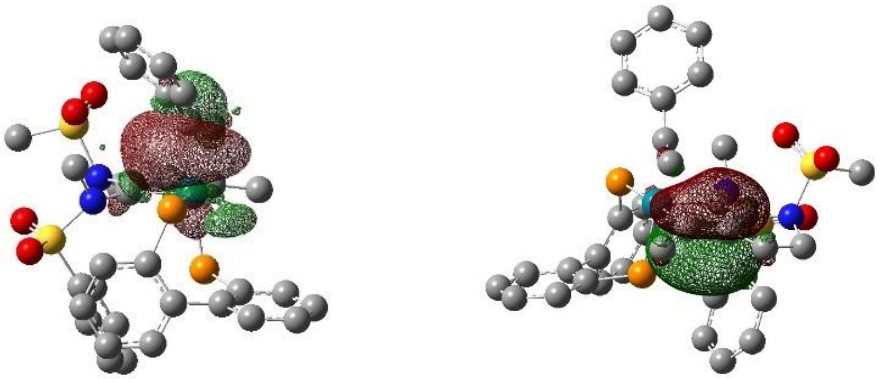


Figure 4.5: Calculated HOMO-9 (left) and HOMO-9 (right) for ***TS2$_{Minor}$**. Iso value 0.02. Hydrogen atoms are omitted for clarity.

Analysis of the forming Rh–C and C–C bond lengths was also used to gain understanding of the transition states. The forming Rh–C and C–C bond lengths in ***TS2$_{Major}$** are 2.07 Å and 2.10 Å respectively. The corresponding bond lengths in ***TS2$_{Minor}$** are 2.16 Å and 2.12 Å respectively (**Figure 4.6**). Although a small difference, this may imply a slightly stronger interaction between the Rh atom and the alkyne in the major isomer than in the minor isomer; this is consistent with the initial predictions made in **Section 4.2**, where pathway **A** was predicted to benefit from stabilisation of rhodium by donation from the aryl-alkyne π system.

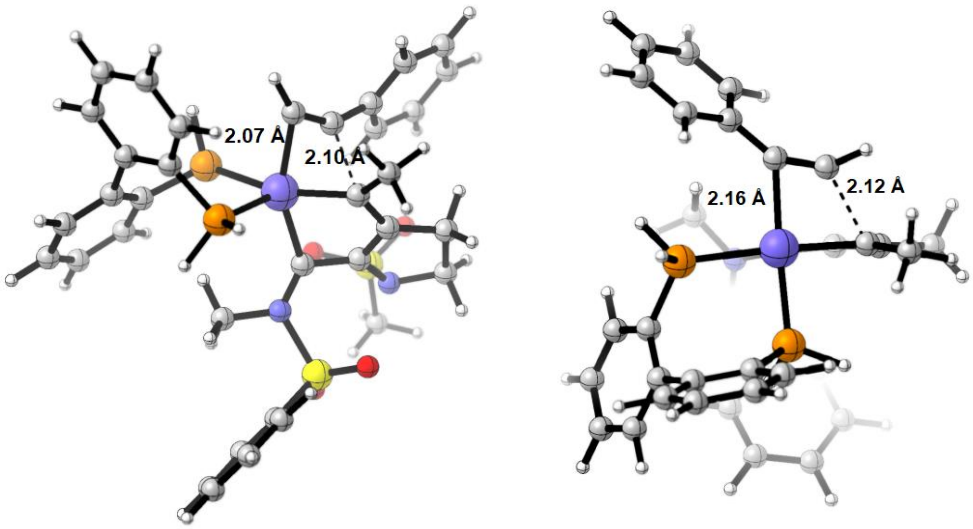


Figure 4.6: Optimised structures of ***TS2$_{Major}$** (left) and ***TS2$_{Minor}$** (right) with bond lengths for the Rh–C and C–C bonds shown.

The simplified bidentate phosphine ligand was once again not an appropriate model for the true ligand system as the ligand adopts a position on the opposite face of the rhodacycle to the approaching alkyne, thus negating the effect of the steric bulk of the phosphine ligand. Therefore, the calculations were repeated using BIPHEP as the ligand.

4.3.4 Modelling the [2+2+2] reaction using BIPHEP

The final ligand to be examined as a model ligand in the calculations for the [2+2+2] cyclotrimerisation was BIPHEP, which had proven effective as a ligand in the experimentally observed cyclotrimerisation reaction (**Section 3.4**, **Table 3.1**, entry **5**). As such, it should be a good substitute for the steric properties of BINAP in a non-enantioselective process such as the process under consideration here. The simplification of BINAP to BIPHEP was made to reduce the computational cost of the calculations, but disappointingly these calculations once again failed to reflect the experimentally observed regioselectivity of the reaction, as shown in **Figure 4.7**. Analagous intermediates and transition states were optimised using BIPHEP as for the simplified bidentate ligand (**Section 4.3.3**).

The formation of the major and minor products was once again modelled and again proceeded through only four intermediates:

†**SM**: rhodacycle and phenylacetylene,

†**Int1**: complex formed between the rhodacycle and phenylacetylene,

†**Int2**: formal [5+2] adduct,

†**Int3**: the reductive elimination product complex.

Although the Gibbs free activation energy of †$\mathbf{TS2_{Major}}$ was once again greater than that of †$\mathbf{TS2_{Minor}}$, the energy difference was smaller than for the simplified bidentate ligand, which implies that further modifications of the model system to more accurately resemble the real system could be beneficial for calculating these values, although the computational resources available limited further development.

As a point of interest, both the catalytic cycles computed with the model bidentate ligand and BIPHEP feature lower Gibbs free activation energies for the reductive elimination step (†**Int2**–†**Int3**) than found for the system using PH_3 ligands. This is a consequence of the natural bite angles of the model bidentate ligand and BIPHEP being close to 90°, which favours reductive elimination to form a square planar Rh(I) species.[165]

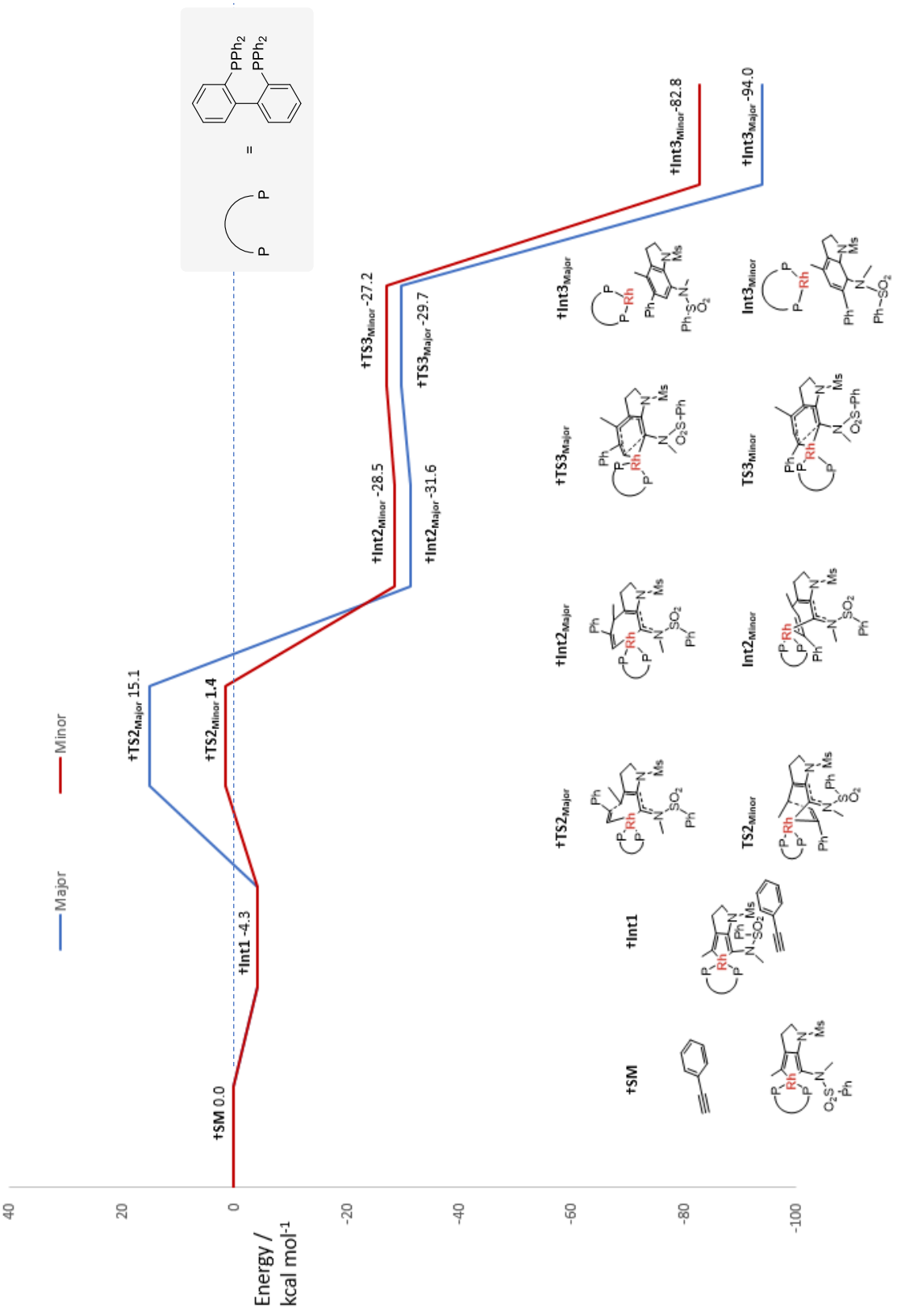


Figure 4.7: Gibbs free energy profile for [2+2+2] cyclotrimerisation computed with BIPHEP ligand. Computed at the PCM(Dichloroethane)-B3LYP-GD3/cc-pVDZ+LANL2DZ(Rh) level of theory.

4.4 Concluding remarks on computational modelling

Although this computational investigation into the factors controlling the regiochemical outcome of the cyclotrimerisation reaction did not provide a complete explanation, it validated the proposed mechanistic pathway as being feasible for yne-yndiamides. It also demonstrates the influence and potential problems of using simplified model ligands on calculated reaction mechanisms.

Turning to consider why the calculations gave results which are inconsistent with the experimental observations, two possible explanations may be considered. Firstly, it is possible that replacing the *N*-benzyl group with the *N*-methyl group in the model used for the calculations is an oversimplification of the structure and does not accurately represent the steric properties of the actual substrate, thus making the formation of the minor isomer more energetically favourable than it is in reality. Secondly, the computational methods used (although precedented for studying similar reactions) may not be appropriate for this particular reaction.

Future work in this area might repeat the calculations using a model which has steric properties which are closer to the true system, however the computational cost of such a model may become prohibitive. Another development would be a rigorous study of other computational methods for studying this transformation, for example by benchmarking geometries and energies of several functionals, basis sets, and pseudopotentials, to identify a robust computational method. Finally, although pathways **C** and **D** are considered to be less feasible than pathways **A** and **B** (**Scheme 4.3**), a full investigation of these pathways would be useful to rule them out as routes to form the experimentally observed major and minor isomers.

This computational investigation into the [2+2+2] cyclotrimerisation of yne-yndiamides with alkynes has laid foundations for further investigations into this transformation, and other regioselective cyclotrimerisation reactions. These transformations are of great synthetic value and their utility will be further increased by improved understanding of the factors which control the regiochemical outcome in non-symmetric contexts.

Chapter 5: Synthesis of diaminopyridines and diaminopyridones from yndiamides

This chapter details the development of syntheses of diaminopyridines and diaminopyridones from yndiamides. Building on the precedent in the literature for reactions of ynamides, two approaches were considered to synthesise these compounds: a Bronsted acid or Lewis acid promoted cationic formal [2+2+2] cyclisation, and a transition metal catalysed cyclotrimerisation approach using metallocycle intermediates generated from yne-yndiamides. This chapter will discuss the limitations of the first approach due to substrate incompatibility with the reaction conditions, and the development of transformations which demonstrate the feasibility of the second approach.

5.1 Introduction to diaminopyridines

Pyridine rings are abundant in small molecule drugs, being the second most commonly encountered nitrogen heterocycle in US FDA approved drugs in 2014.[25] New methods to synthesise substituted pyridines are therefore of great synthetic value in medicinal chemistry applications. Diaminopyridines in particular feature in numerous medicinally relevant molecules (**Figure 5.1**), such as the peptic ulcer treatment pirenzepine and delavirdine, a HIV treatment; such structures are attractive targets for synthesis from yndiamides. Even the simplest member of this class of molecules, 3,4-diaminopyridine (known as amifampridine), is a potassium channel blocker which has been extensively investigated as a treatment for neuromuscular disorders.[166] Substituted diaminopyridines are also encountered in medicinal molecules, such as pirenzepine[167] and delavirdine.[168] This chapter will describe an investigation into various approaches to the synthesis of diaminopyridines from yndiamides.

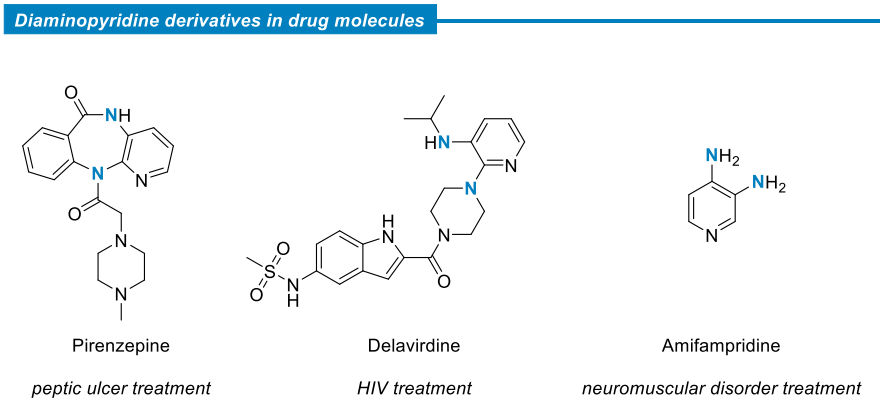


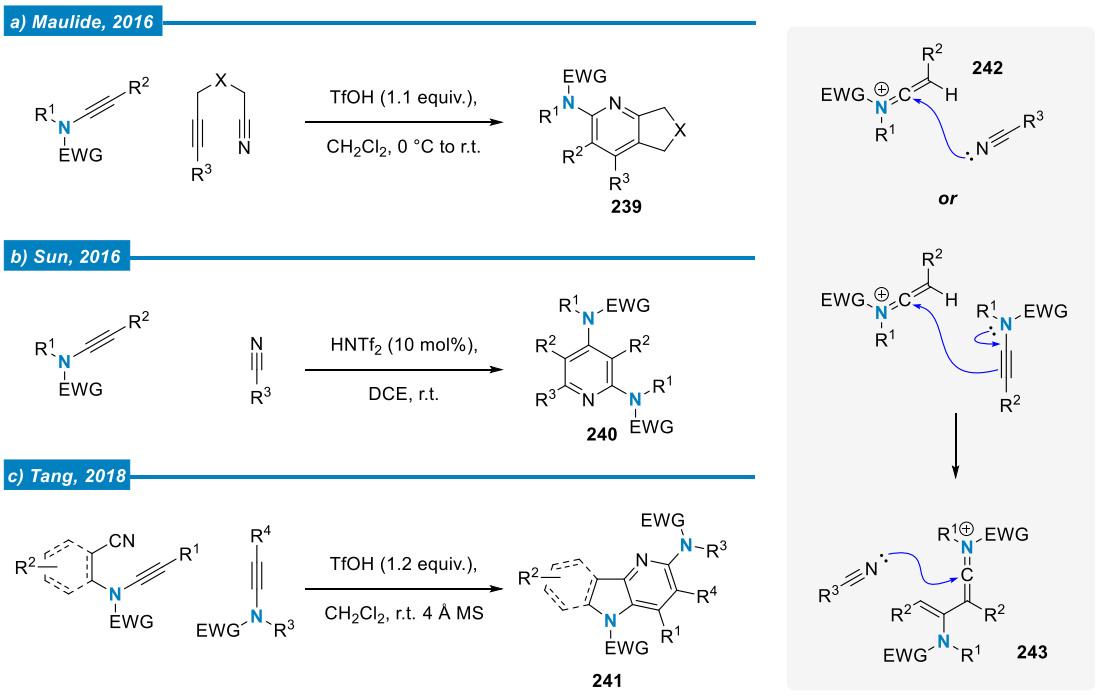
Figure 5.1: Examples of diaminopyridines in biologically relevant molecules.

5.2 Review of Brønsted acid and Lewis acid catalysed syntheses of aminopyridines from ynamides

This section will introduce the formation of aminopyridines from ynamides by Brønsted acid or Lewis acid catalysis. *Formal* cyclotrimerisation reactions between an ynamide, an alkyne and a nitrile will be covered in this section but other variations, such as reactions of

cyanamides,[169] or the formation of aminopyrimidines,[170,171] are less immediately relevant to this investigation and will not be discussed here.

Brønsted acid-promoted cyclisations of ynamides with alkynes and nitriles to form aminopyridines have been reported by Maulide,[172] Sun[173], and Tang[174], forming 2-aminopyridines (**239**), 2,4-diaminopyridines (**240**), and 3-amino-δ-carboline (**241**) derivatives respectively (**Scheme 5.1**). These transformations are thought to proceed *via* keteniminium ions (**242**) formed by protonation of ynamides. The keteniminium ion is attacked by either a nitrile or another molecule of the ynamide. Where the initial attack was by a nitrile, this may be followed by attack by a tethered alkyne or another ynamide. Where the initial attack was by another molecule of the yndiamide, a second keteniminium ion (**243**) is formed, and this may then be attacked by a nitrile. Cationic cyclisation then completes the formation of the pyridine ring.

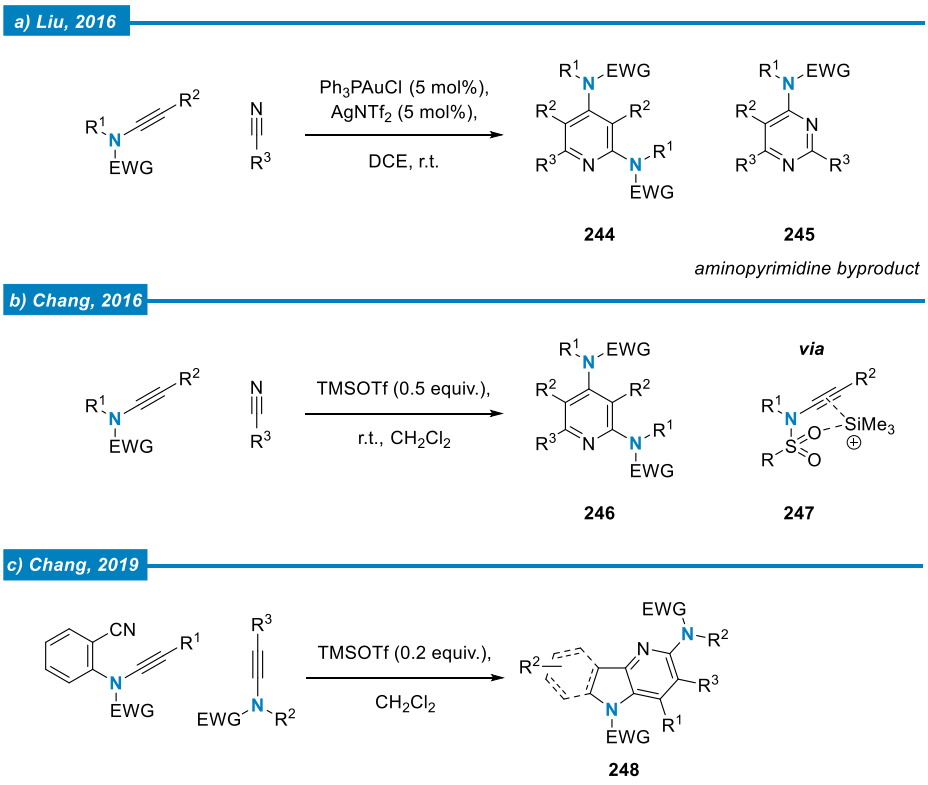


Scheme 5.1: Brønsted acid-catalysed formation of *a)* 2-aminopyridines,[172] *b)* 2,4-diaminopyridines,[173] and 3-amino-δ-carbolines.[174]

Lewis acid catalysis (more specifically π-acid catalysis) has also been used to promote the formation of aminopyridines from ynamides (**Scheme 5.2**).

Gold(I) catalysts were used by Liu and co-workers to form 2,4-diaminopyridines (**244**) by cyclisation of two ynamides with a nitrile and 4-aminopyrimidines (**245**) were also formed as byproducts (**Scheme 5.2a**).[175] This reaction was proposed to occur by activation of the ynamide by gold coordination followed by attack of either a nitrile or another ynamide. If a second molecule of the ynamide attacks, this forms a new keteniminium ion which can then be attacked by the nitrile. In either case, the pyridine ring is formed by a final cationic cyclisation.

In 2016, Chang and co-workers reported that TMSOTf catalysed the cyclisation of two ynamides with a nitrile to form 2,4-diaminopyridines (**246**) (**Scheme 5.2b**).[176] Other Lewis acids, including $BF_3{\cdot}Et_2O$, were able to promote the transformation but gave **246** in lower yield. The yndiamide is proposed to be activated by formation of a complex (**247**) between the carbon-carbon triple bond and the trimethylsilyl cation, followed by attack of either another molecule of the ynamide or a nitrile. Silylium ions are increasingly finding applications in catalysis, including examples of activation of triple bonds,[177] although the mechanism of such catalytic behaviour was not explored extensively in this work. The same group further developed their methodology in 2019 to synthesise 3-amino-δ-carboline derivatives (**248**) (**Scheme 5.2c**).



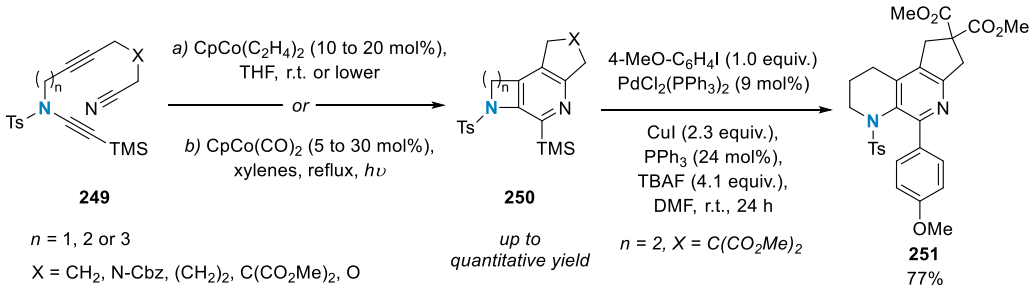
Scheme 5.2: Lewis acid-catalysed formation of *a*) 2,4-diaminopyridines by gold-catalysis,[175] *b*) 2,4-diaminopyridines by silylium catalysis,[176] and *c*) 3-amino-δ-carbolines by silylium catalysis.[178]

5.3 Review of transition-metal catalysed synthesis of aminopyridines from ynamides

In an analogous manner to the use of ynamides to access nitrogen-substituted benzene rings by [2+2+2] cyclotrimerisation reactions with alkynes (**Chapter 3**), ynamides can be used to synthesise nitrogen-substituted pyridines by cyclotrimerisation with an alkyne and a nitrile. The topic of transition metal-catalysed alkyne-alkyne-nitrile cyclotrimerisation has been reviewed multiple times over the past two decades,[179–181] but this section will specifically review the use of ynamides in these transformations.

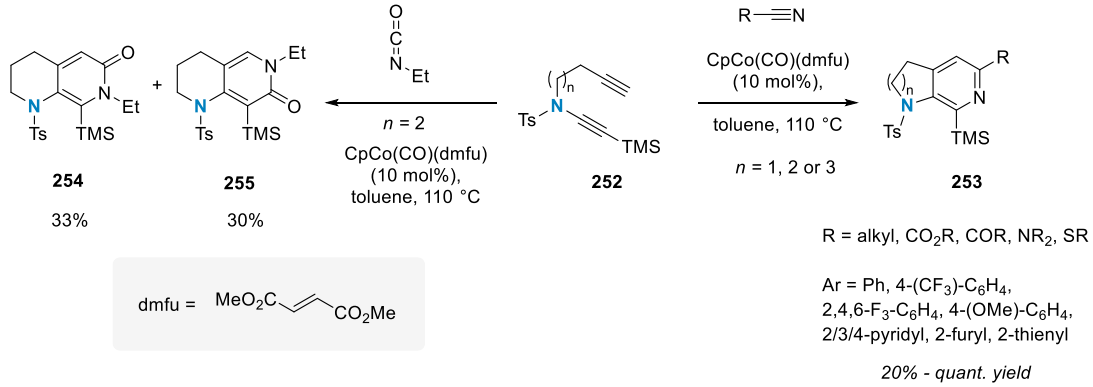
The first report of transition metal-catalysed ynamide cyclotrimerisation with an alkyne and nitrile came from Aubert, Malacria and Gandon in 2009, who carried out fully intramolecular [2+2+2] reactions to form silylated aminopyridines (**249**→**250**) which could then undergo Hiyama cross-coupling to form highly substituted pyridines (e.g. **251**) (**Scheme 5.3**).[182] This work used the air-sensitive Co(I) catalysts $CpCo(C_2H_4)_2$ (at room temperature or lower) and $CpCo(CO)_2$ (in refluxing xylene with visible light irradiation) to achieve the cyclotrimerisations

to form tricyclic pyridines in moderate to quantitative yields. Although these conditions were effective in achieving these particular transformations, the limited range of available Co(I) catalysts and their sensitivity to air and water posed significant barriers to further applications of this reactivity in aminopyridine synthesis.



Scheme 5.3: First report of ynamide-alkyne-nitrile cyclotrimerisation to form tricyclic pyridines.[182]

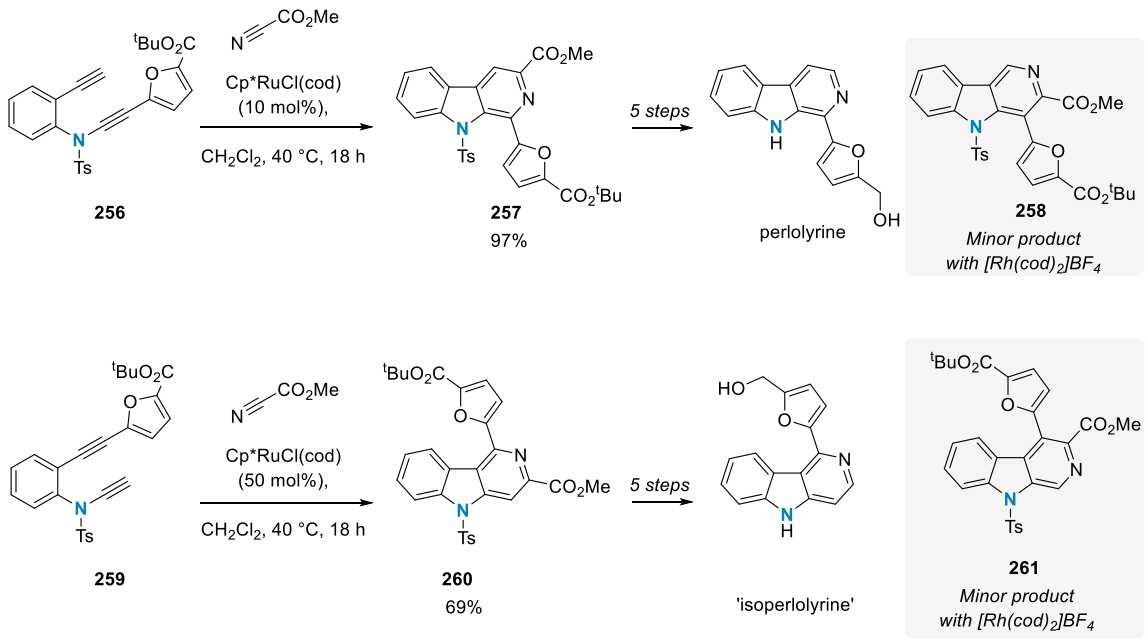
The development of air-stable Co(I) catalysts, reported in 2009, by Aubert, Malacria and Gandon,[183] enabled further development of cyclotrimerisation reactions between yne-yndiamides and nitriles or isocyanates; this was reported in 2011[184] and 2012[185] by the same authors (**Scheme 5.4**). In this work, yne-ynamides (**252**) were reacted with nitriles to form fused pyridines (**253**). In the cases where only the ynamide terminus was substituted and the alkyne terminus remained unsubstituted, the products were formed exclusively as 3-aminopyridines. When the alkyne terminus was also substituted, the products were formed as mixtures of the 3- and 4-aminopyridines (not shown). The authors also reported a single example of reaction of an yne-ynamide with ethyl isocyanate to form pyridones **254** and **255** in an equimolar ratio. Improving on this poor regioselectivity provides a potentially useful application of yndiamides in this chemistry: could the presence of a second nitrogen substituent overcome the poor regioselectivity of this process?



Scheme 5.4: Cobalt-catalysed [2+2+2] cyclotrimerisation of yne-ynamides to form fused pyridines.[185]

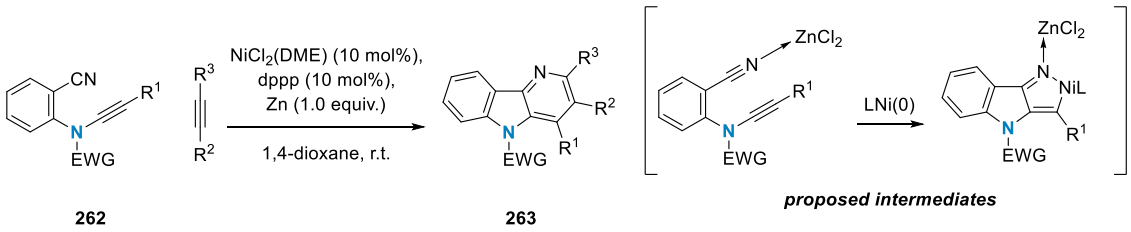
The limited range of air-stable cobalt (I) catalysts and poor regioselectivity may be partly responsible for the limited progress made on cobalt-catalysed synthesis of aminopyridines from ynamides since 2012. However, other pyridines have been prepared in an analogous manner recently, for example 2-aminopyridines from cynamides[186,187] and polysubstituted pyridines prepared from diynes and nitriles using a multicomponent cobalt catalytic system.[188]

The value of the cyclotrimerisation approach to aminopyridine synthesis was demonstrated by Detert and co-workers in 2011[189] in their synthesis of the carboline natural products perlolyrine and 'isoperlolyrine' (**Scheme 5.5**). A cationic rhodium catalyst promoted the cycloaddition between **256** and methyl cyanoformate to form the carbolines **257** (β) and **258** (γ) as a 10:1 mixture. When the neutral ruthenium complex Cp*RuCl(cod) was used instead, the β-isomer (**257**) was formed as the exclusive product and further transformations gave perlolyrine in 15-20% overall yield. The synthesis of 'isoperlolyrine' (previously believed to be the only naturally occurring γ-carboline alkaloid) was achieved by cyclotrimerisation of **259** with methyl cyanoformate to form **260** and **261**; subsequent transformations gave the target compound in 10% overall yield. By comparison to the data for the naturally occurring compound the authors showed that the previously proposed structure of 'isoperlolyrine' was incorrect and it is most likely actually a β-carboline derivative.



Scheme 5.5: Cyclotrimerisation approaches to perlolyrine and 'isoperlolyrine'.[189]

In 2017, Liu and co-workers reported a nickel-catalysed [2+2+2] reaction between nitrile-yndiamides (**262**) and alkynes to form 3-amino-δ-carboline derivatives (**263**) (**Scheme 5.6**).[190] The *in-situ* formation of Ni(0) forms $ZnCl_2$ as a byproduct; this Lewis acid is necessary to form the desired product. The authors suggest that it activates the nitrile moiety, increasing its electrophilicity and promoting oxidative coupling between the ynamide and nitrile at the nickel(0) centre.



Scheme 5.6: Nickel-catalysed [2+2+2] cyclotrimerisation of nitrile-ynamides with alkynes to form δ-carbolines.[190]

As this literature survey has shown, cobalt-catalysis has significant precedent in [2+2+2] cyclotrimerisation reactions forming aminopyridines, and this was selected as the starting point for an investigation of analogous reactivity of yndiamides. However, as **Section 5.5.2** will

describe, these reactions were not effective for yndiamides so alternative approaches were investigated to synthesise diaminopyridone and diaminopyridine derivatives.

5.4 Yndiamides in Brønsted acid and Lewis acid-catalysed approaches to diaminopyridine synthesis

A formal [2+2+2] reaction between an yndiamide, a nitrile and an alkyne was investigated to synthesise diaminopyridine derivatives. An initial concern was the instability of yndiamides under acidic conditions, given that they are known to undergo addition reactions, cyclisation reactions or decomposition depending on the acid used.[24] Yndiamide **188** (**Scheme 5.7**) was selected as the model substrate as the butyl side chains are not able to cyclise onto a keteniminium ion intermediate (c.f. reactions in **Section 1.3**).

5.4.1 Optimisation of Brønsted acid and Lewis acid-catalysed approaches to diaminopyridine synthesis

Treatment of **188** and alkynyl-nitrile **264** with $HNTf_2$[173] gave no reaction, while TfOH[172] unsurprisingly led to decomposition of **188** (**Figure 5.2**). However, a catalytic quantity of TMSOTf[176] effected the cyclisation to form fused diaminopyridine **265** in low yield. The structure of **265** was confirmed by single crystal XRD. More Lewis-acidic catalysts were then screened and $Cu(OTf)_2$ gave a promising 48% yield of **265**. A gold(I) catalyst ($Ph_3PAuNTf_2$) did not promote the cyclisation when the reaction mixture was heated at 80 °C, despite this catalyst being known to form keteniminium ions from yndiamides (**Chapter 2**). Having shown that $Cu(OTf)_2$ promoted the formation of **265**, further optimisation was undertaken. Addition of molecular sieves (to reduce water-mediated decomposition pathways) and use of Cu(OTf)·PhMe (to investigate the action of Cu(I) in this reaction) both gave **265** in lower yield but did not result in complete decomposition of the remaining **188**. Other triflate salts were then screened, with $Sc(OTf)_3$ and $In(OTf)_3$ giving comparable outcomes to $Cu(OTf)_2$. $In(OTf)_3$ was taken forward for further optimisation as it did not effect complete decomposition of the

remaining **188**, and there is precedent for its use in activation of ynamides (including tolerance of Lewis-acid sensitive *N*-benzyl groups).[191] Attempts to moderate the decomposition of **188** by carrying out the reaction at a lower temperature or using slow addition of **264** did not improve the yield of **265**.

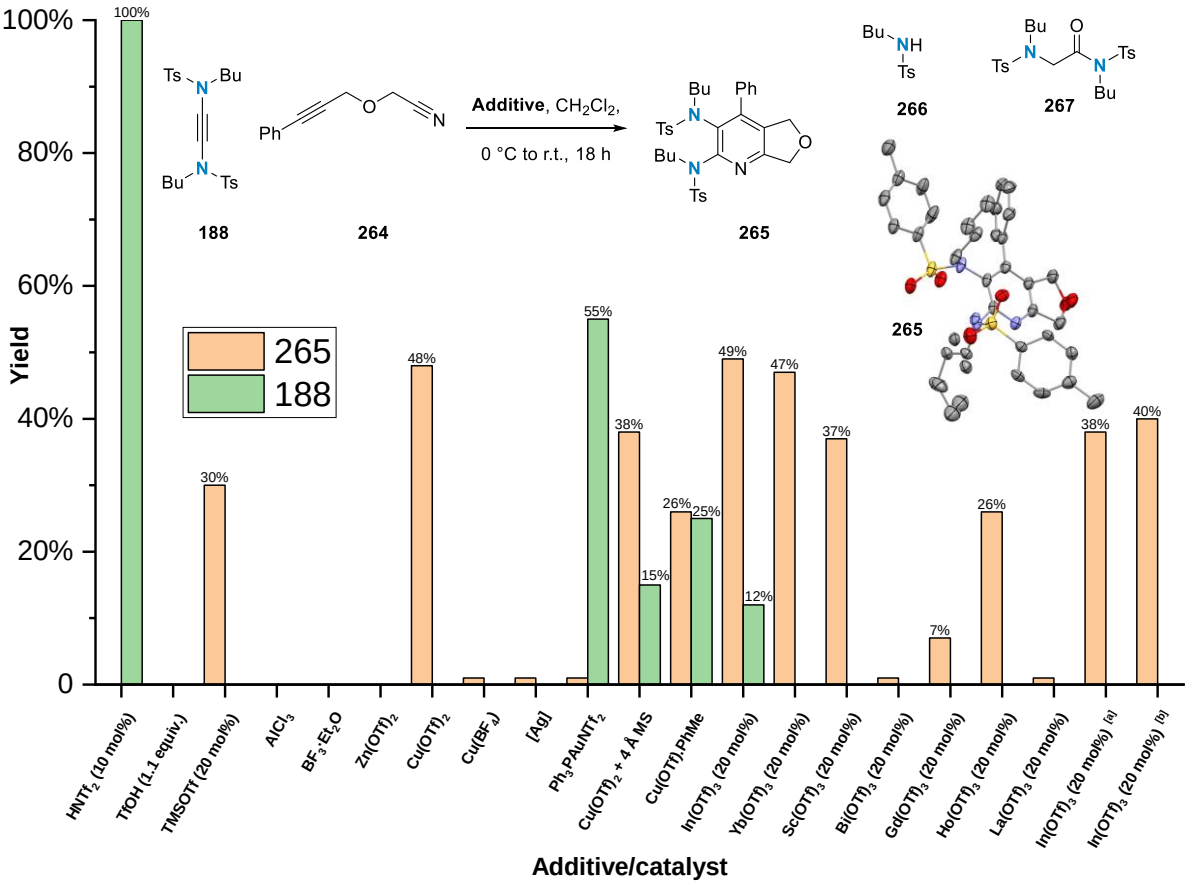
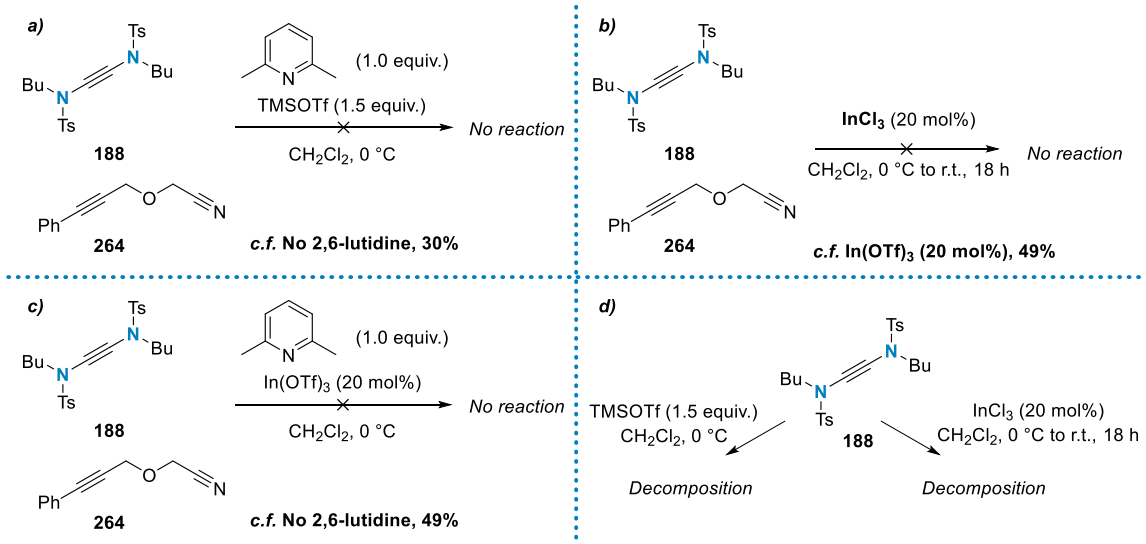


Figure 5.2: Optimisation of formal [2+2+2] cyclotrimerisation of **188** and **264** to form **265** and single-crystal XRD structure of **265**. Displacement plot for **265** is displayed at 50% probability with hydrogen atoms hidden for clarity. All reactions on 0.050 mmol scale under Ar atmosphere. All reactions carried out with temperature increasing from 0 °C to r.t.. All reaction times 18 h. Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [Ag] = $AgBF_4$ or $AgSbF_6$ or AgOTf. [a] Reaction temperature allowed to increase from -78 °C to r.t. [b] Addition of **188** as solution in CH_2Cl_2 over 10 minutes.

Having completed an initial screen of additives and catalysts for the reaction of **188** and **264** to form **265** it was apparent that while some metal triflate salts were able to promote the transformation in moderate yield, in all cases this was accompanied by extensive decomposition to form the hydrolysis products **266** and **267**.

The mechanism of the reaction was probed before advancing the investigation further (**Scheme 5.8**). Addition of 2,6-lutidine (a non-coordinating base) suppressed the reaction in the presence of TMSOTf or $In(OTf)_3$ (**Scheme 5.8a** & **c**); this suggested that the reaction *might* be occurring by a Brønsted acid-promoted reaction, possibly as a result of trace TfOH being formed from TMSOTf or $In(OTf)_3$ – this is despite carrying out the reaction using anhydrous solvent and an inert atmosphere, as both of these Lewis acids are extremely water sensitive. Further evidence for the possible role of TfOH was provided by the observation that $InCl_3$ (which is soluble in CH_2Cl_2) failed to catalyse the transformation – **188** was returned unchanged from these conditions – suggesting the possibility that In^{3+} cations did not promote the cyclisation reaction (**Scheme 5.8b**), although it is not possible to rule out a inhibitory effect of chloride ions on the Lewis acidity of In^{3+}. Interestingly, Weng and co-workers had also previously found $InCl_3$ did not promote the cyclisation of ene-ynamides.[191]

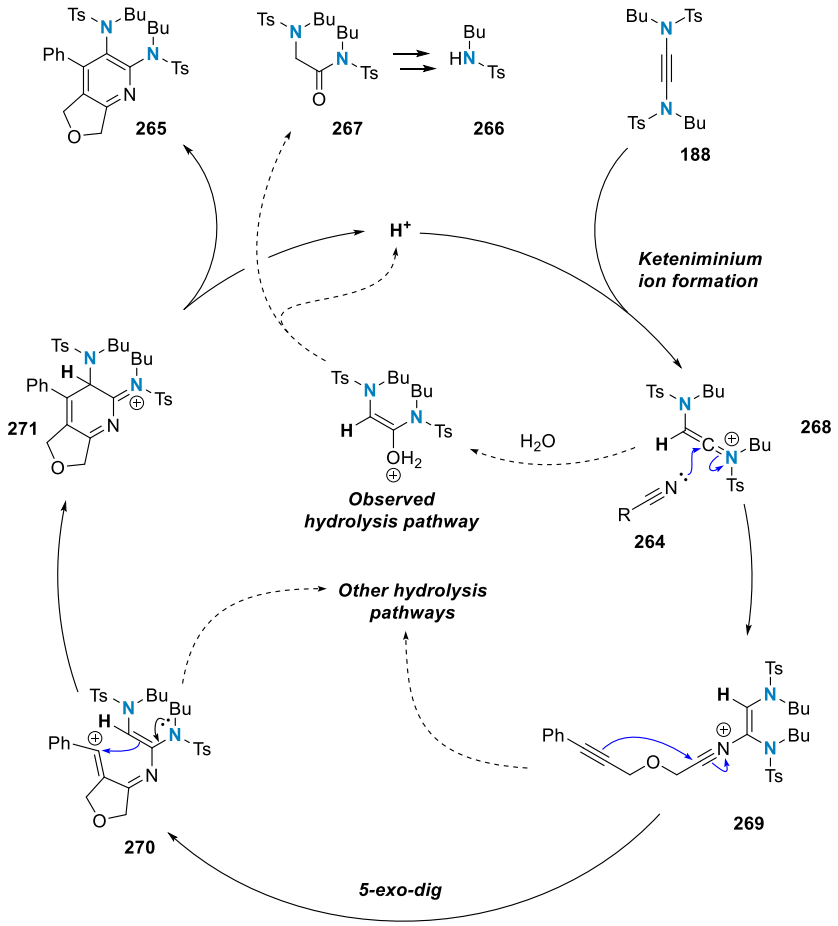


Scheme 5.8: Investigation of the role of In^{3+} and/or *in-situ*-formed TfOH in the cyclisation of **188** and **264**.

Based on the observations in **Scheme 5.8a** it is plausible that the yndiamide (**188**) was being degraded by the Lewis acid catalyst (either directly or by formation of TfOH *in situ*). This was confirmed by treating **188** with TMSOTf and $In(OTf)_3$ in turn – complete decomposition of **188** was observed in both cases (**Scheme 5.8d**). At this point the investigation of Brønsted acids

and Lewis acids to promote diaminopyridine formation was halted as further optimisation would be extremely challenging and the scope of the reaction would likely be limited by the tendency of yndiamides to decompose under the reaction conditions.

A proposed mechanism for the formation of **265**, assuming catalysis by TfOH formed *in situ*, is given in **Scheme 5.9**. Formation of a keteniminium ion (**268**) is likely followed by nucleophilic attack by the nitrile moiety in **264** to form nitrilium ion **269**. A *5-exo-dig* cyclisation of **269** would form the tetrahydrofuran ring (**270**) and cyclisation of the dienamide onto the vinyl cation thus formed would give form the final C–C bond (**271**). Rearomatisation by deprotonation would form **265** and release the proton back into the catalytic cycle. The basic pyridine moiety in **265** probably interferes with the acid-catalysed reaction (in some cases a species corresponding to the protonated form of **265** was observed in the crude ^{1}H NMR spectrum) but the complete consumption of the yndiamide (mostly by hydrolysis) is consistent with there being sufficient water and thus TfOH present (despite using anhydrous solvent and inert conditions) to sustain the cycle. Alternatively, it is plausible that the triflate anion might act as a nucleophile to mediate the decomposition of the keteniminium ion intermediate; such a pathway would not necessitate the presence of water in the reaction mixture until the reaction was quenched or opened to the atmosphere, at which point hydrolysis could occur to form the observed products. However, using the available data, it is not possible to conclusively determine which pathway is in operation.



Scheme 5.9: A proposed mechanistic cycle for the formation of **265** and decomposition of **188** by hydrolysis.

Having found significant limitations in the use of acid catalysis in the formation of diaminopyridines from yndiamides due to the undesired hydrolysis of the yndiamide, it was decided to return to transition metal-catalysis in the pursuit of a robust synthesis of diaminopyridines.

5.5 Yndiamides in transition metal-catalysed cycloisomerisation approaches to diaminopyridine synthesis

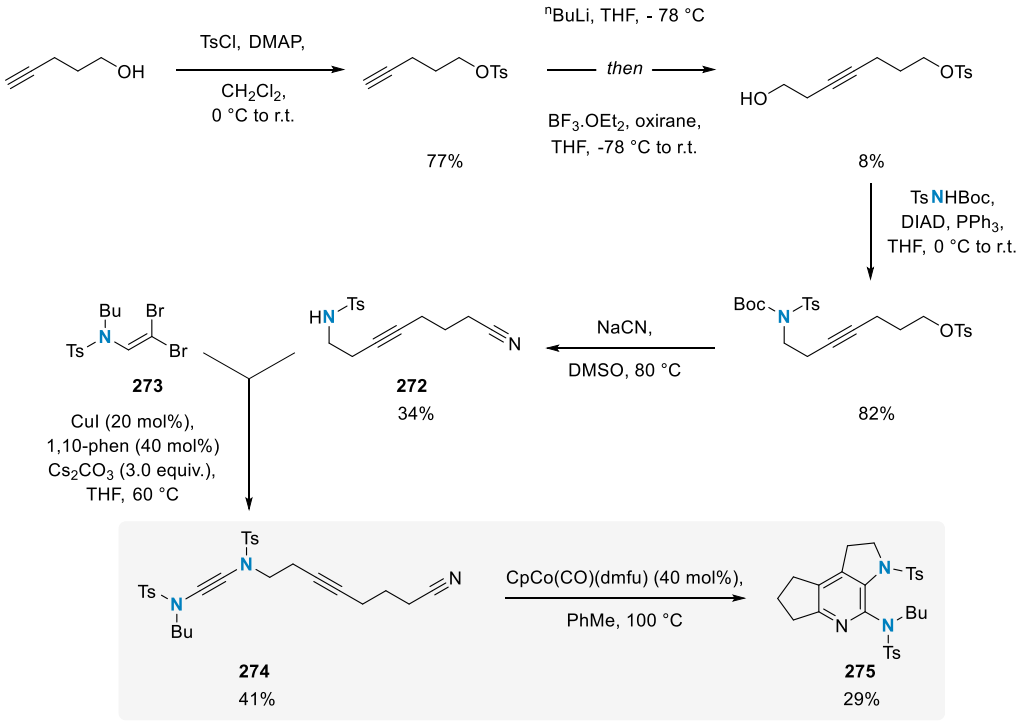
A transition metal-catalysed approach was explored as a means to synthesis diaminopyridine derivatives from yndiamides. This approach was divided into two aspects: cycloisomerisation approaches (**Section 5.5.1**) and intermolecular approaches (**Section 5.5.2**).

5.5.1 Cycloisomerisation approaches to diaminopyridine synthesis from yndiamides

The investigation of the transition metal-catalysed cyclotrimerisation approach to diaminopyridine synthesis commenced by adapting the fully intramolecular [2+2+2] reaction reported by Gandon and co-workers (**Section 5.3**, **Scheme 5.3**)[182] to use yndiamides.

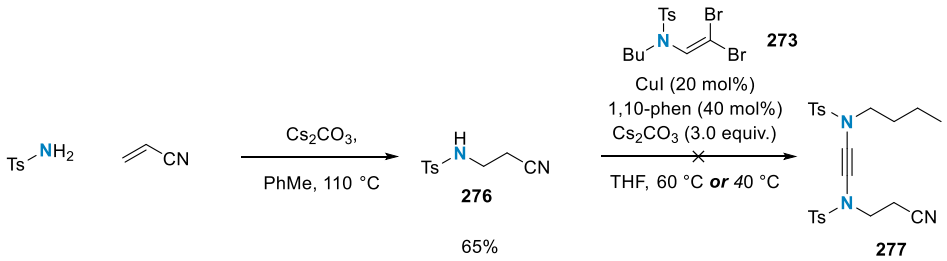
To investigate this reaction for an yndiamide/alkyne/nitrile system, sulfonamide **272** was prepared in four steps according to Gandon and co-workers' procedure; **272** was then coupled with 1,1-dibromoenamide **273** to form the required yndiamide **274** (**Scheme 5.10**). The synthesis of **272** proceeded smoothly except for the two-carbon homologation with oxirane, which was challenging to purify due to polymerisation of oxirane.

Cyclotrimerisation of **274** using catalytic CpCo(CO)(dmfu)[183] (initially 20 mol%) was slow and required the addition of a second portion of catalyst (20 mol%) after 2 hours, as TLC analysis showed that the starting material remained and the catalyst had been consumed.[185] The desired product **275** was obtained in low yield, with the remaining material being decomposed. Although the formation of **275** by this route is low yielding, it demonstrates that yndiamides can be successfully applied to the synthesis of diaminopyridines by a cycloisomerisation reaction, although further optimisation would be required to achieve comparable results to those seen for ynamides. One plausible explanation for the lower yield is inhibition of the catalyst by the electron-rich pyridine product; this may also explain the catalyst decomposition. Additionally, the increased steric bulk around the yndiamide triple bond relative to the ynamide analogue may hinder its involvement in the metallocycle formation.



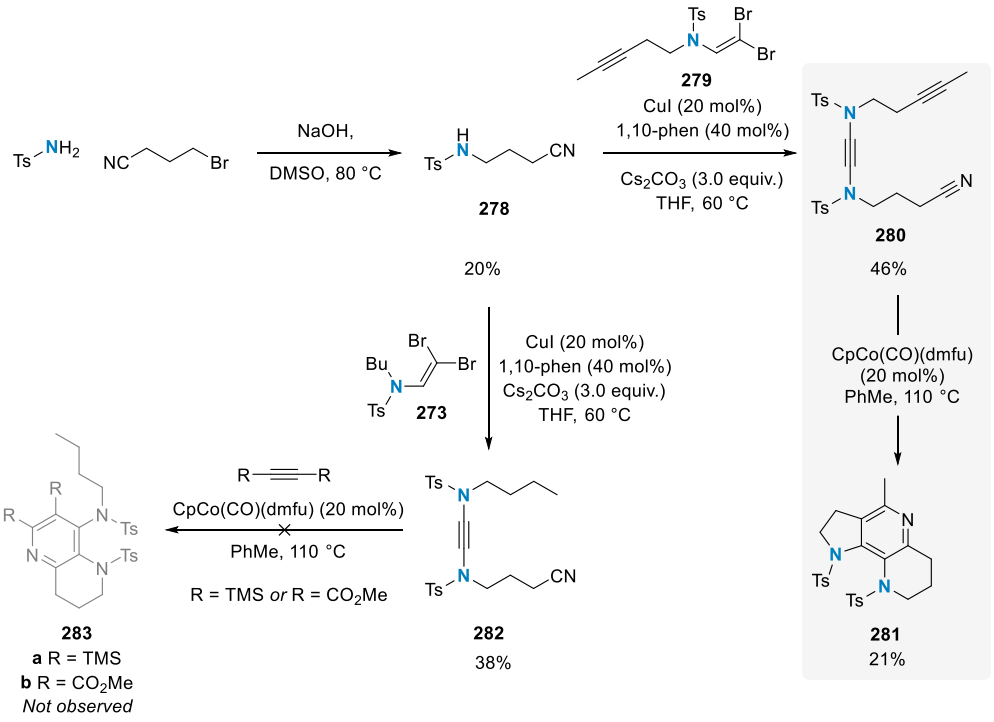
Scheme 5.10: Synthesis of nitrile-yne-yndiamide **274** and cycloisomerisation to form **275**.

An alternative mode of yndiamide-alkyne-nitrile cyclotrimerisation is possible in which the alkyne and the nitrile moieties are on opposite sides of the yndiamide; this would form tricyclic 3,4-diaminopyridines (as opposed to **274** in which they are part of the same side chain, forming a 2,3-diaminopyridine). Before synthesising a substrate with the required structure for this cyclotrimerisation, sulfonamide **276** was investigated as a possible nucleophilic partner in an yndiamide synthesis (**Scheme 5.11**). Disappointingly, the attempted coupling reaction between **276** and 1,1-dibromoenamide **273** did not lead to yndiamide **277** and **273** was returned unchanged. Acrylonitrile was observed in the crude ^{1}H NMR spectrum, suggesting that the failure of the reaction was due to the equilibrium between nitrile sulfonamide **276** and its precursors ($TsNH_2$ and acrylonitrile[192]). Repeating the reaction at a lower temperature (40 °C) was also unsuccessful.



Scheme 5.11: Preparation of nitrile-sulfonamide **276** and attempted preparation of yndiamide **277**.

Sulfonamide **278** (the one-carbon homologue of **276**, intended to avoid the undesired elimination which occurred in the attempted synthesis of **277**) was synthesised and subjected to the standard yndiamide synthesis conditions using alkynyl dibromoenamide **279** as a coupling partner, forming **280** in moderate yield. Cyclotrimerisation of **280** formed tricyclic diaminopyridine **281** in low yield: once again decomposition of the catalyst was observed by TLC after approximately one turnover (**Scheme 5.12**).



Scheme 5.12: Investigation of nitrile-yndiamides as precursors to fused pyridines.

Sulfonamide **278** was also employed in a coupling reaction with dibromoenamide **273**, forming nitrile-yndiamide **282** (**Scheme 5.12**). Disappointingly, attempts to engage this substrate in intermolecular cobalt-catalysed [2+2+2] cyclotrimerisation reactions were unsuccessful, with

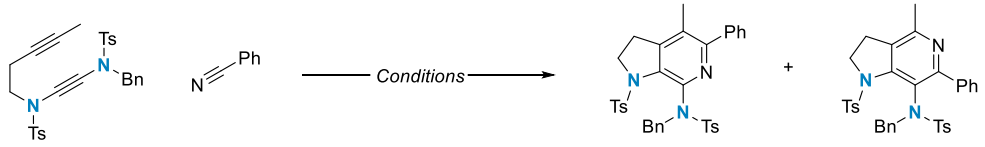
the starting material being returned unchanged and none of the desired products **283a** or **283b** being formed. Intermolecular cyclotrimerisation reactions have previously been reported between alkynyl-nitriles and the two alkynes investigated here (*bis*-TMS-acetylene and dimethyacetylene dicarboxylate).[193] However, it is unsurprising that these transformations with **282** were unsuccessful as the yndiamide is sterically hindered so formation of the initial metallocycle by an intermolecular process is likely to be quite unfavourable (as opposed to the fully intramolecular cyclotrimerisations of **274** or **280**).

5.5.2 Intermolecular diaminopyridine synthesis from nitriles

Having demonstrated the application of intramolecular cyclotrimerisation reactions to the synthesis of tricyclic diaminopyridines, the focus of the investigation turned to achieving *intermolecular* reactivity. As was demonstrated in **Chapter 3** with cycloisomerisations involving an yndiamide and two alkynes, this is more challenging than intramolecular reactivity due to the tendency of simple alkynes to dimerise or trimerise in preference to reacting with the more sterically encumbered yndiamide. In an analogous manner to the investigation in **Chapter 3**, the reaction of an yne-yndiamide (**82u**) with a nitrile was considered to be a promising approach to form diaminopyridines.

Commencing with the cyclotrimerisation of yne-yndiamide **82u** with benzonitrile, a screen of conditions was undertaken (**Table 5.1**), but none of the conditions explored gave satisfactory yield and/or regioselectivity. Using CpCo(CO)(dmfu), a small amount of **284** was isolated (by preparative TLC) and the minor isomer (**285**) was also observed. No reaction was observed with a cationic rhodium catalyst (entry 2) and when a larger excess of benzonitrile was used the yield did not improve significantly (entry 3). The multicomponent cobalt catalytic system reported by Yoshikai and co-workers for nitrile/alkyne cyclotrimerisation (entry 4) was also ineffective.[188]. Adjusting the loading of the cobalt (I) catalyst and changing the concentration were not effective (entries 5 to 9). Microwave irradiation (200 °C) of the reaction mixture

resulted only in complete decomposition of **82u** (entry 10) and using benzonitrile as the solvent did not improve the yield (entry 11). Further changes to the catalyst loading and concentration were then investigated (entries 12 to 14) but only increasing the catalyst loading to 40 mol% (entry 13) improved the yield significantly. This line of investigation was curtailed because of the limited range of air-stable cobalt (I) catalysts available for further optimisations (an attempt to prepare the other commonly referenced cobalt cyclopentadiene complex, CpCo(cod),[194] using a magnesium-anthracene reducing system[195], was unsuccessful).



