Synthesis of mono- and bicyclic azacycles *via* palladium- and ruthenium-catalysed enynamide cycloisomerisation

A thesis submitted to the
Board of the Faculty of Physical Sciences
in partial fulfilment of the requirements for the degree of

Doctor of Philosophy



Patrick Ross Walker

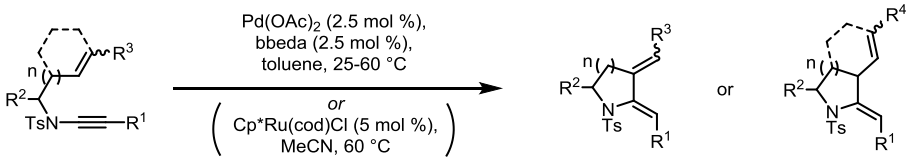
Oriel College, University of Oxford

Supervisor : Dr. Edward Anderson

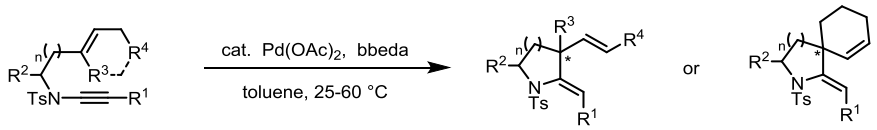
Abstract

The initial aim of this project was to investigate ways of synthesising fused, spirocyclic and linked bicyclic amines. We built on methodology previously developed within our group, employing cyclic dienamides, prepared using the reductive cyclisation of bromoenynamides, as key structural building blocks for further annulation.

In the course of investigating the reactivity of these cyclic dienamides, we discovered a new efficient and general route to their synthesis, by employing palladium- or ruthenium-catalysed enynamide cycloisomerisation. A wide range of attractive dienamide scaffolds were synthesised from simple enynamide precursors in rapid, high yielding and operationally simple reactions, underlining their potential utility as an atom-economical source of azacycles.



Chiral enynamide substrates were used to generate 1,4-dienamides as a single diastereomer at the newly formed (quaternary) stereocentre. This relay of stereochemistry was exploited not only in the formation of monocyclic dienamides, but even in the formation of a spirocyclic product, and this bodes well for further stereocontrolled synthesis of polysubstituted azacycles.



Finally the palladium- and ruthenium-catalysed cycloisomerisation of enynamides was discussed and investigated mechanistically, utilising ^{1}H NMR spectroscopy, timecourse and deuterium-labelling experiments.

Acknowledgments

There have been a great many people throughout my DPhil to whom I owe thanks:

Firstly, I need to thank Dr. Edward Anderson for giving me the opportunity to work within his group and for his continual help and support. I feel like I have learnt a lot from you over the years.

To AstraZeneca for funding and my industrial supervisors Greg Carr, Abid Suleman and Alan Steven for their input.

To the staff of the CRL for their expertise and assistance, particularly those of the NMR and mass spectrometry departments.

To all the members of the EAA group past and present – MC, Dave, Sonia, Jem, Birgit, Diane, Becky, Liz, Craig, Bryony, Shermin, Bobby, Rob, Haraldur, Marius, Glen, Yao, Christian and our Part II and visiting students, for advice, friendship and good humour, especially when things looked bleakest. Craig - your chemistry knowledge is astounding and I greatly appreciate all the time and effort you have put in to helping me over the years, not least in the proof reading of this thesis (even though you are no longer officially a member of this research group). I truly hope that you achieve your ambition to be an academic; Birgit - your efficiency at running the group and sharing of chocolate have been greatly missed; MC - for helping me out in the early days; Dave- for your training and 'banter'; Becky - for your vast knowledge of ynamides and all the work you did in this area; Diane - for your cheerful nature, tireless patience and excellent organisation skills; Liz - for understanding about the perils of NMR experiments; Bryony- for generally putting up with me and for helping to run our 'half lab'; Shermin - for the outside tea breaks; Bobby, Rob, Haraldur and Marius - for all the units of alcohol. To anyone who ever joined in with my singing in the lab.

To the members of the Fletcher and the Hodgson groups, for accepting us into their labs and for making our time there enjoyable. To all the members of the organic teaching labs, including Dr. Malcolm Stuart, for your entertaining company.

To my mum and dad, for always being there and for always trying to understand. Your encouragement has kept me going.

To my girlfriend Ellie, for sticking by me, for keeping me sane (ironically) and for all your love.

Abbreviations

Ac	acetyl
AcO	acetate
Ar	generic aryl group
aq.	aqueous
bbeda	*N*,*N*′-bis(benzylidene)ethylenediamine
b.p.	boiling point
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brsm	based on recovered starting material
Bz	benzoyl
cat.	catalytic
Cbz	carboxybenzyl
cod	cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
dba	dibenzylideneacetone
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethene
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMM	dimethoxymethane
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
E^+	electrophile
e.e.	enantiomeric excess
Eq.	equation
eq.	equivalent(s)
ESI	electrospray ionisation
EWG	electron-withdrawing group
FVT	flash vacuum thermolysis
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence

HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
Hz	hertz
IPA	propan-2-ol
^{i}Pr	*iso*-propyl
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	molar
m-	meta
m.p.	melting point
m/*z*	mass to charge ratio
m-CPBA	3-chloroperbenzoic acid
min	minute(s)
mol	mole(s)
Ms	mesyl, methanesulfonyl
n.d.	not determined
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Ns	nosyl, 4-nitrobenzenesulfonyl
Nuc^-	nucleophile
o-	ortho
p-	para
Ph	phenyl
PIFA	bis(trifluoroacetoxy)iodobenzene
pin	pinacol
PMB	*p*-methoxybenzyl
PNBSA	*p*-nitrobenzenesulfonic acid
PPTS	pyridinium *p*-toluenesulfonate
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
ppm	parts per million
ppt	precipitate
quant.	quantitative
R	generic organic group
RCEM	ring-closing enyne metathesis
R_f	retention factor
rbf	round bottom flask
RT	room temperature

sat.	saturated
t_R	retention time
tert	tertiary
TBAF	tetra-*n*-butylammonium fluoride
$TBAHSO_4$	tetra-*n*-butylammonium hydrogen sulphate
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TCPC	tetracarbomethoxypalladacyclopentadiene
Tf/triflate	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	toluene
TPPO	triphenylphosphine oxide
Ts	tosyl, *p*-toluenesulfonyl
X	halogen
wt%	weight percent

Table of Contents

1. Introduction 1

1.1 Ynamides 1

1.2 Ynamide Synthesis 1

1.2.1 Early ynamide synthesis 1
1.2.2 Metal-catalysed alkynylation of amides 3

1.3 Cycloisomerisation of Ynamides 6

1.3.1 Cycloisomerisation 6
1.3.2 π-Acid activation of the ynamide 6
1.3.3 Ring-closing enyne metathesis (RCEM) 12
1.3.4 Intramolecular cyclotrimerisations (Formal [2+2+2]-cycloaddition) 16

1.4 Previous Group Work 19

1.5 Initial Aims 21

2. Reactions of Cyclic Dienamides 22

2.1 Introduction 22

2.2 Substrate Synthesis 24

2.3 Initial Investigations of Dienamide Reactivity 25

2.4 Formal [4 + 2] Cycloadditions 27

2.4.1 Imines 27
2.4.2 Heteroatom-containing dienophiles (commercially available) 28
2.4.3 Iminium ion salts 30
2.4.4 Nitroso compounds 31

2.5 N-O Bond Cleavage 35

2.6 Bicyclic Dienamides 38

2.7 Heteroatom-Functionalised Sidechain Dienamides 40

2.8 Conclusions and Further Work 42

3. Palladium- and Ruthenium-Catalysed Enynamide Cycloisomerisation 43

3.1 Introduction 43

3.1.1 Origins of the project 43
3.1.2 Enyne cycloisomerisation 44

3.2 Preliminary Result 51

3.3 Reaction Optimisation 52

3.4 Substrate Synthesis 54

3.4.1 Monosubstituted alkenyl ynamides 55
3.4.2 Disubstituted alkenyl ynamides 58
3.4.3 Cycloalkenyl ynamides 62

3.5 Substrate Scope 64

3.5.1 Monosubstituted alkenyl ynamides 64
3.5.2 Disubstituted alkenyl ynamides 66
3.5.3 Cycloalkenyl ynamides 71
3.5.4 Unsuccessful substrates 74

3.6 Stereochemical Control 75

3.6.1 Potential expansion of the methodology 75
3.6.2 Branched disubstituted alkenyl ynamides 77
3.6.3 α-Branched trisubstituted alkenyl ynamides 80

3.7 Conclusions and Further Work 84

4. Mechanistic Considerations 85

4.1 Introduction 85

4.1.1 Palladacycle vs hydropalladation 85
4.1.2 The ruthenacycle mechanism 90

4.2 Proposed Mechanism for Enynamide Cycloisomerisation 92

4.3 The Palladium(II) Acetate Story 97

4.4 Mechanistic Investigations 100

4.4.1 Initial experiments 100
4.4.2 Timecourse spectroscopy 101
4.4.3 Deuterated substrates 109

4.5 Conclusions and Further Work 120

5. Conclusions and Future Work 122

6. Experimental 125

6.1 General Experimental 125

6.2 General Experimental Procedures 127

6.3 Characterisation of Compounds 131

6.3.1 Reactions of cyclic dienamides 131

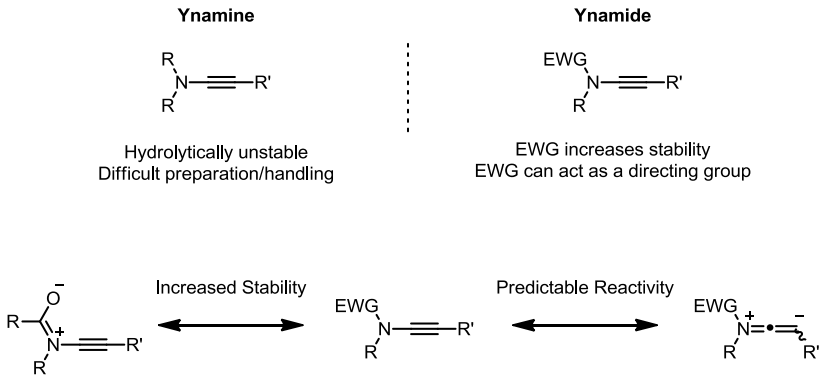
6.3.2 Enynamide precursors *173*
6.3.3 Enynamides *226*
6.3.4 Cycloisomerisation products *256*
6.3.5 Deuterated substrates *291*
6.3.6 Miscellaneous *299*

7. References 301

1. Introduction

1.1 Ynamides

Ynamides - alkynes substituted with an amide derivative through the nitrogen - offer unique opportunities for the incorporation of nitrogen-based functionalities into organic molecules.[1,2] The prevalence of ynamines in synthesis has remained somewhat limited due to their unstable nature and difficult preparation. In contrast, ynamides provide a robust alternative, maintaining the high level of reactivity and predictable regioselectivity, but with the decreased electron density affording enhanced stability (Scheme 1). It is of no surprise, therefore, that the arrival of powerful new methods to synthesise ynamides has led to renewed investigation into the numerous possibilities offered by these versatile building blocks.



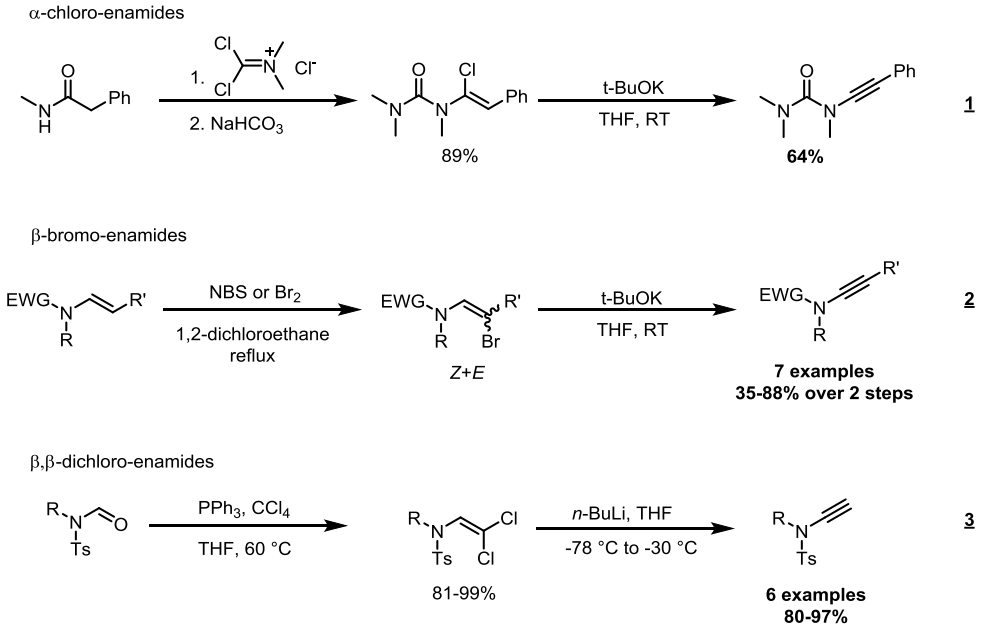
Scheme 1 – The advantages of ynamides.

1.2 Ynamide Synthesis

1.2.1 Early ynamide synthesis

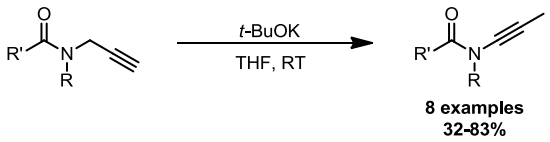
The first reported ynamide formation reaction, described by Viehe and co-workers in 1972, showed that ynamides could be generated from elimination reactions of α-chloro-enamides (Scheme 2, Eq. 1).[3] This work was extended to the elimination of β-bromo-enamides,[4] allowing a number of ynamides to be synthesised in useful yields (Eq. 2), despite only the *Z*

β-bromo-enamides undergoing the elimination. Under similar elimination conditions, β,β-dichloro-enamides were found to generate a number of terminal ynamides,[5,6] which could then undergo subsequent functionalisation of the terminal alkyne (Eq. 3).[7-10] These methods suffered from limited substrate scope however, due in part to the relatively harsh conditions required, such as potent electrophiles (Eq. 1 & 2), excess reagents (Eq. 3) and requirement for strong base.



Scheme 2 – Elimination of halo-enamides.

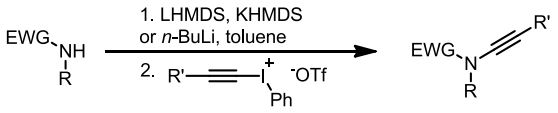
Propargyl amides were found to undergo isomerisation to methyl-substituted ynamides, but only carboxamides could be tolerated as the electron-withdrawing group (Scheme 3).[11]



Scheme 3 – Isomerisation of propargyl amides.

Witulski found that ynamides could also be synthesised by reacting lithium amides with alkynyl iodonium salts (Scheme 4),[12,13] a technique pioneered by Stang for the synthesis of

ynamines.[14] However, the synthesis of the starting alkynyl iodonium salts remained problematic, with typically only silyl and aromatic substitution of the alkyne moiety tolerated.



Scheme 4 – Ynamidation using alkenyl iodonium salts.

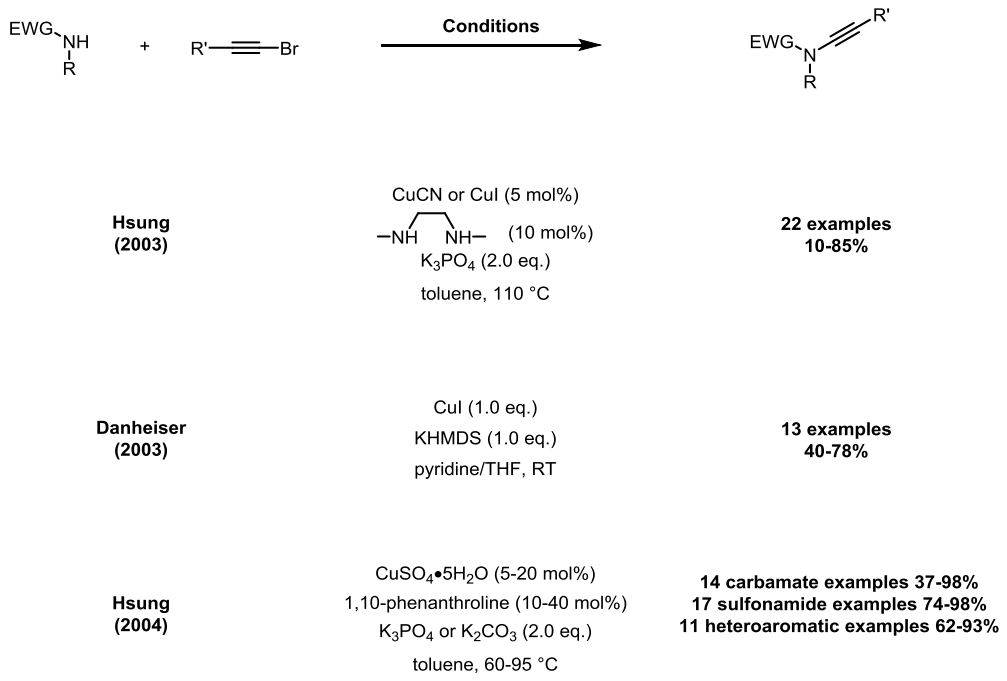
Despite the relative success of these methods in synthesising ynamides, the drawbacks of restricted substrates, harsh conditions and/or lengthy reaction sequences meant that until the emergence of metal-catalysed cross-coupling as a method of ynamide preparation, the development of ynamide reactions in synthesis remained an underdeveloped area.

1.2.2 Metal-catalysed alkynylation of amides

In 2003 Hsung and co-workers developed the first copper-catalysed ynamide formation (Scheme 5),[15] where catalytic CuI, with *N,N'*-dimethylethylenediamine as a ligand and two equivalents of K_3PO_4, were used to carry out the cross-coupling of amides to bromoalkynes. Whilst this method provided a streamlined synthesis of ynamides, the temperature of the reaction remained high and the substrate scope was poor, with only oxazolidinones giving good yields. During the same year, Danheiser and co-workers published an ynamide formation reaction involving initial *in situ* formation of a stoichiometric amide copper salt using KHMDS, followed by coupling to a bromoalkyne.[16] This reaction proceeded in good yield at room temperature even when employing carbamates and sulfonamides as substrates, although a stoichiometric amount of strong base and CuI were required.

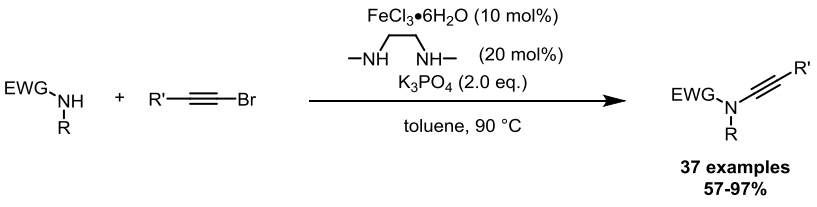
In 2004 Hsung and co-workers published an improved set of ynamide formation conditions,[17] finding that catalytic $CuSO_4 \bullet 5H_2O$, 1,10-phenanthroline as a ligand and two equivalents of base could be employed at 65-95 ºC. The substrate scope was vastly improved with both carbamates and sulfonamides now also proceeding in good yields. These conditions

represented the first catalytic and relatively mild general synthesis of ynamides, and to this date they remain a workhorse for ynamide formation, including within our group.[18]



Scheme 5 – Copper-catalysed ynamide synthesis using bromoalkynes.

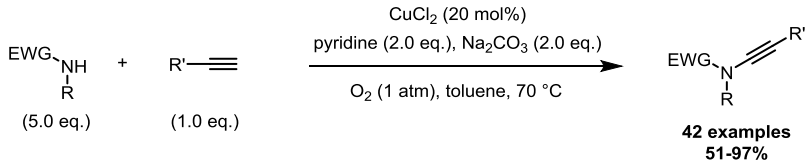
More recently an additional efficient and wide-ranging ynamide synthesis, using catalytic $FeCl_3•6H_2O$ as a cheap and environmentally friendly alternative to copper, was reported by Zhang and co-workers (Scheme 6).[19]



Scheme 6 – Iron-catalysed ynamide formation using bromoalkynes.

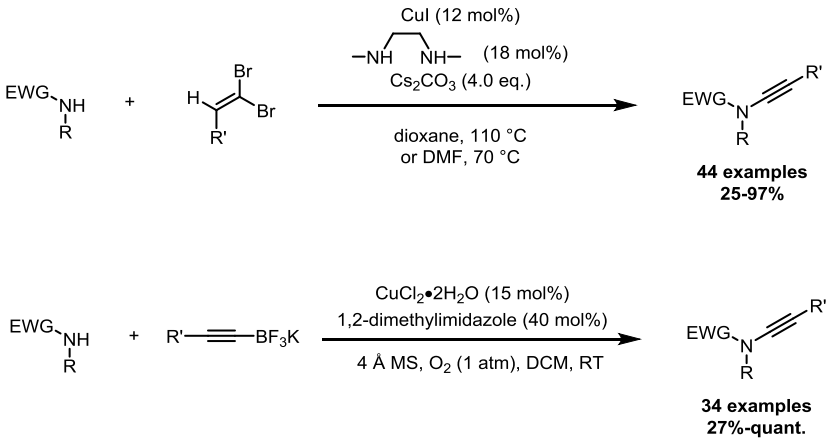
The necessity for the formation of bromoalkynes could be circumvented using the conditions developed by Stahl.[20] Copper-catalysed aerobic oxidative coupling of amides and terminal-alkynes could be performed using Brønsted bases in an atmosphere of oxygen at 90 °C, giving ynamides in good yields (Scheme 7). The major drawback of this methodology is that, in order

to avoid significant dimerisation of the alkyne and maintain satisfactory yields, five equivalents of the amide are necessary.



Scheme 7 – Copper-catalysed aerobic oxidative ynamide formation.

In 2009 Evano and co-workers established an alternative synthesis of ynamides directly from vinyl dibromides (Scheme 8).[21] A catalyst system of CuI and DMEDA was utilised along with Cs_2CO_3 as a base, with the choice of base having a large impact on the outcome of the reaction. Evano also reported the first base-free and room temperature synthesis of ynamides coupling potassium alkynyltrifluoroborates with amides under aerobic copper-catalysed conditions.[22] These methods offer a suitable alternative for ynamide formation in cases where synthesis of the required bromoalkynes proves difficult.



Scheme 8 – Evano's copper-catalysed ynamide formations.

This cornucopia of efficient and practical methods for synthesising ynamides has led to a rapid expansion of interest in their synthetic uses.

1.3 Cycloisomerisation of Ynamides

1.3.1 Cycloisomerisation

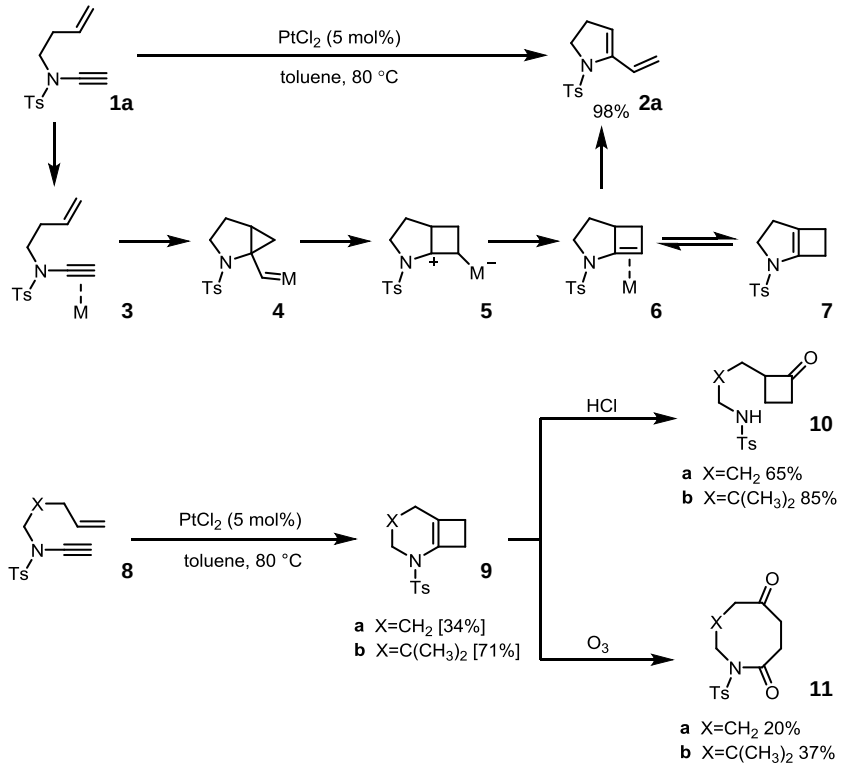
Cycloisomerisation, the skeletal reorganisation of organic molecules with the concurrent formation of one or more rings, represents a highly attractive method of generating valuable organic ring systems from simple acyclic starting materials.[23-25] These operationally simple reactions give access to products with substantial structural complexity, often with high yield and selectivity, whilst being intrinsically atom economic. Where 1,*n*-enynes have been particularly explored as cycloisomerisation substrates, reports of enynamide cycloisomerisation are limited to a handful of examples focusing on π-acid activation of the ynamide,[26-33] or enynamide ring-closing metathesis.[34-38]

1.3.2 π-Acid activation of the ynamide

The activation of ynamides towards cycloisomerisation under platinum catalysis was first reported by Fensterbank and Malacria (Scheme 9).[26] In the presence of $PtCl_2$ at 80°C in toluene, enynamides were found to undergo cycloisomerisation to bicyclic cyclobutenamides. In the 5-membered ring case, cyclobutenamide **6** underwent electrocyclic ring opening to give the formal metathesis dienamide product **2a**. With an extended carbon tether length, cyclobutenamides **9a** and **9b**, although prone to decomposition, could be isolated in moderate yields. Normally however, these unstable products were further functionalised in a one-pot procedure *via* hydrolysis or ozonolysis to give cyclobutanone derivatives **10** or medium-sized nitrogen heterocycles **11** respectively.

The mechanism of the reaction was investigated using DFT calculations by Soriano and Marco-Contelles,[27] who proposed that coordination of the metal to the ynamide triple bond is followed by formation of cyclopropyl metallocarbene species **4**. A 1,2-alkyl shift into the

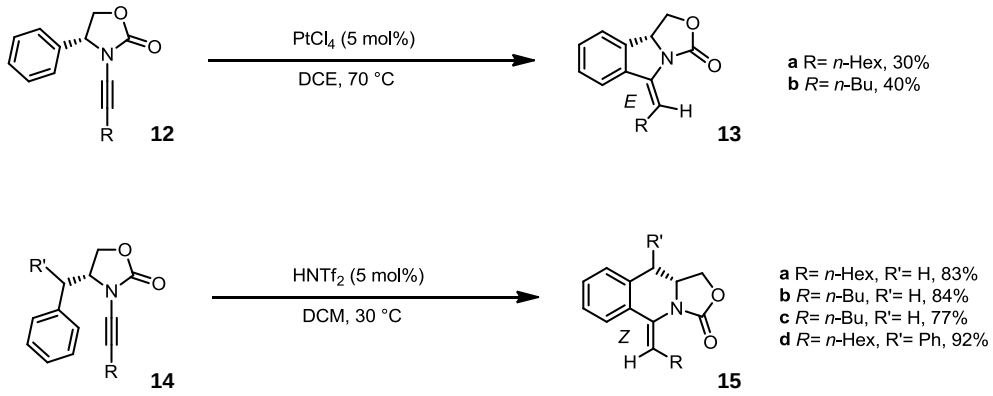
carbene and subsequent demetallation gives cyclobutenamide **6**, which can then undergo either an isomerisation or ring-opening electrocyclisation depending on the amount of ring strain due to the tether length.



Scheme 9 – Platinum-catalysed cycloisomerisation of enynamides.

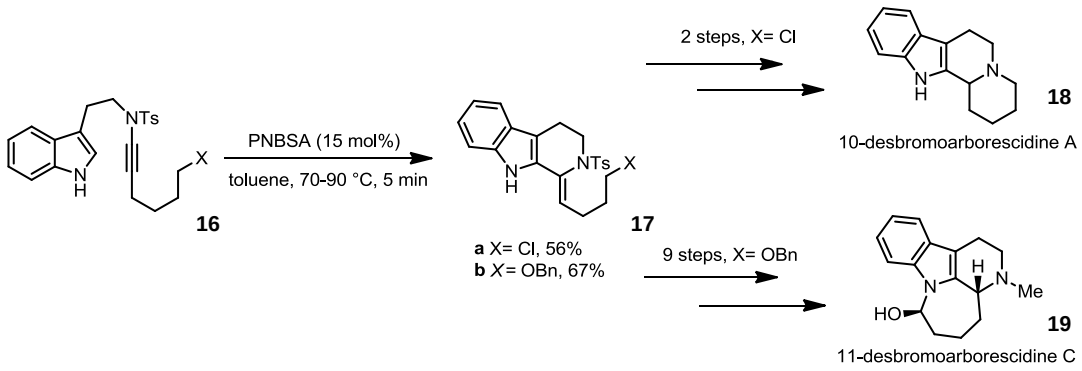
In 2005 Hsung and co-workers investigated the keteniminium Pictet-Spengler cyclisation of arene-ynamides (Scheme 10).[28] To their surprise, transition metal π-acids such as $PtCl_4$ proved unsuccessful in most cases and only moderately useful for *N*-tethered arene-ynamides **12a** and **12b**. Instead, Brønsted acids proved effective at catalysing the reaction, and arene-ynamides **14a-d** were cyclised using 5 mol% $HNTf_2$ to give tetrahydroisoquinolines **15a-d** in good to excellent yields. Interestingly, whilst the reaction is always highly stereoselective, (*Z*)-enamide formation is observed in all cases using Brønsted Acids, whereas the use of $PtCl_4$ gives isoindoles **13a** and **13b** as the (*E*)-enamides. Under Brønsted acid catalysis, the R group of the keteniminium intermediate is orientated away from the incoming arene in order to minimise the steric interaction, leading to the (*Z*)-enamide. With $PtCl_4$, the approach of the arene is

hindered more by the bulky Lewis acid than by the R substituent, leading to arene attack on the same face as R and the (*E*)-enamide product.



Scheme 10 – Brønsted acid-catalysed arene-ynamide cyclisation.

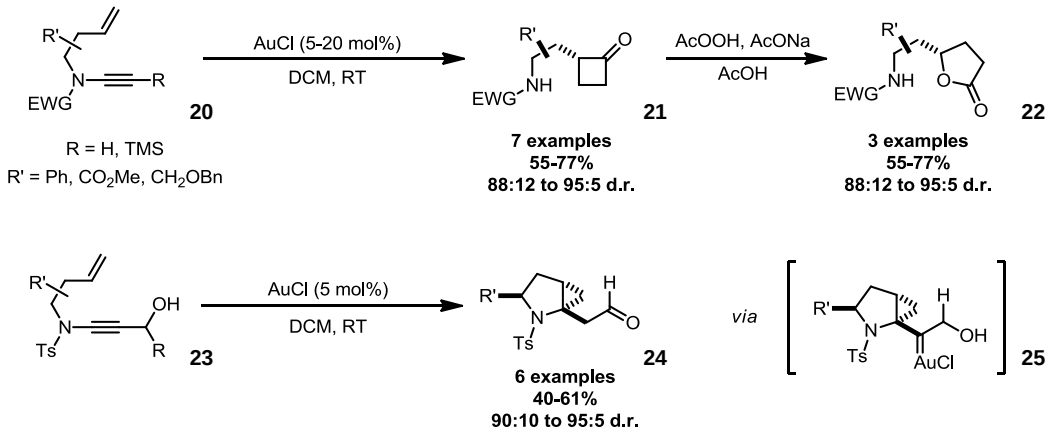
In order to demonstrate the synthetic utility to this methodology, the total syntheses of desbromoarborescidines A and C were completed using the Brønsted acid-catalysed keteniminium Pictet-Spengler cyclisation as the key step (Scheme 11). Notably, this also represented the first use of ynamides in total synthesis.



Scheme 11 – Arene-ynamide cyclisation in total synthesis.

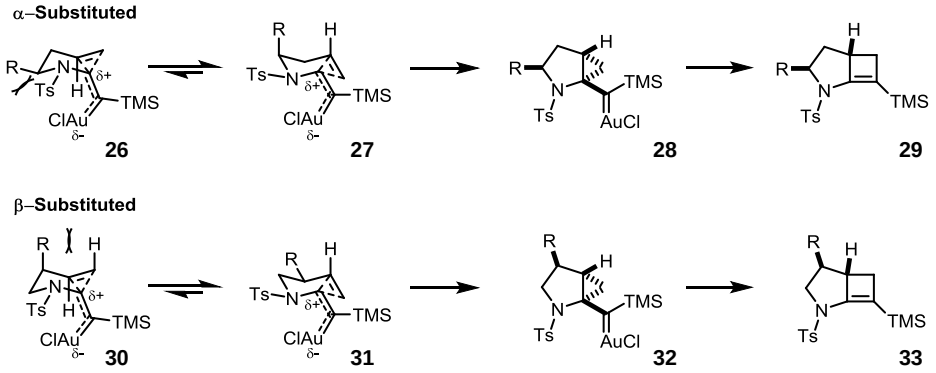
Cycloisomerisation of enynamides **20** and **23** by π-acid activation was achieved at ambient temperature by Cossy and co-workers using a gold(I) chloride catalyst in DCM.[29] Under these mild conditions the electrocyclic ring opening of the cyclobutene was avoided and the stereocentre formed in the reaction was preserved. Ynamides containing both α- and β-substituents **20** were cycloisomerised to give cyclobutanones **21** in good yield and high

diastereoselectivity. When the reaction was carried out using propargylic ynamides **23**, bicyclic cyclopropyl pyrrolidines **24** were generated by an oxygen-mediated 1,2-hydride shift in the cyclopropyl metallocarbene intermediate **25** (rather than the expected ring expansion). This work was later extended to 1,2-disubstituted alkenes generating 2,3-disubstituted cyclobutenones and lactones in high diastereoselectivity.[30]



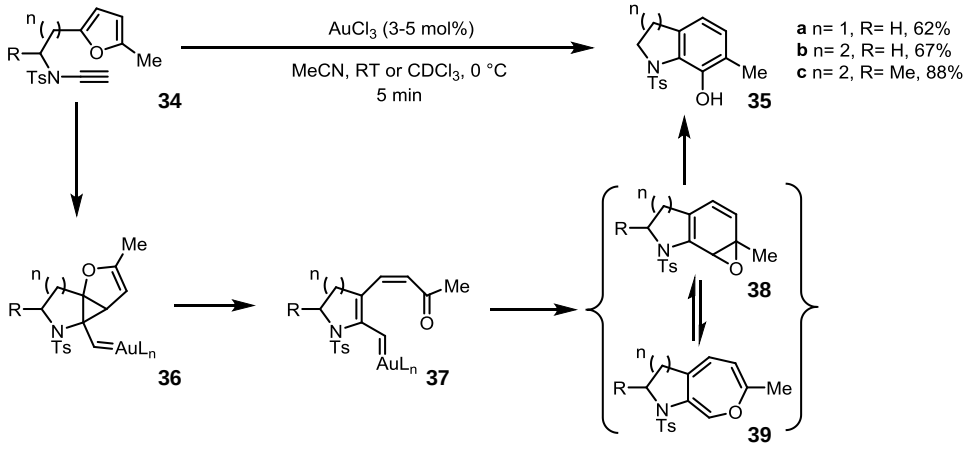
Scheme 12 – Gold-catalysed cycloisomerisation of enynamides.

The authors explained the diastereoselectivity of the reaction by considering a chair like transition state where a π-complex is formed between the developing positive charge on the metal-coordinated ynamide and the alkene double bond. They argued that in the α-substituted case reactive conformer **26** is disfavoured, as stabilisation of the developing carbocation by the nitrogen lone pair increases the unfavourable steric interaction between the α-substituent and the tosyl group (similar to $A^{1,2}$ strain). In the β-substituted case, conformer **31** is favoured, avoiding the 1,3-diaxial interactions present in conformer **30**. In both cases the favoured conformers **27** and **31** lead to the formation of the expected cyclopropyl pyrrolidines **28** and **32**. A 1,2-alkyl shift maintains the high level of diastereoselectivity, generating the silylated cyclobutenes **29** and **33** respectively, which upon desilylation and hydrolysis give observed cyclobutanones **21**.



Scheme 13 – Mechanistic rational for observed diastereoselectivity.

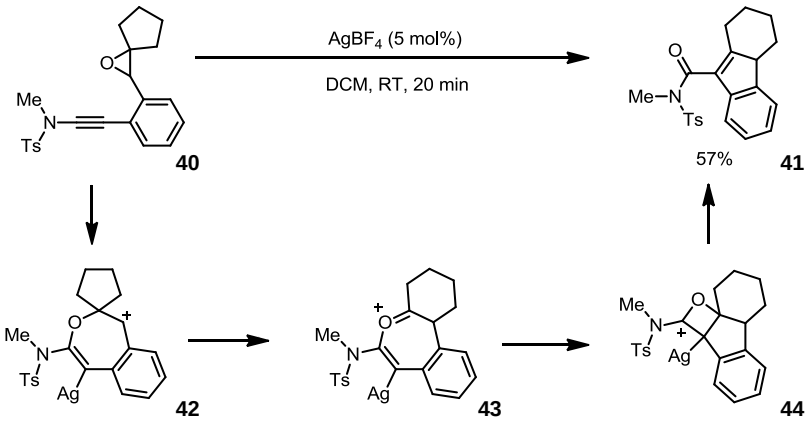
Hashmi *et al* were able to employ $AuCl_3$ as a catalyst in the efficient synthesis of dihydroindoles and tetrahydroquinolines **35** from ynamido-furans **34** (Scheme 14).[31] The mechanism probably involves the initial formation of the same cyclopropyl metallocarbene **36**, previously hypothesised. The additional enol ether present in this case however, promotes a ring opening to give intermediate **37**. The metal carbenoid can then undergo an insertion into the nearby carbonyl to generate epoxide **38**, which isomerises to give the product.



Scheme 14 – Gold-catalysed cycloisomerisation of ynamido-furans.

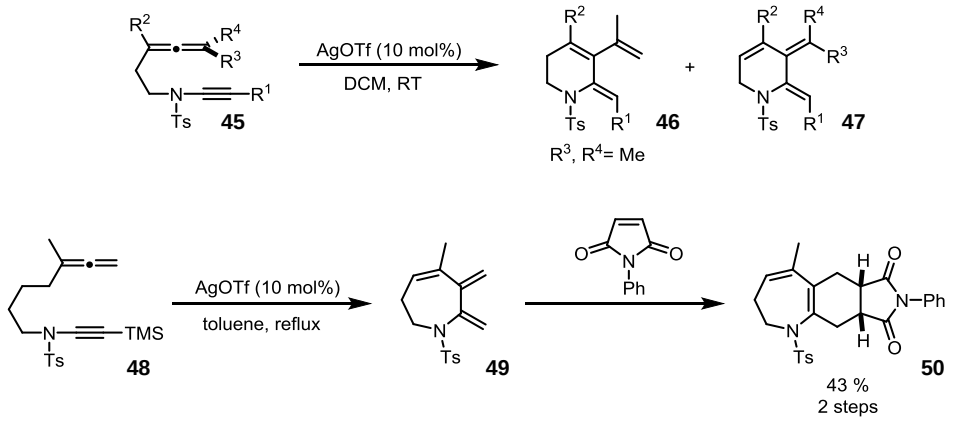
Gold- and silver-catalysed cycloisomerisations of epoxide-alkyne functionalities to generate a diverse range of carbocyclic and heterocyclic frameworks were presented by Liu and co-workers,[32] one silver-catalysed example featuring an ynamide substrate (Scheme 15). It was proposed that coordination of the metal to the ynamide triggers the formation of carbocation

42, which then undergoes a 1,2-alkyl shift to intermediate **43**. Electrocyclic ring closure and subsequent regeneration of the silver catalyst then generates product amide **41**.



Scheme 15 – Silver-catalysed cycloisomerisation of epoxide-ynamide functionalities.

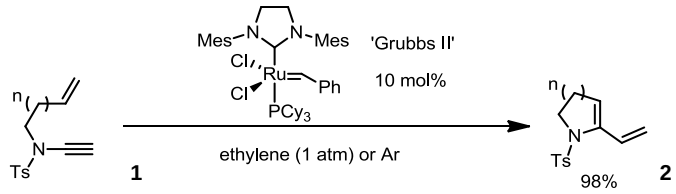
Silver was also found to catalyse the cycloisomerisation of a variety of allenynamides **45** generating nitrogen-containing heterocycles incorporating cross-conjugated trienes (Scheme 16).[33] Both tetrahydropyridine-based trienes **46** and **47**, and azepanes **49** could be generated depending on the tether length. Furthermore, formation of the trienes in the presence *N*-phenylmaleimide produced polycyclic ring systems such as 7,6,5-annulated heterocycle **50** *via* a tandem cycloisomerisation/Diels-Alder sequence.



Scheme 16 – Silver-catalysed cycloisomerisation of allenynamides.

1.3.3 Ring-closing enyne metathesis (RCEM)

In 2002 Mori and co-workers published the first examples of RCEM with an enynamide,[34] where Grubbs second generation catalyst was used with terminal enynamides **1** to give cyclic dienamides **2** in high yields (Scheme 17). For the formation of 5-membered rings (n= 1), the reaction proceeded best in toluene at 80 °C, whereas with a longer tether (n= 2) the optimal reaction was in DCM at reflux. Interestingly, for both cases a comparable yield could be achieved for the reaction using an argon atmosphere, rather than ethylene.

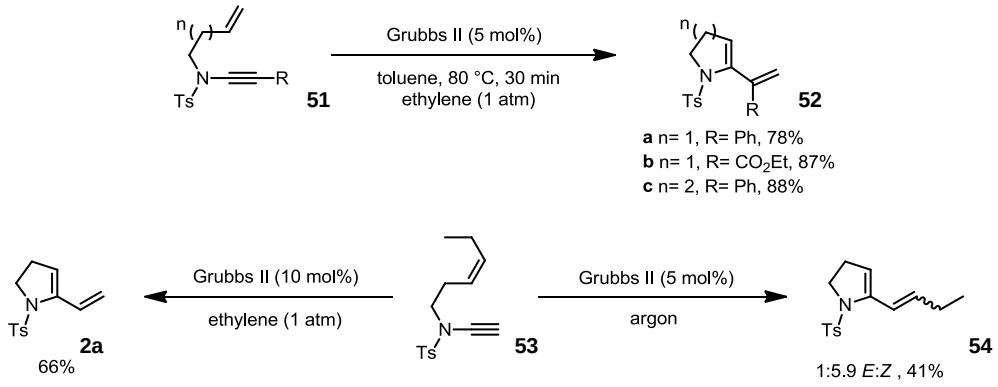


n =	Atmosphere	Solvent/Temp	Time	Product	Yield
1	ethylene	DCM/reflux	4 h	**2a**	66
1	ethylene	toluene/80 °C	15 min	**2a**	83
1	argon	toluene/80 °C	30 min	**2a**	76
2	ethylene	DCM/reflux	6 h	**2b**	85
2	argon	DCM/reflux	5 h	**2b**	82

Scheme 17 - Ruthenium-catalysed RCEM of enynamides.

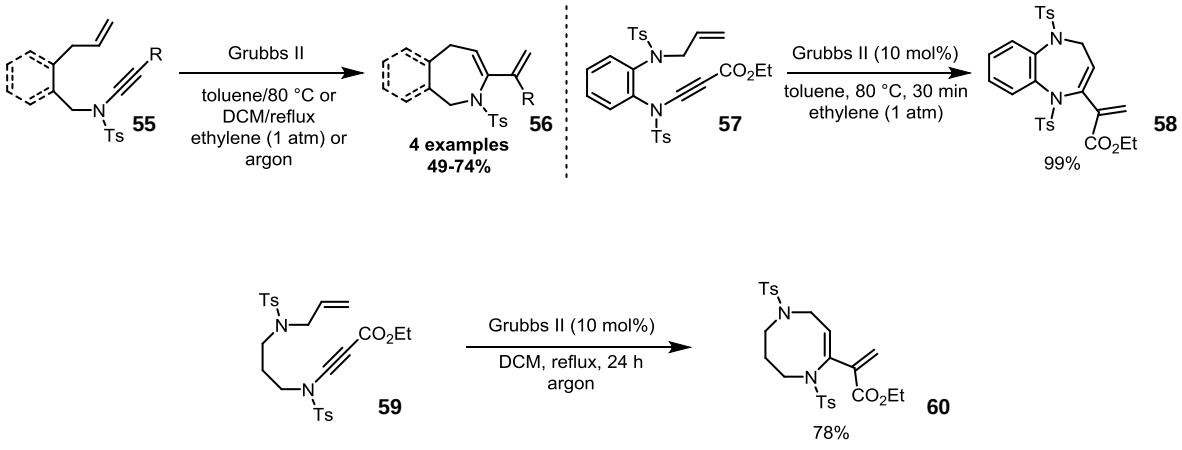
Later, this work was expanded to include terminally substituted ynamides **51**, once again generating cyclic dienamides **52** in good yields (Scheme 18).[35] These dienamides were found to be excellent substrates for Diels-Alder reactions and a number of these were carried out, both on the isolated dienamides and as a one pot procedure from the enynamides. When an enynamide containing a disubstituted alkene moiety **53** was investigated, the product was found to differ between the use of an ethylene or argon atmosphere. In an argon atmosphere, the expected metathesis product **54** was observed as a 1:5.9 mixture of *E*:*Z* isomers. This product represents the direct addition of the ruthenium alkylidene generated by the catalytic cycle to a new molecule of substrate. In the presence of ethylene gas, exchange of the ethylene

with the ruthenium alkylidene, leads to the formation of cyclic dienamide **2a**, possessing a terminal alkene moiety.



Scheme 18 - Synthesis of cyclic dienamides using ruthenium-catalysed RCEM.

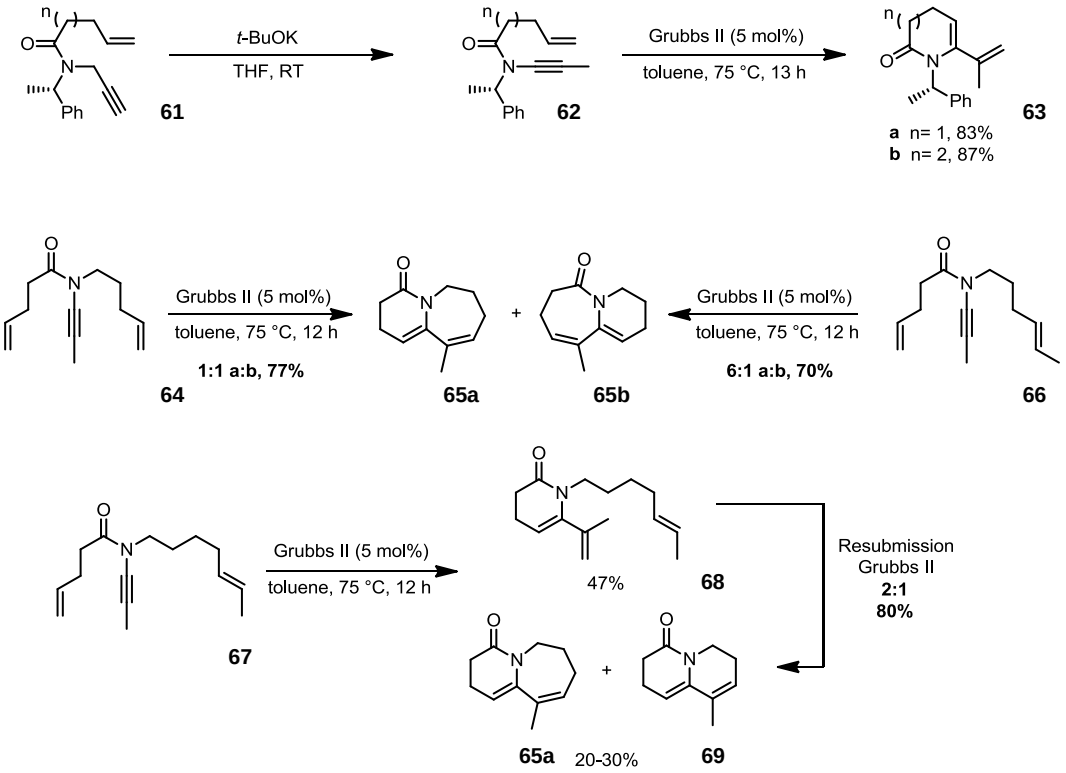
Mori and co-workers also reported the RCEM of enynamides to give medium sized 7- and 8-membered ringed cyclic dienamides (Scheme 19).[36] An additional sulfonamide on the backbone of the molecule could be tolerated, with benzodiazepine derivative **58** being prepared in excellent yield from enynamide **57**. In the 8-membered ring case, enynamide **59** proved to be the only successful substrate, with others either proving unreactive or undergoing dimerisation.



Scheme 19 – Synthesis of medium-sized heterocyclic dienamides.

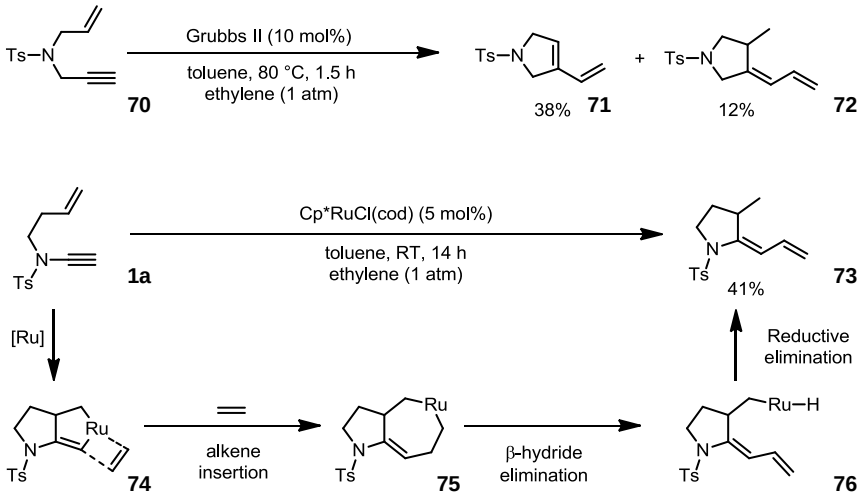
Taking the chiral enynamides **62** generated from the base-induced isomerisation of propargyl amides **61**, Hsung and co-workers were able to promote a RCEM generating chiral cyclic

dienamides **63** (Scheme 20).[11] As expected, these dienamides made excellent substrates for Diels-Alder reactions, although with only moderate diastereoselectivity. In the same paper the first successful tandem RCEM reactions of dienynamides were reported. Both dienynamide **64** and **66** could be used to generate a mixture of 6,7-fused products **65a** and **65b**. Dienynamide **64** gave a 1:1 ratio of products suggesting that RCEM is equally likely from either direction in a ene-yne-ene manner. When the tethers are differentiated as in dienynamide **66**, RCEM favours initiation on the less substituted double bond giving a higher proportion of product **65a**. When dienynamide **67** was subjected to RCEM conditions, the desired 6,8-fused system was not seen; instead monocyclic dienamide **68** was formed in 47% yield along with 20-30% of ring closed products **65a** and **69**. This suggested that the potential second ring closure to form the 8-membered ring was significantly slower and that instead alkene migration was occurring in the monocyclic dienamide intermediate **68**. Indeed, resubmitting monocyclic dienamide **68** to the same reaction conditions led to the formation of a 2:1 mixture of bicyclic products **65a** and **69** in 70% yield.



Scheme 20 – RCEM of chiral enynamides and achiral dienynamides.

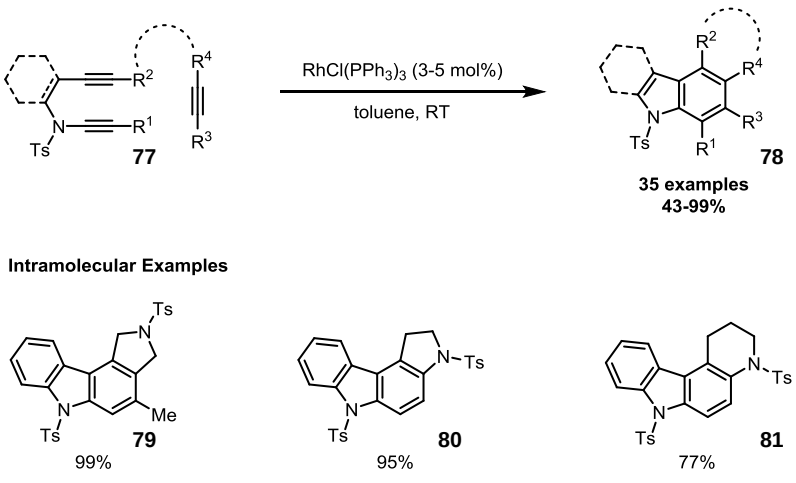
Whilst investigating RCEM, Mori *et al.* discovered that under an ethylene gas atmosphere enyne **70** formed the metathesis product **71** in low yield but also 12% of pyrrolidine **72** (Scheme 21).[37] This pyrrolidine product suggested a possible alternative reaction pathway which the authors chose to investigate by exploring other ruthenium catalysts. As well as numerous enyne substrates, they found that enynamide **1a**, when exposed to catalytic Cp*RuCl(cod) in an ethylene gas atmosphere, underwent a reaction to form unprecedented cyclic dienamide **73**.[38] The reaction was thought to proceed *via* formation of a ruthenacyclopentene **74**, followed by alkene insertion to generate 7-membered ruthenacycle **75**. β-Hydride elimination and then reductive elimination from the resulting ruthenium hydride **76**, gives observed product **73**.



Scheme 21 – Ruthenium-catalysed alkenylative cyclisation of enynes.

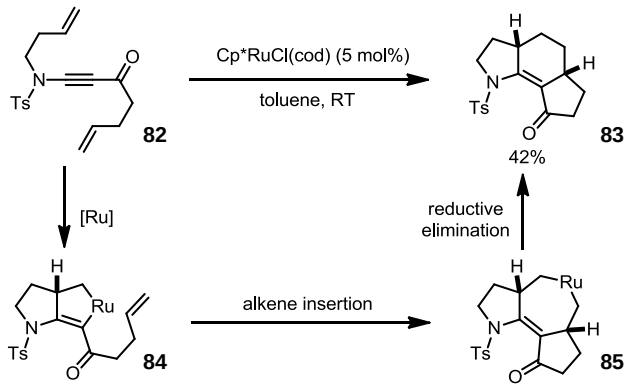
1.3.4 Intramolecular cyclotrimerisations (Formal [2+2+2]-cycloaddition)

In 1999 Witulski and Stengel reported the first examples of rhodium-catalysed formal [2+2+2] cycloadditions of ynamides (Scheme 22).[39] By employing yne-ynamides **77** with a variety of alkynes and Wilkinson's catalyst, the authors were able to generate a diverse range of indoles and carbazoles **78** in good to excellent yields. The regioselectivity of the reaction with unsymmetrical alkynes was found to be highly dependent on both steric factors and the solvent used.[40] Later the substrate scope was expanded, including diyne-ynamide substrates, where the intramolecular version of the reaction offered straightforward access to annulated carbazoles **79**-**81**.[41]



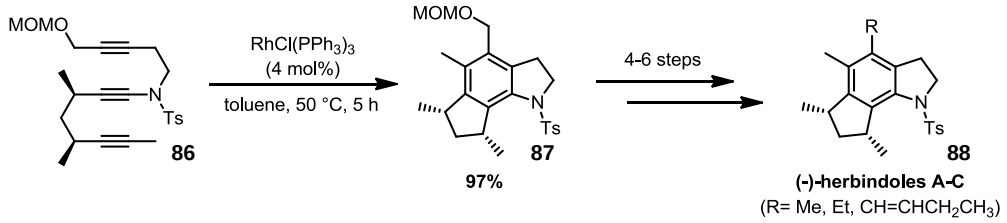
Scheme 22 – Rhodium-catalysed inter- and intramolecular alkyne cyclotrimerisations.

Mori and co-workers presented a paper in which numerous straight-chain 1,11-diene-6-yne substrates underwent cyclotrimerisation under mild conditions using Cp*Ru(cod)Cl as the catalyst, to give tricyclic frameworks in high yields.[42] One such example employed dienynamide **82** to generate heterocyclic tricycle **83**, albeit in a more moderate yield (Scheme 23). In a similar manner to the ruthenium-catalysed alkenylative cyclisation of enynamides (Scheme 21), the mechanism of the reaction is thought to involve the initial formation of ruthenacyclopentene **84**, followed by alkene insertion to give 7-membered ruthenacycle **85**. In this case however, the conformation for β-hydride elimination is restricted and a direct reductive elimination occurs to generate the tricyclic product. Indeed, an attempt to increase tether length of the substrate altered the reaction pathway, with the product once again derived from a β-hydride elimination final step.



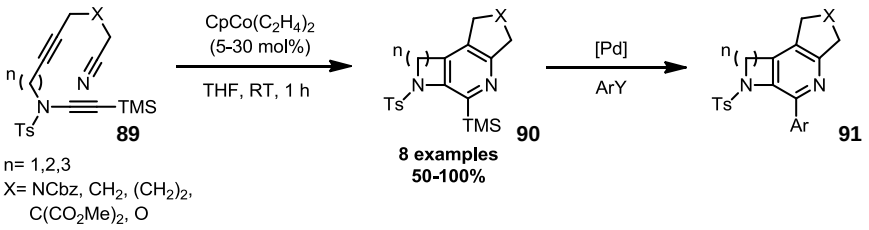
Scheme 23 – Ruthenium-catalysed cyclotrimerisation of dienynamides.

Saito and Sato were able to use the ruthenium-catalysed intramolecular cyclotrimerisation of diyne-ynamides as a key step in the total synthesis of (–)-herbindoles A, B and C **88** (Scheme 24).[43] Tricyclic scaffold **87**, the core of all three natural products, was generated from an acyclic precursor **86** in a single high yielding reaction. Manipulation of the MOM-group side-chain then led to each of the natural products in 4-6 additional steps.



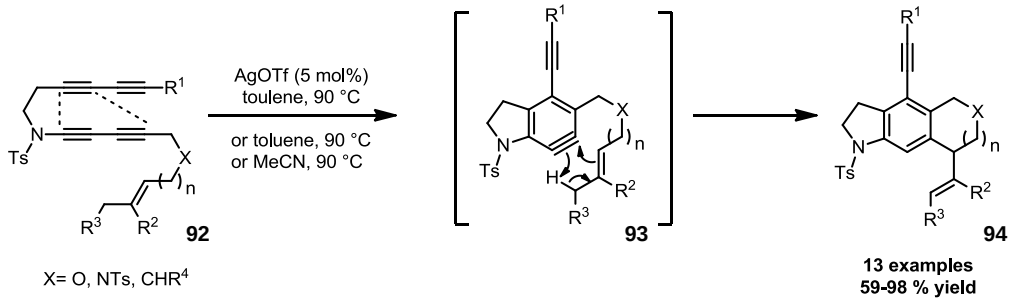
Scheme 24 - Total synthesis of (–)-herbindoles A, B and C.

Aubert and Malacria discovered the first intramolecular [2+2+2] cycloaddition between substrates containing an ynamide, internal alkyne and nitrile (Scheme 25).[44] Acyclic precursors **89**, of varying tether lengths and with or without additional heteroatoms, were cyclised using a $CpCo(C_2H_4)_2$ catalyst to give tricyclic 3-aminopyridines **90**. The authors were pleased to discover that these already interesting 3-aminopyridines **90** could be further functionalised by utilising the TMS group in Hiyama cross-coupling.



Scheme 25 – Cobalt-catalysed intramolecular cyclotrimerisation of yne-ynamide-nitriles.

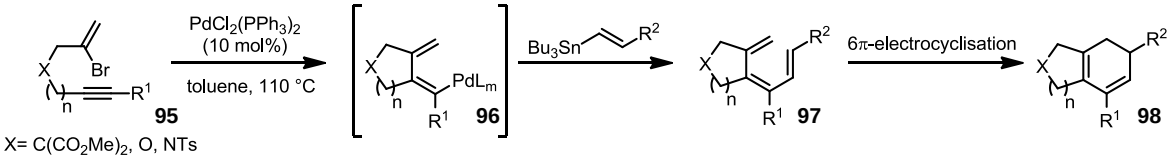
Recently, Lee and co-workers investigated the Alder-ene reactions of arynes **93** generated directly by the cyclotrimerisation of bis-1,3-diynes **92** (Scheme 26).[45] The substituent patterns on the alkene, the tether length and the nature of the connecting heteroatom all affected the efficiency of the reaction and the optimum conditions varied between substrates.



Scheme 26 – Cyclotrimerisation of bis-1,3-diynes and successive Alder-ene reaction.

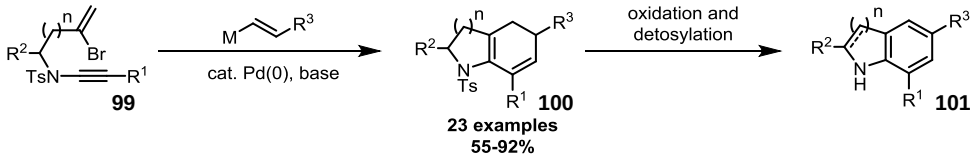
1.4 Previous Group Work

Early work in our research group focused around the development of a palladium-catalysed carbopalladation/cross-coupling/electrocyclisation cascade, as a way of generating complex polycyclic structures **98** in a single step from acyclic bromoenyne precursors **95** (Scheme 27).[46] Palladium(0) is thought to undergo oxidative insertion into the C-Br bond of the vinyl bromide, followed by a *syn*-carbopalladation onto the alkyne to give dienyl-palladium species **96**. A Stille cross-coupling with the already present vinyl stannane coupling partner then generates triene **97**, which undergoes a 6π-electrocyclisation to generate the bicyclic product **98**.



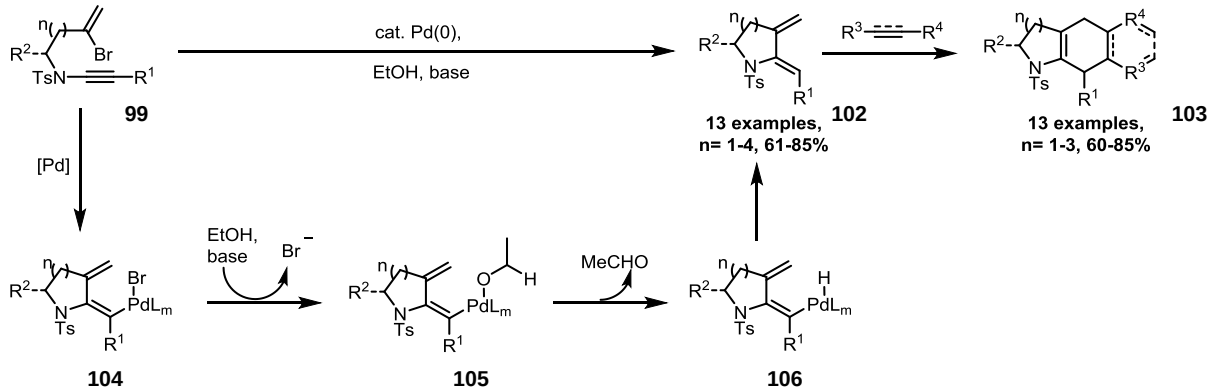
Scheme 27 – Synthesis of polycyclic rings *via* a palladium-mediated cascade reaction.

This reaction was extended to include bromoenynamide substrates **99** as a method for synthesising a diverse range of highly-desirable azacycles (Scheme 28).[47] The vinyl stannanes were largely replaced with more environmentally friendly vinyl boron derivatives. Whilst the dienamides **100** formed from the cascade reaction are important frameworks in their own right, selective and tunable oxidations gave access to the corresponding heteroaromatic bicycles **101**; namely indoles, indolines, tetrahydroquinolines, and benzazepines. Such heteroaromatic bicycles are widespread within organic chemistry, being found in many biologically active molecules, and this methodology provides a general and efficient method for their synthesis.



Scheme 28 - Palladium-catalysed cascade cyclisation of bromoenynamides to azabicycles.

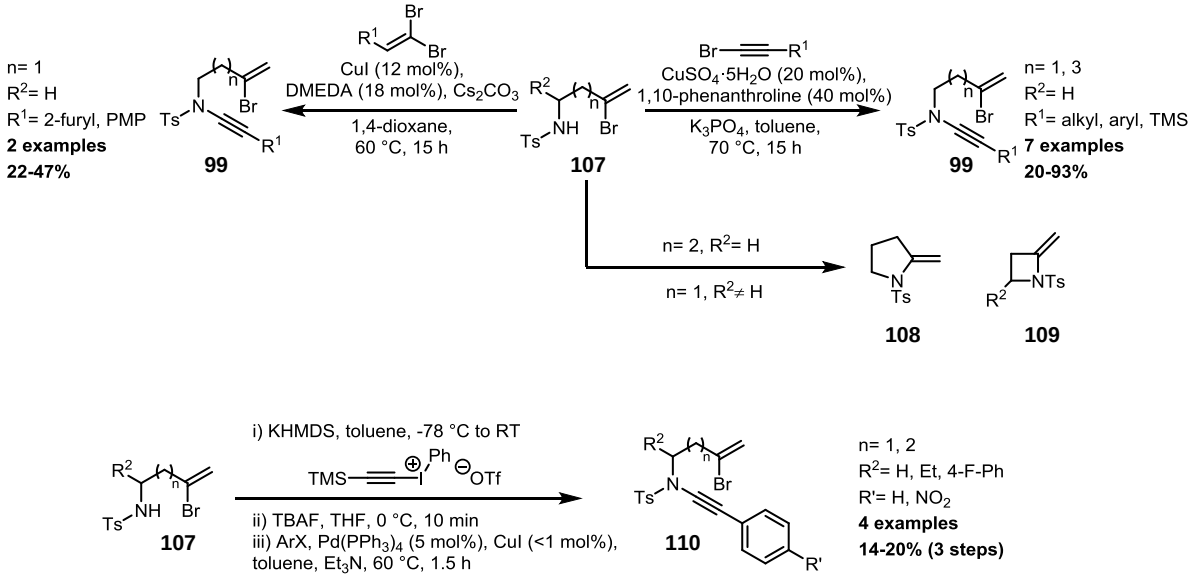
In the absence of a cross-coupling partner and with an alcoholic solvent to act as a hydride source, cyclic dienamides **102** could be isolated (Scheme 29).[48] Mechanistic investigations supported the proposed hypothesis that the initial steps of the reaction were once again oxidative insertion/*syn*-carbopalladation to form dienyl-palladium intermediate **104**. Coordination of EtOH/EtO$^-$ to the metal and subsequent β-hydride elimination generates acetaldehyde and palladium hydride **106**, which then undergoes a reductive elimination to the dienamide product **102**. These dienamides **102** proved to be good substrates for Diels-Alder reactions in order to generate a complementary range of bicyclic and tricyclic azacycles **103**.



Scheme 29 - Reductive cyclisation of bromoenynamides.

