Palladium-Catalysed Cyclisations of Bromoenynamides in the Synthesis and Applications of Amidodienes

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Doctor of Philosophy

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Declaration

The work presented in this thesis was carried out at the Chemistry Research Laboratory at the University of Oxford between Michaelmas 2009 and Trinity 2013 under the supervision of Dr. Edward Anderson. All the work presented is my own, except where otherwise stated, and has not been submitted in full or in part for any other degree at this or any other university.

Rebecca L. Greenaway

April 2013

Dedicated to

Dean Peter Atterbury

(1963-2013)

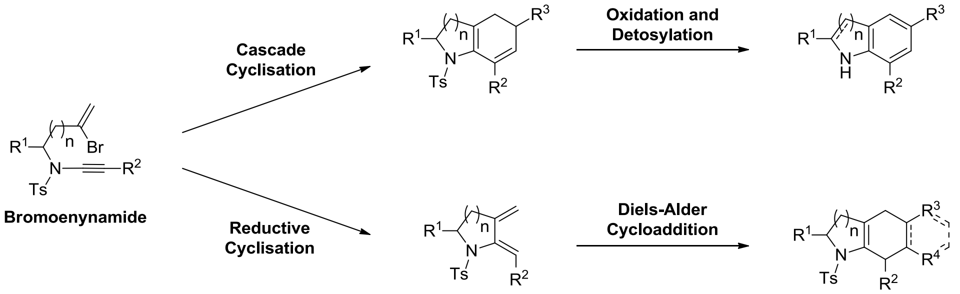
Loving father, friend and inspiration.

Gone, but never forgotten.

Abstract

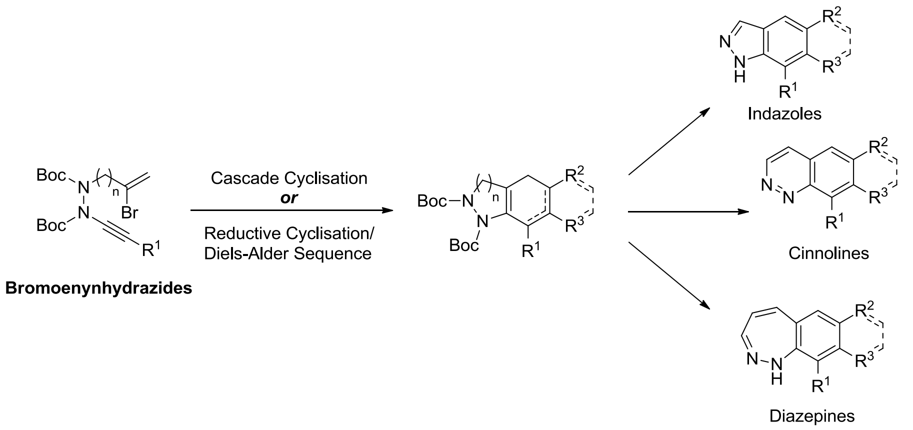
The aim of this work was to investigate palladium-catalysed cyclisations of bromoenynamides in the synthesis of amidodienes, which on further reaction or oxidation can lead to a diverse range of heteroaromatic systems.

Building upon work within the Anderson group on the palladium-catalysed cyclisations of bromoenynes, we have been able to successfully apply a palladium-catalysed carbopalladation/Stille coupling/electrocyclisation cascade to bromoenynamides and then further develop this to incorporate a Suzuki coupling, leading to bicyclic amidodienes which can undergo selective oxidation to a range of heteroaromatics including indolines, indoles, tetrahydroquinolines and benzazepines.

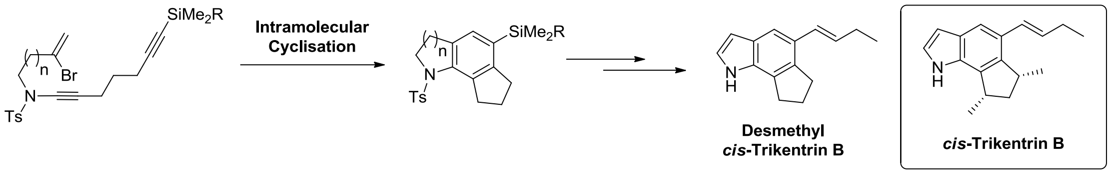


During the investigations into the cascade cyclisation, a reductive cyclisation was discovered which enabled access to a range of monocyclic amidodienes. These could subsequently be subjected to a series of Diels-Alder cycloadditions (thermal, Lewis acid-catalysed, arynes) and oxidations to afford a complimentary range of heteroaromatic systems.

Whilst this methodology was successful with bromoenynamides, extension of its application to bromoenynhydrazides, with the hope of accessing a relatively unusual range of heteroaromatic structures including indazoles, cinnolines and diazepines, proved to be more problematic.



Finally, expansion of the cascade methodology into a fully intramolecular cyclisation, enabled studies towards the synthesis of the trikentrin family of natural products to be conducted.



Acknowledgements

Firstly, thanks must go to Ed ‘Edwardo’ Anderson for being insane enough to offer me a position in his group and for providing me with the opportunity to explore the ‘fantabulous’ world of ynamides and cascade cyclisations (sorry .... domino reactions ...). Always offering inspiration, help, support and being optimistic, I felt it was my role to be the pessimist but it turns out it did all work out in the end!

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for impromptu food and drink; Birgit – for introducing me to feuerzangenbowle and not setting fire to my flat in the process and making me addicted to Carcasonne; Bryony – for teaching me how to crochet and being someone I can talk to about anything; Ross – for providing hugs on bad days and for the ‘Ross-sized’ baked goods; Craig for our chats on the train to liven up the daily commute and for being a walking chemistry textbook; Shermin for persuading me to enjoy the sun at tea breaks; and finally Diane and Liz – we’ve made it through together, had loads of fun both in the lab and out with the late night KFC’s in the office getting us through the rough times.

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Major thanks must go to my parents Ann and Dean, for their constant love, help and support, and for pushing me to reach my full potential; I wouldn’t have made it to where I am without you! Thanks also go to my brother Richard, Mandy, Uncle Raymond and Andrea for being there when it was needed most.

And last but not least, to my best friend and partner Mike, for always being there, making me laugh, for loving and supporting me through everything and putting up with the nutter that I am. It’s been a journey of ups and downs, but here’s to the future!

Abbreviations

Ac	acetyl
acac	acetylacetonate
AcO	acetate
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	argon
BAIB	(diacetoxyiodo)benzene
BDMS	benzyldimethylsilyl
BHT	butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
bpt	boiling point
brsm	based on recovered starting material
Bu	butyl
calc.	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
cod	cyclooctadiene
Conc.	concentration
COSY	correlation spectroscopy
dba	dibenzylideneacetone
DBAD	dimethyl acetylenedicarboxylate
DCE	1,2-dichloroethylene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DIAD	diisopropyl dicarboxylate
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMDO	methyl(trifluoromethyl)dioxirane
DME	1,2-dimethoxyethane
DMEDA	*N,N’*-dimethylethylenediamine

DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1’-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EDTA	ethylenediaminetetraacetic acid
ee	enatiomeric ratio
equiv.	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FI	field ionisation
FT-IR	fourier transform infra-red spectroscopy
FWHM	full width at half maximum
*c*Hex	cyclohexyl
*n*Hex	hexyl chain
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
IPA	isopropyl alcohol
IR	infra-red
LC-MS	liquid chromatography – mass spectrometry
LDA	lithium diisopropylamide
lit.	Literature values
LUMO	lowest unoccupied molecular orbital
Me	methyl
mpt	melting point
MS	molecular sieves
m/z	mass to charge ratio
N	chemical unit of normality
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

1,10-phen	1,10-phenanthroline
*n*Pr	propyl chain
Ns	nosyl/4-nitrobenzenesulfonyl
o	*ortho*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Pin	pinacol
PMP	*para*-methoxyphenyl
PNBSA	*para*-nitrobenzenesulfonic acid
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid monohydrate
py	pyridine
py-imine	(*E*)-2,4,6-trimethyl-*N*-(pyridin-2-ylmethylene)aniline
quant.	quantitative
R	unspecified substituent
rbf	round bottomed flask
RCEM	ring-closing enyne metathesis
R_f	thin layer chromatography retention factor
rr	ratio of regioisomers
RT	room temperature
Salen	*N*,*N′*-bis(salicylidene)ethylenediamine
sat.	saturated
t	*tert*-
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogen sulfate
TBAI	tetrabutylammonium iodide
TBS	*tert* –butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFAc	trifluoroacetate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide

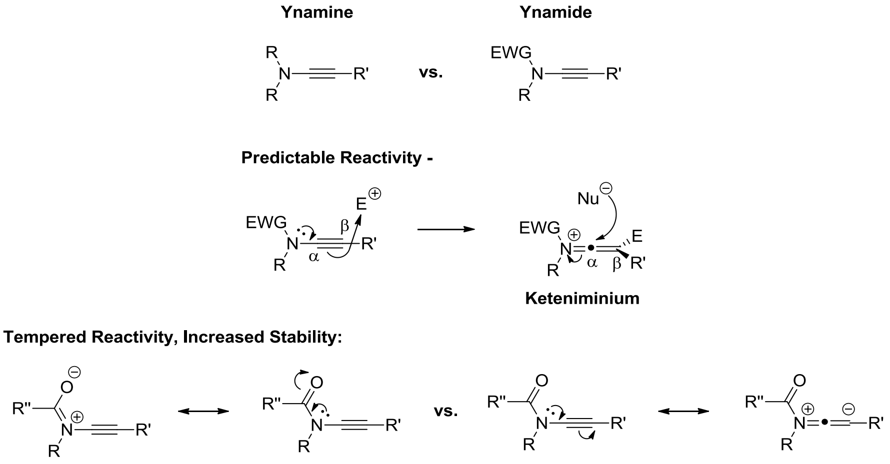
TMEDA	*N,N,N’,N’*-tetramethylethylenediamine
TMS	trimethylsilyl
TMS-EBX	trimethylsilyl ethynyl-1,2-benziodoxol-3(1*H*)-one
Ts	tosyl, *p*-toluenesulfonyl
W/V	mass per volume
X-phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
xyl	xylene

Contents

1. Introduction

1.1. Overview

Ynamides – alkynes substituted with an amide derivative through the nitrogen atom – have seen an increased level of interest over the last decade due to their enhanced stability compared to ynamines (Scheme 1.1).[1,2] By incorporating an electron-withdrawing substituent on the nitrogen, an electron-deficient ynamine is formed which still features the inherent electronic bias imposed by the nitrogen atom that can lead to excellent regio- and stereoselectivities in subsequent reactions, but also benefits from increased stability, making them considerably easier to synthesise, purify and handle.

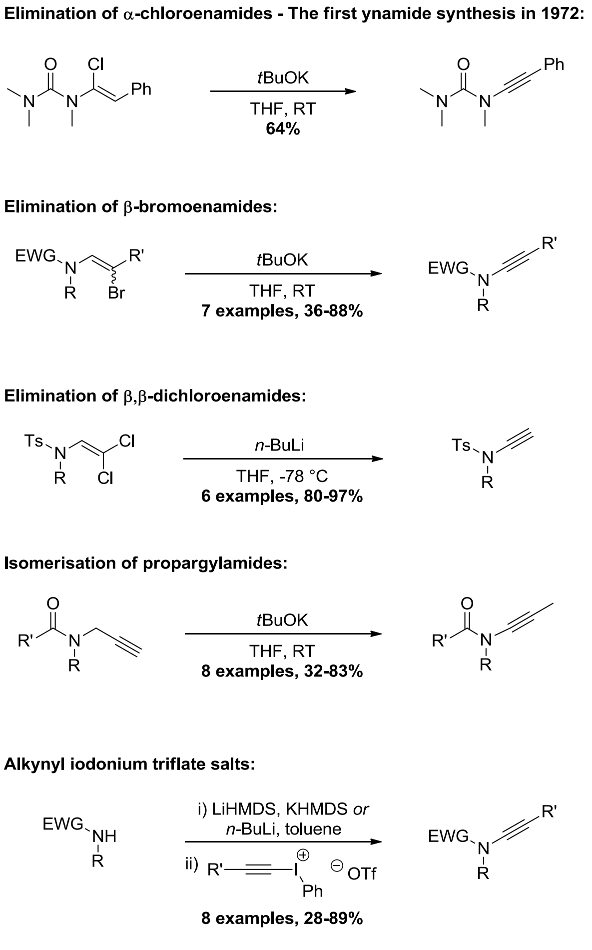


Scheme 1.1 – Ynamines vs. Ynamides

However, whilst there has been an increased level of interest, the applications of ynamides in organic chemistry is still a relatively under-investigated area, in part due to general practical synthetic routes to ynamides only having been reported during the last decade.

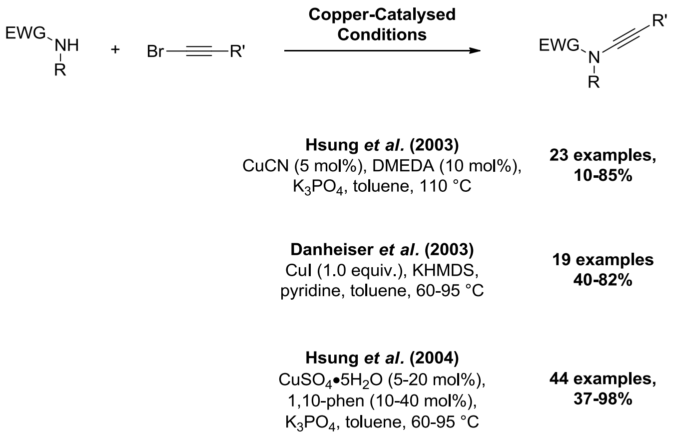
1.2. Ynamide Synthesis

Whilst there had been reports of ynamide formation since 1972, the synthetic routes often suffered from low product scope and often required harsh conditions for ynamide formation.[3] The common methods included elimination of α-chloroenamides, β-bromoenamides[4] or β,β-dichloroenamides[5,6] and subsequent functionalisation of the terminal alkene,[7-9] isomerisation of propargylamides[10] or by the use of alkynyl iodonium salts[11,12] (Scheme 1.2).



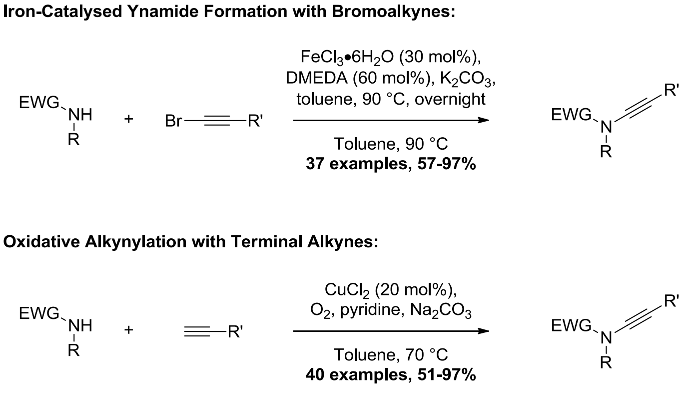
Scheme 1.2 –Traditional 'Pre-copper' Ynamide Formations

However, in 2003 Hsung *et al.* reported the first copper-catalysed coupling of amides with bromoalkynes, using CuCN or CuI as the catalyst and DMEDA as the ligand, providing an atom-economical and direct route to ynamides (Scheme 1.3).[13] Whist this route was a major breakthrough in ynamide formation, some limitations still remained including product scope, with sulfonamides being unsuitable, and high temperatures were required. Danheiser *et al.* overcame this problem by utilising stoichiometric amounts of CuI with KHMDS to access a broader range of ynamides, and this reaction could be conducted at room temperature.[14] This route still had the disadvantage of requiring a strong base, and in 2004 Hsung *et al.* reported an improved catalytic ynamide formation with an alternative copper catalyst and ligand ($CuSO_4$•$5H_2O$, 1,10-phenanthroline) at a reduced temperature, which to this date still proves to be one of the most efficient and direct routes to ynamides.[15,16]



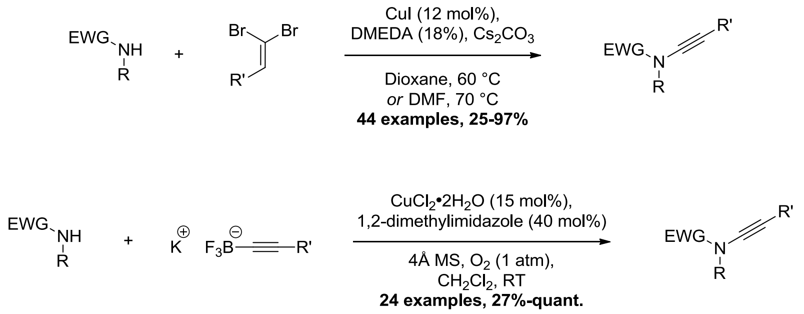
Scheme 1.3 – Copper-Catalysed Ynamide Formations

More recent routes to ynamides following the publication of these copper-catalysed conditions include an iron-catalysed coupling of amides with bromoalkynes[17] and an oxidative alkynylation of amides, with terminal alkynes which has the disadvantage of requiring five equivalents of amide (Scheme 1.4).[18]



Scheme 1.4 – Metal-Catalysed Ynamide Formations with Various Coupling Partners

The latest metal-catalysed formations were reported in 2009 and 2010 by Evano *et al.* who reported a copper-catalysed coupling of amides with dibromoalkenes, which act as synthetic equivalents of bromoalkynes,[19] and also a room-temperature, base-free copper-catalysed coupling with alkynyltrifluoroborates;[20] methods that are particularly useful when the synthesis of bromoalkynes proves difficult (Scheme 1.5).



Scheme 1.5 – Evano's Copper-Catalysed Ynamide Formations

With the development of the more recent copper-catalysed conditions for the formation of ynamides which allow efficient and reliable access to a range of ynamides, alongside the stability of these products and the electronic properties of the alkyne offering interesting reactivity patterns, there has been increased synthetic use and the development of interesting methodology which would otherwise be difficult to achieve using traditional ynamines.[1,2]

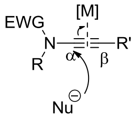
1.3. Applications of Ynamides in Ring-Forming Reactions

The use of ynamides in ring-forming reactions has received a large amount of interest due to the variety of synthetically useful azacycles that can be prepared, and can be generally grouped according to the type of reactions they involve: addition reactions, cycloadditions and cycloisomerisations.

1.3.1. Addition Reactions

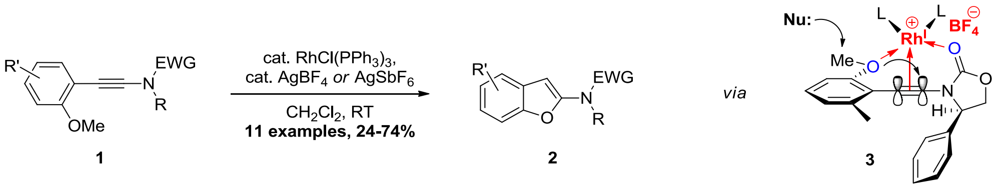
Metal-Catalysed Additions at the α-position

Ynamides are good substrates for the introduction of a substituent at the α-carbon, and this reactivity has been exploited in the development of simple and efficient routes to heterocycles (Scheme 1.6). It is common for a transition metal to activate the alkyne enabling α-addition, although there is the possibility that the electron-withdrawing group can chelate with transition metal catalysts directing addition, and that it can also act as a chiral auxilliary.



Scheme 1.6 – α-Addition to Ynamides

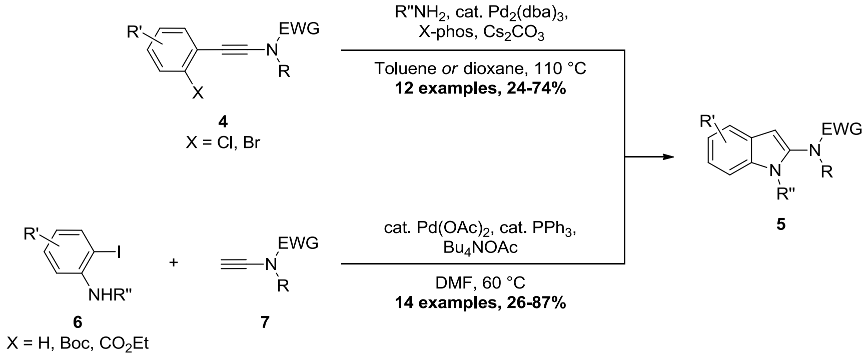
Whilst intermolecular additions are successful for the formation of polysubstituted enamides,[1] intramolecular addition is particularly efficient in the synthesis of heteroaromatic systems. In 2007, Hsung *et al.* reported a rhodium-catalysed demethylation/cyclisation of ynamides containing an *o*-anisole substituent affording benzofurans of the type **2** (Scheme 1.7).[21]



Scheme 1.7 – Rhodium-Catalysed Cyclisation to Benzofurans

Interestingly, this methodology was discovered during investigations into a [2+2+2] cycloaddition with ynamide **1**, which in the presence of a silver salt actually formed the benzofurans **2**. The proposed mechanism involved the abstraction of a $Cl^{\ominus}$ ligand to form silver(I) chloride and complex **3** which possesses additional co-ordination sites. With the catalyst chelating to both the EWG and the alkyne, it may be possible for complexation to occur with the methoxy substituent setting up the demethylation required for cyclisation to occur.

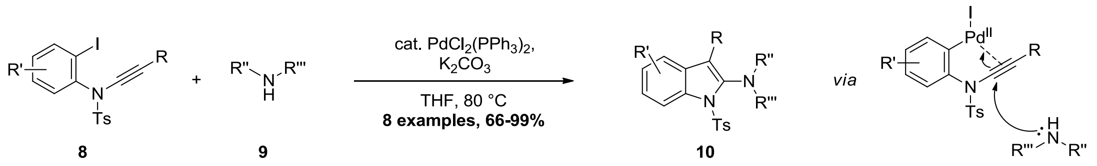
Using a similar strategy, Hsung *et al.* extended the intramolecular cyclisation to incorporate *o*-aminoaryl ynamides in the synthesis of 2-aminoindoles **5**, with the nucleophile being formed *in-situ via* the amination of **4** (Scheme 1.8).[22]



Scheme 1.8 – 2-Aminoindole Formation *via* Intramolecular α-addition

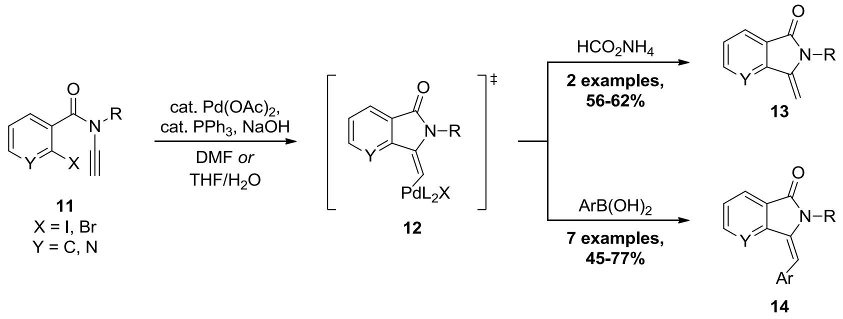
This methodology was further developed by the Skrydstrup group, forming the same *o*-aminoaryl ynamide intermediate but *via* a Sonogashira coupling of an *o*-iodoaniline **6** with a terminal ynamide **7**.[23] This method has the added advantage of being able to access 2-aminoindole **5** with R'' = H, without the need for subsequent deprotection.

In 2003 Witulski *et al.* also reported a complementary method to form 2-aminoindoles **10**, involving a palladium-catalysed activation of ynamide **8**, enabling the intermolecular addition of external amines **9** to the alkyne bond (Scheme 1.9).[24]



Scheme 1.9 – 2-Aminoindole Formation *via* Intermolecular α-activation

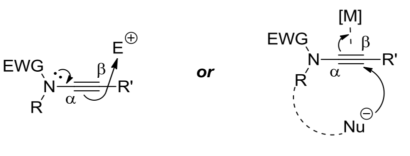
In an alternative ynamide cyclisation to nucleophilic addition at the α-position, Cossy *et al.* reported the first intramolecular carbopalladation of a tethered bromo- or iodo-aniline with a terminal ynamide **11** to form the vinyl palladium intermediate **12** (Scheme 1.10).[25] Further reaction of this intermediate by either a reduction with ammonium formate, or a Suzuki coupling with aryl boronic acids, afforded 3-(methylene)isoindolinones **13** and (*E*)-3-(arylmethylene)isoindolinones **14** stereoselectively.



Scheme 1.10 – Ynamide Carbopalladation in the Synthesis of Isoindolinones

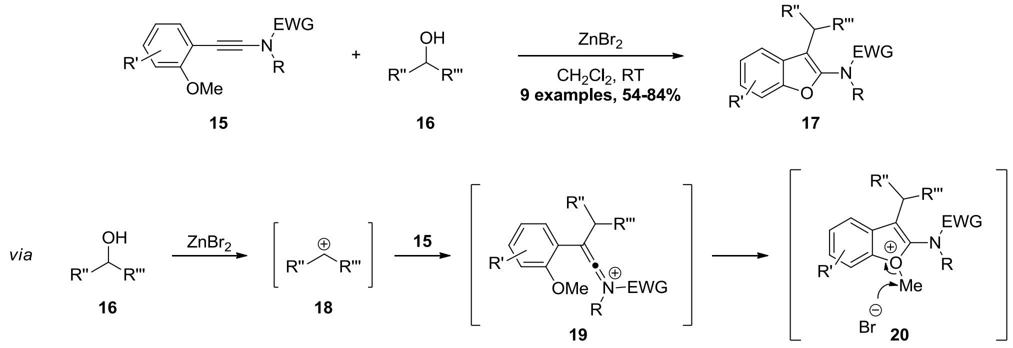
Metal-Catalysed Additions at the β-position

It is also possible to reverse the regioselectivity of reactions with ynamides by introducing an electrophile to exploit the inherent reactivity, or alternatively, by varying the substrate to incorporate an intramolecular process in the presence of a transition metal catalyst, addition at the β-carbon is also possible (Scheme 1.11). It is generally felt that this reversal of regioselectivity is due to either steric interactions or caused by chelation of metal catalyst to the EWG present on the nitrogen.[2]



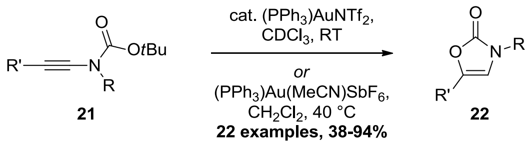
Scheme 1.11 – β-Addition to Ynamides

Recently, Cao *et al.* reported a complimentary synthesis of benzofurans, compared to Scheme 1.7, *via* a novel carbocation-induced electrophilic cyclisation which truly exploited the inherent reactivity of ynamides (Scheme 1.12).[26] By employing a secondary alcohol and a Lewis-acid, they propose that carbocation **18** could be formed which undergoes initial electrophilic β-addition to ynamide **15** forming keteniminium **19**, which can undergo subsequent cyclisation *via* an α-addition and demethylation to afford benzofuran **17**.



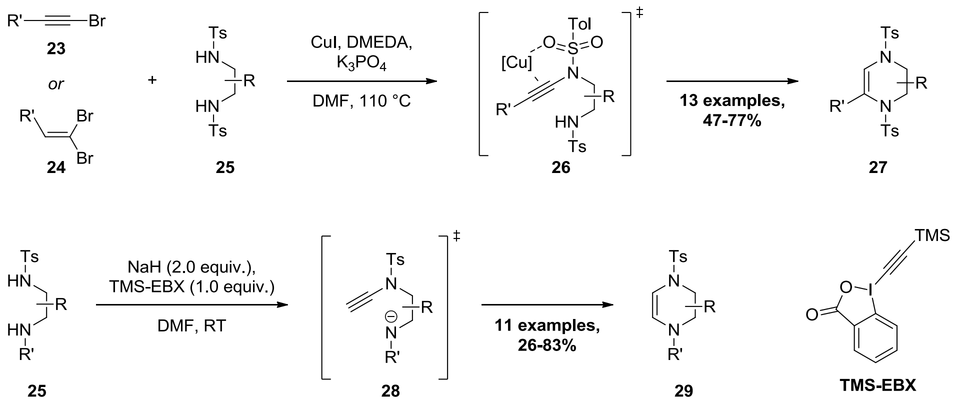
Scheme 1.12 – Electrophilic Cyclisation to Benzofurans

Hashmi demonstrated the ability of the nitrogen electron-withdrawing group to be involved in the gold-catalysed cyclisation with carbamate-protected ynamide **21** (Scheme 1.13).[27,28] Mechanistically, it is thought that the gold activates the alkyne to a 5-*endo*-dig attack by the Boc group, followed by loss of isobutene and protodemetallation to afford the oxazolidinone **22**. Unfortunately, whist a wide range of substituents were tolerated on the nitrogen, only terminal or silylated ynamides were reported.



Scheme 1.13 – Gold-Catalysed Intramolecular β-addition of a Boc Group to an Ynamide

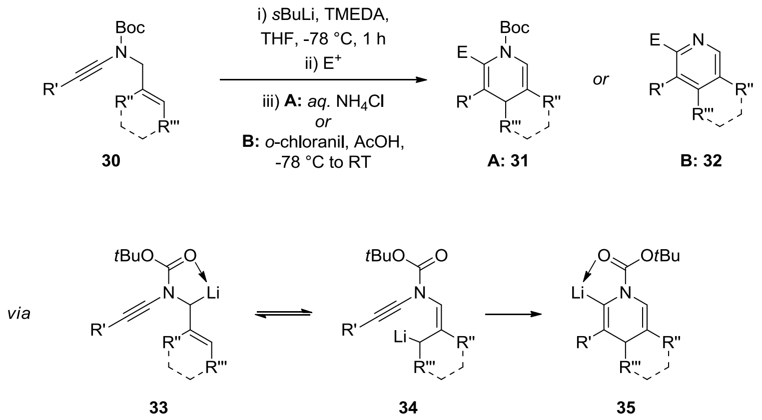
There have been two independently reported syntheses of tetrahydropyrazines **27** and **29** (Scheme 1.14). Urabe *et al.* discovered the unexpected copper-catalysed double amination of bromoalkynes **23** or dibromoalkenes **24** while investigating a dual-ynamide formation.[29] After the first alkynylation has occurred it is thought that the sulfonyl group co-ordinates the copper salt activating the alkyne to an intramolecular 6-*endo*-dig cyclisation.



Scheme 1.14 – Formation of Tetrahydropyrazines

More recently, Cossy and co-workers found that by conducting a formal deprotonation of the diamine **25** and utilising the alkenyl iodonium salt TMS-EBX in an ynamide formation, cyclisation occurred to form an analogous product set.[30]

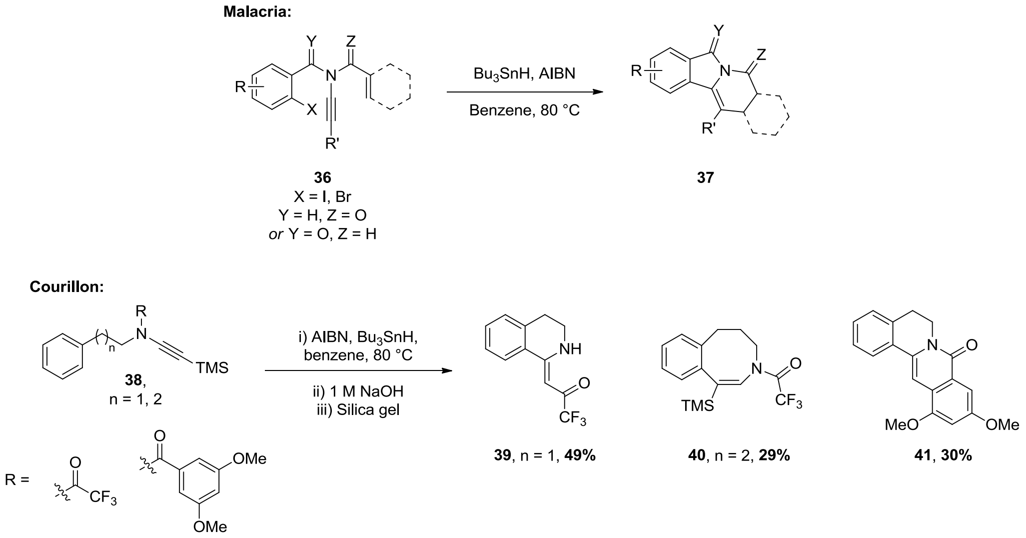
Ynamides have also been utilised in the formation of 1,4-dihydropyridines **31** and pyridines **32** *via* intramolecular carbolithiation (Scheme 1.15).[31] Evano and co-workers discovered that deprotonation of *N*-allyl ynamides **30** resulted in a chelation-stabilised intermediate **33** that exists in equilibrium with intermediate **34**, which can then undergo an intramolecular 6-*endo*-dig carbometallation to form the stabilised vinyllithium **35**. Subsequent electrophilic quench followed by either an aqueous work-up or hydrolysis and oxidation afforded the highly substituted dihydropyridine **31** or pyridine **32** derivatives.



Scheme 1.15 – Formation of 1,4-Dihydropyridines and Pyridines

Radical Cyclisations

There have only been a few ynamide radical processes reported, with only two involving the cyclisation of ynamides in the construction of complex heterocycles. Malacria and co-workers demonstrated a 5-*exo*-dig cyclisation of ynamides **36** followed by a 6-*endo*-trig radical trapping to access isoindolines **37**,[32,33] whilst Courillon *et al.* demonstrated the formation of the 6-membered rings **39** and **41**, and 8-membered ring **40**, *via* a 6-*exo*-dig or 8-*endo*-dig cyclisation of specifically designed ynamides respectively (Scheme 1.16).[34]



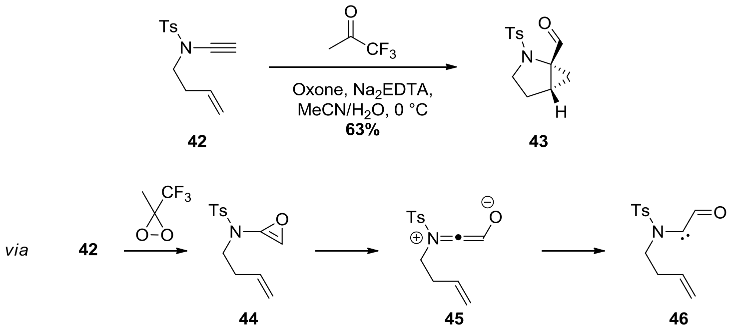
Scheme 1.16 – Radical Cyclisation to Isoindolines and a Range of Heteroaromatics

1.3.2. Cycloadditions

The use of ynamides in cycloadditions is probably one of the most investigated applications, proving to be an extremely powerful tool for the preparation of a range of carbo- and heterocycles, with the outcome often being directed by the polarisation of the triple bond to afford a single regioisomer.

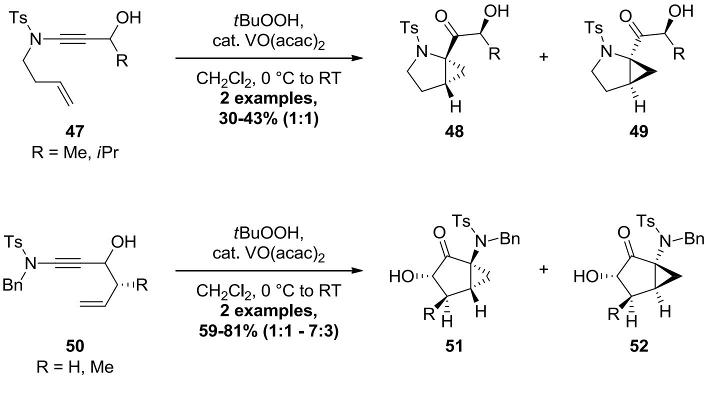
[2+1] Cycloadditions

Cossy and Meyer, as well as Hsung and Al-Rashid, simultaneously reported a novel example of a [2+1] epoxidation/ring-opening/cyclisation strategy *via* a formal push-pull carbene intermediate to access azabicycles **43** (Scheme 1.17).[35,36] Treatment of enynamide **42** with the oxidant methyl(trifluoromethyl)dioxirane results in a chemoselective epoxidation of the ynamide, which is slightly more electron-rich than the alkene due to the delocalisation of the nitrogen lone pair. The resulting oxirene **44** can then undergo ring-opening to generate carbene **46** which is trapped by the alkene to afford the fused pyrrolidine-cyclopropane product **43**.



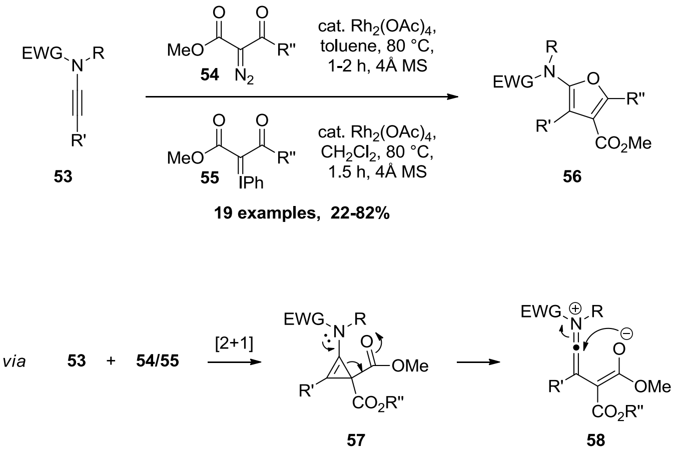
Scheme 1.17 – Oxidation of Enynamides

Unfortunately, this reaction was found to be highly substrate-specific and could not be applied to substituted ynamides with the exception of a secondary propargylic alcohol, which underwent successful epoxidation and cyclisation in the presence of *t*BuOOH and VO(acac)$_2$, tethering the alkene through either the *N*- (**47**) or *C*-terminus (**50**) (Scheme 1.18).



Scheme 1.18 – Oxidation of Propargylic Alcohol Substituted Enynamides

Recently, Hsung also published a rhodium(II)-catalysed cyclopropenation of ynamides with both diazo dimethyl malonates **54** and phenyl iodonium ylides **55**, to access the highly substituted 2-amidofurans **56** (Scheme 1.19).[37] The proposed mechanism by the authors was thought to proceed *via* a rhodium carbene-catalysed [2+1] cycloaddition to form cyclopropene **57**, which after ring-opening and subsequent cyclisation affords the furans **56**.

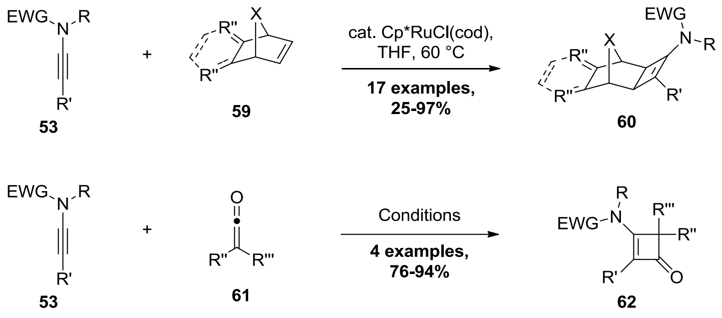


Scheme 1.19 – Rhodium-Catalysed Ynamide Cyclopropenation

[2+2] Cycloadditions

In a continuation of their work on ruthenium catalysed [2+2] cycloadditions, Tam and co-workers reported the reaction of bi- and tri-cyclic bridged alkenes **59** with ynamides **53** (Scheme 1.20).[38,39] On attempting to extend this methodology to incorporate chiral ynamides, it was found that only modest diastereoselectivities were obtained.

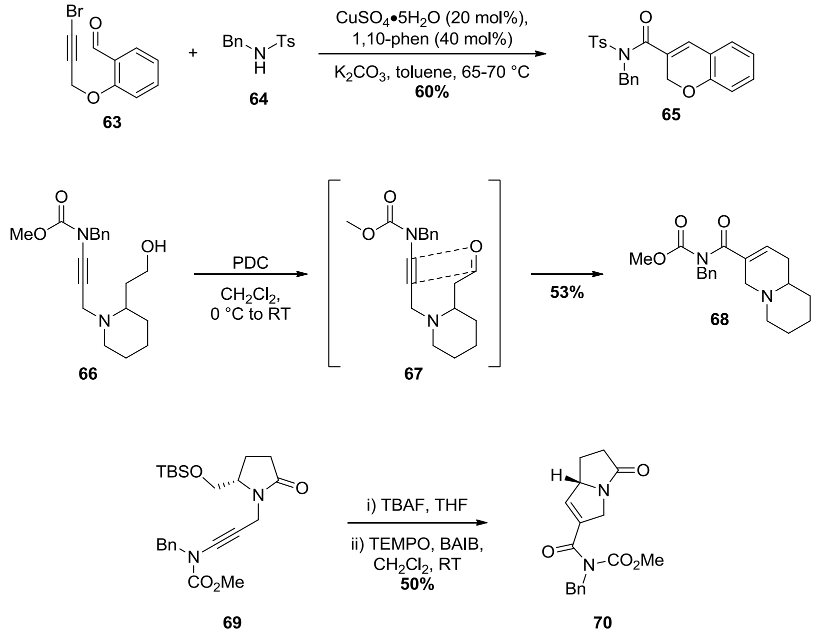
The Danheiser research group also demonstrated the ability of ynamides **53** to undergo [2+2] cycloadditions with a range of ketenes **61** using a variety of conditions to afford a range of aminocyclobutenones **62**.[40]



Conditions:
A: MeCN, RT
B: cat. $Rh_2(OAc)_4$, $PhSCOCHN_2$, CH_2Cl_2, reflux
C: Zn-Cu, CCl_3COCl, Et_2O/DME, 0 °C → RT
D: *i*PrCOCl, NEt_3, CH_2Cl_2, reflux

Scheme 1.20 – [2+2] Cycloadditions

Perhaps a more exciting application of the [2+2] cycloaddition with ynamides is the tandem cross-coupling/cycloaddition/ring-opening sequence which was explored by Hsung and co-workers (Scheme 1.21).[41] Formation of the ynamide from bromoalkyne **63** and sulfonamide **64** *in-situ*, followed by cycloaddition and ring-opening, led to the formation of chromene **65**.

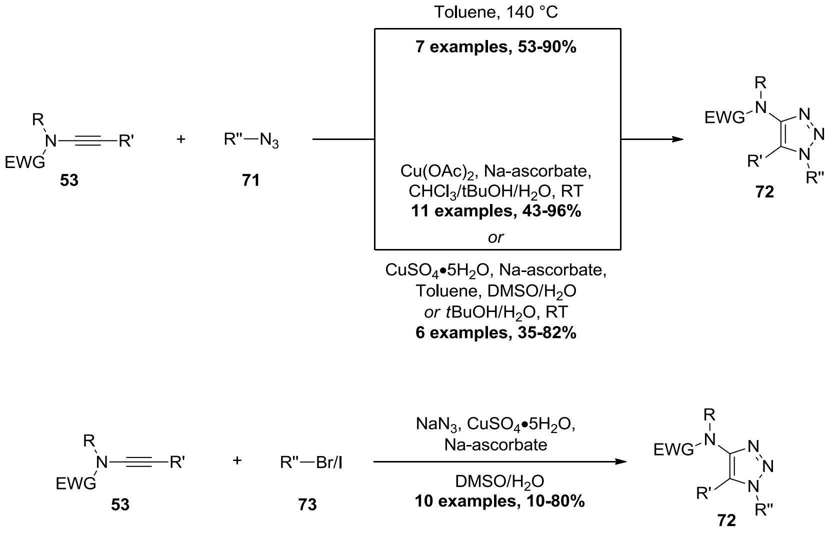


Scheme 1.21 – Tandem [2+2] Cycloaddition/Ring-Opening

In another example, oxidation of a primary alcohol also led to the tandem process occurring, affording quinolizidine **68**. This method was also applied to pyrrolizidine **70** employing a one-pot oxidation/cycloaddition/ring-opening sequence.

Dipolar [3+2] Cycloadditions

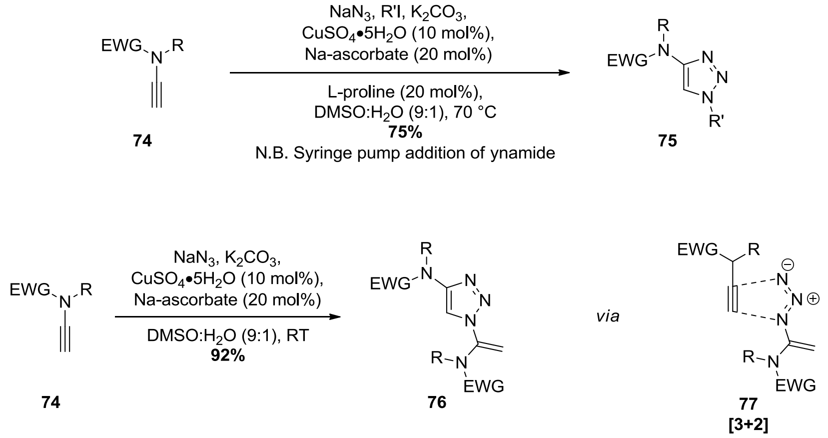
There have been a wide range of reports of “click” chemistry with ynamides since the first publication in 2006 by Ijsselstijn and Cintrat, [42] and by Hsung and co-workers. [39,40] A range of conditions were employed with both thermal and copper-catalysed conditions (either $Cu(OAc)_2$ or $CuSO_4$•$5H_2O$ and Na-ascorbate) proving to be successful affording a range of aminotriazoles **72** (Scheme 1.22).



Scheme 1.22 – Click Cycloadditions with Ynamides

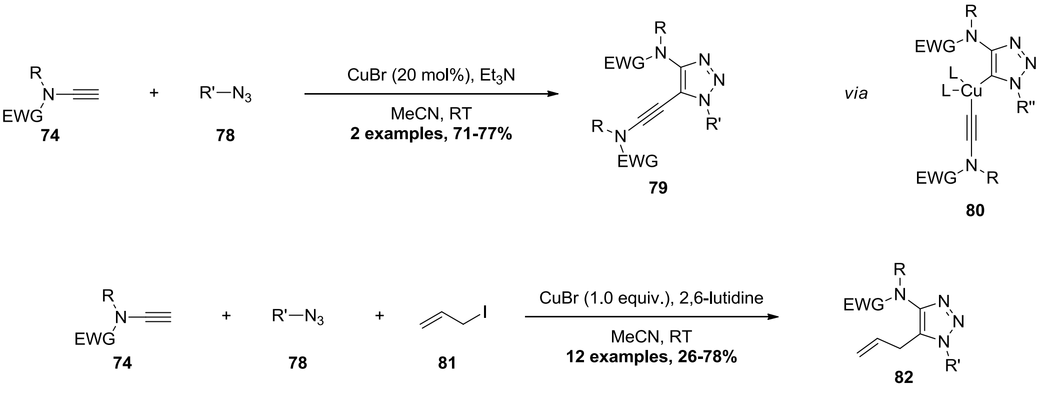
This methodology was further developed to incorporate an azidination/cycloaddition sequence from aryl, alkyl or vinyl iodides or bromides **73** and sodium azide.[43]

Interestingly, during the studies of the one-pot azidination/[3+2] cycloaddition sequence, Hsung *et al*. discovered that if a terminal ynamide **74** was employed vinyl triazole **76** was preferentially formed (Scheme 1.23). This could be overcome by adding the ynamide *via* a syringe pump to afford the expected triazole **75**, but by removing the L-proline and the iodide used for the azidination, the vinyl triazole **76** could also be formed in a 92% yield.[44] After conducting competition experiments with ynamide **74** and a terminal alkyne to investigate the electronics of the cycloaddition, they found that the terminal alkyne did not react, suggesting that hydroazidination was chemoselective for the electron-rich ynamide, which could undergo a cycloaddition with another ynamide as shown by the transition state **77**.



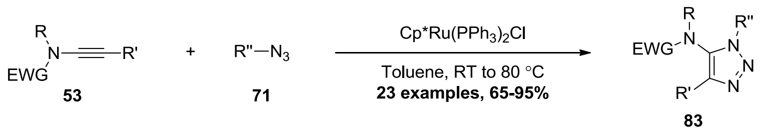
Scheme 1.23 – Hydroazidination/Cycloaddition Sequence for the Formation of Vinyl Triazoles

As the field of 'click' chemistry with ynamides evolved another interesting observation was discovered; when CuBr was utilised alkyne **79** was formed (Scheme 1.24).[45] It was presumed that the product was formed from reductive elimination of the intermediate **80**, which implied the presence of a vinyl copper intermediate which co-ordinated another ynamide. Based on this concept, the methodology was developed to trap this intermediate with allyl iodide instead of an ynamide, which afforded triazoles **82**.



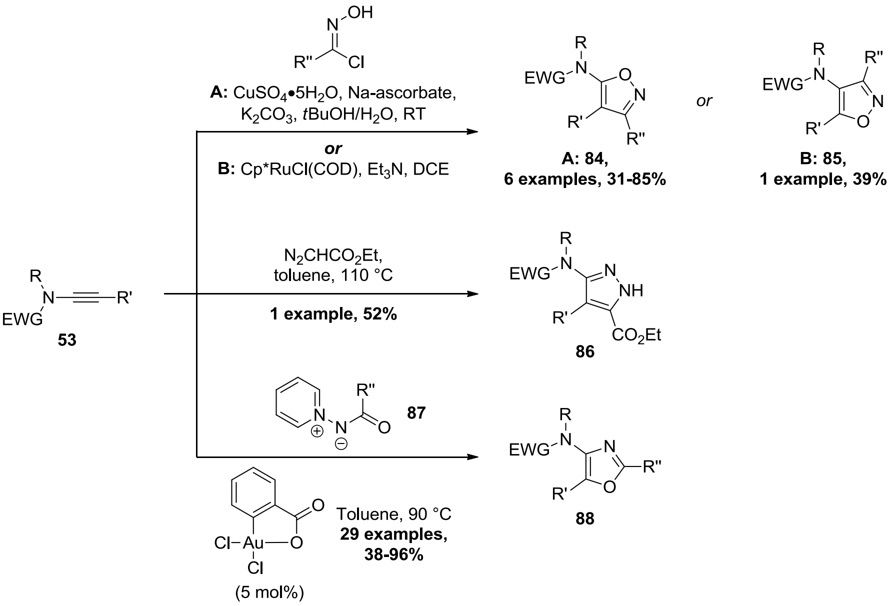
Scheme 1.24 – [3+2] Click Cycloaddition/Cross-Coupling Sequence

It was also found that the regioselectivity of the 'click' cycloaddition could be reversed by replacement of the copper catalyst with a ruthenium catalyst, favouring the formation of the triazole **83** (Scheme 1.25).[46,47]



Scheme 1.25 – Ruthenium-Catalysed Click Cycloaddition with Reversed Regioselectivity

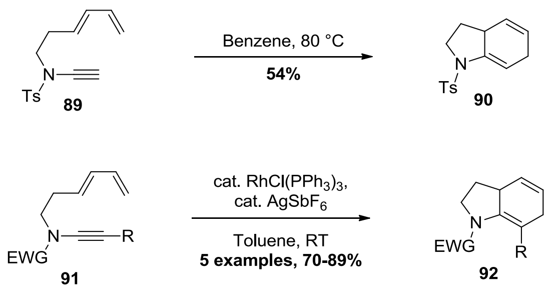
Finally, a range of other dipolar reagents have been successfully employed in [3+2] cycloadditions with ynamides (Scheme 1.26). This includes nitrile oxides, whose regioselectivity can also be reversed by using a ruthenium catalyst[48] instead of a copper catalyst, to form isoxazoles **84** and **85** respectively.[49] Other successful dipolar reagents include diazoacetates[49] to form pyrazole **86**, and aminide **87** in the presence of a gold catalyst to form 1,3-oxazoles **88**.[50]



Scheme 1.26 – [3+2] Cycloadditions with Various Dipolar Reagents

[4+2] Cycloadditions

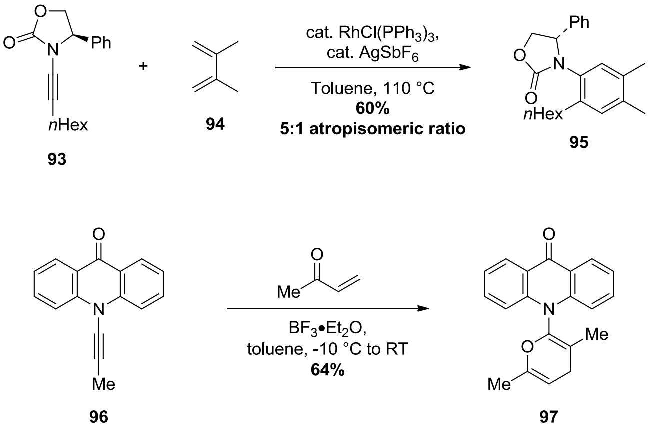
The first intramolecular Diels-Alder cycloaddition was reported by Witulski and co-workers, who discovered that diene-ynamides could undergo either a thermal reaction if a terminal ynamide **89** was used, or a cationic rhodium(I)-catalysed reaction with substituted ynamides **91**, to afford dihydroindolines **90** and **92** (Scheme 1.27).[51]



Scheme 1.27 – [4+2] Intramolecular Cycloadditions with Diene-Ynamides

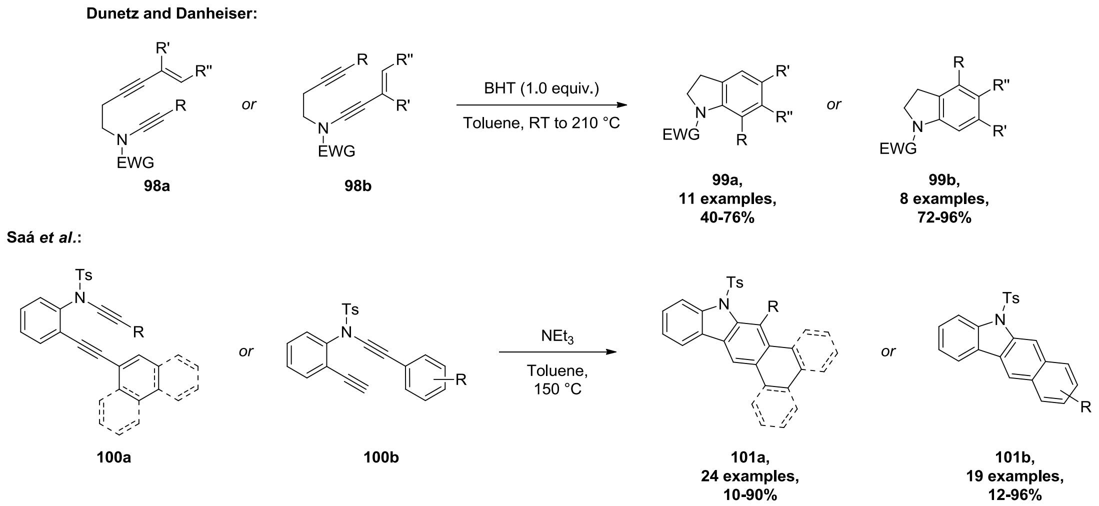
This intramolecular Diels-Alder cycloaddition was also applied to a chiral oxazolidinone-derived ynamide to successfully obtain a tricyclic dihydroindoline as a single diastereomer.[16]

This work was later expanded by Hsung to involve an intermolecular cycloaddition with symmetrical dienes **94** to afford anilide **95** in a 5:1 atropisomeric ratio,[16] and the group also reported a single example of a Lewis acid-catalysed hetero-Diels-Alder reaction of ynamide **96** with methacrolein to afford **97** (Scheme 1.28).[52]



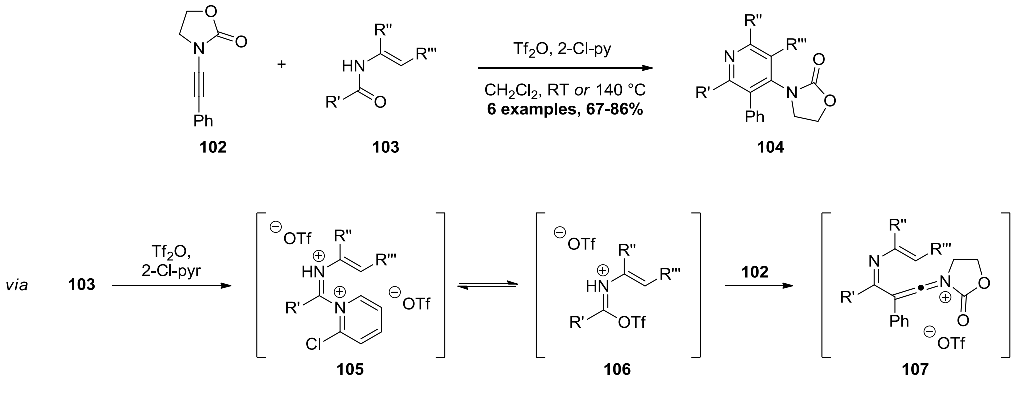
Scheme 1.28 – [4+2] Intermolecular Cycloadditions with Ynamides

In 2005, Dunetz and Danheiser[53] and Saá *et al.* [54,55] independently derived intramolecular thermal [4+2] dehydro-cycloadditions of both enyne-tethered ynamides **98a** and **100a**, and alkyne-tethered enynamides **98b** and **100b** to afford indolines **99** and carbazoles **101** respectively (Scheme 1.29).



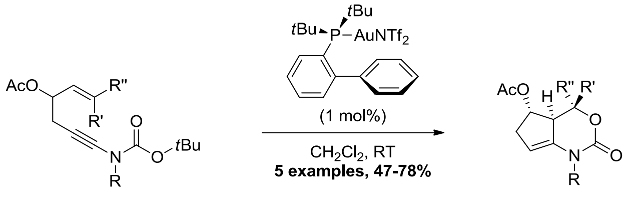
Scheme 1.29 – [4+2] Dehydro-Cycloadditions

A synthesis of highly substituted pyridines **104** *via* an acid-catalysed *aza*-[4+2] cycloaddition of ynamide **102** with enamide **103** has also been reported by Movassaghi and co-workers (Scheme 1.30).[56] The authors proposed that electrophilic activation of enamide **103** using 2-Cl-pyridine in combination with Tf_2O forms the bis-iminium intermediate **105** which is thought to exist in equilibrium with the corresponding triflate adduct **106**, which can subsequently be attacked by the ynamide **102** to form keteniminium **107**. This intermediate can then undergo an intramolecular *aza*-Diels-Alder cycloaddition forming the pyridine **104**, a useful method with the potential for varying all five substituents.



Scheme 1.30 – Acid-Catalysed *aza*-[4+2] Cycloaddition

Finally, there has been a single example of a gold-catalysed hetero-Diels-Alder reaction of *N*-Boc protected ynamides **108** where the EWG partakes in the cycloaddition with the ynamide and trisubstituted alkene to form enamides **109** as single diastereomers, with the selectivity being determined by the acetoxy group being *pseudo*-equatorial to avoid steric interactions with the alkene substituents (Scheme 1.31).[57]

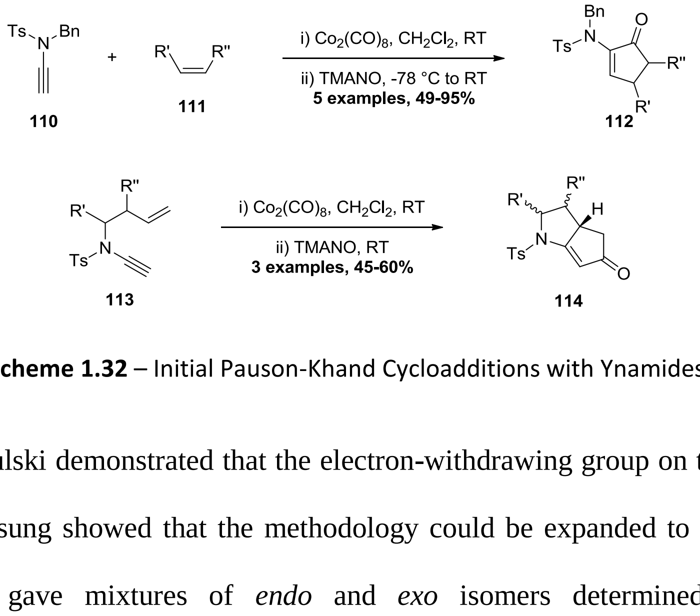


108 **109**

Scheme 1.31 – Gold Catalysed Hetero-Diels-Alder Reaction

[2+2+1] Cycloadditions

Both the inter- and intramolecular Pauson-Khand reactions of ynamides to form cyclopentenones such as **112** and **114** has been thoroughly investigated, with Witulski first reporting the highly regioselective cyclocarbonylation of ynamide **110** with a range of olefins **111**, and by then incorporating an *N*-tethered olefin into ynamide **113** (Scheme 1.32).[11,58]



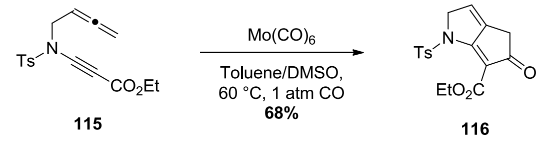
110 **111** **112** **113** **114**

Scheme 1.32 – Initial Pauson-Khand Cycloadditions with Ynamides

Shortly after, Witulski demonstrated that the electron-withdrawing group on the nitrogen could be varied[59] and Hsung showed that the methodology could be expanded to incorporate chiral ynamides which gave mixtures of *endo* and *exo* isomers determined by the alkyne substitution.[60] Generally, it was found that with a terminally substituted ynamide, *endo* addition was favoured, although the mechanistic rationale for this selectivity remains unclear.

The Rainer group has also conducted extensive studies on the use of yne-ynamides using both $CpCo(CO)_2$ and $Fe(CO)_5$ in the formation of cyclobutadiene-metal complexes, but these will not be discussed as a carbo- or heterocycle is not formed without further reaction of such complexes.[12,61]

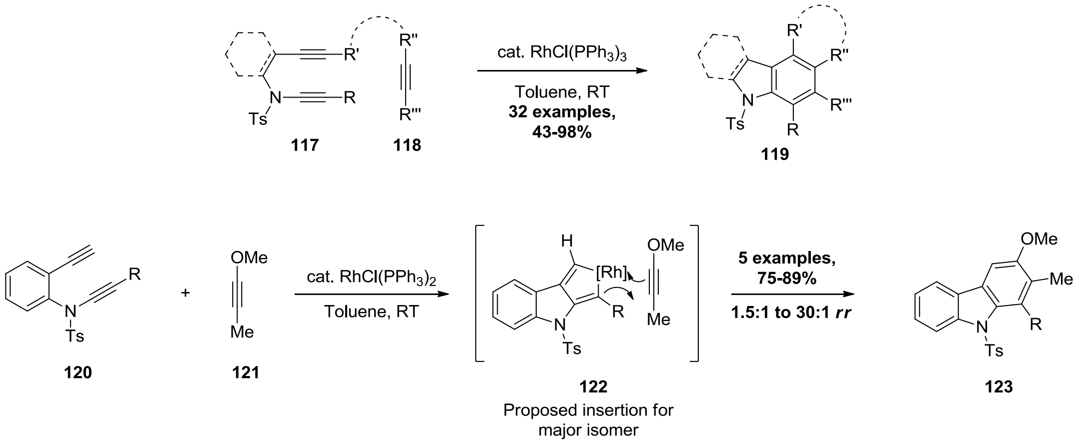
Finally, in 2005 Oh *et al.* reported the $Mo(CO)_6$-catalysed Pauson-Khand reaction of the allene-containing ynamide **115** which formed the bicyclic pentanone **116** in 68% yield (Scheme 1.33).[62]



Scheme 1.33 – Pauson-Khand with Allene-Ynamide

[2+2+2] Cycloadditions (Cyclotrimerisations)

The pioneer of ynamide cyclotrimerisation is Witulski, who in 1999 reported the rapid formation of indolines and carbazoles **119** from yne-ynamides **117**, in an intra- or intermolecular process with a variety of alkynes **118**, catalysed by Wilkinson's catalyst (Scheme 1.34).[63-65]

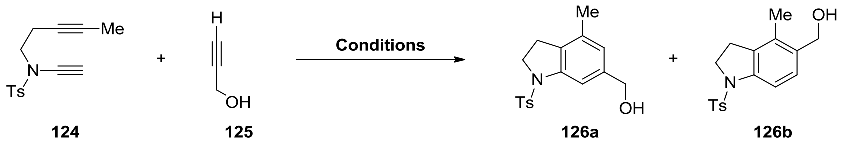


Scheme 1.34 – Rhodium Catalysed Cyclotrimerisation of Yne-ynamides

The regioselectivity was found to be dependent on steric effects and solvent effects, rather than just the polarisation of the triple bond, and could be completely reversed by replacing

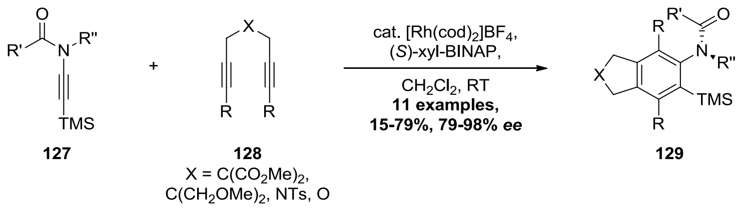
Wilkinson’s catalyst with Grubbs II catalyst, allowing selective access to both 4,5- and 4,6-disubstituted indolines **126a** and **126b** respectively (Table 1.1).[66] The change in regioselectivity was proposed to be due to the Grubbs catalyst inducing a series of metathesis steps beginning with addition of the electrophilic Ru-benzylidene to the electron-rich ynamide motif.

Table 1.1 – Switching the Regioselectivity of Intermolecular Cyclotrimerisation



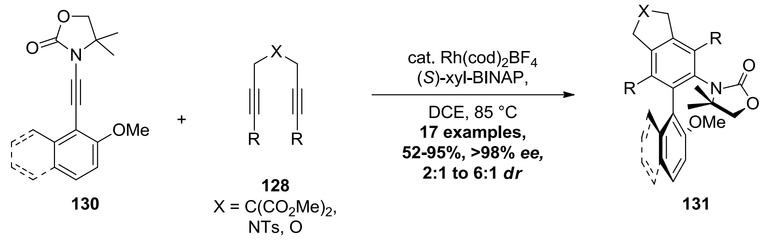
	Conditions	126a:126b	Yield
1	Wilkinson’s catalyst ($RhCl(PPh_3)_3$), toluene, RT	9:1	70%
2	Grubbs II catalyst ($RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, 40 °C	1:20	67%

In 2006, Tanaka reported an asymmetric rhodium-catalysed cyclotrimerisation of diynes **128** with ynamides **127**, with the chiral ligand (*S*)-xyl-BINAP, forming a range of axially chiral anilides **129** in good yield with good to excellent enantiomeric excesses (Scheme 1.35).[67]



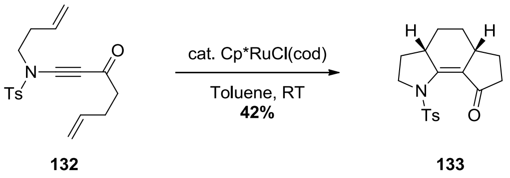
Scheme 1.35 – Cyclotrimerisation of Ynamides to Axially Chiral Anilides

Using this protocol, Hsung and co-workers could also synthesise axially chiral *N,O*-biaryls **131** in modest diastereoselectivities of up to 6:1 *dr*, with both diastereomers having up to 99% *ee* (Scheme 1.36).[68-70]



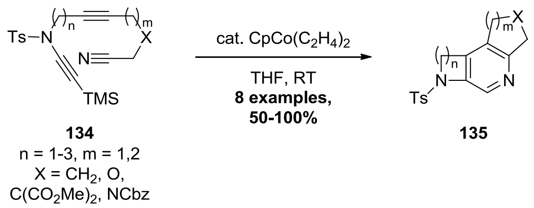
Scheme 1.36 – Cyclotrimerisation of Ynamides to Axially Chiral Biaryls

The work of Mori and Sato demonstrated a simple and effective cyclotrimerisation of ynamide **132** under ruthenium-catalysed conditions providing rapid access to the tricyclic framework **133** (Scheme 1.37).[71]



Scheme 1.37 – Ruthenium-Catalysed Cyclotrimerisation to Tricyclic Framework

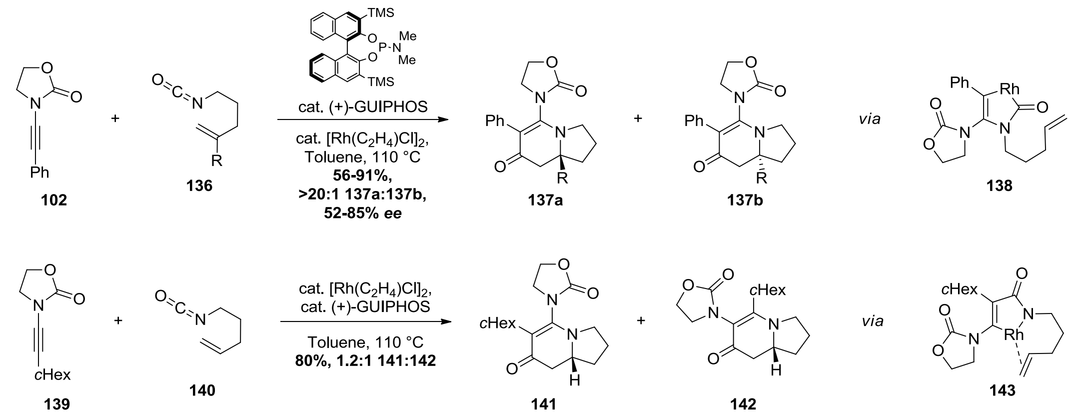
Aubert and co-workers also demonstrated that a tricyclic system could be assembled in a single step and that nitriles could be utilised in cyclotrimerisations with ynamides by submitting **134** to a cobalt-catalysed cyclisation. This substrate, containing an ynamide, a tethered alkyne and a nitrile, formed the tricyclic aminopyridines **135** in a single step in impressive yields (Scheme 1.38).[72]



Scheme 1.38 – Cobalt-Catalysed Cyclotrimerisation Involving a Nitrile

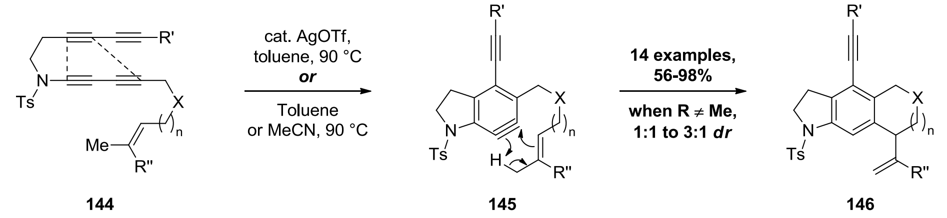
The use of alkenyl isocyanates **136** and **140** in a cyclotrimerisation with achiral ynamides **102** and **139** has also been reported by Rovis *et al* in the presence of the chiral ligand (+)-GUIPHOS to form the vinylogous amides **137a** and **141** in moderate to good enantioselectivity (Scheme 1.39).[73] Interestingly when the cyclohexyl-substituted ynamide **139** was used instead of the phenyl-substituted ynamide **102**, a mixture of regioisomers is obtained with **141** being isolated.

The authors suggest that the different regioisomers are determined by the initial oxidative addition which can lead to either intermediate **138** or **143**, but that the difference in selectivity is due to electronic effects.



Scheme 1.39 – Rhodium-Catalysed [2+2+2] Cycloaddition of Ynamides with Alkenyl Isocyanates

Finally, Lee *et al.* recently published an exciting silver-catalysed [2+2+2] cycloaddition forming aryne **145**, which undergoes an *in situ* Alder-ene reaction to form the tricyclic indolines **146** in impressive yields, with both alkene and alkyne substituents which could be used as handles for further functionalisation (Scheme 1.40).[74]



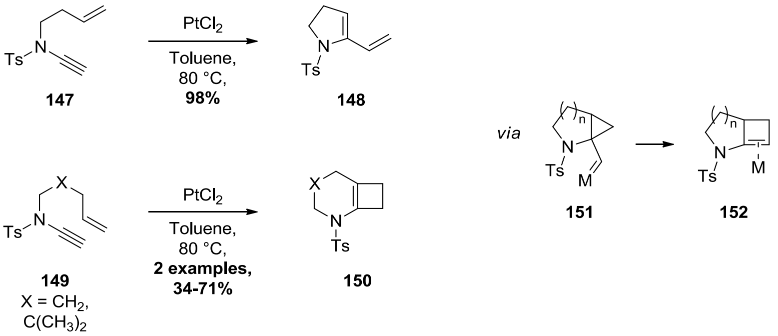
Scheme 1.40 – Ynamide Cyclotrimerisation and Subsequent Alder-ene Reaction

1.3.3. Cycloisomerisations

Cycloisomerisations, like cyclotrimerisations, are particularly appealing transformations offering efficient and atom-economical routes into cyclic systems, but so far the application of ynamides in such reactions has been limited. Generally, the previous reports have focussed on π-acid-catalysed cyclisations and ring-closing enyne metathesis

Metal- and Acid- catalysed cyclisations

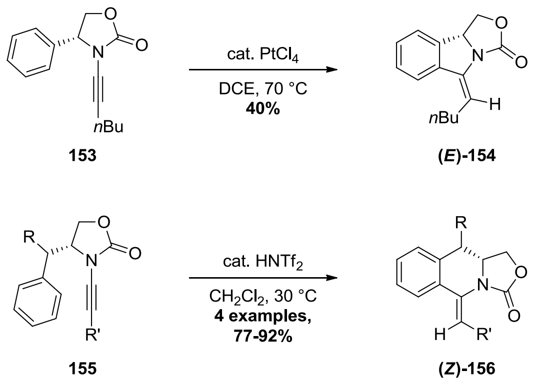
The cycloisomerisation of ene-ynamides was first reported in 2004 by Malacria and co-workers, who developed a platinum-catalysed ene-ynamide cycloisomerisation to form exocyclic amidodiene **148** (Scheme 1.41).[75-77] It was found that by increasing the tether length the bicyclic system **150** was formed instead.



Scheme 1.41 – Platinum-Catalysed Ynamide Cycloisomerisations

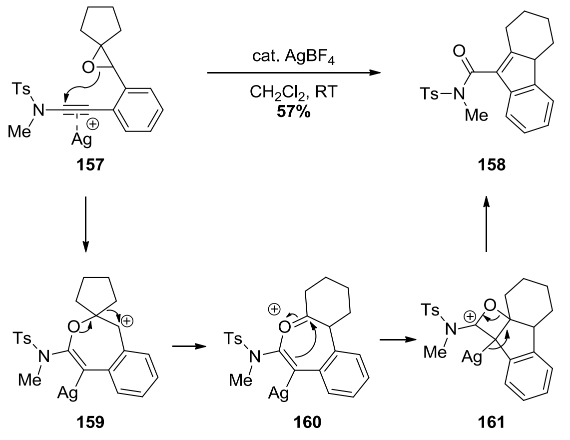
Mechanistically, this transformation has been explored through DFT calculations which suggest that the initial complexation of the electrophilic metal to the electron-rich ynamide, followed by attack of the tethered alkene, forms the intermediate **151**. The key intermediate **152** is then formed from a 1,2-alkyl shift into the carbene, at which point the ring strain which is introduced depending on the tether length leads either to other exocyclic diene **148** or the bicyclic system **150**.[77]

The cycloisomerisation of ynamides was furthered by Hsung in the formation of chiral isoindoles **154** and tetrahydroisoquinolines **156** *via* acid-catalysed keteniminium Pictet-Spengler cyclisations (Scheme 1.42).[78] The use of the Lewis-acid $PtCl_4$ with ynamide **153** afforded isoindole **154** with an (*E*)-exocyclic diene, whereas the use of a Brønsted-acid with ynamide **155** afforded tetrahydroisoquinoline **156** with a (*Z*)-exocyclic diene. The authors rationalised the difference in selectivity by the *Z*-formation being favoured with the Brønsted-acid to minimise steric interactions between the aromatic nucleophile and the substituent on the ynamide terminus, whereas the bulky Lewis-acid favours the *E*-olefin.



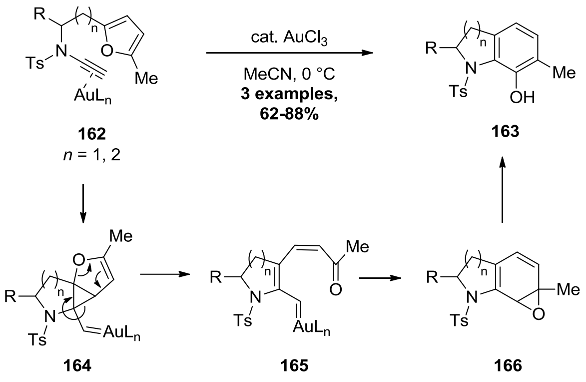
Scheme 1.42 – Acid-Catalysed Keteniminium Pictet-Spengler Cyclisations

A silver-catalysed cycloisomerisation of the epoxide-containing ynamide **157** has also been investigated by the Liu group (Scheme 1.43).[79] The carbocyclic framework **158** was formed by epoxide attack of the activated alkene followed by a 1,2-alkyl shift ring expansion and cyclisation to **161**, with subsequent elimination of silver.



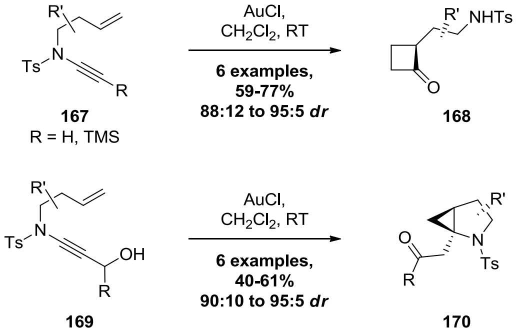
Scheme 1.43 – Silver-Catalysed Cycloisomerisation of Epoxide Containing Ynamides

More recently, gold catalysed cycloisomerisations have been shown to be successful with ynamides. In 2008, Hashmi and co-workers discovered that $AuCl_3$ could be used to catalyse the intramolecular cyclisation of ynamide **162** containing a tethered furan to afford the corresponding indolines **163**, and for larger tether lengths, tetrahydroquinolines (Scheme 1.44).[80]



Scheme 1.44 – Gold-Catalysed Cycloisomerisation of Ynamido-Furans

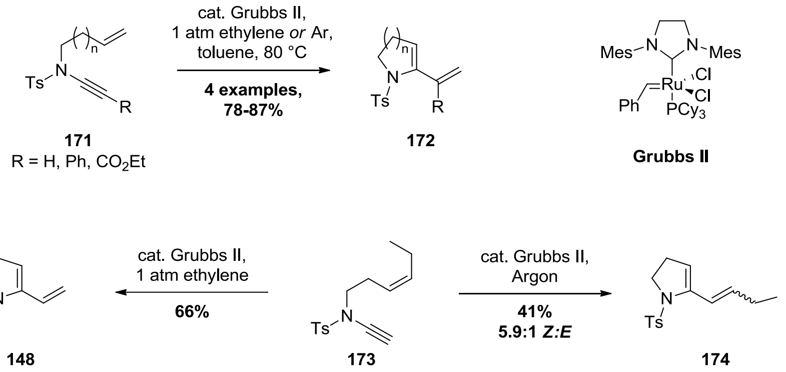
Cossy *et al.* has also demonstrated the ability of AuCl to catalyse the cycloisomerisation of enynamides **167** and **169** to the corresponding cyclobutanones **168** and azabicycles **170** in a highly diastereoselective manner (Scheme 1.45).[81,82]



Scheme 1.45 – Gold-Catalysed Cycloisomerisation of Enynamides

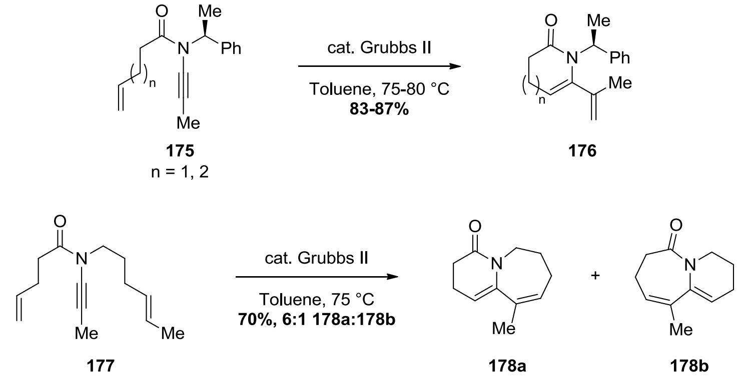
Ring-closing enyne metathesis (RCEM)

The first examples of RCEM with enynamides **171** were reported by Mori in 2002, using Grubbs II catalyst and a terminal ynamide under an atmosphere of ethylene or argon,[83] and was later expanded to incorporate terminally substituted ynamides,[84] to form pyrrolidines or piperidines **172** (Scheme 1.46). These amidodienes were also successfully subjected to Diels-Alder reactions with both DMAD and *N*-phenyl maleimide to afford a range of 1,4-*aza*-dienes.[83] An interesting result was discovered when (*Z*)-enynamide **173** was employed; under an atmosphere of argon the expected product **174** was formed as a mixture of isomers, however, under one atmosphere of ethylene gas amidodiene **148** was formed as a result of ethylene exchange with the ruthenium alkylidene.



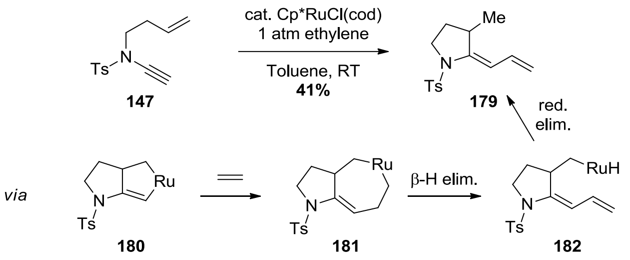
Scheme 1.46 – Mori's RCEM of Enynamides

During the same year as Mori's reported RCEM of enynamides, the Hsung group also demonstrated the ease with which enynamides **175** underwent cyclisation to the cyclic amidodienes **176** (Scheme 1.47).[10] They then demonstrated a tandem RCEM process on diene-ynamide **177** to form the bicyclic lactams **178a** and **178b** in a 6:1 ratio, which was dependent on which alkene underwent the initial cross-metathesis.