82u **284** **285**

Entry	Catalyst	Equiv. PhCN	Solv.	Conc.	Temp.	Conversion	Yield (284/285)
1[a]	**Co-1** [e]	1.5	PhMe	0.10 M	110 °C	86%	6%/<5%
2[a]	**Rh-2** [e]	1.5	PhMe	0.10 M	110 °C	95%	0%/0%
3[a]	**Co-1** [e]	5.0	PhMe	0.10 M	110 °C	61%	13%/<5%
4[a]	CoI_2 [e], dppp [e], Zn [h]	2.0	NMP	0.10 M	80 °C	68%	0%/0%
5[b d]	**Co-1** [e]	5.0	PhMe	0.10 M	110 °C	93%	9%/<5%
6[a]	**Co-1** [e]	5.0	PhMe	0.10 M	110 °C	91%	29%/<5%
7[a]	**Co-1** [e]	5.0	PhMe	0.50 M	110 °C	> 95%	18%/6%
8[a]	**Co-1** [f]	5.0	PhMe	0.50 M	110 °C	73%	23%/7%
9[a]	**Co-1** [f]	10.0	PhMe	0.50 M	110 °C	70%	23%/7%
10[c]	**Co-1** [f]	5.0	DMF	0.015 M	200 °C [j]	85%	0%/0%
11[a]	**Co-1** [f]	Solvent	PhCN	0.10 M	110 °C	74%	7%/<5%
12[a]	**Co-1** [f]	5.0	PhMe	0.10 M [i]	110 °C	77%	13%/<5%
13[a]	**Co-1** [g]	5.0	PhMe	0.10 M	110 °C	93%	29%/13%
14[a]	**Co-1** [f]	5.0	PhMe	1.0 M	110 °C	62%	14%/7%

Table 5.1: All reactions on 0.025 mmol scale under Ar atmosphere. Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. **Rh-2** = (*rac*-BINAP)Rh(cod)SbF6. **Co-1** = CpCo(CO)(dmfu). [a] Reaction time 15 h. [b] Reaction time 8 h. [c] Reaction time 10 min. [d] Irradiated with visible light. [e] 10 mol%. [f] 20 mol%. [g] 40 mol%. [h] 50 mol%. [i] Dropwise addition of **82u** over 1.5 h. [j] Microwave irradiation. In all cases the remaining mass balance was comprised of a complex mixture of decomposition products.

5.5.3 Diaminopyridone synthesis

The synthesis of nitrogen heterocycles by [2+2+2] cyclotrimerisation reactions is not limited to reactions of nitriles, as isocyanates can undergo similar reactions to form 2-pyridones.[196] Pyridones (both the 2- and 4- isomers) are found in pharmaceutical molecules [197] and in natural products (some of which are of potential medicinal value) (**Figure 5.3**).[198] They also can be transformed into pyridines, *via* (for example), chlorination with $POCl_3$.

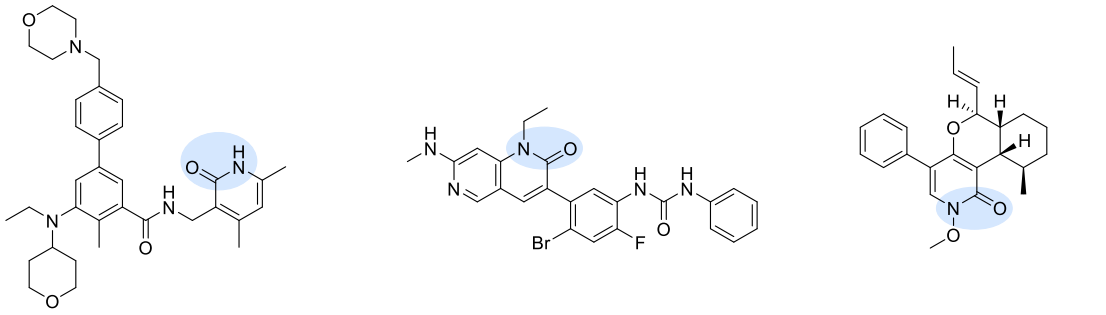
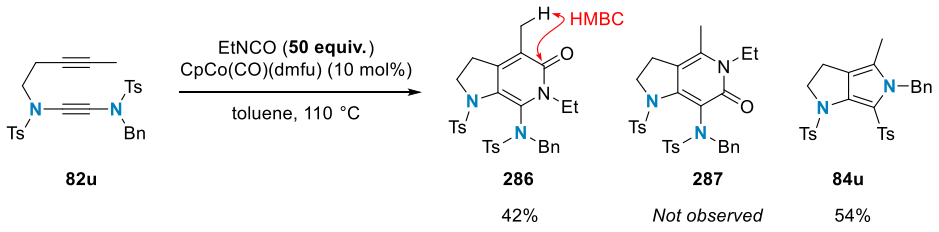


Figure 5.3: 2-Pyridone-containing bioactive molecules.

Cyclotrimerisation reactions between yne-yndiamides and isocyanates are therefore an appealing approach to the synthesis of novel heterocycles bearing adjacent nitrogen substituents.

Inspired by Gandon and co-workers' isocyanate/alkyne/ynamide cyclotrimerisation reaction (**Section 5.3**, **Scheme 5.4**), we investigated similar reactivity of yne-yndiamide **82u** with ethyl isocyanate (**Scheme 5.13**). Remarkably, diaminopyridone **286** was formed as a single regioisomer, albeit in moderate yield; the minor isomer **287** was not observed. The major product from this reaction was **84u**, the cycloisomerisation product previously formed using gold-catalysis (**Chapter 2**).



Scheme 5.13: [2+2+2] Cyclotrimerisation between **82u** and ethyl isocyanate.

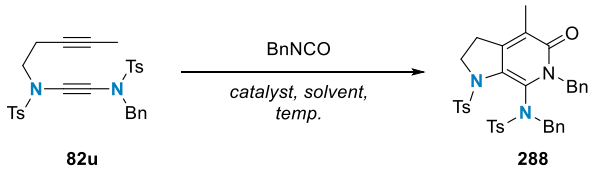
Having formed pyridone **286** as a single isomer, the reaction of yne-yndiamides with isocyanates was further investigated as an indirect (but potentially completely regioselective) approach to substituted diaminopyridines. Instead of using ethyl isocyanate (which is toxic and volatile), the less volatile benzyl isocyanate was employed, although even the boiling point of

this compound was to be an issue in this investigation.

Several transition-metal complexes were explored as potential catalysts for the reaction of **82u** with benzyl isocyanate to form **288** (**Table 5.2**, entries 1 to 5). Only (*rac*-BINAP)Rh(cod)SbF_6 (entry 2) and Cp(CO)Co(dmfu) (entry 5) promoted the formation of **288**, and both of these were only able to promote the cyclisation at 110 °C. The air stable Ni(0) catalyst Ni(cod)(dq)[199] was not effective when used with the dppp ligand (entry 1). $Ni(cod)_2$, although known to promote isocyanate [2+2+2] reactions,[200] was not investigated due to its instability, and neither RuCp*(cod)Cl nor $[IrCl(cod)]_2$ gave any product at either of the temperatures investigated. The other rhodium catalysts investigated did not promote the cyclotrimerisation (entries 6 to 8), so (*rac*-BINAP)Rh(cod)SbF_6 was used for further optimisation. An increase in concentration to 0.25 M slightly reduced the yield (entry 9) and slow addition of reagents did not improve the yield (entries 10 and 11). At this point it is important to note that the starting material in the rhodium-catalysed transformations was generally almost completely consumed, which was indicative of other (decomposition) pathways in operation. The volatility of benzyl isocyanate (b.p. 101–104 °C) was deemed a potential issue so the reaction was performed at 85 °C (entry 12) but this did not improve the yield, neither did a large increase in the equivalents of benzyl isocyanate (entry 13).

After this investigation it appeared that the reaction of **82u** with benzyl isocyanate might follow the path of the previously explored cyclotrimerisation reactions with nitriles, being only a niche transformation applicable to a small number of substrates in low yield. However, a remarkable improvement in yield (73%) was observed when the reaction was performed on a 0.10 mmol scale (entry 14). The most likely explanation for the dramatic increase in yield is the volatility of benzyl isocyanate – when the reaction was performed on a small scale (0.025 mmol) even at a temperature significantly below its boiling point, the relatively large headspace in the vial meant that a significant proportion of the BnNCO was likely in the gas phase, but this was

reduced when the reaction was performed in the same size vial on a larger scale (0.10 mmol). Additionally, the 0.10 mmol scale crude ^{1}H NMR spectrum showed less decomposition, which is consistent with the previously low yields being due to the rhodacycle decomposing rather than reacting with benzyl isocyanate.



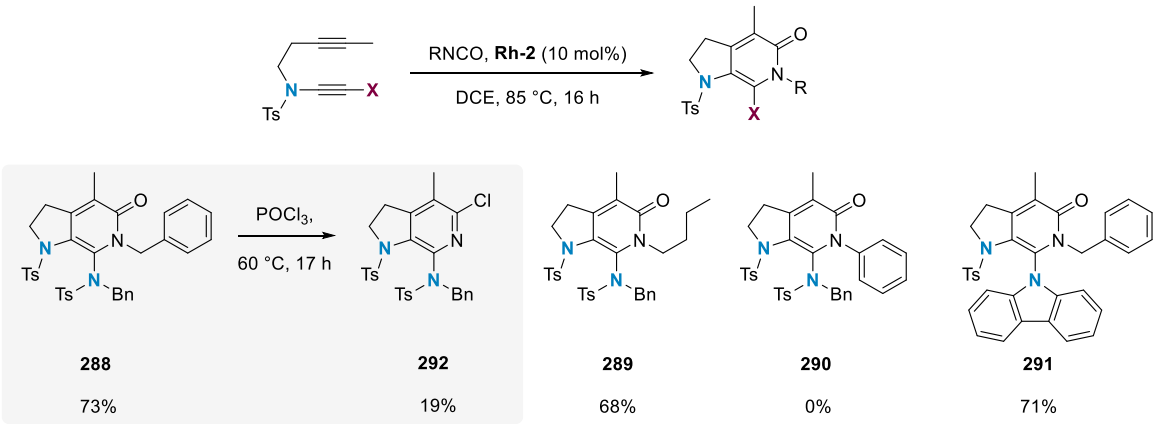
82u **288**

Entry	Catalyst	Solvent/conc.	Equiv. BnNCO	Temp.	Yield
1	Ni(cod)(dq) [b] + dppp [b]	PhMe, 0.050 M	10.0	50 °C	n.d.
				110 °C	n.d.
2	**Rh-2** [b]	PhMe, 0.050 M	10.0	50 °C	n.d.
				110 °C	20%
3	RuCp*(cod)Cl [b]	PhMe, 0.050 M	10.0	50 °C	n.d.
				110 °C	trace
4	$[IrCl(cod)]_2$ [a] + *rac*-BINAP [b]	PhMe, 0.050 M	10.0	50 °C	n.d.
				110 °C	trace
5	**Co-1** [b]	PhMe, 0.050 M	10.0	50 °C	n.d.
				110 °C	10%
6	$(PPh_3)_3RhCl$ [b]	PhMe, 0.050 M	10.0	110 °C	n.d
7	$(PPh_3)_3RhCl$ [b] + $AgSbF_6$ [b]	PhMe, 0.050 M	10.0	110 °C	n.d
8	$[Rh(nbd)Cl]_2$ [a], *rac*-BINAP [b]	PhMe, 0.050 M	10.0	110 °C	n.d
9	**Rh-2** [b]	PhMe, 0.25 M	10.0	110 °C	13%
10	**Rh-2** [b]	PhMe, 0.050 M [c]	10.0	100 °C	trace
11	**Rh-2** [b]	PhMe, 0.050 M [d]	10.0	100 °C	trace
12	**Rh-2** [b]	DCE, 0.050 M	10.0	85 °C	20%
13	**Rh-2** [b]	PhMe, 0.050 M	50.0	110 °C	8%
14*	**Rh-2** [b]	**DCE, 0.050 M**	**10.0**	**85 °C**	**73%***

Table 5.2: All reactions on 0.025 mmol scale under Ar atmosphere unless otherwise stated. All reaction times 16 h. Yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. **Rh-2** = (*rac*-BINAP)Rh(cod)SbF_6. **Co-1** = CpCo(CO)(dmfu). [a] 5 mol%. [b] 10 mol%. [c] Addition of **82u** and **Rh-1** over 1 h. [d] Addition of BnNCO over 4 h. * Reaction on 0.10 mmol scale.

With conditions for the cyclotrimerisation of **82u** with benzyl isocyanate in hand, a small scope

of substrates was explored (**Scheme 5.14**). Yne-yndiamide **82u** was transformed into pyridones **288** and **289** in good yield, although no product formation (**290**) was observed with phenyl isocyanate, with the reaction instead resulting in complete decomposition. Carbazole-yndiamide **199** also underwent the cyclotrimerisation reaction with benzyl isocyanate to form pyridone **291** in good yield as a single regioisomer. Unlike in the reactions of **199** with alkynes (**Chapter 3**), the carbazole substitution in **199** had no effect on the regiochemical outcome of the reaction in comparison to the sulfonamide group in **82u**. Pyridone **288** was also converted to the 2-chloropyridine derivative **292** in low yield by heating in $POCl_3$.



Scheme 5.14: Scope of [2+2+2] cyclotrimerisation reactions between yne-yndiamides and isocyanates and conversion of **288** to 2-chloropyridine **292**.

5.6 Concluding remarks on diaminopyridine synthesis from yndiamides

The formation of diaminopyridines derivatives from yndiamides proved more challenging than the synthesis of the 1,2-diaminobenzene derivatives described in **Chapter 3**, nevertheless several cyclotrimerisation approaches to diaminopyridines were explored and a reaction was developed to prepare fused pyrrolidine-pyridones. This chapter has demonstrated the use of yne-yndiamides to prepare highly substituted diaminopyridones and diaminopyridines. In contrast to reactions of similar ynamides reported in the literature, the pyridone products were formed as single regioisomers; the mechanistic reasons for this may be related to the regiochemical trends observed for cyclotrimerisation reactions with alkynes reported in

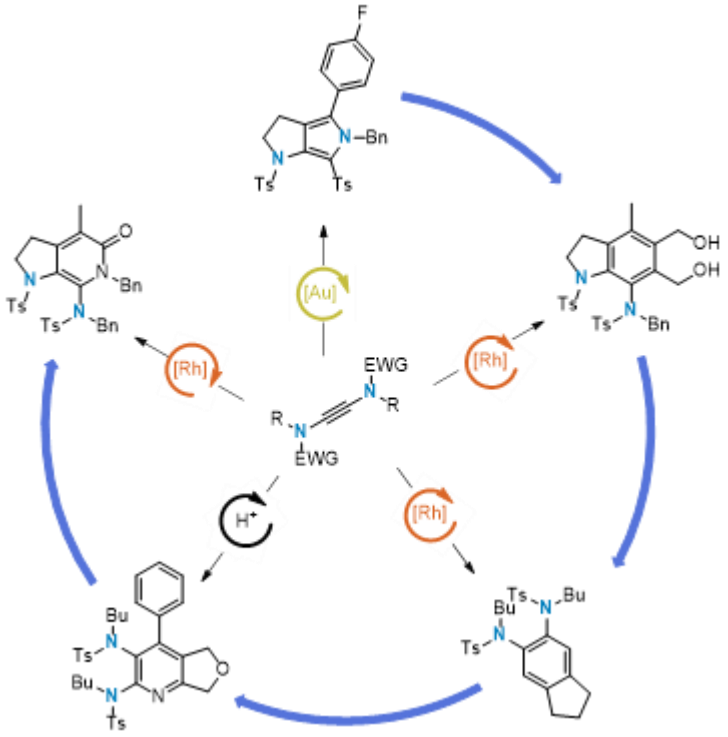
Chapter 3. The regioselective synthesis of such complex nitrogen-rich aromatic structures is a powerful demonstration of the utility of yndiamides in providing access to novel, medicinally relevant, motifs.

Future work in this area might include efforts to develop a robust reaction between simple yndiamides and alkynyl-nitriles (**Section 5.5.2**), including attempting to achieve such a transformation regioselectively. A regioselective synthesis of 2,3-diaminopyridines with orthogonal nitrogen protecting groups (such as Ts- and Ns-) might allow this chemistry to be used in a synthetically useful context. Transition metal-catalysis will probably be required to achieve this reactivity; preliminary investigations of the reaction between yndiamide **188** and 5-cyano-1-pentyne suggest this may be feasible, although extensive optimisation would probably be required to overcome the competing self-dimerisation/trimerisation of 5-cyano-1-pentyne.

Chapter 6: Conclusions and future uses of yndiamides in ring-forming transformations

As **Chapter**s **2**–**5** have described, yndiamides can be applied to the synthesis of a wide variety of 1,2-diamino-substituted ring structures, with the nitrogen atoms present in both aromatic and aliphatic rings, and as endo- and exo-cyclic moieties. These reactions of yndiamides expand known chemical space by introducing nitrogen-substitution onto rings in a single step from linear precursors. Some of these reactions can be used to synthesise multiple nitrogen-rich structures, which further underlines the synthetic utility of these methodologies. This concluding chapter will provide an overview of the progress made in regioselective ring forming transformations of yndiamides and will address some avenues for possible future application of yndiamides in ring synthesis.

6.1 Project summary and conclusions



Scheme 6.1: Overview of novel ring forming reactions of yndiamides described in this thesis.

Chapter 2 detailed the serendipitous discovery and subsequent development of a cycloisomerisation approach to form highly substituted pyrroles *via* a tandem [3+2] cycloaddition/sulfonyl migration process. The two synthetic methodologies developed to achieve this transformation (gold-catalysis and a thermal process) provided valuable points of comparison between the chemistry of yndiamides and ynamides. The novel fused ring systems formed in this cycloisomerisation reaction may be of interest to the medicinal chemistry community, and the significance of the work was further enhanced by novel derivatisation reactions which exploited the reactive functionalities present in the scaffold.

In **Chapter 3** a regioselective rhodium-catalysed [2+2+2] cyclotrimerisation reaction was used to form 7-aminoindoline derivatives from yne-yndiamides by tuning the electronic properties of the aryl alkyne partner, or by changing the substitution on the terminal nitrogen atom of the yndiamide. As a regioselective synthesis of highly-substituted benzene rings, this work is a

valuable demonstration of the synthetic utility of heteroatom-substituted alkynes in [2+2+2] methodologies. This reactivity was expanded to achieve a more challenging cyclotrimerisation reaction between simple yndiamides and diynes. In **Chapter 4** the mechanism of the [2+2+2] reaction of yne-yndiamides was investigated computationally to probe the regioselectivity of the reaction and its dependence on the alkyne electronic properties.

Finally, in **Chapter 5**, [2+2+2] reactivity of yndiamides was applied to the synthesis of diaminopyridine/pyridone derivatives from yndiamides, alkynes and nitriles/isocyanates in both intramolecular and intermolecular contexts. The literature precedent for similar reactions of ynamides was adapted for yndiamides, and these were found to be less reactive than ynamides under cobalt catalysis. However, good reactivity and (remarkably) complete regioselectivity were observed when isocyanates were used as the partner with yne-yndiamides in rhodium-catalysed [2+2+2] reactions, thus demonstrating divergence from the non-regioselective reactivity of similar ynamides.

6.2 Future applications of yndiamides in ring-forming reactions

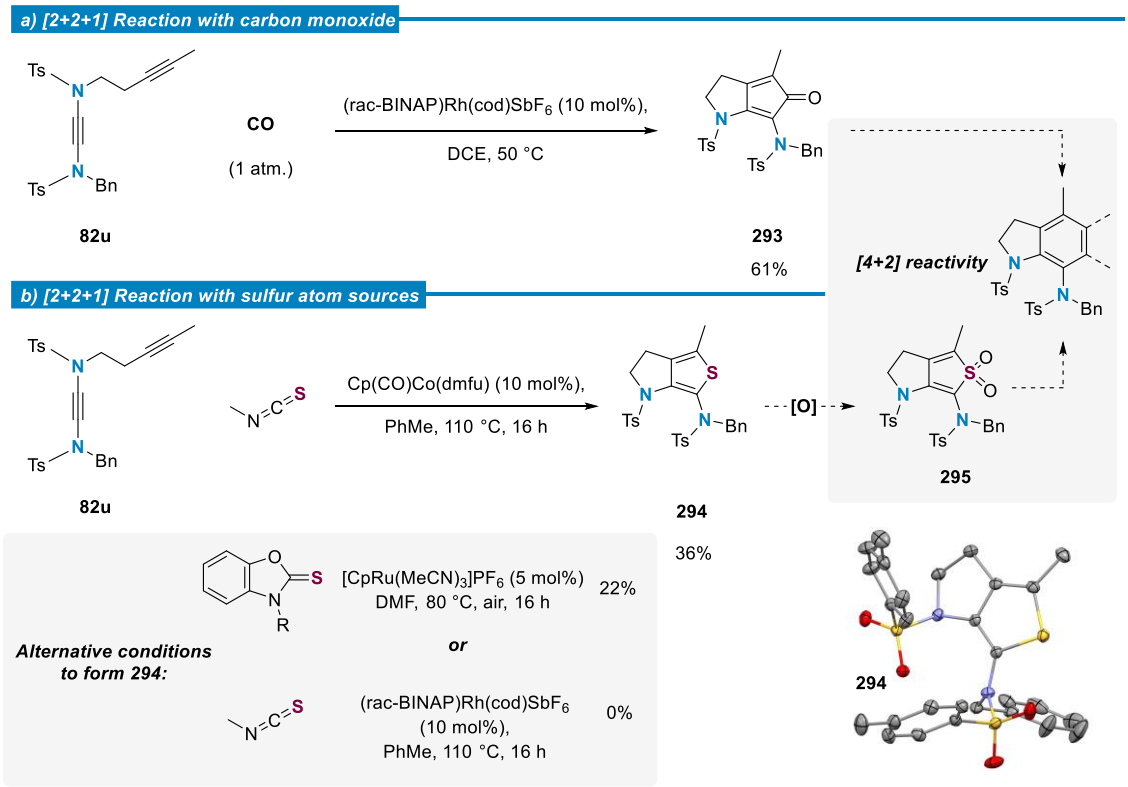
The chemistry discovered in this work, specifically the reactions of yndiamides bearing tethered alkynes, provides inspiration for developing new transformations to form nitrogen-rich ring structures. This section will describe initial results towards [2+2+1] reactivity of yne-yndiamides and some possible future applications of yndiamides in ring synthesis.

6.2.1 Future work: yne-yndiamides in [2+2+1] reactions

The metallocycle intermediates proposed in [2+2+2] cyclotrimerisation reactions of yne-yndiamides (**Chapters 3** and **5**) pose an attractive prospect for capture with one-atom cycloaddition components, resulting in a [2+2+1] cyclotrimerisation to form 5-membered rings with two nitrogen substituents. Two possible one-atom cycloaddition components are carbon monoxide[201,202] and sulfur atom sources.[203] **Scheme 6.2** shows the current state of initial investigations of both of these transformations.

Cyclopentadienone **293** was formed in moderate yield by a rhodium-catalysed reaction of **82u** with carbon monoxide (**Scheme 6.2a**); alternative (safer) sources of carbon monoxide could also be considered for use if this reaction was to be developed further.[204] Cyclopentadienones are often good substrates for Diels-Alder reactions, both self-dimerisation[205] and with other dienophiles,[206] and applying such reactivity (with CO extrusion) could provide another route to doubly nitrogenated arenes.

Thiophene **294** was formed when methyl isothiocyanate acted as a sulfur atom source in a [2+2+1] reaction with **82u** (**Scheme 6.2b**). The thiophene synthesis conditions developed by Yamamoto and co-workers[203] were also investigated but **294** was formed in a low yield. Further optimisation of this transformation could make it more synthetically useful, and additional applications of similar [2+2+1] reactivity may also be possible – for example to form diaminofurans,[207] or diaminopyrroles.[208] Oxidation of the thiophene product (**294**) could allow access to thiophene *S*-*S*-dioxides (**295**), which our group has demonstrated to be valuable substrates in inverse electron demand Diels-Alder reactions,[209] although the electron-donating groups present in **294** may significantly alter the characteristics of the proposed cycloadditions.

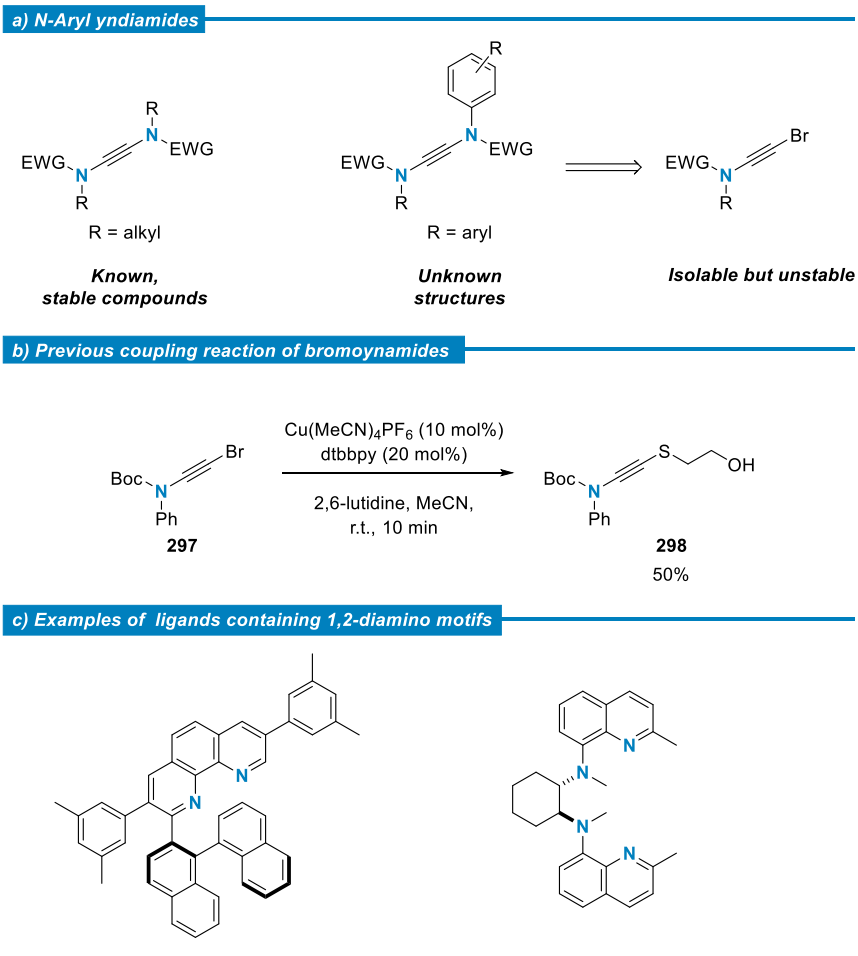


Scheme 6.2: Preliminary results for [2+2+1] cyclotrimerisation reactions to form *a)* cyclopentadienone **293** and *b)* thiophenes **294** and single-crystal XRD structure of **294**. Displacement plot for **294** is displayed at 50% probability with hydrogen atoms hidden for clarity.

6.2.2 Future work: development and application of novel yndiamides

The majority of the yndiamides employed in the reactions detailed in **Chapter**s **2**–**5** are similar to the sulfonamide yndiamides reported in our group's initial work on yndiamides. Perhaps the most significant limitation of yndiamide chemistry thus far is the absence of suitable routes to synthesise *N*-aryl yndiamides and *N*-carbonyl yndiamides, whereas routes exist to synthesise the *ynamide* analogues of these compound classes.[4,210] Initial progress towards the synthesis of *N*-aryl yndiamides was made in the form of the carbazole-yndiamides reported in **Chapter 3**, but more general *N*-arylated yndiamides are yet to be synthesised despite several attempts by our group.[15,128] Developing routes to these compounds and the application of existing yndiamide methodologies (specifically [2+2+2] cyclotrimerisations) might enable the synthesis of more medicinally-relevant compounds.

One possible method to prepare *N*-arylated yndiamides could use bromoynamides (**296**) in cross-coupling reactions with aniline derivatives. In 2015 Takasu and co-workers reported observing an oxazolidone bromoynamide in trace quantities,[211] and a sulfonamide bromoynamide was also used as an intermediate in the synthesis of a bromooxazole by Davies and co-workers in 2016[14] (**Scheme 6.3a**). An oxazolidone bromoynamide was coupled with a thiol by Collins and co-workers to form a thioynamide in their 2020 report of a general C_{sp}-S coupling reaction (**297**→**298**) (**Scheme 6.3b**).[212] The application of similar methodology to a nitrogen coupling partner might provide an alternative route to synthesise yndiamides. The current yndiamide synthesis probably fails for *N*-aryl sulfonamides because the sulfonamide anion is too stabilised by delocalisation to act as a base to assist with the elimination of HBr from the dibromoenamide, but if a bromoynamide could be used this step would no longer be required. However, all existing reports of bromoynamides describe them as extremely unstable and this is likely to pose a significant challenge in the synthesis of yndiamides by this route.



Scheme 6.3: *a)* Proposed synthesis of *N*-aryl yndiamides from bromoynamides. *b)* Literature precedence for coupling of bromoynamides.[212] *c)* Examples of ligands used in iron-catalysis containing 1,2-diamino motifs.[213]

6.3 Closing remarks

Yndiamides have herein been shown to be viable precursors to numerous doubly-nitrogen substituted rings and the reactivity explored provides points of comparison to ynamides. Many of the compounds prepared exhibit structural features which are not commonly encountered in the existing literature. Thus, this work expands the known chemical space, especially in the preparation of nitrogen-rich ring structures which will be of interest to the medicinal chemistry community. Alternatively, yndiamides may find applications in synthesising novel 1,2-diamino ligands, such as phenanthroline derivatives or diaminocyclohexanes, a class of ligands which find use in the vibrant field of iron catalysis (**Scheme 6.3c**).[213] There are doubtless many more applications of yndiamides in ring-forming chemistry remaining to be explored in the quest to exploit yndiamides as valuable building blocks in organic synthesis.

Chapter 7: Experimental

7.1 General Experimental Techniques

Unless stated otherwise, all chemicals were purchased from commercial suppliers (Sigma-Aldrich, Fluorochem, Alfa Aesar, TCI) and used without further purification. 1*H*-Benzo[d][1,2,3]triazole-1-carbaldehyde (BtCHO, formylating agent) was prepared in quantitative yield according to the procedure of Marquez and co-workers.[214]

^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded on a Bruker AVIII400 Spectrometer (400 MHz, 101 MHz, 162 MHz, and 377 MHz respectively) or a Bruker AVII500 (^{1}H: 500 MHz and ^{13}C: 126 MHz) in $CDCl_3$, DMSO-d_6 or MeOD and referenced to residual solvent peaks. Chemical shifts δ are quoted in parts per million (ppm) to the nearest 0.01 for ^{1}H and 0.1 for ^{13}C (for ^{13}C in cases where two peaks have the same chemical shift to the nearest 0.1 ppm, shifts are given to the nearest 0.01 ppm), coupling constants *J* are quoted in Hz to the nearest 0.1 and splitting are recorded as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), hextet (h), doublet of a doublet (dd), doublet of a doublet of a doublet (ddd), broad singlet (br. s) and multiplet (m), or apparent (app) splitting corresponding to one of the above patterns. Assignments were based upon COSY, HSQC, NOESY and HMBC experiments. Chemical shifts and splitting patterns are recorded as observed.

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer fitted with an Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers (cm^{-1}). Absorption maxima with wavenumbers >1000 cm^{-1} are quoted.

Mass spectra were recorded on a Fisons Platform II spectrometer under electrospray ionisation (ESI). High resolution mass spectra are given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM).

Melting points (MP) were obtained using a Gallenkamp melting point machine.

Analytical thin layer chromatography (TLC) was performed on pre-coated SiO_2 aluminium sheets from Merck (TLC Silica Gel 60 F254s). Spots were visualised either by the quenching of UV fluorescence or by staining with vanillin solution, $KMnO_4$ solution, ninhydrin solution or PMA solution. Retention factor (R_f) values are given for compounds formed in reactions which were monitored by TLC.

Preparative flash column chromatography was carried out using Geduran Silica Gel 60 (40–63 μm) from Merck, except in cases where it is stated that phosphate-buffered SiO_2 was used. Phosphate buffered SiO_2 was prepared according to a procedure from Newton and co-workers.[215]

All compounds were named using PerkinElmer ChemDraw software and key atoms were numbered for ease of data interpretation.

Data for compounds prepared by other researchers (Prof. Yubo Jiang, Julia Ragus) are not included in the supporting information, except where the synthesis was repeated on a larger scale by the author.

7.2 General Procedures

General Procedure 1: Sonagashira couplings

To an oven-dried flask equipped with a stirrer bar was added $PdCl_2(PPh_3)_2$ (3 mol%) and CuI (6 mol%). The flask was fitted with a septum and evacuated under high vacuum and backfilled with argon. Et_3N [1.0 mL per mmol of aryl (pseudo)halide] was then added, followed by 3-butyn-1-ol (1.25 equiv.) and the aryl (pseudo)halide. The reaction mixture was stirred at room temperature overnight or until completion was observed by TLC, then diluted with EtOAc, filtered and concentrated *in vacuo*. The crude material was then purified by flash column chromatography.

General Procedure 2: Mitsunobu reactions and carbamate deprotections[216]

To an oven-dried flask equipped with a stirrer bar was added Ph_3P (1.2 equiv.) and methyl tosylcarbamate (1.2 equiv.) under an atmosphere of argon. Anhydrous THF (10 mL per mmol alcohol) and the alcohol (1.0 equiv.) were then added. The reaction mixture was then cooled to 0 °C and DIAD (1.2 equiv.) was added dropwise while stirring vigorously. The reaction mixture was stirred at room temperature overnight or until completion was observed by TLC then the solvent was removed *in vacuo*. The crude material was filtered through a short SiO_2 plug, eluting with 20 % EtOAc in pentane to remove the triphenylphosphine oxide. The filtrate was concentrated *in vacuo*, then dissolved in MeOH (5 mL per mmol alcohol) and K_2CO_3 (2.0 equiv.) was added. The reaction mixture was stirred at room temperature overnight or until completion was observed by TLC, then concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with water, the layers were separated and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*, then purified by flash column chromatography.

General Procedure 3: Sulfonamide preparation

The relevant amine (1.5 equiv.) was dissolved in CH_2Cl_2 (1.0 mL per mmol sulfonyl chloride) at 0 °C and Et_3N (1.5 equiv.) was added. Sulfonyl chloride (1.0 equiv.) was added portionwise at 0 °C and the reaction mixture was stirred at room temperature for 2 h. Water was added and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the product which was used without further purification.

General Procedure 4: 1,1-Dibromoenamide preparation[1]

To an oven-dried flask equipped with a stirrer bar was added a sulfonamide (1.0 equiv.) and anhydrous THF (6.0 mL $mmol^{-1}$ sulfonamide) under an atmosphere of argon. The resulting mixture was cooled to 0 °C and *n*-BuLi (solution in hexanes, 1.1 equiv.) was added slowly at 0 °C. The reaction was stirred at 0 °C for 30 minutes then a solution of 1*H*-Benzo[d][1,2,3]triazole-1-carbaldehyde (BtCHO) (1.2 equiv.) in dry THF (2.0 mL $mmol^{-1}$ sulfonamide) and added dropwise over 10 minutes. The reaction was stirred at room temperature for 18 h then then quenched with water (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with K_2CO_3 (2M, 2 × 100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was used immediately in the next step.

PPh_3 (4.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (6.0 mL $mmol^{-1}$ sulfonamide) under an atmosphere of argon and cooled to −30 °C. A solution of CBr_4 (2.0 equiv.) in anhydrous CH_2Cl_2 (1.0 mL $mmol^{-1}$ sulfonamide) was then added dropwise and the reaction mixture was stirred for 30 minutes at −30 °C. The reaction mixture was then cooled to −40 °C and the crude material from the previous step was added dropwise as a solution in anhydrous CH_2Cl_2 (3.0 mL $mmol^{-1}$ sulfonamide). The reaction mixture was slowly warmed to room temperature and stirred until completion was observed by TLC. The reaction was then concentrated *in vacuo* to

approximately half its original volume *in vacuo* and the crude material was directly purified by flash column chromatography.

General Procedure 5: Yndiamide synthesis[1]

To an oven-dried flask equipped with a stirrer bar were added sulfonamide (1.0 equiv.), 1,1-dibromoenamide (1.1 equiv.), 1,10-phenanthroline (40 mol%), CuI (20 mol%, dispensed in N_2-filled glovebox), and Cs_2CO_3 (3.0 equiv., dispensed in N_2-filled glovebox). The vial was then capped with a septum and evacuated under high vacuum for 10 minutes. The vial was then backfilled with argon and the cycle was repeated twice more. Anhydrous THF (3.0 mL per mmol sulfonamide) was added and the reaction mixture was stirred at 60 °C overnight or until completion was observed by TLC. The reaction mixture was cooled to room temperature and diluted with EtOAc and filtered through a short Celite pad. The crude material was then concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 6: Gold-catalysed cycloisomerisation reactions

To an oven dried vial containing a stirrer bar was added the yndiamide (0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%). The vial was then wrapped in foil and purged with argon, then anhydrous DCE (0.6 mL) was added and the vial was capped. The reaction mixture was then stirred at room temperature for 3 h or until completion was observed by TLC (3 h except where specified), then concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 7: Thermal cycloisomerisation reactions

To an oven dried vial containing a stirrer bar was added the yndiamide (0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.). Anhydrous toluene (2.0 mL) was then added and the vial was purged with argon and capped. The reaction mixture was then heated at 110 °C for

18 h or until completion was observed by TLC (18 h except where specified), then concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 8: Rh-catalysed cyclotrimerisation reactions of yne-yndiamides with alkynes

Yndiamide (0.10 mmol, 1.0 equiv.), (±BINAP)Rh(cod)SbF_6 (5.2 mg, 0.050 mmol, 5 mol%), and alkyne (0.30 mmol, 3.0 equiv.) were added to an oven-dried screw cap vial containing a stirrer bar and fitted with a septum. The vial was then evacuated under high vacuum and backfilled with argon three times, then 1,2-dichloroethane (1.0 mL, anhydrous) was added by syringe. The septum was then replaced quickly with a screw cap and the reaction mixture was stirred at 50 °C for 16 h or until complete consumption of the yndiamide starting material was confirmed by TLC. The solvent was then removed *in vacuo* and a crude ^{1}H NMR spectrum was obtained to measure the regioisomeric ratio. The crude material was then purified by flash column chromatography.

General Procedure 9: Rh-catalysed cyclotrimerisation reactions of yndiamides with diynes

Yndiamide (0.10 mmol, 1.0 equiv.) and (*rac*-BINAP)Rh(cod)SbF_6 (5.2 mg, 0.050 mmol, 5 mol%) were added to an oven-dried vial containing a stirrer bar. The vial was evacuated under high vacuum and backfilled with argon three times, then toluene (0.20 mL, anhydrous) was added by syringe. In a second vial under an atmosphere of argon the diyne (0.50 mmol, 5.0 equiv.) was dissolved in toluene (0.80 mL, anhydrous). The first vial was heated at 100 °C under an atmosphere of argon and the diyne solution was added to the reaction mixture by syringe pump over 3 h, then the reaction mixture was stirred for an additional 15 h at 100 °C. The reaction mixture was then cooled to room temperature and diluted with $CHCl_3$ then concentrated *in vacuo* and a crude ^{1}H NMR spectrum was obtained. The crude material was then purified by flash column chromatography.

Determination of regioisomeric ratio in products 174a–q

The regioisomeric ratio for the cyclotrimerisation of yne-yndiamides with aryl alkynes was determined by analysis of the *crude* ^{1}H NMR spectra. Typically the *N*-benzyl CH_2 protons (approx. 5.4–4.6 ppm) were found to give a good measure of the ratio between the two regioisomers. Analysis of the purified regioisomeric mixtures by examining NOESY, HMBC and COSY correlations allowed the major product to be identified. An example is given below for the reaction of yne-yndiamide **82u** with phenylacetylene to form **174e** in a 6:1 regioisomeric ratio, identification of the major isomer is shown from the NOESY spectrum (**Figure 7.4.1**) and identification of the minor isomer is shown from the COSY spectrum (**Figure 7.4.2**).

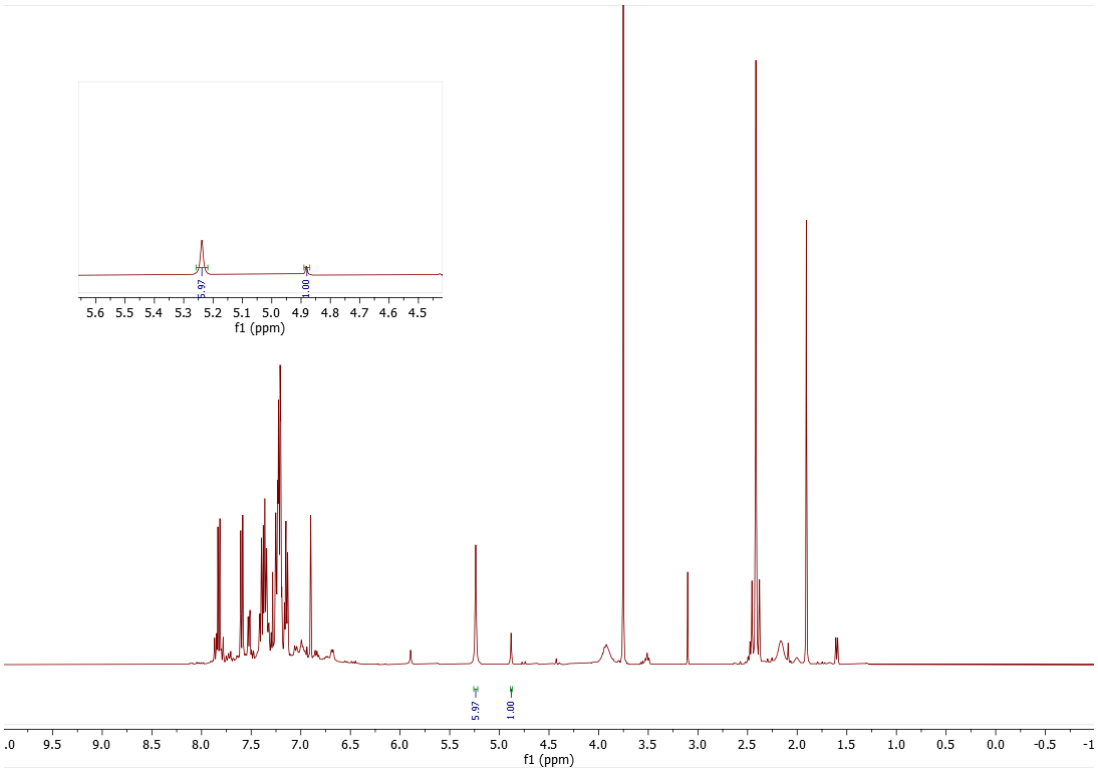


Figure 7.4.1 NOESY spectrum (assignment of major isomer):

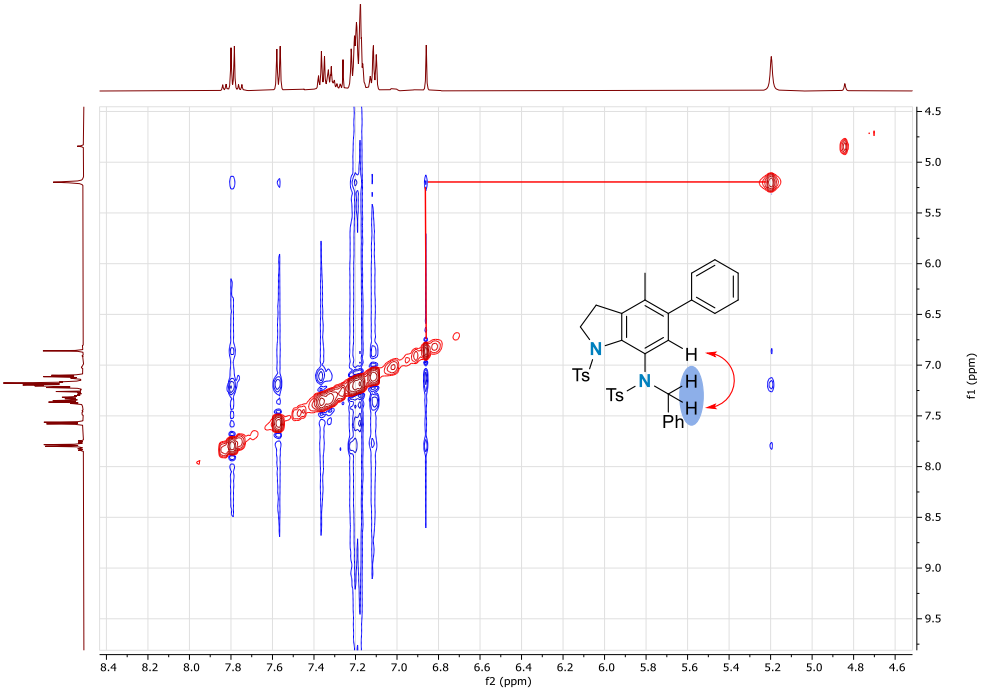
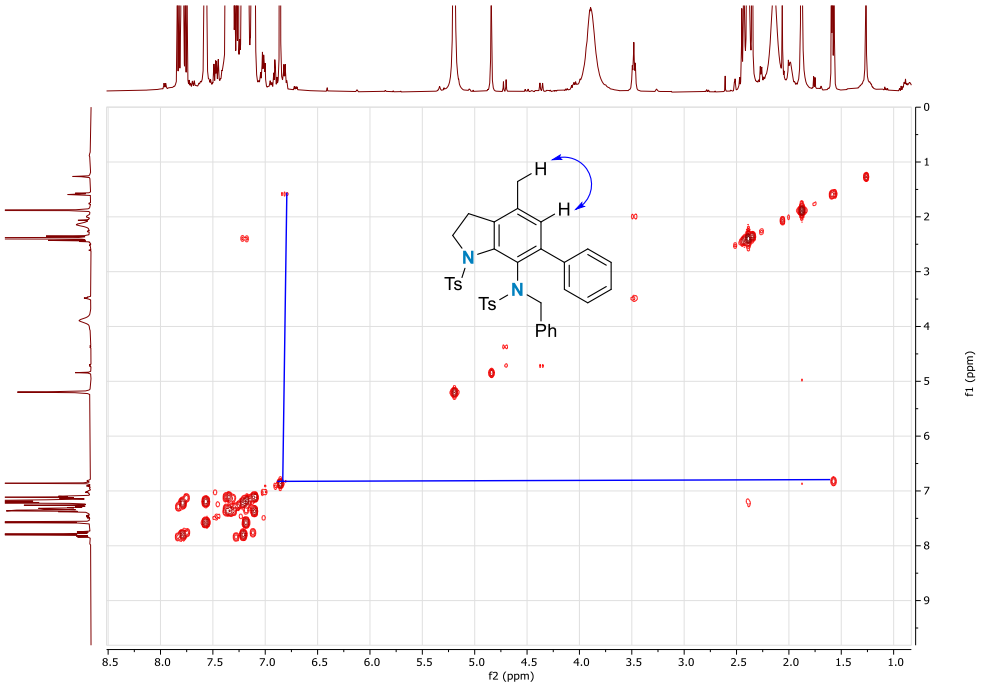


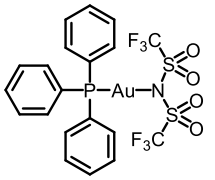
Figure 7.4.2 COSY spectrum (assignment of minor isomer):



7.3 Chapter 2 Characterisation Data

7.3.1 Gold(I) catalysts

Triphenylphosphine gold(I) triflimide



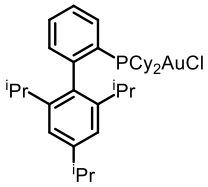
According to the procedure of Tokuyama and co-workers.[217] Triphenylphosphine gold(I) chloride (50.0 mg, 0.10 mmol, 1.0 equiv.) and silver (I) triflimide (38.8 mg, 0.10 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL) under an argon atmosphere. The reaction mixture was then stirred at room temperature in the dark for 15 minutes then filtered through a celite pad and the filtrate was concentrated *in vacuo* and dried under high vacuum in the dark to give the title compound (75.0 mg, 0.10 mmol, >99%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[217]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61–7.46 (15H, m).

^{31}P NMR (162 MHz, CDCl3) δ_P 30.62.

^{19}F NMR (377 MHz, CDCl3) δ_F −75.19.

Chloro[2-dicyclohexyl(2′,4′,6′-trisopropylbiphenyl)phosphine]gold(I)

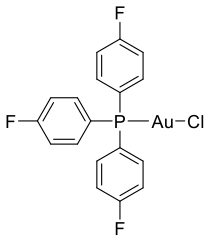


Adapted from a procedure from Davies and co-workers.[218] Dimethylsulfide gold(I) chloride (30.0 mg, 0.10 mmol, 1.0 equiv.) and XPhos (47.6 mg, 0.10 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL) and stirred at room temperature in the dark for 2 h. The solvent was then removed *in vacuo* followed by drying under high vacuum in the dark to give the title compound (68.0 mg, 0.096 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63–7.57 (1H, m), 7.52–7.47 (2H, m), 7.29 (1H, s), 7.08 (2H, s), 2.98 (1H, app. p, J = 6.9 Hz), 2.23 (2H, app. p, J = 6.8 Hz), 2.09 (3H, q, J = 11.9 Hz), 1.90–1.72 (7H, m), 1.68 (3H, br. s), 1.53 (3H, s), 1.38 (3H, s), 1.37 (3H, s), 1.31 (3H, s), 1.29 (3H, s), 1.27–1.16 (6H, m), 0.95 (3H, s), 0.93 (3H, s).

^{31}P NMR (162 MHz, CDCl3) δ_P 35.33.

Tris-(4-fluorophenyl)phosphine gold(I) chloride



According to the procedure of Hashmi and co-workers.[219] Dimethylsulfide gold(I) chloride (25.0 mg, 0.085 mmol, 1.0 equiv.) and tris-(4-fluorophenyl)phosphine (26.9 mg, 0.085 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL) and stirred in the dark at room temperature for 1 h. The solvent was then blown off with N_2 and the resulting solid was dried under high

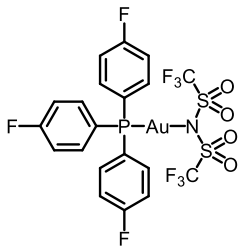
vacuum in the dark to give the title compound (44.2 mg, 0.081 mmol, 95%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[220]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51 (6H, ddd, *J* = 12.7, 8.8, 5.3 Hz), 7.24–7.17 (6H, m).

^{31}P NMR (162 MHz, $CDCl_3$) δ_P 30.72 (d, *J* = 2.9 Hz).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −105.46 (tp, *J* = 8.1, 2.6 Hz).

Tris-(4-fluorophenyl)phosphine gold(I) triflimide



Tri-(4-fluorophenyl)phosphine gold(I) chloride (44.2 mg, 0.081 mmol, 1.0 equiv.) and silver triflimide (31.3 mg, 0.081 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL) and stirred at room temperature in the dark for 1 h then filtered through a celite pad. The solvent was then blown off with N_2 and the resulting solid was then dried under high vacuum in the dark to give the title compound (51.8 mg, 0.065 mmol, 81%) as a colourless solid.

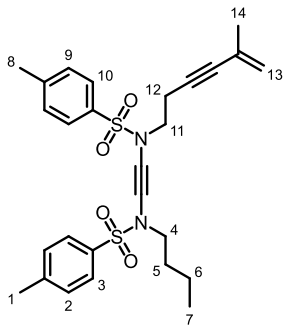
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 (6H, ddd, *J* = 13.2, 8.8, 5.2 Hz), 7.28–7.22 (6H, m).

^{31}P NMR (162 MHz, $CDCl_3$) δ_P 27.87.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −75.13, −104.14 (d, *J* = 3.0 Hz). *Note: possible long range F-P coupling observed.*

7.3.2 Yndiamides

82a ***N*-Butyl-4-methyl-*N*-(((4-methyl-*N*-(5-methylhex-5-en-3-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide**



S86a (0.100 g, 0.38 mmol, 1.0 equiv.), **S87a** (0.172 g, 0.42 mmol, 1.1 equiv.), CuI (14.5 mg, 0.080 mmol, 20 mol%), 1,10-phenanthroline (28.8 mg, 0.16 mmol, 40 mol%) and Cs_2CO_3 (0.371 g, 1.14 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (1.2 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 10%) to give the title compound (43.8 mg, 0.086 mmol, 23%) as a brown oil.

R_f (EtOAc in pentane, 10%) 0.50.

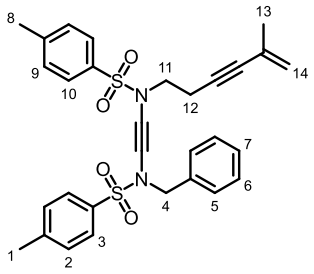
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.70 (4H, m, H3 + H10), 7.33–7.30 (4H, m, H2 + H9), 5.20–5.18 (1H, m, H13), 5.16 (1H, app. q, *J* = 1.5 Hz, H13), 3.53–3.51 (2H, m, H11), 3.32 (2H, t, *J* = 7.3 Hz, H4), 2.54–2.50 (2H, m, H12), 2.45 (6H, overlapping singlets, H1 + H8), 1.83 (3H, t, *J* = 1.5 Hz, H14), 1.58–1.48 (2H, m, H5), 1.31–1.23 (2H, m, H6), 0.88 (3H, t, *J* = 7.3, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 144.7, 135.03, 135.01, 129.91, 129.85, 129.8, 127.8, 127.7, 121.6, 84.4, 83.8, 69.8, 68.5, 51.6, 50.6, 30.0, 23.7, 21.8 (2 C), 19.5, 19.2, 13.7.

HRMS (ES^+) calc. for $C_{27}H_{32}O_4N_2S_2Na$ 535.16860 $[M+Na]^+$, found 535.16943.

IR (thin film, ν_{max}/cm^{-1}) 2969, 2875, 1716, 1684, 1598, 1457, 1363, 1324, 1258, 1166, 1128, 1089, 1068, 1018. *Note: the apparent carbonyl peak at 1716 cm^{-1} cannot be readily assigned to this structure.*

82b ***N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(5-methylhex-5-en-3-yn-1-yl)phenyl)sulfonamido)ethynyl)benzenesulfonamide**



S86a (0.337 g, 1.28 mmol, 1.0 equiv.), **S87b** (0.627 g, 1.41 mmol, 1.1 equiv.), CuI (48.8 mg, 0.26 mmol, 20 mol%), 1,10-phenanthroline (92.3 mg, 0.52 mmol, 40 mol%) and Cs_2CO_3 (1.25 g, 3.84 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (3.8 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 10%) to give the title compound (0.151 g, 0.28 mmol, 22%) as a brown oil.

R_f (EtOAc in pentane, 10%) 0.21.

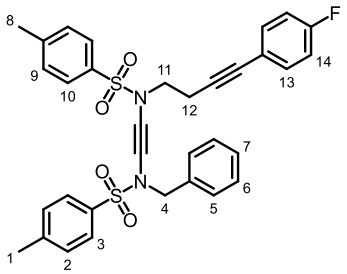
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.4 Hz, ArH), 7.62 (2H, d, *J* = 8.4 Hz, ArH), 7.31–7.24 (7H, m, ArH), 7.20–7.16 (2H, m, ArH), 5.20–5.18 (1H, m, H14), 5.16 (1H, t, *J* = 1.6 Hz, H14), 4.50 (2H, s, H4), 3.42–3.36 (2H, m, H11), 2.45 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.31–2.26 (2H, m, H12), 1.82 (3H, t, *J* = 1.6 Hz, H13).

^{13}C NMR (101 MHz, $CDCl_3$) 144.8, 144.7, 135.03, 134.99, 134.7, 129.9, 129.8, 129.0, 128.6, 128.4, 127.9, 127.7, 126.9, 121.5, 84.4, 83.7, 70.1, 69.4, 56.1, 50.5, 23.7, 21.8 (2 C), 18.9.

HRMS (ES^+) calc. for $C_{30}H_{31}O_4N_2S_2$ ($[M+H]^+$) 547.1696, found 547.1718.

IR (thin film, ν_{max}/cm^{-1}) 2972, 1597, 1455, 1412, 1365, 1186, 1169, 1090, 1019.

82c ***N*-Benzyl-*N*-(((*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylphenyl)sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86c (0.500 g, 1.58 mmol, 1.0 equiv.), **S87b** (0.771 g, 1.73 mmol, 1.1 equiv.), CuI (60.2 mg, 0.316 mmol, 20 mol%), 1,10-phenanthroline (0.114 g, 0.632 mmol, 40 mol%) and Cs_2CO_3 (1.54 g, 4.74 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (5.1 mL) for 44 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (0.421 g, 0.70 mmol, 44%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.4 Hz, ArH), 7.63 (2H, d, *J* = 8.4 Hz, ArH), 7.33–7.27 (7H, m, H5 + H6 + H7 + H13), 7.24–7.21 (2H, m, ArH), 7.20–7.17 (2H, m, ArH), 6.97 (2H, t, *J* = 8.7 Hz, H14), 4.50 (2H, s, H4), 3.47 (2H, t, *J* = 7.1 Hz, H11), 2.44 (3H, s, CH_3), 2.43–2.38 (5H, m, H12 + CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^1J_{C\text{-}F}$ = 248.9 Hz), 144.8, 144.7, 135.0, 134.7, 133.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 129.8 (2C), 128.9, 128.6, 128.4, 127.84, 127.83, 127.7, 119.4 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 85.1 (d, $^5J_{C\text{-}F}$ = 1.4 Hz), 81.5, 70.3, 69.3, 56.1, 50.4, 21.81, 21.79, 19.0.

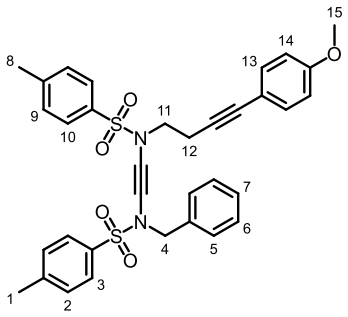
^{19}F NMR (377 MHz, $CDCl_3$): δ_F −111.47.

HRMS (ES^+) calc. for $C_{33}H_{30}FN_2O_4S_2$ ($[M+H]^+$) 601.1626, found 601.1625.

IR (thin film, ν_{max}/cm^{-1}) 2967, 1599, 1507, 1412, 1364, 1221, 1168, 1090.

MP 78–82 °C.

82d ***N*-Benzyl-*N*-(((*N*-(4-(4-methoxyphenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86d (0.670 g, 2.03 mmol, 1.0 equiv.), **S87b** (0.994 g, 2.23 mmol, 1.1 equiv.), CuI (77.3 mg, 0.41 mmol, 20 mol%), 1,10-phenanthroline (0.146 g, 0.82 mmol, 40 mol%) and Cs_2CO_3 (1.98 g, 6.09 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (6.0 mL) with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (0.812 g, 1.33 mmol, 65%) as a brown oil.

R_f (CH_2Cl_2) 0.68.

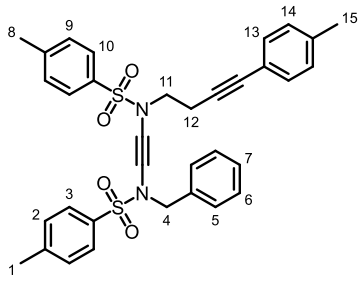
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, ArH), 7.63 (2H, d, *J* = 8.4 Hz, ArH), 7.30–7.25 (7H, m, ArH), 7.24–7.17 (4H, m, ArH), 6.80 (2H, d, *J* = 8.8 Hz, H14), 4.50 (2H, s, H4), 3.80 (3H, s, H15), 3.47 (2H, dd, *J* = 8.1, 7.0 Hz, H11), 2.44 (3H, s, CH_3), 2.41–2.37 (5H, m, H12 + CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.5, 144.73, 144.65, 135.04, 135.01, 134.7, 133.1, 129.84, 129.83, 128.9, 128.6, 128.4, 127.9, 127.7, 115.5, 114.0, 83.8, 82.3, 70.2, 69.4, 56.1, 55.4, 50.6, 21.82, 21.80, 19.1.