For both the cascade reaction (Scheme 28) and the reductive cyclisation (Scheme 29) the bromoenynamide substrates **99** were synthesised *via* alkynylation of the corresponding sulfonamide **107** (Scheme 30). Copper catalysis was the preferred method of ynamide formation, either the conditions pioneered by Hsung using bromoalkynes,[17] or those of Evano using vinyl dibromides.[21] However, under these conditions substrates with a pent-4-enyl chain (n= 2) did not form the desired ynamides, instead undergoing an intramolecular cyclisation to give pyrrolidines **108**. The addition of a substituent to the sulfonamide in the α-position (n= 1,

$R^2 \neq H$) also prevented ynamide formation, with azetidines **109** being formed. Therefore, in order to synthesise pent-4-enyl sulfonamides (n= 2) and α-substituted sulfonamides ($R^2 \neq H$) lithium amides with alkynyl iodonium salts had to be employed. However, the synthesis of the alkynyl iodonium salts remained problematic and alkyl groups could not be tolerated. The overall sequence formed aryl ynamides **110** in low yields; this route clearly did not offer a satisfactory alternative.



Scheme 30 – Synthesis of bromoenynamides.

1.5 Initial Aims

Cyclic 2-amidodienes represent building blocks with much synthetic potential. This project was to investigate ways of synthesising fused, spirocyclic and linked bicyclic amines from these cyclic dienamides, to generate small molecules of general interest to the pharmaceutical industry. This would build on previous worked carried out within the group, employing the cyclic dienamides formed by the reductive cyclisation of bromoenynamides, as well as other ynamide chemistry.

2. Reactions of Cyclic Dienamides

2.1 Introduction

Bicyclic nitrogen-containing frameworks are of fundamental importance in medicinal chemistry, due to their prevalence in numerous natural products and other biologically active molecules.[49] Due to the challenges associated with the preparation of such heterocycles, their synthesis remains a prominent area of investigation, within both the pharmaceutical industry and the wider synthetic community. As well as the preparation of the skeletal framework, the substitution pattern and, for saturated rings, control of both relative and absolute stereochemistry is also important. The initial aims of this project targeted the synthesis of three distinct classes of bicyclic diamines: fused ring systems, spirocyclic systems and linked ring systems (Figure 1), which were deemed to be of interest to our industrial sponsor.

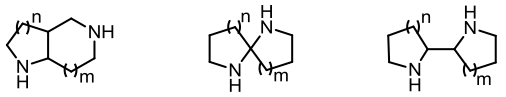
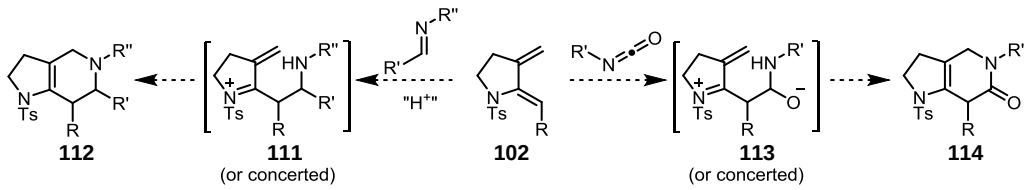


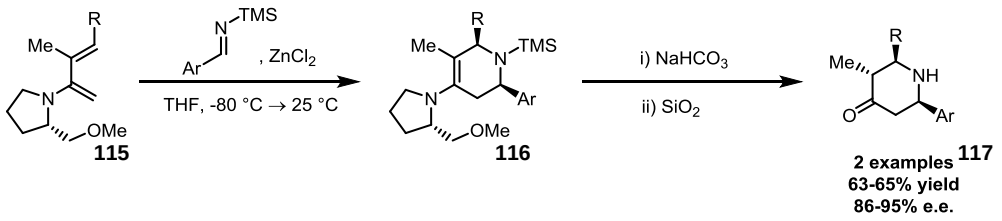
Figure 1 : Bicyclic diamine scaffolds.

Our group had recently developed the reductive cyclisation of bromoenynamides as a way of synthesising cyclic dienamides **102** (Scheme 29).[48] Our strategy for the synthesis of bicyclic diamines was to utilise these cyclic dienamides **102** as key building blocks for further annulation. It was hoped that the reactivity of the 2-amidodiene moiety could be exploited in order to build in a second nitrogen-containing ring using either inter- or intramolecular reactions. For example, it was hoped that cyclic dienamide **102** would undergo [4+2] cycloaddition reactions with aza-dienophiles such as imines and isocyanates, to give fused bicyclic amines **112** or sulfonamide-lactams **114** respectively (Scheme 31).



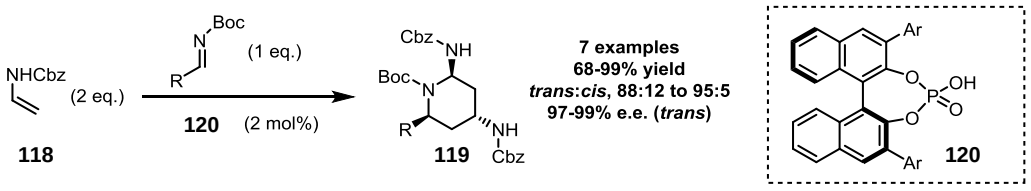
Scheme 31 – Cyclic dienamides as the key building-block.

Indications to the potential reactivity of enamides, in the context of bicyclic amine formation, are given in the literature. Barluenga *et al.* were able to carry out formal [4+2] cycloadditions of chiral 2-aminodienes **115** with an imine, in order to generate highly functionalised piperidones with good enantioselectivity (Scheme 32).[50] In this case, the enamide **116** resulting from the formal [4+2] reaction was hydrolysed to ketone **117** using mild hydrolytic conditions.



Scheme 32 – Cycloadditions of aminodienes and imines.

The nucleophilic/electrophilic nature of enamides was also exploited by Terada *et al.* in the enantioselective formation of piperidine derivatives **119** *via* a chiral monophosphoric acid-catalysed tandem aza-ene type reaction (Scheme 33).[51] The phosphoric acid facilitates an initial asymmetric addition of the enamide to the imine, followed by addition of another equivalent of enamide to the resultant iminium ion. Intramolecular cyclisation then terminates the reaction sequence in an efficient one-pot procedure.

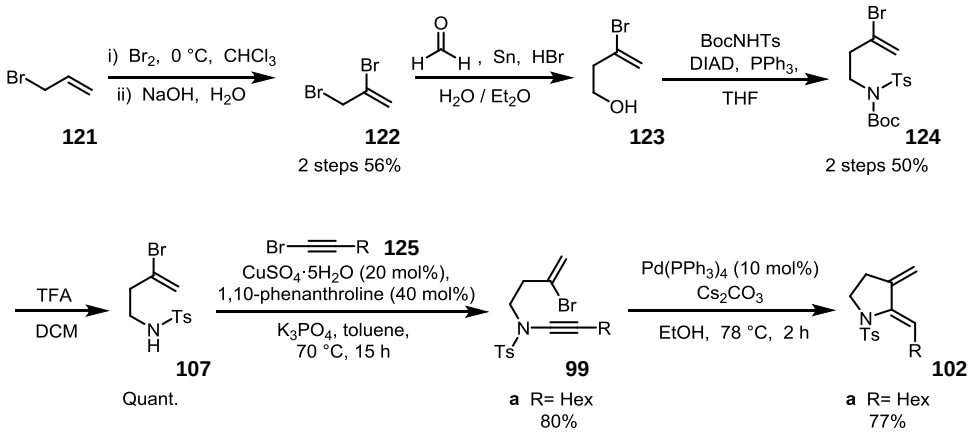


Scheme 33 – Acid-catalysed tandem aza-ene type reaction.

These two papers suggested that we might be able to employ substrate control or a chiral acid catalyst with our cyclic dienamides, in order to generate the additional nitrogen-containing ring in an enantioselective manner.

2.2 Substrate Synthesis

Dienamide **102a** (R= Hex) was chosen as an initial test substrate for our reactivity investigations and therefore was synthesised by our previously reported route on gram scale (Scheme 34). 2,3-Dibromopropene **122** was prepared in two steps from allyl bromide **121** by dibromination using elemental bromine and selective elimination. Although 2,3-dibromopropene **122** is commercially available, it is relatively expensive and we found the quality to be inconsistent. A tin-promoted Barbier allylation of formaldehyde with **122** then generated alcohol **123**.[52] Since purification of alcohol **123** often proved capricious, it was converted to Boc-protected sulfonamide **124** under Mitsunobu conditions before column chromatography, resulting in a 50% yield over two steps.[53] Boc deprotection using TFA gave sulfonamide **107** which could be used without further purification, and was smoothly converted to the corresponding bromoenynamide **99a** using Hsung's copper-catalysed coupling reaction with bromoalkyne **125**.[17] The palladium-catalysed reductive cyclisation of bromoenynamide **99a** then gave our desired cyclic dienamide **102a** in good yield.

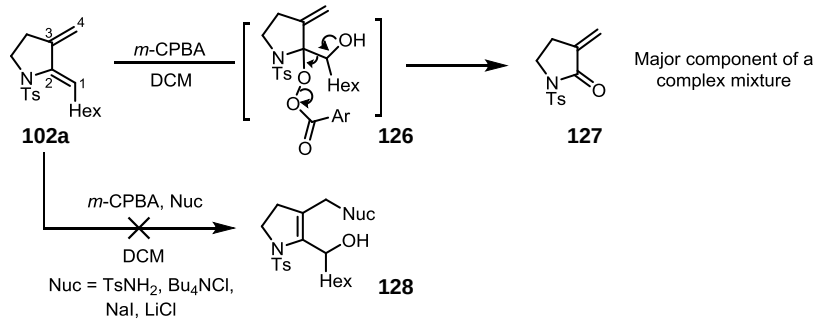


Scheme 34

2.3 Initial Investigations of Dienamide Reactivity

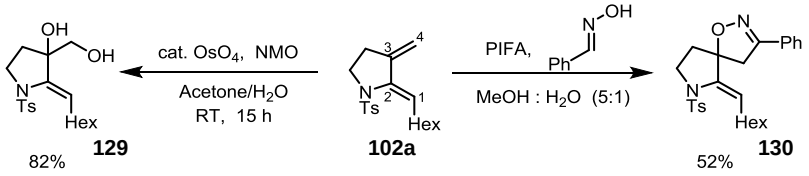
Dienamide **102a** was treated with a number of electrophiles in order to probe the reactivity of the alkenes, and potentially form our first heterocycles. Attempts were made to epoxidise cyclic dienamide **102a**, but using either commercially supplied or recrystallised *m*-CPBA, no epoxide was ever detected (Scheme 35). Instead, γ-lactam **127** was formed along with some unidentified impurities. Mechanistically, this can perhaps be explained by initial epoxidation of the 1,2-double bond of the 2-amidodiene (thought to be more election-rich due to mesomeric donation from the nitrogen lone pair), followed by reaction with a second equivalent of *m*-CPBA to give intermediate **126**, and then elimination of heptanal (as shown). Indeed, we observe the presence of an aldehyde in the crude reaction mixture adding support to this hypothesis. Additionally, using 1.0 eq. of recrystallised *m*-CPBA (i.e. without significant 3-chlorobenzoic acid and/or H_2O) led to only 40% conversion of the starting material.

When a nucleophile was added to the reaction, the hope was this would preferentially open the epoxide to give cyclic enamides **128**. These could then undergo ring-closing reactions to give bicyclic nitrogen-containing frameworks. Unfortunately however, in all the cases where a nucleophile was added only complex mixtures, sometimes containing γ-lactam **127**, were isolated. The use of a Shi epoxidation,[54] or DMDO were also investigated as a means of forming the epoxide, but both met with no success.



Scheme 35

Dienamide **102a** was found to undergo dihydroxylation under Upjohn conditions to form dihydroxylated product **129** in good yield, with exclusive selectivity for the *exo*-methylene moiety (Scheme 36). Preferential reaction of the 3,4-alkene was also observed when dienamide **102a** was treated with a nitrile oxide (generated *in situ* from an oxime and PIFA) in a 1,3-dipolar cycloaddition to give isoxazole **130** as a single regioisomer (thought to be as shown on the basis of ^{13}C NMR spectroscopic chemical shift measurements).



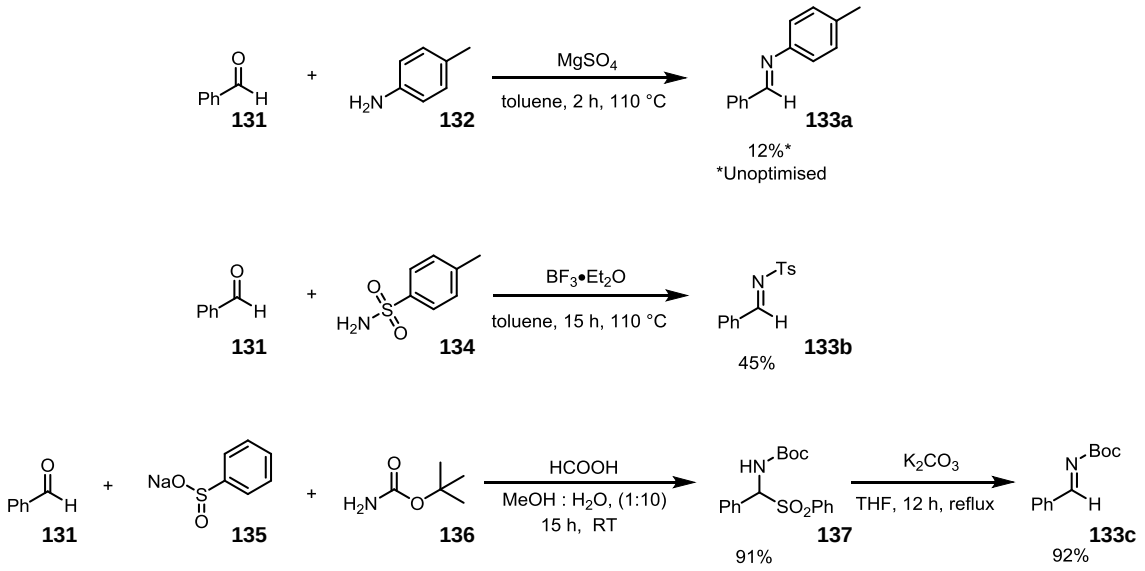
Scheme 36

It is surprising that both dihydroxylation and 1,3-dipolar cycloaddition appear to be occurring on the less electron-rich alkene. However, this potentially highlights the fact that whereas delocalisation of the nitrogen-atom lone pair in enamines and ynamines is widely observed, in contrast, this effect is often less significant for enamides and ynamides. This could be explained by the inductive electron-withdrawing nature of the tosyl group, or the fact that donation of the nitrogen lone pair into the diene system would increase $A^{1,3}$-strain between the tosyl group and the hexyl substituent. Positioning the tosyl group away from the hexyl chain with a tetrahedral geometry around the nitrogen centre reduces unfavourable steric interactions, but the nitrogen lone pair of electrons is no longer correctly orientated for mesomeric donation into the diene system. Therefore, for dienamide **102a**, the 1,2-alkene is only slightly more electron rich than the 3,4-alkene, meaning that other factors (such as sterics) can significantly alter the selectivity.

2.4 Formal [4 + 2] Cycloadditions

2.4.1 Imines

Given the literature precedent for imines undergoing formal [4+2] cycloadditions with 2-aminodienes,[50] we were hopeful that dienamide **102a** might behave in a similar manner. Imines **133a-c** were therefore synthesised using known literature procedures (Scheme 37). No reaction was observed between dienamide and imine, but we anticipated that a phosphoric acid catalyst would help facilitate the reaction, as these have been widely used to catalyse reactions with imine electrophiles, chiral phosphoric acids often allowing for asymmetric induction.[55] Disappointingly, all of these imines failed to react with dienamide **102a** at room temperature even when 10 mol% of acid catalyst was added. When the reactions were heated up to a maximum of 80 °C, starting material was consumed but only complex mixtures were obtained.



Scheme 37

In hindsight this failure to react under phosphoric acid catalysis is perhaps unsurprising, if we consider the postulated mechanism for aza-ene type reactions (Figure 2).[56] The phosphoric acid is thought not only to coordinate to the nitrogen of the imine but also to the N-H of the

enamide through a hydrogen-bonding array. It has been indicated in the literature that lack of this dual activation is highly detrimental to reactivity,[57,58] and in the case of our dienamide **102a** this N-H is absent.

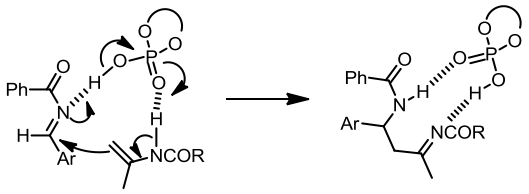
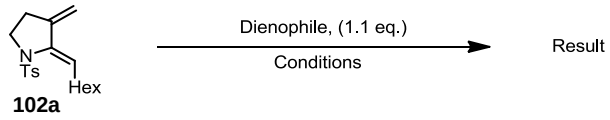


Figure 2 : Mechanistic hypothesis for an aza-ene-type reaction catalysed by a phosphoric acid.

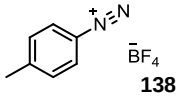
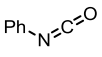
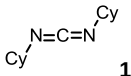
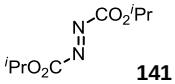
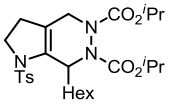
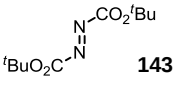
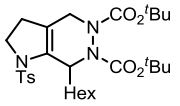
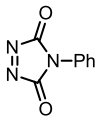
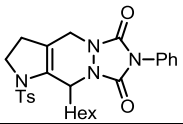
2.4.2 Heteroatom-containing dienophiles (commercially available)

The formal [4+2] cycloaddition of a dienamide **102a** with a number of commercially available nitrogen-containing dienophiles was investigated (Table 1), as an alternative strategy to form heterocycles. Aryldiazonium salt **138** reacted to give a complex mixture, even at room temperature (entry 1). Phenyl isocyanate **139** and DCC **140** were likewise unsuccessful, with no reaction occurring until elevated temperatures ≥100 °C (entries 2 & 3). In stark contrast, DIAD **141** and DTAD **143** both underwent efficient cycloadditions with dienamide **102a** at room temperature giving bicyclic adducts **142** and **144** in good to excellent yield (entries 4 & 5). Formation of cycloadduct **144** was significantly slower than for **142**, probably due to increased steric hindrance of the *t*-Bu groups. We also found that tricyclic adduct **146** could be generated very rapidly in good yield, using highly reactive dienophile PTAD **145** (entry 6).

Table 1 : Formal [4 + 2] cycloadditions of heteroatom-containing dienophiles.



102a

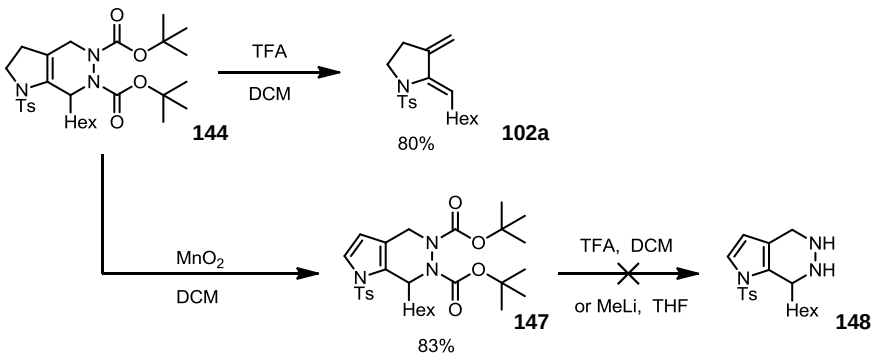
Entry	Dienophile	Conditions[a]	Result	Isolated Yield
1	 **138**	DCM, 25 °C, 6 h	Complex mixture	-
2	 **139**	a) DCM, 25 °C, 15 h b) PPTS[b], DCM, 25 °C, 5 h c) PPTS[b], toluene, 80 °C, 2 h d) PPTS[b], toluene, 100 °C, 2 h	a) n.r. b) n.r. c) n.r. d) Complex mixture	- - - -
3	 **140**	a) DCM, 25 °C, 6 h b) PPTS[b], DCM, 25 °C, 5 h c) PPTS[b], toluene, 80 °C, 2 h d) PPTS[b], toluene, 100 °C, 2 h	a) n.r. b) n.r. c) n.r. d) Complex mixture	- - - -
4	 **141**	DCM, 25 °C, 1.5 h	 **142**	75%
5	 **143**	DCM, 25 °C, 15 h	 **144**	95%
6	 **145**	DCM, 25 °C, 10 min	 **146**	85%

[a] 0.1 M in solvent. [b] 10 mol% PPTS,

It was thought that the formal [4+2] cycloaddition might be accelerated via Brønsted acid catalysis and a number of such acids were screened with dienamide **102a** and DIAD **141**. When 10 mol% of PPTS or phosphoric acid catalyst was added to the reaction, no rate enhancement was observed, whilst catalytic TsOH led to partial hydrolysis of the dienamide.

In an attempt to diversify our products, bicyclic adduct **144** was exposed to TFA in the hope that Boc deprotection would give the unprotected hydrazine **148** (Scheme 38). Instead, dienamide **102a** was returned, perhaps *via* a [4+2] cycloreversion reaction. In order to prevent this, adduct **144** was oxidised using MnO_2 to the corresponding pyrrole **147**. Unfortunately

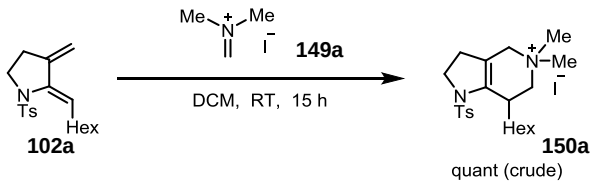
however, attempts to deprotect pyrrole **147** failed, with complex mixtures resulting from both TFA and MeLi deprotection conditions.



Scheme 38

2.4.3 Iminium ion salts

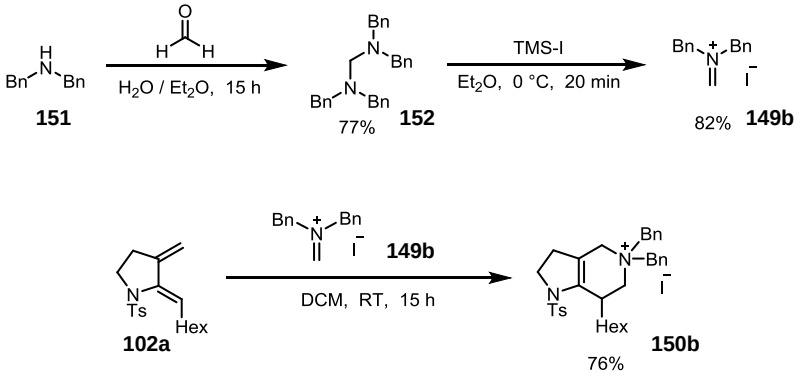
To our surprise, commercially available Echenmoser's salt **149a** was found to undergo a formal [4+2] cycloaddition with dienamide **102a** to give cycloadduct salt **150a** along with some impurities, with quantitative crude mass recovery (Scheme 39). Isolation of the pure product proved problematic due to its highly polar nature. Column chromatography, even using a MeOH/DCM eluent, failed remove the impurities and cycloadduct salt **150a** was therefore characterised as part of a crude mixture. This reaction did however highlight the possibility of utilising other iminium ion salts as dienophiles for our substrates.



Scheme 39

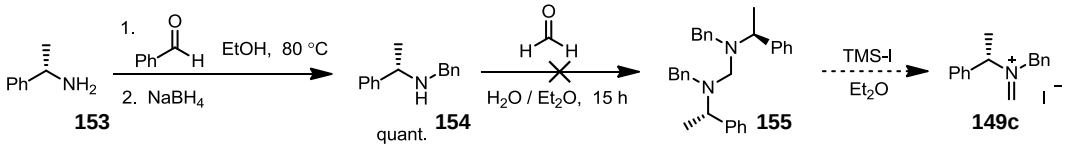
We hypothesised that the dibenzyl analogue of Eschenmoser's salt would allow access to a cycloadduct, mono-debenzylation of which would give an orthogonally protected bicyclic diamine. Iminium ion salt **149b** was therefore synthesised in a two-step process (Scheme 40): Dibenzylamine **151** was stirred with aqueous formaldehyde in order to form aminal **152**. TMSI

was then used to eliminate the silylated dibenzylamine from aminal **152** giving iminium ion salt **149b**, which could be isolated by column chromatography and stored at -20 °C. Pleasingly, iminium ion salt **149b** underwent a formal [4+2] cycloaddition with dienamide **102a** to give cycloadduct salt **150b**, and in this case purification by column chromatography (2→4% MeOH in DCM) was achieved, with the product obtained in good isolated yield.



Scheme 40

It was hoped that by using a chiral iminium ion salt, it would be possible to carry out a diastereoselective cycloaddition. The intention was to synthesise iminium ion **149c**, where one of the substituents on the nitrogen atom carries a stereogenic centre (Scheme 41). Amine **153** was converted to an imine, which was then reduced to benzylamine **154** in quantitative yield. However, we were unable to generate the corresponding aminal **155**, presumably due to the increased steric hindrance of the chiral substituent.

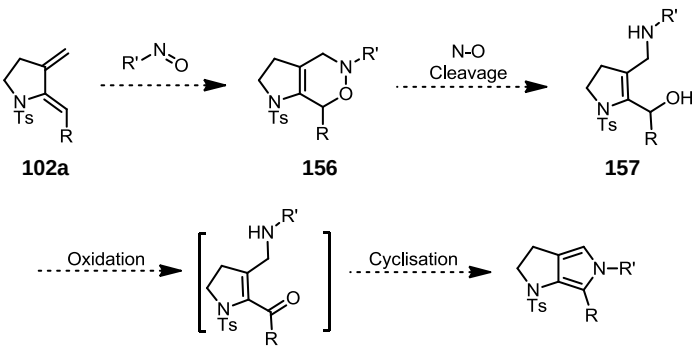


Scheme 41

2.4.4 Nitroso compounds

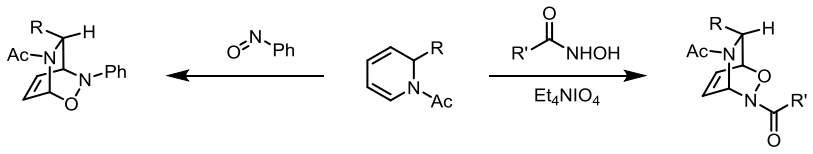
The use of nitroso compounds in hetero-Diels-Alder reactions with dienes is well documented,[59] including a number of asymmetric examples.[60] The cycloaddition of nitroso

compounds with dienamide **102a** also represented a possible route to the formation of bicyclic diamines (Scheme 42). Cleavage of the N-O bond in cycloadduct **156**, followed by oxidation of the resulting alcohol **157** and possible concomitant cyclisation was a particularly attractive route into these structures.



Scheme 42

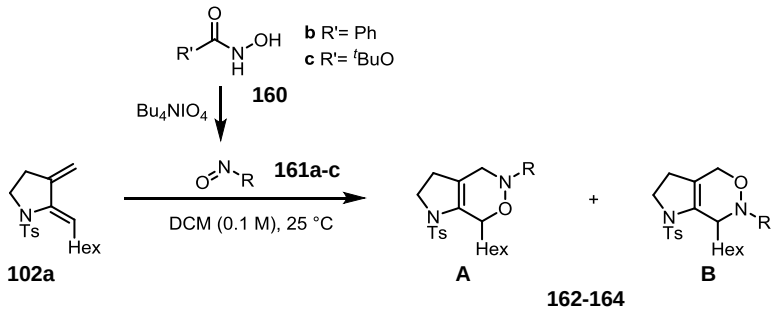
The regioselectivity of cycloadditions involving nitroso compounds is a delicate balance of steric and electronic factors.[59] In general, hetero-Diels-Alder reactions involving nitroso compounds are believed to proceed *via* a concerted but highly asynchronous transition state.[61] The electronic contribution to regioselectivity is determined by the principal interaction between the HOMO of the diene and the LUMO of the dienophile. In most cases the regioselectivity is the same for arylnitroso and acylnitroso species, determined by nature of the strongly electron donating/withdrawing substituents on the diene. There are cases in the literature however, where the regioselectivity of arylnitroso *vs* acylnitroso dienophiles with the same diene is reversed (Scheme 43).[62,63] In particular, 2-substituted dienes are sensitive to the nature of the dienophile, as the diene substituent only produces a weak directing effect.



Scheme 43 – Regioselectivity of arylnitroso *vs* acylnitroso dienophiles.[62,63]

Initially, dienamide **102a** was treated with commercially available nitrosobenzene **161a** in DCM at room temperature to give a 1:3.1 mixture of cycloadduct regioisomers **162A** and **162B** respectively, in a virtually instantaneous reaction (Table 2, entry 1). The presence of two regioisomers was apparent by TLC, but separation could not be achieved by column chromatography. For characterisation purposes, a small amount of each regioisomer was isolated by semi-preparative HPLC. In an effort to improve the regioselectivity, the reaction was performed at -78 °C, but this led to only a very minor improvement with the reaction still complete within 45 min (entry 2).

Table 2 : Formal [4+2] cycloadditions of nitroso compounds.



Entry	Nitroso Compound R =	Product	Temp (°C)	Reaction Time	A:B Ratio	Isolated Yield
1	Ph[a] (1.1 eq.) **161a**	**162**	25	5 min	3.1 : 1	81%
2		**162**	-78	45 min	3.5 : 1	n.d.
3	Bz[b] (2.2 eq.) **161b**	**163**	25	1 h	0 : 1	95%
4	Boc[c] (2.2 eq.) **161c**	**164**	25	1 h	1.8 : 1	98%

[a] Commercially available. [b/c] Generated *in situ* by the addition of *n*-Bu_4NIO_4 (2.3 eq.) followed by the portionwise addition of benzo[b]/Boc[c] hydroxamic acid (2.2 eq.) over 1 h.

We next turned our attention towards acylnitroso compounds, hoping that they would show greater regioselectivity. Acylnitroso compounds **161b** and **161c** (R= Bz, Boc) were generated *in situ* by the portionwise addition of the corresponding hydroxamic acid to *n*-Bu_4NIO_4 (entries 3

& 4).[64] In both cases, an excess (2.2 eq.) of the generated nitroso compound was required in order to achieve full conversion of the dienamide substrate, possibly due to some homo-dimerisation of the nitroso compound. Acylnitroso compound **161b** (R=Bz) underwent a cycloaddition with isolated dienamide **102a** to give cycloadduct **163B** as a single regioisomer and in excellent yield (entry 3). Acylnitroso compound **163c** (R=Boc) formed a 1.8:1 mixture of cycloadducts **164A** and **164B** respectively (entry 4). The regiochemistry in both cases was assigned on the basis of HMBC spectroscopy, considering the correlations to carbonyl carbon.

Changes in regioselectivity between the different nitroso dienophiles were not unexpected.[61] The weakly electron-donating effect of the sulfonamide nitrogen in dienamide **102a** means that for a simple predicted HOMO of this 2-amidodiene (Spartan 14, Hartree-Fock, 3.21G(*) basis set), the coefficient is slightly greater at C(1) than C(4) (Figure 3). An explanation of the observed regioselectivity is that increasing the electron-withdrawing ability of the R-substituent of the nitroso compound increases the LUMO coefficient on the nitrogen atom and therefore favours the formation of regioisomer **B** over **A**. This explains why the regioselectivity is reversed between nitroso compounds **161a** and **161b** (entries 1 & 3). With nitroso compound **161c**, the electron-withdrawing R group means that electronically it also favours the formation of regioisomer **B**. However, formation of regioisomer **A** with the bulky Boc group orientated away from the hexyl chain is sterically more favoured. The result of these two competing factors was a poor regioselectivity of 1.8:1 (entry 4).

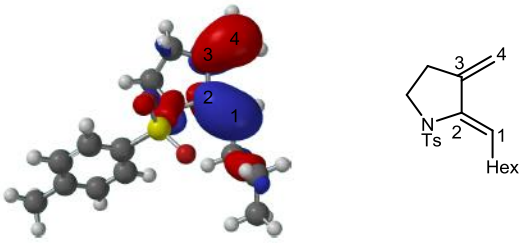
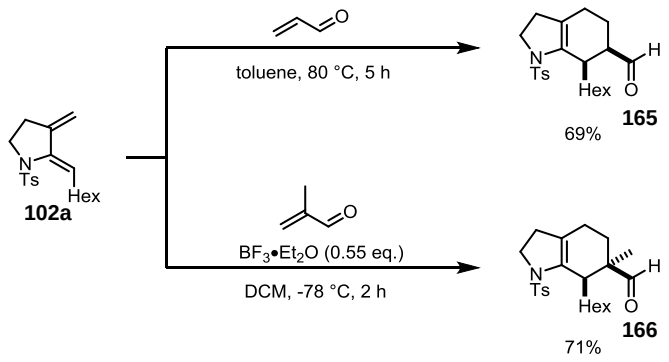


Figure 3 : Calculated HOMO for dienamide **102a**.

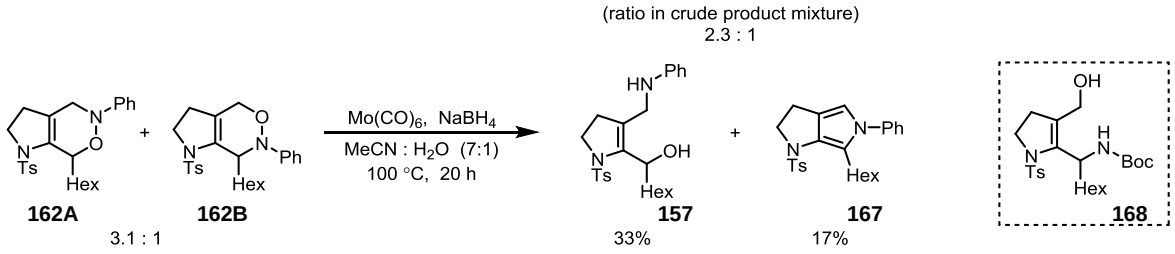
These results are surprising given the observed regioselectivity of the Diels-Alder reactions of dienamide **102a** with acrolein and methacrolein (Scheme 44, previous group work).[48] However, this still agrees with the hypothesis that the sulfonamide nitrogen lone pair is only weakly electron-donating and that the HOMO coefficient on C(1) of the diene is therefore only marginally greater than that of C(4) (the mildly electron-donating hexyl chain also helps to increase the HOMO coefficient on C(4)). For these Diels-Alder reactions with α,β-unsaturated aldehydes, one could explain the regioselectivity by suggesting that bond formation in the transition state is more advanced at the β-position of the dienophile. Sterics would therefore favour orientation of the β-position towards the less sterically hindered *exo*-methylene (C(4)) of dienamide **102a**, this effect overcoming the marginally smaller HOMO coefficient.



Scheme 44 – Regioselectivity of Diels-Alder cycloadditions with dienamide **102a**.[48]

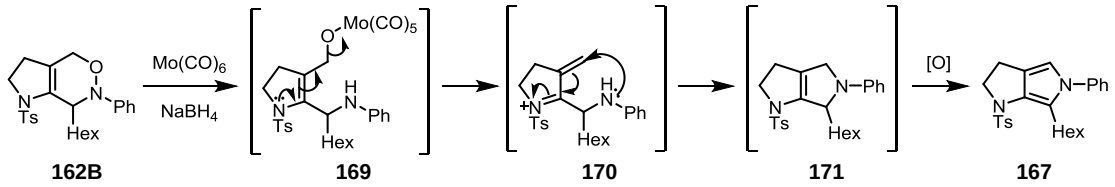
2.5 N-O Bond Cleavage

With several cycloadducts from the nitroso-Diels-Alder reactions in hand, we now attempted to cleave the N-O bond. $Mo(CO)_6$ is one of the most common methods for reductive cleavage of N-O bonds,[59,65-68] and this was investigated first. When the mixture of regioisomers **162A** and **162B** (R=Ph) was subjected to standard $Mo(CO)_6$ cleavage conditions, amino alcohol **157** and surprisingly pyrrole **167** were formed in a 2.3:1 ratio (determined by ^{1}H NMR spectroscopy) (Scheme 45).



Scheme 45

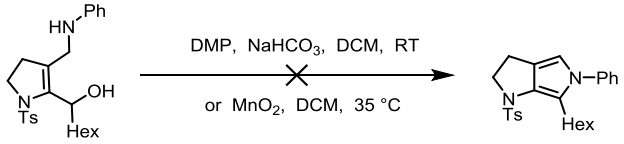
Presumably, amino alcohol **157** arises from starting material regioisomer **162A** but either regioisomer, or indeed both, could be responsible for the formation of pyrrole **167**. When the product mixture was resubjected to the reaction conditions, the product ratio remained constant, which suggested that pyrrole **167** was not being formed from alcohol **157**. Therefore, one might tentatively suggest that pyrrole **167** was formed from regioisomer **162B**, probably *via* amino alcohol **168**. Indeed, the requisite ring closure of intermediate amino alcohol **168** appears more favourable than that of amino alcohol **157**. One could propose a mechanism where the loss of hydroxide from amino alcohol **168** is promoted by coordination to molybdenum,[69] and facilitated by electron donation from the enamide (Scheme 46). The amine then cyclises onto the resultant iminium ion **170** and this is finally oxidised to the pyrrole **167**. This enamide assisted loss of hydroxide is not possible in amino alcohol **157**.



Scheme 46

It was hoped that upon oxidation amino alcohol **157** would cyclise and then aromatise to give pyrrole **167** (Scheme 47). This would allow both regioisomers of the nitroso compound cycloadduct **162** to be converted to the same product. Kouklovsky and co-workers had employed both DMP oxidation and MnO_2 conditions in similar reactions.[64] Unfortunately, with amino alcohol **157** these conditions led to a complex mixture of products. Intramolecular

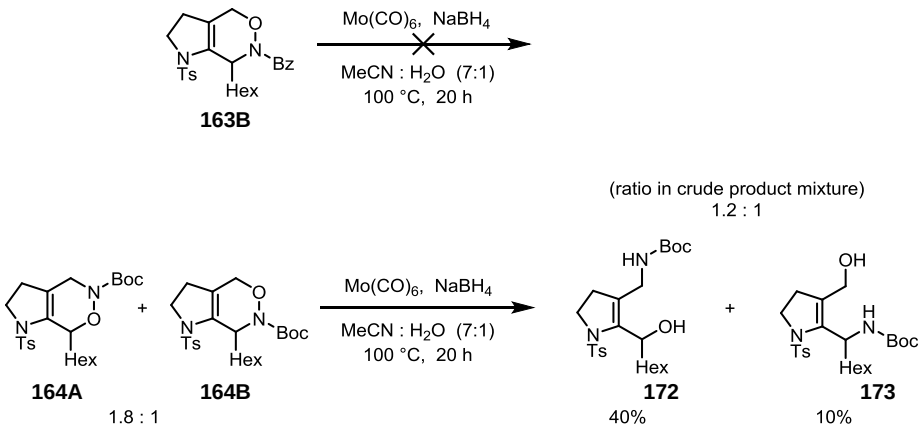
activation under Mitsunobu conditions also failed to promote the cyclisation. The difficulty encountered in trying to cyclise amino alcohol **157**, is further evidence to support the hypothesis that under N-O bond cleavage conditions, pyrrole **167** is only formed from cycloadduct regioisomer **162B**. Some alternative N-O bond cleavage conditions were also attempted with a mixture of regioisomers **162A** and **162B**, but both Zn/AcOH and SmI_2 failed to effect the desired cleavage, despite being utilised in the literature.[70,71]



157 **167**

Scheme 47

Under standard $Mo(CO)_6$ cleavage conditions cycloadduct **163B** (R=Bz) underwent no reaction, with recovery of the starting material (Scheme 48). However, regioisomers **164A** and **164B** (R=Boc) were both converted to the corresponding amino alcohols, with a small amount of unreacted starting material. Amino alcohol **172** was isolated in moderate yield but isolation of amino alcohol **173** proved problematic, resulting in a poor yield.



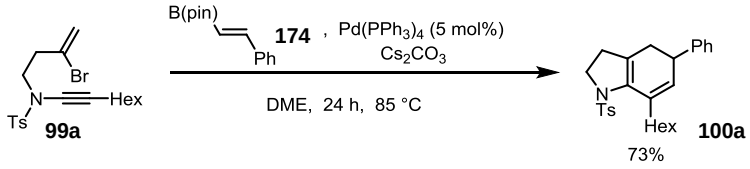
164A **164B** **172** **173**

1.8 : 1 40% 10%

Scheme 48

2.6 Bicyclic Dienamides

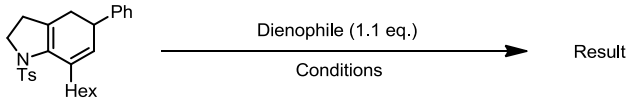
Given the successful formal [4+2] cycloadditions of monocyclic dienamides, it was hoped that bicyclic dienamide **100a** would also undergo similar reactions in order to give tricyclic structures. Bicyclic dienamide **100a** was synthesised in good yield from bromoenynamide **99a**, utilising the palladium-catalysed carbopalladation-Suzuki-electrocyclisation cascade methodology developed by our group (Scheme 49).[47]



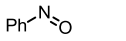
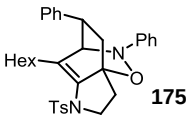
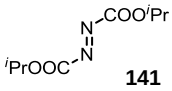
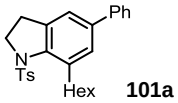
Scheme 49

Gratifyingly, bicyclic dienamide **100a** underwent cycloaddition with nitrosobenzene **161a** to give tricyclic structure **175** as a single regioisomer and diastereomer (Table 3, entry 1), tentitively suggested to be as illustrated based on steric grounds. The reaction was significantly slower than with the monocyclic dienamide substrate, presumably due to the increased steric hindrance. When a [4+2] cycloaddition with DIAD **141** was attempted at room temperature, no reaction was observed. Upon heating the mixture under reflux in toluene, oxidation of the substrate to the corresponding indoline **101a** took place (entry 2). Both Eschenmoser's salt **149a** and iminium ion salt **149b** failed to react with bicyclic dienamide **100a**, even when heated to 110 °C (entries 3 & 4).

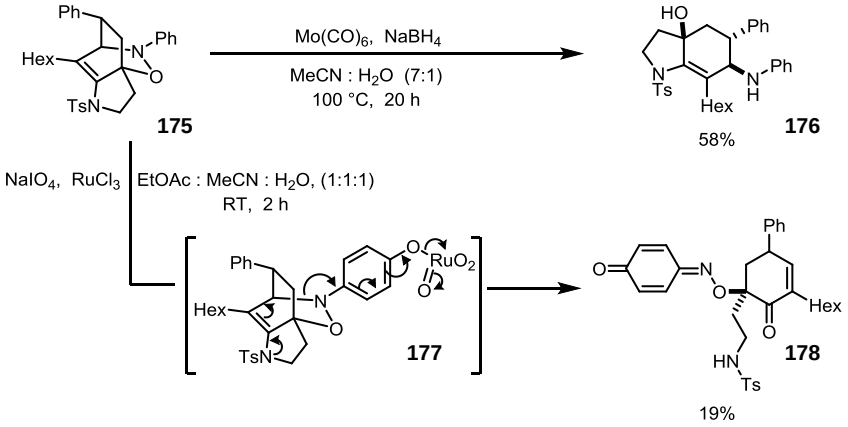
Table 3 : Formal [4+2] cycloadditions with bicyclic dienamides.



100a

Entry	Dienophile	Conditions	Result	Isolated Yield
1	 **161a**	DCM, 25 °C, 18 h	 **175**	68%
2	 **141**	tol, 110 °C, 24 h	 **101a**	56%
3	 **149a**	tol, 110 °C, 24 h	n.r.	-
4	 **149b**	tol, 110 °C, 24 h	n.r.	-

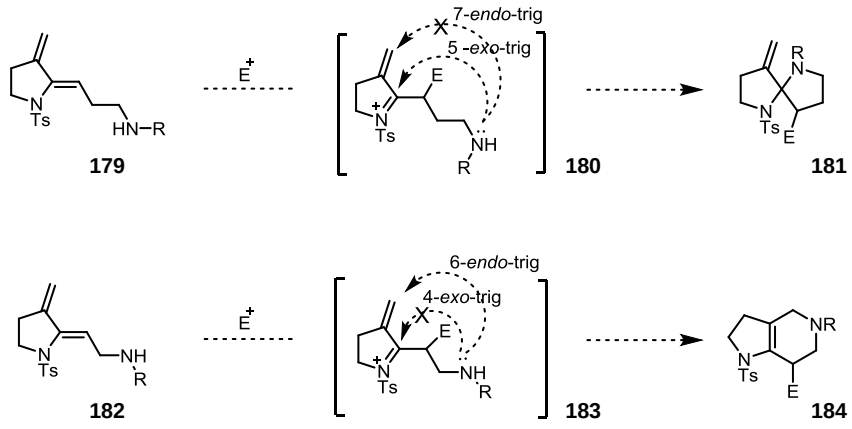
Pleasingly, tricyclic structure **175** underwent cleavage of the N-O bond under $Mo(CO)_6/NaBH_4$ conditions to give bicyclic structure **176** in moderate yield (Scheme 50), the assignment of which agreed with our suggested regioisomer for the starting material. It was hoped that the C=C bond of cycloadduct **175** could be cleaved in order to give a spirocyclic structure. However, under typical conditions using RuO_4, generated in situ from $NaIO_4$ and $RuCl_3$,[72] amide **178** was the only discernible product. This could possibly have arisen from oxidation of the aniline aromatic ring and N-C bond scission promoted by the enamide, followed by hydrolysis of the resulting iminium ion.



Scheme 50

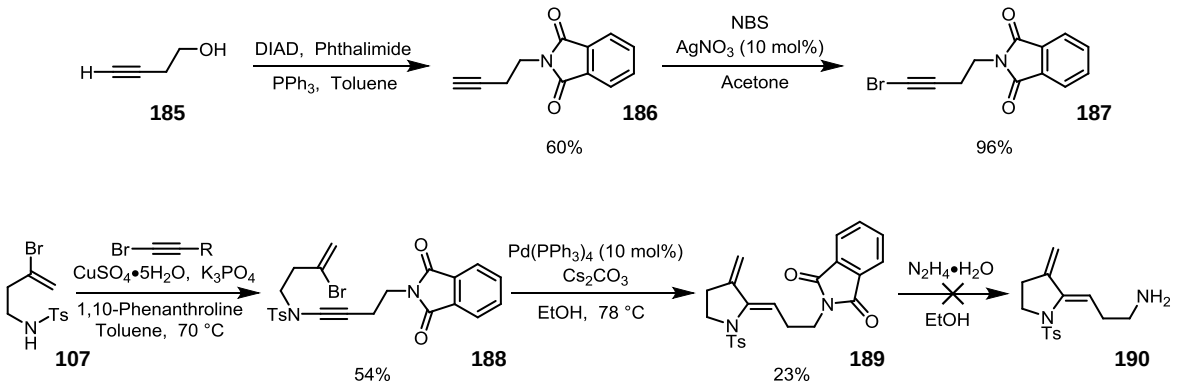
2.7 Heteroatom-Functionalised Sidechain Dienamides

Functionalisation of the side-chain of our monocyclic dienamides presented further opportunities for the synthesis of bicyclic diamines. It was thought that dienamides with sidechains bearing a nucleophilic amino moiety (dienamides **179** and **182**) might undergo intramolecular cyclisation reactions in the presence of an electrophile (E+) (Scheme 51). The type of bicyclic framework formed would hopefully depend on the tether length. With dienamide **179** the 5-*exo*-trig cyclisation directly onto the iminium ion should be favoured over the 7-*endo*-trig, leading to spirocyclic structures **181**. With a shorter tether, dienamide **182** ought to favour the 6-*endo*-trig conjugate addition giving fused bicyclic structures **184**.



Scheme 51

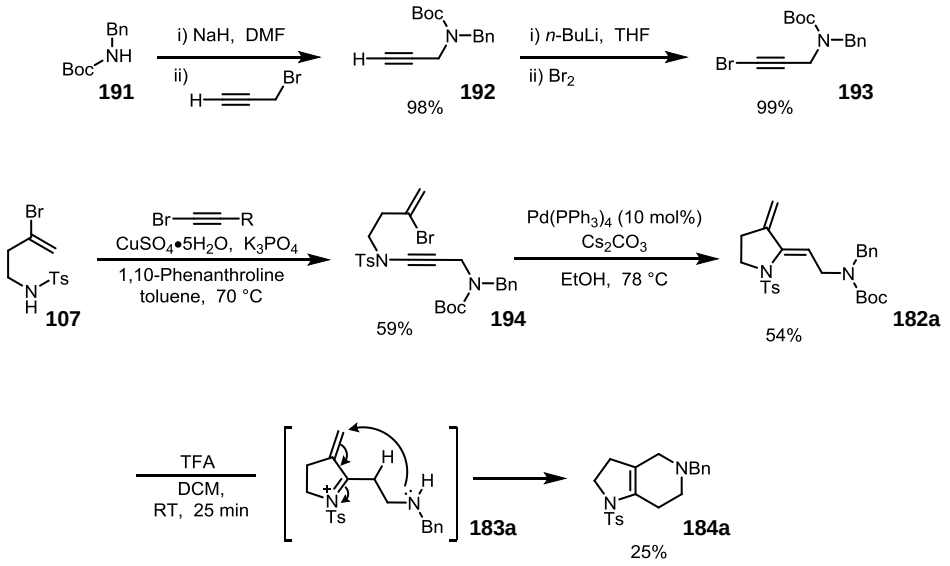
Firstly, attempts were made to synthesise dienamide **190** starting from homopropargyl tosylate and the carbamate anion of Boc-protected benzylamine, but these failed to react. An alternative route involving the formation of phthalimide **186** *via* a Mitsunobu reaction was therefore devised (Scheme 52), in the hope that the free primary amine could be unveiled at the end. Chemoselective bromination of phthalimide **186** at the alkyne terminus using a strong base was unsuccessful but could be achieved in excellent yield using NBS and cat. $AgNO_3$. Sulfonamide **107** was coupled to bromoalkyne **187** using Hsung's conditions to give ynamide **188** in moderate yield. The palladium-catalysed reductive cyclisation of ynamide **188** gave only a low isolated yield (23%) of dienamide **189**, possible due to the poor solubility of the product in organic solvents. Further to this, all attempts to reveal the primary amine were unsuccessful and therefore we were unable to synthesise dienamide **190**.



Scheme 52

A different protecting group strategy was sought, and as such *N*-Boc-benzylamine **191** and propargyl bromide were used to prepare alkyne **192**, which was then brominated using *n*-BuLi and bromine to give bromoalkyne **193** (Scheme 53). Sulfonamide **107** and bromoalkyne **193** were coupled under copper catalysis to give ynamide **194**, which underwent a palladium-catalysed reductive cyclisation to give dienamide **182a** in moderate yield**.** To our delight, dienamide **182a** was found to spontaneously cyclise upon Boc deprotection using TFA to give the anticipated fused bicyclic diamine **184a**, albeit in a low yield. We were unable to improve

this yield under various acidic Boc deprotection conditions, whilst attempts to deprotect the carbamate without cyclisation under thermal conditions (toluene, xylenes) resulted in complex mixtures.



Scheme 53

2.8 Conclusions and Further Work

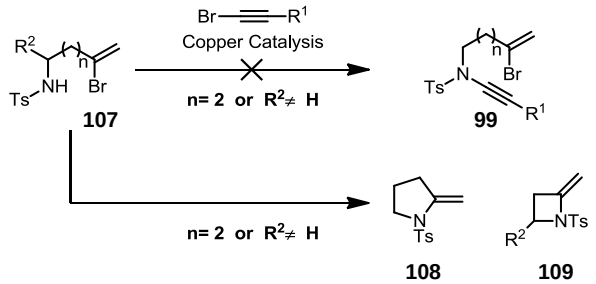
The reactivity of our monocyclic dienamides has been investigated in regards to several different reactions and number of fused aza-bicycles and tricycles have been synthesised. Whilst having no success with formal [4+2] cycloadditions using imines, several other heteroatom-containing dienophiles, including nitroso compounds, were successful. Further functionalisation of the resulting cycloadducts remains an ongoing challenge, and in particular an efficient and general N-O bond cleavage has yet to be realised. The nitroso dienophiles could also be utilised with bicyclic dienamides in order to give tricyclic structures. Finally, through incorporation of a nucleophilic amino functionality into substrates that are competent in the reductive cyclisation, the successful preparation of a fused bicyclic diamine was achieved *via* an acid-catalysed cyclisation reaction. Given these encouraging results, refinement of our strategies, in order to develop more general and efficient routes to these target systems, is worthy of further investigation.

3. Palladium- and Ruthenium-Catalysed Enynamide Cycloisomerisation

3.1 Introduction

3.1.1 Origins of the project

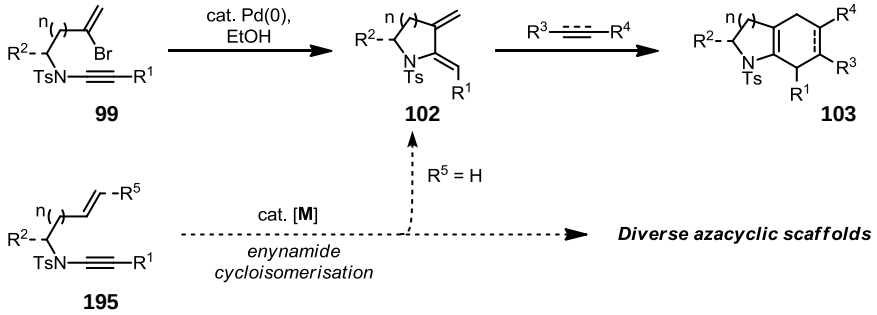
A significant limitation of our methodology for the synthesis of mono- and bicyclic dienamides remained the constraints for synthesis of the parent bromoenynamides. When sulfonamides **107** with a pent-4-enyl tether (n= 2) are subjected to copper-catalysed ynamide formation conditions, the bromoenynamides **99** are not formed, instead undergoing intramolecular cyclisation to give pyrrolidines **108** (Scheme 54). Substituents on the backbone of the tether in the α-position ($R^2 \neq$ H), also prevented ynamide formation under copper catalysis, with the intramolecular cyclisation to form azetidines **109** being favoured.[73] In the small number of cases where pent-4-enyl sulfonamides (n= 2) and α-substituted sulfonamides ($R^2 \neq$ H) could be synthesised, we had to resort to the use of stoichiometric lithium amides with alkynyl iodonium salts, an inefficient reaction sequence.



Scheme 54

It was realised that cycloisomerisation, the skeletal reorganisation of organic molecules with the concurrent formation of one or more rings, could offer an alternative strategy to the reductive cyclisation of bromoenynamides as a means of preparing monocyclic dienamides **102** (Scheme 55). The cycloisomerisation of enynamides **195** would not only provide a highly atom-economic synthesis of dienamides **102**, but also access to a greater diversity of other

azacyclic products. The enynamides **195** could hopefully be synthesised from simple starting materials, with the necessity of installing the vinyl bromide and then carrying it through the remaining synthesis now removed. The absence of the vinyl bromide should also prevent any intramolecular cyclisation during copper-catalysed ynamide formation, allowing enynamides **195** with pent-4-enyl tethers (n=2) or backbone substituents ($R^2 \neq H$) to be easily synthesised. Furthermore, the literature also shows that cycloisomerisation reactions tend to be high yielding, operationally simple, and highly stereo- and regioselective.[23-25] However, unlike 1,6-enyne cycloisomerisation there are very few examples of ynamides being employed in this chemistry.



Scheme 55

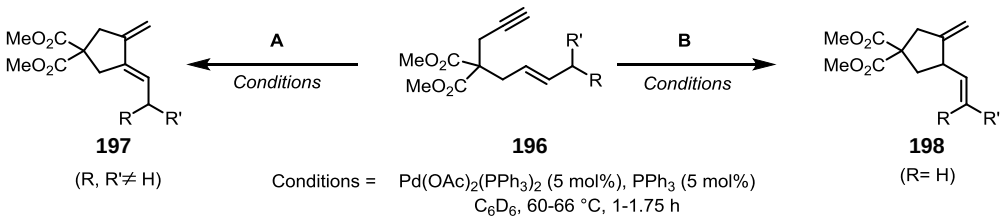
3.1.2 Enyne cycloisomerisation

The thermal cycloisomerisation of enynes (intramolecular ene reaction) has been used as an atom-efficient way of generating carbocycles.[74] However, the very high temperatures required (often >300°C) place severe restrictions on substrate stability and functional group tolerance is poor. Metal-catalysed cycloisomerisations offer higher efficiency at lower temperature and as such have since taken precedent.

3.1.2.1 Palladium-catalysed processes

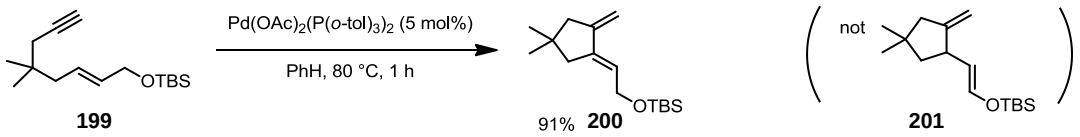
The pioneering studies in the area of palladium-catalysed enyne cycloisomerisation were carried out by Trost and co-workers.[75,76] They began their investigations into this area with the carbocyclisation of 1,6-enynes **196** to 1,3- and 1,4-dienes (**197** and **198**) using $Pd(OAc)_2(PPh_3)_2$

as catalyst (Scheme 56).[77] Substrates containing methyl or methylene groups in the external allylic position (R= H), formed 1,4-dienes **198** (Path B) with a high degree of selectivity for the *(E)*-alkene, whilst when the allylic carbon was disubstituted (R, R'≠ H), the reaction formed exclusively 1,3-dienes **197** (Path A). Phosphine ligands combined with Pd(II) salts produced the best yields, whilst Pd(0) sources were ineffective. Changing the polarity of the solvent did not significantly change the rate of reaction, but yields were maximised in non-polar solvents such as benzene.



Scheme 56 – Early cycloisomerisations of 1,6-enynes to 1,3- and 1,4-dienes.

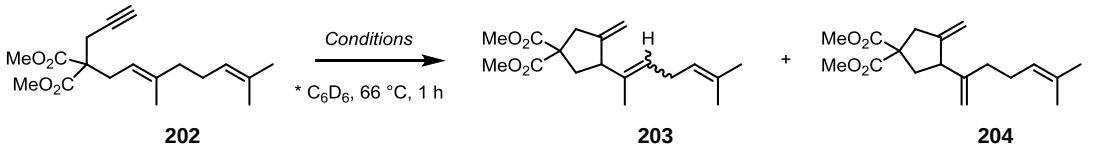
Surprisingly, allylic silyl ethers were found to show a strong preference for 1,3-dienes, with 1,6-enyne **199** generating exclusively 1,3-diene **200** in high yield (Scheme 57).[78] Heck had shown that the favourability of β-hydride elimination increases adjacent to a hydroxyl group,[79] but clearly in this case the silyl ether exercises a strikingly different electronic effect. Trost was able to utilise this regioselectivity as the key step in the racemic total synthesis of (±)-sterepolide.[78]



Scheme 57 – An unusual substituent effect favouring 1,3-dienes.

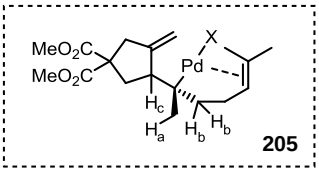
For the formation or 1,4-dienes where two possible regioisomeric products are possible, a difference was observed in the regioselectivity between the thermal-ene reaction and the new palladium-catalysed conditions (Scheme 58).[80] Flash vacuum thermolysis (FVT) of 1,6-enyne **202** at 625 °C led exclusively to triene **203**, arising from removal of the hydrogen from the

methylene group only. In contrast, palladium-catalysed cyclisation favoured the formation of triene **204**, derived from removal of the hydrogen atom from the methyl group. The thermal reaction likely reflects the conformational constraints of the reacting functionalities and their connecting tether. The metal-catalysed reaction presents the possibility that the remote alkene coordinates to the metal (as shown in intermediate **205**), restricting the conformation of the tether so that the methylene hydrogens (H_b) are poorly aligned for *syn*-β-hydride elimination, with the majority of the hydrogens therefore eliminated from the methyl group (H_a) instead. Indeed, when complexing phosphine ligands are added to the metal-catalysed reaction, the preference for triene **204** decreases, presumably due to less coordination from the remote alkene.



202 **203** **204**

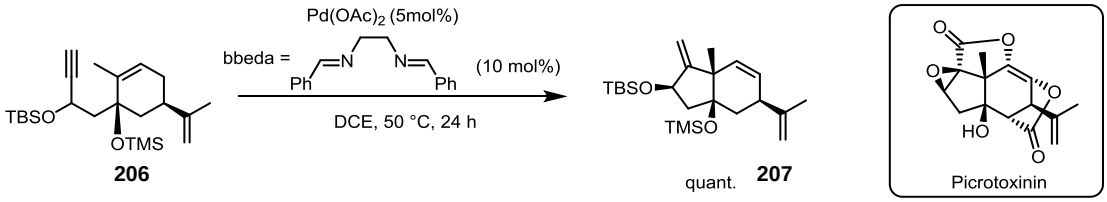
Conditions	Yield	Ratio 203:204
625 °C/FVT	83%	1 : 0.0
$Pd(OAc)_2$ (5 mol%)*	80%	1 : 16.9
$Pd(OAc)_2(P(o\text{-}tol)_3)_2$ (5 mol%)*	n.d.	1 : 2.4
$Pd(OAc)_2(PPh_3)_2$ (5 mol%)*	73%	1 : 2.9



Scheme 58 – Metal-catalysed *vs* thermal ene-reaction.

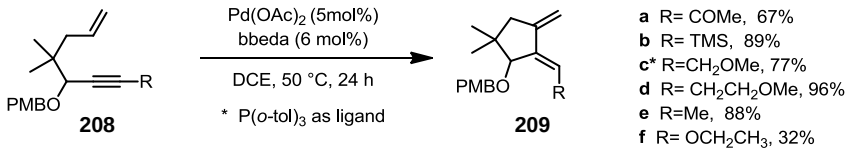
The formation of picrotoxane skeleton **207** from 1,6-enyne **206** was used to demonstrate the ability of palladium-catalysed cycloisomerisation to form quaternary stereocentres (Scheme 59).[81] A test substrate containing only the carbon skeleton of 1,6-enyne **206**, was found to cyclise in good yield using the previously developed conditions of catalytic $Pd(OAc)_2(PPh_3)_2$ in benzene at 60 ºC. However, the added silyl ethers present in 1,6-enyne **206** meant that, upon its exposure to a wide variety of Pd(II) catalysts in the presence of an array of phosphines, phosphites and pyridines, mostly decomposition occurred (<10% yield). This necessitated the development of a new ligand, one which would impart sufficient kinetic

reactivity, whilst preventing further reaction of the products. The ligand chosen was *N*,*N*'-bis(benzylidene)ethylenediamine (bbeda), a stronger σ-donor than phosphines but retaining some π-acceptor properties. Using $Pd(OAc)_2$ (5 mol%) and bbeda (6 mol%), 1,6-enyne **206** underwent cycloisomerisation to form picrotoxane skeleton **207** in quantitative yield, a marked contrast to all previous attempts.



Scheme 59 – Synthesis of the picrotoxane skeleton.

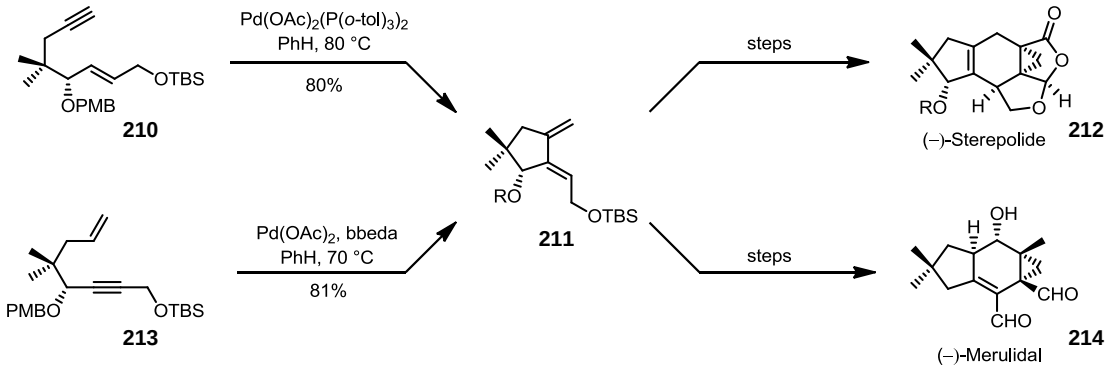
The $Pd(OAc)_2$/bbeda catalyst would turn out to be one of the most generally usefully systems for the palladium-catalysed cycloisomerisation of enynes.[82,83] For example, initial investigations had found alkyl substituents at the alkyne terminus inhibited cycloisomerisation, with at best modest yields under ligand-free $Pd(OAc)_2$ conditions.[84] However, using catalytic $Pd(OAc)_2$ and bbeda a wide variety of such substrates were found to undergo cycloisomerisation in high yield, including a number possessing a propargylic protected-alcohol moiety (Scheme 60).[85]



Scheme 60 – Cycloisomerisation of disubstituted alkyne substrates using $Pd(OAc)_2$/bbeda.

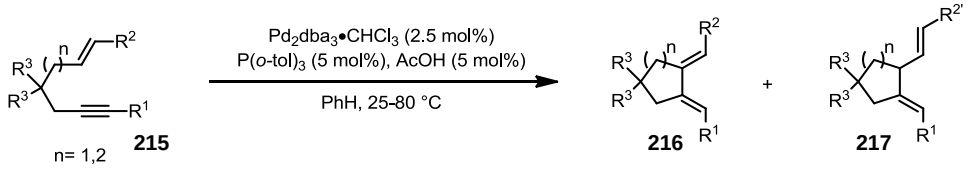
Difficulties encountered with the synthesis of 1,6-enyne **210**, meant that for the asymmetric synthesis of (–)-sterepolide an alternative strategy was devised (Scheme 61).[85] The $Pd(OAc)_2$/bbeda catalyst system allowed the use of substrates bearing an alkyl substituent at the alkyne terminus, and 1,6-enyne **213**, synthesised *via* the asymmetric reduction of the corresponding ketone, was found to undergo cycloisomerisation to give 1,3-diene **211** in high yield. A Diels-Alder reaction, followed by a number of further steps, then converted 1,3-diene

211 into both (–)-sterepolide **212**,[85] and (–)-merulidal **214**,[86] where all the stereocentres are derived from propagation of the stereochemical information at the carbinol centre in 1,3-diene **211**.



Scheme 61 – Total asymmetric synthesis of (–)-sterepolide and (–)-merulidal.

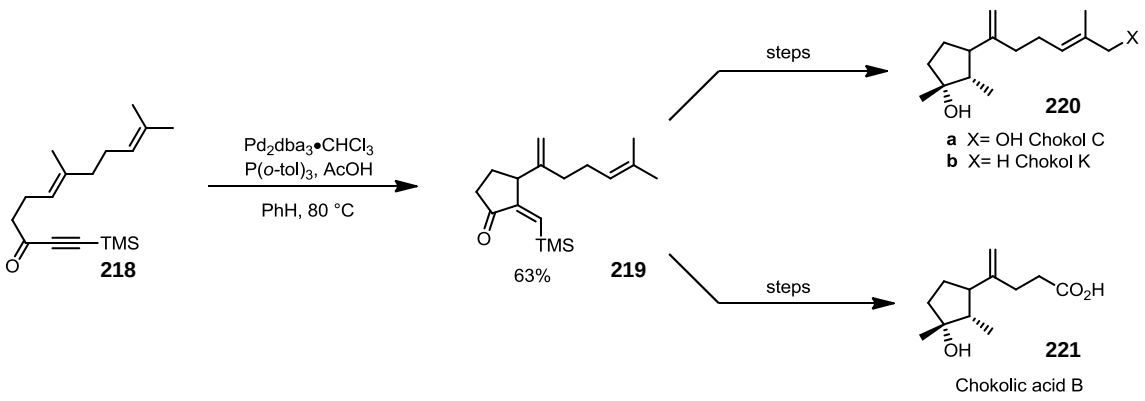
In 1989, Trost and co-workers discovered that Pd_2dba_3•$CHCl_3$ plus a carboxylic acid could also effectively catalyse the cycloisomerisation of enynes.[87] This alternative catalyst system would prove similarly applicable to a wide range of enyne substrates **215** (Scheme 62), with the regioselectivity of the reactions closely mirroring the $Pd(OAc)_2$/bbeda system.[88] However, the reaction profiles of the two systems were not identical, with the efficacy of each catalyst showing a marked difference for certain substrates.