Scheme 1.47 – Hsung's RCEM of Enynamides

Finally, the Mori group also found that by using an alternative ruthenium catalyst, the same enynamide **147** as was used in the Grubbs II catalysed RCEM (Scheme 1.46) could be converted to diene **179** *via* ethylene insertion into the ruthenacyclopentene **180** (Scheme 1.48)[85]



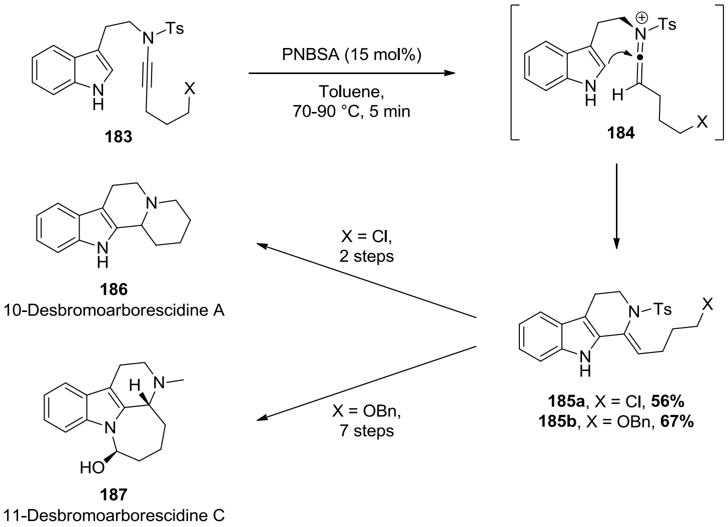
Scheme 1.48 –RCEM of Enynamides to form Alternative Amidodienes

1.3.4. Ynamides in Natural Product Synthesis

There have only been a few reports of the use of ynamides in natural product syntheses, but with the cyclisations of ynamides being able to provide rapid and efficient access to heterocyclic systems as demonstrated, the application of ynamides in synthesis is appealing.

10-Desbromoarborescidine A and 11-Desbromoarborescidine C

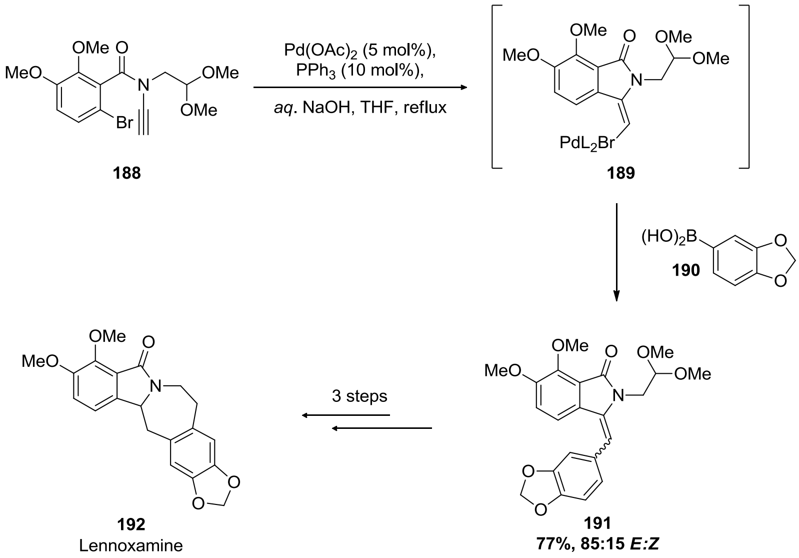
The first example of the use of an ynamide in a natural product synthesis was reported by the Hsung group in 2005. By employing the Brønsted acid-catalysed Pictet Spengler cyclisation of ynamide **183** containing a tethered indole, cyclisation *via* the keteniminium intermediate **184** to the desbromoarborescidine frameworks **185a** and **185b** could be achieved (Scheme 1.49).[78]



Scheme 1.49 – Total Synthesis of Desbromoarborescidines

Lennoxamine

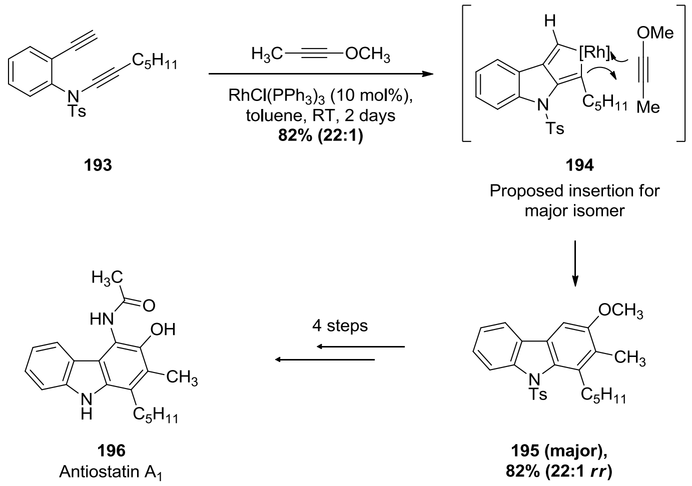
In 2006, Cossy and Meyer published an impressive domino reaction incorporating a carbopalladation of terminal ynamide **188** to form the vinyl palladium(II) intermediate **189**, which could then undergo a subsequent Suzuki-Miyaura coupling with aryl boronic acid **190** to afford the key precursor **191** to the natural product lennoxamine in a good yield and moderate *E/Z* selectivity (Scheme 1.50).[86,87]



Scheme 1.50 – Total Synthesis of Lennoxamine

Antiostatin A$_1$

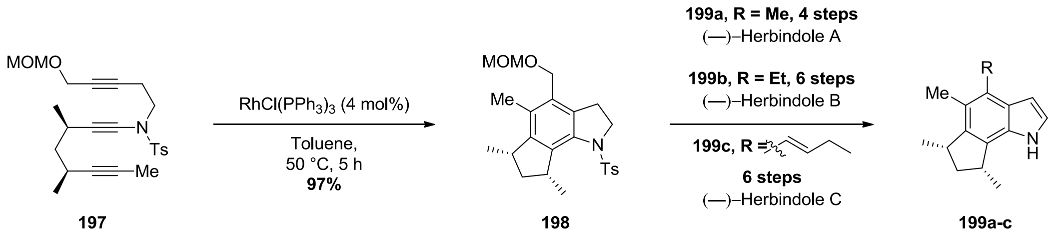
More recently, Witulski *et al.* employed a chemo- and regioselective rhodium-catalysed intermolecular cyclotrimerisation of yne-ynamide **193** with an ynol ether, with the reaction proceeding through intermediate **194** to form the antiostatin framework **195** (Scheme 1.51).[65]



Scheme 1.51 – Total Synthesis of Antiostatin A$_1$

(−)-Herbindoles A, B and C

Finally, Sato *et al.* reported an elegant synthesis of (−)-herbindoles A, B and C *via* a rhodium-catalysed intramolecular [2+2+2] cycloaddition of ynamide **197** containing two alkynes (Scheme 1.52).[88] Not only did this route form all three rings of the herbindole scaffold in a single step in an excellent yield, the indole product **198** could then be derivatised to all three natural products.



Scheme 1.52 – Total Synthesis of (−)-Herbindoles A, B and C

1.4. Conclusions

Based on the recent developments of efficient preparations of ynamides, their polarisation inducing regioselective reactions, their stability to storage and handling and the ability to rapidly form a range of carbo- and heterocyclic frameworks, the field of ynamide cyclisations has rapidly expanded over the last decade. However, there are still a large range of areas that have either not been investigated or have limited examples including the concept of ynamide carbopalladation.

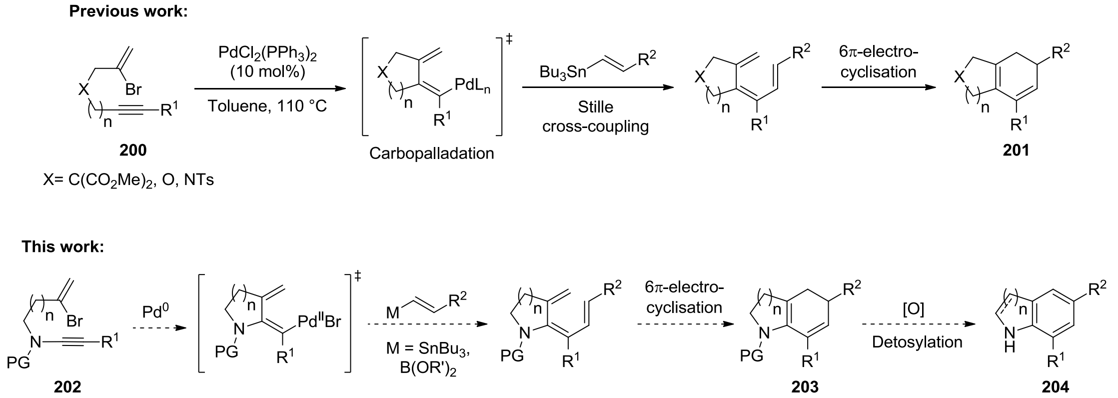
This thesis incorporates the investigations of ynamide carbopalladation in cascade and tandem processes terminating in three different pathways. The first incorporates a Stille or Suzuki coupling with subsequent electrocyclisation to afford a range of *aza*-bicycles (Chapter 2). Furthermore, these bicycles can be selectively oxidised to the synthetically useful indolines and indoles. During the investigations of the Suzuki coupling, a reductive cyclisation was discovered which could be exploited to afford a range of exocyclic amidodienes, and could be subjected to further cycloadditions and oxidation to afford a complementary range of heteroaromatics (Chapter 3). Finally, instead of terminating with a cross-coupling or a reductive process, a fully intramolecular system was developed incorporating further carbopalladations, and its application toward the synthesis of the trikentrin family of natural products was investigated (Chapter 5).

2. Palladium-Catalysed Cascade Cyclisation

2.1. Introduction

2.1.1 Overview

Previous work reported by both the Anderson group,[89,90] and Suffert *et al.*,[91-93] has focused on palladium-mediated cascade cyclisations of bromoenynes **200**, involving a carbopalladation / cross-coupling / electrocyclisation process, giving rise to bicyclic systems of type **201** (Scheme 2.1). Following on from this work, it was envisaged that modification of the alkyne portion of the bromoenyne **200** to a bromoenynamide **202** could lead to significantly more valuable azabicycles **203**, synthetically useful building blocks that could serve as precursors to a wide range of nitrogen-containing heteroaromatics **204**.

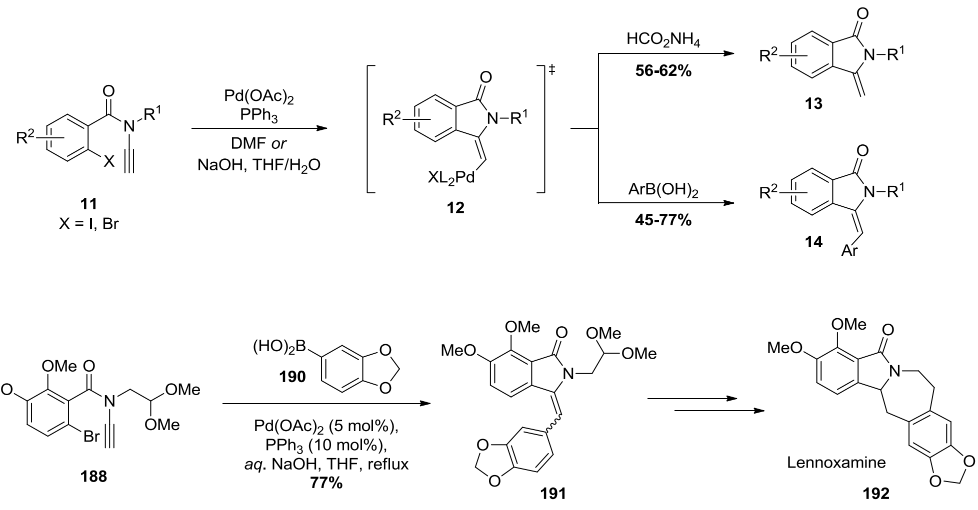


Scheme 2.1 – Bromoenyne and Proposed Bromoenynamide Cascade

Nitrogen-containing heterocycles are among the most important motifs in organic chemistry, with the indole architecture being particularly prevalent, appearing in many natural products and pharmaceuticals. Whilst there are many routes to access these structures, from traditional to the more recent transition metal-catalysed routes,[94-97] such syntheses usually require a pre-functionalised benzene ring onto which the heterocycle is annulated.[98,99] Consequently, these strategies can suffer from a lack of late-stage structural diversity with regard to the benzenoid portion of the heterocycle. One advantage of our envisaged cascade approach is that it would allow formation of both rings of the heterocycle in a single step, enabling greater structural diversity with regards to substitution patterns. It also has the added advantage of allowing access to a wide range of heteroaromatics by varying the substrate tether lengths and ring oxidation states, giving access to not only indoles but also indolines, quinolines and benzazepines (**204**, *n* = 1-3).

2.1.2 Precedent

The area of ynamide carbopalladation was relatively under investigated with, to the best of our knowledge, only a single study by Cossy *et al.* having been reported at the onset of this work.[25] This involved the intramolecular carbopalladation of a terminal ynamide **11** with a tethered aryl halide, and subsequent reaction of the vinyl palladium intermediate **12** in either a reduction with ammonium formate or a Suzuki-Miyaura coupling with an aryl boronic acid (Scheme 2.2).

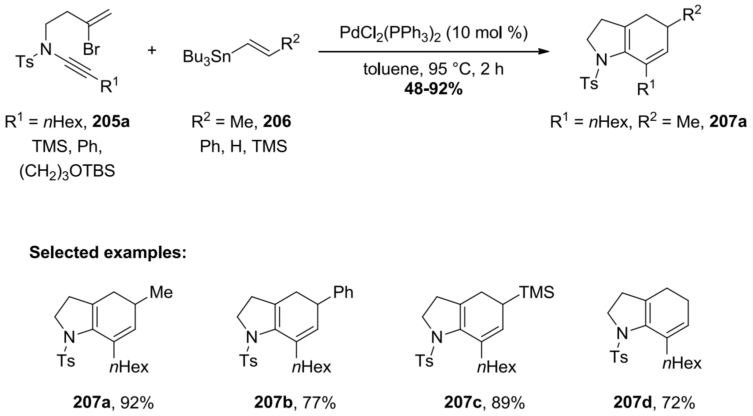


Scheme 2.2 – Cossy *et al.*'s Ynamide Carbopalladation/Suzuki Coupling Sequence[25,86]

Whilst this example represents an elegant domino reaction towards the heteroaromatic isoindoline system, especially when applied in the total synthesis of the natural product lennoxamine **192** (Scheme 2.2),[86] it is worth noting that this strategy still involved annulation of a pre-existing benzene ring, and is therefore of some difference to our own plans.

2.1.3. Preliminary Studies

Preliminary investigations by Oliver Holton, a Part II student, on the proposed cascade cyclisation[100] were conducted with bromoenynamide **205a** (R^1 = *n*Hex) and stannane **206** (R^2 = Me), screening several palladium-catalysts ($Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$). Of these, the previously reported conditions used in the bromoenyne cascade (10 mol% $PdCl_2(PPh_3)_2$, toluene) proved to be superior, giving the electrocyclised product **207a** in a 92% yield when heated at 95 °C for 2 hours (Scheme 2.3). The optimised conditions were then applied to a variety of ynamides and stannanes, which demonstrated that alkyl, aryl and silyl substituents were all tolerated at the ynamide terminus and on the vinyl stannane, affording the corresponding dienamides in reasonable to high yields (48-92%).



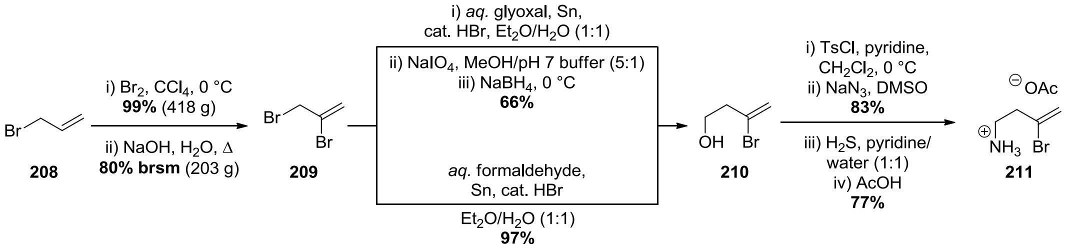
Scheme 2.3 – Preliminary Stille Cascade Cyclisation Results[100]

Building on the success of these preliminary results, the primary aims of our research were threefold: firstly, since sulfonamide groups often require harsh deprotection conditions, such as concentrated acid or strong reducing agents,[101] we sought to investigate ynamide formation with a range of alternative, more labile, protecting groups. Secondly, with an optimal protecting group in hand, the methodology could be further optimised and applied to a wider substrate set. Finally, whilst it is clear that the proposed carbopalladation/Stille coupling/electrocyclisation cascade is highly efficient, it does require the use of toxic organotin reagents. Therefore, inspired by the previously mentioned work of Cossy *et al.*, our aim was to expand the methodology to utilise non-toxic alkenyl boron derivatives in a Suzuki coupling as an alternative to the Stille coupling.

2.2. Carbopalladation/Stille/Electrocyclisation Cascade

2.2.1. Effect of varying the nitrogen EWG on ynamide formation

In order to enable the investigation of the use of an alternative electron-withdrawing substituent to the tosyl group used in the preliminary studies, we first needed to prepare the parent unsubstituted amine **211** (Scheme 2.4).

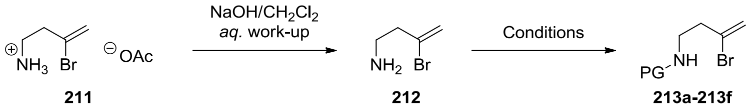


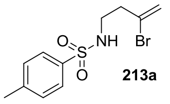
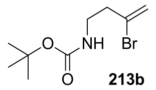
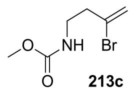
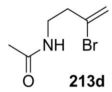
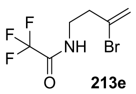
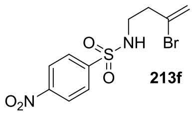
Scheme 2.4 – Synthesis of Parent Unsubstituted Amine

A robust synthetic route was utilised on a multi-hundred gram scale which began with the bromination of allyl bromide **208**[102] and subsequent elimination of 1,2,3-tribromopropane to yield 2,3-dibromopropene **209.**[103] Although **209** is commercially available, it is usually purchased in a rather impure form and is expensive. Initially, in the preparation of alcohol **210**, a double Barbier allylation was utilised between aqueous glyoxal and 2,3-dibromopropene **209** using the procedure of Otera,[104] which afforded an inconsequential mixture of diastereomeric diols in quantitative yield. Oxidative cleavage of this diol with periodate followed by *in situ* reduction of the intermediate aldehyde provided alcohol **210**. Unfortunately, due to the surprising thermal instability of alcohol **210**, satisfactory purification required a rapid distillation which often led to a significant loss in product. A superior method for the preparation of **210** involved direct bromoallylation of aqueous formaldehyde, from which **210** was obtained in quantitative yield and in sufficient purity to be employed directly in subsequent reactions without the need for distillation.

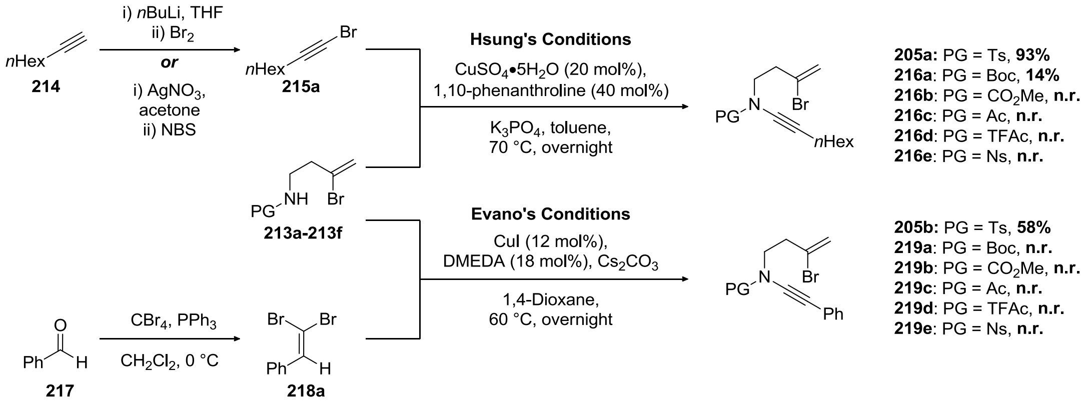
Conversion of alcohol **210** to the amine **211** had previously been achieved in the group according to conditions described by Padwa *et al.*,[105] which entailed alcohol tosylation, azide displacement and a Staudinger reduction with triphenylphosphine to form the amine. However, this route proved problematic on scale-up due to the difficulty in removing the triphenylphosphine oxide by-product, which led to low mass recovery of the desired amine. Consequently, a more effective synthesis was achieved *via* alcohol tosylation, azide displacement and reduction using H_2S (Scheme 2.4), with the amine being conveniently stored as the acetate salt **211**.[106] This ammonium salt **211** could be readily converted to the free amine **212** *via* a basic aqueous work-up directly before being converted to the tosyl, Boc, methoxycarbonyl, acetyl, trifluoroacetyl and nosyl derivatives **213a-213f** (Table 2.1).

Table 2.1 – Varying the EWG on the Nitrogen



	Conditions		Yield
1	TsCl, NEt_3, CH_2Cl_2	 **213a**	89%
2	Boc_2O, NEt_3, DMAP, THF	 **213b**	63%
3	$ClCO_2Me$, pyridine, CH_2Cl_2	 **213c**	51%
4	AcCl, pyridine, Et_2O	 **213d**	70%
5	TFAA, pyridine, CH_2Cl_2	 **213e**	59%
6	NsCl, NEt_3, CH_2Cl_2	 **213f**	39%

With a range of bromoenamides in hand containing a selection of electron-withdrawing groups on the nitrogen, their conversion to bromoenynamides could be investigated. Initially Hsung's efficient copper-catalysed conditions for the coupling of amides with bromoalkynes was utilised, as this method has been shown to tolerate a vinyl bromide.[15,16] The bromoalkynes themselves were simply generated through either lithiation/bromine quench, or by using NBS and catalytic silver(I) nitrate, from commercially available terminal alkynes (Scheme 2.5). Whilst sulfonamide **213a** underwent coupling with bromooct-1-yne **215a** to afford ynamide **205a** (with the vinyl bromide functionality still intact) in an impressive 93% yield, no other amide derivative permitted coupling, with only starting material being recovered. The only exception was carbamate **213b** which yielded 14% of what was tentatively assigned as ynamide **216a** by ^{1}H NMR spectroscopic analysis. However, attempts to improve this coupling did not lead to any greater yield.



Scheme 2.5 – Ynamide Formation Varying the Nitrogen EWG

Evano's copper-catalysed ynamide formation was then evaluated. This involves the coupling of amides with 1,1-dibromoalkenes, which may be generated through the reaction of carbon tetrabromide and triphenylphosphine with commercially available aldehydes.[19] Again, whilst sulfonamide **213a** underwent coupling with dibromoalkene **218a** in reasonable yield to afford ynamide **205b**, no other protecting group was tolerated.

A survey of the literature confirmed there is little diversity in which protecting groups are used in such ynamide formations, with the majority of methods utilising a tosyl or oxazolidinone group, and our findings coincide with this.[1,2] Interestingly, there is evidence that the use of a nosyl protecting group has allowed ynamide formation when employing copper catalysis, but unfortunately our attempts with **213f** yielded no product.[18] Due to the inability to form our desired ynamides with an alternative protecting group, it was decided that sulfonamide **213a** would continue to be used in the cascade cyclisations, with the hope that on accessing heteroaromatic systems, detosylation conditions would meet with success.

2.2.2. Cascade Optimisation

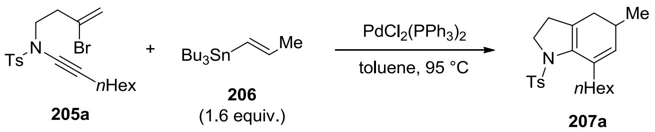
With bromoenynamide **205a** in hand, we began our investigations by attempting to reproduce the cascade cyclisation using the same reaction conditions as employed by Holton with vinyl stannane **206** (Table 2.2, entry 1).[100] This proved more challenging than expected with the reaction not proceeding as cleanly as had previously been observed, with an inferior isolated yield (entry 2).

Initially, comparison of the crude ^{1}H NMR spectra to that of the purified dienamide **207a** showed that decomposition was occurring on the silica gel. In order to combat this decomposition a variety of purification techniques were attempted including the addition of triethylamine to the eluent system, and the use of alumina, which whilst avoiding decomposition gave poor separation of the residual stannane and product. Eventually, it was found that by using an alternative brand of silica gel (Merck Kieselgel 60), the decomposition could be avoided. Unfortunately, whilst the decomposition issues were solved, the unknown impurities which had been present in the crude ^{1}H NMR spectra remained inseparable from the product.

A number of investigations were then attempted in order to identify the cause of these unknown impurities, beginning with the effect of reaction concentration. After both decreasing (entry 3) and increasing (entry 4) the reaction concentration compared to that used in the preliminary investigations, it was discovered that this did not play an important role in governing the amount of impurities formed. This result was promising as we might have expected an increase in the amount of the “direct” (non-carbopalladated) Stille coupled product on increasing the concentration.

The next variable to be investigated was the use of the additive triethylamine, given that the dienamide product **207a** appeared to be acid sensitive (entry 5). However, even with this present the reaction proceeded with the same impurities being formed in similar ratios with a reduced isolated yield, ruling out decomposition of the product in the reaction mixture caused by the presence of trace amounts of acid.

Table 2.2 – Optimisation of carbopalladation/Stille coupling/electrocyclisation cascade



	Catalyst Loading/mol%	Solvent	Concentration	Time/h	Yield[a]
1	10	Anhydrous toluene	16.7 mL.mmol^{-1}	18	92%
2	10	Anhydrous toluene	16.7 mL.mmol^{-1}	4	72%[b]
3	10	Anhydrous toluene	83 mL.mmol^{-1}	1	n.d.[c]
4	10	Anhydrous toluene	8 mL.mmol^{-1}	1	n.d.[c]
5	10	Anhydrous toluene + NEt_3	16.7 mL.mmol^{-1}	2	30[b]
6	10	‘Bottle’ toluene	16.7 mL.mmol^{-1}	0.5	53[b]
7[d]	10	Anhydrous d_8-toluene	16.7 mL.mmol^{-1}	2	83%
8	10	Anhydrous toluene	16.7 mL.mmol^{-1}	4	86%
9	1	Anhydrous toluene	16.7 mL.mmol^{-1}	4	70%
10	1	Anhydrous toluene	16.7 mL.mmol^{-1}	8	78%
11	1	Anhydrous toluene	16.7 mL.mmol^{-1}	18	90%

[a] Isolated yield [b] Contains product and unknown impurities; [c] Isolated yield not determined due to impurities in crude ^{1}H NMR spectra; [d] Conducted as a VT NMR experiment at 90 °C

The requirement for anhydrous and anaerobic conditions in the reaction was then investigated. The use of ‘wet’ bottle toluene in the cyclisation in place of distilled toluene again gave the same impurities but in no greater amount (entry 6). Finally, we conducted the reaction under strictly inert, anhydrous conditions, using anhydrous degassed toluene, oven-dried glassware, and a fresh batch of catalyst pre-weighed in the glovebox. We first opted to conduct this as a VT NMR experiment in d_8-toluene to enable us to monitor the reaction and the formation of any side-products (see Figure 2.1 in **2.2.3.**). To our delight the reaction proceeded cleanly when heated to 90 °C for 2 hours with no impurities being formed and the product isolated in a pleasing 83% yield (entry 7). Pleasingly, when the reaction was then repeated within the lab, and not as a VT NMR experiment, we found the cyclisation to now be reproducible with the product being isolated in an 86% yield (entry 8). With a renewed confidence in the cascade cyclisation we found that it was possible to reduce the catalyst loading from 10 mol% to 1 mol% with no loss in yield, albeit with longer reaction times (entries 9-11).

2.2.3. Mechanistic Considerations

Whilst conducting the VT NMR experiment it was found that the reaction proceeded in d_8-toluene at a probe temperature of 90 °C with the formation of several new peaks visible after 10 minutes (* = 6.63 (1H, d, *J* = 15.5 Hz), 5.30 (1H, s), 4.70 (1H, s), 3.39 (2H, t, *J* = 15.5 Hz), 3.04 ppm (2H, t, *J* = 15.5 Hz)). These peaks were even more prominent at 20 minutes, with product formation now visible (♦ = 5.39 ppm (1H, s)), which gradually increased in intensity over the 120 minute reaction time (Figure 2.1) until all starting material and intermediate had been consumed.

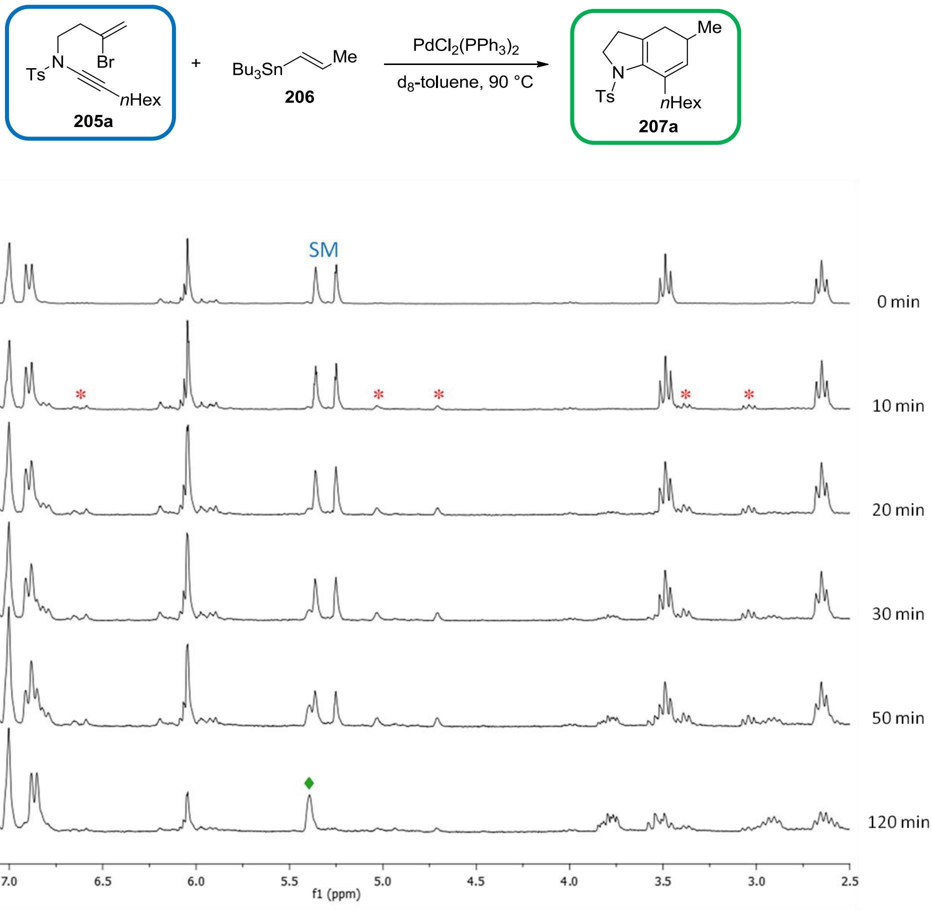
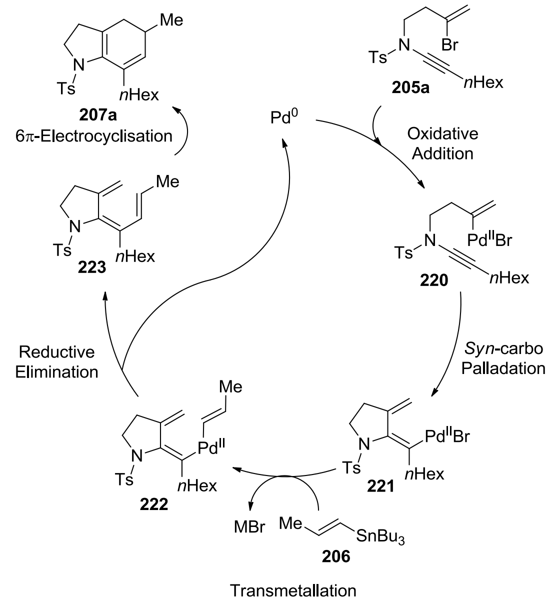


Figure 2.1 – Stacked ^{1}H NMR Spectra Showing Reaction Progress

With the formation of what appeared to be an intermediate visible at a maximum between 10-20 minutes we sought to determine its identity. If the proposed catalytic cycle is considered (Scheme 2.6), ynamide **205a** could undergo oxidative addition followed by a *syn*-carbopalladation to access the dienylpalladium(II) intermediate **221**. This can then undergo transmetallation with the stannane coupling partner with subsequent reductive elimination to afford triene **223**, which after undergoing thermal electrocyclisation would afford the desired bicyclic systems. Taking into account the number of alkene signals visible it seemed unlikely that the intermediate would be **221**, but instead could be the triene **223**.



Scheme 2.6 – Proposed Stille Cascade Catalytic Cycle

To allow us to identify this intermediate the reaction was stopped after approximately 10 minutes and cooled to room temperature. After careful column chromatography, we managed to isolate the intermediate as the predominant component of a mixture, confirming it was indeed the triene **223**. Whilst the isolated material was a mixture of the intermediate **223**, ynamide **205a**, hydrolysed ynamide and product **207a**, irradiation of the key resonances was possible, allowing us to determine the geometry of the triene by ^{1}H NMR spectroscopic nOe studies. Clear mutual enhancements were seen between the exocyclic methylene (H_C) and the alkene peak (H_A), confirming that the intermediate was the *syn*-triene **223** (Figure 2.2).

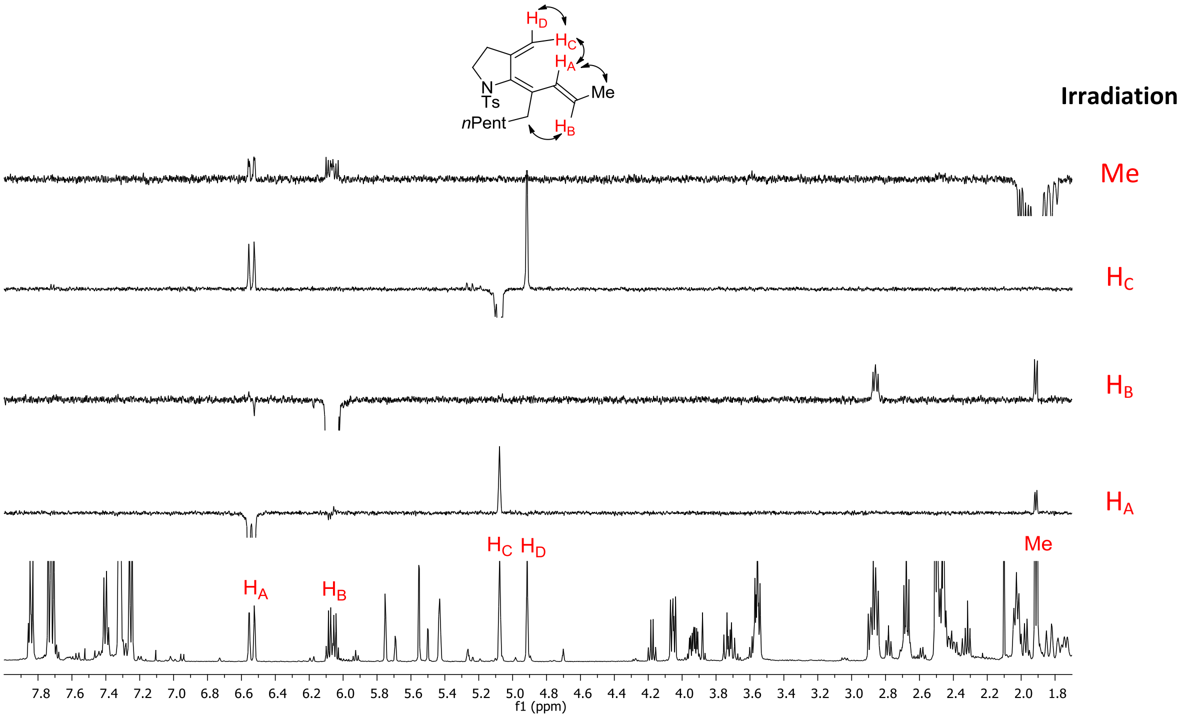


Figure 2.2 – Confirmation of Triene Geometry by nOe Analysis

With the VT NMR experiment and the isolation and identification of *syn*-triene **223** proving successful, another experiment was conducted measuring the ratio of starting material, intermediate and product based on the relative concentrations of the three components compared to the starting ynamide concentration. A graph showing the reaction profile is depicted in Figure 2.3, which clearly reveals the build-up of the *syn*-triene **223** to a maximum concentration between 6-15 minutes. This triene appears to maintain a steady state before it is slowly consumed at later reaction times. Interestingly, there is a lag time in product formation for approximately the first 10 minutes providing support that *syn*-triene **223** is a genuine reaction intermediate.

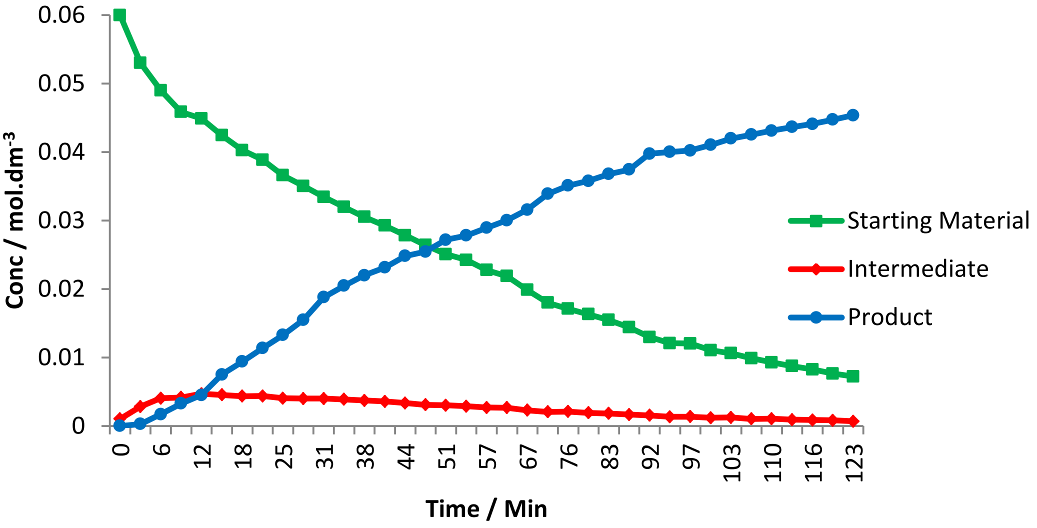


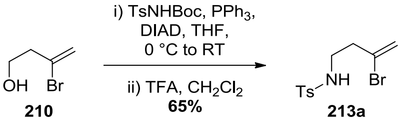
Figure 2.3 – Stille Cascade Reaction Profile

Interestingly, subjecting the *syn*-triene to the thermal cyclisation conditions (d_8-toluene, 90 °C, 10 min), in the absence of the palladium catalyst, led to complete conversion to the bicyclic diene product **207a** suggesting that the electrocyclisation step of the cascade is not reliant on the catalyst, although from these experiments we cannot rule out that the electrocyclisation could be accelerated in the presence of the catalyst.

Whilst the identification of the *syn*-triene **223** is not unexpected based on our proposed mechanism, as far as we are aware this is the first time that this intermediate has been identified in a carbopalladation/cross-coupling/electrocyclisation cascade. Previously, when bromoenynes were used in a similar cascade process in the Anderson group, the *Z*-triene was observed sometimes in quite substantial amounts, although it is worth noting that while the *anti*-triene was observed, it is likely that the pathway does not proceed exclusively *via* this intermediate.[89] With the *anti*-triene often being formed with a bromoenyne containing a silyl-substituent on the alkyne terminus, a VT NMR experiment was conducted using a TMS-substituted bromoenynamide in an attempt to see if increased steric bulk or electronic effects of the silicon would also favour the *anti*-triene. However, during this experiment no intermediate was observed, implying that silyl-substituted ynamides undergo a much more rapid electrocyclisation compared to the *n*hexyl-substituted ynamide **205a**. This implies that the reaction pathway indeed does still proceed *via* the *syn*-triene, as it might be predicted that if *anti*-triene were formed the length of reaction would be increased due to the need for a second isomerisation to occur to set up the electrocyclisation process.

2.2.4. Bromoenynamide Synthesis

Having established a suitable electron withdrawing group on the nitrogen, and an optimised set of cyclisation conditions, we turned our attention to the synthesis of a range of bromoenynamides in order to conduct a substrate screen. Whilst we had obtained sulfonamide **213a** (for ynamide formation) in four steps from alcohol **210** *via* tosylate formation, azide displacement, reduction and subsequent tosyl protection in an overall 56% yield, it required the use of the undesirable reagents sodium azide and hydrogen sulfide gas. Consequently, a more efficient and scalable route was employed involving a Mitsunobu coupling between alcohol **210** and BocNHTs to install the requisite nitrogen atom, with Boc deprotection yielding the desired sulfonamide **213a** in an improved 65% yield in only two steps (Scheme 2.7).[107]

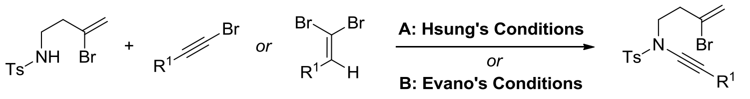


Scheme 2.7 – ‘Parent’ Sulfonamide Formation *via* Mitsunobu Coupling

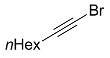
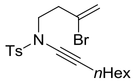
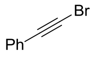
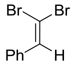
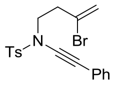
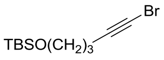
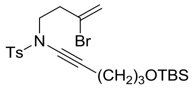
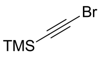
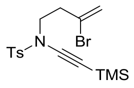
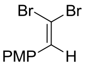
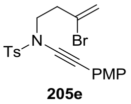
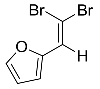
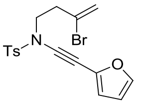
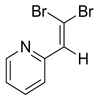
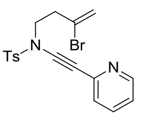
With a facile route to sulfonamide **213a** in hand we first aimed to vary the substituents on the ynamide terminus. Therefore, sulfonamide **213a** was submitted to a range of ynamide formations (Table 2.3) using both Hsung’s[16] ($CuSO_4{\bullet}5H_2O$ (20 mol%), 1,10-phenanthroline (40 mol%), K_3PO_4, toluene, 70 °C) and Evano’s copper-catalysed conditions[19] (CuI (12 mol%), DMEDA (18 mol%), Cs_2CO_3, 1,4-dioxane, 60 °C), with the choice of method being mainly dependent on the cost and availability of the corresponding starting aldehyde or alkyne used in the preparation of the coupling partners. Generally, the reactions proceeded cleanly, with alkyl, aryl, silyl and heteroaromatic substituents all being tolerated to afford the desired bromoenynamides in good yield. The exception to this was the TMS-ynamide **205d** (entry 4), where desilylation occurred under the reaction conditions, and the electron-rich PMP-ynamide

205e. It is worth noting that the yield of ynamide formation under both Hsung's and Evano's conditions had a strong dependence on the dryness of the base (K_3PO_4 or Cs_2CO_3), which correlates with the findings of Dooleweerdt *et al.* who reported that ynamides synthesised using Hsung's conditions were obtained in substantially higher yields using pure and anhydrous K_3PO_4 in comparison to hydrated bases (K_3PO_4•$1.5H_2O$ and K_3PO_4•$7H_2O$).[108]

Table 2.3 – Bromoenynamide Formation



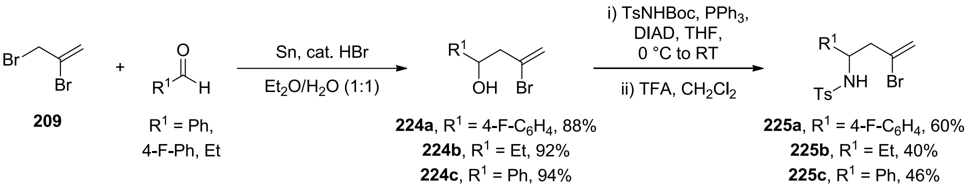
213a 215a-d 218a-d 205a-g

	Coupling Partner	Conditions[a]	Substrate	Yield
1	 215a	A	 205a	93%
2	  215b or 218a	A B	 205b	58% 88%
3	 215c	A	 205c	66%
4	 215d	A	 205d	20%
5	 218b	B	 205e	22%
6	 218c	B	 205f	47%
7	 218d	B	 205g	69%

[a] Conditions A: $CuSO_4$•$5H_2O$ (20 mol%), 1,10-phenanthroline (40 mol%), K_3PO_4, toluene, 70 °C, overnight. Conditions B: CuI (12 mol%), DMEDA (18 mol%), Cs_2CO_3, 1,4-dioxane, 60 °C, overnight

α-Substituted Ynamides

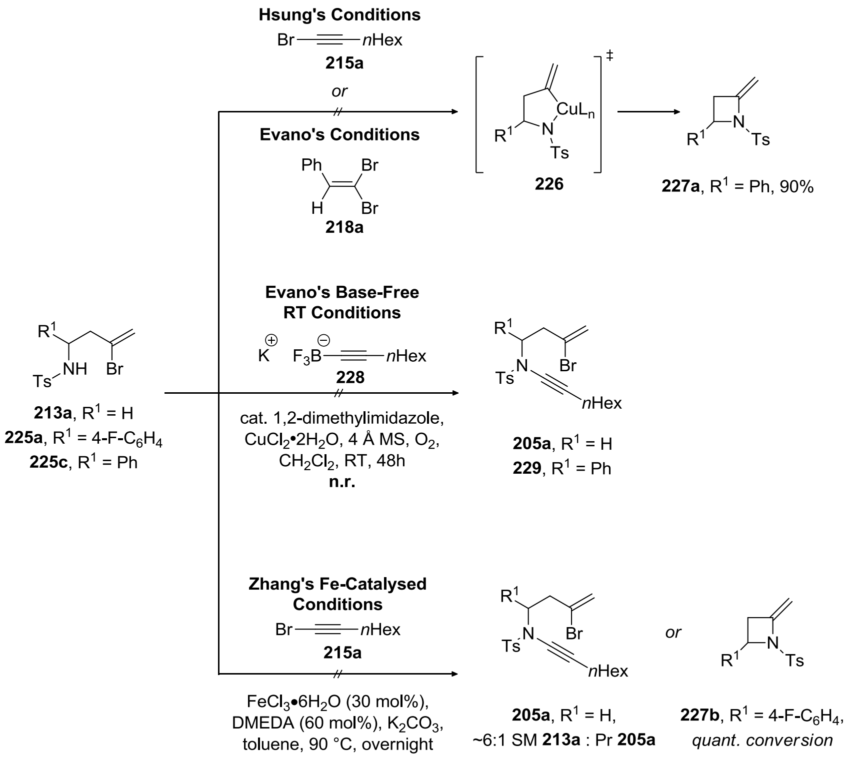
In an effort to introduce greater structural diversity to the final heterocyclic products, it was desirable to demonstrate the synthesis and subsequent cyclisation of bromoenynamides containing substituents along the tether, thereby introducing functionality onto the pyrrole portion of our systems. This was achieved by introducing a substituent adjacent to the nitrogen centre using a Barbier allylation of a range of aldehydes, followed by a Mitsunobu coupling and Boc deprotection (Scheme 2.8), reactions which proceeded in good yields.



Scheme 2.8 – Synthesis of α-Substituted Sulfonamides

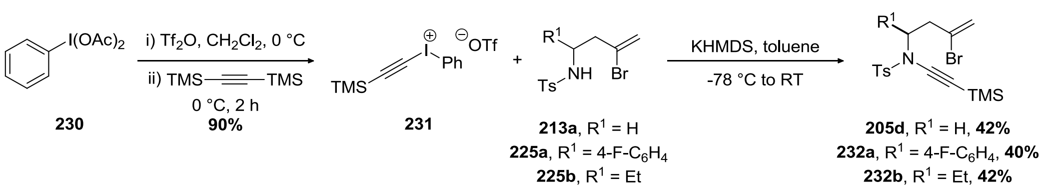
Disappointingly, conversion of these α-substituted sulfonamides **225a-225c** to the corresponding bromoenynamides proved problematic with both of the copper-catalysed conditions used previously, instead favouring intramolecular cyclisation to azetidine **227a** (Scheme 2.9). This result may reflect a slight Thorpe-Ingold effect, or steric hindrance, as similar conditions (CuI, DMEDA, Cs_2CO_3, dioxane) have been shown to cyclise vinyl chloride analogues of **225a-225c** to the corresponding azetidines.[109] making this result somewhat unsurprising in hindsight. Unfortunately, the use of Evano's alternative copper-catalysed, base-free, room temperature coupling of trifluoroborate salt **228** with sulfonamide **225c** (and 'parent' sulfonamide **213a**, which is known to undergo ynamide formation, as a comparison), were also unsuccessful, with no reaction occurring and only the starting sulfonamides being recovered.[20]

In an attempt to avoid the inherent problems of copper-catalysed conditions, Zhang's iron-catalysed coupling of amides with bromoalkynes was investigated (Scheme 2.9),[17] initially with 'parent' sulfonamide **213a**. Whilst **213a** underwent successful ynamide formation using copper-catalysed conditions using bromoalkyne **215a**, the iron-catalysed coupling proved less successful with only partial conversion occurring (**213a:205a** = 6:1). However, whilst full conversion was not possible, the ynamide formation with α-substituted sulfonamide **225a** was still attempted. Interestingly, this also led to quantitative conversion to azetidine **227b**.



Scheme 2.9 – Attempted Syntheses of α-Substituted Bromoenynamides

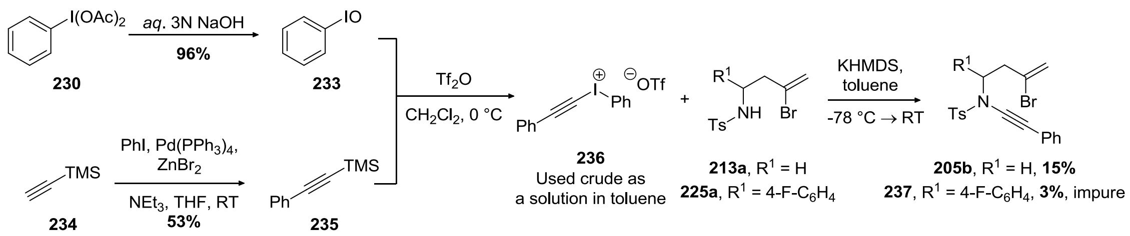
To overcome the failure of these metal-catalysed methods to prepare bromoenynamides from α-substituted sulfonamides, we next examined Witulksi's alkynyliodonium triflate methodology (Scheme 2.10) which had been popular and widely applied in ynamide synthesis prior to the discovery of copper-catalysed alkynylations. This method has the drawback of being predominantly suited only to the synthesis of silyl-substituted ynamides.[11,58] As such iodonium triflate salt **231** was prepared according to literature conditions.[110]



Scheme 2.10 – Witulski's Alkynyliodonium Triflate Methodology

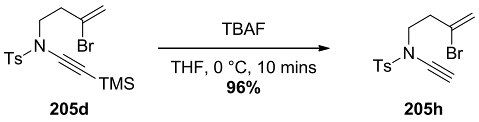
After conducting a brief screen of the most widely used bases (*n*-BuLi, LiHMDS, KHMDS)[1] it was found that in order to avoid bromine-lithium exchange and to obtain a cleaner reaction, the use of KHMDS was most suitable with a reduced temperature of −78 °C instead of the often reported 0 °C. The yields for the formation of the TMS-ynamides **205d** and **232a-b** using this method were reproducible, if moderate and we could now obtain bromoenynamide **205d** in significantly greater yield compared to Hsung's conditions (Table 2.3, entry 4) with no desilylation occurring during the reaction. The isolated yields of α-substituted bromoenynamides **232a** and **232b** were particularly pleasing as the issue of intramolecular cyclisation was avoided. The moderate yields of these reactions are typical of α-branched amides, [11] likely due to the increase in steric hindrance in the nucleophilic addition of the amide to the iodonium triflate salt during *in situ* carbene formation prior to 1,2-migration.

Whilst we were pleased to have obtained silylated α-branched bromoenynamides, it was desirable to have alternative substituents on the ynamide terminus due to the intolerance of silyl-substituted ynamides in later cascade cyclisations. We initially sought to introduce alternative substituents directly through the use of a phenyl-substituted alkynyliodonium triflate salt **236** (Scheme 2.11).[51,63,64] Although the iodonium salt **236** has been previously reported in the literature,[110] it proved difficult to isolate; furthermore, utilising the crude iodonium salt **236** in the ynamide formation with 'parent' sulfonamide **213a** gave bromoenynamide **205b** in only 15% yield. When α-branched sulfonamide **225a** was submitted to the same conditions, even after repeated attempts, the best yield was 3%, with the product still containing impurities.



Scheme 2.11 – Attempted Synthesis of a Phenyl-Substituted α-Branched Ynamide

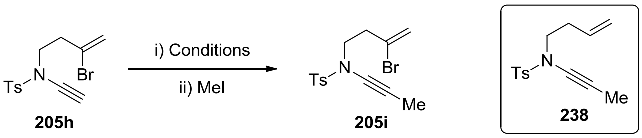
Having failed to introduce an alternative ynamide substituent directly, investigations into desilylation of ynamides **205d** and **232a-b**, and subsequent introduction of alternative functionality, were conducted. Successful desilylation of TMS-ynamide **205d** with TBAF afforded terminal ynamide **205h** (Scheme 2.12) which had a reduced stability towards purification by column chromatography, compared to alkyl- and aryl-substituted ynamides. Therefore this crude reaction mixture was rapidly filtered through a silica plug, concentrated *in vacuo* and used without further purification.



Scheme 2.12 – Ynamide Desilylation

With terminal ynamide **205h** in hand, alkylation was attempted (Table 2.4) following the precedent of Witulski *et al.*, who reported the successful introduction of *n*-butyl and methyl substituents.[51,111]

Table 2.4 – Attempted Alkylation of Terminal Ynamide



	Conditions	Result
1	*n*-BuLi (1.0 equiv.), THF	Eliminated Pr **238**
2	LDA (1.0 equiv.), THF	Only SM recovered **205h**
3	LiHMDS (1.0 equiv.), THF	Only SM recovered **205h**
4	KHMDS (1.0 equiv.), THF	Inseparable mixture ~1:2 Pr **205i**:SM **205h**[a]

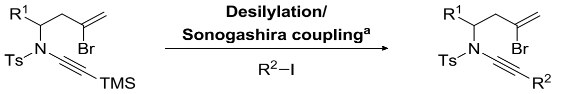
[a] Calculated by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

Unsurprisingly, the use of *n*-BuLi led to bromine-lithium exchange alongside successful reaction with the electrophile methyl iodide (entry 1). Use of alternative bases LDA and

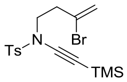
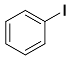
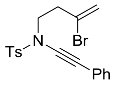
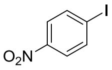
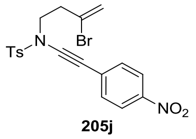
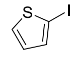
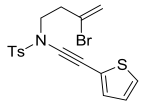
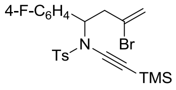
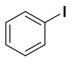
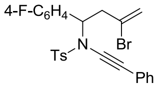
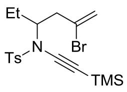
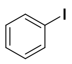
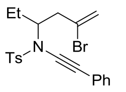
LiHMDS afforded no formation of the desired product **205i** (entries 2-3) and whilst the use of KHMDS did avail desired alkylation, poor conversion was observed and the desired product could not be separated from the starting material (entry 4). It is possible that the failure of these reactions, in particular the failure of LDA and LiHMDS, was due to the small scale on which the reactions were conducted and if any water was present the lithium bases and any anions formed would have been quenched.

Due to the difficulties in introducing functionality *via* alkylation, Hsung's conditions for the Sonogashira coupling of terminal ynamides with aryl iodides were employed on bromoenynamides both with and without an α-substituent (Table 2.5).[7]

Table 2.5 – Sonogashira Coupling of Aryl Iodides with a Terminal Ynamide



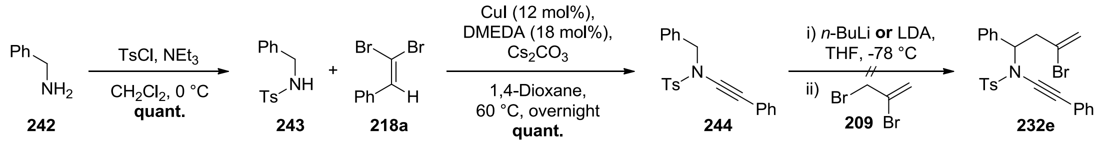
205d, 232a-b → **205b, 205j-k, 232c-d**

	Ynamide	Aryl Iodide	Product	Yield
1	 **205d**	 **239**	 **205b**	17%[b] 50%
2	**205d**	 **240**	 **205j**	52%
3	**205d**	 **241**	 **205k**	28%
4	 **232a**	 **239**	 **232c**	41%
5	 **232b**	 **239**	 **232d**	43%

[a] Conditions: i) TBAF, THF, 0 °C, 10 min, ii) Pd(PPh$_3$)$_4$ (5 mol%), CuI (<1 mol%), toluene, NEt$_3$, 60 °C, 1.5 h; [b] Conducted with CuI (2 mol%) and Pd(PPh$_3$)$_4$ (5 mol%) at RT

As reported, the coupling was highly dependent on the quantity of copper(I) iodide used, with only 17% of bromoenynamide **205ba** isolated using 2 mol% CuI catalyst loading, compared to yields in excess of 50% when <1 mol% CuI was used (entry 1). The significant drop in yield is due to homocoupling of the terminal ynamide as shown by Saá[112,113] (10 mol% CuI, 20 mol% TMEDA, acetone, O_2, RT). Having found reliable conditions for the introduction of functionality onto the ynamide terminus, a range of aryl iodides were coupled with **205b** (entries 2-3), and the α-branched bromoenynamides **232a** and **232b** were coupled with iodobenzene (entries 4-5) to afford the desired products **232c** and **232d**.

In a brief attempt to render the synthesis of α-branched bromoenynamides more efficient, a new three-step route was designed involving the synthesis and α-deprotonation of the literature known ynamide **244**, with subsequent introduction of 2,3-dibromopropene **209** as an electrophile (Scheme 2.13). Whilst the synthesis of ynamide **244** proceeded in quantitative yield, the addition of **209** proved more difficult with only traces of starting material being identified during analysis of the crude ^{1}H NMR spectra after aqueous work-up.



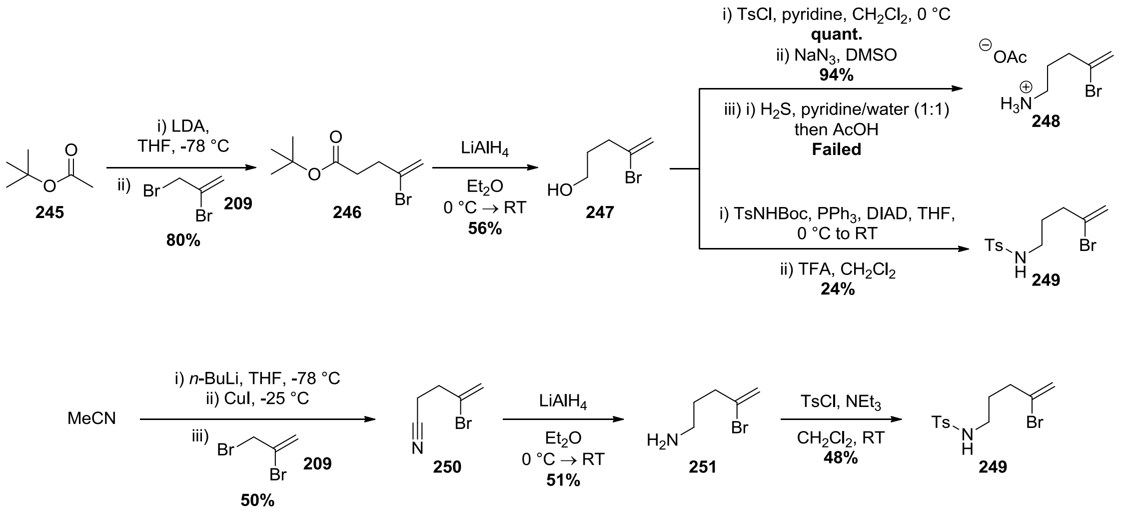
Scheme 2.13 – Alternative Route to α-Substituted Bromoenynamides

Whilst this route would have provided an elegant synthesis of ynamide **232e**, one potential problem in the final step of this scheme could be the elimination of the tosyl group if α-deprotonation occurred to give an ynimine, which would most likely be unstable. Bearing this potential problem in mind and in the interest of time, it was decided that the alkynyliodonium triflate salt/desilylation/Sonogashira route to the same substrates would continue to be utilised, enabling our focus to be shifted onto the synthesis of other bromoenynamides that would expand the substrate set.

Larger Tether Length Ynamides

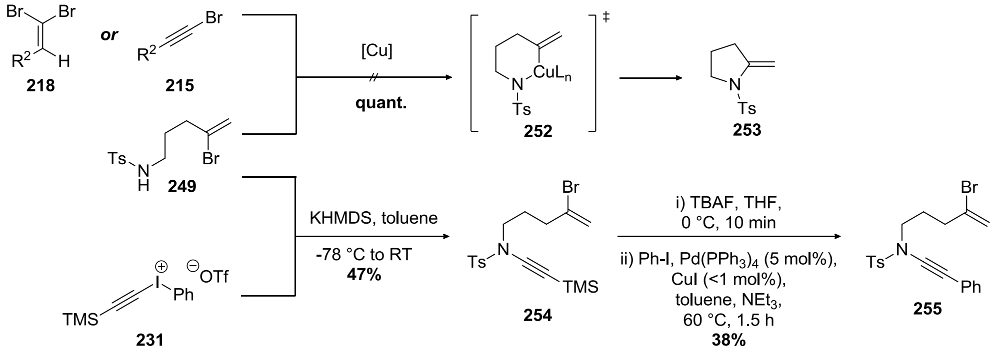
One of the envisioned advantages of our cascade was that we would be able to increase the ynamide tether length to enable access to a range of bicyclic systems. With this in mind we aimed to synthesis bromoenynamides that on submission to the cascade cyclisation would form 6,6- and 7,6-bicyclic ring systems.

Two routes were initially employed (Scheme 2.14), with the first involving enolisation of *tert*-butyl acetate **245** and subsequent reaction with 2,3-dibromopropene **209** to form ester **246**, which could be reduced to alcohol **247**.[114] Conversion of this alcohol to the ammonium salt **248** *via* tosylation/azide displacement, reduction and salt formation was unsuccessful with a complex product mixture being obtained in the final reduction step. A possible explanation for this outcome is the potential 1,3-dipolar cycloaddition reaction of the azide with the vinyl bromide, which could be enabled by the larger tether size. Nevertheless, conversion to sulfonamide **249** by using Mitsunobu coupling/Boc deprotection was successful, albeit in a poor yield of 24%. The second route involved the *in situ* formation and reaction of a cyanomethylcopper species with 2,3-dibromopropene **209**, as reported by Corey and Kuwajima.[115] Subsequent $LiAlH_4$ reduction afforded the free amine **251**, which could then be tosylated to afford **249**.



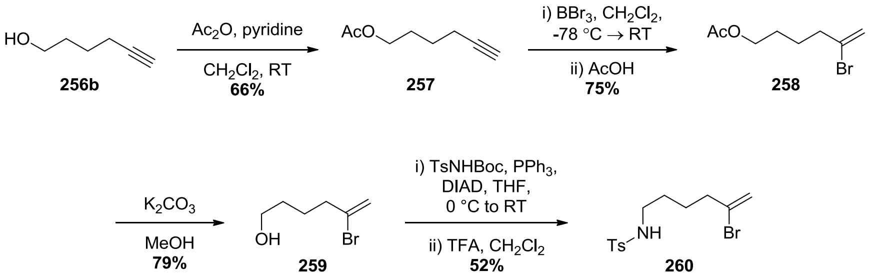
Scheme 2.14 – Synthesis of Larger Tether Length Sulfonamides

After the problems encountered in preparing α-branched bromoenynamides using copper-catalysed conditions, it was not surprising that similar intramolecular cyclisation occurred with sulfonamide **249** *via* putative intermediate **252** to give pyrrolidine **253** (Scheme 2.15). The problem was similarly overcome by employing Witulski's alkynyliodonium triflate salt methodology followed by desilylation and Sonogashira coupling to afford bromonenynamide **255**.



Scheme 2.15 – Larger Tether Length Ynamide Formation

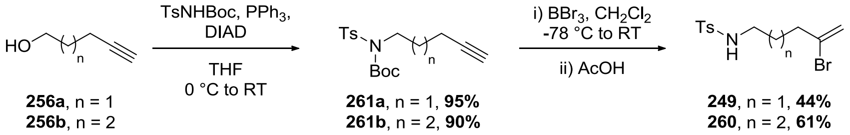
To obtain the homologue of **260** (ie. a precursor to an azepane ring system), alcohol **259** was prepared using a modification of the reported procedure by Trost and Chen.[116] Acetyl protection of alcohol **256b** followed by alkyne bromoboration/protodeborylation introduced the required vinyl bromide functionality as a single regioisomer (Scheme 2.16).[117] Acetate **258** could then be deprotected and submitted to the Mitsunobu coupling/Boc deprotection protocol as previously described.



Scheme 2.16 – Synthesis of Larger Tether Length Sulfonamides

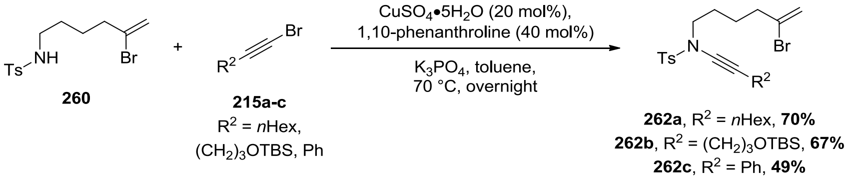
Whilst this method indeed formed sulfonamide **260**, it was realised that the sequence could be shortened by reversing the order of events. By conducting the Mitsunobu coupling on alcohol

256b followed directly by the bromoboration/protodeborylation step, HBr generated in the latter process enabled *in situ* Boc deprotection; as such sulfonamide **260** could be obtained in only 2 steps from a commercially available alcohol (Scheme 2.17). Pleasingly, this route could also be applied to form sulfonamide **249** (n = 1) and if desired could even be utilised for the 'parent' sulfonamide (n = 0).



Scheme 2.17 – Shortened Synthesis of Larger Tether Length Ynamides

Given the behaviour of sulfonamide **249** in ynamide formations, it was surprising to find that Hsung's copper-catalysed conditions were successful in the coupling of homologue **260** with a range of bromoalkynes (Scheme 2.18). No formation of the anticipated piperidine was witnessed, which could possibly be explained by the formation of the required 7-membered intermediate being less favourable compared to the equivalent 5- and 6-membered intermediates.

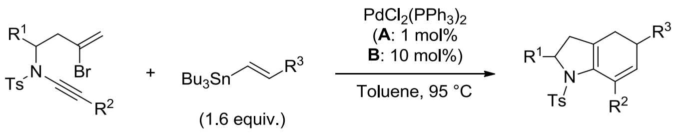


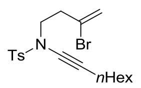
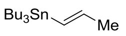
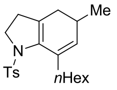
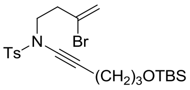
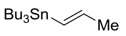
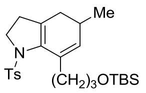
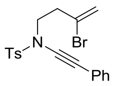
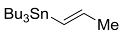
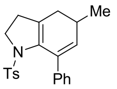
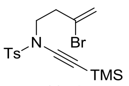
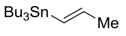
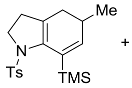
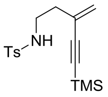
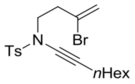
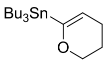
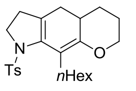
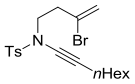
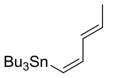
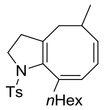
Scheme 2.18 – Larger Tether Length Ynamide Formation

2.2.5 Substrate Screen

With a range of bromoenynamides and optimised cascade cyclisation conditions involving a Stille coupling in hand, we could focus our attention on a substrate screen to study the effects of the substituents on both the ynamide and stannane coupling partner (Table 2.6).

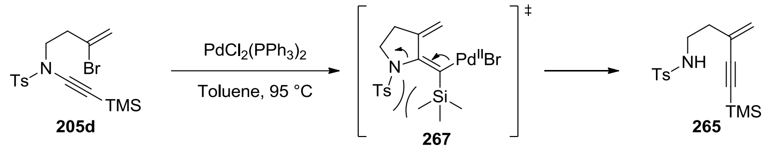
Table 2.6 – Stille Cascade Substrate Screen



	Ynamide	Coupling Partner	Product	Yield
1	 **205a**	 **206**	 **207a**	**A:** 90% **B:** 92%^{b}
2	 **205c**	 **206**	 **207e**	**A:** 76% **B:** 70%^{b}
3	 **205b**	 **206**	 **207f**	**A:** 67% **B:** 48%^{b}
4	 **205d**	 **206**	 +  **207g** **265**	**B:** 66% + 18% **265**
5	 **205a**	 **263**	 **207h**	**B:** 66%
6	 **205a**	 **264**	 **266**	**B:** 68%^{c}

^{a} Isolated yield; ^{b} Isolated yields from preliminary results^{100}; ^{c} Isolated as a 7:1 ratio of **266:269a**

Pleasingly, ynamides with both an alkyl (entries 1-2) and aryl (entry 3) substituent were tolerated with alkenyl stannane **206**, with no loss in yield occurring when the catalyst loading was reduced to 1 mol% compared to the previously used 10 mol%. Whilst a trimethylsilyl group on the ynamide terminus was tolerated under the reaction conditions (entry 4), the side-product **265** was isolated in an 18% yield. This side-product is formed due to *N*- to *C*-alkyne migration and may be explained by the mechanism shown in Scheme 2.19.



Scheme 2.19 – *N*- to *C*-Alkyne Migration

The increased steric bulk of the silyl substituent leads to significant allylic strain in dienylpalladium(II) intermediate **267**, resulting in elimination of palladium and the sulfonamide leaving group before cross-coupling can occur. With a TMS substituent this elimination is competitive with the Stille cross-coupling to give a mixture of products, however it had been previously shown by Holton that when a TIPS group is used this migration is the exclusive product,[100] supporting the belief that increased steric bulk favours this elimination pathway.

During Holton's preliminary investigations a range of stannanes were screened and it was shown that alkyl, aryl and silyl-1,2-substituted *trans* alkenyl stannanes, and terminal alkenyl stannanes, could be successfully employed (**207a-d**, Scheme 2.3 in **2.1.3.**).[100] In an attempt to further expand the scope of the cyclisation dihydropyranyl stannane **263** was utilized, which gave access to the tricyclic 5,6,6-fused ring system **207h** (entry 5). This was a particularly pleasing result given both the steric challenge, and due to the fact that the product contained two activated alkenes in the form of an enamide and an enol ether.

In addition to the 6π-electrocyclisation terminating cascades, we also addressed the corresponding 8π process using dienylstannane **264**.[89,90] Pleasingly, ynamide **205a** successfully underwent cyclisation to the bicyclic 5,8-fused ring system **266** (entry 6) which did not undergo a further 6π-electrocyclisation of the cyclooctatriene. Unfortunately, the reaction was complicated by inseparable impurities and the presence of what appeared to be the exocyclic diene **269a** which was identified during optimization of the Suzuki cascade (see Table 2.7).

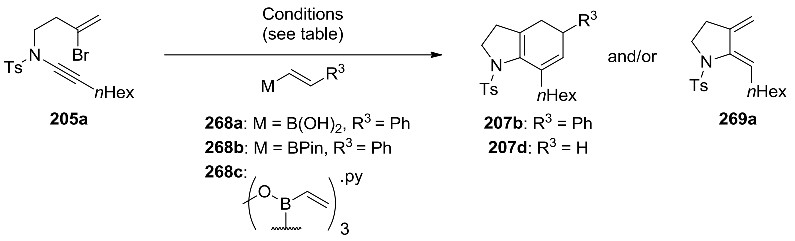
2.3. Carbopalladation/Suzuki/Electrocyclisation Cascade

2.3.1. Cascade Optimisation

Whilst it was clear that the carbopalladation/Stille coupling/electrocyclisation cascade was highly efficient, it did require the use of toxic organotin reagents. We were therefore inclined to move toward a cascade that would allow the incorporation of a vinyl boron derivative in a Suzuki coupling, which in practice proved to be quite challenging.

Since Cossy *et al.* had successfully developed conditions to conduct an intramolecular ynamide carbopalladation terminating in a Suzuki coupling,[25] it seemed logical to initially apply these conditions (5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, THF/H_2O (10:1), *aq.* NaOH, reflux) to our system using bromoenynamide **205a** and alkenyl boronic acid **268a** (Table 2.7, entry 1). Intriguingly, incomplete conversion of the starting material was observed alongside the unexpected formation of exocyclic diene **269a**, which appeared to arise from a reduction of the intermediate dienylpalladium(II) complex. We next tested conditions reported by Oh (10 mol% $Pd(PPh_3)_4$, Cs_2CO_3, anhydrous EtOH, 80 °C) in a related alkyne carbopalladation/Suzuki coupling sequence conducted on bromoenynes with both aryl boronic acids and alkenyl boronic acids (including **268a**). In this reported case, the electrocyclisation process was not seen, possibly due to the reduced reaction temperature.[118] Pleasingly, conversion of the starting material improved but diene **269a** was still formed (entry 2), and when the boronic acid coupling partner was removed, **269a** was actually isolated in an impressive 83% yield (entry 3). At this point we hypothesised that the hydroxylic solvent might be the cause of formation of **269a** *via* a palladium(II) hydride species, and thus carried out a brief screen of anhydrous solvents in the hope that this side reaction could be eradicated. The use of 1,4-dioxane gave a poor yield with, surprisingly, a mixture of both product **207b** and diene **269a** still being formed (entry 4), whilst the use of toluene led to no reaction (entry 5). Eventually, it was found that the use of THF greatly favoured product formation (entry 6), while DME led to exclusive formation of product **207b** (entry 7).

Table 2.7 – Optimisation of carbopalladation/Suzuki coupling/electrocyclisation cascade[a]



	Coupling Partner	Solvent, Time (h)	Pd catalyst (mol%)	Yield	207b:269a
1	**268a**	THF:H_2O (10:1), 5[b]	$Pd(OAc)_2$ (5), PPh_3 (10)	n.d.	1:4:2 **205a:207b:269a**
2	**268a**	EtOH, 18	$Pd(PPh_3)_4$ (10)	n.d.	1:1.2
3	-	EtOH, 2	$Pd(PPh_3)_4$ (10)	83	0:1
4	**268b**	1,4-Dioxane, 18	$Pd(PPh_3)_4$ (5)	24	1:2.5
5	**268b**	Toluene, 5	$Pd(PPh_3)_4$ (5)	n.r.	-
6	**268b**	THF, 18	$Pd(PPh_3)_4$ (5)	80	30:1
7	**268b**	DME, 4	$Pd(PPh_3)_4$ (5)	83	1:0
8	**268b**	DME, 18	$PdCl_2(PPh_3)_2$ (5)	70	10:1
9	**268b**	DME, 18	$PdCl_2$(dppf) (5)	25[c]	1:0
10	**268a**	THF, 18	$Pd(PPh_3)_4$ (5)	67	20:1
11	**268a**	DME, 18	$Pd(PPh_3)_4$ (5)	79	1:0
12	**268c**	THF, 3[d]	$Pd(PPh_3)_4$ (5)	85	1:0

[a] Reactions conducted using **268a** or **268b** (1.5 equiv.) and Cs_2CO_3 (1.5 equiv.) at reflux in degassed, anhydrous solvent; [b] 1 M NaOH used as base; [c] Direct cross-coupling with the vinyl bromide was also observed; [d] **268c** (0.5 equiv.)/H_2O (1.5 equiv.) used

With anhydrous DME being the optimal solvent for selective product formation, a brief screen of palladium catalysts was conducted (entries 7-9), with 5 mol% $Pd(PPh_3)_4$ and Cs_2CO_3 proving to be optimal, the desired product **207b** being isolated in an impressive 83% yield from bromoenynamide **205a** and alkenyl pinacol boronate **268b**. Finally, we investigated how the nature of the alkenylboron species affected the reaction efficiency, with both the boronic acid

268a and boroxin trimer **268c** being tolerated. These formed products **207b** and **207d** respectively, in excellent yields (entries 11-12).

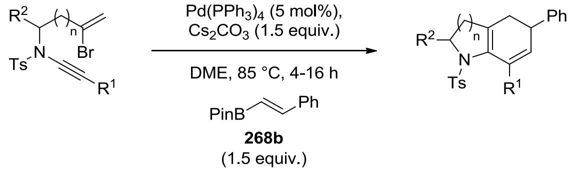
2.3.2. Substrate Screen

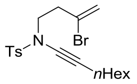
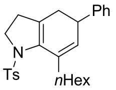
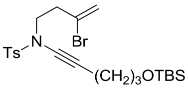
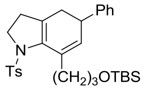
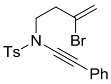
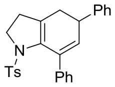
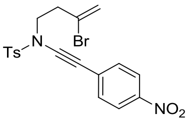
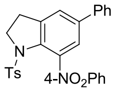
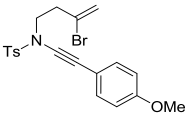
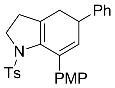
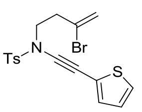
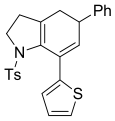
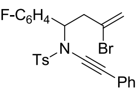
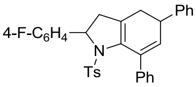
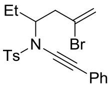
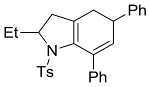
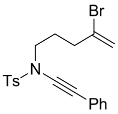
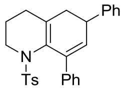
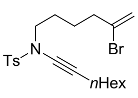
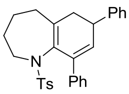
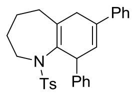
Using the same range of bromoenynamides described in Section **2.2.4.** and the optimised cyclisation conditions (5 mol% $Pd(PPh_3)_4$, Cs_2CO_3, anhydrous DME, reflux), the scope of the reaction was investigated by varying the bromoenynamide (Table 2.8), and then by varying the coupling partner (Table 2.9).

First, the effect of varying the substituent on the ynamide terminus was examined using coupling partner **268b**, with both alkyl and aryl functionality being tolerated to form bicyclic 5,6-fused ring systems (Table 2.8, entries 1-3). The use of the electron-deficient ynamide **205j** proved successful in the cyclisation but afforded indoline **207k**, presumably due to *in situ* aerobic oxidation of the 1,3-diene (entry 4), whilst the use of electron-rich ynamides **205e** and **205k** was significantly less effective with poor yields and inseparable impurities being present in the reaction mixture (entries 5-6). The cascade cyclisation of the α-branched ynamides **232c** and **232d** to the trisubstituted 5,6-bicyclic systems **207n** and **207o** proceeded in good yield with moderate diastereoselectivity (entries 7-8), reflecting a degree of substrate control in the electrocyclisation from the conformation-controlling effects of the tosyl group, phenyl, and α-substituent.

Both the 6,6- and 7.6-fused systems were also successfully accessed from cyclisation of the larger tether length ynamides **255** and **262a** (entries 9-10), however the latter was isolated as a mixture of both the 1,3- and 1,4-diene isomers as shown (see later discussion).