HRMS (ES^+) calc. for $C_{34}H_{33}N_2O_5S_2$ ($[M+H]^+$) 613.1819, found 613.1821.

IR (thin film, ν_{max}/cm^{-1}) 2956, 1606, 1510, 1456, 1412, 1364, 1291, 1248, 1185, 1168, 1090, 1031.

82e ***N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(4-(p-tolyl)but-3-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide**



S86e (0.500 g, 1.60 mmol, 1.0 equiv.), **S87b** (0.779 g, 1.76 mmol, 1.1 equiv.), CuI (60.9 mg, 0.32 mmol, 20 mol%), 1,10-phenanthroline (0.115 g, 0.64 mmol, 40 mol%) and Cs_2CO_3 (1.56 g, 4.80 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.8 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (90.0 mg, 0.15 mmol, 9%) as a brown oil which solidified on standing.

R_f (EtOAc in pentane, 20%) 0.45.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.67 (2H, m, ArH), 7.65–7.61 (2H, m, ArH), 7.30–7.25 (5H, m, ArH), 7.24–7.20 (4H, m, H9 + ArH), 7.19 (2H, dd, *J* = 7.5, 2.2 Hz, ArH), 7.09–7.06 (2H, m, H10), 4.50 (2H, s, H4), 3.47 (2H, dd, *J* = 8.1, 7.1 Hz, H11), 2.44 (3H, s, CH_3), 2.41–2.36 (5H, m, CH_3 + H12), 2.33 (3H, s, H15).

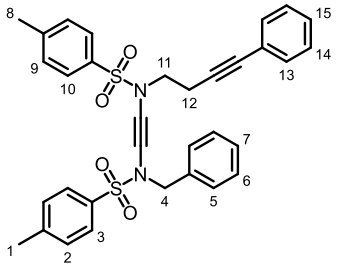
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.74, 144.66, 138.2, 135.04, 135.01, 134.8, 131.7, 129.9, 129.8, 129.1, 129.0, 128.6, 128.4, 127.9, 127.7, 120.3, 84.6, 82.6, 70.2, 69.4, 56.1, 50.5, 21.82, 21.79, 21.6, 19.1.

HRMS (ES^+) calc. for $C_{34}H_{33}N_2O_4S_2$ ($[M+H]^+$ 597.1854, found 597.1876.

IR (solid, ν_{max}/cm^{-1}) 2950, 1597, 1509, 1445, 1406, 1356, 1166, 1090.

MP 82–86 °C.

82f *N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(4-phenylbut-3-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide



S86f (0.173 g, 0.58 mmol, 1.0 equiv.), **S87b** (0.284 g, 0.64 mmol, 1.1. equiv.), CuI (22.1 mg, 0.12 mmol, 20 mol%), 1,10-phenanthroline (41.8 mg, 0.23 mmol, 40 mol%) and Cs_2CO_3 (0.566 g, 1.74 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (1.7 mL) for 18 h with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (0.174 g, 0.30 mmol, 52%) as a brown oil.

R_f (CH_2Cl_2) 0.57.

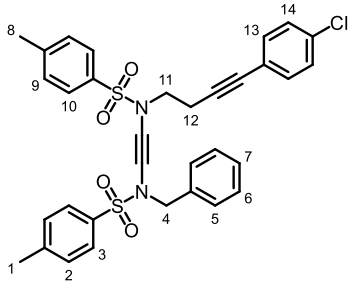
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, ArH), 7.63 (2H, d, *J* = 8.3 Hz, ArH), 7.36–7.31 (2H, m, ArH), 7.32–7.23 (7H, m, ArH), 7.24–7.17 (5H, m, ArH), 4.50 (2H, s, H4), 3.48 (2H, dd, *J* = 8.0, 7.1 Hz, H11) 2.45–2.38 (8H, m, H1 + H8 + H12).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.63, 144.56, 134.9 (2 C), 134.6, 131.6, 129.72, 129.71, 128.8, 128.5, 128.3, 128.2, 128.0, 127.7, 127.6, 123.2, 85.3, 82.4, 70.1, 69.2, 56.0, 50.3, 21.68, 21.66, 18.9.

HRMS (ES^+) calc. for $C_{33}H_{31}O_4N_2S_2$ ($[M+H]^+$) 583.1720, found 583.1718.

IR (thin film, ν_{max}/cm^{-1}) 2923, 2852, 1597, 1492, 1413, 1364, 1169, 1090, 1019, 814.

82g ***N*-Benzyl-*N*-(((*N*-(4-(4-chlororophenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86g (0.527 g, 1.58 mmol, 1.0 equiv.), **S87b** (0.771 g, 1.73 mmol, 1.10 equiv.), CuI (60.2 mg, 0.32 mmol, 20 mol%), 1,10-phenanthroline (0.114 g, 0.64 mmol, 40 mol%) and Cs_2CO_3 (1.54 g, 4.74 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.7 mL) for 44 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (0.421 g, 0.68 mmol, 43%) as a colourless solid.

R_f (EtOAc in pentane, 20%) 0.44.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.3 Hz, ArH), 7.63 (2H, d, *J* = 8.3 Hz, ArH), 7.32–7.20 (13H, m, H2 + H5 + H6 + H7 + H9 + H13 + H14), 4.51 (2H, s, H4), 3.49 (2H, t, *J* = 7.5 Hz, H11), 2.47–2.38 (8H, m, H1 + H8 + H12).

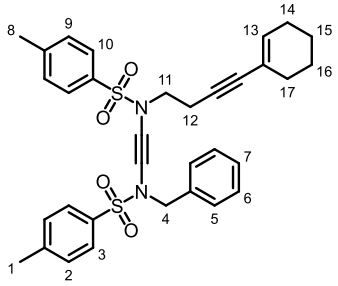
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 144.7, 135.0 (2 C), 134.7, 134.1, 133.0, 129.83, 129.82, 128.9, 128.7, 128.6, 128.4, 127.8, 127.7, 121.8, 86.5, 81.5, 70.3, 69.3, 56.1, 50.4, 21.79, 21.77, 19.1.

HRMS (ES^+) calc. for $C_{33}H_{30}{}^{35}ClN_2O_4S_2$ ($[M+H]^+$) 617.1330, found 617.1329.

IR (thin film, ν_{max}/cm^{-1}) 2980, 1597, 1484, 1453, 1324, 1153, 1090, 1014.

MP 133–137 °C.

82h ***N*-Benzyl-*N*-(((*N*-(4-(cyclohex-1-en-1-yl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86h (0.550 g, 1.82 mmol, 1.0 equiv.), **S87b** (0.883 g, 2.00 mmol, 1.1 equiv.), CuI (69.3 mg, 0.36 mmol, 20 mol%), Cs_2CO_3 (1.77 g, 5.46 mmol, 3.0 equiv.) and 1,10-phenanthroline (0.131 g, 0.72 mmol, 40 mol%) were used in **General Procedure 5** with anhydrous THF (5.5 mL) for 21 h. Purification by flash column chromatography (SiO_2, Et_2O in pentane, 5 to 20%) to give the title compound (0.121 g, 0.21 mmol, 12%) as a yellow oil.

R_f (Et_2O in pentane, 20%) 0.29.

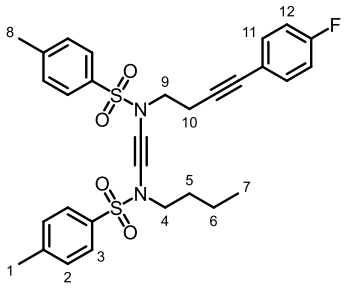
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.4 Hz, ArH), 7.62 (2H, d, *J* = 8.3 Hz, ArH), 7.31–7.24 (7H, m, ArH), 7.20–7.16 (2H, m, ArH), 6.00–5.97 (1H, m, H13), 4.50 (2H, s, H4), 3.40–3.35 (2H, m, H11), 2.45 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.27 (2H, t, *J* = 7.7 Hz, H12), 2.08–2.01 (4H, m, H14 + H15), 1.66–1.50 (4H, m, H16 + H17).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 144.6, 135.1, 135.0, 134.7, 134.4, 129.84, 129.82, 128.9, 128.6, 128.4, 127.9, 127.7, 120.7, 84.3, 82.4, 70.1, 69.4, 56.1, 50.7, 29.5, 25.7, 22.5, 21.8 (2 C), 21.7, 19.0.

HRMS (ES^+) calc. for $C_{33}H_{35}O_4N_2S_2$ ($[M+H]^+$) 587.2033, found 587.2031.

IR (thin film, ν_{max}/cm^{-1}) 2993, 2894, 2880, 1405, 1363, 1167, 1089.

82i ***N*-Butyl-*N*-(((*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86c (0.351 g, 1.11 mmol, 1.0 equiv.), **S87a** (0.500 g, 1.22 mmol, 1.1. equiv.), CuI (42.3 mg, 0.22 mmol, 20 mol%), 1,10-phenanthroline (79.9 mg, 0.44 mmol, 40 mol%) and Cs_2CO_3 (1.08 g, 3.33 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (3.3 mL) for 60 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.326 g, 0.58 mmol, 52%) as a brown oil.

R_f (20% EtOAc in pentane) 0.48.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.72 (4H, m, ArH), 7.35–7.25 (6H, m, ArH), 6.99–6.94 (2H, m, H12), 3.60 (2H, t, *J* = 7.4 Hz, H9), 3.31 (2H, t, *J* = 7.4 Hz, H4), 2.64 (2H, t, *J* = 7.4 Hz, H10), 2.44 (3H, s, CH_3), 2.41 (3H, s, CH_3), 1.54–1.47 (2H, m, H5), 1.31–1.21 (2H, m, H6), 0.86 (3H, t, *J* = 7.4 Hz, H7).

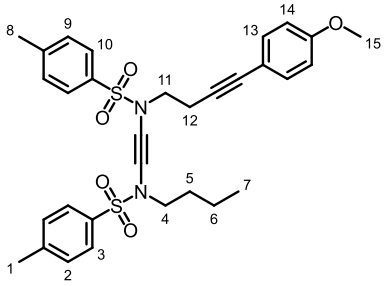
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^1J_{C-F}$ = 249.0 Hz), 144.8, 144.7, 135.1, 133.6 (d, $^3J_{C-F}$ = 8.3 Hz), 129.88, 129.86, 127.8, 127.7, 127.2, 119.4 (d, $^4J_{C-F}$ = 3.4 Hz), 115.6 (d, $^2J_{C-F}$ = 22.1 Hz), 85.1, 81.6, 70.0, 68.5, 51.6, 50.6, 30.0, 21.79, 21.77, 19.5, 19.3, 13.7.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.45.

HRMS (ES+) calc. for $C_{30}H_{32}O_4N_2S_2F$ ($[M+H]^+$) 567.1782, found 567.1782.

IR (thin film, ν_{max}/cm^{-1}) 2959, 2932, 1598, 1507, 1457, 1412, 1363, 1221, 1186, 1168, 1090.

82j ***N*-Butyl-*N*-(((*N*-(4-(4-methoxyphenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86d (0.365 g, 1.11 mmol, 1.0 equiv.), **S87a** (0.500 g, 1.22 mmol, 1.1 equiv.), CuI (42.3 mg, 0.22 mmol, 20 mol%), 1,10-phenanthroline (79.9 mg, 0.44 mmol, 40 mol%) and Cs_2CO_3 (1.08 g, 3.33 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (3.3 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (90.2 mg, 0.15 mmol, 14%) as a brown oil.

R_f (20% EtOAc in pentane) 0.36.

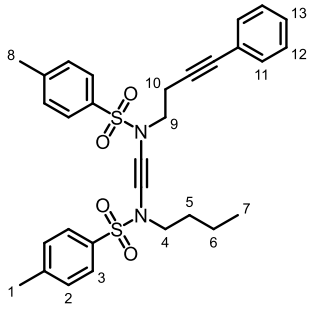
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.4 Hz, ArH), 7.72 (2H, d, *J* = 8.4 Hz, ArH), 7.31 (2H, dt, *J* = 7.9, 0.7 Hz, ArH), 7.29–7.25 (4H, m, ArH), 6.80 (2H, d, *J* = 8.8 Hz, H14), 3.80 (3H, s, H15), 3.59 (2H, dd, *J* = 7.9, 7.1 Hz, H11), 3.31 (2H, dd, *J* = 7.7, 6.8 Hz, H4), 2.62 (2H, dd, *J* = 7.9, 7.1 Hz, H12), 2.44 (3H, s, CH_3), 2.41 (3H, s, CH_3), 1.54–1.48 (2H, m, H5), 1.32–1.21 (2H, m, H6), 0.86 (3H, t, *J* = 7.4 Hz, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.5, 144.72, 144.66, 135.1, 135.0, 133.2, 129.88, 129.86, 127.81, 127.75, 115.5, 114.0, 83.8, 82.4, 69.9, 68.5, 55.4, 51.6, 50.7, 30.0, 21.81, 21.79, 19.5, 19.4, 13.7.

HRMS (ES^+) calc. for $C_{31}H_{34}O_5N_2NaS_2$ ($[M+Na]^+$) 601.1801, found 601.1799.

IR (thin film, ν_{max}/cm^{-1}) 2966, 1606, 1509, 1463, 1412, 1363, 1290, 1247, 1166, 1089, 1031.

82k ***N*-Butyl-4-methyl-*N*-(((4-methyl-*N*-(4-phenylbut-3-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide**



S86f (0.331 g, 1.11 mmol, 1.0 equiv.), **S87a** (0.500 g, 1.22 mmol, 1.1. equiv), CuI (42.3 mg, 0.22 mmol, 20 mol%), 1,10-phenanthroline (79.9 mg, 0.44 mmol, 40 mol%) and Cs_2CO_3 (1.08 g, 3.33 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (3.3 mL) for 44 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 15%) to give the title compound (0.291 g, 0.53 mmol, 48%) as a brown oil.

R_f (20% EtOAc in pentane) 0.67.

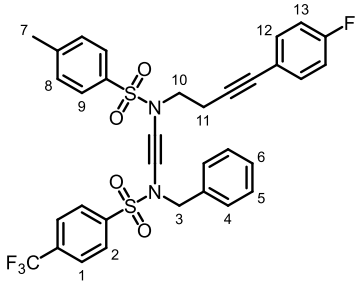
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.71 (4H, m, ArH), 7.35–7.30 (4H, m, ArH), 7.30–7.24 (5H, m, ArH), 3.61 (2H, dd, *J* = 7.9, 7.1 Hz, H9), 3.31 (2H, dd, *J* = 7.8, 6.7 Hz, H4), 2.64 (2H, dd, *J* = 7.9, 7.1 Hz, H10), 2.44 (3H, s, CH_3), 2.40 (3H, s, CH_3), 1.56–1.47 (2H, m, H5), 1.31–1.21 (2H, m, H6), 0.86 (3H, t, *J* = 7.4 Hz, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 144.7, 135.0, 131.8, 129.9 (3 C), 128.4, 128.1, 127.8, 127.7, 123.3, 85.4, 82.6, 69.9, 68.5, 51.6, 50.6, 30.0, 21.9, 21.8, 19.5, 19.4, 13.7.

HRMS (ES^+) calc. for $C_{30}H_{33}O_4N_2S_2$ ($[M+H]^+$) 549.1876, found 549.1876.

IR (thin film, ν_{max}/cm^{-1}) 2959, 2931, 1597, 1491, 1456, 1412, 1363, 1186, 1168, 1090.

82m ***N*-Benzyl-*N*-(((*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylphenyl)sulfonamido) ethynyl)-4-(trifluoromethyl)benzenesulfonamide**



88 (0.776 g, 1.55 mmol, 1.1 equiv.), **S3** (0.444 g, 1.41 mmol, 1.0 equiv.), CuI (53.7 mg, 0.28 mmol, 20 mol%), 1,10-phenanthroline (0.102 g, 0.56 mmol, 40 mol%) and Cs_2CO_3 (1.37 g, 4.23 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.2 mL) for 24 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (0.283 g, 0.43 mmol, 30%) as a brown oil.

R_f (EtOAc in pentane, 20%) 0.54.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87 (2H, d, *J* = 8.3 Hz, ArH), 7.69 (2H, d, *J* = 8.3 Hz, ArH), 7.64–7.60 (2H, m, ArH), 7.34–7.29 (2H, m, H12), 7.29–7.27 (1H, m, H6), 7.26–7.21 (4H, m, ArH), 7.17–7.14 (2H, m, ArH), 6.96 (2H, t, *J* = 8.7 Hz, H13), 4.55 (2H, s, H3), 3.55 (2H, t, *J* = 7.4 Hz, H10), 2.51 (2H, t, *J* = 7.4 Hz, H11), 2.41 (3H, s, H7).

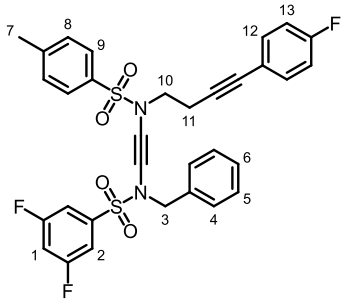
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.5 (d, $^1J_{C\text{-}F}$ = 249.2 Hz), 144.9, 141.4, 135.2 (q, $^2J_{C\text{-}F}$ = 33.2 Hz), 135.0, 134.2, 133.6 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.9, 128.9, 128.71, 128.65, 128.3, 127.7, 126.3 (q, $^4J_{C\text{-}F}$ = 3.6 Hz), 123.3 (q, $^1J_{C\text{-}F}$ = 273.0 Hz), 119.3 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 84.9, 81.7, 69.9, 69.7, 56.7, 50.4, 21.8, 19.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −63.17, −111.34.

HRMS (ES^+) calc. for $C_{33}H_{27}O_4N_2F_4S_2$ ($[M+H]^+$) 655.1343, found 655.1340.

IR (thin film, ν_{max}/cm^{-1}) 2928, 1600, 1508, 1407, 1369, 1323, 1230, 1171, 1134, 1109, 1091, 1063.

82n *N*-Benzyl-3,5-difluoro-*N*-(((*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)benzenesulfonamide



88 (0.776 g, 1.55 mmol, 1.1 equiv.), **S5** (0.400 g, 1.41 mmol, 1.0 equiv.), CuI (53.7 mg, 0.28 mmol, 20 mol%), 1,10-phenanthroline (0.102 g, 0.56 mmol, 40 mol%) and Cs_2CO_3 (1.37 g, 4.23 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.2 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.272 g, 0.44 mmol, 31%) as a brown oil.

R_f (EtOAc in pentane, 10%) 0.32.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.4 Hz, H9), 7.34–7.27 (6H, m, ArH), 7.26–7.22 (5H, m, ArH), 7.04 (1H, tt, *J* = 8.4, 2.3 Hz, H1), 6.96 (2H, t, *J* = 8.7 Hz, H13), 4.57 (2H, s, H3), 3.53 (2H, t, *J* = 7.4 Hz, H10), 2.50 (2H, t, *J* = 7.4 Hz, H11), 2.42 (3H, s, H7).

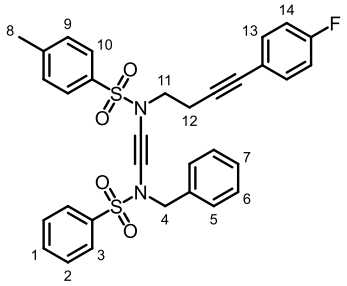
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.7 (dd, $^1J_{C\text{-}F}$ = 255.2, $^3J_{C\text{-}F}$ = 11.5 Hz), 162.5 (d, $^1J_{C\text{-}F}$ = 249.1 Hz), 145.0, 140.9 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 134.9, 134.1, 133.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 130.0, 129.0, 128.82, 128.77, 127.6, 119.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 111.6–111.2 (m), 109.3 (t, $^2J_{C\text{-}F}$ = 25.0 Hz), 84.9, 81.7, 69.9, 69.7, 56.9, 50.5, 21.8, 19.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −105.18, −111.41.

HRMS (ES^+) calc. for $C_{32}H_{26}O_4N_2F_3S_2$ ($[M+H]^+$) 623.1281, found 623.1278.

IR (thin film, ν_{max}/cm^{-1}) 3088, 2942, 1604, 1507, 1442, 1413, 1369, 1299, 1221, 1167, 1129, 1091.

82o *N*-((*N*-Benzylphenylsulfonamido)ethynyl)-*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide



S86c (0.241 g, 0.76 mmol, 1.0 equiv.), **S87a** (0.361 g, 0.84 mmol, 1.1 equiv.), CuI (29.0 mg, 0.15 mmol, 20 mol%), 1,10-phenanthroline (54.7 mg, 0.30 mmol, 40 mol%) and Cs_2CO_3 (0.741 g, 2.28 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (2.3 mL) for 21 h, with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) followed by recrystallisation from heptane/Et_2O (2:1) to give the title compound (0.120 g, 0.20 mmol, 27%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.44.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, dd, *J* = 8.5, 1.2 Hz, ArH), 7.65–7.60 (3H, m, ArH), 7.52–7.47 (2H, m, ArH), 7.34–7.30 (2H, m, ArH), 7.28–7.24 (3H, m, ArH), 7.23–7.20 (2H, m, ArH), 7.19–7.16 (2H, m, ArH), 6.97 (2H, t, *J* = 8.7 Hz, H14), 4.52 (2H, s, H4), 3.49 (2H, dd, *J* = 7.8, 7.0 Hz, H11), 2.45–2.40 (5H, m, H12 + H8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^1J_{C\text{-}F}$ = 248.8 Hz), 144.7, 137.9, 135.0, 134.6, 133.7, 133.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.8, 129.2, 128.9, 128.6, 128.4, 127.8, 127.7, 119.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 85.1, 81.5, 70.1, 69.4, 56.2, 50.4, 21.8, 19.1.

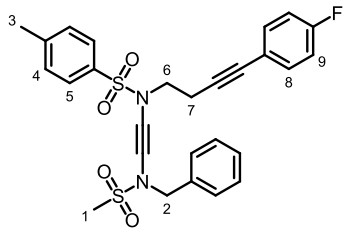
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.45.

HRMS (ES^+) calc. for $C_{32}H_{28}O_4N_2FS_2$ ($[M+H]^+$) 587.1469, found 587.1467.

IR (thin film, ν_{max}/cm^{-1}) 3000, 1600, 1507, 1448, 1413, 1366, 1221, 1170, 1090.

MP 83–87 °C.

82p *N*-((*N*-Benzylmethylsulfonamido)ethynyl)-*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide



S86c (0.250 g, 0.79 mmol, 1.0 equiv.), **S87g** (0.320 g, 0.87 mmol, 1.1 equiv.), CuI (30.1 mg, 0.16 mmol, 20 mol%), 1,10-phenanthroline (57.0 mg, 0.32 mmol, 40 mol%) and Cs_2CO_3 (0.770 g, 2.37 mmol, 3.0 equiv.) in anhydrous THF (2.4 mL) were used in **General Procedure 5** for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (83.5 mg, 0.16 mmol, 20%) as a brown oil which solidified on standing.

R_f (20% EtOAc in pentane) 0.47.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.3 Hz, H5), 7.42–7.37 (5H, m, ArH), 7.32 (2H, dd, *J* = 8.8, 5.4 Hz, H8), 7.27–7.23 (2H, m, H4), 6.97 (2H, t, *J* = 8.7 Hz, H9), 4.61 (2H, s, H2), 3.59 (2H, t, *J* = 7.4 Hz, H6), 2.77 (3H, s, H1), 2.62 (2H, t, *J* = 7.4 Hz, H7), 2.40 (3H, s, H3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.5 (d, $^1J_{C\text{-}F}$ = 248.8 Hz), 145.0, 135.0, 134.9, 133.7 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 130.0, 129.1, 129.0, 128.9, 127.8, 119.4, 115.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 85.1, 81.7, 70.1, 70.0, 56.4, 50.5, 39.0, 21.8, 19.4.

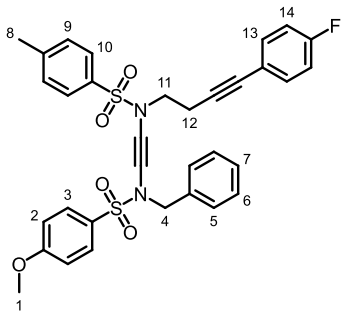
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.40.

HRMS (ES^+) calc. for $C_{27}H_{26}O_4N_2FS_2$ 525.1313, found 525.1313.

IR (solid, ν_{max}/cm^{-1}) 1600, 1508, 1358, 1341, 1156, 958, 837, 786, 730, 699, 664.

MP 87–91 °C.

82q *N*-Benzyl-*N*-(((*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methoxybenzenesulfonamide



S86c (68.9 mg, 0.22 mmol, 1.0 equiv.), **S87e** (0.110 g, 0.24 mmol, 1.10 equiv.), CuI (8.3 mg, 0.040 mmol, 20 mol%), 1,10-phenanthroline (15.6 mg, 0.080 mmol, 40 mol%) and Cs_2CO_3 (0.233 g, 0.65 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (0.7 mL) for 40 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 30%) to give the title compound (55.0 mg, 0.089 mmol, 41%) as a brown oil. *This compound was unstable and decomposed before ^{13}C and IR data could be obtained.*

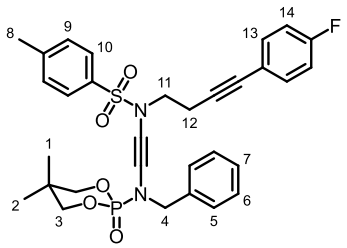
R_f (EtOAc in pentane, 20%) 0.55.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 9.0 Hz, ArH), 7.62 (2H, d, *J* = 8.4 Hz, ArH), 7.33–7.27 (5H, m, ArH), 7.24–7.20 (2H, m, ArH), 7.20–7.16 (2H, m, ArH), 6.98 (2H, d, *J* = 8.8 Hz, ArH), 6.93 (2H, d, *J* = 9.1 Hz, ArH), 4.50 (2H, s, H4), 3.86 (3H, s, H1), 3.48 (2H, dd, *J* = 7.9, 7.0 Hz, H11), 2.45–2.40 (5H, m, H12 + H8).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.47.

HRMS (ES^+) calc. for $C_{33}H_{30}O_5N_2FS_2$ ($[M+H]^+$) 617.1575, found 617.1572.

82r ***N*-((Benzyl(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)amino)ethynyl)-*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide**



88 (0.181 g, 0.71 mmol, 1.0 equiv.) and **S8** (0.388 g, 0.78 mmol, 1.0 equiv.), CuI (26.9 mg, 0.14 mmol, 20 mol%), 1,10-phenanthroline (50.8 mg, 0.28 mmol, 40 mol%) and Cs_2CO_3 (0.655 g, 2.13 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (2.1 mL) for 48 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20 to 50%) to give the title compound (0.124 g, 0.21 mmol, 29%) as a brown oil.

R_f (EtOAc in pentane, 50%) 0.43.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 (2H, d, *J* = 8.3 Hz, H10), 7.36–7.25 (7H, m, H5 + H6 + H7 + H13), 7.22–7.19 (2H, m, H9), 6.97 (2H, t, *J* = 8.7 Hz, H14), 4.42 (2H, d, *J* = 8.3 Hz, H4), 4.24 (2H, dd, *J* = 10.8, 9.1 Hz, H3), 4.14–4.03 (2H, m, H3), 3.50 (2H, t, *J* = 7.3 Hz, H11), 2.52 (2H, t, *J* = 7.3 Hz, H12), 2.41 (3H, s, H8), 1.14 (3H, s, CH_3), 0.90 (3H, s, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.4 (d, $^1J_{C\text{-}F}$ = 248.9 Hz), 144.5, 136.5, 134.9, 133.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.8, 128.7, 128.6, 128.1, 127.7, 119.4 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 85.3, 81.6, 79.0 (d, $^2J_{C\text{-}P}$ = 7.0 Hz), 72.7 (d, $^3J_{C\text{-}P}$ = 5.5 Hz), 63.9 (d, $^3J_{C\text{-}P}$ = 5.5 Hz), 55.7 (d, $^2J_{C\text{-}P}$ = 7.5 Hz), 50.4, 32.2 (d, $^3J_{C\text{-}P}$ = 7.0 Hz), 21.77, 21.76, 20.8, 19.2.

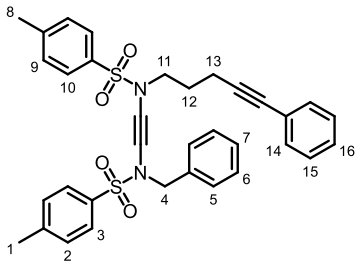
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.40.

^{31}P NMR (162 MHz, $CDCl_3$) δ_P −3.63.

HRMS ES^+ calc. for $C_{31}H_{33}O_5N_2FPS$ ($[M+H]^+$) 595.1826, found 595.1824.

IR (thin film, ν_{max}/cm^{-1}) 3000, 1736, 1598, 1509, 1362, 1291, 1244, 1170, 1045, 1011. *Note: the peak at 1736 cm^{-1} cannot be readily assigned to this structure.*

82s *N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(5-phenylpent-4-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide



S82s (0.500 g, 1.60 mmol, 1.0 equiv.), **S87b** (0.783 g, 1.76 mmol, 1.0 equiv.), CuI (61.0 mg, 0.32 mmol, 20 mol%), 1,10-phenanthroline (0.115 g, 0.64 mmol, 40 mol%) and Cs_2CO_3 (1.56 g, 4.80 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.8 mL) with purification by flash column chromatography to give the title compound (0.598 g, 0.10 mmol, 63%) as a brown oil.

R_f (CH_2Cl_2) 0.63.

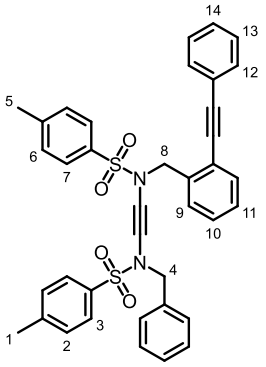
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.4 Hz, ArH), 7.63 (2H, d, *J* = 8.3 Hz, ArH), 7.39–7.36 (2H, m, ArH), 7.30–7.27 (5H, m, ArH), 7.26–7.24 (5H, m, ArH), 7.19–7.17 (2H, m, ArH), 4.50 (2H, s, H4), 3.38 (2H, t, *J* = 6.9 Hz, H11), 2.44 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.20 (2H, t, *J* = 6.9 Hz, H13), 1.62 (2H, app. p, *J* = 6.9 Hz, H12).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 144.6, 135.0, 134.9, 134.7, 131.7, 129.84, 129.81, 129.0, 128.6, 128.4, 128.4, 127.9, 127.8, 127.7, 123.8, 88.5, 81.6, 69.7, 69.5, 56.0, 50.6, 26.9, 21.80, 21.78, 16.4.

HRMS (ES^+) calc. for $C_{34}H_{33}O_4N_2S_2$ ($[M+H]^+$) 597.1876, found 597.1875.

IR (thin film, ν_{max}/cm^{-1}) 1597, 1491, 1412, 1364, 1168, 1090.

82t ***N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(2-(phenylethynyl)benzyl)phenyl) sulfonamido)ethynyl)benzenesulfonamide**



S82t (0.578 g, 1.60 mmol, 1.0 equiv.), **S87b** (0.780 g, 1.76 mmol, 1.1 equiv.), CuI (77.3 mg, 0.41 mmol, 20 mol%), 1,10-phenathroline (0.146 g, 0.82 mmol, 40 mol%) and Cs_2CO_3 (1.98 g, 6.09 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.8 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20% + 1% CH_2Cl_2) to give the title compound (0.348 g, 0.54 mmol, 34%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67–7.63 (2H, m, ArH), 7.56–7.52 (2H, m, ArH), 7.52–7.49 (2H, m, ArH), 7.47 (1H, dd, *J* = 7.6, 1.4 Hz, ArH), 7.38–7.33 (3H, m, ArH), 7.25–7.15 (8H, m, ArH), 7.13 (1H, dd, *J* = 7.6, 1.4 Hz, ArH), 7.08–7.05 (1H, m, ArH), 7.04–7.00 (2H, m, ArH), 4.72 (2H, s, CH_2), 4.38 (2H, s, CH_2), 2.43 (3H, s, CH_3), 2.40 (3H, s, CH_3).

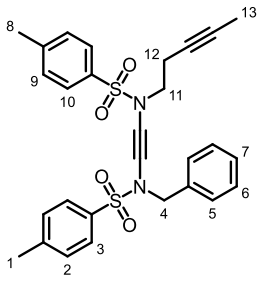
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.4, 136.1, 135.1, 134.83, 134.77, 132.3, 131.8, 129.8, 129.7, 128.8, 128.72, 128.65, 128.51 (2 C), 128.49, 128.1, 128.0, 127.9, 127.8, 123.2, 122.9, 94.8, 86.8, 70.2, 70.1, 56.1, 53.9, 21.81, 21.76.

HRMS (ES^+) calc. for $C_{38}H_{33}N_2O_4S_2$ ($[M+H]^+$) 645.1876, found 645.1871.

IR (solid, ν_{max}/cm^{-1}) 1597, 1493, 1454, 1413, 1358, 1166, 1087, 1020.

MP 104–106 °C.

82u ***N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(pent-3-yn-1-yl)phenyl)sulfonamido) ethynyl)benzenesulfonamide**



S86u (1.00 g, 4.22 mmol, 1.0 equiv.), **S87b** (2.05 g, 4.64 mmol, 1.1 equiv.), CuI (0.160 g, 0.84 mmol, 20 mol%), 1,10-phenanthroline (0.303 g, 1.68 mmol, 40 mol%) and Cs_2CO_3 (4.11 g, 12.7 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (12.6 mL) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (1.10 g, 2.12 mmol, 50%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.57.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.4 Hz, ArH), 7.62 (2H, d, *J* = 8.4 Hz, ArH), 7.30–7.26 (7H, m, ArH), 7.19–7.17 (2H, m, ArH), 4.50 (2H, s, H4), 3.33 (2H, dd, *J* = 8.3, 7.1 Hz, H11), 2.45 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.13–2.11 (2H, m, H12), 1.70 (3H, t, *J* = 2.6 Hz, H13).

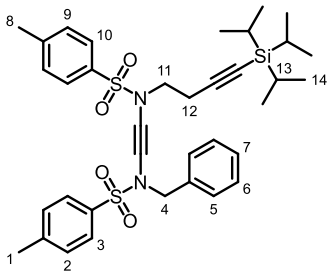
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 144.6, 135.1, 135.0, 134.7, 129.8 (2 C), 128.9, 128.6, 128.4, 127.8, 127.7, 77.8, 74.7, 69.9, 69.4, 56.1, 50.8, 21.8 (2 C), 18.4, 3.6.

HRMS (ES^+) calc. for $C_{28}H_{29}O_4N_2S_2$ ($[M+H]^+$) 521.1563, found 521.1562.

IR (thin film, ν_{max}/cm^{-1}) 2980, 1597, 1412, 1364, 1168, 1090.

MP 88–90 °C.

82v ***N*-Benzyl-4-methyl-*N*-(((4-methyl-*N*-(4-(triisopropylsilyl)but-3-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide**



S86v (0.500 g, 1.32 mmol, 1.0 equiv.), **S87b** (0.646 g, 1.45 mmol, 1.1 equiv.), CuI (50.3 mg, 0.26 mmol, 20 mol%), 1,10-phenanthroline (95.2 mg, 0.52 mmol, 40 mol%) and Cs_2CO_3 (1.29 g, 3.96 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (3.8 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.269 g, 0.41 mmol, 31%) as an orange oil.

R_f (EtOAc in pentane, 20%) 0.63.

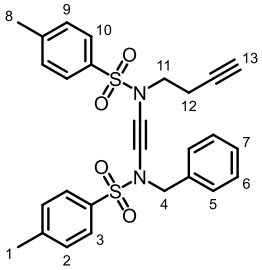
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69–7.65 (2H, m, ArH), 7.61 (2H, d, *J* = 8.4 Hz, ArH), 7.31–7.26 (7H, m, ArH), 7.19–7.15 (2H, m, ArH), 4.50 (2H, s, H4), 3.40–3.34 (2H, m, H11), 2.45 (6H, s, H1 + H8), 2.23–2.17 (2H, m, H12), 1.06–1.04 (21H, m, H13 + H14).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 144.7, 135.03, 135.00, 134.7, 129.9, 129.8, 128.9, 128.6, 128.4, 127.9, 127.7, 103.5, 83.0, 70.0, 69.4, 56.1, 50.6, 21.81, 21.80, 19.5, 18.7, 11.3.

HRMS (ES^+) calc. for $C_{36}H_{47}O_4N_2S_2Si$ ($[M+H]^+$), 663.2741, found 663.2727.

IR (thin film, ν_{max} /cm^{-1}) 2942, 2864, 1597, 1457, 1411, 1366, 1168, 1090.

82w ***N*-Benzyl-*N*-(((*N*-(but-3-yn-1-yl)-4-methylphenyl)sulfonamido)ethynyl)-4-methyl benzenesulfonamide**



82v (0.211 g, 0.32 mmol, 1.0 equiv.) was dissolved in THF (4.5 mL) and was treated with TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 30 minutes then concentrated *in vacuo* and the crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.116 g, 0.22 mmol, 69%) as a brown oil which solidified on standing.

R_f (EtOAc in pentane, 10%) 0.20.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.4 Hz, ArH), 7.55 (2H, d, *J* = 8.4 Hz, ArH), 7.25–7.17 (7H, m, ArH), 7.13–7.09 (2H, m, ArH), 4.43 (2H, s, H4), 3.31 (2H, dd, *J* = 8.3, 7.1 Hz, H11), 2.38 (6H, s, H1 + H8), 2.09 (2H, ddd, *J* = 8.3, 7.1, 2.7 Hz, H12), 1.81 (1H, t, *J* = 2.7 Hz, H13).

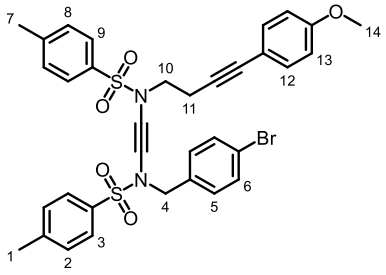
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8 (2 C), 135.0, 134.9, 134.7, 129.9, 129.8, 129.0, 128.6, 128.4, 127.9, 127.8, 79.8, 70.5, 70.1, 69.3, 56.0, 50.3, 21.8 (2 C), 18.1.

HRMS (ES^+) calc. for $C_{27}H_{26}O_4N_2NaS_2$ ($[M+Na]^+$) 529.1226, found 529.1224.

IR (thin film, ν_{max}/cm^{-1}) 2920, 2850, 1597, 1455, 1411, 1362, 1166, 1089.

MP 107–109 °C.

82x *N*-(4-Bromobenzyl)-*N*-(((*N*-(4-(4-methoxyphenyl)but-3-yn-1-yl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide



S86c (0.500 g, 1.52 mmol, 1.0 equiv.), **S87c** (0.876 g, 1.67 mmol, 1.1 equiv.), CuI (57.9 mg, 0.30 mmol, 20 mol%), 1,10-phenanthroline (0.110 g, 0.60 mmol, 40 mol%) and Cs_2CO_3 (1.48 g, 4.56 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.6 mL) for 18 h with purification by flash column chromatography (two columns, SiO_2, EtOAc in pentane, 0 to 30%, then CH_2Cl_2) to give the title compound (0.198 g, 0.29 mmol, 19%) as a yellow oil.

R_f (30% EtOAc in pentane) 0.48.

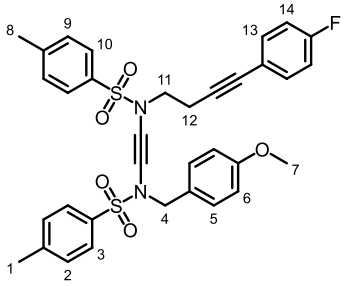
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.3 Hz, ArH), 7.56 (2H, d, *J* = 8.3 Hz, ArH), 7.31 (2H, d, *J* = 8.4 Hz, ArH), 7.24–7.20 (3H, m, ArH), 7.19–7.15 (3H, m, ArH), 6.99 (2H, d, *J* = 8.4 Hz, H6), 6.73 (2H, d, *J* = 8.8 Hz, H13), 4.38 (2H, s, H4), 3.73 (3H, s, H14), 3.45–3.40 (2H, m, H10), 2.40–2.36 (5H, m, CH_3 + H11), 2.34 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.5, 144.9, 144.8, 135.1, 134.9, 133.9, 133.2, 131.8, 130.5, 129.9 (2 C), 127.83, 127.79, 122.5, 115.5, 114.0, 83.7, 82.4, 70.1, 69.6, 55.5, 55.4, 50.6, 21.83, 21.81, 19.2.

HRMS (ES^+) calc. for $C_{34}H_{32}O_5N_2{}^{81}BrS_2$ ($[M+H]^+$) 693.0913, found 693.0903.

IR (thin film, ν_{max}/cm^{-1}) 2983, 1606, 1597, 1510, 1489, 1456, 1443, 1406, 1363, 1291, 1247, 1168, 1089, 1033, 1011.

82y ***N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-*N*-(((*N*-(4-methoxybenzyl)-4-methylphenyl) sulfonamido)ethynyl)-4-methylbenzenesulfonamide**



S86c (0.500 g, 1.58 mmol, 1.0 equiv.), **S87d** (0.822 g, 1.74 mmol, 1.1 equiv.), CuI (60.2 mg, 0.32 mmol, 20 mol%), 1,10-phenanthroline (0.114 g, 0.64 mmol, 40 mol%) and Cs_2CO_3 (1.54 g, 4.74 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (4.8 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.397 g, 0.63 mmol, 40%) as an orange oil.

R_f (20% EtOAc in pentane) 0.39.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.67 (2H, m, ArH), 7.65–7.62 (2H, m, ArH), 7.34–7.31 (2H, m, H13), 7.31–7.27 (2H, m, ArH) 7.24 (2H, dt, *J* = 8.0, 0.7 Hz, ArH), 7.12–7.09 (2H, m, H5), 7.00–6.94 (2H, m, H14), 6.80–6.76 (2H, m, H6), 4.43 (2H, s, H4), 3.77 (3H, s, H7), 3.48 (2H, dd, *J* = 7.9, 7.1 Hz, H11), 2.45–2.38 (8H, m, H1 + H8 + H12).

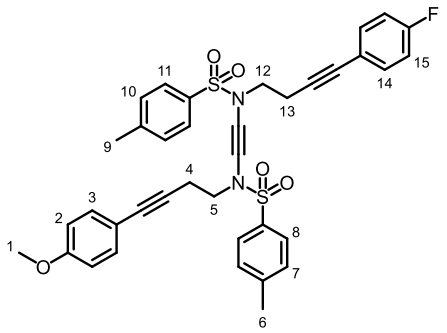
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^1J_{C\text{-}F}$ = 248.8 Hz), 159.8, 144.70, 144.68, 135.13, 135.08, 133.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 130.5, 129.84, 129.82, 127.8, 127.7, 126.8, 119.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 114.0, 85.2, 81.5, 70.2, 69.4, 55.6, 55.4, 50.5, 21.81, 21.79, 19.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.47.

HRMS (ES^+) calc. for $C_{34}H_{32}O_5N_2FS_2$ ($[M+H]^+$) 631.1731, found 631.1728.

IR (thin film, ν_{max}/cm^{-1}) 2982, 1612, 1598, 1507, 1455, 1411, 1362, 1305, 1249, 1221, 1167, 1090, 1033.

119 *N*-(4-(4-Fluorophenyl)but-3-yn-1-yl)-*N*-(((*N*-(4-(4-methoxyphenyl)but-3-yn-1-yl)-4-methylphenyl)sulfonamido)ethynyl)-4-methylbenzenesulfonamide



S86d (0.250 g, 0.76 mmol, 1.0 equiv.), **88** (0.421 g, 0.84 mmol, 1.1 equiv.), CuI (29.0 mg, 0.15 mmol, 20 mol%), 1,10-phenathroline (54.7 mg, 0.30 mmol, 40 mol%) and Cs_2CO_3 (0.741 g, 2.28 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (2.3 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (0.222 g, 0.33 mmol, 44%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.21.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.73 (4H, m, H8 + H11), 7.33–7.30 (2H, m, H14), 7.27–7.25 (6H, m, H7 + H10 + H3), 6.98–6.94 (2H, m, H15), 6.80–6.78 (2H, m, H2), 3.78 (3H, s, H1), 3.61–3.56 (4H, m, H5 + H12), 2.65–2.59 (4H, m, H4 + H13), 2.40 (6H, s, H6 + H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, J = 248.8 Hz, $^1J_{C\text{-}F}$), 159.5, 144.87, 144.85, 134.9 (d, J = 3.1 Hz, $^4J_{C\text{-}F}$), 133.6 (d, J = 8.3 Hz, $^3J_{C\text{-}F}$), 133.2, 129.9 (2 C), 127.8 (2 C), 119.39, 119.35, 115.6 (d, J = 22.1 Hz, $^2J_{C\text{-}F}$), 115.4, 114.0, 85.1, 83.8, 82.5, 81.6, 69.5, 69.3, 55.4, 50.7, 50.5, 21.8 (2 C), 19.4, 19.3.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.40.

HRMS (ES^+) calc. for $C_{37}H_{34}FN_2O_5S_2$ ($[M+H]^+$) 669.1888, found 669.1883.

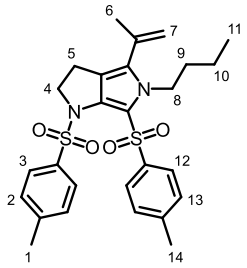
IR (thin film, ν_{max}/cm^{-1}) 1604, 1508, 1413, 1365, 1247, 1168, 1091, 1033.

7.3.3 Ynamides

Ynamides **98a**–**c** were prepared by Prof. Yubo Jiang, according to the procedure of Hsung and co-workers.[4]

7.3.4 Yndiamide cycloisomerisation products

84a 5-Butyl-4-(prop-1-en-2-yl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82a (20.0 mg, 0.038 mmol, 1.0 equiv.) and BHT (26.5 mg, 0.12 mmol, 3.0 equiv.) were dissolved in dry toluene (0.8 mL) with 3 Å molecular sieves. The reaction mixture was heated at 100 °C for 16 h then concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (9.5 mg, 0.018 mmol, 48%) as a brown oil.

R_f (EtOAc in pentane, 10%) 0.45

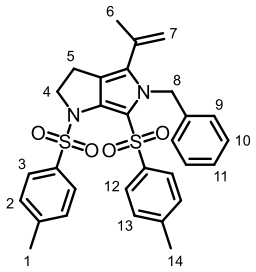
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.21–8.18 (2H, m, ArH), 7.82–7.78 (2H, m, ArH), 7.33–7.30 (2H, m, ArH), 7.25–7.22 (2H, m, ArH), 5.30–5.28 (1H, m, H7), 4.98 (1H, dq, *J* = 1.6, 0.9 Hz, H7), 4.12 (2H, t, *J* = 6.9 Hz, H4), 4.05–3.98 (2H, m, H8), 2.42 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.32 (2H, t, *J* = 6.9 Hz, H5), 1.91 (3H, dd, *J* = 1.6, 0.9 Hz, H6), 1.14–1.05 (2H, m, H9), 1.01–1.92 (2H, m, H10), 0.68 (3H, t, *J* = 7.2 Hz, H11).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.8, 140.1, 138.2, 135.8, 134.7, 133.8, 129.6, 129.5, 128.4, 128.3, 122.4, 119.3, 117.7, 59.7, 46.6, 33.7, 23.9, 23.2, 21.7 (2C), 19.9, 13.7.

HRMS (ES^+) calc. for $C_{27}H_{32}O_4N_2S_2Na$ 535.16957 $[M+Na]^+$, found 535.16952.

IR (thin film, ν_{max}/cm^{-1}) 2959, 1597, 1496, 1453, 1361, 1326, 1240, 1166, 1130, 1081, 1019.

84b 5-Benzyl-4-(prop-1-en-2-yl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82b (54.6 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** for 42 h, with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (37.6 mg, 0.069 mmol, 69%) as a cream solid.

82b (54.6 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (42.1 mg, 0.077 mmol, 77%) as a cream solid. *Crystals suitable for XRD were prepared by vapour diffusion of pentane into a concentrated solution of **84b** in Et_2O.*

R_f (EtOAc in pentane, 20%) 0.22.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (2H, d, *J* = 8.4 Hz, ArH), 7.80 (2H, d, *J* = 8.3 Hz, ArH), 7.25–7.22 (2H, m, ArH), 7.08–7.05 (3H, m, ArH), 6.99–6.96 (2H, m, ArH), 6.60–6.56 (2H, m, H9), 5.42 (2H, s, H8), 5.18 (1H, t, *J* = 1.5 Hz, H7), 4.92–4.90 (1H, m, H7), 4.20 (2H, t, *J* = 7.0 Hz, H4), 2.41 (3H, s, CH_3), 2.35 (2H, t, *J* = 7.0, H5), 2.25 (3H, s, CH_3), 1.72–1.71 (3H, m, H6).

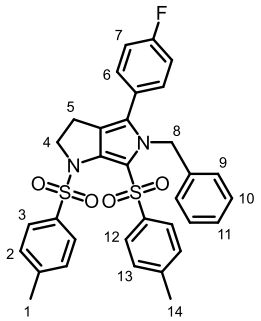
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.5, 138.8, 138.5, 138.1, 135.7, 134.37, 134.36, 129.5, 129.2, 128.32, 128.29, 128.1, 126.7, 125.5, 122.5, 119.5, 118.4, 59.7, 49.3, 23.9, 23.2, 21.8, 21.6.

HRMS (ES^+) calc. for $C_{30}H_{30}O_4N_2NaS_2$ ($[M+Na]^+$) 569.1539, found 569.1536.

IR (thin film, ν_{max}/cm^{-1}) 2950, 1597, 1496, 1454, 1361, 1326, 1168, 1129, 1081, 915.

MP 157 °C (decomposition).

84c 5-Benzyl-4-(4-fluorophenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82c (60.2 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (42.6 mg, 0.071 mmol, 71%) as a cream solid.

82c (60.2 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (54.3 mg, 0.091 mmol, 91%) as a cream solid.

1.0 mmol scale reactions

82c (0.602 g, 1.0 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (73.9 mg, 0.10 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 30%) to give the title compound (0.430 g, 0.72 mmol, 72%) as a cream solid.

82c (0.602 g, 1.0 mmol, 1.0 equiv.) and BHT (0.220 g, 1.0 mmol, 1.0 equiv.) were dissolved in anhydrous toluene (20 mL) and heated at 110 °C for 18 h in a flask equipped with a reflux condenser then concentrated *in vacuo* and purified by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 30%), with purification of later fractions by recrystalisation ($CHCl_3$/pentane) to give the title compound (0.456 g, 0.76 mmol, 76%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.20.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.98–7.94 (2H, m, ArH), 7.87–7.83 (2H, m, ArH), 7.26 (2H, d, J = 8.1 Hz, ArH), 7.08–7.03 (3H, m, ArH), 7.02–6.95 (6H, m, ArH), 6.48–6.44 (2H, m, H9), 5.34 (2H, s, H8), 4.22 (2H, t, J = 7.0 Hz, H4), 2.43 (3H, s, CH_3), 2.37 (2H, t, J = 7.0 Hz, H5), 2.27 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.9 (d, $^1J_{C\text{-}F}$ = 249.7 Hz), 144.2, 143.6, 138.8, 138.7, 137.7, 135.8, 132.5, 131.3 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.5, 129.3, 128.4, 128.3, 128.2, 126.8, 126.3 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 125.5, 123.7, 118.9, 116.0 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 59.8, 49.3, 23.5, 21.8, 21.6.

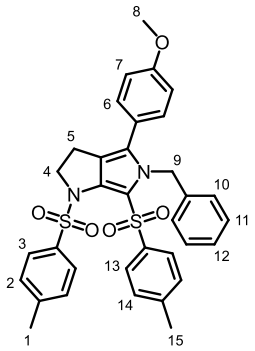
^{19}F NMR (377 MHz, $CDCl_3$): δ_F −111.68.

HRMS (ES^+) calc. for $C_{33}H_{30}FN_2O_4S_2$ ($[M+H]^+$) 601.1626, found 601.1625.

IR (thin film, ν_{max}/cm^{-1}) 3050, 1596, 1495, 1453, 1323, 1227, 1151, 1082.

MP 86–90 °C.

84d 5-Benzyl-4-(4-methoxyphenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82d (61.2 mg, 0.10 mmol, 1.0 equiv) and $Ph_3PAuNTf_2$ (7.4 mg, 0.10 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (16.3 mg, 0.027 mmol, 27%) as a cream solid.

82d (61.2 mg, 0.10 mmol, 1.0 equiv) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv) used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (56.0 mg, 0.092 mmol, 92%) as a cream solid.

R_f (EtOAc in pentane, 30%) 0.40.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (2H, d, *J* = 8.4 Hz, ArH), 7.83 (2H, d, *J* = 8.4 Hz, ArH), 7.27–7.24 (2H, m, ArH), 7.05–6.96 (7H, m, ArH), 6.82–6.79 (2H, m, H7), 6.49–6.45 (2H, m, H10), 5.36 (2H, s, H9), 4.23 (2H, d, *J* = 7.0 Hz, H4), 3.77 (3H, s, H8), 2.43 (3H, s, CH_3), 2.34 (2H, t, *J* = 7.0 Hz, H5), 2.26 (3H, s, CH_3).

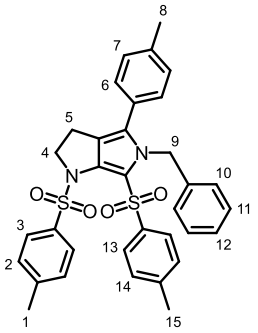
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 160.0, 144.2, 143.4, 139.0, 138.9, 138.0, 135.8, 133.7, 130.8, 129.5, 129.2, 128.4, 128.2, 128.1, 126.6, 125.5, 123.2, 122.5, 118.3, 114.3, 59.8, 55.4, 49.3, 23.5, 21.8, 21.6.

HRMS (ES^+) calc. for $C_{34}H_{33}N_2O_5S_2$ ($[M+H]^+$) 613.1825, found 613.1822.

IR (solid, ν_{max}/cm^{-1}) 2981, 1596, 1520, 1494, 1453, 1360, 1321, 1305, 1292, 1250, 1167, 1150, 1124, 1081, 1045, 1022.

MP 96–100 °C.

84e 5-Benzyl-4-(*p*-tolyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82e (59.6 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.10 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (21.3 mg, 0.036 mmol, 36%) as a cream foam.

82e (59.6 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (37.8 mg, 0.063 mmol, 63%) as a cream foam.

R_f (EtOAc in pentane, 20%) 0.20.

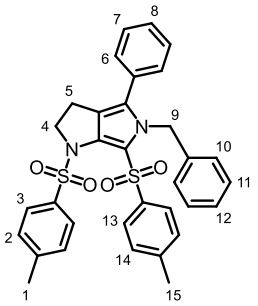
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (2H, d, *J* = 8.4 Hz, ArH), 7.83 (2H, d, *J* = 8.3 Hz, ArH), 7.25 (2H, d, *J* = 7.2 Hz, ArH), 7.10–7.08 (2H, m, ArH), 7.04–6.96 (7H, m, ArH), 6.49–6.46 (2H, m, H10), 5.38 (2H, s, H9), 4.22 (2H, t, *J* = 7.0 Hz, H4), 2.43 (3H, s, CH_3), 2.35 (2H, t, *J* = 7.0 Hz, H5), 2.31 (3H, s, H8), 2.26 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.4, 139.0, 138.9, 138.0, 135.9, 133.9, 129.6, 129.5, 129.3, 129.2, 128.4, 128.21, 128.15, 127.4, 126.6, 125.6, 123.4, 118.5, 59.8, 49.3, 23.5, 21.8, 21.6, 21.4. *One aromatic carbon not found due to overlap.*

HRMS (ES^+) calc. for $C_{34}H_{33}O_4N_2S_2$ ($[M+H]^+$) 597.1876, found 597.1873.

IR (thin film, ν_{max}/cm^{-1}) 1596, 1496, 1455, 1362, 1169, 1152, 1083.

84f 5-Benzyl-4-phenyl-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82f (58.2 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.10 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (34.2 mg, 0.059 mmol, 59%) as a cream solid.

82f (58.2 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (55.4 mg, 0.095 mmol, 95%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.17.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 (2H, d, *J* = 8.4 Hz, ArH), 7.83 (2H, d, *J* = 8.3 Hz, ArH), 7.31–7.24 (5H, m, ArH), 7.12–7.08 (2H, m, ArH), 7.05–7.02 (1H, m, H12), 6.99 (4H, dt, *J* = 8.8, 3.1 Hz, ArH), 6.49–6.45 (2H, m, H10), 5.39 (2H, s, H9), 4.23 (2H, t, *J* = 7.0 Hz, H4), 2.43 (3H, s, CH_3), 2.36 (2H, t, *J* = 7.0 Hz, H5), 2.27 (3H, s, CH_3).

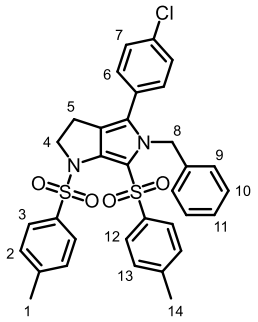
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.5, 139.0, 138.8, 137.8, 135.6, 133.7, 130.2, 129.5, 129.4, 129.2, 128.84, 128.79, 128.3, 128.2, 128.1, 126.7, 125.5, 123.6, 118.8, 59.8, 49.4, 23.4, 21.8, 21.6.

HRMS (ES^+) calc. for $C_{33}H_{31}O_4N_2S_2$ ($[M+H]^+$) 583.1720, found 583.1719.

IR (thin film, ν_{max}/cm^{-1}) 2924, 2854, 1597, 1496, 1453, 1362, 1326, 1170.

M.P 103–107 °C.

84g 5-Benzyl-4-(4-chlorophenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82g (61.6 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (40.9 mg, 0.066 mmol, 66%) as a colourless solid.

82g (30.8 mg, 0.050 mmol, 1.0 equiv.) and BHT (11.0 mg, 0.050 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (28.0 mg, 0.045 mmol, 91%) as a colourless solid.

R_f (EtOAc in pentane, 20%) 0.20.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 (2H, d, *J* = 8.4 Hz, ArH), 7.85 (2H, d, *J* = 8.3 Hz, ArH), 7.28–7.23 (4H, m, ArH), 7.06–6.98 (7H, m, ArH), 6.48–6.44 (2H, m, H9), 5.35 (2H, s, H8), 4.22 (2H, t, *J* = 6.9 Hz, H4), 2.43 (3H, s, CH_3), 2.37 (2H, t, *J* = 6.9 Hz, H5), 2.26 (3H, s, CH_3).

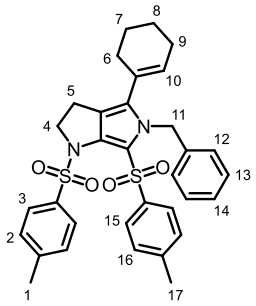
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 143.7, 138.8, 138.6, 137.6, 135.8, 135.1, 132.3, 130.7, 129.6, 129.3, 129.1, 128.7, 128.4, 128.3, 128.2, 126.8, 125.4, 123.9, 119.2, 59.7, 49.4, 23.5, 21.8, 21.6.

HRMS (ES^+) calc. for $C_{33}H_{30}{}^{35}ClN_2O_4S_2$ ($[M+H]^+$) 617.1330, found 617.1328.