Scheme 62 – An alternative palladium catalyst system.

For example, Pd_2dba_3•$CHCl_3$/AcOH/($P(o\text{-tol})_3$) was used to cyclise dienyne **218** to give exclusively triene **219** in good yield (Scheme 63), whereas the palladium(II)-catalysed reactions with other phosphine ligands or bbeda gave poor results. Triene **219** was used as the key intermediate in the synthesis of a number of natural products from the chokol family of

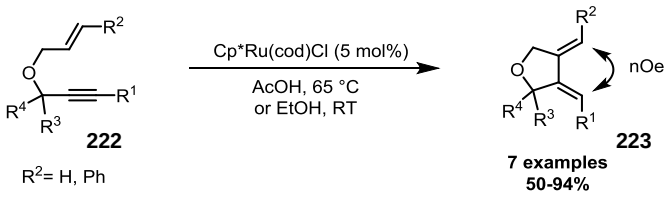
antifungal agents. A similar reaction was also successfully employed as the key step in the synthesis of antiulcerogenic agent (+)-cassiol.[89]



Scheme 63 – Total synthesis of chokol family antifungals.

3.1.2.2 Ruthenium-catalysed processes

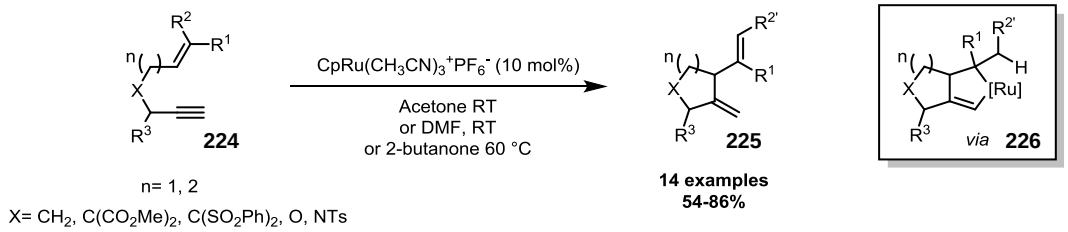
In 1999 Dixneuf and co-workers showed that catalytic Cp*Ru(cod)Cl in the presence of AcOH or EtOH could be used to perform the selective cycloisomerisation of allyl propargyl ethers **222** (1,6-enynes) into 3,4-dialkylidenetetrahydrofurans **223** (1,3-dienes) (Scheme 64).[90] The structures of the products were determined by nOe experiments, which in all cases showed the relative *exo* position of the substituents. However, only substrates incapable of forming 1,4-dienes were utilised (i.e. R^2= H, Ph).



Scheme 64 – A new cycloisomerisation catalyst of enynes.

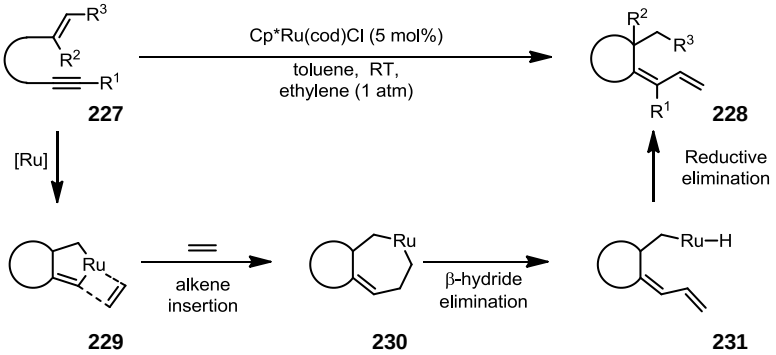
At a similar time, Trost published work describing the ruthenium-catalysed cycloisomerisation of 1,6- (**224**, n=1) and 1,7-enynes (**224**, n= 2) to form 1,4-dienes **225** (Scheme 65).[91] With CpRu(cod)Cl only monosubstituted alkenes participated in the reaction, but the use of cationic ruthenium catalyst $CpRu(CH_3CN)_3^+PF_6^-$ extended the scope to include 1,2-di- and

trisubstituted alkenes. The mechanism was thought to proceed *via* a ruthenacyclopentene intermediate **226**, where subsequent β-hydride elimination and then reductive elimination gives the observed product and regenerates the catalyst. This chemistry also proved effective for intramolecular formal [5+2] cycloadditions using vinylcyclopropyl enynes, a mild and efficient method for the construction of 7-membered rings.[92]



Scheme 65 – Ruthenium-catalysed cycloisomerisation of 1,6- and 1,7-enynes.

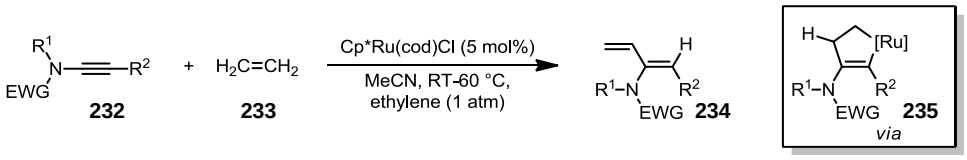
Whilst reinvestigating different ruthenium catalysts for enyne metathesis, Mori and co-workers discovered they could optimise the reaction for a ruthenium-catalysed alkenylative cyclisation (Scheme 66).[37,38] When enynes **227** were exposed to catalytic Cp*Ru(cod)Cl under an atmosphere of ethylene, ethylene was inserted into the ruthenium-sp^2 bond of the initially generated ruthenacyclopentene **229** to give ruthenacycloheptenes **230**. These would then undergo β-hydride elimination and subsequent reductive elimination in order to generate a number of different carbocyclic and heterocyclic compounds with a diene moiety **228**.



Scheme 66 – Ruthenium-catalysed alkenylative cyclisation.

Saito and Sato used the same catalyst system to synthesise 2-amino-1,3-dienes **234**, by coupling ynamides **232** and ethylene gas **233** (Scheme 67).[93] Since the reaction proceeds *via* a

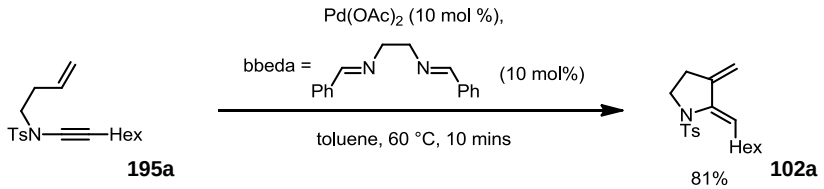
ruthenacyclopentene **235**, the 2-amino-1,3-dienes **234** were formed in a regio- and stereoselective manner. Cp*Ru(cod)Cl also found use in a number of other reactions involving the cyclisation of enyne substrates to give ruthenacyclopentene intermediates, which could then undergo further insertions.[94]



Scheme 67 – Ruthenium-catalysed coupling of ynamides and ethylene.

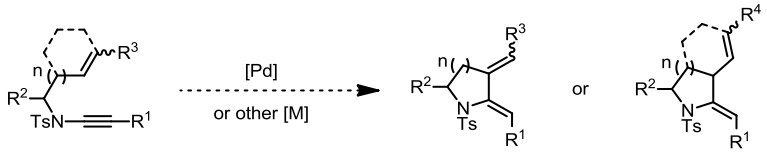
3.2 Preliminary Result

With Trost's seminal studies of enyne cycloisomerisation in mind, we set out to investigate the palladium-catalysed cycloisomerisation of enynamide **195a**. We were delighted to find that, with a $Pd(OAc)_2$ catalyst and *N*,*N*'-*bis*-benzylidene ethylenediamine (bbeda) ligand in toluene at 60 °C, enynamide **195a** underwent rapid cycloisomerisation to give dienamide **102a** in high yield (Scheme 68).



Scheme 68

The hope was that by using a palladium-catalyst system we could take a number of differently substituted enynamides **195** and perform cycloisomerisation reactions to access highly desirable mono and bicyclic 1,3- and 1,4-dienamides (**102** and **236** respectively) (Scheme 69). We would also take the opportunity to examine the feasibility of other metal catalysts, including any differences in reactivity.



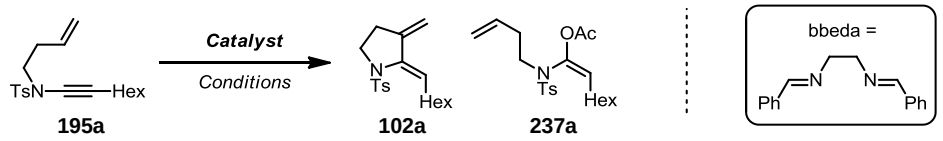
195 **102** **236**

Scheme 69

3.3 Reaction Optimisation

Firstly, our test reaction was subjected to a number of different catalyst systems in order to refine the reaction conditions, as well as to discover if any alternative systems held a similar potency (Table 4). The reactions were all carried out using 5 mol% of metal precatalyst, and with this reduced catalyst loading the $Pd(OAc)_2$/bbeda system still proved highly efficient at converting enynamide **195a** to dienamide **102a** in high yield (entry 1). Triphenylphosphine could also be utilised as a ligand, although traces of enol acetate **237a** were observed (entry 2). In contrast, the use of bulkier P(*o*-tol)$_3$ ligands led to a sluggish reaction (entry 3), as did ligand-free conditions containing only $Pd(OAc)_2$ (entry 4). Interestingly, Trost's alternative catalyst system for enyne cycloisomerisation,[87,88] consisting of Pd_2dba_3•$CHCl_3$/AcOH, also failed to consume the staring material within 1 h and produced increased amounts of enol acetate **237a** (entry 5). Only in the presence of the bbeda ligand did this system provide a rapid and selective reaction (entry 6), with phosphine ligands once again proving ineffective (entries 7 & 8). Cp*RuCl(cod) has also been used in the literature to catalyse the formation of dienes from enynes.[37,38,90-94] We were pleased to find that Cp*RuCl(cod) in MeCN at 60 °C was also a competent catalyst in the formation of dienamide **102a** from enynamide **195a**, albeit with a longer reaction time than $Pd(OAc)_2$/bbeda (entry 9).

Table 4 : Optimisation of catalyst system.



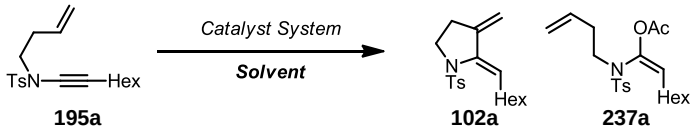
Entry	Catalyst system[a]	Time	102a:195a:237a[b]
1	$Pd(OAc)_2$ / bbeda	10 min	100:0:0
2	$Pd(OAc)_2(PPh_3)_2$	10 min	98:0:2
3	$Pd(OAc)_2(P(o\text{-tol})_3)_2$	1 h	31:62:7
4	$Pd(OAc)_2$	1 h	66:29:4
5	$Pd_2dba_3 \bullet CHCl_3$ / AcOH	1 h	50:44:6
6	$Pd_2dba_3 \bullet CHCl_3$ / AcOH / bbeda	10 min	99:0:1
7	$Pd_2dba_3 \bullet CHCl_3$ / AcOH / PPh_3	1 h	78:12:10
8	$Pd_2dba_3 \bullet CHCl_3$ / AcOH / $P(o\text{-tol})_3$	1 h	19:69:11
9	Cp*Ru(cod)Cl[c]	1.5 h	100:0:0

[a] Conditions: 5 mol % catalyst system, toluene (0.167 M), 60 °C. [b] Measured by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Performed in acetonitrile at 60 °C.

We decided to take our best palladium catalyst systems and perform a short solvent screen (Table 5). For the $Pd(OAc)_2$/bbeda catalyst system, Trost had also used DCE, THF or MeCN instead of toluene for certain reactions. In our screening using DCE or THF as solvent, we observed similar substrate conversion rates to those in toluene, but at the expense of minor impurities being observed in the crude reaction mixture (entries 2 & 3). MeCN showed no sign of impurities but the rate was reduced (entry 4). For $Pd(OAc)_2(PPh_3)_2$, toluene also proved to be the optimal solvent (entry 5), with DCE, THF and MeCN all leading to incomplete reactions over an increased reaction time (entries 6-8). For the $Pd_2dba_3 \bullet CHCl_3$/AcOH/bbeda system, DCE appeared to be comparable with toluene, both solvents offering an efficient reaction (entries 9 & 10). On the other hand, THF and MeCN retarded the reaction, as well as producing a small percentage of unknown impurities

(entries 11 & 12). Taking into account these results, a $Pd(OAc)_2$/bbeda catalyst system in toluene seemed to be the best conditions.

Table 5 : Solvent screen for the best catalyst systems.



195a **102a** **237a**

Entry	Catalyst system[a]	Solvent	Time	102a:195a:237a[b]
1	$Pd(OAc)_2$ / bbeda	toluene	10 min	100:0:0
2	$Pd(OAc)_2$ / bbeda	DCE	10 min	99:0:1*
3	$Pd(OAc)_2$ / bbeda	THF	10 min	100:0:0*
4	$Pd(OAc)_2$ / bbeda	MeCN	1 h	98:1:1
5	$Pd(OAc)_2(PPh_3)_2$	toluene	10 min	98:0:2
6	$Pd(OAc)_2(PPh_3)_2$	DCE	1 h	69:29:2
7	$Pd(OAc)_2(PPh_3)_2$	THF	1 h	98:2:0
8	$Pd(OAc)_2(PPh_3)_2$	MeCN	1 h	36:63:1
9	Pd_2dba_3•$CHCl_3$ / AcOH / bbeda	toluene	10 min	99:0:1
10	Pd_2dba_3•$CHCl_3$ / AcOH / bbeda	DCE	10 min	99:0:1
11	Pd_2dba_3•$CHCl_3$ / AcOH / bbeda	THF	1 h	98:1:1*
12	Pd_2dba_3•$CHCl_3$ / AcOH / bbeda	MeCN	1 h	99:0:1*

*** Reaction also contained approx. 1-8% of unidentified impurities.** [a] Conditions: 5 mol % catalyst system, solvent (0.167 M), 60 °C. [b] Measured by ^1H NMR spectroscopic analysis of the crude reaction mixture.

3.4 Substrate Synthesis

With our optimised conditions for palladium-catalysed cycloisomerisation in hand, as well as contrasting ruthenium-catalysed conditions, we set about synthesising a range of enynamides in order to test the substrate scope of our reaction. The substrates were divided into three classes: monosubstituted alkenyl ynamides **A**, disubstituted alkenyl ynamides **B** and

cycloalkenyl ynamides **C** (Figure 4). The hope was that each of these distinct classes of substrate would give access to different varieties of azacycles. In particular, most disubstituted alkenyl ynamides **B** had the potential to form both 1,3- and 1,4-dienamides. Cycloalkenyl ynamides would hopefully give access to a range of complex bicyclic azacycles, many of which would not be readily accessible through other means.

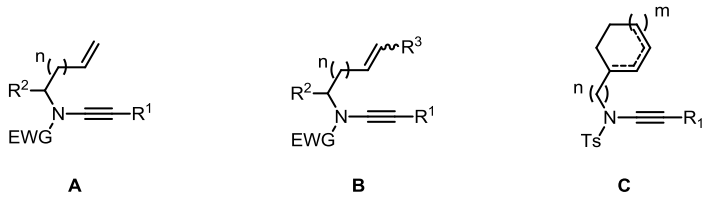
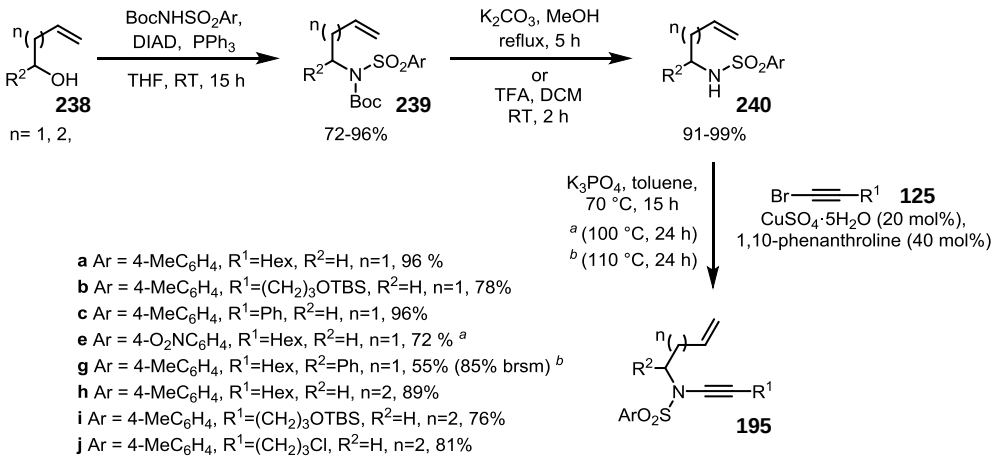


Figure 4 : Classes of enynamide substrate.

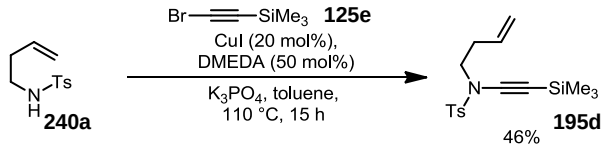
3.4.1 Monosubstituted alkenyl ynamides

A Mitsunobu strategy was employed in order to synthesise the majority of our monosubstituted alkenyl ynamides (Scheme 70). Commercially available alcohols **238** were reacted with $BocNHSO_2Ar$ under Mitsunobu conditions in order to give the Boc-protected sulfonamide **239**. Deprotection using K_2CO_3/MeOH at reflux, or TFA in DCM, then gave the sulfonamide **240** in high yield. This was followed by copper-catalysed ynamide formation, according to the conditions of Hsung,[17] using bromoalkynes **125**. The enynamides **195** were generally formed in good yields after 15 h at 70 °C. The exceptions to this were nosyl-ynamide **195e** and α-branched ynamide **195g** (R^2= Ph), which required temperatures of 100 °C and 110 °C respectively for 24 h. Nosyl-ynamide **195e** did however offer a good alternative to the usual tosyl protecting group, as nosyl deprotection can be carried out under milder conditions.[95]



Scheme 70

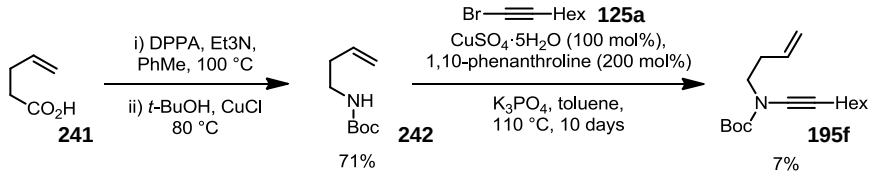
When attempts were made to synthesise TMS-substituted ynamide **195d** (R^1= TMS), our usual ynamide formation conditions proved ineffective. After a number of conditions were investigated without any success, we found that TMS-substituted ynamide **195d** could be synthesised in moderate yield using a CuI/DMEDA catalyst system, with (bromoethynyl)trimethylsilane **125e** and sulfonamide **240a** (Scheme 71). If desired, this substrate has the potential to be converted into various aryl ynamides *via* a TMS-deprotection and subsequent Sonogashira coupling.



Scheme 71

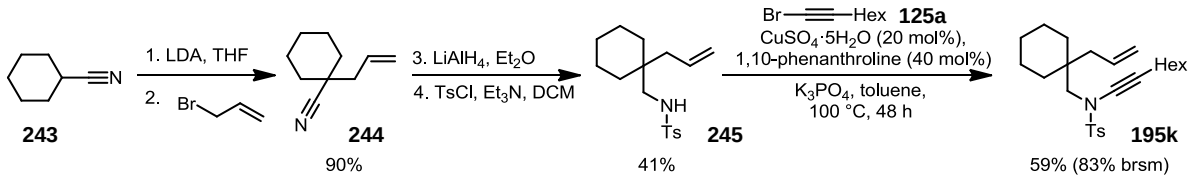
Replacing the sulfonyl protecting group with a Boc group would facilitate revealing of the free amine, as well as improve the amide scope. Boc-protected ynamide **195f** was prepared from pent-4-enoic acid **241** in two steps *via* Curtius rearrangement with subsequent *t*-BuOH trapping of the resulting isocyanate, then ynamide formation according to the procedure of Hsung (Scheme 72, work undertaken by Dr. Craig Campbell.) Despite examples in the literature suggesting the efficient conversion of some carbamates to ynamides under these conditions,[96-98] the formation of ynamide **195f** from carbamate **242** proved problematic. Even

when a full equivalent of copper catalyst was employed over an extended time period, the conversion remained exceedingly poor.



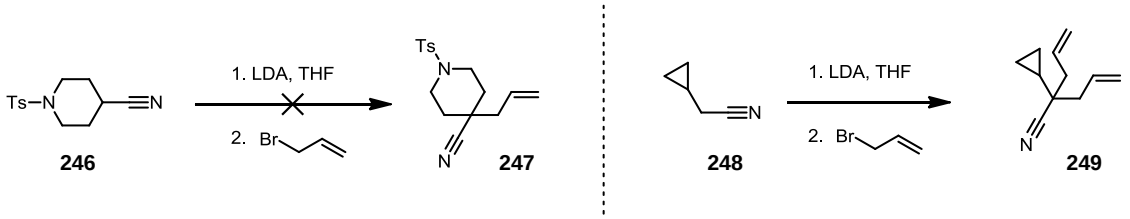
Scheme 72, Work undertaken by Dr. Craig Campbell.

Ynamide **195k**, with a cyclohexane substituent on backbone of the tether, was synthesised from nitrile **243** (Scheme 73). Alkylation at the α-position to the nitrile, reduction to the amine using $LiAlH_4$ and tosylation gave sulfonamide **245**. Subsequent ynamide formation again required an extended time and higher temperature to achieve a 59% yield, but unreacted starting material could be recovered.



Scheme 73

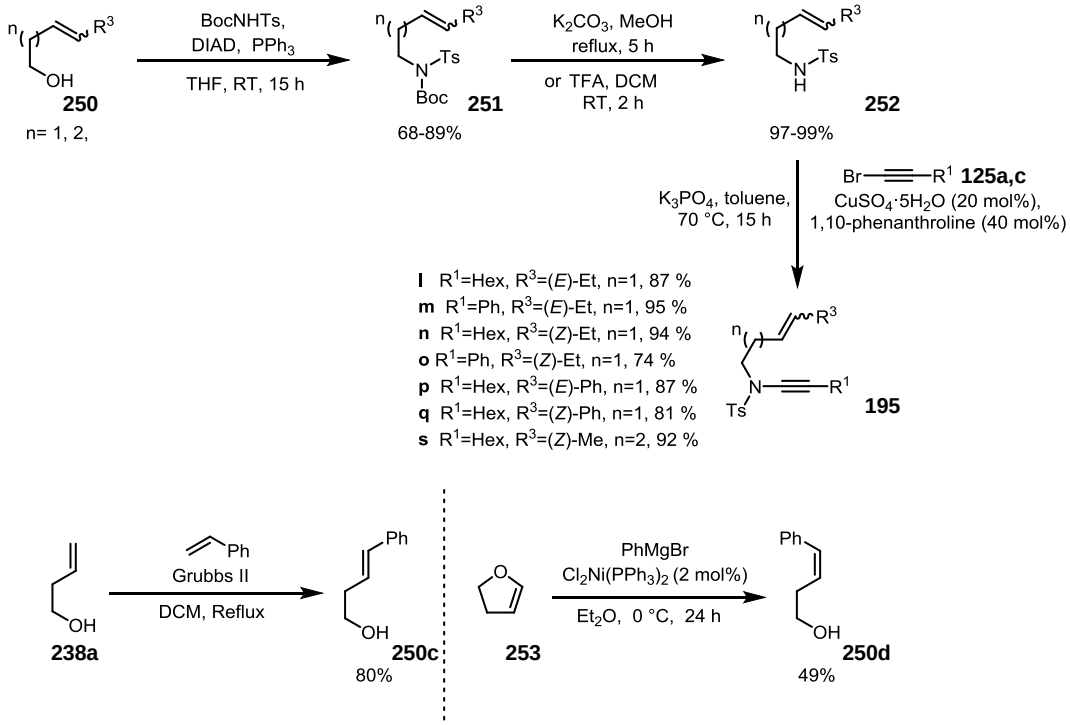
Other attempts to employ the deprotonation of nitriles as a strategy for the formation of different substrates were less successful (Scheme 74). With nitrile **246**, containing a piperidine sulfonamide, alkylation did not occur, possibly due to solubility problems. Nitrile **248** did undergo alkylation, but to give dialkylated nitrile **249** as the major product. This could be converted to the corresponding sulfonamide *via* reduction and tosylation, but exposure of the sulfonamide to ynamide formation conditions produced only traces of ynamide.



Scheme 74

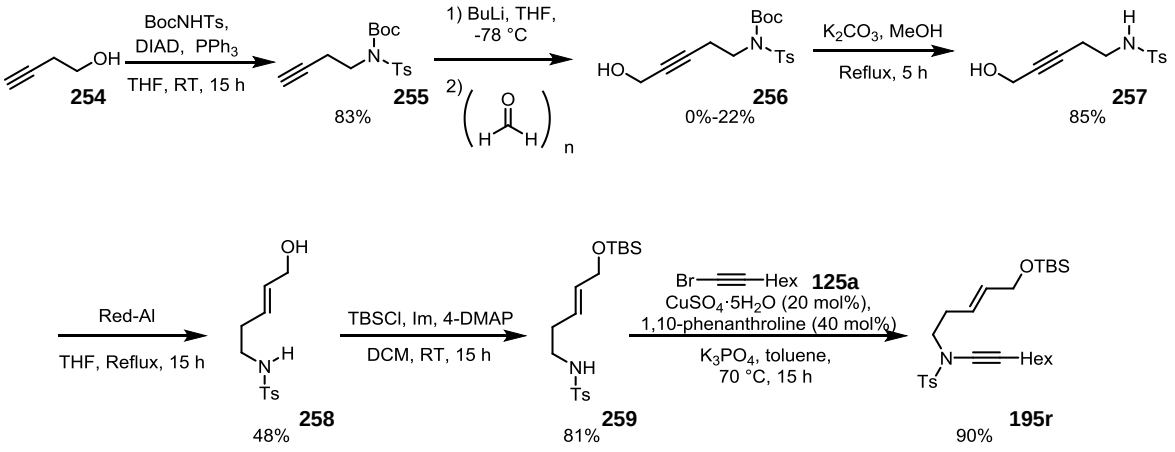
3.4.2 Disubstituted alkenyl ynamides

A similar Mitsunobu strategy was employed where possible in the case of disubstituted alkenyl ynamides (Scheme 75). Once again the alcohols **250** were reacted with BocNHTs to synthesise the corresponding Boc-protected sulfonamides **251**. Deprotection under acidic or basic conditions, followed by copper-catalysed ynamide formation gave the enynamides **195** in good yields. Alcohols **250c** and **250d** were not commercially available, but could each be easily synthesised in a single step. Alcohol **250c** was formed from alcohol **238a** using cross metathesis with styrene and Grubbs II catalyst to install the (*E*)-alkene, and alcohol **250d** was generated using a nickel-catalysed ring opening of 2,3-dihydrofuran **253** with PhMgBr.[99]



Scheme 75

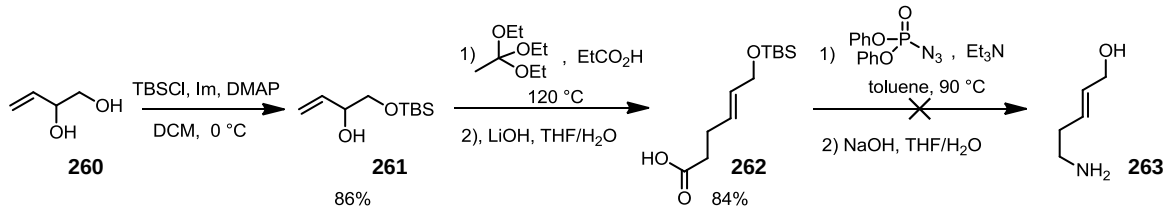
Whilst studying enyne cycloisomerisation with alkyl-substituted alkenes, Trost had found that the use of allylic silyl ethers enhanced the selectivity for the formation of the 1,3-diene.[78] Enynamide **195r** was therefore a desirable substrate in order to compare the effects that an allylic silyl ether would have on our system. Initially enynamide **195r** was synthesised starting from but-3-yn-1-ol **254** (Scheme 76). Following a Mitsunobu reaction, the alkyne group of Boc-protected sulfonamide **255** was deprotonated and the anion added to paraformaldehyde to give alcohol **256** in a low yield. Boc deprotection under basic conditions, followed by a Red-Al reduction of the triple bond then installed the (*E*)-allylic alcohol with high diastereoselectivity, which upon TBS-protection gave sulfonamide **259** in acceptable yield. It proved necessary to carry out the Boc deprotection before attempting the Red-Al reduction. Sulfonamide **259** was then converted to enynamide **195r** in excellent yield, using standard Hsung conditions for ynamide formation. However, the formation of alcohol **256** from Boc-protected sulfonamide **255** turned out to be very capricious and several attempts to repeat the reaction failed to generate any of the desired product. The unreliability of this synthesis route therefore caused us to look at alternative methods of synthesising enynamide **195r**.



Scheme 76

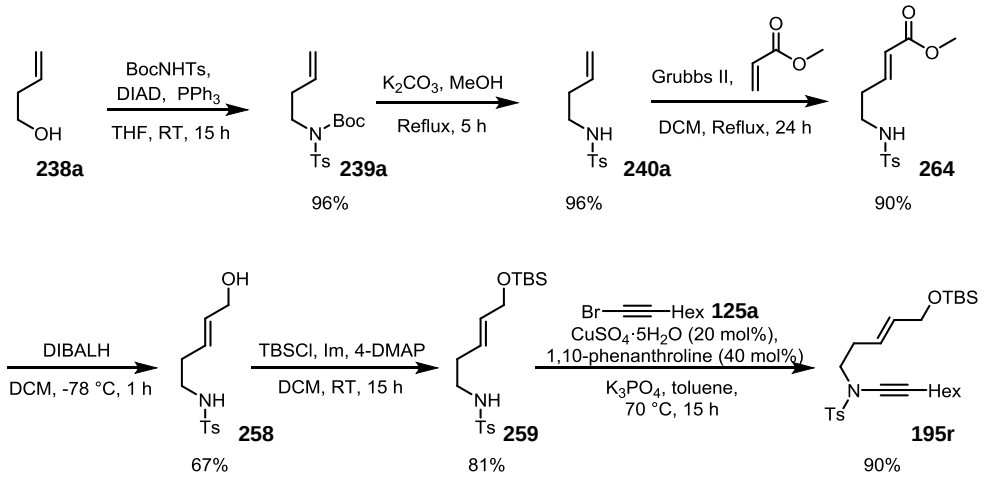
At first, we hoped that a Curtius rearrangement of carboxylic acid **262** would allow us access to amine **263** (Scheme 77). Diol **260** underwent TBS-protection exclusively on the primary alcohol and an Ireland-Claisen rearrangement then gave carboxylic acid **262** in excellent yield

and as a single geometric isomer. Unfortunately however, Curtius rearrangement conditions did not appear to generate the desired isocyanate and only complex mixtures were formed.



Scheme 77

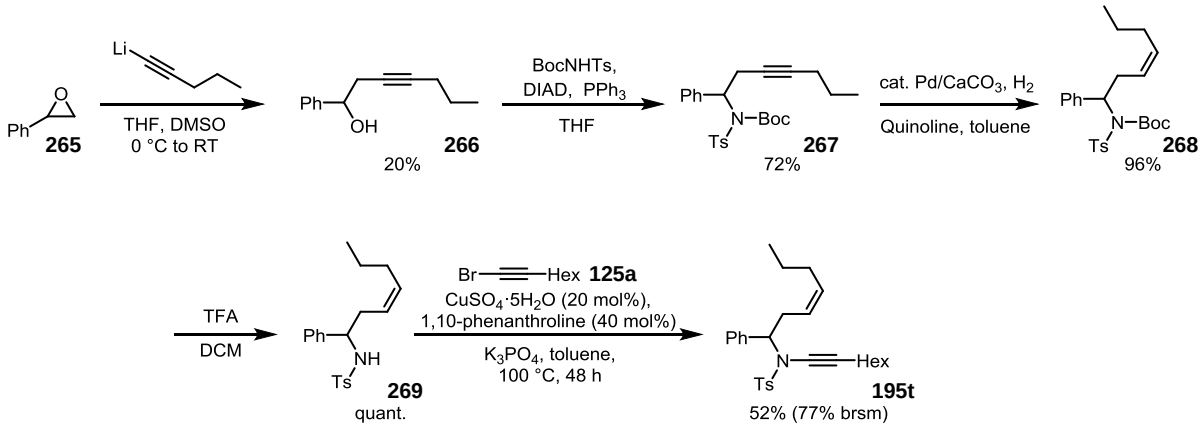
We therefore turned to cross-metathesis as a way of installing the (*E*)-allylic alcohol in enynamide **195r** (Scheme 78). Sulfonamide **240a**, synthesised in the usual way from but-3-en-1-ol **238a**, underwent a Grubbs II catalysed cross metathesis with methyl acrylate to generate enoate **264** in high selectivity ((*E*), *J*=15.6 Hz). DIBALH reduction of the ester then gave alcohol **258** which was common to our original route. Thus, subsequent TBS-protection gave sulfonamide **259**, which was then converted to the corresponding enynamide **195r**.



Scheme 78

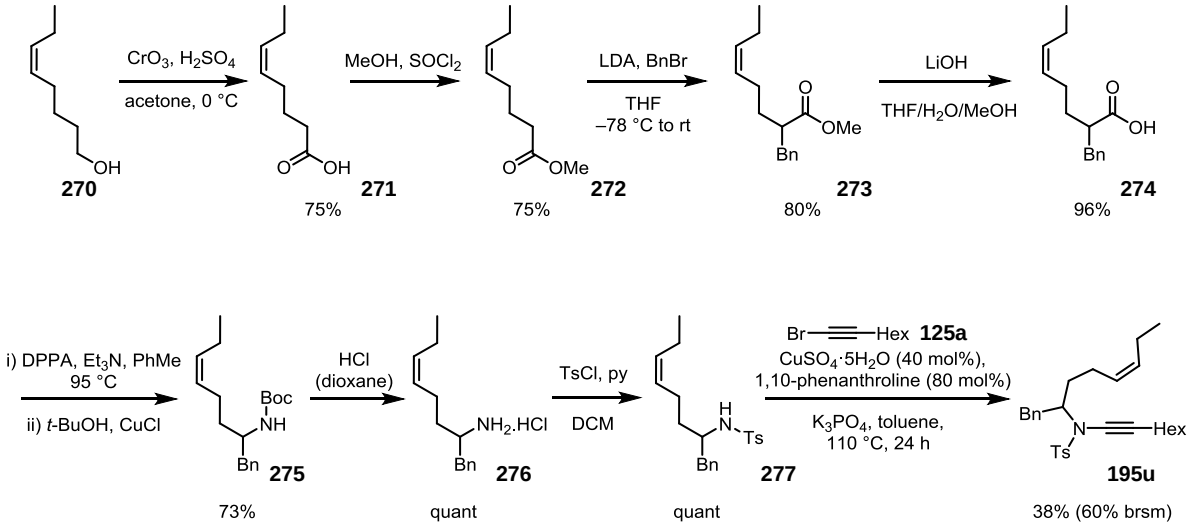
Next we turned our attention to chiral enynamides in the hope of achieving diastereoselective cyclisations. Alcohol **266** was synthesised using the opening of epoxide **265** with an alkynyl anion (Scheme 79). The corresponding Boc-protected sulfonamide **267** underwent a Lindlar reduction in order to install the (*Z*)-double bond. Boc deprotection and ynamide formation

then gave the desired enynamide **195t**. As before, ynamide formation with an α-substituted sulfonamide required an increased reaction time and a higher temperature.



Scheme 79

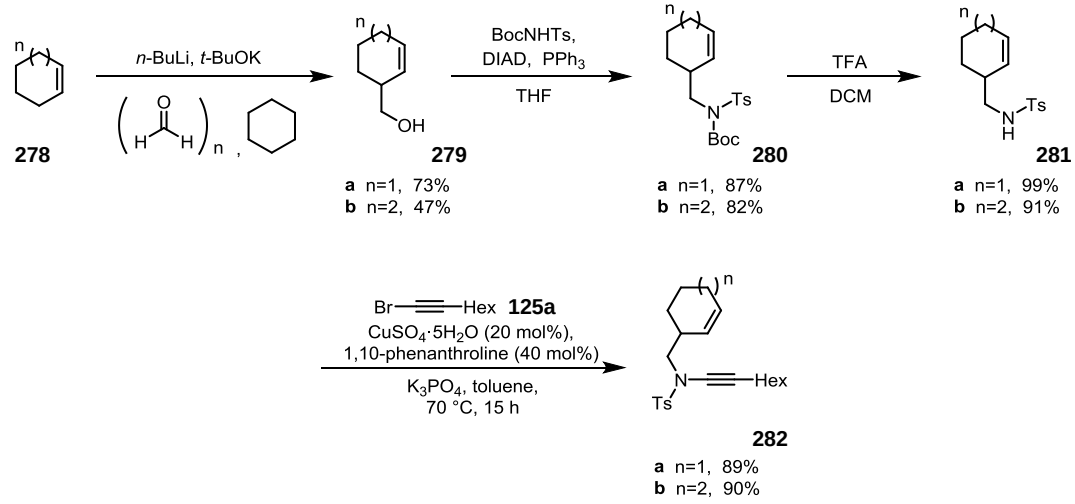
Chiral enynamide **195u** required a more complex strategy to install the α-benzyl substituent (Scheme 80, work undertaken by Dr. Craig Campbell). Carboxylic acid **271** was formed from alcohol **270** *via* a Jones oxidation, but direct α-benzylation of the acid failed. Carboxylic acid **271** was therefore converted to the ester **272**, which did undergo α-benzylation. After LiOH hydrolysis to reveal the desired carboxylic acid, the nitrogen atom was installed using a Curtius rearrangement, the isocyanate being trapped with *t*-BuOH to form Boc-protected amine **275**. The Boc-group was removed under acidic conditions to form the ammonium salt **276**, which was then tosylated to form sulfonamide **277**. Copper-catalysed ynamide formation at reflux in toluene for 24 h gave enynamide **195u** in moderate yield based on recovered starting material.



Scheme 80, Work undertaken by Dr. Craig Campbell.

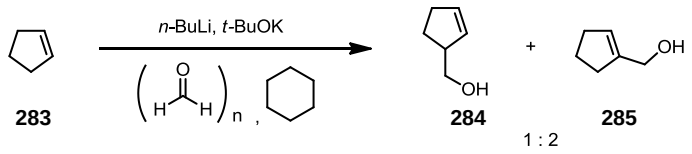
3.4.3 Cycloalkenyl ynamides

Alcohols **279a** and **279b** were synthesised using superbase deprotonation of the corresponding cycloalkene **278** and addition of the allyl anion onto paraformaldehyde (Scheme 81). The superbase, known as Schlosser base, was generated by mixing *n*-BuLi and *t*-BuOK for 15 h. Alcohols **279a** and **279b** were then smoothly converted into cycloalkenyl ynamides **282a** and **282b** *via* our usual method.



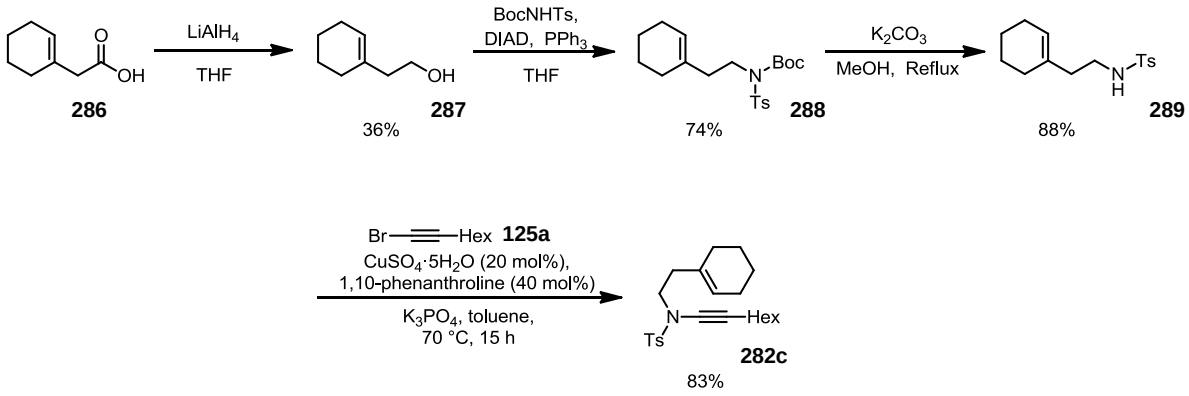
Scheme 81

When cyclopentene **283** was employed as the parent cycloalkene, deprotonation occurred at the desired allylic position, but also directly on the alkene itself (i.e. to afford the vinyl anion) (Scheme 82). This led to a mixture of alcohol products **284** and **285** which could not be separated, and the cyclopentene version of cycloalkenyl ynamides **282a** and **282b** was therefore not synthesised.



Scheme 82

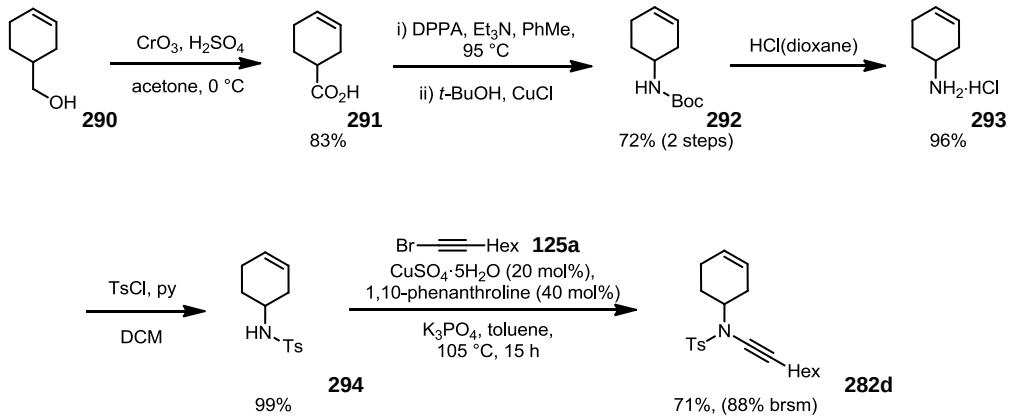
Cycloalkenyl ynamide **282c**, with the tether attached directly to the alkene, held the exciting prospect of possibly forming spirocyclic structures. It was synthesised from commercially available carboxylic acid **286** (Scheme 83). Reduction of this acid using $LiAlH_4$ gave alcohol **287** which was then converted to the ynamide.



Scheme 83

In order to synthesise cycloalkenyl ynamide **282d**, commercially available alcohol **290** was initially oxidised to carboxylic acid **291** (Scheme 85, work undertaken by Dr. Craig Campbell). Curtius rearrangement using DPPA and subsequent trapping of the generated isocyanate with *t*-BuOH gave Boc-protected amine **292**, which was deprotected to the hydrochloride salt **293**.

Tosylation of the amine gave sulfonamide **294**, from which cycloalkenyl ynamide **282d** was synthesised in good yield using standard ynamide formation conditions at 105 °C.



Scheme 84, Work undertaken by Dr. Craig Campbell.

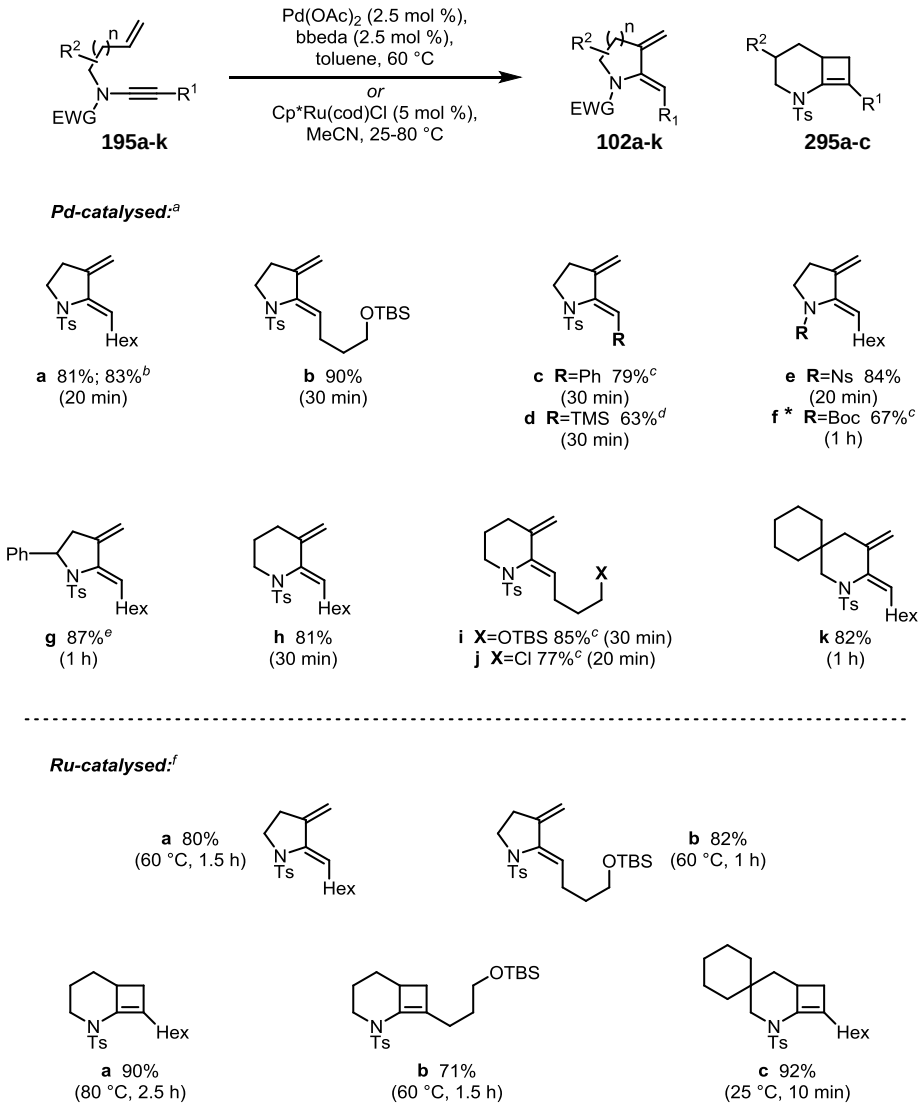
3.5 Substrate Scope

3.5.1 Monosubstituted alkenyl ynamides

We had already shown the potential for cyclic 1,3-dienamides to be formed from monosubstituted alkenyl ynamides using palladium- or ruthenium-catalysed cycloisomerisation, and we set about exploring the substrate scope with the expanded range of substrates (Figure 5). The mechanistic details (i.e. stereochemical models) for these cyclisations will be discussed in Chapter 4. Alkyl-substituted 1,6-enynamides underwent rapid and high yielding cycloisomerisation, using our optimised palladium catalyst system at 60 °C and only 2.5 mol% of catalyst, to give dienamides **102a** and **102b**. The reaction to form dienamide **102a** was also carried out on gram scale, allowing the catalyst loading to be lowered even further to just 1 mol% palladium catalyst without any loss of yield (83%). Aryl-substituted and TMS-substituted ynamides could also be tolerated, forming dienamides **102c** and **102d** in good yield, although higher catalyst loadings of 5 mol% and 10 mol% respectively were required. The nature of the *N*-electron withdrawing group could also be varied, with nosyl-protected

dienamide **102e** and Boc-protected dienamide **102f** (reaction carried out by Dr. Craig Campbell) formed in good to excellent yields.

Figure 5 : Cycloisomerisation of monosubstituted enynamides to 1,3-dienamides and bicyclic cyclobutenes.



[a] Figures in parentheses indicate reaction time; yields are isolated yields. Products isolated as a 97:3 *Z*:*E* ratio of enamides as measured by 1H NMR spectroscopic analysis of the crude reaction mixture. [b] Performed on 1 g scale with 1 mol% catalyst (2.5 h). [c] Performed using 5 mol% catalyst. [d] Performed using 10 mol% catalyst. [e] Isolated as a 92:8 *Z*:*E* ratio of enamides. [f] Figures in parentheses indicate reaction temperature/time; yields are isolated yields. ***** Reaction carried out by Dr. Craig Campbell.

The presence of a substituent adjacent to the ynamide in the α-position did not impede the reaction and α-substituted dienamide **102g** was formed in excellent yield, as a 92:8 *Z*:*E* ratio of enamides ((*Z*) and (*E*) assigned using 1H NMR nOe data). Piperidine dienamide **102h** could be generated using the corresponding 1,7-enynamide, where the tether length is extended by

one methylene unit. This 6-membered ring forming reaction was also tolerant of a silyl ether or a chlorine atom in the alkyl-sidechain, with piperidine dienamides **102i** and **102j** formed in good yields. Finally, a cyclohexyl substituent on the backbone of the molecule also produced an efficient reaction, forming piperidine dienamide **102k** in good yield, albeit with a slightly extended reaction time. With the exception of dienamide **102g**, these palladium-catalysed reactions were found to be high stereoselective, with only trace amounts of the isomeric (*E*)-enamides being observed (*Z*:*E*; 97:3 by ^{1}H NMR spectroscopy).

Alkyl-substituted 1,6-enynamides also proved to be excellent substrates for ruthenium catalysis, with dienamides **102a** and **102b** being formed in good yield using Cp*Ru(cod)Cl (5 mol%) in MeCN at 60 °C. However, when 1,7-enynamides were examined under ruthenium catalysis, a remarkable change in reactivity was observed. 6,4-Fused cyclobutenes **295a-c** were isolated in excellent yields *via* a formal [2+2] cycloaddition,[100,101] along with only trace amounts of the expected 1,3-dienes (<5%) formed under palladium catalysis. It is noteworthy that in the case of 1,7-enynamides, a single starting material can be selectively transformed into two different products, depending only on the choice of catalyst. Normally, the formal [2+2] cycloaddition of ynamides requires a highly strained or electron-deficient alkene (e.g. cyclic enones, nitroalkenes),[102-104] whereas in this intramolecular case the unstrained electron-neutral alkene still reacts with high efficiency. Cyclobutene **295c** even forms rapidly at room temperature, presumable benefiting from a Thorpe-Ingold effect of the cyclohexyl substituent.

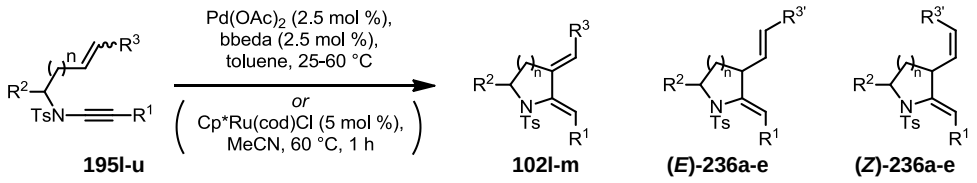
3.5.2 Disubstituted alkenyl ynamides

We next turned our attention towards the cycloisomerisation of enynamides containing 1,2-disubstituted alkenes, which have the potential to form either 1,3- or 1,4-dienes (Table 6). The standard reaction conditions employed were $Pd(OAc)_2$ (2.5 mol %) and bbeda (2.5 mol %) in toluene. Cycloisomerisation of alkyl enynamide **195l** containing an ethyl-substituted (*E*)-alkene

successfully generated 1,4-dienamide **(*E*)-236a**, along with a moderate amount of the (*E*)-1,3-dienamide (entry 1). Aryl-substituted enynamide **195m** behaved in a similar manner, with the ethyl-substituted (*E*)-alkene giving 1,4-dienamide **(*E*)-236b** as the major product (entry 2). The analogous (*Z*)-alkene substrates **195n** and **195o** also favoured the formation of 1,4-dienamides **(*E*)-236a** and **(*E*)-236b**, now to the exclusion of the 1,3-dienamide but with the appearance of minor amount the (*Z*)-1,4-dienamide (entries 3 & 4). Moreover, (*Z*)-alkene substrates **195n** and **195o** appeared to be more reactive than their (*E*)-alkene counterparts, with enynamide **195n** even reacting at room temperature. The assignment of the alkene geometry in the product 1,4-dienamides was made on the basis of coupling constant ((*E*), J=15.0-15.5 Hz; (*Z*), J=10.5-11.0 Hz). The different isomers formed in these reactions probably correspond to the β-hydride elimination of different hydrogen atoms in the final step, and therefore the distribution of products likely reflects the relative ease of each of these eliminations (see chapter 4 for mechanistic discussion).

It was hoped that styrenyl ynamides (such as **195p** and **195q**) would form a single product upon cycloisomerisation, as they lack the hydrogens required to form 1,4-dienes. Pleasingly styrenyl ynamides **195p** and **195q** reacted to give 1,3-dienamdes **(*E*)-102l** and **(*Z*)-102l** respectively as single stereoisomers (assigned using ^{1}H NMR nOe experiments), the stereochemistry of the starting materials thus being faithfully translated into the products (entries 4 & 5). Once again the (*Z*)-alkene substrate proved to be the more reactive of the two isomers, with a reaction time of just 15 min for ynamide **195p**, whilst (*E*)-strenyl ynamide **195q** took 4 h to go to completion at 60 °C.

Table 6 : Cycloisomerisation of disubstituted alkenyl ynamides.[a]



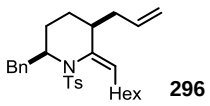
195l-u **102l-m** **(*E*)-236a-e** **(*Z*)-236a-e**

Entry	S/M	n	R^1, R^2, R^3	Temp (°C), Time	Major Product	Yield (%)[b]	Ratio[c]
1	**195l**	1	Hex, H (*E*)-Et	60, 20 min	**(*E*)-236a**	80	22:78:0
2	**195m**	1	Ph H (*E*)-Et	60, 20 min	**(*E*)-236b**	83	27:70:3
3	**195n**	1	Hex H (*Z*)-Et	25, 1 h	**(*E*)-236a**	87	0:86:14
4	**195o**	1	Ph H (*Z*)-Et	60 , 20 min	**(*E*)-236b**	81	0:91:9
5	**195p**	1	Hex H (*E*)-Ph	60, 4 h	**(*E*)-102l**	82	–[d]
6	**195q**	1	Hex H (*Z*)-Ph	60, 15 min	**(*Z*)-102l**	84	–[d]
7	**195r**	1	Hex H (*E*)-CH_2OTBS	60, 20 min[e]	**(*E*)-102m**	53[f]	66:17:17
8	**195s**	2	Hex H (*Z*)-Me	60, 20 min[e]	**236c**	72	7:93
9	**195t**	1	Hex Ph (*Z*)-*n*-Pr	25, 3 h	**(*E*)-236d**	87	0:100:0
10	**195u**	2	Hex Bn (*Z*)-Et	60, 1.5 h[e]	**(*E*)-236e**	86	9:77:14[g]
11[b]	**195m**	1	Ph H (*E*)-Et	60, 1 h	**(*Z*)-236b**	84	33:9:58

[a] Reaction conditions: $Pd(OAc)_2$ (2.5 mol %), bbeda (2.5 mol %), toluene (0.333 M). [b] Isolated overall yield. [c] Ratio of **102:(*E*)-236:(*Z*)-236**. [d] Formed as a single stereoisomer. [e] Performed using 5 mol% catalyst. [f] Yield of pure alcohol following treatment of the reaction mixture with TBAF. [g] 14% (by ratio) of the 1,5-dienamide arising from isomerisation of **(*E*)-236e**. [h] Catalysed by Cp*Ru(cod)Cl (5 mol%).

Trost had shown that for enyne cycloisomerisations of alkyl-substituted alkenes (capable of forming 1,3- and 1,4-dienes), the use of allylic silyl ethers enhanced the selectivity for the formation of the 1,3-diene.[78] Hoping to utilise this approach, we examined the cycloisomerisation of allylic silyl ether **195r** and found that it did indeed improve selectivity for the formation of the 1,3-dienamide (entry 7). For convenience the crude reaction mixture was treated with TBAF, following which the major product alcohol **(*E*)-102m** was easily separable from the aldehyde generated by TBS-deprotection of the minor 1,4-dienamides. A piperidine 1,4-dienamide **236c** was also prepared by the cycloisomerisation of 1,7-enynamide **195s** (entry 8), and in all cases the isolated yield of the cyclised products was excellent.

Finally, we explored the potential of chiral enynamide substrates, which held the possibility of diastereoselective substrate-control of any generated stereocentres. To our delight, α-branched enynamides **195t** and **195u** both cyclised to give product 1,4-dienamides **(*E*)-236d** and **(*E*)-236e** as a single diastereomer at the newly formed stereocentre (entries 9 & 10), the relative stereochemistry assigned using ^{1}H NMR nOe experiments (see conformational analysis below). In the case of dienamide **(*E*)-236e** a small amount of the 1,3-dienamide was also formed, along with 1,5-dienamide **296** (Figure 6) which presumably arises from a palladium hydride-catalysed alkene isomerisation in the product.[105] It is possible that these additional isomers are not observed from enynamide **195t** because the reaction can be carried out at room temperature. These combined results illustrate that cycloisomerisation could be used as a practical and efficient method for the stereocontrolled synthesis of polysubstituted azacycles.



296

Figure 6 : 1,5-Dienamide **296**

When ruthenium-catalysed cycloisomerisation conditions were employed, disubstituted alkenyl ynamides generally proved to be poor substrates, undergoing no reaction with recovery of starting material. The exception to this was aryl enynamide **195m**, containing an ethyl-substituted (*E*)-alkene, which underwent cycloisomerisation to give a mixture of 1,3- and 1,4-dienamides in good yield (Table 6, entry 11). Interestingly, the majority of the 1,4-dienamide formed was **(*Z*)-236b**, the opposite 4,5-diastereomer to that formed under palladium catalysis, which therefore suggests operation of different reaction pathways for the two catalyst systems.

3.5.2.1 Conformational analysis

Assignment of stereochemistry of **(*E*)-236d** as *anti* is based on interpretation of 1D ^{1}H NMR nOe data (Figure 7). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between the alkene sidechain (H6), the benzylic proton (H5), and H4α. Complementary enhancement is seen between H3 and H4β.

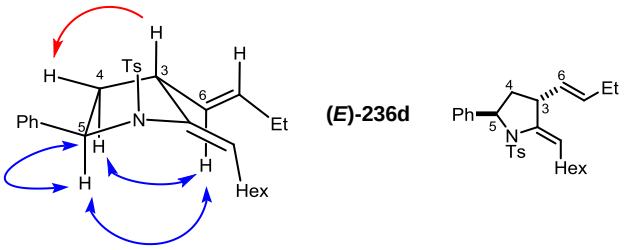


Figure 7 : Assignment of stereochemistry of **(*E*)-236d**.

Assignment of stereochemistry of **(*E*)-236e** as *syn* is also based on interpretation of 1D ^{1}H NMR nOe data (Figure 8). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between protons H6, H5α, H4α, and H3 which suggest these protons to be on the same face of the molecule. Complementary enhancements are seen between the benzyl sidechain (H17a), H4β, H5β, the alkene sidechain H7, and Ts (*ortho*-protons). The enhancements can be explained by considering an interconverting mixture of conformers. For conformers **297** and **298** the enhancements H17a–H4β and H7–H5β

indicate the sidechains must both be on the same face of the molecule, i.e. 1,4-*syn*-substitution. These enhancements are inconsistent with the alternative *anti*-isomer with both sidechains equatorial (conformer **299**), assuming that *bis*-axial conformer **300** is significantly less-populated.

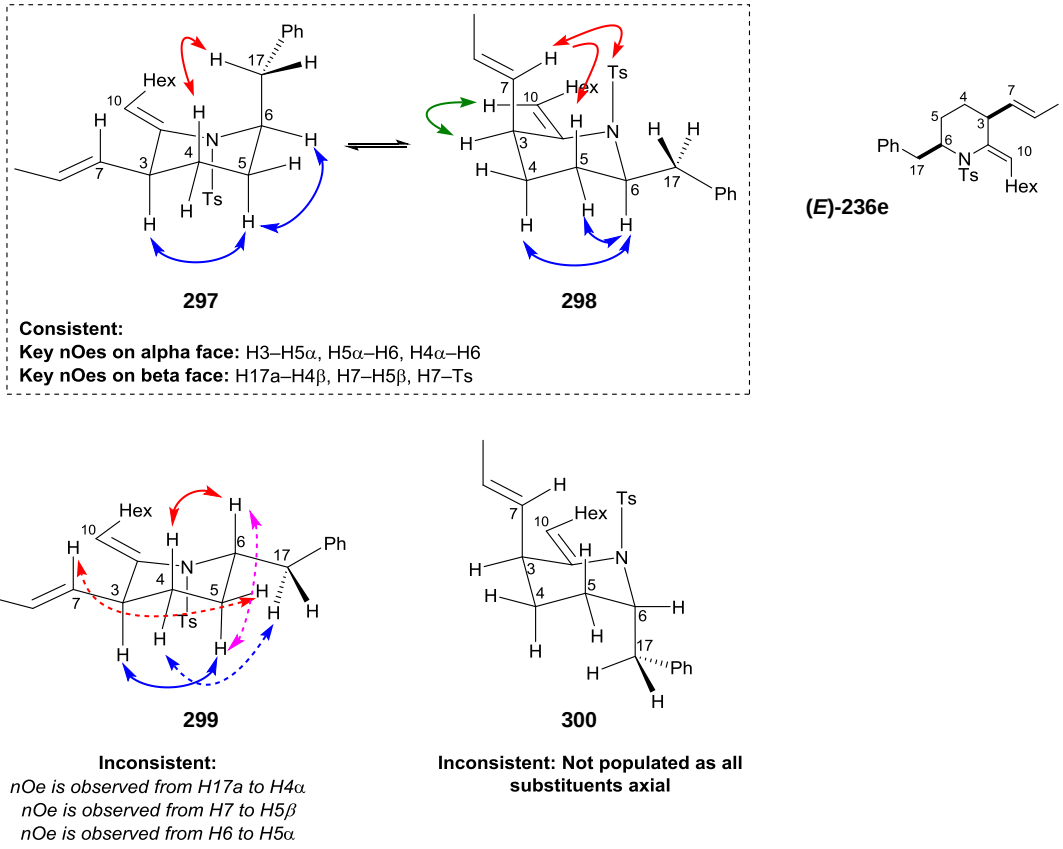


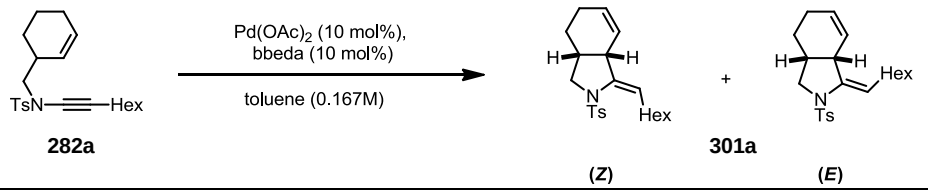
Figure 8 : Assignment of stereochemistry of **(*E*)-236e**.

3.5.3 Cycloalkenyl ynamides

Having established the cycloisomerisation of mono- and disubstituted acyclic alkenyl ynamides, we turned our attention towards cyclic substrates. Cycloalkenyl ynamides have the potential to provide access to a variety of types of bicyclic structure, depending on the position of the alkene within the ring. Pleasingly, the palladium-catalysed cycloisomerisation of 3-functionalised cyclohexenyl ynamide **282a** proceeded smoothly at room temperature, generating 5,6-*cis*-fused bicyclic dienamide **301a** in excellent yield and good diastereoselectivity (Table 7, entry 1). Increasing the reaction temperature to 60 °C led to a greatly reduced

reaction time but at a cost of reduced yield and a greater proportion of the (*E*)-enamide isomer (entry 2). Lowering the temperature to 0 °C had a positive effect on the diastereoselectivity but led to incomplete conversion of the starting material, even when the reaction was left for 24 h (entry 3).

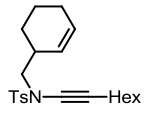
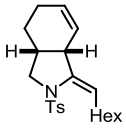
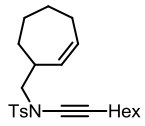
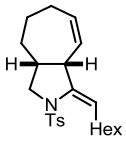
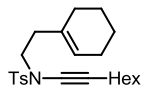
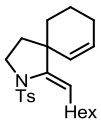
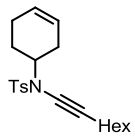
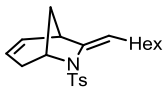
Table 7 : Effect of temperature variation for cyclohexenyl ynamide **282a**.[a]



Entry	Temp	Time	Conversion	Isolated Yield	Ratio (*Z*):(*E*)
1	25 °C	2.5 h	100%	95%	96:4
2	60 °C	<5 min	100%	87%	89:11
3	0 °C	24 h	56%	n.d.	98:2

At lower catalyst loading (2.5 mol%), cyclohexenyl ynamide **282a** still generated 5,6-*cis*-fused bicyclic dienamide **301a** in excellent yield and good diastereoselectivity (Table 8, entry 1). Cycloheptenyl ynamide **282b** also underwent a high yielding reaction at room temperature to give 5,7-*cis*-fused bicyclic dienamide **301b**, along with a small amount of the 5,7-*trans*-fused diastereomer (entry 2). We were also delighted to observe cycloisomerisation of 1-functionalised cyclohexenyl ynamide **282c** at 60 °C to form spirocyclic 1,4-dienamide **301c** in good yield (entry 3).[82] A small quantity of the 1,5-diene (7% by ratio) was also formed, again probably due to palladium-catalysed alkene-migration in the product.[106,107] The structural assignment of cycloisomerisation products **301a-c**, as well as for the minor isomers present, was supported using ^{1}H NMR nOe experiments.

Table 8 : Cycloisomerisation of cycloalkenyl ynamides to azabicyclic 1,4-dienes.[a]

Entry	Substrate		Temp (°C), Time	Major Product		Yield (%)[b]	Ratio
1		**282a**	25, 2.5 h		**301a**	89	96:4[c]
2		**282b**	25, 2.5 h		**301b**	91	90:10[d]
3		**282c**	60, 1 h		**301c**	82	93:7[e]
4*		**282d**	35, 5 h		**301d**	77	91:9[c]

[a] Reaction conditions: $Pd(OAc)_2$ (2.5 mol %), bbeda (2.5 mol %), toluene (0.333 M). [b] Isolated overall yield. [c] Ratio of *Z*:*E* enamides. [d] Ratio of 5,7-*cis*:5,7-*trans* fused rings. [e] Ratio of 1,4-diene:1,5-diene. * Reaction carried out by Dr. Craig Campbell.