Table 2.8 – Substrate Scope: Varying the Ynamide



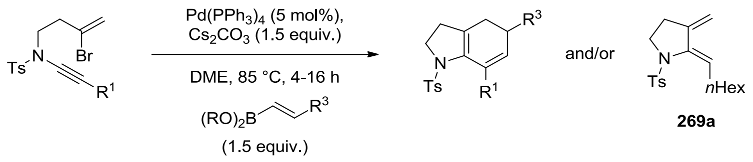
	Ynamide	Product	Yield[a] (dr)[b]
1	 **205a**	 **207b**	83%
2	 **205c**	 **207i**	55%
3	 **205b**	 **207j**	69%
4	 **205j**	 **207k**	61%
5	 **205e**	 **207l**	<37% Impure
6	 **205k**	 **207m**	<23% Impure
7	 **232c**	 **207n**	77% (*dr* 3:1)
8	 **232d**	 **207o**	68% (*dr* 1.4:1)
9	 **255**	 **270**	61%
10	 **262a**	 **271** +  ***iso*-271**	74%[c]

[a] Isolated yield; [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction; [c] Isolated as a 1.3:1 mixture of 1,3- and 1,4-diene isomers

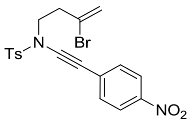
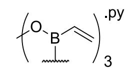
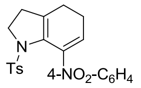
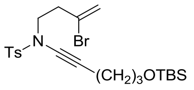
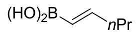
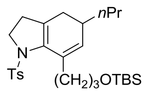
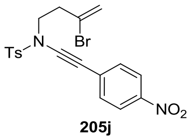
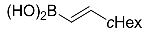
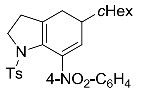
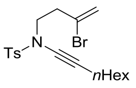
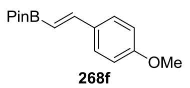
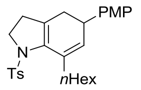
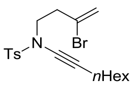
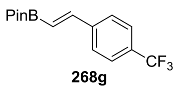
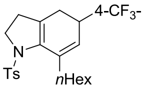
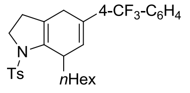
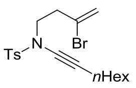
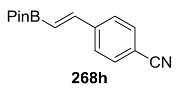
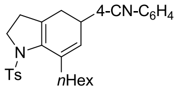
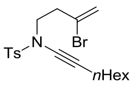
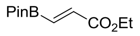
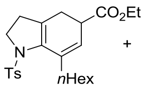
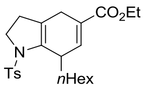
Satisfied with the scope of the reaction with respect to the substituent on the ynamide terminus, the scope with respect to the coupling partner was investigated. Pleasingly, the unsubstituted boroxin trimer **268c**, and the alkyl- and cycloalkyl-substituted vinyl boronic acids **268d** and **268e** underwent successful couplings with ynamides **205j** and **205c** (Table 2.9, entries 1-3). Interestingly, during the cascade cyclisation of **205j** with cyclohexenyl boronic acid **268e** (Table 2.9, entry 3) no *in situ* oxidation of the 1,3-diene to the indoline was observed, as compared to the reaction of **205j** with styrenyl pinacol boronate **268b** (Table 2.8, entry 4) where only the oxidised indoline was isolated. It is worth noting that when the alkenyl boronic acids **268d** and **268e** were replaced with their boronic ester counterparts, the cascade was much less efficient with hardly any product being formed even with extended reaction times. This could reflect a reduced rate of transmetallation or hydrolysis of the alkenyl boronic ester compared to the boronic acid, as alkenyl boronic acids are known to be more reactive than the corresponding boronic esters.[119,120]

The use of the electron-rich aryl-substituted vinylboronate **268f** also underwent coupling with ynamide **205a** but with the formation of the exocyclic diene **269a** being observed, suggesting that the formation of a palladium hydride species was now occurring in DME (see discussion in Chapter 3). Fortunately, the product was separable from this side-product and could be isolated in a reasonable 55% yield (entry 4). Disappointingly, this trend of forming both product and the exocyclic diene **269a** was also seen when electron-deficient aryl-substituted vinylboronates **268g** and **268h** were utilised. With an electron-withdrawing *para*-trifluoromethyl substituent the formation of exocyclic diene was more favoured compared to the electron-rich example, but again the product was separable and obtained in a 67% yield, with the added complication of the product being a mixture of 1,3- and 1,4-diene (entry 5). The formation of the exocyclic diene was even more pronounced when a mesomerically electron-withdrawing *para*-nitrile substituent was present with no product being formed, and full conversion of ynamide **205a** to exocyclic diene **269a** occurring (entry 6). The amount of exocyclic diene formed in these examples seemed to reflect the rate of transmetallation of the boron coupling partner with the dienylpalladium(II) complex. The cascade cyclisation with the ester-containing boronic ester **268i** did not suffer from any exocyclic diene formation, but was again complicated by the isolation of a mixture of diene isomers (entry 7).

Table 2.9 – Substrate Screen: Varying the Coupling Partner

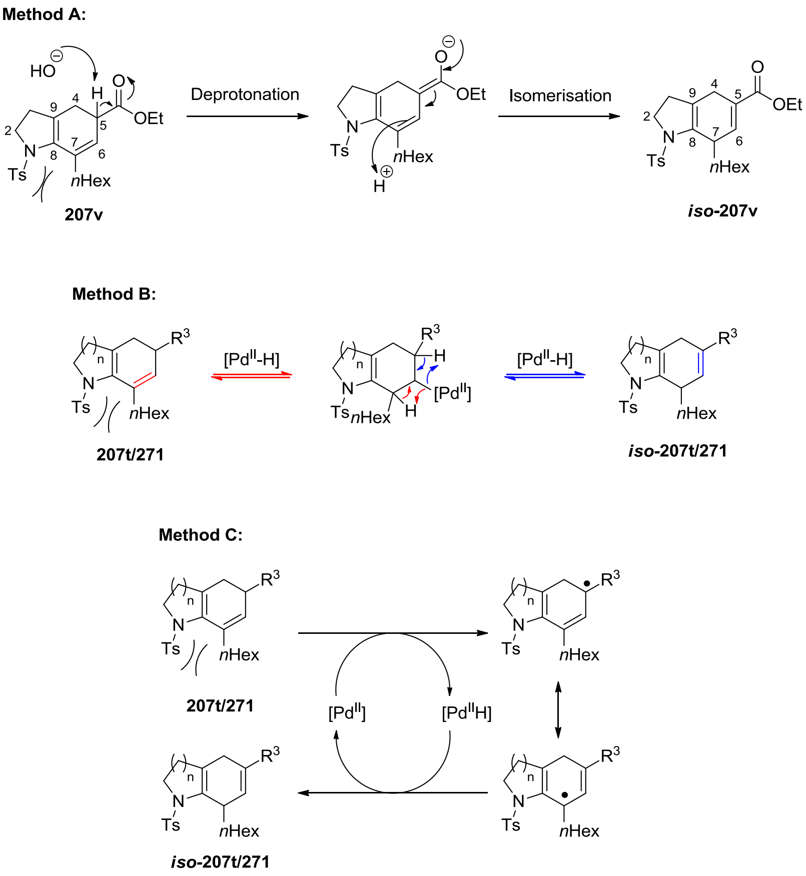


269a

	Ynamide	Coupling Partner	Product	Yield[a]
1[b]	 **205j**	 **268c**	 **207p**	54%
2	 **205c**	 **268d**	 **207q**	62%
3	 **205j**	 **268e**	 **207r**	74%
4	 **205a**	 **268f**	 **207s**	55% (10:1 **207s:269a**)[c]
5	 **205a**	 **268g**	 **207t** +  ***iso*-207t**	67%[d] (3.5:1 **207t:269a**)[c]
6	 **205a**	 **268h**	 **207u**	n.d. (0:1 **207u:269a**)[c]
7	 **205a**	 **268i**	 **207v** +  ***iso*-207v**	67%[e]

[a] Isolated yield; [b] **268c** (0.5 equiv.)/H_2O (1.5 equiv.) used; [c] Determined by ^1H NMR spectroscopic analysis of the crude reaction; [d] Isolated as a 3:1 mixture of 1,3- and 1,4-diene isomers; [e] Isolated as a 1.2:1 mixture of 1,3- and 1,4-diene isomers

The formation of a 1,4-diene in the 7,6-bicyclic ring system **271** (Table 2.8, entry 10), and with **207t** and **207v** (Table 2.9, entries 5 & 7), may be due to isomerisation of the 1,3-diene product of the cascade cyclisations. Its formation is interesting as in doing so, except for the ester containing product ***iso*-207v**, the molecule appears to become unconjugated. The simplest explanation for the isomerisation of **207v** would be the deprotonation of the 1,3-diene product adjacent to the electron-withdrawing ester to form a stabilised anion followed by isomerisation (Scheme 2.20, method A).



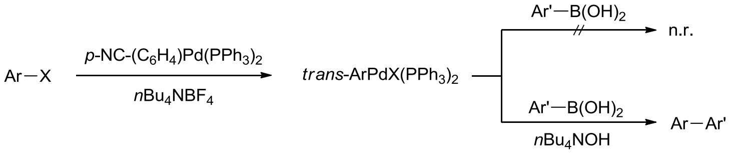
Scheme 2.20 – Proposed Mechanisms for the Isomerisation of 1,3-Amidodienes

However, this mechanism seems less viable as an explanation for the isomerisation of **207t** and of the 7,6-system **271**. Since it seems likely that a palladium(II) hydride species is being formed in DME, due to the exocyclic diene being formed during the cascade (Table 2.9, entries 4-6), a more plausible mechanism explaining the mixture of diene isomers could involve the reversible addition/ß-hydride elimination of this Pd(II)-H species across the alkenes in the cyclised product (Scheme 2.20, method B). This proposal is further supported by the literature reported isomerisation/migration of olefins using palladium hydride complexes by Gauthier *et al.*, who suggest the same mechanism.[121] Alternatively, Baiker *et al.* suggest a palladium-catalysed hydrogen-abstraction to afford an allylic radical, which could then undergo isomerisation and re-capture of a hydrogen atom, regenerating the palladium(II) and forming the 1,4-diene (Scheme 2.20, method C).[122,123]

It is possible that this process happens to relieve axial strain induced by the interaction between the tosyl and *n*hexyl substituents in the 1,3-diene, and to enable the nitrogen lone pair to become conjugated with the C8/C9 alkene which would prevent further isomerisation.

2.3.3. Mechanistic Insight and Future Considerations

Recent studies conducted by Jutand *et al.* have concentrated on elucidating the mechanism of the Suzuki reaction, with an initial focus on the role of the base and hydroxide ions. [124] Reactions were conducted using an aryl halide and aryl boronic acid in the presence of the catalyst (*p*-NC-C_6H_4)Pd(PPh_3)$_3$ in DMF, with and without a base. In the absence of a base, whilst oxidative addition occurred, no reaction was observed with the aryl boronic acid. However, on the addition of hydroxide ions the reaction did proceed, confirming that the presence of a base is required to induce cross-coupling (Scheme 2.21).



Scheme 2.21 – Investigation into the Role of the Base in a Suzuki Coupling

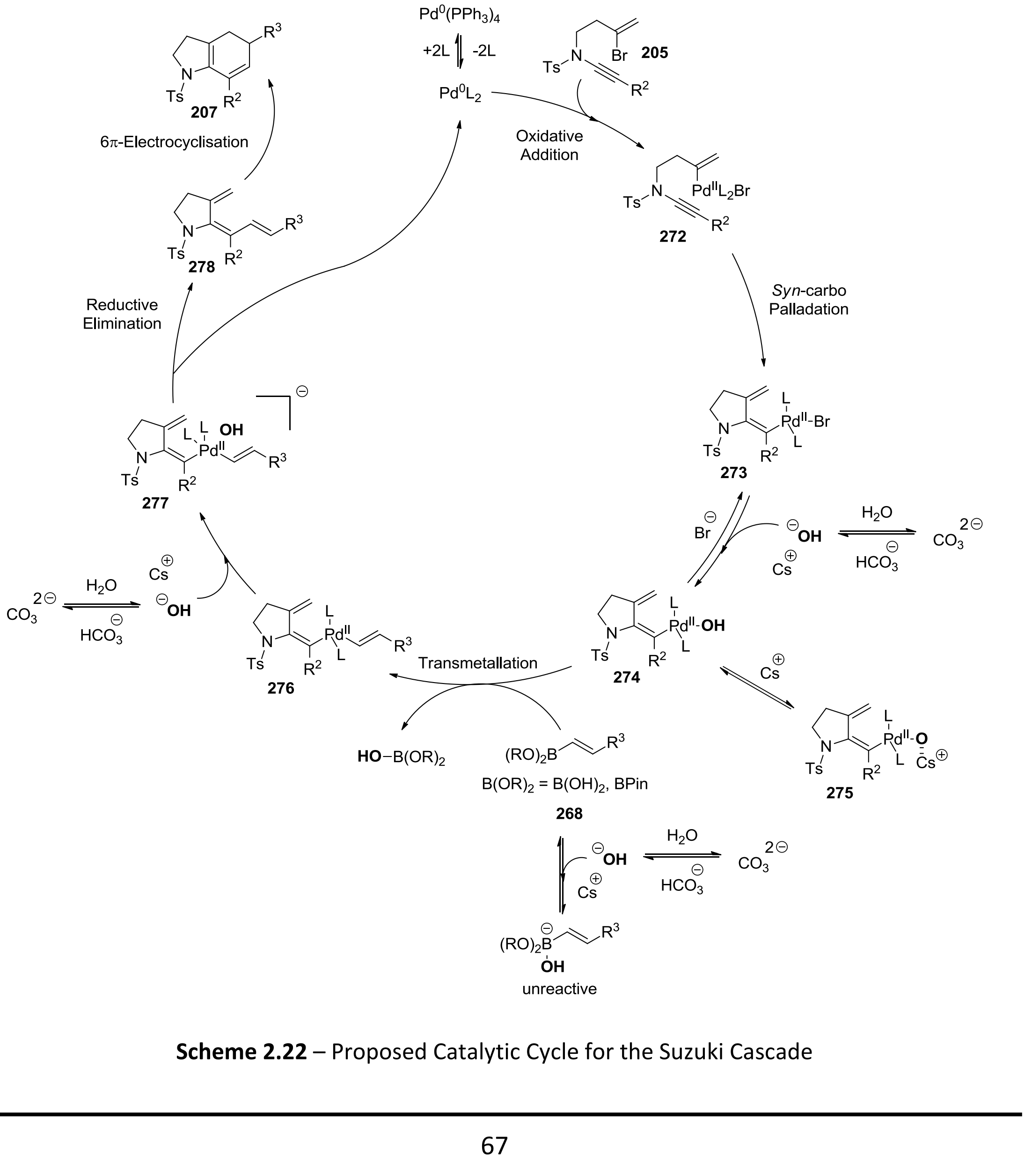
Having confirmed that a base is required, further investigations discovered that the hydroxide ions unexpectedly played three roles. The first is the formation of the key reactive complex for transmetallation to occur (*trans*-[ArPdOH(PPh_3)$_2$)]. Secondly, hydroxide promotes the reductive elimination by forming a penta-coordinate palladium species with *trans*-

[ArPdAr'(PPh_3)$_2$)]. The final role of the hydroxide ion is an inhibitor of the reaction by forming the unreactive 'boronate' Ar'B(OH)$_3^{\ominus}$ species – an intermediate previously thought to be more nucleophilic and therefore more reactive in the transmetallation step.[125]

Following on from these findings, Jutand *et al.* also reported in 2012 the effect of using carbonate (Cs_2CO_3) bases instead of hydroxide (*n*Bu_4NOH), including a study of the effect of the metal counterion.[126] It was found that the counterion did affect the rate of transmetallation, decreasing reactivity by complexation to the *trans*-[ArPdOH(PPh_3)$_2$)] intermediate, and inhibiting co-ordination of the aryl boronic acid to varying degrees depending on the cationic species ($Na^{\oplus} > Cs^{\oplus} > K^{\oplus} >$ *n*$Bu_4N^{\oplus}$). The reaction involving use of Cs_2CO_3 was also compared to that using *n*Bu_4NOH, and it was discovered that carbonates actually result in a slower reaction, even if water is added to form more $^{\ominus}$OH to accelerate the reaction. Further studies confirmed that when a carbonate is used, a similar catalytic cycle occurs with the carbonate reacting with water to form the active palladium-hydroxide species. However, as the concentration of hydroxide generated from the reaction of the carbonate with water is low, a slower reaction results due to decreased rates of both transmetallation and reductive elimination compared to the use of *n*Bu_4NOH.

Overall, these findings show the importance of the base in the Suzuki reaction in terms of both counterion effects and the concentration of hydroxide present in the reaction. Interestingly, our Suzuki cascade utilises anhydrous conditions (Pd(PPh_3)$_4$, Cs_2CO_3, anhydrous DME, inert atmosphere, sealed vial, 85 °C), and based on Jutand's findings should not proceed efficiently. If these findings are transferable to our cascade, the fact that the cascade cyclisation is successful suggests that some 'adventitious' water is present, most likely originating from the cesium carbonate used which is somewhat hygroscopic in nature, and was not rigorously dried with heat or vacuum before use. Combination of this hypothesis with the reported findings allows a catalytic cycle to be proposed (Scheme 2.22).

Oxidative addition of bromoenynamide **205**, followed by *syn*-carbopalladation leads to the intermediate **273** which can then undergo the required conversion to the active intermediate **274** due to the presence of hydroxide ions formed from the reaction of $CO_3^{2\ominus}$ with water. This active intermediate **274** can then undergo transmetallation with the boronic species **268**. However, the rate of transmetallation will be affected due to both the counterion $Cs^{\oplus}$ complexing to **274** and the $^{\ominus}OH$ forming the unreactive 'boronate' species, although if our reaction does not contain much water this may not be a problem. Once transmetallation has occurred, **276** can then undergo reductive elimination to **278**, promoted by hydroxide co-ordination forming the penta-coordinate species **277**, regenerating Pd^0 and forming triene **278** which can undergo subsequent thermal electrocyclisation.



Scheme 2.22 – Proposed Catalytic Cycle for the Suzuki Cascade

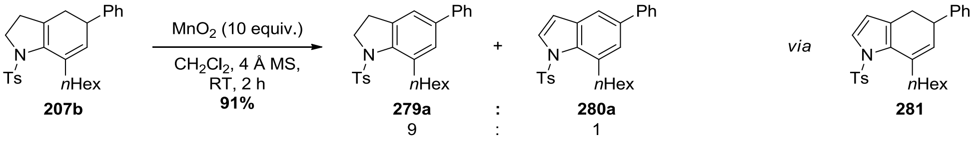
Based on this proposal in which hydroxide ions play a crucial role, it would be interesting to investigate the use of pre-dried Cs_2CO_3 in the cascade cyclisation to see if this indeed prevents the reaction from occurring, confirming the need for water to be present as proposed by Jutand. Also, as a screen of bases was not conducted during the initial optimisation of our Suzuki cascade, it would be interesting to investigate the use of a hydroxide base (e.g. CsOH instead of Cs_2CO_3) and also alter the counterion (e.g. $n\mathrm{Bu}_4^{\oplus}$ instead of $\mathrm{Cs}^{\oplus}$) to see if there is any improvement to the yield and reaction times. However, the formation of the exocyclic diene **269a** could be an issue with it potentially being formed in even greater amounts if the base is changed. This prediction is based on the findings that the use of Cossy's conditions of *aqueous* NaOH in THF predominantly formed this diene (Table 2.7, entry 1), whilst in Chapter 3 the use of Cs_2CO_3 with THF gave less than 5% conversion to the same diene (Table 3.1, entry 9 in **3.3** suggesting that an increased concentration of hydroxide ions may actually have a detrimental effect on our cascade.

2.4. Conversion of 1,3-Amidodienes to the Corresponding Heteroaromatics

2.4.1. Oxidations

Both the cascade strategies incorporating either a Stille or Suzuki coupling enabled a range of bromoenynamides to be successfully cyclised with a variety of coupling partners, resulting in a large selection of bicyclic 1,3-amidodiene frameworks being formed. Whilst one could envisage a number of uses for these products, for example, reduction of the diene or Diels-Alder cycloadditions, we opted to oxidise them with the aim of accessing a range of bicyclic heteroaromatic systems including indolines, indoles, tetrahydroquinolines and benzazepines.

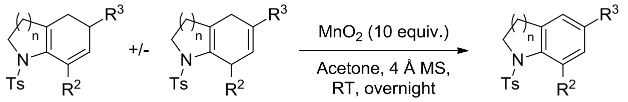
Preliminary investigations by Holton on the oxidation of bicyclic amidodienes **207a** and **207b** explored a wide range of oxidants (Pd/C, Ru/Al_2O_3, PCC, DDQ, CAN, $PdCl_2/CuCl_2$, air, O_2). Unfortunately, this often resulted in a mixture of indoline and indole being formed, or incomplete reaction, or the formation of side-products, with a particularly interesting occurrence of a Diels-Alder cycloaddition with DDQ. Eventually it was found that the use of unactivated MnO_2 in CH_2Cl_2 could affect clean conversion to a mixture of both the indole and indoline, albeit with slow conversion.[100] In these studies, it was found that the use of freshly activated MnO_2 showed an increased reactivity in CH_2Cl_2 at room temperature and gave a mixture of indoline **279a** and indole **280a** in ~9:1 ratio respectively with the reaction proceeding cleanly (Scheme 2.23). On attempting to resubmit this mixture of indoline and indole to the same reaction conditions in the hope of achieving complete oxidation to the indole, it was disappointing to find that no further reaction occurred. This suggests that oxidation to the indole **280a** may not proceed *via* the indoline **279a**, but instead the pyrrolidine ring oxidises first to form the pyrrole **281** in small amounts which then goes on to become fully oxidised, presumably quite rapidly as no pyrrole oxidation product (ie. a dihydroindole **281**) was observed.

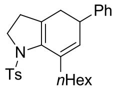
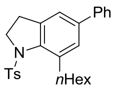
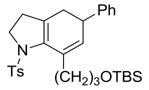
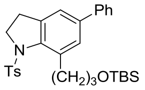
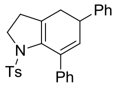
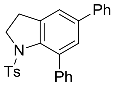
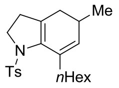
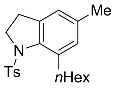
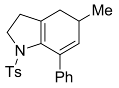
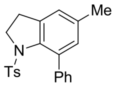
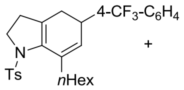
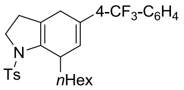
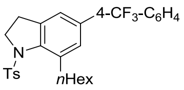
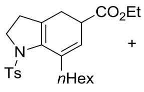
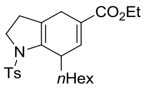
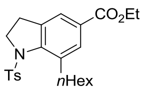
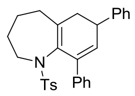
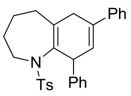
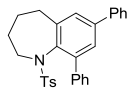


Scheme 2.23 – Unselective Oxidation of Cascade Product

Based on this initial result, the optimisation of the use of this reagent was studied. Pleasingly, the replacement of CH_2Cl_2 with the moderately deactivating acetone gave the indoline **279a** selectively from amidodiene **207b** (Table 2.10, entry 1). Following this finding the conditions were successfully applied to a range of amidodienes bearing alkyl and aryl substituents on the benzenoid portion of the ring, formed from both the Stille and Suzuki cascade cyclisations (entries 2-5). Additionally, the mixtures of 1,3- and 1,4-dienes isolated from the cascade could also be successfully oxidised to the corresponding indolines **279f** and **279g** and benzazepine **282** in good yields (entries 6-8).

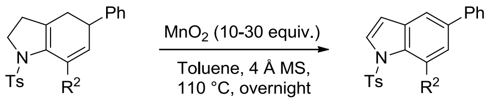
Table 2.10 – Selective Oxidation of Cascade Products to Indolines and Benzazepines



	Amidodiene	Product	Yield
1	 **207b**	 **279a**	86%
2	 **207i**	 **279b**	62%
3	 **207j**	 **279c**	53%
4	 **207a**	 **279d**	68%
5	 **207f**	 **279e**	63%
6	 **207t** +  ***iso*-207t**	 **279f**	70%
7	 **207v** +  ***iso*-207v**	 **279g**	94%
8[a]	 **271** +  ***iso*-271**	 **282**	91%

[a] CH_2Cl_2 used as the solvent due to no risk of oxidation of the left hand ring

Pleased with having found conditions for selective oxidation conditions to the indoline, we next investigated selective oxidation conditions for the conversion of 5,6-amidodienes to indoles. By employing more forcing literature conditions, involving the use of MnO_2 in toluene at reflux with extended reaction times, it was now possible to obtain indoles **280a** and **280b** in good yields (Scheme 2.24), with no indoline present.[127] It is worth noting that benzaldehyde was present in the ^{1}H NMR spectra of the crude reaction mixture, suggesting oxidation of toluene had occurred, thus potentially lowering the yield of the product due to consumption of MnO_2.



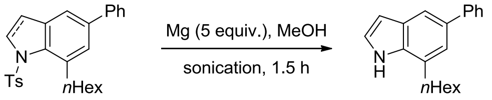
207b, R^2 = *n*Hex
207j, R^2 = Ph

280a, R^2 = *n*Hex, **53%**
280b, R^2 = Ph, **50%**

Scheme 2.24 – Selective Oxidation of Cascade Products to Indoles

2.4.2. Detosylations

The final hurdle in this area was to find milder detosylation conditions to heteroaromatic systems, given that no other protecting group enabled ynamide formation. Pleasingly, detosylation of both indoline **279a** and indole **280a** could be achieved using the relatively mild conditions of magnesium in methanol (Scheme 2.25).[128]

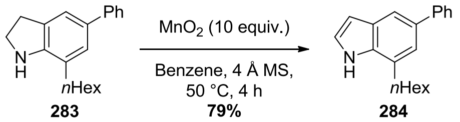


Indoline **279a**
Indole **280a**

Indoline **283**, **63%**
Indole **284**, **71%**

Scheme 2.25 – Detosylation of Indolines and Indoles

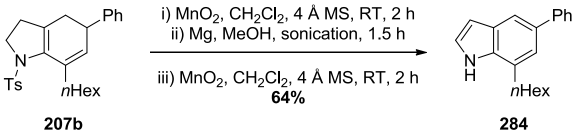
It is worth noting that it is considerably easier to oxidise the detosylated indoline **283** to the detosylated indole **284** than with the tosyl group in place as seen earlier. Utilising MnO_2 in benzene with mild heating at 50 °C for 4 hours yielded indole **284** in 79% yield (Scheme 2.26).



283 **284**

Scheme 2.26 – Oxidation of Detosylated Indolines

Lastly, due to the increased difficulty in oxidising 1,3-amidodiene **207b** directly to the corresponding indole before detosylation, these procedures were combined in an oxidation/detosylation/oxidation sequence allowing **207b** to be rapidly converted to the detosylated indole **284** in a 64% yield with a single purification step (Scheme 2.27). This three-step sequence could be performed within a single day, facilitating access to the fully-oxidised heteroaromatics.



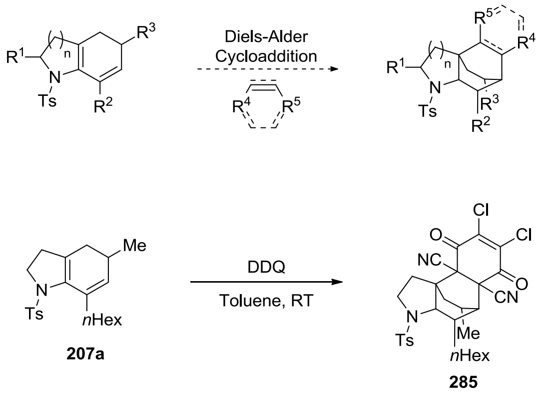
Scheme 2.27 – Three-step Sequential Oxidation/Detosylation of Cascade Products

2.5. Conclusions and Future Work

We have demonstrated that bromoenynamides can be used as substrates in a palladium-catalysed carbopalladation/Stille coupling/electrocyclisation of bromoenynes, and we have further extended this to incorporate a Suzuki coupling to form a wide range of bicyclic amidodienes. These studies have added further knowledge to the relatively under-investigated area of ynamide carbopalladation, and include a number of novel aspects, including the first example of ynamide carbopalladation/Stille or alkenyl Suzuki coupling sequence, and the first example of a carbopalladative Suzuki coupling resulting in a triene which undergoes *in situ* electrocyclisation. The 1,3-amidodienes formed could then undergo selective and tuneable oxidations to the corresponding heteroaromatic systems.[129]

Overall, this route provides a general method to a range of bicyclic systems with the ability to vary both the ring sizes and to install a variety of functional groups regiospecifically, giving access to not only indolines and indoles, but also tetrahydroquinolines and benzazepines. The major limitation of this methodology remains in the reduced ability to synthesise a range of bromoenynamides that would allow introduction of functionality in any position on the bicyclic systems, with the vinyl bromide functionality often causing problems by being responsible for issues of intramolecular cyclisation or reduced reactivity in formation.

Further areas of investigation could focus on the use of the cascade 1,3-amidodiene products in Diels-Alder reactions given the interesting cycloaddition observed of **207a** with DDQ discovered by Holton, forming the bridged azacycle **285** (Scheme 2.28), and on experimenting with alternative bases in the Suzuki cascade.

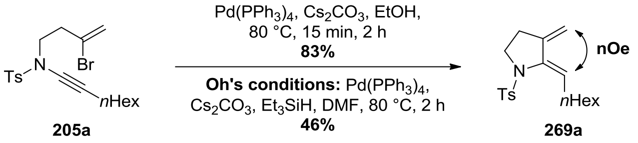


Scheme 2.28 – Diels-Alder Cycloadditions with Cascade 1,3-Amidodiene Products

3. Reductive Cyclisation/Diels-Alder Cycloaddition Sequence

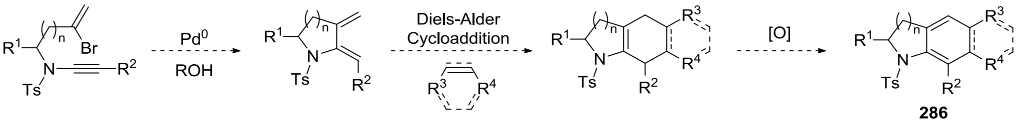
3.1. Introduction

In the earlier described optimisation of the carbopalladation/Suzuki coupling/electrocyclisation cascade we discovered the interesting formation of the exocyclic diene **269a** as a single geometric isomer (determined by ^{1}H NMR nOe experiments), which was isolated in an 83% yield when an alcoholic solvent was used, in the absence of a coupling partner. This suggested a reductive pathway could be occurring without the use of a traditional reductant such as triethylsilane or ammonium formate, and in fact produced **269a** in a far superior yield compared to Oh's conditions which had been utilised on analogous bromoenynes (Scheme 3.1).[130]



Scheme 3.1 – Reductive Cyclisations

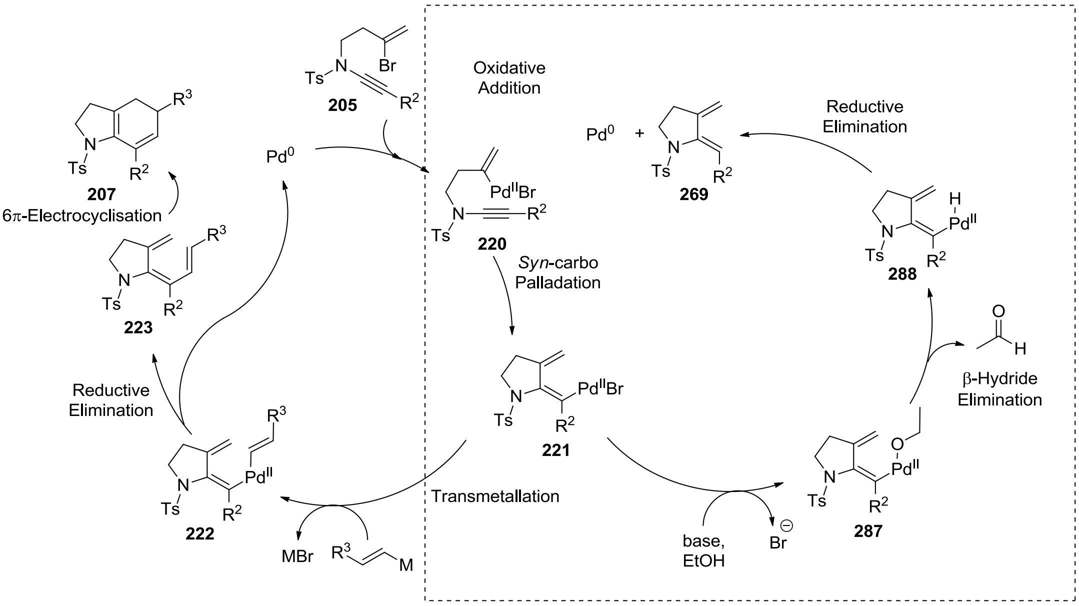
We realised that these exocyclic dienamides could themselves be valuable building blocks for the synthesis of further functionalised heteroaromatic compounds, and therefore set out to understand their formation and to optimise this reductive cyclisation, subsequently applying it to the same bromoenynamides used in the cascade methodology. It was envisaged that the dienamides would make ideal Diels-Alder cycloaddition substrates, which on oxidation would provide a complementary range of bi- and tricyclic heteroaromatic systems **286** with different substitution patterns to those obtained utilising the cascade methodology.



Scheme 3.2 – Envisaged Reductive Cyclisation/Diels-Alder Cycloaddition Sequence

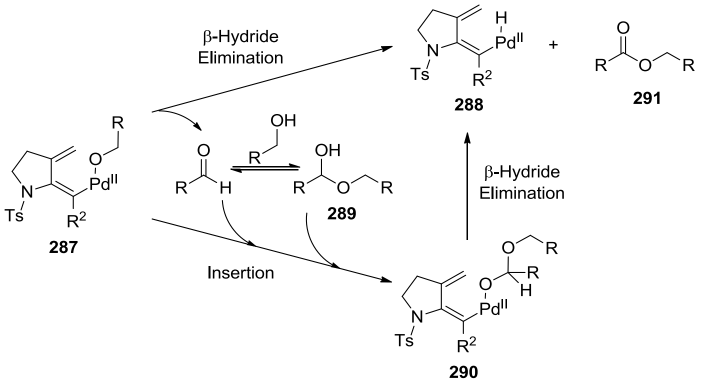
3.2. Mechanistic Insight

With the formation of the exocyclic amidodiene being quite surprising, we were initially intrigued as to the mechanism of its formation. We proposed that bromoenynamide **205** still underwent initial oxidative addition, followed by *syn*-carbopalladation to form dienylpalladium(II) intermediate **221**, at which point a competing pathway to transmetallation could occur. In order to access the exocyclic diene **269** a palladium hydride species **288** is required, which could be formed by co-ordination of ethoxide to **221** and subsequent ß-hydride elimination. Finally, reductive elimination would furnish the product and regenerate the palladium(0) catalyst (Scheme 3.3).



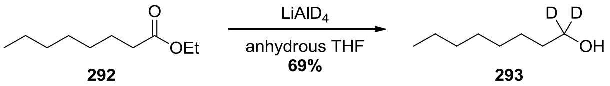
Scheme 3.3 – Proposed Reductive Cyclisation Catalytic Cycle

Preliminary support for this mechanism was found by employing a 10:1 solvent mixture of toluene (which had been shown to give no conversion to product, Table 3.1, entry 5) and octanol as the hydride source. With this less volatile alcohol, exocyclic diene **269a** was still formed, and whilst there was no clear aldehyde peak present in the crude ^{1}H NMR spectra, there was instead evidence for the formation of significant amounts of octyl octanoate. This result suggested that the alcohol was not only undergoing oxidation to the corresponding aldehyde allowing formation of the palladium hydride species, but that the aldehyde was then undergoing further oxidation to the ester *via* the palladium-hemiacetal species **290**, generated from either aldehyde insertion into palladium-alkoxide **287** or by co-ordination of hemiacetal **289** (Scheme 3.4),[131] suggesting that the hemiacetal itself is a superior hydride source. This palladium-catalysed oxidation of an alcohol to an aldehyde and ester has been previously reported in the literature, adding further weight to our suggested mechanism.[131-135]



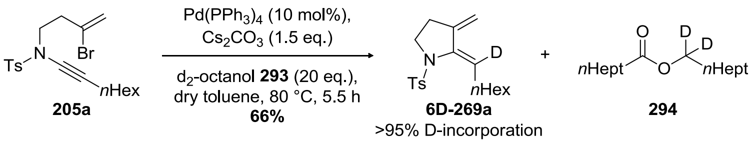
Scheme 3.4 – Reaction Pathway for the Formation of an Ester By-product

With this preliminary experiment supporting the proposed catalytic cycle, we decided to conduct deuterium labelling studies using deuterated octanol (prepared by reduction of ethyl octanoate with lithium aluminium deuteride, Scheme 3.5),[136] which could to be used as a deuteride source in the reductive cyclisation. If deuterium incorporation was observed this would provide evidence that alkoxide co-ordination and ß-hydride elimination was indeed responsible for the formation of the palladium hydride species.



Scheme 3.5 – Formation of d_2-octanol

Pleasingly, reaction of **205a** with d_2-octanol **293** in toluene, under inert atmosphere and anhydrous conditions, led to >95% deuterium incorporation (Scheme 3.6), suggesting that the α-hydrogens of the alcohol are indeed acting as the hydride source.



Scheme 3.6 – Deuterium Labelling Experiment

It is worth noting that no 'direct' reduction of the vinyl bromide to an alkene was observed, suggesting that the rate of *syn*-carbopalladation is much more rapid than alkoxide co-ordination/β-hydride elimination.

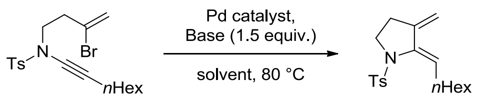
3.3. Reaction Optimisation

With an understanding of the mechanism of the reductive cyclisation now established, we could move onto a more focussed optimisation. Initially, taking the conditions used in the Suzuki cascade (EtOH, Cs_2CO_3, $Pd(PPh_3)_4$) a range of catalyst loadings were investigated (Table 3.1, entries 1-4).

Pleasingly, reducing the catalyst loading from 10 mol% to 1 mol% had no detriment to the yield; at this lowest catalyst loading, however, the reaction did not consistently reach completion due to catalyst deactivation. Therefore, in a compromise of lowering the catalyst loading but also enabling reproducibility of results, a loading of 2.5 mol% was selected.

A solvent screen was then conducted to test whether ethanol was the optimal choice (Table 3.1, entries 5-10). As mentioned earlier, the use of toluene gave no product (entry 5), which is not unexpected due to the supporting evidence that an alkoxide is required for co-ordination and ß-hydride elimination to occur. Use of ethanol as a co-solvent in toluene proved successful with no loss in yield, albeit with a longer reaction time (entry 6), conditions which proved useful in the later optimisation of the reductive cyclisation of ynamides with longer tether lengths. The use of isopropanol as an alternative to ethanol was also unsurprisingly successful but required a slightly longer reaction time. This could reflect a reduced rate of ß-hydride elimination, or as a ketone would be formed instead of an aldehyde, further oxidation to an ester would not occur, adding further weight to the idea that the hemiacetal is a superior hydride source, i.e. oxidation of IPA always proceeds *via* the alcohol and not the hemiketal (entry 7).

Table 3.1 – Optimisation of Reductive Cyclisation



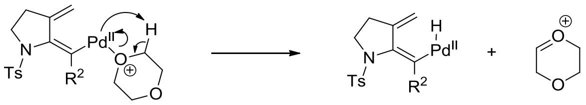
205a **269a**

	Pd catalyst (mol%)	Base (1.5 eq.)	Solvent, Conc (M)[a]	Time	Yield (%), Conv.[b]
1	$Pd(PPh_3)_4$ (10)	Cs_2CO_3	EtOH (0.02)	15 min	83 (100)
2	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	EtOH (0.02)	15 min	79 (100)
3	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	EtOH (0.02)	1 h	83 (100)
4	$Pd(PPh_3)_4$ (1)	Cs_2CO_3	EtOH (0.02)	1 h	80 (100)
5	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene[c] (0.02)	22 h	n.r. (0)
6	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Tol:EtOH, 30:1 (0.02)[c]	4 h	83 (100)
7	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	IPA (0.02)	30 min	75 (100)
8	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	1,4-Dioxane[c] (0.02)	19 h	33 (50)
9	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	THF[c] (0.02)	19 h	n.d. (<5)
10	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	DME[c] (0.02)	3 h	45 (100)
11	$PdCl_2(PPh_3)_2$ (2.5)	Cs_2CO_3	EtOH (0.02)	1 h	66 (100)
12	$PdCl_2$(dppf) (2.5)	Cs_2CO_3	EtOH (0.02)	1 h	70 (100)
13	$Pd(OAc)_2$ (2.5), PPh_3 (5)	Cs_2CO_3	EtOH (0.02)	1 h	58 (100)
14	$Pd(PPh_3)_4$ (2.5)	NaOH	EtOH (0.02)	1 h	62 (100)
15	$Pd(PPh_3)_4$ (2.5)	K_3PO_4	EtOH (0.02)	18 h	62 (100)
16	$Pd(PPh_3)_4$ (2.5)	K_2CO_3	EtOH (0.02)	1 h	62 (100)
17	$Pd(PPh_3)_4$ (2.5)	-	EtOH (0.02)	2 h	0 (0)
18	-	-	EtOH (0.02)	2.5 h	0 (0)
19	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	EtOH (0.045)	15 min	83 (100)
20	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	EtOH (0.09)	5 min	75[d] (100)
21	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	EtOH (0.18)	5 min	79[d] (100)

[a] Solvent used “as is” directly from the bottle unless otherwise stated; [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [c] Anhydrous and degassed solvent used; [d] Product formed with a new unknown impurity.

The use of anhydrous 1,4-dioxane or DME also unexpectedly led to diene formation (entry 8 and 10), albeit in reduced yields; an interesting result, as the mechanism for the formation of the required palladium hydride species **288** using these solvents is unclear. The use of THF was unsuccessful with less than 5% conversion occurring (entry 9), which is consistent with the observed formation of traces of this diene in the Suzuki cascade (Table 2.7 in **2.3.1.**). Interestingly, DME led to greater conversion to the exocyclic diene than THF, an opposite trend to that seen during the optimisation of the Suzuki cascade (Table 2.7 in **2.3.1.**), although diene formation in DME was sometimes observed during the substrate screen of the Suzuki cascade (Table 2.8 in **2.3.2.**). This could potentially be explained by a slower rate of palladium hydride formation compared to transmetallation during the Suzuki cascade and therefore no exocyclic diene was formed, but with no coupling partner present the reductive cyclisation pathway is somehow occurring.

Whilst there is no reported explanation of the mechanism of palladium(II) hydride formation from 1,4-dioxane or 1,2-dimethoxyethane, similar such results have been noted before. Keay *et al.* found evidence for an unexpected hydride transfer from 1,4-dioxane, suggesting that either the 1,4-dioxane can transfer a hydride *via* a ß-hydride elimination pathway to form oxocarbenium species **296** (Scheme 3.7) or that it can directly donate a hydride.[137]



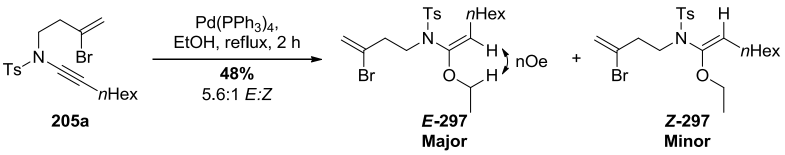
295 **288** **296**

Scheme 3.7 – Suggested Mechanism for 1,4-Dioxane as a Hydride Source

Lautens *et al.* reported hydride transfer from 1,2-dimethoxyethane in the presence of a palladium catalyst, and observed that methanol was produced.[138] By conducting deuterium labelling studies they also confirmed the CH_2 protons were acting as the hydride source, and not the CH_3 groups. Even after having confirmed the hydride source, the mechanism of hydride transfer was still unclear and they also suggested Keay's ß-hydride elimination pathway as a plausible mechanism (Scheme 3.7).

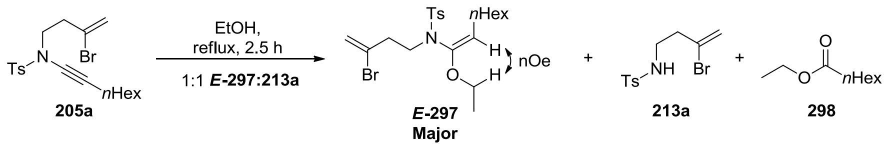
Having found no improvement in the isolated yield by changing the solvent, a brief screen of palladium catalysts - $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)$, $Pd(OAc)_2$ + $2PPh_3$ (entries 11-13) and bases – NaOH, K_3PO_4, K_2CO_3 (entries 14-16) was conducted, all of which were successful but less effective. Finally, the effect of reaction concentration was investigated (entries 19-21), and whilst the concentration could be doubled with no loss in yield, any further increase in concentration led to formation of the desired product and a new unknown impurity. Based on the outcome of these results, the original conditions from the Suzuki cascade with a reduced catalyst loading and an increased concentration were found to be optimal (entry 19).

Interestingly, in the absence of a base (entry 17) the α-alkoxyenamide **297** was obtained as a mixture of geometric isomers (*E*:*Z* = 5.6:1) with no trace of the cyclised product, confirming that a base is required in order to obtain the exocyclic diene **269a** (Scheme 3.8). There have been a few reports of transition metal-catalysed addition of nucleophiles at the α-position of ynamides,[2] including hydrostannylation with $Pd(PPh_3)_4$ in THF[139] and intramolecular examples,[21] making this addition somewhat unsurprising.



Scheme 3.8 – α-Alkoxyenamide Formation

We were interested in whether this was a palladium-catalysed reaction, and therefore a control reaction was conducted by excluding both the base and palladium catalyst (entry 18) and as expected no cyclisation occurred. However, after 2.5 hours all the starting material had been consumed, with α-alkoxyenamide **297** formed as only the *E*-isomer, along with the 'parent' sulfonamide **213a** in a 1:1 ratio respectively (Scheme 3.9), based on analysis of the ^1H NMR spectra of the crude reaction mixture. The presence of **213a** can be explained by further solvolysis of **297** to a keto-sulfonamide, which after nucleophilic attack with more EtOH would yield the sulfonamide **213a** and the ester **298**, which was also identifiable in the crude reaction mixture.



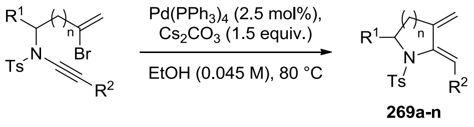
Scheme 3.9 – α-Alkoxyenamide Formation and Hydrolysis to 'Parent' Sulfonamide

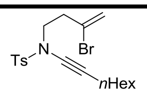
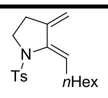
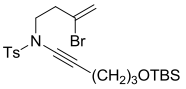
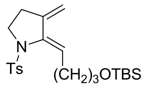
This reaction suggests that formation of α-alkoxyenamide **297** may not be due to palladium catalysis and also shows the ease of which ynamides can undergo hydrolysis under thermal conditions in hydroxylic solvents. This again highlights the rapid nature of the *5-exo-dig* carbopalladation, since no α-enamide formation, and rarely solvolysis, is observed during the reductive cyclisation (Table 3.1).

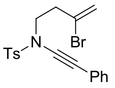
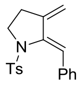
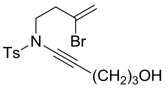
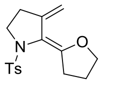
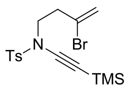
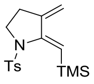
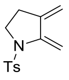
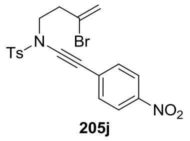
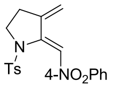
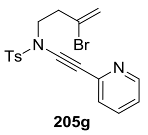
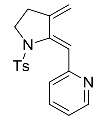
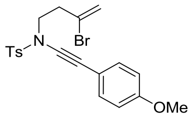
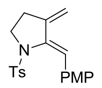
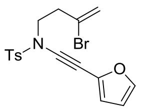
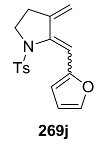
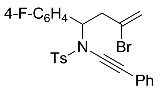
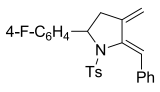
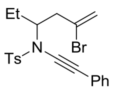
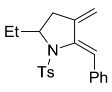
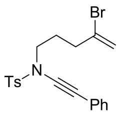
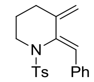
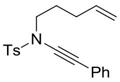
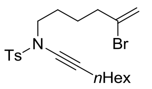
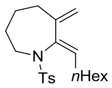
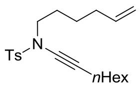
3.4. Substrate Screen

With an optimised set of conditions in hand, the scope of the cyclisation could be explored using the same range of bromoenynamides synthesised for use in the cascade cyclisation (Table 3.2). Beginning with the investigation of the effect of the substituent on the ynamide terminus, it was found that both alkyl and aryl substituents were tolerated (entries 1-3), albeit with aryl groups affording a reduced isolated yield of the exocyclic amidodiene **269c**. Pleasingly, it was found that when the reductive cyclisation was conducted on a larger scale, the catalyst loading could be reduced to 1 mol% with no detrimental effect (entries 1 & 3).

Table 3.2 – Reductive Cyclisation Substrate Scope

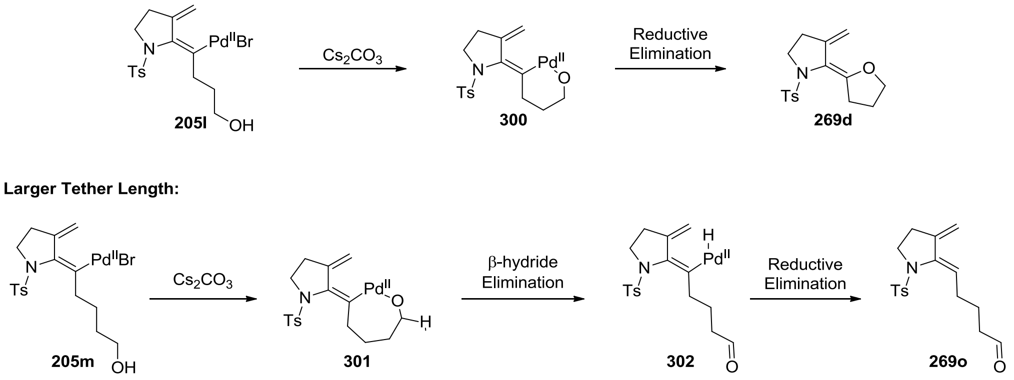


	Ynamide	Product	Yield
1	 **205a**	 **269a**	83% 84%[a]
2	 **205c**	 **269b**	83%

	Ynamide	Product	Yield
3	 **205b**	 **269c**	65% 65%[b]
4[c]	 **205l**	 **269d**	100% conv. 0% yield[d]
5[e]	 **205d**	 **269e** +  **269f**	66%[d] 1.3:1 **269e:269f**
6	 **205j**	 **269g**	0%[f]
7	 **205g**	 **269h**	0%[f]
8	 **205e**	 **269i**	61%[d]
9	 **205f**	 **269j**	66%[g] 1:4.2 *E:Z*
10	 **232c**	 **269k**	75%
11	 **232d**	 **269l**	68%
12	 **255**	 **269m** +  **299a**	71% 6:1 **269m:299a**
13	 **262a**	 **269n** +  **299b**	59% 1:3.3 **269n:299b**

[a] Performed on a 2.42 mmol (1 g) scale with 1 mol% catalyst; [b] Performed on a 1.24 mmol (0.5 g) scale with 1 mol% catalyst; [c] Conducted in toluene; [d] Product prone to decomposition on silica gel and in $CDCl_3$; [e] Conducted with 10 mol% catalyst and $NaHCO_3$ as the base; [f] Complex crude reaction mixture containing product but could not be isolated; [g] Product prone to isomerisation on silica gel and in $CDCl_3$

On attempting to conduct the reductive cyclisation on an ynamide containing a tethered alcohol (entry 4) in toluene, formed by the desilylation of **205c** with TBAF, quantitative conversion to exocyclic diene **269d** was observed containing a fused enamine/enol ether system which proved unstable to purification by column chromatography on silica gel. Initially, it had been hoped that this alcohol would itself serve as the hydride source, giving an aldehyde product. Presumably, due to the tether length used, reductive elimination proved to be more favourable forming the observed bicyclic system **269d**, but there is the possibility that if the tether length was increased by a further methylene unit, the aldehyde containing exocyclic diene **269o** could be formed (Scheme 3.10).



Scheme 3.10 – Reductive Elimination vs. ß-hydride Elimination

When a silyl-substituted ynamide **205d** was used in the reductive cyclisation, no exocyclic diene could be isolated after purification. On analysis of the ^{1}H NMR spectra of the crude reaction mixture it was possible to see very small amounts of the TMS-diene **269e** and the desilylated diene **269f** to confirm that the reaction was occurring. By opting to use a milder base, such as NaHCO$_3$ which did require a higher catalyst loading due to the increased reaction time, it was possible to obtain the silyl-substituted exocyclic diene as a mixture of geometric isomers. Rapid purification by column chromatography then allowed us to isolate amidodiene **269e** as a 1.3:1 mixture with the terminal amidodiene **269f**, which interestingly was formed during purification, in a pleasing 66% yield (entry 5). Unfortunately, the product mixture proved unstable with hydrolysis occurring during characterisation in CDCl$_3$.

The use of the electron-deficient ynamides **205j** and **205g** proved unsuccessful in the cyclisation, affording complex reaction mixtures with only trace amounts of the desired dienamides identified (entries 6 & 7). The use of electron-rich ynamides **205e** and **205f** afforded amidodienes **269i** and **269j** in good yield (entries 8 & 9). However, **269i** was prone to decomposition, and **269j** to isomerisation, during purification on silica gel or on standing in $CDCl_3$ (Figure 3.1).

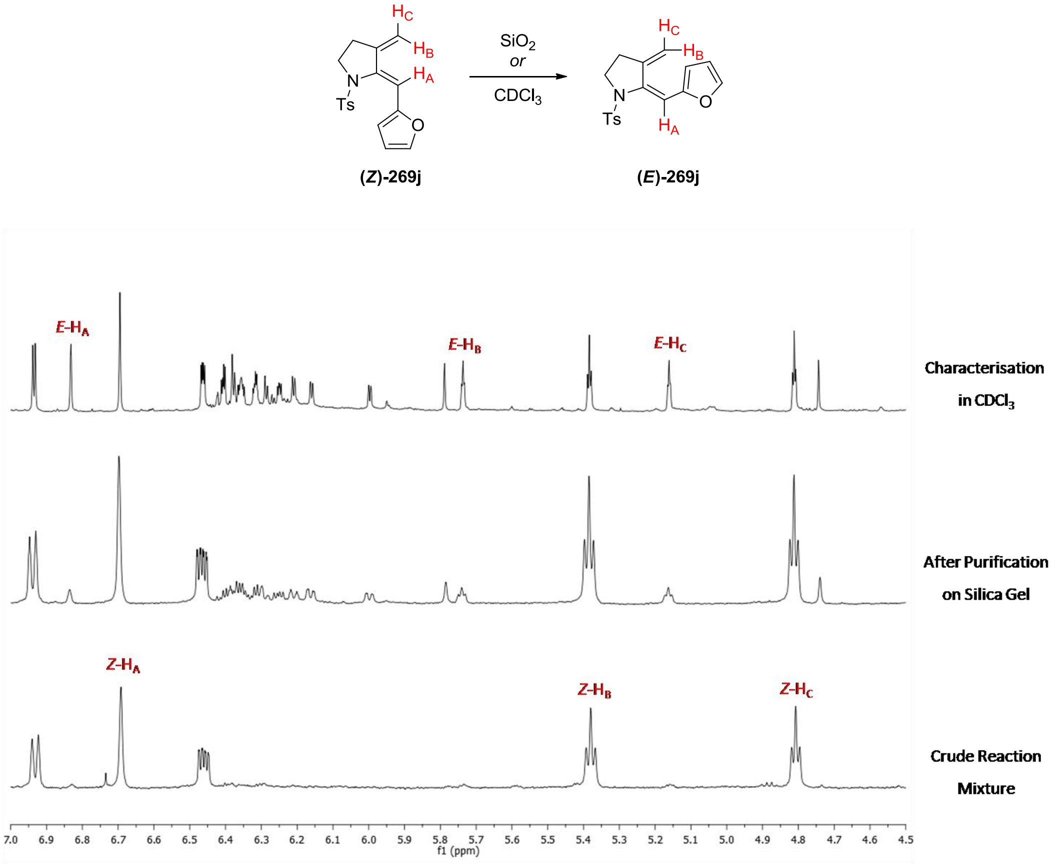


Figure 3.1 – ^1H NMR Spectra Showing Amidodiene Isomerisation

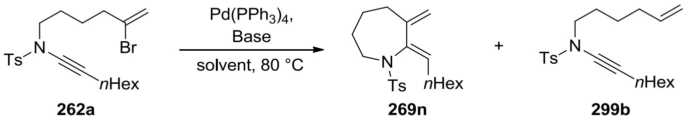
The introduction of a substituent adjacent to the sulfonamide enabled the successful synthesis of α-branched cyclic dienamides **269k** and **269l** (entries 10 & 11). Finally, the reductive cyclisation of the larger tether length ynamides **255** and **262a** proved more difficult, with the corresponding amidodienes being formed alongside significant, or even predominant, formation of the debrominated ynamides **299a** and **299b** (entries 12 & 13). This demonstrates that the larger tether 6- and 7-*exo-dig* carbopalladations are slower, due to the increased flexibility in the system, enabling alkoxide co-ordination and ß-hydride elimination to occur prior to carbopalladation, which results in the formation of side-products **299a** and **299b**.

3.5. Further Investigations

With selective formation of the 6- and 7-membered amidodienes being desirable, conditions which allowed sufficient time for carbopalladation to occur prior to alkoxide co-ordination and/or β-hydride elimination were required. Therefore, optimisation of the reductive cyclisation of bromoenynamide **262a** was conducted using the more challenging 7-membered system, due to it giving predominantly debrominated starting material under the standard conditions (Table 3.3, entry 1).

Initial attempts to reduce the rate of hydride transfer involved the use of alternative solvents, with IPA yielding more of the undesired side-product **299b**, but DME selectively forming amidodiene **269n** in 41% yield, a pleasing result but one that we felt could be improved upon (entries 2 & 3). Next, a range of mixed solvent systems (with toluene) were investigated (entries 4-9) which revealed a dependence on the nature of the alcohol cosolvent, with the general trend that alcohols with increased branching tended to produce less of the undesired enynamide **299b** (MeOH>EtOH>IPA>cyclopentanol/cyclohexanol). This suggests that the degree of branching of the alcohol influences the rate at which ß-hydride elimination occurs. Pleasingly, use of the cyclic secondary alcohols cyclopentanol and cyclohexanol enabled selective formation of the 7-membered amidodiene **269n** in a 68% and 62% yield respectively (entries 8 & 9). This observation suggests that both cyclopentanol and cyclohexanol have a reduced rate of hydride transfer compared to the other attempted alcohols, allowing the 7-*exo-dig* carbopalladation to occur prior to the ß-hydride elimination.

Table 3.3 – Optimisation of the Reductive Cyclisation on Larger Ring Systems



	Pd catalyst (mol%)	Base (1.5 eq.)	Solvent[a]	Time	Yield, Ratio **269n**:**299b**[a]
1	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	EtOH	1 h	60%, 1:3.3
2	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	IPA	2 h	55%, 1:4.6
3	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	DME	2 h	41%, 1:0
4	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene/EtOH (10:1)	2 h	45%, 1:0.4
5	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene/IPA (10:1)	2 h	68%, 1:0.2
6	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene/MeOH (10:1)	1 h	52%, 1:1
7	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene/CF_3CH_2OH (10:1)	1 h	0%[b]
8	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene/cyclopentanol (10:1)	2 h	68%, 1:0
9	$Pd(PPh_3)_4$ (2.5)	Cs_2CO_3	Toluene/cyclohexanol (10:1)	2 h	62%, 1:0
10	$Pd(PPh_3)_4$ (10)	Na_2CO_3	EtOH	15 min	n.d.,[c] 1:0
11	$Pd(PPh_3)_4$ (10)	$NaHCO_3$	EtOH	4 h	40% conv.,[a] 1:0
12	$Pd(PPh_3)_4$ (2.5)	K_2CO_3	EtOH	1.75 h	68%, 1:0.15
13	$Pd(PPh_3)_4$ (2.5)	K_2CO_3	Toluene/EtOH (10:1)	5 h	30% conv.,[a] 1:0
14	$Pd(PPh_3)_4$ (10)	K_2CO_3	Toluene/EtOH (10:1)	2 h	67%, 1:0
15	$Pd(PPh_3)_4$ (2.5)	K_2CO_3	Toluene/EtOH (1:1)	3.5 h	69%, 1:0

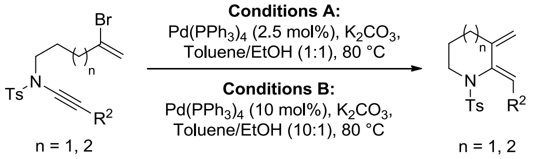
[a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture; [b] Mostly decomposition; [c] Product and unknown impurity formed

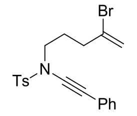
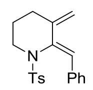
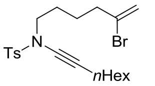
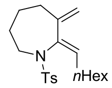
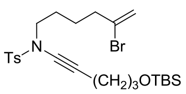
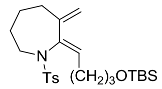
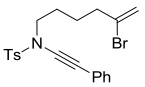
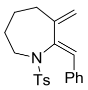
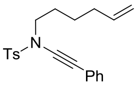
We next turned our attention to the effect of using different bases in the reductive cyclisation with EtOH as the solvent. Changing from Cs_2CO_3 to Na_2CO_3 proved effective at eliminating the formation of enynamide **299b**, although a new unknown impurity was then formed (entry 10), whilst the use of $NaHCO_3$ effected exclusive formation of the exocyclic amidodiene but with only 40% conversion observed after 4 hours (entry 11). Finally, the use of K_2CO_3 in EtOH greatly reduced the extent of direct reduction of the vinyl bromide, but did not eliminate the problem (entry 12). Overall, the variation in the quantity of enynamide **299b** formed, in relation to the inorganic base ($Cs^{\oplus}$>$K^{\oplus}$>$Na^{\oplus}$), likely reflects the rate of alkoxide co-ordination which in itself would be influenced by the dissociation of the metal counterion from the alkoxide and its subsequent effect on alkoxide nucleophilicity.

In attempt to further reduce the amount of side-product we investigated the use of mixed solvent systems with the optimal base, K_2CO_3, which had proved effective at reducing the amount of enynamide **299b** formed with a reasonable reaction time and had not introduced any new impurities (entries 13-15). Pleasingly, when a 10:1 ratio of toluene/EtOH was used, selective formation of the amidodiene was observed, but at 2.5 mol% catalyst loading the rate of reaction decreased considerably with only 30% conversion after 5 hours (entry 13). By increasing the catalyst loading to 10 mol% (entry 12), or by increasing the solvent ratio to 1:1 toluene/EtOH (entry 13), the amidodiene could now be formed selectively and was isolated in a 67% and 69% yield respectively, our best results so far.

With the modified cyclisation conditions in hand, the synthesis of larger ring systems could be demonstrated with alkyl substituents on the ynamide terminus (Table 3.4), which selectively gave piperidine **269m** (entry 1) and azepanes **269n** and **269p** (entries 2 & 3). However, when an aryl substituent was present on the ynamide terminus, the modified conditions again afforded a mixture of amidodiene **269q** and debrominated ynamide **299c** (entry 4, conditions A). This was overcome by reducing the EtOH/toluene ratio from 1:1 to 10:1, and increasing the catalyst loading from 2.5 mol% to 10 mol% (as in Table 3.3, entry 14), which successfully afforded azepane **269q** in 61% yield (entry 4, conditions A).

Table 3.4 – Larger Tether Length Substrate Screen



	Ynamide	Product	Yield
1	 **255**	 **269m**	**A:** 73%
2	 **262a**	 **269n**	**A:** 69%
3	 **262b**	 **269p**	**A:** 65%
4	 **262c**	 **269q** +  **299c**	**A:** 45% 1:0.4 **269q:299c** **B:** 61% 1:0 **269q:299c**

3.6. Diels-Alder Cycloadditions

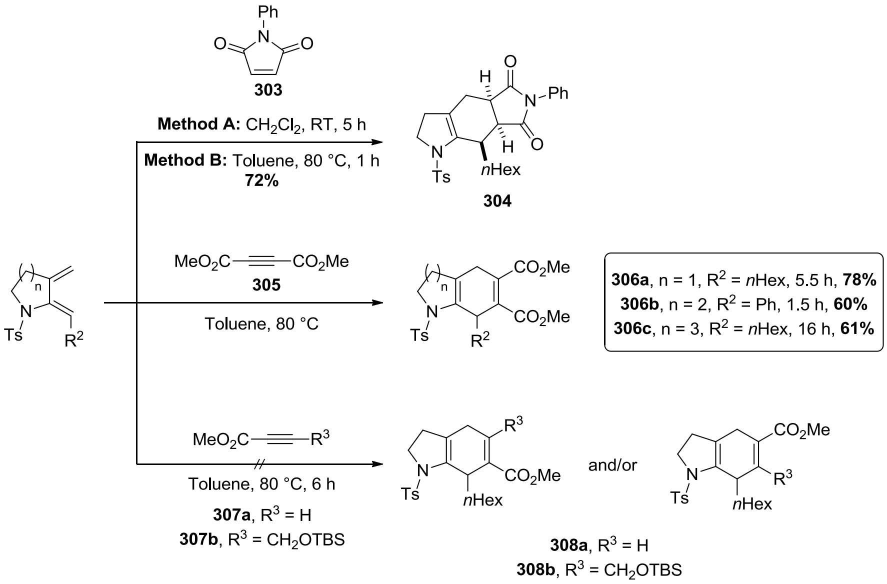
The exocyclic amidodienes, whilst generally stable to storage for prolonged periods under an inert atmosphere in the freezer, are still relatively reactive, even towards polymerisation. Thus, we wished to exploit the significant apparent reactivity profiles with a range of Diels-Alder cycloaddition reactions in an attempt to synthesise both azabicycles and azatricycles, which included the investigation of thermal, Lewis-acid catalysed, cobalt-catalysed, aryne and asymmetric processes.

3.6.1. Thermal Cycloadditions

The thermal Diels-Alder cycloaddition of cyclic 5-, 6- and 7-membered dienes with an adjacent *N*-tosyl substituent to the diene is known with both dimethylacetylene dicarboxylate (DMAD) and *N*-phenyl maleimide as dienophiles.[83,84,140] Pleasingly, the cycloaddition with *N*-phenyl maleimide was successful in CH_2Cl_2 at room temperature, and in toluene at elevated temperatures, affording tricycle **304** as a single diastereomer (Scheme 3.11). However, if the amidodiene was heated above 80 °C decomposition became apparent, and therefore in all subsequent cycloadditions this temperature was not exceeded.

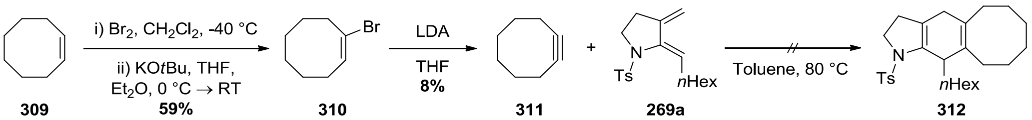
The Diels-Alder reaction of amidodienes **269a**, **269m** and **269n** with DMAD also proved successful, affording the 5,6-, 6,6- and 7,6-cycloadducts in good yield but with varying reaction times. The differing rates of reaction suggest that the diene reactivity is highly dependent on the tethering ring size (6-membered>5-membered>7-membered), presumably due to the differing bond angles based on the ring size and the flexibility of the ring affecting the dihedral angle of the diene.

To our dismay, the reaction of the amidodiene with the unsymmetrical alkynyl dienophiles **307a** or **307b** proved unsuccessful, with no reaction occurring despite precedent on an acyclic *N*-tosyl dienamide.[141] This suggests that the HOMO of the diene and the LUMO of the dienophile, which now only contains a single electron-withdrawing group, are no longer of a sufficiently similar energy to allow the reaction to occur.



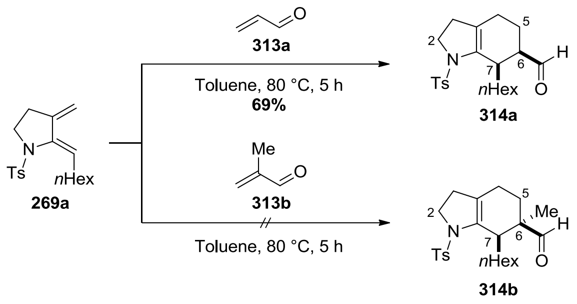
Scheme 3.11 – Thermal Diels-Alder Cycloadditions

The use of cyclooctyne as a dienophile[142] was also appealing as it would provide access to a 5,6,8-tricyclic system (Scheme 3.12). The bromination of cyclooctene, followed by dehydrobromination with KO*t*Bu and then LDA afforded cyclooctyne **311**,[143,144] which on submission to our Diels-Alder conditions with amidodiene **269a** did not afford any of the desired product, even with prolonged reaction times, only resulting in diene hydrolysis.



Scheme 3.12 – Thermal Cycloaddition with Cyclooctyne

Finally, for thermal cycloadditions we investigated the use of the unsymmetrical enals acrolein and methacrolein (Scheme 3.13). We were excited to find that acrolein could be successfully reacted to form the cycloadduct **314a** as both a single regio- and diastereomer (assigned based on COSY analysis and nOe enhancements respectively, see below), although the equivalent reaction with methacrolein was unsuccessful with only starting material being recovered.

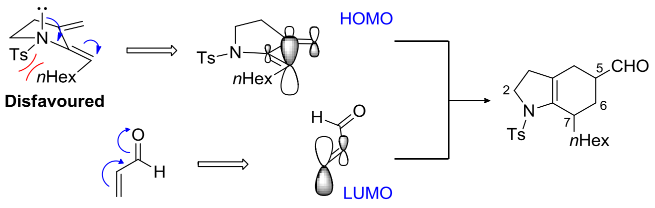


Scheme 3.13 – Thermal Cycloaddition with Acrolein and Methacrolein

This result was particularly interesting due to the regioselectivity observed (assigned from a ^{1}H-^{1}H NMR COSY correlation between H6 and H7 on **314a**), providing us with a complimentary substitution pattern to that obtained in the cascade cyclisations. Our initial prediction of the regioselectivity, based on electronic considerations, was that the nitrogen lone pair would have an electron-donating effect, therefore forming the largest HOMO coefficient on the *n*hexyl-substituted alkene of the diene. On orientation to react with the largest coefficient of the LUMO of acrolein, the expected product would have a 5,7-disubstitution pattern (Figure 3.2, predicted regioselectivity).

However, the observed 6,7-substitution pattern implies that the sulfonamide nitrogen atom actually has a negligible mesomeric electron donating effect which could be due to the inductive electron-withdrawing nature of the tosyl group, or, could be explained by considering the steric interactions between the tosyl and *n*hexyl substituent induced by a tetrahedral geometry around the nitrogen centre. In order for the nitrogen lone pair to donate electronically into the diene system, the interaction between the tosyl and *n*hexyl substituent would induce axial strain, making this an unfavourable intermediate. Alternatively, if the tosyl group and *n*hexyl substituent were to position themselves away from each other the axial strain would be relieved, leading to the nitrogen lone pair no longer being able to donate electronically into the diene system. Instead, it would appear that the mildly electron-donating dienyl alkyl groups are actually forming the largest HOMO coefficient on the exocyclic methylene, or that steric effects are playing a more important role, giving the observed regioselectivity (Figure 3.2).

Predicted Regioselectivity:



Observed Regioselectivity:

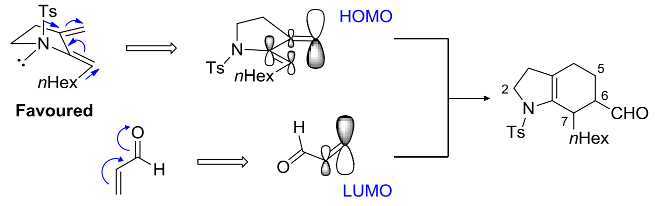
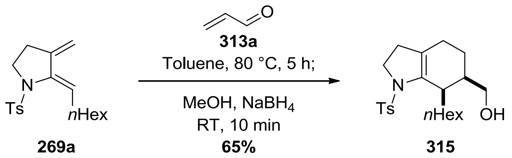


Figure 3.2 – Predicted and Observed Regioselectivity

With the regioselectivity confirmed, in order to identify the diastereomer formed, a series of nOe experiments were conducted and by considering the four possible conformers (with the pyrrolidine ring omitted for clarity) it was determined that the product ***endo*-314a** was the most highly populated conformer (Figure 3.3). This is the only conformer which is consistent with all the nOe enhancements, with the alternative conformers containing inconsistencies, supporting an *endo*-cycloaddition.

It is also worthwhile noting that the product **314a** was prone to epimerisation at the C6 centre and therefore, in order to enable isolation, a one-pot two-step procedure was designed involving the Diels-Alder cycloaddition followed by dilution with MeOH and reduction with $NaBH_4$ to afford alcohol **315** (Scheme 3.14).



Scheme 3.14 – One-pot Diels-Alder Cycloaddition/Reduction

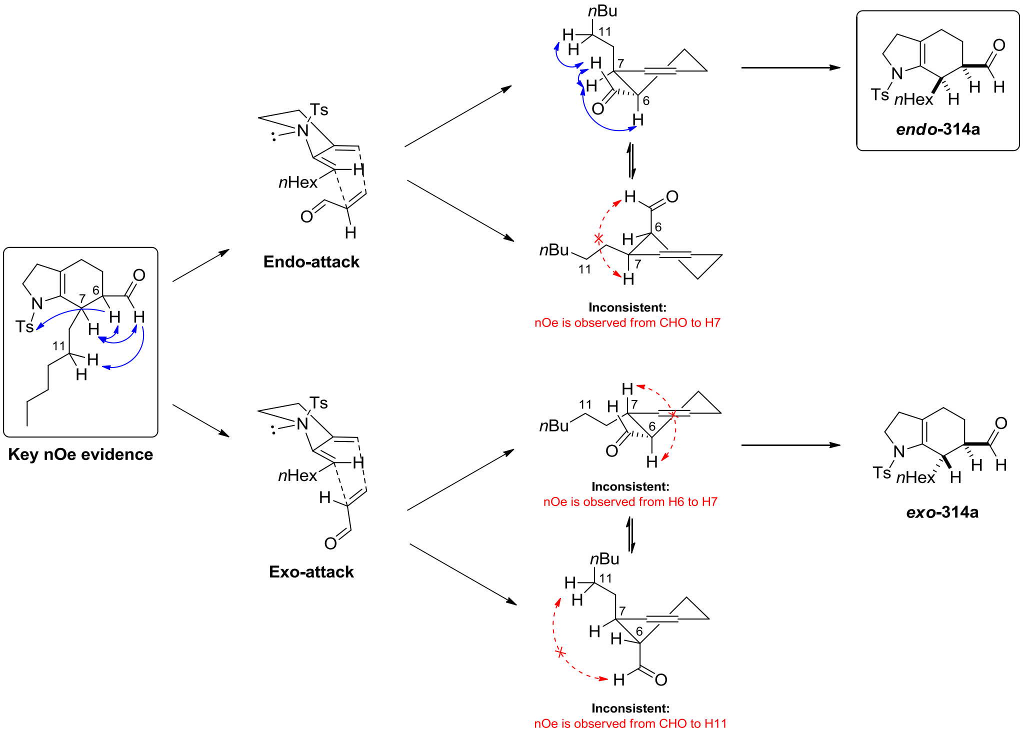
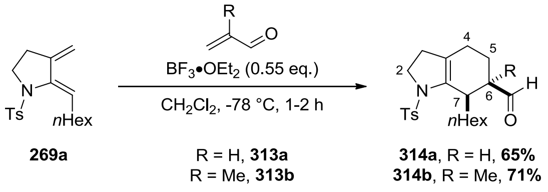


Figure 3.3 – nOe Evidence and Conformational Considerations

3.6.2. Lewis-Acid Catalysed Cycloadditions

Having discovered that acrolein underwent a thermal Diels-Alder reaction with amidodiene **269a** with unexpected regioselectivity, our attention turned to Lewis-acid catalysed conditions which might allow the introduction of additional dienophiles. By employing BF_3•OEt_2 as the catalyst it became possible to not only conduct the cycloaddition of **269a** with acrolein with a reduced reaction time, but the equivalent reaction with methacrolein also proved successful with cycloadduct **314b** being obtained as a single regio- and diastereomer (Scheme 3.15).[145] This represented our first example of an azacycle containing a quaternary carbon, which again was something we could not achieve using the cascade cyclisation methodology.



Scheme 3.15 – Lewis-Acid Catalysed Diels-Alder Cycloadditions

The regioisomer of **314b** was assigned based on a ^1H-^1H NMR COSY correlation between H4 and H5, and the lack of a correlation between H7 and H6 as would be expected in the other regioisomer. Using the same method for **314a**, the diastereomer could then be assigned by comparison of a series of nOe enhancements with the four possible conformers which again suggested the product ***endo*-314b** with the conformation shown was formed (Figure 3.4).

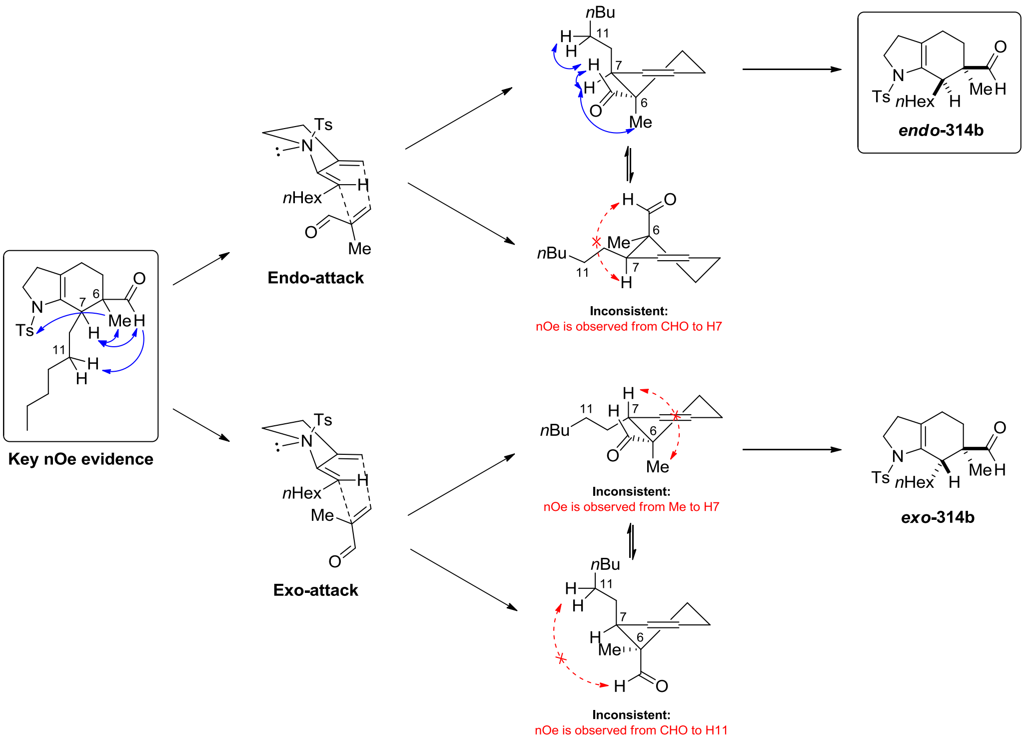
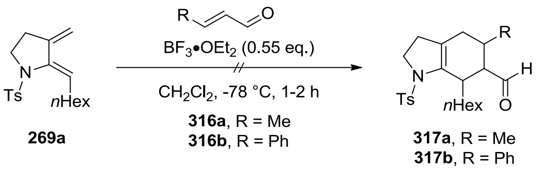


Figure 3.4 – nOe Evidence and Conformational Considerations

Following the successful Lewis-acid catalysed cycloadditions with acrolein and methacrolein, in an attempt to introduce an α,ß-disubstituted unsymmetrical alkene to enable a tri-substituted 6-membered ring to be formed, the previously successful conditions were attempted with the dienophiles crotonaldehyde **316a** and cinnamaldehyde **316b** (Scheme 3.16). Disappointingly, cycloadducts **317a** and **317b** were not formed, with only partial recovery of the starting material potentially due to hydrolysis of the exocyclic-amidodiene on the addition of MeOH/H_2O, suggesting that the additional substituent is preventing the cycloaddition from occurring, potentially due to increased steric interactions.

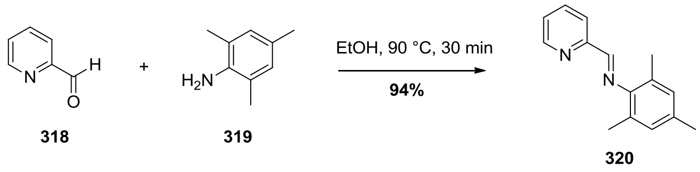


Scheme 3.16 – Lewis-Acid Catalysed Diels-Alder Cycloadditions

3.6.3. Cobalt-Catalysed Cycloadditions

Having demonstrated the ability to conduct cycloadditions of amidodiene **269a** with symmetrical alkynes and unsymmetrical α-substituted enals, we were inspired by the work of Hilt *et al.*[146] who have reported the selective *meta*- and *para*-directing cobalt-catalysed Diels-Alder reaction of acyclic dienes with terminal and disubstituted unsymmetrical alkynes. By varying the ligands on the catalyst from $CoBr_2$(dppe), which gave *para*-substituted products,[147] to $CoBr_2$(py-imine), a *meta*-selective Diels-Alder reaction was also possible.[148,149]

In order to attempt these conditions, which have proved very successful on non-activated substrates, the first step was to form the required catalysts which were not commercially available. The py-imine ligand **320** was readily synthesised from the reaction of pyridine carboxaldehyde **318** and 2,4,6-trimethylaniline **319** (Scheme 3.17).[150]



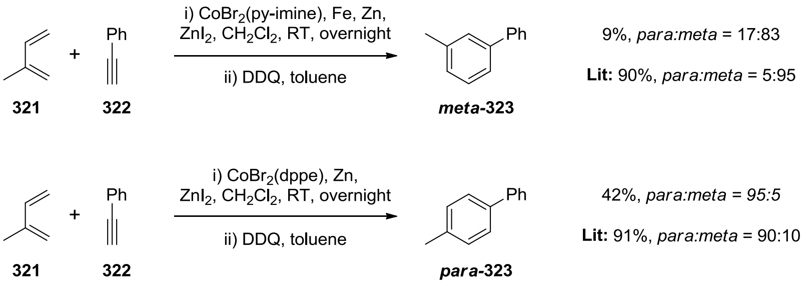
Scheme 3.17 – Synthesis of Py-imine Ligand

With the py-imine ligand **320** and commercially available dppe in hand, the two catalysts could be simply formed by stirring each ligand with anhydrous $CoBr_2$ in anhydrous THF overnight, followed by removal of the solvent *in vacuo* (Scheme 3.18).[151]

$$\mathrm{CoBr_2(dppe)} \xleftarrow[\text{quant.}]{\text{dppe, THF, RT}} \mathrm{CoBr_2} \xrightarrow[\text{quant.}]{\text{py-imine } \mathbf{320}\text{, THF, RT}} \mathrm{CoBr_2(py\text{-}imine)}$$

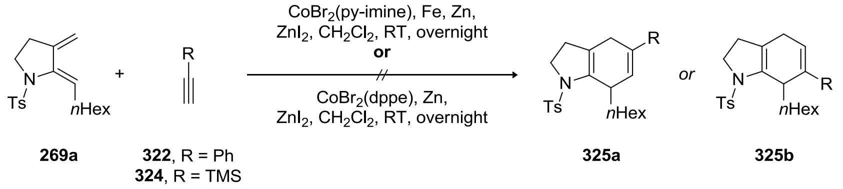
Scheme 3.18 – Formation of Cobalt Catalysts

Before attempting the cobalt-catalysed cycloadditions with our amidodienes, the homemade catalysts were tested with known literature examples to confirm that we could reproduce similar results (Scheme 3.19).[149] Pleasingly, similar *para*:*meta* ratios of product were obtained, although the yields were considerably lower, which was felt to be due to the reactions not being conducted in a sealed Schlenk tube which would have prevented loss of the volatile diene **321**.