IR (thin film, ν_{max}/cm^{-1}) 3029, 1597, 1485, 1452, 1361, 1323, 1166, 1125, 1090, 1013.

MP 166–170 °C.

84h 5-Benzyl-4-(cyclohex-1-en-1-yl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82h (58.6 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** for 18 h with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (18.0 mg, 0.031 mmol, 31%) as a yellow solid.

R_f (EtOAc in pentane, 20%) 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 (2H, d, *J* = 8.4 Hz, ArH), 7.79 (2H, d, *J* = 8.3 Hz, ArH), 7.22 (2H, d, *J* = 7.8 Hz, ArH), 7.09–7.07 (3H, m, H13 + H14), 7.02 (2H, d, *J* = 7.8 Hz, ArH),

6.65–6.58 (2H, m, H12), 5.68 (1H, tt, *J* = 3.8, 1.8 Hz, H10), 5.34 (2H, s, H11), 4.18 (2H, t, *J* = 7.0 Hz, H4), 2.40 (3H, s, CH_3), 2.30–2.36 (5H, m, H5 + CH_3), 2.05–2.00 (2H, m, H9), 1.72 (2H, dd, *J* = 4.5, 2.4 Hz, H6), 1.50–1.44 (4H, m, H7 + H8).

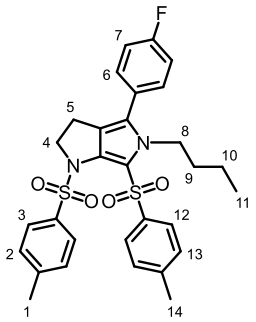
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 143.3, 139.3, 138.7, 138.3, 135.8, 135.6, 131.9, 129.4, 129.2, 128.4, 128.33, 128.26, 128.1, 126.8, 126.0, 122.0, 117.5, 59.7, 49.5, 28.7, 25.5, 23.6, 22.5, 21.8, 21.6, 21.5.

HRMS (ES^+) calc. for $C_{33}H_{35}O_4N_2S_2$ ($[M+H]^+$) 587.2033, found 587.2030.

IR (solid, ν_{max}/cm^{-1}) 2923, 1597, 1495, 1453, 1361, 1323, 1296, 1165, 1148, 1123, 1081.

MP 87–91 °C.

84i 5-Butyl-4-(4-fluorophenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82i (56.6 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (22.1 mg, 0.039 mmol, 39%) as a pale brown foam.

82i (56.6 mg, 0.10 mmol, 1.0 equiv.) and BHT (2.3 mg, 0.010 mmol, 10 mol%) used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc: pentane, 0 to 20%) to give the title compound (35.9 mg, 0.063 mmol, 63%) as a pale brown foam.

R_f (EtOAc in pentane, 20%) 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (2H, d, *J* = 8.4 Hz, ArH), 7.85 (2H, d, *J* = 8.3 Hz, ArH), 7.35–7.31 (2H, m, ArH), 7.29–7.25 (2H, m, ArH), 7.18 (2H, dd, *J* = 8.7, 5.3 Hz, H6), 7.09 (2H, t, *J* = 8.7 Hz, H7), 4.14 (2H, t, *J* = 6.9 Hz, H4), 4.03–3.98 (2H, m, H8), 2.42 (6H, overlapping s, 2 × CH_3), 2.33 (2H, t, *J* = 6.9 Hz, H5), 0.94–0.84 (2H, m, H9), 0.81–0.73 (2H, m, H10), 0.50 (3H, t, *J* = 7.2 Hz, H11).

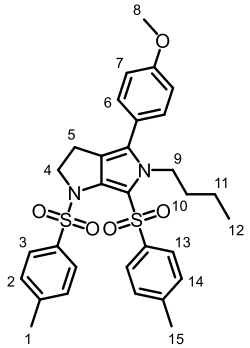
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.8 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 144.2, 144.0, 139.9, 138.5, 135.8, 131.7, 131.3 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.6, 129.5, 128.4, 128.3, 126.7 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 123.5, 118.3, 116.1 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 59.8, 46.4, 33.2, 23.4, 21.8, 21.7, 19.7, 13.4.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.86.

HRMS (ES^+) calc. for $C_{30}H_{32}O_4N_2S_2F$ ($[M+H]^+$) 567.1782, found 567.1782.

IR (thin film, ν_{max}/cm^{-1}) 2960, 2930, 1597, 1506, 1494, 1451, 1358, 1325, 1224, 1158, 1132, 1089.

84j 5-Butyl-4-(4-methoxyphenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82j (57.8 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 30%) to give the title compound (15.9 mg, 0.028 mmol, 28%) as a cream foam.

R_f (EtOAc in pentane, 20%) 0.29.

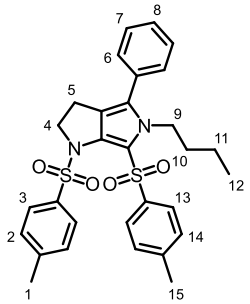
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (2H, d, *J* = 8.4 Hz, ArH), 7.84 (2H, d, *J* = 8.3 Hz, ArH), 7.34–7.31 (2H, m, ArH), 7.28–7.25 (2H, m, ArH), 7.12 (2H, d, *J* = 8.8 Hz, H6), 6.91 (2H, d, *J* = 8.8 Hz, H7), 4.14 (2H, t, *J* = 6.9 Hz, H4), 4.06–3.98 (2H, m, H9), 3.82 (3H, s, H8), 2.43 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.30 (2H, t, *J* = 6.9 Hz, H5), 0.91 (2H, tdd, *J* = 7.8, 6.3, 3.9 Hz, H10), 0.82–0.72 (2H, m, H11), 0.50 (3H, t, *J* = 7.3 Hz, H12).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.9, 144.1, 143.8, 140.2, 138.6, 135.9, 132.9, 130.7, 129.6, 129.5, 128.4, 128.3, 123.03, 122.96, 117.7, 114.3, 59.8, 55.5, 46.4, 33.2, 23.4, 21.8, 21.7, 19.7, 13.5.

HRMS (ES^+) calc. for $C_{31}H_{35}O_5N_2S_2$ ($[M+H]^+$) 579.1982, found 579.1976.

IR (thin film, ν_{max}/cm^{-1}) 2959, 2930, 1613, 1596, 1520, 1494, 1453, 1360, 1324, 1304, 1290, 1250, 1164, 1132, 1082, 1025.

84k 5-Butyl-4-phenyl-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82k (54.8 mg, 0.10 mmol, 1.0 equiv.) and BHT (66.0 mg, 0.3 mmol, 3.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%), to give the title compound (38.8 mg, 0.071 mmol, 71%) as a brown oil.

R_f (EtOAc in pentane, 20%) 0.35.

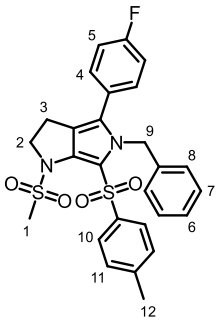
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.23 (2H, d, *J* = 8.4 Hz, ArH), 7.84 (2H, d, *J* = 8.3 Hz, ArH), 7.38 (3H, tdt, *J* = 7.0, 5.3, 1.8 Hz, ArH), 7.33 (2H, d, *J* = 7.7 Hz, ArH), 7.29–7.25 (2H, m, ArH), 7.21–7.18 (2H, m, ArH), 4.15 (2H, t, *J* = 6.9 Hz, H4), 4.08–4.03 (2H, m, H9), 2.43 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.31 (2H, t, *J* = 6.9 Hz, H5), 0.96–0.98 (2H, m, H10), 0.81–0.72 (2H, m, H11), 0.49 (3H, t, *J* = 7.3 Hz, H12).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.9, 140.0, 138.5, 135.8, 132.9, 130.7, 129.6, 129.5, 129.4, 128.9, 128.7, 128.4, 128.3, 123.4, 118.1, 59.8, 46.4, 33.2, 23.4, 21.8, 21.7, 19.6, 13.4.

HRMS (ES^+) calc. for $C_{30}H_{33}O_4N_2S_2$ ($[M+H]^+$) 549.1876, found 549.1875.

IR (thin film, ν_{max}/cm^{-1}) 2150, 1596, 1519, 1494, 1447, 1360, 1322, 1293, 1226, 1151, 1126, 1080.

84l 5-Benzyl-4-(4-fluorophenyl)-1-(methylsulfonyl)-6-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82l (52.4 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (phosphate buffered SiO_2, CH_2Cl_2) to give the title compound (37.9 mg, 0.072 mmol, 72%) as a yellow oil.

82l (32.5 mg, 0.060 mmol, 1.0 equiv.) and BHT (13.2 mg, 0.060 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 20%) to give the title compound (22.5 mg, 0.043 mmol, 72%) as a yellow oil.

R_f (CH_2Cl_2) 0.47.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.86–7.83 (2H, m, H11), 7.16–7.11 (2H, m, H4), 7.00–6.97 (2H, m, H5), 6.96–6.89 (5H, m, H11 + H7 + H6), 6.37–6.33 (2H, m, H8), 5.20 (2H, s, H9), 4.51 (2H, t, *J* = 7.1 Hz, H2), 3.41 (3H, s, H1), 2.83 (2H, t, *J* = 7.1 Hz, H3), 2.23 (3H, s, H12).

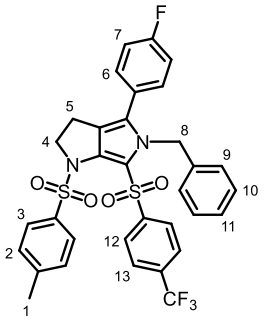
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.0 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 143.6, 139.5, 138.6, 137.5, 132.7, 131.3 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.3, 128.2, 127.7, 126.5, 126.3 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 125.2, 122.2, 116.1, 116.0 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 59.6, 49.0, 42.8, 24.4, 21.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.73.

HRMS (ES^+) calc. for $C_{27}H_{26}O_4N_2FS_2$ ($[M+H]^+$) 525.1313, found 525.1314.

IR (thin film, ν_{max}/cm^{-1}) 2970, 1607, 1597, 1521, 1495, 1453, 1361, 1326, 1295, 1227, 1186, 1153, 1127, 1082.

84m 5-Benzyl-4-(4-fluorophenyl)-1-tosyl-6-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82m (65.4 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** for 24 h, with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (38.4 mg, 0.059 mmol, 59%) as a cream solid.

82m (65.4 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 10%) to give the title compound (46.1 mg, 0.070 mmol, 70%) as a cream solid.

R_f (20% EtOAc in pentane) 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.14–8.11 (2H, m, H12), 7.89–7.86 (2H, m, H3), 7.40–7.37 (2H, m, ArH, H2), 7.32–7.29 (2H, m, H13), 7.18–7.14 (2H, m, H6), 7.08–6.93 (5H, m, H7 + H10 + H11), 6.44–6.41 (2H, m, H9), 5.35 (2H, s, H8), 4.26 (2H, t, J = 7.0 Hz, H4), 2.50 (2H, t, J = 7.0 Hz, H5), 2.44 (3H, s, H1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.1 (d, $^1J_{C\text{-}F}$ = 250.3 Hz), 144.9, 144.5, 140.3, 137.3, 135.8, 134.0 (q, $^2J_{C\text{-}F}$ = 32.7 Hz), 133.8, 131.4 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.7, 128.5, 128.4, 128.3, 127.4, 125.9 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 125.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 125.1, 123.8, 123.3 (q, $^1J_{C\text{-}F}$ = 272.9 Hz), 116.8, 116.2 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 59.7, 49.2, 23.6, 21.8.

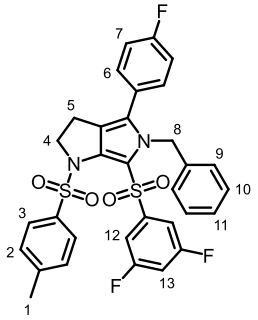
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −63.28, −111.07.

HRMS (ES^+) calc. for $C_{33}H_{27}O_4N_2F_4S_2$ ($[M+H]^+$) 655.1343, found 655.1340.

IR (thin film, ν_{max}/cm^{-1}) 2963, 2927, 1597, 1518, 1495, 1452, 1360, 1308, 1226, 1163, 1132, 1090.

MP 87–91 °C.

84n 5-Benzyl-6-((3,5-difluorophenyl)sulfonyl)-4-(4-fluorophenyl)-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82n (62.2 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 1.0 equiv.) were used in **General Procedure 6** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (28.1 mg, 0.045 mmol, 45%) as a pale cream foam.

82n (62.2 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (50.3 mg, 0.081 mmol, 81%) as a pale cream solid.

R_f (20% EtOAc in pentane) 0.24.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.87 (2H, d, J = 8.3 Hz, H3), 7.61–7.57 (2H, m, H12), 7.31 (2H, d, J = 8.3 Hz, H2), 7.15 (2H, dd, J = 8.7, 5.3 Hz, H6), 7.11–7.05 (3H, m, H10 + H11), 7.02 (2H, t, J = 8.7 Hz, H7), 6.68 (1H, tt, J = 8.5, 2.4 Hz, H13), 6.54–6.51 (2H, m, H9), 5.35 (2H, s, H8), 4.26 (2H, t, J = 7.0 Hz, H4), 2.49 (2H, t, J = 7.0 Hz, H5), 2.45 (3H, s, H1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.1 (d, $^1J_{C\text{-}F}$ = 250.3 Hz), 162.3 (dd, $^1J_{C\text{-}F}$ = 253.4 Hz, $^3J_{C\text{-}F}$ =11.5 Hz), 144.9 (t, $^3J_{C\text{-}F}$ = 8.4 Hz), 144.5, 140.3, 137.3, 135.7, 133.9, 131.4 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.7, 128.5, 128.3, 127.5, 125.9 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 125.1, 123.8, 116.5, 116.2 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 111.7–111.5 (m), 108.2 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 59.7, 49.2, 23.6, 21.8.

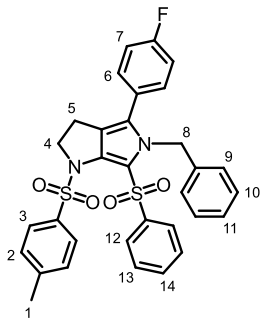
^{19}F NMR (470 MHz, $CDCl_3$) δ_F −106.47, −111.00.

HRMS (ES^+) calc. for $C_{32}H_{26}O_4N_2F_3S_2$ ($[M+H]^+$) 623.1281, found 623.1277.

IR (solid, ν_{max}/cm^{-1}) 1606, 1597, 1453, 1440, 1329, 1295, 1166, 1123.

MP 80–84 °C.

84o 5-Benzyl-4-(4-fluorophenyl)-6-(phenylsulfonyl)-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82o (58.6 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (46.3 mg, 0.079 mmol, 79%) as a cream solid.

82o (58.6 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (46.7 mg, 0.080 mmol, 80%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.25.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.10–8.07 (2H, m, ArH), 7.85–7.81 (2H, m, ArH), 7.37–7.32 (1H, m, ArH), 7.28–7.21 (4H, m, ArH), 7.09–6.95 (7H, m, ArH), 6.47 (2H, dd, *J* = 7.9, 1.6 Hz,

H9), 5.35 (2H, s, H8), 4.22 (2H, t, *J* = 7.0 Hz, H4), 2.43 (3H, s, H1), 2.36 (2H, t, *J* = 7.0 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.0 (d, $^1J_{C-F}$ = 249.9 Hz), 144.4, 141.7, 139.1, 137.6, 135.7, 132.9, 132.8, 131.3 (d, $^3J_{C-F}$ = 8.3 Hz), 129.6, 128.6, 128.4, 128.3, 128.1, 127.1, 126.3 (d, $^4J_{C-F}$ = 3.6 Hz), 125.5, 123.8, 118.5, 116.0 (d, $^2J_{C-F}$ = 21.7 Hz), 59.7, 49.4, 23.4, 21.8.

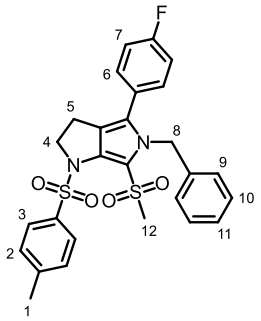
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.56.

HRMS (ES^+) calc. for $C_{32}H_{28}O_4N_2FS_2$ 587.1469 ($[M+H]^+$), found 587.1467.

IR (solid, ν_{max}/cm^{-1}) 2985, 2150, 1596, 1519, 1494, 1447, 1360, 1322, 1293, 1226, 1151, 1126, 1080.

MP 128–132 °C.

84p 5-Benzyl-4-(4-fluorophenyl)-6-(methylsulfonyl)-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82p (52.4 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (13.3 mg, 0.025 mmol, 25%) as a brown oil.

R_f (EtOAc in pentane, 20%) 0.15.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.3 Hz, H3), 7.38–7.31 (4H, m, ArH), 7.29 (1H, d, *J* = 7.6 Hz, H11), 7.24–7.19 (2H, m, ArH), 7.13–7.05 (2H, m, ArH), 6.98–6.93 (2H, m,

ArH), 5.49 (2H, s, H8), 4.22 (2H, t, *J* = 7.1 Hz, H4), 2.70 (3H, s, H12), 2.48 (3H, s, H1), 2.41–2.35 (2H, m, H5).

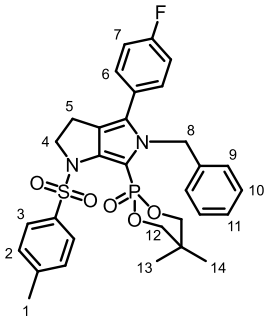
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 138.7, 138.6, 135.4, 132.3, 131.5 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.6, 129.1, 128.3, 128.1, 126.4, 126.3, 122.6, 117.5, 116.3 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 59.1, 49.5, 43.5, 23.4, 21.9. ***C**-F peak not found. Sample decomposed before higher resolution ^{13}C spectrum could be obtained.*

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.37.

HRMS (ES^+) $C_{27}H_{26}O_4N_2FS_2$ ($[M+H]^+$) 525.1313, found 525.1312.

IR (thin film, ν_{max}/cm^{-1}) 2361, 2342, 1596, 1522, 1508, 1496, 1455, 1358, 1318, 1227, 1167, 1148, 1118.

84r 2-(5-Benzyl-4-(4-fluorophenyl)-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrol-6-yl)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide



82r (59.4 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 40%) followed by trituration with pentane to give the title compound (25.5 mg, 0.043 mmol, 43%) as a cream solid. *Crystals suitable for XRD analysis were grown by vapour diffusion of pentane into a concentrated solution of **84p** in EtOAc + 1% MeOH.*

R_f (50% EtOAc in pentane) 0.21.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 (2H, d, *J* = 8.3 Hz, H3), 7.22–7.18 (3H, m, ArH), 7.09–7.04 (2H, m, H2), 7.02–6.91 (6H, m, ArH), 5.38 (2H, s, H8), 4.20 (2H, t, *J* = 7.1 Hz, H4), 3.97 (2H, dd, *J* = 10.6, 3.7 Hz, H12), 3.94–3.82 (2H, m, H12), 2.38 (3H, s, H1), 1.88 (2H, t, *J* = 7.1 Hz, H5), 1.36 (3H, s, CH_3), 0.80 (3H, s, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.7 (d, $^{1}J_{C\text{-}F}$ = 249.2 Hz), 144.2, 141.3 (d, $^{1}J_{C\text{-}P}$ = 11.8 Hz), 138.0, 131.9 (d, $^{3}J_{C\text{-}P}$ = 9.0 Hz), 131.0 (d, $^{4}J_{C\text{-}P}$ = 8.2 Hz), 129.3, 128.6, 128.4, 127.5, 127.3 (d, $^{4}J_{C\text{-}F}$ = 2.8 Hz), 127.2, 123.6 (d, $^{2}J_{C\text{-}P}$ = 10.9 Hz), 115.9 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 110.2, 108.4, 77.2 (d, $J_{C\text{-}P}$ = 6.9 Hz), 59.1, 51.2, 32.5 (d, $J_{C\text{-}P}$ = 7.1 Hz), 22.8, 22.6, 21.8, 21.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −112.39.

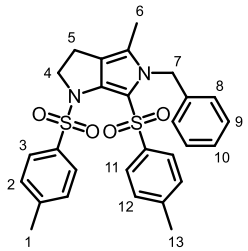
^{31}P NMR (162 MHz, $CDCl_3$) δ_P 0.27.

HRMS (ES^+) calc. for $C_{31}H_{33}O_5N_2FPS$ ($[M+H]^+$) 595.1826, found 595.1825.

IR (thin film, ν_{max}/cm^{-1}) 2958, 1596, 1522, 1496, 1453, 1404, 1357, 1277, 1225, 1167, 1090, 1059, 1007.

MP 176–180 °C.

84u 5-Benzyl-4-methyl-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** for 42 h, with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (34.8 mg, 0.067 mmol, 67%) as a brown oil.

R_f (CH_2Cl_2) 0.17.

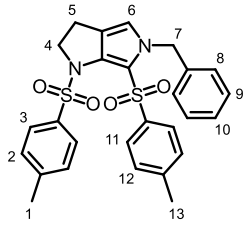
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97–7.93 (2H, m, ArH), 7.83–7.79 (2H, m, ArH), 7.24–7.27 (2H, m, ArH), 7.09–7.13 (3H, m, H9 + H10), 7.02–6.99 (2H, m, ArH), 6.63–6.60 (2H, m, H8), 5.32 (2H, s, H7), 4.21 (2H, t, *J* = 6.9 Hz, H4), 2.42 (3H, s, CH_3), 2.36 (2H, t, *J* = 6.9 Hz, H5), 2.25 (3H, s, CH_3), 1.94 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.3, 139.5, 137.9, 137.1, 136.0, 129.5, 129.2, 128.8, 128.5, 128.3, 127.9, 126.9, 125.4, 121.9, 117.1, 59.8, 48.6, 23.2, 21.8, 21.5, 11.5.

HRMS (ES^+) calc. for $C_{28}H_{29}O_4N_2S_2$ 521.1563 ($[M+H]^+$), found 521.1561.

IR (thin film, ν_{max}/cm^{-1}) 2981, 1598, 1497, 1454, 1339, 1167, 11421, 1083.

84w 5-Benzyl-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82w (50.6 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (11.0 mg, 0.022 mmol, 22%) as a cream foam.

R_f (20% EtOAc in pentane) 0.19.

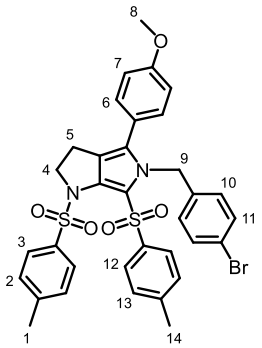
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.99 (2H, d, *J* = 8.4 Hz, H11), 7.75 (2H, d, *J* = 8.2 Hz, H3), 7.24–7.20 (5H, m, H12 + H9 + H10), 7.13 (2H, d, *J* = 8.2 Hz, H2), 6.89 (2H, dd, *J* = 6.9, 2.6 Hz, H8), 6.38 (1H, s, H6), 5.29 (2H, s, H7), 4.18 (2H, t, *J* = 7.0 Hz, H4), 2.41 (3H, s, CH_3), 2.36–2.32 (5H, m, CH_3 + H5).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.1, 143.7, 139.4, 138.6, 137.0, 135.7, 129.6, 129.4, 128.7, 128.3, 127.9, 127.8, 127.2, 123.2, 120.3, 118.1, 59.8, 52.5, 23.7, 21.8, 21.7.

HRMS (ES^+) calc. for $C_{27}H_{27}O_4N_2S_2$ ($[M+H]^+$) 507.1407, found 507.1409.

IR (thin film, ν_{max}/cm^{-1}) 2924, 1597, 1582, 1496, 1454, 1402, 1355, 1322, 1306, 1248, 1163, 1130, 1085, 1018.

84x 5-(4-Bromobenzyl)-4-(4-methoxyphenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b] pyrrole



82x (69.0 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 15%) to give the title compound (49.7 mg, 0.072 mmol, 72%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.13.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.92 (2H, d, *J* = 8.5 Hz, H12), 7.87 (2H, d, *J* = 8.4 Hz, H3), 7.27 (2H, d, *J* = 8.4 Hz, H2), 7.10 (2H, d, *J* = 8.5 Hz, H11), 7.05–6.99 (4H, m, H6 + H13), 6.83 (2H, d, *J* = 8.8 Hz, H7), 6.33 (2H, d, *J* = 8.5 Hz, H10), 5.28 (2H, s, H9), 4.22 (2H, t, *J* = 6.9 Hz, H4), 3.77 (3H, s, H8), 2.46–2.39 (5H, m, H1 + H5), 2.33 (3H, s, H14).

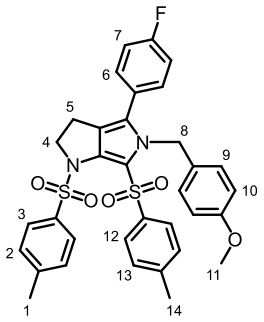
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 160.1, 144.2, 143.9, 139.1, 138.7, 137.0, 135.9, 133.6, 131.3, 130.7, 129.5, 129.2, 128.3, 128.1, 127.2, 123.3, 122.2, 120.6, 118.0, 114.4, 59.8, 55.4, 48.6, 23.6, 21.8, 21.7.

HRMS (ES^+) calc. for $C_{34}H_{32}O_5N_2{}^{81}BrS_2$ ($[M+H]^+$) 693.0913, found 693.0906.

IR (solid, ν_{max}/cm^{-1}) 3000, 1663, 1593, 1494, 1431, 1319, 1294, 1169, 1110, 1020, 1011.

MP 110–114 °C.

84y 4-(4-Fluorophenyl)-5-(4-methoxybenzyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



82y (63.1 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (12.0 mg, 0.019 mmol, 19%) as a cream solid.

82y (63.1 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) used in **General Procedure 7** with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (41.6 mg, 0.066 mmol, 66%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.22.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (2H, d, *J* = 8.4 Hz, H12), 7.82 (2H, d, *J* = 8.2 Hz, H3), 7.24 (2H, dt, *J* = 8.2, 0.7 Hz, H2), 7.08–7.03 (4H, m, H13 + H6), 6.98 (2H, t, *J* = 8.6 Hz, H7), 6.53 (2H, d, *J* = 8.8 Hz, H9), 6.39 (2H, d, *J* = 8.8 Hz, H10), 5.27 (2H, s, H8), 4.20 (2H, t, *J* = 6.9 Hz, H4), 3.72 (3H, s, H11), 2.42 (3H, s, H1), 2.34 (2H, t, *J* = 6.9 Hz, H5), 2.30 (3H, s, H14).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.9 (d, $^1J_{C\text{-}F}$ = 249.7 Hz), 158.6, 144.2, 143.5, 138.9, 138.7, 135.7, 132.4, 131.3 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 129.7, 129.5, 129.2, 128.3, 128.2, 126.9, 126.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 123.7, 118.7, 116.0 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 113.6, 59.7, 55.3, 48.9, 23.4, 21.8, 21.6.

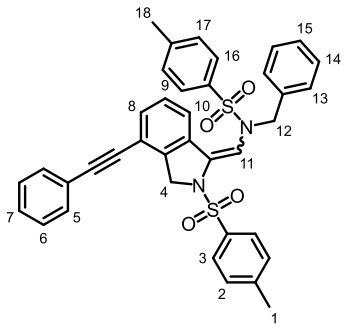
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.74.

HRMS (ES^+) calc. for $C_{34}H_{32}O_5N_2FS_2$ ($[M+H]^+$) 631.1731, found 631.1729.

IR (thin film, ν_{max}/cm^{-1}) 2980, 1612, 1597, 1514, 1494, 1452, 1403, 1362, 1326, 1307, 1293, 1248, 1170, 1151, 1125, 1082, 1035.

MP 97–101 °C.

90 *N*-Benzyl-4-methyl-*N*-((4-(phenylethynyl)-2-tosylisoindolin-1-ylidene)methyl) benzenesulfonamide



82t (64.4 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** for 3 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 10%) to give **90** (19.9 mg, 0.031 mmol, 31% as a 10 : 1 mixture of *E/Z* isomers, major isomer could not be determined, *NMR data given for major isomer in mixture*) as a yellow oil and **91** (14.1 mg, 0.022 mmol, 22%) as a yellow oil.

R_f (EtOAc in pentane, 20%) 0.29.

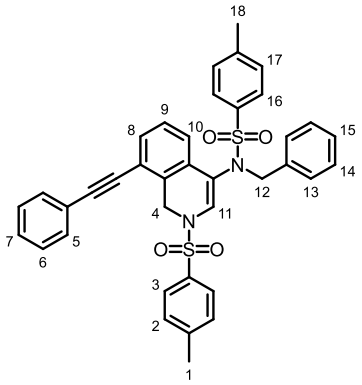
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.4 Hz, ArH), 7.45–7.37 (4H, m, ArH), 7.28–7.19 (7H, m, ArH), 7.19–7.16 (2H, m, ArH), 7.14–7.11 (2H, m, ArH), 7.06 (1H, dd, *J* = 7.5, 1.6 Hz, ArH), 7.03–6.98 (1H, m, ArH), 6.96 (1H, td, *J* = 7.5, 1.9 Hz, ArH), 6.76–6.66 (1H, m, ArH), 6.41 (1H, s, H11), 4.94 (2H, s, H12), 4.54–4.39 (1H, m, H4), 4.27 (1H, br. s, H4), 2.43 (3H, s, CH_3), 2.38 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.8, 137.3, 136.3, 134.9, 132.4, 131.6, 130.3, 129.9, 129.7, 129.3, 128.7, 128.4, 128.3, 128.1, 128.0, 127.84, 127.78, 127.3, 125.4, 124.0, 122.9, 122.2, 121.3, 93.9, 87.2, 51.8, 47.2, 21.73, 21.69.

HRMS (ES^+) calc. for $C_{38}H_{33}N_2O_4S_2$ ($[M+H]^+$) 645.1876, found 645.1877.

IR (thin film, ν_{max}/cm^{-1}) 3041, 2930, 1598, 1494, 1454, 1349, 1165, 1090, 1034.

91 *N*-Benzyl-4-methyl-*N*-(8-(phenylethynyl)-2-tosyl-1,2-dihydroisoquinolin-4-yl) benzenesulfonamide



*See procedure for **90**.*

R_f (EtOAc in pentane, 20%) 0.35.

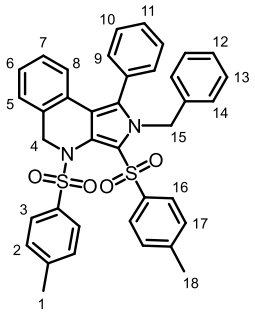
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.3 Hz, ArH), 7.54–7.51 (2H, m, ArH), 7.41–7.38 (5H, m, ArH), 7.35–7.31 (2H, m, ArH), 7.26–7.19 (6H, m, ArH), 7.13–7.10 (2H, m, ArH), 7.05–6.99 (2H, m, ArH), 6.41 (1H, s, H11), 4.77 (2H, d, *J* = 7.0 Hz, H12), 4.70 (1H, d, *J* = 14.5 Hz, H4), 4.52–4.43 (1H, m, H4), 2.48 (3H, s, CH_3), 2.34 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 144.1, 135.6, 135.5, 134.9, 131.7, 131.2, 130.5, 129.9 (2 C), 129.4, 128.87, 128.85, 128.8, 128.7 (2 C), 128.2, 128.0, 127.4, 127.2, 122.9, 122.4, 122.3, 120.1, 94.9, 85.9, 54.3, 45.6, 21.8, 21.7.

HRMS (ES^+) calc. for $C_{38}H_{32}O_4N_2NaS_2$ ($[M+H]^+$) 667.1696, found 667.1693.

IR (thin film, ν_{max}/cm^{-1}) 2923, 1597, 1493, 1443, 1350, 1163, 1091.

92 2-Benzyl-1-phenyl-3,4-ditosyl-4,5-dihydro-2*H*-pyrrolo[3,4-c]isoquinoline



82t (64.4 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** for 72 h with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 10%) followed by trituration with pentane to give the title compound (10.4 mg, 0.016 mmol, 16%) as a white solid.

R_f (EtOAc in pentane, 20%) 0.46.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.01 (2H, d, *J* = 8.4 Hz, ArH), 7.40 (2H, d, *J* = 8.3 Hz, ArH), 7.38–7.34 (1H, m, ArH), 7.26 (3H, br. s, ArH), 7.13–7.03 (5H, m, ArH), 6.93 (1H, br. s, ArH), 6.89–6.86 (2H, m, ArH), 6.83 (2H, d, *J* = 8.2 Hz, ArH), 6.67 (1H, ddd, *J* = 7.8, 6.0, 2.9 Hz, ArH), 6.60 (2H, dd, *J* = 8.0, 1.6 Hz, H14), 6.25–6.20 (1H, m, ArH), 5.66 (1H, d, *J* = 17.1 Hz, H15), 5.03 (1H, d, *J* = 17.1 Hz, H15), 4.86 (1H, d, *J* = 16.6 Hz, H4), 4.55 (1H, d, *J* = 16.6 Hz, H4), 2.30 (3H, s, CH_3), 2.18 (3H, s, CH_3).

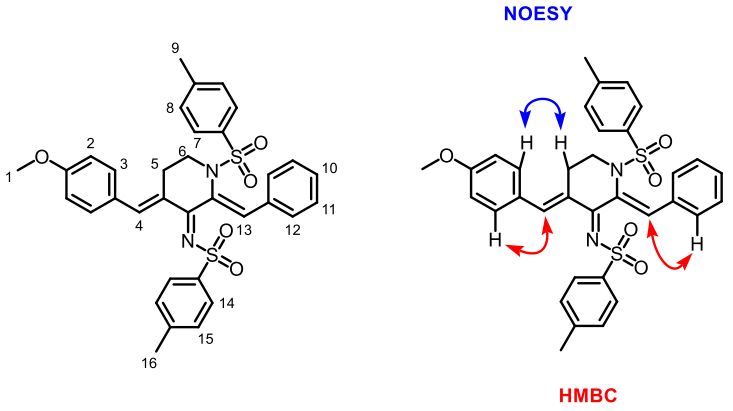
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 143.4, 138.5, 137.6, 135.0, 134.4, 130.6, 130.4, 129.6, 129.3, 128.8, 128.6, 128.4, 128.34, 128.31, 127.7, 127.0, 126.8, 126.4, 126.2, 125.6, 123.4, 122.9, 115.6, 52.2, 49.2, 21.6, 21.5. *Two aromatic carbon peaks not observed due to overlap.*

HRMS (ES^+) calc. for $C_{38}H_{33}O_4N_2S_2$ ($[M+H^+]$) 645.1876, found 645.1871.

IR (thin film, ν_{max}/cm^{-1}) 3058, 2971, 1597, 1496, 1454, 1349, 1327, 1186, 1165, 1148, 1087, 1028.

MP 113–115 °C.

93d ***N*-((*Z*)-2-((*Z*)-benzylidene)-4-((*E*)-4-methoxybenzylidene)-1-tosylpiperidin-3-ylidene)-4-methylbenzenesulfonamide**



*See procedure for **84d**, title compound formed as by-product (38.7 mg, 0.063 mmol, 63%) as a yellow solid.*

R_f (CH_2Cl_2) 0.30.

^{1}H NMR (500 MHz, DMSO-d_6) δ_H 7.91–7.89 (2H, m, H12), 7.85 (2H, d, *J* = 8.3 Hz, ArH), 7.72 (1H, s, H13), 7.57 (2H, d, *J* = 8.3 Hz, ArH), 7.46–7.44 (5H, m, ArH), 7.09 (2H, d, *J* = 8.9 Hz, H3), 7.03 (2H, d, *J* = 7.7 Hz, ArH), 6.97 (2H, d, *J* = 8.9 Hz, H2), 6.84 (1H, s, H4), 3.92 (1H, br. s, H6), 3.81 (3H, s, H1), 3.78 – 3.71 (1H, m, H6), 2.81 (1H, br. s, H5), 2.44–2.36 (4H, m, CH_3 + H5), 2.18 (3H, s, CH_3).

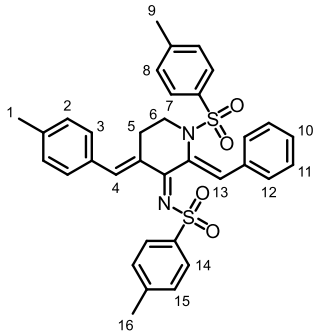
^{13}C NMR (126 MHz, DMSO-d_6) δ_C 173.8, 160.4, 143.9, 143.1, 140.8, 139.0, 135.3, 133.4, 132.3, 131.1, 130.8, 129.72, 129.66, 129.2, 128.8, 128.6, 128.0, 127.3, 126.7, 126.5, 114.1, 55.4, 44.2, 24.2, 21.05, 21.04.

HRMS (ES^+) calc. for $C_{34}H_{33}N_2O_5S_2$ ($[M+H]^+$) 613.1825, found 613.1833.

IR (thin film, ν_{max}/cm^{-1}) 3129, 1598 (C=N), 1510, 1355, 1302, 1256, 1171, 1088, 1030.

MP 140–142 °C.

93e *N*-((*Z*)-2-((Z)-Benzylidene)-4-((*E*)-4-methylbenzylidene)-1-tosylpiperidin-3-ylidene)-4-methylbenzenesulfonamide



*See procedure for **84e**, title compound formed as by-product (12.4 mg, 0.021 mmol, 21%) as a yellow solid.*

R_f (EtOAc in pentane, 20%) 0.22.

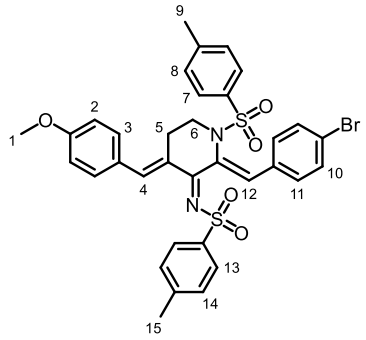
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (2H, d, *J* = 8.3 Hz, ArH), 7.88–7.85 (2H, m, ArH), 7.74 (1H, s, H13), 7.66 (2H, d, *J* = 8.3 Hz, ArH), 7.38–7.36 (3H, m, ArH), 7.35–7.33 (2H, m, ArH), 7.15 (2H, d, *J* = 7.8 Hz, ArH), 7.12 (1H, s, H4), 7.03–7.01 (2H, m, ArH), 6.98 (2H, d, *J* = 8.1 Hz, ArH), 3.83 (2H, br. s, H6), 2.95–2.85 (1H, m, H5), 2.69–2.55 (1H, m, H5), 2.46 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.26 (3H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.5, 144.0, 143.3, 141.8, 140.4, 139.8, 139.5, 135.7, 133.6, 132.1, 131.5, 130.9, 130.2, 129.8, 129.6, 129.3, 128.7, 128.0, 127.5, 127.2, 45.6, 25.2, 21.7, 21.64, 21.56. *One aromatic carbon peak not found due to overlap.*

HRMS (ES^+) calc. for $C_{34}H_{33}N_2O_4S_2$ ($[M+H]^+$) 597.1876, found 597.1892.

IR (thin film, ν_{max}/cm^{-1}) 2923, 1597 (C=N), 1541, 1412, 1360, 1314, 1167, 1088.

93x *N*-((*Z*)-2-((*Z*)-4-Bromobenzylidene)-4-((*E*)-4-methoxybenzylidene)-1-tosylpiperidin-3-ylidene)-4-methylbenzenesulfonamide



82x (69.0 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 1.0 equiv.) were used in **General Procedure 6** for 3 h with purification by flash column chromatography (phosphate buffered SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (27.6 mg, 0.040 mmol, 40%) as a cream foam.

R_f (EtOAc in pentane, 20%) 0.17.

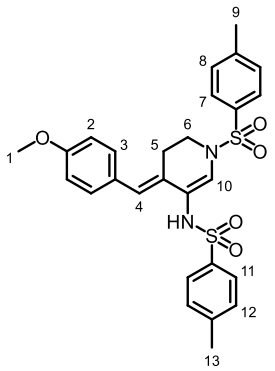
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.91 (2H, d, *J* = 8.4 Hz, ArH), 7.69 (2H, d, *J* = 8.6 Hz, ArH), 7.65 (1H, s, H12), 7.62 (2H, d, *J* = 8.2 Hz, ArH), 7.47 (2H, d, *J* = 8.6 Hz, ArH), 7.33 (2H, d, *J* = 8.1 Hz, ArH), 7.14 (1H, s, H4), 7.08 (2H, d, *J* = 8.8 Hz, ArH), 7.01 (2H, d, *J* = 8.0 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 3.94–3.70 (5H, m, H1 + H6), 2.45 (3H, s, CH_3), 2.40–2.32 (1H, m, H5), 2.26 (3H, s, CH_3) *Note: 1H corresponding to H5 not resolved due to extremely broad peaks.*

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 174.0, 160.8, 144.2, 143.3, 142.2, 139.4, 138.2, 135.7, 132.7, 132.6, 132.3, 131.9, 131.7, 129.8, 129.6, 128.6, 127.9, 127.5, 127.1, 125.1, 114.1, 55.6, 45.3, 25.5, 21.73, 21.70.

HRMS *Not found by alternative ionisation.*

IR (thin film, ν_{max}/cm^{-1}) 2927, 1598 (C=N), 1509, 1488, 1457, 1350, 1250, 1163, 1090, 1035, 1010.

94 (*E*)-*N*-(4-(4-Methoxybenzylidene)-1-tosyl-1,4,5,6-tetrahydropyridin-3-yl)-4-methylbenzenesulfonamide



According to the procedure of Boyer.[66] **93d** (10.0 mg, 0.016 mmol, 1.0 equiv.) was dissolved in toluene (0.7 mL) and Al_2O_3 (Brockmann III) (0.160 g, 10.0 g per mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was then purified directly by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (3.9 mg, 0.0074 mmol, 74%) as a yellow oil.

R_f (EtOAc in pentane, 20%) 0.13.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.3 Hz, ArH), 7.51 (2H, d, *J* = 8.3 Hz, ArH), 7.39–7.37 (2H, m, ArH), 7.18–7.16 (2H, m, ArH), 7.07 (1H, s, H4), 6.77 (2H, d, *J* = 8.9 Hz, H3), 6.72 (2H, d, *J* = 8.9 Hz, H2), 5.79 (1H, s, H10), 5.58 (1H, s, NH), 3.77 (3H, s, H1), 3.20 (2H, dd, *J* = 6.7, 5.3 Hz, H5), 2.60–2.56 (2H, m, H6), 2.46 (3H, s, CH_3), 2.39 (3H, s, CH_3).

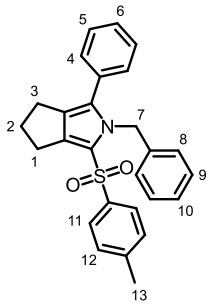
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 158.7, 144.6, 143.9, 137.0, 133.9, 130.3, 130.1, 129.6, 128.5, 127.7, 127.5, 127.3, 126.6, 121.1, 117.3, 113.8, 55.4, 43.6, 24.8, 21.8, 21.7.

HRMS (ES^+) calc. for $C_{27}H_{29}N_2O_5S_2$ ($[M+H]^+$) 525.1512, found 525.1497.

IR (thin film, ν_{max}/cm^{-1}) 3270, 1600, 1510, 1359, 1252, 1165, 1090, 1021.

7.3.5 Ynamide cycloisomerisation products

103a 2-Benzyl-1-phenyl-3-tosyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole



102a (42.8 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, Et_2O in pentane, 0 to 20%) to give the title compound (17.0 mg, 0.040 mmol, 40%) as a colourless oil.

R_f (Et_2O in pentane, 20%) 0.44.

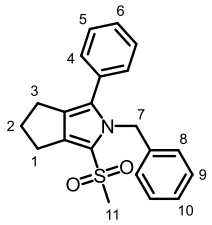
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (2H, d, *J* = 8.3 Hz, H11), 7.29-7.25 (3H, m, ArH), 7.21–7.18 (2H, m, ArH), 7.05–7.03 (1H, m, ArH), 7.01–6.95 (4H, m, ArH), 6.59–6.56 (2H, dt, *J* = 7.2, 1.2 Hz, ArH), 5.42 (2H, s, H7), 3.09 (2H, t, *J* = 7.4 Hz, CH_2), 2.68 (2H, dd, *J* = 7.8, 6.7 Hz, CH_2), 2.41 (2H, app. h, *J* = 6.9 Hz, H2), 2.30 (3H, s, H13).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 142.9, 140.7, 139.9, 138.5, 133.5, 131.6, 130.7, 129.32, 129.27, 128.7, 128.3, 128.2, 126.8, 126.5, 125.8, 120.7, 48.9, 30.1, 27.7, 25.7, 21.6.

HRMS (ES^+) calc. for $C_{27}H_{26}O_2NS$ ($[M+H]^+$) 428.1679, found 428.1679.

IR (thin film, ν_{max}/cm^{-1}) 2980, 2968, 2917, 1455, 1319, 1147, 1080, 1026.

103b 2-Benzyl-1-(methylsulfonyl)-3-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole



102b (35.1 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (16.5 mg, 0.047 mmol, 47%) as a sticky colourless gum.

R_f (EtOAc in pentane, 20%) 0.60.

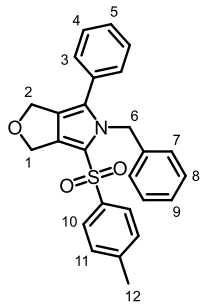
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.33 (5H, m, ArH), 7.30–7.22 (3H, m, ArH), 6.97–6.95 (2H, m, ArH), 5.48 (2H, s, H7), 2.96 (2H, t, *J* = 7.5 Hz, CH_2), 2.72–2.68 (2H, m, CH_2), 2.43 (3H, s, H11), 2.38 (2H, app. p, *J* = 7.5 Hz, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 141.1, 138.9, 133.6, 131.5, 130.4, 129.5, 128.9, 128.8, 128.4, 127.7, 126.5, 119.9, 48.8, 45.0, 30.1, 27.2, 25.6.

HRMS (ES^+) calc. for $C_{21}H_{22}O_2NS$ ($[M+H]^+$) 352.1366, found 352.1365.

IR (thin film, ν_{max}/cm^{-1}) 2922, 2851, 1496, 1454, 1373, 1313, 1211, 1174, 1142, 1107.

103c 5-Benzyl-4-phenyl-6-tosyl-3,5-dihydro-1*H*-furo[3,4-c]pyrrole



102c (42.9 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) followed by trituration with pentane to give the title compound (21.6 mg, 0.050 mmol, 50%) as a colourless solid.

R_f (EtOAc in pentane, 10%) 0.24.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 (2H, d, *J* = 8.4 Hz, H10), 7.30–7.27 (3H, m, H4 + H5), 7.18–7.14 (2H, m, H3), 7.08–7.03 (1H, m, H9), 7.01–6.95 (4H, m, H11 + H8), 6.57–6.53 (2H, m, H7), 5.42 (2H, s, H6), 5.24 (2H, t, *J* = 1.6 Hz, H1), 4.93 (2H, t, *J* = 1.6 Hz, H2), 2.30 (3H, s, H12).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 143.6, 138.8, 137.6, 136.8, 131.5, 130.6, 129.5, 129.0 (2 C), 128.8, 128.4, 127.3, 127.1, 126.7, 125.6, 120.1, 69.4, 68.2, 48.9, 21.6.

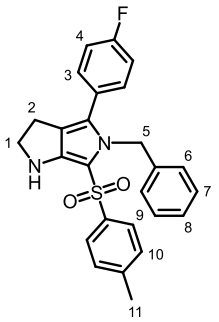
HRMS ES^+ calc. for $C_{26}H_{24}O_3NS$ ($[M+H]^+$) 430.1471, found 430.1470.

IR (thin film, ν_{max}/cm^{-1}) 2866, 1597, 1494, 1453, 1340, 1303, 1203, 1149, 1127, 1082, 1028.

MP 132–136 °C.

7.3.6 Derivatisation products

104 5-Benzyl-4-(4-fluorophenyl)-6-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



84c (30.0 mg, 0.050 mmol), magnesium turnings (12.0 mg, 0.50 mmol, 10.0 equiv.) and NH_4Cl (5.4 mg, 0.10 mmol, 2.0 equiv.) were dissolved in anhydrous MeOH (1.0 mL) and anhydrous THF (1.0 mL) in a vial, and the vial was purged with argon. The reaction mixture was then sonicated at room temperature. After approximately 10 minutes the reaction mixture turned a dark blue colour, and after 30 minutes it turned black. The reaction progress was monitored by TLC, and after 40 minutes complete consumption of the starting material was observed. The reaction mixture was quenched with saturated NH_4Cl (aq) (5 mL) and diluted with EtOAc (10 mL). The organic layer was separated and washed again with water (2 × 5 mL). The organic layer was dried over $MgSO_4$, then concentrated *in vacuo*. The crude material was purified by flash column chromatography (phosphate buffered SiO_2, SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (19.1 mg, 0.043 mmol, 82%) as a brown oil.

R_f (30% EtOAc in pentane) 0.44.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (2H, d, *J* = 8.3 Hz, ArH), 7.21–7.17 (2H, m, ArH), 7.21–7.17 (7H, m, ArH), 6.58–6.55 (2H, m, H6), 5.14 (2H, s, H5), 4.50 (1H, s, NH), 3.94 (2H, t, *J* = 7.9 Hz, H1), 2.87 (2H, t, *J* = 7.9 Hz, H2), 2.29 (3H, s, H11).

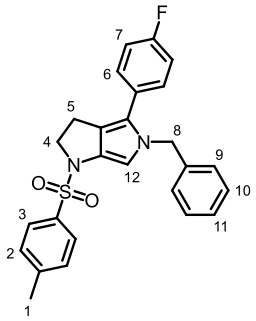
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.7 (d, $^1J_{C\text{-}F}$ = 248.5 Hz), 151.2, 142.7, 140.5, 138.6, 134.2, 130.9 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 129.3, 128.2, 127.3, (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 126.51, 126.48, 125.8, 117.5, 115.9 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 107.1, 53.5, 48.6, 24.4, 21.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −112.67.

HRMS (ES^+) calc. for $C_{26}H_{24}O_2N_2FS$ ($[M+H]^+$) 447.1537, found 447.1534.

IR (thin film, ν_{max}/cm^{-1}) 3400, 2953, 2925, 2855, 1600, 1553, 1455, 1406, 1325, 1225, 1147, 1130, 1081, 1051, 1016.

105 5-Benzyl-4-(4-fluorophenyl)-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



84c (30.0 mg, 0.050 mmol, 1.0 equiv.) and Pd/C (10% w/w, 30.0 mg) were dissolved in MeOH (1.0 mL) and stirred at room temperature under an atmosphere of H_2 (1 atm) for 2 days, then Pd/C (10% w/w, 15.0 mg) was added and the reaction mixture was stirred under an atmosphere for H_2 (1 atm) for an additional 2 days. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) (9.6 mg, 0.022 mmol, 43%) as a colourless oil.

R_f (20% EtOAc in pentane) 0.51.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, H3), 7.31–7.27 (3H, m, H10 + H11), 7.25–7.22 (2H, m, H2), 7.11 (2H, dd, *J* = 8.9, 5.4 Hz, H6), 7.01–6.93 (4H, m, H7 + H9), 6.60 (1H, s, H12), 5.01 (2H, s, H8), 4.02 (2H, dd, *J* = 8.1, 7.5 Hz, H4), 2.70 (2H, t, *J* = 7.5 Hz, H5), 2.43 (3H, s, H1).

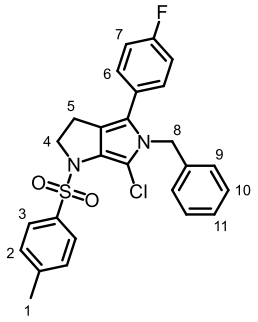
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.0 (d, $^1J_{C\text{-}F}$ = 247.2 Hz), 143.9, 139.0, 133.0, 132.8, 130.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.5, 128.8, 128.12 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 128.06, 127.6, 126.4, 125.3, 118.2, 115.7 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 106.7, 56.1, 51.3, 23.9, 21.8.

^{19}F NMR (376 MHz, CDCl3) δ_F −114.56.

HRMS (ES^+) calc. for $C_{26}H_{24}O_2N_2FS$ ($[M+H]^+$) 447.1537, found 447.1534.

IR (thin film, ν_{max}/cm^{-1}) 2922, 1597, 1570, 1504, 1453, 1350, 1224, 1163, 1109, 1090, 1030, 1006.

106 5-Benzyl-6-chloro-4-(4-fluorophenyl)-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole



$AlCl_3$ (33.3 mg, 0.25 mmol, 5.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) under an argon atmosphere and cooled to 0 °C. **84c** (30.0 mg, 0.050 mmol, 1.0 equiv.) was then added as a solution in anhydrous CH_2Cl_2 (0.5 mL) and the reaction was stirred at 0 °C for 15 minutes, then warmed to room temperature and stirred for a further 45 minutes. The reaction mixture was purified directly by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (20.0 mg, 0.042 mmol, 83%) as a pale yellow oil.

R_f (20% EtOAc in pentane) 0.50.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.2 Hz, H3), 7.31–7.26 (3H, m, H10 + H11), 7.23 (2H, d, *J* = 8.2 Hz, H2), 7.03–6.99 (2H, m, H6), 6.96 (2H, dd, *J* = 9.8, 7.6 Hz, H7), 6.89–

6.86 (2H, m, H9), 5.09 (2H, s, H8), 4.20 (2H, t, *J* = 7.5 Hz, H4), 2.43 (3H, s, H1), 2.37 (2H, t, *J* = 7.5 Hz, H5).

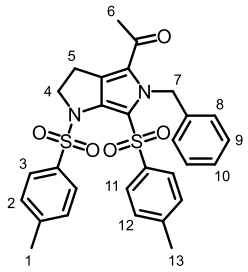
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.2 (d, $^1J_{C\text{-}F}$ = 248.2 Hz), 144.0, 138.1, 133.9, 130.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.5, 128.8, 128.2, 127.9, 127.7 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 127.5, 126.0, 125.0, 121.1, 115.8 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 104.3, 58.3, 48.5, 23.5, 21.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −113.65.

HRMS (ES^+) calc. for $C_{26}H_{23}O_2N_2ClFS$ ($[M+H]^+$) 481.1147, found 481.1148.

IR (thin film, ν_{max}/cm^{-1}) 2995, 1657, 1596, 1547, 1504, 1444, 1402, 1354, 1321, 1225, 1185, 1167, 1122, 1088.

110 1-(5-Benzyl-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrol-4-yl)ethan-1-one



84b (13.7 mg, 0.025 mmol, 1.0 equiv.) was dissolved in MeOH (5.0 mL) and CH_2Cl_2 (5.0 mL); the reaction mixture was then cooled to −78 °C and the flask was purged with oxygen for 2 minutes. Ozone was passed through the reaction mixture until a blue colour was observed after 5 minutes, followed by a further 5 minutes passing ozone through the reaction mixture. Dimethyl sulfide (73 μL, 1.0 mmol, 40.0 equiv.) was added and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was concentrated *in vacuo* and purified directly by flash column chromatography (SiO_2, MeOH in CH_2Cl_2, 5%) to give the title compound (13.0 mg, 0.024 mmol, 95%) as a sticky yellow gum.

R_f (MeOH in CH_2Cl_2, 10%) 0.68.

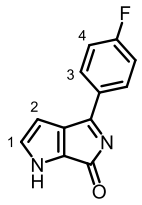
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.97 (2H, d, *J* = 8.4 Hz, H11), 7.87 (2H, d, *J* = 8.2 Hz, H3), 7.28 (2H, d, *J* = 8.2 Hz, H2), 7.08–7.03 (5H, m, H12 + H9 + H10), 6.63–6.61 (2H, m, H8), 5.83 (2H, s, H7), 4.25 (2H, t, *J* = 6.9 Hz, H4), 2.77 (2H, t, *J* = 6.9 Hz, H5), 2.43 (3H, s, H1), 2.27 (3H, s, H13), 2.22 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 188.5, 144.6 (2 C), 137.9, 137.7, 136.9, 135.5, 131.6, 129.7, 129.6, 128.4 (2 C), 128.2, 126.6, 125.7, 125.4, 59.1, 50.4, 30.1, 27.3, 21.8, 21.6. *One aromatic carbon peak not observed due to overlap.*

HRMS (ES^+) calc. for $C_{29}H_{29}O_5N_2S_2$ ($[M+H]^+$) 549.1512, found 549.1514.

IR (thin film, ν_{max}/cm^{-1}) 2929, 1675 (C=O), 1597, 1496, 1453, 1362, 1334, 1258, 1168, 1156, 1125, 1091.

111 4-(4-Fluorophenyl)pyrrolo[3,4-b]pyrrol-6(1*H*)-one



84c (30.0 mg, 0.050 mmol, 1.0 equiv.) was dissolved in DMSO (5.0 mL) and potassium *tert*-butoxide (1.0 M in THF, 0.50 mL, 0.50 mmol, 10.0 equiv.) was added and the reaction mixture was purged with O_2, then stirred at room temperature for 18 h. The reaction mixture was quenched with NH_4Cl (aq., satd., 10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with LiCl (10% aq., 10 mL) and dried over $MgSO_4$, then concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (4.2 mg, 0.020 mmol, 39%) as a white gum.

R_f (EtOAc in pentane, 50%) 0.55

^{1}H NMR (500 MHz, MeOD) δ_H 7.88 (2H, dd, *J* = 8.8, 5.5 Hz, H3), 7.26 (2H, t, *J* = 8.8 Hz, H4), 7.01 (1H, d, *J* = 2.9 Hz, CH), 6.52 (1H, d, *J* = 2.9 Hz, CH) *NH peak not observed.*

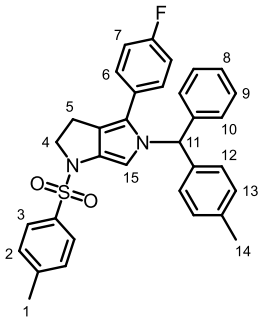
^{13}C NMR (101 MHz, MeOD) δ_C 194.2, 167.5, 164.5 (d, $^{1}J_{C\text{-}F}$ = 253.0 Hz), 137.5, 133.25 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 123.2, 121.3, 117.4 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 116.2 (d, $^{2}J_{C\text{-}F}$ = 22.2 Hz). *One carbon peak not observed due to overlap.*

^{19}F NMR (377 MHz, MeOD) δ_F -109.20.

HRMS (ES^-) calc. for $C_{12}H_6O_2N_2F$ ($[M\text{-}H]^-$) 213.0470, found 213.0467.

IR (thin film, ν_{max}/cm^{-1}) 2490, 1655, 1618, 1603, 1558, 1527, 1508, 1458, 1383, 1307, 1288, 1244, 1157, 1098.

112 4-(4-Fluorophenyl)-5-(phenyl(p-tolyl)methyl)-1-tosyl-1,2,3,5-tetra hydropyrrolo[3,4-b]pyrrole



84c (30.0 mg, 0.050 mmol, 1.0 equiv.) was dissolved in anhydrous DMSO (1.0 mL) under an atmosphere of argon and potassium *tert*-butoxide (1.0 M in THF, 0.10 mL, 0.10 mmol, 2.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 18 h then LiCl (aq., 5% w/v) (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, then concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (11.3 mg, 0.021 mmol, 42%) as a brown oil.