Finally, we were delighted to find that enynamide **282d** cycloisomerised to give bridged azabicycle **301d** in good yield (entry 4, reaction carried out by Dr. Craig Campbell), the structure of which bears close resemblance to the core of the alkaloid peduncularine (Figure 9).[108,109] A temperature of 35 °C allowed the reaction to go to completion, whilst offering a superior yield to higher temperatures. It is noteworthy that this methodology provides efficient access to three distinct and important classes of azabicycle, namely fused, spirocyclic and bridged ring systems, many of which are challenging to prepare.

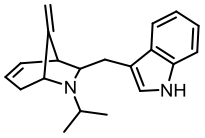


Figure 9 : (–)-peduncularine

3.5.4 Unsuccessful substrates

Despite the success of this methodology, a small number of substrates were found to be unamenable to our reaction conditions. Three monosubstituted enynamides were synthesised in the typical manner using the corresponding commercially available alcohol and synthesised bromoalkyne, but failed to give the desired outcome under cycloisomerisation conditions (Figure 10). Ester enynamide **195v** produced a complex mixture of products under both palladium- and ruthenium-catalysed cycloisomerisation conditions. To our surprise, aryl enynamide **195w** only showed substrate degradation under either set of reaction conditions, despite alkyl enynamides of the same chain length being excellent substrates. Alkyl enynamide **195x** also failed to react, and thus this methodology does not appear to be applicable to the formation of 7-membered rings.

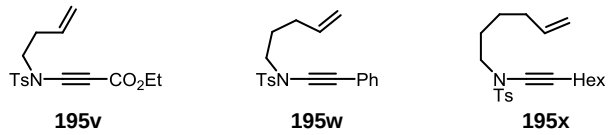
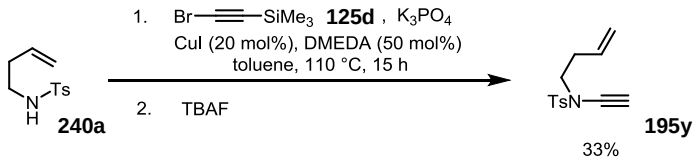


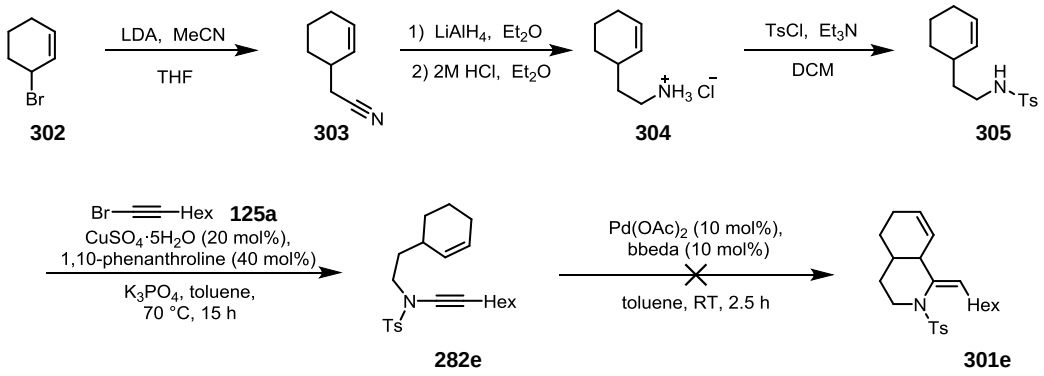
Figure 10 : Monosubstituted enynamides that did not cyclise.

Terminal enynamide **195y** was synthesised in a one pot procedure from sulfonamide **240a** (Scheme 85). After formation of the TMS-enynamide under CuI/DMEDA conditions, TBAF was added to the crude reaction mixture in order to from the deprotected ynamide. Unfortunately however, enynamide **195y** proved too reactive, forming a complex mixture of products under cycloisomerisation conditions.



Scheme 85

Cyclohexenyl ynamide **282e** was synthesised starting from cyclohexenyl bromide **302** (Scheme 86). The bromide was substituted with the anion of acetonitrile to give nitrile **303**, which was then reduced using $LiAlH_4$ and isolated as the hydrochloride salt **304**. Tosylation and then ynamide formation under standard conditions gave the ynamide. When cyclohexenyl ynamide **282e** was subjected to palladium-catalysed cycloisomerisation conditions, the starting material was consumed but a complex mixture of products was formed. There was perhaps a small amount of the desired 6,6-fused system but this could not be separated from the mixture.

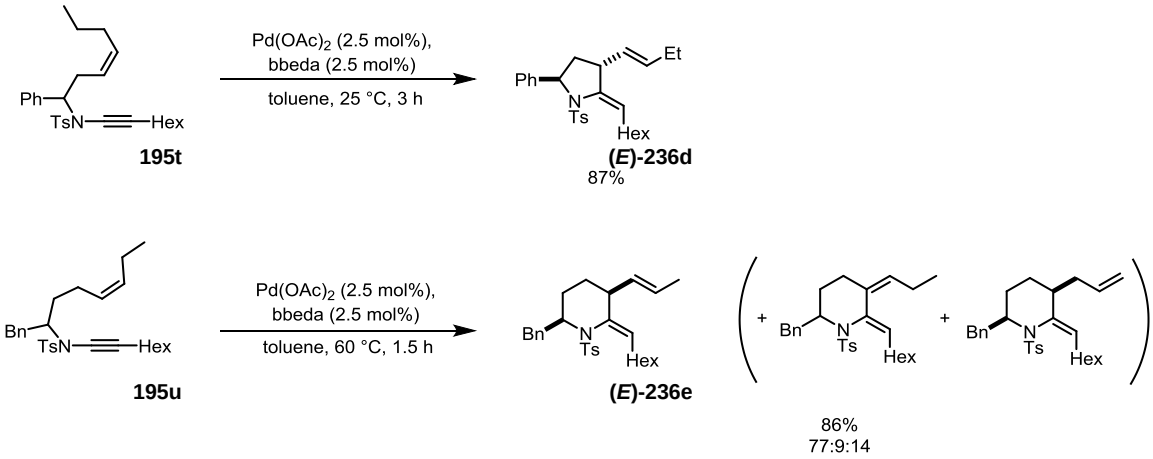


Scheme 86

3.6 Stereochemical Control

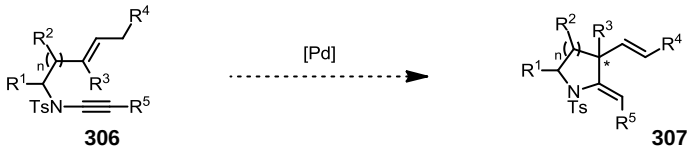
3.6.1 Potential expansion of the methodology

In the course of our investigations, we had found that chiral enynamide substrates could be used to form cyclic 1,4-dienamides as single diastereomers at the newly formed stereocentre. These results are repeated below (Scheme 87), where α-branched enynamides **195t** and **195u** both cyclised to give product 1,4-dienamides **(*E*)-236d** and **(*E*)-236e** as a single diastereomer, the relative stereochemistries of which were assigned using ^{1}H NMR nOe experiments.



Scheme 87

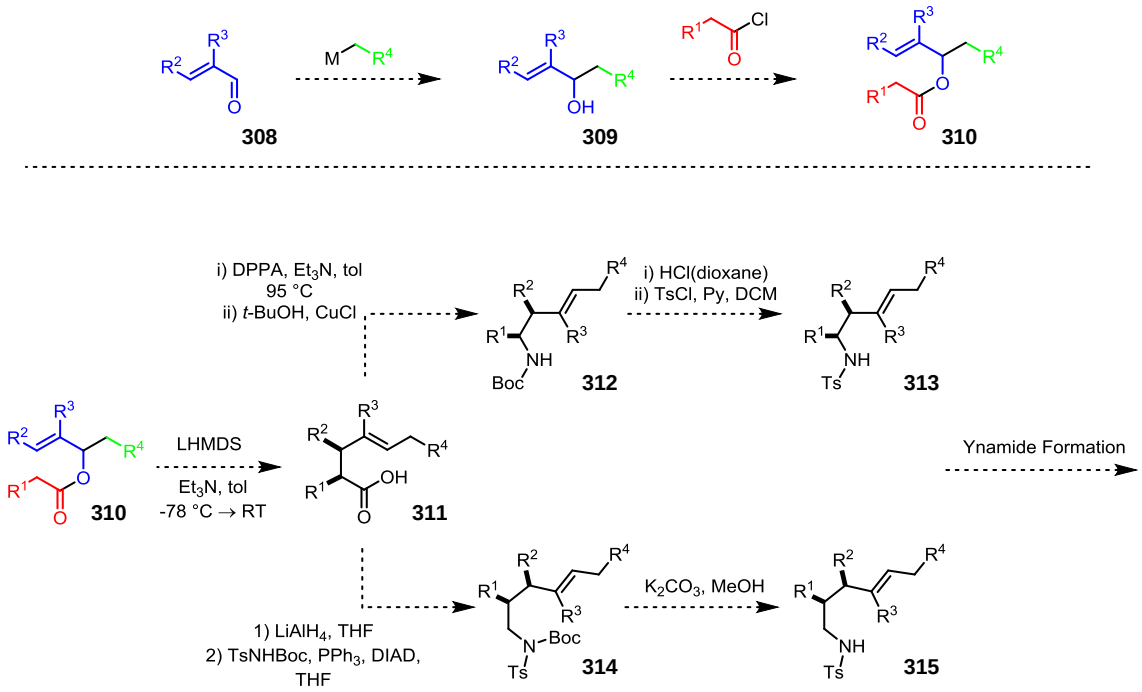
The hope was that if we could synthesise highly branched enynamides **306** (Scheme 88), these could undergo cycloisomerisation in a diastereoselective manner, giving access to highly functionalised 1,4-dienamides **307**. In time, enantioselective enynamide synthesis should even allow substrate-controlled formation of 1,4-dienamides as single enantiomers.



Scheme 88

We decided to employ an Ireland-Claisen strategy towards the synthesis of such highly branched enynamides (Scheme 89). This would allow the potential for a wide variety of substituents to be incorporated at each position, as well as effectively controlling the relative stereochemistry of substituents on the backbone of the molecule. The required esters **310** could be synthesised starting with the addition of an organometallic into α,β-unsaturated aldehydes **308**, with the alcohol **309** generated then reacted with an acyl chloride. An Ireland-Claisen reaction would then generate the carboxylic acid **311**. Using LHMDS at low temperature ensures the formation of an (*E*)-enolate,[110] and where applicable the chair transition state should lead to the formation of a single diastereomer. From the carboxylic acid **311**, a Curtius rearrangement using DPPA and subsequent trapping of the generated

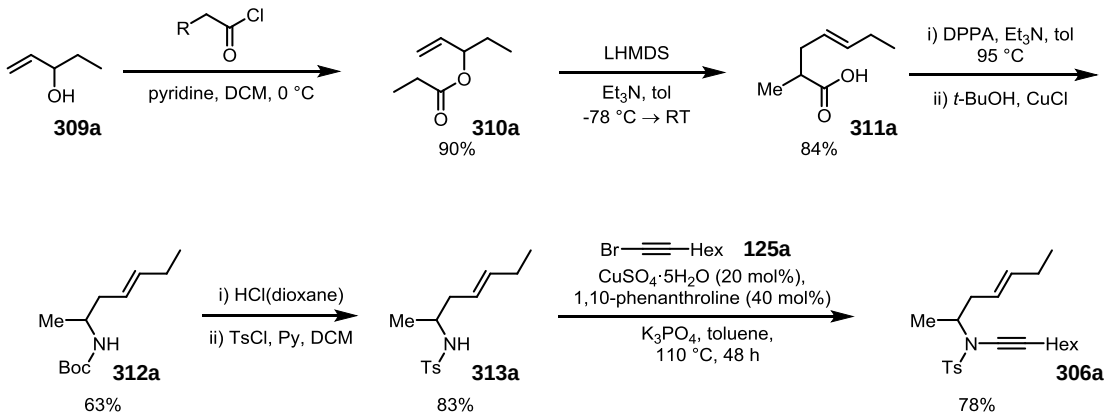
isocyanate with *t*-BuOH would give the Boc-protected amine **312**. Deprotection to the hydrochloride salt, tosylation of the amine and subsequent ynamide formation would then complete the synthesis. Alternatively, a direct reduction of the carboxylic acid **311** to the corresponding alcohol, followed by a Mitsunobu reaction and subsequent Boc deprotection, would generate a one carbon homologous sulfonamide **315**, with possible substituents at the β- and γ-positions.



Scheme 89

3.6.2 Branched disubstituted alkenyl ynamides

The planned route was initially applied to the synthesis of enynamide **306**, with a methyl substituent in the α-position (Scheme 90). We were pleased to find that the synthesis of sulfonamide **313a** proceeded as planned, with each step occurring in moderate to excellent yield. The copper-catalysed ynamide formation required heating at reflux in toluene for 48 h, but a good yield of 78% was obtained.



Scheme 90

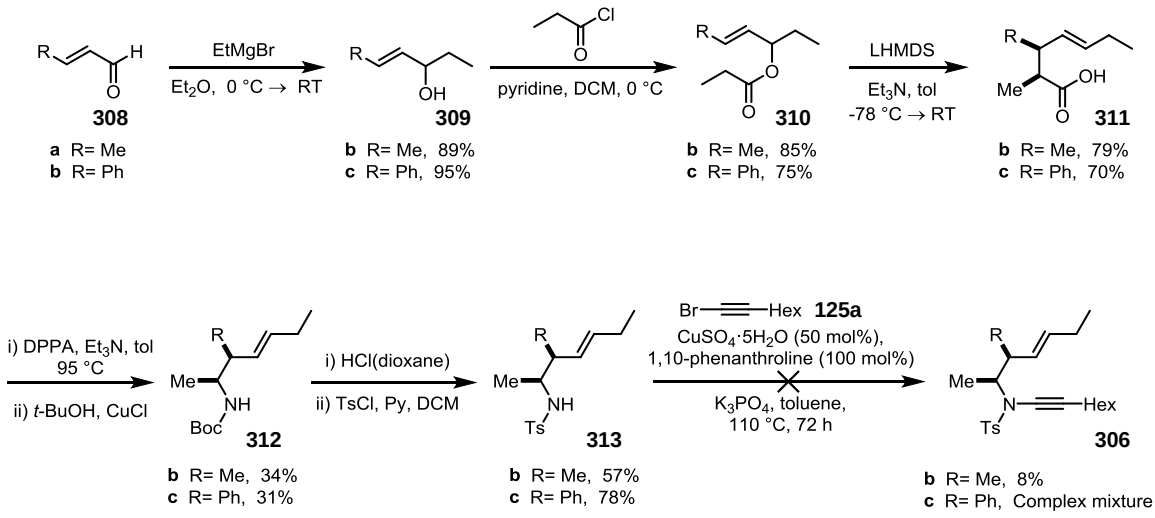
Palladium-catalysed cycloisomerisation of enynamide **306a** proceeded slowly and produced an approximate 1:1 mixture of 1,3- and 1,4-dienamides (**316a** and **(*E*)-307a**) in a moderate overall yield (Scheme 91). The two isomers could not be separated and therefore the relative stereochemistry of the newly-formed stereocentre in 1,4-dienamide **(*E*)-307a** was not determined, although the 1,4-dienamide **(*E*)-307a** did appear to be predominantly a single diastereomer. Enynamide **306a** also had to be handled with increased care relative to other enynamides as it appeared considerably more prone to decomposition.



Scheme 91

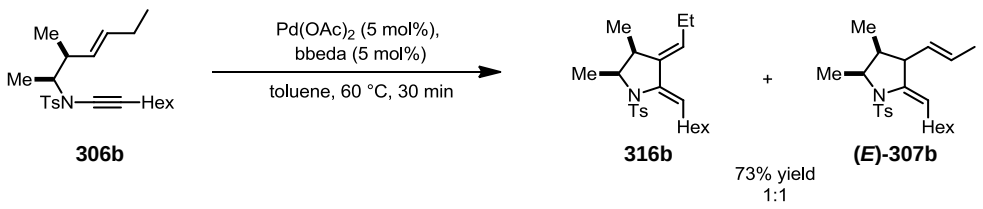
The same synthesis route was also employed in attempting to form branched enynamides **306b** and **306c** (Scheme 92). Esters **310b** and **310c** were synthesised as before starting from crotonaldehyde **308a** and cinnamaldehyde **308b** respectively, each step proceeding in good yield. A low temperature Ireland-Claisen reaction then generated carboxylic acids **311b** and **311c**, as what appeared to be single diastereomers by 1H NMR spectroscopy. The subsequent Curtius rearrangements proved to be more challenging and gave Boc-protected amines **312b**

and **312c** in low yield, which were nevertheless converted to their respective sulfonamides. Disappointingly, sulfonamides **313b** and **313c** proved to be very poor substrates for copper-catalysed ynamide formation. Despite a number of different conditions being attempted, including high temperature for an extended time with an increased catalyst loading of copper sulfate, branched enynamide **306c** (R= Ph) was not formed. Sulfonamide **313b** showed only 17% conversion after 72 h under reflux with 50 mol% of catalyst, affording a small amount of the desired branched enynamide **306b** after isolation (8% yield).



Scheme 92

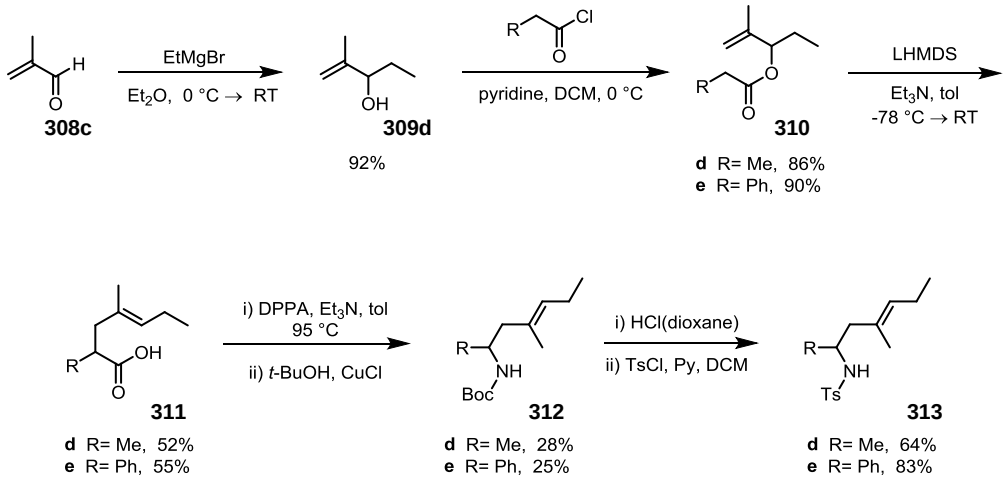
With only a very small amount of material available, branched enynamide **306b** was found to undergo cycloisomerisation to form an approximately 1:1 mixture of the 1,3- and 1,4-dienamide (**316b** and **(*E*)-307b**), as well as a small percentage of other unidentified isomers (Scheme 93).



Scheme 93

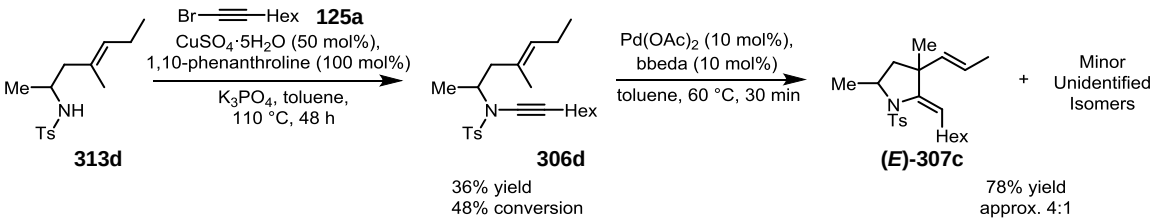
3.6.3 α-Branched trisubstituted alkenyl ynamides

The use of enynamides containing a 1,1,2-trisubstituted alkene prevents the reaction from forming 1,3-dienamides, and in forming 1,4-dienamides, a quaternary stereocentre is generated. However, we were concerned that any diastereoselectivity imparted by substituents on the backbone in the formation of the newly-formed stereocentre may be reduced due to the increased steric demands of a methyl group (*vs* a hydrogen atom). Nonetheless, sulfonamides **313d** and **313e** were synthesised using our established Ireland-Claisen rearrangement route (Scheme 94), although once again the yields of the Curtius rearrangement step were disappointingly low.



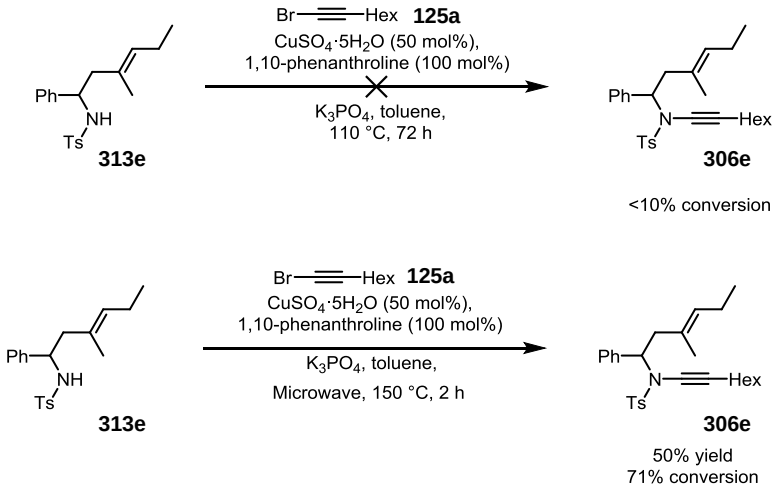
Scheme 94

Sulfonamide **313d** was converted to branched enynamide **306d** in low yield using 50 mol% of copper catalyst under reflux in toluene for 48 h, with only 48% conversion of the starting material. Enynamide **306d** was found to undergo palladium-catalysed cycloisomerisation to give 1,4-dienamide **(*E*)-307c** but with around 20% by ratio of other isomers.



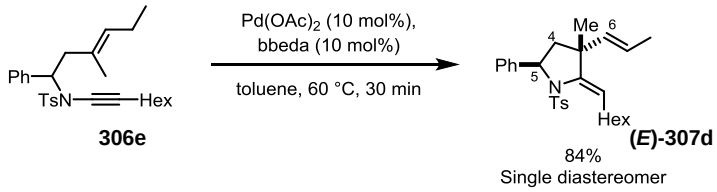
Scheme 95

Sulfonamide **313e** showed only a trace of the desired enynamide **306e** when subjected to the same ynamide formation conditions (Scheme 96), namely 50 mol% of copper catalyst heating under reflux in toluene for 72 h. Pleasingly however, this problem could be overcome by employing the same catalytic system in the microwave at 150 °C for 2 h, which gave 71% conversion of the starting material by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, and an isolated yield of 50%.



Scheme 96

To our delight, we found that α-branched enynamide **306e** underwent palladium-catalysed cycloisomerisation to give exclusively the highly-substituted cyclic 1,4-dienamide **(*E*)-307d** as a single diastereomer (Scheme 97). Complete substrate control was exerted over the newly-formed stereocentre, and the relative stereochemistry of the substituents across the ring was assigned through ^{1}H NMR nOe experiments. The (*E*)-geometry of the alkene was determined from the coupling constant (J=15.4 Hz).



Scheme 97

A possible minimum energy conformation for product dienamide **(*E*)-307d** was calculated using Spartan 14 molecular modelling software (Hartree-Fock, 3.21G(*) basis set) (Figure 11). In agreement with the suggested conformation, ^{1}H NMR nOe experiments show enhancements between protons on the alpha face of the molecule (as depicted below) between the alkene sidechain (H6), the benzylic proton (H5), and H4α. Complementary enhancement is seen between the methyl group and H4β, as well as from the Ph (*ortho*-protons) to H4β.

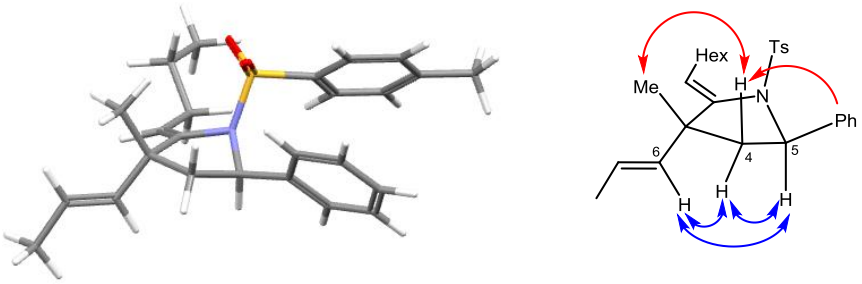
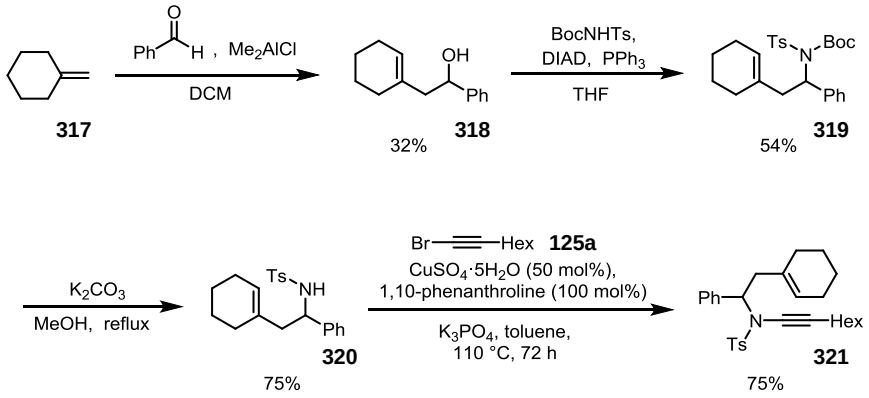


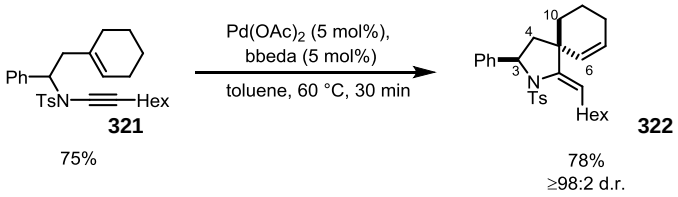
Figure 11 : Possible minimum energy conformation for dienamide **(*E*)-307d**.

Finally, we wanted to test whether the same stereocontrol could be exerted over the formation of a spirocyclic centre, a particularly challenging prospect given the steric similarities of the groups requiring to be differentiated. Methylenecyclohexane **317** underwent a Lewis acid-catalysed ene-reaction with benzaldehyde to form cyclohexenyl alcohol **318** (Scheme 98). A Mitsunobu reaction with BocNHTs and subsequent Boc deprotection then gave sulfonamide **320**, which was converted to cyclohexenyl ynamide **321** in good yield.



Scheme 98

We were elated to find that cyclohexenyl ynamide **321** underwent rapid palladium-catalysed cycloisomerisation at 60 °C in toluene to give spirocyclic 1,4-dienamide **322** in excellent yield and ≥98:2 d.r. (Scheme 99). Once more the relative stereochemistry of the product was assigned using ^{1}H NMR nOe experiments and was found to be as illustrated below. It is of some note that this methodology is able to generate azacycles possessing quaternary stereocentres with such excellent stereocontrol exercised by the substrate.



Scheme 99

A possible minimum energy conformation for spirocyclic dienamide **322** was again calculated using Spartan 14 molecular modelling software (Hartree-Fock, 3.21G(*) basis set) (Figure 11). In agreement with the illustrated diastereomer and the suggested conformation, ^{1}H NMR nOe experiments show enhancements between protons on the alpha face of the molecule (as depicted below) between the alkene moiety of the cyclohexenyl substituent (H6), the benzylic proton (H3), and H4α. Complementary enhancement is seen between CH_2-10 and H4β, as well as between the Ph (*ortho*-protons) and H4β.

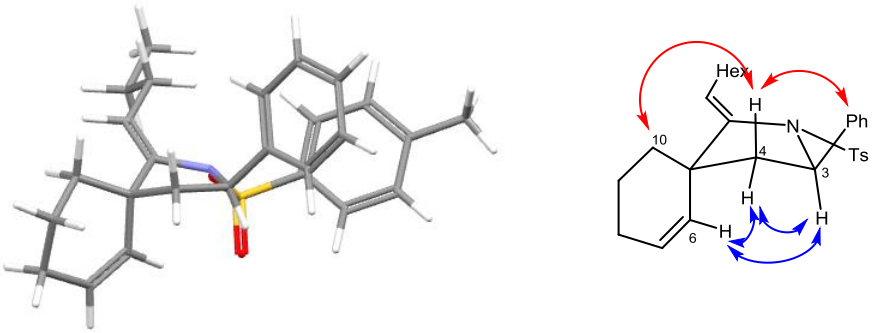


Figure 12 : Possible minimum energy conformation for spirocyclic dienamide **322**.

3.7 Conclusions and Further Work

We have presented the first examples of palladium-catalysed enynamide cycloisomerisation, together with a contrasting ruthenium-catalysed process. Mono-, di-, and trisubstituted alkenyl ynamides were found to undergo rapid and high yielding reactions giving access a wide range of attractive dienamide scaffolds, often in a highly stereo- and regioselective manner. The reactions are tolerant of a range of substituents on both the ynamide and alkene, underlining their potential utility as an atom-economical source of azacycles. In particular, the palladium-catalysed cycloisomerisation of cycloalkenyl ynamides provides efficient access to three distinct and important classes of azabicycle, namely fused, spirocyclic and bridged ring systems and efforts to further derivatise these products are ongoing..

Chiral enynamide substrates were used to generate 1,4-dienamides as a single diastereomer at the newly formed stereocentre. This was extended to include enynamides with a 1,1,2-trisubstituted alkene moiety, the resulting dienamide possessing a newly-formed quaternary stereocentre. This relay of stereochemistry was not only exploited in the formation of monocyclic dienamides, but also in the formation of a spirocyclic product, suggesting the potential for further stereocontrolled synthesis of polysubstituted azacycles.

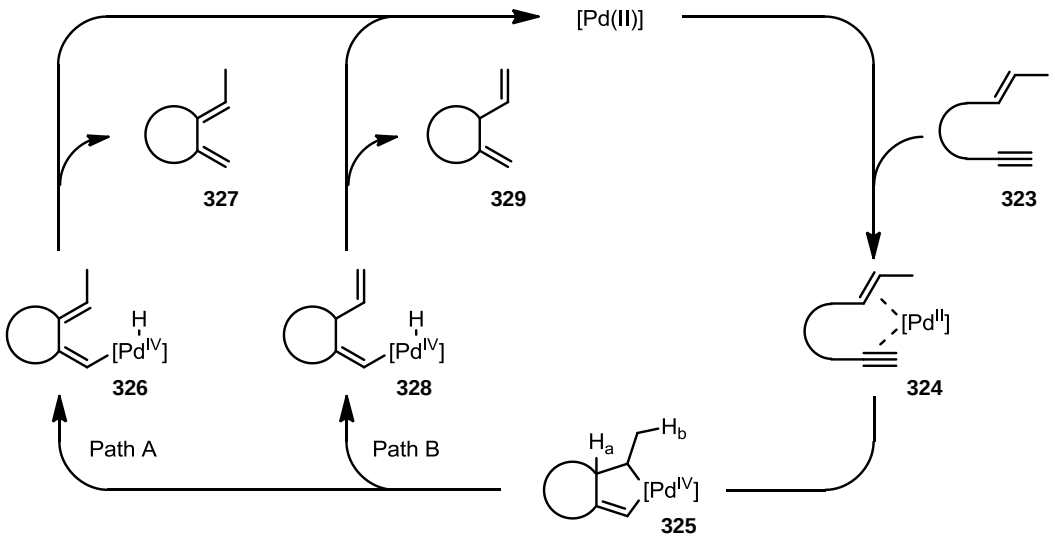
4. Mechanistic Considerations

4.1 Introduction

Having established the methodology for palladium- and ruthenium-catalysed cycloisomerisation of enynamides, we wanted to consider and investigate the mechanistic aspects of the reactions.

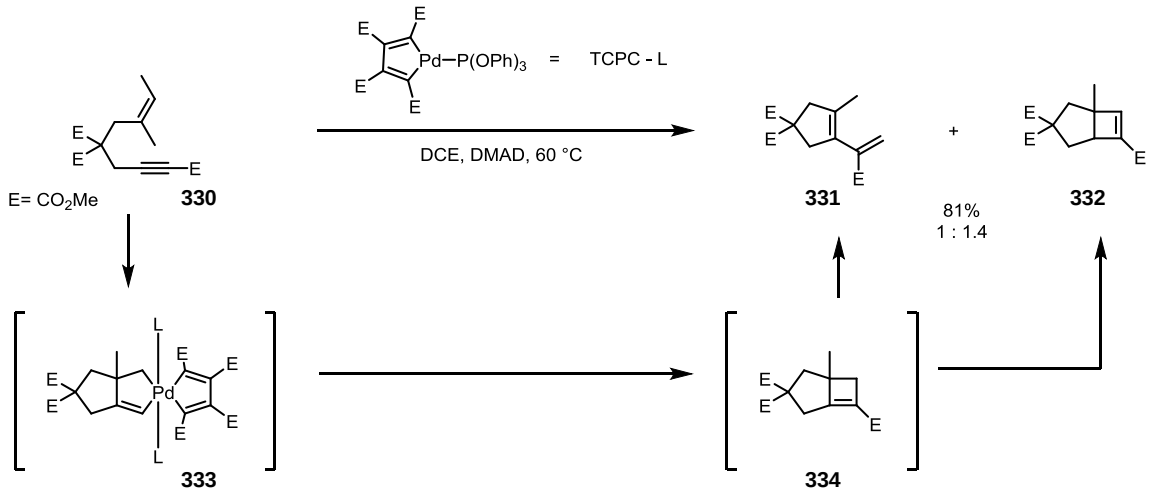
4.1.1 Palladacycle vs hydropalladation

For the cycloisomerisation of enynes using $Pd(OAc)_2$ as the catalyst, Trost initially proposed a mechanism that involves a palladacycle intermediate (Scheme 100).[77,85] Cyclisation of the alkyne onto a π-allyl palladium species was deemed highly unlikely, since it failed to account for the competitive formation of 1,3-dienes or for substrates which lacked allylic hydrogens.[82] Instead, it was proposed that coordination of Pd(II) to both the alkene and alkyne enables oxidative cyclisation to form a palladacyclopentene **325** containing a Pd(IV) species. At this point, β-hydride elimination of either H_a (Path A) or H_b (Path B) generates palladium hydride species **326** or **328** respectively. Reductive elimination then regenerates the Pd(II) catalyst and forms the corresponding 1,3- or 1,4-diene (**327** or **329**).



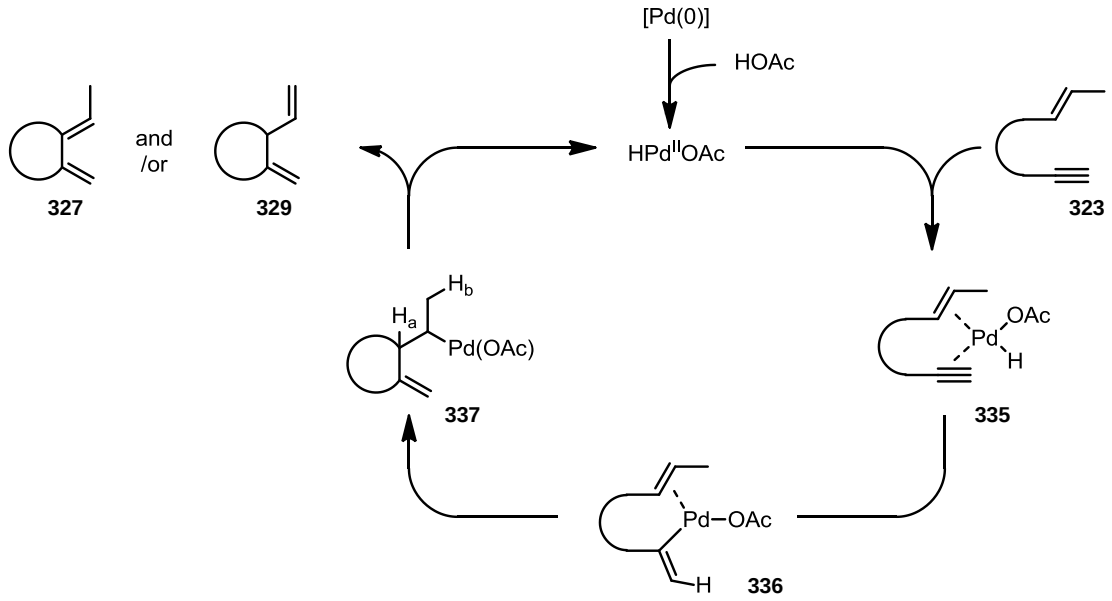
Scheme 100 – The palladacycle mechanism.

Support for the palladacycle mechanism was derived from the observed formation of related metallocyclopentenes with other transition metals, such as cobalt, zirconium and titanium.[111] In addition, when 1,6-enyne **330** was treated with tetracarbomethoxypalladacyclopentadiene (TCPC) in the presence of triphenyl phosphite a mixture of unexpected 1,3-diene **331** and cyclobutene **332** was formed (Scheme 101).[75] Both products appear to have been derived from a common intermediate, namely cyclobutene **334**. Product cyclobutene **332** represents a double bond isomerisation, whereas 1,3-diene **331** is formed by an electrocyclic ring opening. The only plausible route to intermediate cyclobutene **334**, involves the initial formation of palladacyclopentene **333** containing a Pd(IV) species, followed by a reductive elimination. Whilst variations in the mechanism operating with TCPC were observed with different substrates,[112] all were thought to involve a palladacycle.[113,114] However, the distribution of products with the TCPC-catalysed reaction was markedly different from those using $Pd(OAc)_2$, and all attempts to trap a palladacyclopentene when using $Pd(OAc)_2$ were unsuccessful. TCPC probably represent a specific case where the ligand is sufficiently electropositive to help stabilise the Pd(IV) state; the involvement of Pd(II)/Pd(IV) cycles is still not widely precedented in organopalladium chemistry, except with strong oxidants such as C_6F_5I and $PhI(OAc)_2$.[115]



Scheme 101 – Evidence for a palladacyclopentene intermediate using TCPC.

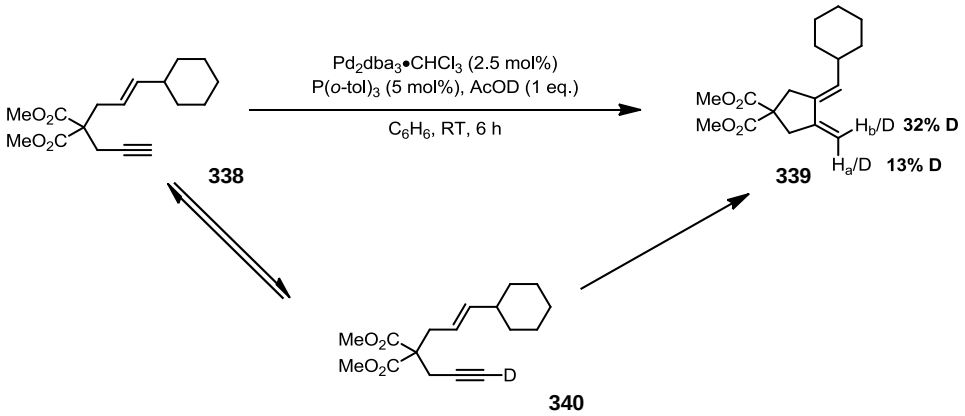
The alternative catalyst system for the cycloisomerisation of enynes using Pd_2dba_3•$CHCl_3$/AcOH was thought to proceed *via* a hydropalladation mechanism (Scheme 102).[76,88] Oxidative addition of Pd(0) into acetic acid generates a palladium(II) hydride species, which effects a regioselective *syn*-hydropalladation across the alkyne. Vinylpalladium species **336** then undergoes an intramolecular *syn*-carbopalladation across the alkene to generate cyclic alkylpalladium **337**. Subsequent β-hydride elimination of either H_a or H_b then gives either the 1,3- or 1,4-diene (**327** or **329**) respectively. Whist C-H bond strength would favour the elimination of the allylic proton H_a (1,3-diene), lower steric hindrance around H_b or geometric restrictions placed on the dihedral angle between C-H_a and C-Pd (*syn*-geometric orientation required for β-hydride elimination), favour elimination of H_b (1,4-diene).



Scheme 102 – The hydropalladation mechanism

In an effort to corroborate the proposal of formation of such palladium hydride species, NMR spectroscopic monitoring was attempted by Trost. Combination of Pd_2dba_3•$CHCl_3$ and AcOH in deuterated solvent led to no discernible change by NMR spectroscopy, meaning that any formation of a palladium hydride species was likely fast and reversible.[88] However, when 1,6-enyne **338**, known to favour the formation of 1,3-dienes, was cycloisomerised using Pd_2dba_3•$CHCl_3$ and one equivalent of AcOD, the resulting 1,3-diene product **339** showed

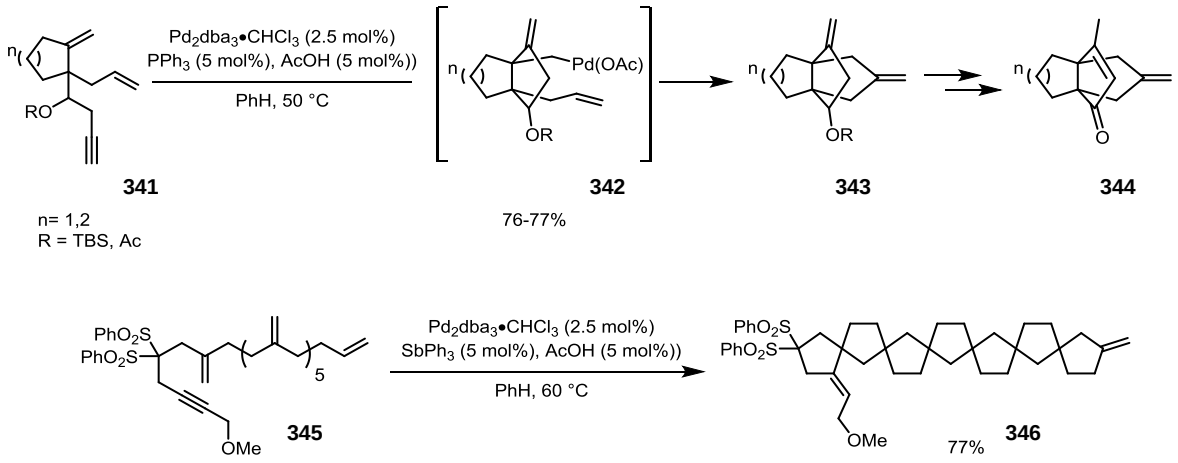
deuterium incorporation at the newly-formed *exo*-methylene moiety (Scheme 103). The hydropalladation mechanism shown in Scheme 102, would predict the *syn*-addition of an initially generated palladium deuteride to give deuterium at H_b and this position does indeed show the most significant level of deuterium incorporation (32% D). Since one equivalent of AcOH is generated during the reaction, the low overall amount of deuterium incorporation is not unexpected. The oxidative addition of Pd(0) to AcOH had been shown by ^{1}H NMR spectroscopy to be fast and reversible, so the percentage deuterium incorporation is determined by the hydropalladation step and any kinetic isotope effect would be thought to favour hydrogen incorporation over deuterium. The deuterium incorporation at the H_a position (13% D) was shown to be a consequence of hydrogen-deuterium exchange of the acetylene proton in the starting material, easily observed using a substrate which could undergo no further reaction.



Scheme 103 – Evidence for the palladium(II) hydride.

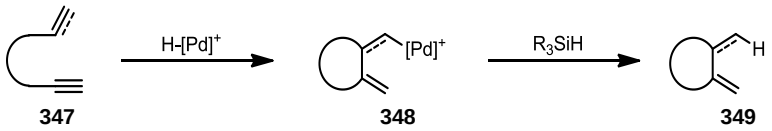
Further evidence supporting the proposed hydropalladation mechanism for Pd_2dba_3•$CHCl_3$/AcOH, comes from the interception of the proposed alkylpalladium intermediate. If the β-hydride elimination step is precluded due to a lack of hydrogen atoms at the β-position, and the molecule contains extra π-unsaturation, further *syn*-carbopalladations can occur generating additional rings. For example, dienyne substrates **341** were used to generate [4.3.3] and [3.3.3] propellanes **343** in a single step, which could then be converted to

propellenones as a single diastereomer **344** (Scheme 104).[116] Fused, bridged and spirocyclic ring systems could all also be generated in this manner, including a spirocyclic system **346** where seven rings were generated in a single step.



Scheme 104 – Palladium-catalysed cyclisations of polyenynes.

Further to this, when the reaction was conducted in the presence of a hydride donor such as R_3SiH, an overall reductive cyclisation of enynes or diynes was achieved (Scheme 105).[117,118] Instead of β-hydride elimination, transmetallation to form the palladium hydride and subsequent reductive elimination produced Pd(0) and the product. In order to regenerate the Pd(II) hydride active catalyst a full equivalent of AcOH was used. The cycloreduction of an enyne was employed as the key step in the total synthesis of antitumor agent phyllanthocin.[119] Application of this cycloreduction to diynes could be used to generate synthetically useful 1,3-dienes, even in cases where the enyne cycloisomerisation reaction proved problematic, and this strategy was utilised in the efficient total synthesis of siccanin.[120] Finally the alkylpalladium intermediate could even be intercepted in a Stille-type cross coupling with various vinyltin reagents, to give carbocycles bearing allyl appendages.[121]



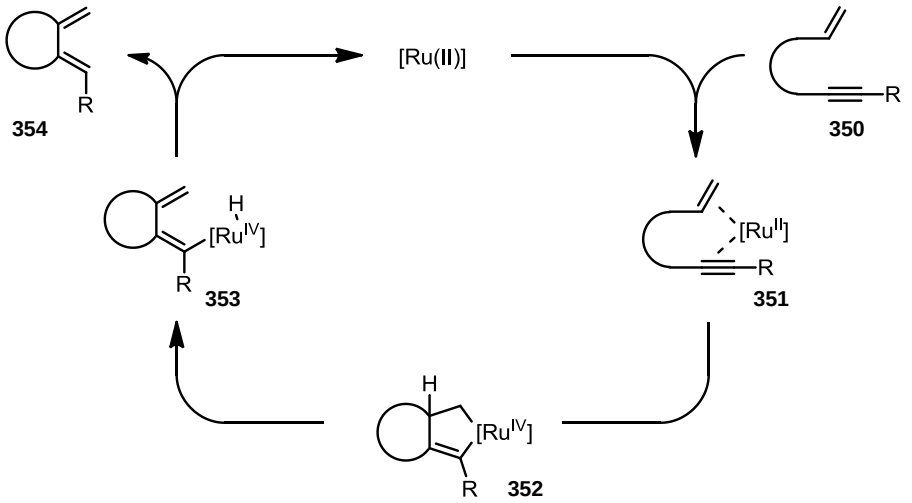
Scheme 105 – Palladium-catalysed reductive cyclisation of enynes and diynes.

Establishing that the Pd_2dba_3•$CHCl_3$/AcOH system operated *via* hydropalladation of a palladium(II) hydride raised the possibility that the $Pd(OAc)_2$-catalysed reactions were in fact the result of the same process. One could envisage a situation where a palladium(II) hydride species was generated *in situ* from $Pd(OAc)_2$ in a Wacker type process, perhaps involving a small amount of sacrificial substrate. If the $Pd(OAc)_2$-catalysed reactions followed a hydropalladation mechanism, it would eliminate the need to invoke a Pd(IV) species and instead would involve only hydro- and carbopalladation of alkenes and alkynes, both of which are highly precedented. Furthermore, the effects of substituents on regioselectivity are mirrored for both catalyst systems, suggesting a similar mechanism.[88] However, it should be noted that the reaction profiles are not identical and that the efficiency of the two catalysts can in certain cases differ considerably, with some substrates favouring a specific catalyst system even when the apparent ligands are the same. It is even possible that both the hydropalladation and the palladacycle mechanism operate for $Pd(OAc)_2$, depending on the substrate and ligands.

4.1.2 The ruthenacycle mechanism

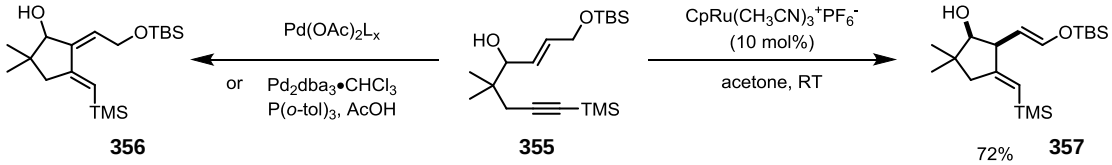
As previously discussed (Chapter 3), experimental evidence strongly suggested that the ruthenium-catalysed reactions of enyne substrates **350** proceeded *via* a ruthenacycle mechanism (Scheme 106).[94] Coordination of both the alkene and alkyne to Ru(II) promotes the formation of a ruthenacyclopentene **352** (Ru(IV)), which can undergo a β-hydride elimination in order to generate a vinylruthenium species **353**. Reductive elimination then regenerates the Ru(II) catalyst and forms the corresponding diene **354**. Any additional

π-unsaturated systems present can insert into the intermediate ruthenacycle, changing the outcome of the reaction.[92]



Scheme 106 – The ruthenacycle mechanism for enyne cycloisomerisation.

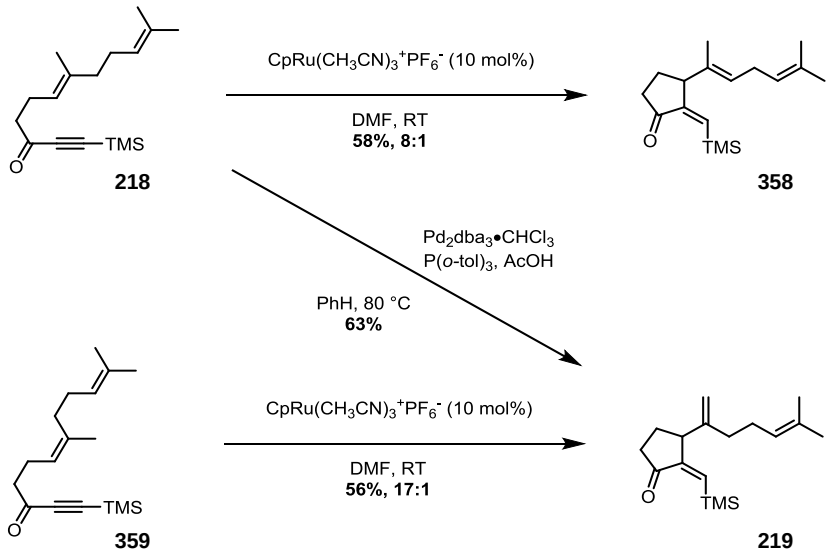
Trost and co-workers investigated the regio- and diastereoselectivity of the ruthenium-catalysed cycloisomerisation of enynes using allylic silyl ether substrate **355**. When using either $Pd(OAc)_2$ or Pd_2dba_3•$HCCl_3$/AcOH, substrate **355** had previously been found to undergo cycloisomerisation to form exclusively 1,3-diene **356**.[78,88] In contrast, $CpRu(CH_3CN)_3^+PF_6^-$ generated exclusively silyl enol ether **357** as a single diastereomer.[91]



Scheme 107 – Substituent effects on regioselectivity for ruthenium-catalysed enyne cycloisomerisation.

Dienyne substrate **218** had been found to give exclusively triene **219** under Pd_2dba_3•$HCCl_3$/AcOH cycloisomerisation conditions (Scheme 108),[122] and similar substrates showed the same pattern of reactivity with $Pd(OAc)_2$.[80] Surprisingly, cycloisomerisation of dienyne **218** using $CpRu(CH_3CN)_3^+PF_6^-$ gave triene **358** as the major isomer (8:1, **358**:**219**), arising from elimination of the hydrogen from the methylene group to form the more

substituted alkene. The alternative product could be formed under ruthenium catalysis by changing the geometry of the alkene moiety in the starting material, and dienyne **359** was found to form triene **219** in good yield and selectivity (17:1, **219**:**358**) using $CpRu(CH_3CN)_3^+PF_6^-$. These ruthenium-catalysed conditions therefore favour the formation of the ene-type product and selective formation of each 1,4-diene can be accomplished by choosing the geometry of the starting enyne.



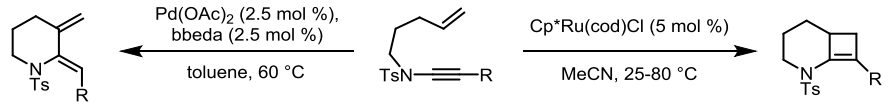
Scheme 108 – Inherent regioselectivity for palladium- and ruthenium-catalysed enyne cycloisomerisation.

The significant differences in selectivity observed between palladium- and ruthenium-catalysed cycloisomerisation conditions provides additional evidence supporting distinct mechanisms for each metal, a fact recognised by Trost.[91] Since a metallacycle is normally operating under ruthenium-catalysed conditions, it would suggest that hydrometallation is the principal mechanism of the palladium-catalysed reactions, even when employing $Pd(OAc)_2$ as the catalyst.

4.2 Proposed Mechanism for Enynamide Cycloisomerisation

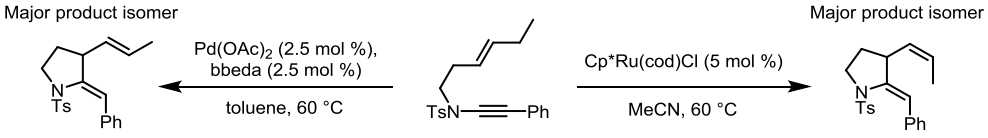
For the cycloisomerisation of enynamides, the contrasting outcomes we have observed under $Pd(OAc)_2$/bbeda and Cp*Ru(cod)Cl catalysed conditions also suggest separate mechanisms

for each catalyst system. Under palladium catalysis, 1,7-enynamides were found to form piperidine dienamides (Scheme 109), whereas under ruthenium catalysis 6,4-fused cyclobutenes **295** were generated in a formal [2+2] cycloaddition.



Scheme 109

In addition, whilst enynamides containing a 1,2-disubstituted alkene generally underwent efficient cycloisomerisation under palladium-catalysed conditions, they proved to be poor substrates for ruthenium catalysis. For enynamide **195m**, which did undergo cycloisomerisation with either metal, the major product isomer formed was different in each case (as part of a mixture of isomers) (Scheme 110).



Scheme 110

The distribution of products in our $Pd(OAc)_2$/bbeda-catalysed reactions has also at times suggested the existence of a palladium(II) hydride. Cycloisomerisation products **(*E*)-236e** and **301c** both contained small amounts of the 1,5-diene (**296** and **362** respectively) in the product mixture (Figure 13). This suggests alkene migration in the product, *via* addition of palladium(II) hydride to the alkene with the palladium at the 5-position, followed by β-hydride elimination away from the enamide ring.

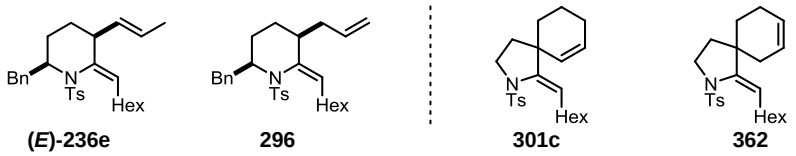
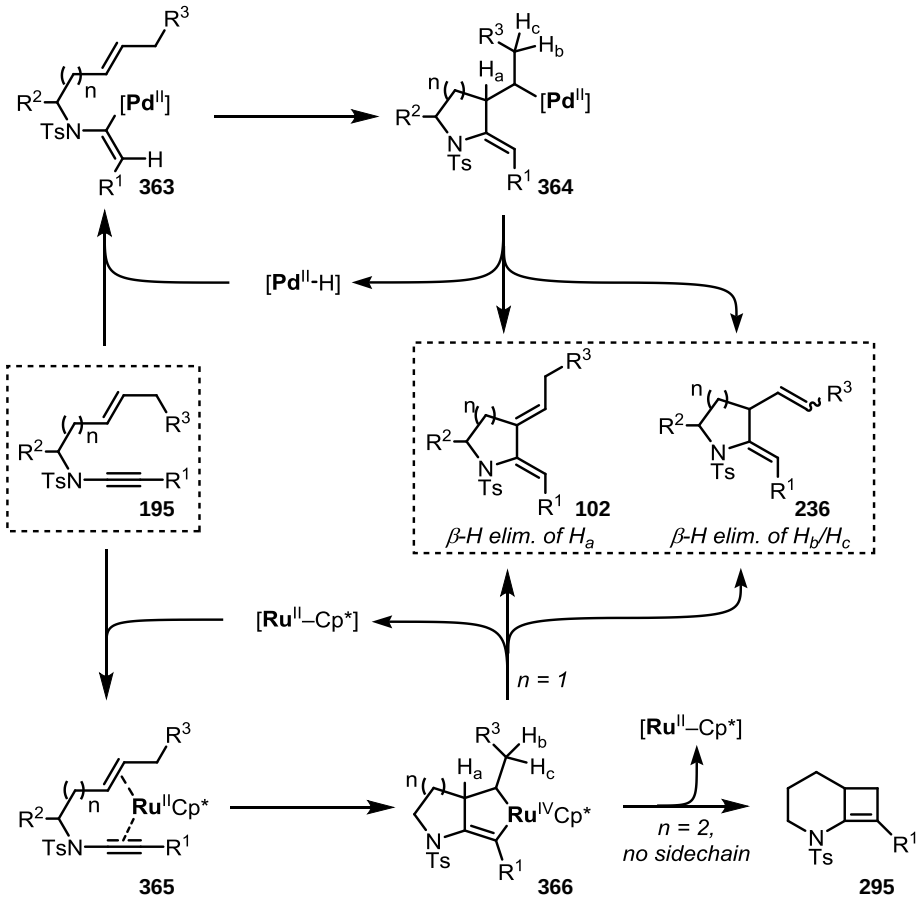


Figure 13 : Cycloisomerisation products containing small amounts of 1,5-diene.

We therefore propose the following distinct mechanisms for the cycloisomerisation of enynamides under $Pd(OAc)_2$/bbeda and Cp*Ru(cod)Cl catalysed conditions (Scheme 111). With $Pd(OAc)_2$/bbeda, a palladium(II) hydride species is generated *in situ* by an undetermined initiation step, which then effects regioselective *syn*-hydropalladation across the ynamide to form vinylpalladium species **363.** Ensuing intramolecular *syn*-carbopalladation across the alkene generates alkylpalladium **364**, which (depending on the substrate) has a choice of hydrogen atoms with which to undergo β-hydride elimination. Elimination of H_a generates the corresponding 1,3-dienamide **102**, whereas elimination of H_b or H_c leads to the (*E*)- or (*Z*)-1,4-dienamide **236**.



Scheme 111

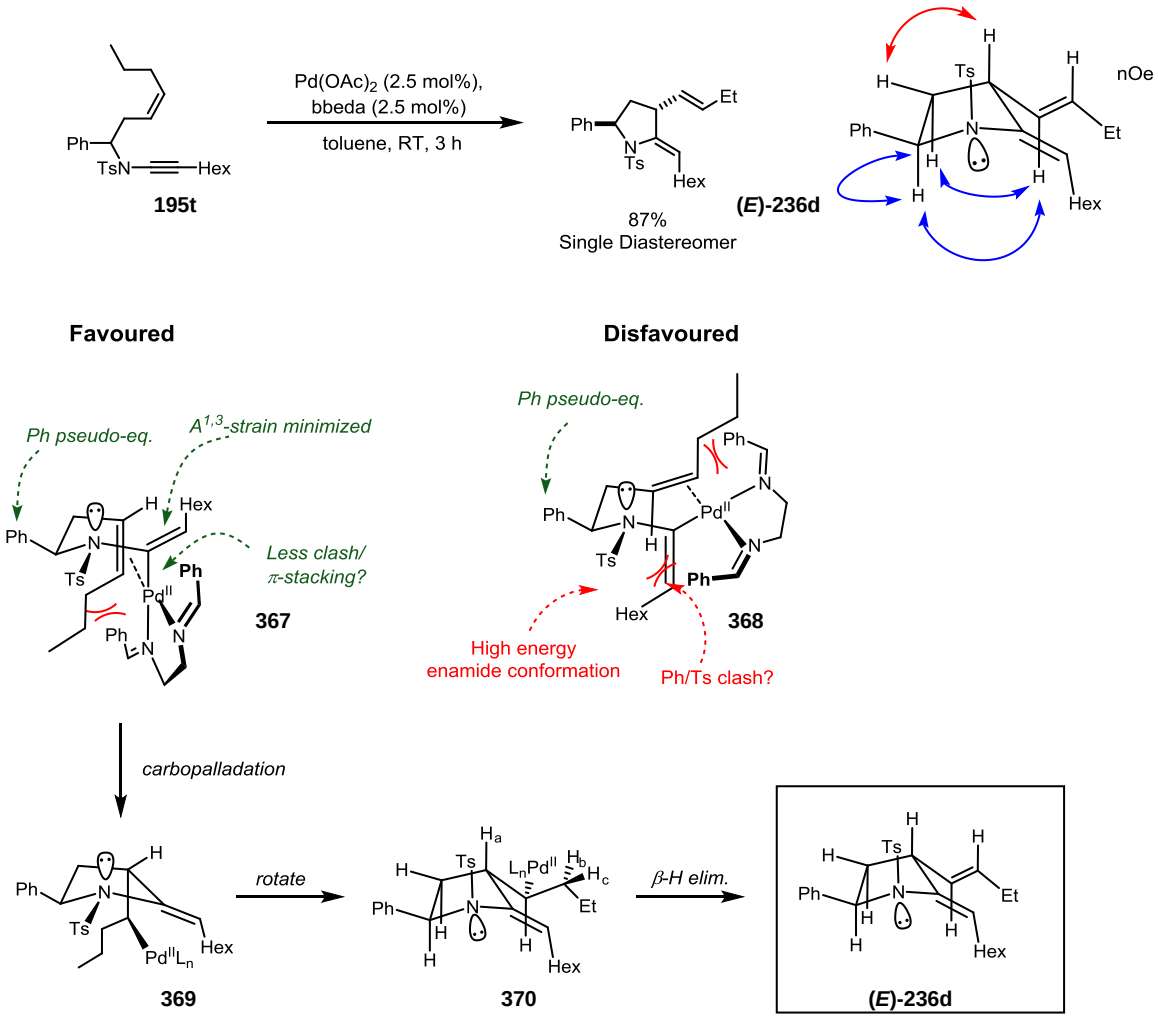
For Cp*Ru(cod)Cl, initial coordination of both the alkene and the ynamide enable formation of a ruthenacyclopentene **366** containing a Ru(IV) species. When the tethering ring is

6-membered (n= 2), direct reductive elimination can occur generating 6,4-fused cyclobutene products **295**. However, with a 5-membered tethering ring, reductive elimination is slowed due to the increased developing ring stain in the 5,4-fused product. Instead, β-hydride elimination now outcompetes reductive elimination in order to generate dienamide products, but in differing ratios to those obtained under palladium catalysis.

Our investigations had shown that, under palladium catalysis, chiral enynamide substrates could be used to form cyclic 1,4-dienamides as a single diastereomer at the newly formed stereocentre. A possible rationale for this stereoselectivity is presented below, with the example of enynamide **195t** (Scheme 112). Following initial hydropalladation, the C-Pd and C=C bonds must be parallel for the ensuing *syn*-carbopalladation and the newly forming five-membered ring substituents should be organised to minimise unfavourable electronic and steric effects. Assuming that the phenyl substituent is placed in a pseudo-equatorial position, the C-Pd and C=C bonds can therefore both occupy either a pseudo-axial (**367**) or pseudo-equatorial orientation (**368**).

Where delocalisation of the nitrogen-atom lone pair in enamines and ynamines is widely observed, in contrast, this effect is often less significant for enamides and ynamides. Additionally, with sulfonamides, the nitrogen atom is sp^3 hybridised and thus can orientate the sulfonyl group in either a pseudo-equatorial or pseudo-axial orientation on the newly forming five-membered ring. In conformation **367** the lone pair of electrons on the nitrogen atom is orientated on the side of the enamide that minimises $A^{1,3}$-strain, whereas in conformation **368** the enamide is forced into a higher energy conformation, with two *gauche* interactions on the 'inside' of the enamide, and with the lone pair of electrons eclipsed with the C-Pd bond. With the bbeda ligand in a square planar arrangement, conformation **368** also shows increased steric clash with the tosyl group. Conformation **367** is therefore favoured and upon *syn*-carbopalladation intermediate **369** is generated, which rotates to give lower energy

conformation **370** in keeping with our proposed conformation of the product. β-Hydride elimination of H_a in order to form the 1,3-dienamide is disfavoured, as the coplanar alignment of C-H_a and C-Pd necessary results in the orientation of the alkyl chain towards the enamide, increasing steric repulsion. This explanation is supported by the general lack of 1,3-dienamides observed with substrates containing (*Z*)-alkenes (for substrates with an (*E*)-alkene, coplanar alignment of C-H_a and C-Pd is more favourable as it orientates the alkyl chain away from the ring). The 1,4-dienamide is therefore formed in preference, with β-hydride elimination of H_b favoured over H_c due to less steric clash in the conformation leading to the more stable (*E*)-alkene isomer. This gives the observed 1,4-dienamide product **(*E*)-236d**, with the phenyl and alkene substituents *anti* across the ring.

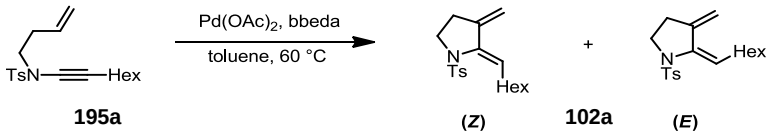


Scheme 112

4.3 The Palladium(II) Acetate Story

During the course of our investigations we discovered that, for the cycloisomerisation of enynamides, the batch quality of $Pd(OAc)_2$ can have a substantial impact on the *E*/*Z* diastereoselectivity of the product enamide (Table 9). When our first batch of $Pd(OAc)_2$ was used as the catalyst, enynamide **195a** underwent cycloisomerisation to give dienamide **102a** as a 97:3 ratio of *Z*:*E* isomers (entry 1). To our surprise however, when we performed the reaction with a new batch of $Pd(OAc)_2$ from the same supplier, the *Z*:*E* ratio was 80:20, a significant increase in the proportion of the (*E)*-dienamide. We therefore set about testing various different samples of commercially available $Pd(OAc)_2$ and found that although some matched our initial result (97:3; *Z*:*E*), others also showed an increased amount of (*E*)-dienamide. One sample even went as far as generate the (*E*)-dienamide as the major isomer (38:62; *Z*:*E*) (entry 3).

Table 9 : Changes in diastereoselectivity with different batches of commercial $Pd(OAc)_2$.