Scheme 3.19 – Literature Known Cycloadditions with Homemade Cobalt Catalysts

Having tested the catalysts and feeling confident that the loss of starting material would not be an issue with amidodiene **269a**, both sets of conditions were attempted with phenylacetylene **322** and trimethylsilylacetylene **324** (Scheme 3.20). Disappointingly, no cycloadducts were formed with only isomerisation of **269a** from the *Z*-alkene to the *E*-alkene visible in the crude ^{1}H NMR spectra.



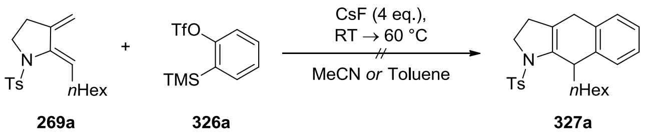
Scheme 3.20 – Cobalt-Catalysed Cycloadditions

There have been reported examples of acyclic dienes with bulky substituents on the diene terminus[152] and with multiply substituted dienes[153,154] which suggests that it is not sterics preventing amidodiene **269a** from reacting. There has also been a report of some unpublished results demonstrating that a trimethylsiloxy substituent adjacent to an acyclic diene is tolerated, suggesting that an electron-donating substituent does not prevent the reaction from occurring.[146] However, as far as we are aware, no cyclic (constrained) dienes have been utilised under the same reaction conditions which could suggest that it is the cyclic nature of our amidodiene that explains the lack of reactivity.

3.6.4. Aryne Cycloadditions

Having found successful conditions for both thermal and Lewis-acid catalysed cycloadditions, but having had no luck with cobalt-catalysed conditions, we were attracted to extending these Diels-Alder processes by using arynes. This would provide access to tricyclic systems which would not be readily synthesised through our other methodology.

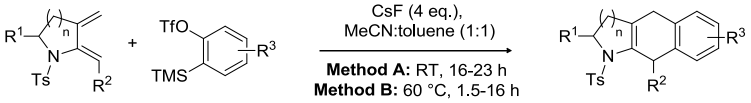
Initial investigations utilising the well known literature conditions of CsF in MeCN with benzyne precursor **326a** at room temperature proved unsuccessful with no reaction occurring (Scheme 3.21).[155,156] However, it became apparent that amidodiene **269a** was insoluble in MeCN and therefore the reaction was slowly elevated in temperature to 60 °C in the hope that this would enable the amidodiene to undergo the cycloaddition with benzyne. Unfortunately, this had no effect on the reactivity and therefore the reaction was attempted in the alternative solvent toluene, which provided a suitable means of dissolving the starting material, but disappointingly cycloadduct **327a** could still not be obtained.

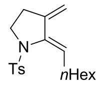
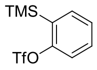
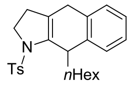
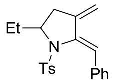
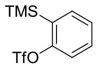
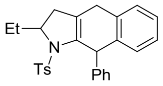
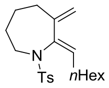
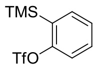
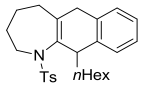
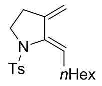
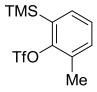
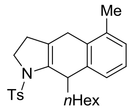
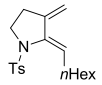
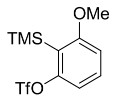
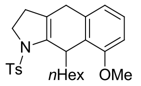
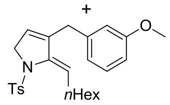
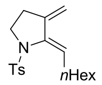
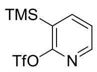
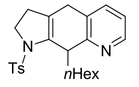


Scheme 3.21 – Initial Investigations into Aryne Cycloadditions

This result suggested that MeCN was required for aryne formation, and pleasingly it was found that by using a 1:1 ratio of MeCN:toluene, at room temperature for 19 hours, cycloadduct **327a** could be obtained in 81% yield.[157] It was also possible to greatly reduce the reaction time to 2 hours when the reaction was conducted at 60 °C, although a slight loss in yield occurred (Table 3.5, entry 1).

Table 3.5 – Aryne Substrate Screen



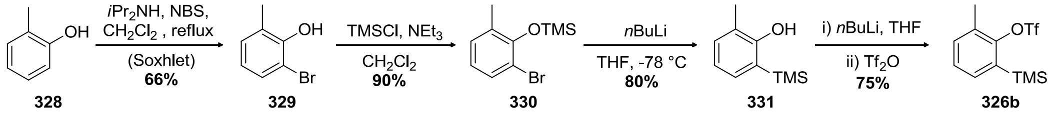
	Amido-diene	Aryne Precursor	Product	Conditions, Time	Yield	*dr/rr*[a]
1	 **269a**	 **326a**	 **327a**	**A**, 19 h **B**, 2 h	81% 63%	N/A
2	 **269l**	 **326a**	 **327b**	**B**, 1.5 h	72%	1:0
3	 **269n**	 **326a**	 **327c**	**B**, 16 h	85%	N/A
4	 **269a**	 **326b**	 **327d**	**A**, 21 h	65%	2:1
5	 **269a**	 **326c**	 **327f** +  ene-product **328**	**A**, 23 h **B**, 2 h	76% 71%	3.1:1(:1.2 **328**) 4.1:1(:1.7 **328**)
6	 **269a**	 **326d**	 **327h**	**A**, 21 h **B**, 2 h	0% 0%	N/A

[a] Ratio indicates ratio of diastereomers (*dr*) or regioisomers (*rr*) in the crude reaction mixture as determined by ^{1}H NMR spectroscopic analysis; major isomer shown

Taking these conditions it was possible to demonstrate the reactivity of benzyne with an α-branched amidodiene **269l** (entry 2). We were pleased to find that only a single diastereomer was formed, whose configuration could not be determined, but which nonetheless either reflects the effect that the sulfonamide and its two adjacent substituents have on the conformation of the diene or the effect of an additional substituent based on steric interactions, both of which would control the facial selectivity of the cycloaddition. The reaction with a 7-membered amidodiene

269n also proved successful (entry 3), although this reaction would not occur at room temperature, which again reflects the influence of ring size and flexibility on diene reactivity.

Satisfied that the cycloaddition with benzyne could be tolerated with a range of amidodienes, the aryne precursor was then varied (entries 4-6). The methyl-substituted aryne precursor **326b** was selected to investigate the effect of steric interactions in the cycloaddition. Utilising literature procedures, **326b** could be synthesised *via* Soxhlet bromination of phenol **328**, followed by silyl protection, Brook rearrangement and triflate formation (Scheme 3.22).[158-161]

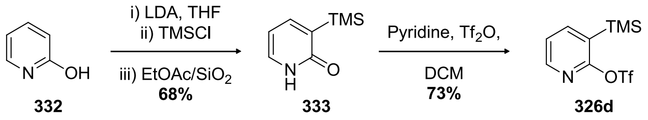


Scheme 3.22 – Aryne Precursor Formation

On employing the methyl-substituted aryne precursor **326b** with amidodiene **269a** a mixture of regioisomers was observed, with the major isomer **327d** bearing the methyl substituent distal to the hexyl side chain of the diene to minimise steric interactions (entry 4).

Next, the commercially available methoxy-substituted aryne precursor **326c** was utilised which again gave a mixture of regioisomers (entry 5). However, the major isomer **327f** now placed the methoxy substituent near the hexyl side chain, supporting our view that the sulfonamide nitrogen has a negligible electron-donating effect in the cycloaddition, which was initially observed with the dienophiles acrolein/methacrolein. Notably, the side-product **328** was also observed, arising from an ene reaction with a hydrogen atom on the pyrrolidine ring, whose intermediate, like that for the major cycloaddition isomer, could also be derived from the advanced bond formation at the exo-methylene terminus. However, it is possible that due to a disfavourable steric interaction between the methoxy substituent and the hexyl side chain, instead of a cycloaddition occurring, a competitive ene reaction occurred.

Lastly, 2,3-pyridyne **326d** was selected as a dienophile based on reported computational studies which predict that C2 attack would be favoured, giving promise that a regioselective cycloaddition would be possible.[162] The 2,3-pyridyne precursor could be synthesised utilising similar literature conditions as to those used for the methyl-substituted aryne precursor **326b** (Scheme 3.23).[163]

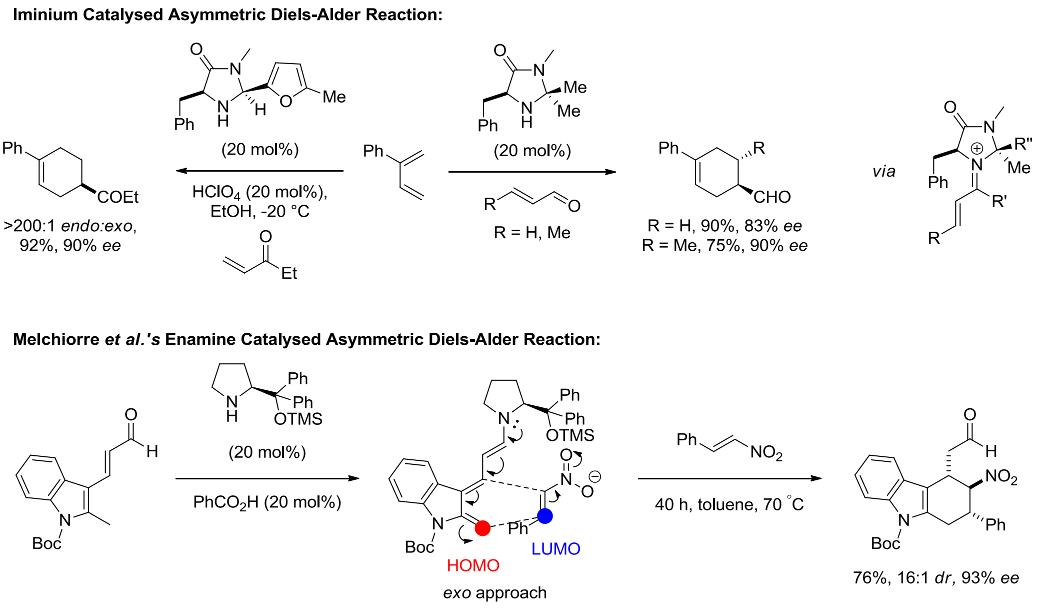


Scheme 3.23 – 2,3-Pyridyne Precursor Formation

Disappointingly, no reaction occurred with amidodiene **269a** at both room temperature and at 60 °C, with the 2,3-pyridyne precursor being consumed almost immediately based on TLC analysis of the crude reaction mixture (entry 6). The mixture also changed from colourless to black, an observation which had not been seen previously with all the other aryne cycloadditions. This suggested that whilst the desired pyridyne was being formed, it was too reactive and short-lived in order for a cycloaddition to occur with the amidodiene. Therefore, the very slow dropwise addition of a dilute solution of the pyridyne precursor **326d** to a solution of the amidodiene **269a** and CsF in MeCN/toluene was attempted over 8 hours. Unfortunately, this method also proved unsuccessful and only amidodiene **269a** was recovered. There is a single reported example of the successful cycloaddition of 2,3-pyridyne with a highly electron-rich methoxy-substituted furan, in which issues of pyridyne formation were encountered if water was present, but even after carefully flame-drying of the CsF before use with inert anhydrous conditions, the reaction still did not occur.[163]

3.6.5. Preliminary Investigations Into Asymmetric Cycloadditions

Following on from the success of the cycloadditions thus far, we were attracted to the prospect of developing an asymmetric process, and proposed a two-pronged approach. Whilst there are many asymmetric cycloadditions controlled by chiral Lewis-acids,[164,165] we thought to investigate the use of chiral organocatalysts.[166] Firstly, based on the findings by Melchiorre *et al.*,[167] an enamine-based activation of the diene with Jørgensen's organocatalyst would be attempted. Secondly, a traditional iminium-based activation of the dienophile could be explored using MacMillan's catalyst (Scheme 3.24).[168,169]



Scheme 3.24 – Literature Examples of Asymmetric Diels-Alder Reactions

Therefore, overall, two modes of activation were to be investigated: the iminium catalysis would involve the LUMO-lowering activation of the α,β-unsaturated aldehydes or ketone dienophile, whilst the enamine catalysis would involve the HOMO-raising addition of the enamine nucleophilic diene to the dienophile (Figure 3.5).

Whilst the *endo*-cycloadduct was obtained with the thermal and Lewis-acid catalysed cycloadditions with acrolein, if MacMillan's chiral organocatalyst is introduced in an iminium catalysed process, the increased steric interaction may now favour the *exo*-cycloadduct. With regards to the enamine catalysis, Melchiorre *et al.* suggest that the favoured transition state would be an *exo* approach due to π(Ph)-π(diene) interactions, and the avoidance of electrostatic repulsion formed during *endo* approach.

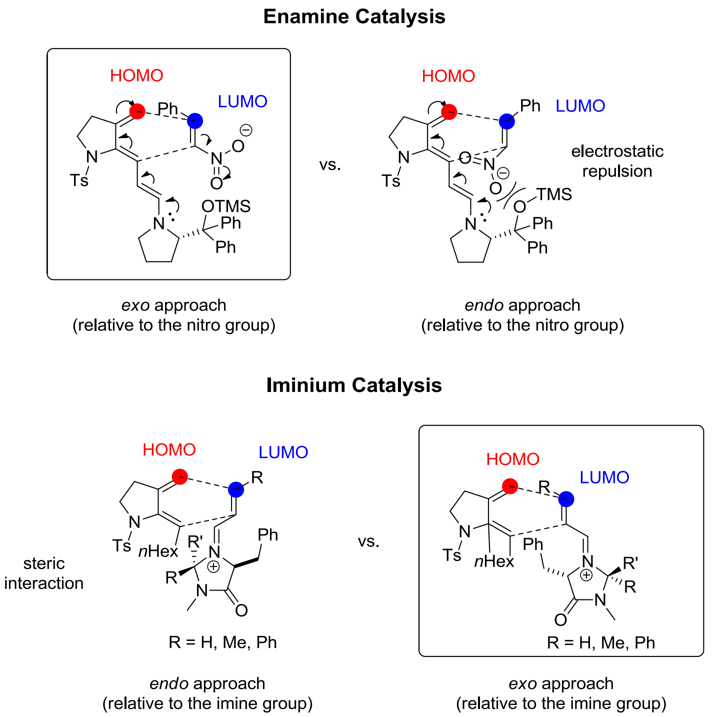
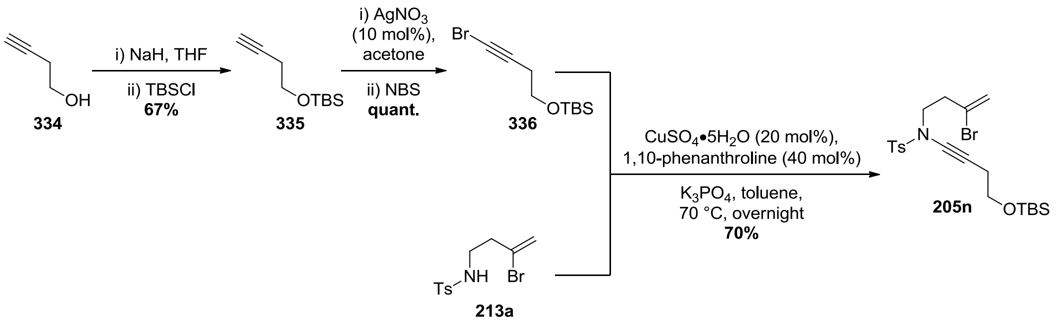


Figure 3.5 – Iminium and Enamine Activation in Diels-Alder Reactions

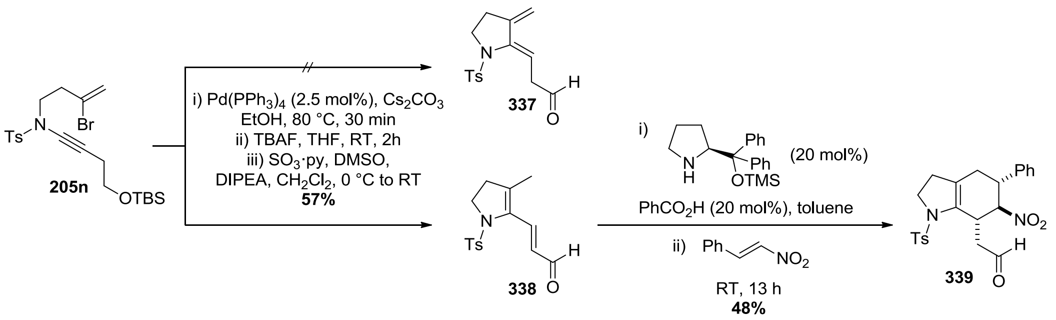
Enamine Catalysis

In order to investigate the proposed enamine-catalysed asymmetric Diels-Alder reaction, the synthesis of a modified amidodiene compared to those used in the substrate screen was required. Firstly, bromoenynamide **205n** was synthesised with the previously described methods in Chapter 2, which contains one less methylene unit on the ynamide terminus than previously used (Scheme 3.27).



Scheme 3.27 – Bromoenynamide Formation

With bromoenynamide **205n** in hand, the reductive cyclisation could be conducted but disappointingly, the exocyclic diene formed proved to be prone to polymerisation. Therefore, a three-step procedure was employed avoiding the need for multiple purification steps (Scheme 3.28), beginning with the reductive cyclisation followed by a solvent switch to THF and desilylation of the crude material. The free alcohol could then be rapidly filtered through a short plug of Celite® before concentration *in vacuo* and submission to a Parikh-Doering oxidation. Initially, aldehyde **337** was the targeted product but the fully isomerised product **338** was actually isolated, which whilst similar to the literature reported examples,[167] could prove to be problematic during enamine formation due to deprotonation being possible in two positions.



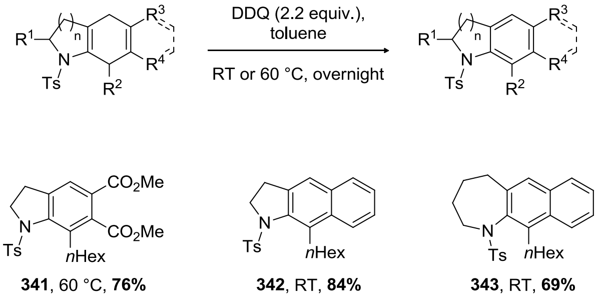
Scheme 3.28 – Enamine-Catalysed Asymmetric Cycloaddition

Pleasingly, on submission of **338** to the literature optimised conditions with nitrostyrene, the desired cycloadduct product was obtained as a single diastereomer. However, the benzoic acid which was used for catalyst salt formation was inseparable from the cycloadduct product **339** during column chromatography. Finally, whilst it was not possible to conduct the reaction with the opposite enantiomer of Jørgensen's catalyst to enable determination of the *ee* of the reaction (due to lack of substrate **338** and time constraints), the specific rotation was found to be −39.7 ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −39.7 (c = 0.14, CHCl$_3$)) which demonstrates that the reaction did involve some level of enantioselectivity.

3.7. Oxidations of 1,4-Amidodienes

Finally, we recognised that the cycloaddition products with alkynes and arynes could be oxidised to the corresponding bicyclic heteroaromatics with complimentary substitution patterns to those obtained using our cascade methodology, and also to tricyclic heteroaromatic systems which we could not previously access.

Pleasingly, whilst our previous oxidant of choice MnO_2 afforded a mixture of oxidation states, the 1,4-amidodienes could be cleanly oxidised using DDQ. Application of these conditions successfully provided access to indoline **341**, benzoindoline **342** and naphthoazepine **343** in good yields (Scheme 3.29).



Scheme 3.29 – Oxidations of 1,4-Amidodienes

3.8. Conclusions and Future Work

In conclusion, we have developed the first example of a carbopalladation/reductive cyclisation process on an alkyne which utilises an alcohol as the hydride source, generated *via* ß-hydride elimination of a palladium alkoxide. The reaction allows conversion of a wide range of bromoenynamides to cyclic amidodienes which in themselves are viable substrates for Diels-Alder cycloadditions with electron-deficient alkenes and alkynes including arynes, providing a straightforward route to bi- and tricyclic azacycles. There is also the potential to develop an enamine-catalysed asymmetric Diels-Alder process as shown by the preliminary investigations, and to investigate the possibility of an iminium-catalysed asymmetric cycloaddition using

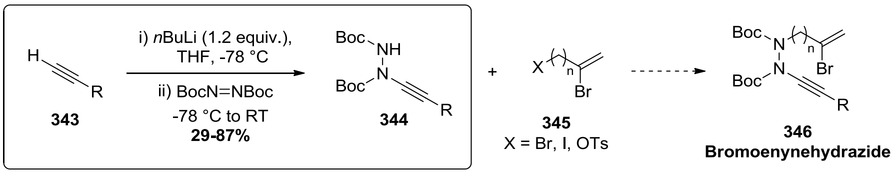
MacMillan’s catalyst. Finally, the 1,4-amidodienes formed from these cycloadditions can also be submitted to oxidation conditions to afford a complimentary range of bi- and tricyclic heteroaromatic systems compared to those obtained using the cascade methodology.[170]

4. Palladium-Catalysed Cyclisations of Bromoenynhydrazides

4.1. Introduction

Following the successful development of the palladium-catalysed cascade cyclisation and reductive cyclisation/Diels-Alder sequence with bromoenynamides, we were keen to investigate the application of the same methodologies on an alternative range of substrates.

In 2012, Beveridge and Batey reported a general synthesis of ynhydrazides **344** from commercially available alkynes and diazodicarboxylates (Scheme 4.1).[171] Having had no success in forming an ynhydrazide in the same manner as an ynamide (using Hsung's copper-mediated cross coupling conditions as described earlier), they turned to the use of *in situ* generated lithium acetylides and their subsequent addition to DBAD (di-*tert*-butyl azodicarboxylate). We postulated that if following acetylide addition to DBAD, the generated carbamate anion could be quenched by addition of another electrophile such as **345**, bromoenynhydrazides **346** could be formed in a single one-pot sequence.

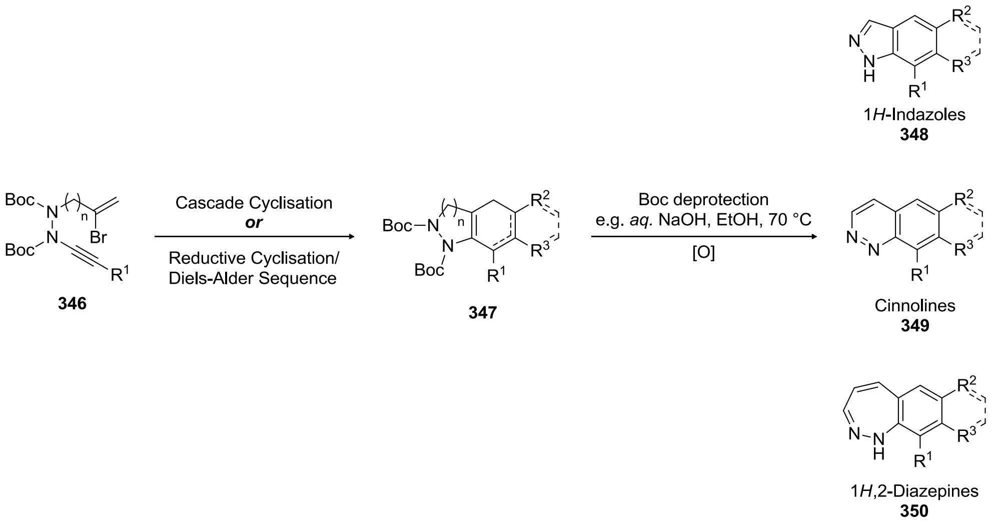


Scheme 4.1 – Synthesis of Bromoenynhydrazides

These analogous substrates to bromoenynamides would offer a number of advantages: firstly, the substrates could potentially be made in a single step compared to the 3 or 4 normally required for the bromoenynamides; secondly, a readily manipulated Boc group can be utilised instead of the previously required tosyl group and finally, with a large range of commercially available terminal alkynes available there is the opportunity for a broad substrate scope.

It was envisaged that with a large range of substrates in hand, application of our previously developed methodologies would lead to the both the 1,3- and 1,4-amidodienes **347**, which on

Boc deprotection[172] and oxidation could lead to a complimentary, and relatively unusual range of heteroaromatic structures including indazoles **348**, cinnolines **349** and diazepines **350** (Scheme 4.2).



Scheme 4.2 – Proposed Bromoenynhydrazides Cyclisations

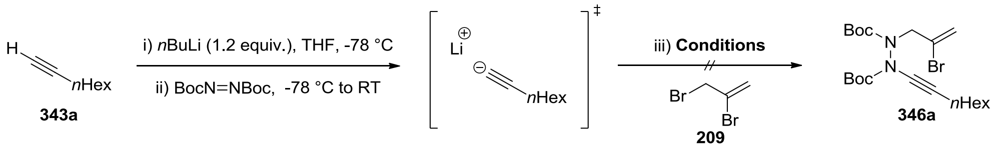
Generally, these classes of structures are comparatively rare in nature compared to indolines, indoles, tetrahydroquinolines and benzazepines. However, both indazoles[156,173] and cinnolines[172] are known to exhibit a wide range of pharmacological activity and are therefore of great synthetic interest.

Our proposed palladium-catalysed cyclisations with bromoenynhydrazides offer the same synthetic advantages as to those with bromoenynamides, namely, the formation of both rings in a single step in the cascade cyclisation enabling greater structural diversity, as again the majority of synthetic routes to such scaffolds involve heterocycle annulation onto a pre-functionalised benzene ring.[174,175] The methodology also has the added advantage of providing access to a range of ring sizes (5,6-, 6,6- and 7,6-heteroaromatics) by simply varying the substrate tether length, whereas currently, different routes are utilised to access each individual scaffold.

4.2. Bromoenynhydrazide Synthesis

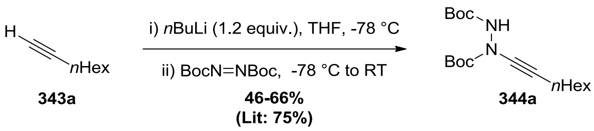
Initial investigations began with a one-pot procedure in an attempt to access bromoenynhydrazide **346a** (Table 4.1). It was hoped that after lithium acetylide addition to DBAD (monitored by TLC analysis), the newly formed nitrogen anion would react with 2,3-dibromopropene **209** directly. Unfortunately, whilst the ynhydrazide intermediate **344a** was formed, no reaction occurred on addition of **209**, even after a prolonged reaction time at room temperature (entry 1) or at an elevated temperature (entry 2). It is worth noting that similar unsuccessful results with other electrophiles were also found by Craig Campbell, a post-doctoral research assistant in the group, with the exception of allyl bromide which was successfully introduced to form an enynhydrazide in a 59% yield.

Table 4.1 – One-pot Synthesis of Bromoenynhydrazides



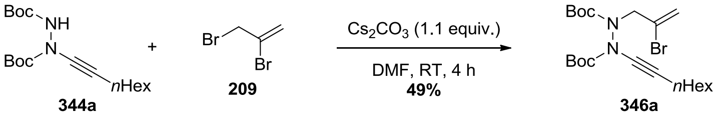
	Conditions	Yield
1	RT, 18 h	n.r.
2	60 °C, 18 h	n.r.

Following this unsuccessful one-pot procedure, the ynhydrazide **344a** was formed according to the reported literature procedure (Scheme 4.3). Notably, whilst the product was formed the isolated yields were always inferior to the reported yields, and on attempting to introduce phenylacetylene and cyclohexylacetylene the literature results proved difficult to reproduce with none of the desired products being isolated, an issue which was also reported by fellow chemists within the group.



Scheme 4.3 – Ynhydrazide Formation

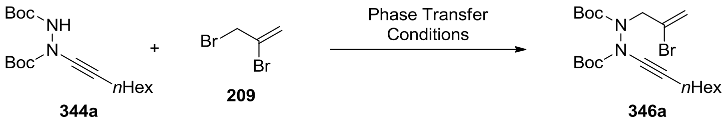
Rather than examining the process as a single step, we next attempted to address the alkylation step separately using the isolated ynhydrazide **344a**. Several methods to introduce 2,3-dibromopropene **209** were investigated, beginning with traditional allylation conditions which had been shown to be successful on di-*tert*-butyl hydrazine-1,2-dicarboxylates (Scheme 4.4).[176] Pleasingly, the use of Cs_2CO_3 and DMF afford the desired bromoenynhydrazide **346a** in a 49% yield.



Scheme 4.4 – Allylation of Ynhydrazides

Whilst our first synthesis of the desired bromoenynhydrazides **346a** was thus only two simple steps, it was desirable to try and improve the isolated yield and therefore phase transfer conditions were next investigated. Two separate sets of conditions had been reported to be successful with similar hydrazides and alkylating agents, and so were attempted (Table 4.2).[177,178] The use of benzyltriethylammonium chloride as the phase transfer catalyst in the presence of K_2CO_3 afforded **346a** in 53% yield, offering no real improvement over the standard allylation conditions (entry 1). However, concurrent use of *two* phase transfer catalysts tetrabutylammonium hydrogen sulfate (TBAHS) and tetrabutylammonium iodide (TBAI), in the presence of *two* bases (K_2CO_3 and NaOH), led to the isolation of bromoenynhydrazide **346a** in a pleasing 74% yield (entry 2).

Table 4.2 – Preliminary Investigations of Phase Transfer Conditions

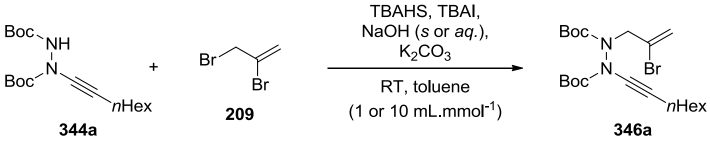


	Conditions	Yield
1	$BnEt_3N^+Cl^-$ (0.1 equiv.), K_2CO_3 (4 equiv.), MeCN, 17 h, RT	53%
2	TBAHS (0.1 equiv.), TBAI (0.1 equiv.), NaOH (3.5 equiv.), K_2CO_3 (2.0 equiv.), toluene, 2 h, RT	74%

In spite of the success of these conditions, it was felt that with the use of two catalysts and two bases, there was room for improvement (Table 4.3). First, the requirement for both bases was tested and it was found that in the absence of NaOH the reaction did not occur, suggesting it is a requirement for the phase-transfer conditions to work (entry 2). If the reaction mixture did not contain K_2CO_3 the reaction still proceeded but with an inferior isolated yield, even after an extended reaction time (entries 3 & 4). Finally, as both sets of conditions had used solid bases with 'bottle' solvents, a biphasic system was investigated. Pleasingly, if a 25% aqueous solution of NaOH was utilised, the desired product could be isolated in a 72% yield (entry 5). Initially, there was concern that with such an excess of NaOH the product might suffer from decomposition *via* bromide elimination, but we were relieved to find that even with prolonged reaction times the yield was not reduced (entry 6).

Secondly, the requirement for both phase transfer catalysts was investigated, and repeated with each of the combinations of bases previously discussed. It was found that in the absence of TBAI the yields were greatly reduced (entries 7-10) and the same effect was also observed when TBAHS was removed (entries 11-14). Therefore, it was deduced that both catalysts were required for optimum performance, with the iodide counterion from TBAI potentially substituting the bromide, thus promoting the coupling. Based on these findings, the optimised conditions to be used in future reactions were either a combination of both solid bases and both catalysts (entry 1), or aqueous NaOH and both catalysts (entries 5 & 6).

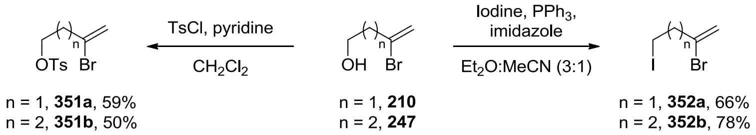
Table 4.3 – Optimisation of Phase Transfer Conditions



	TBAHS (0.1 eq.)	TBAI (0.1 eq.)	NaOH (solid, 3.5 eq.) *or* (*aq.* 25% NaOH, 10 mL.mmol^{-1})	K_2CO_3 (2.0 eq.)	Toluene (mL.mmol^{-1})	Time	Yield[a]
1	✓	✓	Solid	✓	1	2 h	74%
2	✓	✓	×	✓	1	18 h	n.r.
3	✓	✓	Solid	×	1	3.5 h	61%
4	✓	✓	Solid	×	1	26 h	63%
5	✓	✓	Aq.	×	10	1 h	72%
6	✓	✓	Aq.	×	10	26 h	73%
7	✓	×	Solid	✓	1	2 h	55%
8	✓	×	×	✓	1	27 h	n.r.
9	✓	×	Solid	×	1	2 h	55%
10	✓	×	Aq.	×	10	1 h	34%
11	×	✓	Solid	✓	1	2 h	46%
12	×	✓	×	✓	1	27 h	n.r.
13	×	✓	Solid	×	1	2 h	n.d.[b]
14	×	✓	Aq.	×	10	1 h	58%

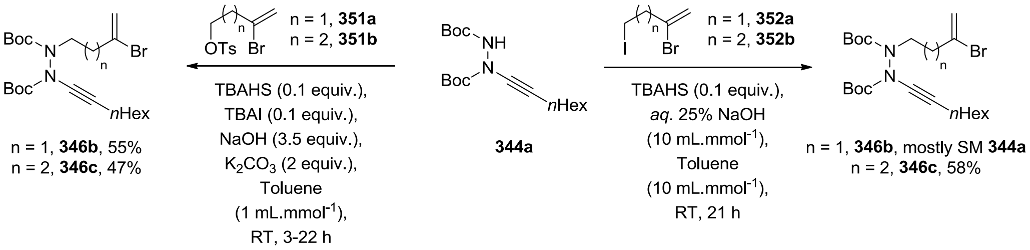
[a] Isolated Yield; [b] Unidentified side-product formed.

Having optimised the phase transfer conditions, we next turned to the synthesis of larger tether length bromoenynhydrazides. First, a synthesis of the coupling partners was required. These could be conveniently formed by either tosylation or iodination of the previously formed alcohols **210** and **247**, which were initially used during the formation of bromoenynamides (Scheme 4.5).



Scheme 4.5 – Tosylation and Iodination of Alcohols

Submission of the tosylates **351a** and **351b** and ynhydrazide **344a** to the phase transfer conditions using both bases pleasingly afforded the larger tether length bromoenynhydrazides **346b** and **346c** (Scheme 4.6).



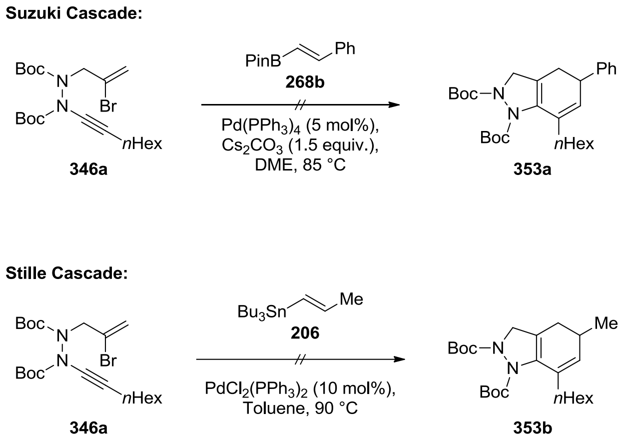
Scheme 4.6 – Larger Tether Length Bromoenynhydrazide Formation

However, when the iodides **352a** and **352b** were submitted to conditions with TBAHS and *aq.* NaOH (TBAI not included as iodide leaving group already present), only the reaction with **352b** was successful forming the bromoenynhydrazide **346c**, which would give us access to a 7-membered ring in future reactions. This may suggest that iodide **346b** could be undergoing competing elimination or $^{\ominus}$OH substitution, preventing reaction with ynhydrazide **344a**. However, with the use of catalytic TBAI with 2,3-dibromopropene **209** or tosylates **351a** and **351b**, only small quantities of the iodide would be produced at any one time which would be rapidly coupled, enabling the desired bromoenynhydrazides to be formed.

It is worth noting that the characterisation of the bromoenynhydrazides proved difficult, with broad signals in the NMR spectra due to rotameric forms of both carbonates, which even on conducting a VT NMR at 90 °C in d_8-toluene were still relatively unresolved.

4.3. Palladium Catalysed Cascade Cyclisation

Satisfied that the bromoenynhydrazides could be successfully formed in only two steps, preliminary studies were conducted to discover if they would be viable substrates in the cascade cyclisation. Employing the optimised conditions from both the Suzuki and Stille cascade with bromoenynhydrazide **346a** in an attempt to form the 5,6-systems **353a** and **353b** proved more difficult than expected (Scheme 4.7).



Scheme 4.7 – Palladium-Catalysed Cyclisation of Bromoenynhydrazides

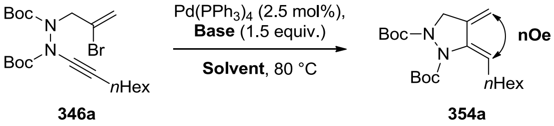
Disappointingly, neither the Suzuki or Stille cascade formed the desired amidodienes with the crude ^{1}H NMR spectra being very complex and somewhat unclear. It is possible that the bromoenynhydrazide is more electron-rich than the corresponding bromoenynamides. For comparison, when a bromoenynamide containing an electron-rich substituent was used in the cascade cyclisations only impure products were formed in low yields (Table 2.8, entries 5 & 6), suggesting that the difference in the electronic properties may have a detrimental effect on the cyclisation.

In an attempt to discover if the Stille cascade would be more successful at a lower temperature, and to see if any of the desired product had been formed, a VT NMR experiment was conducted using the same conditions as in Scheme 4.7 in d$_8$-toluene slowly raising the temperature by 10 °C up to 90 °C. Unfortunately, this did not help matters; at low temperatures no reaction was observed, and heating again led to a complex mixture of products. Given the complexity of the process, we turned our attention to the reductive cyclisation.

4.4. Reductive Cyclisation/Diels-Alder Cycloaddition Sequence

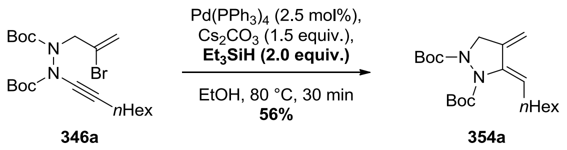
Following the unsuccessful cascade cyclisations, bromoenynhydrazides **346a** was submitted to the optimised reductive cyclisation conditions (Table 4.4). It was gratifying to find that the exocyclic diene **354a** could be formed as a single geometric isomer (determined by nOe analysis) in a 55% yield (entry 1). Since this yield was inferior to the bromoenynamide analogue (83%) the reaction was repeated and the product was isolated in an unimproved 49% (entry 2). The optimised conditions for the 6- and 7-membered rings was also attempted to see if any improvement could be made with regards to the yield, but unfortunately the product was still formed in a similar amount (entry 3).

Table 4.4 – Reductive Cyclisation of Bromoenynhydrazides



	Base	Solvent	Time	Yield
1	Cs_2CO_3	EtOH	1 h	55%
2	Cs_2CO_3	EtOH	1 h	49%
3	K_2CO_3	Toluene/EtOH (1:1)	22 h	53%

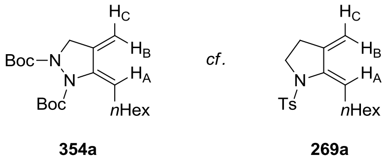
Pleased with having obtained the desired exocyclic diene, but in a moderate yield, the cyclisation was attempted in the presence of the reductant triethylsilane (Scheme 4.8). Interestingly, even in the presence of a ‘traditional’ reductant alongside the ethanol there was no improvement in the isolated yield, suggesting that in this example the triethylsilane is not a superior hydride source as one might have predicted.



Scheme 4.8 – Reductive Cyclisation with Triethylsilane

On analysis of the chemical shifts of the diene protons in comparison to the analogous sulfonamide diene **269a**, it is possible to see that the enamide proton H_A is further upfield, and *exo*-methylene protons H_B and H_C are further downfield (Table 4.5). This change in shift can be explained by the nitrogen lone pair adjacent to the alkene having an electron-donating effect, compared to the sulfonamide diene which, based on experimental data from the cycloadditions, had an electron-withdrawing effect. Therefore, if electron donation is possible in **354a**, H_A will be shielded moving the chemical shift upfield, which is clearly observed with the resonance being 5.61 ppm for **354a**, compared to 5.87 ppm for **269a**.

Table 4.5 – Comparison of Proton Shifts[a]



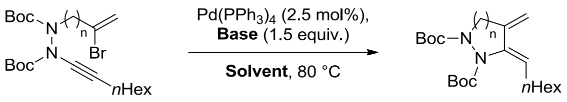
	354a (Boc)	269a (Ts)
H_A	5.61 ppm	5.87 ppm
H_B	5.30 ppm	5.20 ppm
H_C	4.90 ppm	4.64 ppm

[a] Assignment based on COSY and NOESY analysis

This suggests that the alkene with an adjacent *N*-Boc group is more electron-rich compared to that with an adjacent *N*-tosyl group, and by analogy so will the starting alkyne. Therefore, since the reductive cyclisation of electron-rich bromoenynamides was successful in a yield range of 61-66% (Table 3.2, entries 8 & 9), which is not dissimilar to the yield of 55% with bromoenynhydrazides, it demonstrates the sensitivity of the methodology to the electronic properties of the system. This difference should also have an effect on the regioselectivity of any subsequent cycloadditions.

Having deduced that the more electron-rich nature of the bromoenynhydrazides, and potentially the exocyclic diene product, were affecting the yield of product using these conditions, we were intrigued as to whether the more difficult substrates with longer tether lengths would also undergo successful cyclisation. Utilising the previously optimised conditions for the cyclisation of bromoenynamides to form 6- and 7-membered rings, the cyclisations of bromoenynhydrazides **346b** and **346c** were attempted (Table 4.6).

Table 4.6 – Reductive Cyclisation of Larger Tether Lengths



346b, n = 2
346c, n = 3

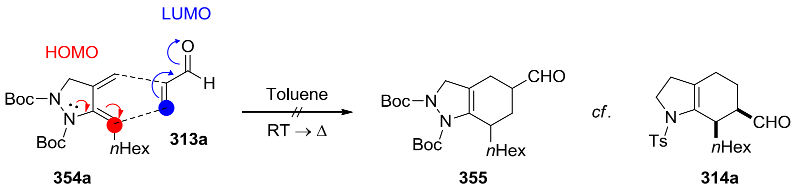
354b, n = 2
354c, n = 3

	Enynhydrazide	Base	Solvent	Time	Yield
1	**346b** (n =2)	K_2CO_3	Toluene/EtOH (1:1)	0.5 h	52%[a]
2	**346c** (n = 3)	K_2CO_3	Toluene/EtOH (1:1)	1 h	0%[b]
3	**346c** (n = 3)	Cs_2CO_3	EtOH	1.5 h	15%

[a] On characterisation some peaks over-integrating suggesting product contains impurities; [b] Crude ^{1}H NMR spectra very messy with no clear sign of product.

Whilst the cyclisation of **346b** appeared to be successful, on characterisation there appeared to be a large over-integration in the alkyl region suggesting that the isolated product was impure (entry 1). Disappointingly the cyclisation of **346c** proved unsuccessful with none of the desired product formed (entry 2), however, by employing the conditions for formation of the 5-membered ring, **354c** was isolated in a 15% yield (entry 3).

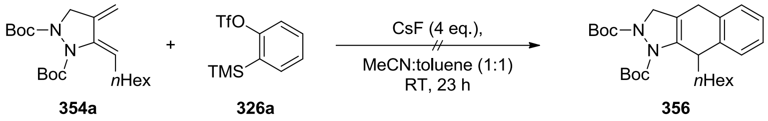
Even though it was disappointing that the reductive cyclisation conditions did not prove to be widely applicable to bromoenynhydrazides, especially for the larger ring sizes, we were particularly interested to discover if the cycloaddition with acrolein would afford the opposite regioisomer to that observed with the dienyl sulfonamides. With the exocyclic diene proton chemical shifts suggesting that the nitrogen lone pair has an electron-donating effect, it would now be expected that the largest HOMO coefficient would be on the enamide alkene, which should orient reaction with the LUMO of acrolein to afford the regioisomer **355** (Scheme 4.9).



Scheme 4.9 – Cycloaddition Between Exocyclic Diene **354a** and Acrolein

Unfortunately, on conducting the Diels-Alder reaction between **354a** and acrolein **313a** at a range of temperatures, the desired product was not formed with what appeared only to be starting material decomposition detected, potentially due to its increased reactivity compared to the sulfonamide diene **269a**.

Finally, the cycloaddition with benzyne was attempted to afford tricycle **356**, but again none of the desired cycloadduct was formed with **354a** having been consumed, which again suggested decomposition of the starting material (Scheme 4.10).

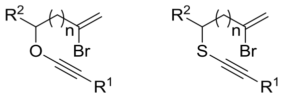


Scheme 4.10 – Benzyne Cycloaddition

4.5. Conclusions and Future Work

In conclusion, we have demonstrated the synthesis of bromoenynhydrazides and attempted their application in both our previously developed cascade methodologies and reductive cyclisation/Diels-Alder cycloaddition sequence. Unfortunately, due to bromoenynhydrazides being more electron-rich than bromoenynamides this proved difficult with only the reductive cyclisation to the 5-membered exocyclic diene being successful. However, on comparison to the electron-rich bromoenynamides which were investigated in both methodologies the outcome is consistent: electron-rich substrates tend to be less effective in the cascade cyclisation but work moderately well in the reductive cyclisation. This could be explained by the electron-rich substrate disfavouring the transmetallation step during the cascade cyclisation, whereas in the reductive cyclisation, as an alkoxide is formed which can associate and dissociate with the palladium catalyst, the reaction can still occur.

Based on our desire to investigate the application of the same palladium-catalysed cyclisations on an alternative range of substrates to afford complimentary sets of heteroaromatic systems, and the relative unsuccess of bromoenynhydrazides, future work could focus on the use of ynol or thiol ethers **357** and **358** (Scheme 4.11).



357 **358**

Scheme 4.11 – Proposed Alternative Substrates

5. Palladium-Catalysed Intramolecular Cyclisation

5.1. Introduction

As one of the final aims of the project the development and application of a bromoenynamide cascade cyclisation to a natural product was envisaged.

The trikentrin family of natural products comprises five indole alkaloids that were isolated from the marine sponge *Trikentrion flabelliforme*, found on the Australian coast, by Capon and co-workers in 1986.[179] The entire family showed antimicrobial activity against cultures of the gram positive bacteria *Bacillus subtilis*. A common structural feature of trikentrins is the 1,3-dimethylcyclopentane group fused to the indole ring, and the presence of one or two alkyl/alkenyl substituents on the benzenoid portion of the tricycle. This extensive substitution, particularly on (+)-*cis*-trikentrin B, made this an ideal target to demonstrate the capability of the cascade cyclisation methodology (Figure 5.1).

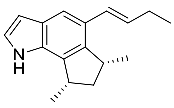
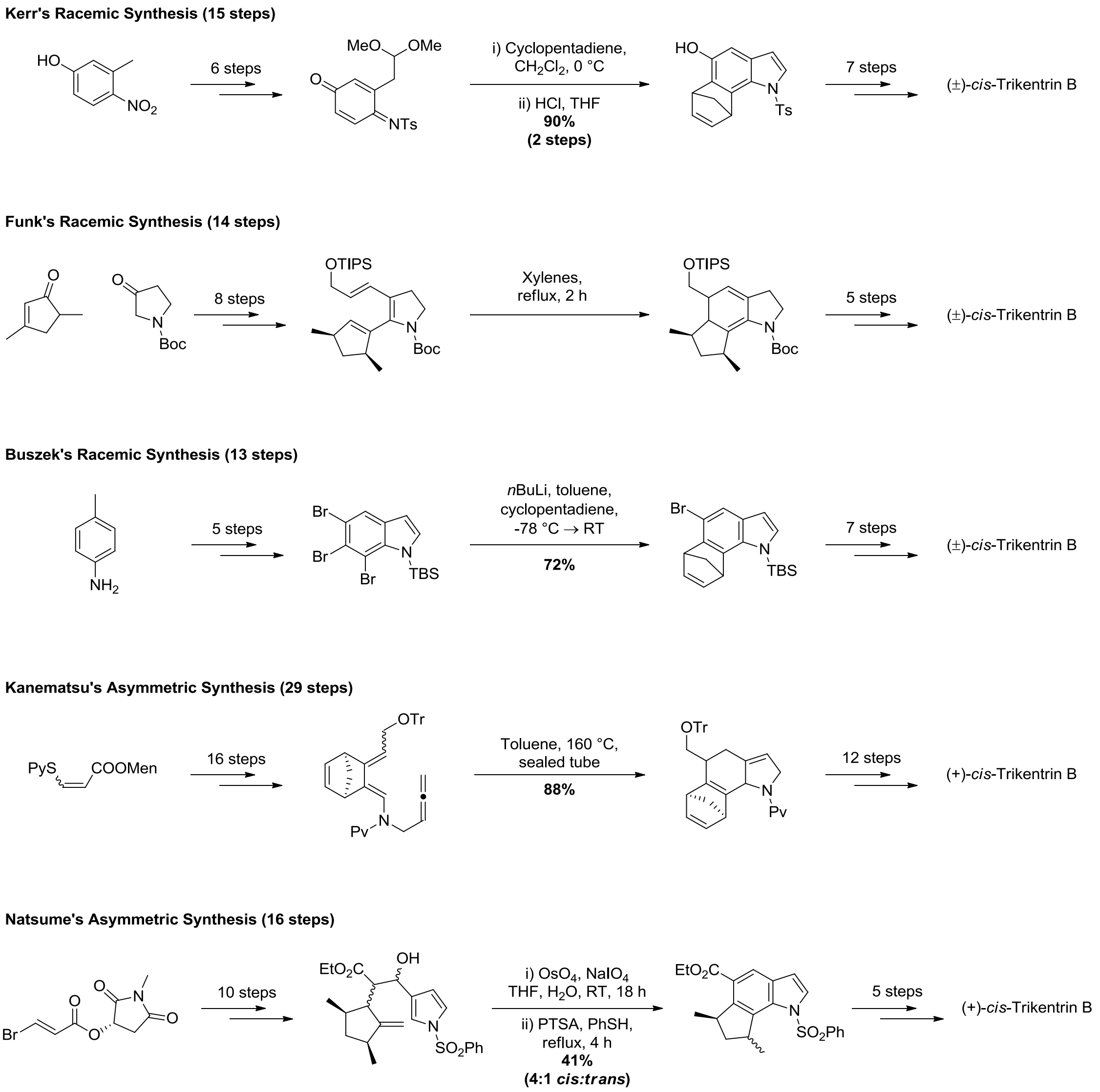


Figure 5.1 – (+)-*cis*-Trikentrin B

Whilst there have been thorough investigations into the synthesis of the trikentrin family, alongside the structurally similar herbindoles,[180] there have been five reported racemic synthetic routes to (±)-*cis*-trikentrin B namely by Kanematsu (1989, 18 steps, intramolecular Diels-Alder of allenic dienamides),[181] Natsume (1990, 7 steps, indolisation of pyrroles),[182] Kerr (2005, 15 steps, Diels-Alder reaction of iminoquinones),[183] Funk (2006, 14 steps, electrocyclic ring closure),[184] and finally by Buszek (2013, 13 steps, 6,7-indole aryne Diels-Alder reaction and Stille coupling).[185] Furthermore, there have been two developments of these routes into asymmetric syntheses by Natsume (1993, 16 steps)[186] and Kanematsu (1996, 29 steps).[187] The various methods with their key steps are depicted in Scheme 5.1.



Kerr's Racemic Synthesis (15 steps)

Funk's Racemic Synthesis (14 steps)

Buszek's Racemic Synthesis (13 steps)

Kanematsu's Asymmetric Synthesis (29 steps)

Natsume's Asymmetric Synthesis (16 steps)

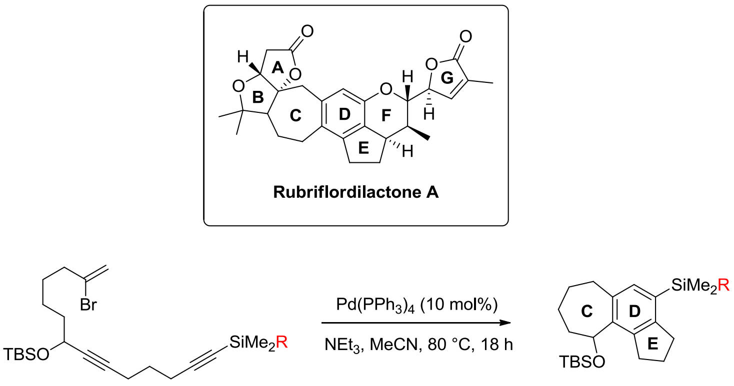
Scheme 5.1 – Total Syntheses of (±)- and (+)-*cis*-trikentrin B

Whilst (+)-*cis*-trikentrin B can be obtained as a single enantiomer and diastereomer using either Kanematsu's or Natsume's asymmetric syntheses, the first method suffers from a larger number of steps and the second, whilst a shorter route, involved the HPLC separation of the two diastereomers obtained after the indolisation of the pyrrole is conducted (Scheme 5.1). Bearing this in mind, it was hoped that our envisaged cascade cyclisation would allow access to single enantiomers much more rapidly and efficiently.

It is also worth noting the cyclotrimerisation methodology utilised by Sato *et al.* in the synthesis of the structurally related herbindoles from diyne-ynamides, demonstrating the synthetic utility of ynamides in natural product synthesis (Scheme 1.52).

5.2. Retrosynthetic Analysis of *cis*-Trikentrin B

The envisaged retrosynthesis was inspired by work conducted within the group on the fully intramolecular palladium-catalysed cyclisation of bromoendiynes in the formation of the CDE rings of rubriflordilactone A (Scheme 5.2).[90,188]

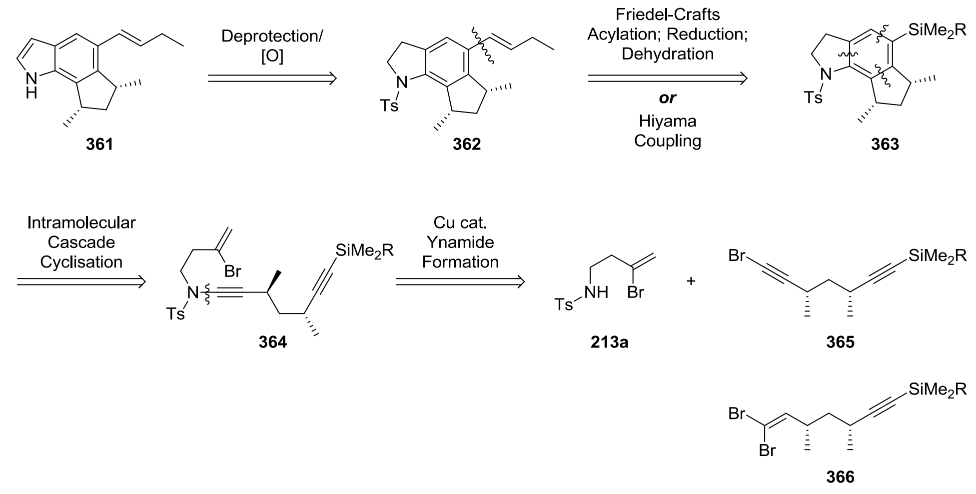


359a, R = Me
359b, R = Bn

360a, R = Me, **62%**
360b, R = Bn, **76%**

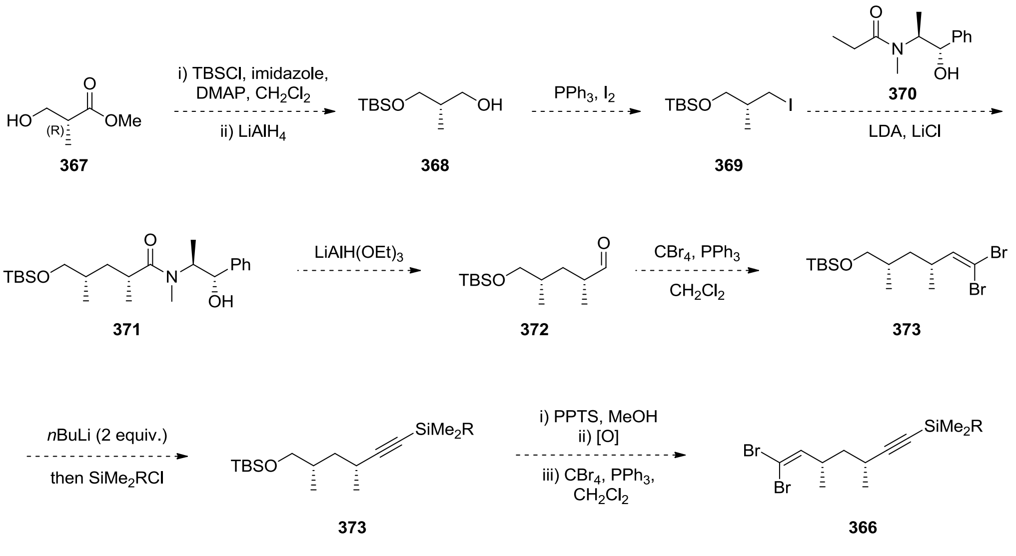
Scheme 5.2 – Intramolecular Cascade Cyclisation of Bromoenynes

Retrosynthetically, this initially would involve the key tosylated indoline intermediate **362**, which, based on our studies into the detosylation and oxidation to indoles in Chapter 2, should not prove problematic (Scheme 5.3). Next, removal of the side chain and replacement with a silyl group would form indoline **363**, with the silyl substituent providing us with a handle for the introduction of the side chain *via* either a more traditional Friedel-Crafts acylation/reduction/dehydration procedure or, by incorporating a Hiyama coupling into the synthesis, methodology which is also often utilised within the Anderson group. Indoline **363** can then be disconnected to bromoenynamide **364** containing a tethered alkyne, which itself can be formed using copper-catalysed coupling conditions with 'parent' sulfonamide **213a** and bromoalkyne **365** or dibromoalkene **366**.



Scheme 5.3 – Retrosynthesis of (+)-*cis*-trikentrin B

The proposed synthesis to dibromoalkene **366** involves 11 steps in total, with the longest linear sequence being 10 steps. Firstly, alcohol protection and ester reduction of the commercially available starting material **367** affords alcohol **368** which can then undergo iodination to **369** (Scheme 5.4).



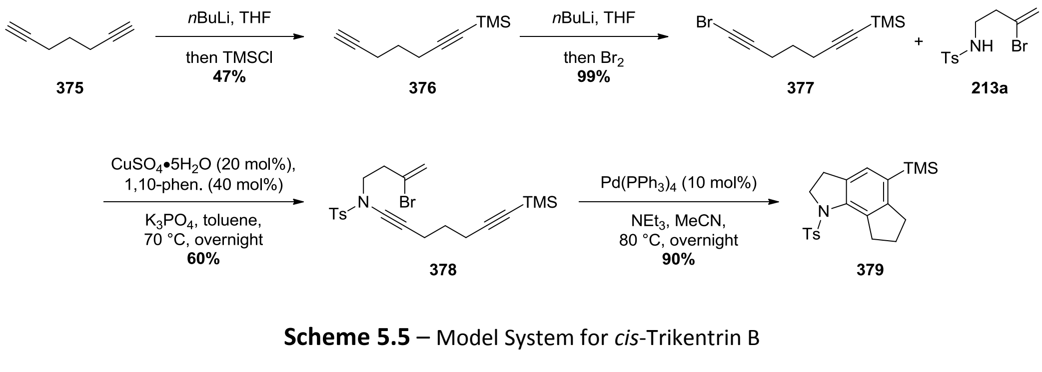
Scheme 5.4 – Asymmetric Synthesis of Dibromoalkene Coupling Partner

The primary iodide **369** can then be subjected to a Myers' asymmetric alkylation with **370** (formed from the *N*-acylation of pseudoephedrine), which we predict would give good stereocontrol due to the reported ≥99% *d.e.* for the same pseudoephedrine amide **370** with a similar chiral iodide.[189] Subsequent reduction of the amide to aldehyde **372** enables application of the Corey-Fuchs protocol giving access to the silyl-substituted alkyne **373**. Finally, deprotection of the silyl ether, oxidation and formation of the vinyl dibromide group affords the required coupling partner to take part in an ynamide formation. It is worth noting that if the dibromoalkene **366** proves unsuccessful in Evano's copper-catalysed ynamide coupling, it could be treated with KHMDS to form the bromoalkyne, at which point Hsung's conditions can be attempted.

However, as the route to the required coupling partner involves a large number of steps, it was decided that a model system would initially be investigated in the absence of the chiral methyl substituents.

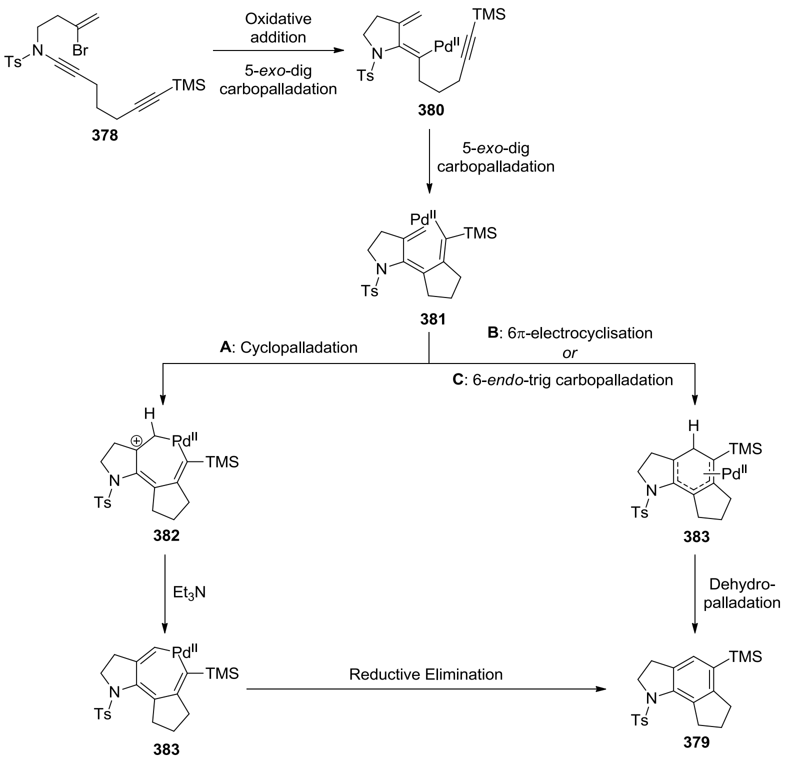
5.3. Preliminary Studies into the Synthesis of desmethyl *cis*-Trikentrin B

Prior to my commencement of the project, preliminary studies had been conducted on the model system for the trikentrin framework by Oliver Holton, a Part II student in the group (Scheme 5.5).[100] Deprotonation of 1,6-heptadiyne and subsequent trapping with TMSCl afforded a mixture of the mono-substituted diyne **376** and the doubly-silylated diyne, which was removed during the later purification of bromoalkyne **377**. With bromoalkyne **377** in hand, Hsung's copper-catalysed ynamide formation was conducted to afford bromoenynamide **378**, which on submission to the previously reported conditions used for bromoendiyne cyclisation (see Scheme 5.2) gave the tricyclic indoline **379** in an impressive 90% yield– pleasingly, all three rings of the trikentrin framework had been assembled in a single step.



Scheme 5.5 – Model System for *cis*-Trikentrin B

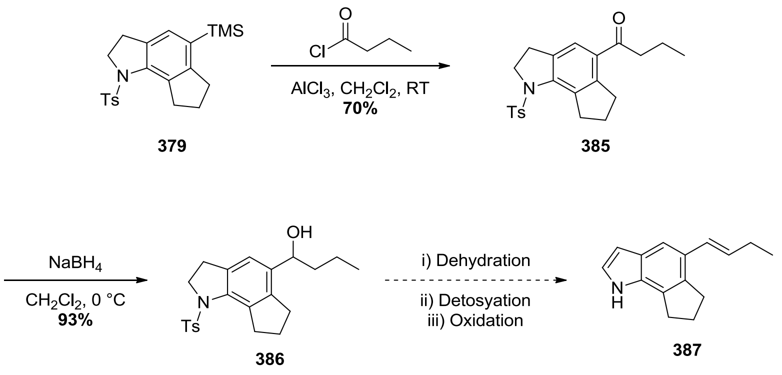
Mechanistically, the intramolecular cascade cyclisation can be rationalised by an oxidative addition and 5-*exo*-dig carbopalladation as previously described, followed by another 5-*exo*-dig carbopalladation with the tethered alkyne to form the triene intermediate **381** (Scheme 5.6).



Scheme 5.6 – Possible Mechanisms for Intramolecular Cyclisation

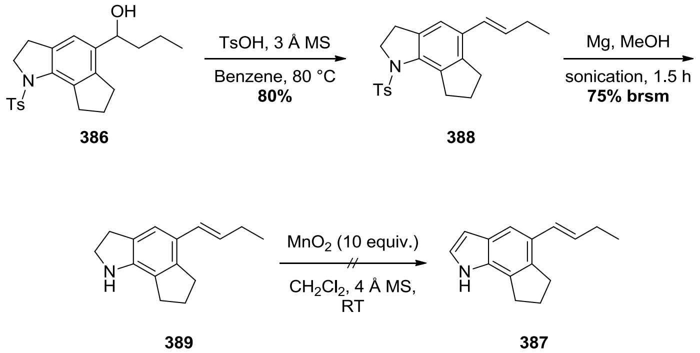
At this point the product could be formed by a number of plausible mechanisms; firstly, a cyclopalladation could occur followed by deprotonation by triethylamine to form trienyl-palladacycle **383**, which can undergo reductive elimination to furnish the product **379**. Alternatively, triene **381** could undergo either a 6π-electrocyclisation, or a 6-*endo*-trig carbopalladation to obtain intermediate **383**, which after dehydropalladation forms the same product **379**.

Continuing with the synthesis of the framework of *cis*-trikentrin B, in order to install the alkenyl side-chain a Friedel-Crafts acylation was conducted with *ipso*-substitution of the trimethylsilyl group to afford **385**, which could be reduced to alcohol **386** (Scheme 5.7). Finally, all that remained was to conduct a dehydration to the *trans*-alkene followed by detosylation to then allow oxidation to the indole **387**.



Scheme 5.7 – Endgame for Model System of *cis*-Trikentrin B

However, due to time constraints, Holton did not manage to complete the synthesis of the model system and therefore, with sufficient alcohol **386** still remaining the final three steps were attempted (Scheme 5.8). Pleasingly, dehydration of alcohol **386** with *p*-toluenesulfonic acid afforded the *trans*-alkene **388**.[190] However, on submission to our previously used detosylation conditions (Scheme 2.26) the reaction did not go to completion with a 1:0.85 ratio of **388**:**389** obtained, as measured in the ^{1}H NMR spectra of the crude reaction mixture. After purification by column chromatography to remove the residual tosylated starting material **388**, the oxidation to indole **387** was attempted with the clean detosylated indoline **389**, but unfortunately no product or starting material was recovered. Disappointingly, the detosylation and oxidation conditions could not be re-attempted due to lack of material. It is worth noting that if when repeated the product is still not obtained, the conditions reported by Sato *et al.* can be utilised, which were used for the same reaction on a similar herbindole structure (i) Na, naphthalene, THF, −78 °C; ii) Co^{II}(salen), O_2, MeOH, RT).[191]



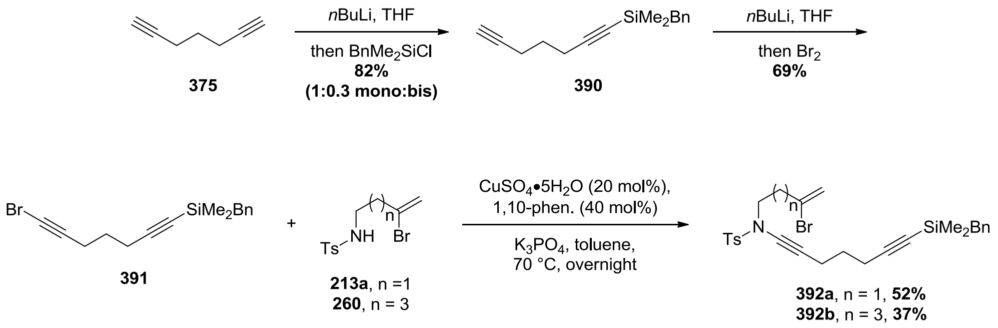
Scheme 5.8 – Final Steps of Model System

Overall, this route has a longest linear sequence of 9 steps; in combination with the asymmetric synthesis of the dibromoalkene **366** this would result in a total 18 steps for the synthesis of *cis*-trikentrin B itself, with a longest linear sequence of 17 steps.

5.4. Alternative Synthesis of *cis*-Trikentrin B

A slight modification on the already described route was planned with the Friedel-Crafts acylation/reduction/dehydration steps being replaced with a Hiyama coupling, enabling the direct introduction of the alkenyl side-chain in a single step. In order to allow this route to be attempted, an alternative silyl substituent to the TMS group was required which would provide a handle for the coupling. Therefore, based on the various silyl groups which may be utilised in Hiyama couplings[192] and the findings on which silyl group is optimal on the alkyne terminus in the bromoendiyne cyclisation,[188] the benzyldimethylsilyl (BDMS) group was selected.

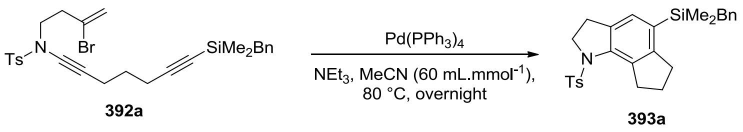
Incorporation of this substituent was conducted by utilising the same methodology as described earlier (Scheme 5.9), although the ynamide coupling was conducted with both the 'parent' sulfonamide **213a** and with the larger tether length sulfonamide **260** to investigate an alternative cyclisation which would form a 7,6,5-tricyclic system.



Scheme 5.9 – Incorporation of the BDMS Substituent

Pleasingly, application of the cyclisation conditions to bromoenynamide **392a** afforded the trikentrin framework **393a** containing the BDMS group in an impressive 91% yield (Table 5.1, entry 1). Investigations into lowering the catalyst loading proved detrimental to the isolated yield (entry 2).

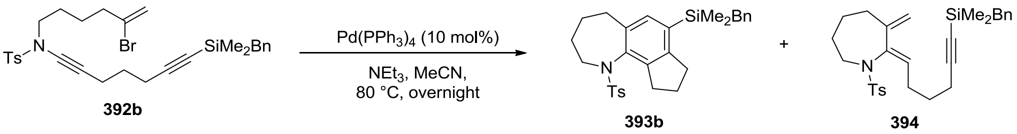
Table 5.1 – Intramolecular Palladium-Catalysed Cyclisation to Trikentrin Framework



	Catalyst Loading/mol%	Yield
1	10	91%
2	5	73%

The intramolecular cyclisation of bromoenynamide **392b** proved more difficult with the successful conditions from the earlier investigations affording a 1:0.7 mixture of the cyclised product **393b** and the exocyclic diene **394**, potentially due to the increased flexibility of the 7-membered ring preventing alignment of the tethered alkyne for carbopalladation to occur (Table 5.2, entry 1). However, on increasing the concentration full conversion to the desired product was possible (entry 2).

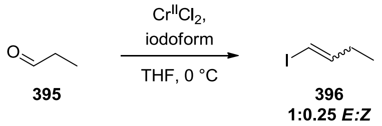
Table 5.2 – Intramolecular Palladium-Catalysed Cyclisation to 7,6,5-system



	Solvent Concentration	Yield	393b/394
1	60 mL.mmol^{-1}	81%	1:0.7
2	6.2 mL.mmol^{-1}	78%	1:0

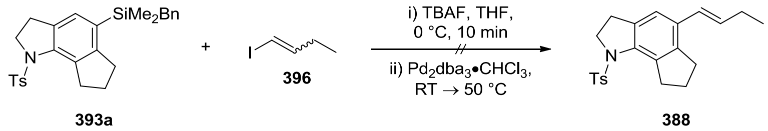
Having discovered that the reaction concentration can be greatly increased, it may be possible to reduce the catalyst loading in the cyclisation of bromoenynamide **392a** if it was also conducted at 6.2 mL.mmol^{-1}, instead of the previously used 60 mL.mmol^{-1}.

With the BDMS-substituted indole **393a** in hand the Hiyama coupling could be investigated with alkenyl iodide **396**. Takai's olefination conditions were employed with propionaldehyde to obtain the required (*E*)-vinyl iodide (Scheme 5.10),[193] which could not be synthesised according to standard literature conditions due to the difficulty in obtaining 1-butyne.[194] Unfortunately, a 1:0.25 mixture of *E:Z* isomers **396** was formed due to the small alkyl group and the product proved to be volatile. Therefore, after careful concentration using Kügelrohr distillation, **396** was kept as a solution in THF for use in the Hiyama coupling, as even though it was a mixture of isomers, generally *trans*-alkenyl iodides tend to be more reactive than the *cis*-isomers.



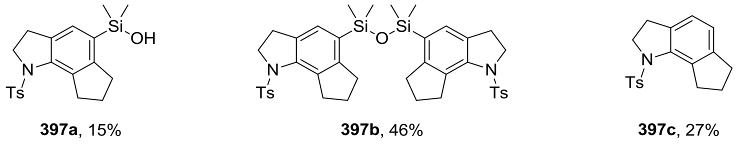
Scheme 5.10 – Takai Olefination

A survey of the literature found that for a BDMS group, the reaction conditions employed for a Hiyama coupling were TBAF and $Pd_2dba_3 \cdot CHCl_3$ in THF ranging from room temperature to 50 °C.[192] However, in all the reported examples an alkenyl silane and aryl iodide were utilised; opposite reactivity to our proposed system. Nonetheless, the literature conditions were attempted with indoline **393a** and iodobutene **396** (Scheme 5.11).



Scheme 5.11 – Initial Attempt at a Hiyama Coupling

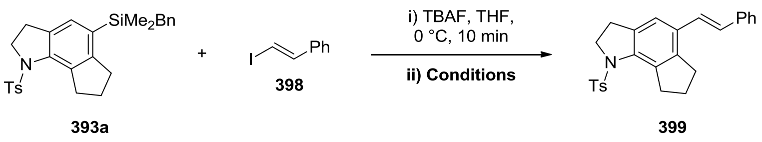
Unfortunately, the desired coupled product was not formed, with the isolated products being a combination of the silanol **397a**, disiloxane **397b** and desilylated indoline starting material **397c** (Scheme 5.12).



Scheme 5.12 – Product Mixture from Failed Hiyama Coupling

Whilst this was not the desired outcome, it did confirm that the activation of BDMS to the silanol required for the cross-coupling had occurred, suggesting that it was the transmetallation step that was the issue.[195] Therefore, based on findings within the group the alkenyl iodide **396** was replaced with styrenyl iodide **398** which had been proven to be more successful in Hiyama couplings, and a small screen of catalyst systems were selected to be tested after pre-activation of BDMS with TBAF, based on couplings between silanols/disiloxanes and aryl/alkenyl iodides (Table 5.3).[192] Again, there appeared to be an absence of literature precedence for a coupling between an aryl silanol/disiloxane and an alkenyl iodide, with the opposite reactivity being more common.

Table 5.3 – Hiyama Coupling Catalyst Screen

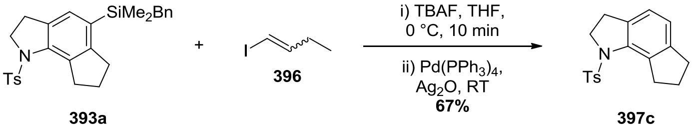


	Conditions	Yield	Outcome
1	$Pd_2dba_3{\bullet}CHCl_3$, RT → 50 °C[196]	N/A	Silanol and disiloxane formed
2	$[allylPdCl]_2$, RT → 50 °C[197]	N/A	Silanol and disiloxane formed
3	$Pd(dba)_2$, RT → 50 °C[198,199]	N/A	Silanol and disiloxane formed
4	$Pd(PPh_3)_4$, Ag_2O, RT, 22 h[200]	68%	

Disappointingly, variation of the palladium catalyst initially proved unsuccessful with mixtures of silanol and disiloxane present in the crude ^1H NMR spectra (entries 1-3). However, on employing a combination of $Pd(PPh_3)_4$ and Ag_2O[200] the coupled product **399** was obtained in a pleasing 68% yield (entry 4).

It is possible that the Hiyama coupling in the presence of silver(I) oxide was successful as it is reported to promote transmetallation by interacting with the organopalladium(II) iodide complex formed by oxidative addition of the styrenyl iodide to palladium(0).[201] Due to the strong affinity of iodide for silver cations, it is proposed that this interaction may cause iodide abstraction forming a cationic palladium species which would accelerate transmetallation.

Having met with success on the Hiyama coupling of **393a** with styrenyl iodide **398** *via* pre-activation of the BDMS group to the silanol and disiloxane (as monitored by TLC analysis) and the catalyst system $Pd(PPh_3)_4$ and Ag_2O, the conditions were applied to the coupling with alkenyl iodide **396** in an attempt to obtain the desired trikentrin framework (Scheme 5.13). It was disappointing to find that the coupling proved unsuccessful with desilylated starting material being isolated in a 67% yield.



Scheme 5.13 – Successful Hiyama Coupling Conditions on the Trikentrin Framework

Whilst the Hiyama coupling would have reduced the total number of steps in the natural product synthesis and demonstrated a combination of methodologies commonly used within the group, due to the difficulty in introducing the required side-chain (and the cost and toxicity of $CrCl_2$ employed in the iodide preparation), the Friedel-Crafts acylation/reduction and dehydration was selected as the optimal route.

5.5. Conclusions and Future Work

In conclusion, we have demonstrated the ability for bromoenynamides to successfully undergo palladium-catalysed intramolecular cyclisations to assemble the trikentrin core in a single step.

The introduction of the alkenyl side chain has also been investigated with a Friedel-Crafts acylation/reduction/dehydration procedure affording the desired framework which only needs to be detosylated and oxidised to finalise the model system.

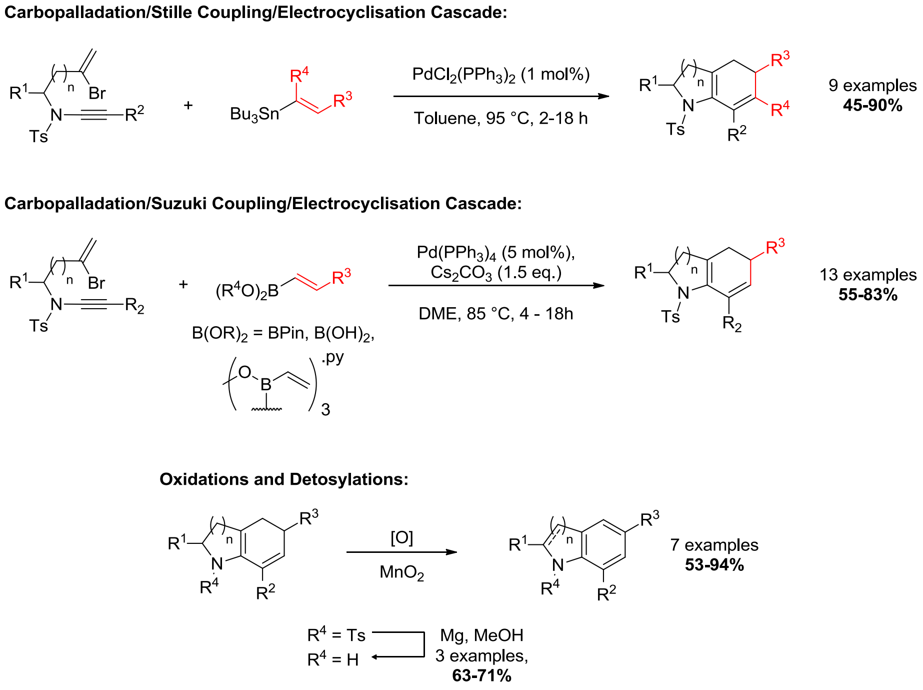
During investigations into the model system a series of analogues have also been synthesised including variation of the silyl substituent, variation of the ring size and introduction of alternative side chains by utilising a Hiyama coupling demonstrating the versatility of this methodology.

Future work to achieve the total synthesis of *cis*-trikentrin B would involve the synthesis of the chiral dibromoalkene/dibromoalkyne required for ynamide formation (see Scheme 5.4) and its use in the developed methodology. It is worth noting that if the *anti*-dimethyl substituted dibromoalkene was also synthesised, it would also be possible to apply the same methodology to form the natural product *trans*-trikentrin B.

6. Conclusions and Future Work

6.1. Palladium-Catalysed Cascade Cyclisations

Overall, we have successfully applied a palladium-catalysed carbopalladation/Stille cross-coupling/electrocyclisation cascade to bromoenynamides and developed this methodology to incorporate a Suzuki coupling, avoiding the toxicity issues inherent in the use of organotin reagents and enabling a range of bicyclic amidodienes to be obtained. The formed 1,3-amidodienes could then undergo selective and tuneable oxidations to the corresponding heteroaromatic systems, with the work having been published in *Chemistry – A European Journal* (Scheme 6.1).[129]

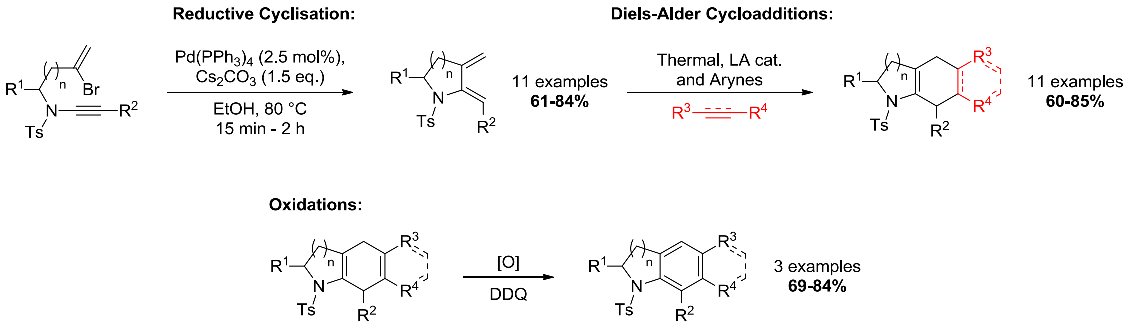


Scheme 6.1 – Palladium-Catalysed Cascade Cyclisations

These studies have added further knowledge to the relatively under-investigated area of ynamide carbopalladation, and include a number of novel aspects, including the first example of ynamide carbopalladation/Stille or alkenyl Suzuki coupling sequence, and the first example of a carbopalladative Suzuki coupling resulting in a triene which undergoes *in situ* electrocyclisation.