R_f (EtOAc in pentane, 20%) 0.47.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.62 (2H, d, *J* = 8.2 Hz, H3), 7.33–7.30 (3H, m, H8 + H9), 7.22 (2H, d, *J* = 8.2 Hz, H2), 7.14 (2H, d, *J* = 7.9 Hz, H13), 7.09–7.04 (2H, m, H6), 7.03–7.00 (2H, m, H10), 6.99–6.93 (4H, m, H7 + H12), 6.42 (1H, s, H15), 6.34 (1H, s, H11), 4.04–3.95 (2H, m, H4), 2.67 (2H, t, *J* = 7.7 Hz, H5), 2.44 (3H, s, H1), 2.38 (3H, s, H14).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.1 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 143.9, 141.1, 130.7 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 132.7, 132.5, 130.74, 130.68, 129.43, 129.41, 128.7, 128.3, 128.20 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 128.18, 128.1, 127.8, 125.7, 118.2, 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 105.4, 63.9, 56.2, 23.7, 21.8, 21.3.

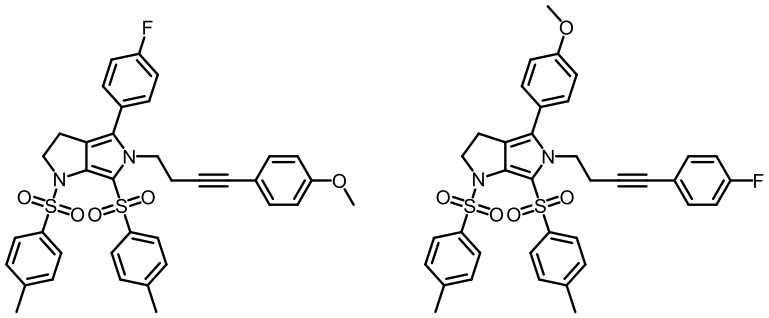
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −114.34.

HRMS (ES^+) calc. for $C_{33}H_{30}O_2N_2FS$ ($[M+H]^+$) 537.2007, found 537.2006.

IR (thin film, ν_{max}/cm^{-1}) 2921, 1597, 1541, 1503, 1451, 1350, 1224, 1163, 1110, 1091, 1032, 1003.

7.3.6 Mechanistic experiment substrates

124 and **125** **4-(4-Fluorophenyl)-5-(4-(4-methoxyphenyl)but-3-yn-1-yl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole** and **5-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-(4-methoxyphenyl)-1,6-ditosyl-1,2,3,5-tetrahydropyrrolo[3,4-b]pyrrole**



123 (66.8 mg, 0.10 mmol, 1.0 equiv.) and $Ph_3PAuNTf_2$ (7.4 mg, 0.010 mmol, 10 mol%) were used in **General Procedure 6** with purification by flash column chromatography (SiO_2, EtOAc

in pentane, 10 to 20%) to give the title compounds as an inseparable (1:1) mixture (16.1 mg, 0.024 mmol, 24%) as a sticky pale brown gum.

123 (66.8 mg, 0.10 mmol, 1.0 equiv.) and BHT (22.0 mg, 0.10 mmol, 1.0 equiv.) were used in **General Procedure 7** for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compounds as an inseparable (1 : 1) mixture (45.3 mg, 0.068 mmol, 68%) as a sticky pale brown gum.

*Data is given for the 1:1 mixture of **124** and **125**.*

R_f (EtOAc in pentane, 20%) 0.24.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.23–8.20 (4H, m), 7.82 (4H, d, *J* = 8.2 Hz), 7.35–7.31 (4H, m), 7.25 –7.16 (10H, m), 7.14 (2H, d, *J* = 8.8 Hz), 7.08 (2H, t, *J* = 8.6 Hz), 6.96 (2H, t, *J* = 8.7 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 4.38–4.33 (4H, m), 4.15–4.11 (4H, m), 3.82 (3H, s), 3.80 (3H, s), 2.41 (3H, s), 2.40 (3H, s), 2.37 (3H, s), 2.36 (3H, s), 2.30–2.26 (4H, m), 2.22–2.18 (4H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.9 (d, $^1J_{C\text{-}F}$ = 249.7 Hz), 162.4 (d, $^1J_{C\text{-}F}$ = 248.9 Hz), 160.0, 159.5, 144.2, 144.1, 144.0, 139.7, 139.5, 139.00, 138.95, 135.7, 135.6, 133.5 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 133.1, 133.0 (2 C), 132.1, 131.5 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 130.8, 129.8, 129.7, 129.6, 129.5, 128.4, 128.3 (2 C), 126.4 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 123.7, 123.3, 122.5, 119.5 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 118.3, 117.7, 116.2 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 115.4, 114.5, 114.0, 85.4, 83.9, 82.5, 81.4, 59.63, 59.61, 55.5, 55.4, 45.2, 45.0, 23.4, 23.3, 21.9, 21.81, 21.79, 21.73, 21.70, 21.69. *One aromatic carbon peak not observed due to overlap.*

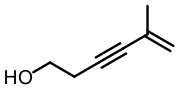
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.46, −111.60.

HRMS (ES^+) calc. for $C_{37}H_{34}FN_2O_5S_2$ ($[M+H]^+$) 669.1888, found 669.1883.

IR (thin film, ν_{max}/cm^{-1}) 1598, 1508, 1455, 1361, 1323, 1249, 1170, 1149, 1126, 1082, 1034.

7.3.7 Yndiamide precursors: alcohols

S85a 5-Methylhex-5-en-3-yn-1-ol



But-3-yn-1-ol (1.96 mL, 26.0 mmol, 1.0 equiv.) and 2-bromopropene (2.77 mL, 31.2 mmol, 1.2 equiv.) were used in **General Procedure 1** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (1.87 g, 17.0 mmol, 65%) as a brown oil.

R_f (EtOAc in pentane, 20%) 0.33.

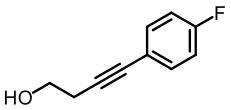
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.24–5.21 (1H, m), 5.17 (1H, t, *J* = 1.8 Hz), 3.72 (2H, t, *J* = 6.4 Hz), 2.59–2.54 (2H, m), 2.12–1.99 (1H, m), 1.86 (3H, t, *J* = 1.2 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 126.9, 121.4, 85.5, 83.8, 61.2, 23.80, 23.76.

HRMS (APCI) calc. for $C_7H_{11}O$ ($[M+H]^+$) 111.0804, found 111.0807.

IR (thin film, ν_{max}/cm^{-1}) 3344, 1679, 1613, 1437, 1373, 1296, 1182, 1044, 899, 750, 696, 609.

S85c 4-(4-Fluorophenyl)but-3-yn-1-ol



But-3-yn-1-ol (2.94 mL, 39.0 mmol, 1.0 equiv.) and 4-fluoroiodobenzene (5.40 mL, 46.8 mmol, 1.2 equiv.) were used in **General Procedure 1** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (4.88 g, 29.8 mmol, 76%) as a brown oil. *NMR data is consistent with that reported in the literature.*[221]

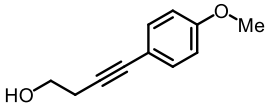
R_f (EtOAc in pentane, 20%) 0.33.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.36 (2H, m), 7.01–6.95 (2H, m), 3.81 (2H, t, *J* = 6.3 Hz), 2.68 (2H, t, *J* = 6.3 Hz), 1.82 (1H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^{1}J_{C\text{-}F}$ = 248.9 Hz), 133.6 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 119.5, 115.6 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 86.2, 81.6, 61.3, 23.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.60.

S85d 4-(4-Methoxyphenyl)but-3-yn-1-ol



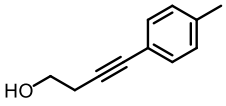
But-3-yn-1-ol (1.50 mL, 19.8 mmol, 1.25 equiv.), 4-iodoanisole (3.71 g, 15.8 mmol, 1.0 equiv.), CuI (90.3 mg, 3.0 mol%) and $PdCl_2(PPh_3)_2$ (0.332 g, 3.0 mol%) were dissolved in Et_3N (15 mL) and DMF (5 mL) and stirred under an atmosphere of Ar at 50 °C for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc in pentane, 20 to 40%) to give the title compound (1.35 g, 7.68 mmol, 48%) as an orange solid. *NMR data is consistent with that reported in the literature*.[222]

R_f (EtOAc in pentane, 20%) 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 (2H, d, *J* = 8.8 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 3.83–3.75 (5H, m), 2.67 (2H, t, *J* = 6.3 Hz), 1.98 (1H, t, *J* = 6.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.5, 133.2, 115.6, 114.0, 84.8, 82.4, 61.4, 55.4, 24.0.

S85e 4-(*p*-Tolyl)but-3-yn-1-ol



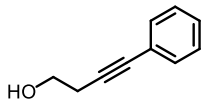
But-3-yn-1-ol (2.00 mL, 26.4 mmol, 1.0 equiv.) and 4-iodotoluene (6.91 g, 31.7 mmol, 1.2 equiv.) were used in **General Procedure 1** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (3.91 g, 24.4 mmol, 92%) as a brown oil. *NMR data is consistent with that reported in the literature.*[223]

R_f (EtOAc in pentane, 20%) 0.23.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 3.81 (2H, dd, *J* = 6.3 Hz, 6.3 Hz), 2.69 (2H, t, *J* = 6.3 Hz), 2.34 (3H, s), 1.82 (1H, t, *J* = 6.3 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.2, 131.7, 129.2, 120.4, 85.6, 82.8, 61.4, 24.0, 21.6.

S85f 4-Phenylbut-3-yn-1-ol



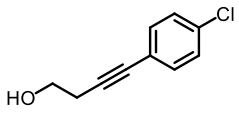
But-3-yn-1-ol (1.50 mL, 19.8 mmol, 1.0 equiv.) and iodobenzene (2.66 mL, 23.8 mmol, 1.2 equiv.) were used in **General Procedure 1** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (1.96 g, 13.4 mmol, 68%) as a brown oil. *NMR data is consistent with that reported in the literature.*[224]

R_f (EtOAc in pentane, 20%) 0.21.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.40 (2H, m), 7.32 – 7.24 (3H, m, *J* = 5.0, 1.9 Hz), 3.81 (2H, t, *J* = 6.3 Hz), 2.69 (2H, t, *J* = 6.3 Hz), 1.89 (1H, br. s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 131.8, 128.4, 128.1, 123.5, 86.5, 82.7, 61.3, 24.0.

S85g 4-(4-Chlorophenyl)but-3-yn-1-ol



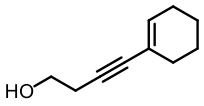
But-3-yn-1-ol (1.50 mL, 19.8 mmol, 1.3 equiv.) and 1-chloro-4-iodobenzene (3.78 g, 15.8 mmol, 1.0 equiv.) were used in **General Procedure 1** for 48 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 30%) to give the title compound (2.57 g, 14.3 mmol, 90%) as a brown solid. *NMR data is consistent with that reported in the literature.*[225]

R_f (EtOAc in pentane, 20%) 0.24.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35–7.32 (2H, m), 7.28–7.25 (2H, m), 3.82 (2H, dd, *J* = 6.0, 6.0 Hz), 2.69 (2H, t, *J* = 6.0 Hz), 1.82–1.77 (1H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 134.1, 133.0, 128.7, 122.0, 87.6, 81.5, 61.2, 24.0.

S85h 4-(Cyclohex-1-en-1-yl)but-3-yn-1-ol



Cyclohex-1-en-1-yl trifluoromethanesulfonate (1.00 g, 4.35 mmol, 1.0 equiv.) and 3-butyn-1-ol (0.42 mL, 5.54 mmol, 1.3 equiv.) were used in **General Procedure 1** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.400 g, 2.67 mmol, 61%) as an orange oil. *NMR data is consistent with that reported in the literature.*[226]

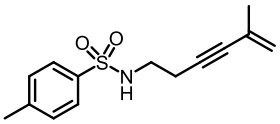
R_f (EtOAc in pentane, 20%) 0.38.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.06 (1H, tt, *J* = 3.9, 1.7 Hz), 3.72 (2H, q, *J* = 6.1 Hz), 2.57 (2H, t, *J* = 6.1 Hz), 2.15–2.01 (4H, m), 1.78 (1H, d, *J* = 6.1 Hz), 1.66–1.52 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 134.4, 120.7, 84.6, 83.3, 61.4, 29.6, 25.7, 23.9, 22.5, 21.7.

7.3.8 Yndiamide precursors: sulfonamides

S86a 4-Methyl-*N*-(5-methylhex-5-en-3-yn-1-yl)benzenesulfonamide



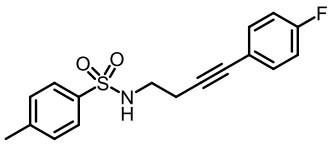
S85a (1.48 g, 13.5 mmol, 1.0 equiv.), methyl tosylcarbamate (3.70 g, 16.2 mmol, 1.2 equiv.), DIAD (3.27 mL, 16.2 mmol, 1.2 equiv.) and PPh_3 (4.25 g, 16.2 mmol, 1.2 equiv.) were used in **General Procedure 2** followed by deprotection with K_2CO_3 (3.73 g, 27.0 mmol, 2.0 equiv.) with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (2.12 g, 8.09 mmol, 60%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[53]

R_f (EtOAc in pentane, 20%) 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78–7.75 (2H, m), 7.31 (2H, dt, *J* = 7.8, 0.7 Hz), 5.21–5.17 (2H, m), 4.70 (1H, t, *J* = 6.4 Hz), 3.11 (2H, app. q, *J* = 6.5 Hz), 2.46 (2H, t, *J* = 6.5 Hz), 2.43 (3H, s), 1.84 (3H, t, *J* = 1.3 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.2, 129.9, 127.2, 126.6, 121.9, 84.6, 84.3, 42.0, 23.7, 21.7, 20.7.

S86c *N*-(4-(4-Fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide



S85c (1.46 g, 8.89 mmol, 1.0 equiv.), methyl tosylcarbamate (2.45 g, 10.7 mmol, 1.2 equiv), Ph_3P (2.80 g, 10.7 mmol, 1.2 equiv.), DIAD (2.10 mL, 10.7 mmol, 1.2 equiv.) were used in **General Procedure 2** followed by deprotection with K_2CO_3 (2.46 g, 17.8 mmol, 2.0 equiv.) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the

title compound (0.989 g, 3.12 mmol, 35%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[227]

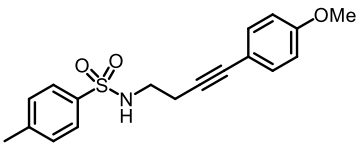
R_f (EtOAc in pentane, 20%) 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79–7.75 (2H, m), 7.33–7.25 (2H, m), 7.27 (2H, d, *J* = 8.0 Hz), 6.95 (2H, t, *J* = 8.7 Hz), 5.20 (1H, t, *J* = 6.7 Hz), 3.16 (2H, app. q, *J* = 6.7 Hz), 2.54 (2H, t, *J* = 6.7 Hz), 2.39 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^1J_{C\text{-}F}$ = 249.1 Hz), 143.6, 137.1, 133.6 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.9, 127.2, 119.2 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 85.5, 81.7, 42.0, 21.6, 20.8.

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −111.27.

S86d *N*-(4-(4-Methoxyphenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide



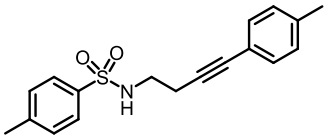
S85d (1.35 g, 7.66 mmol, 1.0 equiv.), methyl tosylcarbamate (2.11 g, 9.19 mmol, 1.2 equiv), PPh_3 (2.41 g, 9.19 mmol, 1.2 equiv.), DIAD (1.8 mL, 9.19 mmol, 1.2 equiv.) were used in **General Procedure 2** followed by deprotection with K_2CO_3 (2.12 g, 15.32 mmol, 2.0 equiv.). The crude material was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound as a cream solid (0.670 g, 2.04 mmol, 27%). *NMR data is consistent with that reported in the literature.*[228]

R_f (EtOAc in pentane, 20%) 0.40.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.3 Hz), 7.32–7.26 (4H, m), 6.82 (2H, d, *J* = 8.8 Hz), 4.74 (1H, t, *J* = 6.2 Hz), 3.81 (3H, s), 3.18 (2H, app. q, *J* = 6.5 Hz), 2.55 (2H, t, *J* = 6.5 Hz), 2.42 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.6, 143.7, 137.2, 133.2, 129.9, 127.3, 115.1, 114.1, 84.0, 82.9, 55.4, 42.1, 21.7, 20.8.

S86e 4-Methyl-*N*-(4-(*p*-tolyl)but-3-yn-1-yl)benzenesulfonamide



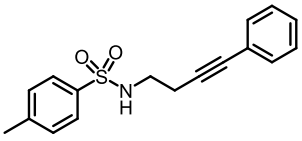
S85e (1.95 g, 12.2 mmol, 1.0 equiv.), methyl tosylcarbamate (3.35 g, 14.6 mmol, 1.2 equiv), Ph_3P (3.83 g, 14.6 mmol, 1.2 equiv.), DIAD (2.9 mL, 14.6 mmol, 1.2 equiv.) were used in **General Procedure 2** followed by deprotection with K_2CO_3 (3.37 g, 24.4 mmol, 2.0 equiv.). The crude material was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (2.46 g, 7.86 mmol, 64%) as a brown solid. *NMR data is consistent with that reported in the literature.*[228]

R_f (CH_2Cl_2) 0.62.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 7.24 (2H, d, *J* = 7.9 Hz), 7.10 (2H, d, *J* = 7.9 Hz), 4.78 (1H, s), 3.18 (2H, app. q, *J* = 6.5 Hz), 2.56 (2H, t, *J* = 6.5 Hz), 2.42 (3H, s), 2.34 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 138.4, 137.2, 131.7, 129.9, 129.2, 127.3, 119.9, 84.8, 83.2, 42.1, 21.7, 21.6, 20.9.

S86f 4-Methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide



S85f (1.93 g, 13.2 mmol, 1.0 equiv.), methyl tosylcarbamate (3.63 g, 15.8 mmol, 1.2 equiv), Ph_3P (4.14 g, 15.8 mmol, 1.2 equiv.), DIAD (3.1 mL, 15.8 mmol, 1.2 equiv.) were used in

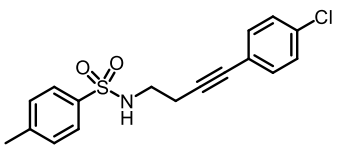
General Procedure 2 followed by deprotection with K_2CO_3 (3.65 g, 26.4 mmol, 2.0 equiv.). The crude material was purified by flash column chromatography (SiO_2, CH_2Cl_2 + 1% MeOH) to give the title compound as an orange solid (1.79 g, 5.99 mmol, 45%). *NMR data is consistent with that reported in the literature.*[228]

R_f (CH_2Cl_2) 0.65

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79–7.76 (2H, m), 7.37–7.33 (2H, m), 7.32–7.28 (5H, m), 4.73 (1H, t, *J* = 6.2 Hz), 3.20 (2H, app. q, *J* = 6.5 Hz), 2.58 (2H, t, *J* = 6.5 Hz), 2.42 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.1, 131.8, 129.9, 128.4, 128.3, 127.2, 123.0, 85.7, 83.0, 42.1, 21.6, 20.9.

S86g *N*-(4-(4-Chlorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide



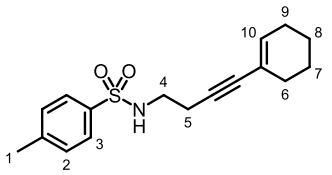
S85g (2.00 g, 11.1 mmol, 1.0 equiv.), methyl tosylcarbamate (3.05 g, 13.3 mmol, 1.2 equiv.), DIAD (2.61 mL, 13.3 mmol, 1.2 equiv.) and PPh_3 (3.49 g, 13.3 mmol, 1.2 equiv.) were used in **General Procedure 2** followed by deprotection with K_2CO_3 (3.06 g, 22.2 mmol, 2.0 equiv.) with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (1.25 g, 3.75 mmol, 34%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[228]

R_f (EtOAc in pentane, 20%) 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.4 Hz), 7.30–7.22 (6H, m), 5.12 (1H, t, *J* = 6.2 Hz), 3.17 (2H, app. q, *J* = 6.6 Hz), 2.56 (2H, t, *J* = 6.6 Hz), 2.40 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.1, 134.2, 133.0, 129.9, 128.7, 127.2, 121.6, 86.9, 81.7, 42.0, 21.6, 20.9.

S86h ***N*-(4-(Cyclohex-1-en-1-yl)but-3-yn-1-yl)-4-methylbenzenesulfonamide**



S85h (0.400 g, 2.67 mmol, 1.0 equiv.), methyl tosylcarbamate (0.730 g, 3.20 mmol, 1.2 equiv.), DIAD (0.63 mL, 3.20 mmol, 1.2 equiv.) and PPh_3 (0.839 g, 3.20 mmol, 1.2 equiv.) were used in **General Procedure 2** followed by deprotection with K_2CO_3 (0.734 g, 6.40 mmol, 2.0 equiv.) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.589 g, 1.94 mmol, 73%) as an orange oil.

R_f (EtOAc in pentane, 20%) 0.60.

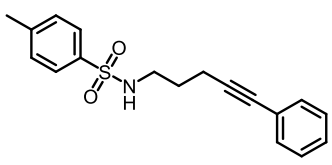
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77–7.74 (2H, m, H3), 7.31 (2H, d, *J* = 7.9 Hz, H2), 6.01 (1H, dq, *J* = 4.1, 1.8 Hz, H10), 4.72 (1H, t, *J* = 6.4 Hz, NH), 3.09 (2H, q, *J* = 6.4 Hz, H4), 2.46–2.41 (5H, m, H5 + H1), 2.10–2.02 (4H, m, 2 × CH_2), 1.65–1.53 (4H, m, 2 × CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.2, 134.9, 129.9, 127.3, 120.4, 85.0, 82.6, 42.1, 29.5, 25.7, 22.4, 21.7, 21.6, 20.6.

HRMS (ES^+) calc. for $C_{17}H_{22}O_2NS$ ($[M+H]^+$) 304.1366, found 304.1364.

IR (thin film, ν_{max}/cm^{-1}) 3284, 2928, 1598, 1435, 1327, 1159, 1094.

S82s 4-Methyl-*N*-(5-phenylpent-4-yn-1-yl)benzenesulfonamide



4-Methyl-*N*-(pent-4-yn-1-yl)benzenesulfonamide (1.00 g, 4.21 mmol, 1.0 equiv) was used in **General Procedure 1** with iodobenzene (1.40 mL, 12.6 mmol, 3.0 equiv.) with purification by

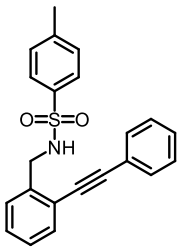
flash column chromatography (SiO_2, EtOAc in pentane, 10%) to give the title compound (1.16 g, 3.71 mmol, 88%) as a brown solid. *NMR data is consistent with that reported in the literature.*[229]

R_f (EtOAc in pentane, 20%) 0.35.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78–7.75 (2H, m), 7.35–7.32 (2H, m), 7.29–7.26 (5H, m), 4.74 (1H, d, *J* = 6.3 Hz), 3.13 (2H, q, *J* = 6.8 Hz), 2.44 (2H, t, *J* = 6.8 Hz), 2.40 (3H, s), 1.77 (2H, p, *J* = 6.8 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.6, 137.0, 131.7, 129.9, 128.4, 128.0, 127.3, 123.6, 88.4, 81.9, 42.5, 28.4, 21.6, 16.9.

S82t 4-Methyl-*N*-(2-(phenylethynyl)benzyl)benzenesulfonamide



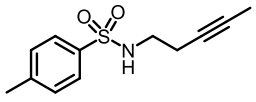
N-(2-Iodobenzyl)-4-methylbenzenesulfonamide (1.50 g, 3.88 mmol, 1.0 equiv.), phenylacetylene (0.51 mL, 4.65 mmol, 1.2 equiv.), $PdCl_2(PPh_3)_2$ (0.162 g, 0.233 mmol, 6 mol%) and CuI (22.0 mg, 0.115 mmol, 3 mol%) were added to a flask which was evacuated under high vacuum and backfilled with argon. Anhydrous THF (5.0 mL) and Et_3N (2.0 mL) were then added and the reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and filtered, then concentrated in vacuo and passed through a SiO_2 plug, then purified by recrystallisation from hot ethanol to give the title compound (0.630 g, 0.998 mmol, 26%) as a brown solid. *NMR data is consistent with that reported in the literature.*[230]

R_f (EtOAc in pentane, 10%) 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.4 Hz), 7.48–7.33 (6H, m), 7.30–7.22 (3H, m), 7.18 (2H, d, *J* = 8.0 Hz), 4.92 (1H, t, *J* = 6.5 Hz), 4.37 (2H, d, *J* = 6.5 Hz), 2.37 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.5, 137.9, 137.1, 132.5, 131.7, 129.8, 129.0, 128.9 (2 C), 128.6, 128.0, 127.3, 122.7, 122.5, 94.6, 86.6, 46.5, 21.7.

S86u 4-Methyl-*N*-(pent-3-yn-1-yl)benzenesulfonamide



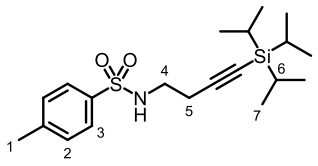
3-Pentyn-1-ol (0.65 mL, 7.02 mmol, 1.0 equiv.) was dissolved in dry THF (100 mL) and PPh_3 (2.11 g, 8.07 mmol, 1.2 equiv.) and methyl tosylcarbamate (1.85 g, 8.07 mmol, 1.2 equiv.) were added and the reaction mixture was cooled to 0 °C. DIAD (1.58 mL, 8.07 mmol, 1.2 equiv.) was added dropwise over 10 minutes at 0 °C. The reaction was then stirred for 1 h at room temperature, then concentrated and the residue directly purified by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 30%). The fractions were concentrated and the residue was dissolved in MeOH (50 mL) and K_2CO_3 (1.94 g, 14.0 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 1 h, then concentrated and subjected to an EtOAc / NH_4Cl work up. The combined organic layers were dried over $MgSO_4$ and concentrated to give the title compound (1.12 g, 4.73 mmol, 67% over two steps) as a colourless solid. *NMR data is consistent with that reported in literature*.[228]

R_f (EtOAc in pentane, 20%) 0.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.73 (2H, m), 7.32–7.28 (2H, m), 4.94 (1H, t, *J* = 6.4 Hz), 3.03 (2H, app. q, *J* = 6.4 Hz), 2.41 (3H, s), 2.30–2.21 (2H, m), 1.72 (3H, t, *J* = 2.5 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.6, 137.1, 129.8, 127.2, 78.5, 75.1, 42.2, 21.6, 20.0, 3.5.

S86v 4-Methyl-*N*-(4-(triisopropylsilyl)but-3-yn-1-yl)benzenesulfonamide



N-(But-3-yn-1-yl)-4-methylbenzenesulfonamide (1.00 g, 4.50 mmol, 1.0 equiv.) was dissolved in dry THF (10 mL) and cooled to −78 °C. ^{n}BuLi (2.1 M in hexanes, 4.3 mL, 9.00 mmol, 2.0 equiv.) was added dropwise at −78 °C and the reaction was stirred at −78 °C for 1 h. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The reaction mixture was then cooled again to −78 °C and TIPSCl (1.1 mL, 5.00 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was allowed warm to room temperature and stirred at room temperature for 1 h, before adding 1M HCl (10 mL) and stirring at room temperature for 16 h. The reaction mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (0.980 g, 2.59 mmol, 57%) as a colourless oil.

R_f (EtOAc in pentane, 20%) 0.53.

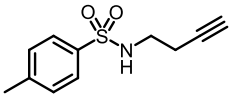
^{1}H NMR (400 MHz, $CDCl_3$) δ_H δ 7.75 (2H, d, *J* = 8.3 Hz, H3), 7.32–7.29 (2H, m, H2), 4.65 (1H, t, *J* = 6.2 Hz, N**H**), 3.11 (2H, app. q, *J* = 6.4 Hz, H4), 2.43 (3H, s, H1), 2.40 (2H, t, *J* = 6.4 Hz, H5), 1.05–1.02 (21H, m, H6 + H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.2, 129.9, 127.2, 104.2, 83.9, 42.1, 21.7, 21.1, 18.7, 11.2.

HRMS (ES^+) calc. for $C_{20}H_{33}O_2NNaSSi$ ($[M+Na]^+$) 402.1893, found 402.1893.

IR (cm^{-1}) 3362, 3176, 1675, 1627, 1431, 1350, 1201, 1183, 1138, 1075.

S86w *N*-(But-3-yn-1-yl)-4-methylbenzenesulfonamide



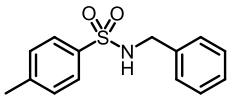
3-Butyn-1-ol (2.16 mL, 28.5 mmol, 1.0 equiv.), PPh_3 (8.58 g, 32.7 mmol, 1.2 equiv), methyl tosylcarbamate (7.50 g, 32.7 mmol, 1.2 equiv.) and DIAD (6.42 mL, 32.7 mmol, 1.2 equiv.) were used in **General Procedure 2** with anhydrous THF (200 mL) followed by deprotection with K_2CO_3 (7.88 g, 57.0 mmol, 2.0 equiv.) in MeOH (200 mL) with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (3.54 g, 15.9 mmol, 56%) as a colourless solid. *NMR data is consistent with that reported in literature.*[228]

R_f (EtOAc in pentane, 20%) 0.39.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77–7.74 (2H, m), 7.32–7.29 (2H, m), 4.74 (1H, t, *J* = 7.4 Hz), 3.12 (2H, app. q, *J* = 6.5 Hz), 2.43 (3H, s), 2.35 (2H, td, *J* = 6.5, 2.6 Hz), 2.00 (1H, t, *J* = 2.6 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.1, 129.9, 127.2, 80.4, 71.0, 41.8, 21.6, 19.9.

S1 *N*-Benzyl-4-methylbenzenesulfonamide



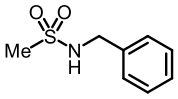
Benzylamine (3.06 mL, 28.0 mmol, 1.2 equiv) and *p*-toluenesulfonyl chloride (4.45 g, 23.3 mmol, 1.0 equiv.) were used in **General Procedure 3** to give the title compound (4.78 g, 18.3 mmol, 79%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[231]

R_f (EtOAc in pentane, 20%) 0.33.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.3 Hz), 7.30 (2H, m), 7.27 (3H, m), 7.19 (2H, m), 4.77 (1H, t, *J* = 6.2 Hz), 4.12 (2H, d, *J* = 6.2 Hz), 2.44 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.0, 136.4, 129.9, 128.8, 128.03, 128.00, 127.3, 47.4, 21.7.

S2 *N*-Benzylmethanesulfonamide

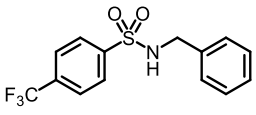


Benzylamine (2.20 mL, 20.0 mmol, 1.0 equiv.) and methanesulfonyl chloride (1.70 mL, 22.0 mmol, 1.1 equiv.) were used in **General Procedure 3** to give the title compound to give the title compound (3.05 g, 16.5 mmol, 82%) as a yellow solid which was used without further purification. *NMR data is consistent with that reported in the literature.*[232]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.29 (5H, m), 4.76 (1H, br. s), 4.32 (2H, s), 2.86 (3H, dd, *J* = 3.0, 1.9 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.8, 129.1, 128.3, 128.1, 47.4, 41.3.

S3 *N*-Benzyl-4-(trifluoromethyl)benzenesulfonamide



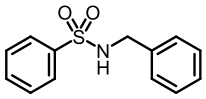
Benzylamine (2.0 mL, 18.4 mmol, 1.5 equiv.) and 4-(trifluoromethyl)benzenesulfonyl chloride (3.00 g, 12.3 mmol, 1.0 equiv.) were used in **General Procedure 3** to give the title compound (3.28 g, 10.4 mmol, 85%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[231]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 (2H, d, *J* = 8.3 Hz), 7.73 (2H, d, *J* = 8.3 Hz), 7.28–7.23 (3H, m), 7.16 (2H, dd, *J* = 6.8, 2.9 Hz), 5.12 (1H, t, *J* = 6.1 Hz), 4.19 (2H, d, *J* = 6.1 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 135.8, 134.5 (d, $^2J_{C\text{-}F}$ = 32.9 Hz), 128.9, 128.3, 128.0, 127.7, 126.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 123.4 (d, $^1J_{C\text{-}F}$ = 272.8 Hz), 47.5.

^{19}F NMR (377 MHz, CDCl3) δ_F –63.15.

S4 *N*-Benzylbenzenesulfonamide

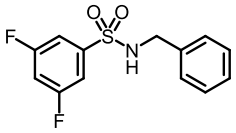


Benzylamine (4.00 mL, 36.8 mmol, 1.5 equiv.) and benzenesulfonyl chloride (3.10 mL, 24.6 mmol, 1.0 equiv.) were used in **General Procedure 3** to give the title compound (5.06 g, 20.5 mmol, 83%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[233]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89–7.86 (2H, m), 7.61–7.56 (1H, m), 7.53–7.47 (2H, m), 7.29–7.24 (3H, m), 7.23–7.18 (2H, m), 5.29 (1H, t, *J* = 6.2 Hz), 4.14 (2H, d, *J* = 6.2 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 139.9, 136.3, 132.7, 129.2, 128.7, 127.91, 127.87, 127.1, 47.2.

S5 *N*-Benzyl-3,5-difluorobenzenesulfonamide



3,5-Difluorophenylsulfonyl chloride (5.00 g, 23.5 mmol, 1.0 equiv.) and benzylamine (3.85 mL, 35.3 mmol, 1.5 equiv.) were used in **General Procedure 3** to give the title compound (5.25 g, 18.6 mmol, 79%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 (2H, ddd, *J* = 5.3, 2.3, 1.2 Hz, ArH), 7.32–7.25 (3H, m, ArH), 7.23–7.17 (2H, m, ArH), 7.00 (1H, tt, *J* = 8.4, 2.3 Hz, ArH), 4.91 (1H, t, *J* = 6.1 Hz, NH), 4.20 (2H, d, *J* = 6.1 Hz, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.9 (dd, $^1J_{C\text{-}F}$ = 254.6, 11.6 Hz) , 143.7 (d, $^3J_{C\text{-}F}$ = 8.3 Hz) , 135.7, 129.0, 128.4, 128.0, 110.9–110.6 (m), 108.4 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 47.6.

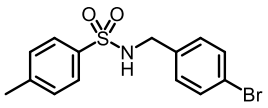
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −105.58.

HRMS (ES^-) calc. for $C_{13}H_{10}O_2NF_2S$ ($[M\text{-}H]^-$) 282.0406, found 282.0401.

IR (thin film, ν_{max}/cm^{-1}) 3298, 3284, 1606, 1495, 1438, 1363, 1332, 1309, 1297, 1152, 1123, 1087, 1063.

MP 87–91 °C.

S6 *N*-(4-Bromobenzyl)-4-methylbenzenesulfonamide

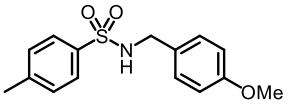


4-Bromobenzylamine (3.29 g, 17.7 mmol, 1.5 equiv.) and *p*-toluenesulfonyl chloride (2.24 g, 11.8 mmol, 1.0 equiv.) were used in **General Procedure 3** to give the title compound (3.55 g, 10.4 mmol, 88%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[234]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8.4 Hz), 7.32–7.30 (2H, m), 7.08 (2H, d, *J* = 8.4 Hz), 4.62 (1H, t, *J* = 6.4 Hz), 4.09 (2H, d, *J* = 6.4 Hz), 2.44 (2H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.9, 137.0, 135.5, 132.0, 130.0, 129.7, 127.3, 122.1, 46.8, 21.7.

S7 *N*-(4-Methoxybenzyl)-4-methylbenzenesulfonamide



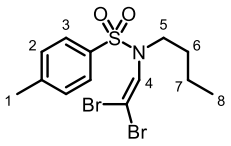
p-Toluenesulfonyl chloride (5.00 g, 23.5 mmol, 1.0 equiv.) and 4-methoxybenzylamine (4.60 mL, 35.3 mmol, 1.5 equiv.) were used in **General Procedure 3** to give the title compound (6.27 g, 21.5 mmol, 92%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[233]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77–7.74 (2H, m), 7.33–7.29 (2H, m), 7.10 (2H, d, *J* = 8.6 Hz), 6.81–6.78 (2H, m), 4.62 (1H, br. s), 4.05 (2H, s), 3.77 (3H, s), 2.44 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.5, 143.6, 137.1, 129.9, 129.4, 128.4, 127.3, 114.2, 55.4, 47.0, 21.7.

7.3.9 Yndiamide precursors: 1,1-dibromoenamides

S87a *N*-Butyl-*N*-(2,2-dibromovinyl)-4-methylbenzenesulfonamide



N-Butyl-4-methylbenzenesulfonamide (5.00 g, 22.0 mmol, 1.0 equiv.), and ^{n}BuLi (2.0 M in hexanes) (11.0 mL, 11.0 mmol, 1.0 equiv.) and . BtCHO (3.96 g, 26.4 mmol, 1.2 equiv.) were used in **General Procedure 4** (stage 1, 15 h) with anhydrous THF (100 mL), followed by CBr_4 (14.6 g, 44.0 mmol, 2.0 equiv.) and Ph_3P (23.2 g, 88.0 mmol, 4.0 equiv.) (stage 2, 18 h) with anhydrous CH_2Cl_2 (160 mL) with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (6.01 g, 14.7 mmol, 67%) as a colourless solid.

R_f (EtOAc in pentane, 5%) 0.33.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.4 Hz, H3), 7.35–7.31 (2H, m, H2), 6.65 (1H, s, H4), 3.34–3.28 (2H, m, H5), 2.44 (3H, s, H1), 1.53–1.45 (2H, m, H6), 1.35 (2H, dt, *J* = 14.8, 7.3 Hz, H7), 0.90 (3H, t, *J* = 7.3 Hz, H8).

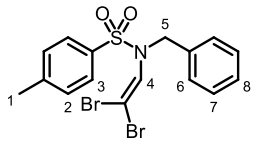
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 135.7, 131.7, 130.0, 127.5, 95.7, 49.1, 30.6, 21.7, 20.0, 13.8.

HRMS (ES^+) calc. for $C_{13}H_{18}O_2N^{79}Br_2S$ $[M+H]^+$ 409.9420, found 409.9419.

IR (thin film, ν_{max}/cm^{-1}) 2871, 1599 1493, 1467. 1387, 1353, 1327, 1293, 1240, 1182, 1164, 1122, 1089, 1059, 1036.

MP 83–85 °C.

S87b *N*-Benzyl-*N*-(2,2-dibromovinyl)-4-methylbenzenesulfonamide



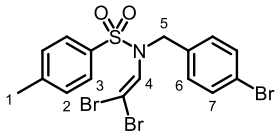
N-Benzyl-4-methylbenzenesulfonamide (3.00 g, 11.4 mmol, 1.0 equiv.), and ^{n}BuLi (2.2 M in hexanes) (5.20 mL, 11.4 mmol, 1.0 equiv.) and BtCHO (2.01 g, 13.7 mmol, 1.2 equiv.) were used in **General Procedure 4** (stage 1, 15 h) with anhydrous THF (115 mL), followed by CBr_4 (7.16 g, 21.6 mmol, 2.0 equiv.) and Ph_3P (11.3 g, 43.2 mmol, 4.0 equiv.) (stage 2, 2 h) with anhydrous CH_2Cl_2 (115 mL) with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (1.76 g, 3.96 mmol, 35%) as a colourless solid. *NMR data is consistent with that reported in the literature.*[1]

R_f (EtOAc in pentane, 20 %) 0.68.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.3 Hz), 7.37–7.27 (7H, m), 6.62 (1H, s), 4.54 (2H, s,), 2.46 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 136.0, 135.2, 131.5, 130.0, 128.8, 128.7, 128.2, 127.6, 98.7, 52.9, 21.8.

S87c *N*-(4-Bromobenzyl)-*N*-(2,2-dibromovinyl)-4-methylbenzenesulfonamide



N-(4-Bromobenzyl)-4-methylbenzenesulfonamide (3.00 g, 8.85 mmol, 1.0 equiv.), NaH (60% w/w) (0.389 g, 9.74 mmol, 1.1 equiv.) and BtCHO (1.56 g, 10.6 mmol, 1.2 equiv.) were used in **General Procedure 4** (stage 1, 2 h) with anhydrous THF (90 mL), followed by CBr_4 (5.87 g, 17.7 mmol, 2.0 equiv.) and PPh_3 (9.27 g, 35.4 mmol, 4.0 equiv.) (stage 2, 18 h) with anhydrous CH_2Cl_2 (90 mL), after which the reaction was incomplete. Stage 2 was repeated, and purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 30%) gave the title compound (1.10 g, 2.10 mmol, 24%) as a colourless solid.

R_f (EtOAc in pentane, 20%) 0.74.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.4 Hz, H3), 7.44 (2H, d, *J* = 8.4 Hz, H6), 7.37–7.31 (2H, m, H2), 7.16 (2H, d, *J* = 8.4 Hz, H7), 6.63 (1H, s, H4), 4.49 (2H, s, H5), 2.46 (3H, s, H1).

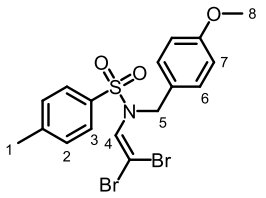
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.6, 135.8, 134.4, 131.9, 131.3, 130.4, 130.1, 127.6, 122.3, 97.2, 52.2, 21.8.

HRMS (ES^+) calc. for $C_{16}H_{15}O_2N^{79}Br_2{}^{81}BrS$ 525.8327, found 525.8326.

IR (thin film, ν_{max}/cm^{-1}) 2879, 1700, 1596, 1489, 1406, 1359, 1293, 1222, 1164, 1090, 1041, 1012.

MP 134–138 °C.

S87d *N*-(2,2-Dibromovinyl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide



N-(4-Methoxybenzyl)-4-methylbenzenesulfonamide (3.49 g, 12.6 mmol, 1.0 equiv.), ^{n}BuLi (1.4 M in hexanes, 9.00 mL, 12.6 mmol, 1.0 equiv.) and BtCHO (2.22 g, 15.1 mmol, 1.2 equiv.) were used in **General Procedure 4** (stage 1, 30 min) with anhydrous THF (125 mL), followed by CBr_4 (8.36 g, 25.2 mmol, 2.0 equiv.) and PPh_3 (13.2 g, 50.4 mmol, 4.0 equiv.) (stage 2, 18 h) with anhydrous CH_2Cl_2 (126 mL) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 30%) to give the title compound (2.18 g, 4.40 mmol, 37%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.50.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.1 Hz, H3), 7.33 (2H, d, *J* = 8.1 Hz, H2), 7.19 (2H, d, *J* = 8.7 Hz, H6), 6.83 (2H, d, *J* = 8.7 Hz, H7), 6.56 (1H, s, H4), 4.47 (2H, s, H5), 3.79 (3H, s, H8), 2.45 (3H, s, H1).

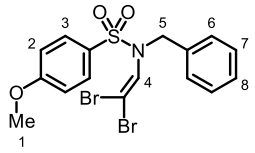
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.6, 144.3, 135.9, 131.5, 130.2, 130.0, 127.6, 127.1, 114.0, 97.5, 55.4, 52.4, 21.7.

HRMS (ES^+) calc. for $C_{17}H_{17}O_3N^{79}Br^{81}BrSNa$ ($[M+Na]^+$) 497.9168, found 497.9167.

IR (solid, ν_{max}/cm^{-1}) 2921, 1615, 1596, 1514, 1457, 1439, 1354, 1329, 1300, 1249, 1166, 1088, 1057, 1024.

MP 132–136 °C.

S87e *N*-Benzyl-*N*-(2,2-dibromovinyl)-4-methoxybenzenesulfonamide



N-Benzyl-4-methoxybenzenesulfonamide (1.76 g, 6.35 mmol, 1.0 equiv.), ^{n}BuLi (1.9 M in hexanes, 3.30 mL, 6.35 mmol, 1.0 equiv.) and BtCHO (1.12 g, 7.62 mmol, 1.2 equiv.) were used in **General Procedure 4** with anhydrous THF (65 mL) (stage 1, 30 min), then Ph_3P (6.66 g, 25.4 mmol, 4.0 equiv.) and CBr_4 (4.21 g, 12.7 mmol, 2.0 equiv.) (stage 2, 18 h) with anhydrous CH_2Cl_2 (65 mL) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 10%) to give the title compound (0.190 g, 0.41 mmol, 7%) as a colourless solid.

R_f (EtOAc in pentane, 20%) 0.51.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 9.0 Hz, H3), 7.32–7.27 (5H, m, H6 + H7 + H8), 7.02–6.98 (2H, m, H2), 6.63 (1H, s, H4), 4.55 (2H, s, H5), 3.89 (3H, s, H1).

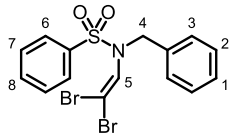
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.6, 135.3, 131.6, 130.5, 129.8, 128.8, 128.7, 128.2, 114.6, 97.1, 55.8, 52.9.

HRMS (ES^+) calc. for $C_{16}H_{16}O_3N^{79}Br^{81}BrS$ ($[M+H]^+$) 461.9192, found 461.9192.

IR (solid, ν_{max}/cm^{-1}) 2974, 1696, 1595, 1576, 1495, 1456, 1439, 1350, 1319, 1306, 1261, 1183, 1159, 1113, 1091, 1049, 1024.

MP 111–115 °C.

S87f *N*-Benzyl-*N*-(2,2-dibromovinyl)benzenesulfonamide



N-Benzyl-benzenesulfonamide (3.00 g, 12.1 mmol, 1.0 equiv.), ^{n}BuLi (2.0 M in hexanes) (6.05 mL, 12.1 mmol, 1.0 equiv.) and BtCHO (2.13 g, 14.5 mmol, 1.2 equiv.) were used in **General Procedure 4** with anhydrous THF (120 mL) (stage 1, 1 h), then Ph_3P (12.7 g, 48.4 mmol, 4.0 equiv.) and CBr_4 (8.07 g, 24.2 mmol, 2.0 equiv.) with anhydrous CH_2Cl_2 (120 mL) (stage 2, 18 h) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (0.361 g, 0.84 mmol, 7%) as a colourless solid.

R$_f$ (EtOAc in pentane, 20%) 0.75.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87–7.83 (2H, m, ArH), 7.66–7.61 (1H, m, ArH), 7.58–7.52 (2H, m, ArH), 7.33–7.25 (5H, m, ArH), 6.65 (1H, s, H5), 4.57 (2H, s, H4).

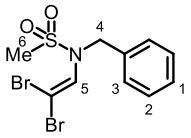
^{13}C NMR (101 Hz, $CDCl_3$) δ_C 138.9, 135.1, 133.4, 131.3, 129.4, 128.8, 128.7, 128.3, 127.5, 97.6, 52.9.

HRMS (ES^+) calc. for $C_{15}H_{14}O_2N^{79}Br^{81}BrS$ ($[M+H]^+$) 431.9086, found 431.9087.

IR (solid, ν_{max}/cm^{-1}) 3065, 2980, 1699, 1495, 1446, 1350, 1324, 1165, 1088, 1046, 1025.

MP 84–88 °C.

S87g *N*-Benzyl-*N*-(2,2-dibromovinyl)methanesulfonamide



N-Benzylmethanesulfonamide (2.00 g, 10.7 mmol, 1.0 equiv.), ^{n}BuLi (2.1 M in hexanes) (5.10 mL, 10.7 mmol, 1.0 equiv.) and BtCHO (1.90 g, 12.9 mmol, 1.2 equiv.) were used in **General Procedure 4** with anhydrous THF (55 mL) (stage 1, 1 h), then Ph_3P (11.2 g, 42.8 mmol, 4.0 equiv.) and CBr_4 (7.10 g, 21.4 mmol, 2.0 equiv.) with anhydrous CH_2Cl_2 (150 mL) (stage 2, 16 h) with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10%) to give the title compound (1.68 g, 4.57 mmol, 43%) as a pale yellow solid.

R_f (EtOAc in pentane, 10%) 0.70.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39–7.32 (5H, m, H1 + H2 + H3), 6.83 (1H, s, H5), 4.73 (2H, s, H4), 2.96 (3H, s, H6).

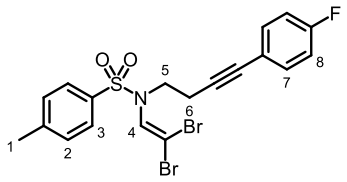
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 135.3, 131.8, 128.9, 128.8, 128.4, 96.3, 52.6, 41.0.

HRMS (ES^+) calc. for $C_{10}H_{11}NO_2{}^{79}Br^{81}BrNaS$ ($[M+Na]^+$) 391.8749, found 391.8750.

IR (thin film, ν_{max}/cm^{-1}) 3029, 1325, 1152, 1037.

MP 98–102 °C.

88 *N*-(2,2-Dibromovinyl)-*N*-(4-(4-fluorophenyl)but-3-yn-1-yl)-4-methylbenzene sulfonamide



N-(4-(4-Fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (4.00 g, 12.6 mmol, 1.0 equiv.), ^{n}BuLi (1.4 M in hexanes) (9.00 mL, 12.6 mmol, 1.0 equiv.) and BtCHO (2.22 g, 15.1 mmol, 1.2 equiv.) were used in **General Procedure 4** (stage 1, 1.5 h) with anhydrous THF (125 mL), then CBr_4 (8.36 g, 25.2 mmol, 2.0 equiv.) and PPh_3 (13.2 g, 50.4 mmol, 4.0 equiv.) (stage 2, 20 h) with anhydrous CH_2Cl_2 (125 mL), with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (3.34 g, 6.68 mmol, 53%) as a brown oil which solidified to give a pale brown solid on standing.

R_f (EtOAc in pentane, 20%) 0.73.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.70 (2H, m, H3), 7.38–7.34 (2H, m, H7),), 7.33–7.31 (2H, m, H2), 6.97 (2H, t, *J* = 8.7 Hz, H8), 6.86 (1H, s, H4), 3.62 (2H, t, *J* = 7.3 Hz, H5), 2.71 (2H, t, *J* = 7.3 Hz, H6), 2.43 (3H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.4 (d, $^{1}J_{C\text{-}F}$ = 248.9 Hz), 144.5, 135.8, 133.6 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 131.5, 130.1, 127.5, 119.4 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 115.6 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz), 96.3, 85.7, 81.9, 48.3, 21.7, 20.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −111.42.

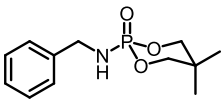
HRMS (ES^+) calc. for $C_{19}H_{17}O_2N^{79}Br^{81}BrFS$ ($[M+H]^+$) 501.9305, found 501.9304.

IR (thin film, ν_{max}/cm^{-1}) 2921, 1599, 1506, 1449, 1353, 1221, 1161, 1092.

MP 72–76 °C.

7.3.10 Yndiamide precursors: phosphoramidite

S8 2-(Benzylamino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide



$POCl_3$ (0.90 mL, 9.60 mmol, 1.0 equiv.) and Et_3N (3.00 mL, 21.4 mmol, 2.2 equiv.) were dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C. 2,2-Dimethyl-1,3-propanediol (1.00 g, 9.60 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 0 °C for 30 minutes. Benzylamine (1.26 mL, 11.5 mmol, 1.2 equiv.) and Et_3N (1.3 mL, 9.30 mmol, 0.97 equiv.) were added and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was washed with 6 M HCl (50 mL) and water (50 mL), then the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc) to give the title compound (1.41 g, 5.53 mmol, 58%) as a colourless solid.

R_f (EtOAc) 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.27 (5H, m), 4.34 (2H, dd, *J* = 10.9, 4.1 Hz), 4.22 (2H, dd, *J* = 10.1, 6.9 Hz), 3.94–3.72 (2H, m), 3.31 (1H, p, *J* = 6.9 Hz), 1.24 (3H, s), 0.93 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 139.3 (d, *J* = 6.3 Hz), 128.7, 127.5, 127.4, 78.5 (d, *J* = 7.1 Hz), 45.4, 31.9 (d, *J* = 4.9 Hz), 22.1, 20.9.

^{31}P NMR (162 MHz, $CDCl_3$) δ_P 5.12

7.3.11 X-Ray Crystallography

Low temperature single crystal X-ray diffraction data were collected using Oxford Diffraction (Rigaku) SuperNovae diffractometers at 150 K. These data were reduced using CrysAlisPro, solved using SuperFlip66 and the structures were refined using CRYSTALS. Further details about the refinements are documented in the CIF. *X-Ray data for **84b** and **84c** was collected and processed by Dr Kirsten Christensen, X-ray data for **84r** was collected and processed by Helena Pickford.*

Table 7.3.1. Crystal data and structure refinement for 84b.

CCDC Identification code	2090823	
Empirical formula	$C_{30}H_{30}N_2O_4S_2$	
Formula weight	546.71	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 15.7521(2) Å	α= 90°
	b = 10.66930(10) Å	β= 109.8954(15)°
	c = 16.8095(2) Å	γ = 90°.
Volume	2656.46(6) $Å^3$	
Z	4	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	2.141 mm^{-1}	
F(000)	1152	
Crystal size	0.14 × 0.10 × 0.04 mm^3	
Theta range for data collection	2.983 to 77.125°	
Index ranges	-19<=h<=19, –13<=k<=13, –21<=l<=18	
Reflections collected	16846	
Independent reflections	5563 [$R_{(int)}$ = 0.026]	

Completeness to theta = 74.812°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.92 and 0.83
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5562 / 0 / 344
Goodness-of-fit on F^2	1.0053
Final R indices [I>2sigma(I)]	R_1 = 0.0316, wR_2 = 0.0801
R indices (all data)	R_1 = 0.0362, wR_2 = 0.0842
Extinction coefficient	24(3)
Largest diff. peak and hole	0.37 and –0.38 e.Å^{-3}

Table 7.3.2. Crystal data and structure refinement for 84c.

CCDC Identification code	2090822	
Empirical formula	$C_{33}H_{29}FO_4S_2$	
Formula Weight	600.73	
Temperature	150 K	
Wavelength	1.54180	
Crystal system	Monoclinic	
Space Group	P 21/n	
Unit cell dimensions	a = 9.81670(10) Å	α = 90°
	b = 19.1257(2) Å	β = 90.8906(12)°
	c = 15.4248(2) Å	γ = 90°
Volume	2895.68(6) Å^3	
Z	4	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	2.070 mm^{-1}	
F(000)	1256	
Crystal size	0.10 × 0.10 × 0.10 mm^3	

Theta range for data collection	3.68 to 76.30°
Index ranges	-12<=h<=12, 0<=k<=24, 0<=l<=19
Reflections collected	26037
Independent reflections	6014 [$R_{(int)}$ = 0.058]
Completeness to theta = 76.30°	99.0%
Absorption correction	Multi Scan
Max. and min. transmission	0.98 and 0.87
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6011 / 0 / 379
Goodness-of-fit on F2	1.0019
Final R indices [I>2sigma(I)]	R_1 = 0.0437, wR_2 = 0.1103
R indices (all data)	R_1 = 0.0539, wR_2 = 0.1240
Largest diff. peak and hole	0.41 and –0.45 e.Å-3

Table 7.3.3. Crystal data and structure refinement for 84r.

CCDC Identification code	2090824	
Empirical formula	$C_{32}H_{36}FN_2O_6PS$	
Formula weight	626.68	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 13.1065(2) Å	α = 90°
	b = 15.4749(2) Å	β = 99.4605(12)°
	c = 15.6201(2) Å	γ = 90°
Volume	3125.01(8) $Å^3$	
Z	4	
Density (calculated)	1.332 Mg/m^3	
Absorption coefficient	1.846 mm^{-1}	

F(000)	1320
Crystal size	0.12 × 0.09 × 0.04 mm^3
Theta range for data collection	4.049 to 76.165°.
Index ranges	-16<=h<=16, −17<=k<=19, −19<=l<=19
Reflections collected	57821
Independent reflections	6534 [$R_{(int)}$ = 0.038]
Completeness to theta	= 76.165° 99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.93 and 0.82
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	6534 / 286 / 416
Goodness-of-fit on F2	1.0017
Final R indices [I>2sigma(I)]	R_1 = 0.0318, wR_2 = 0.0832
R indices (all data)	R_1 = 0.0365, wR_2 = 0.0877
Largest diff. peak and hole	0.47 and −0.47 e.Å-3

Table 7.3.4. Crystal data and structure refinement for 93d.

Empirical formula	$C_{34}H_{32}N_2O_5S_2$	
Formula weight	612.77	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 16.0767(15) Å	α = 90°
	b = 10.3510(8) Å	β = 108.545(11)°
	c = 19.393(2) Å	γ = 90°
Volume	3059.6(5) $Å^3$	
Z	4	
Density (calculated)	1.330 Mg/m^3	

Absorption coefficient	1.946 mm^{-1}
F(000)	1288
Crystal size	0.17 x 0.04 x 0.03 mm^3
Theta range for data collection	4.317 to 77.276°.
Index ranges	-18<=h<=20, -13<=k<=12, -24<=l<=24
Reflections collected	22339
Independent reflections	6330 [$R_{(int)}$ = 0.127]
Completeness to theta	= 74.185° 99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.94 and 0.65
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	6329 / 0 / 388
Goodness-of-fit on F2	1.0170
Final R indices [I>2sigma(I)]	R_1 = 0.0747, wR_2 = 0.1610
R indices (all data)	R_1 = 0.1553, wR_2 = 0.2272
Largest diff. peak and hole	0.80 and –0.79 e.Å-3

7.4 Chapter 3 Characterisation Data

7.4.1 Rhodium(I) catalysts

Synthesis of (*rac*-BIPHEP)Rh(cod)SbF$_6$ (Rh-1)

[Rh(cod)$_2$]SbF$_6$ (20.0 mg, 0.034 mmol, 1.0 equiv.) and *rac*-BIPHEP (18.8 mg, 0.034 mmol, 1.0 equiv.) were dissolved in anhydrous CH_2Cl_2 (1.0 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the solid was washed with Et_2O (5 × 1.0 mL) and dried under high vacuum to give the title compound (27.1 mg, 0.028 mmol, 83%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.41 (16H, m), 7.38–7.27 (6H, m), 7.11–7.04 (2H, m), 7.02–6.96 (2H, m), 6.35–6.32 (2H, m), 4.75–4.69 (2H, m), 4.65–4.56 (2H, m), 2.84–2.72 (2H, m), 2.57–2.49 (2H, m), 2.24–2.15 (2H, m), 2.08–1.95 (2H, m).

^{31}P NMR (162 MHz, $CDCl_3$) δ_P 24.36 (d, J = 145.6 Hz).

Synthesis of (*rac*-BINAP)Rh(cod)SbF$_6$ (Rh-2)

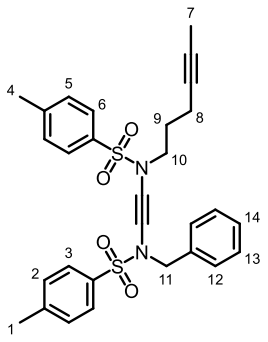
[Rh(cod)$_2$]SbF$_6$ (0.149 g, 0.27 mmol, 1.0 equiv.) and *rac*-BINAP (0.168 g, 0.27 mmol, 1.0 equiv.) were dissolved in anhydrous CH_2Cl_2 (7.5 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the solid was washed with Et_2O (5 × 1.0 mL) and dried under high vacuum to give the title compound (0.230 g, 0.22 mmol, 80%) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85–7.78 (2H, m), 7.64 (2H, d, J = 9.3 Hz), 7.56–7.52 (2H, m), 7.49–7.41 (10H, m), 7.38–7.31 (4H, m), 7.30–7.24 (2H, m), 6.93–6.87 (2H, m), 6.76–6.68 (2H, m), 6.68–6.60 (4H, m), 6.40–6.34 (2H, m), 4.75–4.68 (2H, m), 4.57–4.50 (2H, m), 2.63–2.51 (2H, m), 2.37–2.18 (4H, m), 2.08–1.99 (2H, m).