195a **(*Z*)** **102a** **(*E*)**

Entry	$Pd(OAc)_2$ Source	Ratio	
		Z	***E***
1	Acros (Batch 1)	97	3
2	Acros (Batch 2)	80	20
3	Alfa Aesar	38	62

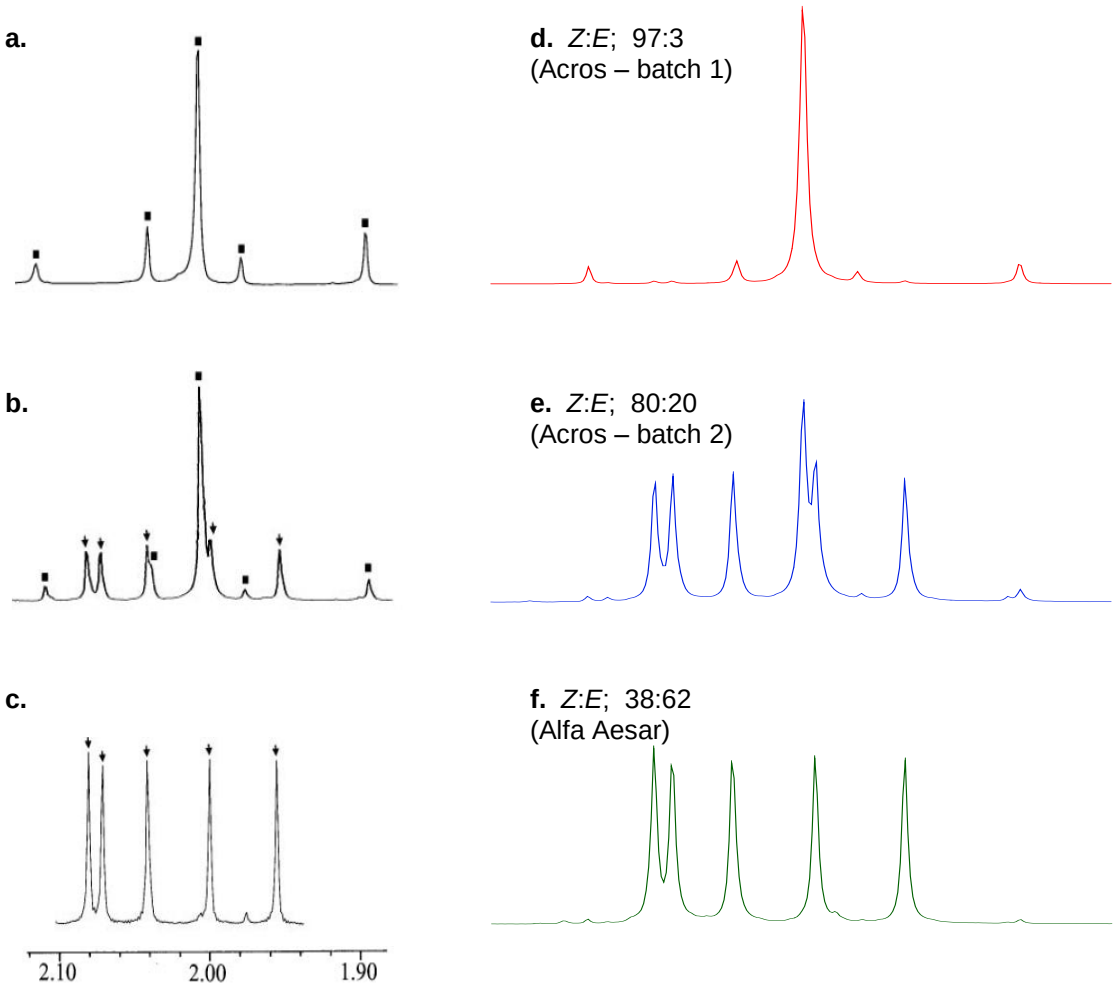
Whilst searching for an explanation for this variation in diastereoselectivity between different $Pd(OAc)_2$ batches, we came across a paper from the Cotton group entitled 'Non-trivial behaviour of palladium(II) acetate'.[123] The authors discussed the fact that commercial $Pd(OAc)_2$ is normally manufactured *via* the oxidation of freshly formed palladium powder using a mixture of HNO_3 and AcOH. Pure solid palladium(II) acetate exists as a trimer

($Pd_3(OAc)_6$), but a common contaminant is $Pd_3(OAc)_5NO_2$, where one of the acetate groups has been replaced by nitrite. To avoid this, nitrogen oxide gases must be eliminated promptly during the manufacture process by bubbling N_2 gas through the reaction mixture. However, many sources of commercially available palladium(II) acetate still contain 10-20% $Pd_3(OAc)_5NO_2$ and sometimes more.[124] Whilst this impurity is immaterial in many cases, it is no doubt responsible for a number of unexpected and irreproducible results.[125] Since the structure and physical properties of $Pd_3(OAc)_6$ and $Pd_3(OAc)_5NO_2$ are similar, these complexes cannot be effectively separated by recrystallisation.

In the solid state the $Pd_3(OAc)_6$ trimer has D_{3h} symmetry with each of the palladium atoms in a square planar environment and six bridging acetate groups. In scrupulously dry $CDCl_3$, all of the acetate groups remain equivalent and ^1H NMR spectroscopy produces a single intense peak. Under normal conditions, the small quantity of H_2O present in the $CDCl_3$ disrupts a small amount of the trimer, producing a single intense signal (the trimer) surrounded by a number of smaller peaks (hydrolysis complex) (Figure 14, **a**).[123] For $Pd_3(OAc)_5NO_2$ the trinuclear motif is preserved, but the replacement of an acetate group by nitrite breaks the D_{3h} symmetry, and the remaining acetate groups occupy five different environments. This leads to five signals of equal intensity in the ^1H NMR spectrum (**c**). It is interesting that for this complex no extraneous peaks are observed even in the presence of small amounts of water, suggesting that $Pd_3(OAc)_5NO_2$ is less labile than $Pd_3(OAc)_6$. Commercially available palladium(II) acetate which can contain up to 20% $Pd_3(OAc)_5NO_2$ therefore produces a ^1H NMR spectrum which is a combination of the individual spectra (**b**).

When we compared the ^1H NMR spectra of our commercial palladium(II) acetate samples, we were astonished to find that the observed diastereoselectivity in our cycloisomerisation reactions corresponded with the amount of $Pd_3(OAc)_5NO_2$ present. Our original sample of palladium(II) acetate, which produced dienamide **102a** as a 97:3 mixture of *Z*:*E* isomers,

consisted of pure $Pd_3(OAc)_6$ trimer (**d**). Our second sample, where the *Z*:*E* ratio was 80:20, contained a mixture of $Pd_3(OAc)_6$ and $Pd_3(OAc)_5NO_2$ (**e**). To our surprise, the third sample of palladium(II) acetate, which had produced the (*E*)-dienamide as the major isomer (38:62; *Z*:*E*), contained only $Pd_3(OAc)_5NO_2$. It is concerning that commercially available samples of palladium(II) acetate have been found to possess such high and inconsistent percentages of $Pd_3(OAc)_5NO_2$, particularly when this impurity can affect the reaction outcome.



Literature spectra[123]

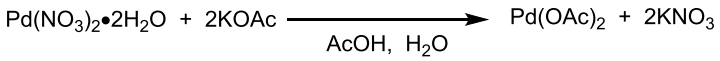
[Reproduced without permission from the authors]

a. Pure $Pd_3(OAc)_6$ in $CDCl_3$
b. $Pd_3(OAc)_6$ prepared according to commercial procedure
c. $Pd_3(OAc)_5(NO_2)$

Our $Pd(OAc)_2$ samples

Figure 14 : The composition of our $Pd(OAc)_2$ samples.

We overcame this problem by using high purity palladium(II) acetate (99+% (99.95+%Pd)) from Strem Chemicals Inc., which can be purchased at minimal extra cost. These palladium(II) acetate samples were found to contain at most only trace amounts of $Pd_3(OAc)_5NO_2$. In addition, we also synthesised pure palladium(II) acetate by combining $Pd(NO_3)_2 \bullet 2H_2O$ and potassium acetate in aqueous acetic acid at room temperature (Scheme 113),[124] a route which circumvents the formation of $Pd_3(OAc)_5NO_2$.



Scheme 113

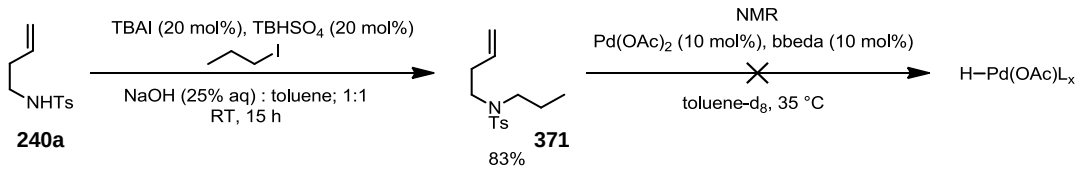
4.4 Mechanistic Investigations

4.4.1 Initial experiments

Our mechanistic hypothesis for the palladium-catalysed cycloisomerisation of enynamides proposed the initial *in situ* formation of a palladium hydride and we attempted to observe such a species using ^{1}H NMR spectroscopy. The hydride signal of palladium hydride species in ^{1}H NMR spectroscopy typically appears between 0 and -25 ppm.[126] Firstly $Pd_2dba_3 \bullet CHCl_3$/AcOH/bbeda were mixed in toluene-d_8 in an NMR tube, this being the catalyst system with most evidence to support progression *via* the hydropalladation mechanism. Unfortunately, no palladium hydride species was observed, a result consistent with the findings of Trost,[88] and supporting the hypothesis that any palladium hydride formation is fast and reversible.

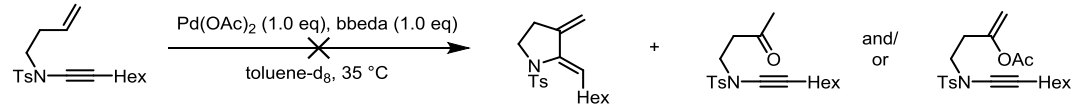
Nevertheless, it was deemed worthwhile confirming that no palladium hydride could be observed by ^{1}H NMR spectroscopy when using $Pd(OAc)_2$. It had been hypothesised that the initial palladium(II) hydride was generated *in situ* from $Pd(OAc)_2$, perhaps in a Wacker type process with a small amount of sacrificial substrate. In order to account for this possibility,

alkene **371** was synthesised from sulfonamide **240a** and *n*-propyl iodide under phase transfer catalysis conditions (Scheme 114). This substrate was designed to test palladium(II) hydride formation whist remaining otherwise unreactive. However, when alkene **371** was added to $Pd(OAc)_2$/bbeda in an NMR tube, no palladium hydride species was observed and the substrate showed no obvious signs of oxidation. In fact, when $Pd(OAc)_2$ and bbeda were mixed together in toluene-d_8, in the absence of a viable cycloisomerisation substrate, the ^{1}H NMR became highly complex, and after an extended period of time a colourless precipitate started to form in the NMR tube.



Scheme 114

An attempt was also made to observe any by-products of a palladium hydride-generating initiation step by careful examination of the crude reaction mixture from a cycloisomerisation of enynamide **195a** using stoichiometric catalyst - the idea being that the percentage of any such by-product might be increased (Scheme 115). However, no such ketone **372** or enol acetate **373** (the potential products of Wacker oxidation) were discernible by ^{1}H NMR spectroscopy or TLC.



Scheme 115

4.4.2 Timecourse spectroscopy

We started our ^{1}H NMR spectroscopy timecourse investigations by observing the progression of enynamide **195a** to 1,3-dienamide **102a** under $Pd(OAc)_2$/bbeda catalysed cycloisomerisation conditions (Figure 15). The reaction was carried out in an NMR tube using

10 mol% of catalyst and toluene-d_8 (0.167 M). A temperature of 35 °C was found to be optimal to perform these experiments, as it slowed the reaction sufficiently, allowing us to take more measurements before the reaction was complete; if the temperature was reduced further, the reaction was deemed to be at risk of not going to completion. 1,4-Dimethoxybenzene was used as an internal standard against which the amount of starting material and product at a given time was measured as a percentage of the total starting material originally present (proportional to concentration).

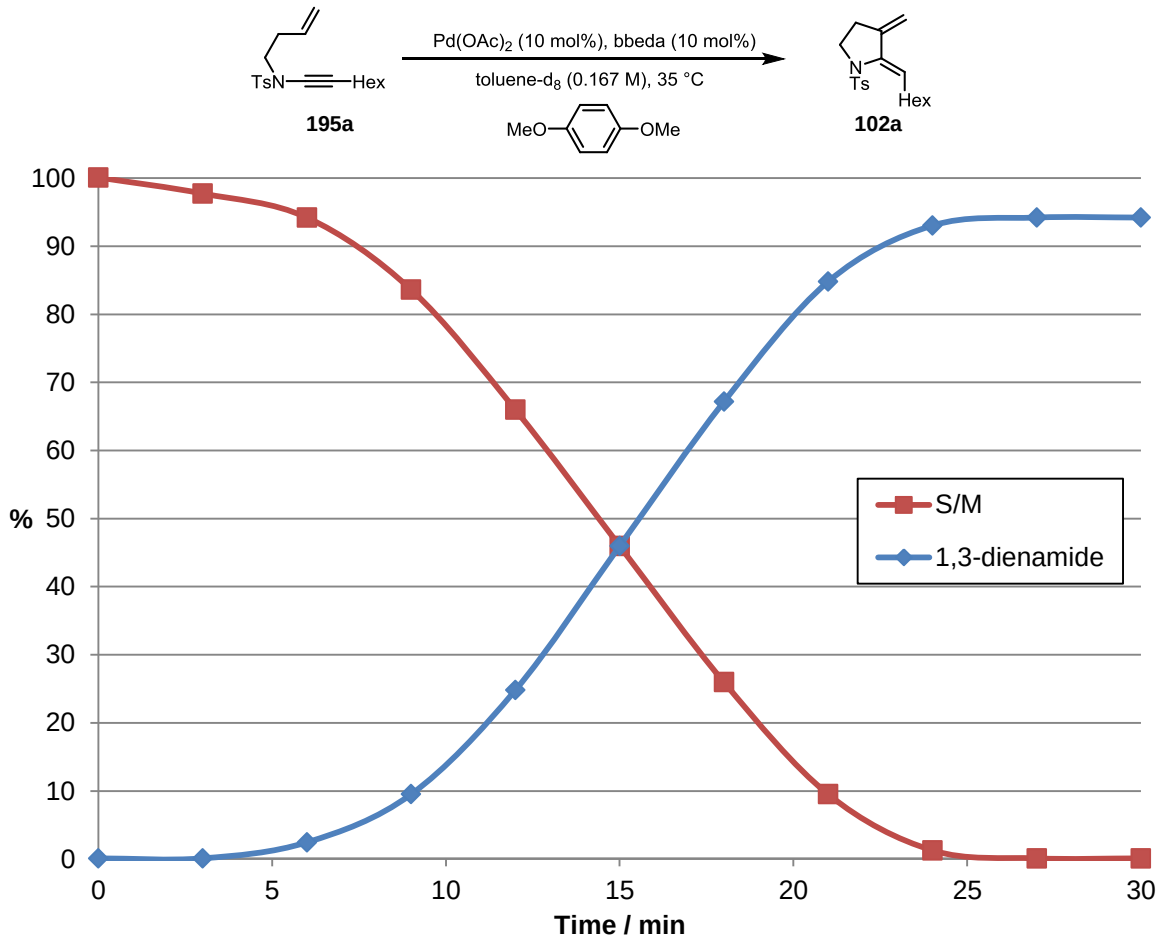


Figure 15 : Reaction profile for $Pd(OAc)_2$/bbeda-catalysed cycloisomerisation.

Whilst one must be aware of the potential errors in a quantitative interpretation of these peak integrations (e.g. differing T_1 relaxation times were not accounted for in this experiment), they nonetheless provide a good overall impression of the reaction course. In this case, the reaction appeared to show an initial period (approx. 4 min) where a small amount of starting material

was consumed without the formation of any 1,3-dienamide **102a**. After this, the rate of formation of 1,3-dienamide **102a** increases to an almost constant rate, before the expected trailing off at the end when the starting material is nearly full consumed. This 'lag period' observed at the start of the reaction lends weight to the argument that the reactive catalyst species is generated *in situ*, perhaps by reaction with a small percentage of sacrificial substrate. However, the active species may be something other than a palladium(II) hydride and the initiation time might simply correspond the breakdown of the $Pd_3(OAc)_6$ trimer.

The reaction profile for the formation of 1,3-dienamide **102a** with $Pd(OAc)_2$/bbeda was then compared to that of two other catalyst systems effective in the same transformation, namely Pd_2dba_3•$CHCl_3$/AcOH/bbeda and Cp*Ru(cod)Cl (Figure 16). The palladium-catalysed reactions were carried out in toluene-d_8 at 35 °C as before, but the slower ruthenium-catalysed reaction required 60 °C in CD_3CN for a comparable reaction time. The Pd_2dba_3•$CHCl_3$/AcOH/bbeda conditions were found to be somewhat unreliable at 35 °C in an NMR tube, the lack of effective stirring and lower temperature contributing to the failure of a number of attempted experiments where precipitation was observed before the reaction was complete. However, a successful run is shown in Figure 16 and the shape of the reaction profile remained constant even in those cases where the reaction failed to reach complete conversion. The Pd_2dba_3•$CHCl_3$/AcOH/bbeda system did not show the initial lag observed with $Pd(OAc)_2$/bbeda, implying that the active catalyst species is present from the beginning, an expected result given that the palladium(II) hydride formation from Pd(0)/AcOH is thought to be fast and reversible. The Cp*Ru(cod)Cl system also showed a maximum rate at the start, the rate decreasing as the substrate was consumed. Predictably, this shows that the reactive ruthenium catalyst species is also immediately present and potentially highlights the difference in mechanism from $Pd(OAc)_2$/bbeda.

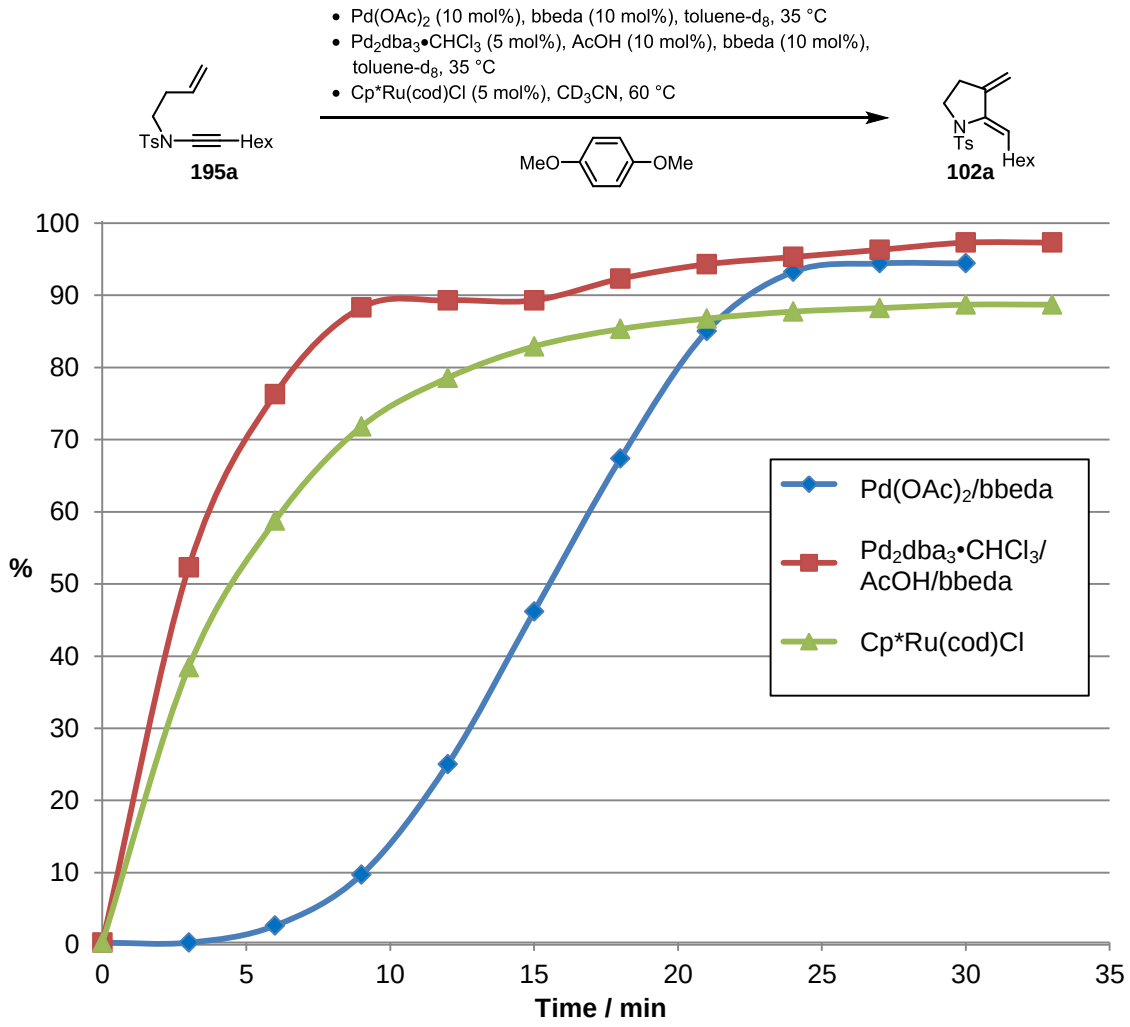


Figure 16 : Reaction profile for different catalyst systems (formation of 1,3-dienamide).

When the cycloisomerisation of disubstituted alkenyl ynamide **195n** under $Pd(OAc)_2$/bbeda conditions was examined by ^1H NMR spectroscopy, the reaction showed a similar overall profile to previous monosubstituted alkenyl ynamide **195a** (Figure 17). Once again there was an initial lag period, after which the rate of the reaction started to increase. The (*Z*)-alkene in the starting material led to the expected mixture of (*E*)- and (*Z*)-1,4-dienamides **236a**, with both products being generated in a roughly constant ratio throughout the course of the reaction (i.e. nether 1,4-dienamide isomer appears to be generated by isomerisation of the other). This suggests that the observed product ratio is indicative of the reaction itself, specifically the efficacy of β-hydride elimination for each of the possible hydrogen atoms.

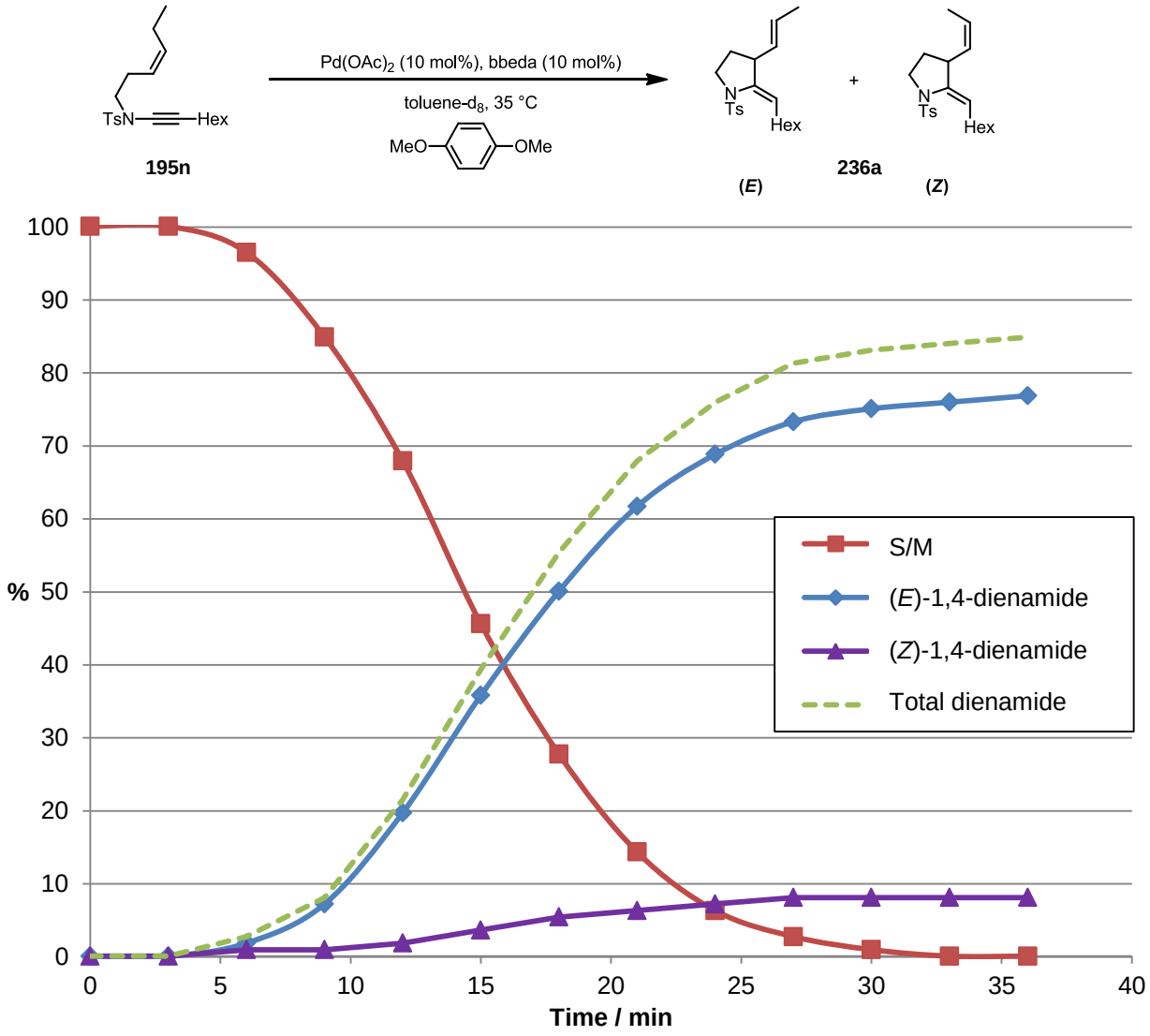


Figure 17 : Reaction profile for the formation (*E*)- and (*Z*)-1,4-dienamides.

Enynamide **195l**, the (*E*)-alkene analogue, also followed the same overall pattern by ^{1}H NMR spectroscopy, although the induction lag time was a little less pronounced (Figure 18). This time the products were the expected mixture of 1,4 - and 1,3-dienamide (**(*E*)-236a** and **(*E*)-102n** respectively), with the ratio between products again remaining approximately constant throughout the reaction, once again suggesting no interconversion between the two.

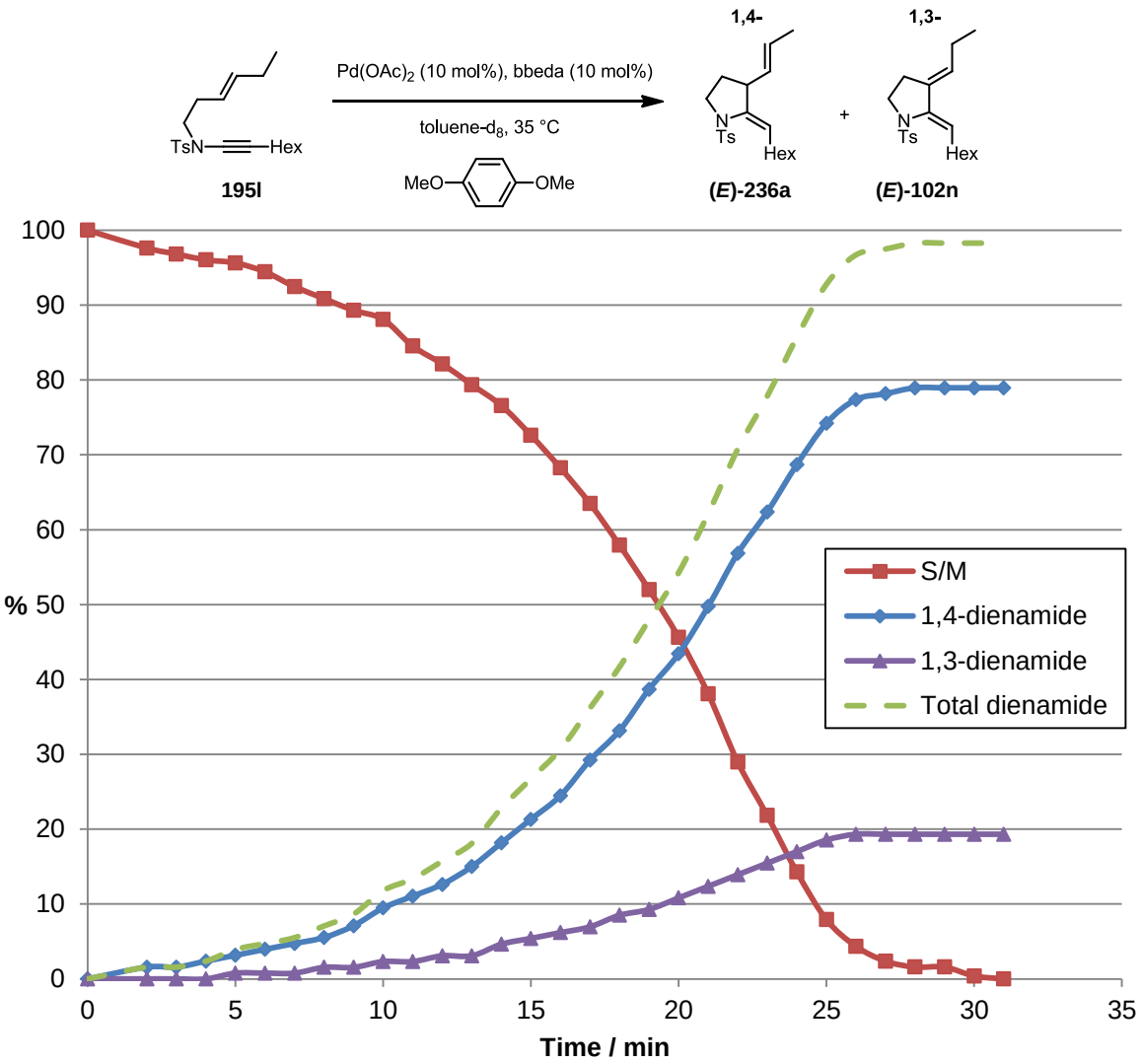


Figure 18 : Reaction profile for the formation 1,4- and 1,3-dienamides.

Whilst investigating the $Pd(OAc)_2$-catalysed cycloisomerisation of enynamide **195l**, we discovered that, in contrast to the majority of our substrates, the reaction also proceeded in the absence of additional ligands (without bbeda), albeit with an extended reaction time. The reaction profile under these ligand free conditions was compared to the standard conditions by considering the total amount of dienamide products formed with time in each case (Figure 19). The initial lag period was once again evident in both cases, and surprisingly the rate of each reaction remained comparable in the early stages, both rates reaching a similar maximum. However, whilst the rate of the $Pd(OAc)_2$/bbeda reaction then remained relatively high until the substrate was nearly consumed, the rate of the ligand-free reaction started to

decreased significantly after only 40-50% conversion, resulting in a flattening of the graph and a significantly longer reaction time to completely consume the starting material. One might tentatively suggest that the bbeda ligand is involved in increasing catalyst turnover, perhaps by decreasing catalyst coordination to product molecules, or otherwise maintains a higher concentration of active catalyst by slowing catalyst degradation.

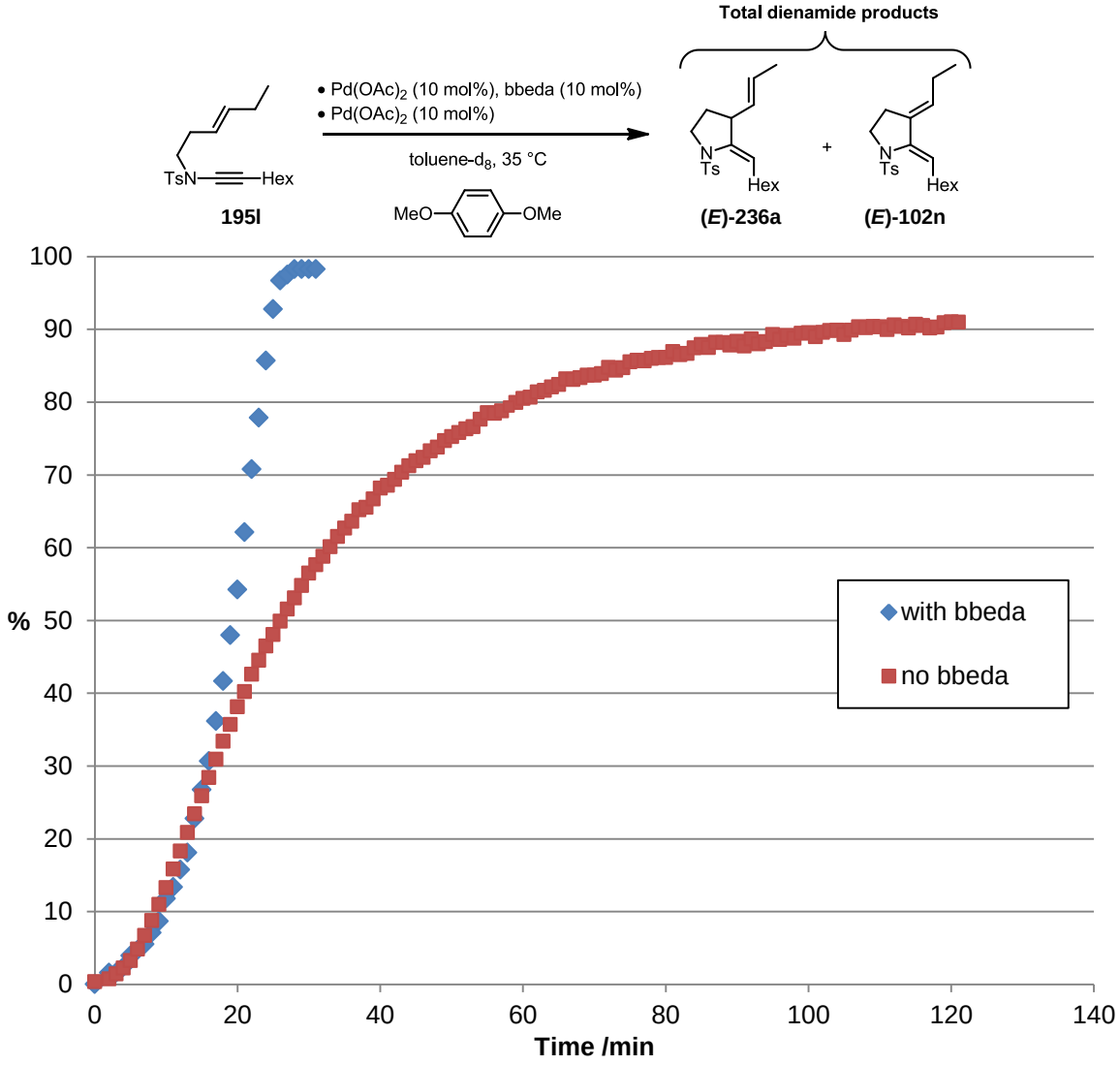


Figure 19 : Comparison with ligand free cycloisomerisation.

The reaction profile for the cycloisomerisation of enynamide **195a** was also investigated using $Pd_3(OAc)_5NO_2$ (Figure 20). Both the (*Z*)- and (*E*)- isomers of dienamide **102a** appeared to be generated in approximately equal amounts from the start of the reaction, but after around 40% conversion the rates started to diverge such that a higher proportion of the

(*Z*)-dienamide was produced. The final ratio of *Z*:*E* isomers remained approximately constant suggesting negligible amounts of interconversion. To our surprise, this NMR experiment resulted in a final mixture of *Z*:*E* isomers of 59:41, in contrast to the 38:62 ratio previously observed with this catalyst. This could be explained by the reduced amount of stirring in an NMR tube, or the lower temperature; nevertheless, both experiments certainly showed a greatly increased amount of (*E*)-isomer.

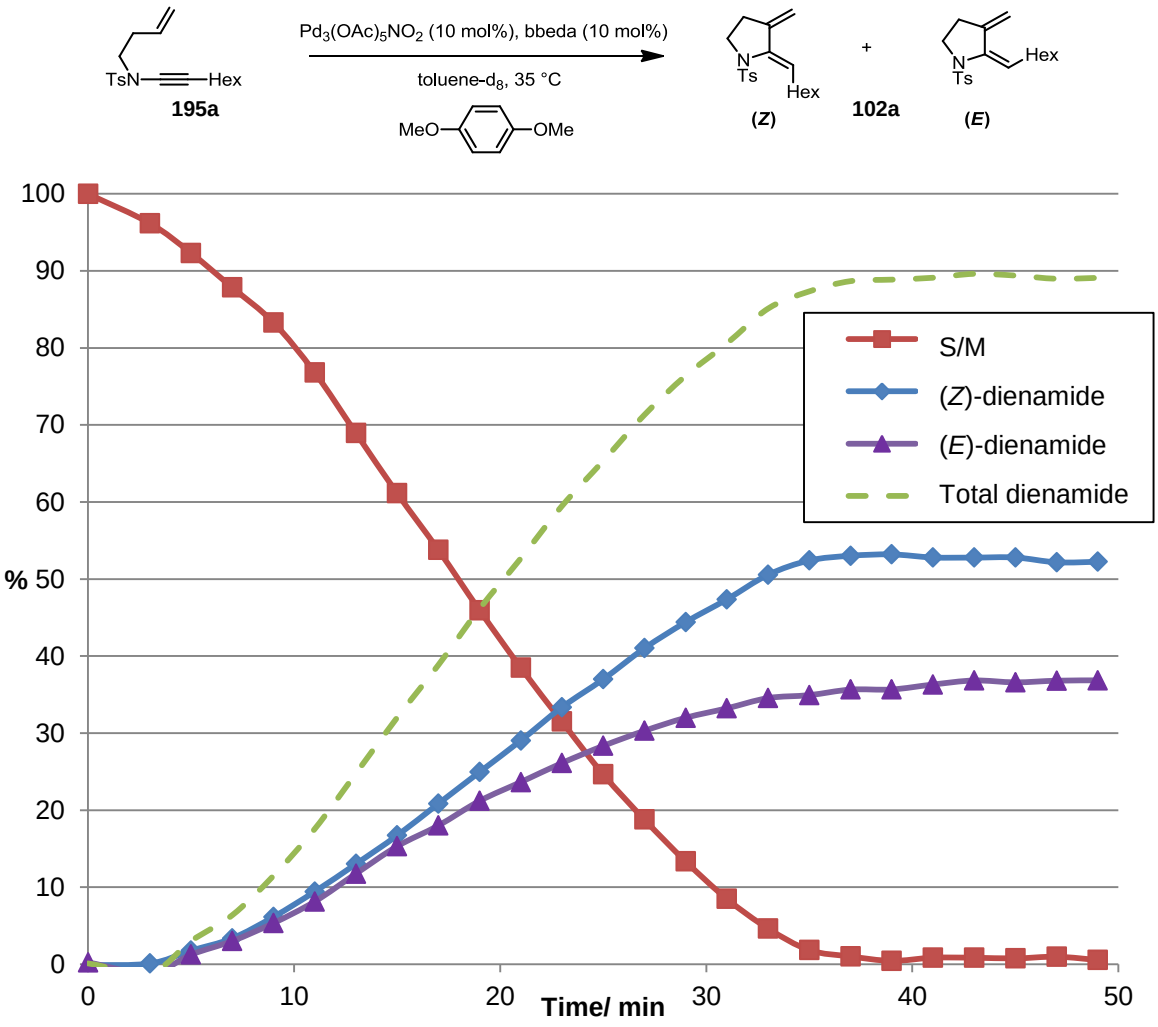
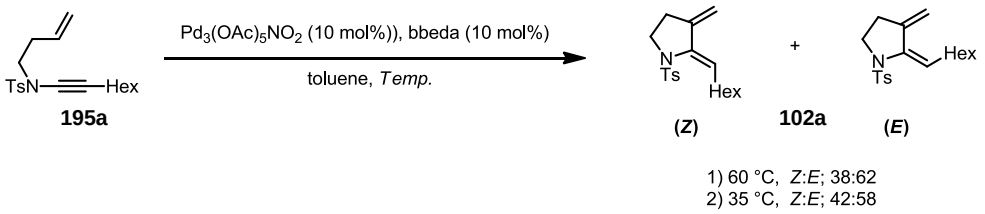


Figure 20 : Reaction profile for cycloisomerisation using $Pd_3(OAc)_5NO_2$.

In order to rule out the possibility that the change in diastereoselectivity for the NMR timecourse experiment had been a result of the reduced temperature, the reaction was performed at 35 °C in the laboratory (Scheme 116). In a laboratory setting, this reduced

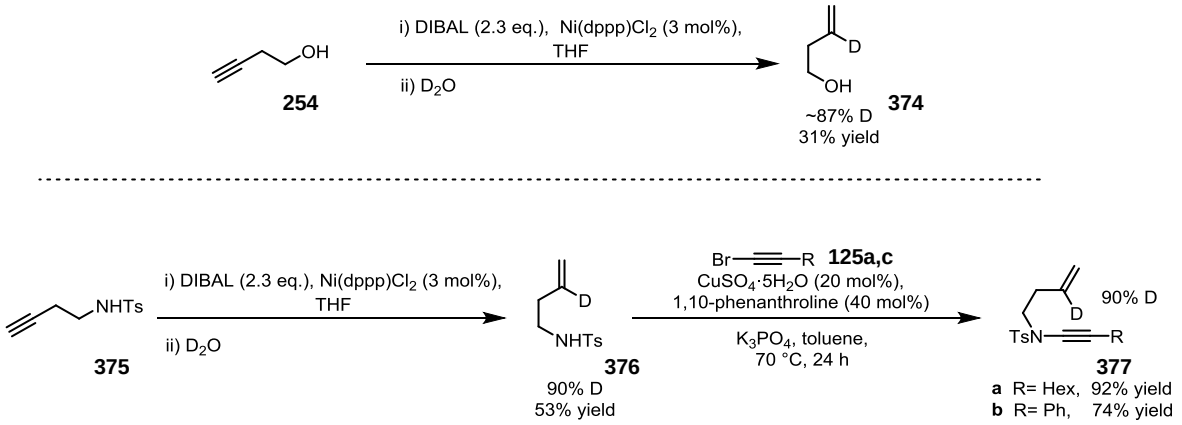
temperature had minimal effect on the diastereoselectivity of the reaction, affording an approximate 40:60 ratio of *Z*:*E* isomers at both temperatures.



Scheme 116

4.4.3 Deuterated substrates

We hoped that through the use of deuterated substrates we could gain further insight into the mechanism of the palladium-catalysed cycloisomerisation reaction. Initial attempts to synthesise deuterated enynamides **377** involved the nickel-catalysed hydroalumination of but-3-yn-1-ol **254**, followed by quenching with D_2O (Scheme 117).[127] This gave deuterated product **374** with ~87% deuterium incorporation but in low yield and purity. Therefore, we were delighted to find that the same reaction conditions could be applied directly to corresponding propargyl sulfonamide **375**, resulting in 90% deuterium incorporation and a moderate yield of sulfonamide **376**. Standard copper-catalysed ynamide formation conditions then gave deuterated enynamides **377a** and **377b** (R= Hex and R= Ph respectively), in good yield and without any loss of deuterium.



Scheme 117

In order to allow a more quantitative analysis of the data obtained from our NMR experiments with deuterated substrates, the variation in peak integrations caused by different T_1 relaxation times was measured before and after the reaction. By comparing spectra taken using the normal settings against ones with a greatly extended time between individual scans, correction factors were calculated for each peak and applied to our measurements throughout the experiment. Deuterated enynamide **377a** was exposed to $Pd(OAc)_2$/bbeda (10 mol%) in toluene-d_8 (0.167 M) in an NMR tube at 35 °C, in order to generate a reaction profile (Figure 21). Surprisingly, the initial consumption of starting material seemed almost linear and the lag time normally seen for the generation of dienamide was much less apparent for this experiment. Until approximately 20% conversion of the starting material, the reaction appeared to generate only the proton-containing 1,3-dienamide **102a** (i.e. no deuterium incorporation). After approximately 20% conversion, the rate of formation of the deuterium-containing 1,3-dienamide **378** began to increase, reaching an almost constant rate. At the same time, the rate of formation of proton-containing 1,3-dienamide **102a** started to decrease. At approximately 70% conversion of the starting material, the reaction contained a 1:1 ratio of 1,3-dienamides **102a** and **378** (i.e. 50% deuterium incorporation in the product). After complete consumption of the starting material, the mixture contained a 48% yield of deuterium-containing 1,3-dienamide **378** and a 36% yield of proton-containing 1,3-dienamide

102a (determined using ^{1}H NMR spectroscopy), corresponding to 57% deuterium incorporation at the 1-position of the diene. There was also what appeared to be approximately 5% deuterium incorporation at each of the *exo*-methylene protons in the product, which is presumably due to a small amount of reversible addition of palladium deuteride across the product alkene.

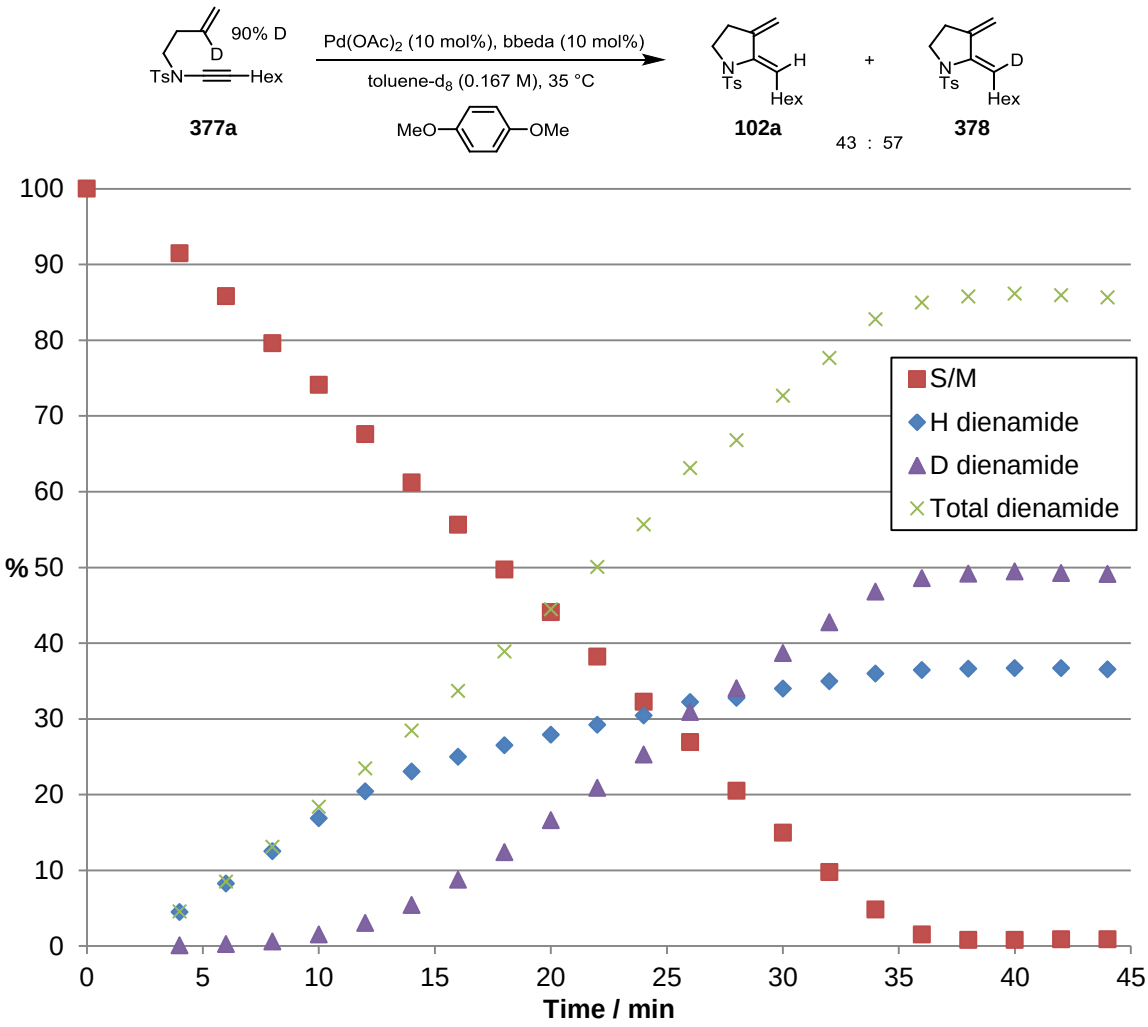
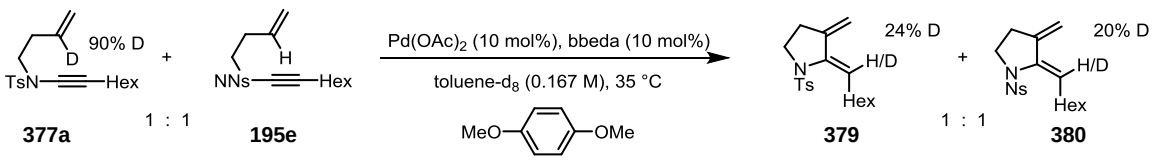


Figure 21 : Reaction profile for deuterated substrate **377a**.

The palladacycle mechanism for the $Pd(OAc)_2$-catalsyed cycloisomerisation of enynes (Scheme 100), would predict complete transference of deuterium form the starting material to the 1-position of the 1,3-dienamide product. The hydropalladation mechanism would also predict complete transference once the catalytic cycle was established (Scheme 111). However, a proton from a different position/source may be responsible for the generation of the initial

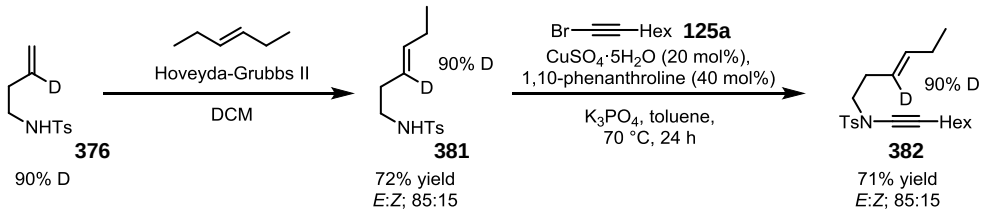
palladium(II) hydride species. Therefore, one might expect an initial percentage of 1,3-dienamide formed without any deuterium incorporation, and in general terms this is what we observe, perhaps offering support to the hydropalladation mechanism. In spite of that, with 90% deuterium incorporation in the starting material, and 10 mol% catalyst loading, the minimum expected deuterium incorporation in the final product would be approximately 80%, higher than the observed value. The only position of the 1,3-dienamide product showing significant deuterium incorporation was the 1-position (57% D), with perhaps small amounts of deuterium incorporated into the *exo*-methylene moiety (~5% for each hydrogen position). At this stage the question therefore remained, where were the additional hydrogen atoms in the product mixture coming from? In discovering that, we also hoped to be able to offer an explanation as to how the initial palladium(II) hydride species is generated.

A crossover experiment was next performed using deuterated tosyl-ynamide **377a** and nosyl-ynamide substrate **195e**, both present from the start in a 1:1 ratio (Scheme 118). The palladacycle mechanism, involving the intramolecular transfer of deuterium, would predict no deuterium incorporation in the nosyl-1,3-dienamide **380**, whereas the hydropalladation mechanism would predict some deuterium incorporation in both the tosyl- and the nosyl-product (**379** and **380** respectively). After complete consumption of the starting material, the tosyl-product **379** showed 24% deuterium incorporation at the 1-position of the diene and the nosyl-product **380** 20%. This crossover of deuterium lends further evidence to the hypothesis of the reaction proceeding *via* a hydropalladation mechanism. Whilst the total deuterium incorporation across both products is low, it is nonetheless consistent with the amount previously seen when using only a deuterated substrate.



Scheme 118

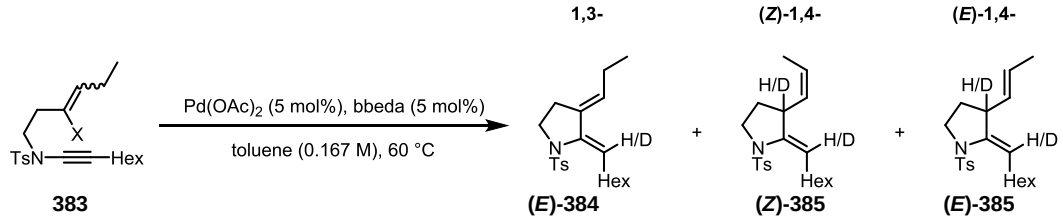
We wanted to discover if using deuterated substrates would have any effect on the ratio of 1,3- and 1,4-dienamides formed from disubstituted alkenyl ynamides. Cross-metathesis of deuterated sulfonamide **376** with (*E*)-hex-3-ene and Hoveyda-Grubbs II catalyst, was used to synthesise sulfonamide **381** as an 85:15 ratio of *E*:*Z* isomers (Scheme 119). Standard copper-catalysed ynamide formation conditions then gave deuterated ynamide **382**, containing a 1,2-disubstituted alkene moiety, in good yield.



Scheme 119

In order to investigate the cycloisomerisation of deuterated enynamide **382**, we first considered the ratio of products obtained using the corresponding substrates containing no deuterium (Table 11). When (*E*)-enynamide **195l** underwent cycloisomerisation, the 1,3-dienamide **(*E*)-384** and 1,4-dienamide **(*E*)-385** were formed in a 23:77 ratio (entry 1). With enynamide **195n**, containing the (*Z*)-alkene moiety, 1,4-dienamides **(*Z*)-385** and **(*E*)-385** were formed in 16:84 ratio (entry 2). From these two results it was calculated that, assuming the molecules react independently, an 85:15 *E*:*Z* mixture of starting material should give the ratio of 1,3- and 1,4-dienamide products shown in the table (**(*E*)-384**:**(*Z*)-385**:**(*E*)-385**; 20:2:78)(entry 3). One would predict that, for deuterated enynamide **382**, the increased strength of the C-D bond (*vs* C-H) would disfavour β-deuteride elimination in order to form 1,3-dienamide **(*E*)-365**, and the amount of 1,4-dienamide should increase. This is indeed the case, with the cycloisomerisation of deuterated enynamide **382** giving dienamides **(*E*)-384**:**(*Z*)-385**:**(*E*)-385** in a 10:4:86 ratio (entry 4). This shows the dependence of the distribution of products on the ease of β-hydride elimination leading to each.

Table 10 : A kinetic isotope effect on the ratio of dienamide products.



Entry	Starting Material			Ratio		
	#	X =	*E*:*Z*	(*E*)-384	(*Z*)-385	(*E*)-385
1	**195l**	H	100 : 0	23	-	77
2	**195n**	H	0 : 100	-	16	84
3*	-	H	85 : 15	20	2	78
4	**382**	D (90%)	85 : 15	10	4	86

***** Predicted product ratio based on results for individual diastereomers.

The reaction profile for the cycloisomerisation of deuterated enynamide **377b** (phenyl-substituted ynamide), showed a similar pattern to deuterated enynamide **377a** (hexyl-substituted ynamide), albeit with a significantly longer reaction time. Once again, at the start of the reaction only proton-containing 1,3-dienamide **102c** was formed. After around 25% conversion the deuterium containing 1,3-dienamide **386** started to be produced and at the same time the rate of formation of proton-containing 1,3-dienamide **102c** started to decrease. At the end of the reaction the crude mixture contained 1,3-dienamides **102c** and **386** in a 44:56 ratio, corresponding to a 56% deuterium incorporation at the 1-position of the diene. This comparable deuterium incorporation to the case with hexyl-substituted ynamide **377a**, showed that the extra protons found in the product mixture were not derived from the hexyl chain.

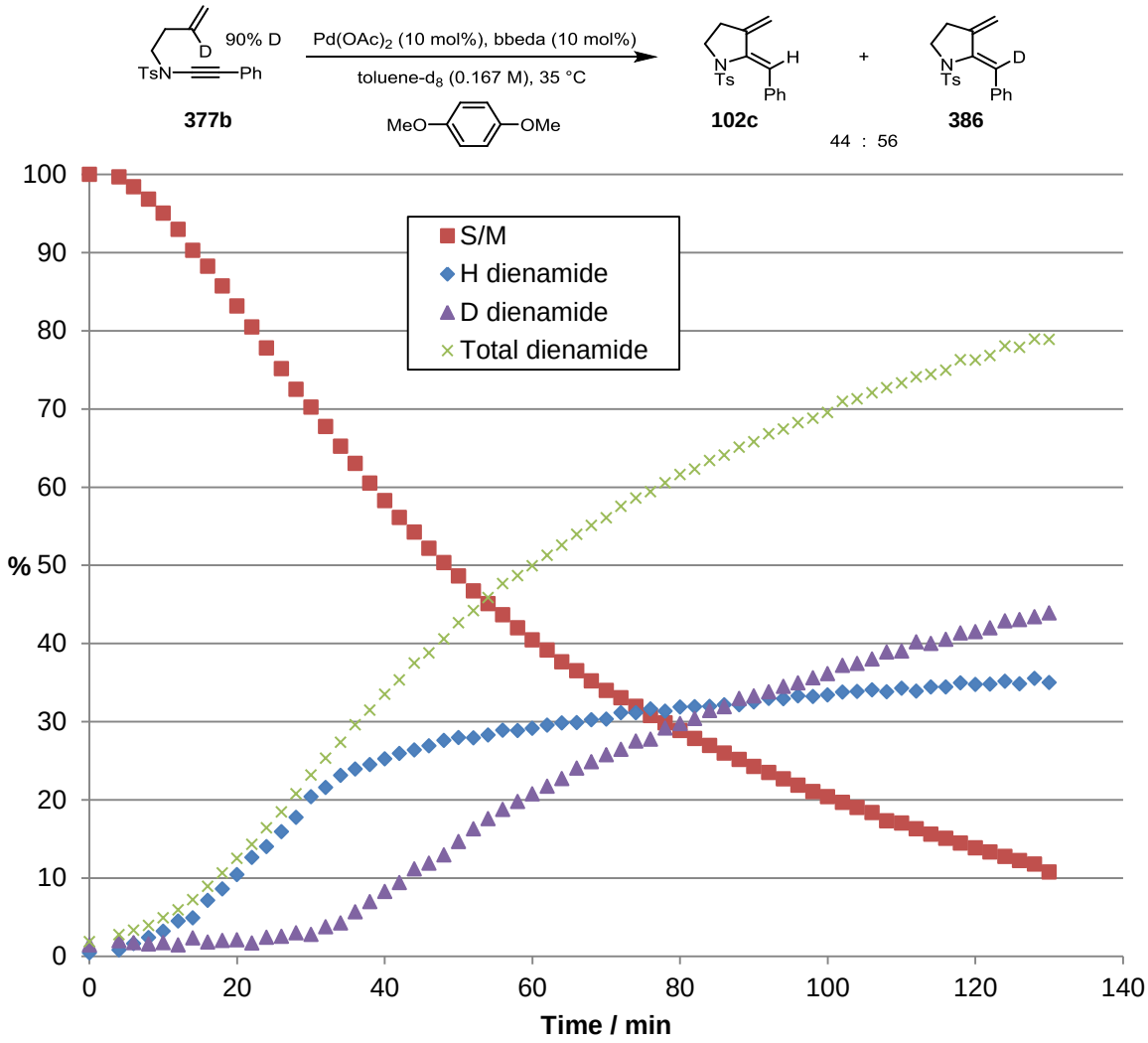
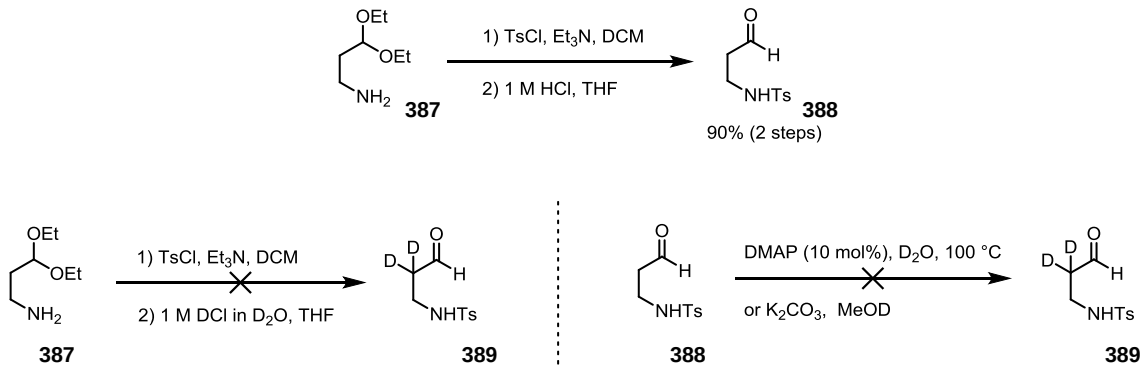


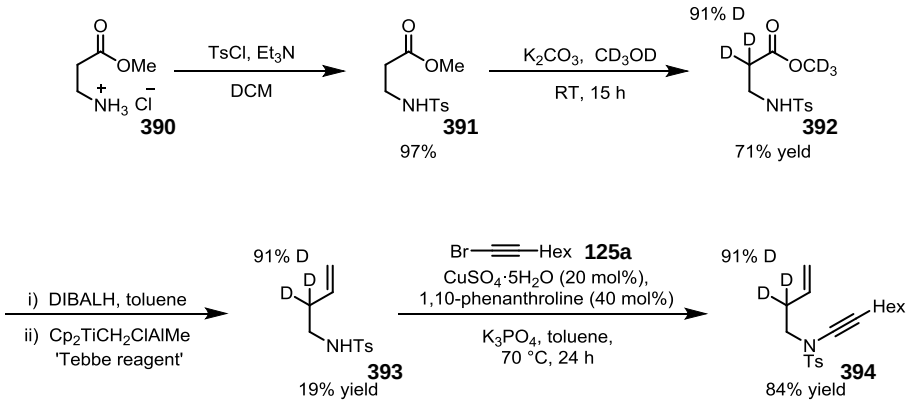
Figure 22 : Reaction profile for deuterated substrate **377b**.

It was hoped that by synthesising an enynamide substrate with a deuterated allylic position, we would be able to determine if a hydrogen from this position was responsible for generating the initial active palladium(II) hydride. Aldehyde **388** was generated from commercially available acetal **387** *via* tosylation and acid-catalysed hydrolysis (Scheme 120). It was hoped that by using DCl in D_2O instead of aqueous HCl, it would be possible to synthesise deuterated aldehyde **389** directly. However, this reaction did not appear to show significant deuteration at the desired position. Attempts to synthesise deuterated aldehyde **389** from isolated aldehyde **388** using DMAP/D_2O or K_2CO_3/MeOD were similarly unsuccessful.



Scheme 120

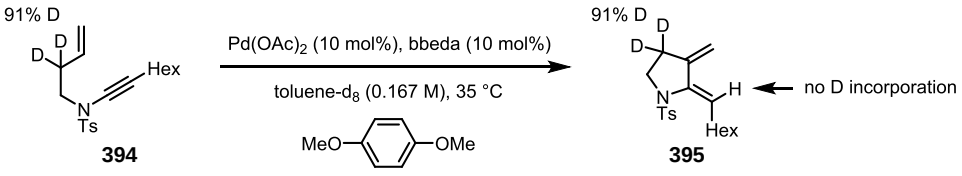
Therefore, an alternative strategy was needed to synthesise deuterated enynamide **394** (Scheme 121). Ammonium salt **390** was tosylated and the resulting sulfonamide **391** deuterated at the α-position to the ester using K_2CO_3 in CD_3OD. Ester **392** was reduced using DIBALH but the aldehyde reacted to produce only a complex mixture under Wittig conditions. Instead, the aldehyde was converted to an alkene using 'Tebbe reagent',[128] giving alkenyl sulfonamide **393** in low yield (19% over 2 steps). Copper-catalysed ynamide formation then gave enynamide **394** in good yield, retaining 91% deuterium incorporation at the allylic position.



Scheme 121

Cycloisomerisation of deuterated enynamide **394** with $Pd(OAc)_2$/bbeda generated 1,3-dienamide **395**, showing no deuterium incorporation at the 1-position of the diene and no loss of deuterium from the allylic position on the ring (Scheme 122). It would appear that the

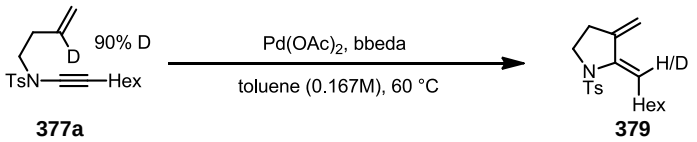
allylic protons are not responsible for generating the initial palladium hydride and that they do not readily exchange with other positions.



Scheme 122

The cycloisomerisation of deuterated enynamide **377a** was repeated using 10 mol% catalyst in the laboratory at 60 °C, in order to confirm the result obtained from the NMR experiment and to ensure that the deuterium incorporation was independent of temperature (Table 11, entry 1). The reaction was then performed using lower catalyst loadings, whilst keeping the substrate concentration constant (entries 2 & 3). If the extra hydrogen atoms incorporated into the product came from the acetate groups or the bbeda ligand, one would expect the deuterium incorporation to increase at lower catalyst loadings. Instead, the deuterium incorporation remained consistent throughout all the experiments.

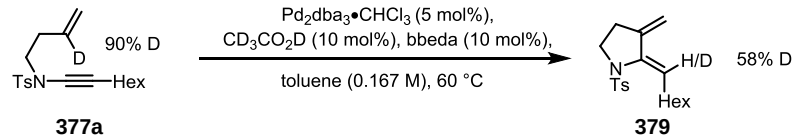
Table 11 : Variation of deuterium incorporation with catalyst loading.



Entry	Catalyst Loading	D incorporation
1	10 mol%	62%
2	5 mol%	63%
3	2.5 mol%	51%

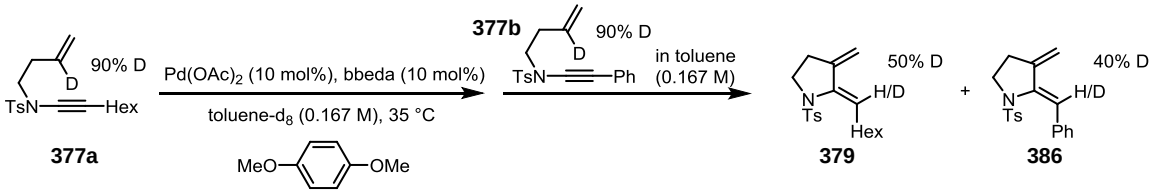
Interestingly, when deuterated enynamide **377a** underwent cycloisomerisation with the alternative Pd_2dba_3•$CHCl_3$/carboxylic acid/bbeda system, using CD_3CO_2D as the acid, the product 1,3-dienamide **379** showed 58% deuterium incorporation at the 1-position, an almost identical amount to the case with $Pd(OAc)_2$/bbeda (Scheme 123). This was something of a surprise, as we had expected that these conditions would show an increased amount of

deuterium incorporation, as the initial active catalyst species should be a palladium(II) deuteride.



Scheme 123

When deuterated enynamide **377a** underwent $Pd(OAc)_2$-catalysed cycloisomerisation, we had observed that deuterium incorporation into the product 1,3-dienamide only began after approximately 20% conversion. This appeared to suggest initial formation of palladium(II) hydride but a turnover of palladium(II) deuteride once the catalytic cycle was established. We therefore envisaged that if we added alternative deuterated substrate **377b** to the reaction after the palladium(II) deuteride cycle had been established, 1,3-dienamide **386** (derived from that substrate) might be formed with a higher deuterium incorporation than previously seen (Scheme 124). The reaction of deuterated enynamide **377a** was followed by ^1H NMR spectroscopy and at approximately 50% conversion of the starting material, a solution of deuterated enynamide **377b** in toluene-d_8 was added. To our surprise the deuterium incorporation into 1,3-dienamide **386** did not increase suggesting that the deuterium incorporation is mainly independent of any initiation process.