6.2. Reductive Cyclisation/Diels-Alder Sequence

We have also developed the first example of a carbopalladation/reductive cyclisation process on an alkyne which utilises an alcohol as the hydride source, generated *via* ß-hydride elimination of a palladium alkoxide. The reaction allows conversion of a wide range of bromoenynamides to cyclic amidodienes which in themselves are viable substrates for Diels-Alder cycloadditions with electron-deficient alkenes and alkynes including arynes, providing a straightforward route to bi- and tricyclic azacycles. The 1,4-amidodienes formed from these cycloadditions can also be submitted to oxidation conditions to afford a complimentary range of bi- and tricyclic heteroaromatic systems compared to those obtained using the cascade methodology, with the results reported in *Advanced Synthesis and Catalysis* (Scheme 6.2).[170]

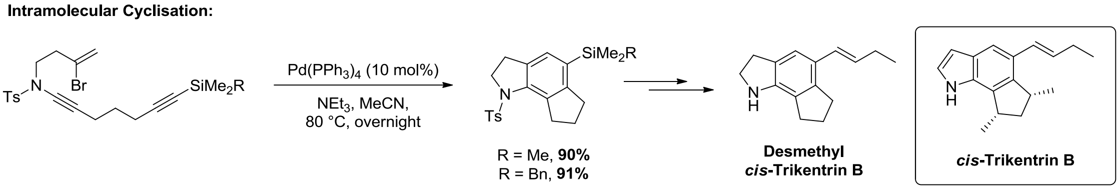


Scheme 6.2 – Reductive Cyclisation/Diels-Alder Cycloaddition

Future work could include further development of an enamine-catalysed asymmetric Diels-Alder process given the promising results from the preliminary investigations, and to investigate the possibility of an iminium-catalysed asymmetric cycloaddition using MacMillan’s catalyst.

6.3. Studies Towards the Trikentrin Natural Product Family

We have successfully demonstrated the ability for bromoenynamides to successfully undergo palladium-catalysed intramolecular cyclisations to assemble the trikentrin core in a single step. Investigations into the introduction of the alkenyl side chain have also been investigated and future work could involve the synthesis of the chiral dibromoalkene/dibromoalkyne required for ynamide formation (see Scheme 5.4) and its use in the developed methodology enabling formation of the natural product (+)-*cis*-trikentrin B (Scheme 6.3).



Scheme 6.3 – Palladium-Catalysed Intramolecular Cyclisation

Overall, these routes provide a general method to a range of heterocycles with the ability to vary both the ring sizes and to install a variety of functional groups regiospecifically, giving access to not only indolines and indoles, but also tetrahydroquinolines and benzazepines. The major limitation of this methodology remains in the reduced ability to synthesise a range of bromoenynamides that would allow introduction of functionality in any position on the bicyclic systems, with the vinyl bromide functionality often causing problems by being responsible for issues of intramolecular cyclisation or reduced reactivity in formation. Therefore, future work within the group is focussing on cycloisomerisations of enynamides to provide an alternative route to azacycles, with the ynamide synthesis being less problematic, enabling a greater substrate scope.

7. Experimental

7.1. General Comments

NMR Spectra: ^1H Nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ 7.26), C_6D_6 (δ 7.16) or d_8-toluene (δ 2.31) at ambient probe temperatures on the following instruments: Bruker AV400 (400 MHz), Varian Inova Unity 400 (400 MHz), Bruker AMX 500 (500 MHz), Bruker AVANCE III 500 (500 MHz), Bruker DRX500 (500 MHz) or Varian Inova 600 (600 MHz). Data are presented as follows: chemical shift, integration, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sex = sextet, sept = septet, m = multiplet, br = broad, app = apparent), coupling constants (*J* / Hz) and assignment. Chemical shifts are expressed in ppm on a δ scale relative to δ_{TMS} (δ = 0 ppm) and coupling constants, *J,* are given in Hz. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, by analysis of 2D NMR (COSY, HSQC, HMBC, NOESY) and irradiation of protons in nOe experiments, or by analogy to fully interpreted spectra for structurally related compounds. ^{13}C NMR Spectra were recorded using an internal deuterium lock using solvents $CDCl_3$ (δ 77.0), C_6D_6 (δ 128.6) and d_8-toluene (δ 21.4) at ambient probe temperatures on the following instruments: Bruker AV400 (101 MHz), Varian Inova Unity 400 (101 MHz), Bruker AMX 500 (126 MHz), Bruker AVANCE III 500 (126 MHz), Bruker DRX500 (126 MHz) or Varian Inova 600 (151 MHz).

Infra-red spectra: Recorded on a Perkin Elmer Paragon 1000 spectrometer or a Perkin Elmer Spectrum One spectrometer, with the sample prepared as a thin film between NaCl plates, or using a PIKE-Miracle Diamond /Universal ZnSe ATR module.

Mass spectra: Low resolution mass spectra (*m/*z) were recorded on a Micromass LCT Premier Open Access mass spectrometer. Accurate mass (HRMS) data was recorded by the Departmental Mass Spectrometry Service at the University of Oxford and were determined under the conditions of ESI on a Bruker MicroTOF (resolution = 5000 FWHM) using tetraoctylammonium bromide as a lock-mass in both positive and negative ion modes, or under the conditions of FI, or under the conditions of CI on a Micromass GCT (resolution = 7000 FWHM) using isoamyl acetate as a lock-mass. High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm. The parent ion $[M]^+$, $[M+H]^+$ or $[M+Na]^+$ is quoted.

Melting points: Obtained using a Reichert-Koffler block and are uncorrected.

Other techniques: Reactions were monitored by thin layer chromatography (TLC) or by liquid chromatography-mass spectroscopy (LC-MS). TLC was conducted on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV_{254}) or on pre-coated glass-backed plates (Macherey-Nagel SIL G-25 with fluorescent indicator UV_{254}). Spots were visualized either by quenching of UV fluorescence (254 nm) or by staining with potassium permanganate or vanillin dip. LC-MS was conducted on an Acquity Ultra Performance LC with Micromass ZQ2000. Flash column chromatography was performed manually according to the method described by Still, Khan and Mitra[1] with silica gel 60 (0.040-0.063 mm) (MN Kieselgel 60M) applying head pressure by means of nitrogen, or on a Combiflash Rf with RediSep Rf Normal Phase disposable columns.

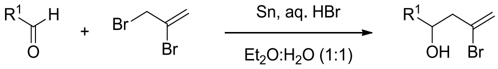
Materials: All reagents, obtained from Acros, Aldrich, Lancaster, Strem and Fluorochem fine chemicals suppliers were used directly as supplied or purified by the methods described by Amerago and Chai.[2]

All non-aqueous reactions were performed in oven dried apparatus under argon or nitrogen atmospheres, using anhydrous solvents, at room temperature unless otherwise indicated, and employed standard techniques for handling air sensitive materials.

The anhydrous solvents were purchased as sure-seal bottles from Aldrich or dried by pre-storing over activated 3Å molecular sieves and then passing through an activated alumina column on a solvent tower under an argon atmosphere. Triethylamine (NEt_3) and pyridine were stored over solid potassium hydroxide. *N,N'*-dimethylethylenediamine (DMEDA) and diisopropylamine (DIPA) were distilled from and stored over calcium hydride and pH 7 buffer was prepared by adding 0.1 M NaOH (29.1 mL) to 0.1 M potassium dihydrogen phosphate (50 mL).

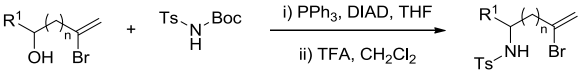
7.2. General Experimental Procedures

General Procedure A: *Barbier Allylation*



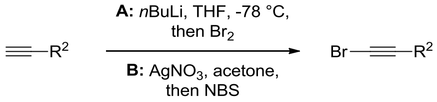
The procedure of Otera *et al*. was used for this preparation.[104] To a mixture of tin powder (1.3 equiv.) and 2,3-dibromopropene (1.3 equiv.) in water/Et_2O (3 $mL.mmol^{-1}$, 1:1) was added aqueous HBr (several drops) and the appropriate aldehyde (1.0 equiv.). The resulting mixture was stirred overnight at RT before being diluted with water and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the corresponding alcohols which were used without further purification.

General Procedure B: *Mitsunobu Coupling and N-Boc deprotection*



The procedure of Lu and Li was used for this preparation.[107] To a solution of triphenylphosphine (2.0 equiv.), TsNHBoc (1.3 equiv.) and the appropriate alcohol (1.0 equiv.) in anhydrous THF (3 $mL.mmol^{-1}$) at 0 °C was added DIAD (1.5 equiv.) dropwise. Reaction was stirred at RT overnight before being concentrated *in vacuo*. The residue was dissolved in Et_2O then sonicated for 5 min and the resulting precipitate (triphenylphosphine oxide) removed by filtration. To the filtrate was added hexanes which was further sonicated for 5 min and the resulting precipitate removed by filtration before being concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded the desired Ts/Boc compound which was taken up in CH_2Cl_2 (2 $mL.mmol^{-1}$) before the dropwise addition of TFA (0.5 $mL.mmol^{-1}$) at 0 °C. The resulting reaction mixture was stirred at RT for 18 h before being cooled to 0 °C and slowly quenched by the dropwise addition of sat. *aq*. $NaHCO_3$. The organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1) → (5:1)) afforded the corresponding sulfonamides.

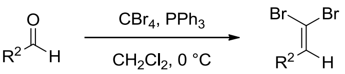
General Procedure C: *Synthesis of bromoalkynes*



Method A: The procedure of Hsung *et al.* was used for this reaction.[16] To a stirred solution of the terminal alkyne (1.0 equiv.) in anhydrous THF (3M) at −78 °C was added *n*-BuLi (2.5 M, 1.2 equiv.) dropwise. The resulting solution was stirred at −78 °C for 30 min before the dropwise addition of bromine (1.4 equiv.). The reaction mixture was then stirred for a further 15 min before being quenched with sat. *aq.* $Na_2S_2O_3$ solution. The reaction was extracted with Et_2O, and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* (some THF not removed due to product volatility) to obtain the corresponding bromoalkynes which were used without further purification.

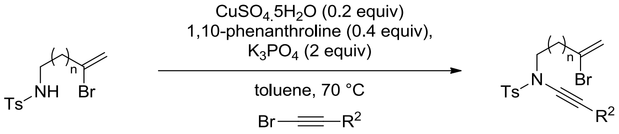
Method B: To a solution of terminal alkyne (1.0 equiv.) in acetone (2 mL.mmol^{-1}) was added $AgNO_3$ (0.1 equiv.). After stirring for 5 min, *N*-bromosuccinimide (1.1 equiv.) was added and the resulting mixture stirred for a further 4 h at RT. The reaction mixture was concentrated *in vacuo* before the addition of petroleum ether and filtration through cotton wool to remove the white precipitate. The resulting solution was concentrated *in vacuo* to obtain the corresponding bromoalkynes which were used without further purification.

General Procedure D: *Synthesis of dibromoalkenes*



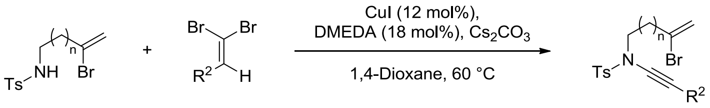
The procedure of Kim *et al.* was used for this reaction.[202] To a stirred solution of the appropriate aldehyde (1.0 equiv.) and carbon tetrabromide (2.0 equiv.) in anhydrous CH_2Cl_2 (0.24 M) at 0 °C, under Ar, was added triphenylphosphine (4.0 equiv.) in portions over 15 min. The resulting solution was stirred at 0 °C for 1 h before being quenched with petroleum ether (125 mL). The precipitate was filtered through a silica plug and the filtrate concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding dibromoalkene.

General Procedure E: *Hsung route to bromoenynamides*



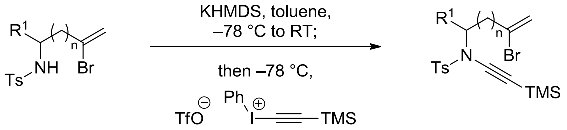
The procedure of Hsung *et al.* was used for this reaction.[16] To a mixture of sulfonamide (1.0 equiv.), K_3PO_4 (2.0 equiv.), $CuSO_4.5H_2O$ (0.2 equiv.) and 1,10-phenanthroline (0.4 equiv.) was added a solution of bromoalkyne (1.5 equiv.) in toluene (4 $mL.mmol^{-1}$). The mixture was heated to 70 °C for 16 h before being cooled to RT and concentrated *in vacuo*. Purification by column chromatography afforded the corresponding bromoenynamide.

General Procedure F: *Evano route to bromoenynamides*



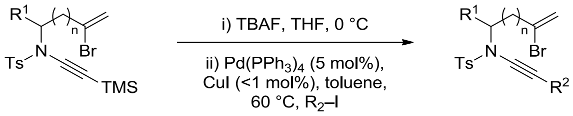
The procedure of Evano *et al.* was used for this reaction.[19] To an oven-dried vial, equipped with stirrer bar, was added sulfonamide (1.0 equiv.), the appropriate dibromoalkene (1.5 equiv.), Cs_2CO_3 (4.0 equiv.) and CuI (0.12 equiv.). The vial was sealed with a septum, evacuated and refilled with Ar (×3) before the addition of anhydrous 1,4-dioxane (0.27 M) and DMEDA (0.18 equiv.). The septum was replaced with a screw cap and the reaction heated at 60 °C overnight before being cooled to RT, filtered through a Celite® plug (EtOAc eluent) and concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding bromoenynamide.

General Procedure G: *Danheiser / Witulski route to TMS-bromoenynamides*



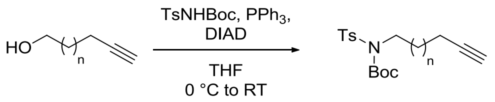
A modification of the procedure of Danheiser *et al.* was used for this reaction.[203] To a solution of the sulfonamide (1.0 equiv.) in toluene (9 mLmmol^{-1}) at –78 °C was added a solution of KHMDS (1.1 equiv., 0.5 M in toluene) dropwise. The mixture was warmed to RT and stirred for 30 min before being re-cooled to –78 °C. A solution of [(trimethylsilyl)ethynyl](phenyl)iodonium triflate **231** (1.2 equiv.) in anhydrous toluene (14 mL.mmol^{-1}) was then added dropwise over 10 min before being allowed to warm to RT and stirred for a further 18 h. The resulting mixture was concentrated *in vacuo* and purified by column chromatography to afford the corresponding bromoenynamide.

General Procedure H: *Deprotection / Sonogashira coupling*



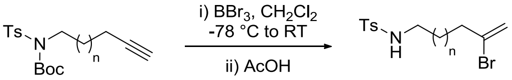
The procedure of Hsung *et al.* was used for this reaction.[7] To a solution of the TMS-bromoenynamide (1.0 equiv.) in anhydrous THF (20 mL.mmol^{-1}) at 0 °C was added TBAF (1.3 equiv., 1 M in THF) dropwise under Ar. The reaction mixture was stirred at 0 °C for 10 min before being quenched with sat. *aq.* NH_4Cl. The aqueous layer was extracted with Et_2O (×3), and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue (1.0 equiv.) was added to an oven-dried vial along with iodide coupling partner (2.0 equiv.) in NEt_3 (~5.33 mL.mmol^{-1}) and anhydrous degassed toluene (Ar bubbling 10 min, ~2.66 mL.mmol^{-1}). $Pd(PPh_3)_4$ (0.05 equiv.), weighed out in the glovebox, was added and the resulting solution stirred at RT for 10 min before the addition of CuI (0.01 equiv. / smallest possible amount on spatula tip). The reaction mixture was heated to 60 °C for 1.5 h before being cooled to RT and concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding functionalized bromoenynamide.

General Procedure I: *Mitsunobu coupling of alkyn-1-ol substrates*



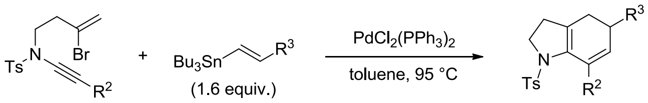
To an ice-cooled solution of PPh_3 (2.0 equiv.), TsNHBoc (1.3 equiv.) and the appropriate alkyn-1-ol (1.0 equiv.) in anhydrous THF (0.32 M) was added DIAD (1.5 equiv.) dropwise. Reaction mixture was then stirred at RT overnight before being concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding Mitsunobu products.

General Procedure J: *Bromoboration/protodeborylation and in-situ Boc-deprotection*



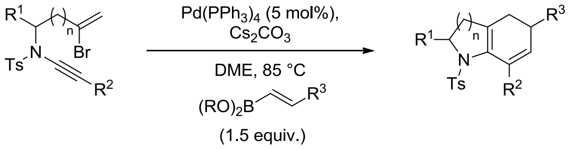
A modified procedure of Moran and Morken was used for this preparation.[117] To an oven-dried rbf charged with stirrer bar was added BBr_3 (1M in DCM, 0.5 equiv.) under Ar. The solution was cooled to −78 °C before the dropwise addition of the alkyne Mitsunobu product (1.0 equiv.) pre-dissolved in anhydrous CH_2Cl_2 (0.57 M). The resulting reaction mixture was allowed to warm to RT over 4.5 h before the addition of glacial AcOH (2.14 $mL.mmol^{-1}$ of BBr_3). After stirring for a further 1 h the reaction was quenched by the addition of water and then extracted with CH_2Cl_2 (x3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding sulfonamides.

General Procedure K: *Stille cascade cyclisation to amidodienes*



To an oven dried vial, equipped with a stirrer bar, was added $PdCl_2(PPh_3)_2$ (1 or 10 mol%) in the glove box, and the vial sealed with a rubber septum. To this was added *via* syringe a degassed (Ar bubbling, 15 min) solution of the bromoenynamide (1.0 equiv.) and stannane coupling partner (1.6 equiv) in anhydrous toluene (16.7 mL.mmol^{-1}). The rubber septum was replaced rapidly with a screw cap, and the reaction mixture heated to 95 °C until the reaction was complete as analysed by TLC. On completion, the reaction was cooled to RT, and concentrated *in vacuo*. Purification *via* column chromatography afforded the bicyclic dienamide.

General Procedure L: *Suzuki cascade cyclisation to amidodienes*

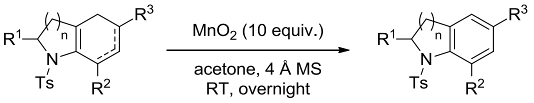


To an oven dried vial, equipped with a stirrer bar, was added $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (1.5 equiv.) in a glove box, and the vial sealed with a rubber septum. To this was added a degassed (Ar bubbling, 15 min) solution of the corresponding bromoenynamide (1.0 equiv.) and vinylboronate species (1.5 equiv.) in anhydrous DME (16.7 mL.mmol^{-1}). The rubber septum was replaced rapidly with a screw cap, and the reaction mixture heated to reflux until the reaction was complete as analysed by TLC. On completion, the reaction was cooled to RT and concentrated *in vacuo*. Purification *via* column chromatography afforded the bicyclic dienamide.

General Procedure M: *Preparation of MnO_2*

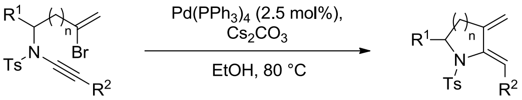
The procedure from the *Encyclopaedia of Reagents for Organic Synthesis* was used for this preparation.[204] To a stirred solution of $MnSO_4$ (5.00 g, 29.58 mmol, 1.55 equiv.) in water (95 mL) at 60 °C was added a solution of $KMnO_4$ (3.12 g, 19.74 mmol, 1.0 equiv.) in water (60 mL). The resulting suspension was stirred at 60 °C for 1 h before being cooled to RT, filtered and the precipitate washed with water until free from sulphate ions. The dark brown solid was then dried at 60 °C until a constant weight was obtained. This was then stored at RT until required for oxidations.

General Procedure N: *Oxidation of 1,3-amidodienes to indolines*



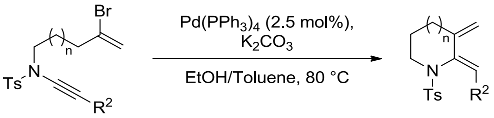
To a solution of an amidodiene (1.0 equiv.) in acetone (7.8 mL.mmol^{-1}) was added a few 4 Å molecular sieves and activated MnO_2 (10 equiv.). The resulting suspension was stirred at RT overnight before being diluted with EtOAc and filtered through a Celite® pad. The filtrate was concentrated *in vacuo* to afford the corresponding indolines.

General Procedure O: *Reductive cyclisation of bromoenynamides to pyrrolidines and piperidines* (*n = 1, 2)*



To a solution of bromoenynamide (1.0 equiv.) in EtOH (0.045 M) was added $Pd(PPh_3)_4$ (2.5 mol%) and Cs_2CO_3 (1.5 equiv.). The reaction mixture was heated to 80 °C until complete as analysed by TLC, before being allowed to cool to RT and filtered through a Celite® plug eluting with EtOAc. The filtrate was concentrated *in vacuo*, and the residue purified *via* column chromatography to afford the corresponding exocyclic dienes.

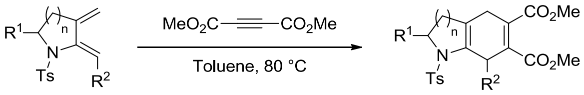
General Procedure P: *Reductive cyclisation of bromoenynamides* to piperidines (*n*=2) and azepanes (*n = 3)*



Method A: To a solution of bromoenynamide (1.0 equiv.) in toluene/EtOH (10:1, 0.045 M) was added $Pd(PPh_3)_4$ (10 mol%) and K_2CO_3 (1.5 equiv.). The reaction mixture was heated to 80 °C until complete as analysed by TLC (3 × TLC runs on the same plate in 20:1 petroleum ether / EtOAc to give separation of SM and product) before being allowed to cool to RT and filtered through a Celite® plug eluting with EtOAc. The filtrate was concentrated *in vacuo* and the residue purified *via* column chromatography to afford the corresponding exocyclic dienes.

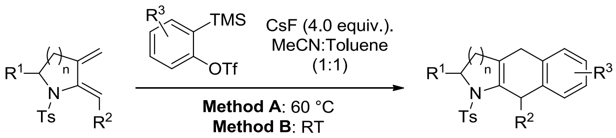
Method B: To a solution of the appropriate bromoenynamide (1.0 equiv.) in toluene/EtOH (1:1, 0.045 M) was added $Pd(PPh_3)_4$ (2.5 mol%) and K_2CO_3 (1.5 equiv.). The reaction mixture was heated to 80 °C until the reaction was complete as analysed by TLC (3 × TLC runs on the same plate in 20:1 petroleum ether / EtOAc to give separation) before being allowed to cool to RT and filtered through a Celite® plug eluting with EtOAc. The filtrate was concentrated *in vacuo*, and the residue purified *via* column chromatography to afford the corresponding exocyclic dienes.

General Procedure Q: *Diels-Alder Cycloaddition with DMAD*



To a solution of exocyclic dienamide (1.0 equiv.) in anhydrous toluene (0.033 M) was added dimethyl acetylenedicarboxylate (5.0 equiv.). The resulting reaction mixture was heated under Ar at 80 °C until the reaction was complete as analysed by TLC, before being cooled to RT and concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding azabicycle.

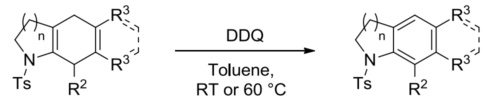
General Procedure R: *Diels-Alder Cycloaddition with Arynes*



Method A: To an oven-dried vial equipped with a stirrer bar was added CsF (4.0 equiv.) in the glovebox, and the vial sealed with a rubber septum. On removal from the glovebox, to this was added a solution of the dienamide (1.0 equiv.) in anhydrous toluene (typically 4.0-4.5 $mL.mmol^{-1}$) and anhydrous MeCN (typically 4.0-4.5 $mL.mmol^{-1}$) under an Ar atmosphere, followed by the addition of the appropriate aryne precursor (2.0 equiv.). The rubber septum was rapidly replaced with a screw cap and the resulting reaction mixture heated to 60 °C until the reaction was complete as analysed by TLC. On completion, the reaction was cooled to RT and concentrated *in vacuo,* and the residue was purified *via* column chromatography to afford the corresponding azatricycle.

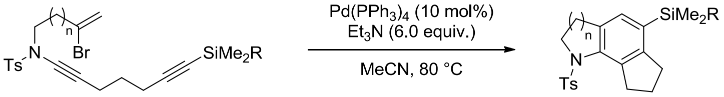
Method B: To an oven-dried vial equipped with a stirrer bar was added CsF (4.0 equiv.) in a glovebox, and the vial sealed with a rubber septum. On removal from the glovebox, a solution of the dienamide (1.0 equiv.) in anhydrous toluene (typically 4.0-4.5 mL.mmol^{-1}) and anhydrous MeCN (typically 4.0-4.5 mL.mmol^{-1}) was added under an Ar atmosphere, followed by the addition of the appropriate aryne precursor (2.0 equiv.). The rubber septum was rapidly replaced with a screw cap and the resulting reaction mixture stirred at RT until the reaction was complete as analysed by TLC. On completion the reaction was concentrated *in vacuo,* and the residue was purified *via* column chromatography to afford the corresponding azatricycle.

General Procedure S: *Oxidations of 1,4-amidodienes*



To a vial equipped with stirrer bar and containing amidodiene (1.0 equiv.) in anhydrous toluene (0.06 M) was added DDQ (2.2 equiv.) and the vial sealed with a screw cap. The resulting reaction mixture was stirred at RT or at 60 °C until the reaction was complete as analysed by TLC. On completion the reaction was cooled to RT if necessary, than diluted with EtOAc and washed with sat. *aq*. $NaHCO_3$ and sat. *aq*. $Na_2S_2O_3$. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding benzoindolines.

General Procedure T: *Intramolecular Cascade Cyclisation*[100,188]

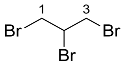


To an oven dried vial, equipped with a stirrer bar, was added Pd(PPh$_3$)$_4$ (10 mol%) in a glove box, and the vial sealed with a rubber septum. To this was added a degassed (Ar bubbling, 15 min) solution of the corresponding bromoenynamide (1.0 equiv.) and triethylamine (6.0 equiv.) in anhydrous MeCN (6.2 or 60 mL.mmol^{-1}). The rubber septum was replaced rapidly with a screw cap, and the reaction mixture heated to 80 °C overnight until the reaction was complete as analyzed by TLC. On completion, the reaction was cooled to RT and concentrated *in vacuo*. Purification *via* column chromatography afforded the corresponding tricycles.

7.3. Palladium-Catalysed Cascade Cyclisations

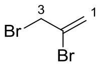
7.3.1. Bromoenynamide Synthesis

1,2,3-Tribromopropane, 400



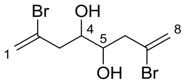
The procedure of Johnson and McEwen was used for this reaction.[102] To a three-necked flask equipped with stirrer bar was added allyl bromide (181.50 g, 1.50 mol, 1.0 equiv.) and carbon tetrachloride (250 mL). The flask was fitted with a dropping funnel, calcium chloride exit tube and a thermometer. To the dropping funnel was added bromine (255.00 g, 1.60 mol, 1.1 equiv.), pre-washed with an equal volume of conc. H_2SO_4. With stirring, the reaction mixture was cooled to −5 °C before the bromine was added dropwise so that the temperature never exceeded 0 °C. After complete addition the reaction mixture was allowed to warm to RT and stirred for a further 30 min. The dropping funnel and thermometer were removed and replaced with stoppers, and the drying tube replaced with distillation apparatus. The reaction mixture was heated to 120 °C at atmospheric pressure and then slowly to 150 °C to distil off the remaining bromine, allyl bromide and carbon tetrachloride. The collecting flask was replaced and the pressure reduced to 26 mbar to remove the remaining starting materials and solvent until the thermometer registered a sudden rise at which point only the title product **400** remained in the distilling flask as a pale yellow oil (418.64 g, 1.49 mmol, 99%); **R$_f$** 0.33 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.42 (1H, tt, *J* = 7.0, 4.0 Hz, H2), 3.99 (2H, dd, *J* = 7.0, 4.0 Hz, H1/H3), 3.90 (2H, dd, *J* = 7.0, 4.0 Hz, H1/H3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 48.7, 35.4. Data in accordance with literature values.[205]

2,3-Dibromoprop-1-ene, 209



The procedure of Lespieau and Bourgeul was used for this reaction.[103] To a rbf, connected to efficient distillation equipment, was added 1,2,3-tribromopropane **400** (418.64 g, 1.49 mol, 1.0 equiv.), water (22 mL) and NaOH pellets (104.40 g, 2.61 mol, 1.75 equiv.). An exotherm is observed, then the mixture was heated further using a heat gun, with stirring, until vigorous ebullition occurs, whereupon spontaneous distillation of the reaction product takes place and the heat is removed. When the reaction subsided, the flask was heated as before and the mass became solid as the volatile components were removed. Once all the volatile components were removed, the distillate was separated with the addition of more water (150 mL). The lower (organic) layer was vacuum distilled to yield the title product **209** as a colourless oil (203.01 g, 1.19 mmol, 80% brsm); **bpt** 68 °C at 75 mbar; **R$_f$** 0.54 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2962, 1734, 1640, 1621, 1418, 1384, 1311, 1215, 1191, 1101, 938; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 6.03 (1H, dt, *J* = 2.0, 1.0 Hz, H1), 6.53 (1H, d, *J* = 2.0, H1'), 4.19 (2H, d, *J* = 1.0 Hz, H3); **^{13}C NMR** (101 MHz, CDCl$_3$) 127.6, 121.2, 36.8; **HRMS** (CI) calc. for $C_3H_4{}^{79}Br_2$ 197.8680, found 197.8684.

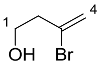
2,7-Dibromoocta-1,7-diene-4,5-diol, 401 *(unassigned mixture of diastereoisomers)*



The procedure of Otera *et al*. was used for this reaction.[104] To a mixture of tin powder (29.7 g, 0.25 mol, 2.3 equiv.) and 2,3-dibromopropene **209** (26 mL, 0.25 mol, 2.3 equiv.) in water/Et$_2$O (240 mL / 240 mL) was added HBr (several drops) and *aq.* glyoxal solution (12.6 mL, 0.11 mol, 40% wt, 1.0 equiv.). The resulting mixture was stirred overnight at RT before being diluted with water and extracted with Et$_2$O. The combined organic layers were dried (MgSO$_4$) and the solvent removed *in vacuo* to afford the title product **401** as coarse white powder (34.0 g, 0.25 mol, quant.) which was used without further purification; **mpt** 85-86 °C; **R$_f$** 0.72 (Et$_2$O); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 5.76 (2H, app s, H1 or H8), 5.59 (2H, t, *J* = 2.0 Hz, H1 or H8), 4.05 (1H, m, H4 or H5), 3.91 (1H, m, H4 or H5), 2.77 (2H, m, H3 or H6), 2.66 (2H, m, H3 or

H6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 130.4, 130.3, 120.8, 120.6, 71.5, 70.9, 46.4, 44.4. Data in accordance with literature values.[100]

3-Bromobut-3-en-1-ol, 210

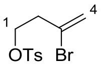


Method A: The procedure of Anderson was used for this reaction.[206] To a solution of 2,7-dibromoocta-1,7-diene-4,5-diol **401** (7.60 g, 25.0 mmol, 1.0 equiv.) in a 5:1 mixture of MeOH/pH 7 buffer (90 mL/18 mL) was added $NaIO_4$ (8.13 g, 38.0 mmol, 1.5 equiv.). The reaction mixture was stirred for 2 h at RT before being cooled to 0 °C followed by the portion-wise addition of $NaBH_4$ (1.93 g, 51.0 mmol, 2.0 equiv.). Once the addition was complete the reaction was allowed to warm to RT and stirred for 20 min before being quenched with water. The mixture was extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by distillation to afford the title product **210** as a colourless liquid (5.12 g, 16.5 mmol, 66%).

Method B: Prepared by General Procedure A using *aq.* formaldehyde (19.4 mL, 0.33 mol, 37% in H_2O) to afford alcohol **210** as a pale yellow oil (48.75 g, 0.32 mol, 97%).

Bpt 74 °C/20 mbar; **R_f** 0.21 (petroleum ether / Et_2O (1:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.71 (1H, app s, H4), 5.53 (1H, app s, H4'), 3.81 (2H, q, J = 6.0 Hz, H1), 2.67 (2H, t, J = 6.0 Hz, H2), 1.87 (1H, t, J = 6.0 Hz, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 130.5, 119.4, 60.0, 44.4. Data in accordance with literature values.[207]

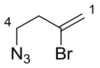
3-Bromobut-3-en-1-yl 4-methylbenzenesulfonate, 351a



To an ice-cooled solution of alcohol **210** (5.11 g, 33.84 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (2.6 mL) was added pyridine (5.5 mL, 67.68 mmol, 2.0 equiv.) and *p*-toluenesulfonyl chloride

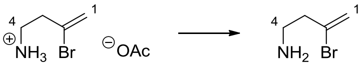
(9.68 g, 50.76 mmol, 1.5 equiv.). After complete addition, the reaction was warmed to RT and stirred for 3 h before being diluted with CH_2Cl_2 and the organic layer washed with *aq*. 1 M HCl. The aqueous layer was extracted with CH_2Cl_2, and the combined organics washed with sat. *aq*. $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / Et_2O (8:1)) afforded the tosylate **351a** as a colourless oil (10.3 g, 33.84 mmol, quant.); **R_f** 0.21 (petroleum ether / Et_2O (8:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.79 (1H, d, *J* = 8.0 Hz, Ts*H*), 7.35 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.65 (1H, app s, H4), 5.48 (1H, d, *J* = 2.0 Hz, H4'), 4.19 (2H, t, *J* 6.0 Hz, H1), 2.74 (2H, t, *J* 6.0 Hz, H2), 2.45 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.0, 132.8, 129.9, 128.0, 127.6, 120.2, 67.2, 40.7, 21.7. Data in accordance with literature values.[106]

4-Azido-2-bromobut-1-ene, 402



The procedure of Pillai was used for this reaction.[106] To sodium azide (1.46 g, 22.48 mmol, 2.0 equiv.) at RT, was added tosylate **351a** (3.43 g, 11.24 mmol, 1.0 equiv.) in DMSO (12.7 mL). After stirring overnight, water was added and the mixture extracted with Et_2O. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford azide **402** as a yellow oil (1.64 g, 9.33 mmol, 83%) which was used without further purification; **R_f** 0.52 (petroleum ether / Et_2O (8:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.73 (1H, dt, *J* = 1.0, 2.0 Hz, H1), 5.55 (1H, d, *J* = 2.0 Hz, H1'), 3.50 (2H, t, *J* = 6.5 Hz, H4), 2.68 (2H, td, *J* = 6.5, 1.0 Hz, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 129.7, 119.6, 49.0, 40.8. Data in accordance with literature values.[106]

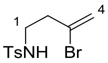
2-Bromobut-1-ene-4-aminium acetate, 211 and 3-bromobut-3-en-1-amine, 212



211 212

The procedure of Pillai was used for this reaction.[106] Hydrogen sulfide was bubbled into a solution of azide **402** (1.94 g, 11.02 mmol, 1.0 equiv.) in pyridine/water (40 mL, 1:1). After 2 h, 2N acetic acid was added to neutralise the mixture, which was then concentrated *in vacuo*, and co-evaporated several times with EtOH. The resulting brown oil was dissolved in water, filtered to remove sulfur and concentrated *in vacuo*, co-evaporating several times with toluene to give the amine salt **211** as a brown oil (1.79 g, 8.48 mmol, 77%). Amine salt **211** was partitioned between sat. *aq*. NaOH and CH_2Cl_2 and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the free amine **212** for subsequent reactions; **R_f** 0.19 (petroleum ether / EtOAc (1:1)) (as free amine); **^{1}H NMR** (400 MHz, D_2O) 5.70 (1H, app s, H1), 5.50 (1H, app s, H1'), 4.67 (3H, br, NH_3^+), 3.07 (2H, t, *J* = 6.5 Hz, H4), 2.66 (2H, t, *J* = 6.5 Hz, H3), 1.78 (3H, s, OAc); **^{13}C NMR** (101 MHz, D_2O) δ_C 180.4, 127.9, 121.6, 38.7, 37.8, 23.0. Data in accordance with literature values.[106]

N-(3-Bromobut-3-en-1-yl)-4-methylbenzenesulfonamide, 213a



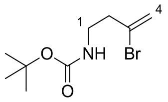
Method A: To a stirred solution of the free amine **212** (200 mg, 1.33 mmol, 1.0 equiv.), and triethylamine (0.74 mL, 5.33 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (4 mL), at 0 °C, was added *p*-toluenesulfonyl chloride (253 mg, 1.33 mmol, 1.0 equiv.). Upon completion by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 and washed with *aq*. 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with sat. *aq*. $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to afford the sulfonamide **213a** as a pale yellow oil (358 mg, 1.18 mmol, 89%) which was used without further purification.

Method B: Prepared by General Procedure B using 3-bromobut-3-en-1-ol **210** (5.57 g, 36.90 mmol) to afford the sulfonamide **213a** as a colourless oil (7.43 g, 23.98 mmol, 65%).

R_f 0.13 (petroleum ether / EtOAc (5:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.60 (1H, app s, H4), 5.48 (1H, d, *J* = 1.5 Hz, H4'), 4.83 (1H, br t, *J* = 6.0 Hz, N*H*), 3.16 (2H, t, *J* = 6.5 Hz, H1), 2.57 (2H, t, *J* = 6.5 Hz, H2), 2.43

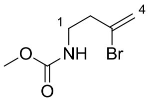
(3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 143.6, 136.9, 129.8, 129.6, 127.1, 120.0, 41.3, 41.0, 21.5. Data in accordance with literature values.[100]

tert-Butyl (3-bromobut-3-en-1-yl)carbamate, 213b



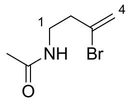
To a solution of free amine **212** (200 mg, 1.33 mmol, 1.0 equiv.) in THF (5 mL) was added triethylamine (0.09 mL, 0.66 mmol, 0.5 equiv.) and di-*tert*-butyl dicarbonate (275 mg, 1.26 mmol, 0.95 equiv.). The reaction mixture was stirred at RT under Ar for 24 h before the addition of DMAP (16 mg, 0.13 mmol, 0.1 equiv.). After stirring at RT for a further 48 h the reaction was heated to reflux for 5 h. Upon completion by TLC analysis the reaction mixture was quenched with *aq*. 1 M HCl solution. The mixture was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried (MgSO$_4$) and concentrated *in vacuo* to afford the title product **213b** as a brown oil (210 mg, 0.84 mmol, 63%) and was used without further purification; **R$_f$** 0.55 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3351, 2977, 1698, 1630, 1519, 1366, 1251; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 5.64 (1H, app s, H4), 5.49 (1H, app s, H4'), 4.68 (1H, br, N*H*), 3.33 (2H, d, *J* = 6.0 Hz, H1), 2.61 (2H, t, *J* = 6.0 Hz, H2), 1.43 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 155.8, 131.0, 119.0, 79.4, 41.9, 38.6, 28.4; **HRMS** (ES+) calc. for $C_9H_{16}{}^{79}BrNNaO_2$ [M+Na]$^+$ 272.0257, found 272.0257.

Methyl (3-bromobut-3-en-1-yl)carbamate, 213c



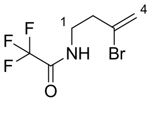
To a solution of free amine **212** (60 mg, 0.40 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (1 mL) was added pyridine (65 µL, 0.80 mmol, 2.0 equiv.) then methyl chloroformate (37 µL, 0.48 mmol, 1.2 equiv.). The resulting reaction mixture was stirred at RT under Ar overnight and then was diluted with CH$_2$Cl$_2$ and washed with *aq*. 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with sat. *aq*. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **213c** as a pale brown oil (42 mg, 0.20 mmol, 51%) which was used without further purification; **R$_f$** 0.57 (petroleum ether / EtOAc (2:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.65 (1H, app s, H4), 5.50 (1H, app s, H4'), 4.87 (1H, br s, N*H*), 3.66 (3H, s, CO_2CH_3), 3.39 (2H, q, *J* = 6.0 Hz, H1), 2.62 (2H, t, *J* 6.0 Hz, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.9, 130.8, 119.2, 52.1, 41.5, 38.9. Data in accordance with literature values.[100]

N-(3-Bromobut-3-en-1-yl)acetamide, 213d



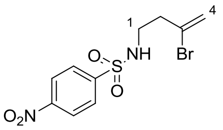
To a solution of free amine **212** (200 mg, 1.33 mmol, 1.0 equiv.) in Et_2O (4 mL) was added pyridine (0.2 mL, 2.66 mmol, 2.0 equiv.) then acetyl chloride (0.1 mL, 1.6 mmol, 1.25 equiv.). The resulting reaction mixture was stirred at RT under Ar. Upon completion as determined by TLC analysis, the reaction mixture was quenched with sat. *aq*. $NaHCO_3$ solution. The mixture was extracted with Et_2O and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **213d** as a colourless oil (180 mg, 0.93 mmol, 70%) which was used without further purification; **R$_f$** 0.10 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.00 (1H, br s, N*H*), 5.63 (1H, dt, *J* = 1.5, 1.0 Hz, H4), 5.47 (1H, d, *J* = 1.5 Hz, H4'), 3.43 (2H, q, *J* = 6.5 Hz, H1), 2.61 (2H, td, *J* = 6.5, 1.0 Hz, H2), 1.96 (3H, s, CH_3). Data in accordance with literature values.[100]

N-(3-Bromobut-3-en-1-yl)-2,2,2-trifluoroacetamide, 213e



To a solution of free amine **212** (145 mg, 0.97 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added pyridine (0.16 mL, 1.94 mmol, 2.0 equiv.) and trifluoroacetic anhydride (0.16 mL, 1.16 mmol, 1.2 equiv.) at 0 °C. The resulting reaction mixture was warmed to RT and stirred under Ar overnight before being diluted with CH_2Cl_2 and washed with *aq*. 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with sat. *aq*. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **213e** as a brown oil (140 mg, 0.57 mmol, 59%) and was used without further purification; **R$_f$** 0.69 (petroleum ether / EtOAc (2:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3313, 3104, 2951, 1708, 1632, 1560, 1432, 1185; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.60 (1H, br s, N*H*), 5.69 (1H, app s, H4), 5.56 (1H, d, *J* = 2.0 Hz, H4'), 3.60 (2H, q, *J* = 6.5 Hz, H1), 2.72 (2H, t, *J* = 6.5 Hz, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.2, 129.4, 120.1, 114.3, 40.2, 37.9; **HRMS** (ES-) calc. for $C_6H_6{}^{79}BrF_3NO$ [M-H]$^-$ 243.9590, found 243.9589.

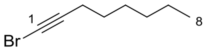
***N*-(3-bromobut-3-en-1-yl)-4-nitrobenzenesulfonamide, 213f**



To a stirred solution of free amine **212** (358 mg, 2.39 mmol, 1.0 equiv.) and triethylamine (1.33 mL, 9.55 mmol, 4.0 equiv.) in CH_2Cl_2 (7 mL), at 0 °C, was added nosyl chloride (530 mg, 2.39 mmol, 1.0 equiv.). Upon completion by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 and washed with *aq*. 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with sat. *aq*. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (3:1)) afforded the title compound **213f** as a pale yellow solid (315 mg, 0.93 mmol, 39%); **mpt** 128-130 °C; **R$_f$** 0.39 (petroleum ether / EtOAc (2:1)); **IR** (nujol mull, ν_{max} / cm^{-1}) 3109, 1608, 1533, 1385, 1351, 1315, 1170; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.45 (2H, d, *J* = 9.0 Hz, Ts*H*), 8.32 (2H, d, *J* = 9.0 Hz, Ts*H*), 5.66 (1H, app s, H4), 5.48 (1H, d, *J* = 2.0 Hz, H4'), 4.00 (2H, t, *J* = 8.0 Hz, H1), 2.80 (2H, t, *J* = 8.0 Hz, H2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 151.0, 144.5, 129.8, 127.7, 124.6, 120.5, 48.4, 41.8; **HRMS** (ES-) calc. for $C_{10}H_{10}BrN_2O_4S$ [M-H]$^-$ 332.9550, found

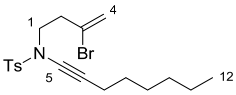
32.9551; **Anal.** calc. for $C_{10}H_{11}{}^{79}BrN_2O_2$: C, 35.83; H, 3.31; N, 8.36; found: C, 35.93; H, 3.23; N, 8.28.

1-Bromooct-1-yne, 215a



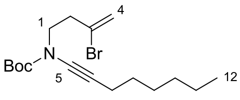
Prepared by General Procedure C Method A using 1-octyne (6.69 mL, 45.37 mmol). Concentration *in vacuo* (some THF not removed due to product volatility) gave the title compound **215a** as a pale orange solution in THF (10.25 g, 45.37 mmol, quant.) and was used without further purification; **R$_f$** 0.70 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.20 (2H, t, J = 7.0 Hz, H3), 1.53 (2H, qu, J = 7.0 Hz, H4), 1.47-1.30 (6H, m, H5-H7), 0.90 (3H, t, J = 7.0 Hz, H8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 80.4, 37.4, 31.3, 28.5, 28.3, 22.5, 19.7, 14.0. Data in accordance with literature values.[208]

N-(3-Bromobut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 205a



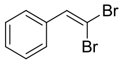
Prepared by General Procedure E using sulfonamide **213a** (1.00 g, 3.29 mmol) and 1-bromo-oct-1-yne **215a** (0.93 g, 4.94 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205a** as a colourless oil (1.26 g, 3.06 mmol, 93%); **R$_f$** 0.39 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2858, 2253, 1703, 1631, 1597, 1169, 1018; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.81 (2H, d, J = 8.0 Hz, Ts*H*), 7.34 (2H, d, J = 8.0 Hz, Ts*H*), 5.64 (1H, br s, H4), 5.45 (1H, br s, H4'), 3.51 (2H, t, J = 7.0 Hz, H1), 2.73 (2H, t, J = 7.0 Hz, H2), 2.46 (3H, s, TsC*H*$_3$), 2.27 (2H, t, J = 7.0 Hz, H7), 1.48 (2H, app qu, J = 7.0 Hz, H8), 1.39-1.23 (6H, m, H9-H11), 0.90 (3H, t, J = 7.0 Hz, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.4, 134.5, 129.6, 129.1, 127.7, 119.5, 72.6, 70.9, 49.7, 39.9, 31.3, 28.8, 28.5, 22.6, 21.6, 18.4, 14.0; **HRMS** (ES$^+$) calc. for $C_{19}H_{26}{}^{79}BrNNaO_2S$ [M+Na]$^+$ 434.0760, found 434.0755.

tert-Butyl (3-bromobut-3-en-1-yl)(oct-1-yn-1-yl)carbamate, 216a



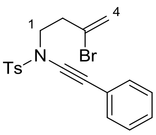
Prepared by General Procedure E using carbamate **213b** (50 mg, 0.20 mmol) and 1-bromo-oct-1-yne **215a** (57 mg, 0.30 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) gave what is tentatively assigned as bromoenynamide **216a** as a colourless oil (10 mg, 14%); **R$_f$** 0.49 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 2928, 2857, 2359, 2263, 1719, 1631, 1455; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 5.68 (1H, app s, H4), 5.48 (1H, app s, H4'), 3.62 (2H, t, *J* = 7.0 Hz, H1), 2.76 (2H, t, *J* = 7.0 Hz, H2), 2.30 (2H, t, *J* = 7.0 Hz, H7), 1.56 (2H, br s, H8), 1.50 (9H, s, C(C*H*$_3$)$_3$), 1.25-1.33 (6H, m, H9-H11), 0.90 (3H, t, *J* = 7.0 Hz, H12); **HRMS** (ES+) calc. for $C_{17}H_{28}{}^{79}BrNNaO_2$ [M+Na]$^+$ 380.1196, found 380.1195.

(2,2-Dibromovinyl)benzene, 218a



Prepared by General Procedure D using benzaldehyde (0.46 mL, 4.52 mmol). Purification *via* column chromatography (hexane / Et$_2$O (20:1)) gave the title compound **218a** as a pale yellow oil (1.16 g, 4.43 mmol, 98%); **R$_f$** 0.62 (hexane / Et$_2$O (20:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.56 (2H, d, *J* = 7.0 Hz, Ph*H*), 7.52 (1H, s, C*H*), 7.41-7.38 (3H, m, Ph*H*); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 136.9, 135.3, 128.6, 128.5, 128.4, 89.7. Data in accordance with literature values.[202]

N-(3-Bromobut-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 205b



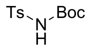
Method A: Prepared by General Procedure F using sulfonamide **213a** (116 mg, 0.38 mmol) and (2,2-dibromovinyl)benzene **218a** (150 mg, 0.57 mmol) with heating for 18 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205b** as a pale yellow oil (90 mg, 0.22 mmol, 58%).

Method B: Prepared by General Procedure E using sulfonamide **213a** (100 mg, 0.33 mmol) and (bromoethynyl)benzene (89 mg, 0.49 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205b** as a yellow oil (116 mg, 0.29 mmol, 88%).

Method C: Prepared by General Procedure H using bromoenynamide **205d** (200 mg, 0.50 mmol) for the desilylation to give the terminal bromoenynamide as a brown oil (158 mg, 0.48 mmol, 96%) and then taking the crude terminal bromoenynamide (50 mg, 0.15 mmol) and iodobenzene (33 µL, 0.30 mmol) for the Sonogashira coupling. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205b** as a yellow oil (30 mg, 0.075 mmol, 50%).

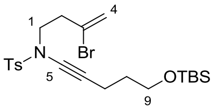
R$_f$ 0.18 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3056, 2926, 2236, 1630, 1597, 1367, 1170; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.90 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.41-7.34 (7H, m, Ts*H* and Ph*H*), 5.73 (1H, d, *J* = 2.0 Hz, H4), 5.53 (1H, d, *J* = 2.0 Hz, H4'), 3.71 (2H, t, *J* = 7.0 Hz, H1), 2.88 (2H, t, *J* = 7.0 Hz, H2), 2.52 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.8, 134.5, 131.3, 129.8, 128.9, 128.3, 127.9, 127.7, 122.7, 119.9, 81.9, 71.1, 49.8, 40.2, 21.6; **HRMS** (FI$^+$) calc. for $C_{19}H_{18}{}^{79}BrNO_2S$ $[M]^+$ 403.0242, found 403.0235.

tert-Butyl tosylcarbamate, 403


$\mathrm{Ts{-}N(H){-}Boc}$

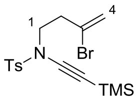
The procedure of Barrett was used for this preparation.[209] To a suspension of *p*-toluenesulfonamide (41.10 g, 240.06 mmol, 1.0 equiv.) in CH_2Cl_2 (200 mL) was added triethylamine (36.2 mL, 266.44 mmol, 1.1 equiv.) and DMAP (2.94 g, 24.06 mmol, 0.1 equiv.) under Ar. To this was added a solution of di-*tert*-butyl dicarbonate (63 mL, 274.23 mmol, 1.15 equiv.) in CH_2Cl_2 (200 mL) dropwise. On complete addition the resulting mixture was stirred for 5 h at RT before being concentrated i*n vacuo*. The crude residue was dissolved in EtOAc (500 mL) and washed with a solution of conc. HCl (34mL) in H_2O (600 mL) and then the organic layer was dried ($MgSO_4$) and concentrated *in vacuo.* Hexanes (500 mL) was added and the mixture sonicated and scratched until precipitation occurred. The solid was filtered, washed with hexane and dried *in vacuo* to afford the title compound **403** as a colourless solid (61.53 g, 225.65 mmol, 94%); **mpt** 115-116 °C, *lit.* 117-119 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.90 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (2H, d, 2H, *J* = 8.5 Hz, Ts*H*), 2.46 (3H, s, TsC*H*$_3$), 1.39 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 148.9, 144.7, 135.9, 129.5, 128.2, 84.0, 27.8, 21.7. Data in accordance with literature values.[209]

N-(3-Bromobut-3-en-1-yl)-*N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methyl benzenesulfonamide, 205c



Prepared by General Procedure E using sulfonamide **213a** (200 mg, 0.66 mmol) and (5-bromopent-4-ynyloxy)(*tert*-butyl)dimethylsilane (274 mg, 0.99 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205c** as a colourless oil (233 mg, 0.44 mmol, 66%); **R$_f$** 0.29 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 2253, 1917, 1631, 1597, 1367, 971; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.34 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.64 (1H, br s, H4), 5.44 (1H, d, *J* = 1.5 Hz, H4'), 3.65 (2H, t, *J* = 6.0 Hz, H9), 3.50 (2H, t, *J* = 7.0 Hz, H1), 2.72 (2H, t, *J* = 7.0 Hz, H2), 2.45 (3H, s, TsC*H*$_3$), 2.35 (2H, t, *J* = 7.0 Hz, H7), 1.70 (2H, tt, *J* = 7.0, 6.0 Hz, H8), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 0.04 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.4, 134.8, 129.6, 129.0, 127.6, 119.5, 72.7, 70.4, 61.5, 49.7, 41.6, 39.9, 32.0, 25.9, 21.6, 14.9, −5.4; **HRMS** (FI^+) calc. for $C_{22}H_{34}{}^{79}BrNO_3SSi$ $[M+H]^+$ 499.1212, found 499.1220.

N-(3-Bromobut-3-en-1-yl)-4-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide, 205d

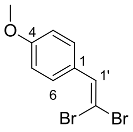


Method A: Prepared by General Procedure E using sulfonamide **213a** (200 mg, 0.66 mmol) and (bromoethynyl)trimethylsilane (175 mg, 0.99 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) gave bromoenynamide **205d** as a pale orange oil (53 mg, 0.13 mmol, 20%).

Method B: Prepared by General Procedure G using sulfonamide **213a** (1.00 g, 3.28 mmol) and [(trimethylsilyl)ethynyl](phenyl)iodonium triflate **231** (1.77 g, 3.94 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205d** as a yellow oil (0.55 g, 1.38 mmol, 42%).

R$_f$ 0.74 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2959. 2220, 2160, 1631, 1371, 1171, 1090; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.81 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.35 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.63 (1H, dt, *J* = 2.0, 1.0 Hz, H4), 5.44 (1H, d, *J* = 2.0 Hz, H4’), 3.55 (2H, t, *J* = 7.0 Hz, H1), 2.73 (2H, td, *J* = 7.0, 0.5 Hz, H2), 2.47 (3H, s, TsC*H*$_3$), 0.17 (9H, s, Si(C*H*$_3$)$_3$);.**^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.8, 134.4, 129.6, 128.8, 127.8, 119.8, 94.4, 73.9, 49.3, 39.9, 21.7, 0.00; **HRMS** (ES+) calc. for $C_{16}H_{23}{}^{79}BrNO_2SSi$ [M+H]$^+$ 400.0397, found 400.0401.

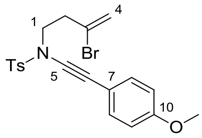
1-(2,2-Dibromovinyl)-4-methoxybenzene, 218b



Prepared by General Procedure D using anisaldehyde (1.8 mL, 14.69 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (98:2)) afforded dibromoalkene **218b** as a pale yellow solid (4.28 g, 14.69 mmol, quant.); **mpt** 36.5 – 38.3 °C; **R$_f$** 0.38 (petroleum ether – EtOAc (99:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.52 (2H, d, *J* = 8.5

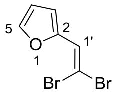
Hz, H2 and H6), 7.42 (1H, s, H1’), 6.90 (2H, d, *J* = 9.0 Hz, H3 and H5), 3.83 (3H, s, C*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ$_c$ 159.8, 136.4, 130.0, 127.9, 113.9, 87.4, 55.4. Data in accordance with literature values.[210]

N-(3-Bromobut-3-en-1-yl)-*N*-((4-methoxyphenyl)ethynyl)-4-methylbenzene sulfonamide, 205e



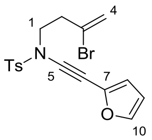
Prepared by General Procedure F using sulfonamide **213a** (500 mg, 1.64 mmol) and 1-(2,2-dibromovinyl)-4-methoxybenzene **218b** (721 mg, 2.47 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded bromoenynamide **205e** as a colourless oil (160 mg, 0.37 mmol, 22%); **R$_f$** 0.23 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν$_{max}$ / cm^{-1}) 2935, 2838, 2237, 1631, 1605, 1568, 1363, 1289, 1248, 1168, 1090; **^{1}H NMR** (400 MHz, CDCl$_3$) δ$_H$ 7.85 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.36 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.5 Hz, H8), 6.83 (2H, d, *J* = 8.5 Hz, H9), 5.67 (1H, d, *J* = 1.0 Hz, H4), 5.46 (1H, d, *J* = 1.5 Hz, H4’), 3.81 (3H, s, OC*H*$_3$), 3.63 (2H, t, *J* = 7.0 Hz, H1), 2.79 (2H, t, *J* = 7.0 Hz, H2), 2.46 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ$_C$ 159.7, 144.9, 134.6, 133.6, 129.9, 129.1, 127.9, 119.9, 114.7, 114.1, 80.5, 70.9, 55.5, 50.00, 40.2, 21.8; **HRMS** (ES$^+$) calc. for $C_{20}H_{20}{}^{79}BrNNaO_3S$ [M+Na]$^+$ 458.0220, found 458.0224; **Elemental analysis** $C_{20}H_{20}BrNO_3S$ requires C, 55.30%; H, 4.64%; N, 3.22%; found C, 55.37%; H, 4.55%; N, 3.27%.

2-(2,2-Dibromovinyl)furan, 218c



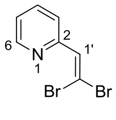
Prepared by General Procedure D using 2-furaldehyde (1.72 mL, 20.82 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (99:1)) afforded dibromoalkene **218c** as a yellow liquid (4.15 g, 16.47 mmol, 79%); **R$_f$** 0.69 (petroleum ether / EtOAc (99:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.44 (1H, d, *J* = 2.0 Hz, H5), 7.41 (1H, s, H1'), 6.95 (1H, dd, *J* = 3.5, 0.5 Hz, H3), 6.48-6.44 (1H, m, H4); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 150.2, 142.7, 126.6, 111.7, 111.6, 87.2. Data in accordance with literature values.[210]

N-(3-Bromobut-3-en-1-yl)-*N*-(furan-2-ylethynyl)-4-methylbenzenesulfonamide, 205f



Prepared by General Procedure F using sulfonamide **213a** (500 mg, 1.64 mmol) and 2-(2,2-dibromovinyl)furan **218c** (627 mg, 2.47 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded bromoenynamide **205f** as a yellow oil (310 mg, 0.78 mmol, 47%); **R$_f$** 0.20 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2227, 1631, 1597, 1491, 1366, 1170, 1118, 1090, 1016, 966; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.84 (2H, d, *J* = 7.5 Hz, Ts*H*), 7.40 (1H, s, H10), 7.37 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.62 (1H, d, *J* = 3.0 Hz, H8), 6.40 (1H, s, H9), 5.67 (1H, s, H4), 5.45 (1H, s, H4'), 3.65 (2H, t, *J* = 7.0 Hz, H1), 2.78 (2H, t, *J* = 7.0 Hz, H2), 2.47 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 145.2, 144.3, 136.7, 134.7, 130.1, 128.8, 127.9, 120.1, 117.6, 111.3, 86.0, 62.2, 50.0, 40.2, 21.9; **HRMS** (ES$^+$) calc. for C$_{17}$H$_{16}$^{79}BrNNaO$_3$S [M+Na]$^+$ 415.9926, found 415.9927; **Elemental analysis** C$_{17}$H$_{16}$BrNO$_3$S requires C, 51.79%; H, 4.09%; N, 3.55%; found C, 51.75%; H, 3.97%; N, 3.64%.

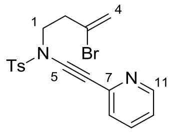
2-(2,2-Dibromovinyl)pyridine, 218d



Prepared by General Procedure D using pyridine-2-carboxaldehyde (1.78 mL, 16.67 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (9:1) → EtOAc) afforded dibromoalkene **218d** as a yellow oil (1.49 g, 5.67 mmol, 30%); **R$_f$** 0.17 (petroleum ether /

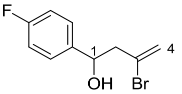
EtOAc (99:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.62 (1H, d, *J* = 5.0 Hz, H6), 7.75-7.67 (2H, m, H3 and H4), 7.64 (1H, s, H1'), 7.23 (1H, ddd, *J* = 7.0, 5.0, 2.0 Hz, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_c 154.0, 149.7, 137.3, 136.4, 123.6, 123.1, 93.3. Data in accordance with literature values.[210]

N-(3-Bromobut-3-en-1-yl)-4-methyl-*N*-(pyridin-2-ylethynyl)benzenesulfonamide, 205g



Prepared by General Procedure F using sulfonamide **213a** (210 mg, 0.69 mmol) and 2-(2,2-dibromovinyl)pyridine **218d** (273 mg, 1.03 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (10:1) + 5% NEt_3 → petroleum ether / EtOAc (4:1) + 5% NEt_3) afforded bromoenynamide **205g** as a pale yellow oil (196 mg, 0.48 mmol, 69%); **R_f** 0.10 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2233, 1631, 1583, 1561, 1469, 1366, 1169, 1089, 966; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H (400 MHz, $CDCl_3$) 8.52 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz, H11), 7.85 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.62 (1H, td, *J* = 7.5, 2.0 Hz, H9), 7.37 (1H, dt, *J* = 8.0, 1.0 Hz, H8), 7.34 (1H, d, *J* = 8.5 Hz, Ts*H*), 7.17 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz, H10), 5.68 (1H, s, H4), 5.44 (1H, d, *J* = 2.0 Hz, H4'), 3.67 (2H, t, *J* = 7.0 Hz, H1), 2.82 (2H, t, *J* = 7.0 Hz, H2), 2.42 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_c 150.0, 145.2, 143.4, 136.2, 134.5, 130.1, 128.7, 127.8, 126.6, 122.3, 120.2, 82.2, 71.7, 49.8, 40.2, 21.8; **HRMS** (ES^+) calc. for $C_{18}H_{17}{}^{79}BrN_2NaO_2S$ $[M+Na]^+$ 427.0086, found 427.0078.

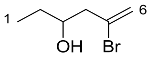
3-Bromo-1-(4-fluorophenyl)but-3-en-1-ol, 224a



Prepared by General Procedure A using 4-fluorobenzaldehyde (5.2 mL, 48.18 mmol) to afford alcohol **224a** as a pale pink oil (7.63 g, 42.39 mmol, 88%); **R_f** 0.21 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.38-7.33 (2H, m, 4-FPh*H*), 7.09-7.02 (2H, m, 4-

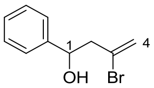
FPh*H*), 5.67 (1H, app s, H4), 5.55 (1H, d, *J* = 1.5 Hz, H4'), 5.04 (1H, dd, *J* = 8.5, 4.5 Hz, H1), 2.84 (1H, ddd, *J* = 14.5, 8.5, 1.0 Hz, H2), 2.72 (1H, ddd, *J* = 14.5, 5.0, 1.0 Hz, H2'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.3 (d, $J_{C\text{-}F}$ = 245.8 Hz), 138.6, 129.8, 127.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 120.2, 115.3 (d, $J_{C\text{-}F}$ = 21.4 Hz), 71.0, 51.2. Data in accordance with literature values.[211]

5-Bromohex-5-en-3-ol, 224b



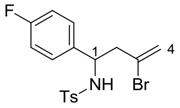
Prepared by General Procedure A using propionaldehyde (0.25 mL, 3.44 mmol) to afford alcohol **224b** as a colourless oil (572 mg, 3.16 mmol, 92%); **R_f** 0.23 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.70 (1H, app s, H6), 5.55 (1H, app s, H6'), 3.88-3.84 (1H, m, H3), 2.58 (1H, dd, *J* = 14.5, 4.0 Hz, H4), 2.51 (1H, dd, *J* = 14.5, 8.5 Hz, H4'), 1.75 (1H, br s, O*H*), 1.57-1.49 (2H, m, H2), 0.99 (3H, t, *J* = 7.5 Hz, H1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 130.9, 119.6, 70.4, 49.0, 29.3, 9.9. Data in accordance with literature values.[212]

3-Bromo-1-phenylbut-3-en-1-ol, 224c



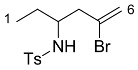
Prepared by General Procedure A using benzaldehyde (0.19 mL, 1.89 mmol) to afford alcohol **224c** as a colourless oil (409 mg, 1.79 mmol, 94%); **R_f** 0.51 (petroleum ether / EtOAc (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43-7.33 (4H, m, Ph*H*), 7.33-7.26 (1H, m, Ph*H*), 5.68 (1H, s, H4), 5.55 (1H, d, *J* = 1.5 Hz, H4'), 5.05 (1H, dd, *J* = 9.0, 4.5 Hz, H1), 2.85 (1H, dd, *J* = 14.5, 9.0 Hz, H2), 2.76 (1H, ddd, *J* = 14.5, 4.5, 1.0 Hz, H2'); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.0, 130.2, 128.7, 128.0, 126.0, 120.2, 71.8, 51.5. Data in accordance with literature values.[104]

N-(3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide, 225a



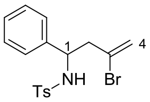
Prepared by General Procedure B using 3-bromo-1-(4-fluorophenyl)but-3-en-1-ol **224a** (2.00 g, 8.16 mmol) to afford the sulfonamide **225a** as a pale yellow oil (1.99 g, 4.90 mmol, 60%); **R$_f$** 0.29 (petroleum ether / EtOAc (3:1)); **^{1}H NMR** (200 MHz, CDCl$_3$) δ_H7.58 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.18 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.09-7.06 (2H, m, 4-FPh*H*), 6.88 (2H, t, *J* = 8.5 Hz, 4-FPh*H*), 5.51 (1H, dt, *J* = 2.0, 1.0 Hz, H4), 5.40 (1H, d, *J* = 2.0 Hz, H4'), 5.06 (1H, d, *J* = 5.5 Hz, N*H*), 4.59 (1H, q, *J* = 6.5 Hz, H1), 2.82 (1H, ddd, *J* = 14.5, 8.0, 1.0 Hz, H2), 2.70 (1H, ddd, *J* = 14.5, 6.0, 1.0 Hz, H2'), 2.40 (3H, s, TsCH_3); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 162.2 (d, J_{C-F} = 246.6 Hz), 143.5, 136.8, 135.1 (d, J_{C-F} = 3.1 Hz), 129.4, 128.4, 128.4, 127.3, 120.9, 115.4 (d, J_{C-F} = 21.7 Hz), 55.6, 49.2, 21.5. Data in accordance with literature values.[100]

N-(5-Bromohex-5-en-3-yl)-4-methylbenzenesulfonamide, 225b



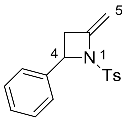
Prepared by General Procedure B using 5-bromohex-5-en-3-ol **224b** (572 mg, 3.20 mmol) to afford the sulfonamide **225b** as a colourless oil (425 mg, 1.28 mmol, 40%); **R$_f$** 0.06 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3281, 1631, 1599, 1451, 1430, 1324, 1158, 1093, 1068, 893; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.78 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.56 (1H, app s, H6), 5.40 (1H, app s, H6'), 4.46 (1H, d, *J* = 8.0 Hz, N*H*), 3.47 (1H, app sex, *J* = 6.5 Hz, H3), 2.52 (1H, dd, *J* = 14.5, 6.5 Hz, H4), 2.45 (1H, dd, *J* = 14.5, 7.0 Hz, H4'), 2.44 (3H, s, TsCH_3), 1.64-1.61 (1H, m, H2), 1.42 (1H, app sept, *J* = 7.0 Hz, H2'), 0.83 (3H, t, *J* = 7.5 Hz, H1); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.4, 137.8, 129.7, 129.6, 127.3, 120.1, 53.6, 46.4, 26.9, 21.6, 9.5; **HRMS** (ES+) calc. for $C_{13}H_{18}{}^{79}BrNNaO_2S$ [M+Na]$^+$ 354.0134, found 354.0122.

N-(3-Bromo-1-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 225c



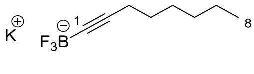
Prepared by General Procedure B using 3-bromo-1-phenylbut-3-en-1-ol **224c** (409 mg, 1.80 mmol) to afford the sulfonamide **225c** as a pale yellow solid (317 mg, 0.83 mmol, 46%); **mpt** 77.5-81.0 °C; **R_f** 0.40 (petroleum ether / EtOAc (3:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.21-7.08 (7H, m, Ts*H* and Ph*H*), 5.63 (1H, d, *J* = 7.0 Hz, N*H*), 5.49 (1H, app s, H4), 5.34 (1H, d, *J* = 1.5 Hz, H4’), 4.62 (1H, q, *J* = 7.0 Hz, H1), 2.85 (1H, dd, *J* = 14.5, 8.0 Hz, H2), 2.72 (1H, dd, *J* = 14.5, 6.5 Hz, H2’), 2.38 (3H, s, TsCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.2, 139.5, 137.1, 129.4, 128.7, 128.5, 127.7, 127.3, 126.7, 120.7, 56.3, 49.2, 21.5. Data in accordance with literature values.[107]

2-Methylene-4-phenyl-1-tosylazetidine, 227a



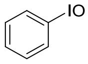
Isolated side-product prepared by General Procedure F using *N*-(3-bromo-1-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide **225c** (100 mg, 0.26 mmol) and (2,2-dibromovinyl)benzene **218a** (104 mg, 0.39 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave azetidine **227a** as a pale yellow solid (69 mg, 0.24 mmol, 90 %); **R_f** 0.29 (petroleum ether / EtOAc (10:1)); **mpt** 110-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.44-7.27 (7H, m, Ts*H* and Ph*H*), 5.03 (1H, q, *J* = 2.5 Hz, H5), 4.91 (1H, dd, *J* = 8.0, 2.5 Hz, H4), 4.32 (1H, q, *J* = 2.5 Hz, H5’), 3.01-2.95 (1H, m, H3), 2.72-2.67 (1H, m, H3’), 2.46 (3H, s, TsCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.0, 144.2, 139.2, 133.5, 129.6, 128.6, 128.3, 127.9, 126.4, 89.9, 62.9, 35.6, 21.6. Data in accordance with literature values.[109]

Potassium trifluoro(oct-1-yn-1-yl)borate, 228



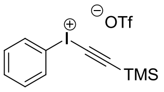
The procedure of Evano was used for this preparation.[20] To a solution of oct-1-yne (0.27 mL, 1.82 mmol, 1.0 equiv.) in anhydrous THF (3.6 mL) was added *n*-BuLi (0.73 mL, 1.82 mmol, 2.5 M, 1.0 equiv.) dropwise at −78 °C before being stirred for 1 h. Trimethyl borate (0.30 mL, 2.72 mmol, 1.5 equiv.) was then added dropwise and stirred for a further 1 h at −78 °C before being allowed to warm to −20 °C over 1 h. KHF_2 (851 mg, 10.89 mmol, 6.0 equiv.) was then added as a sat. *aq*. solution and the resulting mixture stirred vigorously for 1 h at −20 °C and then at RT for 1 h. The resulting reaction mixture was concentrated *in vacuo* and dried under high vacuum to remove any residual water. The resulting solid was extracted with boiling acetone and the solution filtered and concentrated *in vacuo* to afford a white powder. This solid was re-dissolved in hot acetone and precipitated with Et_2O, then stored in the freezer at −20 °C overnight to complete precipitation of the solid, which was subsequently filtered and dried to afford the title compound **228** as a white crystalline powder (215 mg, 1.00 mmol, 55%); **mpt** decomposed >248 °C; **IR** (nujol, ν_{max} / cm^{-1}) 2187, 1274, 1145, 1120, 968, 722; **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 1.98-1.95 (2H, m, H3), 1.33-1.23 (8H, m, H4-H7), 0.86 (3H, t, *J* = 7.0 Hz, H8); **^{13}C NMR** (101 MHz, d_6-DMSO**)** δ_C 31.8, 29.9, 28.9, 23.0, 19.8, 14.8; **HRMS** (ES-) calc. for $C_8H_{13}BF_3$ $[M-K]^-$ 177.1069, found 177.1073.

Iodosobenzene, 233



The procedure of Saltzman and Sharefkin was used for this preparation.[213] To a 50 mL beaker was added iodosobenzene diacetate (10 g, 31.05 mmol, 1.0 equiv.) and 3N *aq*. NaOH (48 mL) with vigorous stirring. The thick emulsion was stirred for a further 15 min before being left to stand for an additional 45 min. To the emulsion was added water (32 mL) and the solid filtered off. The collected solid was triturated in water (64 mL), refiltered and washed with more water (64 mL) and the solid dried under vacuum. The solid was then triturated in chloroform (24 mL), filtered and dried under vacuum to afford the title product **233** as a pale yellow solid which was used without further purification or analysis due to its insolubility (6.55 g, 96%).

[(Trimethylsilyl)ethynyl](phenyl)iodonium triflate, 231

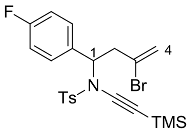


Method A: The procedure of Stang and co-workers was used for this preparation.[110] A mixture of iodosobenzene **233** (4.78 g, 21.71 mmol, 1.0 equiv.) and trifluoromethanesulfonic anhydride (1.82 mL, 10.86 mmol, 0.5 equiv.) in CH_2Cl_2 (21 mL) was stirred at 0 °C for 10 min (until the suspension became a clear homogenous yellow solution). To the resulting mixture was added bis(trimethylsilyl)acetylene (3.7 g, 21.71 mmol, 1.0 equiv.) in CH_2Cl_2 (21 mL) and was stirred for a further 30 min at 0 °C before being concentrated *in vacuo*. The crude product was triturated in Et_2O and the precipitate collected by filtration, washed with more Et_2O and dried *in vacuo* to afford the title product **231** as a white solid (7.48 g, 16.50 mmol, 76%).

Method B: The procedure of Fujiwara was used for this preparation.[214] A solution of iodosobenzene diacetate (8.28 g, 24.90 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (25 mL) was stirred for 5 min under Ar. Fresh trifluoromethanesulfonic anhydride from an ampoule (2.1 mL, 12.45 mmol, 0.5 equiv.) was then added dropwise at 0 °C and the resulting homogenous yellow solution stirred for 30 min. Bis(trimethylsilyl)acetylene (4.24 g, 24.90 mmol, 1.0 equiv.) was added and the reaction stirred for a further 2 h before the addition of Et_2O to precipitate the product. The solid was filtered, washed further with Et_2O and dried i*n vacuo* to afford the desired product **231** as a colourless solid (10.18 g, 22.41 mmol, 90%).

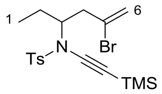
mpt 139-144 °C, *lit*. 143-146 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.08 (2H, d, J = 8.0 Hz, Ph*H*), 7.69 (1H, t, J = 7.5 Hz, Ph*H*), 7.58 (2H, t, J = 8.0 Hz, Ph*H*), 0.26 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 133.7, 132.8, 130.2, 121.1, 120.5, 117.4, 44.5, 0.84. Data in accordance with literature values.[215]

N-(3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)-4-methyl-*N*-((trimethylsilyl)ethynyl) benzene sulfonamide, 232a



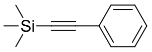
Prepared by General Procedure G using sulfonamide **225a** (1.99 g, 5.00 mmol), KHMDS (11 mL, 5.50 mmol) and [(trimethylsilyl)ethynyl](phenyl)iodonium triflate **231** (2.70 g, 6.00 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **232a** as a pale yellow oil (0.98 g, 1.98 mmol, 40%); **R$_f$** 0.48 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3045, 2959, 2925, 2159, 1718, 1632, 1604, 1512, 1370, 844; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.61 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.30 (2H, dd, *J* = 8.5, 5.0 Hz, 4-FPh*H*), 7.19 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.93 (2H, t, *J* = 8.5 Hz, 4-FPh*H*), 5.56 (1H, br s, H4), 5.33 (1H, dd, *J* = 5.5, 3.5 Hz, H1), 5.30 (1H, d, *J* = 2.0 Hz, H4'), 3.15 (1H, dd, *J* = 14.5, 9.0 Hz, H2), 2.77 (1H, dd, *J* = 15.0, 6.0 Hz, H2'), 2.41 (3H, s, TsC*H$_3$*), 0.19 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 162.5 (d, $J_{C\text{-}F}$ = 247.5 Hz), 144.4, 134.9, 133.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.1, 128.8, 128.7, 128.1, 127.9, 120.8, 115.3 (d, $J_{C\text{-}F}$ = 21.5 Hz), 92.7, 60.0, 45.7, 21.6, 0.02; **HRMS** (ES$^+$) calc. for $C_{22}H_{25}{}^{79}BrFNNaO_2SSi$ [M+Na]$^+$ 516.0435, found 516.0422.

N-(5-Bromohex-5-en-3-yl)-4-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide, 232b



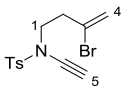
Prepared by General Procedure G using sulfonamide **225b** (1.01 g, 3.03 mmol), KHMDS (6.7 mL, 3.34 mmol), and [(trimethylsilyl)ethynyl](phenyl)iodonium triflate **231** (1.64 g, 3.64 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **232b** as an orange oil (0.55g, 1.28 mmol, 42%); **R$_f$** 0.31 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2965, 2159, 1699, 1632, 1598, 1363, 1249, 1169, 1091, 988, 844.8; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.48 (1H, br s, H6), 5.18 (1H, br s, H6'), 4.20-4.11 (1H, m, H3), 2.60 (1H, dd, *J* = 14.5, 8.5 Hz, H4), 2.45 (3H, s, TsC*H*$_3$), 2.43 (1H, dd, *J* = 14.5, 5.5 Hz, H4'), 1.59-1.53 (2H, m, H2), 0.91 (3H, t, *J* = 7.5 Hz, H1), 0.17 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.2, 135.4, 129.1, 127.8, 119.9, 91.8, 75.8, 60.2, 44.8, 30.8, 25.5, 21.5, 10.5, −0.0034; **HRMS** (ES+) calc. for $C_{18}H_{26}{}^{79}BrNNaO_2SSi$ [M+Na]$^+$ 450.0529, found 450.0517.

Trimethyl(phenylethynyl)silane,235



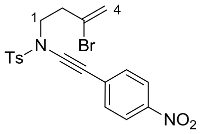
The procedure of Negishi was used for this preparation.[216] To a solution of ZnBr$_2$ (5.00 g, 22.20 mmol, 1.2 equiv.) weighed out in a glovebox, in anhydrous THF (463 mL) was added anhydrous NEt$_3$ (12.4 mL, 88.80 mmol, 4.8 equiv.) and the resulting solution stirred under Ar at RT for 5 min. Iodobenzene (2.1 mL, 18.50 mmol, 1.0 equiv.), ethynyltrimethylsilane (3.07 mL, 22.20 mmol, 1.2 equiv.) and Pd(PPh$_3$)$_4$, pre-weighed in a glovebox, (1.08 g, 0.93 mmol, 0.05 equiv.) were added to the solution before being stirred at RT for 18 h. Reaction mixture diluted with Et$_2$O and washed with sat. *aq*. NH$_4$Cl followed by sat. *aq*. NaHCO$_3$, and the organic layer dried (MgSO$_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether) afforded the desired product **235** as a colourless oil (1.72 g, 9.80 mmol, 53%); **R$_f$** 0.53 (petroleum ether); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.48-7.46 (2H, m, Ph*H*), 7.32-7.28 (3H, m, Ph*H*), 0.26 (9H, s, Si(CH$_3$)$_3$; **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 131.9, 128.5, 128.2, 123.1, 105.1, 94.1, −0.05. Data in accordance with literature values.[216]

N-(3-Bromobut-3-en-1-yl)-N-ethynyl-4-methylbenzenesulfonamide,205h



To a solution of the TMS-bromoenynamide **205d** (300 mg, 0.75 mmol, 1.0 equiv) in anhydrous THF (15 mL) at 0 °C was added TBAF (0.98 mL, 0.98 mmol, 1.3 equiv, 1 M in THF) dropwise under Ar. The reaction mixture was stirred at 0 °C for 10 min before being quenched with sat. *aq.* NH_4Cl. The aqueous layer was extracted with Et_2O (×3), and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford terminal bromoenynamide **205h** as a brown solid (237 mg, 0.72 mmol, 96%); **R$_f$** 0.31 (petroleum ether – EtOAc (10:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.37 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.66 (1H, dt, *J* = 2.0, 1.0 Hz, H4), 5.46 (1H, d, *J* = 2.0 Hz, H4'), 3.56 (2H, t, *J* = 7.0 Hz, H1), 2.78 (1H, s, H5), 2.75 (2H, td, *J* = 7.0, 1.0 Hz, H2), 2.47 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz) δ_C 145.0, 134.4, 129.9, 128.6, 127.7, 119.9, 75.5, 59.8, 49.4, 39.8, 21.7. Data in accordance with literature values.[100]

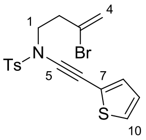
N-(3-Bromobut-3-en-1-yl)-4-methyl-*N*-((4-nitrophenyl)ethynyl)benzenesulfonamide, 205j



Prepared by General Procedure H using bromoenynamide **205d** (200 mg, 0.50 mmol) for the desilylation to give the terminal bromoenynamide as a brown oil (158 mg, 0.48 mmol, 96%) and then taking the crude terminal bromoenynamide (50 mg, 0.15 mmol) and 1-iodo-4-nitrobenzene (75 mg, 0.30 mmol) for the Sonogashira coupling. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205j** as a yellow solid (35 mg, 0.078 mmol, 52%) which was used immediately in the cascade cyclisation; **R$_f$** 0.18 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3082, 2921, 1698, 1631, 1599, 1523, 1347, 1166; **^{1}H NMR** (500 MHz, d$_6$-DMSO) δ_H 8.22 (2H, d, *J* = 9.0 Hz, 4-NO_2Ph*H*), 7.91 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.62 (2H, d, *J* = 9.0 Hz, 4-NO_2Ph*H*), 7.55 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.82 (1H, d, *J* = 2.0 Hz, H4), 5.55 (1H, d, *J* = 2.0 Hz, H4′), 3.71 (2H, t, *J* = 6.5 Hz, H1), 2.84 (2H, d, *J* = 6.5 Hz, H2), 2.45 (3H, s, TsC*H*$_3$); **^{13}C NMR** (126 MHz, d$_6$-DMSO) δ_C 146.0, 145.6, 133.3, 131.0, 130.3, 129.3, 129.0, 127.6, 123.9, 120.6, 87.9, 70.6, 49.2, 40.1, 21.1; **HRMS** (FI+) calc. for $C_{19}H_{17}{}^{79}BrN_2O_4S$ $[M]^+$ 448.0092, found 448.0211 and calc. for the amide $C_{19}H_{19}{}^{79}BrN_2O_5S$ $[M+H_2O]$ 466.0198, found 466.0253.