^{31}P NMR (162 MHz, $CDCl_3$) δ_P 25.42 (d, J = 146.2 Hz).

7.4.2 Yndiamides

193 *N*-Benzyl-*N*-(((*N*-(hex-4-yn-1-yl)-4-methylphenyl)sulfonamido)ethynyl)-4-methyl benzenesulfonamide



N-(Hex-4-yn-1-yl)-4-methylbenzenesulfonamide (0.128 g, 0.51 mmol, 1.0 equiv.), **S87b** (0.250 g, 0.56 mmol, 1.1 equiv.), CuI (19.5 mg, 0.10 mmol, 20 mol%), 1,10-phenanthroline (36.9 mg, 0.20 mmol, 40 mol%) and Cs_2CO_3 (0.500 g, 1.53 mmol, 3.0 equiv.) were submitted to **General Procedure 5** with anhydrous THF (1.5 mL) for 40 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (0.215 g, 0.40 mmol, 79%) as a viscous yellow oil.

R_f (EtOAc in pentane, 20%) 0.43.

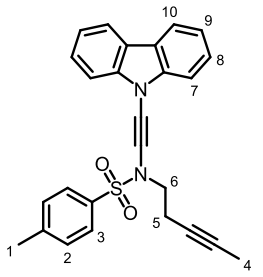
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.4 Hz, ArH), 7.62 (2H, d, *J* = 8.4 Hz, ArH), 7.32–7.25 (7H, m, ArH), 7.20–7.15 (2H, m, ArH), 4.49 (2H, s, H11), 3.30 (2H, t, *J* = 7.1 Hz, H10), 2.45 (3H, s, CH_3), 2.44 (3H, s, CH_3), 1.92 (2H, tq, *J* = 7.1, 2.6 Hz, H8), 1.75 (3H, t, *J* = 2.6 Hz, H7), 1.48 (2H, p, *J* = 7.1 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 144.6, 135.1, 135.0, 134.8, 129.82, 129.78, 128.9, 128.6, 128.3, 127.9, 127.7, 77.6, 76.6, 69.7, 69.5, 56.1, 50.7, 27.2, 21.8 (2 C), 15.8, 3.6.

HRMS (ES^+) calc. for $C_{29}H_{31}O_4N_2S_2$ ($[M+H]^+$) 535.1718, found 535.1697.

IR (thin film, ν_{max}/cm^{-1}) 2976, 1363, 1168, 1089, 1013.

199 *N*-((9*H*-Carbazol-9-yl)ethynyl)-4-methyl-*N*-(pent-3-yn-1-yl)benzenesulfonamide



S86u (0.237 g, 1.0 mmol, 1.0 equiv.), **197a** (0.385 g, 1.1 mmol, 1.1 equiv.), CuI (38.0 mg, 0.20 mmol, 20 mol%), 1,10-phenanthroline (72.0 mg, 0.40 mmol, 40 mol%) and Cs_2CO_3 (0.975 g, 3.0 mmol, 3.0 equiv.) were submitted to **General Procedure 5** with anhydrous THF (3.0 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10%) followed by recrystallisation from pentane/Et_2O (1:1 v/v) to give the title compound (80.0 mg, 0.19 mmol, 19%) as a brown solid.

R_f (EtOAc in pentane, 10%) 0.34.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.00 (2H, d, *J* = 7.9 Hz, H3), 7.90 (2H, d, *J* = 8.4 Hz, ArH), 7.46 (4H, dd, *J* = 3.9, 0.8 Hz, ArH), 7.38 (2H, d, *J* = 7.9 Hz, H2), 7.33 (2H, dt, *J* = 8.1, 4.1 Hz, ArH), 3.70 (2H, t, *J* = 7.4 Hz, H6), 2.60 (2H, app. tp, *J* = 7.5, 2.7 Hz, H5), 2.50 (3H, s, H1), 1.71 (3H, t, *J* = 2.7 Hz, H4).

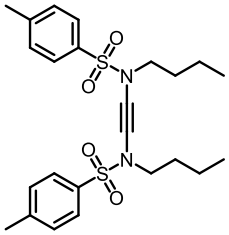
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.9, 141.4, 134.9, 129.9, 128.1, 126.8, 123.9, 122.4, 120. 4, 111.6, 78.2, 74.8, 72.2, 65.0, 51.4, 21.9, 19.0, 3.6.

HRMS (ES^+) calc. for $C_{26}H_{23}O_2N_2S$ ($[M+H]^+$) 427.1475, found 427.1476.

IR (solid, ν_{max}/cm^{-1}) 2981, 2972, 2889, 1496, 1464, 1377, 1224, 1170, 1089.

MP 127–129 °C.

188 *N,N'*-(Ethyne-1,2-diyl)bis(*N*-butyl-4-methylbenzenesulfonamide)



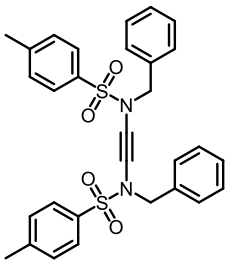
BuNHTs (0.504 g, 2.22 mmol, 1.0 equiv.), **S87a** (1.00 g, 2.44 mmol, 1.1 equiv.), CuI (84.0 mg, 0.44 mmol, 20 mol%), 1,10-phenanthroline (0.160 g, 0.88 mmol, 40 mol%) and Cs_2CO_3 (2.16 g, 6.66 mmol, 3.0 equiv.) were submitted to **General Procedure 5** with anhydrous THF (7.0 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10%) followed by recrystallisation from pentane/Et_2O (1:1) to give the title compound (0.815 g, 1.71 mmol, 77%) as a white solid. *NMR data is consistent with that reported in the literature.*[21]

R_f (EtOAc in pentane, 10%) 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (4H, d, *J* = 8.0 Hz), 7.31 (4H, d, *J* = 8.0 Hz), 3.32 (4H, t, *J* = 7.2 Hz), 2.45 (6H, s), 1.58–1.46 (4H, m), 1.34–1.19 (4H, m), 0.87 (6H, t, *J* = 7.3 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 135.1, 129.8, 127.7, 68.9, 51.6, 30.0, 21.8, 19.5, 13.7.

212 *N,N'*-(Ethyne-1,2-diyl)bis(*N*-benzyl-4-methylbenzenesulfonamide)



BnNHTs (0.800 g, 3.06 mmol, 1.0 equiv.), **S87b** (1.49 g, 3.36 mmol, 1.1 equiv.), CuI (0.117 g, 0.62 mmol, 20 mol%), 1,10-phenanthroline (0.222 g, 1.24 mmol, 40 mol%) and Cs_2CO_3 (3.02 g, 9.18 mmol, 3.0 equiv.) were submitted to **General Procedure 5** with anhydrous THF

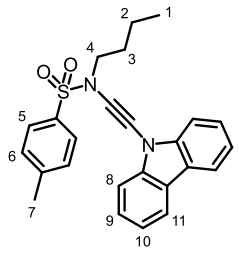
(10.0 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10%) followed by recrystallisation from pentane/Et_2O (1:1) to give the title compound (1.01 g, 1.86 mmol, 61%) as a white solid. *NMR data is consistent with that reported in the literature.*[21]

R_f (EtOAc in pentane, 10%) 0.17.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56–7.54 (4H, m), 7.28–7.17 (10H, m), 7.04–7.01 (4H, m), 4.39 (4H, s), 2.44 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 135.0, 134.7, 129.7, 128.8, 128.5, 128.2, 127.8, 70.1, 56.1, 21.8.

198a *N*-((9*H*-carbazol-9-yl)ethynyl)-*N*-butyl-4-methylbenzenesulfonamide



BuNHTs (2.27 g, 10.0 mmol, 1.00 equiv.), **197a** (3.86 g, 11.0 mmol, 1.1 equiv.), CuI (0.381 g, 2.00 mmol, 0.20 equiv.), Cs_2CO_3 (9.75 g, 30.0 mmol, 3.0 equiv) and 1,10-phenanthroline (0.720 g, 4.0 mmol, 0.40 equiv.) were submitted to **General Procedure 5** with anhydrous THF (30 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 10%) followed by recrystallisation from Et_2O to give the title compound as a cream solid (2.67 g, 6.42 mmol, 64%).

R_f (EtOAc in pentane, 10%) 0.60.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.01 (2H, dd, *J* = 7.7, 2.0 Hz, ArH), 7.89 (2H, d, *J* = 8.5 Hz, H5), 7.49–7.44 (4H, m, ArH), 7.38 (2H, d, *J* = 8.5 Hz, H6), 7.36–7.29 (2H, m, ArH), 3.55 (2H, t, *J* = 7.2 Hz, H4), 2.50 (3H, s, H7), 1.79–1.71 (2H, m, H3), 1.48–1.39 (2H, m, H2), 0.95 (3H, t, *J* = 7.4 Hz, H1).

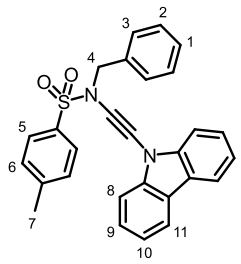
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.7, 141.4, 134.9, 129.9, 128.0, 126.7, 123.8, 122.3, 120.4, 111.5, 72.5, 64.4, 52.0, 30.2, 21.8, 19.6, 13.8.

HRMS (ES^+) calc. for $C_{25}H_{25}O_2N_2S_1$ 417.16313 $[M+H]^+$, found 417.16306.

IR (thin film, ν_{max}/cm^{-1}) 2925, 1597, 1495, 1453, 1364, 1306, 1224, 1169, 1115, 1088.

MP 115–117 °C.

198b *N*-((9*H*-Carbazol-9-yl)ethynyl)-*N*-benzyl-4-methylbenzenesulfonamide



BnNHTs (0.339 g, 1.30 mmol, 1.0 equiv), **197a** (0.500 g,1.43 mmol, 1.1 equiv.), CuI (49.5 mg, 0.26 mmol, 20 mol%), 1,10-phenanthroline (93.6 mg, 0.52 mmol, 40 mol%) and Cs_2CO_3 (1.27 g, 3.90 mmol, 3.0 equiv.) were submitted to **General Procedure 5** with anhydrous THF (3.9 mL) for 20 h with purification by flash column chromatography (SiO_2, CH_2Cl_2 and EtOAc in pentane, 15:5:80) to give the title compound (0.366 g, 0.81 mmol, 63%) as a brown solid.

R_f (Pentane : CH_2Cl_2 : EtOAc, 80:15:5) 0.50.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.98 (2H, dt, *J* = 7.7, 1.0 Hz, H11), 7.82 (2H, d, *J* = 8.3 Hz, H3), 7.44–7.37 (4H, m, ArH), 7.34–7.31 (7H, m, ArH), 7.30–7.26 (2H, m, ArH), 4.75 (2H, s, H4), 2.49 (3H, s, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.8, 141.3, 135.0, 134.9, 129.8, 129.0, 128.7, 128.5, 128.1, 126.7, 123.8, 122.3, 120.4, 111.5, 72.9, 65.4, 56.5, 21.8.

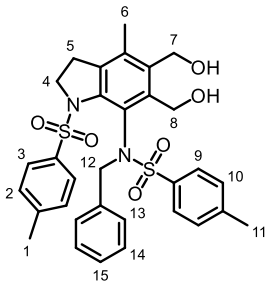
HRMS (ES^+) calc. for $C_{28}H_{22}O_2N_2SNa$ ($[M+Na]^+$) 473.1294, found 473.1295.

IR (thin film, ν_{max}/cm^{-1}) 2956, 1598, 1494, 1462, 1455, 1365, 1336, 1306, 1223, 1186, 1168, 1090.

MP 109–112 °C.

7.4.3 7-Aminoindoline products

158 *N*-Benzyl-*N*-(5,6-bis(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-butyne-1,4-diol (25.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, MeOH in CH_2Cl_2, 5 to 10%) to give the title compound (52.5 mg, 0.087 mmol, 87%) as a brown solid.

Scaled-up synthesis (1.0 mmol scale)

82u (0.520 g, 1.0 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-butyne-1,4-diol (0.258 g, 3.0 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, MeOH in CH_2Cl_2, 1 to 2%) to give the title compound (0.558 g, 0.92 mmol, 92%) as a brown solid.

R_f (MeOH in CH_2Cl_2, 10%) 0.43.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.2 Hz, ArH), 7.42–7.38 (4H, m, ArH), 7.35–7.31 (3H, m, ArH), 7.28 (2H, d, *J* = 8.2 Hz, ArH), 7.22 (2H, d, *J* = 8.2 Hz, ArH), 5.37 (1H, d, *J* = 14.6 Hz, H12), 5.25 (1H, d, *J* = 14.6 Hz, H12), 4.55 (2H, s, H7), 4.21 (1H, d, *J* = 13.5 Hz,

H8), 3.85 (1H, d, *J* = 13.5 Hz, H8), 3.77 (1H, ddd, *J* = 12.8, 7.2, 2.4 Hz, H5), 3.69 (1H, s, OH), 3.12 (1H, ddd, *J* = 12.8, 10.6, 7.8 Hz, H5), 2.70 (1H, s, OH), 2.44 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.17 (3H, s, H6), 2.16–2.06 (2H, m, H4).

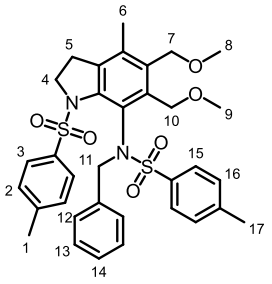
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.5, 144.1, 143.5, 140.7, 140.53, 140.46, 138.5, 136.3, 136.2, 135.2, 131.2, 129.7, 129.4, 128.8, 128.5, 128.3, 128.2, 127.8, 59.6, 59.5, 56.1, 53.4, 29.3, 21.78, 21.75, 16.1.

HRMS (ES^+) calc. for $C_{32}H_{34}O_6N_2S_2Na$ ($[M+Na]^+$) 629.1750, found 629.1750.

IR (thin film, ν_{max}/cm^{-1}) 3487, 2924, 1598, 1452, 1355, 1328, 1155, 1090, 1039, 1028, 1001.

MP 135–137 °C.

159 *N*-Benzyl-*N*-(5,6-bis(methoxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 1,4-dimethoxybut-2-yne (34.2 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 40%) to give the title compound (20.8 mg, 0.033 mmol, 33%) as a viscous yellow oil.

R_f (EtOAc in pentane, 40%) 0.39.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.3 Hz, ArH), 7.54 (2H, d, *J* = 8.3 Hz, ArH), 7.42–7.39 (2H, m, ArH), 7.24–7.14 (7H, m, ArH), 5.14 (1H, d, *J* = 13.9 Hz, H11), 5.07 (1H, d, *J* = 13.9 Hz, H11), 4.49 (1H, d, *J* = 11.5 Hz, CH_2), 4.41 (1H, d, *J* = 11.4 Hz, CH_2), 4.08 (1H, d,

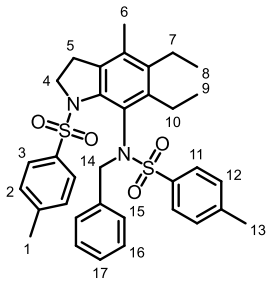
J = 11.0 Hz, CH_2), 4.00 (1H, d, *J* = 11.0 Hz, CH_2), 3.95–3.89 (1H, m, H4), 3.64–3.56 (1H, m, H4), 3.31 (3H, s, CH_3), 3.16 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.23–2.17 (1H, m, H5), 2.13–2.03 (4H, m, H5 + H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 142.9, 141.3, 140.3, 139.9, 138.9, 137.6, 136.5, 135.6, 135.0, 131.8, 130.8, 129.6, 129.1, 128.4, 128.3, 128.0, 127.9, 68.7, 68.4, 58.4, 58.1, 56.5, 53.0, 29.1, 21.8, 21.7, 16.2.

HRMS (ES^+) calc. for $C_{34}H_{38}O_6N_2S_2Na$ ($[M+Na]^+$) 657.2063, found 657.2059.

IR (thin film, ν_{max}/cm^{-1}) 2932, 1448, 1330, 1159, 1090, 1003.

160 *N*-Benzyl-*N*-(5,6-diethyl-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 3-hexyne (24.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 0 to 20%) to give the title compound (31.0 mg, 0.051 mmol, 51%) as a sticky white gum.

R_f (EtOAc in pentane, 20%) 0.32.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.3 Hz, ArH), 7.44–7.41 (4H, m, ArH), 7.20–7.12 (7H, m, ArH), 5.08 (1H, d, *J* = 13.6 Hz, H14), 5.02 (1H, d, *J* = 13.6 Hz, H14), 3.97–3.92 (1H, m, H4), 3.72–3.64 (1H, m, H4), 2.64 (2H, qd, *J* = 7.3, 2.3 Hz, H7), 2.55 (1H, dt, *J* = 14.8,

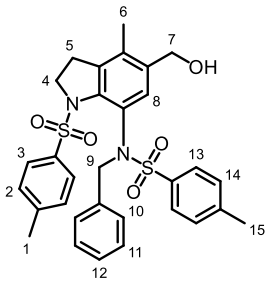
7.4 Hz, H10), 2.43–2.39 (7H, m, H1 + H13 + H10), 2.23–2.17 (1H, m, H5), 2.05–1.98 (4H, m, H6 + H4), 1.09–1.03 (6H, m, H8 + H9).

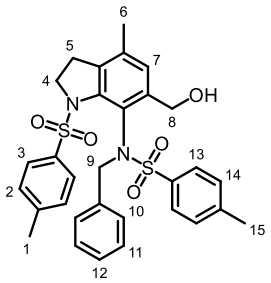
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 145.2, 144.2, 142.6, 142.3, 139.5, 139.2, 137.6, 135.8, 134.9, 133.4, 131.6, 130.7, 129.4, 129.0, 128.4 (2 C), 127.8, 127.6, 56.3, 52.9, 29.2, 22.8, 22.7, 21.8, 21.7, 16.2, 16.0, 14.8.

HRMS (ES^+) calc. for $C_{34}H_{38}O_4N_2NaS_2$ ($[M+Na]^+$) 625.2165, found 625.2164.

IR (thin film, ν_{max}/cm^{-1}) 2966, 2925, 1598, 1495, 1455, 1353, 1334, 1159, 1090, 1040.

161a ***N*-Benzyl-*N*-(5-(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzene sulfonamide** and **161b** ***N*-Benzyl-*N*-(6-(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide**





82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with propargyl alcohol (16.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 20 to 50%) to give the title compounds **161a** (37.6 mg, 0.065 mmol, 65%) as a white solid and **161b** (14.7 mg, 0.026 mmol, 26%) as a white solid.

161a

R_f (EtOAc in pentane, 50%) 0.27.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.3 Hz, ArH), 7.50 (2H, d, *J* = 8.4 Hz, ArH), 7.28–7.24 (2H, m, ArH), 7.19–7.14 (7H, m, ArH), 6.97 (1H, s, H8), 5.17 (2H, s, H9), 4.47 (2H,

d, *J* = 6.1 Hz, H7), 3.91–3.69 (2H, m, H4), 2.42 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.11–2.01 (2H, m, H5), 1.93 (3H, s, H6), 1.40 (1H, t, *J* = 6.1, OH).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.2, 143.3, 139.2, 138.8, 137.7, 137.6, 137.1, 135.0, 131.5, 130.2, 129.6, 129.5, 129.4, 128.8, 128.5, 128.3, 128.0, 127.5, 63.1, 53.1, 52.9, 28.3, 21.8, 21.7, 15.0.

HRMS (ES^+) calc. for $C_{31}H_{33}O_5N_2S_2$ ($[M+H]^+$) 577.1825, found 577.1823.

IR (thin film, ν_{max}/cm^{-1}) 2975, 2364, 1597, 1353, 1167, 1157, 1090.

MP 130–132 °C.

161b

R_f (EtOAc in pentane, 50%) 0.42.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.4 Hz, ArH), 7.45 (2H, d, *J* = 8.2 Hz, ArH), 7.38 (2H, dd, *J* = 6.5, 2.9 Hz, ArH), 7.29–7.25 (5H, m, ArH), 7.21 (2H, d, *J* = 8.2 Hz, ArH), 7.13 (1H, s, H7), 5.25 (1H, d, *J* = 14.6 Hz, H9), 5.19 (1H, d, *J* = 14.6 Hz, H9), 4.11 (1H, dd, *J* = 12.8, 5.2 Hz, H8), 3.80 (1H, ddd, *J* = 12.9, 6.4, 4.3 Hz, H4), 3.72 (1H, dd, *J* = 12.8, 9.0 Hz, H8), 3.38 (1H, dt, *J* = 12.8, 8.7 Hz, H4), 2.44–2.42 (6H, m, H1 + H15), 2.09–2.04 (5H, m, H5 + H6), 1.94 (1H, dd, *J* = 9.0, 5.2 Hz, OH).

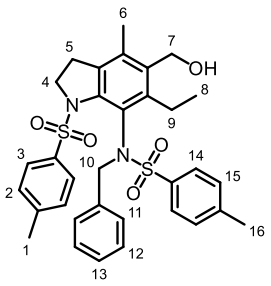
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.5, 144.4, 143.4, 141.0, 139.2, 138.5, 136.3, 135.6, 135.1, 131.6, 131.0, 129.6, 129.3, 128.6, 128.3, 128.0, 61.6, 55.4, 53.5, 28.4, 21.8, 21.7, 18.9 (*Two aromatic carbon peaks could not be identified due to overlap).*

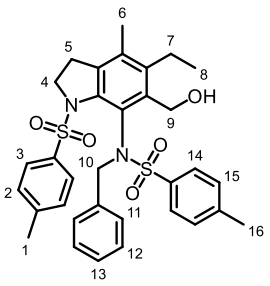
HRMS (ES^+) calc. for $C_{31}H_{32}O_5N_2NaS_2$ ($[M+Na]^+$) 599.1645, found 599.1641.

IR (thin film, ν_{max}/cm^{-1}) 3552, 2924, 1598, 1496, 1448, 1355, 1328, 1155, 1090, 1041.

MP 105–107 °C.

162a ***N*-Benzyl-*N*-(6-ethyl-5-(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide** and **162b** ***N*-Benzyl-*N*-(5-ethyl-6-(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide**





82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-pentyn-1-ol (25.2 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 50%) to give the title compounds **162a** (29.6 mg, 0.049 mmol, 49%) as a brown oil and **162b** (31.4 mg, 0.051 mmol, 51%) as a pale cream foam.

162a ***N*-Benzyl-*N*-(6-ethyl-5-(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide**

R_f (EtOAc in pentane, 50%) 0.23.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, H14), 7.49 (2H, d, *J* = 8.3 Hz, H3), 7.45–7.41 (2H, m, ArH), 7.24–7.21 (2H, m, ArH), 7.20–7.11 (5H, m, ArH), 5.10 (1H, d, *J* = 13.6 Hz, H10), 5.03 (1H, d, *J* = 13.6 Hz, H10), 4.69 (2H, s, H7), 3.97–3.92 (1H, m, H4), 3.72–3.64 (1H, m, H4), 2.75–2.65 (1H, m, H9), 2.58 (1H, dt, *J* = 14.7, 7.5 Hz, H9), 2.44 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.27–2.21 (1H, m, H5), 2.17 (3H, s, H6), 2.13–2.05 (1H, m, H5), 1.06 (3H, t, *J* = 7.5 Hz, H8). *OH peak not found.*

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 146.7, 144.4, 142.8, 141.8, 139.1, 138.1, 137.7, 136.0, 135.5, 135.0, 131.6, 131.0, 129.6, 129.0, 128.3 (2 C), 127.9, 127.8, 59.6, 56.2, 53.0, 29.1, 23.0, 21.8, 21.7, 16.9, 16.2.

HRMS (ES^+) calc. for $C_{33}H_{36}O_5N_2NaS_2$ ($[M+Na]^+$) 627.1958, found 627.1960.

IR (thin film, ν_{max}/cm^{-1}) 2957, 2925, 1455, 1332, 1163, 1089, 1030, 1005.

162b *N*-Benzyl-*N*-(5-ethyl-6-(hydroxymethyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide

R_f (EtOAc in pentane, 50%) 0.50.

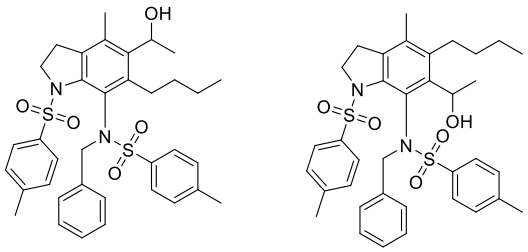
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.3 Hz, ArH), 7.41 (2H, d, *J* = 8.3 Hz, ArH), 7.33 (2H, dd, *J* = 7.6, 1.9 Hz, ArH), 7.30–7.25 (6H, m, ArH), 7.20 (1H, d, *J* = 8.3 Hz, H13), 5.27 (1H, d, *J* = 14.5 Hz, H10), 5.19 (1H, d, *J* = 14.5 Hz, H10), 4.13 (1H, dd, *J* = 13.0, 4.4 Hz, H9), 3.83–3.71 (2H, m, H9 + H4), 3.33–3.27 (1H, ddd, *J* = 12.7, 9.5, 7.8 Hz, H4), 2.89–2.82 (1H, dq, *J* = 14.9, 7.5 Hz, H7), 2.62 (1H, dt, *J* = 14.9, 7.5 Hz, H7), 2.46–2.42 (6H, m, H1 + H16), 2.35–2.30 (1H, m, OH), 2.22–2.09 (2H, m, H5), 2.03 (3H, s, H6), 1.02 (3H, t, *J* = 7.5 Hz, H8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.5, 144.3, 143.3, 141.8, 140.0, 138.7, 138.5, 136.1, 135.2, 134.4, 131.0, 129.6, 129.3, 128.8, 128.5, 128.3, 128.2, 128.0, 58.5, 55.7, 53.3, 29.5, 22.7, 21.8, 21.7, 16.0, 14.7.

HRMS (ES^+) calc. for $C_{33}H_{36}O_5N_2NaS_2$ ($[M+Na]^+$) 627.1958, found 627.1949.

IR (thin film, ν_{max}/cm^{-1}) 3541, 2960, 2924, 1598, 1454, 1356, 1328, 1155, 1090, 1039.

163a ***N*-Benzyl-*N*-(6-butyl-5-(1-hydroxyethyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide** and **163b** ***N*-Benzyl-*N*-(5-butyl-6-(1-hydroxyethyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide** *(isolated as 1.1 : 1.0 r.r., crude 1.1 : 1.0 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with oct-3-yn-2-ol (37.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 50%) to give the title compounds as an inseparable mixture (31.7 mg, 0.049 mmol, 49%) as a yellow foam. *NMR data is given for the mixture of isomers.*

R_f (EtOAc in pentane, 50%) 0.60.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.01 (2H, d, *J* = 8.2 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 7.55 (2H, dt, *J* = 5.7, 1.6 Hz), 7.46 (2H, dd, *J* = 6.7, 3.0 Hz), 7.44 (2H, d, *J* = 8.2 Hz), 7.38–7.33 (8H, m), 7.30 (2H, d, *J* = 7.4 Hz), 7.22 (2H, d, *J* = 8.1 Hz), 7.18 (4H, d, *J* = 7.9 Hz), 5.47 (1H, d, *J* = 14.4 Hz), 5.36 (1H, d, *J* = 14.4 Hz), 5.27 (1H, d, *J* = 13.9 Hz), 5.20 (1H, qd, *J* = 7.0, 3.1 Hz), 5.02 (1H, d, *J* = 13.9 Hz), 4.87 (1H, qd, *J* = 6.8, 3.8 Hz), 3.94 (1H, ddd, *J* = 12.8, 7.2, 1.6 Hz), 3.66 (1H, ddd, *J* = 12.8, 7.2, 2.6 Hz), 3.58 (1H, ddd, *J* =1 2.8, 11.0, 7.8 Hz), 3.19–3.06 (2H, m), 2.98–2.90 (2H, m), 2.75–2.67 (1H, m), 2.55 (1H, ddd, *J* = 12.8, 10.6, 4.8 Hz), 2.46 (3H, s), 2.45 (3H, s), 2.43 (3H, s), 2.39 (3H, s), 2.22–2.15 (2H, m), 2.08 (2H, ddd, *J* = 14.9, 10.4, 7.4 Hz), 2.01 (3H, s), 1.99 (3H, s), 1.46–1.40 (3H, m), 1.36–1.29 (6H, m), 1.27–1.18 (3H, m), 0.95 (3H, t, *J* = 7.1 Hz), 0.91 (3H, t, *J* =7.3 Hz), 0.79 (3H, d, *J* = 6.9 Hz).

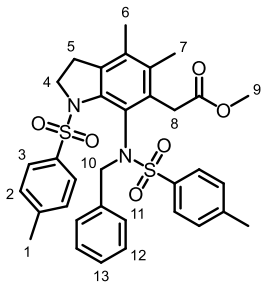
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 145.5, 145.1, 144.4, 143.5, 143.4, 143.3, 143.2, 139.8, 139.6, 139.0, 138.6, 138.5, 138.4, 136.5, 136.3, 135.6, 135.4, 134.9, 134.8, 131.7, 130.9, 129.53,

129.47, 129.46, 129.1, 128.66, 128.65, 128.6, 128.51, 128.46, 128.24, 128.19, 128.14, 128.11, 127.7, 67.4, 66.4, 55.0, 54.4, 53.3, 53.0, 33.7, 33.3, 29.9, 29.8, 29.5, 29.4, 23.3, 23.2, 23.0, 21.79, 21.77, 21.76, 21.7, 21.3, 16.1, 16.0, 14.2, 14.1 O*ne aromatic carbon peak not identified due to overlap*.

HRMS (ES^+) calc. for $C_{36}H_{42}O_5N_2S_2Na$ ($[M+Na]^+$) 669.2427, found 669.2421.

IR (thin film, ν_{max}/cm^{-1}) 3300, 2986, 2160, 2500, 2028, 1977, 1673, 1349, 1162, 1089, 1029.

164 Methyl 2-(7-((*N*-benzyl-4-methylphenyl)sulfonamido)-4,5-dimethyl-1-tosyl indolin-6-yl)acetate



82u (0.260 g, 0.50 mmol, 1.0 equiv.) was used in **General Procedure 8** with methyl pent-3-ynoate (0.168 g, 1.50 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 50%) to give the title compound (0.267 g, 0.42 mmol, 84%) as a pale cream solid.

R_f (EtOAc in pentane, 30%) 0.28

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.4 Hz, ArH), 7.52 (2H, d, *J* = 8.3 Hz, ArH), 7.44–7.42 (2H, m, ArH), 7.24–7.15 (7H, m, ArH), 5.18 (1H, d, *J* = 14.1 Hz, H10), 5.08 (1H, d, *J* = 14.1 Hz, H10), 3.85 (1H, ddd, *J* = 12.8, 6.7, 2.8 Hz, H4), 3.59 (3H, s, H9), 3.54–3.43 (3H, m, H4 + H8), 2.43 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.20–2.14 (2H, m, H5), 2.03 (3H, s, CH_3), 2.00 (3H, s, CH_3).

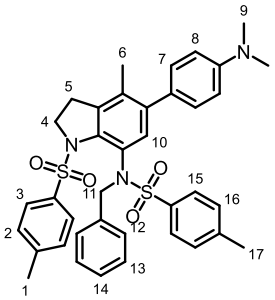
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.7, 144.3, 142.9, 139.5, 138.9, 138.7, 137.6, 136.1, 135.8, 135.2, 134.1, 131.4, 131.2, 129.6, 129.1, 128.34, 128.27, 128.2, 127.8, 56.2, 53.2, 52.0, 36.2, 29.4, 21.8, 21.7, 17.1, 16.9.

HRMS (ES^+) calc. for $C_{34}H_{37}N_2O_6S_2$ ($[M+H]^+$) 633.2088, found 633.2057.

IR (thin film, ν_{max}/cm^{-1}) 2953, 1739, 1455, 1337, 1162, 1090, 1017.

MP 85–87 °C.

174a ***N*-Benzyl-*N*-(5-(4-(dimethylamino)phenyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide** *(isolated as >20:1 r.r., crude >20:1 r.r.).*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-ethynyl-*N*,*N*-dimethylaniline (43.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (53.2 mg, 0.080 mmol, 80%) as a brown solid.

R_f (EtOAc in pentane, 30%) 0.22.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.4 Hz, H15), 7.57 (2H, d, *J* = 8.3 Hz, H3), 7.23–7.14 (9H, m, ArH), 7.02 (2H, d, *J* = 8.8 Hz, H7), 6.88 (1H, s, H10), 6.72 (2H, d, *J* = 8.8 Hz, H8), 5.20 (2H, s, H11), 3.88 (2H, br. s, H4), 3.00 (6H, s, H9), 2.39–2.38 (6H, m, H1 + H17), 2.12 (2H, br. s, H5), 1.91 (3H, s, H6).

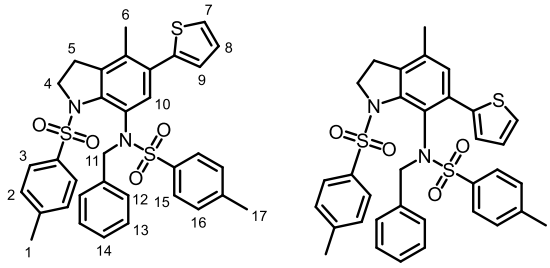
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.7, 144.0, 143.1, 140.7, 139.2, 139.0, 137.3, 136.5, 135.1, 130.87, 130.85, 130.2, 130.1, 129.6, 129.5, 129.3, 128.4, 128.3, 128.2, 128.1, 127.4, 112.0, 53.3, 53.0, 40.7, 28.9, 21.72, 21.65, 17.1.

HRMS (ES^+) calc. for $C_{38}H_{40}O_4N_3S_2$ ($[M+H]^+$) 666.2455, found 666.2452.

IR (thin film, ν_{max}/cm^{-1}) 1611, 1525, 1477, 1445, 1352, 1165, 1090.

MP 115–118 °C.

174b ***N*-Benzyl-4-methyl-*N*-(4-methyl-5-(thiophen-2-yl)-1-tosylindolin-7-yl)benzene sulfonamide** and ***N*-benzyl-4-methyl-*N*-(4-methyl-6-(thiophen-2-yl)-1-tosylindolin-7-yl) benzenesulfonamide** *(isolated as. 19:1 r.r., crude 10:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-ethynylthiophene (32.4 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compounds as an inseparable mixture (42.0 mg, 0.067 mmol, 67%) as a pale brown amorphous solid. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.40.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (2H, d, *J* = 8.3 Hz, H15), 7.56 (2H, d, *J* = 8.4 Hz, H3), 7.31 (1H, dd, *J* = 5.1, 1.2 Hz, H9), 7.24 (2H, d, *J* = 8.0 Hz, H16), 7.20–7.16 (7H, m, H2 + H12 + H13 + H14), 7.05–7.03 (2H, m, H8 + H10), 6.86 (1H, dd, *J* = 3.5, 1.1 Hz, H7), 5.20 (2H, s,

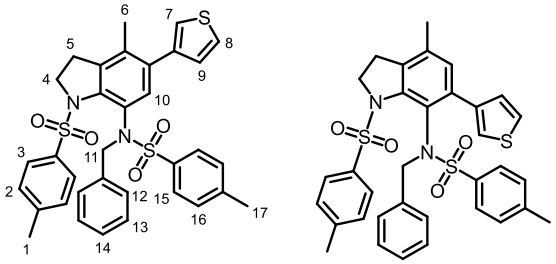
H11), 3.88 (2H, br. s, H4), 2.41 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.19–2.11 (2H, m, H5), 2.03 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.2, 143.3, 141.6, 139.6, 138.8, 137.6, 137.0, 135.0, 132.8, 131.4, 131.3, 130.2, 129.6, 129.5, 129.4, 128.4, 128.3, 128.0, 127.6, 127.2, 127.0, 125.6, 53.1, 52.9, 28.9, 21.74, 21.68, 17.4.

HRMS (ES^+) calc. for $C_{34}H_{33}O_4N_2S_3$ ($[M+H]^+$) 629.1957, found 629.1957.

IR (thin film, ν_{max}/cm^{-1}) 2927, 1356, 1169, 1159, 1091.

174c ***N*-Benzyl-4-methyl-*N*-(4-methyl-5-(thiophen-3-yl)-1-tosylindolin-7-yl)benzene sulfonamide** and ***N*-benzyl-4-methyl-*N*-(4-methyl-6-(thiophen-3-yl)-1-tosylindolin-7-yl) benzenesulfonamide** *(isolated as 9:1 r.r., crude 9:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 3-ethynylthiophene (32.4 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compounds as an inseparable mixture (41.0 mg, 0.065 mmol, 65%) as a pale brown amorphous solid. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 20%) 0.22.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.3 Hz, H15), 7.56 (2H, d, *J* = 8.3 Hz, H3), 7.31 (1H, dd, *J* = 4.9, 3.0 Hz, H9), 7.25–7.17 (9H, m, ArH), 6.99 (1H, dd, *J* = 3.0, 1.3 Hz, H8),

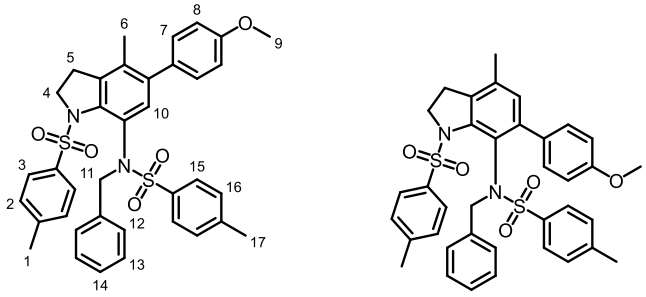
6.92 (1H, dd, *J* = 4.9, 1.3 Hz, H7), 6.89 (1H, s, H10), 5.18 (2H, s, H11), 3.90–3.81 (2H, m, H4), 2.41 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.15–2.11 (2H, m, H5), 1.95 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.3, 140.6, 139.4, 138.7, 137.4, 137.2, 135.07, 135.05, 131.14, 131.11, 130.0, 129.7, 129.5, 129.3, 128.9, 128.5, 128.3, 128.0, 127.6, 125.1, 123.2, 53.3, 52.9, 28.9, 21.7, 21.7, 17.2.

HRMS (ES^+) calc. for $C_{34}H_{33}O_4N_2S_3$ ($[M+H]^+$) 629.1597, found 629.1595.

IR (thin film, ν_{max}/cm^{-1}) 2977, 1598, 1354, 1167, 1159, 1091.

174d *N*-Benzyl-*N*-(5-(4-methoxyphenyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide and ***N*-benzyl-*N*-(6-(4-methoxyphenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide** *(isolated as 7:1 r.r., crude 8:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-ethynylanisole (39.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 40%) to give the title compounds as an inseparable mixture (59.8 mg, 0.092 mmol, 92%) as a yellow foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.37.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.4 Hz, H15), 7.57 (2H, d, *J* = 8.4 Hz, H3), 7.23–7.16 (9H, m, ArH), 7.03 (2H, d, *J* = 8.7 Hz, H7), 6.89 (2H, d, *J* = 8.7 Hz, H8), 6.83 (1H,

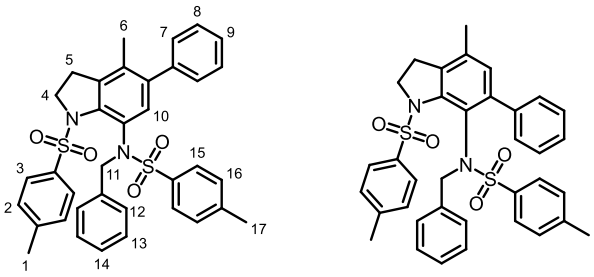
s, H10), 5.18 (2H, s, H11), 3.89–3.84 (5H, m, H4 + H9), 2.39 (6H, s, H1 + H17), 2.17–2.07 (2H, m, H5), 1.88 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 158.9, 144.1, 143.2, 140.2, 139.3, 138.8, 137.2, 137.1, 135.1, 132.7, 131.1, 130.9, 130.5, 130.0, 129.7, 129.5, 129.3, 128.5, 128.3, 128.1, 127.5, 113.6, 55.5, 53.2, 53.0, 28.9, 21.8, 21.7, 17.0.

HRMS (ES^+) calc. for $C_{37}H_{37}O_5N_2S_2$ ($[M+H]^+$) 653.2138, found 653.2134.

IR (thin film, ν_{max}/cm^{-1}) 2979, 2160, 2029, 1977, 1673, 1606, 1454, 1352, 1245, 1158, 1089, 1028.

174e ***N*-Benzyl-4-methyl-*N*-(4-methyl-5-phenyl-1-tosylindolin-7-yl)benzenesulfonamide** and ***N*-benzyl-4-methyl-*N*-(4-methyl-6-phenyl-1-tosylindolin-7-yl)benzenesulfonamide** *(isolated as 6:1 r.r., crude 6:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with phenylacetylene (30.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (48.0 mg, 0.077 mmol, 77%) as a yellow foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.45.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.3 Hz, H15), 7.57 (2H, d, *J* = 8.3 Hz, H3), 7.38–7.30 (3H, m, ArH), 7.23–7.16 (8H, m, ArH), 7.12–7.09 (3H, m, ArH), 6.86 (1H, s, H10),

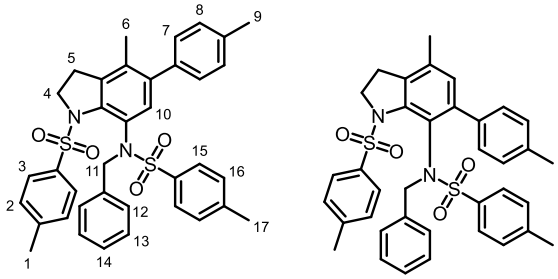
5.20 (2H, s, H11), 3.97–3.81 (2H, m, H4), 2.40–2.38 (6H, m, H1 + H17), 2.18–2.10 (2H, m, H5), 1.88 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.1, 143.2, 140.5, 140.3, 139.3, 138.7, 137.3, 137.1, 135.1, 131.0, 130.9, 130.0, 129.6, 129.5, 129.4, 129.3, 128.5, 128.3, 128.2, 128.0, 127.5, 127.2, 53.2, 52.9, 28.9, 21.7, 21.6, 17.0.

HRMS (ES^+) calc. for $C_{36}H_{35}O_4N_2S_2$ ($[M+H]^+$) 623.2033, found 623.2031.

IR (thin film, ν_{max}/cm^{-1}) 2980, 1597, 1474, 1354, 1158, 1090.

174f *N*-Benzyl-4-methyl-*N*-(4-methyl-5-(*p*-tolyl)-1-tosylindolin-7-yl)benzene sulfonamide and ***N*-benzyl-4-methyl-*N*-(4-methyl-6-(*p*-tolyl)-1-tosylindolin-7-yl)benzenesulfonamide** *(isolated as 7:1 r.r., crude 6:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-methylphenylacetylene (34.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (36.0 mg, 0.057 mmol, 57%) as a cream amorphous solid. *NMR data is given for the major isomer in the isolated mixture.*

R_f (Et_2O in pentane, 20%) 0.25.

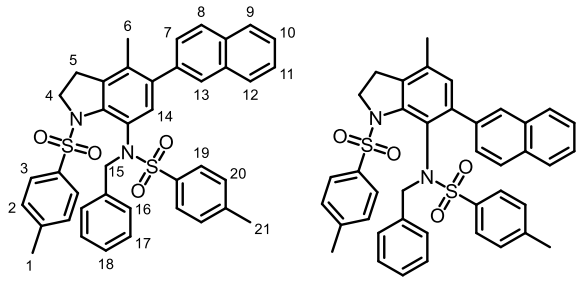
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, H15), 7.58 (2H, d, *J* = 8.3 Hz, H3), 7.23–7.14 (11H, m, ArH), 7.00 (2H, d, *J* = 8.1 Hz, H8), 6.84 (1H, s, H10), 5.19 (2H, s, H11), 3.88 (2H, br. s, H4), 2.39 (9H, s, H1 + H9 + H17), 2.13 (2H, br. s, H5), 1.88 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.2, 140.5, 139.3, 138.8, 137.4, 137.2, 137.1, 136.9, 135.11, 131.05, 130.9, 130.1, 129.6, 129.5, 129.3 (2 C), 128.9, 128.5, 128.3, 128.1, 127.5, 53.3, 53.0, 28.9, 21.8, 21.7, 21.3, 17.0.

HRMS (ES^+) calc. for $C_{37}H_{37}O_4N_2S_2$ ($[M+H]^+$) 637.2189, found 637.2189.

IR (thin film, ν_{max}/cm^{-1}) 2981, 1721, 1598, 1356, 1278, 1162, 1091. *The apparent carbonyl peak observed at 1721 cm^{-1} (sharp, strong) cannot be readily assigned to this structure.*

174g ***N*-Benzyl-4-methyl-*N*-(4-methyl-5-(naphthalen-2-yl)-1-tosylindolin-7-yl)benzene sulfonamide** and ***N*-benzyl-4-methyl-*N*-(4-methyl-6-(naphthalen-2-yl)-1-tosylindolin-7-yl) benzenesulfonamide** *(isolated as 5:1 r.r., crude 5:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-ethynylnapthalene (45.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (52.0 mg, 0.077 mmol, 77%) as a cream amorphous solid. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.37.

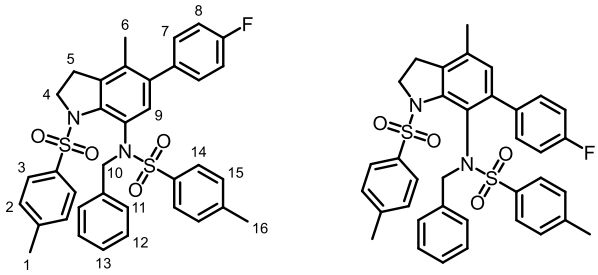
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85–7.78 (6H, m, ArH), 7.63 (2H, d, *J* = 8.4 Hz, ArH), 7.55–7.50 (3H, m, ArH), 7.27–7.19 (9H, m, ArH), 6.87 (1H, s, H14), 5.21 (2H, s, H15), 3.96–3.87 (2H, m, H4), 2.41 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.24–2.16 (2H, m, H5), 1.94 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.2, 140.4, 139.4, 138.7, 137.8, 137.1, 135.2, 133.3, 132.4, 131.6, 131.2, 130.0, 129.8, 129.6, 129.5, 129.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.64, 127.61, 127.58, 126.5, 126.2, 53.3, 53.9, 29.0, 21.8, 21.6, 17.1.

HRMS (ES^+) calc. for $C_{40}H_{37}O_4N_2S_2$ ($[M+H]^+$) 673.2189, found 673.2188.

IR (thin film, ν_{max}/cm^{-1}) 2979, 1355, 1169, 1051, 1033, 1018.

174h *N*-Benzyl-*N*-(5-(4-fluorophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzene sulfonamide *(isolated as single (major) isomer, crude 5:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 1-ethynyl-4-fluorobenzene (36.0 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (35.0 mg, 0.055 mmol, 55%) as an orange foam and a mixture of the title compound and the minor isomer (22.5 mg, 0.035 mmol, 35%) as a brown oil. *NMR data is given for the isolated major isomer.*

R_f (EtOAc in pentane, 20%) 0.22.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (2H, d, J = 8.4 Hz, H15), 7.57 (2H, d, J = 8.4 Hz, H3), 7.24–7.16 (9H, m, ArH), 7.05–7.02 (4H, m, H7 + H8), 6.77 (1H, s, H9), 5.17 (2H, s, H10), 3.88 (2H, br. s, H4), 2.40 (6H, s, H1 + H16), 2.15 (2H, br. s, H5), 1.86 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.2 (d, $^1J_{C\text{-}F}$ = 246.5 Hz), 144.2, 143.3, 139.43, 139.35, 138.6, 137.7, 137.1, 136.2 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 135.1, 131.4, 130.94 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 130.93,

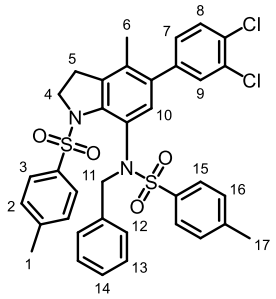
130.0, 129.8, 129.5, 129.3, 128.5, 128.3, 128.0, 127.6, 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 53.2, 52.9, 28.9, 21.74, 21.66, 16.9.

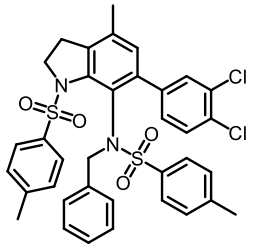
^{19}F NMR (377 MHz, $CDCl_3$) δ_F −115.36.

HRMS (ES^+) calc. for $C_{36}H_{34}O_4N_2FS_2$ ($[M+H]^+$) 641.1939, found 641.1934.

IR (thin film, ν_{max}/cm^{-1}) 2977, 2932, 1598, 1506, 1353, 1222, 1158, 1090, 1018.

174i ***N*-Benzyl-*N*-(5-(3,4-dichlorophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide** and ***N*-benzyl-*N*-(6-(3,4-dichlorophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide** *(isolated as 4:1 r.r., crude 4:1 r.r.)*





82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 3,4-dichlorophenylacetylene (51.3 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (44.9 mg, 0.065 mmol, 65%) as a pale brown foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.37.

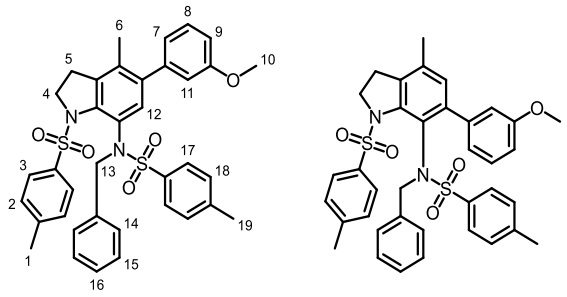
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, H15), 7.60 (2H, d, *J* = 8.3 Hz, H3), 7.41 (1H, d, *J* = 8.3 Hz, H8), 7.25–7.18 (8H, m, ArH), 7.10 (1H, d, *J* = 2.1 Hz, H9), 7.06 (1H, d, *J* = 3.8 Hz, ArH), 6.93 (1H, dd, *J* = 8.3, 2.1 Hz, H7), 6.61 (1H, s, H10), 5.16 (2H, s, H11), 3.90–3.84 (2H, m, H4), 2.42–2.40 (6H, m, H1 + H17), 2.20–2.13 (2H, m, H5), 1.88 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 143.5, 140.2, 139.6, 138.5, 137.7, 137.0, 135.2, 132.4, 131.50, 131.48, 131.3, 130.9, 130.8, 130.1, 130.0, 129.9, 129.61, 129.59, 129.4, 128.43, 128.39, 128.0, 127.8, 53.3, 52.9, 29.0, 21.8, 21.7, 16.9.

HRMS (ES^+) calc. for $C_{36}H_{33}O_4N_2Cl_2S_2$ ($[M+H]^+$) 691.1253, found 691.1252.

IR (thin film, ν_{max}/cm^{-1}) 2975, 2948, 1465, 1356, 1159, 1091.

174j ***N*-Benzyl-*N*-(5-(3-methoxyphenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzene sulfonamide** and ***N*-benzyl-*N*-(6-(3-methoxyphenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide** *(isolated as 5:1 r.r., crude 4:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 3-ethynylanisole (39.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO2, EtOAc in pentane, 10 to 40%) to give the title compounds as an inseparable mixture (65.0 mg, 0.099 mmol, 99%) as an orange oil. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.33.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.4 Hz, H17), 7.57 (2H, d, *J* = 8.2 Hz, H3), 7.30–7.27 (2H, m, ArH), 7.22–7.15 (8H, m, ArH), 7.14–7.11 (1H, m, ArH), 6.85 (1H, s, ArH), 6.70–6.68 (1H, m, ArH), 6.64 (1H, t, *J* = 1.7 Hz, ArH), 5.18 (2H, s, H13), 3.95–3.85 (2H, m,

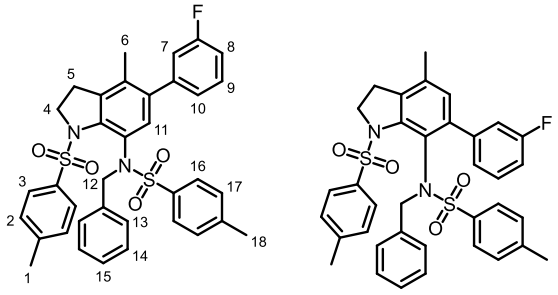
H4), 3.83 (3H, s, H10), 2.40 (3H, s, CH3), 2.39 (3H, s, CH3), 2.20–2.10 (2H, m, H5), 1.88 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 159.4, 144.1, 143.2, 141.7, 140.4, 139.3, 138.7, 137.4, 137.1, 135.1, 130.8, 130.4, 130.1, 129.6, 129.5, 129.4, 129.2, 128.5, 128.3, 128.1, 127.5, 122.0, 115.3, 112.5, 55.5, 53.2, 53.0, 28.9, 21.8, 21.7, 17.0.

HRMS (ES^+) calc. for $C_{37}H_{37}N_2O_5S_2$ ($[M+H]^+$) 653.2138, found 653.2150.

IR (thin film, ν_{max}/cm^{-1}) 3063, 3030, 2952, 2920, 1598, 1470, 1355, 1167, 1159, 1090, 1046.

174k ***N*-Benzyl-*N*-(5-(3-fluorophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzene sulfonamide** and ***N*-benzyl-*N*-(6-(3-fluorophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide** *(isolated as 8:1 r.r., crude 3:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 1-ethynyl-3-fluorobenzene (36.0 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 20%) to give the title compounds as an inseparable mixture (11.7 mg, 0.018 mmol, 18%) as a yellow foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 20%) 0.19.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, H16), 7.58 (2H, d, *J* = 8.4 Hz, H3), 7.31 (1H, td, *J* = 8.0, 6.0 Hz, H9), 7.25–7.17 (9H, m, ArH), 7.03–6.99 (1H, m, H8), 6.87 (1H,

dt, J = 7.8, 1.2 Hz, H10), 6.78–6.74 (2H, m, H7 + H11), 5.17 (2H, s, H12), 3.88 (2H, br. s, H4), 2.40 (6H, m, H1 + H18), 2.17 (2H, br. s, H5), 1.88 (3H, s, H6).

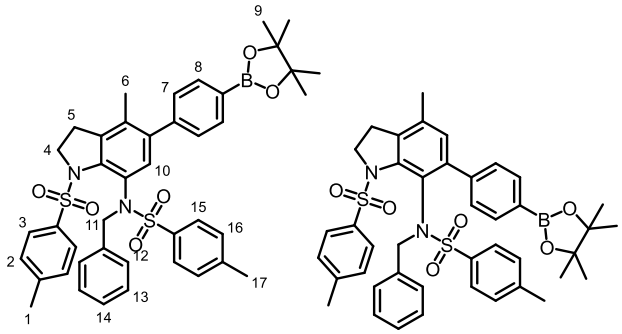
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 162.6 (d, $^1J_{C\text{-}F}$ = 246.4 Hz), 144.2, 143.5, 142.5, 139.5, 139.1, 138.5, 138.0, 137.0, 135.1, 131.2, 130.9, 130.0, 129.8, 129.63 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 129.56, 129.4, 128.5, 128.4, 128.1, 127.7, 125.2 (d, $^4J_{C\text{-}F}$ =2.9 Hz), 116.4 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 114.1 (d, $^2J_{C\text{-}F}$ = 20.7 Hz), 53.2, 52.9, 28.9, 21.8, 21.7, 17.0. *One $^3J_{C\text{-}F}$ doublet observed as singlet due to overlap.*

^{19}F NMR (471 MHz, $CDCl_3$) δ_F −113.45.

HRMS (ES^+) calc. for $C_{36}H_{34}O_4N_2FS_2$ ($[M+H]^+$) 641.1939, found 641.1937.

IR (thin film, ν_{max}/cm^{-1}) 2981, 2919, 1714, 1597, 1495, 1454, 1353, 1161, 1091, 1032.

174l ***N*-Benzyl-4-methyl-*N*-(4-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-tosylindolin-7-yl)benzenesulfonamide** and ***N*-benzyl-4-methyl-*N*-(4-methyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-tosylindolin-7-yl)benzene sulfonamide** *(isolated as 8 : 1 r.r., crude 3:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-ethynylphenylboronic acid pinacol ester (68.4 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (62.9 mg, 0.084 mmol, 84%) as a yellow foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.33.

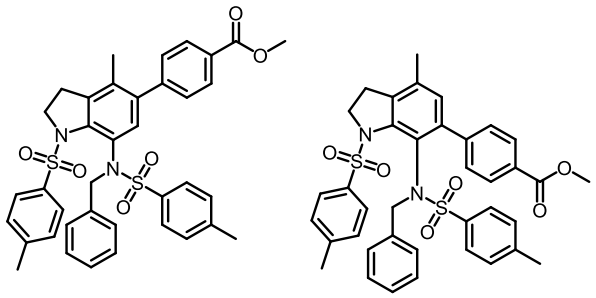
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.1 Hz, ArH), 7.76 (2H, d, *J* = 8.3 Hz, ArH), 7.61 (2H, d, *J* = 8.3 Hz, ArH), 7.22–7.19 (4H, m, ArH), 7.17–7.15 (5H, m, H12 + H13 + H14), 7.10 (2H, d, *J* = 8.1 Hz), 6.76 (1H, s, H10), 5.19 (2H, s, H11), 3.92–3.85 (2H, m, H4), 2.40 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.24–2.12 (2H, m, H5), 1.88 (3H, s, H6), 1.38 (12H, s, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 143.2, 143.1, 140.3, 139.4, 138.8, 137.8, 137.0, 135.2, 134.6, 131.1, 131.0, 130.0, 129.7, 129.5, 129.4, 128.8, 128.32, 128.30, 128.0, 127.6, 84.0, 53.3, 52.9, 28.9, 25.0, 21.74, 21.65, 17.0 *One aromatic carbon peak not found.*

HRMS (ES^+) calc. for $C_{42}H_{46}O_6N_2BS_2$ ($[M+H]^+$) 749.2891, found 749.2885.

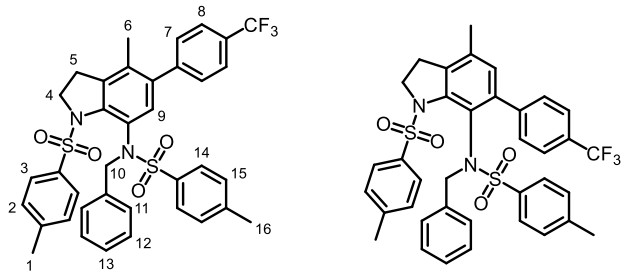
IR (thin film, ν_{max}/cm^{-1}) 2980, 1608, 1358, 1161, 1089.