Scheme 124

We therefore began to suspect that the extra hydrogen atoms incorporated into the dienamide products when using deuterated substrates could be the result of very small amounts of H_2O present in the reaction mixture. No extreme measures had been taken to exclude traces of water from the substrates, catalysts or ligands, and the toluene-d_8 had been used as supplied

but stored under an inert atmosphere. The ^{1}H NMR experiments had also not been carried out under an inert atmosphere, as we had generally found these reaction to proceed satisfactorily even in the presence of air. To test this hypothesis palladium-catalysed cycloisomerisation of deuterated enynamide **377a** was performed in the presence of excess D_2O (10 eq.); now the rapid formation of hydrogen-containing 1,3-dienamide **102a** at the beginning of the reaction was not observed (Figure 23). Instead, deuterium-containing 1,3-dienamide **378** was consistently formed as the major product throughout the reaction, with a small proportion of hydrogen-containing 1,3-dienamide **102a** formed concurrently.

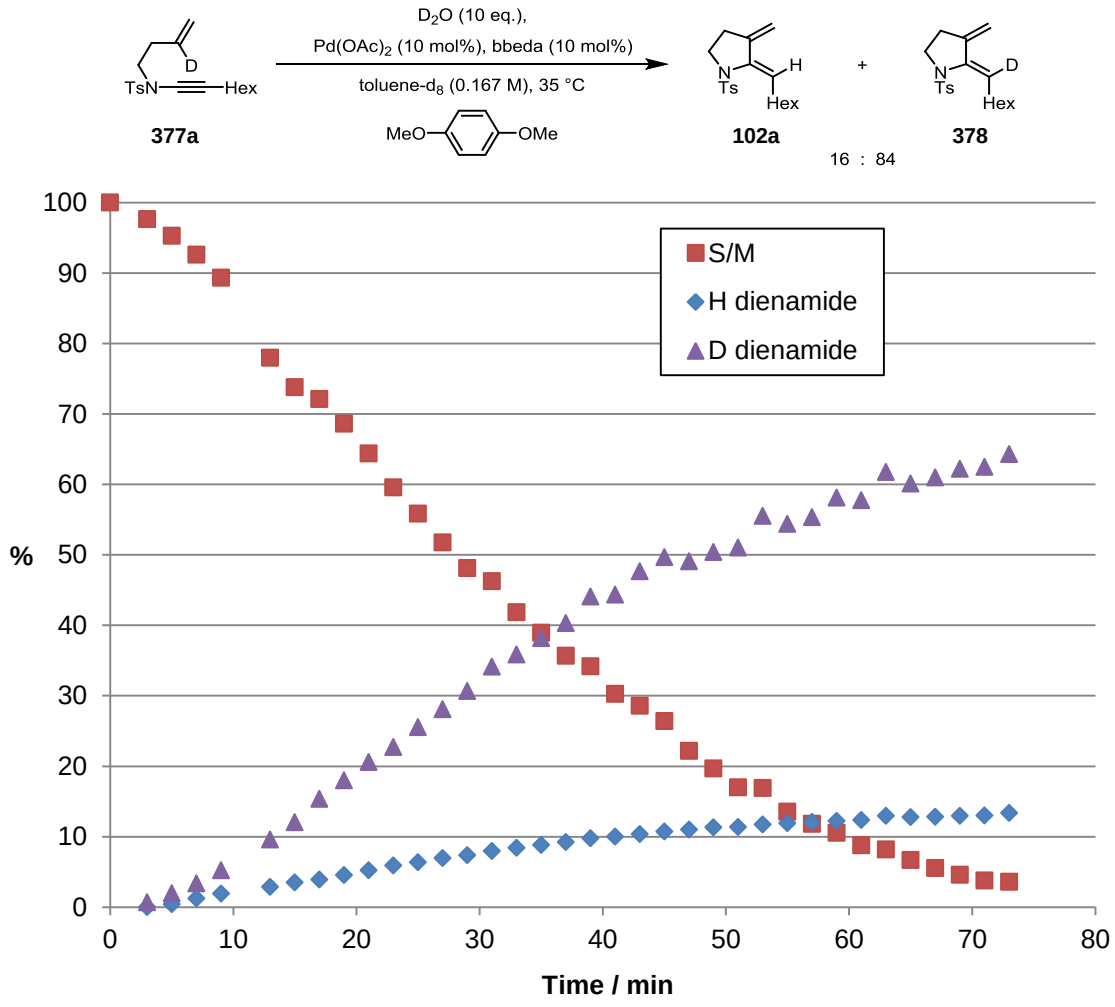


Figure 23 : D_2O suppression of palladium(II) hydride.

This result suggests that hydrogen/deuterium exchange between palladium(II) hydride/deuteride and H_2O/D_2O is fast and reversible. The source of H_2O is likely to be the

toluene-d_8 NMR solvent. Since a significant amount of hydrogen is incorporated even in the presence of 10 equivalents of D_2O, it may also suggest that there is a kinetic isotope effect favouring hydrogen incorporation over deuterium in the hydropalladation step. Therefore in our previous ^{1}H NMR experiments with deuterated substrates, deuterium incorporation into the product only began in earnest once H_2O had been predominantly consumed. Given the low molecular weight of H_2O, its ability to provide two hydrogen atoms per molecule and the preference for hydropalladation over deuteropalladation, only a very small amount of H_2O would be required to produce the observed effect.

A rapid exchange between any palladium deuteride species and traces of water makes it difficult to distinguish between the outcomes of the palladacycle and hydropalladation mechanisms with deuterated substrates. As such it is difficult to conclude definitively as to the mechanism of $Pd(OAc)_2$-catalysed cycloisomerisation on enynamides, but there remains strong evidence to support hydropalladation as at least one of the processes in operation. Discovering the exact manner of how the initial palladium(II) hydride/deuteride is generated also remains a significant challenge, given the rapid H/D exchange, and the relatively small proportion of final product derived from this species.

4.5 Conclusions and Further Work

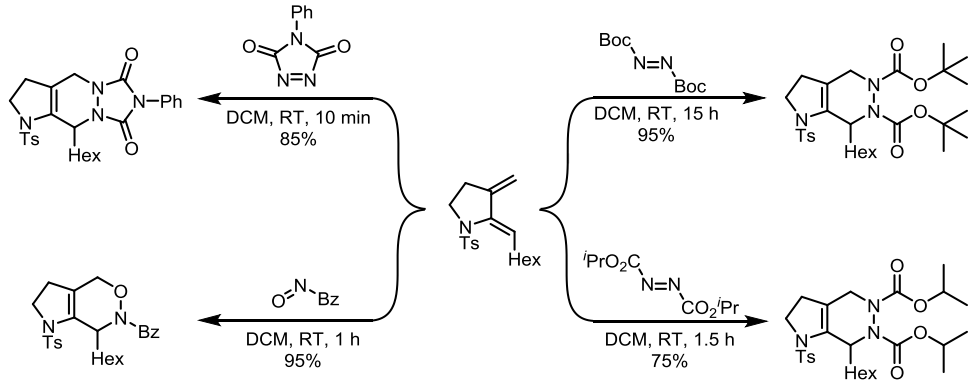
In conclusion we have proposed feasible mechanisms for the palladium- and ruthenium-catalysed cycloisomerisation of enynamides, in the case of palladium catalysis also discussing a number of alternatives. For $Pd(OAc)_2$-catalysed cycloisomerisation we favour a hydropalladation mechanism following an initial *in situ* formation of palladium(II) hydride, and evidence supporting this pathway has been presented. Our attempts to observe the palladium(II) hydride species formed by ^{1}H NMR spectroscopy were unsuccessful, although this result is not unexpected given that all evidence points toward palladium hydride formation being fast and reversible on the NMR timescale. The reaction profile for different substrates

and catalyst systems has been observed using ^{1}H NMR spectroscopy, including the evolution of reactions with multiple product isomers. For $Pd(OAc)_2$-catalysed reactions and in contrast to other catalyst systems, we observe a delay in conversion at the start of the reaction, presumably corresponding to the time needed to generate the active catalyst species. The mechanism and reaction profile of palladium-catalysed enynamide cycloisomerisation was also investigated using deuterated substrates and a kinetic isotope effect could be used to manipulate the distribution of products.

We discovered that the amount of $Pd_3(OAc)_5(NO_2)$ present in commercially available palladium(II) acetate can have a substantial impact on the diastereoselectivity of the reaction. During the industrial process used to manufacture $Pd_3(OAc)_6$, generation of $Pd_3(OAc)_5(NO_2)$ is only avoided through the prompt elimination of nitrogen oxide gases and therefore different batches often contain widely varying amounts. This problem can be overcome either by purchasing high grade palladium(II) acetate at minimal extra cost, or by synthesising palladium acetate using an alternative procedure from $Pd(NO_3)_2$.

5. Conclusions and Future Work

In conclusion, we started by investigating ways of synthesising fused, spirocyclic and linked bicyclic amines, utilising cyclic dienamides as the key structural building block. These cyclic dienamides were initially synthesised using the reductive cyclisation of bromoenynamides, methodology previously developed within our group. The reactivity of our monocyclic dienamides was investigated in regards to several different reactions and a number of fused aza-bicycles and tricycles were synthesised. Despite a lack of success with the formal [4+2] cycloaddition of imines, several other heteroatom-containing dienophiles did undergo efficient reactions with monocyclic dienamides, including nitroso compounds (Scheme 125). The addition of nitroso dienophiles to bicyclic dienamides could also be used to generate tricyclic structures.

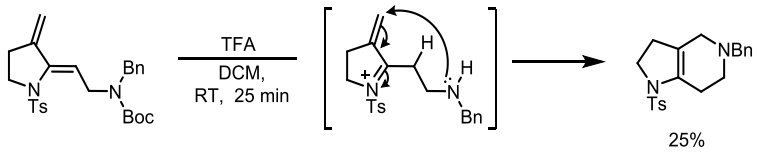


Scheme 125

Further functionalisation of these cycloadducts remains an ongoing challenge, and despite our investigations, an efficient N-O bond cleavage protocol has yet to be realised. There also remains the potential to examine both inter- and intramolecular asymmetric organocatalytic Diels-Alder reactions, as a method of introducing molecular complexity in a stereocontrolled manner.

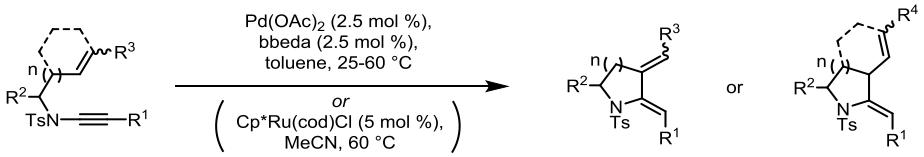
Through incorporating nucleophilic amino functionality into the side chain of a cyclic dienamide, an acid-catalysed cyclisation reaction was used to successfully prepare a fused

bicyclic diamine (Scheme 126). Utilising this strategy to develop a more efficient and general synthesis of theses azacyclic systems is worthy of further investigation.



Scheme 126

In the course of investigating the reactivity of these cyclic dienamides, we discovered a new efficient and general route to their synthesis, utilising the first examples of palladium-catalysed enynamide cycloisomerisation, together with a contrasting ruthenium-catalysed process. Mono-, di-, and trisubstituted alkenyl ynamides underwent cycloisomerisation to give a diverse range of attractive dienamide scaffolds (Scheme 127). These reactions were rapid, high yielding and intrinsically atom economic, as well as tolerant of a range of substituents on both the ynamide and alkene, underlining their potential utility as an atom-economical source of azacycles.



Scheme 127

Indeed, we were able to exploit the palladium-catalysed cycloisomerisation of cycloalkenyl ynamides to access three distinct and important classes of azabicycle, namely fused, spirocyclic and bridged ring systems (Figure 24). Efforts to further derivatise these dienamides are ongoing, including application of this chemistry to natural product synthesis.

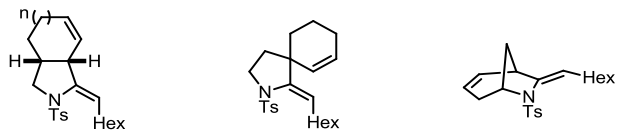
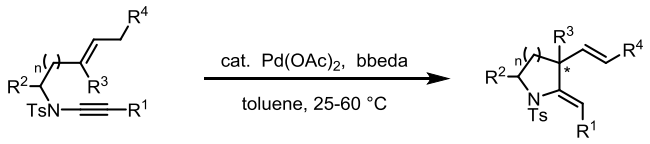


Figure 24 : Fused, spirocyclic and bridged ring dienamides.

Chiral enynamide substrates were used to generate 1,4-dienamides as single diastereomers at the newly formed stereocentre (Scheme 128), and this bodes well for future stereocontrolled synthesis of polysubstituted azacycles. The relay of stereochemistry was even found to be applicable to enynamides with a 1,1,2-trisubstituted alkene moiety, the resulting 1,4-dienamides possessing a newly-formed quaternary stereocentre.



Scheme 128

This was not only exploited in the formation of monocyclic dienamides (Figure 25), but a chiral cycloalkenyl ynamide was also used in the diastereoselective generation of a spirocyclic product.

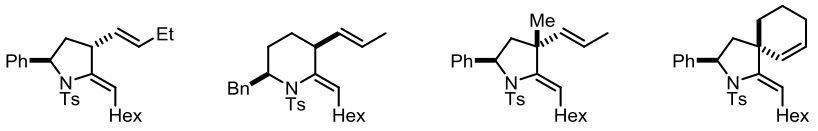


Figure 25 : Examples of the diastereoselective formation of 1,4-dienamides.

Finally, mechanistic hypotheses for the palladium- and ruthenium-catalysed cycloisomerisation of enynamides were discussed, based on our own findings and those of the literature for the cycloisomerisation of enynes. The palladium-catalysed cycloisomerisations of enynamides were investigated mechanistically, utilising ^{1}H NMR spectroscopy, timecourse and deuterium-labelling experiments. Whilst we favour a hydropalladation mechanism for the $Pd(OAc)_2$-catalysed cycloisomerisation of enynamides and much of the evidence supports this, further work is needed to confirm this hypothesis.

6. Experimental

6.1 General Experimental

NMR Spectra: Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AVII500 (500/125 MHz), Bruker DPX400 (400/100 MHz) or Bruker AV400 (400/100 MHz). Proton and carbon chemical shifts (δ_H, δ_C) are quoted in ppm and referenced to tetramethylsilane. ^{1}H NMR spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ 7.26) and C_6D_6 (δ 7.16). ^{13}C NMR Spectra were recorded using an internal deuterium lock using solvents $CDCl_3$ (δ 77.0) and C_6D_6 (δ 128.06). Assignments were made on the basis of chemical shift, coupling constants, COSY, HSQC, HMBC, nOe, NOESY data and comparison with spectra of related compounds. Resonances are described using the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sext. (sextet), sept. (septet), m (multiplet), br. (broad), ap. (apparent), dd (double doublet) and so on. Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.1 Hz. H and H' refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry.

Mass Spectra: Low resolution mass spectra were recorded on a Micromass LCT Premier spectrometer (ESI). High resolution mass spectra were recorded by the Mass Spectrometry service of the Chemistry Research laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (ESI). *m*/*z* values are reported in Daltons with their percentage abundances and relevant fragment ions in parentheses. High resolution values are calculated to four decimal places from the molecular formula, all found values being within a tolerance of 5 ppm.

Infrared Spectra: Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer, as a thin film on NaCl plates or a diamond ATR module. Absorption maxima

(ν_{max}) are described as s (strong), m (medium), w (weak), br. (broad) and are quoted in wavenumbers (cm^{-1}).

Melting Points: Melting points were recorded on a Leica Galen III Compound Microscope and are uncorrected.

Elemental Analysis. Samples were analysed by Mr. Stephen Boyer, Science Centre, London Metropolitan University.

HPLC: Semi-preparative high performance liquid chromatography was carried out using a Zorbax RX-SIL column.

Chromatography techniques: TLC was performed on Merck Keiselgel 60 F_{254} 0.2 mm precoated plates and visualised using basic potassium permanganate dip, acidic vanillin dip or ultraviolet light. Retention factors are reported with the solvent system in parentheses. Column chromatography was performed on Merck Keiselgel 60 SiO_2 (40-63 μm) and the solvent system used is recorded in parentheses.

Solvents were either used as commercially supplied, or as purified by standard techniques. Pet. ether refers to the fraction of light petroleum ether boiling at 40-60 °C. Brine refers to a saturated aqueous solution of sodium chloride. Unless otherwise stated, reactions were carried out in oven-dried flasks under an atmosphere of dry argon.

6.2 General Experimental Procedures

Procedure 1 : Bromination of primary alkynes using *n*-BuLi

According to the procedure of Hsung et al.[18] To a solution of alkyne (1.0 eq.) in dry THF (1 mL/mmol of alkyne) at -78 °C was added dropwise *n*-BuLi solution (2.5 M in hexane, 1.2 eq.). The reaction mixture was stirred for 30 min at -78 °C. Bromine (1.4 eq.) was added dropwise and the reaction stirred for a further 15 min at -78 °C. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (2 mL/mmol of alkyne), allowed to warm to RT and then extracted with Et_2O (3 × 0.6 mL/mmol of alkyne). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Procedure 2 : Bromination of primary alkynes using $AgNO_3$

To a suspension of alkyne (1.0 eq.) in acetone (1 mL/mmol) was added $AgNO_3$ (2.5 mol%). The reaction mixture was stirred for 5 min and NBS (1.1 eq.) added. The reaction mixture was stirred at RT for 15 h, filtered through a pad of silica (pet. ether) and concentrated *in vacuo*.

Procedure 3 : Conversion of an alcohol to a sulfonamide

To a solution of alcohol (1.0 eq.), triphenylphosphine (2.0 eq.) and *tert*-butyl tosylcarbamate (1.3 eq.) in THF (4 mL/mmol of alcohol) at 0 °C was added dropwise DIAD (1.5 eq.). The reaction mixture was stirred at RT overnight, filtered and then concentrated *in vacuo*. The residue was then taken up in Et_2O:pet. ether (5 mL:5 mL/mmol of alcohol), sonicated for 5 min and filtered. The filtrate was concentrated *in vacuo* to approximately 15 mL/mmol of alcohol at which point the resulting ppt was removed by filtration before being concentrated *in vacuo* to dryness.

Procedure 4 : Boc deprotection using TFA

To a solution of carbamate (1.0 eq.) in DCM (3 mL/mmol of carbamate) was added dropwise TFA (10.0 eq.). The reaction mixture was stirred at RT for 1 h, cooled to 0 °C, quenched with sat. aq. Na_2CO_3 (3 mL/mmol of carbamate) and transferred to a separating funnel. The

organic layer was separated and the aqueous layer extracted with DCM (2 × 2 mL/mmol of carbamate). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Procedure 5 : Boc deprotection using K_2CO_3 and MeOH

To a solution of carbamate (1.0 eq.) in MeOH (8 mL/mmol carbamate) was added K_2CO_3 (5.0 eq.). The reaction mixture was stirred under reflux for 5 h, allowed to cool to RT and concentrated *in vacuo* to approx. 5 mL. The mixture was then added to H_2O (10 mL/mmol carbamate) and extracted with DCM (3 × 10 mL/mmol carbamate). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Procedure 6 : Copper (II) catalysed ynamide formation

According to the procedure of Hsung and co-workers.[18] To a mixture of sulfonamide (1.0 eq.), K_3PO_4 (2.0 eq.), $CuSO_4 \bullet 5H_2O$ (0.2 eq.) and 1,10-phenanthroline (0.4 eq.) was added a solution of bromoalkyne (1.2-1.5 eq.) in toluene (2 mL/mmol of sulfonamide). The reaction mixture was stirred at 70 °C for 15 h before being allowed to cool to RT. The reaction mixture was filtered through Celite eluting with Et_2O and the filtrate concentrated *in vacuo*.

Procedure 7 : Intramolecular reductive carbopalladation cyclisation

To a solution of ynamide (1.0 eq.) in EtOH (40 mL/mmol of ynamide) was added $Pd(PPh_3)_4$ (0.1 eq.) and Cs_2CO_3 (1.5 eq.). The resulting mixture was stirred under reflux for 2 h, allowed to cool to RT and then concentrated *in vacuo*. The residue was taken up in Et_2O (40 mL/mmol of ynamide) and H_2O (40 mL/mmol of ynamide), the organic layer separated and the aqueous layer extracted with further Et_2O (2 × 40 mL/mmol of ynamide). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Procedure 8 : Palladium-catalysed cycloisomerisation of alkenyl-ynamides

To a solution of ynamide (1.0 eq.) in dry toluene (0.167M-0.333M) was added a 1:1 ratio of *N*,*N*′-bis(benzylidene)ethylenediamine (bbeda) and $Pd(OAc)_2$ (2.5-10 mol%). The reaction mixture was stirred at 60 °C for the stated time and concentrated *in vacuo*.

Procedure 9 : Claisen rearrangement

To a solution of LiHMDS (3.0 eq.) in toluene (12 mL/mmol of ester) at -78 ºC was added Et_3N (30 eq.), followed by a solution of ester (1.0 eq.) in toluene (2.5 mL/mmol of ester). The reaction mixture was allowed to warm to RT overnight and then poured onto 2 M aq. NaOH (12 mL/mmol of ester). The aqueous layer was separated, washed with *t*-BuOMe (8 mL/mmol of ester), cooled to 0 ºC, acidified with concentrated HCl and extracted with *t*-BuOMe (3 × 10 mL/mmol of ester). These organic washings were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo.*

Procedure 10 : NMR timecourse experiments

To an NMR tube was added a solution of ynamide (0.075 mmol, 1.0 eq.) and 1,4-dimethoxybenzene (internal standard) (2.6 mg, 0.019 mmol, 0.25 eq.) in deuterated solvent (0.45 mL, 0.167 M). The tube was placed in the NMR spectrometer and heated to the stated reaction temperature. NMR spectra were taken of the starting material using first an extended time between individual scans to obtain a quantitative spectrum (D_1(relaxation delay)=60 s) and then the normal ^{1}H NMR settings desired for following the reaction (typically NS(number of scans)=10, D_1=1 s). The tube was removed from the NMR machine, the solution added to the stated catalyst system and the reaction mixture swiftly returned to the NMR machine. Spectra were collected at regular intervals to observe the variation in concentration of reactants and products with time. Once the reaction was complete, a quantitative spectrum of the products was obtained using an extended time between individual scans (D_1=60 s).

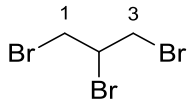
The spectra were automatically phased, corrected and integrated (relative to the internal standard) using the TOPSPIN multi_integ3 function. Variations in peak integrations caused by different T_1 relaxation times were then accounted for (N.B. only for deuterated substrates) By comparing the spectra of the starting materials and products taken under the normal settings (D_1=1 s) against the quantitative spectra (D_1=60 s), a correction factor was calculated

for each peak of interest and applied to the measurements throughout. The corrected integration values were plotted using Microsoft Excel as a percentage of the total starting material originally present (proportional to concentration).

6.3 Characterisation of Compounds

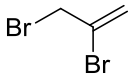
6.3.1 Reactions of cyclic dienamides

1,2,3-Tribromopropane, S1



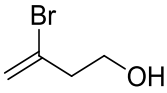
According to the modified procedure of Johnson and McEwen.[129] To a three-necked flask with a stirrer bar was added allyl bromide (181.5 g, 1.50 mol, 1.0 eq.) and $CHCl_3$ (250 mL). The flask was fitted with a dropping funnel, calcium chloride exit tube and a thermometer. To the dropping funnel was added bromine (255.0 g, 1.60 mol, 1.1 eq.), pre-washed with conc. H_2SO_4 (80 mL). The stirred reaction mixture was cooled to -5 °C using an ice/salt bath 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 and allyl bromide. The pressure was reduced to 26 mbar to remove the remainder of these until the thermometer registered a sudden rise at which point only the title compound remained in the distilling flask as a pale yellow oil (386.1 g, 1.38 mol, 92%); R_f = 0.95 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 4.37 (1H, tt, *J*=6.9, 4.3 Hz, C**H**), 3.94 (2H, dd, *J*=11.0, 4.3 Hz, C**H**H'-1, C**H**H'-3), 3.84 (2H, dd, *J*=11.0, 6.9 Hz, CH**H'**-1, CH**H'**-3); δ_C (100 MHz, $CDCl_3$) 48.2 (**C**H), 34.9 (**C**H_2). Data are consistent with literature values.[130]

2,3-Dibromoprop-1-ene, 122



According to the modified procedure of Lespieau and Bourgeul.[131] To a rbf, connected to efficient distillation equipment, was added 1,2,3-tribromopropane **S1** (78.0 mL, 666 mmol, 1.0 eq.), H_2O (12 mL) and NaOH pellets (46.6 g, 1.17 mol, 1.75 eq.). An exotherm was observed, then the mixture was heated further using a heat gun, with stirring, until vigorous ebullition occurred, whereupon spontaneous distillation of the reaction product took place and the heat was 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 further H_2O (75 mL). The organic layer was vacuum distilled to yield the title compound as a colourless oil (81.71 g, 409 mmol, 61%); b.p. 66 °C/75 mbar; R_f = 0.77 (1:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 6.03-6.01 (1H, m, =C**H**H'), 5.62 (1H, d, *J*=2.0 Hz, =CH**H'**), 4.18 (2H, s, C**H**$_2$Br); δ_C (100 MHz, $CDCl_3$) 127.6 (=**C**Br), 121.1 (=**C**HH'), 36.8 (**C**H_2Br). Data are consistent with literature values.[132]

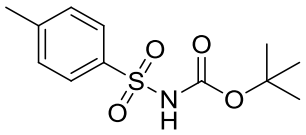
3-Bromobut-3-en-1-ol, 123



To a mixture of tin (21.4 g, 180 mmol, 1.2 eq.) and 2,3-dibromopropene **122** (30.0 g, 150 mmol, 1.0 eq.) in Et_2O:H_2O (100 mL:100 mL) was added hydrogen bromide solution (2.5 mL, 48 wt% in H_2O) followed by formaldehyde (429 mg, 37 wt% in H_2O, 14.3 mmol, 1.0 eq.). The reaction mixture was stirred at RT overnight, the layers separated and the aqueous layer extracted with further Et_2O (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a yellow oil (24.2 g,

160 mmol, quant.) which was used without further purification; R_f = 0.44 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.72 (1H, ap. s, =C**H**H'), 5.54 (1H, d, *J*=1.5 Hz, =CH**H'**), 3.82 (2H, t, *J*=5.9 Hz, C$\mathbf{H_2}$OH), 2.68 (2H, t, *J*=5.9, =CBrC$\mathbf{H_2}$), 2.33 (1H, br. s, CH_2O**H**); δ_C (100 MHz, $CDCl_3$) 130.4 (=**C**Br), 119.1 (=**C**HH'), 59.9 (**C**H_2OH), 44.3 (=CBr**C**H_2). Data are consistent with literature values.[133]

***tert*-Butyl tosylcarbamate, S2**



Method A

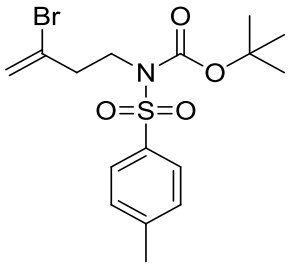
To a suspension of 4-methylbenzenesulfonamide (50.0 g, 284 mmol, 1.0 eq.) in DCM (180 mL) was added triethylamine (43.5 mL, 312 mmol, 1.1 eq.) and 4-dimethylaminopyridine (3.47 g, 28.4 mmol, 0.1 eq.). A solution of di-*tert*-butyl-dicarbonate (74.9 mL, 326 mmol, 1.15 eq.) in DCM (300 mL) was added dropwise. The reaction mixture was stirred at RT for 2 h and then concentrated *in vacuo*. EtOAc (500 mL) and 1 M aq. HCl (400 mL) were added and the mixture separated. The organic extract was washed with H_2O (300 mL) and brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Trituration with hot hexane (200 mL) gave the title compound as a colourless solid (78.5 g, 289 mmol, quant.); m.p. 117-122 °C; R_f = 0.51 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, *J*=8.0 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.0 Hz, *m*-Ts**H**), 2.44 (3H, s, ArC$\mathbf{H_3}$), 1.37 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 149.3 (**C**=O), 144.7 (**Ts**), 135.9 (**Ts**), 129.5 (*m*-**Ts**H), 128.2 (*o*-**Ts**H), 84.0 (**C**$(CH_3)_3$), 27.8 (C(**C**$H_3)_3$), 21.6 (Ar**C**H_3). Data are consistent with literature values.[134,135]

Method B

To a solution of *tert*-butanol (8.0 g, 108 mmol, 1.0 eq.) in DCM (200mL) at 0 °C was added *p*-toluenesulfonyl isocyanate (17.3 mL, 113 mmol, 1.05 eq.). The reaction mixture was stirred

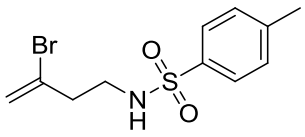
at RT for 2 h and concentrated *in vacuo*. The resulting solid was recrystallised from 5:1, Et_2O: DCM to give the title compound as a colourless solid (22.0 g, 80.9 mmol, 75%). Data are in accordance with Method A.

tert-Butyl (3-bromobut-3-en-1-yl)(tosyl)carbamate, 124



Synthesised from 3-bromobut-3-en-1-ol **123** (2.00 g, 13.2 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound as a colourless solid (3.94 g, 9.73 mmol, 74%); m.p. 57-62 °C; R_f = 0.66 (1:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J*=8.2 Hz, *o*-**Ts**H), 7.30 (2H, d, *J*=8.2 Hz, *m*-**Ts**H), 5.70-5.67 (1H, m, =C**H**H'), 5.49 (1H, d, *J*=1.8 Hz, =CH**H'**), 4.06-4.00 (2H, m, C$\mathbf{H_2}$N), 2.91-2.84 (2H, m, =CBrC$\mathbf{H_2}$), 2.44 (3H, s, ArC$\mathbf{H_3}$), 1.36 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.7 (**C**=O), 144.3 (**Ts**), 137.1 (**Ts**), 129.5 (=**C**Br), 129.3 (*m*-**Ts**H), 127.9 (*o*-**Ts**H), 119.3 (=**C**HH'), 84.5 (**C**$(CH_3)_3$), 45.7 (**C**H_2N), 42.0 (=CBr**C**H_2), 27.8 (C(**C**H_3)$_3$), 21.6 (Ar**C**H_3). Data are consistent with literature values.[132]

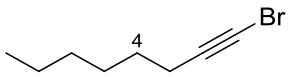
***N*-(3-Bromobut-3-en-1-yl)-4-methylbenzenesulfonamide, 107**



Synthesised from *tert*-butyl (3-bromobut-3-en-1-yl)(tosyl)carbamate **124** (11.05 g, 27.3 mmol) using Procedure 4 to give the title compound as a colourless solid (8.30 g, 27.3 mmol, quant.) which was used without further purification; m.p. 42-46 °C; R_f = 0.38 (1:1, pet. ether:Et_2O); δ_H

(400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.31 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.60 (1H, dt, *J*=1.8, 1.0 Hz, =C**H**H'), 5.48 (1H, d, *J*=1.8 Hz, CH**H'**), 4.67 (1H, br. t, *J*=6.3 Hz, N**H**), 3.17 (2H, ap. q, *J*=6.3 Hz, C$\mathbf{H_2}$NH), 2.56 (2H, td, *J*=6.3, 1.0 Hz, =CBrC$\mathbf{H_2}$), 2.43 (3H, s, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 143.6 (**Ts**), 136.8 (**Ts**), 129.8 (*m*-**Ts**H), 129.6 (=**C**Br), 127.1 (*o*-**Ts**H), 120.1 (=**C**HH'), 41.3 (=CBr**C**H_2), 40.9 (**C**H_2NH), 21.5 (Ar**C**H_3). Data are consistent with literature values.[132]

1-Bromooct-1-yne, 125a



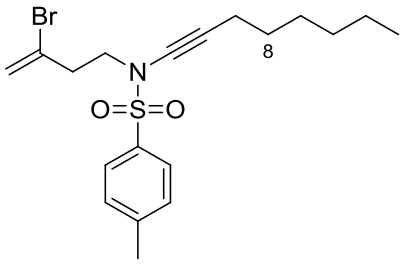
Method A

Synthesised from oct-1-yne (6.69 mL, 45.4 mmol) using Procedure 1 to give the title compound as a pale yellow oil (8.32 g, 44.0 mmol, 96%) which was used without further purification. R_f = 0.83 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 2.19 (2H, t, *J*=7.2 Hz, ≡CC$\mathbf{H_2}$), 1.50 (2H, ap. quin., *J*=7.2 Hz, C$\mathbf{H_2}$-4), 1.43-1.20 (6H, m, (C$\mathbf{H_2}$)$_3$$CH_3$), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 80.4 (≡**C**CH_2), 37.4 (≡**C**Br), 31.3 ((**C**H_2)$_3$$CH_3$), 28.5 ((**C**$H_2$)$_3$$CH_3$), 28.3 (**C**$H_2$-4), 22.5 ((**C**$H_2$)$_3$$CH_3$), 19.6 (≡C**C**$H_2$), 14.0 (**C**$H_3$). Data are consistent with literature values.[136]

Method B

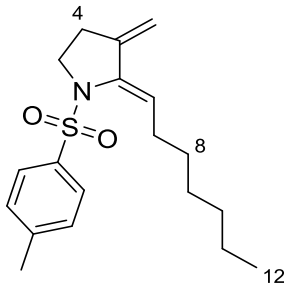
Synthesised from oct-1-yne (15.0 mL, 102 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (pet. ether) to give the title compound as a colourless oil (18.4 g, 97.5 mmol, 96%); Data are in accordance with Method A.

_N_-(3-Bromobut-3-en-1-yl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 99a



Synthesised from *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide **107** (2.40 g, 7.89 mmol) and 1-bromooctyne **125a** (2.24 g, 11.8 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10:1, pet. ether:EtOAc) to give the title compound as a yellow oil (2.54 g, 6.15 mmol, 80%); R_f = 0.64 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.33 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.65-5.61 (1H, m, =C**H**H'), 5.44 (1H, d, *J*=2.0 Hz, =CH**H'**), 3.50 (2H, t, *J*=7.1 Hz, C$\mathbf{H_2}$NTs), 2.72 (2H, t, *J*=7.1 Hz, =CBrC$\mathbf{H_2}$), 2.45 (3H, s, ArC$\mathbf{H_3}$), 2.26 (2H, t, *J*=7.0 Hz, ≡CC$\mathbf{H_2}$), 1.47 (2H, ap. quin., *J*=7.0 Hz, C$\mathbf{H_2}$-8), 1.40-1.17 (6H, m, (C$\mathbf{H_2}$)$_3$CH$_3$), 0.88 (3H, t, *J*=6.9 Hz, (CH$_2$)$_3$C$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 144.4 (**Ts**), 134.5 (**Ts**), 129.6 (*m*-**Ts**H), 129.1 (=**C**Br), 127.7 (*o*-**Ts**H), 119.5 (=**C**HH'), 72.6 (≡**C**NTs), 70.9 (≡**C**CH$_2$), 49.7 (**C**H$_2$NTs), 39.9 (=CBr**C**H$_2$), 31.3 ((**C**H$_2$)$_3$CH$_3$), 28.8 (**C**H$_2$-8), 28.5 ((**C**H$_2$)$_3$CH$_3$), 22.6 ((**C**H$_2$)$_3$CH$_3$), 21.6 (Ar**C**H$_3$), 18.4 (≡C**C**H$_2$), 14.0 ((CH$_2$)$_3$**C**H$_3$). Data are consistent with literature values.[47]

(*Z*)-2-Heptylidene-3-methylene-1-tosylpyrrolidine, 102a



Method A

Synthesised from *N*-(3-bromobut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **99a** (1.50 g, 3.63 mmol) using Procedure 7. The resulting crude material was purified by column chromatography (10:1, pet. ether:EtOAc + 1% Et_3N) to give the title compound as a pale yellow oil (955 mg, 2.86 mmol, 78%); R_f = 0.49 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.68 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.23 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.87 (1H, t, *J*=7.4 Hz, =C**H**CH_2), 5.20 (1H, t, *J*=2.3 Hz, =C**H**H'), 4.64 (1H, t, *J*=2.3 Hz, =CH**H'**), 3.53 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 2.53 (2H, q, *J*=7.6 Hz, =CHC$\mathbf{H_2}$), 2.42 (2H, s, ArC$\mathbf{H_3}$), 1.83 (2H, tt, *J*=7.4, 2.3 Hz, C$\mathbf{H_2}$-4), 1.48-1.23 (8H, m, C$\mathbf{H_2}$-(8-11)), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-12); δ_C (125 MHz, $CDCl_3$) 143.8 (**Ar**CH_3), 143.2 (=**C**), 136.5 (=**C**), 136.0 (**Ar**SO_2), 129.5 (*m*-**Ts**H), 127.7 (*o*-**Ts**H), 122.1 (=**C**HCH_2), 103.5 (=**C**HH'), 48.5 (**C**H_2NTs), 31.7 (**C**H_2-(8-11)), 29.7 (=CH**C**H_2), 29.5 (**C**H_2-(8-11)), 29.1 (**C**H_2-(8-11)), 29.0 (**C**H_2-4), 22.7 (**C**H_2-(8-11)), 21.6 (Ar**C**H_3), 14.1 (**C**H_3-12). Data are consistent with literature values.[48]

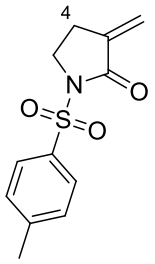
Method B

See cycloisomerisation products.

Method C

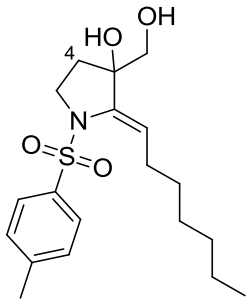
See cycloisomerisation products.

3-Methylene-1-tosylpyrrolidin-2-one, 127



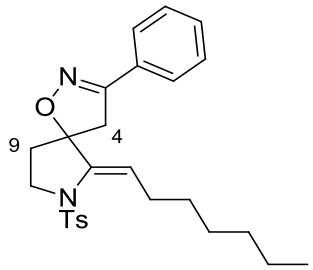
To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (10.0 mg, 0.030 mmol, 1.0 eq.) in DCM (0.3 mL) at 0 °C was added recrystallised *m*-CPBA (14.5 mg, 90% in H_2O, 0.084 mmol, 2.8 eq.). The reaction mixture was stirred at RT for 3 h. The reaction mixture was diluted with DCM (10 mL) and washed with sat. aq. $Na_2S_2O_3$ (2 × 10 mL) and then 1 M aq. NaOH (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (3:1, pet. ether:EtOAc) to give the title compound as a yellow oil (5.0 mg, 0.020 mmol, 66%); R_f = 0.23 (3:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.97 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.34 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 6.10 (1H, t, *J*=2.8 Hz, =C**H**H'), 5.46 (1H, t, *J*=2.4 Hz, =CH**H'**), 3.91-3.86 (2H, m, C$\mathbf{H_2}$NTs), 2.81 (2H, tdd, *J*=7.1, 2.8, 2.4 Hz, C$\mathbf{H_2}$-4); 2.43 (3H, s, ArC$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 165.5 (**C**=O), 145.3 (**Ts**), 137.6 (**Ts**), 134.9 (=**C**), 129.7 (*m*-**Ts**H), 128.3 (*o*-Ts**H**), 120.8 (=**C**HH'), 43.7 (**C**H_2NTs), 24.1 (**C**H_2-4), 21.7 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2924 m (C-H), 1726 m (C=O), 1359 m (SO_2), 1169 s (SO_2), 1112 m, 913 m; LRMS *m*/*z* (ESI+) 525.1 ([2M+Na]$^+$, 100%), 274.1 ([M+Na]$^+$, 96%). Data are consistent with literature values.[54,137]

(*Z*)-2-Heptylidene-3-(hydroxymethyl)-1-tosylpyrrolidin-3-ol, 129



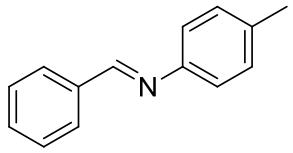
To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (20 mg, 0.060 mg, 1.0 eq.) and *N*-methylmorpholine *N*-oxide (7.7 mg, 0.066 mmol, 1.1 eq.) in acetone:H_2O (0.5 mL:0.1 mL) was added OsO_4 (2.5 wt% in *t*-BuOH, 4.5 μL, 36 μmol, 0.6 mol%). The reaction mixture was stirred at RT overnight, quenched with solid Na_2SO_3 (90 mg), diluted with water (2 mL) and stirred for a further 1 h. The reaction mixture was extracted with DCM (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10%→30% EtOAc in pet. ether) to give the title compound as a yellow oil (18.0 mg, 0.049 mmol, 82%); R_f = 0.15 (1:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.71 (2H, d, *J*=8.4 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.4 Hz, *m*-Ts**H**), 5.33 (1H, t, *J*=7.2 Hz, =C**H**CH_2), 3.62-3.51 (2H, m, C**HH'**NTs), 3.23 (1H, dd, *J*=11.3, 4.4 Hz, C**H**H'OH), 3.07 (1H, dd, *J*=11.3, 7.9 Hz, CH**H'**OH), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.38 (2H, ap. q, *J*=7.2 Hz, =CHC$\mathbf{H_2}$), 1.92 (1H, s, C-O**H**), 1.85-1.63 (3H, m, C**HH'**-4, CHH'O**H**), 1.45-1.20 (8H, m, (C$\mathbf{H_2}$)$_4$$CH_3$), 0.88 (3H, t, *J*=7.0 Hz, $(CH_2)_4$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 144.2 (**Ts**), 139.2 (=**C**), 135.4 (**Ts**), 129.7 (*m*-**Ts**H), 127.7 (*o*-**Ts**H), 121.2 (=**C**HCH_2), 79.2 (**C**-OH), 66.5 (**C**HH'OH), 47.2 (**C**HH'NTs), 33.2 (**C**HH'-4), 31.7 ((**C**H_2)$_4$$CH_3$), 29.7 ((**C**$H_2$)$_4$$CH_3$), 29.1 (=CH**C**$H_2$), 29.0 ((**C**$H_2$)$_4$$CH_3$), 22.6 ((**C**$H_2$)$_4$$CH_3$), 21.6 (Ar**C**$H_3$), 21.6 ($(CH_2)_4$**C**$H_3$); IR (thin film) ν_{max}/cm^{-1} 3467 br. m (O-H), 2925 m (C-H), 1352 m (SO_2), 1162 s (SO_2), 914 m; LRMS *m*/*z* (ESI+) 757.4 ([2M+Na]$^+$, 100%), 390.2 ([M+Na]$^+$, 87%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 390.1707; $C_{19}H_{29}NNaO_4S^+$ requires 390.1710.

(*Z*)-6-Heptylidene-3-phenyl-7-tosyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene, 130



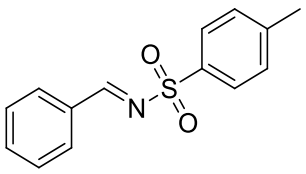
According to the procedure of Delft and co-workers.[138] To a solution of (*E*)-benzaldehyde oxime (17 mg, 97%, 0.14 mmol, 1.5 eq.) in MeOH:H_2O (80 μL:20 μL) was added iodobenzene bis(trifluoroacetate) (58 mg, 0.135 mmol, 1.5 eq.). The reaction mixture was stirred for 2 min and a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in MeOH:H_2O (80 μL:20 μL) was added. The reaction mixture was stirred for 4 h and then concentrated *in vacuo*. DCM (20 mL) was added and the solution dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5:1, pet. ether:EtOAc) to give the title compound as a yellow oil (21 mg, 0.046 mmol, 52%); R_f = 0.33 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.76 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.50-7.45 (2H, m, Ar**H**), 7.42-7.33 (5H, m, Ar**H**), 5.43 (1H, dd, *J*=7.9, 6.3 Hz, =C**H**), 3.68-3.57 (2H, m, C**HH'**NTs), 2.84 (1H, d, *J*=17.0 Hz, C**H**H'-4), 2.72 (1H, d, *J*=17.0 Hz, C**H**H'-4), 2.48 (3H, s, ArC$\mathbf{H_3}$), 2.48-2.37 (2H, m, =CHC$\mathbf{H_2}$), 2.08-2.01 (1H, m, C**H**H'-9), 1.74-1.67 (1H, m, CH**H'**-9), 1.46-1.20 (4H, m, (C$\mathbf{H_2}$)$_4$$CH_3$), 0.88 (3H, t, *J*=6.9 Hz, (CH_2)$_4$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 155.8 (**C**), 144.2 (**C**), 137.7 (**C**), 135.3 (**C**), 130.2 (**C**), 129.7 (**Ar**H), 129.2 (=**C**H), 128.7 (**Ar**H), 128.1 (**Ar**H), 126.4 (**Ar**H), 121.7 (**Ar**H), 90.1 (**C**-O), 47.4 (**C**HH'NTs), 44.5 (**C**HH'-4), 36.3 (**C**HH'-9), 31.7 ((**C**H_2)$_4$$CH_3$), 29.5 ((**C**$H_2$)$_4$$CH_3$), 29.0 ((**C**$H_2$)$_4$$CH_3$), 29.0 (=CH**C**$H_2$), 22.6 ((**C**$H_2$)$_4$$CH_3$), 21.6 (Ar**C**$H_3$), 14.1 (($CH_2$)$_4$**C**$H_3$); IR (thin film) ν_{max}/cm^{-1} 2926 w (C-H), 1358 m, (SO_2), 1166 s (SO_2); LRMS *m*/*z* (ESI+) 927.5 ([2M+Na]$^+$, 100%), 475.2 ([M+Na]$^+$, 54%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 475.2007; $C_{26}H_{32}N_2NaO_3S^+$ requires 475.2026.

_N_-Benzylidene-4-methylaniline, 133a



According to the procedure of Hania.[139] To a solution of *p*-toluidine (2.00 g, 18.7 mmol, 1.0 eq.) in toluene (20 mL) was added benzaldehyde (1.90 mL, 18.7 mmol, 1.0 eq.) and $MgSO_4$ (8.99 g, 74.7 mmol, 4.0 eq.). The reaction mixture was heated under reflux for 2 h before being filtered and concentrated *in vacuo*. The product was crystallised from EtOAc (10 mL) at -78 °C, filtered and dried to yield the title compound as a brown solid (438 mg, 2.24 mmol, 12%); m.p. 27-28 °C; R_f = 0.56 (3:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 8.49 (1H, s, C**H**=N), 7.96-7.89 (2H, m, *o*-Ph**H**), 7.52-7.45 (3H, m, *m*-Ph**H**, *p*-Ph**H**), 7.25-7.15 (4H, m, Tol**H**), 2.40 (3H, s, C$\mathbf{H}_3$); δ_C (100 MHz, $CDCl_3$) 159.6 (**C**H=N), 149.4 (**Ar**), 136.3 (**Ar**), 135.8 (**Ar**), 131.2 (**Ph**-H), 129.7 (**Tol**H), 128.7 (**Ph**H), 120.8 (**Tol**H), 21.0 (**C**H_3). Data are consistent with literature values.[140]

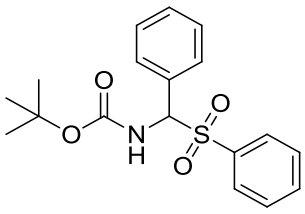
_N_-Benzylidene-4-methylbenzenesulfonamide, 133b



According to the procedure of Smith and co-workers.[141] To a solution of benzaldehyde (2.00 mL, 19.7 mmol, 1.0 eq.) and *p*-toluenesulfonamide (3.37 g, 19.7 mmol, 1.0 eq.) in toluene (60 mL), refluxing using a Dean-Stark apparatus, was added $BF_3 \cdot Et_2O$ (41 μL, 0.31 mmol, 0.016 eq.). The mixture was heated under reflux for 20 h. The solution was the cooled and washed with 2 M aq. NaOH (2 × 50 mL) and H_2O (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude product was purified by recrystallisation from EtOAc/hexane to give the title compound as a colourless solid (2.30 g,

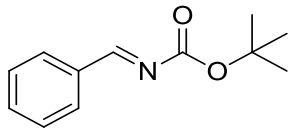
8.88 mmol, 45%); m.p. 111-113 °C (Lit. m.p. 105-112 °C); R_f = 0.43 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 9.03 (1H, s, N=C**H**), 7.96-7.86 (4H, m, Ar**H**), 7.65-7.30 (5H, m, Ar**H**), 2.43 (3H, s, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 170.1 (N=**C**H), 144.6 (**Ar**), 135.1 (**Ar**), 134.9 (**Ar**H), 132.3 (**Ar**), 131.2 (**Ar**H), 129.8 (**Ar**H), 129.1 (**Ar**H), 128.0 (**Ar**H), 21.6 (Ar**C**H_3). Data are consistent with literature values.[141,142]

***tert*-Butyl (phenyl(phenylsulfonyl)methyl)carbamate, 137**



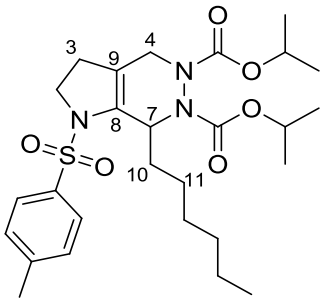
According to the procedure of Greene and co-workers.[143] To a solution of *tert*-benzyl carbamate (1.15 g, 9.80 mmol, 1.0 eq.) and benzenesulfinic acid sodium salt (1.61 g, 9.8 mmol, 1.0 eq.) in H_2O (10 mL) was added benzaldehyde (3.00 mL, 29.5 mmol, 3.0 eq.) in MeOH (1.0 mL). The solution was adjusted to pH~2 with the addition of formic acid (88%, approx. 2 mL), then the reaction mixture was stirred at RT for 15 h. The resulting colourless ppt was filtered and washed with H_2O and then pet. ether to yield the title compound as a colourless solid (3.09 g, 8.89 mmol, 91%); m.p. 166-170 °C (Lit. m.p. 164-165 °C); R_f = 0.51 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.98-7.85 (2H, m, Ar**H**), 7.70-7.35 (8H, m, Ar**H**), 6.00-5.84 (2H, m, N**H**, C**H**), 1.25 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 153.5 (**C**=O), 136.9 (**Ar**), 129.9 (**Ar**H), 129.8 (**Ar**), 129.4 (**Ar**H), 129.0 (**Ar**H), 128.9 (**Ar**H), 128.7 (**Ar**H), 81.2 (**C**$(CH_3)_3$), 73.9 (**C**H), 28.0 (C(**C**H_3)$_3$). Data are consistent with literature values.[143,144]

tert-Butyl benzylidenecarbamate, 133c



According to the procedure of Greene and co-workers.[143] A stirred mixture of *tert*-butyl (phenyl(phenylsulfonyl)methyl)carbamate **137** (1.50 g, 4.32 mmol, 1.0 eq.) and K_2CO_3 (3.58 g, 25.9 mmol, 6.0 eq.) in THF (50 mL) was heated under reflux for 12 h. The mixture was allowed to cool, filtered through Celite and concentrated *in vacuo* to yield the title compound as a colourless oil (813 mg, 3.96 mmol, 92%); R_f = 0.34 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 8.87 (1H, s, N=C**H**), 7.90 (2H, m, Ar**H**), 7.60-7.42 (3H, m, Ar**H**), 1.59 (9H, s, C(C**H**$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 169.6 (**C**), 162.6 (**C**), 134.0 (**Ar**), 133.5 (**Ar**H), 130.2 (**Ar**H), 128.8 (**Ar**H), 82.2 (**C**(CH$_3$)$_3$), 27.9 (C(**C**H$_3$)$_3$). Data are consistent with literature values.[143]

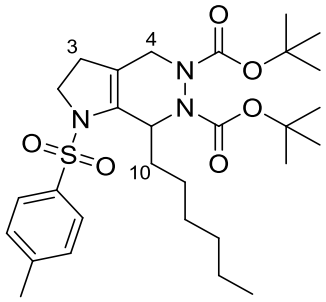
Diisopropyl 7-hexyl-1-tosyl-2,3-dihydro-1*H*-pyrrolo[2,3-*d*]pyridazine-5,6(4*H*,7*H*)-dicarboxylate, 142



To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM (1.0 mL) was added dropwise DIAD (19.5 μL, 0.099 mmol, 1.1 eq.). The reaction mixture was stirred at RT for 3 h, added to further DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5:1, pet.

ether:EtOAc) to give the title compound as a colourless oil (36 mg, 0.067 mmol, 75%); R_f = 0.41 (3:1, pet. ether:EtOAc); δ_H (500 MHz, d_8-toluene, 363 K) 7.80 (2H d, *J*=7.7 Hz, *o*-Ts**H**), 6.95 (2H, d, *J*=7.7 Hz, *m*-Ts**H**), 5.76-5.62 (1H, br. m, C**H**-7), 5.07-4.94 (2H, m, C**H**$(CH_3)_2$, C**H**$(CH_3)_2$), 4.28 (1H, d, *J*=16.5 Hz, C**H**H'-4), 3.53 (1H, d, *J*=16.5 Hz, CH**H'**-4), 3.51-3.40 (2H, m, C**HH'**NTs), 2.21 (1H, m, C**H**H'-10), 2.00 (3H, s, ArC**H$_3$**), 1.84-1.71 (2H, m, C**HH'**-11) 1.70-1.59 (2H, m, CH**H'**-10, C**H**H'-3), 1.60-1.49 (1H, m, CH**H'**-3), 1.43-1.25 (6H, m, (C**H$_2$**)$_3$$CH_3$), 1.25-1.05 (12H, m, CH(C**H$_3$**)$_2$, CH(C**H$_3$**)$_2$), 0.99-0.83 (3H, m, $(CH_2)_4$C**H$_3$**); δ_C (125 MHz, d_8-toluene, 363 K) 156.5 (**C**=O), 155.5 (**C**=O), 143.7 (**Ar**CH_3), 139.1(=**C**-8), 135.8 (**Ar**SO_2), 130.0 (*m*-**Ts**H), 128.8 (*o*-**Ts**H), 118.6 (=**C**-9), 70.6 (C**H**$(CH_3)_2$), 70.0 (C**H**$(CH_3)_2$), 56.5 (C**H**-7), 49.9 (**C**HH'NTs), 43.8 (**C**HH'-4)), 32.8 ((**C**H_2)$_3$$CH_3$), 32.2 (**C**HH'-10), 30.5 ((**C**H_2)$_3$$CH_3$), 29.4 (**C**HH'-3), 27.6 (**C**HH'-11), 23.3 ((**C**H_2)$_3$$CH_3$), 22.5 (CH(**C**$H_3$)(C'$H_3$)), 22.4 (CH(**C**$H_3$)(C'$H_3$)), 22.3 CH$(CH_3)$(**C'**$H_3$), 22.2 CH$(CH_3)$(**C'**$H_3$), 21.3 (Ar**C**$H_3$), 14.4 ($(CH_2)_4$C**H$_3$**); IR (thin film) ν_{max}/cm^{-1} 2928 m (C-H), 1720 br. s (C=O), 1381 m (SO_2), 1168 m (SO_2), 1105 m; LRMS *m*/*z* (ESI+) 558.3 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 558.2602; $C_{27}H_{41}N_3NaO_6S^+$ requires 558.2608.

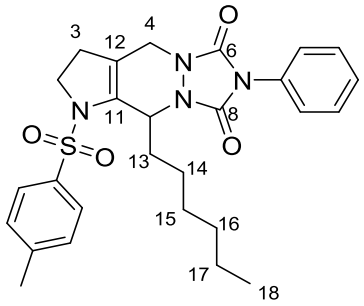
di-*tert*-Butyl 7-hexyl-1-tosyl-2,3-dihydro-1*H*-pyrrolo[2,3-*d*]pyridazine-5,6(4*H*,7*H*)-dicarboxylate, 144



To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM (1.0 mL) was added dropwise DTAD (23 mg, 0.099 mmol, 1.1 eq.). The reaction mixture was stirred at RT for 15 h, added to further DCM (10 mL) and washed with

sat. aq. $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10%→20% EtOAc in pet. ether) to give the title compound as a colourless oil (48 mg, 0.085 mmol, 95%); ^{1}H NMR spectrum is broad due to the highly rotameric nature of the product. Due to the thermal instability of this compound, variable temperature analysis was not attempted and ^{13}C NMR spectroscopic analysis is not reported as signal coalescence could not be obtained; R_f = 0.38 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.83-7.62 (2H, br. m, *m*-Ts**H**), 7.32-7.20 (2H, br. m, *o*-Ts**H**), 5.44-5.19 (1H, br. m, C**H**), 4.25 (1H, d, *J*=16.7 Hz, C**H**H'-4), 3.83-3.74 (1H, m, C**H**H'NTs), 3.68-3.48 (2H, br. m, CH**H'**NTs, CH**H'**-4), 2.46-2.37 (3H, br. m, ArC**H**$_3$), 2.15-2.05 (2H, m, C**HH'**-3), 2.00-1.90 (1H, m, C**H**H'-10), 1.68-1.22 (9H, m, CH**H'**-10, (C**H**$_2$)$_4$CH$_3$), 0.93-0.83 (3H, br. m, (CH$_2$)$_4$C**H**$_3$); IR (thin film) ν_{max}/cm^{-1} 2928 m (C-H), 1703 s (C=O), 1393 m, 1367 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 586.3 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 586.2930; $C_{29}H_{45}N_3NaO_6S^+$ requires 586.2921.

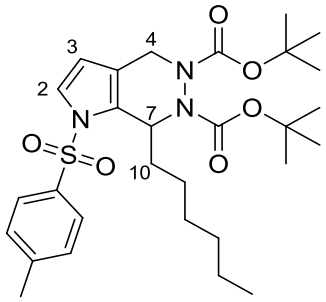
10-Hexyl-7-phenyl-1-tosyl-2,3,7,10-tetrahydropyrrolo[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-6,8(1*H*,4*H*)-dione, 146



To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM (0.5 mL) was added a solution of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (18 mg, 97%, 0.099 mmol, 1.1 eq.) in DCM (0.5 mL). The reaction mixture was stirred at RT for 10 min. The reaction mixture was added to DCM (10 mL), washed with sat. aq. $NaHCO_3$

(10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (3:2, pet. ether:EtOAc) to give the title compound as a colourless oil (39 mg, 0.077 mmol, 85%); R_f = 0.29 (3:2, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.57-7.53 (2H, m, *o*-Ph**H**), 7.49 (2H, t, *J*=7.5 Hz, *m*-Ph**H**), 7.39 (1H, t, *J*=7.5 Hz, *p*-Ph**H**), 7.35 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.47 (1H, br. s, C**H**), 4.25 (1H, dd, *J*=16.1, 0.6 Hz, C**H**H'-4), 3.98-3.81 (3H, m, CH**H'**-4, C**HH'**NTs), 2.45 (3H, s, ArC**H$_3$**), 2.29-2.20 (1H, m, C**H**H'-3), 2.20-2.09 (2H, m, CH**H'**-3, C**H**H'-13), 2.06-1.96 (1H, m, CH**H'**-13), 1.48-1.21 (8H, m, (C**H$_2$**)-(14-17)), 0.87 (3H, t, *J*=6.7 Hz, C**H$_3$**-18); δ_C (125 MHz, $CDCl_3$) 153.0 ((**C**-6)=O), 150.6 ((**C**-8)=O), 144.5 (**Ar**CH_3), 136.0 (=**C**-11), 133.2 (**Ar**SO_2), 131.2 (**Ph**), 130.0 (*m*-**Ts**H), 129.2 (*m*-**Ph**H), 128.2 (*p*-**Ph**H), 127.6 (*o*-**Ts**H), 125.3 (*o*-**Ph**H), 118.6 (=**C**-12), 54.2 (**C**H), 50.2 (**C**HH'NTs), 44.3 (**C**HH'-4), 32.1 (**C**HH'-13), 31.6 (**C**H_2-16), 29.2 (**C**HH'-3), 29.2 (**C**H_2-15), 24.9 (**C**H_2-14), 22.6 (**C**H_2-17), 21.6 (Ar**C**H_3), 14.0 (**C**H_3-18); IR (thin film) ν_{max}/cm^{-1} 2927 w (C-H), 1777 w (C=O), 1715 s (C=O), 1354 m (SO_2), 1164 m (SO_2); LRMS *m/z* (ESI+) 921.5 ($[2M+Na]^+$, 28%), 531.2 ($[M+Na]^+$, 98%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 531.2049; $C_{27}H_{32}N_4NaO_4S^+$ requires 531.2036.

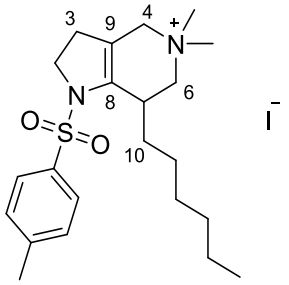
di-*tert*-Butyl 7-hexyl-1-tosyl-1*H*-pyrrolo[2,3-*d*]pyridazine-5,6(4*H*,7*H*)-dicarboxylate, 147



To a solution of di-*tert*-butyl 7-hexyl-1-tosyl-2,3-dihydro-1*H*-pyrrolo[2,3-*d*]pyridazine-5,6(4*H*,7*H*)-dicarboxylate **144** (42 mg, 0.075 mmol, 1.0 eq.) in DCM (2.0 mL) was added γ-MnO_2 (129 mg, 1.69 mmol, 20 eq.). The reaction mixture was stirred at RT for 2 h, filtered

through Celite eluting with DCM and concentrated *in vacuo* to give the title compound as a colourless oil (35 mg, 0.062 mmol, 83%); Product is highly rotameric. Due to the thermal instability of this compound, variable temperature analysis was not attempted and ^{13}C NMR spectroscopic analysis is not given as signal coalescence could not be obtained; R_f = 0.63 (3:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.85-7.56 (2H, br. m, *m*-Ts**H**), 7.35-7.20 (2H, br. m, *o*-Ts**H**), 7.15-6.97 (1H, br. m, C**H**-2), 6.14-6.02 (1H, br. m, C**H**-3), 5.57-5.15 (1H, br. m, C**H**-7), 4.77-4.54 (1H, m, C**H**H'-4), 4.19-3.92 (1H, br. m, CH**H'**-4), 2.46-2.31 (3H, br. m, ArC**H**$_3$), 1.94-1.79 (1H, m, C**H**H'-10), 1.75-1.14 (9H, m, CH**H'**-10, (C**H**$_2$)$_4$CH$_3$), 0.96-0.79 (3H, br. m, (CH$_2$)$_4$C**H**$_3$); IR (thin film) ν_{max}/cm^{-1} 2928 m (C-H), 1704 s (C=O), 1368 s (SO_2), 1149 s, 1136 s, 1120 s; LRMS *m/z* (ESI+) 584.3 ([M+Na]$^+$, 94%); HRMS *m/z* (ESI+) found [M+Na]$^+$ 584.2763; $C_{29}H_{43}N_3NaO_6S^+$ requires 584.2765.

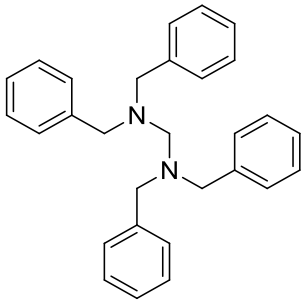
7-Hexyl-5,5-dimethyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[3,2-*c*]pyridin-5-ium iodide, 150a



To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM was added Eschenmoser's salt (19 mg, 0.099 mmol, 1.1 eq.). The reaction mixture was stirred at RT for 18 h and concentrated *in vacuo* to give a crude mixture containing the title compound as a yellow semi-solid (80% purity, 45 mg, 0.087 mmol, 96%); R_f = 0.36 (5.0% MeOH in DCM); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.35 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 4.52 (1H, d, *J*=16.4 Hz, C**H**H'-4), 4.18 (1H, d, *J*=16.4 Hz, CH**H**-4), 4.04 (1H, ddd, *J*=12.7, 8.9, 2.0 Hz, C**H**H'NTs), 3.94-3.89 (1H, m, C**H**H'-6), 3.79-3.69 (1H, m,

CH**H'**NTs), 3.73 (3H, s, $N^+C\mathbf{H_3}$), 3.39 (1H, ap. t, *J*=12.0 Hz, CH**H'**-6), 3.22 (3H, s, $N^+C\mathbf{H_3}$), 3.09 (1H, br. s, C**H**), 2.45 (3H, s, Ar$C\mathbf{H_3}$), 2.22-2.02 (3H, m, C**HH'**-3, C**H**H'-10), 1.63-1.51 (1H, m, CH**H'**-10), 1.33-1.22 (8H, m, $(C\mathbf{H_2})_4CH_3$), 0.87 (3H, t, *J*=7.1 Hz, $(CH_2)_4C\mathbf{H_3}$); 145.3 (**Ar**CH_3), 137.0 (=**C**-8), 134.1 (**Ar**SO_2), 130.3 (*m*-**Ts**H), 127.4 (*o*-**Ts**H), 119.3 (=**C**-9), 65.2 (**C**HH'-6), 61.9 (**C**HH'-4), 55.9 ($N^+\mathbf{C}H_3$), 50.2 (**C**HH'NTs), 49.1 ($N^+\mathbf{C}H_3$), 32.0 (**C**H), 31.5 ($(\mathbf{C}H_2)_4CH_3$), 30.3 (**C**HH'-10), 29.5 (**C**HH'-3), 29.2 ($(\mathbf{C}H_2)_4CH_3$), 25.6 ($(\mathbf{C}H_2)_4CH_3$), 22.6 ($(\mathbf{C}H_2)_4CH_3$), 21.7 (Ar**C**H_3), 14.1 ($(CH_2)_4\mathbf{C}H_3$); IR (thin film) ν_{max}/cm^{-1} 2927 w (C-H), 1349 w (SO_2), 1163 s (SO_2), 915 m; LRMS *m*/*z* (ESI+) 391.3 ([M^+], 100%); HRMS *m*/*z* (ESI+) found $[M]^+$ 391.2410; $C_{22}H_{35}N_2O_2S^+$ requires 391.2414.