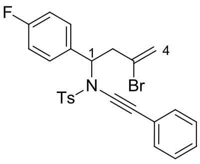
N.B. Bromoenynamide **205j** is highly susceptible to ambient hydrolysis, and decomposition on silica and in acidic media.

N-(3-Bromobut-3-en-1-yl)-4-methyl-*N*-(thiophen-2-ylethynyl)benzenesulfonamide, 205k



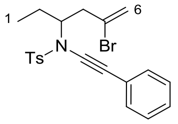
Prepared by General Procedure H using bromoenynamide **205d** (200 mg, 0.50 mmol) for the desilylation to give the terminal bromoenynamide as a brown oil (158 mg, 0.48 mmol, 96%) and then taking the crude terminal bromoenynamide (50 mg, 0.15 mmol) and 2-iodothiophene (31 µL, 0.30 mmol) for the Sonogashira coupling. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205k** as a yellow oil (17 mg, 0.042 mmol, 28%); **R$_f$** 0.32 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2924, 2229, 1631, 1597, 1433, 1368, 1170, 1091; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.85 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.38 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.29 (1H, dd, *J* = 5.0, 1.0 Hz, H10), 7.19 (1H, dd, *J* = 3.5, 1.0 Hz, H8), 6.99 (1H, dd, *J* = 5.0, 3.5 Hz, H9), 5.67-5.66 (1H, m, H4), 5.47 (1H, d, *J* = 2.0 Hz, H4’), 3.66 (2H, t, *J* = 7.0 Hz, H1), 2.79 (2H, t, *J* = 7.0 Hz, H2), 2.48 (3H, s, TsC*H*$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.9, 134.4, 133.1, 129.8, 128.8, 127.9, 127.7, 127.0, 122.6, 119.9, 85.4, 64.6, 49.9, 40.1, 21.7; **HRMS** (ES+) calc. for $C_{17}H_{16}{}^{79}BrNNaO_2S_2$ [M+Na]$^+$ 431.9698, found 431.9683.

N-(3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzene sulfonamide, 232c



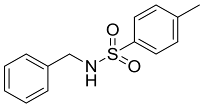
Prepared by General Procedure H using bromoenynamide **232a** (400 mg, 0.80 mmol) for the desilylation to give the terminal bromoenynamide as a brown oil (309 mg, 0.73 mmol, 91%), and then taking the crude terminal bromoenynamide (309 mg, 0.73 mmol) and iodobenzene (0.16 mL, 1.46 mmol) for the Sonogashira coupling. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **232c** as a yellow oil (156 mg, 0.32 mmol, 43%); **R$_f$** 0.42 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3065, 2926, 1700, 1631, 1603, 1511, 1496, 1359, 1228, 1163; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.39 – 7.32 (7H, m, 4-FPh*H* and Ph*H*), 7.21 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.96 (2H, t, *J* = 8.5 Hz, 4-FPh*H*), 5.61 (1H, br s, H4), 5.46 (1H, dd, *J* = 9.0, 6.0 Hz, H1), 5.34 (1H, d, *J* = 2.0 Hz, H4'), 3.20 (1H, dd, *J* = 14.5, 9.0 Hz, H2), 2.89 (1H, dd, *J* = 14.5, 6.0 Hz, H2'), 2.41 (3H, s, TsC*H*$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 162.6 (d, $J_{C\text{-}F}$ = 24.5), 144.5, 135.0, 133.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 131.3, 129.3, 128.9 (d, $J_{C\text{-}F}$ = 8.5 Hz), 128.4, 128.1, 128.0, 127.8, 122.6, 120.8, 115.4 (d, $J_{C\text{-}F}$ = 21.5 Hz), 80.0, 74.0, 60.6, 45.9, 21.6; **HRMS** (FI+) calc. for $C_{25}H_{21}{}^{79}BrFNO_2S$ [M]$^+$ 497.0463, found 497.1133.

***N*-(5-Bromohex-5-en-3-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 232d**



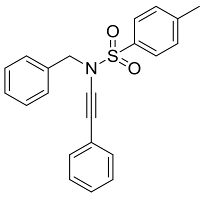
Prepared by General Procedure H using bromoenynamide **232b** (300 mg, 0.70 mmol) for the desilylation to give the terminal bromoenynamide as a brown oil (219 mg, 0.61 mmol, 87%), and then taking the crude terminal bromoenynamide (219 mg, 0.61 mmol) and iodobenzene (0.13 mL, 1.22 mmol) for the Sonogashira coupling. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **232d** as a yellow oil (110 mg, 0.25 mmol, 41%); **R$_f$** 0.37 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2233, 1364, 1171, 1091, 980, 908, 813, 732, 691, 671; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.88 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.39-7.36 (2H, m, Ph*H*), 7.34-7.29 (5H, m, Ph*H* and Ts*H*), 5.53 (1H, br s, H6), 5.24 (1H, d, *J* = 1.5 Hz, H6'), 4.28 (1H, app qu, *J* = 7.0 Hz, H3), 2.67 (1H, dd, *J* = 14.5, 8.0 Hz, H4), 2.52 (1H, dd, *J* = 14.5, 6.0 Hz, H4'), 2.45 (3H, s, TsC*H*$_3$), 1.64 (2H, app qu, *J* = 7.5 Hz, H2), 0.96 (3H, t, *J* = 7.5 Hz, H1); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.4, 135.7, 131.3, 129.5, 129.3, 128.3, 127.9, 127.8, 122.9, 120.1, 79.2, 73.1, 60.8, 45.2, 25.7, 21.6, 10.7; **HRMS** (ES+) calc. for $C_{21}H_{22}{}^{79}BrNNaO_2S$ $[M+Na]^+$ 456.0427, found 456.0427.

***N*-Benzyl-4-methylbenzenesulfonamide, 243**



To a stirred solution of benzylamine (1.00 g, 9.33 mmol, 1.0 equiv.) and triethylamine (1.95 mL, 14.00 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (20 mL), at 0 °C, was added *p*-toluenesulfonyl chloride (1.78 g, 9.33 mmol, 1.0 equiv.). Upon completion by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 and washed with *aq*. 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers washed with sat. *aq*. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **243** as a pale yellow solid (2.44 g, 9.33 mmol, quant.) which was used without further purification; **mpt** 108-110 °C; **R$_f$** 0.06 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.20-7.31 (5H, m, Ph*H*), 4.67 (1H, br s, N*H*), 4.13 (2H, d, *J* = 6.0 Hz, C*H*$_2$), 2.45 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.6, 136.8, 136.2, 129.7, 128.7, 127.9, 127.8, 127.2, 47.3, 21.5. Data in accordance with literature values.[217]

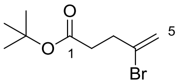
***N*-Benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 244**



Prepared by General Procedure F using sulfonamide **243** (200 mg, 0.77 mmol) and (2,2-dibromovinyl)benzene **218a** (301 mg, 1.15 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded bromoenynamide **244** as a yellow solid (278 mg, 0.77 mmol, quant.); **mpt** 58-61 °C; **R$_f$** 0.19 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400

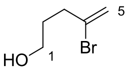
MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.34 (7H, m, Ar*H* and Ts*H*), 7.25 (5H, m, Ar*H*), 4.60 (2H, s, C*H*$_2$), 2.46 (3H, s, TsC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.6, 134.4, 131.1, 129.7, 128.9, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 122.8, 82.7, 71.4, 55.7, 21.7. Data in accordance with literature values.[19]

tert-Butyl-4-bromopent-4-enoate, 246



The procedure of Baldwin *et al.* was used for this preparation.[114] To a freshly prepared 1 M solution of LDA (17.2 mL, 17.2 mmol, 1.5 equiv.), made from 2.5 M *n*-BuLi (8 mL) added dropwise to an ice-cooled solution of DIPA (2.8 mL) in THF (9.2 mL) at −78 °C, was added a solution of *tert*-butyl acetate (2.3 mL, 17.2 mmol, 1.5 equiv.) in anhydrous THF (36 mL) dropwise. Reaction mixture stirred for 30 min at −78 °C before the dropwise addition of 2,3-dibromopropene **209** (1.2 mL, 11.5 mmol, 1.0 equiv.). After further stirring at −78 °C for 2 h the reaction was quenched with sat. *aq*. NH_4Cl and allowed to warm to RT before being extracted with Et_2O. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded the title product **246** as a colourless oil (2.15 g, 9.20 mmol, 80%); **R$_f$** 0.54 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.63 (1H, d, *J* = 1.5 Hz, H5), 5.43 (1H, d, *J* = 1.5 Hz, H5’), 2.72 (2H, t, *J* = 7.5 Hz, H2), 2.49 (2H, td, *J* = 7.5 Hz, H3), 1.45 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.2, 132.5, 117.3, 80.7, 36.8, 34.1, 28.1. Data in accordance with literature values.[114]

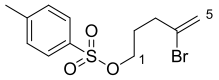
4-Bromopent-4-en-1-ol, 247



The procedure of Baldwin *et al.* was used for this preparation.[114] To a solution of $LiAlH_4$ (382 mg, 10.07 mmol, 1.1 equiv.) in anhydrous Et_2O (18 mL) at 0 °C was added a solution of *tert*-

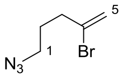
butyl 4-bromopent-4-enoate **246** (2.15 g, 9.15 mmol, 1.0 equiv.) in anhydrous Et_2O (18 mL). The reaction mixture was then stirred at RT for 2 h before being quenched with sat. *aq*. NaOH. The aqueous layer was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **247** as a pale yellow oil (0.85 g, 5.12 mmol, 56%); **R_f** 0.58 (petroleum ether / EtOAc (1:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.62 (1H, d, *J* = 1.5 Hz, H5), 5.43 (1H, d, *J* = 1.5 Hz, H5'), 3.69 (2H, t, *J* = 6.0 Hz, H1), 2.55 (2H, t, *J* = 7.5 Hz, H3), 1.84 (2H, qu, *J* = 7.5 Hz, H2), 1.39 (1H, br s, O*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 133.9, 117.0, 61.4, 37.7, 30.8. Data in accordance with literature values.[114]

4-Bromopent-4-en-1-yl 4-methylbenzenesulfonate, 351b



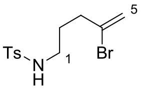
To an ice-cooled solution of 4-bromopent-4-en-1-ol **247** (845 mg, 5.12 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (16 mL) was added pyridine (0.83 mL, 10.24 mmol, 2.0 equiv.) and *p*-toluenesulfonyl chloride (1.46 g, 7.68 mmol, 1.5 equiv.). After addition, the reaction was warmed to RT and stirred for 3 h, before being diluted with CH_2Cl_2 and the organic layer washed with *aq*. 1 M HCl. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were washed with sat. *aq*. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / Et_2O (8:1)) afforded the tosylate **351b** as a pale yellow oil (1.94 g, 5.12 mmol, quant.) and was used without further purification; **R_f** 0.24 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2959, 1631, 1596, 1492, 1444, 1364, 1293, 1176, 1121, 1098; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.34 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.51 (1H, app s, H5), 5.37 (1H, d, *J* = 1.5 Hz, H5'), 4.05 (2H, t, *J* = 6.0 Hz, H1), 2.47 (2H, t, *J* = 7.0 Hz, H3), 2.45 (3H, s, TsCH_3), 1.91 (2H, qu, *J* = 7.0 Hz, H2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.9, 130.2, 129.9, 127.9, 127.0, 118.1, 68.7, 37.1, 27.0, 21.6; **HRMS** (ES+) calc. for $C_{12}H_{15}{}^{79}BrNNaO_3S$ $[M+Na]^+$ 340.9817, found 340.9820.

5-Azido-2-bromopent-1-ene, 404



The procedure of Pillai was used for this preparation.[106] To sodium azide (0.67 g, 10.24 mmol, 2.0 equiv.) at RT was added tosylate **351b** (1.63 g, 5.12 mmol, 1.0 equiv.) in DMSO (6 mL). After stirring overnight, water was added and the mixture extracted with Et_2O. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford azide **404** as a pale yellow oil (0.47 g, 4.81 mmol, 94%) and was used without further purification; **R_f** 0.57 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3417, 2929, 2099, 1630, 1435, 1291, 1142, 1025; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.60 (1H, app s, H5), 5.42 (1H, d, *J* = 1.5 Hz, H5’), 3.29 (2H, t, *J* = 7.0 Hz, H1), 2.49 (2H, t, *J* = 7.0 Hz, H3), 1.82 (2H, qu, *J* = 7.0 Hz, H2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 132.7, 117.8, 49.8, 38.2, 27.1; **MS** (ES+) found 232.05 $[M+MeCN]^+$.

N-(4-Bromopent-4-en-1-yl)-4-methylbenzenesulfonamide, 249



Method A: Prepared by General Procedure B using 4-bromopent-4-en-1-ol **247** (1.80 g, 10.91 mmol) to afford sulfonamide **249** as a colourless oil (0.82 g, 2.62 mmol, 24%).

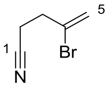
Method B: To a stirred solution of 4-bromopent-4-en-1-amine **251** (100 mg, 0.61 mmol, 1.0 equiv.) and NEt_3 (0.34 mL, 2.44 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (2 mL) at 0 °C, was added *p*-toluenesulfonyl chloride (116 mg, 0.61 mmol, 1.0 equiv.). Upon completion by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 and washed with *aq*. 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with sat. *aq*. $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound **249** as a pale yellow oil (94 mg, 0.29 mmol, 48%) which was used without further purification.

Method C: Prepared by General Procedure J using *tert*-butyl pent-4-yn-1-yl(tosyl)carbamate **261a** (6.108 g, 18.10 mmol). Purification *via* column chromatography (petroleum ether / EtOAc

(10:1 → 3:1)) afforded the title compound **249** as a light brown oil (2.57 g, 7.96 mmol, 44%).

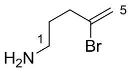
R$_f$ 0.13 (petroleum ether / EtOAc + 1% NEt_3 (10:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.54 (1H, m, H5), 5.36 (1H, d, *J* = 2.0 Hz, H5'), 5.03 (1H, br s, N*H*), 2.94 (2H, q, *J* = 6.5 Hz, H1), 2.42 (5H, m, TsCH_3 and H3), 1.72 (2H, qu, *J* = 7.0 Hz, H2). Data in accordance with literature values.[218]

4-Bromopent-4-enenitrile, 250



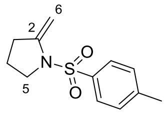
The procedure of Corey was used for this preparation.[115] To a solution of anhydrous MeCN (91 µL, 1.75 mmol, 3.5 equiv.) in anhydrous THF (2.6 mL) was added *n*-BuLi (0.3 mL, 0.75 mmol, 2.5 M, 1.5 equiv.) at −78 °C and the reaction was stirred for 40 min at −78 °C before being allowed to warm to −25 °C. Copper(I) iodide (333 mg, 1.75 mmol, 3.5 equiv.) was added and the resulting brick-red mixture stirred for 15 min at −25 °C before the dropwise addition of 2,3-dibromopropene **209** (52 µL, 0.5 mmol, 1.0 equiv.) in anhydrous THF (1.5 mL). After stirring for a further 1 h at −25 °C, sat. *aq*. NH_4Cl was added and the aqueous layer extracted with Et_2O. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product **250** as a pale orange oil (40 mg, 0.25 mmol, 50%) and was used immediately without further purification; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.79 (1H, dt, *J* = 2.0, 1.0 Hz, H5), 5.59 (1H, d, *J* = 1.0 Hz, H5'), 2.74 (2H, m, H2), 2.65 (2H, m, H3).

4-Bromopent-4-en-1-ylamine, 251



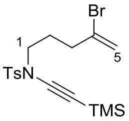
To a solution of 4-bromopent-4-enenitrile **250** (40 mg, 0.25 mmol, 1.0 equiv.) in anhydrous Et_2O (1 mL) was added $LiAlH_4$ (19 mg, 0.50 mmol, 2.0 equiv.) at 0 °C. The reaction mixture was warmed to RT and stirred overnight before being diluted with Et_2O and water (1 mL). The resulting mixture was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title product **251** as a colourless oil (21 mg, 0.13 mmol, 51%) and was used without further purification; **R$_f$** 0.22 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.58 (1H, q, *J* = 1.5 Hz, H5), 5.39 (1H, d, *J* = 1.5 Hz, H5'), 2.72 (2H, t, *J* = 7.0 Hz, H1), 2.48 (td, *J* = 7.0, 1.5 Hz, H3), 1.70 (2H, qu, *J* = 7.0 Hz, H2), 1.42 (2H, br s, N*H*$_2$). Data in accordance with literature values.[219]

2-Methylene-1-(4-methylbenzenesulfonyl)pyrrolidine, 253



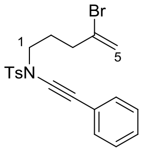
Isolated side-product prepared by General Procedure E using *N*-(4-bromopent-4-en-1-yl)-4-methylbenzenesulfonamide **249** (20 mg, 0.063 mmol) and 1-bromooct-1-yne **215a** (18 mg, 4.94 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) gave pyrrolidine **253** as a brown oil (quantitative conversion as analysed by ^{1}H NMR spectroscopic analysis); **R$_f$** 0.23 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.06 (1H, app s, H6), 4.24 (1H, q, *J* = 1.0 Hz, H6'), 3.66 (2H, t, *J* = 6.5 Hz, H5), 2.44 (3H, s, TsC*H*$_3$), 2.40-2.33 (2H, m, H3), 1.80-1.73 (2H, m, H4). Data in accordance with literature values.[220]

N-(4-Bromopent-4-en-1-yl)-4-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide, 254



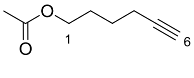
Prepared by General Procedure G using sulfonamide **249** (1.00 g, 3.14 mmol), KHMDS (6.9 mL, 3.45 mmol), and [(trimethylsilyl)ethynyl](phenyl)iodonium triflate **231** (1.69 g, 3.76 mmol). Purification via column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **254** as a pale yellow oil (0.61 g, 1.47 mmol, 47%); **R$_f$** 0.31 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 2899, 2161, 1630, 1597, 1367, 1249, 1212, 814; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.79 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.35 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.63 (1H, q, *J* = 1.5 Hz, H5), 5.44 (1H, d, *J* = 1.5 Hz, H5'), 3.31 (2H, t, *J* = 7.0 Hz, H1), 2.48 (2H, t, *J* = 7.0 Hz, H3), 2.46 (3H, s, TsC*H$_3$*), 1.91 (2H, qu, *J* = 7.0 Hz, H2), 0.16 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.7, 134.2, 132.7, 129.6, 127.7, 117.9, 94.7, 73.5, 49.8, 37.9, 25.9, 21.6, 0.07; **HRMS** (ES+) calc. for $C_{17}H_{24}{}^{79}BrNNaO_2SSi$ [M+Na]$^+$ 438.0352, found 438.0337.

N-(4-Bromopent-4-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 255



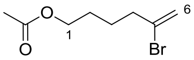
Prepared by General Procedure H using bromoenynamide **254** (67 mg, 0.16 mmol) for the desilylation to give the terminal bromoenynamide as a brown oil (54 mg, 0.16 mmol, quant.), and then taking the crude terminal bromoenynamide (54 mg, 0.16 mmol) and iodobenzene (36 μL, 0.32 mmol) for the Sonogashira coupling. Purification by column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **255** as a yellow oil (25 mg, 0.06 mmol, 38%); **R$_f$** 0.47 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3059, 2928, 2236, 1631, 1598, 1494, 1441, 1366, 1170, 1091; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34-7.27 (5H, m, Ts*H* and Ph*H*), 7.10 (2H, d, *J* = 7.5 Hz, Ph*H*), 5.62 (1H, br s, H5), 5.44 (1H, d, *J* = 2.0 Hz, H5'), 3.80-3.76 (2H, m, H1), 2.48-2.43 (2H, m, H3), 2.46 (3H, s, TsC*H$_3$*), 1.96 (2H, qu, *J* = 7.5 Hz, H2); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 171.0, 145.0, 136.5, 133.4, 132.7, 129.9, 129.3, 128.6, 127.6, 127.2, 117.4, 46.0, 38.7, 27.7, 21.6; **HRMS** (ES+) calc. for $C_{20}H_{20}{}^{79}BrNNaO_2S$ [M+Na]$^+$ 440.0290, found 440.0274.

Hex-5-yn-1-yl acetate, 257



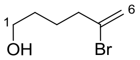
The procedure of Trost and Chen was used for this preparation.[116] To a solution of 5-hexyn-1-ol (2.44 mL, 20.38 mmol, 1.0 equiv.) and pyridine (1.91 mL, 23.64 mmol, 1.16 equiv.) in CH_2Cl_2 (11.2 mL) under Ar was added acetic anhydride (2.23 mL, 23.64 mL, 1.16 equiv.) dropwise. The resulting reaction mixture was stirred at RT overnight before being diluted with CH_2Cl_2 and washed with H_2O (×2). The combined aqueous layers were extracted with CH_2Cl_2 (×2) and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Crude residue purified by vacuum distillation (pyridine and acetic acid removed at 40-50 °C at ~2 mbar) to afford the title compound **257** as a colourless oil (1.89 g, 13.45 mmol, 66%); **bpt** 60-68 °C at ~2 mbar; **R_f** 0.38 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.09 (2H, t, *J* = 6.5 Hz, H1), 2.23 (2H, td, *J* = 7.0, 2.5 Hz, H4), 2.05 (3H, s, C*H*$_3$), 1.96 (1H, t, *J* = 2.5 Hz, H6), 1.76 (2H, m, H2), 1.60 (2H, m, H3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 171.1, 83.8, 68.7, 63.9, 27.6, 24.9, 20.9, 18.0. Data in accordance with literature values.[221]

5-Bromohex-5-en-1-yl acetate, 258



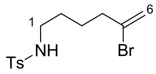
A modified procedure of Moran and Morken was used for this preparation.[117] To an oven dried flask, evacuated and refilled with Ar (×3), was added boron tribromide (5.67 mL, 5.67 mmol, 1 M in CH_2Cl_2, 0.5 equiv.) and the solution cooled to −78 °C. Hex-5-yn-1-yl acetate **257** (1.59 g, 11.34 mmol, 1.0 equiv.) was added dropwise and on complete addition reaction warmed to RT over 3h. Glacial acetic acid (11.1 mL) was added and reaction mixture stirred for a further 1 h. Reaction quenched with H_2O, extracted with CH_2Cl_2 (×3) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether – EtOAc (10:1)) afforded the title compound **258** as a pale yellow oil (1.88 g, 8.50 mmol, 75%); **R_f** 0.38 (petroleum ether – EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2951, 1738, 1630, 1456, 1432, 1388, 1366, 1240, 1042; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.59 (1H, app s, H6), 5.42 (1H, app s, H6'), 4.09 (2H, t, *J* = 6.0 Hz, H1), 2.46 (2H, t, *J* = 6.5 Hz, H4), 2.06 (3H, s, C*H*$_3$), 1.65 (4H, m, H2 and H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 171.2, 134.1, 117.0, 64.1, 40.9, 27.3, 24.3, 21.0; **HRMS** (FI+) calc. for $C_8H_{13}{}^{79}BrO_2$ [M]$^+$ 220.0099, found 220.0093.

5-Bromohex-5-en-1-ol, 259



The procedure of Trost was used for this preparation.[116] To a solution of 5-bromohex-5-en-1-yl acetate **258** (1.88 g, 8.50 mmol, 1.0 equiv.) in MeOH (25 mL) was added K_2CO_3 (3.53 g, 25.51 mmol, 3.0 equiv.) and the resulting suspension stirred at RT for 30 min before being neutralised with *aq*. 1N HCl. Reaction mixture extracted with CH_2Cl_2 (×3) and the combined organic layers dried (MgSO$_4$) and concentrated i*n vacuo.* Purification *via* column chromatography (petroleum ether / EtOAc (4:1)) afforded the title compound **259** as a pale yellow oil (1.20 g, 6.71 mmol, 79%); **R$_f$** 0.12 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3304 (br), 2940, 2867, 1630, 1456, 1431, 1123, 1063, 886; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.50 (1H, dt, *J* = 1.5, 1.0 Hz, H6), 5.41 (1H, d, *J* = 1.5 Hz, H6'), 3.68 (2H, t, *J* = 6.0 Hz, H1), 2.47 (2H, td, *J* = 7.0, 1.0 Hz, H4), 1.72-1.56 (4H, m, H2 and H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 134.3, 116.7, 62.6, 41.1, 31.4, 24.1; **HRMS** (FI+) calc. for $C_6H_{11}{}^{79}BrO$ [M]$^+$ 177.9993, found 177.9993.

N-(5-Bromohex-5-en-1-yl)-4-methylbenzenesulfonamide, 260

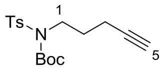


Method A: Prepared by General Procedure B using 5-bromohex-5-en-1-ol **259** (1.20 g, 6.70 mmol) to afford sulfonamide **260** as a colourless oil (1.15 g, 3.48 mmol, 52%).

Method B: Prepared by General Procedure J using *tert*-butyl *N*-hex-5-ynyl-*N*-(p-tolylsulfonyl)carbamate **261b** (100 mg, 0.28 mmol, 1.0 equiv.). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (1:1)) afforded the title compound **260** as a colourless oil (37 mg, 0.086 mmol, 30%).

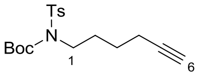
R$_f$ 0.10 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3279, 2941, 2867, 1630, 1599, 1433, 1156, 1093, 887; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.52 (1H, app s, H6), 5.37 (1H, app s, H6'), 4.60 (1H, t, *J* = 6.0 Hz, N*H*), 2.96 (2H, q, *J* = 6.5 Hz, H1), 2.44 (3H, s, TsC*H*$_3$), 2.37 (2H, t, *J* = 7.0 Hz, H4), 1.55-1.46 (4H, m, H2 and H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.5, 137.0, 133.8, 129.8, 127.1, 117.0, 42.9, 40.7, 28.3, 24.8, 21.6; **HRMS** (ES+) calc. for $C_{13}H_{18}{}^{79}BrNNaO_2S$ [M+Na]$^+$ 354.0134, found 354.0127.

tert-Butyl pent-4-yn-1-yl(tosyl)carbamate, 261a



Prepared by General Procedure I using 4-pentyn-1-ol (0.22 mL, 2.38 mmol). Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded **261a** as a white solid (768 mg, 2.28 mmol, 95%); **mpt** 97.4-100.6 °C; **R$_f$** 0.27 (petroleum ether / EtOAc (5:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3278, 3007, 2984, 2960, 2929, 1726, 1597, 1443, 1369, 1346, 1320, 1257, 1118; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.78 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.92 (2H, dd, *J* = 8.0, 7.0 Hz, H1), 2.44 (3H, s TsC*H*$_3$), 2.28 (2H, td, *J* = 7.0, 2.5 Hz, H3), 1.99 (2H, qu, *J* = 7.0 Hz, H2), 1.98 (1H, t, *J* = 2.5 Hz, H5), 1.34 (9H, s, *t*Bu); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 144.3, 138.1, 137.5, 129.4, 128.0, 84.4, 83.2, 69.1, 46.4, 29.0, 28.0, 21.8, 16.2; **HRMS** (ES$^+$) calc. for $C_{17}H_{23}NNaO_4S^+$ [M+Na]$^+$ 360.1240, found 360.1237.

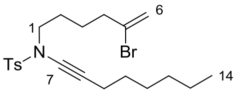
tert-Butyl *N*-hex-5-ynyl-*N*-(p-tolylsulfonyl)carbamate, 261b



Prepared by General Procedure I using 5-hexyn-1-ol (1.00 g, 10.19 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (8:2)) afforded **261b** as a colourless solid (3.31 g, 9.43 mmol, 93%); **mpt** 65.3-67.9 °C; **R$_f$** 0.41 (petroleum ether / EtOAc (5:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3286, 2979, 1724, 1598, 1456, 1352, 1289, 1256, 1184, 1087 ;

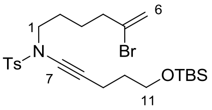
^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.78 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.85 (2H, t, *J* = 7.5 Hz, H1), 2.44 (3H, s, TsC*H*$_3$), 2.26 (2H, td, *J* = 7.0, 2.5 Hz, H4), 1.97 (1H, t, *J* = 2.5 Hz, H6), 1.88 (2H, qu, *J* = 7.5 Hz, H2), 1.60 (2H, qu, *J* = 7.5 Hz, H3), 1.34 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 151.0, 144.1, 137.4, 129.2, 127.8, 84.2, 84.0, 68.7, 46.6, 29.3, 27.9, 25.6, 21.6, 18.1; **HRMS** (ES+) calc. for $C_{18}H_{25}NNaO_4S$ [M+Na]$^+$ 374.1397, found 374.1391.

***N*-(5-Bromohex-5-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 262a**



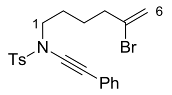
Prepared by General Procedure E using sulfonamide **260** (467 mg, 1.40 mmol) and 1-bromooct-1-yne **215a** (397 mg, 2.10 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **262a** as a pale yellow oil (437 mg, 0.99 mmol, 70%); **R$_f$** 0.25 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2930, 2859, 2252, 1630, 1598, 1457, 1401, 1363, 1169; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.78 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.56 (1H, br s, H6), 5.40 (1H, br s, H6'), 3.28 (2H, t, *J* = 6.5 Hz, H1), 2.45 (3H, s, TsC*H*$_3$), 2.43 (2H, t, *J* = 7.0 Hz, H4), 2.26 (2H, t, *J* = 7.0 Hz, H9), 1.66-1.57 (4H, m, H2 and H3), 1.48 (2H, app qu, *J* = 7.0 Hz, H10), 1.37-1.26 (6H, m, H11, H12 and H13), 0.89 (3H, t, *J* = 7.0 Hz, H14); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.3, 134.6, 133.9, 129.6, 127.7, 116.9, 72.9, 70.4, 51.0, 40.7, 31.4, 28.9, 28.5, 26.5, 24.5, 22.6, 21.7, 18.5, 14.1; **HRMS** (ES+) calc. for $C_{21}H_{30}{}^{79}BrNNaO_2S$ [M+Na]$^+$ 462.1073, found 462.1064.

***N*-(5-Bromohex-5-en-1-yl)-*N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methyl benzene sulfonamide, 262b**



Prepared by General Procedure E using sulfonamide **260** (348 mg, 1.05 mmol) and ((5-bromopent-4-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (438 mg, 1.58 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the bromoenynamide **262b** as a pale yellow oil (377 mg, 0.71 mmol, 67%); $\mathbf{R_f}$ 0.34 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 1630, 1471, 1363, 1254, 1169, 1101, 974; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.55 (1H, d, *J* = 1.4 Hz, H6), 5.39 (1H, d, *J* = 1.5 Hz, H6'), 3.64 (2H, t, *J* = 6.0 Hz, H11), 3.27 (2H, t, *J* = 6.5 Hz, H1), 2.44 (3H, s, TsC*H*$_3$), 2.42 (2H, t, *J* = 7.0 Hz, H4), 2.34 (2H, t, *J* = 7.0 Hz, H9), 1.68 (2H, dt, *J* = 13.5, 6.5 Hz, H10), 1.65-1.57 (4H, m, H2 and H3), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 0.03 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.4, 134.7, 134.0, 129.8, 127.7, 117.1, 73.1, 70.0, 61.7, 51.1, 40.8, 32.2, 26.6, 26.1, 24.6, 21.8, 18.5, 15.1, −5.2; **HRMS** (ES^+) calc. for $C_{24}H_{38}{}^{79}BrNNaO_3SSi$ $[M+Na]^+$ 550.1417, found 550.1418.

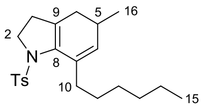
***N*-(5-Bromohex-5-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 262c**



Prepared by General Procedure E using sulfonamide **260** (500 mg, 1.50 mmol) and (bromoethynyl)benzene (407 mg, 2.25 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the bromoenynamide **262c** as an orange oil (316 mg, 0.73 mmol, 49%); $\mathbf{R_f}$ 0.50 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2946, 1695, 1630, 1597, 1495, 1454, 1354, 1164, 1088, 907; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.84 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.41-7.33 (4H, m, Ts*H* and Ph*H*), 7.32-7.27 (3H, m, Ph*H*), 5.56 (1H, d, *J* = 1.0 Hz, H6), 5.40 (1H, d, *J* = 1.5 Hz, H6'), 3.42 (2H, t, *J* = 7.0 Hz, H1), 2.45 (5H, m, TsC*H*$_3$ and H4), 1.73 (2H, dt, *J* = 13.5, 7.0 Hz, H2), 1.63 (2H, dt, *J* = 13.0, 6.5 Hz, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.8, 134.6, 133.9, 131.5, 129.9, 128.4, 128.0, 127.8, 122.9, 117.2, 82.3, 70.9, 51.3, 40.8, 26.7, 24.6, 21.8; **HRMS** (FI^+) calc. for $C_{21}H_{22}{}^{79}BrNO_2S$ $[M]^+$ 431.0555, found 431.0327.

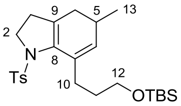
7.3.2. Carbopalladation/Stille/Electrocyclisation Cascade

7-Hexyl-5-methyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207a



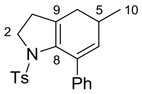
Prepared by General Procedure K using bromoenynamide **205a** (50 mg, 0.12 mmol) and (*E*)-tributyl(prop-1-en-1-yl)stannane (63 mg, 0.19 mmol) with 1 mol% $PdCl_2(PPh_3)_2$ and heating for 18 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) afforded amidodiene **207a** as a pale yellow oil (40.7 mg, 0.109 mmol, 90%); **R_f** 0.13 (petroleum ether / EtOAc (10:1) + 1% NEt_3); **IR** (thin film, ν_{max} / cm^{-1}) 2926, 2855, 1598, 1493, 1352, 1164, 1132; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.38 (1H, s, H6), 3.87 (1H, m, H2), 3.68 (1H, m, H2'), 2.63 (1H, m, H5), 2.44 (3H, s, TsCH_3), 2.39 (2H, m, H4), 1.93 (1H, m, H3), 1.73 (1H, m, H3'), 1.69-1.24 (10H, m, H10-H14), 1.07 (3H, d, *J* = 6.5 Hz, H16), 0.88 (3H, t, *J* = 6.5 Hz, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.7, 138.5, 134.1, 133.1, 132.5, 129.1, 128.4, 128.2, 51.5, 32.0, 31.9, 31.8, 30.5, 29.5, 28.9, 28.8, 22.6, 21.6, 20.2, 14.1; **HRMS** (ES+) calc. for $C_{22}H_{31}NNaO_2S$ $[M+Na]^+$ 396.1968, found 396.1961.

7-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-5-methyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207e



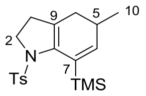
Prepared by General Procedure K using bromoenynamide **205c** (50 mg, 0.10 mmol) and (*E*)-tributyl(prop-1-en-1-yl)stannane (53 mg, 0.16 mmol) with 1 mol% $PdCl_2(PPh_3)_2$ and heating for 18 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) afforded amidodiene **207e** as a pale yellow oil (34 mg, 0.076 mmol, 76%); **R_f** 0.25 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2738, 1597, 1493, 1353, 1254, 1165; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.68 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.26 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.40 (1H, s, H6), 3.90-3.84 (1H, m, H2), 3.7-3.63 (1H, m, H2'), 3.67 (2H, t, *J* = 9.0 Hz, H12), 3.63 (2H, t, *J* = 7.0 Hz, H10), 2.66 (1H, m, H5), 2.44 (3H, s, TsC*H*$_3$), 2.42-2.35 (2H, m, H4), 1.98-1.90 (1H, dd, *J* = 17.5, 8.0 Hz, H3), 1.83-1.69 (1H, m, H3'), 1.70-1.50 (2H, qu, *J* = 7.5 Hz, H11), 1.06 (3H, d, *J* = 7.0 Hz, H13), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.06 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 143.7, 138.3, 133.3, 133.0, 132.7, 129.2, 128.7, 128.4, 62.9, 51.5, 31.9, 30.5, 29.6, 28.2, 26.0, 21.6, 20.2, 18.4, 13.5, −5.2; **HRMS** (ES+) calc. for $C_{25}H_{39}NNaO_3SSi$ [M+Na]$^+$ 484.2312, found 484.2304.

5-Methyl-7-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207f



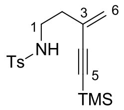
Prepared by General Procedure K using bromoenynamide **205b** (50 mg, 0.12 mmol) and (*E*)-tributyl(prop-1-en-1-yl)stannane (63 mg, 0.19 mmol) with 1 mol% PdCl$_2$(PPh$_3$)$_2$ and heating for 18 h. Purification *via* column chromatography (petroleum ether + 1% NEt$_3$ → petroleum ether / EtOAc (10:1) + 1% NEt$_3$) afforded amidodiene **207f** as a yellow oil (29.5 mg, 0.08 mmol, 67%); **R$_f$** 0.16 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2925, 1598, 1493, 1446, 1353, 1164, 1090; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.62 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.43 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.34 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.25 (3H, d, *J* = 8.0 Hz, Ph*H* and Ts*H*), 5.82 (1H, d, *J* = 3.5 Hz, H6), 3.95 (1H, m, H2), 3.82 (1H, m, H2'), 2.62 (1H, m, H5), 2.44 (3H, s, TsC*H*$_3$), 2.09 (1H, dd, *J* = 17.5, 8.0 Hz, H4), 1.97 (2H, m, H4' and H3), 1.86 (1H, m, H3'), 1.18 (3H, d, *J* = 7.0 Hz, H10); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 143.6, 139.3, 136.3, 134.1, 133.5, 133.2, 132.2, 129.2, 128.2, 127.8, 1727.0, 126.7, 50.7, 31.4, 31.1, 30.0, 21.6, 20.1; **HRMS** (ES+) calc. for $C_{22}H_{23}NNaO_2S$ [M+H]$^+$ 388.1342, found 388.1332.

5-Methyl-1-tosyl-7-(trimethylsilyl)-2,3,4,5-tetrahydro-1*H*-indole, 207g



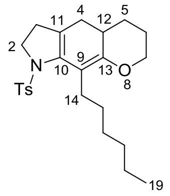
Prepared by General Procedure K using bromoenynamide **205d** (20 mg, 0.05 mmol) and (*E*)-tributyl(prop-1-en-1-yl)stannane (26 mg, 0.08 mmol) with 10 mol% $PdCl_2(PPh_3)_2$ and heating for 4.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded **207g** as a colourless oil (12 mg, 0.033 mmol, 66%); **R$_f$** 0.53 (petroleum ether – EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 1350, 1246, 1163, 1090, 901, 841; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.24 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.92 (1H, d, *J* = 2.5 Hz, H6), 3.81 (1H, ddd, *J* = 12.5, 8.0, 3.0 Hz, H2), 3.62 (1H, dt, *J* = 13.0, 9.5 Hz, H2'), 2.42 (3H, s, TsC*H*$_3$), 2.40-2.29 (1H, m, H5), 1.89 (1H, dd, *J* = 17.5, 8.0 Hz, H4), 1.79-1.65 (2H, m, H3 and H4'), 1.56 (1H, dt, *J* = 17.0, 6.0 Hz, H3'), 1.08 (3H, d, *J* = 7.0 Hz, H10), 0.25 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_c 143.7, 143.7, 140.0, 134.7, 133.1, 129.6, 129.2, 128.5, 50.5, 31.4, 30.4, 30.3, 21.8, 19.9, 1.02; **HRMS** (ES+) calc. for $C_{19}H_{28}NO_2SSi$ $[M+H]^+$ 362.1605, found 362.1597.

4-Methyl-*N*-(3-methylene-5-(trimethylsilyl)pent-4-yn-1-yl)benzenesulfonamide, 265



Isolated as a side-product from the formation of 5-methyl-1-tosyl-7-(trimethylsilyl)-2,3,4,5-tetrahydro-1*H*-indole **207g**, using General Procedure K, as a yellow oil (3 mg, 0.0093 mmol, 18%); **R$_f$** 0.23 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2959, 1599, 1437, 1332, 1250, 1161, 1094, 909; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.43 (1H, d, *J* = 1.0 Hz, H6), 5.23 (1H, d, *J* = 1.5 Hz, H6'), 4.52 (1H, t, *J* = 6.0 Hz, N*H*), 3.17 (2H, q, *J* = 6.5 Hz, H1), 2.43 (3H, s, TsC*H*$_3$), 2.28 (2H, t, *J* = 6.5 Hz, H2), 0.14 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_c 143.6, 137.2, 129.9, 127.7, 127.3, 125.2, 104.0, 96.0, 41.6, 37.0, 21.7, −0.08; **HRMS** (ES$^+$) calc. for $C_{16}H_{23}NNaO_2SSi^+$ $[M+Na]^+$ 344.1111, found 344.1110.

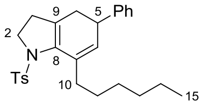
9-Hexyl-8-tosyl-2,3,4,4a,5,6,7,8-octahydropyrano[3,2-f]indole, 207h



Prepared by General Procedure K using bromoenynamide **205a** (50 mg, 0.12 mmol) and tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane (71 mg, 0.19 mmol) with 10 mol% $PdCl_2(PPh_3)_2$ and heating for 15 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded **207h** as a pale yellow oil (32 mg, 0.077 mmol, 64%); $\mathbf{R_f}$ 0.22 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 2926, 2857, 2255, 1677, 1627, 1598, 1454, 1351, 1162, 1119, 1089, 910; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.26 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.96 (2H, dt, *J* = 7.0, 3.5 Hz, H7), 3.68 (1H, ddd, *J* = 12.5, 8.5, 6.0 Hz, H2), 3.55 (1H, ddd, *J* = 12.5, 9.0, 6.5 Hz, H2’), 2.81 (1H, ddd, *J* = 13.5, 9.0, 7.0 Hz, H14), 2.42 (3H, s, TsC*H*$_3$), 2.38-2.31 (1H, m, H14’), 2.24-2.12 (1H, m, H12), 2.10-2.01 (1H, m, H4/5), 1.94-1.84 (3H, m, H4’, H5’ and H6), 1.85-1.76 (2H, m, H4/5 and H6’), 1.48-1.40 (2H, m, H3 and H15), 1.37-1.22 (7H, m, H15’ and H16-H18), 1.05 (1H, dddd, *J* = 13.0, 8.5, 7.0, 6.0 Hz, H3’), 0.87 (3H, t, *J* = 7.0 Hz, H19); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ_c 147.8, 143.8, 136.0, 135.5, 129.7, 127.9, 126.4, 103.3, 66.0, 51.3, 38.0, 34.5, 31.9, 29.2, 28.6, 27.8, 27.2, 25.2, 23.0, 22.9, 21.7, 14.3; **HRMS** (ES$^+$) calc. for $C_{24}H_{34}NO_3S^+$ $[M+H]^+$ 416.2254, found 416.2242.

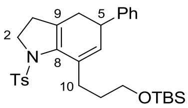
7.3.3. Carbopalladation/Suzuki/Electrocyclisation Cascade

7-Hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207b



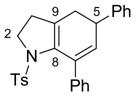
Prepared by General Procedure L using bromoenynamide **205a** (50 mg, 0.12 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (41 mg, 0.18 mmol) with heating for 4 h, *or* with (*E*)-styrylboronic acid (27 mg, 0.18 mmol) with heating for 18 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) gave amidodiene **207b** as a pale yellow oil (43 mg, 0.099 mmol, 83% and 41 mg, 0.094 mmol, 79% respectively); $\mathbf{R_f}$ 0.38 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926, 2856, 1598, 1493, 1452, 1351, 1164, 1089, 1019; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.39-7.30 (5H, m, Ph*H*), 7.22 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.62 (1H, s, H6), 3.94-3.89 (1H, m, H2), 3.71-3.65 (1H, dt, *J* = 13.5, 9.5 Hz, H2’), 3.64-3.57 (1H, m, H5), 2.77-2.70 (1H, m, H10), 2.50-2.40 (1H, m, H10’), 2.44 (3H, s, TsCH_3), 2.36-2.27 (1H, m, H4), 2.24-2.16 (1H, m, H4’), 1.69-1.63 (2H, m, H3), 1.57-1.52 (1H, m, H11), 1.50-1.44 (1H, m, H11’), 1.41-1.27 (6H, m, H12-H14), 0.90 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 145.0, 143.8, 138.8, 135.3, 133.0, 131.9, 129.2, 128.5, 128.4, 127.5, 126.5, 125.4, 51.5, 41.1, 32.4, 32.1, 31.8, 30.4, 28.9, 28.8, 22.7, 21.6, 14.1; **HRMS** (ES+) calc. for $C_{27}H_{33}NNaO_2S$ $[M+Na]^+$ 458.2124, found 458.2112.

7-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207i



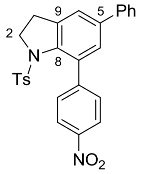
Prepared by General Procedure L using bromoenynamide **205c** (30 mg, 0.06 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (21 mg, 0.09 mmol) with heating for 15 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded amidodiene **207i** as a pale yellow oil (17 mg, 0.033 mmol, 55%); **R$_f$** 0.38 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2857, 1598, 1493, 1352, 1251, 1164; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.38-7.27 (5H, m, Ph*H*), 7.22 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.64 (1H, s, H6), 3.95-3.88 (1H, m, H2), 3.73-3.68 (1H, m, H2'), 3.68 (2H, t, *J* = 7.0 Hz, H12), 3.60 (2H, m, H10), 2.77 (1H, m, H5), 2.59-2.46 (2H, m, H4), 2.44 (3H, s, TsC*H*$_3$), 2.36-2.16 (2H, m, H3), 1.85-1.78 (1H, m, H11), 1.75-1.69 (1H, m, H11'), 0.91 (9H, s, OSi(CH$_3$)$_2$*t-Bu*), 0.08 (6H, s, OSi(C*H*$_3$)$_2$*t*-Bu); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.9, 143.8, 138.6, 134.6, 133.0, 132.2, 129.2, 128.5, 128.4, 127.5, 126.5, 125.8, 63.0, 51.5, 41.1, 32.4, 31.9, 30.4, 28.3, 26.0, 21.7, 18.4, −5.2; **HRMS** (ES+) calc. for $C_{30}H_{41}NNaO_3SSi$ [M+Na]$^+$ 546.2469, found 546.2472.

5,7-Diphenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207j



Prepared by General Procedure L using bromoenynamide **205b** (50 mg, 0.12 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (41 mg, 0.18 mmol) with heating for 15 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded amidodiene **207j** as a pale yellow oil (35 mg, 0.083 mmol, 69%); **R$_f$** 0.40 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3059, 3028, 2926, 2892, 2845, 2253, 1598, 1493, 1447, 1353, 1164, 1090; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.62 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.48 (2H, dd, *J* = 8.0, 1.0 Hz, Ph*H*), 7.37-7.34 (6H, m, Ph*H*), 7.31-7.26 (2H, m, Ph*H*), 7.23 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.06 (1H, d, *J* = 3.5 Hz, H6), 4.04-3.99 (1H, m, H2), 3.86-3.80 (1H, dt, *J* = 13.0, 9.0 Hz, H2'), 3.80-3.76 (1H, m, H5), 2.52-2.31 (2H, m, H4), 2.45 (3H, s, TsC*H*$_3$), 1.97 (2H, app t, *J* = 9.0 Hz, H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.4, 143.7, 139.0, 136.7, 135.1, 133.6, 132.6, 129.4, 129.2, 128.6, 128.2, 127.9, 127.6, 127.1, 126.9, 126.7, 50.7, 41.9, 32.2, 31.1, 21.6; **HRMS** (ES+) calc. for $C_{27}H_{25}NNaO_2S$ [M+Na]$^+$ 450.1498, found 450.1491.

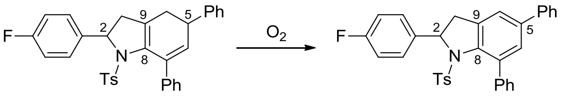
7-(4-Nitrophenyl)-5-phenyl-1-tosylindoline, 207k



Prepared by General Procedure L using bromoenynamide **205j** (30 mg, 0.067 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (23 mg, 0.10 mmol) with heating for 18 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) gave indoline **207k** as a yellow oil (19 mg, 0.041 mmol, 61%); $\mathbf{R_f}$ 0.09 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 1597, 1515, 1463, 1449, 1344, 1164, 1109, 1089; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.31 (2H, d, *J* = 8.5 Hz, 4-NO_2Ph*H*), 7.89 (2H, d, *J* = 8.5 Hz, 4-NO_2Ph*H*), 7.61 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.55 (1H, s, H6), 7.47 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.40 (1H, t, *J* = 7.0 Hz, Ph*H*), 7.38 (1H, s, H4), 7.34 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.12 (2H, t, *J* = 7.5 Hz, H2), 2.44-2.37 (5H, m, TsCH_3 and H3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 147.4, 146.8, 144.4, 140.8, 139.9, 139.6, 139.4, 134.4, 133.4, 129.6, 129.2, 129.0, 128.4, 127.9, 127.5, 127.1, 123.8, 123.6, 52.4, 29.1, 21.7; **HRMS** (ES+) calc. for $C_{27}H_{22}N_2NaO_4S$ $[M+Na]^+$ 493.1192, found 493.1180.

2-(4-Fluorophenyl)-5,7-diphenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207n

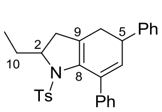
2-(4-Fluorophenyl)-5,7-diphenyl-1-tosyl-2,3-dihydro-1*H*-indole, [O]-207n



Prepared by General Procedure L using bromoenynamide **232c** (30 mg, 0.06 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (20 mg, 0.09 mmol) with heating for 17 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (20:1) + 1% NEt_3)) gave amidodiene **207n** as a pale yellow oil (24 mg, 0.046 mmol, 77%) as a mixture of diastereomers (4:1); $\mathbf{R_f}$ 0.14 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74-7.66 (2H, m, Ts*H*), 7.49-7.42 (3H, m, Ar*H*), 7.37-7.29 (25H, m, Ar*H*), 7.16-7.04 (3H, m, TsH_{maj} + PhH_{min}), 6.82-6.74 (3H, m, 4-FPhH_{min} + PhH_{min}), 6.34-6.27 (1H, m, H6_{min}), 6.06 (1H, br d, *J* = 2.0 Hz, H6_{maj}), 5.29-5.16 (1H, m, H5_{maj}), 5.06-4.97 (1H, m, H5_{min}), 4.24 (1H, dd, *J* = 6.0, 1.5 Hz, H2_{min}), 3.92-3.71 (1H, m, H2_{maj}), 3.33-3.16 (1H, m, H4_{min}), 3.33-3.16 (1H, dd, *J* = 22.5, 6.5 Hz, H4'$_{min}$), 2.68-2.19 (6H, H$4_{maj,}$ H$3_{maj+min}$), 2.50 (3H, s, TsC$H_{3\ maj}$), 2.45 (3H, s, TsC$H_{3\ min}$); **HRMS** (ES+) calc. for $C_{33}H_{28}FNNaO_2S$+ $[M+Na]^+$ 544.1717, found 544.1715.

Attempted separation of the diastereomers by semi-preparative HPLC (1:99 IPA / hexane) led to the products undergoing aerobic oxidation to the indoline **[O]-207n** as a colourless oil; **IR** (thin film, ν_{max} / cm^{-1}) 3061, 3029, 2927, 2850, 1600, 1496, 1446, 1353, 1089, 861; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.78 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.66 (1H, d, *J* = 1.5 Hz, H4), 7.44 (2H, d, *J* = 8.0 Hz, Ph*H*), 7.43-7.40 (2H, m, Ph*H*), 7.27 (2H, t, *J* = 8.0 Hz, Ar*H*), 7.24-7.18 (5H, m, Ar*H*), 7.16-7.12 (1H, *obscured*, Ph*H*), 7.07 (1H, br s, H6), 6.74-6.69 (2H, m, 4-FPh*H*), 6.59 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.46 (1H, d, *J* = 8.5 Hz, H2), 2.66 (1H, dd, *J* = 16.0, 8.5 Hz, H3), 2.44 (1H, d, *J* = 16.0 Hz, H3'); **^{13}C NMR** (126 MHz, C_6D_6) δ_C 162.2 (d, *J* = 246 Hz), 143.8, 141.4, 141.1, 140.9 (br), 139.7 (br), 138.4, 138.1 (br), 138.0, 137.2, 136.7, 130.2, 129.8, 129.4, 129.1 (d, *J* = 4 Hz), 128.9, 128.9, 128.9, 128.8, 128.7, 128.5, 128.3, 127.9, 127.7, 122.7, 116.2 (d, *J* = 22 Hz), 66.1, 36.0, 21.5; **HRMS** (ES+) calc. for $C_{33}H_{26}FNNaO_2S$+ $[M+Na]^+$ 542.1560, found 544.1556.

2-Ethyl-5,7-diphenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207o



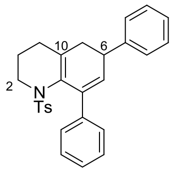
Prepared by General Procedure L using bromoenynamide **232d** (30 mg, 0.069 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (23 mg, 0.10 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (20:1) + 1% NEt_3) gave amidodiene **207o** as a yellow oil (21 mg, 0.047 mmol, 68%) as a mixture of diastereomers (1.5:1); **R_f** 0.18 (petroleum ether – EtOAc (10:1)); **^{1}H NMR** (200

MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.0 Hz, TsH_{min}), 7.63 (2H, d, *J* = 8.0 Hz, TsH_{maj}),7.50-7.41 (4H, m, *J* = 7.5 Hz, Ph*H*), 7.36-7.32 (10H, m, Ph*H* and Ts*H*), 6.28-6.26 (1H, m, $H6_{min}$), 6.02 (1H, br s, $H6_{maj}$), 4.98-4.93 (1H, m, $H5_{min}$), 4.15-4.01 (1H, m, $H5_{maj}$), 3.86 (1H, q, *J* = 6.5 Hz, $H2_{min}$), 3.82-3.66 (1H, m, $H2_{maj}$), 3.27 (2H, dd, *J* = 21.5, 6.5 Hz, H4), 3.03 (2H, dd, *J* = 21.5, 7.0 Hz, H4’), 2.51 (3H, s, $TsCH_{3\,maj}$), 2.43 (3H, s, $TsCH_{3\,min}$), 2.30-1.67 (4H, m, H3 and H3’), 1.63-1.48 (1H, m, H10),1.39-1.25 (3H, m, H10), 1.10 (3H, t, *J* = 7.5 Hz, $H11_{maj}$), 0.68 (3H, t, *J* = 7.5 Hz, $H11_{min}$).

Semi-preparative HPLC purification (1:99 IPA / hexane) to separate the diastereomers for analysis gave only the minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.45 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.36-7.32 (5H, m, Ph*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ph*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.22 (1H, t, *J* = 7.5 Hz, Ph*H*), 6.28-6.24 (1H, m, H6), 4.98-4.93 (1H, m, H5), 3.86 (1H, q, *J* = 6.5 Hz, H2), 3.27 (1H, dd, *J* = 21.5, 6.5 Hz, H4), 3.03 (1H, dd, *J* = 21.5, 7.0 Hz, H4’), 2.42 (3H, s, $TsCH_3$), 2.00 (1H, dddd, *J* = 16.0, 8.0, 1.5, 1.0 Hz, H3), 1.79-1.64 (2H, d, *J* = 16.0 Hz, H3’), 1.39-1.25 (2H, m, H10), 0.68 (3H, t, *J* = 7.5 Hz, H11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 143.3, 141.9, 140.1, 135.7, 134.6, 131.7, 129.4, 128.7, 128.4, 128.2, 127.5, 127.4, 126.6, 126.2, 125.1, 124.6, 62.8, 43.3, 36.5, 29.5, 28.5, 21.6, 9.2; **HRMS** (ES+) calc. for $C_{29}H_{29}NNaO_2S$ $[M+Na]^+$ 478.1811, found 478.1807.

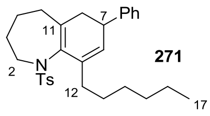
6,8-Diphenyl-1-tosyl-1,2,3,4,5,6-hexahydroquinoline, 270



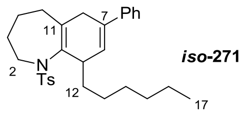
Prepared by General Procedure L using bromoenynamide **255** (30 mg, 0.072 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (25 mg, 0.11 mmol) with heating for 17 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (20:1) + 1% NEt_3)) gave amidodiene **270** as a colourless solid (19 mg, 0.044 mmol, 61%); **mpt** 115-118 °C; **R$_f$** 0.15 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 2927, 2856, 1617, 1598, 1466, 1326, 1257, 1166, 1125, 1016, 910, 733, 688, 678; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.35-7.27 (12H, m, Ts*H* and Ph*H*), 7.08 (5H, m, Ts*H* and Ph*H*), 5.93 (1H, s, H7), 3.90-3.80 (1H, m, H6), 3.70-3.60 (1H, m, H2), 3.12-2.96 (1H, m, H2'), 2.62-2.51 (1H, m, H5), 2.37 (3H, s, TsC*H*$_3$), 2.37-2.25 (2H, m, H4), 2.18-2.00 (2H, m, H5' and H3), 1.75-1.63 (1H, m, H3'); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 145.0, 143.2, 140.4, 139.0, 135.8, 131.4, 129.8, 129.4, 129.1, 128.5, 128.0, 127.8, 127.7, 126.5, 126.3, 45.4, 41.0, 39.0, 30.3, 26.8, 21.5, 20.4; **HRMS** (ES+) calc. for $C_{28}H_{27}NNaO_2S$ [M+Na]$^+$ 464.1655, found 464.1653.

N.B. NMR Spectra very broad, even upon variable temperature analysis at 100 °C in *d*$_8$-toluene.

9-Hexyl-7-phenyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-benzo[*b*]azepine, 271 and 9-hexyl-7-phenyl-1-tosyl-2,3,4,5,6,9-hexahydro-1H-benzo[*b*]azepine, *iso*-271



271



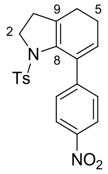
***iso*-271**

Prepared by General Procedure L using bromoenynamide **262a** (50 mg, 0.11 mmol) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (39 mg, 0.17 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether + 1% NEt$_3$ → petroleum ether / EtOAc (10:1) + 1% NEt$_3$) gave a 1.3:1 mixture of the 1,3 and 1,4-amidodienes **271** (*maj*) and ***iso*-271** (*min*), respectively, as a yellow oil (38 mg, 0.082 mmol, 74%) which were oxidised to benzazepine **282** before full characterisation.

NMR Data represented for the mixture of regioisomers: **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.82 (2H, d, *J* = 8.0 Hz, Ts*H*$_{maj}$), 7.71-7.67 (1H, m, Ph*H*$_{maj}$), 7.61-7.57 (1H, m, Ph*H*$_{min}$), 7.54-7.48 (4H, m, Ph*H*$_{min}$ and Ts*H*$_{min}$),7.44 (2H, t, *J* = 7.5 Hz, Ph*H*$_{min}$), 7.39 (2H, t, *J* = 7.5 Hz, Ph*H*$_{maj}$), 7.36-7.21 (4H, Ts*H*$_{maj}$ and Ph*H*$_{maj+min}$), 7.02 (2H, d, *J* = 8.0 Hz, Ts*H*$_{min}$), 5.74 (1H, d, *J* = 6.5 Hz, H8$_{min}$), 5.57 (1H, br s, H8$_{maj}$), 4.24-4.17 (2H, m, H2$_{maj+min}$), 3.71-3.64 (1H, m, H7$_{maj}$), 3.44 (1H, t, *J* = 8.0 Hz, H9$_{min}$), 3.00-2.90 (4H, m, H2$_{maj+min}$), 2.75-2.55 (1H, m, C*H*$_{min}$), 2.55-2.45

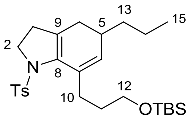
(1H, m, H6*maj*), 2.45 (3H, s, TsCH_3 *maj*), 2.33 (3H, s, TsCH_3 *min*), 2.30-2.20 (2H, m, H2'*maj + min*), 2.12 (2H, app dd, *J* = 17.0, 6.5 Hz, H6'*maj*), 1.80-1.23 (20H, CH_2s), 1.12-1.00 (4H, CH_2 *maj + min*), 0.95-0.75 (10H, m, H17 *maj + min* and CH_2 *maj + min*); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 145.8, 144.3, 143.5, 143.4, 143.0, 142.7, 140.9, 140.6, 140.3, 140.2, 139.3, 139.2, 139.0, 138.8, 138.1, 137.6, 134.0, 134.0, 129.6, 129.3, 128.7, 128.4, 128.2, 128.1, 127.6, 127.5, 127.5, 127.4, 127.1, 127.1, 126.8, 126.3, 126.3, 126.1, 124.8, 121.3, 50.4, 49.1, 49.1, 41.1, 40.9, 40.1, 36.7, 33.8, 33.0, 32.3, 32.0, 31.9, 31.8, 31.7, 31.5, 30.8, 29.5, 29.3, 29.2, 28.8, 28.6, 28.3, 28.1, 27.8, 23.6, 23.5, 22.7, 22.6, 22.6, 22.6, 21.4, 14.1, 14.1 (46).

7-(4-Nitrophenyl)-1-tosylindoline, 207p



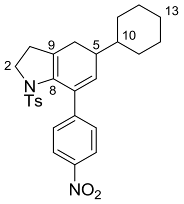
To a vial, equipped with a stirrer bar, was added Pd(PPh$_3$)$_4$ (3.9 mg, 0.0034 mmol, 5 mol%) and Cs$_2$CO$_3$ (32 mg, 0.10 mmol, 1.5 equiv.) in the glove box. To this was added a degassed (Ar bubbling, 15 min) solution of bromoenynamide **205j** (30 mg, 0.067 mmol, 1.0 equiv.) and vinylboronic anhydride pyridine complex (24 mg, 0.10 mmol, 1.5 equiv.) in DME (1.1 mL), followed by water (1.8 µL, 0.10 mmol, 1.5 equiv.). The rubber septum was replaced with a screw cap, and the reaction mixture heated to reflux for 15.5 h. On completion, the reaction was cooled to RT and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1 → 3:1)) afforded the bicyclic dienamide **207p** as a yellow oil (14mg, 0.036 mmol, 54%); **R$_f$** 0.24 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 1597, 1513, 1344, 1164, 910, 731; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 8.20 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.60 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.57 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.27 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.20 (1H, t, *J* = 5.0 Hz, H6), 3.89 (2H, t, *J* = 8.0 Hz, H2), 2.44 (3H, s, TsCH_3), 2.43-2.34 (2H, m, H5), 2.14 (2H, d, *J* = 8.5 Hz, H4), 1.91 (2H, t, *J* = 7.5 Hz, H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 146.7, 146.6, 146.1, 144.2, 135.8, 133.9, 133.0, 129.5, 128.3, 128.1, 127.7, 123.5, 50.6, 31.2, 23.7, 22.8, 21.8; **HRMS** (ES+) calc. for $C_{21}H_{20}N_2NaO_4S$ $[M+Na]^+$ 419.1036, found 419.1035.

7-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-5-propyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207q



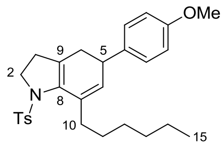
Prepared by General Procedure L using bromoenynamide **205c** (30 mg, 0.06 mmol) and (*E*)-pent-1-en-1-ylboronic acid (10 mg, 0.09 mmol) with heating for 15.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded amidodiene **207q** as a colourless oil (18 mg, 0.037 mmol, 62%); $\mathbf{R_f}$ 0.19 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 1471, 1256, 1165, 1092, 836; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.25 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.44 (1H, s, H6), 3.86 (1H, ddd, *J* = 13.0, 8.0, 3.5 Hz, H2), 3.67 (1H, dt, *J* = 13.0, 9.5 Hz, H2'), 3.62 (2H, t, *J* = 7.0 Hz, H12), 2.71-2.62 (1H, m, H10), 2.43 (3H, s, $TsCH_3$), 2.42-2.36 (1H, m, H10'), 2.33-2.24 (1H, m, H5), 1.94 (1H, dd, *J* = 17.5, 8.0 Hz, H4), 1.82-1.72 (1H, m, H4'), 1.74-1.59 (4H, m, H3 and H11), 1.47-1.28 (4H, m, H13 and H14), 0.93 (3H, t, *J* = 7.0 Hz, H15), 0.90 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 143.9, 138.6, 133.5, 133.3, 132.8, 129.3, 128.6, 127.5, 63.1, 51.6, 36.9, 34.5, 32.0, 30.7, 29.9, 28.4, 26.2, 21.8, 20.4, 18.6, 14.3, −5.07; **HRMS** (ES+) calc. for $C_{27}H_{43}NNaO_3SSi$ $[M+Na]^+$ 512.2625, found 512.2627.

5-Cyclohexyl-7-(4-nitrophenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207r



Prepared by General Procedure L using bromoenynamide **205j** (30 mg, 0.067 mmol) and (*E*)-(2-cyclohexylvinyl)boronic acid (23 mg, 0.10 mmol) with heating for 18 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) afforded amidodiene **207r** as a yellow oil (23 mg, 0.049 mmol, 74%); **R_f** 0.26 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2923, 1597, 1514, 1343, 1164, 909, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.20 (2H, d, *J* = 9.0 Hz, 4-NO_2Ph*H*), 7.59 (4H, app t, *J* = 9.0 Hz, Ts*H* and 4-NO_2Ph*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.05 (1H, d, *J* = 3.0 Hz, H6), 3.96 (1H, ddd, *J* = 13.0, 8.5, 3.5 Hz, H2), 3.84 (1H, dt, *J* = 13.0, 9.5 Hz, H2'), 2.45 (3H, s, TsCH_3), 2.40-2.34 (1H, m, H5), 2.14 (1H, app t, *J* = 16.0 Hz, H4), 2.07-2.03 (1H, m, H4'), 2.01-1.97 (1H, m, H3), 1.90-1.78 (3H, m, H3' and alkyl CH_2), 1.74-1.67 (2H, m, CH_2), 1.53-1.47 (1H, m, H10), 1.31-1.14 (4H, m, *c*Hex CH_2), 1.08 (2H, qt, *J* = 12.0, 3.0 Hz, H13); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 146.4, 146.2, 144.0, 135.4, 134.1, 133.1, 132.9, 132.7, 129.3, 128.1, 127.6, 123.3, 50.6, 40.8, 31.2, 30.8, 30.5, 26.5, 26.4, 25.6, 21.7; **HRMS** (ES+) calc. for $C_{27}H_{30}N_2NaO_4S$ $[M+Na]^+$ 501.1818, found 501.1818.

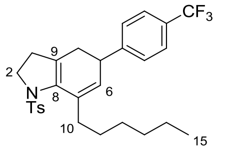
7-Hexyl-5-(4-methoxyphenyl)-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 207s



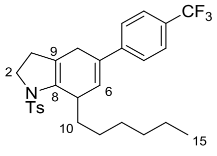
Prepared by General Procedure L using bromoenynamide **205a** (30 mg, 0.073 mmol) and (*E*)-2-(4-methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28 mg, 0.11 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) gave the amidodiene **207s** as a colourless oil (18 mg, 0.040 mmol, 55%); **R_f** 0.13 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 1740, 1512, 1464, 1350, 1247, 1163, 1036, 909, 815, 733, 676; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.71-7.67 (2H, m, Ts*H*), 7.26-7.22 (4H, m, Ts*H* and 4-MeOPh*H*), 6.92-9.88 (2H, m, 4-MeOPh*H*), 3.97-3.85 (1H, m, H2), 3.83 (3H, m, TsCH_3), 3.75-3.64 (1H, dt, *J* = 13.0, 9.0 Hz, H2'), 3.59-3.50 (1H, m, H5), 2.81-2.62 (1H, m, H10), 2.53-2.35 (1H, m, H10'), 2.44 (3H, s, TsCH_3), 2.30-2.12 (2H, m, H4), 1.74-1.60 (2H, m, H3), 1.57-1.47 (1H, m, H11), 1.47-1.27 (6H, m, H12-H14), 0.90 (3H, t, *J* = 6.3 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 158.2, 143.8, 138.8, 137.1, 135.1, 133.1, 131.9, 129.2, 128.4, 128.4, 125.9, 113.8, 55.3, 51.5, 40.3, 32.6, 32.1, 31.8, 30.4, 28.9, 28.8, 22.7, 21.7, 14.1; **HRMS** (ES+) calc. for $C_{28}H_{35}NNaO_3S$ $[M+Na]^+$ 488.2230, found 488.2230.

N.B. Partial aerobic oxidation to the indoline product was observed upon ^{13}C NMR spectroscopic analysis.

7-Hexyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1*H*-indole, 207t and **7-hexyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-2,3,4,7-tetrahydro-1*H*-indole, *iso*-207t**



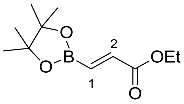
207t



***iso*-207t**

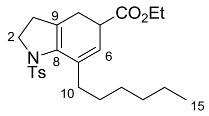
Prepared by General Procedure L using bromoenynamide **205a** (30 mg, 0.073 mmol) and (*E*)-4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)styryl)-1,3,2-dioxaborolane (32 mg, 0.11 mmol) with heating for 16 h. Purification by column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) gave a 3.7:1 mixture of the 1,3 and 1,4-aminodienes **207t** and ***iso*-207t** as a yellow oil (24 mg, 0.049 mmol, 67%) which were oxidised to the indoline **279f** before full characterisation.

(*E*)-Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate, 268i

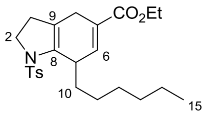


The procedure of Yun *et al.* was used for this preparation.[222] To an oven-dried rbf was added CuCl weighed out in a glovebox (15 mg, 0.15 mmol, 0.03 equiv.), NaO^{t}Bu (29 mg, 0.61 mmol, 0.06 equiv.) and Xantphos (89 mg, 0.15 mmol, 0.03 equiv.) and had anhydrous THF (4.6 mL) added under Ar. The reaction mixture was stirred at RT for 30 min before the addition of bis(pinacolato)diboron (1.42 g, 5.61 mmol, 1.1 equiv.) and anhydrous THF (3.1 mL). After stirring for a further 10 min ethyl propiolate (0.52 mL, 5.10 mmol, 1.0 equiv.) was added, followed by anhydrous MeOH (0.41 mL), and finally the sides of the flask were rinsed with anhydrous THF (2 mL) before the flask was sealed and stirred at RT for 20 h. The crude reaction mixture was filtered through a Celite® plug, eluting with THF, and the filtrate concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether – Et_2O (19:1)) afforded the title compound **268i** as a colourless oil (0.724 g, 3.21 mmol, 63%); **R$_f$** 0.23 (petroleum ether / Et_2O (19:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.75 (1H, d, *J* = 18.0 Hz, H1), 6.65 (1H, d, *J* = 18.0 Hz, H2), 4.21 (2H, q, *J* = 7.0 Hz, C*H$_2$*), 1.34-1.24 (15H, m, 5 x CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.0, 154.1, 138.7, 84.0, 60.6, 24.7, 14.2. Data in accordance with literature values.[222]

Ethyl 7-hexyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole-5-carboxylate, 207v and **ethyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydro-1*H*-indole-5-carboxylate, *iso*-207v**



207v

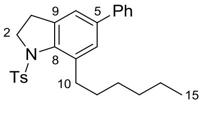


***iso*-207v**

Prepared by General Procedure L using bromoenynamide **205a** (30 mg, 0.073 mmol) and boronic ester **268i** (32 mg, 0.11 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether + 1% NEt_3 → petroleum ether / EtOAc (10:1) + 1% NEt_3) gave a 1.2:1 mixture of the 1,3 and 1,4-aminodienes **207v** and ***iso*-207v** as a yellow oil (24 mg, 0.049 mmol, 67%) which were oxidised to the indoline **279g** before full characterisation.

7.3.4. Oxidations and Detosylations of Cascade Amidodienes

7-Hexyl-5-phenyl-1-tosylindoline, 279a

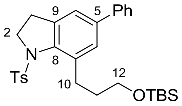


Prepared by General Procedure N using amidodiene **207b** (100 mg, 0.23 mmol, 1.0 equiv.) to afford indoline **279a** as a yellow oil (85 mg, 0.20 mmol, 86%); **R$_f$** 0.31 (petroleum ether /

EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926, 2856, 1730, 1598, 1466, 1354, 1167, 1090, 1021; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.57 (2H, dd, *J* = 8.5, 1.0 Hz, Ph*H*), 7.46-7.40 (5H, m, Ts*H*, H4 or H6 and Ph*H*), 7.35 (1H, tt, *J* = 7.5, 1.0 Hz, Ph*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.12 (1H, s, H4 or H6), 3.99 (2H, t, *J* = 7.5 Hz, H2), 3.12-3.08 (2H, m, H10), 2.39 (3H, s, TsCH_3), 2.17 (2H, t, *J* = 7.5 Hz, H3), 1.72 (2H, app qu, *J* = 8.0 Hz, H11), 1.43-1.25 (6H, m, H12-H14), 0.89 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.0, 140.7, 140.6, 139.9, 138.2, 137.6, 134.7, 129.4, 128.7, 127.8, 127.7, 127.3, 127.0, 120.5, 52.9, 32.4, 31.8, 30.3, 29.4, 29.0, 22.7, 21.6, 14.1; **HRMS** (ES+) calc. for $C_{27}H_{31}NNaO_2S$ $[M+Na]^+$ 456.1968, found 456.1963.

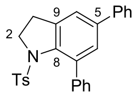
N.B. On performing this reaction in CH_2Cl_2, a 9:1 ratio of indoline **279a**:indole **280a** was obtained.

7-(3-((tert-Butyldimethylsilyl)oxy)propyl)-5-phenyl-1-tosylindoline, 279b



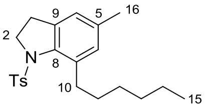
Prepared by General Procedure N using amidodiene **207i** (24 mg, 0.046 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford indoline **279b** as a pale yellow oil (14.8 mg, 0.029 mmol, 62%); **R$_f$** 0.43 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3061, 3031, 2954, 2928, 2894, 2856, 1450, 1357, 1168, 1101, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.57 (2H, dd, *J* = 8.5, 1.0 Hz, Ph*H*), 7.45-7.40 (5H, m, Ts*H*, H4 or H6 and Ph*H*), 7.35 (1H, tt, *J* = 7.5, 1.0 Hz, Ph*H*), 7.15 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.12 (1H, s, H4 or H6), 3.99 (2H, t, *J* = 7.0 Hz, H2), 3.72 (2H, t, *J* = 6.5 Hz, H12), 3.13 (2H, t, *J* = 8.0 Hz, H10), 2.39 (3H, s, TsCH_3), 2.17 (2H, t, *J* = 7.0 Hz, H3), 2.00 (2H, app tt, *J* = 8.0, 6.5 Hz, H11), 0.91 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, Si(CH_2)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.0, 140.6, 139.9, 138.3, 136.9, 134.6, 129.4, 128.7, 128.5, 128.4, 127.9, 127.7, 127.3, 127.0, 120.7, 63.2, 52.9, 33.3, 29.0, 28.8, 26.0, 21.6, −5.26; **HRMS** (ES+) calc. for $C_{30}H_{39}NNaO_3SSi$ $[M+Na]^+$544.2312, found 544.2300.

5,7-Diphenyl-1-tosylindoline, 279c



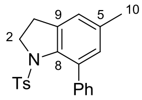
Prepared by General Procedure N using amidodiene **207j** (35 mg, 0.081 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford indoline **279c** as a yellow oil (18 mg, 0.043 mmol, 53%); **R$_f$** 0.06 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3060, 3030, 2957, 2922, 2852, 2362, 2343, 2253, 1597, 1496, 1462, 1441, 1357, 1165, 1089; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.74 (2H, dd, *J* = 8.0, 1.5 Hz, Ph*H*), 7.61 (2H, dd, *J* = 8.0, 1.5 Hz, Ph*H*), 7.56 (1H, d, *J* = 1.5 Hz, H4 or H6), 7.47-7.43 (4H, m, Ph*H*), 7.38-7.33 (2H, m, Ph*H*), 7.35 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.30 (1H, m, H4 or H6), 7.14 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.09 (2H, t, *J* = 7.5 Hz, H2), 2.41 (2H, t, *J* = 7.5 Hz, H3), 2.39 (3H, s, TsC*H*$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.8, 140.5, 140.32, 140.28, 139.4, 138.9, 135.8, 134.8, 129.3, 128.8, 128.7, 128.3, 128.32, 128.30, 127.6, 127.5, 127.0, 122.1, 52.3, 29.2, 21.6; **HRMS** (ES+) calc. for $C_{27}H_{23}NNaO_3S$ [M+Na]$^+$448.1342, found 448.1340.

7-Hexyl-5-methyl-1-tosylindoline, 279d



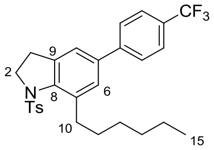
Prepared by General Procedure N using amidodiene **207a** (38 mg, 0.102 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford indoline **279d** as a colourless oil (26 mg, 0.069 mmol, 68%); **R$_f$** 0.31 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.38 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.15 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.97 (1H, s, H4), 6.68 (1H, s, H6), 3.92 (2H, t, *J* = 7.5 Hz, H2), 2.99 (2H, t, *J* = 8.0 Hz, H3), 2.39 (3H, s, TsC*H*$_3$), 2.30 (3H, s, H16), 2.05 (2H, t, *J* = 7.5 Hz, H10), 1.67 (2H, qu, *J* = 7.5 Hz, H11), 1.41-1.27 (6H, m, H12-H14), 0.89 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 143.8, 138.8, 137.6, 137.0, 136.6, 134.7, 129.3, 129.3, 127.8, 122.6, 52.9, 32.2, 31.8, 30.3, 29.4, 28.8, 22.7, 21.6, 21.2, 14.1. Data in accordance to previously reported values.[100]

5-Methyl-7-phenyl-1-tosylindoline, 279e



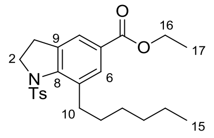
Prepared by General Procedure N using amidodiene **207f** (38 mg, 0.102 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford indoline **279e** as a yellow oil (16.3 mg, 0.064 mmol, 63%); **R_f** 0.17 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 2920, 2360, 2256, 1577,1401, 1182; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.67 (2H, dd, *J* = 8.0, 1.5 Hz, Ph*H*), 7.43 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.32 (3H, m, Ph*H* and Ts*H*), 7.12 (3H, d, *J* = 8.0 Hz, Ts*H* and H6), 6.87 (1H, s, H4), 4.02 (2H, t, *J* = 7.5 Hz, H2), 2.38 (3H, s, TsC*H*$_3$), 2.36 (3H, s, H10), 2.78 (2H, t, *J* = 7.5 Hz, H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.6, 140.6, 138.3, 137.6, 136.9, 135.3, 134.8, 130.4, 129.2, 128.3, 128.2, 127.6, 126.9, 124.2, 52.2, 29.1, 21.6, 21.2; **HRMS** (ES+) calc. for $C_{22}H_{21}NNaO_2S$ [M+Na]+ 386.1185, found 386.1189.

7-Hexyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)indoline, 279f



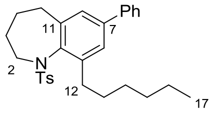
Prepared by General Procedure N using amidodienes **207t** and **iso-207t** (15 mg, 0.030 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford indoline **279f** as a colourless oil (14 mg, 0.028 mmol, 94%); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.69 (2H, d, *J* = 9.0 Hz, 4-F$_3$C-Ph*H*), 7.67 (2H, d, *J* = 9.0 Hz, 4-F$_3$C-Ph*H*), 7.43 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.41 (1H, d, *J* = 1.5 Hz, H6), 7.17 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.13 (1H, d, *J* = 1.5 Hz, H4), 4.00 (2H, t, *J* = 8.0 Hz, H2), 3.11 (2H, t, *J* = 8.0 Hz, H3), 2.40 (3H, s, TsC*H*$_3$), 2.20 (2H, t, J = 7.0 Hz, H10), 1.45-1.37 (2H, m, H11), 1.73 (2H, app q, *J* = 7.5 Hz, H11), 1.46-1.22 (6H, m, H12-H14), 0.89 (3H, t, *J* = 6.5 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.2, 144.1, 141.5, 138.5, 138.4, 137.9, 134.7, 129.4, 128.0, 127.7, 127.5, 127.3, 125.7 (q, *J* = 3.8 Hz), 125.3, 120.7, 52.9, 32.4, 31.7, 30.3, 29.3, 29.0, 22.6, 21.6, 14.1; **HRMS** (ES+) calc. for $C_{28}H_{30}F_3NNaO_2S^+$ $[M+Na]^+$ 524.1841, found 524.1838.