174m Methyl 4-(7-((*N*-benzyl-4-methylphenyl)sulfonamido)-4-methyl-1-tosylindolin-5-yl)benzoate and **methyl 4-(7-((*N*-benzyl-4-methylphenyl)sulfonamido)-4-methyl-1-tosylindolin-6-yl)benzoate**



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with methyl 4-ethynylbenzoate (48.0 mg, 0.30 mmol, 3.0 equiv.) for 16 h. *The yield of this compound was calculated by quantitative ^{1}H NMR on the crude reaction mixture as clean material could not be isolated.*

174n *N*-Benzyl-4-methyl-*N*-(4-methyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)indolin-7-yl)benzenesulfonamide and ***N*-benzyl-4-methyl-*N*-(4-methyl-1-tosyl-6-(4-(trifluoromethyl)phenyl)indolin-7-yl)benzenesulfonamide** *(isolated as 5:1 r.r., crude 2:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-ethynyl-α,α,α-trifluorotoluene (51.0 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (49.2 mg, 0.071 mmol, 71%) as a yellow foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 20%) 0.26.

^{1}H NMR (500 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.3 Hz, H14), 7.62–7.57 (4H, m, ArH), 7.24–7.17 (11H, m, ArH), 6.76 (1H, s, H9), 5.17 (2H, s, H10), 3.95–3.82 (2H, m, H4), 2.41–2.40 (6H, m, H1 + H16), 2.25–2.12 (2H, m, H5), 1.88 (3H, s, H6).

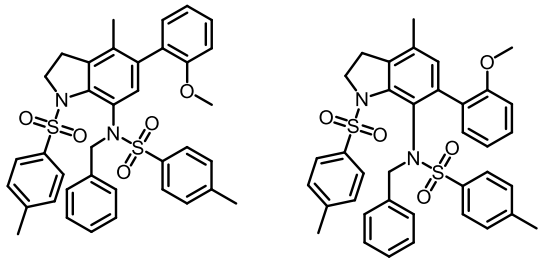
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.3, 143.4, 139.6, 138.9, 138.5, 138.3, 137.0, 135.1, 134.3 (q, $^2J_{C\text{-}F}$ = 53.5 Hz), 131.4, 130.9, 130.1, 129.8, 129.7, 129.61, 129.58, 129.4, 128.5, 128.4, 128.0, 127.6, 125.2 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 53.2, 52.9, 28.9, 21.8, 21.7, 17.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F −62.44.

HRMS (ES^+) calc. for $C_{37}H_{34}O_4N_2F_3S_2$ ($[M+H]^+$) 691.1907, found 691.1902.

IR (thin film, ν_{max}/cm^{-1}) 2920, 2850, 1599, 1512, 1477, 1355, 1266, 1224, 1158, 1091.

174o ***N*-Benzyl-*N*-(5-(2-methoxyphenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzene sulfonamide** and ***N*-benzyl-*N*-(6-(2-methoxyphenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide** *(isolated as 2:1 r.r., crude 2:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-ethynylanisole (39.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as an inseparable mixture (58.9 mg, 0.090 mmol, 90%) as a yellow foam. *NMR data is given for the mixture of isomers in the mixture as the peaks could not be assigned individually.*

R_f (EtOAc in pentane, 20%) 0.35.

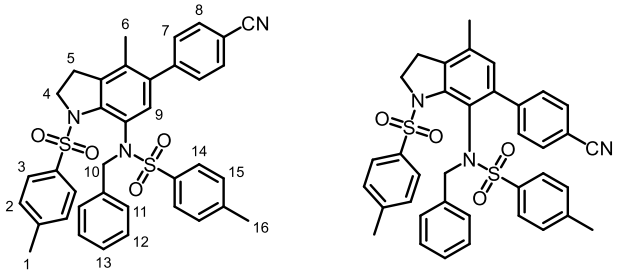
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (1H, d, *J* = 8.3 Hz), 7.74 (2H, d, *J* = 8.2 Hz), 7.71 (1H, d, *J* = 8.3 Hz), 7.54 (1H, d, *J* = 8.4 Hz), 7.39–7.27 (4H, m), 7.23–7.06 (13H, m), 7.00–6.64 (5H, m), 5.18 (2H, s), 4.81 (1H, s), 3.99–3.81 (5H, m), 3.71 (2H, s), 3.49 (1H, t, *J* = 7.2 Hz), 2.43 (2H, s), 2.39 (3H, s), 2.36 (3H, s), 2.33 (2H, s), 2.22–2.10 (2H, m), 2.03 (1H, d, *J* = 11.4 Hz), 1.72 (3H, s), 1.62 (2H, d, *J* = 7.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 160.1, 156.7, 144.0, 143.9, 143.8, 143.0, 142.7, 138.5, 137.7, 137.5, 137.2, 136.0, 135.5, 135.1, 134.3, 133.4, 132.5, 131.3, 130.6, 130.4, 129.5, 129.44, 129.38, 129.2, 129.01, 128.96, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.44, 127.35, 127.3, 126.2, 120.6, 120.4, 112.9, 112.0, 111.2, 110.6, 96.3, 91.2, 55.8, 55.6, 54.5, 53.3, 52.9, 48.2, 29.8, 28.8, 27.0, 21.8, 21.64, 21.58, 16.6, 16.1 *Four aromatic peaks not found for minor isomer.*

HRMS (ES^+) calc. for $C_{37}H_{37}O_5N_2S_2$ ($[M+H]^+$) 653.2138, found 653.2136.

IR (thin film, ν_{max}/cm^{-1}) 2900, 1597, 1494, 1462, 1381, 1355, 1246, 1160, 1090.

174p ***N*-Benzyl-*N*-(5-(4-cyanophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methylbenzene sulfonamide** and ***N*-benzyl-*N*-(6-(4-cyanophenyl)-4-methyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide** *(isolated as 2:1 r.r., crude 2:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-ethynylbenzonitrile(38.1 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compounds as

an inseparable mixture (21.1 mg, 0.033 mmol, 33%) as an orange foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 30%) 0.35.

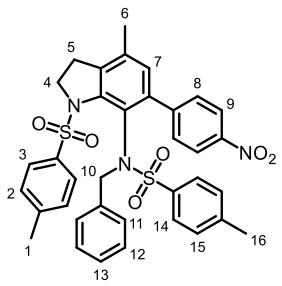
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.4 Hz, H14), 7.66–7.62 (2H, m, ArH), 7.58 (2H, d, *J* = 8.3 Hz, H3), 7.25–7.14 (11H, m, ArH), 6.71 (1H, s, H9), 5.15 (2H, s, H10), 3.91–3.88 (2H, m, H4), 2.41 (6H, s, H1 + H16), 2.22–2.16 (2H, m, H5), 1.87 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 145.0, 144.3, 143.5, 139.8, 138.7, 138.4, 138.3, 136.9, 135.0, 132.0, 131.4, 134.0, 130.1, 129.8, 129.6, 129.4, 128.5, 128.4, 128.09, 127.97, 127.7, 118.9, 111.1, 53.2, 52.9, 28.9, 21.8, 21.7, 16.9.

HRMS (ES^+) calc. for $C_{37}H_{34}O_4N_3S_2$ ($[M+H]^+$) 648.1985, found 648.1983.

IR (thin film, ν_{max}/cm^{-1}) 2922, 2227 (nitrile), 1598, 1475, 1455, 1355, 1158, 1090.

174q' *N*-Benzyl-4-methyl-*N*-(4-methyl-6-(4-nitrophenyl)-1-tosylindolin-7-yl)benzene sulfonamide



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 1-ethynyl-4-nitrobenzene (44.1 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, Et_2O in pentane, 10 to 40%) to give the title compound (23.2 mg, 0.035 mmol, 35%) as a viscous brown oil.

R_f (EtOAc in pentane, 40%) 0.44.

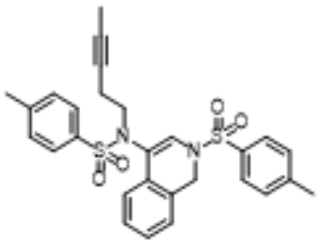
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (2H, d, *J* = 8.8 Hz, H9), 7.82 (2H, d, *J* = 8.3 Hz, H14), 7.78 (2H, d, *J* = 8.3 Hz, H3), 7.32–7.28 (4H, m, ArH), 7.27–7.23 (2H, m, H8), 7.18–7.11 (5H, m, ArH), 6.80–6.73 (1H, m, H7), 4.85 (2H, s, H10), 3.46 (2H, t, *J* = 7.3 Hz, H4), 2.44 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.03–1.96 (2H, m, H5), 1.60 (3H, d, *J* = 7.1 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 147.3, 146.3, 144.4, 143.3, 137.8, 135.7, 135.4, 134.8, 132.0, 130.6, 129.6, 129.4, 129.2, 128.6, 128.2, 128.0, 127.8, 126.9, 123.7, 111.3, 96.1, 92.9, 54.2, 48.2, 26.7, 21.8, 21.7, 16.0.

HRMS (ES^+) calc. for $C_{36}H_{34}O_6N_3S_2$ ($[M+H]^+$) 668.1884, found 668.1890.

IR (thin film, ν_{max}/cm^{-1}) 1597, 1521, 1345, 1164, 1089.

180 4-Methyl-*N*-(pent-3-yn-1-yl)-*N*-(2-tosyl-1,2-dihydroisoquinolin-4-yl) benzenesulfonamide



R_f (EtOAc in pentane, 20%) 0.35

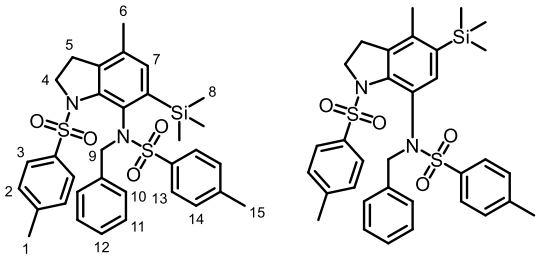
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.2 Hz), 7.61 (2H, d, *J* = 8.4 Hz), 7.30 (2H, d, *J* = 5.2 Hz), 7.28 (2H, d, *J* = 5.3 Hz), 7.17 – 7.09 (3H, m), 6.97 – 6.92 (1H, m), 6.58 (1H, s), 4.65 (1H, d, *J* = 14.2 Hz), 4.55 (1H, d, *J* = 14.2 Hz), 3.66 – 3.48 (2H, m), 2.46 (3H, s), 2.41 (3H, s), 2.40 – 2.34 (1H, m) 2.31 – 2.17 (1H, m), 1.69 (3H, t, *J* = 2.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.7, 143.8, 136.3, 134.6, 130.2, 130.1, 129.8, 128.4, 128.3, 128.1, 127.8, 127.3, 127.2, 125.5, 122.4, 122.0, 78.1, 75.5, 50.1, 47.3, 21.8, 21.7, 19.5, 3.5.

HRMS (ES^+) calc. for $C_{28}H_{28}O_4N_2S_2Na$ ($[M+Na]^+$) 543.1383, found 543.1382.

IR (thin film, ν_{max} / cm^{-1}) 1454, 1350, 1165, 1091, 1044.

181a ***N*-Benzyl-4-methyl-*N*-(4-methyl-1-tosyl-6-(trimethylsilyl)indolin-7-yl)benzene sulfonamide** and ***N*-benzyl-4-methyl-*N*-(4-methyl-1-tosyl-5-(trimethylsilyl)indolin-7-yl)benzenesulfonamide** *(isolated as 6:1 r.r., crude 6:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** (using a sealed tube) with trimethylsilylacetylene (0.14 mL, 1.0 mmol, 10.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, Et_2O in pentane, 10 to 40% + 1% Et_3N) to give the title compounds as an inseparable mixture (43.8 mg, 0.071 mmol, 71%) as a yellow foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (Et_2O in pentane, 30%) 0.18.

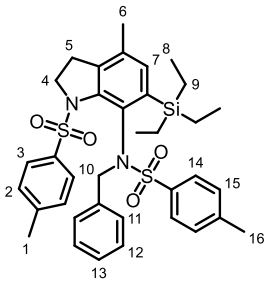
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.3 Hz, H13), 7.69 (2H, d, *J* = 8.3 Hz, H3), 7.29–7.26 (2H, m, ArH), 7.25–7.21 (2H, m, ArH), 7.17–7.11 (4H, m, ArH), 7.10–7.06 (1H, m, ArH), 6.82 (1H, qt, *J* = 7.1, 2.6 Hz, H7), 4.76 (2H, s, H9), 3.47 (2H, t, *J* = 7.3 Hz, H4), 2.42 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.03–1.97 (2H, m, H5), 1.57–1.53 (3H, m, H6), 0.16 (9H, s, H8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 144.0, 142.9, 138.0, 135.9, 135.4, 134.3, 130.4, 129.5, 129.0, 128.5, 128.3, 127.8, 127.5, 126.5, 112.3, 105.2, 102.1, 54.1, 48.0, 27.0, 21.7, 21.6, 15.6, −0.3.

HRMS (ES^+) calc. for $C_{33}H_{39}O_4N_2S_2Si$ ($[M+H]^+$) 619.2115, found 619.2116.

IR (thin film, ν_{max}/cm^{-1}) 2920, 1598, 1456, 1355, 1250, 1163, 1090, 1018, 1008.

181b ***N*-Benzyl-4-methyl-*N*-(4-methyl-1-tosyl-6-(triethylsilyl)indolin-7-yl)benzene sulfonamide** *(isolated as > 20:1 r.r., crude > 20:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with triethylsilylacetylene (42.1 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (22.3 mg, 0.034 mmol, 34%) as a pale brown amorphous solid.

R_f (EtOAc in pentane, 20%) 0.54.

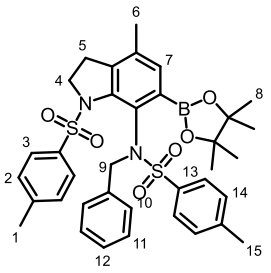
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.3 Hz, H13), 7.65 (2H, d, *J* = 8.3 Hz, H3), 7.30–7.27 (4H, m, ArH, H2 + H15), 7.16–7.05 (5H, m, ArH, H11 + H12 + H13), 6.88 (1H, dt, *J* = 7.1, 2.7 Hz, H7), 4.72 (2H, s, H10), 3.49 (2H, t, *J* = 7.2 Hz, H4), 2.42 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.08–1.96 (2H, m, H5), 1.56 (3H, d, *J* = 7.1 Hz, H6), 0.98 (9H, t, *J* = 7.6 Hz, H8), 0.62 (6H, q, *J* = 7.6 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 144.0, 142.8, 137.9, 135.9, 135.4, 134.3, 130.5, 129.5, 129.0, 128.4, 128.3, 127.8, 127.4, 126.4, 112.7, 103.7, 102.8, 54.3, 47.9, 27.1, 21.7, 21.6, 15.6, 7.5, 4.3.

HRMS (ES^+) calc. for $C_{36}H_{45}O_4N_2S_2Si$ ($[M+H]^+$) 661.2585, found 661.2578.

IR (thin film, ν_{max}/cm^{-1}) 2980, 1355, 1164, 1090, 1007.

183 ***N*-Benzyl-4-methyl-*N*-(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosylindolin-7-yl)benzenesulfonamide** *(isolated as > 20:1 r.r., crude 6:1 r.r.)*



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (45.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 40%) to give the title compound (17.7 mg, 0.026 mmol, 26%) as a viscous brown oil.

R_f (EtOAc in pentane, 20%) 0.24.

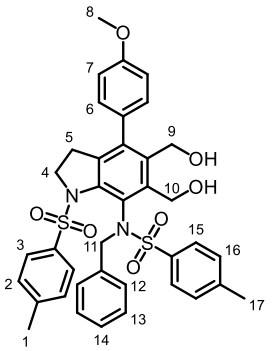
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.2 Hz, H13), 7.51 (2H, d, *J* = 8.3 Hz, H3), 7.37 (1H, s, H7), 7.23 (2H, d, *J* = 8.2 Hz, H14), 7.21–7.14 (7H, m, ArH), 5.15 (2H, s, H9), 3.93–3.69 (2H, m, H4), 2.43 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.11 (3H, s, H6), 2.05–2.00 (2H, m, H5), 1.29 (12H, s, H8).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.0, 142.8, 140.3, 139.8, 139.2, 138.3, 137.4, 137.0, 135.1, 129.8, 129.6, 129.2, 128.6, 128.52, 128.47, 128.2, 127.9, 127.4, 83.7, 53.6, 52.6, 28.2, 25.1, 21.8, 21.7, 18.2.

HRMS (ES^+) calc. for $C_{36}H_{42}O_6N_2BS_2$ ($[M+H]^+$) 673.2577, found 673.2572.

IR (thin film, ν_{max}/cm^{-1}) 2968, 1597, 1354, 1167, 1144, 1091.

190 *N*-Benzyl-*N*-(5,6-bis(hydroxymethyl)-4-(4-methoxyphenyl)-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide



82d (61.2 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-butyne-1,4-diol (25.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, Et_2O in CH_2Cl_2, 10 to 20%) to give the title compound (15.0 mg, 0.21 mmol, 21%) as a viscous colourless oil.

R_f (Et_2O in CH_2Cl_2, 10%) 0.46.

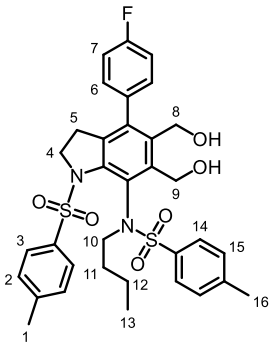
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.4 Hz, ArH), 7.46–7.41 (5H, m, ArH), 7.37–7.34 (3H, m, ArH), 7.31–7.28 (4H, m, ArH), 6.92 (1H, d, *J* = 8.5 Hz, H7), 6.78 (1H, d, *J* = 8.6 Hz, H6), 6.60 (1H, d, *J* = 8.5 Hz, H6), 5.43 (1H, d, *J* = 14.7 Hz, H11), 5.30 (1H, d, *J* = 14.7 Hz, H11), 4.45–4.41 (1H, m, CH_2), 4.36–4.26 (2H, m, H9 + OH), 4.18 (1H, dd, *J* = 12.0, 10.1 Hz, CH_2), 3.90 (1H, dd, *J* = 13.3, 10.6 Hz, H9), 3.81 (3H, s, H8), 3.69 (1H, ddd, *J* = 12.9, 7.4, 2.1 Hz, CH_2), 3.15–3.01 (2H, m, CH_2 + OH), 2.48 (3H, s, CH_3), 2.45 (3H, s, CH_3), 1.92 (1H, ddd, *J* = 16.1, 10.8, 7.6 Hz, CH_2), 1.72 (1H, ddd, *J* = 16.1, 7.6, 2.1 Hz, CH_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 159.3, 144.6, 143.7, 141.8, 141.0, 140.9, 140.6, 138.5, 136.1, 135.0, 131.2, 131.0, 130.0, 129.9, 129.8, 129.4, 128.8, 128.6, 128.2, 128.0, 114.0, 113.5, 60.5, 59.4, 56.6, 55.4, 53.8, 30.3, 21.78, 21.77.

HRMS (ES^+) calc. for $C_{38}H_{38}O_7N_2S_2Na$ ($[M+Na]^+$) 721.2013, found 721.2007.

IR (thin film, ν_{max}/cm^{-1}) 3443, 2922, 2359, 1609, 1598, 1514, 1441, 1357, 1328, 1289, 1246, 1167.

191 *N*-Butyl-*N*-(4-(4-fluorophenyl)-5,6-bis(hydroxymethyl)-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide



82i (56.6 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-butyne-1,4-diol (25.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (33.5 mg, 0.051 mmol, 51%) as a cream foam.

R_f (EtOAc in pentane, 30%) 0.24.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (2H, d, *J* = 8.3 Hz, ArH), 7.54 (1H, ddd, *J* = 8.2, 5.4, 2.3 Hz, H6), 7.37 (2H, d, *J* = 8.3 Hz, ArH), 7.33–7.30 (2H, m, ArH), 7.26–7.23 (2H, m, ArH), 7.12 (1H, td, *J* = 8.6, 2.8 Hz, H7), 6.94 (1H, td, *J* = 8.6, 2.8 Hz, H7), 6.61 (1H, ddd, *J* = 8.2, 5.4, 2.3 Hz, H6), 5.11 (1H, d, *J* = 12.7 Hz), 4.85 (1H, t, *J* = 11.4 Hz), 4.71–4.69 (1H, m), 4.25 (1H, d, *J* = 5.8 Hz), 3.92–3.88 (2H, m, H10), 3.68 (2H, ddd, *J* = 13.0, 6.6, 2.5 Hz), 3.14 (1H, ddd, *J* = 12.9, 10.9, 8.6 Hz), 2.46 (3H, s, CH_3), 2.44 (3H, s, CH_3), 1.77–1.64 (4H, m, H5 + H11), 1.34 (1H, q, *J* = 7.4 Hz, H12), 0.91 (3H, t, *J* = 7.4 Hz, H13) *OH protons not observed*.

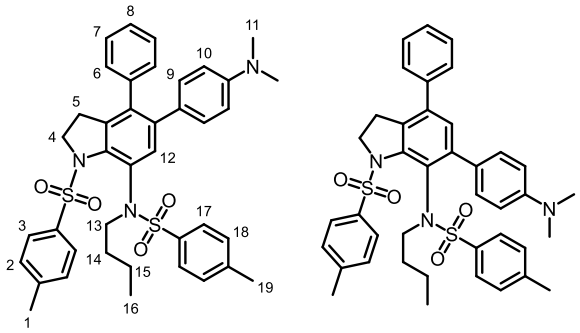
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 162.5 (d, $^1J_{C\text{-}F}$ = 247.5 Hz), 144.6, 143.84, 143.82, 141.8, 140.6, 140.2, 140.1, 137.5, 134.9, 133.7 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 131.7 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 131.4, 130.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.7, 129.5, 128.3, 128.0, 115.7 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 115.2 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 60.4, 60.0, 53.4, 52.9, 30.5, 29.9, 21.76, 21.75, 20.6, 14.1. *Two additional aromatic carbon signals observed due to diastereotopic character of 4-C_6H_4F ring.*

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −113.85.

HRMS (ES^+) calc. for $C_{34}H_{37}O_6N_2FNaS_2$ ($[M+Na]^+$) 675.1969, found 675.1967.

IR (thin film, ν_{max}/cm^{-1}) 2988, 1598, 1511, 1358, 1331, 1165, 1090, 1032.

192 *N*-Butyl-*N*-(5-(4-(dimethylamino)phenyl)-4-phenyl-1-tosylindolin-7-yl)-4-methyl benzenesulfonamide and ***N*-butyl-*N*-(6-(4-(dimethylamino)phenyl)-4-phenyl-1-tosylindolin-7-yl)-4-methylbenzenesulfonamide** *(isolated as 5:1 r.r., crude 5:1 r.r.)*



82k (54.8 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 4-ethynyl-*N*,*N*-dimethylaniline (43.6 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compounds as an inseparable mixture (20.0 mg, 0.029 mmol, 29%) as a brown foam. *NMR data is given for the major isomer in the isolated mixture.*

R_f (EtOAc in pentane, 20%) 0.19.

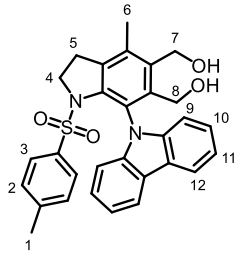
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.2 Hz, H17), 7.71 (2H, d, *J* = 8.2 Hz, H3), 7.33 (2H, d, *J* = 8.2 Hz, ArH), 7.28 (2H, d, *J* = 8.2 Hz, ArH), 7.22–7.15 (3H, m, ArH), 7.06 (1H, s, H12), 6.87–6.80 (4H, m, ArH), 6.50 (2H, d, *J* = 8.9 Hz, H10), 3.93–3.87 (2H, m, H4), 3.79–3.70 (2H, m, H13), 2.90 (6H, s, H11), 2.46 (3H, s, CH_3), 2.45 (3H, s, CH_3), 2.30–2.12 (2H, m, H5), 1.67 (2H, app. p, *J* = 7.9 Hz, H14), 1.29–1.17 (2H, m, H15), 0.85 (3H, t, *J* = 7.4 Hz, H16).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 149.3, 144.0, 143.3, 139.9, 139.5, 139.2, 137.1, 135.8, 132.1, 130.5, 129.7, 129.52, 129.50, 129.4 (2 C), 128.6, 128.14, 128.11, 128.06, 127.8, 126.9, 111.8, 53.1, 50.5, 40.5, 30.33, 30.27, 21.7 (2 C), 20.6, 13.9.

HRMS (ES^+) calc. for $C_{40}H_{44}O_4N_3S_2$ 694.2768, found 694.2764.

IR (thin film, ν_{max}/cm^{-1}) 2979, 1611, 1525, 1355, 1167, 1089.

202 (7-(9*H*-Carbazol-9-yl)-4-methyl-1-tosylindoline-5,6-diyl)dimethanol



199 (42.6 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with 2-butyne-1,4-diol (25.8 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 50%) to give the title compound (29.9 mg, 0.058 mmol, 58%) as a brown foam.

R_f (EtOAc in pentane, 50%) 0.25.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 7.7 Hz, H3), 7.27–7.23 (2H, m, ArH), 7.17–7.09 (2H, m, H2), 6.94 (2H, d, *J* = 8.1 Hz, ArH), 6.53 (4H, s, ArH), 4.69 (2H, d, *J* = 4.1 Hz, CH_2), 4.17 (2H, t, *J* = 7.3 Hz, H4), 3.97 (2H, d, *J* = 2.8 Hz, CH_2), 3.05 (1H, br. s, OH), 2.97 (2H, t, *J* = 7.3 Hz, H5), 2.38 (3H, s, H6), 2.15 (3H, s, H1), 1.86 (1H, br. s, OH).

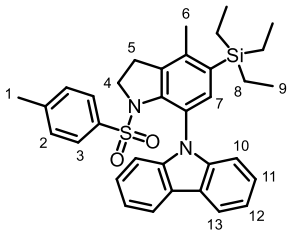
Note: the abnormally low chemical shift of the tosyl-CH_3 protons (2.15 ppm) is generally seen for all carbazole-substituted 7-aminoindolines prepared in this work, and also those prepared by Julia Ragus.[128]

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 142.6, 141.5, 140.8, 139.2, 138.8, 138.5, 136.0, 135.7, 128.6, 125.9, 125.5, 125.3, 123.5, 120.1, 120.0, 110.6, 59.5, 58.8, 52.9, 30.6, 21.6, 16.3.

HRMS (ES^+) calc. for $C_{30}H_{28}O_4N_2SNa$ ($[M+Na]^+$) 535.1662, found 535.1662.

IR (solid, ν_{max}/cm^{-1}) 3353, 2947, 2907, 1770, 1759, 1373, 1315, 1246.

203 9-(4-Methyl-1-tosyl-6-(triethylsilyl)indolin-7-yl)-9*H*-carbazole *(isolated as > 20:1 r.r., crude > 20:1 r.r.)*



199 (42.6 mg, 0.10 mmol, 1.0 equiv.) was used in **General Procedure 8** with triethylsilylacetylene (42.1 mg, 0.30 mmol, 3.0 equiv.) for 16 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 50%) to give the title compound (8.0 mg, 0.014 mmol, 14%) as a brown foam.

R_f (EtOAc in pentane, 10%) 0.34.

^{1}H NMR (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* = 7.6 Hz, ArH), 7.38 (1H, s, H7), 7.35 (2H, t, *J* = 7.7 Hz, ArH), 7.24–7.21 (4H, m, ArH), 6.79 (2H, d, *J* = 8.2 Hz, H3), 6.72 (2H, d, *J* = 8.2 Hz, H2), 4.19 (2H, t, *J* = 7.4 Hz, H4), 2.87 (2H, t, *J* = 7.4 Hz, H5), 2.36 (3H, s, H6), 2.25 (3H, s, H1), 0.94 (9H, t, *J* = 7.7 Hz, H9), 0.85–0.80 (6H, m, H8).

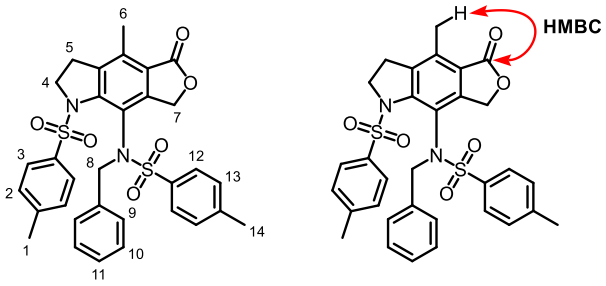
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 143.1, 140.5, 139.6, 139.4, 138.2, 135.7, 135.6, 135.1, 128.8, 126.5, 126.3, 125.7, 123.7, 120.1, 119.6, 110.6, 52.1, 30.0, 21.6, 19.6, 7.7, 4.2

HRMS (ES^+) calc. for $C_{34}H_{39}N_2O_2SSi$ ($[M+H]^+$) 567.2496, found 567.2510

IR (thin film, ν_{max}/cm^{-1}) 2989, 2947, 1597, 1464, 1453, 1365, 1336, 1233, 1168, 1003.

7.4.4 7-Aminoindoline derivatisation products

205 *N*-Benzyl-4-methyl-*N*-(4-methyl-5-oxo-1-tosyl-2,3,5,7-tetrahydro-1*H*-furo[3,4-f] indol-8-yl)benzenesulfonamide



158 (30.3 mg, 0.050 mmol, 1.0 equiv.), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0.8 mg, 0.0050 mmol, 10 mol%) and *bis*-acetoxyiodobenzene (33.8 mg, 0.11 mmol, 2.1 equiv.) were dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (26.6 mg, 0.044 mmol, 88%) as a white solid.

R_f (EtOAc in pentane, 20%) 0.30.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 (2H, d, *J* = 8.4 Hz, H12), 7.52 (2H, d, *J* = 8.3 Hz, H3), 7.32–7.28 (4H, m, ArH), 7.25–7.19 (5H, m, ArH), 5.22 (1H, d, *J* = 16.1 Hz, H7), 5.07–4.98 (2H, m, H8), 4.05 (1H, d, *J* = 16.1 Hz, H7), 3.89–3.76 (2H, m, H4), 2.45 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.34 (3H, s, H6), 2.22–2.15 (1H, m, H5), 2.11 (1H, dt, *J* = 15.5, 7.4 Hz, H5).

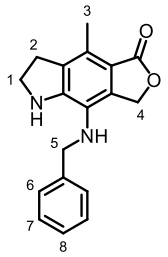
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.2, 150.4, 145.0, 144.9, 144.1, 141.1, 137.1, 136.0, 135.3, 134.7, 129.92, 129.86, 129.5, 129.0, 128.7, 128.6, 127.9, 125.6, 123.4, 69.4, 53.5, 53.4, 27.7, 21.81, 21.77, 14.1.

HRMS (ES^+) calc. for $C_{32}H_{31}O_6N_2S_2$ ($[M+H]^+$) 603.1618, found 603.1619.

IR (solid, ν_{max}/cm^{-1}) 2889, 1759 (C=O), 1461, 1242, 1157, 1089.

MP 110–112 °C.

206 8-(Benzylamino)-4-methyl-1,2,3,7-tetrahydro-5*H*-furo[3,4-f]indol-5-one



205 (30.1 mg, 0.050 mmol, 1.0 equiv.), magnesium turnings (24.0 mg, 1.0 mmol, 20 equiv.) and NH_4Cl (5.3 mg, 0.10 mmol, 2.0 equiv.) were dissolved in MeOH (1.0 mL) and the vial was purged with argon then sealed. The reaction mixture was sonicated for 30 minutes then diluted with CH_2Cl_2 (10 mL) and washed with water (2 × 5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (11.0 mg, 0.037 mmol, 75%) as a white solid.

R_f (EtOAc in pentane, 40%) 0.33.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34–7.27 (3H, m, H7 + H8), 7.25–7.21 (2H, m, H6), 4.86 (2H, s, H4), 4.19 (2H, s, H5), 3.69 (2H, t, *J* = 8.6 Hz, H1), 3.05 (2H, t, *J* = 8.6 Hz, H2), 2.47 (3H, s, H3). *NH peaks not observed.*

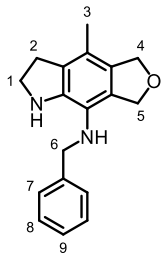
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 171.8, 149.2, 140.1, 138.5, 130.8, 129.3, 129.0, 127.83, 127.75, 122.8, 114.1, 66.9, 50.8, 47.9, 28.3, 13.7.

HRMS (ES^+) calc. for $C_{18}H_{19}O_2N_2$ ($[M+H]^+$) 295.1441, found 295.1441.

IR (solid, ν_{max}/cm^{-1}) 3389, 2981, 1708 (C=O), 1599, 1520, 1462, 1381, 1312, 1160, 1023.

MP 138–140 °C.

207 *N*-Benzyl-4-methyl-2,3,5,7-tetrahydro-1*H*-furo[3,4-f]indol-8-amine



158 (15.2 mg, 0.025 mmol, 1.0 equiv.) and magnesium turnings (12.0 mg, 0.050 mmol, 2.0 equiv.) were dissolved in MeOH (0.5 mL) in a vial fitted with a screw cap and heated at 50 °C for 18 h. The reaction mixture was cooled to room temperature and poured into saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* then purified by flash column chromatography (SiO_2, MeOH in CH_2Cl_2, 5%) to give the title compound (2.5 mg, 0.0089 mmol, 36%) as a pale yellow oil.

R_f (MeOH in CH_2Cl_2, 5%) 0.26.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34–7.26 (5H, m, H7 + H8 + H9), 4.70 (2H, s, CH_2), 4.60 (2H, s, CH_2), 4.11 (2H, s, H6), 3.50 (2H, t, *J* = 8.4 Hz, H1), 3.00 (2H, t, *J* = 8.4 Hz, H2), 2.26 (3H, s, H3). *NH protons not observed.*

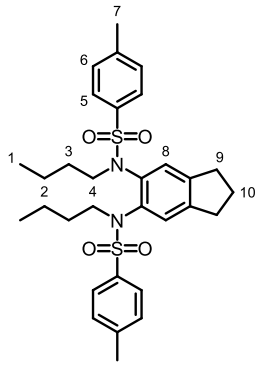
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 146.0, 140.5, 132.4, 129.6, 129.01, 128.98, 128.8, 128.34, 128.25, 127.5, 59.5, 58.6, 52.3, 47.5, 30.0, 15.8.

HRMS (ES^+) calc. for $C_{18}H_{21}N_2O$ ($[M+H]^+$) 281.1648, found 281.1650.

IR (thin film, ν_{max}/cm^{-1}) 3332, 2924, 2852, 1604, 1455, 1411, 1321, 1284, 1109, 1071.

7.4.5 1,2-Diaminobenzene products

211 *N*,*N*'-(2,3-Dihydro-1*H*-indene-5,6-diyl)bis(*N*-butyl-4-methylbenzenesulfonamide)



188 (47.6 mg, 0.10 mmol, 1.0 equiv.) and 1,6-heptadiyne (46.0 mg, 0.50 mmol, 5.0 equiv.) were used in **General Procedure 9** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 10%) to give the title compound (35.0 mg, 0.062 mmol, 62%) as a cream solid.

R_f (EtOAc in pentane, 20%) 0.30.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.81 (4H, d, *J* = 8.1 Hz, H5), 7.34 (4H, d, *J* = 8.1 Hz, H6), 6.90 (2H, s, H8), 3.75–3.64 (4H, m, H4), 2.86 (4H, dt, *J* = 8.1, 4.0 Hz, H9), 2.46 (6H, s, H7), 2.11 (2H, p, *J* = 7.5 Hz, H10), 1.52–1.32 (4H, m, H3), 1.15 (4H, app. h, *J* = 7.4 Hz, H2), 0.80 (6H, t, *J* = 7.4 Hz, H1).

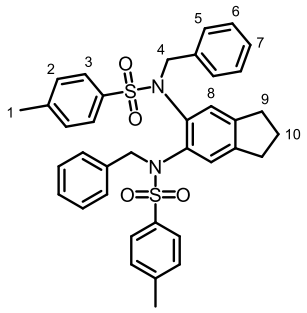
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 145.1, 143.5, 138.3, 137.1, 129.7, 128.2, 126.7, 51.5, 32.8, 29.7, 25.6, 21.7, 20.2, 13.8.

HRMS (ES^+) calc. for $C_{31}H_{41}O_4N_2S_2$ ($[M+H]^+$) 569.2502, found 569.2501.

IR (thin film, ν_{max}/cm^{-1}) 2974, 1350, 1331, 1305, 1162, 1095.

MP 168–170 °C.

213 *N*,*N*'-(2,3-Dihydro-1*H*-indene-5,6-diyl)bis(*N*-benzyl-4-methylbenzenesulfonamide)



212 (54.4 mg, 0.10 mmol, 1.0 equiv.) and 1,6-heptadiyne (46.0 mg, 0.50 mmol, 5.0 equiv.) were used in **General Procedure 9** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 20%) to give the title compound (39.8 mg, 0.063 mmol, 63%) as a cream solid.

Scaled up procedure (1.0 mmol scale)

212 (0.544 g, 1.0 mmol, 1.0 equiv.) and 1,6-heptadiyne (0.460 g, 5.0 mmol, 5.0 equiv.) were used in **General Procedure 9** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10%) to give the title compound (0.372 g, 0.58 mmol, 58%) as a cream solid.

Note: this compound exhibited restricted rotation about the C(aryl)-N axis leading to broadening in the ^{1}H NMR spectrum; this was confirmed by a variable temperature (25–85 °C) ^{1}H NMR experiment.

R_f (EtOAc in pentane, 20%) 0.40.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (4H, d, *J* = 8.3 Hz, H3), 7.28–7.26 (4H, m, H2), 7.22–7.11 (6H, m, ArH), 7.09–7.04 (4H, m, ArH), 6.54 (2H, s, H8), 5.04–4.99 (4H, m, H4), 2.73–2.67 (4H, m, H9), 2.45 (6H, s, H1), 2.03 (2H, p, *J* = 7.5 Hz, H10).

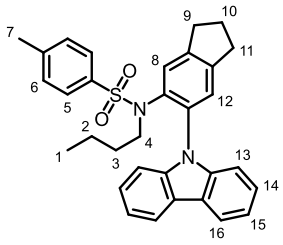
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 143.5, 138.5, 136.8, 136.0, 130.4, 129.6, 128.4, 128.1, 128.0, 127.7, 55.3, 32.7, 25.4, 21.7.

HRMS (ES^+) calc. for $C_{37}H_{37}O_4N_2S_2$ ($[M+H]^+$) 637.2189, found 637.2182.

IR (thin film, ν_{max}/cm^{-1}) 1493, 1342, 1157, 1090, 1041. *C-H signals extremely weak.*

MP 177–179 °C.

214a *N*-(6-(9*H*-Carbazol-9-yl)-2,3-dihydro-1*H*-inden-5-yl)-*N*-butyl-4-methylbenzenesulfonamide



198a (1.00 g, 2.40 mmol, 1.0 equiv.) and 1,6-heptadiyne (1.37 mL, 12.0 mmol, 5 equiv.) were used in **General Procedure 9** (*modification: dissolve **198a** and **Rh-2** in 10 mL PhMe and add 1,6-heptadiyne in 20 mL PhMe*) with purification by flash column chromatography (SiO_2, Et_2O in pentane, 10%) followed by trituration (Et_2O in pentane, 10%) to give the title compound (0.650 g, 1.28 mmol, 53%) as a white solid.

R_f (Et_2O in pentane, 10%) 0.16.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.13 (2H, d, *J* = 7.7 Hz, H5), 7.59 (1H, s, H8), 7.38–7.33 (2H, m, ArH), 7.29–7.23 (3H, m, ArH), 7.22 (1H, s, H12), 7.19–7.17 (3H, m, ArH), 6.94–6.92 (2H, m, ArH), 3.09 (2H, t, *J* = 7.5 Hz, H9), 2.98 (2H, t, *J* = 7.5 Hz, H11), 2.80 (2H, t, *J* = 8.4 Hz, H4), 2.29 (3H, s, H7), 2.22 (2H, q, *J* = 7.5 Hz, H10), 1.24 (2H, qd, *J* = 8.4, 6.7 Hz, H3), 0.83–0.78 (2H, m, H2), 0.59 (3H, t, *J* = 7.3 Hz, H1).

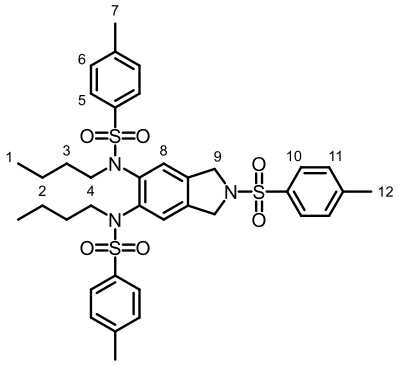
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 146.3, 146.1, 143.4, 142.3, 136.6, 136.5, 133.8, 129.3, 128.1, 127.6, 127.1, 125.9, 123.3, 120.2, 119.8 (2 C), 51.0, 33.1, 32.8, 29.6, 25.9, 21.5, 19.8, 13.6.

HRMS (ES^+) calc. for $C_{32}H_{33}N_2O_2S$ $[M+H]^+$ 509.2263, found 509.2257.

IR (thin film, ν_{max}/cm^{-1}) 2981, 2888, 1382, 1157, 1088.

M.P 169–171 °C.

215 *N,N'*-(2-Tosylisoindoline-5,6-diyl)bis(*N*-butyl-4-methylbenzenesulfonamide)



188 (54.4 mg, 0.10 mmol, 1.0 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (0.124 g, 0.50 mmol, 5.0 equiv.) were used in **General Procedure 9** with purification by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (66.2 mg, 0.092 mmol, 92%) as a sticky yellow oil.

R_f (CH_2Cl_2) 0.39.

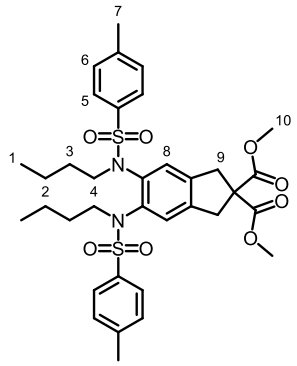
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.74 (6H, m, H5 + H10), 7.35–7.33 (6H, m, H6 + H11), 6.85 (2H, s, H8), 4.54 (4H, s, H9), 3.66–3.65 (4H, m, H4), 2.47 (6H, s, H7), 2.43 (3H, s, H12), 1.33–1.32 (4H, s, H3), 1.13 (4H, app. h, *J* = 7.3 Hz, H2), 0.78 (6H, t, *J* = 7.3 Hz, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 144.0, 139.1, 137.7, 136.9, 133.5, 130.1, 129.9, 128.1, 127.7, 125.2, 53.5, 51.4, 29.7, 21.72, 21.68, 20.1, 13.8.

HRMS (ES^+) calc. for $C_{37}H_{46}O_6N_3S_3$ ($[M+H]^+$) 724.2543, found 724.2537.

IR (thin film, ν_{max}/cm^{-1}) 2959, 2930, 1598, 1494, 1345, 1163, 1090, 1037.

216 Dimethyl 5,6-bis((*N*-butyl-4-methylphenyl)sulfonamido)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate



188 (54.4 mg, 0.10 mmol, 1.0 equiv.) and dimethyl 2,2-di(prop-2-yn-1-yl)malonate (0.104 g, 0.50 mmol, 5.0 equiv.) were used in **General Procedure 9** with purification by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 30%) to give the title compound (54.8 mg, 0.080 mmol, 80%) as a white solid. *Crystals suitable for single crystal XRD were prepared by vapour diffusion of pentane into a concentrated solution of **216** in pentane.*

R_f (EtOAc in pentane, 20%) 0.23.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (4H, d, *J* = 8.4 Hz, H5), 7.36–7.31 (4H, m, H6), 6.85 (2H, s, H8), 3.78 (6H, s, H10), 3.71–3.62 (4H, m, H4), 3.58–3.55 (4H, m, H9), 2.46 (6H, s, H7), 1.48–1.30 (4H, m, H3), 1.14 (4H, app. p, *J* = 7.4 Hz, H2), 0.80 (6H, t, *J* = 7.3 Hz, H1).

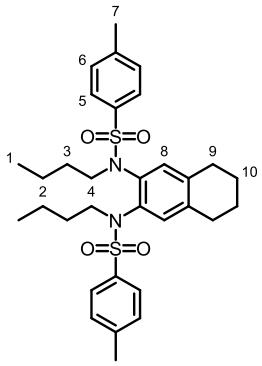
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.8, 143.7, 140.7, 138.3, 137.9, 129.7, 128.2, 126.5, 60.5, 53.3, 51.6, 40.4, 29.7, 21.7, 20.1, 13.8.

HRMS (ES^+) calc. for $C_{35}H_{45}O_8N_2S_2$ ($[M+H]^+$) 685.2612, found 685.2596.

IR (thin film, ν_{max}/cm^{-1}) 2959, 1736, 1494, 1435, 1345, 1274, 1247, 1162, 1089.

MP 135–137 °C.

217 *N*,*N*'-(5,6,7,8-Tetrahydronaphthalene-2,3-diyl)bis(*N*-butyl-4-methylbenzene sulfonamide)



188 (54.4 mg, 0.10 mmol, 1.0 equiv.) and 1,7-octadiyne (53.1 mg, 0.50 mmol, 5.0 equiv.) were used in **General Procedure 9** with purification by flash column chromatography (SiO_2, CH_2Cl_2) and recrystalisation (Et_2O in pentane, 10 %) to give the title compound (10.0 mg, 0.017 mmol, 17%) as a white solid.

R_f (EtOAc in pentane, 10%) 0.26.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (4H, d, J = 8.3 Hz, H5), 7.37–7.30 (4H, m, H6), 6.70 (2H, s, H8), 3.75–3.59 (4H, m, H4), 2.66–2.62 (4H, m, H9), 2.46 (6H, s, H7), 1.80–1.75 (4H, m, H10), 1.52 –1.31 (4H, m, H3), 1.21–1.12 (4H, m, H2), 0.81 (6H, t, J = 7.3 Hz, H1).

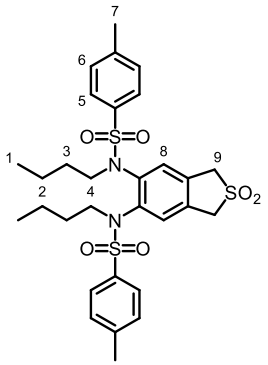
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.5, 138.2, 137.9, 136.2, 131.3, 129.6, 128.2, 51.5, 29.8, 29.0, 22.7, 21.7, 20.2, 13.8.

HRMS (ES^+) calc. for $C_{32}H_{43}O_4N_2S_2$ ($[M+H]^+$) 583.2659, found 583.2649.

IR (solid, ν_{max}/cm^{-1}) 2958, 2934, 1498, 1343, 1153, 1089, 1043.

MP 189–191 °C.

218 *N,N'*-(2,2-Dioxido-1,3-dihydrobenzo[c]thiophene-5,6-diyl)bis(*N*-butyl-4-methylbenzenesulfonamide)



188 (54.4 mg, 0.10 mmol, 1.0 equiv.) and 3-(prop-2-yn-1-ylsulfonyl)prop-1-yne (71.0 mg, 0.50 mmol, 5.0 equiv.) were used in **General Procedure 9** using 1,4-dioxane as the solvent at 90 °C, with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 40%) to give the title compound (16.0 mg, 0.026 mmol, 26%) as a viscous brown oil.

R_f (EtOAc in pentane, 30%) 0.26.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (4H, d, *J* = 8.0 Hz, H5), 7.36 (4H, d, *J* = 8.0 Hz, H6), 7.05 (2H, s, H8), 4.33 (4H, s, H9), 3.70–3.61 (4H, m, H4), 2.48 (6H, s, H7), 1.46–1.28 (4H, m, H3), 1.20–1.11 (4H, m, H2), 0.81 (6H, t, *J* = 7.4 Hz, H1).

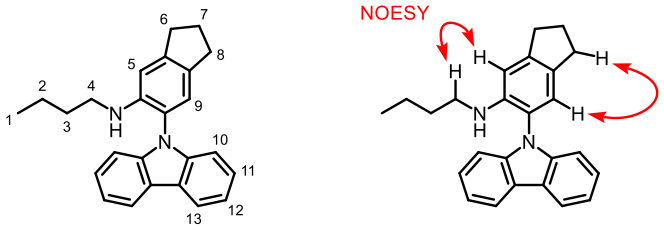
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 140.1, 131.8, 130.0 (2 C), 128.7, 128.1, 56.9, 51.4, 29.8, 21.8, 20.1, 13.8.

HRMS (ES^+) calc. for $C_{30}H_{39}O_6N_2S_3$ ($[M+H]^+$) 619.1965, found 619.1963.

IR (thin film, ν_{max}/cm^{-1}) 2962, 2932, 1493, 1344, 1321, 1163, 1089, 1037.

7.4.6 1,2-Diaminobenzene derivatisation products

229 *N*-Butyl-6-(9*H*-carbazol-9-yl)-2,3-dihydro-1*H*-inden-5-amine



214a (25.4 mg, 0.050 mmol, 1.0 equiv.), magnesium turnings (6.0 mg, 0.25 mmol, 10.0 equiv.) and NH_4Cl (2.7 mg, 0.050 mmol, 1.0 equiv.) were dissolved in MeOH (1.0 mL) and the reaction mixture was purged with argon. The reaction mixture was then sonicated for 30 minutes and then diluted with EtOAc (10 mL) and washed with brine (10 mL) then water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, Et_2O in pentane, 10%) to give the title compound (3.0 mg, 0.0085 mmol, 17%) as a colourless oil.

R_f (Et_2O in pentane, 10%) 0.70.

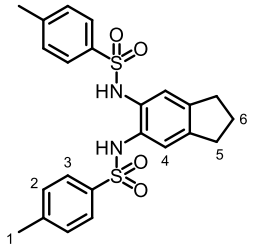
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.15–8.13 (2H, m, ArH), 7.40–7.37 (2H, m, ArH), 7.29–7.25 (2H, m, ArH), 7.18–7.16 (2H, m, ArH), 7.04 (1H, s, H9), 6.80 (1H, s, H5), 3.04 (2H, t, *J* = 7.1 Hz, H4), 2.99 (2H, t, *J* = 7.4 Hz, H6), 2.86 (2H, t, *J* = 7.4 Hz, H8), 2.14z (2H, app. p, *J* = 7.4 Hz, H7), 1.37–1.31 (2H, m, H3), 1.18–1.10 (2H, m, H2), 0.78 (3H, t, *J* = 7.3 Hz, H1). *NH signal not found.*

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 146.1, 144.2, 141.3, 132.5, 126.0, 125.0, 123.5, 120.4, 120.3, 119.8, 110.5, 107.8, 43.6, 33.6, 32.2, 31.4, 26.0, 20.2, 13.9.

HRMS (ES^+) calc. for $C_{25}H_{27}N_2$ ($[M+H]^+$) 355.2169, found 355.2173.

IR (thin film, ν_{max}/cm^{-1}) 3422, 2868, 2846, 1625, 1582, 1508, 1478, 1451, 1314, 1232.

230 *N*,*N*'-(2,3-Dihydro-1*H*-indene-5,6-diyl)bis(4-methylbenzenesulfonamide)



213 (15.7 mg, 0.025 mmol, 1.0 equiv.) was dissolved in MeOH (1.0 mL) and Pd/C (10% w/w) (6.2 mg, 40% w/w) was added and the reaction mixture was purged with H_2 for 5 minutes then stirred under an atmosphere of H_2 for 60 h. The reaction mixture was then filtered through Celite® and concentrated *in vacuo* then purified by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (5.1 mg, 0.011 mmol, 45%) as a colourless oil which was then recrystallised from $CDCl_3$ to give white crystals.

R_f (EtOAc in pentane, 30%) 0.31.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.56 (4H, d, *J* = 8.2 Hz, H3), 7.23 (4H, d, *J* = 8.2 Hz, H2), 6.81 (2H, s, H4), 6.50 (2H, s, NH), 2.74 (4H, t, *J* = 7.5 Hz, H5), 2.40 (6H, s, H1), 2.01 (2H, p, *J* = 7.5 Hz, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.3, 144.2, 136.0, 129.7, 129.2, 127.7, 122.9, 32.7, 25.5, 21.8.

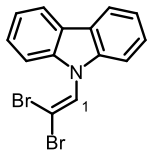
HRMS (ES^+) calc. for $C_{23}H_{25}O_4N_2S_2$ ($[M+H]^+$) 457.1250, found 457.1245.

IR (thin film, ν_{max}/cm^{-1}) 3410, 2890, 2877, 1717, 1457, 1351, 1162.

MP 155-157 °C.

7.4.7 Carbazole-yndiamide precursors: 1,1-dibromoenamides

197a 9-(2,2-Dibromovinyl)-9*H*-carbazole



Carbazole (5.00 g, 29.9 mmol, 1.0 equiv.) was dissolved in formic acid (50 mL) and the reaction mixture was heated to 100 °C and stirred for 2 h then cooled to room temperature. The formic acid was removed *in vacuo* and the resulting solid was dried under high vacuum for 1 h to give *N*-formyl carbazole which was used in the next stage without further purification.

Triphenylphosphine (31.4 g, 120 mmol, 4.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (180 mL) at −30 °C under an atmosphere of argon and CBr_4 (19.8 g, 59.8 mmol, 2.0 equiv.) was added slowly as a solution in anhydrous CH_2Cl_2 (30 mL). The reaction mixture was then cooled to −40 °C and stirred at this temperature for 30 minutes. *Note: at this stage an additional 200 mL of anhydrous CH_2Cl_2 was added due to insolubility of the PPh_3/CBr_4 adduct on this scale, this additional solvent is not normally required on smaller scales.* The crude *N*-formylcarbazole from the first stage was then added over 30 minutes as a solution in anhydrous CH_2Cl_2 (90 mL) and the reaction mixture was allowed to slowly warm to room temperature then was stirred at room temperature for 16 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 20%) to give the title compound as a white solid (8.81 g, 25.2 mmol, 84%).

R_f (EtOAc in pentane, 10%) 0.90.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.09–8.07 (2H, m, ArH), 7.73 (1H, s, H1), 7.51–7.50 (2H, m, ArH), 7.39–7.37 (2H, m, ArH), 7.35–7.29 (2H, m, ArH).

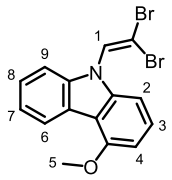
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.9, 129.8, 126.3, 123.9, 121.0, 120.6, 110.8, 95.7.

HRMS (ES^+) calc. for $C_{14}H_{10}N^{79}Br^{81}Br$ 351.9154 ($[M+H]^+$), found 351.9152.

IR (thin film, ν_{max}/cm^{-1}) 2925, 1608, 1591, 1476, 1446, 1357, 1334, 1313, 1284, 1222, 1154, 1118.

M.P 104–106 °C.

197b 9-(2,2-Dibromovinyl)-4-methoxy-9*H*-carbazole



$POCl_3$ (2.84 mL, 30.6 mmol, 3.0 equiv.) was dissolved in DMF (40 mL) at 0 °C, then 1-methoxy-9-*H*-carbazole (2.00 g, 10.2 mmol, 1.0 equiv.) was added slowly as a solution in DMF (60 mL). The reaction mixture was stirred at room temperature for 2 h then water was added and the precipitate was collected by filtration. The precipitate was dissolved in EtOAc and washed with brine and the organic layer was dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give 4-methoxy-9*H*-carbazole-9-carbaldehyde (1.29 g, 5.73 mmol, 56%) as a yellow solid; this was used without further purification in the next step.

Triphenylphosphine (4.67 g, 17.8 mmol, 4.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (30 mL) at –30 °C under an atmosphere of argon and CBr_4 (2.94 g, 8.88 mmol, 2.0 equiv.) was added slowly as a solution in anhydrous CH_2Cl_2 (5.0 mL). The reaction mixture was then cooled to –40 °C and stirred at this temperature for 30 minutes. 4-Phenyl-9*H*-carbazole-9-carbaldehyde (1.00 g, 4.44 mmol, 1.0 equiv.) from the first stage was then added over 30 minutes as a solution in anhydrous CH_2Cl_2 (25 mL) and the reaction mixture was allowed to slowly warm to room temperature then was stirred at room temperature for 16 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, EtOAc in pentane, 10%) to give the title compound (1.03 g, 2.71 mmol, 71%) as a white solid.

R_f (EtOAc in pentane, 10%) 0.56

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.35 (1H, d, *J* = 7.8 Hz, ArH), 7.69 (1H, s, H1), 7.49–7.30 (4H, m, ArH), 7.00 (1H, d, *J* = 8.1 Hz, ArH), 6.78 (1H, d, *J* = 8.1 Hz, ArH), 4.09 (3H, s, H5).

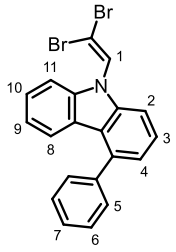
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.4, 140.2, 138.0, 129.9, 127.1, 125.3, 123.4, 123.2, 121.1, 113.0, 110.2, 103.6, 102.2, 95.9, 55.7.

HRMS (ES^+) calc. for $C_{15}H_{21}ON^{79}Br^{81}Br$ ($[M+H]^+$) 381.9260, found 381.9260.

IR (thin film, ν_{max}/cm^{-1}) 2936, 1587, 1453, 1437, 1344, 1267, 1228, 1176, 1157, 1111, 1061.

MP 79–81 °C.

197c 9-(2,2-Dibromovinyl)-4-phenyl-9*H*-carbazole



4-Phenyl-9*H*-carbazole (0.430 g, 1.76 mmol, 1.0 equiv.) was dissolved in formic acid (10 mL) and the reaction mixture was heated to 100 °C and stirred for 16 h then cooled to room temperature. The formic acid was removed *in vacuo* and the resulting solid was dried under high vacuum for 1 h to give 4-phenyl-9*H*-carbazole-9-carbaldehyde which was used in the next stage without further purification.

Triphenylphosphine (1.85 g, 7.04 mmol, 4.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (15 mL) at –30 °C under an atmosphere of argon and CBr_4 (1.17 g, 3.52 mmol, 2.0 equiv.) was added slowly as a solution in anhydrous CH_2Cl_2 (3.0 mL). The reaction mixture was then cooled to –40 °C and stirred at this temperature for 30 minutes. The crude 4-phenyl-9*H*-carbazole-9-carbaldehyde from the first stage was then added over 30 minutes as a solution in anhydrous

CH_2Cl_2 (15 mL) and the reaction mixture was allowed to slowly warm to room temperature then was stirred at room temperature for 16 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 20%) to give the title compound (0.353 g, 0.83 mmol, 47%) as a white solid.

R_f (pentane) 0.21.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (1H, s, H1), 7.66–7.60 (2H, m, ArH), 7.58–7.50 (4H, m, ArH), 7.49–7.46 (1H, m, ArH), 7.45–7.35 (3H, m, ArH), 7.21 (1H, dd, *J* = 7.4, 1.0 Hz, ArH), 7.09–7.04 (1H, m, ArH).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 141.0, 139.2, 139.1, 138.1, 129.7, 129.3, 128.6, 127.8, 127.3, 126.1, 126.0, 123.6, 122.7, 121.3, 120.6, 110.6, 109.7, 96.5.

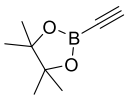
HRMS (ES^+) calc. for $C_{20}H_{14}N^{79}Br^{81}Br$ ($[M+H]^+$) 427.9467, found 427.9467.

IR (thin film, ν_{max}/cm^{-1}) 3055, 1588, 1454, 1422, 1334, 1314, 1289, 1153.

MP 99–101 °C.