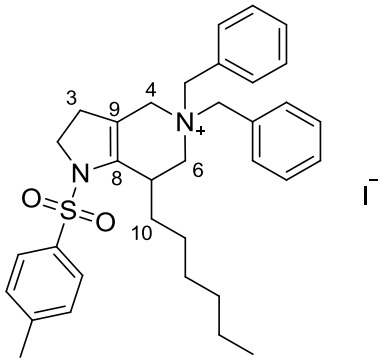
N,N,N',N'-Tetrabenzylmethanediamine, 152



According to the modified procedure of Heaney et al.[145] To a mixture of formaldehyde (94 μL, 37 wt% in H_2O, 1.23 mmol, 1.0 eq.) in H_2O:Et_2O (1.5 mL:0.5 mL) at 0 °C was added dropwise dibenzylamine (500 mg, 97%, 2.46 mmol, 2.0 eq.). The reaction mixture was stirred at RT overnight and then saturated with solid KOH. The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5:1, pet. ether:EtOAc) to give the title compound as a colourless solid (385 mg, 0.95 mmol, 77%); m.p. 94-98 °C; R_f = 0.50 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.17-7.34 (20H, m, Ar**H**), 3.60 (8H, C$\mathbf{H_2}$Ph), 3.08 (2H, N-C$\mathbf{H_2}$-N); δ_C (100 MHz, $CDCl_3$) 139.7 (**Ar**), 129.0 (**Ar**H), 128.1

(**Ar**H), 126.7 (**Ar**H), 72.3 (N-**C**H_2-N), 56.1 (**C**H_2Ph). Data are consistent with literature values.[146]

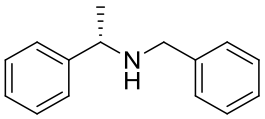
5,5-Dibenzyl-7-hexyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[3,2-*c*]pyridin-5-ium iodide, 150b



To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM was added *N*-benzyl-*N*-methylene-1-phenylmethanaminium iodide **149b** (33 mg, 0.099 mmol, 1.1 eq.). The reaction mixture was stirred at RT for 18 h and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (4.5% MeOH in DCM) to give the title compound as a yellow semi-solid (46 mg, 0.069 mmol, 76%); R_f = 0.53 (5.0% MeOH in DCM); δ_H (500 MHz, $CDCl_3$) 7.81 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.60 (2H, d, *J*=6.9 Hz, *o*-Ph**H**), 7.58-7.52 (1H, m, *p*-Ph**H**), 7.51-7.40 (5H, m, Ar**H**), 7.29-7.23 (4H, m, *m*-Ts**H**, Ar**H**), 5.48 (1H, d, *J*=12.9 Hz, C**H**H'Ph), 5.32 (1H, d, *J*=12.6 Hz, C**H**H'Ph), 4.62-4.49 (3H, m, CH**H'**Ph, CH**H'**Ph, C**H**H'-6), 4.25 (1H, ddd, *J*=12.9, 8.8, 2.2 Hz, C**H**H'NTs), 3.90-3.71 (3H, m, C**HH'**-4, CH**H'**NTs), 3.37 (1H, br. s, C**H**), 2.76 (1H, dd, *J*=12.2, 11.4 Hz, CH**H'**-6), 2.38-2.14 (3H, m, C**HH'**-3, C**H**H'-10), 2.28 (3H, s, ArC$\mathbf{H_3}$) 1.49-1.39 (1H, m, CH**H'**-10), 1.37-1.14 (8H, m, (C$\mathbf{H_2}$)$_4$$CH_3$), 0.89 (3H, t, *J*=6.9 Hz, $(CH_2)_4$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 145.3 (**Ar**CH_3), 137.6 (=**C**-8), 134.6 (**Ar**SO_2), 133.8 (*o*-**Ph**H), 133.1 (**Ar**H), 131.1 (*p*-**Ph**H), 131.0 (**Ar**H), 130.6 (*m*-**Ts**H), 129.5 (**Ar**H), 129.4 (**Ar**H), 127.3 (*o*-**Ts**H), 126.4 (**Ph**), 125.9 (**Ph**), 118.4 (=**C**-9), 64.2 (**C**HH'Ph), 60.3 (**C**HH'Ph), 58.4

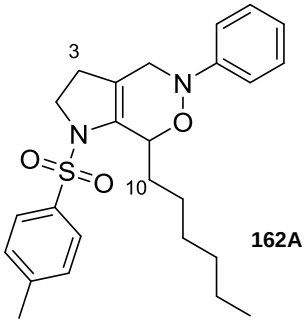
(**C**HH'-6), 52.2 (**C**HH'-4), 50.3 (**C**HH'NTs), 31.8 (**C**H), 31.3 ((**C**H_2)$_4$$CH_3$), 30.6 (**C**HH'-10), 29.7 (**C**HH'-3), 29.0 ((**C**H_2)$_4$$CH_3$), 25.3 ((**C**$H_2$)$_4$$CH_3$), 22.5 ((**C**$H_2$)$_4$$CH_3$), 21.5 (Ar**C**$H_3$), 14.0 ((CH$_2$)$_4$**C**$H_3$); IR (thin film) ν_{max}/cm^{-1} 2927 w (C-H), 1352 m (SO_2), 1162 s (SO_2), 916 m; LRMS *m/z* (ESI+) 543.3 ([M^+], 100%); HRMS *m/z* (ESI+) found $[M]^+$ 543.3033; $C_{34}H_{43}N_2O_2S^+$ requires 543.3040.

(*S*)-*N*-Benzyl-1-phenylethanamine, 154

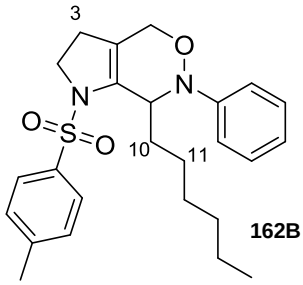


To a solution of (*S*)-1-phenylethylamine (1.05 mL, 8.25 mmol, 1.0 eq.) in EtOH (10 mL) was added dropwise a solution of benzaldehyde (847 μL, 8.25 mmol, 1.0 eq.) in EtOH (5 mL). The mixture was heated under reflux for 2 h and then allowed to cool to RT. $NaBH_4$ (687 mg, 18.2 mmol, 2.2 eq.) was added portionwise, the reaction mixture heated under reflux for 2 h and then concentrated *in vacuo*. The residue was dissolved in DCM (20 mL), washed with 1 M aq. NaOH (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound as a colourless oil (1.91 g, 9.04 mmol, quant.); R_f = 0.66 (EtOAc); δ_H (400 MHz, $CDCl_3$) 7.38-7.17 (10H, m, Ar**H**), 3.79 (1H, ap. q, *J*=6.7 Hz, C**H**), 3.64 (1H, d, *J*=13.1 Hz, C**H**H'), 3.57 (1H, d, *J*=13.1 Hz, CH**H'**), 1.59 (1H, br. s, N**H**), 1.35 (3H, d, *J*=6.8 Hz, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 145.5 (**Ar**), 140.6 (**Ar**), 128.4 (**Ar**H), 128.3 (**Ar**H), 128.1 (**Ar**H), 126.9 (**Ar**H), 126.8 (**Ar**H), 126.7 (**Ar**H), 57.5 (**C**H), 51.6 (C**HH'**), 24.5 (**C**H_3); Data are consistent with literature values.[147]

7-Hexyl-5-phenyl-1-tosyl-1,2,3,4,5,7-hexahydropyrrolo[3,2-*d*][1,2]oxazine, 162A and **7-Hexyl-6-phenyl-1-tosyl-1,2,3,4,6,7-hexahydropyrrolo[2,3-*d*][1,2]oxazine, 162B**



162A



162B

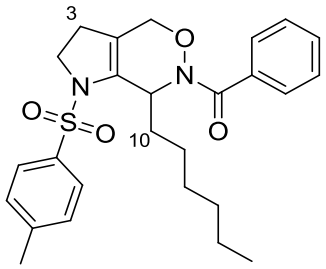
To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM (1.0 mL) was added nitrosobenzene (11 mg, 0.099 mmol, 1.1 eq.). The reaction mixture was stirred at RT for 10 min. The reaction mixture was added to DCM (10 mL), washed with sat. aq. $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5:1, pet. ether:EtOAc) to give regioisomeric products **162A** and **162B** in a 3.1:1 ratio as a yellow oil (32 mg, 0.073 mmol, 81%); For characterisation 2 mg of each regioisomer was separated by semi-preparative HPLC:

Product **162A**: HPLC (1.5% IPA in hexane, 6.5 mL/min, t_R = 5.68 min); R_f = 0.31 (5:1, pet. ether:EtOAc); δ_H (700 MHz, $CDCl_3$) 7.67 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.32 (2H, dd, *J*=8.3, 7.4 Hz *m*-Ph**H**), 7.29 (2H, d, *J*=8.1 Hz, *p*-Ts**H**), 7.09 (2H, d, *J*=8.3 Hz, *o*-Ph**H**), 7.00 (1H, t, *J*=7.4 Hz, *p*-Ph**H**), 5.05 (1H, br. d, *J*=8.5 Hz, C**H**), 3.84-3.73 (3H, m, C**HH'**NTs, C**H**H'NPh), 3.65 (1H, d, *J*=15.0 Hz, CH**H'**NPh), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.20-2.09 (2H, m, C**H**H'-3, C**H**H'-10), 1.98-1.90 (1H, m, CH**H'**-3), 1.90-1.82 (1H, m, C**H**H'-10), 1.44-1.19 (8H, m, (C$\mathbf{H_2}$)$_4$CH$_3$), 0.91-0.87 (3H, m, (CH$_2$)$_3$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 150.0 (**C**), 144.0 (**C**), 139.2 (**C**), 133.1 (**C**), 129.7 (*m*-**Ts**H), 128.9 (*m*-**Ph**H), 127.8 (*o*-**Ts**H), 122.1 (*p*-**Ph**H), 115.4 (*o*-**Ph**H), 78.3 (C**H**), 51.6 (**C**HH'NPh), 50.2 (**C**HH'NTs), 31.8 ((**C**H$_2$)$_4$CH$_3$), 31.4 (**C**HH'-10), 29.6 (**C**HH'-3), 29.3 ((**C**H$_2$)$_4$CH$_3$) 29.2 ((**C**H$_2$)$_4$CH$_3$), 22.7 ((**C**H$_2$)$_4$CH$_3$), 21.6 (Ar**C**H$_3$), 14.1

($(CH_2)_4\mathbf{C}H_3$); IR (thin film) ν_{max}/cm^{-1} 2926 w (C-H), 1354 m (SO_2), 1163 s (SO_2); LRMS *m/z* (ESI+) 903.5 ($[2M+Na]^+$, 100%), 463.2 ($[M+Na]^+$, 100%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 463.2034; $C_{25}H_{32}N_2NaO_3S^+$ requires 463.2026.

Product **162B**: HPLC (1.5% IPA in hexane, 6.5 mL/min, t_R = 5.30 min); R_f = 0.27 (5:1, pet. ether:EtOAc); δ_H (700 MHz, $CDCl_3$) 7.70 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.31 (2H, dd, *J*=8.4, 7.5 Hz, *m*-Ph**H**), 7.24 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 7.09 (2H, d, *J*=8.4 Hz, *o*-Ph**H**), 6.97 (1H, t, *J*=7.5 Hz, *p*-Ph**H**), 4.84 (1H, br. s, C**H**), 4.43 (1H, d, *J*=15.2 Hz, C**H**H'O), 4.16 (1H, d, *J*=15.2 Hz, C**H**H'O), 3.84-3.71 (2H, m, C**HH'**NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.12-2.05 (1H, m, C**H**H'-3), 1.97-1.90 (1H, m, CH**H'**-3), 1.90-1.83 (2H, m, C**HH'**-10), 1.51-1.42 (2H, m, C**HH'**-11), 1.32-1.18 (6H, m, $(C\mathbf{H_2})_3CH_3$), 0.92-0.79 (3H, m, $(CH_2)_3C\mathbf{H_3}$); IR (thin film) ν_{max}/cm^{-1} 2925 w (C-H), 1353 m (SO_2), 1163 s (SO_2); LRMS *m/z* (ESI+) 463.2 ($[M+Na]^+$, 80%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 463.2030; $C_{25}H_{32}N_2NaO_3S^+$ requires 463.2026.

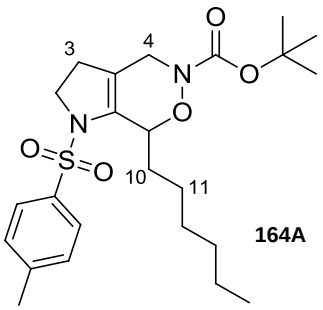
(7-Hexyl-1-tosyl-2,3-dihydropyrrolo[2,3-*d*][1,2]oxazin-6(1*H*,4*H*,7*H*)-yl)(phenyl)methanone, 163A



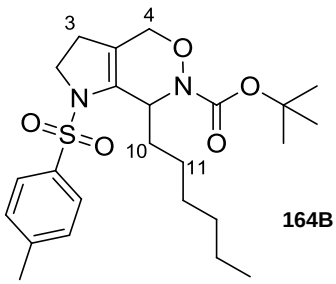
To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM (1.0 mL) was added Bu_4NIO_4 (90 mg, 0.207 mmol, 2.3 eq.). Benzohydroxamic acid (27 mg, 0.198 mmol, 2.2 eq.) was then added portionwise over 1 h. The reaction mixture was partitioned between DCM (5 mL) and sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with further DCM (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was

purified by column chromatography (30%→40% EtOAc in pet. ether) to give the title compound as a yellow oil and as a single regioisomer (40 mg, 0.085 mmol, 95%); R_f = 0.50 (3:2, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J*=6.9 Hz, *o*-Ph**H**), 7.60 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.54-7.48 (1H, m, *p*-Ph**H**), 7.28-7.52 (2H, m, *m*-Ph**H**), 7.36 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 4.79 (1H, br. d, *J*=6.9 Hz, C**H**), 4.45 (1H, d, *J*=17.2 Hz, C**H**H'O), 4.16 (1H, d, *J*=17.2 Hz, C**H**H'O), 3.82-3.67 (2H, m, C**HH'**NTs), 2.47 (3H, s, ArC$\mathbf{H_3}$), 2.09 (1H, dd, *J*=15.4, 9.5 Hz, C**H**H'-3), 2.04-1.97 (1H, m, C**H**H'-10), 1.85-1.74 (1H, m, CH**H'**-3), 1.58-1.50 (1H, m, CH**H'**-10), 1.27-1.05 (8H, m, (C$\mathbf{H_2}$)$_4$CH$_3$), 0.85 (3H, t, *J*=7.3 Hz, (CH$_2$)$_4$C$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 170.2 (**C**=O), 144.5 (**Ar**CH$_3$), 136.9 (=**C**), 133.3 (**Ph**), 132.5 (**Ar**SO$_2$), 131.2 (*p*-**Ph**H), 129.9 (*m*-Ts**H**), 128.8 (*o*-**Ph**H), 128.0 (*m*-**Ph**H), 127.6 (*o*-**Ts**H), 123.9 (=**C**), 80.8 (**C**H), 50.0 (**C**HH'NTs), 43.4 (**C**HH'O), 31.7 ((**C**H$_2$)$_4$CH$_3$), 31.1 (**C**HH'-10), 29.4 (**C**HH'-3), 28.8 ((**C**H$_2$)$_4$CH$_3$), 24.9 ((**C**H$_2$)$_4$CH$_3$), 22.5 ((**C**H$_2$)$_4$CH$_3$), 21.7 (Ar**C**H$_3$), 14.1 ((CH$_2$)$_4$**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 2928 w (C-H) 1642 w (C=C), 1354 m (SO$_2$), 1164 s (SO$_2$); LRMS *m*/*z* (ESI+) 959.5 ([2M+Na]$^+$, 100%), 491.2 ([M+Na]$^+$, 33%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 491.1974; $C_{26}H_{32}N_2NaO_4S^+$ requires 491.1975.

***tert*-Butyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydropyrrolo[3,2-*d*][1,2]oxazine-5(1*H*)-carboxylate, 164A** and ***tert*-Butyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydropyrrolo[2,3-*d*][1,2]oxazine-6(1*H*)-carboxylate, 164B**



164A



164B

To a solution of (*Z*)-2-heptylidene-3-methylene-1-tosylpyrrolidine **102a** (30 mg, 0.090 mmol, 1.0 eq.) in DCM (1.0 mL) was added Bu_4NIO_4 (90 mg, 0.207 mmol, 2.3 eq.). *N*-Boc-

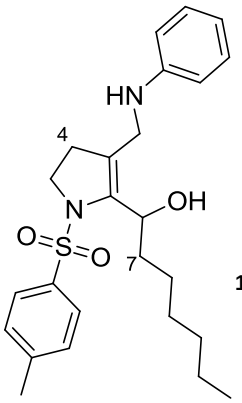
hydroxylamine (26 mg, 0.198 mmol, 2.2 eq.) was then added portionwise over 1 h. The reaction mixture was partitioned between DCM (5 mL) and sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with further DCM (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (15%→25% EtOAc in pet. ether) to give regioisomeric products **164A** and **164B** in a 1.8:1 ratio as a pale yellow oil (41 mg, 0.088 mmol, 98%); For characterisation 3 mg of each regioisomer was separated by semi-preparative HPLC:

Product **164A**: HPLC (10% IPA in hexane, 6.0 mL/min, t_R = 3.27 min); R_f = 0.73 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.61 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 7.30 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 4.99 (1H, br. d, *J*=8.8 Hz, C**H**), 4.04-3.90 (2H, m, C**HH'**-4), 3.76-3.70 (2H, m, C**HH'**NTs), 2.44 (3H, s, ArC**H$_3$**), 2.12-2.02 (2H, m, C**H**H'-10, C**H**H'-3), 1.91-1.79 (1H, CH**H'**-3), 1.78-1.68 (1H, m, CH**H'**-10), 1.68-1.59 (1H, m, C**H**H'-11) 1.55 (9H, s, C(C**H$_3$**)$_3$), 1.55-1.46 (1H, m, CH**H'**-11), 1.44-1.23 (6H, m (C**H$_2$**)$_4$$CH_3$), 0.89 (3H, t, *J*=6.9 Hz, $(CH_2)_4$C**H$_3$**); δ_C (125 MHz, $CDCl_3$) 155.0 (**C**=O), 144.3 (**Ar**CH_3), 137.6 (=**C**), 132.8 (**Ar**SO_2), 129.7 (*o*-**Ts**H), 127.6 (*m*-**Ts**H), 81.8 (**C**$(CH_3)_3$, 79.1 (**C**H), 50.0 (**C**HH'NTs), 45.1 (**C**HH'-4), 31.8 ((**C**H_2)$_3$$CH_3$), 31.2 (**C**HH'-10), 29.3 (**C**HH'-3), 29.0 ((**C**H_2)$_3$$CH_3$), 28.3 (C(**C**$H_3$)$_3$), 25.4 (**C**HH'-11), 22.7 ((**C**H_2)$_3$$CH_3$), 21.6 (Ar**C**$H_3$), 14.1 ($(CH_2)_3$**C**$H_3$); IR (thin film) ν_{max}/cm^{-1} 2928 w (C-H), 1702 br. w (C=O), 1355 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 951.5 ($[2M+Na]^+$, 100%), 487.2 ($[M+Na]^+$, 77%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 487.2236; $C_{24}H_{36}N_2NaO_5S^+$ requires 487.2237.

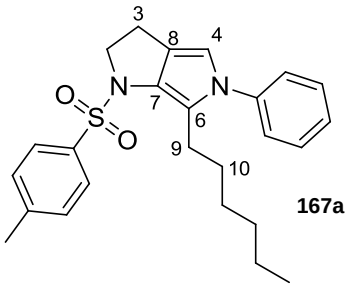
Product **164B**: HPLC (10% IPA in hexane, 6.0 mL/min, t_R = 4.10 min); R_f = 0.62 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 7.28 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 5.21 (1H, br. d, *J*=9.1 Hz, C**H**), 4.53 (1H, d, *J*=14.8 Hz, C**H**H'-4), 4.12 (1H, d, *J*=14.8 Hz, CH**H'**-4), 3.82 (1H, ddd, *J*=12.0, 10.4, 9.1 Hz, C**H**H'NTs), 3.63 (1H, ddd, *J*=12.0, 10.1, 5.0 Hz, CH**H'**NTs), 2.43 (3H, s, ArC**H$_3$**), 2.18-2.10 (1H, m, C**H**H'-3), 2.09-1.96 (2H, m,

CH**H'**-3, C**H**H'-10), 1.78-1.67 (1H, m, CH**H'**-10), 1.56 (9H, s, C(C**H**$_3$)$_3$), 1.52-1.45 (2H, m, C**HH'**-11), 1.44-1.27 (6H, m, (C**H**$_2$)$_3$CH$_3$), 0.88 (3H, t, *J*=6.7 Hz, (CH$_2$)$_3$C**H**$_3$); δ_C (125 MHz, $CDCl_3$) 143.9 (**Ar**CH_3), 136.7 (=**C**), 133.1 (**Ar**SO_2), 129.7 (*o*-**Ts**H), 127.8 (*m*-**Ts**H), 119.2 (=**C**) 81.8 (**C**(CH$_3$)$_3$, 67.6 (**C**HH'-4), 55.4 (**C**H), 49.3 (**C**HH'NTs), 31.8 ((**C**H$_2$)$_3$CH$_3$), 31.3 (**C**HH'-10), 28.7 ((**C**H$_2$)$_3$CH$_3$), 28.6 (**C**HH'-3), 28.4 (C(**C**H$_3$)$_3$), 26.3 (**C**HH'-11), 22.6 ((**C**H$_2$)$_3$CH$_3$), 21.6 (Ar**C**H$_3$), 14.2 ((CH$_2$)$_3$**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 2927 w (C-H); 1704 br. w (C=O), 1364 m (SO_2), 1165 s (SO_2); LRMS *m*/*z* (ESI+) 951.4 ([2M+Na]$^+$, 100%), 487.2 ([M+Na]$^+$, 76%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 487.2232; $C_{24}H_{36}N_2NaO_5S^+$ requires 487.2237.

1-(3-((Phenylamino)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)heptan-1-ol, 157a and **6-Hexyl-5-phenyl-1-tosyl-1,2,3,5-tetrahydropyrrolo[3,4-*b*]pyrrole, 167a**



157a



167a

To a solution of 7-hexyl-5-phenyl-1-tosyl-1,2,3,4,5,7-hexahydropyrrolo[3,2-*d*][1,2]oxazin **162A** and 7-hexyl-6-phenyl-1-tosyl-1,2,3,4,6,7-hexahydropyrrolo[2,3-*d*][1,2]oxazine **162B** (3.1:1 ratio, 30 mg, 0.068 mmol, 1.0 eq.) in MeCN:H_2O (0.7 mL:0.1 mL) was added $Mo(CO)_6$ (29 mg, 0.109 mmol, 1.6 eq.). The reaction mixture was stirred at RT for 10 min and $NaBH_4$ (6 mg, 0.136 mmol, 2.0 eq.) added. The reaction mixture was heated to 90 °C for 20 h and filtered through Celite eluting with DCM. The solution was then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude products were separated and purified by column

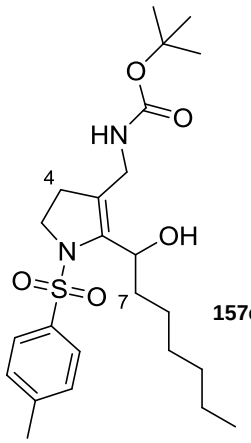
chromatography (dry loaded; 15%→25% EtOAc in pet. ether) to give title compound **157a** as a yellow oil (10 mg, 0.023 mmol, 33%) and title compound **167a** as a yellow oil (5 mg, 0.012 mmol 17%);

Product **157a**: R_f = 0.41 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.79 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.21-7.13 (4H, m, *m*-Ph**H**, *m*-Ts**H**), 6.74 (1H, t, *J*=7.4 Hz, *p*-Ph**H**), 6.55 (2H, d, *J*=8.2 Hz, *o*-Ph**H**), 4.63 (1H, t, *J*=7.3 Hz, C**H**OH), 3.88 (2H, br. d, *J*=2.8 Hz, C$\mathbf{H_2}$NH), 3.72 (1H, ddd, *J*=12.5, 8.9, 3.2 Hz, C**H**H'NTs), 3.61 (1H, ddd, *J*=12.5, 11.0, 9.3 Hz CH**H'**NTs), 2.39 (3H, s, ArC$\mathbf{H_3}$), 2.00-1.90 (3H, m, C$\mathbf{H_2}$-7, C**H**H'-4), 1.80-1.68 (1H, m, CH**H'**-4), 1.40-1.20 (8H, m (C$\mathbf{H_2}$)$_4$CH$_3$), 0.89 (3H, t, *J*=6.8 Hz, (CH$_2$)$_4$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 147.5 (**Ph**), 144.2 (**Ar**CH_3), 140.4 (=**C**), 133.7 (**Ar**SO_2), 132.6 (=**C**), 129.6 (*m*-**Ts**H), 129.3 (*m*-**Ph**H), 127.7 (*o*-**Ts**H), 118.0 (*p*-**Ph**H), 112.9 (*o*-**Ph**H), 67.2 (**C**HOH), 50.4 (**C**HH'NTs), 41.1 (**C**H_2NH), 35.3 (**C**H_2-7), 31.8 ((**C**H_2)$_4$CH$_3$), 30.6 (**C**HH'-4), 29.1 ((**C**H_2)$_4$CH$_3$), 26.2 ((**C**H_2)$_4$CH$_3$), 22.6 ((**C**H_2)$_4$CH$_3$), 21.6 (Ar**C**H$_3$), 14.1 ((CH$_2$)$_4$**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 3513 br. w (O-H), 3415 br. w (N-H), 2926 m (C-H), 1603 m (Ar), 1506 w, 1340 m (SO_2), 1159 (SO_2); LRMS *m*/*z* (ESI+) 907.5 ([2M+Na]$^+$, 100%), 465.2 ([M+Na]$^+$, 51%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 465.2185; $C_{25}H_{34}N_2NaO_3S^+$ requires 465.2182.

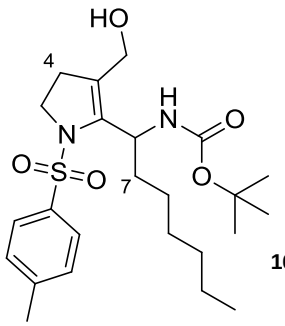
Product **167a**: R_f = 0.69 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.58 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.45 (2H, ap. t, *J*=7.6 Hz, *m*-Ph**H**), 7.36 (1H, t, *J*=7.4 Hz, *p*-Ph**H**), 7.27 (2H, d, *J*=8.0 Hz, *o*-Ph**H**), 7.19 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 6.19 (1H, s, C**H**-4), 4.17 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.83 (2H, dd, *J*=7.2, 8.3 Hz, C**HH'**-9), 2.39 (3H, s, ArC$\mathbf{H_3}$), 2.10 (2H, t, *J*=7.1 Hz C$\mathbf{H_2}$-3), 1.48-1.39 (2H, m, C**HH'**-10), 1.28-1.10 (6H, m, (C$\mathbf{H_2}$)$_3$CH$_3$), 0.80 (3H, t, *J*=7.1 Hz, (CH$_2$)$_3$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 143.5 (**Ar**CH_3) , 140.7 (**Ph**), 134.5 (**Ar**SO_2), 130.6 (**C**-7), 129.3 (*m*-**Ts**H), 129.1 (*m*-**Ph**H), 127.7 (*o*-**Ts**H), 127.1 (*p*-**Ph**H), 126.3 (*o*-**Ph**H), 122.4 (**C**-6), 121.6 (**C**-8), 112.1 (**C**-4), 58.6 (**C**H_2NTs), 31.3 ((C$\mathbf{H_2}$)$_3$CH$_3$), 29.7 ((C$\mathbf{H_2}$)$_3$CH$_3$), 28.9 ((C$\mathbf{H_2}$)$_3$CH$_3$), 28.4 (**C**HH'-10), 24.5 (**C**HH'-9), 22.9 (**C**H_2-3), 22.5 ((C$\mathbf{H_2}$)$_3$CH$_3$), 21.6 (Ar**C**H$_3$),

14.0 ($(CH_2)_3\mathbf{C}H_3$); IR (thin film) ν_{max}/cm^{-1} 2926 m (C-H), 1370 m, 1349 m (SO_2), 1163 s (SO_2); LRMS *m*/*z* (ESI+) 867.5 ($[2M+Na]^+$, 100%), 423.2 ($[M+H]^+$, 92%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 445.1920; $C_{25}H_{30}N_2NaO_2S^+$ requires 445.1920.

***tert*-Butyl ((2-(1-hydroxyheptyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-3-yl)methyl)carbamate, 157c** and ***tert*-Butyl (1-(3-(hydroxymethyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)heptyl)carbamate, 168c**



157c



168c

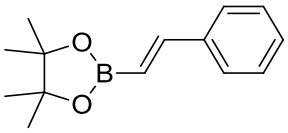
To a solution of *tert*-butyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydropyrrolo[3,2-*d*][1,2]oxazine-5(1*H*)-carboxylate **164A** and *tert*-butyl 7-hexyl-1-tosyl-2,3,4,7-tetrahydropyrrolo[2,3-*d*][1,2]oxazine-6(1*H*)-carboxylate **164B** (1.8:1 ratio, 20 mg, 0.043 mmol, 1.0 eq.) in MeCN:H_2O (0.7 mL:0.1 mL) was added $Mo(CO)_6$ (17 mg, 0.086 mmol, 1.6 eq.). The reaction mixture was stirred at RT for 10 min and $NaBH_4$ (3 mg, 0.136 mmol, 2.0 eq.) added. The reaction mixture was heated to 100 °C for 18 h and filtered through Celite eluting with DCM. The solution was then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude products were separated and purified by column chromatography (25%→60% EtOAc in pet. ether) to give title compound **157c** as a yellow oil (8.0 mg, 0.017 mmol, 40%) and title compound **168c** as a yellow oil (2.0 mg, 45 μmol, 10%):

Product **157c**: R_f = 0.33 (3:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.80 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 4.66-4.57 (1H, br. m, C**H**OH), 4.57-4.49 (1H, br. m.

N**H**), 4.05 (1H, br. d, *J*=9.5 Hz, O**H**), 3.96 (1H, dd, *J*=15.2, 6.1 Hz, C**H**H'NH), 3.78 (1H, dd, *J*=15.2, 6.1 Hz, CH**H'**NH), 3.75-3.68 (1H, m, C**H**H'NTs), 3.67-3.59 (1H, m, CH**H'**NTs), 2.44 (3H, s, ArC**H**$_3$), 1.97-1.84 (3H, m, C**H**H'-4, C**HH'**-7), 1.79-1.70 (1H, m, CH**H'**-4), 1.41 (9H, s, C(C**H**$_3$)$_3$), 1.38-1.20 (8H, m, (C**H**$_2$)$_4$CH$_3$), 0.89 (3H, t, *J*=6.8 Hz, (CH$_2$)$_4$C**H**$_3$); δ_C (125 MHz, $CDCl_3$) 155.8 (**C**=O), 144.2 (**Ar**CH_3), 140.9 (=**C**), 133.9 (**Ar**SO_2), 130.5 (=**C**) 129.6 (*m*-**Ts**H), 127.7 (*o*-Ts**H**), 79.8 (**C**$(CH_3)_3$), 67.6 (**C**HOH), 50.3 (**C**HH'NTs), 37.3 (**C**HH'NH), 35.6 (**C**HH'-7), 31.8 ((**C**H$_2$)$_4$CH$_3$), 30.4 (**C**HH'-4), 29.7 ((**C**H$_2$)$_4$CH$_3$), 29.1 ((**C**H$_2$)$_4$CH$_3$), 28.3 (C(**C**H$_3$)$_3$), 22.6 ((**C**H$_2$)$_4$CH$_3$), 21.6 (Ar**C**H$_3$), 14.1 ((CH$_2$)$_4$**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 3401 br. w (O-H), 2926 m (C-H), 1692 m (C=O), 1345 m (SO_2), 1161 s (SO_2); LRMS *m*/*z* (ESI+) 955.5 ([2M+Na]$^+$, 100%), 489.3 ([M+Na]$^+$, 30%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 489.2396; $C_{24}H_{38}N_2NaO_5S^+$ requires 489.2394.

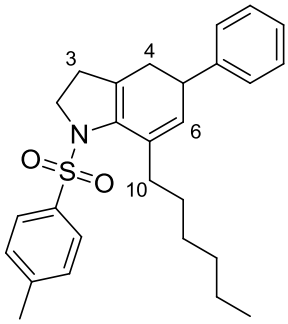
Product **168c:** R_f = 0.11 (3:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.70 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.27 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 6.01 (1H, d, *J*=9.8 Hz, N**H**), 4.76 (1H, q, *J*=8.4 Hz, C**H**NH), 4.45 (1H, dd, *J*=12.6, 2.5 Hz, C**H**H'OH), 3.95-3.83 (2H, m, CH**H'**OH, CHH'O**H**), 3.78 (1H, ddd, *J*=12.4, 8.8, 2.1 Hz, C**H**H'NTs), 3.64 (1H, td, *J*=12.4, 9.5 Hz, CH**H'**NTs), 2.43 (3H, s, ArC**H**$_3$), 2.12-1.95 (2H, m, C**H**H'-4, C**H**H'-7), 1.94-1.79 (2H, m, CH**H'**-4, CH**H'**-7), 1.50 (9H, s, C(C**H**$_3$)$_3$), 1.36-1.20 (8H, m, (C**H**$_2$)$_4$CH$_3$), 0.88 (3H, t, *J*=6.9 Hz, (CH$_2$)$_4$C**H**$_3$); δ_C (125 MHz, $CDCl_3$) 156.4 (**C**=O), 144.1 (**Ar**CH_3), 138.6 (=**C**), 134.9 (**Ar**SO_2), 133.9 (=**C**), 129.7 (*m*-**Ts**H), 127.2 (*o*-**Ts**H), 80.1 (**C**$(CH_3)_3$), 57.9 (**C**HH'OH), 50.7 (**C**HH'NTs), 46.9 (**C**HNH), 32.0 (**C**HH'-7), 31.7 ((**C**H$_2$)$_4$CH$_3$), 31.4 (**C**HH'-4), 28.9 ((**C**H$_2$)$_4$CH$_3$), 28.5 (C(**C**H$_3$)$_3$), 26.4 ((**C**H$_2$)$_4$CH$_3$), 22.6 (Ar**C**H$_3$), 21.6 ((**C**H$_2$)$_4$CH$_3$), 14.0 ((CH$_2$)$_4$**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 3428 br. w (O-H), 2928 m (C-H), 1711 m (C=O), 1689 m (C=O), 1502 m, 1346 m (SO_2), 1162 s (SO_2); LRMS *m*/*z* (ESI+) 955.5 ([2M+Na]$^+$, 96%), 489.2 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 489.2396; $C_{24}H_{38}N_2NaO_5S^+$ requires 489.2394.

(*E*)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane, 174



To a mixture of pinacolborane (1.42 mL, 97%, 10.1 mmol, 1.05 eq.) and phenylacetylene (1.08 mL, 98%, 9.60 mmol, 1.0 eq.) was added Schwartz reagent (248 mg, 0.96 mmol, 0.1 eq.). The reaction mixture was stirred at RT for 15 h and pet. ether (30 mL) added. The mixture was filtered through a silica pad and concentrated *in vacuo* to yield the title compound as a colourless solid (1.67 g, 7.24 mmol, 75%); m.p. 27-30 °C; R_f = 0.71 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.52-7.46 (2H, m, Ar**H**), 7.40 (1H, d, *J*=18.3 Hz, =C**H**Ph), 7.37-7.27 (3H, m, Ar**H**), 6.18 (1H, d, *J*=18.2 Hz, =C**H**B), 1.32 (12H, s, C**H**$_3$); δ_C (125 MHz, $CDCl_3$) 149.5 (=**C**HPh), 137.4 (**Ar**), 128.9 (Ar**H**), 128.5 (**Ar**H), 127.0 (**Ar**H), 83.3 (**C**$(CH_3)_2$), 24.8 (C(**C**$H_3)_2$). Data are consistent with literature values.[148]

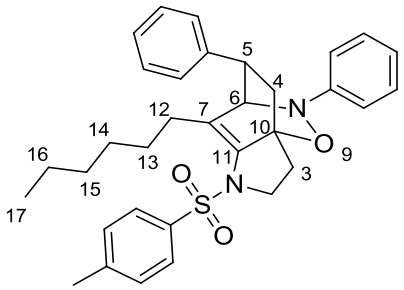
7-Hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole, 100a



To a mixture of $Pd(PPh_3)_4$ (56 mg, 0.048 mmol, 0.05 eq.) and vacuum dried Cs_2CO_3 (474 mg, 1.45 mmol, 1.5 eq.) was added a solution of *N*-(3-bromobut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **99a** (400 mg, 0.97 mmol, 1.0 eq.) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane **174** (335mg, 1.45 mmol, 1.5 eq.) in dry degassed DME (4.0 mL). The reaction mixture was heated under reflux for 24 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give

the title compound as a yellow oil (298 mg, 0.68 mmol, 71%); R_f = 0.50 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=7.9 Hz, *o*-Ts**H**), 7.41-7.25 (5H, m, Ar**H**), 7.22 (2H, d, *J*=7.9 Hz, *m*-Ts**H**), 5.62 (1H, s, C**H**-6), 3.96-3.87 (1H, m, C**H**H'NTs), 3.74-3.65 (1H, m, CH**H'**NTs), 3.65-3.55 (1H, m, C**H**Ph), 2.82-2.68 (1H, m, C**H**H'-10), 2.51-2.40 (1H, m , CH**H'**-10), 2.44 (3H, s, ArC**H$_3$**), 2.38-2.16 (2H, m, C**HH'**-4), 1.70-1.62 (2H, m, C**HH'**-3), 1.60-1.29 (8H, m, (C**H$_2$**)$_4$CH$_3$), 0.90 (3H, t, *J*=6.4 Hz, (CH$_2$)$_4$C**H$_3$**); δ_C (125 MHz, $CDCl_3$) 145.0 (**C**), 143.8 (**C**), 138.8 (**C**), 135.3 (**C**), 133.0 (**C**), 131.9 (**C**), 129.2 (Ar**H**), 128.5 (**Ar**H), 128.4 (**Ar**H), 127.5 (**Ar**H), 126.5 (**Ar**H), 125.4 (**C**H-6), 51.5 (**C**HH'NTs), 41.1 (**C**HPh), 32.4 (**C**HH'-4), 32.1 (**C**HH'-10), 31.8 ((**C**H$_2$)$_4$CH$_3$), 30.4 (**C**HH'-3), 28.9 ((**C**H$_2$)$_4$CH$_3$), 28.8 ((**C**H$_2$)$_4$CH$_3$), 22.7 ((**C**H$_2$)$_4$CH$_3$), 21.6 (Ar**C**H$_3$), 14.1 ((CH$_2$)$_4$**C**H$_3$). Data are consistent with literature values.[47]

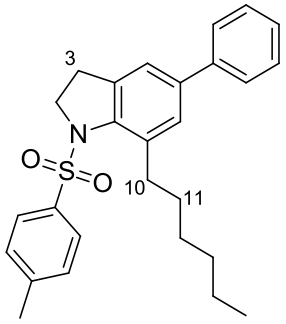
7-Hexyl-5,8-diphenyl-1-tosyl-1,2,3,4,5,6-hexahydro-3a,6-(epoxyimino)indole, 175



To a solution of 7-hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole **100a** (76 mg, 0.174 mmol, 1.0 eq.) in DCM (2.0 mL) was added nitrosobenzene (21 mg, 0.192 mmol, 1.1 eq.). The reaction mixture was stirred at RT for 18 h, added to further DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5:1, pet. ether:EtOAc) to give the title compound as a yellow oil (71 mg, 0.131 mmol, 75%); R_f = 0.28 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.38-7.32 (2H, m, C-Ar**H**) 7.29-7.17 (7H, m, Ar**H**), 6.97-6.93 (3H, m, N-Ar**H**), 4.31 (1H, d,

J=2.8 Hz C**H**-6), 4.08 (1H, ddd, *J*=12.3, 7.9, 2.2 Hz, C**H**H'NTs), 3.84 (1H, ddd, *J*=12.3, 10.9, 6.8 Hz, CH**H'**NTs), 3.81-3.76 (1H, m, C**H**Ph), 2.51 (1H, dd, *J*=13.0, 9.6 Hz, C**H**H'-4), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.06 (1H, ddd, *J*=14.0, 6.8, 2.2 Hz, C**H**H'-3), 1.93 (1H, ddd, *J*=14.1, 11.9, 5.0 Hz, C**H**H'-12), 1.76 (1H, ddd, *J*=14.1, 11.9, 5.0 Hz, CH**H'**-12), 1.71 (1H, ddd, *J*=14.0, 10.9, 7.9 Hz, CH**H'**-3), 1.34 (1H, dd, *J*=13.0, 5.4 Hz, CH**H'**-4), 1.06 (2H, quin., *J*=7.3 Hz, C$\mathbf{H_2}$-16), 0.96-0.82 (4H, m, C$\mathbf{H_2}$-14, C$\mathbf{H_2}$-15), 0.77 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-17), 0.60-0.42 (2H, m, C$\mathbf{H_2}$-13); δ_C (125 MHz, $CDCl_3$) 151.1 (N-**Ph**), 144.1 (**Ar**CH_3), 142.1 (CH-**Ph**), 136.3 (**Ar**SO_2), 135.7 (=**C**-11), 129.8 (*m*-**Ts**H), 128.5 (N-*m*-**Ph**H), 128.4 (CH-*m*-**Ph**H), 128.1 (CH-*o*-**Ph**H), 127.5 (*o*-**Ts**H), 126.9 (CH-*p*-**Ph**H), 125.6 (=**C**-7), 122.7 (N-*p*-**Ph**H), 117.8 (N-*o*-**Ph**H), 81.1 (**C**-10), 69.5 (**C**H-6), 51.4 (**C**HH'NTs), 42.8 (**C**HPh), 37.8 (**C**HH'-4), 32.4 (**C**HH'-12), 31.9 (**C**HH'-3), 31.4 (**C**H_2-15), 29.4 (**C**H_2-14), 25.7 (**C**H_2-13), 22.3 (**C**H_2-16), 21.6 (Ar**C**H_3), 14.0 (**C**H_3-17); IR (thin film) ν_{max}/cm^{-1} 2927 w (C-H), 1597 w, 1488, w, 1355 m (SO_2), 1165 s (SO_2); LRMS *m/z* (ESI+) 565.3 ($[M+Na]^+$, 100%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 565.2490; $C_{33}H_{38}N_2NaO_3S^+$ requires 565.2495.

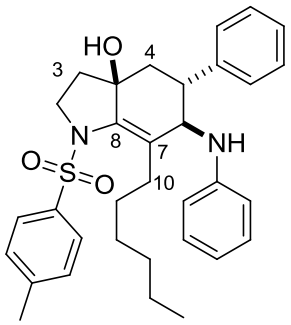
7-Hexyl-5-phenyl-1-tosylindoline, 101a



To a solution of 7-hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole **100a** (30 mg, 0.069 mmol, 1.0 eq.) in toluene (0.75 mL) was added DIAD (15 μL, 0.076 mmol, 1.0 eq.) dropwise. The reaction mixture was heated under reflux for 24 h, diluted with DCM (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was washed with further DCM (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in*

vacuo. The resulting crude product was purified by column chromatography (17:3, pet. ether:Et_2O) to give the title compound as a yellow oil (15 mg, 0.035 mmol, 50%); R_f = 0.54 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.57 (2H, d, *J*=7.8 Hz, *o*-Ph**H**), 7.47-7.38 (5H, m, *o*-Ts**H**, *m*-Ph**H**, Ar**H**), 7.34 (1H, t, *J*=7.4 Hz, *p*-Ph**H**), 7.15 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 7.11 (1H, s, Ar**H**), 3.98 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 3.09 (2H, dd, *J*=8.3, 7.4 Hz, C$\mathbf{H_2}$-10), 2.38 (3H, s, ArC$\mathbf{H_3}$), 2.16 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$-3), 1.77-1.68 (2H, m, C$\mathbf{H_2}$-11), 1.45-1.20 (6H, m, (C$\mathbf{H_2}$)$_3$CH$_3$), 0.89 (3H, t, *J*=7.0 Hz, (CH$_2$)$_3$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 144.0 (**C**), 140.7 (**C**), 140.6 (**C**), 139.9 (**C**), 138.2 (**C**), 137.6 (**C**), 134.7 (**C**), 129.4 (*m*-**Ts**H), 128.8 (**Ar**H), 127.8 (*o*-**Ts**H, *m*-**Ph**H), 127.3 (*p*-**Ph**H), 127.0 (*o*-**Ph**H), 120.6 (**Ar**H), 52.9 (**C**H$_2$NTs), 32.4 (**C**H$_2$-10), 31.8 ((**C**H$_2$)$_3$CH$_3$), 30.3 (**C**H$_2$-11), 29.4 ((**C**H$_2$)$_3$CH$_3$), 29.0 (**C**H$_2$-3), 22.7 ((**C**H$_2$)$_3$CH$_3$), 21.6 (Ar**C**H$_3$), 14.1 ((CH$_2$)$_3$**C**H$_3$). Data are consistent with literature values.[47]

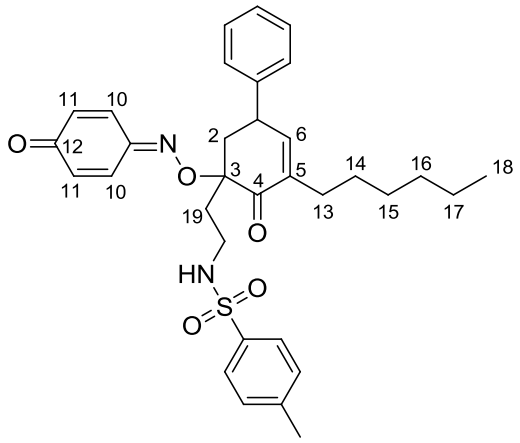
7-Hexyl-5-phenyl-6-(phenylamino)-1-tosyl-2,3,3a,4,5,6-hexahydro-1*H*-indol-3a-ol, 176



To a solution of 7-hexyl-5,8-diphenyl-1-tosyl-1,2,3,4,5,6-hexahydro-3a,6-(epoxyimino)indole **175** (24 mg, 0.044 mmol, 1.0 eq.) in MeCN:H_2O (0.7 mL:0.1 mL) was added $Mo(CO)_6$ (17 mg, 0.066 mmol, 1.6 eq.). The reaction mixture was stirred at RT for 10 min and $NaBH_4$ (5 mg, 0.132 mmol, 3.0 eq.) added. The reaction mixture was heated to 90 °C for 20 h and filtered through Celite eluting with DCM. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5:1, pet. ether:EtOAc) to give the title compound as a yellow oil (14 mg, 0.026 mmol, 58%);

R_f = 0.27 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.87 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.37 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 7.28-7.22 (2H, m CH-*m*-Ph**H**), 7.22-7.17 (1H, m, CH-*p*-Ph**H**), 7.15 (2H, d, *J*=7.3 Hz, CH-*o*-Ph**H**), 7.06 (2H, ap. t, *J*=7.9 Hz, NH-*m*-Ph**H**), 6.65 (1H, t, *J*=7.3 Hz, NH-*p*-Ph**H**), 6.48 (2H, d, *J*=7.9 Hz, NH-*o*-Ph**H**), 3.91 (1H, d, *J*=9.8 Hz, C**H**NH), 3.80 (1H, ddd, *J*=10.1, 9.5 7.8 Hz, C**H**H'NTs), 3.64 (1H, br. s, N**H**), 3.44 (1H, ddd, *J*=10.1, 9.5, 1.6 Hz, CH**H'**NTs), 3.35 (1H, ddd, *J*=13.0, 10.0, 2.5 Hz, C**H**Ph), 2.72 (1H, ddd, *J*=14.6, 9.1, 7.3 Hz, C**H**H'-10), 2.45 (3H, s, ArC$\mathbf{H_3}$), 2.23-2.15 (2H, m, CH**H'**-10, C**H**H'-4), 2.12 (1H, ddd, *J*=13.0, 7.8, 1.6 Hz, C**H**H'-3), 2.03 (1H, br. s, O**H**), 1.87 (1H, ap. t, *J*=13.4 Hz, CH**H'**-4), 1.72 (1H, ddd, *J*=13.0, 9.5, 9.5 Hz, C**H**H'-3), 1.46-1.04 (8H, m, (C$\mathbf{H_2}$)$_4$CH$_3$), 0.83 (3H, t, *J*=6.9 Hz, (CH$_2$)$_4$C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 147.5 (NH-**Ph**), 144.3 (**Ar**CH$_3$), 143.2 (CH-**Ph**), 136.5 (**C**-8), 135.5 (**C**-7), 135.0 (**Ar**SO$_2$), 129.7 (*m*-**Ts**H), 129.0 (NH-*m*-**Ph**H), 128.4 (CH-*m*-**Ph**H), 128.2 (*o*-**Ts**H), 127.9 (CH-*o*-**Ph**H), 126.7 (CH-*p*-**Ph**H), 117.6 (NH-*p*-**Ph**H), 114.4 (NH-*o*-**Ph**H), 74.7 (**C**-OH), 60.9 (**C**HNH), 47.6 (**C**HH'NTs), 42.1 (**C**HPh), 40.4 (**C**HH'-4), 38.0 (**C**HH'-3), 31.5 ((**C**H$_2$)$_4$CH$_3$), 29.6 (**C**HH'-10), 28.8 ((**C**H$_2$)$_4$CH$_3$), 27.4 ((**C**H$_2$)$_4$CH$_3$), 22.6 ((**C**H$_2$)$_4$CH$_3$), 21.6 (Ar**C**H$_3$), 14.1 ((CH$_2$)$_4$**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 3504 w (O-H), 3396 w (N-H), 2926 m (C-H), 1601 m, 1497 m, 1325 m (SO$_2$), 1159 s (SO$_2$); LRMS *m*/*z* (ESI+) 567.3 ([M+Na]$^+$, 93%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 567.2652; $C_{33}H_{40}N_2NaO_3S^+$ requires 567.2652.

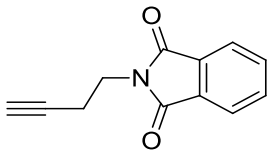
_N_-(2-(5-Hexyl-4-oxo-3-(((4-oxocyclohexa-2,5-dien-1-ylidene)amino)oxy)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-3-yl)ethyl)-4-methylbenzenesulfonamide, 178



According to the procedure of Miller and co-workers.[72] To a solution of 7-hexyl-5,8-diphenyl-1-tosyl-1,2,3,4,5,6-hexahydro-3a,6-(epoxyimino)indole **175** (35 mg, 0.064 mmol, 1.0 eq.) in EtOAc:MeCN (0.5 mL:0.5 mL) was added a solution of $NaIO_4$ (62 mg, 0.290 mmol, 4.5 eq.) in H_2O (0.5 mL), followed by $RuCl_3$ (0.5 mg, 0.0016 mmol, 0.025 eq.). The reaction mixture was stirred at RT, open to air, for 2 h. The reaction mixture was partitioned between EtOAc (5 mL) and brine (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (4:1, pet. ether:EtOAc) to give the title compound as a yellow oil (7 mg, 0.012 mmol, 19%); R_f = 0.25 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.61 (1H, dd, *J*=10.4, 2.5 Hz, C**H**-10), 7.40-7.34 (2H, m, *m*-Ph**H**), 7.33-7.28 (1H, m, *p*-Ph**H)**, 7.26 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 7.17 (2H, d, *J*=7.3 Hz, *o*-Ph**H**), 7.10 (1H, dd, *J*=10.1, 2.5 Hz, C**H**-10'), 6.62 (1H, br. s, C**H**-6), 6.54-6.47 (2H, m, C**H**-11, C**H**-11'), 4.72 (1H, t, *J*=6.0 Hz, N**H**), 3.87-3.80 (1H, m, C**H**Ph), 3.07-3.00 (2H, m, C**HH'**NH), 2.75 (1H, ddd, *J*=14.7, 4.9, 1.6 Hz, C**H**H'-2), 2.43-2.35 (1H, m, C**H**H'-13), 2.40 (3H, s, ArC$\mathbf{H_3}$), 2.20-2.11 (3H, m, C**HH'**-19, CH**H'**-13), 2.09-2.02 (1H, m, CH**H'**-2), 1.42-1.19 (8H, m, (C$\mathbf{H_2}$)$_4$), 0.88-0.82 (3H, m, C$\mathbf{H_3}$-18); 194.7 (4-**C**=O), 187.0 (12-**C**=O), 149.9 (**C**=N), 147.1 (**C**H-6), 143.4 (**Ar**CH_3), 142.8 (**Ph**), 138.3 (**C**-5), 136.7

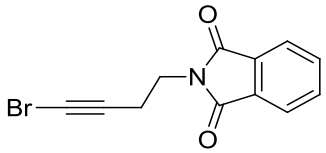
(**C**H-10'), 136.7 (**Ar**SO_2), 132.8 (**C**H-11), 130.5 (**C**H-11'), 129.7 (*m*-**Ts**H), 129.1 (*m*-**Ph**H), 127.5 (*o*-**Ph**H), 127.4 (*p*-**Ph**H), 127.1 (*o*-**Ts**H), 123.9 (**C**H-10), 85.1 (**C**-3), 41.4 (**C**HH'-2), 39.7 (**C**HPh), 38.2 (**C**HH'NH), 33.5 (**C**HH'-19), 31.6 (**C**H_2-16), 30.0 (**C**HH'-13), 28.9 (**C**H_2-15), 28.3 (**C**H_2-14), 22.6 (**C**H_2-17), 21.5 (Ar**C**H_3), 14.0 (**C**H_3-18); IR (thin film) ν_{max}/cm^{-1} 3279 br. w (N-H), 2925 m (C-H), 1685 m (C=O), 1641, s, (C=O), 1329 m (SO_2), 1159 s (SO_2), 1094 m, 988 s; LRMS *m/z* (ESI+) 597.3 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI+) found [M+Na]$^+$ 597.2401; $C_{33}H_{38}N_2NaO_5S^+$ requires 597.2394.

2-(But-3-yn-1-yl)isoindoline-1,3-dione, 186



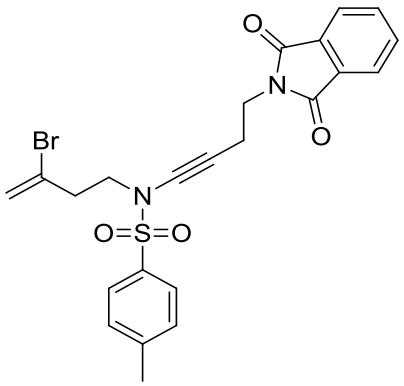
To a solution of phthalimide (5.65 g, 38.4 mmol, 1.0 eq.), 3-butyn-1-ol (3.24 mL, 42.8 mmol, 1.1 eq.) and triphenylphosphine (11.2 g, 42.8 mmol, 1.1 eq.) in toluene (45 mL) at -5 °C was added DIAD (8.81 mL, 44.7 mmol, 1.15 eq.) dropwise. The reaction mixture was stirred at RT for 2 h. MeOH (25 mL) was added and the reaction mixture stirred for a further 30 min. The colourless ppt was washed with MeOH (50 mL) and pet. ether (50 mL) and dried *in vacuo* to yield the title compound as a colourless solid (4.56 g, 22.9 mmol, 60%); m.p. 121-126 °C (Lit. m.p. 135-138 °C); δ_H (400 MHz, $CDCl_3$) 7.88-7.82 (2H, m, Ar**H**), 7.74-7.68 (2H, m, Ar**H**), 3.87 (2H, t, *J*=7.1 Hz, NC**H**$_2$), 2.60 (2H, td, *J*=7.1, 2.6 Hz, ≡CC**H**$_2$), 1.95 (1H, t, *J*=2.6 Hz, ≡C**H**); δ_C (100 MHz, $CDCl_3$) 168.0 (**C**=O), 134.0 (**Ar**H), 131.9 (**Ar**), 123.3 (**Ar**H), 80.2 (≡**C**CH_2), 70.2 (≡**C**H), 36.5 (N**C**H_2), 18.3 (≡C**C**H_2). Data are consistent with literature values.[149]

2-(4-Bromobut-3-yn-1-yl)isoindoline-1,3-dione, 187



To a suspension of 2-(but-3-yn-1-yl)isoindoline-1,3-dione **186** (200 mg, 1.00 mmol, 1.0 eq.) in acetone (10 mL) was added $AgNO_3$ (17.0 mg, 0.10 mmol, 0.1 eq.). The reaction mixture was stirred for 5 min and NBS (197 mg, 1.10 mmol, 1.1 eq.) added. The reaction mixture was stirred at RT for 1 h, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (1:1, pet. ether:Et_2O) to yield the title compound as a colourless solid (266 mg, 0.95 mmol, 96%); m.p. 86-89 °C; R_f = 0.39 (1:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.88-7.82 (2H, m, Ar**H**), 7.75-7.69 (2H, m, Ar**H**), 3.85 (2H, t, *J*=7.1 Hz, NC**H**$_2$), 2.61 (2H, t, *J*=7.1 Hz, ≡CC**H**$_2$); δ_C (100 MHz, $CDCl_3$) 167.9 (**C**=O), 134.0 (**Ar**H), 131.9 (**Ar**H), 123.2 (**Ar**H), 76.2 (≡**C**CH_2), 40.5 (≡**C**Br), 36.3 (N**C**H_2), 19.6 (≡C**C**H_2).

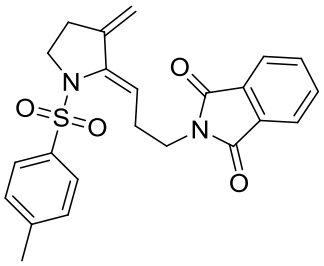
***N*-(3-Bromobut-3-en-1-yl)-*N*-(4-(1,3-dioxoisoindolin-2-yl)but-1-yn-1-yl)-4-methylbenzenesulfonamide, 188**



Synthesised from *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide **107** (1.50 g, 4.93 mmol) and 2-(4-bromobut-3-yn-1-yl)isoindoline-1,3-dione **187** (2.06 g, 7.40 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (3:1, pet. ether:EtOAc) to give the title compound as a yellow oil (1.24 g, 2.47 mmol, 50%); R_f = 0.28

(3:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.87-7.81 (2H, m, Ar**H**), 7.77-7.69 (4H, m, Ar**H**), 7.29 (2H, d, *J*=8.0 Hz, Ar**H**), 5.63-6.60 (1H, m, =C**H**H'), 5.40 (1H, d, *J*=1.7 Hz, =CH**H'**), 3.83 (2H, t, *J*=7.1 Hz, C$\mathbf{H_2}$N(phthalimide)), 3.45 (2H, t, *J*=7.2 Hz, C$\mathbf{H_2}$NTs), 2.71 (2H, t, *J*=7.1 Hz, ≡CC$\mathbf{H_2}$), 2.65 (2H, t, *J*=7.2 Hz, =CBrC$\mathbf{H_2}$), 2.43 (3H, s, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 167.8 (**C**=O), 144.4 (**C**), 134.4 (**C**), 134.0 (**Ar**H), 131.8 (**C**), 129.6 (**Ar**H), 128.8 (**C**), 127.4 (**Ar**H), 123.2 (**Ar**H), 119.5 (=**C**HH'), 74.3 (≡**C**), 66.7 (≡**C**), 49.5 (**C**H_2NTs), 39.6 (=CBr**C**H_2), 36.7 (**C**H_2N(phthalimide)), 21.5 (Ar**C**H_3), 18.4 (≡C**C**H_2); IR (thin film) ν_{max}/cm^{-1} 2923 w (C-H), 1712 s (C=O), 1396 m, 1364 m (SO_2), 1169 m (SO_2); LRMS *m*/*z* (ESI+) 523.1 ($[M+Na]^+$, ^{79}Br, 97%), 525.1 ($[M+Na]^+$, ^{81}Br, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$, ^{81}Br, 525.0271; $C_{23}H_{21}{}^{81}BrN_2NaO_4S^+$ requires 525.0278.

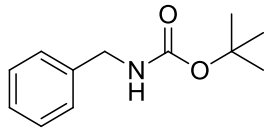
(*Z*)-2-(3-(3-Methylene-1-tosylpyrrolidin-2-ylidene)propyl)isoindoline-1,3-dione, 189



Synthesised from *N*-(3-bromobut-3-en-1-yl)-*N*-(4-(1,3-dioxoisoindolin-2-yl)but-1-yn-1-yl)-4-methylbenzenesulfonamide **188** (600 mg, 1.20 mmol) using Procedure 7, except the reaction mixture was stirred for 4 h. The resulting crude material was purified by column chromatography (1% MeOH in DCM) to give the title compound as a green/yellow oil (115 mg, 0.36 mmol, 31%); R_f = 0.34 (1% MeOH in DCM); δ_H (400 MHz, $CDCl_3$) 7.86-7.79 (2H, m, Ar**H**(phthalimide)) 7.72-7.66 (2H, m, Ar**H**(phthalimide)), 7.64 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.21 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.85 (1H, t, *J*=7.3 Hz, =C**H**(CH_2)), 5.21 (1H, t, *J*=2.4 Hz, =C**H**H'), 4.66 (1H, t, *J*=2.1 Hz, =CH**H'**), 3.86 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$N(phthalimide)), 3.46 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.93 (2H, ap. q, *J*=7.0 Hz, =CH(C$\mathbf{H_2}$)), 2.38 (3H, s, ArC$\mathbf{H_3}$), 1.82-1.75 (2H, m, =C(C$\mathbf{H_2}$)); δ_C (100 MHz, $CDCl_3$) 168.3

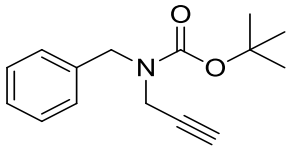
(**C**=O), 143.8 (**C**), 142.8 (**C**), 138.4 (**C**), 135.6(**C**), 133.8 (**Ar**H(phthalimide)) 132.1 (**C**), 129.5 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 123.1 (**Ar**H (phthalimide)), 116.4 (=**C**H(CH_2)), 104.8 (=**C**HH'), 48.5 (**C**H_2NTs), 37.5 (**C**H_2N(phthalimide)), 29.2 (=CH(**C**H_2)), 28.8 (=C(C**H_2**)) , 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2985 w (C-H), 1737 s (C=O), 1373 m (SO_2), 1236 s, 1044 s; LRMS *m*/*z* (ESI+) 867.3 ($[2M+Na]^+$, 96%), 445.1 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 445.1178; $C_{23}H_{22}N_2NaO_4S^+$ requires 445.1192.

***tert*-Butyl benzylcarbamate, 191**



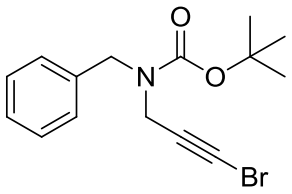
To a suspension of benzylamine (6.37 mL, 40.0 mmol, 1.0 eq.) in DCM (50 mL) was added triethylamine (6.13 mL, 44.0 mmol, 1.1 eq.). A solution of di-*tert*-butyl-dicarbonate (10.5 mL, 45.8 mmol, 1.15 eq.) in DCM (80 mL) was added dropwise. The reaction mixture was stirred at RT for 2 h and then washed with sat. aq. NH_4Cl (2 × 100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Trituration with hot hexane (60 mL) gave the title compound as a colourless solid (4.00 g, 19.2 mmol, 48%); m.p. 49-52 °C (Lit. m.p. 55-57 °C); R_f = 0.29 (4:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.38-7.21 (5H, m, Ar**H**), 4.91 (1H, br. s, N**H**), 4.31 (2H, d, *J*=5.6 Hz, PhC**H_2**), 1.47 (9H, s, C(C**H_3**)$_3$); δ_C (100 MHz, $CDCl_3$) 155.9 (**C**=O), 138.9 (**Ph**CH_2), 128.5 (**Ph**H), 127.4 (**Ph**H), 127.2 (**Ph**H), 79.4 (**C**$(CH_3)_3$), 44.6 (Ph**C**H_2), 28.4 (C(**C**H_3)$_3$). Data are consistent with literature values.[150,151]

tert-Butyl benzyl(prop-2-yn-1-yl)carbamate, 192



To a suspension of sodium hydride (695 mg, 60 wt% in mineral oil, 17.4 mmol, 1.2 eq.) in DMF (40 mL) at 0 °C was added dropwise *tert*-butyl benzylcarbamate **191** (3.00 g, 14.5 mmol, 1.0 eq.). The reaction mixture was stirred for 30 min. Propargyl bromide (2.59 g, 17.4 mmol, 1.2 eq.) was added dropwise at 0 °C. The reaction mixture was stirred at RT for 3 h and then quenched with sat. aq. NH_4Cl. (40 mL). The reaction mixture was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with H_2O (3 × 150 mL) and brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound as a yellow oil (3.74 g, 15.3 mmol, 88%); R_f = 0.62 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.40-7.21 (5H, m, Ar**H**) 4.55 (2H, s, PhC**H**$_2$), 4.11-3.83 (2H, m, ≡CC**H**$_2$), 2.21 (1H, s, ≡C**H**), 1.49 (9H, s, C(C**H**$_3$)$_3$); LRMS *m*/*z* (ESI+) 514.3 ([2M+Na]$^+$, 100%), 268.1 ([M+Na]$^+$, 92%). Data are consistent with literature values.[152,153]

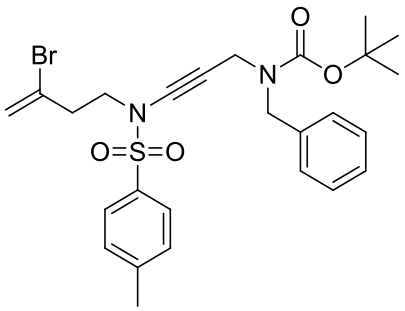
tert-Butyl benzyl(3-bromoprop-2-yn-1-yl)carbamate, 193



Synthesised from *tert*-butyl benzyl(prop-2-yn-1-yl)carbamate **192** (1.50 g, 6.11 mmol) using Procedure 1 to give the title compound as a brown oil (1.96 g, 6.05 mmol, 99%) which was used without further purification; R_f = 0.54 (3:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.40-7.21 (5H, m, Ar**H**), 4.54 (2H, s, ArC**H**$_2$), 4.12-3.84 (2H, br. m, ≡CC**H**$_2$), 1.50 (9H, s, C(C**H**$_3$)$_3$); LRMS *m*/*z* (ESI+) 669.1 ([2M+Na]$^+$, ^{79}Br^{79}Br, 87%), 671.1 ([2M+Na]$^+$, ^{79}Br^{81}Br,

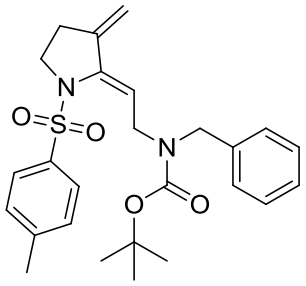
100%), 673.1 ([2M+Na]$^+$, Br^{81}Br^{81}, 83%), 346.1 ([M+Na]$^+$, ^{79}Br, 81%), 348.1 ([M+Na]$^+$, ^{81}Br, 83%).

***tert*-Butyl benzyl(3-(*N*-(3-bromobut-3-en-1-yl)-4-methylphenylsulfonamido)prop-2-yn-1-yl)carbamate, 194**



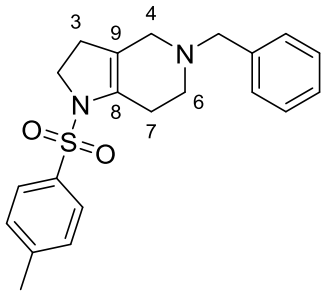
Synthesised from *N*-(3-bromobut-3-en-1-yl)-4-methylbenzenesulfonamide **107** (1.00 g, 3.29 mmol) and *tert*-butyl benzyl(3-bromoprop-2-yn-1-yl)carbamate **193** (1.60 g, 4.93 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (5:1, pet. ether:EtOAc) to give the title compound as a yellow oil (948 mg, 1.73 mmol, 53%); R_f = 0.30 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J*=8.2 Hz Ar**H**), 7.40-7.20 (7H, m, Ar**H**), 5.62 (1H, s, =C**H**H'), 5.44 (1H, s, =CH**H'**), 4.49 (2H, s, PhC$\mathbf{H_2}$), 4.22-3.98 (2H, br. m, ≡CC$\mathbf{H_2}$), 3.53 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$NTs), 2.69 (2H, t, *J*=7.9 Hz, =CBrC$\mathbf{H_2}$), 2.46 (3H, s, ArC$\mathbf{H_3}$), 1.47 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 155.1 (**C**=O), 144.7 (**C**), 134.5 (**C**), 129.8 (**Ar**H), 128.8 (**C**), 128.5 (**Ar**H), 127.6 (**C**), 127.3 (**Ar**H), 119.7 (=**C**HH'), 80.4 (≡**C**, **C**(CH$_3$)$_3$), 67.1 (≡**C**), 49.5 (**C**H$_2$NTs), 49.2 (Ph**C**H$_2$), 39.9 (=CBr**C**H$_2$), 28.3 (C(**C**H$_3$)$_3$), 21.6 (Ar**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 2253 w (C≡C), 1694 m (C=O), 1366 m (SO_2), 1170 s (SO_2); LRMS *m*/*z* (ESI+) 569.1 ([M+Na]$^+$, ^{79}Br, 99%), 571.1 ([M+Na]$^+$, ^{81}Br, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$, ^{81}Br, 571.1062; $C_{26}H_{31}{}^{81}BrN_2NaO_4S^+$ requires 571.1061.