Ethyl 7-hexyl-1-tosylindoline-5-carboxylate, 279g



Prepared by General Procedure N using the mixture of 1,3- and 1,4-amidodienes **207v** and **iso-207v** (71 mg, 0.16 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford indoline **279g** as a colourless oil (62 mg, 0.145 mmol, 91%); **R_f** 0.25 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 2927, 2857, 1715, 1597, 1465, 1360, 1288, 1204, 1169, 1155; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.88 (1H, s, H6), 7.54 (1H, s, H4), 7.37 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.37 (2H, q, *J* = 7.0 Hz, H16), 3.99 (2H, t, *J* = 7.5 Hz, H2), 3.09-3.05 (2H, m, H10), 2.40 (3H, s, TsCH_3), 2.16 (2H, t, *J* = 7.5 Hz, H3), 1.73-1.66 (2H, m, H11), 1.41 (2H, t, *J* = 7.0 Hz, H17), 1.37-1.25 (6H, m, H12-H14), 0.89 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 166.4, 145.3, 144.2, 137.9, 137.4, 134.5, 130.7, 129.5, 128.9, 127.6, 123.0, 61.0, 52.9, 32.3, 31.7, 30.1, 29.3, 28.6, 22.6, 21.6, 14.3, 14.1; **HRMS** (ES+) calc. for $C_{24}H_{31}NNaO_4S$ $[M+Na]^+$ 452.1866, found 452.1848.

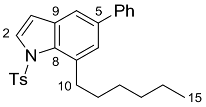
9-Hexyl-7-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine, 282



Prepared by General Procedure N using the mixture of 1,3- and 1,4-amidodienes **271** and **iso-271** (31 mg, 0.067 mmol) with purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) to afford benzazepine **282** as a pale yellow oil (21 mg, 0.045

mmol, 70%); **R$_f$** 0.16 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2928, 1468, 1342, 1156, 1093, 908, 763, 732, 678, 649; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.70 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.59 (2H, d, *J* = 8.0 Hz, PhH), 7.44 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.37 (1H, d, *J* = 2.0 Hz, H6), 7.35 (1H, t, *J* = 7.5 Hz, Ph*H*), 7.28 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.16 (1H, d, *J* = 2.0 Hz, H8), 4.35 (1H, dt, *J* = 14.5, 3.5 Hz, H2), 3.05 (1H, ddd, *J* = 14.5, 12.0, 2.5 Hz, H2’), 2.97 (1H, ddd, *J* = 14.5, 10.0, 6.0 Hz, H12), 2.61 (1H, ddd, *J* = 14.5, 10.0, 5.5 Hz, H12’), 2.44 (3H, s, TsC*H*$_3$), 2.43-2.40 (1H, m, H5), 2.34 (1H, td, *J* = 12.5, 1.5 Hz, H5’), 1.93-1.84 (1H, m, H3), 1.80-1.77 (1H, m, H4), 1.66-1.50 (3H, m, H13 and H3’), 1.34-1.22 (7H, m, H14-H16 and H4), 0.89 (3H, t, *J* = 7.0 Hz, H17); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 144.3, 143.5, 143.2, 140.9, 140.6, 139.2, 137.6, 129.6, 128.7, 127.6, 127.3, 127.1, 126.9, 126.1, 50.4, 33.8, 32.3, 31.7, 30.8, 29.5, 28.1, 25.9, 22.6, 21.5, 14.1; **HRMS** (ES+) calc. for $C_{29}H_{35}NNaO_2S$ [M+Na]$^+$ 484.2281, found 484.2283.

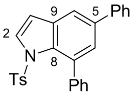
7-Hexyl-5-phenyl-1-tosyl-1*H*-indole, 280a



To a solution of amidodiene **207b** (100 mg, 0.23 mmol, 1.0 equiv.) in toluene (1.8 mL) was added a few 4Å molecular sieves and activated MnO$_2$ (600 mg, 6.89 mmol, 30 equiv.). The resulting suspension was stirred at 110 °C for 44 h before being allowed to cool to RT, diluted with EtOAc and filtered through a Celite® pad. The filtrate was concentrated *in vacuo* and purified *via* column chromatography (petroleum ether / EtOAc (10:1)) to afford indole **280a** as a yellow oil (53 mg, 0.12 mmol, 53%); **R$_f$** 0.35 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3034, 2954, 2926, 2856, 1660, 1599, 1495, 1464, 1440, 1402, 1366, 1171, 1124, 1098; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.80 (1H, d, *J* = 4.0 Hz, H2), 7.61-7.57 (5H, m, Ts*H*, Ph*H* and H4 or H6), 7.44 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.34 (1H, tt, *J* = 7.5, 1.5 Hz, Ph*H*), 7.32 (1H, s, H4 or H6), 7.23 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.74 (1H, d, *J* = 4.0 Hz, H3), 3.04 (2H, m, H10), 2.38 (3H, s, TsC*H*$_3$), 1.52 (2H, app qu, *J* = 8.0 Hz, H11), 1.34-1.21 (6H, m, H12-H14), 0.89

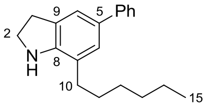
(3H, t, J = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.5, 141.0, 137.1, 136.5, 133.9, 133.7, 130.8, 130.5, 129.8, 128.7, 127.2, 127.0, 126.5, 126.4, 117.4, 109.5, 33.6, 31.8, 31.4, 29.5, 22.6, 21.6, 14.1; **HRMS** (ES+) calc. for $C_{27}H_{29}NNaO_2S$ $[M+Na]^+$ 454.1811, found 454.1821.

5,7-Diphenyl-1-tosyl-1H-indole, 280b



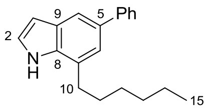
To a solution of amidodiene **207j** (20 mg, 0.047 mmol, 1.0 equiv.) in toluene (0.4 mL) was added a few 4Å molecular sieves and activated MnO_2 (41 mg, 0.47 mmol, 10 equiv.). The resulting suspension was stirred at 110 °C for 20 h before being allowed to cool to RT, diluted with EtOAc and filtered through a Celite® pad. The filtrate was concentrated *in vacuo* and purified *via* column chromatography (petroleum ether / EtOAc (10:1)) to afford indole **280b** as a colourless oil (10mg, 0.023 mmol, 50%); **R_f** 0.38 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3058, 2920, 2361, 1702, 1597, 1494, 1460, 1439, 1377, 1237, 1189, 1175, 1123, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.74 (1H, d, J = 3.5 Hz, H2), 7.70 (1H, d, J = 2.0 Hz, H4), 7.60 (2H, dd, J = 8.0, 1.5 Hz, Ph*H*), 7.42 (2H, t, J = 7.5 Hz, Ph*H*), 7.38-7.28 (7H, m, Ph*H* and H6), 7.18 (2H, d, J = 8.5 Hz, Ts*H*), 7.09 (2H, d, J = 8.5 Hz, Ts*H*), 6.79 (1H, d, J = 3.5 Hz, H3), 2.35 (3H, s, $TsCH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.2, 140.8, 140.5, 136.9, 135.2, 134.1, 133.0, 131.3, 131.1, 129.6, 129.3, 128.7, 128.0, 127.4, 127.2, 127.1, 126.6, 118.6, 110.3, 21.5; **HRMS** (ES+) calc. for $C_{27}H_{21}NNaO_2S$ $[M+Na]^+$ 446.1185, found 446.1166.

7-Hexyl-5-phenylindoline, 283



The procedure of Nyasse and co-workers was used for this preparation.[128] To a solution of indoline **279a** (80 mg, 0.18 mmol, 1.0 equiv.) in MeOH (2.2 mL) was added magnesium granules (22 mg, 0.92 mmol, 5.0 equiv.) and the mixture was sonicated for 1.5 h. The reaction was diluted with CH_2Cl_2 and poured into *aq.* 1M HCl. The organic layer was separated, washed with sat. *aq.* $NaHCO_3$ (×2), and then brine before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded indoline **283** as a colourless oil (31 mg, 0.11 mmol, 63%); **R_f** 0.58 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3384, 3030, 2954, 2927, 2854, 1599, 1469, 1307, 1280, 1263, 1168; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.58 (2H, dd, *J* = 8.0, 1.0 Hz, Ph*H*), 7.42 (2H, t, *J* = 8.0 Hz, Ph*H*), 7.31-7.27 (1H, m, Ph*H*), 7.29 (1H, s, H4), 7.17 (1H, s, H6), 3.65 (2H, t, *J* = 8.5 Hz, H2), 3.14 (2H, t, *J* = 8.5 Hz, H3), 2.53 (2H, m, H10), 1.68 (2H, app qu, *J* = 8.0 Hz, H11), 1.48-1.30 (6H, m, H12-H14), 0.94 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 149.3, 142.0, 132.3, 129.7, 128.6, 126.6, 126.4, 126.0, 123.9, 121.1, 47.5, 31.8, 31.6, 30.1, 29.4, 29.1, 22.7, 14.1; **HRMS** (ES+) calc. for $C_{20}H_{26}N$ $[M+H]^+$ 280.2060, found 280.2064.

7-Hexyl-5-phenyl-1*H*-indole, 284



Method A: The procedure of Nyasse and co-workers was used for this preparation.[128] To a solution of indole **280a** (16 mg, 0.037 mmol, 1.0 equiv.) in MeOH (0.44 mL) was added magnesium granules (5 mg, 0.18 mmol, 5.0 equiv.) and the mixture was sonicated for 1.5 h. The reaction was diluted with CH_2Cl_2 and poured into *aq.* 1M HCl. The organic layer was separated, washed with sat. *aq.* $NaHCO_3$ (×2), and then brine before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded indole **284** as a colourless oil (7 mg, 0.026 mmol, 71%).

Method B: A modified procedure of Chandra *et al.* was used for this preparation.[223] To a solution of detosylated indoline **283** (25 mg, 0.09 mmol, 1.0 eq.) in anhydrous benzene (1.4 mL) was added 4Å molecular sieves (346 mg) and activated MnO_2 (78 mg, 0.90 mmol, 10.0

eq.) and the resulting suspension stirred at 50 °C for 4 h before being cooled to RT. The reaction was diluted with EtOAc, filtered through a Celite® pad and the filtrate concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded indole **284** as a brown oil (19 mg, 0.071 mmol, 79%).

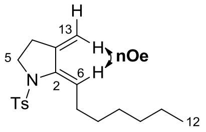
Method C: To a solution of amidodiene **207b** (110 mg, 0.25 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added a few 4Å molecular sieves and activated MnO_2 (219 mg, 2.52 mmol, 10 equiv.) and the resulting suspension was stirred at RT for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a Celite® pad. The filtrate was concentrated *in vacuo* and the residue re-dissolved in MeOH (3 mL), then magnesium granules (31 mg, 1.26 mmol, 5.0 equiv.) were added. After sonication for 1.5 h (RT) the reaction was diluted with CH_2Cl_2 (15 mL) and poured into *aq.* 1M HCl (10 mL). The organic layer was separated, washed with sat. *aq.* $NaHCO_3$ (×2) and then brine (10 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (2 mL) and a few 4Å molecular sieves and activated MnO_2 (219 mg, 2.52 mmol, 10 equiv.) were added before stirring the reaction mixture for a further 2 h. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a Celite® pad, and then concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave indole **284** as a pale brown oil (44 mg, 0.16 mmol, 64%).

$\mathbf{R_f}$ 0.35 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3436, 3026, 2956, 2929, 2856, 1598, 1497, 1471, 1445, 1426, 908; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.14 (1H, br s, H1), 7.72 (1H, s, H4 or H6), 7.66 (2H, dd, *J* = 8.0, 1.0 Hz, Ph*H*), 7.45 (2H, t, *J* = 8.0 Hz, Ph*H*), 7.32 (1H, tt, *J* = 7.5, 1.0 Hz, Ph*H*), 7.28 (1H, s, H4 or H6), 7.25 (2H, app t, *J* = 3.0 Hz, H2), 6.63 (1H, dd, *J* = 3.0, 2.0 Hz, H3), 2.90 (2H, t, *J* = 8.0 Hz, H10), 1.80 (2H, app qu, *J* = 8.0 Hz, H11), 1.48-1.43 (2H, m, H12), 1.37-1.31 (4H, m, H13 and H14), 0.91 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 142.8, 134.5, 133.6, 128.6, 128.2, 127.4, 126.2, 125.3, 124.3, 121.5, 117.0, 103.4, 31.8, 31.5, 29.7, 29.4, 22.6, 14.1; **HRMS** (ES+) calc. for $C_{20}H_{24}N$ $[M+H]^+$ 278.1903, found 278.1896.

7.4. Reductive Cyclisation/Diels-Alder Cycloaddition Sequence

7.4.1. Reductive Cyclisation

(*Z*)-2-Heptylidene-3-methylene-1-tosylpyrrolidine, 269a



Method A: Prepared by General Procedure O using bromoenynamide **205a** (30 mg, 0.072 mmol or 1 g, 2.42 mmol) with $Pd(PPh_3)_4$ (2 mg, 0.0018 mmol, 2.5 mol% or 28 mg, 0.0242 mmol, 1 mol%) and heating for 1 h. Purification *via* column chromatography (petroleum ether → ether / EtOAc (95:5)) afforded the dienamide **269a** as a yellow oil (20 mg, 0.06 mmol, 84% or 673 mg, 2.02 mmol, 84%).

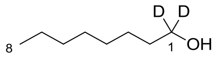
Method B: The procedure by Oh was used for this preparation.[130] To a solution of bromoenynamide **205a** (100 mg, 0.24 mmol, 1.0 equiv.) in anhydrous DMF (1 mL) was added Cs_2CO_3 (156 mg, 0.48 mmol, 2.0 equiv.) and triethylsilane (77 µL, 0.48 mmol, 2.0 equiv.) before the solution was degassed (bubbling Ar, 10 min). To this mixture was added $Pd(PPh_3)_4$ (8 mg, 0.0072 mmol, 0.03 equiv.), pre-weighed in the glovebox, before heating the reaction under Ar at 80 °C for 2 h. On completion by TLC analysis the reaction mixture was concentrated under a stream of N_2. The residue was partitioned between water and Et_2O and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1) + 1% NEt_3) afforded the dienamide **269a** as a colourless oil (37 mg, 0.11 mmol, 46%).

R_f 0.33 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2925, 1166, 1091, 801, 415; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.23 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.87 (1H, t, *J* = 7.5 Hz, H6), 5.20 (1H, t, *J* = 2.0 Hz, H13), 4.64 (1H, t, *J* = 2.0 Hz, H13'), 3.53 (2H, t, *J* = 7.5 Hz, H5), 2.53 (2H, q, *J* = 7.5 Hz, H7), 2.41 (3H, s, TsC*H*$_3$), 1.84 (2H, tt, *J* = 7.5, 2.0 Hz, H4), 1.45 (2H, qu, *J* = 7.5 Hz, H8), 1.39-1.29 (6H, m, H9, H10, H11), 0.89 (3H, t, *J* =

7.0 Hz, H12); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.8, 143.3, 136.5, 136.0, 129.5, 127.8, 122.1, 103.5, 48.5, 31.8, 29.7, 29.5, 29.1, 29.0, 22.7, 21.6, 14.1; **HRMS** (ES+) calc. for $C_{19}H_{27}NO_2S$ $[M+Na]^+$ 356.1660, found 356.1656.

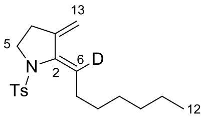
The stereochemistry of **269a** was assigned through ^{1}H NMR nOe experiments. A strong enhancement was seen between H6 and H13. Stereochemistry of remaining dienes was assigned by analogy, or by equivalent nOe experiments.

1,1-Dideuterio-*n*-octyl alcohol, 293



To a stirred suspension of LiAlD$_4$ (15.64 mL, 5.80 mmol, 1.0 equiv., 0.37 M in THF) under Ar was added a solution of ethyl octanoate (1 g, 5.805 mmol, 1.0 equiv.) in anhydrous THF (1.74 mL) dropwise over 30 min. The resulting suspension was then stirred at reflux for 4 h before being cooled to 0 °C and slowly quenched by the dropwise addition of water (50 mL). The reaction was extracted with Et$_2$O (×3) and the combined organic layers dried (MgSO$_4$) and concentrated *in vacuo* to afford alcohol **293** as a pale yellow liquid (533 mg, 4.00 mmol, 69%); **R$_f$** 0.48 (petroleum ether / EtOAc (1:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 1.55 (2H, t, *J* = 6.5 Hz, H2), 1.42 (1H, s, O*H*), 1.38-1.17 (10H, m, H3-H7), 0.87 (3H, t, *J* = 7.0 Hz, H8); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 62.5, 32.7, 32.0, 29.5, 29.4, 25.8, 22.8, 14.2. Data in accordance with literature values.[136]

D-Labelled (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine, 6D-269a

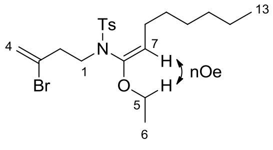


>95% D-incorporation

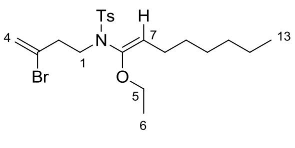
To an oven-dried Schlenk tube with stirrer bar was added Pd(PPh$_3$)$_4$ (5.5 mg, 0.0048 mmol, 10 mol%) and Cs$_2$CO$_3$ (23 mg, 0.072 mmol, 1.5 equiv.). The tube was sealed with a septum and evacuated / refilled with Ar (×3). In a separate oven-dried vial was added bromoenynamide

205a (20 mg, 0.048 mmol, 1.0 equiv.) and the vial sealed with a suba-seal followed by evacuation/refill with Ar (× 3) and the addition of anhydrous toluene (1 mL, 0.045 M). The bromoenynamide solution was transferred to the Schlenk tube followed by the addition of 1,1-d_2-octanol-OH **293** (126 mg, 0.96 mmol, 20 equiv.). The resulting reaction mixture was stirred at 80 °C for 3 h before being allowed to cool to RT and filtered through a Celite® plug eluting with EtOAc. The filtrate was concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (95:5)) afforded the D-labelled exocyclic diene **6D-269a** as a colourless oil (10.7 mg, 0.032 mmol, 66%, >95% D-incorporation); $\mathbf{R_f}$ 0.53 (petroleum ether / EtOAc (5:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2927, 2855, 1597, 1457, 1354, 1166, 1091, 1043; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.23 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.20 (1H, t, *J* = 2.5 Hz, H13), 4.65 (1H, t, *J* = 2.0 Hz, H13'), 3.53 (2H, t, *J* = 7.5 Hz, H5), 2.53 (2H, t, *J* = 7.5 Hz, H7), 2.41 (3H, s, TsCH_3), 1.83 (2H, tt, *J* = 7.5, 2.5 Hz, H4), 1.49-1.41 (2H, m, H8), 1.39-1.24 (6 H, m, H9-H11), 0.89 (3H, t, *J* = 7.0 Hz, H12); D:H incorporation determined by integration of the ^{1}H NMR signals for H6 in unlabelled product present (0.03H, 5.87 ppm) and H13/13' (1H, 5.20 and 4.65 ppm); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 143.9, 143.4, 136.6, 136.1, 129.6, 127.9, 121.9 (t), 103.6, 48.7, 31.9, 29.8, 29.6, 29.3, 29.2, 22.8, 21.7, 14.3; **HRMS** (FI$^+$) calc. for $C_{19}H_{26}DNO_2S$ [M]$^+$ 334.1825, found 334.2015.

(*E*)-*N*-(3-Bromobut-3-en-1-yl)-*N*-(1-ethoxyoct-1-en-1-yl)-4-methylbenzene sulfonamide, (*E*)-297 and (*Z*)-*N*-(3-bromobut-3-en-1-yl)-*N*-(1-ethoxyoct-1-en-1-yl)-4-methylbenzene sulfonamide, (*Z*)-297



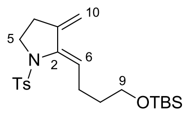
(*E*)-297
Major



(*Z*)-297
Minor

To a solution of bromoenynamide **205a** (30 mg, 0.072 mmol, 1.0 equiv.) in EtOH (3.4 mL, 0.02 M) was added $Pd(PPh_3)_4$ (2.1 mg, 0.0019 mmol, 2.5 mol%). The resulting reaction mixture was heated to reflux for 2 h before being allowed to cool to RT and filtered through a Celite® plug eluting with EtOAc. The filtrate was taken and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (95:5)) afforded the α-alkoxyenamide **297** as a colourless oil in a ratio of 5.6:1 *E*:*Z* respectively (16 mg, 0.035 mmol, 48%); **R_f** 0.64 (petroleum ether / EtOAc (5:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926, 2855, 1735, 1672, 1631, 1599, 1496, 1456, 1353, 1306, 1163, 1113, 1091; **^{1}H NMR** *Major E-isomer* (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.65 (1H, d, *J* = 1.5 Hz, H4), 5.44 (1H, d, *J* = 2.0 Hz, H4'), 4.63 (1H, t, *J* = 7.0 Hz, H7), 3.65 (2H, q, *J* = 7.0 Hz, H5), 3.40 (2H, br s, H1), 2.60 (2H, t, *J* = 7.5 Hz, H2), 2.42 (3H, s, $\mathrm{TsC}H_3$), 2.18 (2H, q, *J* = 7.5 Hz, H8), 1.38-1.27 (8H, m, H9-H12), 1.11 (3H, t, *J* = 7.0 Hz, H6), 0.89 (3H, t, *J* = 7.0 Hz, H13); **^{1}H NMR** *Minor Z-isomer* (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.61 (1H, app s, H4), 5.42 (1H, d, *J* = 2.0 Hz, H4'), 4.41 (1H, t, *J* = 7.5 Hz, H7), 3.74 (2H, q, *J* = 7.0 Hz, H5), 3.53 (2H, dd, *J* = 8.0, 6.5 Hz, H1), 2.66 (2H, dd, *J* = 8.0, 7.0 Hz, H2), 2.43 (3H, s, $\mathrm{TsC}H_3$), 2.05 (2H, q, *J* = 7.0 Hz, H8), 1.38-1.27 (8H, m, H9-H12), 1.21 (3H, t, *J* = 7.0 Hz, H6), 0.89 (3H, t, *J* = 7.0 Hz, H13); *E:Z* ratio determined by integration of the ^{1}H NMR signals for H4:5.65 and 5.61 ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C *Mixture of E/Z isomers; for distinguishable resonances (m) represents the minor Z-isomer* 145.1, 143.4, 136.6, 130.1, 129.4 (m), 129.2, 128.1, 128.0 (m), 118.9 (m), 118.5, 112.1 (m) 104.1, 64.6 (m), 63.3, 47.3 (m), 46.3, 40.3 (m), 40.1, 31.8, 31.7 (m), 30.1, 29.3 (m), 29.2, 28.9 (m), 27.2, 25.3 (m), 22.7, 21.5, 15.0 (m), 14.1; **HRMS** (ES+) calc. for $C_{21}H_{32}BrNNaO_3S$ $[M+Na]^+$ 480.1178, found 480.1185.

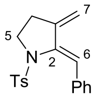
(*Z*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)butylidene)-3-methylene-1-tosylpyrrolidine, 269b



Prepared by General Procedure O using bromoenynamide **205c** (50 mg, 0.10 mmol) with heating for 1 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (90:10)) afforded the dienamide **269b** as a pale yellow oil (35 mg, 0.083 mmol, 83%);

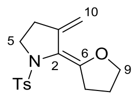
R$_f$ 0.52 (petroleum ether / EtOAc (5:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2857, 1675, 1598, 1472, 1438, 1332, 1254, 1160, 1092; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.61 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.83 (1H, t, *J* = 7.5 Hz, H6), 5.13 (1H, t, *J* = 2.0 Hz, H10), 4.57 (1H, t, *J* = 2.0 Hz, H10'), 3.61 (2H, t, *J* = 6.5 Hz, H9), 3.46 (2H, t, *J* = 7.5 Hz, H5), 2.51 (2H, q, *J* = 7.5 Hz, H7), 2.34 (3H, s, TsC*H*$_3$), 1.77 (2H, tt, *J* = 7.0, 2.0 Hz, H4), 1.64 (2H, qu, *J* = 7.0 Hz, H8), 0.84 (9H, s, SiC(C*H*$_3$)$_3$), 0.00 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.8, 143.2, 136.7, 136.0, 129.5, 127.8, 121.4, 103.7, 63.1, 48.5, 32.7, 29.1, 26.3, 26.0, 21.6, 18.4, −5.24; **HRMS** (ES+) calc. for $C_{22}H_{35}NNaO_3SSi$ [M+Na]$^+$ 444.1999, found 444.4989.

(*Z*)-2-Benzylidene-3-methylene-1-tosylpyrrolidine, 269c



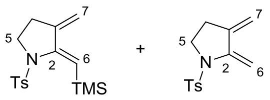
Prepared by General Procedure O using bromoenynamide **205b** (50 mg, 0.12 mmol or 0.5 g, 1.24 mmol) with Pd(PPh$_3$)$_4$ (3.5 mg, 0.003 mmol, 2.5 mol% or 14 mg, 0.012 mmol, 1 mol%) and heating for 30 min. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded dienamide **269c** as a yellow oil (26 mg, 0.079 mmol, 65% or 263 mg, 0.81 mmol, 65%); **R$_f$** 0.23 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3062, 3028, 2925, 2255, 1729, 1647, 1598, 1494, 1449, 1353, 1162, 1089, 910; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.81 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.69 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.24 (3H, app. d, *J* = 8.5 Hz, Ts*H* and Ph*H*), 6.73 (1H, s, H6), 5.44 (1H, t, *J* = 2.5 Hz, H7), 4.84 (1H, t, *J* = 2.5 Hz, H7'), 3.67 (2H, t, *J* = 7.5 Hz, H5), 2.42 (3H, s, TsC*H*$_3$), 1.88 (2H, tt, *J* = 7.5, 2.5 Hz, H4); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 144.3, 144.2, 136.2, 135.8, 135.7, 129.7, 129.6, 128.1, 128.0, 127.8, 117.9, 105.1, 48.7, 28.9, 21.7; **HRMS** (ES$^+$) calc. for $C_{19}H_{19}NNaO_2S$ [M+Na]$^+$ 348.1029, found 348.1023.

(*E*)-2-(Dihydrofuran-2(3*H*)-ylidene)-3-methylene-1-tosylpyrrolidine, 269d



Prepared by General Procedure O using bromoenynamide **205l** (38 mg, 0.099 mmol) with $Pd(PPh_3)_4$ (12 mg, 0.0099 mmol, 10 mol%) in anhydrous toluene (4.5 mL) and heating for 1 h. ^{1}H NMR analysis of the crude compound confirmed conversion to **269d** but on attempted purification *via* column chromatography decomposition occurred: **R$_f$** 0.41 (petroleum ether / EtOAc (4:1)); **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 5.49 (1H, s, H10), 4.82 (1H, s, H10'), 4.43 (2H, t, *J* = 7.0 Hz, H9), 3.58 (2H, t, *J* = 7.5 Hz, H5), 3.21 (2H, t, *J* = 7.5 Hz, H4), 2.47 (3H, s, TsCH_3), 2.10 (2H, qu, *J* = 7.0 Hz, H8), 1.84 (2H, tt, *J* = 7.5, 2.0 Hz, H7).

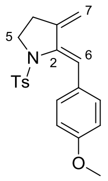
(*Z*)-3-Methylene-1-tosyl-2-((trimethylsilyl)methylene)pyrrolidine, 269e and 2,3-di-methylene -1-tosylpyrrolidine, 269f



269e **269f**

Prepared by General Procedure O using bromoenynamide **205d** (20 mg, 0.05 mmol) but with $NaHCO_3$ (6 mg, 0.075 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol, 10 mol%) with heating for 8 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1) + 1% NEt_3) afforded a mixture of dienamides **269e** and **269f** in a 1.3:1 ratio respectively (9.7 mg, 66%) which were prone to decomposition in $CDCl_3$ during characterisation; **R$_f$** 0.54 (petroleum ether / EtOAc (4:1)); **^{1}H NMR** (200 MHz, $CDCl_3$) *Mixture of products; for distinguishable resonances **e** or **f** stated*: δ_H 7.75 (2H, d, *J* = 8.5 Hz, TsH_f), 7.64 (2H, d, *J* = 8.5 Hz, TsH_e), 7.35-7.16 (4H, m, TsH_{e+f}), 5.79 (1H, s, H6_e), 5.36 (2H, app dd, *J* = 4.5, 2.5 Hz, H7_{e+f}), 5.12 (1H, d, *J* = 1.5 Hz, H6_f), 4.92 (1H, t, *J* = 2.0 Hz, H7'$_f$), 4.84 (1H, d, *J* = 1.5 Hz, H6'$_f$), 4.78 (1H, t, *J* = 2.0 Hz, H7'$_e$), 3.67 (2H, t, *J* = 7.5 Hz, H5_f), 3.55 (2H, t, *J* = 7.5 Hz, H5_e), 2.57-2.43 (2H, m, H4_f), 2.40 (6H, s, TsC$H_{3\ e+f}$), 1.78 (2H, tt, *J* = 7.5, 2.5 Hz, H4_e), 0.27 (9H, s, Si(CH_3)$_{3\ e}$).

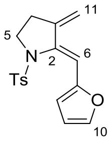
(*Z*)-2-(4-Methoxybenzylidene)-3-methylene-1-tosylpyrrolidine, 269i



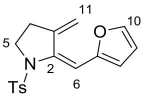
Prepared by General Procedure O using bromoenynamide **205e** (20 mg, 0.046 mmol) with heating for 1 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded dienamide **269i** as a yellow oil (10 mg, 0.028 mmol, 61%); **R$_f$** 0.30 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3485, 3304, 3033, 2955, 2839, 1724, 1600, 1511, 1462, 1442, 1350, 1250, 1162, 1090; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 8.02 (2H, d, *J* = 8.5 Hz, PMP*H*), 7.72 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.83 (2H, d, *J* = 9.0 Hz, PMP*H*), 6.75 (1H, s, H6), 6.67 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.21 (1H, t, *J* = 2.5 Hz, H7), 4.51 (1H, t, *J* = 2.0 Hz, H7'), 3.35 (2H, t, *J* = 7.5 Hz, H5), 3.28 (3H, s, OC*H*$_3$), 1.81 (3H, s, TsC*H*$_3$), 1.44 (2H, tt, *J* = 7.5, 2.5 Hz, H4); **^{13}C NMR** (126 MHz, C_6D_6) δ_C 159.9, 145.3, 143.5, 136.8, 134.6, 132.0, 130.6, 129.5, 128.4, 118.8, 113.9, 103.4, 54.8, 48.7, 28.9, 21.1; **HRMS** (ES$^+$) calc. for $C_{20}H_{21}NNaO_3S$ [M+Na]$^+$ 378.1134, found 378.1129.

N.B. This compound was prone to decomposition / isomerisation on SiO_2 and in $CDCl_3$

(*Z*)-2-(Furan-2-ylmethylene)-3-methylene-1-tosylpyrrolidine, (*Z*)-269j and (*E*)-2-(furan-2-ylmethylene)-3-methylene-1-tosylpyrrolidine, (*E*)- 269j



(*Z*)-269j



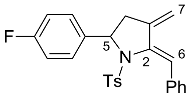
(*E*)-269j

Prepared by General Procedure O using bromoenynamide **205f** (40 mg, 0.101 mmol) with heating for 1 h. ^{1}H NMR analysis of the crude compound confirmed only *Z*-isomer formed: **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.42 (1H, d, *J* = 2.0 Hz, H10), 7.26 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.93 (1H, d, *J* = 3.5 Hz, H8), 6.69 (1H, s, H6), 6.46 (1H, dd, *J* = 3.5, 2.0 Hz, H9), 5.38 (1H, t, *J* = 2.5 Hz, H11), 4.81 (1H, t, *J* = 2.0 Hz, H11'), 3.60 (2H, t, *J* = 7.5 Hz, H5), 2.42 (3H, s, TsCH_3), 1.80 (2H, tt, *J* = 7.0, 2.5 Hz, H4).

Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded dienamide **269j** as an inseparable 1:4.2 *E:Z* mixture as a pale yellow oil (21 mg, 0.067 mmol, 66%); $\mathbf{R_f}$ 0.36 (petroleum ether / EtOAc (4:1)); **IR** (thin film, mixture, ν_{max} / cm^{-1}) 2925.1783, 1758, 1717, 1683, 1597, 1344, 1162, 1090; **(*Z*)-269j**: **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.74 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.43 (1H, d, *J* = 1.5 Hz, H10), 7.26 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.94 (1H, d, *J* = 3.5 Hz, H8), 6.70 (1H, s, H6), 6.46 (1H, dd, *J* = 3.5, 2.0 Hz, H9), 5.38 (1H, t, *J* = 2.5 Hz, H11), 4.81 (1H, t, *J* = 2.0 Hz, H11'), 3.60 (2H, t, *J* = 7.5 Hz, H5), 2.42 (3H, s, TsCH_3), 1.80 (2H, tt, *J* = 7.5, 2.5 Hz, H4); **(*E*)-269j**: **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.99 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.54 (1H, d, *J* = 8.5 Hz, H10), 7.42 (2H, d, *J* = 7.5 Hz, Ts*H*), 7.32 (1H, d, *J* = 9.5 Hz, H8), 7.13 (1H, dd, *J* = 8.0, 5.0 Hz, H9), 6.83 (1H, s, H6), 5.74 (1H, t, *J* = 2.0 Hz, H11), 5.16 (1H, t, *J* = 2.0 Hz, H11'), 3.68 (2H, t, *J* = 7.0 Hz, H5), 2.40 (3H, s, TsCH_3), 2.36 (2H, dt, *J* = 7.5, 3.5 Hz, H4); **^{13}C NMR** (126 MHz, C$_6$D$_6$) δ_C *Mixture of E/Z isomers* 151.8, 151.3, 144.5, 143.6, 143.5, 142.3, 141.2, 141.0, 136.7, 136.2, 130.3, 130.0, 129.7, 129.6, 129.5, 129.4, 113.1, 113.0, 112.4, 111.9, 110.9, 108.4, 104.2, 101.9, 48.9, 48.6, 31.4, 28.7, 21.1, 21.0; **HRMS** (ES$^+$, mixture) calc. for $C_{17}H_{17}NNaO_3S$ [M+Na]$^+$ 338.0821, found 338.0814.

N.B. *E:Z* ratio determined by integration of the ^{1}H NMR signals for H12 at 5.74 and 5.38 ppm. Stereochemical assignment by analogy with **269a** and related compounds. **269j** was prone to acid-catalysed isomerisation / decomposition to varying degrees on SiO$_2$ and in CDCl$_3$ – purification on alumina was not investigated.

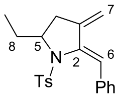
(*Z*)-2-Benzylidene-5-(4-fluorophenyl)-3-methylene-1-tosylpyrrolidine, 269k



Prepared by General Procedure O using bromoenynamide **232c** (30 mg, 0.06 mmol) with heating for 1 h. Purification *via* column chromatography (petroleum ether → petroleum ether /

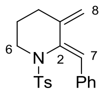
EtOAc (10:1)) afforded dienamide **269k** as a colourless oil (18.8 mg, 0.045 mmol, 75%); **R_f** 0.21 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3062, 3028, 2963, 2923, 1599, 1510, 1494, 1448, 1358, 1266, 1227, 1184, 1164, 1089, 1030; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.91 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.74 (2H, d, *J* = 6.5 Hz, Ts*H*), 7.21 (2H, ddd, *J* = 7.0, 5.0, 2.5 Hz, 4-FPh*H*), 7.14 (2H, m, *Ph*H), 7.01 (1H, t, *J* = 7.5 Hz, Ph*H*), 6.76 (1H, s, H6), 6.73-6.67 (4H, m, Ts*H* and 4-FPh*H*), 5.24 (1H, dd, *J* = 3.0, 1.5 Hz, H7), 5.15 (1H, d, *J* = 8.5 Hz, H5), 4.57 (1H, dd, *J* = 3.0, 1.5 Hz, H7'), 2.01 (1H, dd, *J* = 16.5, 1.5 Hz, H4), 1.91-1.85 (1H, m, H4'), 1.83 (3H, s, TsC*H*$_3$); **^{13}C NMR** (126 MHz, C_6D_6) δ_C 162.7 (d, *J* = 246.0 Hz), 144.5, 143.8, 137.7 (d, *J* = 3.5 Hz), 136.6, 136.1, 135.5, 130.1, 129.7, 128.5, 128.41, 128.40, 128.35, 119.0, 115.8 (d, *J* = 21.5 Hz), 105.1, 62.4, 35.8, 21.2; **HRMS** (ES^+) calc. for $C_{25}H_{22}FNNaO_2S$ $[M+Na]^+$ 442.1247, found 442.1240.

(*Z*)-2-Benzylidene-5-ethyl-3-methylene-1-tosylpyrrolidine, 269l



Prepared by General Procedure O using bromoenynamide **232d** (20 mg, 0.046 mmol) with heating for 30 min. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded dienamide **269l** as a pale yellow oil (11 mg, 0.031 mmol, 68%); **R_f** 0.46 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3084, 3059, 3026, 2969, 2932, 2876, 1575, 1493, 1449, 1356, 1165, 1089; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 8.04 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.70 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.25 (2H, t, *J* = 8.0 Hz, Ph*H*), 7.07 (1H, t, *J* = 8.0 Hz, Ph*H*), 6.77 (1H, s, H6), 6.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.24 (1H, t, *J* = 2.5 Hz, H7), 4.56 (1H, t, *J* = 2.0 Hz, H7'), 3.89 (1H, tdd, *J* = 9.0, 5.0, 2.5 Hz, H5), 1.82 (3H, s, TsC*H*$_3$), 1.57-1.51 (2H, m, H4), 1.42 (1H, ddq, *J* = 13.5, 8.5, 7.0 Hz, H8), 1.14 (1H, ddq, *J* = 13.0, 11.0, 6.0 Hz, H8'), 1.05 (3H, t, *J* = 7.0 Hz, H9); **^{13}C NMR** (126 MHz, C_6D_6) δ_c 145.1, 143.4, 137.0, 136.5, 135.4, 130.2, 129.5, 128.4, 128.3, 128.0, 119.3, 104.8, 62.0, 34.2, 28.9, 21.1, 11.1; **HRMS** (ES^+) calc. for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$ 376.1342, found 376.1338.

(*Z*)-2-Benzylidene-3-methylene-1-tosylpiperidine, 269m

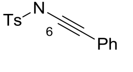


Prepared by General Procedure O using bromoenynamide **255** (35 mg, 0.0838 mmol) with heating for 30 min. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded dienamide **269m** as a pale yellow oil (17 mg, 0.050 mmol, 60%).

Prepared by General Procedure P Method B using bromoenynamide **255** (4 mg, 0.00958 mmol) with heating for 1 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded dienamide **269m** as a pale yellow oil (2.4 mg, 0.00707 mmol, 73%).

R$_f$ 0.42 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2920, 2230, 1598, 1448, 1351, 1161, 1092, 909, 842, 815, 732; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.67-7.60 (2H, m, Ph*H*), 7.62 (2H, d, *J* = 8.5 Hz Ts*H*), 7.35-7.28 (2H, m, Ph*H*), 7.23-7.20 (1H, m, Ph*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.69 (1H, s, H7), 5.23 (1H, d, *J* = 1.5 Hz, H8), 4.74 (1H, dd, *J* = 3.0, 1.5 Hz, H8’), 3.80-3.63 (2H, br s, H6), 2.38 (3H, s, TsC*H*$_3$), 2.15 (2H, t, *J* = 6.0 Hz, H4), 1.43 (2H, qu, *J* = 6.5 Hz, H5); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_c 144.1, 143.3, 137.0, 135.8, 135.3, 129.2, 129.1, 128.5, 128.2, 128.1, 127.8, 110.2, 47.3, 32.0, 22.8, 21.5; **HRMS** (ES$^+$) calc. for $C_{20}H_{21}NNaO_2S$ [M+Na]$^+$ 362.1185, found 362.1186.

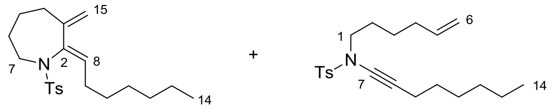
4-Methyl-*N*-(pent-4-en-1-yl)-*N*-(phenylethynyl)benzenesulfonamide, 299a



Isolated as a side-product from the formation of **269m**, using General Procedure O, as a colourless oil (3.2 mg, 0.0094 mmol, 11%); **R$_f$** 0.57 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2930, 2237, 1598, 1365, 1170, 1091, 910; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.84 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.39-7.33 (4H, m, Ts*H* and Ph*H*), 7.30-7.27 (3H, m, Ph*H*), 5.78 (1H, ddd, *J* = 17.0, 6.5, 3.5 Hz, H4), 5.04 (1H, ddd, *J* = 17.0, 3.5, 1.5 Hz, H5), 5.00 (1H, ddd, *J*

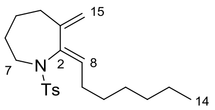
= 10.0, 3.0, 1.0 Hz, H5'), 3.41 (2H, t, *J* = 6.5 Hz, H1), 2.45 (3H, s, TsC*H*$_3$), 2.13 (2H, q, *J*= 7.0 Hz, H3), 1.81 (2H, qu, *J* = 7.5 Hz, H2); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_c 144.8, 137.2, 134.7, 131.5, 129.9, 128.4, 127.9, 127.8, 123.0, 115.8, 82.5, 70.8, 51.2, 30.5, 27.3, 21.8; **HRMS** (ES$^+$) calc. for $C_{20}H_{21}NNaO_2S$ [M+Na]$^+$ 362.1185, found 362.1179.

N-(Hex-5-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 299b



Prepared by General Procedure O using bromoenynamide **262a** (25 mg, 0.057 mmol) with heating for 1 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (9:1)) afforded a 1:3.3 ratio (as determined by ^{1}H NMR spectroscopic analysis) of **269n** (see characterisation below) and **299b** as a pale yellow oil (12 mg, 0.034 mmol, 59%); Data for **299b** (as inseparable mixture with **269n**): **R$_f$** 0.50 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2931, 2859, 1740, 1598, 1452, 1371, 1242, 1169, 1092, 1047; **^{1}H NMR** (500 MHz, MeOD) δ_H 7.81 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.47 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.82 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, H5), 5.03 (1H, ddd, *J* = 17.0, 3.5, 1.5 Hz, H6$_{trans}$), 4.98 (1H, dd, *J* = 10.0, 1.0 Hz, H6$_{cis}$), 3.31 (2H, t, *J* = 7.0 Hz, H1), 2.50 (3H, s, TsC*H*$_3$), 2.31 (2H, t, *J* = 6.5 Hz, H9), 2.09 (2H, q, *J* = 7.0 Hz, H4), 1.69-1.61 (2H, m, H2), 1.51 (2H, dt, *J* = 14.0, 7.0 Hz, H10), 1.47-1.39 (4H, m, H3 and H11), 1.38-1.30 (4H, m, H12 and H13), 0.96 (3H, t, *J* = 7.0 Hz, H14); **^{13}C NMR** (126 MHz, MeOD) δ_C 146.1, 139.4, 136.0, 130.8, 128.7, 115.3, 74.3, 71.2, 52.4, 34.2, 32.5, 30.0, 29.4, 28.2, 26.6, 23.7, 21.6, 19.0, 14.4; **HRMS** (ES$^+$) calc. for $C_{21}H_{31}NNaO_2S$ [M+Na]$^+$ 384.1968, found 384.1954.

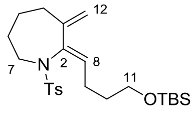
(*Z*)-2-Heptylidene-3-methylene-1-tosylazepane, 269n



Prepared by General Procedure P Method B using bromoenynamide **262a** (50 mg, 0.113 mmol) with heating for 3.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded dienamide **269n** as a yellow oil (28 mg, 0.078 mmol, 69%); **R$_f$** 0.5 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2927, 2856, 2256, 1598, 1495, 1450, 1401, 1344, 1157, 1098, 908; N.B. Rate of conformation interconversion leads to broadening of some peaks: **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.71 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.24 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.92 (1H, t, *J* = 7.5 Hz, H8), 5.12 (1H, s, H15), 4.73 (1H, d, *J* = 1.5 Hz, H15'), 2.40 (3H, s, TsC*H*$_3$), 2.15-2.09 (2H, br s, H4), 1.89 (2H, dt, *J* = 13.5, 7.0 Hz, H9), 1.64 (2H, dt, *J* = 11.5, 6.0 Hz, H6), 1.49 (2H, br s, H5), 1.31-1.15 (8H, m, H10–H13), 0.87 (3H, t, *J* = 7.0 Hz, H14); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 149.2, 142.9, 139.3, 138.9, 134.3, 129.4, 127.4, 110.2, 52.2, 34.5, 31.8, 30.8, 29.4, 28.9, 28.0, 26.2, 22.7, 21.6, 14.2; **HRMS** (ES$^+$) calc. for $C_{21}H_{31}NNaO_2S$ [M+Na]$^+$ 384.1968, found 384.1954.

H7 broadened into baseline in RT ^{1}H NMR therefore ^{1}H NMR was also conducted at 70 °C in C_6D_6 to resolve the peak: **^{1}H NMR** δ_H (250 MHz, C_6D_6, 70 °C) 7.80 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.83 (2H, dd, *J* = 8.5, 0.5 Hz, Ts*H*), 5.93 (1H, t, *J* = 7.5, H8), 5.18 (1H, s, *J* = 0.5 Hz, H15), 4.70 (1H, d, *J* 1.5 Hz, H15'), 3.50 (2H, t, *J* = 5.0 Hz, H7), 2.18-2.09 (2H, m, H4), 2.04 (2H, dt, *J* = 14.5, 7.5 Hz, H9), 1.96 (3H, s, TsC*H*$_3$), 1.49 (2H, dt, *J* = 11.5, 6.0 Hz, H6), 1.36-1.16 (10H, m, H5 and H10–13), 0.87 (3H, t, *J* = 6.5 Hz, H14).

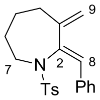
(*Z*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)butylidene)-3-methylene-1-tosylazepane, 269p



Prepared by General Procedure P Method B using bromoenynamide **262b** (20 mg, 0.037 mmol) with heating for 2 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded dienamide **269p** as a colourless oil (10.6 mg, 0.024 mmol, 65%); **R$_f$** 0.4 (petroleum ether / EtOAc (20:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2952, 2930, 2857, 1472, 1447, 1387, 1344, 1255, 1159, 1099, 909; N.B. Rate of conformation interconversion leads to broadening of some peaks: **^{1}H NMR** 500 MHz, C_6D_6) δ_H 7.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.97 (1H, t, *J* = 7.5 Hz, H8), 5.22 (1H, s, H12), 4.72 (1H, d, *J* = 1.5 Hz, H12'), 3.45 (2H, t, *J* = 6.5 Hz, H11), 2.18 (2H, dt, *J* = 14.5, 7.5 Hz, H9), 2.11-2.04 (2H, m, H4), 1.89 (3H, s, TsC*H*$_3$), 1.50 (2H, app q, *J* = 7.5 Hz, H10), 1.46-1.39 (2H, br s, H6), 1.28-1.20 (2H, br s, H5), 0.98 (9H, s, SiC(C*H*$_3$)$_3$), 0.05 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, C_6D_6) δ_C 149.6, 142.4, 140.3, 140.1, 133.8, 129.4, 127.8, 110.2, 62.9, 52.2, 34.8, 32.4, 30.8, 26.5, 26.2, 24.9, 21.1, 18.5, −5.2; **HRMS** (ES$^+$) calc. for $C_{24}H_{39}NNaO_3SSi$ [M+Na]$^+$ 472.2312, found 472.2298.

H7 broadened into baseline in RT ^{1}H NMR therefore heated ^{1}H NMR conducted at 70 °C in C_6D_6 to resolve the peak: **^{1}H NMR** (250 MHz, C_6D_6, 70 °C) δ_H 7.81 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.97 (1H, t, *J* = 7.5 Hz, H8), 5.18 (1H, s, H12), 4.70 (1H, d, *J* = 1.5 Hz, H12'), 3.50 (4H, t, *J* = 6.5 Hz, H11 and H7), 2.19 (2H, dt, *J* = 15.0, 7.5 Hz, H9), 2.13-2.04 (2H, m, H4), 1.95 (3H, s, TsC*H*$_3$), 1.49 (4H, ddd, *J* = 11.5, 7.0, 1.0 Hz, H10 and H6), 1.35-1.22 (2H, m, H5), 0.97 (9H, s, SiC(C*H*$_3$)$_3$), 0.06 (6H, s, Si(C*H*$_3$)$_2$).

(*Z*)-2-Benzylidene-3-methylene-1-tosylazepane, 269q



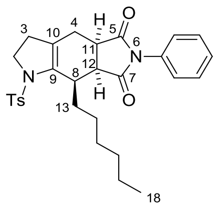
Prepared by General Procedure P Method A using bromoenynamide **262c** (20 mg, 0.0462 mmol) with heating for 2 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded dienamide **269q** as a colourless oil (10 mg, 0.0283, 61%); **R$_f$** 0.28 (petroleum ether / EtOAc (20:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3026, 2930, 2856, 1598, 1493, 1446, 1343, 1305, 1158, 1097, 1044; NB. N.B. Rate of conformation interconversion leads to broadening of some peaks: **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.80 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.55 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.06 (2H, t, *J* = 7.5 Hz, Ph*H*), 6.98 (1H, tt, *J* = 7.5, 2.0 Hz, Ph*H*), 6.71 (1H, s, H8), 6.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.35 (1H, d, *J* = 1.5 Hz, H9), 4.80 (1H, dd, *J* = 3.0, 1.5 Hz, H9'), 2.12-2.01 (2H, br s, H4), 1.84 (3H, s, TsC*H*$_3$), 1.35-1.05

(2H, br m, H5 and H6); **^{13}C NMR** (126 MHz, C_6D_6) δ_C 170.2, 154.9, 150.9, 142.6, 140.0, 139.6, 134.9, 130.3, 129.6, 129.3, 128.7, 128.4, 128.4, 111.9, 51.1, 34.4, 30.5, 26.3, 21.1; **HRMS** (ES$^+$) calc. for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$ 376.1342, found 376.1329.

H7 missing on RT ^{1}H NMR therefore ^{1}H NMR conducted at 70 °C in C_6D_6 to resolve the peak: **^{1}H NMR** (250 MHz, C_6D_6, 70 °C) δ_H 7.74 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.46 (2H, dd, *J* = 8.0, 1.5 Hz, Ph*H*), 7.10-6.96 (3H, m, Ph*H* and *p*-Ph*H*), 6.72 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.71 (1H, s, H8), 5.32 (1H, d, *J* = 1.5 Hz, H9), 4.80 (1H, q, *J* = 1.5 Hz, H9'), 3.54-3.39 (2H, br s, H7), 2.23-2.13 (2H, m, H4), 1.90 (3H, s, TsC*H*$_3$), 1.52 (2H, dt, *J* = 11.0, 5.5 Hz, H6), 1.38-1.24 (2H, m, H5).

7.4.2. Diels-Alder Cycloadditions

(4*aR*,7*aS*,8*R*)-8-Hexyl-6-phenyl-1-tosyl-2,3,4,4a,7a,8-hexahydropyrrolo[3,4-*f*]indole-5,7(1*H*,6*H*)-dione, 304



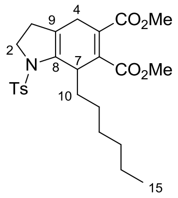
To a solution of dienamide **269a** (20 mg, 0.06 mmol, 1.0 equiv.) in anhydrous toluene (1.8 mL, 0.033 M) was added *N*-phenyl maleimide (20 mg, 0.12 mmol, 2.0 equiv.). The reaction mixture was heated to 80 °C for 1 h before being allowed to cool to RT and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (1:1)) afforded **304** as a colourless oil (18 mg, 0.043 mmol, 72%); **R$_f$** 0.68 (petroleum ether / EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926, 2856, 1714, 1598, 1496, 1456, 1380, 1352, 1289, 1161, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.49 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.41 (1H, t, *J* = 7.5 Hz, Ph*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 7.5 Hz, Ph*H*), 3.91-3.83 (2H, m, H8 and H2), 3.76 (1H, ddd, *J* = 11.5, 9.5, 6.0 Hz, H2'), 3.21 (1H, ddd, *J* = 20.0, 10.0, 6.5 Hz, H11), 3.17 (1H, dd, *J* = 10.0, 6.0 Hz, H12), 2.62 (1H, dd, *J* = 18.0, 6.5 Hz, H4), 2.49 (1H, dd, *J* = 18.0, 10.0 Hz, H4'), 2.45 (3H, s, TsC*H*$_3$), 2.30-2.23 (1H, m, H3), 2.21-2.14 (1H, m, H3’), 1.47-1.40 (2H, m, H13), 1.36-1.20 (8H, m, H14-H17), 0.86 (3H, t, *J* = 7.0 Hz, H18); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 178.7, 176.5, 143.9, 139.6, 134.1, 131.7, 129.8, 129.3, 128.7, 127.6, 126.3, 122.4, 49.9, 45.2, 38.3, 34.1, 31.7, 30.48, 30.46, 29.6, 27.2, 22.6, 21.9, 21.6, 14.1; **HRMS** (ES+) calc. for $C_{29}H_{34}N_2NaO_4S$ $[M+Na]^+$ 529.2131, found 529.2121.

The stereochemical assignment of the product is proposed based on the following ^{1}H NMR nOesy signals:

H12 → H8

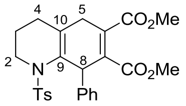
No nOe from H12 to H13 supports this stereoisomer.

Dimethyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydro-1*H*-indole-5,6-dicarboxylate, 306a



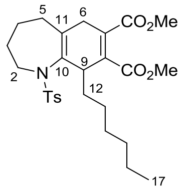
Prepared by General Procedure Q using dienamide **269a** (20 mg, 0.059 mmol) with heating for 5.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (6:4)) afforded **306a** as a yellow oil (18 mg, 0.046 mmol, 78%); **R_f** 0.18 (petroleum ether / EtOAc (3:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 1728, 1645, 1597, 1352, 1262, 1163, 734; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.63 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.11 (1H, dd, *J* = 7.0, 3.5 Hz, H7), 3.84 (3H, s, CO$_2$C*H*$_3$), 3.78-3.72 (5H, m, CO$_2$C*H*$_3$ and H2), 3.07 (1H, dd, *J* = 23.0, 7.5 Hz, H4), 2.76 (1H, dd, *J* = 23.0, 6.5 Hz, H4’), 2.42 (3H, s, TsC*H*$_3$), 2.19 (1H, ddt, *J* = 14.0, 12.0, 4.5 Hz, H10), 2.06 (1H, dt, *J* = 14.5, 7.0 Hz, H3), 1.94-1.84 (1H, m, H3’), 1.64-1.53 (1H, m, H10’), 1.32-1.19 (6H, m, H12-H14), 1.22-1.10 (1H, m, H11), 1.05 (1H, dq, *J* = 12.5, 6.5 Hz, H11’), 0.86 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_c 169.0, 167.1, 144.0, 140.9, 135.2, 133.7, 129.9, 129.0, 127.7, 123.1, 52.5, 52.4, 49.8, 38.5, 31.9, 30.6, 30.5, 29.4, 28.4, 24.0, 22.8, 21.7, 14.2; **HRMS** (ES+) calc. for $C_{23}H_{33}NNaO_6S$ $[M+Na]^+$ 498.1926, found 498.1921.

Dimethyl 8-phenyl-1-tosyl-1,2,3,4,5,8-hexahydroquinoline-6,7-dicarboxylate, 306b



Prepared by General Procedure Q using dienamide **269m** (14 mg, 0.041 mmol) with heating for 1.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (4:1)) afforded **306b** as a colourless oil (9.6 mg, 0.025 mmol, 60%); $\mathbf{R_f}$ 0.12 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3062, 3029, 2952, 1723, 1598, 1454, 1435, 1340, 1268, 1243, 1159, 1046; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.52 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.26-7.18 (7H, m, Ts*H* and Ph*H*), 5.44 (1H, t, *J* = 5.5 Hz, H8), 3.77 (3H, s, CO$_2$C*H*$_3$), 3.80-3.74 (1H, m, H2), 3.58 (3H, s, CO$_2$C*H*$_3$), 3.30 (1H, dd, *J* = 23.0, 7.0 Hz, H5), 3.00 (1H, dd, *J* = 23.0, 5.5 Hz, H5'), 2.57 (1H, ddd, *J* = 14.0, 9.0, 7.5 Hz, H2), 2.41 (3H, s, TsC*H*$_3$), 2.02 (1H, dt, *J* = 18.5, 8.0 Hz, H4), 1.74 (1H, d, *J* = 18.5 Hz, H4'), 1.53-1.45 (2H, m, H3); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 167.8, 167.4, 143.7, 140.7, 138.1, 137.1, 131.5, 129.7, 129.0, 128.8, 128.6, 127.5, 127.3, 123.4, 52.5, 52.2, 47.4, 46.7, 33.4, 26.4, 21.7, 20.5; **HRMS** (ES$^+$) calc. for $C_{26}H_{27}NNaO_6S$ $[M+Na]^+$ 504.1451, found 504.1443.

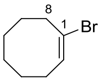
Dimethyl 9-hexyl-1-tosyl-2,3,4,5,6,9-hexahydro-1*H*-benzo[*b*]azepine-7,8-dicarboxy-late, 306c



Prepared by General Procedure Q using dienamide **269n** (30 mg, 0.0829 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (4:1)) afforded **306c** as a colourless oil (25.4 mg, 0.0504 mmol, 61%); $\mathbf{R_f}$ 0.26 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2930, 2857, 1726, 1656, 1598, 1436, 1345, 1265, 1220, 1156; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.73 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.13 (1H, d, *J* = 15.0 Hz, H2), 3.86-3.81 (1H, m, H9), 3.78 (3H, s, CO$_2$C*H*$_3$), 3.75 (3H, s, CO$_2$C*H*$_3$), 3.18 (1H, dd, *J* = 23.0, 7.5 Hz, H6), 2.89 (1H, dd, *J* = 23.0, 5.0 Hz, H6'), 2.69

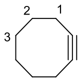
(1H, t, J = 13.5 Hz, H2'), 2.41 (3H, s, TsCH_3), 1.86 (1H, t, J = 13.5 Hz, H5), 1.81-1.72 (1H, m, H3), 1.71-1.59 (4H, m, H3', H4 and H5'), 1.55-1.47 (2H, m, H12), 1.29-1.13 (7H, m, H13 and H14-16), 1.11-1.01 (1H, m, H13'), 0.83 (3H, t, J = 7.0 Hz, H17); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 168.2, 167.2, 143.4, 139.4, 138.6, 136.0, 132.8, 129.7, 129.6, 127.3, 52.4, 52.3, 50.1, 42.1, 34.9, 32.5, 31.8, 30.5, 29.7, 29.5, 24.3, 23.6, 22.7, 21.7, 14.2; **HRMS** (FI$^+$) calc. for $C_{27}H_{37}NO_6S$ [M]$^+$ 503.2342, found 503.2165.

(*E*)-1-Bromocyclooct-1-ene, 310



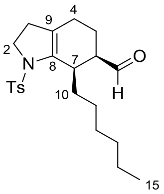
The procedure of Fairbanks *et al.* was used for this preparation.[143,144] To a solution of cyclooctene (1.2 mL, 9.07 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (3.1 mL, 0.35 mL.mmol^{-1}) was added bromine (0.46 mL, 9.07 mmol, 1.0 equiv.) at −40 °C. The solvent was then removed *in vacuo* and the residue dissolved in anhydrous Et_2O (3.6 mL, 0.4 mL.mmol^{-1}) before the addition of KO*t*Bu in THF (8 mL, 13.61 mmol, 1.5 equiv., 1.7 M in THF) over 20 min with vigorous stirring, whilst maintaining the temperature at 0 °C. After complete addition, reaction stirred for 1 h at RT before pouring the mixture into ice-water (25 mL) and extracting the product with Et_2O (× 3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (petroleum ether) afforded the bromocyclooctene **310** as a colourless oil (1.01 g, 5.35 mmol, 59%); **R$_f$** 0.52 (petroleum ether); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 6.03 (1H, t, J = 8.5 Hz, H2), 2.65-2.56 (2H, m, CH_2), 2.09 (2H, t, J = 6.5 Hz, CH_2), 1.69-1.58 (2H, m, CH_2), 1.58-1.44 (6H, m, (CH_2)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 131.8, 124.9, 35.3, 30.0, 28.8, 27.6, 26.5, 25.6. Data in accordance with literature values.[144]

Cyclooctyne, 311



The procedure of Fairbanks *et al.* was used for this preparation.[143,144] A solution of LDA was made by the dropwise addition of *n*-BuLi (0.65 mL, 1.63 mmol, 0.5 equiv., 2.5 M in THF) to anhydrous diisopropylamine (0.24 mL, 1.73 mmol, 0.53 equiv.) in anhydrous THF (0.7 mL) at −25 °C with stirring for 15 min. To this solution was added bromocyclooctene **310** (618 mg, 3.26 mmol, 1.0 equiv.) at once before allowing the temperature to gradually rise to RT over 45 min, at which point the reaction was stirred for a further 90 min. The reaction mixture was poured into water, extracted with Et_2O (×3) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (pentanes) afforded the desired product **311** as a colourless oil (14 mg, 0.13 mmol, 4%, 8% brsm); **R$_f$** 0.23 (petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.16 (4H, t, *J* = 6.5 Hz, H1), 1.86 (4H, d, *J* = 4.0 Hz, H2), 1.62 (4H, d, *J* = 4.5 Hz, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_c 94.7, 34.7, 29.8, 21.0. Data in accordance with literature values.[144]

(6*RS*,7*RS*)-7-Hexyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-indole-6-carbaldehyde, 314a



Method A: An oven dried flask equipped with stirrer bar was evacuated and refilled with Ar (x 3) before the addition of dienamide **269a** (20 mg, 0.06 mmol, 1.0 equiv.) and acrolein (20 µL, 0.30 mmol, 5.0 equiv.) in anhydrous CH_2Cl_2 (1 mL, 0.06 M). The resulting solution was cooled to –78 °C, then $BF_3•OEt_2$ (7 µL, 0.0.033 mmol, 0.55 equiv.) was added dropwise. The reaction was stirred at –78 °C for 1 h before being quenched with MeOH:H_2O (1:1, 1 mL) and allowed to warm to RT. The mixture was extracted with CH_2Cl_2 (×3) and the combined organic layers dried ($MgSO_4$), then concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded **314a** as pale yellow oil (15 mg, 0.0386 mmol, 65%).

Method B: To a solution of dienamide **269a** (20 mg, 0.06 mmol, 1.0 equiv.) in anhydrous toluene (1.8 mL) in an oven-dried vial equipped with stirrer bar was added acrolein (20 μL, 0.30 mmol, 5.0 equiv.). The vial was sealed with a screw cap and the resulting mixture heated at 80 °C for 5 h before being allowed to cool to RT and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded **314a** as colourless oil (16.1 mg, 0.0413 mmol, 69%).

R$_f$ 0.26 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2857, 1714, 1456, 1330, 1162, 1093, 912; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 9.87 (1H, s, C*H*O), 7.65 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.83 (1H, ddd, *J* = 12.0, 9.0, 3.0 Hz, H2), 3.67 (1H, dd, *J* = 21.5, 11.5 Hz, H2’), 3.57 (1H, br s, H7), 2.62 (1H, dt, *J* = 11.0, 4.5 Hz, H6), 2.43 (3H, s, TsC*H*$_3$), 2.08 (1H, dd, *J* = 17.0, 5.5 Hz, H4), 1.96-1.71 (5H, m, H3, H4’ and H5), 1.67 (1H, ddd, *J* = 11.5, 9.0, 5.5 Hz, H10), 1.48-1.33 (3H, m, H10’ and H11), 1.32-1.19 (6H, m, H12-14), 0.86 (3H, t, *J* = 6.5 Hz, H15); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 203.7, 143.9, 139.1, 134.4, 129.7, 127.5, 127.0, 51.9, 50.2, 34.8, 31.8, 31.6, 31.5, 29.9, 28.4, 23.8, 22.8, 21.7, 17.9, 14.2; **HRMS** (ES$^+$) calc. for $C_{22}H_{31}NNaO_3S$ [M+Na]$^+$ 412.1917, found 412.1908.

The regiochemistry of the cycloaddition was confirmed by ^{1}H–^{1}H NMR COSY correlation from H6 to H7.

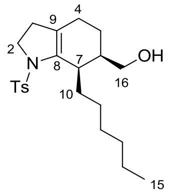
The stereochemical assignment of the product is proposed based on the following ^{1}H NMR nOe enhancements:

Irradiation of H6 → H7, TsH

Irradiation of H7 → H6, CHO

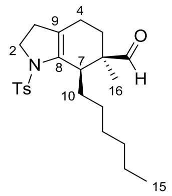
Irradiation of CHO → H11

((6*RS*,7*RS*)-7-Hexyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-indol-6-yl)methanol, 315



To a solution of dienamide **269a** (35 mg, 0.105 mmol, 1.0 equiv.) in anhydrous toluene (3.2 mL) in an oven-dried vial equipped with stirrer bar was added acrolein (35 µL, 0.524 mmol, 5.0 equiv.). The vial was sealed with a plastic cap and the resulting mixture heated at 80 °C for 5 h before being allowed to cool to RT. MeOH (3.2 mL) was then added followed by $NaBH_4$ (4 mg, 0.105 mmol, 1.0 equiv.) and the resulting mixture stirred at RT for 10 min before being quenched with sat. *aq.* NH_4Cl (<0.1 mL). Copious amounts of $MgSO_4$ was added before filtering the reaction and concentrating *in vacuo*. An off-white solid was obtained to which was added $CHCl_3$ and the solid removed by filtration. Concentration of the filtrate afforded **315** as a yellow oil which was not purified further (27 mg, 0.069 mmol, 65%); **R_f** 0.10 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3531 (br), 2928, 2857, 2255, 1466, 1343, 1163, 1090, 1049, 1018, 909, 731; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.85-3.72 (2H, m, H2 and H16), 3.70-3.51 (2H, m, H2' and H16'), 3.14 (1H, br s, H7), 2.41 (3H, s, TsC*H*$_3$), 2.02 (1H, dd, *J* = 17.5, 6.0 Hz, H4), 1.97-1.87 (1H, m, H6), 1.87-1.62 (5H, m, H3, H4' and 2 x C*H*H'), 1.53 (1H, t, *J* = 5.5 Hz, O*H*), 1.50-1.38 (4H, m, H11 and 2 x CH*H*'), 1.27 (6H, s, H12-14), 0.87 (3H, t, *J* 6.5 Hz, H15); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_c 143.6, 140.2, 134.5, 129.6, 127.6, 126.6, 65.0, 50.1, 41.7, 35.1, 31.9, 31.7, 30.4, 30.1, 28.5, 24.7, 22.9, 21.7, 20.8, 14.3; **HRMS** (ES$^+$) calc. for $C_{22}H_{33}NNaO_3S$ $[M+Na]^+$ 414.2073, found 414.2054.

(6*RS*,7*RS*)-7-Hexyl-6-methyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-indole-6-carbaldehyde, 314b



An oven dried flask equipped with stirrer bar was evacuated and refilled with Ar (×3) before the addition of dienamide **269a** (30 mg, 0.089 mmol, 1.0 equiv.) and methacrolein (74 μL, 0.45 mmol, 5.0 equiv.) in anhydrous CH_2Cl_2 (1.5 mL, 0.06 M). The resulting solution was cooled to –78 °C before the dropwise addition of BF_3•OEt_2 (6 μL, 0.049 mmol, 0.55 equiv.). The reaction was stirred at –78 °C for 2 h before being quenched with MeOH:H_2O (1:1, 1 mL) and allowed to warm to RT. The mixture was extracted with CH_2Cl_2 (×3) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded **314b** as colourless oil (25.7 mg, 0.064 mmol, 71%); $\mathbf{R_f}$ 0.26 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3298, 2930, 2857, 1724, 1598, 1495, 1342, 1161, 1092; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.64 (1H, s, C*H*O), 7.70 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.87 (1H, ddd, *J* = 12.5, 9.5, 3.5 Hz, H2), 3.73 (1H, dt, *J* = 12.0, 10.0 Hz, H2’), 3.02 (1H, br s, H7), 2.43 (3H, s, TsCH_3), 2.15-1.92 (3H, m, H3 and H4), 1.92-1.75 (2H, m, H4’ and H5), 1.54 (1H, ddd, *J* = 12.0, 8.5, 4.0 Hz, H10), 1.50-1.37 (3H, m, H5’, H10’ and H11), 1.37-1.13 (7H, m, H11’ and H12-14), 1.02 (3H, s, H16), 0.86 (3H, t, *J* = 7.0 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_c 205.2, 143.9, 137.7, 135.3, 129.7, 127.7, 123.9, 50.1, 49.7, 40.8, 32.6, 31.7, 31.6, 30.0, 28.6, 23.1, 22.8, 21.7, 21.5, 19.7, 14.2; **HRMS** (ES^+) calc. for $C_{23}H_{33}NNaO_3S^+$ $[M+Na]^+$ 426.2073, found 426.2070.

The regiochemistry of the cycloaddition was confirmed by ^1H–^1H NMR COSY correlation from H4 to H5, and a lack of correlation from H7 to H5 as would be expected in the regioisomer.

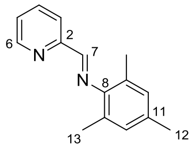
The stereochemical assignment of the product is proposed based on the following ^{1}H NMR nOe enhancements:

Irradiation of Me → H7, TsH

Irradiation of H7 → Me, CHO

Irradiation of CHO → H11

(*E*)-2,4,6-trimethyl-*N*-(pyridin-2-ylmethylene)aniline, 320



The procedure of Burstein and co-workers was used for this reaction.[150] A solution of 2-pyridinecarboxaldehyde (3.57 mL, 37.3 mmol, 1.0 equiv.) and 2,4,6-trimethylaniline (5.2 mL, 37.3 mmol, 1.0 equiv.) in EtOH (50 mL, 0.75 M) was heated to 90 °C for 30 min before being allowed to cool to RT. Reaction mixture concentrated *in vacuo* and the residue was taken up in CH_2Cl_2 (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the py-imine ligand **320** as a yellow solid (7.88 g, 35.13 mmol, 94%); **mpt** 72.9-75.6 °C ; $\mathbf{R_f}$ 0.52 (EtOAc); $\mathbf{^1H}$ **NMR** (400 MHz, $CDCl_3$) δ_H 8.71 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz, H6), 8.33 (1H, s, H7), 8.27 (1H, dt, *J* = 8.0, 1.0 Hz, H3), 7.83 (1H, td, *J* = 7.5, 1.5 Hz, H4), 7.39 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz, H5), 6.90 (2H, s, H10), 2.29 (3H, s, H12), 2.14 (6H, s, H13); $\mathbf{^{13}C}$ **NMR** (101 MHz, $CDCl_3$) δ_C 163.4, 154.5, 149.6, 147.8, 136.7, 133.4, 128.8, 126.8, 125.2, 121.2, 20.7, 18.2. Data in accordance with literature values.[150]

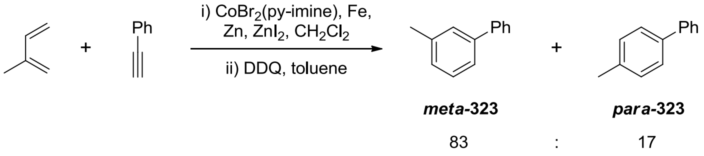
$CoBr_2$(py-imine)

The procedure of Hilt *et al.* was used for this reaction.[151] The complex was synthesised by suspending anhydrous $CoBr_2$ (1.00 g, 4.57 mmol, 1.0 equiv.) and the py-imine ligand **320** (1.03 g, 4.57 mmol, 1.0 equiv.) in anhydrous THF (18 mL, 0.25 M) at RT. After stirring overnight the solvent was removed *in vacuo* to obtain the catalyst as a brown/green solid (2.02 g, 4.57 mmol, quant.) which was used without further purification.

$CoBr_2$(dppe)

The procedure of Hilt *et al.* was used for this reaction.[151] The complex was synthesised by suspending anhydrous $CoBr_2$ (1.00 g, 4.57 mmol, 1.0 equiv.) and ethylenebis(diphenyl phosphine) (1.82 g, 4.57 mmol, 1.0 equiv.) in anhydrous THF (18 mL, 0.25 M) at RT. After stirring overnight the solvent was removed *in vacuo* to obtain the catalyst as a brown/green solid (2.82 g, 4.57 mmol, quant.) which was used without further purification.

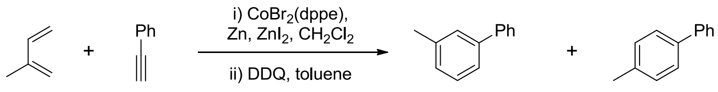
3-Methyl-1,1'-biphenyl, *meta*-323



The procedure of Hilt *et al.* was used for this reaction.[149] To an oven-dried schlenk tube charged with stirrer bar was added $CoBr_2$(py-imine) (45 mg, 0.10 mmol, 0.05 equiv.), zinc iodide (64 mg, 0.20 mmol, 0.1 equiv.), zinc powder (13 mg, 0.20 mmol, 0.1 equiv.) and iron powder (11 mg, 0.20 mmol, 0.1 equiv.). The schlenk tube was sealed with a suba-seal, then evacuated/refilled with N_2 (×3) before adding anhydrous CH_2Cl_2 (1 mL) followed by isoprene (136 mg, 2.00 mmol, 1.0 equiv.) and phenyl acetylene (204 mg, 2.00 mmol, 1.0 equiv.). The resulting suspension was stirred at RT for 19 h before being filtered over a small amount of silica gel (eluent: Et_2O) and the solvent removed *in vacuo*. The residue was taken up in toluene (10 mL), and the crude product oxidised with DDQ (545 mg, 2.40 mmol, 1.2 equiv.). After 2h at RT the solution was diluted with Et_2O and washed with an aqueous sodium hydroxide (10%)/sodium thiosulphate (10%) solution. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (99:1)) afforded the *meta*- and *para*-products **323** in a ratio of 83:17 respectively as a colourless oil (30 mg, 0.18 mmol, 9%); **^{1}H NMR** Mixture of *meta*- and *para*-products 1H:0.2H respectively (400 MHz, $CDCl_3$) δ_H 7.58 (2.4H, d, *J* = 8.0 Hz, 2 x ArC*H* $_{meta\ \mathrm{and}\ para}$), 7.49 (0.4H, d, *J* = 7.5 Hz, 2 x ArC*H* $_{para}$), 7.51 – 7.37 (4.4H, m, 4 x ArC*H* $_{meta}$ and 2 x

ArCH_{para}), 7.33 (2.2H, t, J = 7.5 Hz, 2 x ArCH_{meta} and ArCH_{para}), 7.25 (0.4H, d, J = 7.0 Hz, ArCH_{para}), 7.17 (1H, d, J = 7.5 Hz, ArCH_{meta}), 2.42 (3H, s, C$H_{3\ meta}$), 2.40 (0.6H, s, C$H_{3\ para}$); *meta:para* ratio determined by integration of the ^{1}H NMR signals for CH_3:2.42 and 2.40 ppm. Data in accordance with literature values.[224]

4-Methyl-1,1'-biphenyl, *para*-323



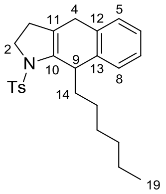
***meta*-323** : ***para*-323**

5 : 95

The procedure of Hilt *et al.* was used for this reaction.[149] To an oven-dried schlenk tube charged with stirrer bar was added CoBr$_2$(dppe) (62 mg, 0.10 mmol, 0.05 equiv.), zinc iodide (64 mg, 0.20 mmol, 0.1 equiv.) and zinc powder (13 mg, 0.20 mmol, 0.1 equiv.). The schlenk tube was sealed with a suba-seal, then evacuated/refilled with N$_2$ (× 3) before adding anhydrous CH$_2$Cl$_2$ (1 mL) followed by isoprene (136 mg, 2.00 mmol, 1.0 equiv.) and phenyl acetylene (204 mg, 2.00 mmol, 1.0 equiv.). The resulting suspension was stirred at RT for 19 h before being filtered over a small amount of silica gel (eluent: Et$_2$O) and the solvent removed *in vacuo*. The residue was taken up in toluene (10 mL), and the crude product oxidised with DDQ (545 mg, 2.40 mmol, 1.2 equiv.). After 2h at RT the solution was diluted with Et$_2$O and washed with an aqueous sodium hydroxide (10%)/sodium thiosulphate (10%) solution. The combined organic layers were dried (MgSO$_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (99:1)) afforded the *meta*- and *para*-products **323** in a ratio of 5:95 respectively as colourless crystals (142 mg, 0.84 mmol, 42%); **mpt** <26 °C; **^{1}H NMR** Mixture of *meta*- and *para*-products 0.05H:1H respectively (400 MHz, CDCl$_3$) δ_H 7.58 (2.1H, dd, J = 8.0, 1.0 Hz, 2 x ArC$H_{meta\ \mathrm{and}\ para}$), 7.50 (2H, d, J = 7.0 Hz, 2 x ArCH_{para}), 7.51 – 7.36 (2.2H, m, 4 x ArCH_{meta} and 2 x ArCH_{para}), 7.32 (1.1H, t, J = 7.5 Hz, 2 x ArCH_{meta} and ArCH_{para}), 7.25 (2H, d, J = 7.0 Hz, ArCH_{para}), 7.17 (0.05H, d, J = 7.5 Hz, ArCH_{meta}), 2.42

(0.15H, s, C$H_{3\ meta}$), 2.40 (3H, s, C$H_{3\ para}$); *meta:para* ratio determined by integration of the ^{1}H NMR signals for CH_3:2.42 and 2.40 ppm. Data in accordance with literature values.[224]

9-Hexyl-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole, 327a

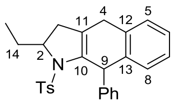


Method A: Prepared by General Procedure R Method A using dienamide **269a** (30 mg, 0.089 mmol) and 2-(trimethylsilyl)phenyltriflate (44 µL, 0.18 mmol) with heating for 2 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded **327a** as a yellow oil (23 mg, 0.056 mmol, 63%).

Method B: Prepared by General Procedure R Method B using dienamide **269a** (60 mg, 0.18 mmol) and 2-(trimethylsilyl)phenyltriflate (87 µL, 0.36 mmol) with stirring at RT for 19 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded **327a** as a pale yellow oil (60 mg, 0.146 mmol, 81%).

R$_f$ 0.24 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3288, 3067, 2955, 2928, 2857, 1706, 1598, 1493, 1456, 1351, 1163, 1091; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.59 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.30 (1H, dd, *J* = 7.5, 1.5 Hz, Ar*H*), 7.24 (1H, dd, *J* = 7.0, 1.5 Hz, Ar*H*), 7.20 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.19 (1H, ddd, *J* = 14.5, 7.5, 1.5 Hz, Ar*H*), 7.10 (1H, d, *J* = 7.5 Hz, Ar*H*), 4.35 (1H, d, *J* = 3.5 Hz, H9), 3.84 (1H, ddd, *J* = 12.0, 10.0, 9.0 Hz, H2), 3.72 (1H, ddd, *J* = 12.0, 9.5, 5.0 Hz, H2'), 3.46 (1H, dd, *J* = 21.5, 4.0 Hz, H4), 3.16 (1H, dd, *J* = 21.5, 3.5 Hz, H4'), 2.36 (3H, s, TsCH_3), 2.26-2.12 (2H, m, H3 and H14), 2.10-1.90 (1H, m, H3'), 1.83 (1H, ddt, *J* = 13.5, 11.0, 4.5 Hz, H14'), 1.31 (1H, d, *J* = 5.0 Hz, H15), 1.24-1.06 (6H, m, H16-H18), 0.89 (1H, ddd, *J* = 10.5, 8.0, 6.6 Hz, H15'), 0.82 (3H, t, *J* = 7.0 Hz, H19); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_c 143.6, 138.2, 137.3, 133.9, 133.6, 129.7, 128.9, 128.2, 127.7, 126.4, 126.1, 123.7, 49.8, 39.3, 35.8, 32.0, 30.9, 30.7, 29.6, 24.4, 22.8, 21.7, 14.2; **HRMS** (ES$^+$) calc. for $C_{25}H_{31}NNaO_2S$ $[M+Na]^+$ 432.1968, found 432.1962.

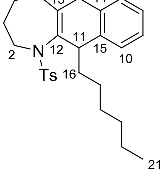
2-Ethyl-9-phenyl-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole, 327b



Prepared by General Procedure R Method A using dienamide **232d** (8 mg, 0.0226 mmol) and 2-(trimethylsilyl)phenyltriflate (11 µL, 0.0453 mmol) with heating for 1.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded **327b** as a pale yellow oil (7 mg, 0.0163 mmol, 72%); **R$_f$** 0.52 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3061, 3028, 2966, 2931, 2876, 1699, 1598, 1494, 1453, 1348, 1165, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.23 (4H, d, *J* = 4.5 Hz, Ar*H*), 7.21-7.13 (7H, m, Ar*H* and Ts*H*), 5.49 (1H, dd, *J* = 7.5, 4.0 Hz, H9), 3.85 (1H, td, *J* = 8.0, 1.5 Hz, H2), 3.64 (1H, dd, *J* = 21.5, 4.5 Hz, H4), 3.31 (1H, dd, *J* = 21.5, 4.0 Hz, H4'), 2.38 (3H, s, TsC*H*$_3$), 2.04-1.97 (1H, m, H3), 1.70 (1H, d, *J* = 16.0 Hz, H3'), 1.31-1.20 (2H, m, H14), 0.63 (3H, t, *J* = 7.5 Hz, H15); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.4, 143.5, 137.9, 136.8, 134.7, 132.4, 130.6, 129.5, 128.8, 128.5, 128.3, 127.6, 126.9, 126.4, 126.4, 124.6, 63.2, 45.7, 36.3, 30.9, 28.7, 21.7, 9.2; **HRMS** (ES$^+$) calc. for $C_{27}H_{27}NNaO_2S$ $[M+Na]^+$ 452.1655, found 452.1638.

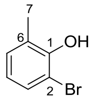
N.B. The stereochemistry of this product could not be definitively assigned by NMR spectroscopic analysis including nOe experiments.