7.4.8 Monoalkyne component synthesis

182 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a solution of i-PrOB(pin) (1.40 mL, 7.5 mmol, 1.5 equiv.) in THF (10 mL) at –78 °C was added slowly ethynyl magnesium bromide (0.5 M in THF, 10.0 mL, 1.0 equiv.) and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction then quenched with HCl (1.0 M in Et_2O, 10 mL, 10.0 mmol, 2.0 equiv.) and concentrated *in vacuo*. The crude material was then purified by Kugelrohr distilliation to give the title compound as one of several components in a mixture (0.559 g, colourless oil), the purity of which was assessed by

quantitative ^{1}H NMR using DCE as the NMR standard. The mixture was found to contain 1.7 mmol of the desired compound and this mixture was used without further purification in the next step. *NMR data is consistent with that reported in the literature.*[235]

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.48 (1H, s), 1.28 (12H, s).

7.4.9 X-Ray Crystallography

Low temperature single crystal X-ray diffraction data were collected using Oxford Diffraction (Rigaku) SuperNovae diffractometers at 150 K. These data were reduced using CrysAlisPro, solved using SuperFlip66 and the structures were refined using CRYSTALS. Further details about the refinements are documented in the CIF. *X-Ray data for **198b** and **211** was collected and processed by Dr Kirsten Christensen, X-ray data for **216** was collected by Helena Pickford and processed by Dr Amber Thompson.*

Table 7.4.1. Crystal data and structure refinement for 198b.

Empirical formula	$C_{28}H_{22}N_2O_2S$	
Formula weight	450.56	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.5324(5) Å	α = 65.080(4)°
	b = 11.4101(4) Å	B = 64.086(4)°
	c = 11.8680(5) Å	γ = 64.089(4)°
Volume	1106.11(9) Å^3	
Z	2	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	1.529 mm^{-1}	
F(000)	472	
Crystal size	0.22 x 0.18 x 0.08 mm^3	

Theta range for data collection	4.321 to 76.187°.
Index ranges	-13<=h<=13, -13<=k<=14, -14<=l<=14
Reflections collected	19271
Independent reflections	4570 [$R_{(int)}$ = 0.024]
Completeness to theta	= 73.091° 99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.88 and 0.72
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4569 / 0 / 298
Goodness-of-fit on F2	0.9922
Final R indices [I>2sigma(I)]	R_1 = 0.0324, wR_2 = 0.0876
R indices (all data)	R_1 = 0.0349, wR_2 = 0.0901
Largest diff. peak and hole	0.28 and –0.39 e.Å^{-3}

Table 7.4.2. Crystal data and structure refinement for 211.

Empirical formula	$C_{32}H_{32}N_2O_2S$	
Formula weight	508.68	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.1358(5) Å	α = 70.974(4)°
	b = 10.9432(5) Å	B = 84.961(4)°
	c = 13.6368(6) Å	γ = 71.099(4)°
Volume	1352.57(12) Å^3	
Z	2	
Density (calculated)	1.249 Mg/m^3	
Absorption coefficient	1.304 mm^{-1}	
F(000)	540	
Crystal size	0.21 x 0.20 x 0.10 mm^3	

Theta range for data collection	4.501 to 76.264°.
Index ranges	-12<=h<=12, -11<=k<=13, -15<=l<=17
Reflections collected	12885
Independent reflections	5603 [$R_{(int)}$ = 0.024]
Completeness to theta	= 73.976° 99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.88 and 0.84
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	5603 / 0 / 335
Goodness-of-fit on F2	1.1092
Final R indices [I>2sigma(I)]	R_1 = 0.0388, wR_2 = 0.0895
R indices (all data)	R_1 = 0.0445, wR_2 = 0.0994
Largest diff. peak and hole	0.30 and –0.33 e.Å^{-3}

Table 7.4.3. Crystal data and structure refinement for 216.

Empirical formula	$C_{35}H_{44}N_2O_8S_2$	
Formula weight	684.87	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.8574(4) Å	α = 107.013(4)°
	b = 12.3419(5) Å	B = 102.544(4)°
	c = 12.8565(7) Å	γ = 95.780(3)
Volume	1728.77(14) Å^3	
Z	2	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	1.839 mm^{-1}	
F(000)	728	

Crystal size	0.12 x 0.08 x 0.02 mm^3
Theta range for data collection	3.805 to 76.277°.
Index ranges	-10<=h<=14, -15<=k<=15, -15<=l<=16
Reflections collected	17490
Independent reflections	7124 [$R_{(int)}$ = 0.040]
Completeness to theta	= 72.463° 99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.96 and 0.93
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	7120 / 0 / 424
Goodness-of-fit on F2	1.0006
Final R indices [I>2sigma(I)]	R_1 = 0.0414, wR_2 = 0.0951
R indices (all data)	R_1 = 0.0554, wR_2 = 0.1084
Largest diff. peak and hole	0.67 and –0.46 e.$Å^{-3}$

7.4.10 Dynamic HPLC Data

*Dynamic HPLC data in **Section 7.4.10** was collected and processed by DPhil student Pearse Solon. The author obtained the initial HPLC separation of the atropisomers of **158** and contributed to discussions of the chromatographic approach to investigate the rotational barrier.*

DHPLC was performed on a Dionex Ultimate 3000 system comprising of a Dionex LPG-3400SD pump, WPS-3000SL autosampler, TCC-3000SD column compartment fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø × 25 cm), corresponding guard column (0.4 cm ø × 1 cm), and a 3 μL heat exchanger, and a DAD-3000RS diode array detector. Wavelengths (λ) are reported in nm, retention times (τ_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}. Chromatograms were analysed using DCXplorer MMXVII[236] and barriers were calculated using the method described by Mayor and co-workers.[237]

DHPLC measurements were performed with a Chiralpak® IC (250 mm, i.d. 4.6 mm, particle size 5 μm) column (*n*-hexane:ethanol, 70:30, 1.0 mL/min) at temperatures between 15.0 and 50.0 °C.

Table 7.4.9 Dynamic HPLC data for 158

T [ºC]	tR1 [min]	tR2 [min]	wh1 [s]	wh2 [s]	h1 [%]	hp [%]	h2 [%]	A1	A2	k1 [1/s]
15	11.18	35.09	28.0	60.4	100	0.53	0.42	50.82	49.18	1.83E-04
	11.17	35.09	28.0	58.8	100	0.50	0.40	50.77	49.23	1.72E-04
	11.17	35.06	27.8	60.6	100	0.50	0.44	50.71	49.29	1.75E-04
20	10.49	28.55	22.8	81.2	100	0.93	40.48	50.05	49.95	3.00E-04
	10.48	28.53	22.8	81.4	100	0.94	40.43	50.03	49.97	3.04E-04
	10.48	28.52	22.8	80.8	100	0.92	40.45	50.07	49.93	3.00E-04
25	9.86	25.42	19.2	65.0	100	1.61	40.39	49.99	50.01	5.32E-04
	9.86	25.41	19.2	65.4	100	1.64	40.36	50.00	50.00	5.41E-04
	9.86	25.41	19.2	64.8	100	1.63	40.39	49.98	50.02	5.37E-04
30	9.31	22.71	16.8	53.0	100	2.94	41.04	49.94	50.06	9.17E-04
	9.31	22.71	16.6	52.6	100	2.94	41.08	49.88	50.12	9.27E-04

	9.31	22.71	16.6	52.8	100	2.95	41.09	49.91	50.09	9.28E-04
35	8.83	20.37	14.8	43.6	100	5.73	42.86	49.86	50.14	1.57E-03
	8.83	20.37	14.8	43.2	100	5.72	42.90	49.86	50.14	1.56E-03
	8.83	20.36	14.8	43.6	100	5.72	42.78	49.84	50.16	1.56E-03
40	8.41	18.34	13.4	36.6	100	12.67	45.88	49.76	50.24	2.65E-03
	8.40	18.33	13.4	36.6	100	12.69	45.91	49.75	50.25	2.66E-03
	8.40	18.32	13.2	36.6	100	12.69	45.89	49.76	50.24	2.68E-03
45	8.01	16.55	12.2	32.0	100	34.12	51.45	49.57	50.43	4.58E-03
	8.02	16.56	12.2	32.0	100	34.13	51.26	49.63	50.37	4.58E-03
	8.02	16.56	12.2	32.0	100	34.08	51.22	49.60	50.40	4.58E-03
50	7.72	15.05	11.8	30.0	77.7	100	48.24	49.11	50.89	7.68E-03
	7.72	15.03	11.6	30.2	76.74	100	48.04	48.90	51.10	7.70E-03
	7.72	15.03	11.6	30.2	77.02	100	47.93	49.03	50.97	7.71E-03

dH (kcal/mol)	19.76
dS (cal/mol)	-7.12
dG (kcal/mol)	21.89
$T_{1/2}$ (min) @ 25°C	21.0

7.5 Chapter 4 Supporting Information

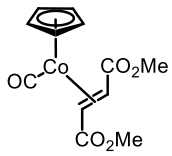
Geometry optimisation and frequency calculations for intermediates and transition states were carried out in Gaussian 16 using the b3lyp functional and cc-pVDZ basis set for all non-metal atoms, with the LANL2DZ pseudopotential for rhodium. The PCM solvent model was used with dichloroethane as the solvent. Single point energy calculations using the optimised geometries (DLPNO-CCSD(T)/def2-TZVP) were carried out in ORCA – dichloroethane was again used as the solvent, defined by its diffraction index and dielectric constant. All output energies were given in Hartrees and were converted to kcal/mol for displaying in energy diagrams.

The data presented in this thesis, including calculated energies, Cartesian coordinates and Python scripts used for data processing, has been submitted as Supplementary Material. The contents of the Supplementary Material are listed in an appendix which is publicly-available on the Oxford University Research Archive (ORA) at **https://ora.ox.ac.uk/objects/uuid:f5ceda87-4998-44b5-934e-cc089e851272**.

7.6 Chapter 5 Characterisation Data

7.6.1 Cobalt(I) catalyst

Synthesis of CpCo(CO)(dmfu)



According to the procedure of Gandon and co-workers. Dicarbonylcyclopentadienylcobalt (I) (0.21 mL, 1.50 mmol, 1.0 equiv.) and dimethyl fumarate (0.216 g, 1.50 mmol, 1.0 equiv.) were dissolved in toluene (30 mL) and heated at 110 °C under visible light irradiation for 3 h. The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (SiO_2, EtOAc in pentane, 30%) to give the title compound (0.179 g, 0.60 mmol, 40 %) as a red solid. *NMR data is consistent with that reported in the literature.*[183]

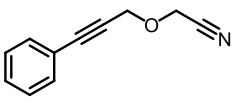
R_f (EtOAc in pentane, 20%) 0.35.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H) 4.99 (5H, s), 3.86 (1H, d, *J* = 10.5 Hz), 3.71 (3H, s), 3.62 (3H, s), 3.28 (1H, d, J = 10.5 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 199.4, 176.5, 175.8, 87.3, 51.7, 51.6, 38.4, 37.2.

7.6.2 Formal [2+2+2] approach to diaminopyridines

264 2-((3-Phenylprop-2-yn-1-yl)oxy)acetonitrile



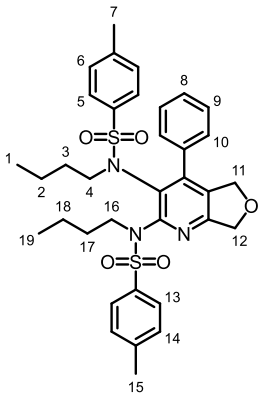
Prepared according to the literature procedure. NMR data is consistent with that reported in the literature.[238]

R_f (EtOAc in pentane, 20%) 0.53.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49–7.45 (2H, m), 7.38–7.30 (3H, m), 4.55 (2H, s), 4.43 (2H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 131.9, 129.1, 128.5, 121.9, 115.7, 88.7, 82.2, 59.0, 54.2.

265 *N*,*N*'-(4-Phenyl-5,7-dihydrofuro[3,4-b]pyridine-2,3-diyl)bis(*N*-butyl-4-methyl benzenesulfonamide)



Yndiamide **188** (23.8 mg, 0.050 mmol, 1.0 equiv.), $Cu(OTf)_2$ (3.6 mg, 0.010 mmol, 20 mol%) and alkynyl nitrile **264** (12.9 mg, 0.075 mmol, 1.5 equiv.) were dissolved in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature then stirred for 18 h. The reaction mixture was directly purified by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (16.4 mg, 0.025 mmol, 51%) as a white gum. Crystals of suitable quality for single crystal XRD were grown by dissolving **265** in HCl in Et_2O (1M, 1.0 mL) and allowing the solution to slowly evaporate. *Analysis of the XRD data revealed that **265** had in fact not crystallised with HCl.*

R_f (EtOAc in pentane, 30%) 0.23.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89 (2H, d, *J* = 8.3 Hz, ArH), 7.46–7.37 (3H, m, H8 + H9), 7.36–7.31 (4H, m, H10 + ArH), 7.24 (2H, d, *J* = 8.3 Hz, ArH), 7.07 (2H, d, *J* = 8.0 Hz, ArH), 5.04 (2H, t, *J* = 2.0 Hz, H12), 4.92 (1H, dt, *J* = 13.4, 2.0 Hz, H11), 4.77 (1H, dt, *J* = 13.4, 2.0 Hz, H11), 3.89–3.80 (1H, m, CH_2), 3.73 (1H, ddd, *J* = 14.0, 11.9, 5.0 Hz, CH_2), 3.55 (1H, ddd,

J = 14.0, 11.9, 5.0 Hz, CH_2), 3.39 (1H, td, *J* = 12.8, 5.2 Hz, CH_2), 2.47 (3H, s, CH_3), 2.36 (3H, s, CH_3), 1.54–1.05 (10H, m, CH_2), 0.78 (3H, t, *J* = 6.4 Hz, CH_3), 0.74 (3H, t, *J* = 6.4 Hz, CH_3). *Note: integration of the peak at 1.54–1.05 (10H) is greater than required for the structure of* ***265****, this peak is extremely broad and accurate integration was not possible.*

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.4, 154.3, 148.7, 143.8, 143.2, 137.3, 136.4, 135.7, 133.9, 132.3, 129.7, 129.3, 129.2, 128.8, 128.7, 127.9, 73.0, 72.3, 51.9, 51.5, 30.1, 28.8, 21.8, 21.6, 20.4, 20.3, 13.7, 13.7 *One aromatic carbon not found.*

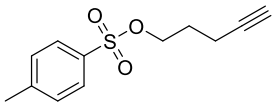
HRMS (ES^+) calc. for $C_{35}H_{42}O_5N_3S_2$ ($[M+H]^+$) 648.2560, found 648.2559.

IR (solid, ν_{max}/cm^{-1}) 2981, 2159, 2029, 1976, 1577, 1458, 1395, 1154, 1087, 1057.

MP 220–222 °C.

7.6.3 Transition metal-catalysed approaches to 1,2-diaminopyridines

S9 Pent-4-yn-1-yl 4-methylbenzenesulfonate



Pent-4-yn-1-ol (5.00 mL, 53.7 mmol, 1.0 equiv.), Et_3N (9.70 mL, 69.8 mmol, 1.3 equiv.) and DMAP (0.122 g, 1.07 mmol, 2 mol%) were dissolved in CH_2Cl_2 (150 mL) and the solution was cooled to 0 °C. Next, *p*-toluenesulfonyl chloride (10.8 g, 56.4 mmol, 1.1 equiv.) was added portion-wise at 0 °C and the reaction mixture was stirred at room temperature for 16 h, after which aqueous NaOH solution (100 mL, 1 M) was added and the reaction mixture was stirred at room temperature for 15 minutes. The reaction mixture was then washed with brine (2 × 50 mL) and water (50 mL) then the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (SiO_2, EtOAc in pentane, 10%) to give the title compound (9.67 g, 40.6 mmol, 76%) as a pale yellow oil.

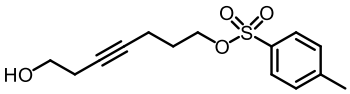
Adapted from the procedure of Liu and co-workers. NMR data is consistent with that reported in the literature.[239]

R_f (Et_2O in pentane, 20%) 0.44.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.4 Hz), 7.37–7.33 (2H, m), 4.15 (2H, t, *J* = 6.1 Hz), 2.45 (3H, s), 2.28–2.23 (2H, m), 1.89–1.82 (3H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 133.1, 130.0, 128.1, 82.3, 69.6, 68.9, 27.9, 21.8, 14.9.

S10 7-Hydroxyhept-4-yn-1-yl 4-methylbenzenesulfonate



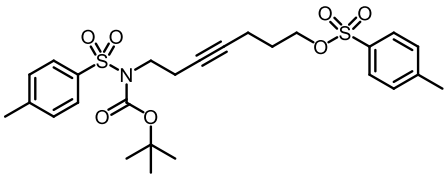
S9 (1.00 g, 4.20 mmol, 1.0 equiv.) was dissolved in anhydrous THF (4.0 mL) at −78 °C and *n*-BuLi (2.1 M in hexanes, 2.43 mL, 5.10 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at −78 °C for 30 minutes then ethylene oxide (2.5 M in THF, 5.0 mL, 12.5 mmol, 3.0 equiv.) and $BF_3{\cdot}OEt_2$ (0.63 mL, 5.10 mmol, 1.2 equiv.) were added and the reaction mixture was stirred at –78 °C for 2 h, following which TLC analysis showed remaining starting material. The reaction mixture was warmed to room temperature and stirred for a further 16 h, then quenched with NH_4Cl (aq., satd.) and extracted with Et_2O (3 × 10 mL). The combined organic layers were then washed with brine and dried over $MgSO_4$, then concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (93.9 mg, 0.33 mmol, 8%) as a pale yellow oil. *Adapted from the procedure of Malacria and co-workers. NMR data is consistent with that reported in the literature.*[182]

R_f (EtOAc in pentane, 40%) 0.20.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.1 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 4.15 (2H, t, *J* = 6.1 Hz), 3.66–3.62 (2H, m), 2.45 (3H, s), 2.35 (2H, tt, *J* = 6.1, 2.4 Hz), 2.25 (2H, tt, *J* = 6.8, 2.4 Hz), 1.88–1.87 (1H, m), 1.85–1.78 (2H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.9, 133.2, 130.0, 128.1, 80.1, 78.2, 69.1, 61.4, 28.2, 23.2, 21.8, 15.2.

S11 7-((*N*-(*Tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)hept-4-yn-1-yl 4-methylbenzenesulfonate



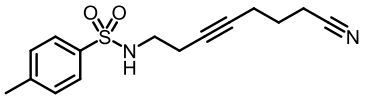
S10 (83.0 mg, 0.29 mmol, 1.0 equiv.) was dissolved in THF (5.0 mL) at 0 °C under an atmosphere of argon, and triphenylphosphine (91.8 mg, 0.35 mmol, 1.2 equiv.) and TsNHBoc (91.9 mg, 0.35 mmol, 1.2 equiv.) were added followed by dropwise addition of DIAD (0.07 mL, 0.35 mmol, 1.2 equiv.) by syringe pump over 10 minutes. The reaction mixture was stirred for 16 h at room temperature, then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, CH_2Cl_2) to give the title compound (0.127 g, 0.24 mmol, 82%) as a pale yellow oil. *Adapted from the procedure of Malacria and co-workers. NMR data is consistent with that reported in the literature, with the exception of the chemical shift of the carbon atom at 77.5 ppm, which in the literature is reported at 70.2 ppm.*[182]

R_f (CH_2Cl_2) 0.45.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82–7.79 (2H, m), 7.78 (2H, d, *J* = 8.5 Hz), 7.37–7.34 (2H, m), 7.30 (2H, d, *J* = 8.1 Hz), 4.13 (2H, t, *J* = 6.1 Hz), 3.88 (2H, dd, *J* = 8.1, 6.9 Hz), 2.55–2.49 (2H, m), 2.44 (6H, br. s), 2.21 (2H, tt, *J* = 6.9, 2.4 Hz), 1.80 (2H, p, *J* = 6.5 Hz), 1.33 (9H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 150.9, 144.9, 144.4, 137.5, 133.2, 130.0, 129.4, 128.1, 128.0, 84.6, 80.2, 77.5, 69.2, 45.8, 28.2, 28.0, 21.77, 21.75, 20.3, 15.2.

272 *N*-(7-Cyanohept-3-yn-1-yl)-4-methylbenzenesulfonamide



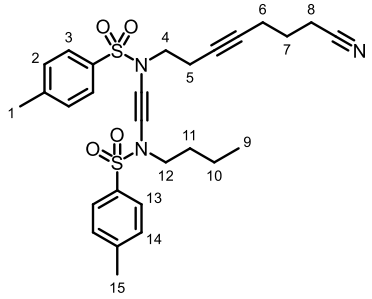
S11 (0.125 g, 0.23 mmol, 1.0 equiv.) was dissolved in DMSO (0.40 mL) and NaCN (22.5 mg, 0.46 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at 80 °C for 20 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O (10 mL) and washed with water (10 mL) and LiCl (aq, 5% w/w, 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 20 to 40%) to give the title compound (22.5 mg, 0.076 mmol, 34%) as a pale yellow oil. *Adapted from the procedure of Malacria and co-workers. NMR data is consistent with that reported in the literature.*[182]

R_f (EtOAc in pentane, 40%) 0.29.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.3 Hz), 7.35–7.27 (2H, m), 4.91 (1H, t, *J* = 6.4 Hz), 3.06 (2H, q, *J* = 6.4 Hz), 2.46–2.41 (5H, m), 2.35–2.27 (4H, m), 1.80 (2H, p, *J* = 6.8 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.7, 137.2, 129.9, 127.2, 119.4, 80.1, 78.3, 42.1, 24.6, 21.7, 20.2, 18.0, 16.3.

274 *N*-Butyl-*N*-(((*N*-(7-cyanohept-3-yn-1-yl)-4-methylphenyl)sulfonamido) ethynyl)-4-methylbenzenesulfonamide



272 (22.5 mg, 0.078 mmol, 1.0 equiv.), **S87a** (35.3 mg, 0.086 mmol, 1.1 equiv.), CuI (3.0 mg, 0.0016 mmol, 20 mol%), 1,10-phenathroline (5.6 mg, 0.0032 mmol, 40 mol%) and Cs_2CO_3 (76.1 mg, 0.23 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (0.30 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) to give the title compound (17.2 mg, 0.032 mmol, 41%) as a pale yellow oil.

R_f (EtOAc in pentane, 30%) 0.40.

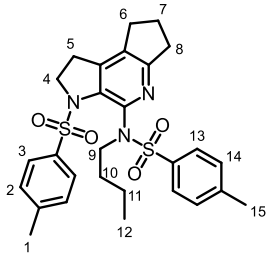
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.73–7.70 (4H, m, H3 + H13), 7.34–7.31 (4H, m, H2 + H14), 3.47 (2H, t, *J* = 7.4 Hz, H4), 3.30 (2H, t, *J* = 7.3 Hz, H12), 2.48 (2H, t, *J* = 6.9 Hz, H8), 2.46 (3H, s, CH_3), 2.45 (3H, s, CH_3), 2.44–2.41 (2H, m, H5), 2.31 (2H, tt, *J* = 6.9, 2.4 Hz, H6), 1.82 (2H, p, *J* = 6.9 Hz, H7), 1.55–1.47 (2H, m, H11), 1.31–1.24 (2H, m, H10), 0.87 (3H, t, *J* = 7.4 Hz, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.8, 144.7, 135.1 (2 C), 129.90, 129.88, 127.74, 127.70, 119.5, 79.9, 77.7, 69.8, 68.4, 51.5, 50.9, 30.0, 24.8, 21.8 (2 C), 19.5, 18.7, 18.0, 16.2, 13.7.

HRMS (ES^+) calc. for $C_{28}H_{34}O_4N_3S_2$ ($[M+H]^+$) 540.1985, found 540.1987.

IR (thin film, ν_{max}/cm^{-1}) 2947, 1597, 1413, 1363, 1168, 1090, 1020. *Nitrile stretch not observed.*

275 *N*-Butyl-4-methyl-*N*-(3-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[b]pyrrolo [3,2-d]pyridin-4-yl)benzenesulfonamide



274 (17.0 mg, 0.032 mmol, 1.0 equiv.) and CpCo(CO)dmfu (1.9 mg, 0.0064 mmol, 20 mol%) were dissolved in anhydrous PhMe (0.50 mL) under an atmosphere of argon and stirred at 100 °C for 2 h, after which TLC analysis showed remaining starting material and consumption of the catalyst, so an additional portion of CpCo(CO)dmfu (1.9 mg, 0.0064 mmol, 20 mol%) was added and the reaction mixture was stirred for a further 6 h. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (5 mL) and washed with water (5 mL) and brine (5 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by preparative TLC (Et_2O in pentane, 80%) to give the title compound (5.0 mg, 0.0093 mmol, 29%) as a colourless oil.

R_f (Et_2O in pentane, 80%) 0.31.

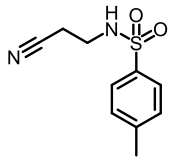
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.87 (2H, d, *J* = 8.3 Hz, H3), 7.80 (2H, d, *J* = 8.3 Hz, H13), 7.31–7.26 (4H, m, H2 + H14), 4.04 (2H, t, *J* = 7.3 Hz, H4), 3.78–3.75 (2H, m, H9), 2.92 (2H, t, *J* = 7.7 Hz, H8), 2.73 (2H, t, *J* = 7.7 Hz, H6), 2.48–2.46 (2H, m, H5), 2.45 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.16 (2H, p, *J* = 7.7 Hz, H7), 1.55–1.47 (2H, m, H10), 1.21–1.12 (2H, m, H11), 0.79 (3H, t, *J* = 7.4 Hz, H12).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.1, 145.0, 144.14, 144.10, 143.1, 137.6, 135.7, 134.2, 132.6, 129.7, 129.1, 128.9, 128.2, 52.7, 48.7, 33.6, 30.1, 28.9, 28.6, 23.5, 21.8, 21.7, 20.4, 13.9.

HRMS (ES^+) calc. for $C_{28}H_{34}O_4N_3S_2$ ($[M+H]^+$) 540.1985, found 540.1984.

IR (thin film, ν_{max}/cm^{-1}) 2859, 1404, 1361, 1167, 1090.

S12 *N*-(2-Cyanoethyl)-4-methylbenzenesulfonamide

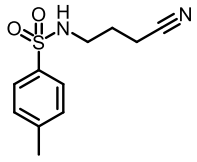


p-Toluenesulfonamide (2.07 g, 12.1 mmol, 1.0 equiv.), acrylonitrile (1.60 mL, 24.3 mmol, 2.0 equiv.) and Cs_2CO_3 (7.89 g, 24.2 mmol, 2.0 equiv.) were dissolved in toluene (80 mL) and heated at 110 °C for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with CH_2Cl_2 and washed with water (3 × 10 mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (1.77 g, 7.90 mmol, 65%) as a cream solid. *According to the procedure of Roglans and co-workers. NMR data is consistent with that reported in the literature.*[192]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.1 Hz), 7.31 (2H, d, *J* = 8.1 Hz), 5.24 (1H, s), 3.20 (2H, t, *J* = 6.7 Hz), 2.57 (2H, t, *J* = 6.7 Hz), 2.42 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.1, 136.7, 130.1, 127.1, 117.8, 39.1, 21.6, 19.5.

278 *N*-(3-Cyanopropyl)-4-methylbenzenesulfonamide



p-Toluenesulfonamide (1.32 g, 7.72 mmol, 2.0 equiv.) and NaOH (0.154 g, 3.86 mmol, 1.0 equiv.) were dissolved in DMSO (7.0 mL) and the reaction mixture was stirred at 60 °C, then 4-bromobutanitrile (0.38 mL, 3.86 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 60 °C for a further 2 h. The reaction mixture was then poured into water (60 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were concentrated *in vacuo*,

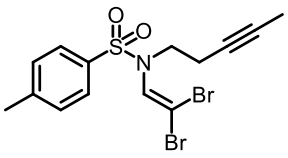
diluted with EtOAc (50 mL) and washed with water (2 × 20 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 20%) to give the title compound (0.186 g, 0.78 mmol, 20%) as a white solid. *Adapted from the procedure of Moeller and co-workers. Note: The ^{1}H NMR data reported in the literature contains an additional peak at 3.75 ppm which was not found in this work – inclusion of this peak is not consistent with the integration required for the structure shown. The NMR data is otherwise consistent with that reported in the literature.*[240]

R_f (EtOAc in pentane, 40%) 0.22.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.2 Hz), 7.33 (2H, d, *J* = 8.2 Hz), 4.92 (1H, t, *J* = 6.4 Hz), 3.05 (2H, q, *J* = 6.5 Hz), 2.45–2.42 (5H, m), 1.86 (2H, p, *J* = 6.9 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.0, 136.6, 130.1, 127.2, 119.1, 41.7, 25.9, 21.7, 14.5.

279 *N*-(2,2-Dibromovinyl)-4-methyl-*N*-(pent-3-yn-1-yl)benzenesulfonamide



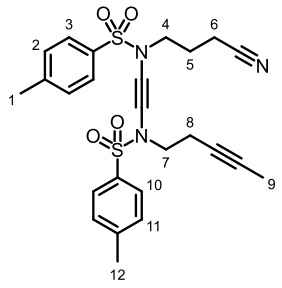
Prepared according to the literature procedure. Data is consistent with that reported in the literature.[1]

R_f (EtOAc in pentane, 20%) 0.65.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.2 Hz), 7.32 (2H, d, *J* = 8.2 Hz), 6.79 (1H, s), 3.48 (2H, dd, *J* = 8.0, 7.0 Hz), 2.44–2.37 (5H, m), 1.74 (3H, t, *J* = 2.6 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.4, 135.8, 131.5, 130.0, 127.4, 95.9, 78.3, 75.2, 48.6, 21.7, 19.7, 3.6.

280 *N*-(3-Cyanopropyl)-4-methyl-*N*-(((4-methyl-*N*-(pent-3-yn-1-yl)phenyl) sulfonamido)ethynyl)benzenesulfonamide



278 (90.0 mg, 0.38 mmol, 1.0 equiv.), **279** (0.176 g, 0.42 mmol, 1.1 equiv.), CuI (14.5 mg, 0.076 mmol, 20 mol%), 1,10-phenathroline (27.4 mg, 0.15 mmol, 40 mol%) and Cs_2CO_3 (0.371 g, 1.14 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (1.2 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) followed by recrystallisation (Et_2O/pentane) to give the title compound (86.5 mg, 0.17 mmol, 46%) as a white solid.

R_f (EtOAc in pentane, 30%) 0.28.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.72 (4H, m, H3 + H10), 7.36–7.33 (4H, m, H2 + H11), 3.48–3.43 (4H, m, H4 + H7), 2.47–2.45 (6H, m, H1 + H12), 2.39 (2H, t, *J* = 7.2 Hz, H6), 2.36–2.31 (2H, m, H5), 1.99–1.92 (2H, m, H8), 1.70 (3H, t, *J* = 2.5 Hz, H9).

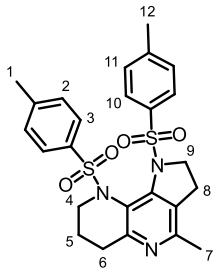
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.2, 145.0, 135.0, 134.4, 130.1, 130.0, 127.8 (2 C), 118.8, 78.1, 74.5, 69.4, 69.2, 50.8, 50.4, 24.5, 21.83, 21.81, 18.7, 14.5, 3.6.

HRMS (ES^+) calc. for $C_{25}H_{28}O_4N_3S_2$ ($[M+H]^+$) 498.1516, found 498.1519.

IR (thin film, ν_{max}/cm^{-1}) 2921, 1597, 1414, 1364, 1168, 1090, 1019. *Nitrile and alkyne stretches not observed.*

MP 80–82 °C.

281 4-Methyl-1,9-ditosyl-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-c][1,5] naphthyridine



280 (24.9 mg, 0.050 mmol, 1.0 equiv.) and CpCo(CO)(dmfu) (3.0 mg, 0.010 mmol, 20 mol%) were dissolved in anhydrous PhMe (0.50 mL) under an atmosphere of argon and stirred at 100 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (5 mL), washed with water (10 mL) and brine (10 mL) and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 40 to 70%) to give the title compound (5.1 mg, 0.010 mmol, 21%) as a pale yellow oil.

R_f (EtOAc in pentane, 40%) 0.14.

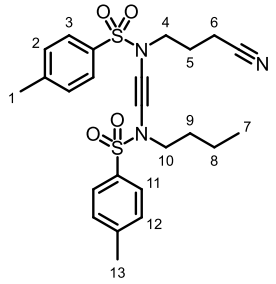
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.3 Hz, ArH), 7.54 (2H, d, *J* = 8.3 Hz, ArH), 7.30 (2H, d, *J* = 8.3 Hz, ArH), 7.26 (2H, d, *J* = 8.3 Hz, ArH), 4.42–4.36 (1H, m, H9), 3.97–3.91 (1H, m, H9), 3.91–3.85 (1H, m, H4), 3.63 (1H, dt, *J* = 13.0, 6.3 Hz, H4), 2.69–2.64 (2H, m, H8), 2.62–2.55 (1H, m, H6), 2.45 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.37 (3H, s, H7), 2.13–2.06 (1H, m, H5), 1.86–1.80 (1H, m, H6), 1.74–1.66 (1H, m, H5).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 157.7, 151.6, 147.8, 144.3, 143.9, 136.2, 136.0, 129.9, 129.8, 129.7, 127.8, 127.7, 122.7, 52.0, 44.9, 29.3, 27.7, 23.5, 21.8 (2 C), 21.7.

HRMS (ES^+) calc. for $C_{25}H_{28}O_4N_3S_2$ ($[M+H]^+$) 498.1516, found 498.1516.

IR (thin film, ν_{max}/cm^{-1}) 2952, 1597, 1582, 1441, 1420, 1359, 1166, 1093.

282 *N*-Butyl-*N*-(((*N*-(3-cyanopropyl)-4-methylphenyl)sulfonamido)ethynyl)-4-methylbenzenesulfonamide



278 (90.0 mg, 0.38 mmol, 1.0 equiv.), **S87a** (0.172 g, 0.42 mmol, 1.1 equiv.), CuI (14.5 mg, 0.076 mmol, 20 mol%), 1,10-phenathroline (27.4 mg, 0.15 mmol, 40 mol%) and Cs_2CO_3 (0.371 g, 1.14 mmol, 3.0 equiv.) were used in **General Procedure 5** with anhydrous THF (1.2 mL) for 18 h with purification by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 20%) followed by recrystallisation (Et_2O/pentane) to give the title compound (70.7 mg, 0.15 mmol, 38%) as a white solid.

R_f (EtOAc in pentane, 20%) 0.23.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75–7.69 (4H, m, H3 + H11), 7.36–7.31 (4H, m, H2 + H12), 3.45 (2H, t, *J* = 6.5 Hz, H4), 3.32 (2H, t, *J* = 7.2 Hz, H10), 2.46 (6H, s, H1 + H13), 2.39 (2H, t, *J* = 7.3 Hz, H6), 1.95 (2H, app. p, *J* = 6.8 Hz, H5), 1.56–1.47 (2H, m, H9), 1.33–1.24 (2H, m, H8), 0.88 (3H, t, *J* = 7.3 Hz, H7).

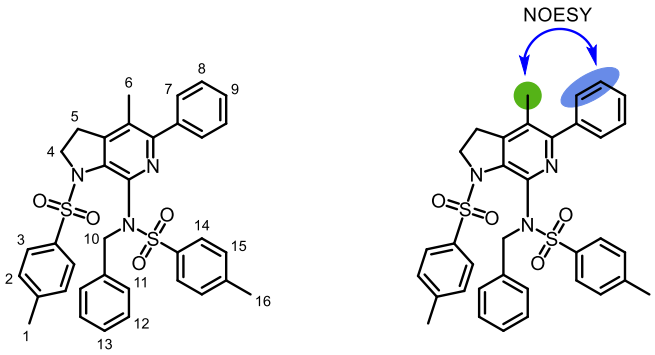
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 145.1, 144.9, 135.0, 134.5, 130.0, 129.9, 127.8, 127.7, 118.8, 69.9, 68.5, 51.4, 50.3, 30.1, 24.5, 21.83, 21.81, 19.5, 14.5, 13.7.

HRMS (ES^+) calc. for $C_{24}H_{30}O_4N_3S_2$ ($[M+H]^+$) 488.1672, found 482.1678.

IR (thin film, ν_{max}/cm^{-1}) 2956, 2903, 1597, 1457, 1414, 1364, 1168, 1089. *Nitrile stretch not observed.*

MP 83–85 °C.

284 *N*-Benzyl-4-methyl-*N*-(4-methyl-5-phenyl-1-tosyl-2,3-dihydro-1*H*-pyrrolo [2,3-c]pyridin-7-yl)benzenesulfonamide



82u (26.0 mg, 0.050 mmol, 1.0 equiv.), benzonitrile (25.8 mg, 0.25 mmol, 5.0 equiv.) and CpCo(CO)(dmfu) (1.5 mg, 0.005 mmol, 10 mol%) were dissolved in anhydrous toluene (0.5 mL) under an atmosphere of argon and stirred at 110 °C for 15 h. The reaction mixture was cooled to room temperature and purified directly by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 30%) to give the title compound (5.0 mg as a 3.1:1 mixture of isomers) as a yellow oil. This mixture was further purified by preparative TLC (CH_2Cl_2) to give the title compound (4.0 mg, 0.0064 mmol, 13%) as a colourless oil as the single isomer shown.

R_f (CH_2Cl_2) 0.42.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.89 (2H, d, *J* = 8.2 Hz, H14), 7.63 (2H, d, *J* = 8.2 Hz, H3), 7.47–7.40 (5H, m, H7 + H8 + H9), 7.17 (2H, d, *J* = 8.2 Hz, H2), 7.08 (2H, d, *J* = 8.2 Hz, H15), 7.04–6.97 (5H, m, H11 + H12 + H13), 5.31 (2H, s, H10), 3.97 (2H, br. s, H4), 2.39 (6H, s, H1 + H16), 2.19 – 2.13 (2H, m, H5), 1.98 (3H, s, H6).

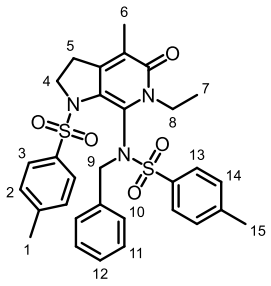
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.9, 149.8, 144.4, 142.7, 142.6, 139.2, 139.0, 136.8, 134.5, 131.1, 129.8, 129.6, 129.1, 128.8, 128.7, 128.31, 128.28, 128.0, 127.9, 127.0, 125.3, 52.4, 51.4, 28.4, 21.8, 21.7, 16.4.

HRMS (ES^+) calc. for $C_{35}H_{34}O_4N_3S_2$ ($[M+H]^+$) 624.1985, found 624.1982.

IR (thin film, ν_{max}/cm^{-1}) 2926, 1597, 1567, 1456, 1413, 1358, 1166, 1091, 1022.

7.6.4 Diaminopyridone synthesis

286 *N*-Benzyl-*N*-(6-ethyl-4-methyl-5-oxo-1-tosyl-2,3,5,6-tetrahydro-1*H*-pyrrolo [2,3-c]pyridin-7-yl)-4-methylbenzenesulfonamide



82u (26.0 mg, 0.050 mmol, 1.0 equiv.), ethyl isocyanate (0.20 mL, 2.50 mmol, 50.0 equiv.) and CpCo(CO)(dmfu) (3.0 mg, 0.010 mmol, 20 mol%) were dissolved in anhydrous toluene (1.0 mL) under an atmosphere of argon and stirred at 110 °C for 15 h. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (5 mL), washed with water (10 mL) and brine (10 mL) and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (SiO_2, EtOAc in pentane, 30%) to give the title compound (11.9 mg, 0.020 mmol, 40%) as a brown oil. *Note: this reaction also formed **84u** (14.2 mg, 0.027 mmol, 54%) as a brown oil.*

R_f (EtOAc in pentane, 30%) 0.10.

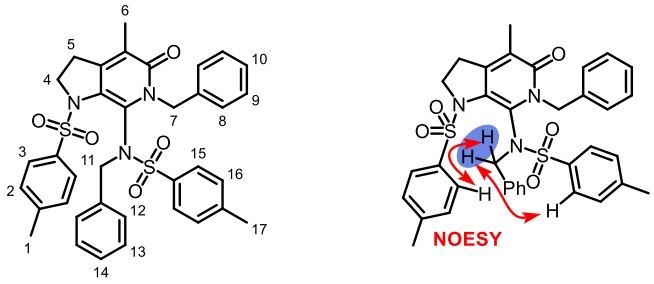
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.4 Hz, ArH), 7.48 (2H, d, *J* = 8.3 Hz, ArH), 7.37 (2H, dd, *J* = 7.9, 1.8 Hz, ArH), 7.23–7.16 (7H, m, ArH), 5.06 (1H, d, *J* = 13.9 Hz, H9), 5.00 (1H, d, *J* = 13.9 Hz, H9), 3.82 (1H, ddd, *J* = 13.0, 7.7, 2.0 Hz, H4), 3.73 (1H, dq, *J* = 13.8, 6.9 Hz, H8), 3.59–3.48 (2H, m, H4 + H8), 2.38 (6H, s, H1 + H15), 2.18–2.11 (1H, m, H5), 1.85–1.76 (4H, m, H5 + H6), 1.04 (3H, app. t, *J* = 6.9 Hz, H7).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.1, 148.1, 145.0, 144.2, 137.6, 134.6, 134.2, 133.6, 131.2, 130.0, 129.5, 128.7, 128.6, 128.5, 128.2, 125.2, 124.9, 56.1, 52.5, 42.0, 28.4, 21.84, 21.79, 14.1, 13.2.

HRMS (ES^+) calc. for $C_{31}H_{34}O_5N_3S_2$ ($[M+H]^+$) 592.1934, found 592.1935.

IR (thin film, ν_{max}/cm^{-1}) 2980, 1664, 1617, 1569, 1354, 1345, 1161, 1089.

288 *N*-Benzyl-*N*-(6-benzyl-4-methyl-5-oxo-1-tosyl-2,3,5,6-tetrahydro-1*H*-pyrrolo [2,3-c]pyridin-7-yl)-4-methylbenzenesulfonamide



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) and (*rac*-BINAP)Rh(cod)SbF_6 (10.4 mg, 0.010 mmol, 10 mol%) were dissolved in anhydrous DCE (2 mL) and benzyl isocyanate (133 µL, 1.00 mmol, 10.0 equiv.) was added. The vial was sealed with a screw cap and tape and the reaction mixture was heated at 85 °C for 16 h, then cooled to room temperature and purified by flash column chromatography (SiO_2, EtOAc in pentane, 30 to 60%) to give the title compound (53.1 mg, 0.073 mmol, 73% with dibenzyl urea) as a sticky brown foam. *NMR data is given for the title compound in the mixture.*

R_f (EtOAc in pentane, 60%) 0.27.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.4 Hz, H3), 7.54 (2H, d, *J* = 8.4 Hz, H15), 7.32–7.31 (2H, m, H2), 7.24–7.22 (4H, m, ArH), 7.19–7.16 (2H, m, ArH), 7.14–7.09 (4H, m, ArH), 6.93 –6.91 (2H, m, ArH), 5.09 (1H, d, *J* = 16.0 Hz, H7), 4.98 (2H, s, H11), 4.75 (1H, d, *J* = 16.0 Hz, H7), 3.96 (1H, ddd, *J* = 12.9, 7.9, 2.3 Hz, H4), 3.74 (1H, ddd, *J* = 12.9, 10.2, 7.4

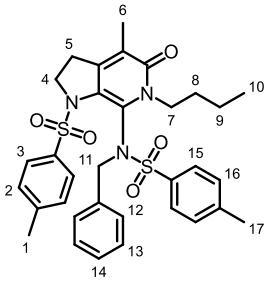
Hz, H4), 2.47 (3H, s, H1), 2.40 (3H, s, H17), 2.32 (1H, ddd, *J* = 16.5, 7.4, 2.3 Hz, H5), 2.08 (1H, dt, *J* = 16.5, 9.1 Hz, H5), 1.89 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.0, 148.5, 145.0, 143.8, 137.5, 137.2, 134.5, 134.1, 133.7, 131.1, 129.9, 129.3, 128.7, 128.4, 128.3, 128.2, 127.5, 126.7, 125.7, 125.2, 125.1, 56.1, 52.2, 49.4, 28.4, 21.7, 21.6, 13.9.

HRMS (ES^+) calc. for $C_{36}H_{36}O_5N_3S_2$ ($[M+H]^+$) 654.2091, found 654.2088.

IR (thin film, ν_{max}/cm^{-1}) 1624, 1570, 1454, 1355, 1162, 1088. *C-H signals extremely weak.*

289 *N*-Benzyl-*N*-(6-butyl-4-methyl-5-oxo-1-tosyl-2,3,5,6-tetrahydro-1*H*-pyrrolo [2,3-c]pyridin-7-yl)-4-methylbenzenesulfonamide



82u (52.0 mg, 0.10 mmol, 1.0 equiv.) and (*rac*-BINAP)Rh(cod)SbF_6 (10.4 mg, 0.010 mmol, 10 mol%) were dissolved in anhydrous DCE (2 mL) and butyl isocyanate (113 μL, 1.00 mmol, 10.0 equiv.) was added. The vial was sealed with a screw cap and tape and the reaction mixture was heated at 85 °C for 16 h, then cooled to room temperature and purified by flash column chromatography (SiO_2, EtOAc in pentane, 20 to 50%) followed by trituration (Et_2O/pentane) to give the title compound (42.0 mg, 0.068 mmol, 68%) as a pale brown solid.

R_f (EtOAc in pentane, 40%) 0.24.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 8.4 Hz, H15), 7.54 (2H, d, *J* = 8.4 Hz, H3), 7.44 (2H, dd, *J* = 7.9, 1.7 Hz, ArH), 7.30–7.23 (7H, m, ArH), 5.12 (1H, d, *J* = 13.9 Hz, H11), 5.06 (1H, d, *J* = 13.9 Hz, H11), 3.89 (1H, ddd, *J* = 13.4, 8.1, 2.5 Hz, H4), 3.69–3.58 (2H, m,

H4 + H7), 3.42 (1H, ddd, *J* = 13.1, 11.6, 4.5 Hz, H7), 2.45 (6H, s, H1 + H17), 2.18 (1H, ddd, *J* = 16.3, 7.8, 2.5 Hz, H5), 1.88 (3H, s, H6), 1.86–1.80 (1H, m, H5), 1.62–1.55 (1H, m, H8), 1.33–1.29 (1H, m, H8), 1.21–1.09 (2H, m, H9), 0.82 (3H, t, *J* = 7.3 Hz, H10).

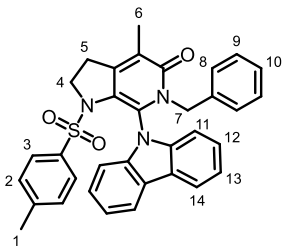
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 163.2, 148.0, 145.0, 144.2, 137.5, 134.6, 134.3, 133.7, 131.2, 130.0, 129.5, 128.7, 128.6, 128.5, 128.2, 125.1, 124.7, 56.0, 52.4, 47.1, 29.4, 28.3, 21.82, 21.76, 20.4, 14.0, 13.7.

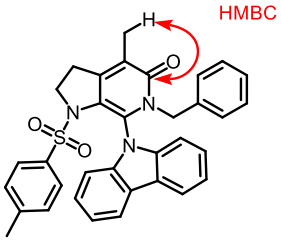
HRMS (ES^+) calc. for $C_{33}H_{38}N_3O_5S_2$ ($[M+H]^+$) 620.2247, found 620.2266.

IR (thin film, ν_{max}/cm^{-1}) 1665, 1620, 1567, 1349, 1161, 1088, 1026. *C-H signals extremely weak.*

MP 88–90 °C.

291 6-Benzyl-7-(9*H*-carbazol-9-yl)-4-methyl-1-tosyl-1,2,3,6-tetrahydro-5*H*-pyrrolo[2,3-c]pyridin-5-one





199 (42.6 mg, 0.10 mmol, 1.0 equiv.) and (*rac*-BINAP)Rh(cod)SbF_6 (10.4 mg, 0.010 mmol, 10 mol%) were dissolved in anhydrous DCE (2 mL) and benzyl isocyanate (133 μL, 1.00 mmol, 10.0 equiv.) was added. The vial was sealed with a screw cap and tape and the reaction mixture was heated at 85 °C for 16 h, then cooled to room temperature and purified by flash column chromatography (SiO_2, EtOAc in pentane, 20 to 40%, then a second column, MeOH in $CHCl_3$, 1%) followed by recrystallisation from $CHCl_3$ to give the title compound (45.0 mg, 0.071 mmol, 71% with dibenzyl urea) as a cream solid. *NMR data is given for the title compound in the mixture.*

R_f (EtOAc in pentane, 40%) 0.33.

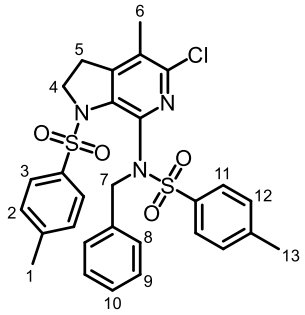
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97–7.92 (2H, m, H3), 7.33–7.22 (5H, m, ArH), 6.96 (2H, d, *J* = 8.0 Hz, ArH), 6.88–6.83 (1H, m, ArH), 6.80–6.76 (5H, m, ArH), 6.48–6.38 (2H, m, ArH), 5.12 (2H, s, H7), 3.92 (2H, t, *J* = 7.1 Hz, H4), 2.79–2.67 (2H, m, H5), 2.27 (3H, s, H1), 2.16 (3H, s, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.5, 148.5, 143.6, 139.4, 136.4, 135.2, 129.1, 128.3, 128.0, 127.2, 127.1, 126.6, 126.2, 125.0, 123.9, 123.3, 121.0, 120.3, 110.8, 52.1, 47.9, 29.9, 21.6, 14.5.

HRMS (ES^+) calc. for $C_{34}H_{30}N_3O_3S$ ($[M+H]^+$) 560.2002, found 560.2006.

IR (thin film, ν_{max}/cm^{-1}) 1674, 1452, 1334, 1226, 1166, 1091, 1080. *C-H signals extremely weak.*

292 *N*-Benzyl-*N*-(5-chloro-4-methyl-1-tosyl-2,3-dihydro-1*H*-pyrrolo[2,3-c]pyridin-7-yl)-4-methylbenzenesulfonamide



288 (26.5 mg, 0.04 mmol, 1.0 equiv.) was dissolved in $POCl_3$ (0.50 mL) and the vial was flushed with argon then sealed with a screw cap and heated at 60 °C for 17 h then cooled to room temperature and the reaction mixture was added dropwise to NH_4OH (aq.) (50 mL). EtOAc (25 mL) was added and the organic layer was separated then the aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) to give the title compound (4.3 mg, 0.074 mmol, 19%) as a brown oil.

R_f (EtOAc in pentane, 30%) 0.29

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.02 (2H, d, *J* = 8.3 Hz, ArH), 7.55 (2H, d, *J* = 8.3 Hz, ArH), 7.26 (2H, d, *J* = 8.3 Hz, ArH), 7.18 (2H, d, *J* = 8.3 Hz, ArH), 7.06–7.03 (3H, m, H9 + H10), 6.96–6.94 (2H, m, H8), 5.26 (2H, s, H7), 3.94–3.87 (2H, m, H4), 2.44 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.08 (2H, t, *J* = 7.4 Hz, H5), 1.96 (3H, s, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 151.1, 145.9, 144.7, 143.2, 142.4, 138.6, 136.3, 134.1, 131.7, 129.8, 129.2, 129.0, 128.6, 128.2, 128.1, 127.2, 126.4, 52.7, 51.2, 28.5, 21.79, 21.75, 15.8.

HRMS (ES^+) calc. for $C_{29}H_{28}{}^{35}ClN_3O_4S_2$ ($[M+H]^+$) 582.1283, found 582.1283.

IR (thin film, ν_{max} / cm^{-1}) 3007, 2995, 1358, 1219, 1169, 1090, 913, 779.

7.6.5 X-Ray Crystallography

Low temperature single crystal X-ray diffraction data were collected using Oxford Diffraction (Rigaku) SuperNovae diffractometers at 150 K. These data were reduced using CrysAlisPro, solved using SuperFlip66 and the structures were refined using CRYSTALS. Further details about the refinements are documented in the CIF. *X-Ray data for **265** was collected and processed by Dr Kirsten Christensen.*

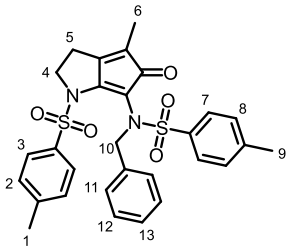
Table 7.6.1. Crystal data and structure refinement for 265.

Empirical formula	$C_{35}H_{41}N_3O_5S_2$	
Formula weight	647.86	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P c a 21	
Unit cell dimensions	a = 18.2280(2) Å	α = 90°
	b = 12.43540(10) Å	β = 90°
	c = 14.66890(10) Å	γ = 90°
Volume	3325.04(5) $Å^3$	
Z	4	
Density (calculated)	1.294 Mg/m^3	
Absorption coefficient	1.823 mm^{-1}	
F(000)	1376	
Crystal size	0.25 x 0.20 x 0.16 mm^3	
Theta range for data collection	3.554 to 76.194°.	
Index ranges	-22<=h<=22, -15<=k<=14, -15<=l<=18	
Reflections collected	38081	
Independent reflections	6123 [$R_{(int)}$ = 0.047]	
Completeness to theta	= 76.194° 99.9 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.75 and 0.62
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	6121 / 17 / 440
Goodness-of-fit on F2	1.0008
Final R indices [I>2sigma(I)]	R_1 = 0.0312, wR_2 = 0.0808
R indices (all data)	R_1 = 0.0333, wR_2 = 0.0834
Absolute structure parameter	-0.33(7)
Extinction coefficient	30(5)
Largest diff. peak and hole	0.24 and –0.35 e.Å^{-3}

7.7 Chapter 6 Characterisation data

293 *N*-Benzyl-4-methyl-*N*-(4-methyl-5-oxo-1-tosyl-1,2,3,5-tetrahydrocyclopenta[b] pyrrol-6-yl)benzenesulfonamide



82u (26.0 mg, 0.050 mmol, 1.0 equiv.) and (*rac*-BINAP)Rh(cod)SbF_6 (5.2 mg, 0.005 mmol, 10 mol%) were dissolved in anhydrous DCE (0.50 mL), the vial was fitted with a septum, and the solution was purged with carbon monoxide. The reaction mixture was then heated at 50 °C under an atmosphere of carbon monoxide for 18 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, EtOAc in pentane, 10 to 30%) then recrystallised from Et_2O/pentane to give the title compound (16.7 mg, 0.030 mmol, 61%) as an orange solid.

R_f (EtOAc in pentane, 30%) 0.23.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.03 (2H, d, *J* = 8.3 Hz, H3), 7.81 (2H, d, *J* = 8.4 Hz, H7), 7.35 (2H, d, *J* = 8.3 Hz, H2), 7.27 (2H, d, *J* = 8.4 Hz, H8), 7.22–7.17 (5H, m, H11 + H12+ H13), 4.77 (1H, d, *J* = 13.6 Hz, H10), 4.59 (1H, d, *J* = 13.6 Hz, H10), 4.06–4.02 (1H, m, H4), 3.79–3.75 (1H, m, H4), 2.61–2.50 (2H, m, H5), 2.43 (6H, s, H1 + H9), 1.56 (3H, t, *J* = 2.5 Hz, H6).

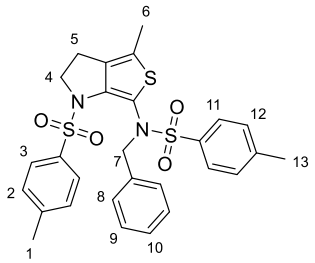
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 199.7, 155.8, 150.0, 145.5, 143.1, 137.7, 135.7, 134.1, 130.2 (2 C), 129.2, 128.8, 128.5, 128.0, 127.6, 120.3, 98.7, 54.9, 53.4, 21.9, 21.82, 21.76, 8.3.

HRMS (ES^+) calc. for $C_{29}H_{29}N_2O_5S_2$ ($[M+H]^+$) 549.1512, found 549.1499.

IR (thin film, ν_{max}/cm^{-1}) 1709, 1629, 1597, 1455, 1374, 1343, 1295, 1275, 1254, 1162, 1090, 1050.

MP 95–97 °C.

294 *N*-Benzyl-4-methyl-*N*-(4-methyl-1-tosyl-2,3-dihydro-1*H*-thieno[3,4-b]pyrrol-6-yl)benzenesulfonamide



82u (26.0 mg, 0.050 mmol, 1.0 equiv.), Cp(CO)Co(dmfu) (3.0 mg, 0.010 mmol, 20 mol%) and methyl isothiocyanate (36.6 mg, 0.50 mmol, 10.0 equiv.) were dissolved in anhydrous toluene (0.50 mL) under an atmosphere of argon and the reaction vial was sealed and heated at 110 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (10 mL) then washed with brine (10 mL) and water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, EtOAc in pentane, 5 to 20%) to give the title compound (10.0 mg, 0.018 mmol, 36%) as a brown oil. *Crystals suitable for XRD analysis were grown by vapour diffusion of pentane into a concentrated solution of **294** in Et_2O.*

R_f (EtOAc in pentane, 30%) 0.28.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.88 (2H, d, *J* = 8.3 Hz, ArH), 7.37 (2H, d, *J* = 8.3 Hz, ArH), 7.34–7.23 (7H, m, ArH), 7.16–7.13 (2H, m, ArH), 5.06 (2H, br. s, H7), 3.92 (2H, t, *J* = 7.3 Hz, H4), 2.41 (3H, s, CH_3), 2.39 (3H, s, CH_3), 1.99 (3H, s, H6), 1.84 (2H, t, *J* = 7.3 Hz, H5).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.1, 143.8, 137.0, 136.7, 136.2, 135.1, 134.8, 129.6, 129.4, 129.1, 128.8, 128.4, 127.7, 127.6, 127.4, 122.3, 57.9, 54.4, 24.2, 21.76, 21.75, 13.8.

HRMS (ES^+) calc. for $C_{28}H_{29}O_4N_2S_3$ ($[M+H]^+$) 553.1284, found 553.1285.

IR (thin film, ν_{max}/cm^{-1}) 1598, 1495, 1454, 1352, 1163, 1091.

MP 149–151 °C.

Table 7.7.1. Crystal data and structure refinement for 294.

Empirical formula	$C_{28}H_{28}N_2O_4S_3$	
Formula weight	552.74	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.8678(6) Å	α = 73.234(5)°
	b = 10.7577(6) Å	β = 69.662(5)°
	c = 13.9448(7) Å	γ = 82.600(5)°
Volume	1328.35(14) $Å^3$	
Z	2	
Density (calculated)	1.382 Mg/m^3	
Absorption coefficient	2.862 mm^{-1}	
F(000)	580	
Crystal size	0.20 x 0.09 x 0.05 mm^3	
Theta range for data collection	4.294 to 76.275°.	
Index ranges	-12<=h<=12, -13<=k<=13, -13<=l<=17	
Reflections collected	12254	
Independent reflections	5487 [$R_{(int)}$ = 0.036]	
Completeness to theta	= 73.224° 99.6 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.87 and 0.78
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	5486 / 0 / 384
Goodness-of-fit on F2	1.0050
Final R indices [I>2sigma(I)]	R_1 = 0.0385, wR_2 = 0.0899
R indices (all data)	R_1 = 0.0460, wR_2 = 0.1019
Largest diff. peak and hole	0.51 and −0.50 e.$Å^{-3}$

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