11-Hexyl-1-tosyl-2,3,4,5,6,11-hexahydro-1*H*-naphtho[2,3-*b*]azepane, 327c



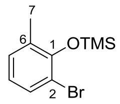
Prepared by General Procedure R Method A using dienamide **269n** (30 mg, 0.0829 mmol) and 2-(trimethylsilyl)phenyltriflate (40 μL, 0.165 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded **327c** as a colourless oil (31 mg, 0.0708 mmol, 85%); **R_f** 0.56 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2928, 2856, 1598, 1494, 1454, 1341, 1156, 1091, 1026, 909; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.25 (2H, d, *J* = 7.0 Hz, Ts*H*), 7.20-7.05 (4H, m, Ar*H*), 4.20 (1H, d, *J* = 14.5 Hz, H2), 3.97 (1H, br s, H11), 3.65 (1H, dd, *J* = 21.0, 4.0 Hz, H6), 3.21 (1H, dd, *J* = 21.0, 2.0 Hz, H6'), 2.88 (1H, t, *J* = 12. 5 Hz, H2'), 2.42 (3H, s, TsCH_3), 1.98 (1H, t, *J* = 13.5 Hz, H5), 1.84-1.75 (2H, m, H5' and H3), 1.73-1.61 (4H, m, H3', H4 and H16), 1.61-1.54 (1H, m, H16'), 1.31-1.07 (7H, m, H17 and H18-20), 0.91-0.86 (1H, m, H17'), 0.81 (3H, t, *J* = 7.0 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 143.1, 139.1, 138.6, 137.1, 135.2, 134.0, 129.6, 128.1, 127.4, 127.3, 126.1, 125.9, 50.7, 44.5, 37.8, 35.0, 33.2, 31.9, 29.8, 29.6, 25.0, 23.9, 22.7, 21.7, 14.2; **HRMS** (ES^+) calc. for $C_{27}H_{35}NNaO_2S$ $[M+Na]^+$ 460.2281, found 460.2264.

2-Bromo-6-methylphenol, 329



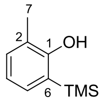
The procedure of Velder *et al.* was used for this preparation.[158] In a flame dried flask equipped with Soxhlet apparatus and flushed with Ar was added *o*-creosol (9.9 g, 91.5 mmol, 1.0 equiv.) and diisopropylamine (1.3 mL, 9.15 mmol, 0.1 equiv.) in CH_2Cl_2 (250 mL). The thimble was filled with *N*-bromosuccinimide (16.28 g, 177.98, 1.0 equiv.) and the system heated to reflux for 24 h, during which time the NBS was slowly consumed. The reaction was cooled to RT, treated with 2M sulphuric acid (250 mL) and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (× 3) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (40:1)) afforded the desired brominated phenol **329** as a colourless oil (11.30 g, 60.39 mmol, 66%); **R$_f$** 0.55 (petroleum ether / EtOAc (20:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (1H, d, *J* = 7.5 Hz, H3), 7.07 (1H, d, *J* = 7.5 Hz, H5), 6.72 (1H, t, *J* = 8.0 Hz, H4), 5.57 (1H, s, OH), 2.31 (3H, s, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 150.5, 130.5, 129.5, 126.1, 121.3, 110.3, 16.8. Data in accordance with literature values.[158]

(2-Bromo-6-methylphenoxy)trimethylsilane, 330



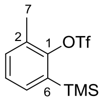
The procedure of Ikawa *et al.* was used for this preparation.[159,161] To an oven-dried 2-neck rbf fitted with condenser and suba-seal, was added phenol **329** (1.00 g, 5.35 mmol, 1.0 equiv.). The system was evacuated and refilled with Ar (×3) before the addition of anhydrous THF (5.35 mL) and HMDS (3.34 mL, 16.04 mmol, 3.0 equiv.) *via* syringe. The reaction mixture was refluxed for 19 h before being cooled to RT, concentrated *in vacuo* and azeotroped with toluene to afford the silylated product **330** as a yellow oil (1.25 g, 4.81 mmol, 90%) which was used without further purification; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.35 (1H, ddd, *J* = 8.0, 1.5, 0.5 Hz, H3), 7.07 (1H, ddd, *J* = 7.5, 1.5, 0.5 Hz, H5), 6.75 (1H, t, *J* = 7.5 Hz, H4), 2.25 (3H, s, H7), 0.33 (9H, s, $Si(CH_3)_3$).

2-Methyl-6-(trimethylsilyl)phenol, 331



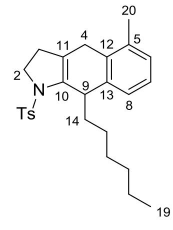
The procedure of Ikawa *et al.* was used for this preparation.[160] To an oven-dried rbf containing a stirrer bar under Ar, was added the silylated starting material **330** (0.5 g, 1.92 mmol, 1.0 equiv.) and anhydrous Et_2O (11 mL). The solution was cooled to −78 °C and *n*-BuLi (0.85 mL, 2.12 mmol, 1.1 equiv., 2.5 M in THF) was added dropwise before allowing the reaction mixture to slowly warm to RT, and then stirred for a further 18 h. The reaction was quenched with sat. *aq.* NH_4Cl and the organic layer separated, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford phenol **331** as a colourless oil (278 mg, 1.53 mmol, 80%) which was used without further purification; **^{1}H NMR** (200 MHz, CDCl$_3$) δ_H 7.27-7.19 (1H, m, H5), 7.14 (1H, ddd, *J* = 7.5, 1.5, 0.5 Hz, H3), 6.86 (1H, t, *J* = 7.5 Hz, H4), 4.75 (1H, s, O*H*), 2.24 (3H, s, H7), 0.32 (9H, s, Si(C*H*$_3$)$_3$).

2-Methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate, 326b



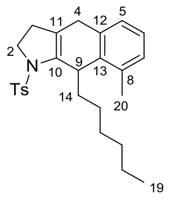
The procedure of Ikawa *et al.* was used for this preparation.[160] To an oven-dried rbf containing a stirrer bar under Ar, was added the phenol **331** (278 mg, 1.54 mmol, 1.0 equiv.) and anhydrous Et$_2$O (5.6 mL).The solution was cooled to −78 °C before the dropwise addition of *n*-BuLi (0.68 mL, 1.69 mmol, 1.1 equiv., 2.5 M in THF) and the mixture was warmed to RT and stirred for 1 h before being re-cooled to −78 °C. Trifluoroacetic anhydride (0.29 mL, 1.69 mmol, 1.1 equiv.) was slowly added dropwise and after complete addition the reaction was warmed to RT and stirred for 3 h. The reaction mixture was quenched with sat. *aq.* NaHCO$_3$, extracted with Et$_2$O (× 3) and the combined organic layers washed with brine, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether) afforded the desired benzyne precursor **326b** as a colourless oil (365 mg, 1.15 mmol, 75%); **R$_f$** 0.27 (petroleum ether); **IR** (thin film, ν_{max} / cm^{-1}) 1401, 1252, 1212, 1141, 1105, 1062, 875, 844; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.41 (1H, dd, *J* = 7.0, 2.5 Hz, H5), 7.33-7.25 (2H, m, H3 and H4), 2.39 (3H, s, H7), 0.39 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_c 151.4, 134.9, 134.7, 133.9, 131.5, 128.1, 118.8 (qu, $J_{C\text{-}F}$ 319.7 Hz), 17.5, 0.12; **^{19}F NMR** (377 MHz, CDCl$_3$) δ_F −73.37; **HRMS** (FI$^+$) calc. for $C_{11}H_{15}F_3O_3SSi$ [M]$^+$ 312.0463, found 312.0474.

9-Hexyl-5-methyl-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole 327d and **9-hexyl-8-methyl-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole, 327e**



327d

+



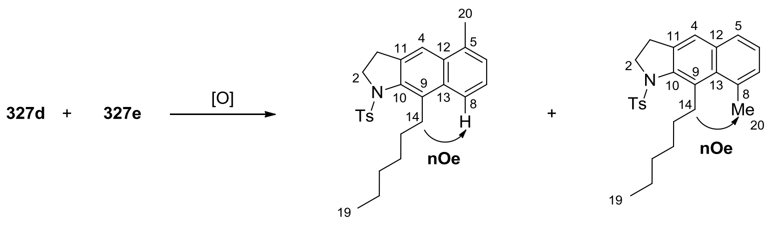
327e

Prepared by General Procedure R Method B using dienamide **269a** (30 mg, 0.089 mmol) and benzyne precursor **326b** (56 mg, 0.18 mmol) with stirring at RT for 21 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (20:1)) afforded **327d** and **327e** in a 2:1 ratio as a colourless oil (24.9 mg, 0.058 mmol, 65%). Due to the product being susceptible to aerobic oxidation on standing, or partial decomposition, this mixture of regioisomers was oxidised to the indoline for full characterisation. The assignment of the major and minor products as **327d** and **327e** respectively is made on the basis of nOe experiments on the oxidised compounds **[O]-327d** and **[O]-327e** (see data below). Ratios determined by integration of the ^{1}H NMR signals for H9 in **327d** (4.93 ppm) and **327e** (5.16 ppm).

R_f 0.30 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (200 MHz, C_6D_6) δ_H *Mixture of regioisomers; for distinguishable resonances **d** or **e** stated;* 7.84 (2H, d, *J* = 8.5 Hz, TsH_e), 7.79 (2H, d, *J* = 8.5 Hz, TsH_d), 7.24 (1H, d, *J* = 7.0 Hz, Ar*H*), 7.18 (1H, t, *J* = 2.5 Hz, Ar*H*), 7.14 (1H, s, Ar*H*), 7.05 (2H, d, *J* = 6.5 Hz, Ar*H*), 7.01-6.90 (1H, m, Ar*H*), 6.70 (4H, d, *J* = 8.0 Hz, TsH_{d+e}), 5.16 (1H, br s, H9_e), 4.93 (1H, br s, H9_d), 3.92-3.69 (4H, m, H2_{d+e}), 3.37 (1H, dd, *J* = 21.0, 1.5 Hz, H4_e), 3.07 (1H, dd, *J* = 21.0, 3.0 Hz, H4_d), 2.94-2.61 (2H, m, H4’$_{d+e}$), 2.58 (3H, s, H20_d), 2.40-2.07 (4H, m, H14_{d+e}), 2.04 (3H, s, H20_d), 1.85 (3H, s, TsMe$_d$), 1.92-1.72 (4H, m, H3_{d+e}), 1.82 (3H, s, TsMe$_d$), 1.53-1.21 (16H, m, H15-18_{d+e}), 1.08-0.86 (6H, m, H15-18_{d+e}).

N.B. Mixture of regioisomers oxidised to benzoindolines to enable characterisation and identification:

9-Hexyl-5-methyl-1-tosyl-2,3-dihydro-1*H*-benzo[*f*]indole, [O]-327d and **9-hexyl-8-methyl-1-tosyl-2,3-dihydro-1*H*-benzo[*f*]indole, [O]-327e**

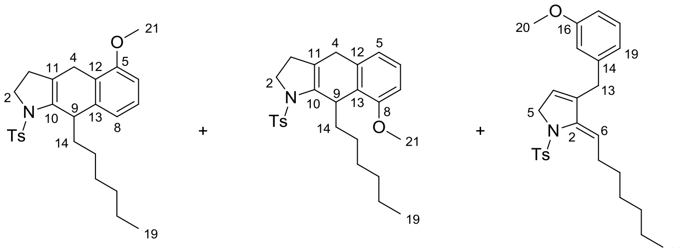


[O]-327d (major)   **[O]-327e** (minor)

To the mixture of **327d** and **327e** (15 mg, 0.0354 mmol, 1.0 equiv.) in anhydrous toluene (0.6 mL) was added DDQ (17 mg, 0.078 mmol, 2.2 equiv.) and the resulting mixture stirred at RT for 24 h. Reaction mixture diluted with EtOAc and washed with sat. *aq*. $NaHCO_3$ and sat. *aq.* $Na_2S_2O_3$. The organic layer was subsequently dried (MgSO4) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1) → (10:1)) afforded **[O]-327d** and **[O]-327e** in a 2.8:1 ratio as a colourless oil (8.5 mg, 0.0202 mmol, 57%). Ratios determined by integration of the ^{1}H NMR signals for H14 in **[O]-327d** (3.54 ppm) and **[O]-327e** (3.68 ppm). Regioisomers assigned by nOe enhancements from irradiation of the same protons, as indicated.

R$_f$ 0.30 (petroleum ether – EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3057, 2957, 2927, 2857, 1597, 1466, 1440, 1419, 1356, 1265, 1163, 1090, 909; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H *Mixture of regioisomers; for distinguishable resonances* ***d*** *or* ***e*** *stated;* 8.00 (1H, d, *J* = 8.5 Hz, H8$_d$), 7.82 (1H, dd, *J* = 8.0, 6.5 Hz, Ar*H*), 7.55 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.51 (1H, s, H4$_d$), 7.40 (1H, dd, *J* = 8.5, 7.0 Hz, Ar*H*), 7.37 (4H, d, *J* = 12.5 Hz, Ts*H*$_{d+e}$), 7.32-7.27 (3H, m, Ar*H*), 7.11 (4H, d, *J* = 8.0 Hz, Ts*H*$_{d+e}$), 4.01 (4H, t, *J* = 7.0 Hz, H2$_{d+e}$), 3.68 (2H, t, *J* = 7.5 Hz, H14$_e$), 3.54 (2H, t, *J* = 8.0 Hz, H14$_d$), 2.92 (3H, s, H20$_e$), 2.62 (3H, s, H20$_d$), 2.38 (3H, s, TsMe$_d$), 2.36 (3H, s, TsMe$_e$), 2.28 (2H, t, *J* = 7.0 Hz, H3$_d$), 2.24 (2H, t, *J* = 6.5 Hz, H3$_e$), 1.65 (2H, dt, *J* = 15.5, 7.5 Hz, H15$_d$), 1.44-1.15 (14 H, m, H15$_e$ and H16-18$_{d+e}$), 0.87 (3H, t, *J* = 7.0 Hz, H19$_d$), 0.81 (3H, t, *J* = 7.0 Hz, H19$_e$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C *Mixture of regioisomers; for distinguishable resonances (m) represents the minor regioisomer;* 144.1, 141.3 (m), 138.9, 136.0, 135.9 (m), 135.3, 135.2 (m), 135.1 (m), 135.0 (m), 134.9 (m), 134.4, 133.7, 132.8 (m), 132.6, 132.5, 129.9 (m), 129.6, 129.5 (m), 128.0 (m), 127.9, 127.8 (m), 127.5 (m), 126.6, 125.2, 123.9, 122.3 (m), 117.7, 53.1, 52.9 (m), 32.7 (m), 32.2 (m), 31.9, 31.8 (m), 30.8, 29.7, 29.3, 29.3, 29.2 (m), 28.9 (m), 25.0 (m), 22.9, 22.8 (m), 21.8, 21.7 (m), 20.1, 14.3, 14.2 (m); **HRMS** (ES$^+$) calc. for $C_{26}H_{31}NNaO_2S$ [M+Na]$^+$ 444.1968, found 444.1951.

9-Hexyl-5-methoxy-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole, 327g and **9-hexyl-8-methoxy-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole, 327f** and **(*Z*)-2-heptylidene-3-(3-methoxybenzyl)-1-tosyl-2,5-dihydro-1H-pyrrole, 328**



327g
(minor)

327f
(major)

328

Method A: Prepared by General Procedure R Method A using dienamide **269a** (30 mg, 0.089 mmol) and 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (59 mg, 0.18 mmol) with heating for 2 h. ^{1}H NMR (200 MHz, $CDCl_3$) analysis of the crude mixture showed three products formed: **327g:327f:328** (assigned as the product of an ene reaction with H4 in **269a** by analysis of COSY, HSQC and HMBC of mixture of products) in a 1:4.4:1.7 ratio. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the mixture of the three products **327g:327f:328** in a 1:3.7:1.4 ratio, as a colourless oil (28 mg, 0.064 mmol, 71%).

Method B: Prepared by General Procedure R Method B using dienamide **269a** (30 mg, 0.089 mmol) and 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (59 mg, 0.18 mmol) with stirring at RT for 23 h. ^{1}H NMR (200 MHz, $CDCl_3$) analysis of the crude mixture showed three products formed – **327g:327f:328** (assigned as the product of an ene reaction with H4 in **269a** by analysis of COSY, HSQC and HMBC of mixture of products) in a 1:3.1:1.2 ratio.

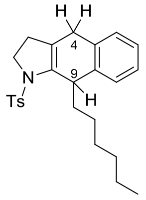
Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the mixture of three products – **327g:327f:328** in a 1:2.7:1 ratio, as a colourless oil (30 mg, 0.068 mmol, 76%).

Ratios determined by integration of the ^{1}H NMR signals for H9 in **327g** (4.36 ppm) and **327f** (4.67 ppm) and for H4 in **328** (5.10 ppm).

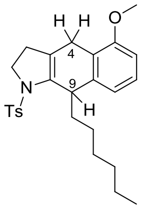
Data for **328** (as mixture with **327g** and **327f** – see data below for isolated Diels-Alder products): $\mathbf{R_f}$ 0.30 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2953, 2926, 2855, 1598, 1583, 1470, 1351, 1255, 1163; $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ_H 7.56 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.18 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.12 (1H, t, *J* = 8.0 Hz, H18), 6.72 (1H, d, *J* = 8.0 Hz, H17), 6.45 (1H, d, *J* = 7.5 Hz, H19), 6.43 (1H, s, *J* = 1.5 Hz, H15), 5.24 (1H, t, *J* = 7.0 Hz, H6), 5.10 (1H, br s, H4), 4.15 (2H, br d, *J* = 1.0 Hz, H5), 3.76 (3H, s, H20), 3.23 (2H, d, *J* = 1.5 Hz, H13), 2.55 (2H, dd, *J* = 14.5, 7.5 Hz, H7), 2.42 (3H, s, TsCH_3), 1.42 (2H, dt, *J* = 14.5, 7.0 Hz, H8), 1.37-1.04 (6H, m, H9-11), 0.89 (3H, t, *J* = 7.0 Hz, H12); $^{\mathbf{13}}$**C NMR** (126 MHz, $CDCl_3$) δ_C (for distinguishable resonances compared to isolated **327g** and **327f** below) 159.7, 143.7, 141.9, 141.4, 139.6, 129.4, 129.3, 127.8, 123.6, 121.4, 117.9, 115.1, 111.4, 56.1, 55.2, 33.4, 31.9, 30.2, 29.5, 29.2; **HRMS** (ES$^+$) calc. for $C_{26}H_{33}NNaO_3S$ [M+Na]$^+$ 462.2073, found 462.2074.

Repurification of product from Method B *via* column chromatography on a longer column (petroleum ether → petroleum ether / EtOAc (20:1)) allowed isolation of **327g** and **327f** in a 1:1.4 ratio respectively as a colourless oil (4.5 mg); $\mathbf{R_f}$ 0.30 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2953, 2927, 2855, 1598, 1583, 1470, 1351, 1256, 1163, 1104, 1091; $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ_H *Mixture of regioisomers; for distinguishable resonances **g** or **f** stated;* 7.61 (4H, d, *J* = 8.0 Hz, TsH$_{g+f}$), 7.22 (1H, dd, *J* = 10.5, 5.0 Hz, Ar*H*), 7.19 (4H, d, *J* = 8.0 Hz, TsH_{g+f}), 7.15 (1H, t, *J* = 8.0 Hz, Ar*H*), 6.93 (1H, d, *J* = 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.72 (2H, dd, *J* = 7.5, 4.0 Hz, 2 x Ar*H*), 4.67 (1H, d, *J* = 3.0 Hz, H9$_f$), 4.36 (1H, dd, *J* = 7.0, 3.5 Hz, H9$_g$), 3.92-3.78 (2H, m, H2$_{f+g}$), 3.88 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.77-3.65 (2H, m, H2'$_{g+f}$), 3.46 (1H, dd, *J* = 21.0, 4.0 Hz, H4$_f$), 3.18 (2H, d, *J* = 4.0 Hz, H4$_g$), 3.14 (1H, dd, J = 21.5 Hz, 2.5 Hz, H4’$_f$), 2.38 (3H, s, TsCH_{3f}), 2.36 (3H, s, TsC$H_{3\,g}$), 2.29-2.16 (3H, m, H3$_{g+f}$ and H14$_g$), 2.14-1.97 (3H, m, H3’$_{g+f}$ and H14$_f$), 1.91 (1H, ddt, J = 13.5, 11.5, 4.5 Hz, H14’$_f$), 1.81 (1H, ddt, J = 13.5, 11.5, 4.5 Hz, H14’$_g$), 1.25-1.04 (14H, m, H15$_{g+f}$ and H16-18$_{g+f}$), 0.91-0.85 (2 H, m, H15’$_{g+f}$), 0.83 (6H, t, J = 7.0 Hz, H19$_{g+f}$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 157.3, 156.6, 143.5, 143.4, 139.7, 138.3, 136.6, 135.7, 134.0, 129.7, 129.6, 127.7, 127.6, 127.3, 127.0, 126.7, 123.9, 122.8, 122.7, 121.1, 120.4, 108.1, 107.1, 55.4, 55.3, 49.9, 49.8, 39.2 (a), 35.8 (a), 34.0, 33.7 (b), 32.1, 32.0, 31.3 (b), 30.9, 30.5, 29.7, 29.6, 25.7 (a), 24.7, 24.2, 22.8, 21.7, 21.6, 14.3, 14.2; **HRMS** (ES$^+$) calc. for $C_{26}H_{33}NNaO_3S$ $[M+Na]^+$ 462.2073, found 462.2074.

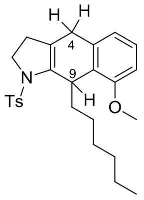
The assignment of the regiochemistry of the products is proposed based on the following ^{1}H NMR analogies to H4/H4’ and H9 in **327a**:



327a



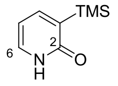
327g
(minor)



327f
(major)

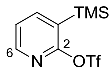
	H4 and H4’	H9	Deduction
327a	**3.46** (1H, dd, J = 21.5, 4.0 Hz) **3.16** (1H, dd, J = 21.5, 3.5 Hz)	**4.35** (1H, d, J = 3.5 Hz)	
327g	***3.18*** (2H, d, J = 4.0 Hz)	**4.36** (1H, dd, J = 7.0, 3.5 Hz)	OMe near H4/H4’ perturbs shift
327f	**3.46** (1H, dd, J = 21.0, 4.0 Hz) **3.14** (1H, dd, J = 21.5 Hz, 2.5 Hz)	***4.67*** (1H, d, J = 3.0 Hz)	OMe near H9; perturbs shift

3-(Trimethylsilyl)pyridin-2(1*H*)-one, 333



The procedure of Caroll *et al.* was used for this preparation.[225] A solution of LDA (1 M in THF) was made by the dropwise addition of *n*-BuLi (20 mL, 2.5 M in THF) to anhydrous diisopropylamine (7 mL) in anhydrous THF (23 mL) at 0 °C with stirring for 15 min. The freshly made LDA (47 mL, 46.27 mmol, 2.2 equiv.) was added dropwise over 15 min to a solution of 2-hydroxypyridine (2.00 g, 21.03 mmol, 1.0 equiv.) in anhydrous THF (50 mL) under Ar at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and then for 1 h whilst warming to RT, at which point it was re-cooled to 0 °C before the dropwise addition of TMSCl (3 mL, 23.13 mmol, 1.1 equiv.) and subsequent stirring for a further 18 h at RT. The reaction mixture was concentrated *in vacuo* before the addition of EtOAc. The precipitate was removed by vacuum filtration and the eluent concentrated *in vacuo*. Purification *via* column chromatography (EtOAc) afforded the desired product **333** as a yellow oil (2.39 g, 14.30 mmol, 68%); **R_f** 0.41 (EtOAc); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.54 (1H, dd, *J* = 6.5, 2.0 Hz, H6), 7.34 (1H, dd, *J* = 6.5, 2.0 Hz, H4), 6.23 (1H, t, *J* = 6.5 Hz, H5), 0.27 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 167.8, 147.5, 135.7, 131.8, 106.7, −1.69. Data in accordance with literature values.[225]

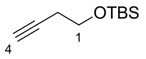
3-(Trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate,326d



The procedure of Caroll *et al.* was used for this preparation.[225] A solution of **333** (2.39 g, 14.28 mmol, 1.0 equiv.) in pyridine (14 mL), under Ar, was cooled to 0 °C before the dropwise addition of trifluoroacetic anhydride (2.64 mL, 15.71 mmol, 1.1 equiv.). The resulting reaction mixture was stirred at RT for 16 h before the solvent was removed *in vacuo*, azeotroping with toluene. The crude residue was dissolved in Et$_2$O and washed with water, and the aqueous layer extracted with Et$_2$O (× 3). The combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1) afforded the pyridyne precursor **326d** as a pale yellow oil (3.15 g, 10.42 mmol, 73%); **R_f** 0.35 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 8.32 (1H, dd, *J* = 4.5, 2.0 Hz, H6), 7.92 (1H, dd, *J* = 7.0, 2.0 Hz, H4), 7.30 (1H, dd, *J* = 7.0, 5.0 Hz, H5), 0.37 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 161.0, 148.9, 147.1, 125.3, 123.3, 118.6 (qu, $J_{C\text{-}F}$ =

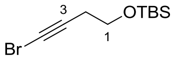
320.6 Hz), 113.8, −1.51. Data in accordance with literature values.[225]

(But-3-yn-1-yloxy)(tert-butyl)dimethylsilane, 335



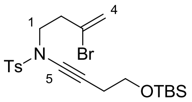
To a stirred solution of NaH (2.05 g, 51.36 mmol, 1.2 equiv., 60% weight in oil) in anhydrous THF (64 mL) under Ar, was added butyn-1-ol (3.00 g, 42.80 mmol, 1.0 equiv.) and the reaction stirred for 30 min. TBSCl (7.74 g, 51.36 mmol, 1. 2 equiv.) was added dropwise and on complete addition the reaction was quenched with sat. *aq.* K_2CO_3 solution. The reaction was diluted with water, extracted with Et_2O (× 3) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afford the silylated product **335** as a colourless oil (5.29 g, 46.96 mmol, 67%); **R$_f$** 0.78 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.74 (2H, t, *J* = 7.0 Hz, H1), 2.40 (2H, td, *J* = 7.0, 2.5 Hz, H2), 1.96 (1H, t, *J* = 2.5 Hz, H4), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.07 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 81.7, 69.4, 61.9, 26.0, 23.0, 18.5, −5.16. Data in accordance with literature values.[226]

((4-Bromobut-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane, 336



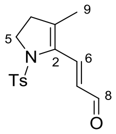
Prepared by General Procedure C Method B using alkyne **335** (2.00 g, 10.84 mmol) to afford bromoalkyne **336** as a pale yellow oil (2.85 g, 10.84 mmol, quant.); **R$_f$** 0.5 (petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.72 (2H, t, *J* = 7.0 Hz, H1), 2.41 (2H, t, *J* = 7.0 Hz, H2), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.07 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 77.7, 61.6, 39.2, 26.0, 24.2, 18.5, −5.17. Data in accordance with literature values.[227]

N-(3-Bromobut-3-en-1-yl)-N-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)-4-methylbenzene sulfonamide, 205n



Prepared by General Procedure E using sulfonamide **213a** (200 mg, 0.66 mmol) and ((4-bromobut-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane **336** (259 mg, 0.99 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) gave bromoenynamide **205n** as a colourless oil (242 mg, 0.46 mmol, 70%); **R$_f$** 0.29 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2953, 2929, 2256, 1364, 1254, 1170, 1092, 910, 836; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.79 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.64 (1H, d, *J* = 1.0 Hz, H4), 5.43 (1H, d, *J* = 2.0 Hz, H4’), 3.67 (2H, t, *J* = 7.0 Hz, H8), 3.50 (2H, t, *J* = 7.0 Hz, H1), 2.72 (2H, t, *J* = 7.0 Hz, H2), 2.48 (2H, t, *J* = 7.0 Hz, H7), 2.45 (3H, s, TsC*H*$_3$), 0.87 (9H, s, SiC(C*H*$_3$)$_3$), 0.05 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 144.7, 134.7, 129.8, 129.1, 127.8, 119.8, 73.7, 68.1, 62.2, 49.8, 40.0, 26.0, 23.0, 21.8, 18.4, –5.16; **HRMS** (ES$^+$) calc. for $C_{21}H_{32}{}^{79}BrNNaO_3SSi$ [M+Na]$^+$ 508.0948, found 508.0933.

(*E*)-3-(3-Methyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)acrylaldehyde, 338



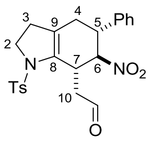
To a solution of bromoenynamide **205n** (90 mg, 0.184 mmol, 1.0 equiv.) in EtOH (4 mL, 0.045 M) was added Pd(PPh$_3$)$_4$ (5.3 mg, 0.0046 mmol, 2.5 mol%) and Cs$_2$CO$_3$ (90 mg, 0.277 mmol, 1.5 equiv.). The reaction mixture was heated to 80 °C for 30 min (until complete as analysed by TLC), before being allowed to cool to RT and filtered through a Celite® plug eluting with EtOAc. The filtrate was concentrated *in vacuo,* and taken up in THF (2 mL) before the addition of TBAF (0.24 mL, 0.24 mmol, 1.3 equiv., 1 M in THF). The reaction was stirred for 2 h at RT (until complete as analysed by TLC) before being diluted with EtOAc, filtered through a silica plug and concentrated *in vacuo* to obtain the exocyclic diene with a free alcohol.

Anhydrous DMSO (0.55 mL, 7.73 mmol, 42.0 equiv.) was added to the sulphur trioxide pyridine complex (237 mg, 1.49 mmol, 8.1 eq.) under Ar and the resulting suspension stirred at RT for 15 min. Anhydrous CH_2Cl_2 (3.4 mL) was added and the mixture cooled to 0 °C and stirred for a further 10 min. A solution of the crude diene formed from the reductive cyclisation/desilylation (53 mg, 0.184 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (3.4 mL) and DIPEA (0.66 mL, 3.77 mmol, 20.5 equiv.) was added and the resulting mixture stirred for 1 h between 0 °C and 10 °C. The reaction was hydrolysed with sat. *aq.* NH_4Cl solution and extracted with Et_2O, before the organic layer was sequentially washed with sat. *aq.* $NaHCO_3$ and sat. *aq.* NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (1:1)) afforded a mixture of the desired product **338** and the unoxidised product in a 0.4:1 ratio (30.8 mg, 57% 0.102 mmol).

The mixture was resubmitted to the oxidation conditions using sulphur trioxide pyridine complex (131 mg, 0.828 mmol), anhydrous DMSO (0.3 mL, 4.29 mmol), anhydrous CH_2Cl_2 (1.9 mL × 2) and DIPEA (0.36 mL, 2.10 mmol) with stirring at RT for 17 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (1:1)) afforded the desired product **338** as a yellow oil (8.6 mg, 0.028 mmol, 28%, overall yield over 4 steps: 16%).

R_f 0.35 (petroleum ether / EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2927, 1681, 1630, 1350, 1164, 1090, 910, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.69 (1H, d, *J* = 8.0 Hz, H8), 7.59 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (1H, d, *J* = 16.0 Hz, H6), 7.29 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.44 (1H, dd, *J* = 16.0, 7.5 Hz, H7), 3.76 (2H, t, *J* = 8.5 Hz, H5), 2.44 (3H, s, TsC*H*$_3$), 2.08 (2H, t, *J* = 8.5 Hz, H4), 1.83 (3H, s, H9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 194.0, 144.4, 142.3, 137.6, 133.9, 133.5, 132.0, 129.8, 128.0, 49.1, 35.5, 21.8, 15.1; **HRMS** (ES$^+$) calc. for $C_{15}H_{17}NNaO_3S$ $[M+Na]^+$ 314.0821, found 314.0833.

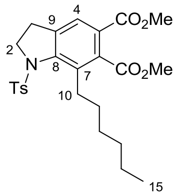
2-((5*R*,6*R*,7*S*)-6-Nitro-5-phenyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-indol-7-yl) acetaldehyde, 339



A modified procedure of Melchiorre *et al.* was used for this preparation without any precaution to air and moisture.[167] To a vial equipped with stirrer bar was added (*S*)-Jørgensen's catalyst (0.9 mg, 0.0027 mmol, 0.2 equiv.) and benzoic acid (0.4 mg, 0.0027 mmol, 0.2 equiv.) in toluene (0.1 mL). The resulting mixture was stirred at RT for 10 min before the addition of a solution of amidodiene **338** (6 mg, 0.021 mmol, 1.5 equiv.) and *trans*-β-nitrostyrene (2 mg, 0.014 mmol, 1.0 equiv.). The reaction was then stirred for 17 h at RT before being diluted with EtOAc, filtered through a silica plug and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (7:3)) afforded cycloadduct **339** as a colourless oil (2.9 mg, 0.0066 mmol, 48%) with residual benzoic acid; **R$_f$** 0.35 (petroleum ether / EtOAc (2:1)); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −39.7 (*c* = 0.14, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 2921, 1724, 1598, 1553, 1349, 1162, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.78 (1H, s, C*H*O), 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.39 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.35-7.27 (3H, m, Ph*H*), 7.25-7.20 (2H, m, Ph*H*), 5.19 (1H, dd, *J* = 11.5, 9.0 Hz, H6), 3.87 (1H, ddd, *J* = 13.0, 8.5, 1.5 Hz, H2), 3.67 (1H, s, *J* = 10.0 Hz, H7), 3.65-3.56 (2H, m, H2' and H10), 3.38 (1H, d, *J* = 5.5 Hz, H5), 2.75 (1H, dd, *J* = 19.0, 3.0 Hz, H10'), 2.48 (3H, s, TsCH_3), 2.47-2.40 (1H, m, H4), 2.22 (1H, dd, *J* = 18.5, 5.0 Hz, H4'), 1.91 (1H, dd, *J* = 16.0, 9.0 Hz, H3), 1.69-1.57 (1H, m, H3'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 199.9, 144.7, 138.6, 134.1, 133.2, 130.6, 129.9, 129.1, 128.2, 128.0, 127.6, 92.0, 50.9, 45.5, 42.0, 37.9, 31.8, 31.1, 21.9; **HRMS** (ES^+) calc. for $C_{23}H_{24}N_2NaO_5S$ $[M+Na]^+$ 463.1298, found 463.1296.

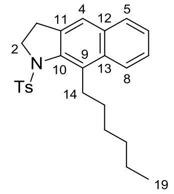
7.4.3. Oxidations

Dimethyl 7-hexyl-1-tosylindoline-5,6-dicarboxylate, 340



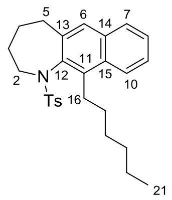
Prepared by General Procedure S using dimethyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydro-1*H*-indole-5,6-dicarboxylate **306a** (20 mg, 0.049 mmol) with stirring at 60 °C for 23 h. Purification *via* column chromatography (petroleum ether / EtOAc (4:1 → 1:1)) afforded **340** as a colourless oil (15.3 mg, 0.032 mmol, 76%); **R$_f$** 0.41 (petroleum ether / EtOAc (3:1 × 3 runs)); **IR** (thin film, ν_{max} / cm^{-1}) 2954, 2929, 2858, 1727, 1438, 1358, 1332, 1280, 1215, 1161, 910; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.53 (1H, s, H4), 7.41 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.18 (2H, d, *J* = 8.0 Hz, Ts*H*), 3.99 (2H, t, *J* = 7.5 Hz, H2), 3.95 (3H, s, CO$_2$C*H*$_3$), 3.86 (3H, s, CO$_2$C*H*$_3$), 3.13 (2H, t, *J* = 8.0 Hz, H10), 2.40 (3H, s, TsC*H*$_3$), 2.15 (2H, t, *J* = 7.0 Hz, H3), 1.53 (2H, dt, *J* = 15.5, 7.5 Hz, H11), 1.35-1.18 (6H, m, H12-14), 0.87 (3H, t, *J* 7.0 Hz, H15); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 169.4, 166.1, 146.0, 144.7, 139.3, 136.6, 135.9, 134.5, 129.8, 127.8, 127.1, 124.0, 53.3, 52.7 (2 × CO$_2$*C*H$_3$), 31.7, 30.3, 29.9, 29.5, 28.8, 22.7, 21.8, 14.2; **HRMS** (ES+) calc. for $C_{25}H_{31}NNaO_6S$ [M+Na]$^+$ 496.1764, found 496.1746.

9-Hexyl-1-tosyl-2,3-dihydro-1*H*-benzo[*f*]indole, 341



Prepared by General Procedure S using 9-hexyl-1-tosyl-2,3,4,9-tetrahydro-1*H*-benzo[*f*]indole **327a** (20 mg, 0.049 mmol) with stirring at RT for 23 h. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded **341** as a colourless oil (16.8 mg, 0.041 mmol, 84%); **R$_f$** 0.39 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2928, 2857, 1354, 1164, 1089, 909; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.12 (1H, d, *J* = 8.5 Hz, H5), 7.71 (1H, d, *J* = 8.0 Hz, H8), 7.50 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, H7), 7.44 (1H, t, *J* = 8.0 Hz, H6), 7.35 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.33 (1H, s, H4), 7.11 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.01 (2H, t, *J* = 7.0 Hz, H2), 3.54 (2H, t, *J* = 8.0 Hz, H14), 2.37 (3H, s, TsCH_3), 2.24 (2H, t, *J* = 7.0 Hz, H3), 1.67 (2H, dt, *J* = 15.5, 7.5 Hz, H15), 1.40 (2H, dt, *J* = 15.0, 7.0 Hz, H16), 1.35-1.25 (4H, m, H17/18), 0.87 (3H, t, *J* = 7.0 Hz, H19); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.1, 139.1, 136.2, 135.2, 133.5, 133.3, 132.5, 129.6, 128.3, 127.9, 125.6, 125.6, 125.5, 121.5, 53.0, 31.9, 30.7, 29.7, 29.1, 28.9, 22.9, 21.7, 14.3; **HRMS** (ES+) calc. for $C_{25}H_{29}NNaO_2S$ $[M+Na]^+$ 430.1811, found 430.1808.

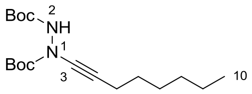
11-Hexyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-naphtho[2,3-*b*]azepane, 342



Prepared by General Procedure S using 11-hexyl-1-tosyl-2,3,4,5,6,11-hexahydro-1*H*-naphtho[2,3-*b*]azepane **327c** (25 mg, 0.057 mmol) with stirring at RT for 23 h. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded **342** as a colourless oil (17.2 mg, 0.0394 mmol, 69%); **R_f** 0.47 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2928, 2857, 1598, 1455, 1342, 1157, 908; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.02-7.97 (1H, m, H7), 7.76-7.71 (1H, m, H10), 7.63 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.45 (2H, t, *J* = 4.5 Hz, H8 and H9), 7.43 (1H, s, H6), 7.26 (2H, d, *J* = 8.0 Hz, Ts*H*), 4.42 (1H, dt, *J* = 14.5, 3.5 Hz, H2), 3.25 (1H, ddd, *J* = 14.0, 11.5, 5.0 Hz, H16), 3.13 (1H, ddd, *J* = 14.5, 12.0, 2.5 Hz, H2'), 3.02-2.94 (1H, m, H16'), 2.54 (1H, ddd, *J* = 14.0, 6.0, 3.0 Hz, H5), 2.49 (1H, d, *J* = 11.5 Hz, H5'), 2.44 (3H, s, TsCH_3), 1.97 (1H, ddt, *J* = 18.5, 11.5, 4.0 Hz, H3), 1.87 (1H, dd, *J* = 10.0, 4.5 Hz, H4), 1.69 (1H, tdd, *J* = 11.5, 8.0, 3.5 Hz, H17), 1.63-1.56 (1H, m, H3'), 1.43-1.33 (3H, m, H17' and H18), 1.33-1.21 (5H, m, H4' and H19-20), 0.89 (3H, t, *J* = 7.0 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 143.3, 141.0, 140.9, 139.1, 135.8, 133.8, 131.7, 129.7, 128.0, 127.7, 126.5, 126.3, 125.6, 125.5, 51.4, 34.1, 31.7, 31.4, 30.2, 28.9, 28.3, 26.9, 22.8, 21.7, 14.2; **HRMS** (ES+) calc. for $C_{27}H_{33}NNaO_2S$ [M+Na]$^+$ 458.2124, found 458.2123.

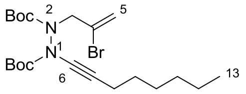
7.5. Palladium-Catalysed Cyclisations of Bromoenynhydrazides

Di-*tert*-butyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 344a



The procedure of Beveridge *et al.* was used for this preparation.[171] To an oven-dried rbf equipped with stirrer bar (evacuated and refilled with Ar × 3) was added oct-1-yne (0.44 mL, 3.00 mmol, 1.0 equiv.) in anhydrous THF (15 mL). The solution was cooled to −78 °C before the dropwise addition of *n*-BuLi (1.44 mL, 3.60 mmol, 1.2 equiv., 2.5 M in THF) over 1-2 min. The resultant reaction was stirred for 15 min at −78 °C before a solution of DBAD (1.03 g, 4.50 mmol, 1.5 equiv.) in anhydrous THF (9 mL) was added dropwise over 1-2 min, after which the cooling bath was removed and the reaction stirred for 30 min at RT. The reaction was quenched by the addition of sat. *aq.* NH_4Cl (15 mL) and then diluted with EtOAc and water. The organic layer was separated, dried ($MgSO_4$), filtered through a short silica plug topped with Celite® and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1 → 10:1) afforded ynhydrazide **344a** as a colourless oil (678 mg, 1.98 mmol, 66%); **R_f** 0.34 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 2.29 (2H, t, *J* = 7.0 Hz, H5), 1.49 (9H, s, CO_2*t*Bu), 1.48 (9H, s, CO_2*t*Bu), 1.43-1.32 (4H, m, H6 and H7), 1.32-1.22 (4H, m, H8 and H9), 0.88 (3H, t, *J* = 7.0 Hz, H10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 154.2, 153.4, 83.8, 82.2, 73.4, 71.2, 31.5, 28.9, 28.6, 28.3, 28.1, 22.7, 18.6, 14.2. Data in accordance with literature values.[171]

Di-*tert*-butyl 1-(2-bromoallyl)-2-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 346a



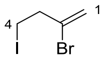
Method A: The procedure of Rasmussen was used for this preparation.[176] To a solution of ynhydrazide **344a** (30 mg, 0.088 mmol, 1.0 equiv.) in DMF (0.5 mL) was added Cs_2CO_3 (31 mg, 0.097 mmol, 1.1 equiv.) and 2,3-dibromopropene **209** (20 µL, 0.17 mmol, 1.5 equiv.) and the resulting mixture stirred at RT for 4 h. The reaction was diluted with water, extracted with CH_2Cl_2 (× 3) and the combined organic layers washed with water (× 3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded bromoenynhydrazide **346a** as a pale yellow oil (16.8 mg, 0.043 mmol, 49%).

Method B: The procedure of Tšupova *et al.* was used for this preparation.[177] To a vial containing K_2CO_3 (40 mg, 0.293 mmol, 2.0 equiv.), ground NaOH (20 mg, 0.511 mmol, 3.5 equiv.), TBAHS (5 mg, 0.0146 mmol, 0.1 equiv.) and TBAI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide **344a** (50 mg, 0.146 mmol, 1.0 equiv.) and 2,3-dibromopropene **209** (29 µL, 0.293 mmol, 2.0 equiv.) in toluene (0.15 mL, 1 $mL.mmol^{-1}$). The resulting mixture was stirred for 2 h at RT before being quenched with sat. *aq.* NH_4Cl, diluted with EtOAc and water and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded bromoenynhydrazide **346a** as a colourless oil (50 mg, 0.108 mmol, 74%).

Method C: To a vial containing TBAHS (5 mg, 0.0146 mmol, 0.1 equiv.) and TBAI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide **344a** (50 mg, 0.146 mmol, 1.0 equiv.) and 2,3-dibromopropene **209** (29 µL, 0.293 mmol, 2.0 equiv.) in toluene (1.5 mL, 10 $mL.mmol^{-1}$). To this was added *aq.* NaOH (1.5 mL, 10 $mL.mmol^{-1}$, 25% w/v) and the biphasic mixture rapidly stirred for 1 h or 26 h at RT before being quenched with sat. *aq.* NH_4Cl, diluted with EtOAc and water and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded bromoenynhydrazide **346a** as a colourless oil (48.3 mg, 0.105 mmol, 72% or 49.3 mg, 0.0106 mmol, 73%).

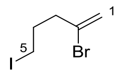
R$_f$ 0.65 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2959, 2933, 1730, 1369, 1301, 1256, 1150; **^{1}H NMR** *Broad signals due to rotameric forms of both carbonates* (500 MHz, CDCl$_3$) δ_H 5.97 (1H, d, *J* = 38.5 Hz, H5), 5.61 (1H, s, H5'), 4.65-4.34 (1H, m, H3), 4.26-4.00 (1H, m, H3'), 2.31 (2H, br s, H8), 1.63-1.44 (20H, m, H9 and 2 × CO$_2$*t*Bu), 1.44-1.33 (2H, m, H10), 1.34-1.22 (4H, m, H11 and H12), 0.89 (3H, t, *J* = 7.0 Hz, H13); **^{13}C NMR** *Broad signals due to rotameric forms of both carbonates* (126 MHz, CDCl$_3$) δ_C 152.9, 127.3, 120.2, 119.3, 83.8, 82.4, 72.3, 56.7, 31.5, 28.9, 28.6, 28.3, 28.1, 22.7, 18.6, 14.2; **HRMS** (ES+) calc. for $C_{21}H_{35}{}^{79}BrN_2NaO_4$ [M+Na]$^+$ 481.1672, found 481.1661.

2-Bromo-4-iodobut-1-ene, 352a



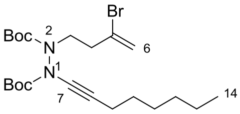
The procedure of Baldwin *et al.* was used for this preparation.[114] To a solution of alcohol **210** (1.00 g, 6.62 mmol, 1.0 equiv.) in Et$_2$O:MeCN (41 mL, 3:1) was added triphenylphosphine (1.91 g, 7.28 mmol, 1.1 equiv.) and imidazole (495 mg, 7.28 mmol, 1.1 equiv.). The resultant solution was cooled in an ice bath and iodine (1.85 g, 7.28 mmol, 1.1 equiv.) was added portionwise. After complete addition the reaction was stirred at RT for 1 h before being filtered under reduced pressure, the solid being thoroughly washed with cold Et$_2$O before the solvent was removed *in vacuo*. The crude mixture was redissolved in Et$_2$O and washed successively with 10% *aq.* Na$_2$S$_2$O$_3$ and brine before being dried (MgSO$_4$) and concentrated *in vacuo*. Petroleum ether was then added to the crude residue and the reaction filtered through a silica plug before concentrating the filtrate *in vacuo* to afford iodide **352a** as a colourless oil (1.15 g, 4.37 mmol, 66%); **R$_f$** 0.68 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 5.68 (1H, dt, *J* = 2.0, 1.0 Hz, H1), 5.56 (1H, d, *J* = 2.0 Hz, H1'), 3.33 (2H, t, *J* = 7.0 Hz, H4), 2.93 (2H, td, *J* = 7.0, 1.0 Hz, H3); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 131.9, 119.2, 45.1, 2.35. Data in accordance with literature values.[228]

2-Bromo-5-iodopent-1-ene, 352b



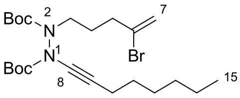
The procedure of Baldwin *et al.* was used for this preparation.[114] To a solution of alcohol **247** (1.00 g, 6.06 mmol, 1.0 equiv.) in Et_2O:MeCN (38 mL, 3:1) was added triphenylphosphine (1.75 g, 6.66 mmol, 1.1 equiv.) and imidazole (453 mg, 6.66 mmol, 1.1 equiv.). The resultant solution was cooled in an ice bath and iodine (1.69 g, 6.66 mmol, 1.1 equiv.) was added portionwise. After complete addition the reaction was stirred at RT for 1 h before being filtered under reduced pressure, the solid being thoroughly washed with cold Et_2O before the solvent was removed *in vacuo*. The crude mixture was redissolved in Et_2O and washed successively with 10% *aq.* $Na_2S_2O_3$ and brine before being dried ($MgSO_4$) and concentrated *in vacuo*. Petroleum ether was then added to the crude residue and the reaction filtered through a silica plug before concentrating the filtrate *in vacuo* to afford iodide **352b** as a colourless oil (1.29 g, 4.72 mmol, 78%); **R_f** 0.70 (petroleum ether / EtOAc (10:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.68 (1H, d, *J* = 1.0 Hz, H1), 5.47 (1H, d, *J* = 1.5 Hz, H1'), 3.19 (2H, t, *J* = 6.5 Hz, H5), 2.56 (2H, t, *J* = 7.0 Hz, H3), 2.06 (2H, qu, *J* = 7.0 Hz, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 132.2, 118.4, 41.7, 31.0, 5.2. Data in accordance with literature values.[114]

Di-*tert*-butyl 1-(3-bromobut-3-en-1-yl)-2-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 346b



The procedure of Tšupova *et al.* was used for this preparation.[177] To a vial containing K_2CO_3 (40 mg, 0.293 mmol, 2.0 equiv.), ground NaOH (20 mg, 0.511 mmol, 3.5 equiv.), TBAHS (5 mg, 0.0146 mmol, 0.1 equiv.) and TBAI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide **344a** (50 mg, 0.146 mmol, 1.0 equiv.) and tosylate **351a** (89 mg, 0.293 mmol, 2.0 equiv.) in toluene (0.15 mL, 1 mL.mmol^{-1}). The resulting mixture was stirred for 22 h at RT before being quenched with sat. *aq.* NH_4Cl, diluted with EtOAc and water and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded bromoenynhydrazide **346b** as a colourless oil (38 mg, 0.080 mmol, 55%); **R$_f$** 0.54 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2979, 2932, 1719, 1368, 1300, 1254, 1147; **^{1}H NMR** *Broad signals due to rotameric forms of both carbonates* (500 MHz, $CDCl_3$) δ_H 5.68 (1H, s, H6), 5.46 (1H, s, H6'), 3.81 (1H, br s, H3), 3.61 (1H, br s, H3'), 2.76 (2H, br d, *J* = 6.0 Hz, H4), 2.30 (2H, br s, H9), 1.58-1.33 (22H, m, H10, H11 and 2 × CO_2tBu), 1.28 (4H, br s, H12 and H13), 0.88 (3H, t, *J* = 6.5 Hz, H14); **^{13}C NMR** *Broad and multiple signals due to rotameric forms of both carbonates* (126 MHz, $CDCl_3$) δ_C 153.1, 152.8, 130.7, 130.5, 118.9, 118.4, 83.7, 81.9, 81.7, 73.1, 72.8, 71.6, 48.7, 47.2, 40.2, 39.4, 31.5, 28.9, 28.6, 28.5, 28.3, 28.1, 22.7, 18.6, 14.2; **HRMS** (ES+) calc. for $C_{22}H_{37}{}^{79}BrN_2NaO_4$ $[M+Na]^+$ 495.1829, found 495.1820.

Di-*tert*-butyl 1-(4-bromopent-4-en-1-yl)-2-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 346c

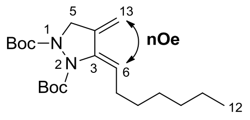


Method A: The procedure of Tšupova *et al.* was used for this preparation.[177] To a vial containing K_2CO_3 (40 mg, 0.293 mmol, 2.0 equiv.), ground NaOH (20 mg, 0.511 mmol, 3.5 equiv.), TBAHS (5 mg, 0.0146 mmol, 0.1 equiv.) and TBAI (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide **344a** (50 mg, 0.146 mmol, 1.0 equiv.) and tosylate **351b** (93 mg, 0.293 mmol, 2.0 equiv.) in toluene (0.15 mL, 1 mL.mmol^{-1}). The resulting mixture was stirred for 3 h at RT before being quenched with sat. *aq.* NH_4Cl, diluted with EtOAc and water and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded bromoenynhydrazide **346c** as a colourless oil (34 mg, 0.069 mmol, 47%).

Method B: To a vial containing TBAHS (5 mg, 0.0146 mmol, 0.1 equiv.) was added a solution of ynhydrazide **344a** (50 mg, 0.146 mmol, 1.0 equiv.) and iodide **352b** (80 mg, 0.293 mmol, 2.0 equiv.) in toluene (1.5 mL, 10 mL.mmol^{-1}). To this was added *aq.* NaOH (1.5 mL, 10 mL.mmol^{-1}, 25% w/v) and the biphasic mixture rapidly stirred for 21 h at RT before being quenched with sat. *aq.* NH_4Cl, diluted with EtOAc and water and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether / EtOAc (10:1)) afforded bromoenynhydrazide **346c** as a colourless oil (41.2 mg, 0.84 mmol, 58%).

R_f 0.49 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2980, 2933, 1740, 1716, 1393, 1303, 1264, 1148; **^{1}H NMR** *Broad signals due to rotameric forms of both carbonates* (500 MHz, $CDCl_3$) δ_H 5.60 (1H, d, *J* = 1.5 Hz, H7), 5.42 (1H, br s, H7’), 3.67-3.49 (1H, m, H3), 3.49-3.34 (1H, m, H3’), 2.51 (2H, t, *J* = 6.5 Hz, H5), 2.28 (2H, t, *J* = 10.5 Hz, H10), 1.86 (2H, dt, *J* = 13.5, 7.0 Hz, H4), 1.57-1.33 (22H, m, H11, H12 and 2 × CO_2tBu), 1.33-1.07 (4H, m, H13 and H14), 0.87 (3H, t, *J* = 6.5 Hz, H15); **^{13}C NMR** *Broad and multiple signals due to rotameric forms of both carbonates* (126 MHz, $CDCl_3$) δ_C 154.4, 154.1, 153.3, 152.8, 133.9, 133.6, 117.1, 83.6, 83.4, 81.7, 81.6, 73.1, 72.7, 71.6, 46.9, 38.8, 31.5, 29.0, 28.6, 28.5, 28.3, 28.1, 25.9, 22.7, 18.6, 14.2; **HRMS** (ES+) calc. for $C_{23}H_{39}{}^{79}BrN_2NaO_4$ $[M+Na]^+$ 509.1985, found 509.1978.

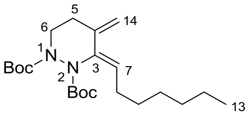
(*Z*)-Di-*tert*-butyl 3-heptylidene-4-methylenepyrazolidine-1,2-dicarboxylate, 354a



Prepared by General Procedure O using bromoenynamide **346a** (90 mg, 0.195 mmol) with heating for 1 h or by General Procedure P Method B using bromoenynamide **346a** (90 mg, 0.195 mmol) with heating for 22 h. Purification *via* column chromatography (petroleum ether / EtOAc (20:1)) afforded the exocyclic diene **354a** as a pale yellow oil (36.5 mg, 0.096 mmol, 49% and 39.5 mg, 0.103 mmol, 53% respectively); **R_f** 0.44 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2978, 2929, 1712, 1456, 1392, 1368, 1326, 1151; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.64-5.57 (1H, m, H6), 5.30 (1H, t, *J* = 2.5 Hz, H13), 4.90 (1H, s, H13’), 4.51 (1H, d, *J* = 15.0 Hz, H5), 3.87 (1H, d, *J* = 15.0 Hz, H5’), 2.26-2.18 (2H, m, H7), 1.56-1.33 (22H, m, H8, H9 and 2 × CO_2tBu), 1.35-1.09 (4H, m, H10 and H11), 0.86 (3H, t, *J* = 7.0 Hz, H12); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 154.3, 141.5, 134.5, 115.9, 102.5, 82.0, 81.3, 50.7, 31.8, 29.5, 29.2, 29.1, 28.3, 28.3, 22.7, 14.2; **HRMS** (ES+) calc. for $C_{21}H_{36}N_2NaO_4$ $[M+Na]^+$ 403.2567, found 403.2567.

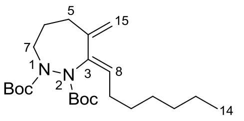
N.B. The stereochemistry of **354a** was assigned through ^{1}H NMR nOe experiments. A strong enhancement was seen between H6 and H13. Stereochemistry of remaining dienes was assigned by analogy.

(*Z*)-Di-*tert*-butyl 3-heptylidene-4-methylenetetrahydropyridazine-1,2-dicarboxylate, 354b



Prepared by General Procedure P Method B using bromoenynamide **346b** (10 mg, 0.021 mmol) with heating for 30 min. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (9:1)) afforded the exocyclic diene **354b** as a colourless oil (4.3 mg, 0.011 mmol, 52%); **R$_f$** 0.43 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 1710, 1456, 1393, 1368, 1255, 1151; **^{1}H NMR** *Broad signals due to rotameric forms of both carbonates* (500 MHz, $CDCl_3$) δ_H 5.72 (1H, s, H7), 5.22 (1H, s, H14), 4.83 (1H, s, H14'), 3.99-3.85 (1H, m, H6), 3.45-3.29 (1H, m, H6'), 2.52-2.41 (1H, m, H5), 2.34-2.18 (2H, m, H5' and H8), 2.16-2.06 (1H, m, H8'), 1.46 (18H, s, 2 × CO_2tBu), 1.36-1.22 (8H, m, H9-H12), 0.87 (3H, t, *J* = 7.0 Hz, H13); **^{13}C NMR** *Broad signals due to rotameric forms of both carbonates* (126 MHz, $CDCl_3$) δ_C 133.2, 128.8, 123.5, 110.1, 96.3, 81.5, 80.7, 44.5, 32.0, 30.8, 29.9, 29.4, 29.1, 28.5, 28.3, 28.1, 22.8, 14.2; **HRMS** (ES+) calc. for $C_{22}H_{38}N_2NaO_4$ $[M+Na]^+$ 417.2724, found 417.2706.

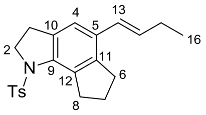
(*Z*)-Di-*tert*-butyl 3-heptylidene-4-methylene-1,2-diazepane-1,2-dicarboxylate, 354c



Prepared by General Procedure O using bromoenynamide **346c** (40 mg, 0.082 mmol) with heating for 1.5 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (9:1)) afforded the exocyclic diene **354c** as a colourless oil (5.2 mg, 0.012 mmol, 15%); **R_f** 0.43 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2930, 1715, 1455, 1392, 1366, 1323, 1152; **^{1}H NMR** *Broad signals due to rotameric forms of both carbonates* (500 MHz, $CDCl_3$) δ_H 5.64 (1H, dd, *J* = 8.5, 5.5 Hz, H8), 5.22 (1H, s, H15), 4.84 (1H, s, H15'), 4.23 (1H, d, *J* = 14.0 Hz, H7), 2.96-2.83 (1H, m, H7'), 2.49-2.40 (1H, m, H5), 2.15-1.98 (3H, m, H5' and H9), 1.85-1.76 (1H, m, H6), 1.71-1.59 (1H, m, H6'), 1.51-1.42 (20H, m, 2 × CO_2*t*Bu and H10), 1.37-1.22 (6H, m, H11-H13), 0.92-0.84 (3H, m, H14); **^{13}C NMR** *Broad signals due to rotameric forms of both carbonates* (126 MHz, $CDCl_3$) δ_C 155.3, 151.4, 147.4, 137.4, 123.0, 113.1, 81.3, 81.0, 47.9, 34.3, 32.0, 30.8, 29.4, 29.0, 28.9, 28.5, 28.4, 22.8, 14.2; **HRMS** (ES+) calc. for $C_{23}H_{40}N_2NaO_4$ $[M+Na]^+$ 431.2880, found 431.2875.

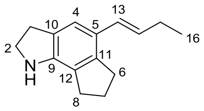
7.6. Palladium-Catalysed Intramolecular Cyclisation

(*E*)-5-(But-1-en-1-yl)-1-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indole, 388



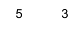
To a solution of 1-(1-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indol-5-yl)butan-1-ol (30 mg, 0.078 mmol, 1.0 equiv.) in anhydrous benzene (0.36 mL) was added *p*-toluenesulfonic acid (1.5 mg, 0.0078 mmol, 0.1 equiv.) and a few 3Å molecular sieves, and the resulting mixture heated at reflux for 16 h. The reaction was allowed to cool to RT, quenched with sat. *aq.* $NaHCO_3$ solution and extracted with Et_2O (×3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (4:1)) afforded the desired product **388** as a pale yellow oil (22.7 mg, 0.062 mmol, 80%); **R_f** 0.52 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2959, 1597, 1454, 1355, 1250, 1164, 1090, 967; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.45 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.99 (1H, s, H4), 6.43 (1H, d, *J* = 16.0 Hz, H13), 6.13 (1H, dt, *J* = 16.0, 6.5 Hz, H14), 3.97 (2H, t, *J* = 7.5 Hz, H2), 3.25 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.94 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.38 (3H, s, TsC*H*$_3$), 2.30-2.19 (4H, m, H3 and H15), 2.07 (2H, qu, *J* = 7.5 Hz, H7), 1.09 (3H, t, *J* = 7.5 Hz, H16); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 143.8, 143.2, 137.6, 136.8, 135.2, 134.8, 133.3, 131.9, 129.6, 127.5, 126.7, 118.9, 52.7, 33.2, 32.1, 28.7, 26.5, 25.9, 21.7, 14.0; **HRMS** (ES+) calc. for $C_{22}H_{25}NNaO_2S$ [M+Na]$^+$ 390.1498, found 390.1500.

(*E*)-5-(But-1-en-1-yl)-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indole, 389



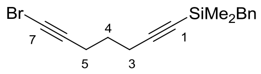
The procedure of Nyasse and co-workers was used for this preparation.[128] To a solution of the tricyclic indoline **388** (14 mg, 0.038 mmol, 1.0 equiv.) in MeOH (0.45 mL) was added magnesium granules (5 mg, 0.19 mmol, 5.0 equiv.) and the mixture was sonicated for 1.5 h. The reaction was diluted with CH$_2$Cl$_2$ and poured into *aq.* 1M HCl. The organic layer was separated, washed with sat. *aq.* NaHCO$_3$ (×2), and then brine before being dried (MgSO$_4$) and concentrated *in vacuo*. Purification by column chromatography (petroleum ether → petroleum ether / EtOAc (3:2)) afforded indoline **389** as a pale yellow oil (3.4 mg, 0.016 mmol, 41%, 75% brsm) which was submitted to unsuccessful oxidation conditions before full characterisation; **R$_f$** 0.34 (petroleum ether / EtOAc (4:1)); **^{1}H NMR** (200 MHz, CDCl$_3$) δ_H 7.12 (1H, s, H4), 6.38 (1H, d, *J* = 16.0 Hz, H13), 6.02 (1H, dt, *J* = 13.5, 6.5 Hz, H14), 3.59 (2H, t, *J* = 8.0 Hz, H2), 3.03 (2H, t, *J* = 8.0 Hz, H3), 2.89 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.73 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.29-2.13 (2H, m, H15), 2.07 (2H, qu, *J* = 7.5 Hz, H7), 1.07 (3H, t, *J* = 7.5 Hz, H16).

Benzyl(hepta-1,6-diyn-1-yl)dimethylsilane, 390



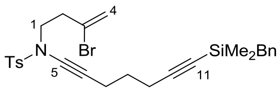
A solution of 1,6-heptadiyne (1 mL, 8.74 mmol, 1.0 equiv.) in anhydrous THF (4.1 mL) was cooled to −78 °C, under Ar, before the dropwise addition of LiHMDS (8.74 mL, 8.74 mmol, 1 M in THF). The reaction mixture was stirred for 45 min at −78 °C before a solution of $BnMe_2SiCl$ (1.9 mL, 10.48 mmol, 1.2 equiv.) in anhydrous THF (2.6 mL) was added. The resulting mixture was stirred for 1 h at −78 °C, and then at RT for 2 h, before quenching with sat. *aq.* NH_4Cl and the addition of Et_2O. After warming to RT the layers were separated and the aqueous layer extracted with Et_2O (×2). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (petroleum ether → petroleum ether / EtOAc (96:4)) afforded an inseparable 1:0.3 mixture (1.97 g, 82%) of the monoprotected diyne **390** (63%) and the bisprotected diyne (19%) as a colourless oil; **R_f** 0.63 (petroleum ether / EtOAc (30:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29-7.20 (2H, m, Bn*H*), 7.15-7.00 (3H, m, Bn*H*), 2.37 (2H, t, *J* = 7.0 Hz, H3), 2.30 (2H, td, *J* = 7.0, 2.5 Hz, H5), 2.19 (2H, s, $SiCH_2$), 1.99 (1H, t, *J* = 2.5 Hz, H7), 1.74 (1H, qu, *J* = 7.0 Hz, H4), 0.12 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.3, 128.5, 128.3, 124.4, 107.6, 83.8, 83.7, 69.0, 27.5, 26.6, 19.1, 17.6, −1.80. Data in accordance with literature values.[90,188]

Benzyl(7-bromohepta-1,6-diyn-1-yl)dimethylsilane, 391



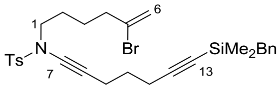
Prepared by General Procedure C Method A using terminal alkyne **390** (0.67 g mono, 2.80 mmol - 1.00 g mixture, 3.64 mmol). Purification *via* column chromatography (petroleum ether) afforded the desired bromoalkyne **391** as a colourless oil (25 mg, 1.93 mmol, 69%); **R_f** 0.46 (petroleum ether); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 2175, 1600, 1493, 1452, 1251, 1208, 1156, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26-7.07 (2H, m, Bn*H*), 7.14-6.86 (3H, m, Bn*H*), 2.32 (4H, dt, *J* = 10.5, 7.0 Hz, H3 and H5), 2.18 (2H, s, $SiCH_2$), 1.71 (2H, qu, *J* = 7.0 Hz, H4), 0.02 (6H, d, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.3, 128.5, 128.3, 124.4, 124.2, 107.5, 83.9, 79.5, 27.4, 26.6, 19.1, 18.9, 0.05, −1.79; **HRMS** (FI+) calc. for $C_{16}H_{19}{}^{79}BrSi$ $[M]^+$ 320.0420, found 320.0477.

***N*-(7-(Benzyldimethylsilyl)hepta-1,6-diyn-1-yl)-N-(3-bromobut-3-en-1-yl)-4-methyl benzenesulfonamide, 392a**



Prepared by General Procedure E using sulfonamide **213a** (150 mg, 0.49 mmol) and benzyl(7-bromohepta-1,6-diyn-1-yl)dimethylsilane **391** (236 mg, 0.74 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the bromoenynamide **392a** as a colourless oil (139 mg, 0.25 mmol, 52%); **R$_f$** 0.42 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2173, 1699, 1599, 1494, 1358, 1250, 1163; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.79 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.21 (2H, t, *J* = 7.5 Hz, Bn*H*), 7.12-7.02 (3H, m, Bn*H*), 5.64 (1H, d, *J* = 1.5 Hz, H4), 5.45 (1H d, *J* = 2.0 Hz, H4’), 3.52 (2H, t, *J* = 7.0 Hz, H1), 2.73 (2H, t, *J* = 7.0 Hz, C*H*$_2$), 2.44 (3H, s, TsC*H*$_3$), 2.37 (2H, t, *J* = 7.0 Hz, C*H*$_2$), 2.28 (2H, t, *J* = 7.0 Hz, C*H*$_2$), 2.18 (2H, s, SiC*H*$_2$), 1.68 (2H, qu, *J* = 7.0 Hz, H8), 0.11 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 144.7, 139.3, 134.6, 129.9, 129.2, 128.5, 128.3, 127.8, 124.4, 119.8, 107.8, 83.8, 73.5, 69.9, 49.8, 40.2, 27.9, 26.6, 21.8, 19.1, 17.7, −1.76; **HRMS** (ES+) calc. for $C_{27}H_{32}{}^{79}BrNNaO_2SSi$ [M+Na]$^+$ 564.0999, found 564.1001.

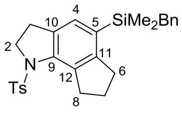
***N*-(7-(Benzyldimethylsilyl)hepta-1,6-diyn-1-yl)-*N*-(5-bromohex-5-en-1-yl)-4-methyl benzene sulfonamide, 392b**



Prepared by General Procedure E using sulfonamide **249** (163 mg, 0.49 mmol) and benzyl(7-bromohepta-1,6-diyn-1-yl)dimethylsilane **391** (236 mg, 0.74 mmol). Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the bromoenynamide **392b** as a colourless oil (106 mg, 0.18 mmol, 37%); **R$_f$** 0.41 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2953, 2173, 1695, 1599, 1355, 1249, 1161, 1088; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.78 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.21

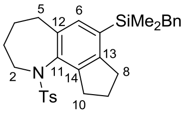
(2H, t, *J* = 7.5 Hz, Bn*H*), 7.12-7.00 (3H, m, Bn*H*), 5.56 (1H, d, *J* = 1.5 Hz, H6), 5.39 (1H, d, *J* = 1.5 Hz, H6'), 3.28 (2H, t, *J* = 6.5 Hz, H1), 2.49-2.40 (5H, m, TsCH_3 and CH_2), 2.37 (2H, t, *J* = 7.0 Hz, CH_2), 2.28 (2H, t, *J* = 7.1 Hz, CH_2), 2.18 (2H, s, *J* = 7.5 Hz, SiCH_2), 1.73-1.54 (6H, m, 3 × CH_2), 0.16-0.04 (6H, m, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 144.6, 139.3, 134.6, 134.0, 129.8, 128.5, 128.3, 127.8, 124.4, 117.1, 107.8, 83.7, 73.7, 69.4, 51.1, 40.8, 28.0, 26.6, 26.5, 24.6, 21.8, 19.1, 17.8, −1.76; **HRMS** (ES+) calc. for $C_{29}H_{38}{}^{79}BrNNaO_3SSi$ [M+Na]$^+$ 610.1417, found 610.1411.

5-(Benzyldimethylsilyl)-1-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indole, 393a



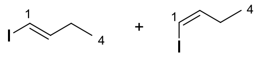
Prepared by General Procedure T using bromoenynamide **392a** (20 mg, 0.036 mmol) with heating for 16 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (9:1)) afforded the desired tricycle **393a** as a colourless oil (15.5 mg, 0.033 mmol, 91%); **R$_f$** 0.28 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 1598, 1493, 1357, 1250, 1165, 1090, 909, 833; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.45 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.19-7.14 (3H, m, Ts*H* and Bn*H*), 7.10-7.04 (2H, m, Bn*H*), 6.93 (1H, s, H4), 6.89 (2H, d, *J* = 7.0 Hz, Bn*H*), 3.97 (2H, t, *J* = 7.5 Hz, H2), 3.20 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.84 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.39 (3H, s, TsCH_3), 2.30 (2H, s, SiCH_2), 2.26 (2H, t, *J* = 7.5 Hz, H3), 2.01 (2H, qu, *J* = 7.5 Hz, H7), 0.25 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 151.9, 143.9, 140.3, 139.9, 136.0, 135.4, 133.3, 130.9, 129.6, 128.5, 128.4, 128.2, 127.5, 124.2, 52.6, 34.6, 32.5, 28.7, 26.4, 26.3, 21.8, −2.47; **HRMS** (ES+) calc. for $C_{27}H_{31}NNaO_2SSi$ [M+Na]$^+$ 484.1737, found 484.1731.

7-(Benzyldimethylsilyl)-1-tosyl-1,2,3,4,5,8,9,10-octahydroindeno[4,5-*b*]azepane, 393b



Prepared by General Procedure T using bromoenynamide **392b** (20 mg, 0.035 mmol) with heating for 19 h. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (9:1)) afforded the desired tricycle **393b** as a colourless oil (13.4 mg, 0.027 mmol, 78%); **R$_f$** 0.28 (petroleum ether / EtOAc (10:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2937, 1599, 1493, 1451, 1344, 1157, 1094, 1036, 908; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.27 (2H, d, *J* = 7.5 Hz, Ts*H*), 7.18 (2H, t, *J* = 7.5 Hz, Bn*H*), 7.07 (1H, t, *J* = 7.5 Hz, Bn*H*), 6.92 (2H, d, *J* = 6.0 Hz, Bn*H*), 4.32 (1H, dt, *J* = 15.4, 3.2 Hz, H2), 3.21-3.11 (1H, m, H8 or H10), 3.02 (1H, ddd, *J* = 14.5, 12.5, 2.5 Hz, H2'), 2.97-2.82 (3H, m, H8 or H10, and H8' and H10'), 2.43 (3H, d, TsC*H*$_3$), 2.37-2.28 (3H, m, SiC*H*$_2$ and H5), 2.16 (1H, d, *J* = 13.0 Hz, H5'), 2.10 (1H, ddt, *J* = 16.0, 8.0, 4.0 Hz, H9), 1.89 (1H, ddt, *J* = 17.5, 12.0, 8.5 Hz, H9'), 1.75-1.61 (2H, m, H3 and H4), 1.60-1.49 (1H, m, H3'), 1.16-1.07 (1H, m, H4'), 0.25 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 150.2, 144.9, 143.2, 139.9, 139.6, 139.2, 137.7, 134.2, 133.7, 129.7, 128.5, 128.2, 127.7, 124.2, 50.3, 34.8, 33.6, 40.00, 28.5, 26.3, 26.1, 25.8, 21.7, −2.64, −2.71; **HRMS** (ES+) calc. for $C_{29}H_{35}NNaO_2SSi$ $[M+Na]^+$ 512.2050, found 512.2049.

(*E*)-1-Iodobut-1-ene and (*Z*)-1-iodobut-1-ene, 396



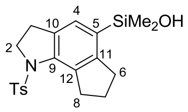
(*E*)-396 (*Z*)-396

To chromium (II) chloride (2.12 g, 17.22 mmol, 10.0 equiv.), dried under vacuum and heat, was added anhydrous THF (48 mL) and the resulting suspension stirred for 30 min at RT before being cooled to 0 °C. A solution of propionaldehyde (0.12 mL, 1.72 mmol, 1.0 equiv.) and iodoform (2.03 g, 5.16 mmol, 3.0 equiv.) in anhydrous THF (8 mL) was added *via* syringe. The resulting brown solution was stirred in the dark for 2.5 h at 0 °C before being diluted with Et_2O and quenched with distilled water. The aqueous layer was extracted with Et_2O (× 2) and the combined organic layers washed sequentially with sat. *aq.* $Na_2S_2O_3$, brine, dried ($MgSO_4$) and concentrated carefully *in vacuo* (no heat on water bath, lowest pressure 500 mbar). The solution was then carefully concentrated *in vacuo* by Kugelrohr distillation (80 °C at 200 mbar) to afford a 1:0.25 mixture of ***E*:*Z*-396** in THF which was stored in the freezer in the dark (46 mg in THF, 0.25 mmol, 15%); $\mathbf{R_f}$ 0.81 (petroleum ether); **(*E*)-396**: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.53 (1H, dt, *J* = 14.5, 6.5 Hz, H2), 5.95 (1H, dt, *J* = 14.5, 1.5 Hz, H1), 2.10-2.01 (2H, m, H3), 0.98 (3H, t, *J* = 7.5 Hz, H4); **(*Z*)-396**: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.18-6.07 (2H, m, H1 and H2), 2.17-2.08 (2H, m, H3), 1.00 (3H, t, *J* = 7.5 Hz, H4). Data in accordance with literature values.[229]

Preliminary Hiyama Coupling:

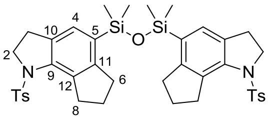
To a solution of the BDMS-substituted indoline **393a** (25 mg, 0.054 mmol, 1.0 equiv.) and vinyl iodide **396** (15 mg, 0.081 mmol, 1.5 equiv.) in THF was added TBAF (0.12 mL, 0.12 mmol, 2.2 equiv.) at 0 °C, and the resulting mixture was stirred for 10 min before the addition of Pd_2dba_3•$CHCl_3$ (1.4 mg, 0.00135 mmol, 2.5 mol%). The reaction mixture was stirred at RT for 2 h and then heated to 50 °C for 1 h before being cooled to RT, diluted with EtOAc, filtered through a short silica plug and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (3:2)) afforded desilylated indoline **397c** (4.7 mg, 0.015 mmol, 27%), disiloxane **397b** (9.5 mg, 0.025 mmol, 46%) and silanol **397a** (3.1 mg, 0.0081 mmol, 15%).

Dimethyl(1-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indol-5-yl)silanol, 397a



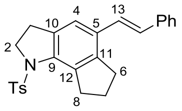
Isolated as a side product from the Hiyama coupling as a yellow oil (3.1 mg, 0.0081 mmol, 15%); $\mathbf{R_f}$ 0.17 (petroleum ether / EtOAc (4:1)); ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.46 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.17 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.09 (1H, s, H4), 3.97 (2H, t, *J* = 7.5 Hz, H2), 3.21 (2H, t, *J* = 7.0 Hz, H6 or H8), 3.01 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.39 (3H, s, TsC*H*$_3$), 2.30 (2H, t, *J* = 7.5 Hz, H3), 2.15-1.97 (2H, m, H7), 0.40 (6H, s, Si(C*H*$_3$)$_2$).

1,1,3,3-Tetramethyl-1,3-bis(1-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indol-5-yl)disiloxane, 397b



Isolated as a side product from the Hiyama coupling as a pale yellow oil (9.5 mg, 0.025 mmol, 46%); **R$_f$** 0.26 (petroleum ether / EtOAc (4:1)); **^{1}H NMR** (200 MHz, CDCl$_3$) δ_H 7.45 (4H, d, *J* = 8.5 Hz, Ts*H*), 7.15 (4H, d, *J* = 8.0 Hz, TsH), 7.00 (2H, s, H4), 3.96 (4H, t, *J* = 7.5 Hz, H2), 3.18 (4H, t, *J* = 7.5 Hz, H6 or H8), 2.93 (H4, t, *J* = 7.5 Hz, H6 or H8), 2.38 (6H, s, TsC*H*$_3$), 2.27 (4H, t, *J* = 7.5 Hz, H3), 2.07-1.77 (4H, m, H7), 0.31 (12H, s, *J* = 3.5 Hz, Si(C*H*$_3$)$_2$).

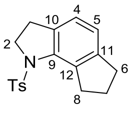
(*E*)-5-Styryl-1-tosyl-1,2,3,6,7,8-hexahydrocyclopenta[*g*]indole, 399



A modified procedure of Hirabayashi *et al.* was used for this preparation.[200] To a solution of the BDMS-substituted indoline **393a** (6 mg, 0.013 mmol, 1.0 equiv.) and styrenyl iodide (4.4 mg, 0.019 mmol, 1.5 equiv.) in THF (0.04 mL) was added TBAF (0.14 µL, 0.014 mmol, 1.1 equiv.) at 0 °C, and the resulting mixture stirred for 10 min. To this was added a pre-made solution of Pd(PPh$_3$)$_4$ (0.8 mg, 0.00065 mmol, 5 mol%) and Ag$_2$O (3.2 mg, 0.014 mmol, 1.1 equiv.) in THF (0.1 mL) and the resulting mixture stirred at RT for 22 h. The reaction was diluted with EtOAc, filtered through a short silica plug and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the desired coupled product **399** as a yellow oil (3.7 mg, 0.0088 mmol, 68%); **R$_f$** 0.37 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2924, 1597, 1454, 1355, 1249, 1164, 1090, 962; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.51-7.38 (4H, m, Ts*H* and Ph*H*), 7.39-7.32 (2H, m, Ph*H*), 7.28-7.23 (1H, m, Ph*H*), 7.21-7.14 (4H, m, Ts*H*, H4 and H13 or H14), 6.97 (1H, d, *J* = 16.5 Hz, H13 or H14), 3.99 (2H, t, *J* = 7.5 Hz, H2), 3.28 (2H, t, *J* = 7.5 Hz, H6 or H8), 3.08-3.01 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.38 (3H, s, TsC*H*$_3$), 2.28 (2H, t, *J* = 7.5 Hz, H3), 2.11 (2H, dt, *J* = 14.5, 7.5

Hz, H7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.4, 144.0, 138.4, 137.7, 137.0, 135.3, 135.0, 131.4, 129.7, 129.0, 128.9, 127.8, 127.5, 126.6, 126.5, 119.0, 52.7, 33.2, 32.2, 28.7, 25.9, 21.7; **HRMS** (ES+) calc. for $C_{26}H_{25}NNaO_2S$ $[M+Na]^+$ 438.1498, found 438.1503.

1-Tosyl-1,2,3,6,7,8-hexahydrocyclopenta[g]indole, 397c



Isolated as a side-product using a modified procedure of Hirabayashi *et al.* for a Hiyama coupling.[200] To a solution of the BDMS-substituted indoline **393a** (6 mg, 0.013 mmol, 1.0 equiv.) and vinyl iodide **396** (3.5 mg, 0.019 mmol, 1.5 equiv.) in THF (0.04 mL) was added TBAF (0.14 μL, 0.014 mmol, 1.1 equiv.) at 0 °C, and the resulting mixture stirred for 10 min. To this was added a pre-made solution of $Pd(PPh_3)_4$ (0.8 mg, 0.00065 mmol, 5 mol%) and Ag_2O (3.2 mg, 0.014 mmol, 1.1 equiv.) in THF (0.1 mL) and the resulting mixture stirred at RT for 17 h. The reaction was diluted with EtOAc, filtered through a short silica plug and concentrated *in vacuo*. Purification *via* column chromatography (petroleum ether → petroleum ether / EtOAc (10:1)) afforded the desilylated indoline **397c** as a colourless oil (2.7 mg, 0.0087 mmol, 67%); **R_f** 0.60 (petroleum ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2956, 1597, 1447, 1355, 1254, 1165, 1091, 908; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.43 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.15 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.99 (1H, d, *J* = 7.5 Hz, H4), 6.83 (1H, d, *J* = 7.5 Hz, H5), 3.98 (2H, t, *J* = 7.5 Hz, H2), 3.24 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.91 (2H, t, *J* = 7.5 Hz, H6 or H8), 2.37 (3H, s, TsC*H*$_3$), 2.25 (2H, t, *J* = 7.5 Hz, H3), 2.06 (2H, qu, *J* = 7.5 Hz, H7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 146.0, 143.9, 139.0, 136.9, 135.2, 134.1, 129.6, 127.5, 122.5, 122.1, 52.7, 33.3, 33.1, 28.7, 26.4, 21.7; **HRMS** (ES+) calc. for $C_{18}H_{19}NNaO_2S$ $[M+Na]^+$ 336.1029, found 336.1031.

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