(*Z*)-*tert*-Butyl benzyl(2-(3-methylene-1-tosylpyrrolidin-2-ylidene)ethyl)carbamate, 182a



Synthesised from *tert*-butyl benzyl(3-(*N*-(3-bromobut-3-en-1-yl)-4-methylphenylsulfonamido)prop-2-yn-1-yl)carbamate **194** (600 mg, 1.10 mmol) using Procedure 7. The resulting crude material was purified by column chromatography (4:1, pet. ether:EtOAc + 1% Et_3N) to give the title compound as a yellow oil (319 mg, 0.68 mmol, 62%); ^{1}H spectrum is broad due to the highly rotameric nature of the product. Due to the thermal instability of this compound, variable temperature analysis was not attempted and ^{13}C NMR spectroscopic analysis is not reported as signal coalescence could not be obtained; R_f = 0.51 (2:3, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.60 (2H, d, *J*=8.3 Hz, Ar**H**), 7.35-7.14 (7H, m, Ar**H**), 5.89-5.66 (1H, br. m, =C**H**(CH_2)), 5.19 (1H, t, *J*=2.4 Hz, =C**H**H'), 4.76-4.62 (1H, br. m, CH**H'**), 4.50-4.17 (4H, br. m, PhC$\mathbf{H_2}$, =CH(C$\mathbf{H_2}$)), 3.47 (2H, t, *J*=7.1 Hz, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 1.80 (2H, t, *J*=7.1 Hz, =CC$\mathbf{H_2}$), 1.50 (9H, s, C(C$\mathbf{H_3}$)$_3$); IR (thin film) ν_{max}/cm^{-1} 2973 w (C-H), 1691 m (C=O), 1359 m (SO_2), 1165 s (SO_2); LRMS *m*/*z* (ESI+) 959.4 ([2M+Na]$^+$, 100%), 491.2 ([M+Na]$^+$, 54%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 491.1969; $C_{26}H_{32}N_2NaO_4S^+$ requires 491.1975.

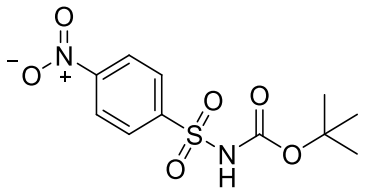
5-Benzyl-1-tosyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[3,2-*c*]pyridine, 184a



To a solution of (*Z*)-*tert*-butyl benzyl(2-(3-methylene-1-tosylpyrrolidin-2-ylidene)ethyl)carbamate **182a** (20 mg, 0.043 mol, 1.0 eq.) in DCM (1.0 mL) was added TFA (47 μL, 0.43 mmol, 10 eq.). The reaction mixture was stirred at RT for 20 min and quenched with sat. aq. $NaHCO_3$ (20 mL). The reaction was transferred to a separating funnel and DCM added (20 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (1:3, pet. ether:Et_2O) to give the title compound as a yellow oil (4 mg, 0.011 mmol, 25%); R_f = 0.28 (1:3, pet. ether:Et_2O); δ_H (500 MHz, $CDCl_3$) 7.67 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.36-7.23 (7H, m, *m*-Ts**H**, Ph**H**), 3.69 (2H, t, *J*=8.6 Hz, C$\mathbf{H_2}$NTs), 3.60 (2H, s, C$\mathbf{H_2}$Ph), 2.88 (2H, br. s, C$\mathbf{H_2}$-4), 2.64 (2H, t, *J*=5.5 Hz, C$\mathbf{H_2}$-6), 2.62-2.56 (2H, m, C$\mathbf{H_2}$-7), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.17 (2H, br. t, *J*=8.6 Hz, C$\mathbf{H_2}$-3); δ_C (125 MHz, $CDCl_3$) 143.5 (**Ar**CH_3), 138.1 (CH_2**Ph**), 134.5 (**Ar**SO_2), 134.3 (=**C**-8), 129.7 (*m*-**Ts**H), 129.0 (*o*-**Ph**H), 128.3 (*m*-**Ph**H), 127.3 (*o*-**Ts**H), 127.2 (*p*-**Ph**H), 119.6 (=**C**-9), 62.0 (**C**H_2Ph), 52.1 (**C**H_2-4), 49.9 (**C**H_2-6), 48.9 (**C**H_2NTs), 29.4 (**C**H_2-3), 25.4 (**C**H_2-7), 21.6 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2923 w (C-H), 1349 m (SO_2), 1162 s (SO_2); LRMS *m*/*z* (ESI+) 737.3 ($[2M+H]^+$, 100%), 391.2 $(M+Na]^+$, 85%), 369.2 ($[M+H]^+$, 99%); HRMS *m*/*z* (ESI+) found $[M+H]^+$ 369.1622; $C_{21}H_{25}N_2O_2S^+$ requires 369.1631.

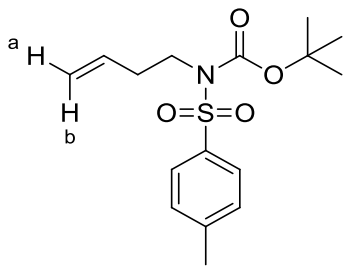
6.3.2 Enynamide precursors

tert-Butyl 4-nitrophenylsulfonylcarbamate, S3



To a suspension of 4-nitrobenzenesulfonamide (10.0 g, 49.5 mmol, 1.0 eq.) in DCM (30 mL) was added triethylamine (7.6 mL, 54.4 mmol, 1.1 eq.) and 4-dimethylaminopyridine (302 mg, 2.5 mmol, 0.05 eq.). A solution of di-*tert*-butyl-dicarbonate (12.5 mL, 54.4 mmol, 1.1 eq.) in DCM (50 mL) was added. The reaction mixture was stirred at RT for 2 h and then concentrated *in vacuo*. EtOAc (100 mL) and 1M aq. HCl (80 mL) were added and the mixture separated. The organic extract was washed with H_2O (60 mL) and brine (600 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Trituration with hot hexane (50 mL) gave the title compound as a colourless solid (13.91 g, 46.0 mmol, 93%); m.p. 150-152 °C (decomp.); R_f = 0.22 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 8.42-8.37 (2H, m, Ns**H**), 8.26-8.22 (2H, m, Ns**H**), 7.63 (1H, br. s, N**H**), 1.40 (9H, s, C(C**H**$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 150.7 (**C**=O), 148.6 (**Ns**), 144.2 (**Ns**), 129.7 (**Ns**H), 124.1 (**Ns**H), 85.1 (**C**$(CH_3)_3$), 27.8 (C(**C**$H_3)_3$).

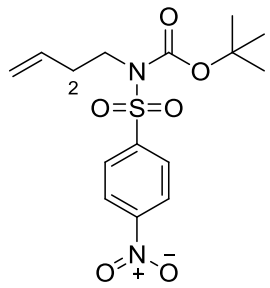
tert-Butyl but-3-en-1-yl(tosyl)carbamate, 239a



Synthesised from but-3-en-1-ol (4.00 g, 55.5 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title

compound as a colourless oil (17.28 g, 53.1 mmol, 96%); R_f = 0.51 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.80 (1H, ddt, *J*=17.2, 10.2, 6.9 Hz, =C**H**), 5.12 (1H, dd, *J*=17.2, 1.5 Hz, =CH^a**H**^{b}), 5.07 (1H, d, *J*=10.2 Hz, =C**H**^{a}H^b), 3.88 (2H, dd, *J*=8.1, 6.8 Hz, C**H**$_2$N), 2.55-2.46 (2H, m, =CHC**H**$_2$), 2.43 (3H, s, ArC**H**$_3$), 1.33 (9H, s, C(C**H**$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**CH_3), 137.4 (**Ar**SO_2), 134.4 (=**C**H), 129.2 (*m*-**Ts**H), 127.8 (*m*-**Ts**H), 117.4 (=**C**H^{a}H^b), 84.1 (**C**(CH_3)), 46.3 (**C**H_2N), 34.5 (=CH**C**H_2), 27.8 (C(**C**$H_3)_3$), 21.6 (Ar**C**H_3). Data are consistent with literature values.[154]

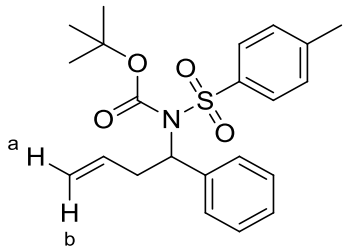
***tert*-Butyl but-3-enyl(4-nitrophenylsulfonyl)carbamate, 239b**



To a solution of 3-buten-1-ol (1.79 mL, 20.8 mmol, 1.0 eq.), triphenylphosphine (8.18 g, 31.2 mmol, 1.5 eq.) and *tert*-butyl 4-nitrophenylsulfonylcarbamate **S3** (7.55 g, 24.9 mmol, 1.2 eq.) in THF (80 mL) at 0 °C was added dropwise DIAD (5.32 mL, 27.0 mmol, 1.3 eq.). The reaction mixture was stirred at RT overnight, filtered and then concentrated *in vacuo*. The residue was then taken up in Et_2O:pet. ether (50 mL:50 mL), sonicated for 5 min and filtered. The filtrate was concentrated *in vacuo* to approximately 15 mL/mmol of alcohol at which point the resulting ppt was removed by filtration before being concentrated *in vacuo* to dryness. The resulting crude material was purified by column chromatography (5%→10% *t*-BuOMe in hexanes) to give the title compound as a brown solid (7.00 g, 19.6 mmol, 94%); m.p. 106-108 °C; R_f = 0.69 (4:1, hexanes:EtOAc); δ_H (400 MHz, $CDCl_3$) 8.38-8.33 (2H, m, Ns**H**), 8.15-8.09 (2H, m, Ns**H**), 5.80 (1H, ddt, *J*=17.1, 10.2, 7.0 Hz, =C**H**), 5.18-5.07 (2H, m,

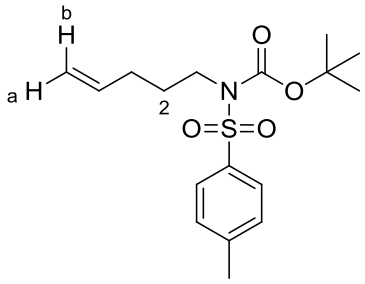
=C**HH'**), 3.95-3.87 (C**H**$_2$N), 2.51 (2H, ap. br. q, *J*=7.2 Hz, C**H**$_2$-2), 1.37 (9H, s, C(C**H**$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.4 (**C**), 150.3 (**C**), 145.8 (**C**), 133.9 (=**C**H), 129.3 (**Ns**H), 123.9 (**Ns**H), 117.9 (=**C**HH'), 85.2 (**C**(CH$_3$)$_3$), 46.7 (**C**H$_2$N), 34.6 (**C**H$_2$-2), 27.9 (C(**C**H$_3$)$_3$); IR (thin film) ν_{max}/cm^{-1} 2980 w (C-H), 1732 s (C=O), 1533 s (NO_2), 1351 s (SO_2/NO_2), 1151 s (SO_2); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 379.0932; $C_{15}H_{20}N_2NaO_6S$ requires 379.0934.

***tert*-Butyl (1-phenylbut-3-en-1-yl)(tosyl)carbamate, 239c**



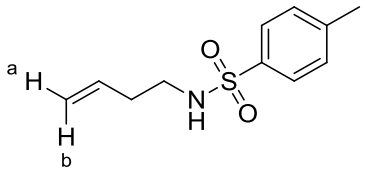
Synthesised from 1-phenylbut-3-en-1-ol (1.00 g, 6.74 mmol) using Procedure 3, except the reaction mixture was heated to 50 °C for 24 h. The resulting crude material was purified by column chromatography (dry loaded, 5%→10% Et_2O in pet. ether) to give the title compound as a colourless oil (2.18 g, 5.43 mmol, 81%); R_f = 0.68 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.43 (2H, d, *J*=7.5 Hz, *o*-Ph**H**), 7.33 (2H, t, *J*=7.5 Hz, *m*-Ph**H**), 7.30-7.25 (1H, m, *p*-Ph**H**), 7.24 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 5.91 (1H, dddd, *J*=17.1, 9.9, 7.8, 6.3 Hz, =C**H**), 5.74 (1H, dd, *J*=9.0, 6.9 Hz, C**H**), 5.20 (1H, dd, *J*=17.1, 1.4 Hz, =C**H**^{a}H^b), 5.12 (1H, br. d, *J*=9.9 Hz, =C**H**^{a}H^b), 3.21-3.00 (2H, m, C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 1.22 (9H, s, C(C**H**$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.7 (**C**=O), 143.9 (**Ph**), 139.7 (**Ar**CH$_3$), 137.2 (**Ar**SO$_2$), 135.0 (=**C**H), 128.9 (*m*-Ts**H**), 128.5 (*o*-Ts**H**), 128.1 (*m*-**Ph**H), 127.7 (*o*-**Ph**H), 127.3 (*p*-**Ph**H), 118.1 (=**C**H^{a}H^b), 84.0 (**C**(CH$_3$)$_3$), 60.1 (**C**H), 36.7 (**C**H$_2$), 27.7 (C(**C**H$_3$)$_3$), 21.5 (Ar**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 2980 w (C-H), 1727 s (C=O), 1598 w (S=O), 1350 m, 1150 s; LRMS *m*/*z* (ESI+) 825.4 ([2M+Na]$^+$, 100%), 424.2 ([M+Na]$^+$, 5%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 424.1553; $C_{22}H_{27}NNaO_4S^+$ requires 424.1553.

***tert*-Butyl pent-4-en-1-yl(tosyl)carbamate, 239d**



Synthesised from pent-4-en-1-ol (1.00 g, 11.6 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 10%→20% Et_2O in pet. ether) to give the title compound as a colourless solid (3.80 g, 11.2 mmol, 96%); m.p. 61-64 °C; R_f = 0.73 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.87 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.83 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz, =C**H**), 5.07 (1H, ddt, *J*=17.1, 1.7, 1.6 Hz, =CH^a**H**^{b}), 5.00 (1H, ddt, *J*=10.3, 1.7, 1.0 Hz, =C**H**^{a}H^b), 3.85-3.78 (2H, m, C**H**$_2$N), 2.43 (3H, s, ArC**H**$_3$), 2.12 (2H, ap. q, *J*=7.3 Hz, =CHC**H**$_2$), 1.86 (2H, quin., *J*=7.6 Hz, C**H**$_2$-2), 1.33 (9H, s, C(C**H**$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**CH_3), 137.5 (**Ar**SO_2, =**C**H), 129.2 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 115.2 (=**C**H^{a}H^b), 84.1 (**C**$(CH_3)_3$), 46.7 (**C**H_2N), 30.8 (=CH**C**H_2), 29.2 (**C**H_2-2), 27.8 (C(**C**H_3)$_3$), 21.6 (Ar**C**H_3). Data are consistent with literature values.[155]

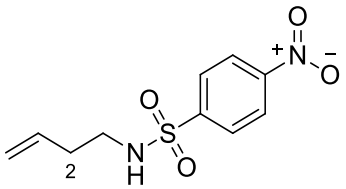
***N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide, 240a**



Synthesised from *tert*-butyl but-3-en-1-yl(tosyl)carbamate **239a** (16.8 g, 51.7 mmol) using Procedure 4 to give the title compound as a colourless oil (11.7 g, 51.9 mmol, quant.) which was used without further purification; R_f = 0.33 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.61 (1H, ddt, *J*=17.0, 10.3,

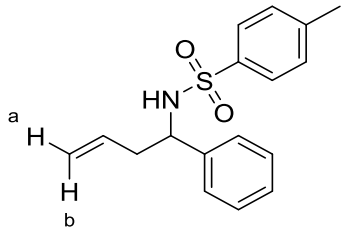
6.8 Hz, =C**H**), 5.05-4.97 (2H, m, =C**H**^{a}**H**^{b}), 4.84 (1H, br. t, *J*=6.1 Hz, N**H**), 2.99 (2H, ap. q, *J*=6.8 Hz, C**H**$_2$NH), 2.41 (3H, s, ArC**H**$_3$), 2.18 (2H, ap. q, *J*=6.8 Hz, =CHC**H**$_2$); δ_C (100 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 136.8 (**Ar**SO_2), 134.1 (=**C**H), 129.6 (*m*-**Ts**H), 127.0 (*o*-**Ts**H), 117.9 (=**C**H^{a}H^{b}), 42.1 (**C**H_2N), 33.5 (=CH**C**H_2), 21.4 (Ar**C**H_3). Data are consistent with literature values.[156]

_N_-(But-3-en-1-yl)-4-nitrobenzenesulfonamide, 240b



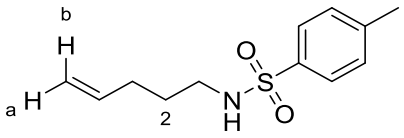
Synthesised from *tert*-butyl but-3-enyl(4-nitrophenylsulfonyl)carbamate **239b** (6.00 g, 16.8 mmol) using Procedure 4 to give the title compound as an off-white solid (3.10 g, 12.1 mmol, 72%) which was used without further purification; m.p. 74-76 °C; R_f = 0.20 (4:1, hexanes:EtOAc); δ_H (400 MHz, $CDCl_3$) 8.36 (2H, m, Ns**H**), 8.05 (2H, m, Ns**H**), 5.62 (1H, ddt, *J*=17.1, 10.3, 6.9 Hz, =C**H**), 5.12-5.02 (2H, m, =C**HH'**), 4.81 (1H, br. t, *J*=5.8 Hz, N**H**), 3.10 (2H, ap. q, *J*=6.6 Hz, C**H**$_2$NH), 2.28-2.20 (2H, m, C**H**$_2$-2); δ_C (100 MHz, $CDCl_3$) 150.1 (**Ns**), 145.9 (**Ns**), 133.6 (=**C**H), 128.3 (**Ns**H), 124.4 (**Ns**H), 118.6 (=**C**HH'), 42.2 (**C**H_2NH), 33.7 (**C**H_2-2); IR (thin film) ν_{max}/cm^{-1} 3292 br. w (N-H), 3105 w (C-H), 1732 s (C=O), 1527 s (NO_2), 1349 s (SO_2/NO_2), 1162 s (SO_2); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 279.0414; $C_{10}H_{12}N_2NaO_4S$ requires 279.0410.

4-Methyl-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide, 240c



Synthesised from *tert*-butyl (1-phenylbut-3-en-1-yl)(tosyl)carbamate **239c** (1.90 g, 4.73 mmol) using Procedure 4 to give the title compound as a colourless solid (1.34 g, 4.45 mmol, 94%) which was used without further purification; m.p. 62-64 °C; R_f = 0.32 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.21-7.10 (5H, m, *m*-Ts**H,** *o*-Ph**H**, *p*-Ph**H**), 7.10-7.03 (2H, m, *m*-Ph**H**), 5.57-5.44 (1H, m, =C**H**), 5.09-5.00 (3H, m, =C**H**^{a}**H**^{b}, N**H**), 4.37 (1H, ap. q, *J*=6.7 Hz, C**H**), 2.51-2.40 (2H, m, C$\mathbf{H_2}$), 2.36 (3H, s, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 143.1 (**Ph**), 140.3 (**Ar**CH_3), 137.5 (**Ar**SO_2), 133.1 (=**C**H), 129.3 (**Ar**H), 128.3 (**Ar**H), 127.3 (**Ar**H), 127.1 (*o*-**Ts**H), 126.5 (*m*-**Ph**H), 119.2 (=**C**H^{a}H^b), 57.1 (**C**H), 41.9 (**C**H_2), 21.4 (Ar**C**H_3). Data are consistent with literature values.[157]

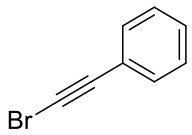
4-Methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide, 240d



Synthesised from *tert*-butyl pent-4-en-1-yl(tosyl)carbamate **239d** (3.76 g, 11.1 mmol) using Procedure 4 to give the title compound as a colourless oil (2.54 g, 10.6 mmol, 96%) which was used without further purification; R_f = 0.60 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, *o*-TsH), 7.30 (2H, d, *J*=8.2 Hz, *m*-TsH), 5.69 (1H, ddt, *J*=17.0, 10.3, 6.7 Hz, =C**H**), 5.00-4.90 (2H, m, =C**H**^{a}**H**^{b}), 4.76 (1H, br. s, N**H**), 2.93 (2H, ap. q, *J*=6.8 Hz, C$\mathbf{H_2}$NH), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.03 (2H, ap. q, *J*=7.0 Hz, =CHC$\mathbf{H_2}$), 1.55 (2H, quin., *J*=7.2 Hz, C$\mathbf{H_2}$-2); δ_C (100 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 137.2 (=**C**H), 136.9 (**Ar**SO_2), 129.7

(*m*-**Ts**H), 127.0 (*o*-**Ts**H), 115.5 (=**C**H^{a}H^b), 42.6 (**C**H$_2$N), 30.6 (=CH**C**H$_2$), 28.6 (**C**H$_2$-2), 21.5 (Ar**C**H$_3$). Data are consistent with literature values.[158]

(Bromoethynyl)benzene, 125b



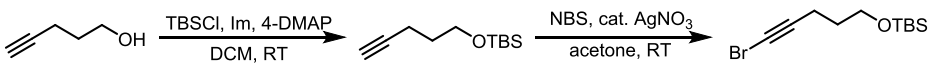
Method A

Synthesised from phenylacetylene (5.00 mL, 45.5 mmol) using Procedure 1 to give the title compound as a pale yellow oil (8.45 g, 46.7 mmol, quant.) which was used without further purification. R_f = 0.68 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.48 (2H, dd, *J*=7.7, 1.9 Hz, *o*-Ph**H**), 7.38-7.29 (3H, m, *m*-Ph**H**, *p*-Ph**H**); δ_C (100 MHz, $CDCl_3$) 132.0 (*o*-**Ph**H), 128.6 (*p*-**Ph**H), 128.3 (*m*-**Ph**H), 122.7 (**Ph**), 80.0 (≡**C**Ph), 49.7 (≡**C**Br). Data are consistent with literature values.[159]

Method B

Synthesised from phenylacetylene (5.00 mL, 45.5 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (pet. ether) to give the title compound as a yellow oil (5.99 g, 33.1 mmol, 73%). Data are in accordance with Method A.

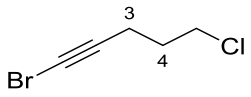
((5-Bromopent-4-yn-1-yl)oxy)(tert-butyl)dimethylsilane, 125c



Scheme 129

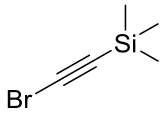
Synthesised by Dr. Craig Campbell according to literature procedure (Scheme 129).[160] Data are consistent with literature values.

1-Bromo-5-chloropent-1-yne, 125d



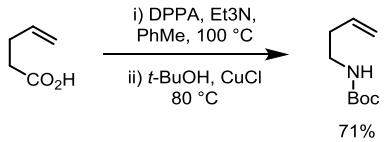
Synthesised from 5-chloropent-1-yne (2.00 g, 19.5 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (pet. ether) to give the title compound as a colourless oil (3.34 g, 18.4 mmol, 94%); R_f = 0.82 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 3.64 (2H, t, *J*=6.4 Hz, C**H**$_2$Cl), 2.41 (2H, t, *J*=6.8 Hz, C**H**$_2$-3), 1.96 (2H, ap. quin., *J*=6.5 Hz, C**H**$_2$-4); δ_C (100 MHz, $CDCl_3$) 78.4 (≡**C**CH_2), 43.4 (**C**H_2Cl), 39.0 (≡**C**Br), 31.0 (**C**H_2-4), 17.1 (**C**H_2-3).

(Bromoethynyl)trimethylsilane, 125e



Synthesised from ethynyltrimethylsilane (5.00 mL, 35.4 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (pet. ether) to give the title compound as a yellow oil (4.83g, 27.3 mmol, 77%); δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 87.0 (≡**C**Si), 61.4 (≡**C**Br), 0.28 ($Si(\mathbf{C}H_3)_3$.

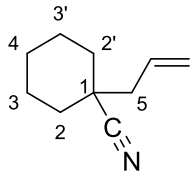
***tert*-Butyl but-3-en-1-ylcarbamate, 242**



Scheme 130

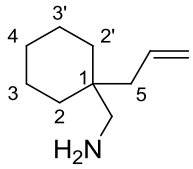
Synthesised by Dr. Craig Campbell according to Scheme 130. Data are consistent with literature values.[161]

1-Allylcyclohexanecarbonitrile, 244



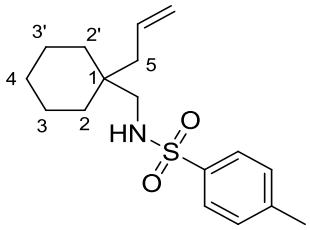
To a solution of diisopropylamine (1.54 mL, 11.0 mmol, 1.2 eq.) in THF (2.5 mL) at -78 °C was added dropwise a solution of *n*-BuLi (4.0 mL, 2.5 M in hexanes, 10.1 mmol, 1.1 eq.). The resulting pale yellow solution was warmed to 0 °C, stirred for 30 min and then cooled to -78 °C. A solution of cyclohexanecarbonitrile (1.09 mL, 9.16 mmol, 1.0 eq.) in THF (2.5 mL) was added dropwise and the reaction mixture stirred at -78 °C for 2 h. Allyl bromide (0.87 mL, 10.1 mmol, 1.1 eq.) was added dropwise, the reaction mixture stirred at RT for 15 h and then 10% aq. NH_4Cl added (30 mL). The layers were separated and the aqueous layer extracted with DCM (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (0%→5% Et_2O in pet. ether) to give the title compound as a colourless oil (1.23 g, 8.24 mmol, 90%); R_f = 0.78 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.88 (1H, ddt, *J*=17.1, 9.9, 7.3 Hz, =C**H**), 5.23-5.11 (2H, m, =C**HH'**), 2.27 (2H, d, *J*=7.3 Hz, C$\mathbf{H_2}$-5), 1.94 (2H, d, *J*=13.1 Hz, C**H**H'-2, C**H**H'-2'), 1.78-1.67 (3H, m, C**H**H'-4, C**H**H'-3, C**H**H'-3'), 1.67-1.53 (2H, m, CH**H'**-3, CH**H'**-3'), 1.29-1.10 (3H, m, CH**H'**-2, CH**H'**-2', CH**H'**-4); δ_C (100 MHz, $CDCl_3$) 131.9 (=**C**H), 123.2 (**C**≡N), 119.5 (=**C**HH'), 44.5 (**C**H_2-5), 38.7 (**C**-1), 35.2 (**C**HH'-2), 25.2 (**C**HH'-4), 22.8 (**C**HH'-3). Data are consistent with literature values.[162]

(1-Allylcyclohexyl)methanamine, S4



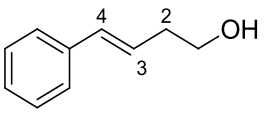
To a suspension of $LiAlH_4$ (305 mg, 8.04 mmol, 2.0 eq.) in dry Et_2O (10 mL) at 0 °C was added a solution of 1-allylcyclohexanecarbonitrile **244** (600 mg, 4.02 mmol, 1.0 eq.) in dry Et_2O (10 mL). The reaction mixture was stirred under reflux for 15 h. The solution was cooled to 0 °C, H_2O (0.3 mL) added dropwise, followed by 4 M aq. NaOH (0.3 mL), further H_2O (0.9 mL) and then excess $MgSO_4$. The reaction mixture was stirred at RT for 1 h, filtered through Celite eluting with Et_2O and concentrated *in vacuo*. The resulting crude material was dissolved in DCM (20 mL) and washed with 2 M aq. HCl (20 mL). The aqueous layer was washed with further DCM (20 mL) and then 50% aq. KOH added until the aqueous layer had pH>12. The aqueous layer was washed with DCM (3 × 20 mL), the organic washings combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (323 mg, 2.11 mmol, 52%); R_f = 0.42 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.76 (2H, ddt, *J*=16.4, 10.6, 7.6 Hz, =C**H**), 5.05-4.96 (2H, m, =C**HH'**), 2.48 (2H, s, C**H**$_2$$NH_2$), 2.02 (2H, d, *J*=7.6 Hz, C**H**$_2$-5), 1.50-1.15 (10H, m, C**HH'**-(2-4)); δ_C (100 MHz, $CDCl_3$) 134.9 (=**C**H), 116.7 (=**C**HH'), 48.7 (**C**H_2NH_2), 39.7 (**C**H_2-5), 36.9 (**C**-1), 33.1 (**C**HH'-2), 26.3 (**C**HH'-4), 21.4 (**C**HH'-3). Data are consistent with literature values.[163]

_N_-((1-Allylcyclohexyl)methyl)-4-methylbenzenesulfonamide, 245



To a solution of (1-allylcyclohexyl)methanamine **S4** (230 mg, 1.50 mmol, 1.0 eq.) and Et_3N (0.42 mL, 3.00 mmol, 2.0 eq.) in DCM (5.0 mL) at 0 ºC was added *p*-toluenesulfonyl chloride (300 mg, 1.58 mmol, 1.05 eq.) portionwise. The reaction mixture was stirred at RT for 15 h, washed with sat. aq. $NaHCO_3$ (5 mL) and then 1.0 M aq. HCl (5 mL). The organic phase was dried, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (20%→40% Et_2O in pet. ether) to give the title compound as a colourless solid (366 mg, 1.19 mmol, 79%); m.p. 67-69 °C; R_f = 0.31 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.30 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.76-5.65 (1H, m, =C**H**), 5.04-4.97 (2H, m, =C**HH'**), 4.48 (1H, t, *J*=6.8 Hz, N**H**), 2.74 (2H, d, *J*=6.9 Hz, C$\mathbf{H_2}$NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.03 (2H, d, *J*=7.6 Hz, C$\mathbf{H_2}$-5), 1.50-1.21 (10H, m, C**HH'**-(2-4)); δ_C (100 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 136.9 (**Ar**SO_2), 134.1 (=**C**H), 129.7 (*m*-**Ts**H), 127.0 (*o*-**Ts**H), 117.8 (=**C**HH'), 49.4 (**C**H_2NTs), 40.5 (**C**H_2-5), 36.3 (**C**-1), 33.3 (**C**HH'-2), 26.0 (**C**HH'-4), 21.5 (Ar**C**H_3), 21.2 (**C**HH'-3). Data are consistent with literature values.[164]

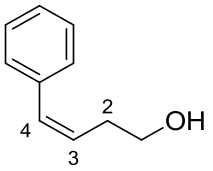
(*E*)-4-Phenylbut-3-en-1-ol, 250c



To a vial containing Grubbs II catalyst (35 mg, 0.055 mmol, 0.03 eq.) was added a solution of 3-buten-1-ol (0.12 mL, 1.39 mmol, 1.0 eq.) and styrene (0.78 mL, 6.93 mmol, 5.0 eq.) in degassed dry DCM (1.0 mL). The reaction mixture was stirred under reflux for 48 h and

concentrated *in vacuo*. The resulting crude material was purified by column chromatography (20%→40% EtOAc in pet. ether) to give the title compound as a yellow oil (88 mg, 0.47 mmol, 42%); R_f = 0.54 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.39-7.34 (2H, m, *o*-Ph**H**), 7.34-7.27 (2H, m, *m*-Ph**H**), 7.25-7.19 (1H, m, *p*-Ph**H**), 6.51 (1H, d, *J*=15.9 Hz, =C**H**-4), 6.21 (1H, dt, *J*=15.9, 7.2 Hz, =C**H**-3), 3.76 (2H, t, *J*=6.2 Hz, C$\mathbf{H_2}$OH), 2.54-2.45 (2H, m, C$\mathbf{H_2}$-2); δ_C (100 MHz, $CDCl_3$) 137.2 (**Ph**), 132.7 (=**C**H-4), 128.5 (*m*-**Ph**H), 127.2 (*p*-**Ph**H), 126.3 (=**C**H-3), 126.0 (*o*-**Ph**H), 62.0 (**C**H_2OH), 36.4(**C**H_2-2). Data are consistent with literature values.[165]

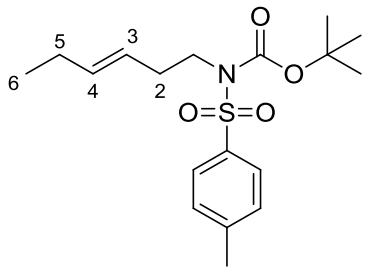
(*Z*)-4-Phenylbut-3-en-1-ol, 250d



To a suspension of $Cl_2Ni(PPh_3)_2$ (224 mg, 0.34 mmol, 0.02 eq.) in dry Et_2O (20 mL) at 0 °C was added PhMgBr (16.8 mL, 2.8 M in Et_2O, 47.8 mmol, 2.2 eq.). The reaction mixture was stirred at room temperature for 30 min and cooled to 0 °C. A solution of 2,3-dihydrofuran (1.50 g, 21.4 mmol, 10 eq.) in dry Et_2O (10 mL) was added and the reaction mixture stirred at 0 °C for 24 h. Sat. aq. NH_4Cl (40 mL) was added, the layers separated and the aqueous layer extracted with further Et_2O (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (30%→40% EtOAc in pet. ether) to give the title compound as a colourless oil (1.56 g, 10.5 mmol, 49%); R_f = 0.38 (3:2, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.40-7.23 (5H, m, Ph**H**), 6.61 (1H, d, *J*=11.6 Hz, =C**H**-4), 5.72 (1H, dt, *J*=11.6, 7.4 Hz, =C**H**-3), 3.76 (2H, t, *J*=6.6 Hz, C$\mathbf{H_2}$OH), 2.64 (2H, dtd, *J*=7.4, 6.6, 1.6 Hz, C$\mathbf{H_2}$-2), 1.69 (1H, br. s, O**H**); δ_C (100 MHz, $CDCl_3$) 137.2 (**Ph**), 131.5 (=**C**H-4), 128.7 (**Ph**H), 128.2 (=**C**H-3),

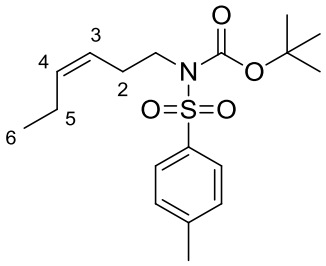
128.2 (**Ph**H), 126.8 (**Ph**H), 62.4 (**C**H_2OH), 31.9 (**C**H_2-2). Data are consistent with literature values.[166]

(*E*)-*tert*-Butyl hex-3-en-1-yl(tosyl)carbamate, 251a



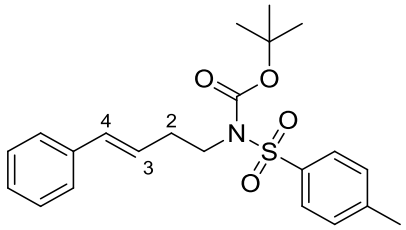
Synthesised from (*E*)-hex-3-en-1-ol (5.00 g, 49.9 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 5%→20% Et_2O in pet. ether) to give the title compound as a colourless solid (15.60 g, 44.1 mmol, 88%); m.p. 61-65 °C; R_f = 0.41 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.30 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.63-5.53 (1H, m, =C**H**-4), 5.39 (1H, dtt, *J*=15.4, 6.8, 1.3 Hz, =C**H**-3), 3.88-3.80 (2H, m, C$\mathbf{H_2}$NTs), 2.48-2.39 (2H, m, C$\mathbf{H_2}$-2), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.08 (2H, ap. quin.d, *J*=7.1, 1.3 Hz, C$\mathbf{H_2}$-5), 1.34 (9H, s, C(C$\mathbf{H_3}$)$_3$), 0.97 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**CH_3), 137.6 (**Ar**SO_2), 135.3 (=**C**H-4), 129.2 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 124.5 (=**C**H-3), 84.0 (**C**$(CH_3)_3$), 46.9 (**C**H_2NTs), 33.4 (**C**H_2-2), 27.9 (C(**C**H_3)$_3$), 25.6 (**C**H_2-5), 21.6 (Ar**C**H_3), 13.6 (**C**H_3-6). Data are consistent with literature values.[154]

(*Z*)-*tert*-Butyl hex-3-en-1-yl(tosyl)carbamate, 251b



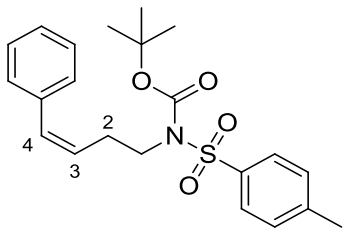
Synthesised from (*Z*)-hex-3-en-1-ol (5.00 g, 49.9 mmol) using Procedure 3. The resulting crude material was filtered through a silica pad (slurry packed in DCM) eluting with DCM (750 mL), concentrated *in vacuo* to approx. 300 mL, washed with 15% aq. H_2O_2 (600 mL), sat. aq. Na_2SO_3 (600 mL) and H_2O (500 mL). The H_2O layer was back extracted with DCM (200 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* to 100 mL, filtered through a silica pad (slurry packed in DCM) eluting with DCM (300 mL) and then concentrated *in vacuo* to dryness to give the title compound as a colourless oil (15.20 g, 43.0 mmol, 68%); R_f = 0.41 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.55-5.46 (1H, m, =C**H**-4), 5.34 (1H, dtt, *J*=10.7, 7.5, 1.3 Hz, =C**H**-3), 3.83-3.76 (2H, m, C$\mathbf{H_2}$NTs), 2.48 (2H, ap. q, *J*=7.5 Hz, C$\mathbf{H_2}$-2), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.08 (2H, ap. quin.d, *J*=7.5, 1.3 Hz, C$\mathbf{H_2}$-5), 1.33 (9H, s, C(C$\mathbf{H_3}$)$_3$), 0.96 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**CH_3), 137.5 (**Ar**SO_2), 134.8 (=**C**H-4), 129.1 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 124.0 (=**C**H-3), 84.0 (**C**$(CH_3)_3$), 46.5 (**C**H_2NTs), 28.1 (**C**H_2-2), 27.8 (C(**C**$H_3)_3$), 21.5 (Ar**C**H_3), 20.5 (**C**H_2-5), 14.2 (**C**H_3-6). Data are consistent with literature values.[154]

(*E*)-*tert*-Butyl (4-phenylbut-3-en-1-yl)(tosyl)carbamate, 251c



Synthesised from (*E*)-4-phenylbut-3-en-1-ol **250c** (120 mg, 0.81 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 20%→30% Et_2O in pet. ether) to give the title compound as a colourless oil (259 g, 0.64 mmol, 80%); R_f = 0.48 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.37-7.23 (6H, m, *m*-Ts**H**, *o*-Ph**H**, *m*-Ph**H**), 7.20 (1H, t, *J*=7.3 Hz, *p*-Ph**H**), 6.46 (1H, d, *J*=15.9 Hz, =C**H**-4), 6.19 (1 H, dt, *J*=15.9, 7.1 Hz, =C**H**-3), 3.96 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.66 (2H, ap. q, *J*=7.2 Hz, C$\mathbf{H_2}$-2), 2.42 (3H, s, ArC$\mathbf{H_3}$), 1.31 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**), 137.4 (**Ar**), 137.3 (**Ar**), 132.6 (=**C**H-4), 129.2 (Ar**H**), 128.5 (Ar**H**), 127.9 (**Ar**H), 127.2 (**Ar**H), 126.1 (**Ar**H), 126.0 (=**C**H-3), 84.1 (**C**(CH$_3$)$_3$), 46.5 (**C**H$_2$NTs), 33.8 (**C**H$_2$-2), 27.8 (C(**C**H$_3$)$_3$), 21.6 (Ar**C**H$_3$); IR (thin film) ν_{max}/cm^{-1} 2979 w (C-H), 1724 m (C=O), 1352 m (SO_2), 1153 s (SO_2); LRMS *m*/*z* (ESI+) 424.1 ([M+Na]$^+$, 100%); HRMS m/z (ESI+) found [M+Na]$^+$ 424.1535; $C_{22}H_{27}NNaO_4S$ requires 424.1553.

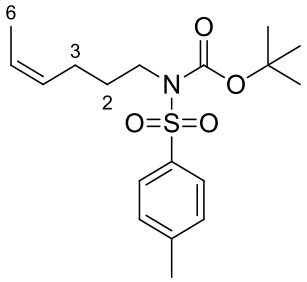
(*Z*)-*tert*-Butyl (4-phenylbut-3-en-1-yl)(tosyl)carbamate, 251d



Synthesised from (*Z*)-4-phenylbut-3-en-1-ol **250d** (500 mg, 3.37 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 20%→30% Et_2O in pet. ether) to give the title compound as a colourless oil (1.13 g, 2.81 mmol, 84%);

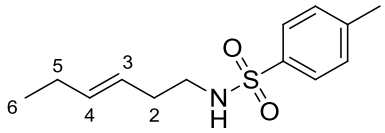
R_f = 0.40 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.38-7.29 (4H, m, *o*-Ph**H**, *m*-Ph**H**), 7.28-7.21 (3H, m, *m*-Ts**H**, *p*-Ph**H**), 6.56 (1H, d, *J*=11.7 Hz, =C**H**-4), 5.68 (1H, dt, *J*=11.7, 7.4 Hz, =C**H**-3), 3.98-3.93 (2H, m, C$\mathbf{H_2}$NTs), 2.79 (2H, ap. qd, *J*=7.4, 1.6, Hz, C$\mathbf{H_2}$-2), 2.43 (3H, s, ArC$\mathbf{H_3}$), 1.30 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (125 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**), 137.4 (**Ar**), 137.0 (**Ar**), 131.4 (=**C**H-4), 129.2 (*m*-**Ts**H), 128.7 (**Ph**H), 128.2 (**Ph**H), 127.9 (*o*-**Ts**H), 127.7 (=**C**H-3), 126.8 (*p*-**Ph**H), 84.2 (**C**$(CH_3)_3$), 46.4 (**C**H_2NTs), 29.4 (**C**H_2-2), 27.8 (C(**C**H_3)$_3$), 21.6 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2980 w (C-H), 1724 m (C=O), 1353 m (SO_2), 1153 s (SO_2); LRMS *m*/*z* (ESI+) 424.1 ([M+Na]$^+$, 76%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 424.1546; $C_{22}H_{27}NNaO_4S$ requires 424.1553.

(*Z*)-*tert*-Butyl hex-4-en-1-yl(tosyl)carbamate, 251e



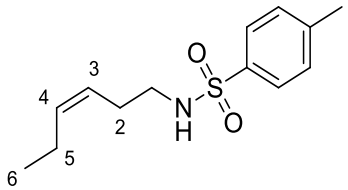
Synthesised from (*Z*)-hex-4-en-1-ol (5.00 g, 49.9 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 5%→30% Et_2O in pet. ether) to give the title compound as a colourless oil (15.62 g, 44.1 mmol, 89%); R_f = 0.50 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.55-5.35 (2H, m, =C**H**, =C**H**), 3.85-3.77 (2H, m, C$\mathbf{H_2}$NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.10 (2H, ap. q, *J*=7.2 Hz, C$\mathbf{H_2}$-3), 1.82 (2H, quin., *J*=7.6 Hz, C$\mathbf{H_2}$-2), 1.61 (3H, dd, *J*=6.3, 1.0 Hz, C$\mathbf{H_3}$-6), 1.33 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.9 (**C**=O), 144.0 (**Ar**CH_3), 137.5 (**Ar**SO_2), 129.2 (*m*-**Ts**H), 129.1 (=**C**H), 127.8 (*o*-**Ts**H), 124.7 (=**C**H), 84.0 (**C**$(CH_3)_3$), 46.8 (**C**H_2NTs), 29.9 (**C**H_2-2), 27.8 (C(**C**H_3)$_3$), 24.1 (**C**H_2-3), 21.6 (Ar**C**H_3), 12.8 (**C**H_3-6).

(*E*)-*N*-(Hex-3-en-1-yl)-4-methylbenzenesulfonamide, 252a



Synthesised from (*E*)-*tert*-butyl hex-3-en-1-yl(tosyl)carbamate **251a** (15.15 g, 42.9 mmol) using Procedure 4 to give the title compound as a colourless oil (10.52 g, 41.5 mmol, 97%) which was used without further purification; R_f = 0.40 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.2 Hz *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.45 (1H, dtt, *J*=15.3, 6.3, 1.1 Hz, =C**H**-4), 5.17 (1H, dtt, *J*=15.3, 6.8, 1.1 Hz, =C**H**-3), 4.79-4.71 (1H, br. m, N**H**), 2.94 (2H, ap. q, *J*=6.8 Hz, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.11 (2H, ap. qd, *J*=6.8, 1.1 Hz, C$\mathbf{H_2}$-2), 1.94 (2H, ap. qdd, *J*=7.5, 6.3, 1.3 Hz, C$\mathbf{H_2}$-5), 0.91 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 143.2 (**Ar**CH_3), 136.9 (**Ar**SO_2), 135.8 (=**C**H-4), 129.6 (*m*-**Ts**H), 127.0 (*o*-**Ts**H), 124.2 (=**C**H-3), 42.6 (**C**H_2NH), 32.3 (**C**H_2-2), 25.4 (**C**H_2-5), 21.4 (ArC$\mathbf{H_3}$), 13.5 (**C**H_3-6). Data are consistent with literature values.[167]

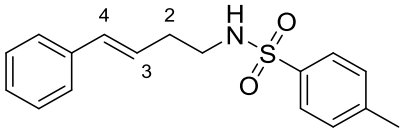
(*Z*)-*N*-(Hex-3-en-1-yl)-4-methylbenzenesulfonamide, 252b



Synthesised from (*Z*)-*tert*-butyl hex-3-en-1-yl(tosyl)carbamate **251b** (7.32 g, 20.7 mmol) using Procedure 4 to give the title compound as a pale yellow oil (5.14 g, 20.2 mmol, 98%) which was used without further purification; R_f = 0.40 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.52-5.42 (1H, m, =C**H**-4), 5.14 (1H, dtt, *J*=10.9, 7.3, 1.4 Hz, =C**H**-3), 4.68 (1H, br. s, N**H**), 2.94 (2H, ap. q, *J*=6.9 Hz, C$\mathbf{H_2}$NH), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.19 (2H, ap. q, *J*=6.8 Hz, C$\mathbf{H_2}$-2), 1.95 (2H, ap. quin.d, *J*=7.5, 1.4 Hz, C$\mathbf{H_2}$-5), 0.91 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 136.9

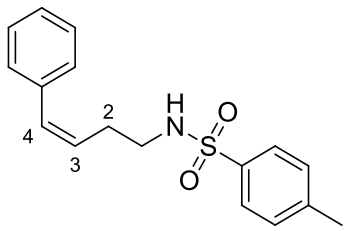
(**Ar**SO_2), 135.3 (=**C**H-4), 129.6 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 124.0 (=**C**H-3), 42.7 (**C**H_2NH), 27.2 (**C**H_2-2), 21.4 (Ar**C**H_3), 20.5 (**C**H_2-5), 14.1 (**C**H_3-6). Data are consistent with literature values.[167]

(*E*)-4-Methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide, 252c



Synthesised from (*E*)-*tert*-butyl (4-phenylbut-3-en-1-yl)(tosyl)carbamate **251c** (250 mg, 0.62 mmol) using Procedure 5 to give the title compound as a colourless oil (192 mg, 0.63 mmol, quant.) which was used without further purification; R_f = 0.33 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.35-7.13 (7H, m, *m*-Ts**H**, Ph**H**), 6.35 (1H, d, *J*=15.9 Hz, =C**H**-4), 5.97 (1H, dt, *J*=15.9, 7.1 Hz, =C**H**-3), 4.73-4.56 (1H, br. m, N**H**), 3.09 (2H, ap. q, *J*=6.5 Hz, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.36 (2H, ap. q, *J*=6.8 Hz, C$\mathbf{H_2}$-4); δ_C (100 MHz, $CDCl_3$) 143.4 (**Ar**), 136.9 (**Ar**), 136.8 (**Ar**), 133.1 (=**C**H-4), 129.7 (**Ar**H), 128.5 (**Ar**H), 127.5 (**Ar**H), 127.1 (**Ar**H), 126.1 (**Ar**), 125.5 (=**C**H-3), 42.5 (**C**H_2NTs), 33.0 (**C**H_2-2), 21.5 (Ar**C**H_3). Data are consistent with literature values.[168]

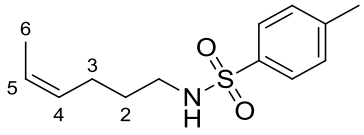
(*Z*)-4-Methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide, 252d



Synthesised from (*Z*)-*tert*-butyl (4-phenylbut-3-en-1-yl)(tosyl)carbamate **251d** (1.00 g, 2.49 mmol) using Procedure 5 to give the title compound as a colourless oil (760 mg, 2.52 mmol, quant.) which was used without further purification; R_f = 0.31 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.34-7.13 (7H, m, Ar**H**),

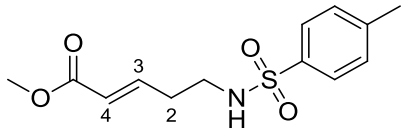
6.50 (1H, d, *J*=11.6 Hz, =C**H**-4), 5.48 (1H, dt, *J*=11.6, 7.2 Hz, =C**H**-3), 4.67 (1H, br. s, N**H**), 3.04 (2H, ap. q, *J*=6.7, C$\mathbf{H_2}$NTs), 2.46 (2H, ap. qd, *J*=7.0, 1.5 Hz, C$\mathbf{H_2}$-2), 2.39 (3H, s, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 143.3 (**Ar**), 136.8 (**Ar**), 136.7 (**Ar**), 131.9 (=**C**H-4), 129.6 (*m*-**Ts**H), 128.6 (**Ph**H), 128.2 (**Ph**H), 127.5 (=**C**H-3), 127.0 (*o*-**Ts**H), 126.9 (**Ph**H), 42.9 (**C**H_2NTs), 28.6 (**C**H_2-2), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3278 br. w (N-H), 3023 w (C-H), 1322 m (SO_2), 1155 s (SO_2); LRMS *m*/*z* (ESI+) 625.2 ($[2M+Na]^+$, 100%), 324.1 ($[M+Na]^+$, 98%); HRMS *m*/*z* (ESI+) found $[M+H]^+$ 324.1024; $C_{17}H_{19}NNaO_2S$ requires 324.1029.

(*Z*)-*N*-(Hex-4-en-1-yl)-4-methylbenzenesulfonamide, 252e



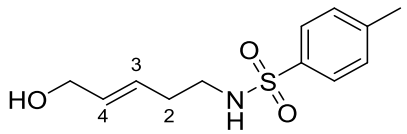
Synthesised from (*Z*)-*tert*-butyl hex-4-en-1-yl(tosyl)carbamate **251e** (13.00 g, 36.8 mmol) using Procedure 5 to give the title compound as a pale yellow oil (9.11 g, 35.9 mmol, 98%) which was used without further purification; R_f = 0.42 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.43 (1H, dqt, *J*=10.8, 6.7, 1.5 Hz, =C**H**-5), 5.31-5.20 (1H, m, =C**H**-4), 4.97-4.85 (1H, br. m, N**H**), 2.92 (2H, ap. q, *J*=6.8 Hz, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.00 (2H, ap. q, *J*=7.3 Hz, C$\mathbf{H_2}$-3), 1.57-1.45 (5H, m, C$\mathbf{H_2}$-2, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 143.2 (**Ar**CH_3), 136.9 (**Ar**SO_2), 129.6 (*m*-**Ts**H), 128.9 (=**C**H-4), 127.0 (*o*-**Ts**H), 125.0 (=**C**H-5), 42.8 (**C**H_2NTs), 29.2 (**C**H_2-2), 23.8 (**C**H_2-3), 21.4 (Ar**C**H_3), 12.7 (**C**H_3-6).

(*E*)-Methyl 5-(4-methylphenylsulfonamido)pent-2-enoate, 264



To a vial containing Grubbs II Catalyst (110 mg, 0.13 mmol, 0.1 eq.) was added a solution of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **240a** (300 mg, 1.33 mmol, 1.0 eq.) in DCM (8.0 mL). The reaction mixture was heated under reflux for 24 h. The resulting crude mixture was purified by column chromatography (20→40% Et_2O in pet. ether) to give the title compound as a brown oil (341 mg, 1.19 mmol, 90%); R_f = 0.42 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 6.78 (1H, dt, *J*=15.6, 7.1 Hz, =C**H**-3), 5.79 (1H, dd, *J*=15.6, 0.7 Hz, =C**H**-4), 5.15-4.98 (1H, br. m, N**H**), 3.69 (3H, s, C$\mathbf{H_3}$O), 3.06 (2H, ap. q, *J*=6.8 Hz, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.36 (2H, ap. qd, *J*=6.8, 0.7 Hz, C$\mathbf{H_2}$-2); δ_C (100 MHz, $CDCl_3$) 166.5 (**C**=O), 144.4 (=**C**H-3), 143.5 (**Ar**CH_3), 136.7 (**Ar**SO_2), 129.7 (*m*-**Ts**H), 127.0 (*o*-**Ts**H), 123.4 (=**C**H-4), 51.5 (**C**H_3O), 41.5 (**C**H_2NTs), 32.2 (**C**H_2-2), 21.5 (Ar**C**H_3). Data are consistent with literature values.[169]

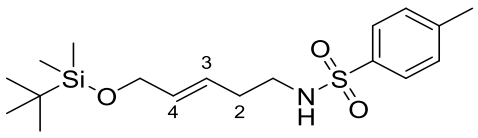
(*E*)-*N*-(5-Hydroxypent-3-en-1-yl)-4-methylbenzenesulfonamide, 258



To a solution of (E)-methyl 5-(4-methylphenylsulfonamido)pent-2-enoate **264** (110 mg, 0.39 mmol, 1.0 eq.) in DCM (4.0 mL) at -78 °C was added DIBALH (1.37 mL, 1 M in hexanes, 1.37 mmol, 3.5 eq.). The reaction mixture was stirred at -78 °C for 1 h and quenched with MeOH (1.0 mL). Celite and Na_2SO_4 were added, the reaction mixture stirred at RT for 2 h, filtered through Celite eluting with DCM and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (50%→75% EtOAc in pet.

ether) to give the title compound as a yellow oil (67 mg, 0.26 mmol, 67%); R_f = 0.19 (1:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.31 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.65 (1H, dt, *J*=15.5, 5.5 Hz, =C**H**-4), 5.52 (1H, dt, *J*=15.5, 6.7 Hz, =C**H**-3), 4.79 (1H, t, *J*=6.1 Hz, N**H**), 4.06 (2H, d, *J*=5.5 Hz, C$\mathbf{H_2}$OH), 3.01 (2H, ap. q, *J*=6.6 Hz, C$\mathbf{H_2}$NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.20 (2H, ap. q, *J*=6.7 Hz, C$\mathbf{H_2}$-2), 1.80-1.65 (1H, br. m, O**H**); δ_C (125 MHz, $CDCl_3$) 143.5 (**Ar**CH_3), 136.9 (**Ar**SO_2), 132.7 (=**C**H-4), 129.7 (*m*-**Ts**H), 127.7 (=**C**H-3), 127.1 (*o*-**Ts**H), 63.1 (**C**H_2OH), 42.3 (**C**H_2NTs), 32.2 (**C**H_2-2), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3279 br. w (O-H), 2924 m (C-H), 1320 m (SO_2), 1154 s (SO_2); LRMS *m*/*z* (ESI+) 278.1 ([M+Na]$^+$, 100%), 533.2 ([2M+Na]$^+$, 95%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 278.0820; $C_{12}H_{17}NNaO_3S^+$ requires 278.0821.

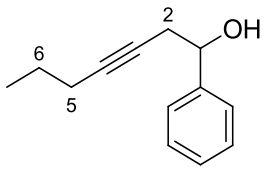
(*E*)-*N*-(5-((*tert*-Butyldimethylsilyl)oxy)pent-3-en-1-yl)-4-methylbenzenesulfonamide, 259



To a solution of TBSCl (48 mg, 0.31 mmol, 1.2 eq.), imidazole (44 mg, 0.65 mmol, 2.5 eq.) and 4-DMAP (trace, 5.2 μmol, 0.02 eq.) at 0 ºC in DCM (0.5 mL) was added a solution of (*E*)-*N*-(5-hydroxypent-3-en-1-yl)-4-methylbenzenesulfonamide **258** (67 mg, 0.26 mmol, 1.0 eq.) in DCM (0.5 mL). The reaction mixture was stirred at RT for 15 h, H_2O (1 mL) and DCM (1mL) added and the layers separated. The organic layer was washed with sat. aq. NH_4Cl (2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (4:1, pet. ether:Et_2O) to give the title compound as a yellow oil (76 mg, 0.21 mmol, 81%); R_f = 0.68 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 5.58-5.39 (2H, m, =C**H**-4, =C**H**-3), 4.80-4.69 (1H, br. m, N**H**), 4.06 (2H, dd, *J*=4.6, 1.2 Hz, C$\mathbf{H_2}$O), 2.97 (2H, ap. q,

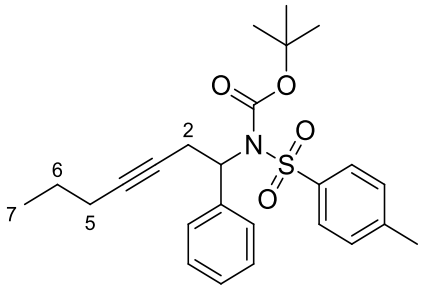
J=6.7 Hz, C**H**$_2$NTs), 2.41 (3H, s, ArC**H**$_3$), 2.22-2.12 (2H, m, C**H**$_2$-2), 0.88 (9H, s, C(C**H**$_3$)$_3$), 0.03 (6H, s, Si(C**H**$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 136.9 (**Ar**SO_2), 132.8 (=**C**H-4), 129.6 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 125.8 (=**C**H-3), 63.3 (**C**H_2O), 42.4 (**C**H_2NTs), 32.1 (**C**H_2-2), 25.9 (C(**C**H_3)$_3$), 21.4 (Ar**C**H_3), 18.3 (**C**$(CH_3)_3$), -5.3 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 3281 br. w (N-H), 2929 w (C-H), 1327 m (SO_2), 1160 s (SO_2); LRMS *m*/*z* (ESI+) 392.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 392.1690; $C_{18}H_{31}NNaO_3SSi^+$ requires 392.1686

1-Phenylhept-3-yn-1-ol, 266



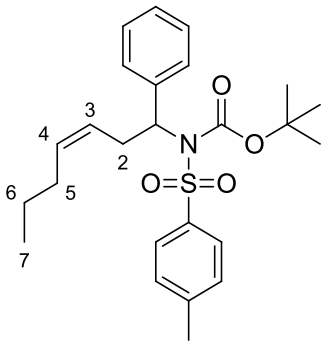
To a solution of 1-pentyne (0.41 mL, 4.16 mmol, 1.25 eq.) in dry THF (5.0 mL) at -78 °C was added dropwise *n*-BuLi (1.6 mL, 2.5 M in hexane, 4.00 mmol, 1.2 eq.). The reaction mixture was allowed to warm to RT and dry DMSO (20 mL) was added over 5 min, followed by dropwise addition of a solution of styrene oxide (0.38 mL, 3.33 mmol, 1.0 eq.) in dry THF (1.0 mL). The reaction mixture was stirred at RT for 3 h, poured into H_2O (15 mL) and extracted with Et_2O (4 × 15 mL). The combined organic layers were washed with brine (3 × 40 mL), dried, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10%→15% EtOAc in pet. ether) to give the title compound as a pale yellow oil (154 mg, 1.03 mmol, 32%); R_f = 0.34 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.40-7.23 (5H, m, Ph**H**), 4.84-4.75 (1H, br. m, C**H**Ph), 2.67-2.48 (3H, m, C**H**$_2$-2, O**H**), 2.18-2.09 (2H, m, C**H**$_2$-5), 1.50 (2H, ap. sext., *J*=7.3 Hz, C**H**$_2$-6), 0.94 (3H, t, *J*=7.3 Hz, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 142.8 (**Ph**), 128.3 (**Ph**H), 127.7 (**Ph**H), 125.7 (**Ph**H), 83.3 (≡**C**), 76.1 (≡**C**), 72.6 (**C**HPh), 30.0 (**C**H_2-2), 22.3 (**C**H_2-6), 20.7 (**C**H_2-5), 13.4 (**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3377 br. w (O-H), 2962 w (C-H); LRMS *m*/*z* (ESI+) 211.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 211.1090; $C_{13}H_{16}NaO$ requires 211.1093.

***tert*-Butyl (1-phenylhept-3-yn-1-yl)(tosyl)carbamate, 267**



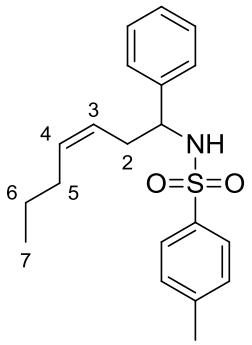
Synthesised from 1-phenylhept-3-yn-1-ol **266** (150 mg, 0.80 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 5%→10% Et_2O in pet. ether) to give the title compound as a colourless oil (253 mg, 0.57 mmol, 72%); R_f = 0.40 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.60 (2H, d, *J*=7.6 Hz, *o*-Ph**H**), 7.35-7.30 (2H, m, *m*-Ph**H**), 7.29-7.24 (3H, *m*-Ts**H**, *p*-Ph**H**), 5.78 (1H, ap. t, *J*=7.9 Hz, C**H**Ph), 3.25 (1H, dtt, *J*=8.6, 8.1, 2.3 Hz, C**H**H'-2), 3.13 (1H, dtt, *J*=8.6, 7.6, 2.3 Hz, CH**H'**-2), 2.43 (3H, s, ArC**H**$_3$), 2.02 (2H, ap. tq, *J*=7.1, 2.3 Hz, C**HH'**-5), 1.42 (2H, ap. qd, 7.3, 3.6 Hz, C**H**$_2$-6), 1.47-1.37 (2H, m, C**H**$_2$-6), 1.24 (9H, s, C(CH_3)$_3$), 0.90 (3H, t, *J*=7.3 Hz, CH_3-7); δ_C (125 MHz, $CDCl_3$) 150.6 (**C**=O), 143.9 (**Ar**), 139.3 (**Ar**), 137.3 (**Ar**), 129.0 (*m*-**Ts**H), 128.6 (*o*-**Ts**H), 128.2 (*m*-**Ph**H), 127.4 (*p*-**Ph**H), 127.2 (*o*-**Ph**H), 84.2 (**C**), 83.4 (**C**), 76.6 (**C**), 59.9 (**C**HPh), 27.8 (C(**C**H$_3$)$_3$), 23.6 (**C**HH'-2), 22.2 (**C**H$_2$-6), 21.6 (Ar**C**H$_3$), 20.8 (**C**HH'-5), 13.5 (**C**H$_3$-7); IR (thin film) ν_{max}/cm^{-1} 2965 w (C-H), 1729 m (C=O), 1358 m (SO_2), 1151 s (SO_2); LRMS *m*/*z* (ESI+) 464.3 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 464.1856; $C_{25}H_{31}NNaO_4S$ requires 464.1866.

(*Z*)-*tert*-Butyl (1-phenylhept-3-en-1-yl)(tosyl)carbamate, 268



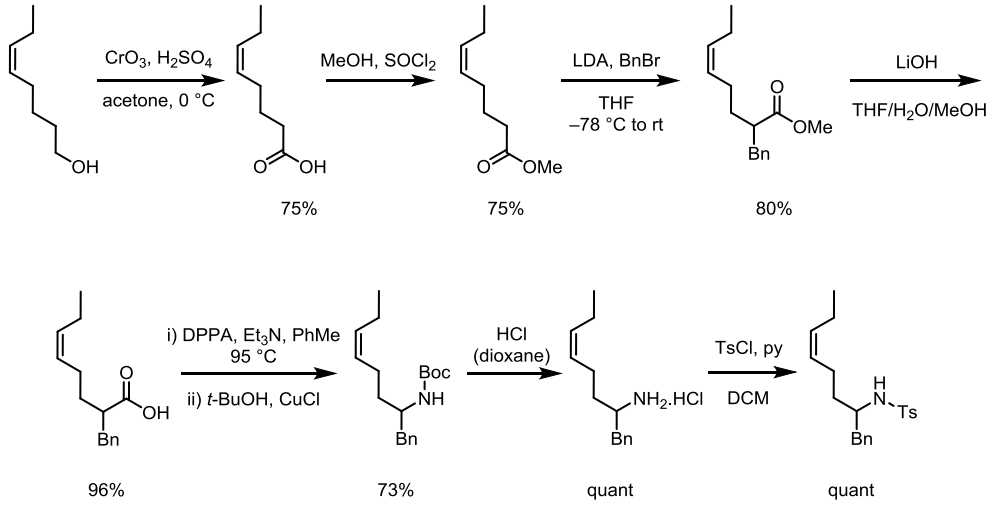
To a solution of *tert*-butyl (1-phenylhept-3-yn-1-yl)(tosyl)carbamate **267** (235 mg, 0.53 mmol, 1.0 eq.) and quinolone (12 μL, 0.11 mmol, 0.2 eq.) in toluene (5.0 mL) was added Pd on $CaCO_3$ (57 mg, 5 wt% Pd, 0.027 mmol, 0.05 eq.). H_2 (balloon, 1 atm) was bubbled through the stirred reaction mixture at room temperature for 1 h. The reaction mixture was stirred for an additional 1 h, filtered through Celite eluting with Et_2O and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (15%→20% Et_2O in pet. ether) to give the title compound as a colourless oil (225 mg, 0.51 mmol, 96%); R_f = 0.47 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.5 Hz, *o*-Ts**H**), 7.44 (2H, d, *J*=7.6 Hz, *o*-Ph**H**), 7.35-7.30 (2H, m, *m*-Ph**H**), 7.29-7.21 (3H, m, *m*-Ts**H**, *p*-Ph**H**), 5.69 (1H, dd, *J*=8.7, 7.1 Hz, C**H**Ph), 5.58-5.45 (2H, m, =C**H**-3, =C**H**-4), 3.23-3.14 (1H, m, C**H**H'-2), 3.05-2.97 (1H, m, CH**H'**-2), 2.42 (3H, s, ArC**H**$_3$), 2.16-2.02 (2H, m, C**HH'**-5), 1.38 (2H, ap. sext.d, *J*=7.4, 1.6 Hz, C**H**$_2$-6), 1.20 (9H, s, C(C**H**$_3$)$_3$), 0.91 (3H, t, *J*=7.4 Hz, C**H**$_3$-7); δ_C (125 MHz, $CDCl_3$) 150.7 (**C**=O), 143.9 (**Ar**), 140.0 (**Ar**), 137.2 (**Ar**), 132.9 (=**C**H-4), 128.9 (*m*-**Ts**H), 128.6 (*o*-**Ts**H), 128.1 (*m*-**Ph**H), 127.8 (*o*-**Ph**H), 127.3 (*p*-**Ph**H), 125.9 (=**C**H-3), 84.0 (**C**), 60.5 (**C**HPh), 30.1 (**C**HH'-2), 29.6 (**C**HH'-5), 27.7 (Ar**C**H$_3$), 22.7 (**C**H$_2$-6), 21.6 (C(**C**H$_3$)$_3$), 13.8 (**C**H$_3$-7); IR (thin film) ν_{max}/cm^{-1} 2961 w (C-H), 1728 s (C=O), 1353 m (SO_2), 1151 s (SO_2); LRMS *m*/*z* (ESI+) 466.2 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 466.2017; $C_{25}H_{33}NNaO_4S$ requires 466.2023.

(*Z*)-4-Methyl-*N*-(1-phenylhept-3-en-1-yl)benzenesulfonamide, 269



Synthesised from (*Z*)-*tert*-butyl (1-phenylhept-3-en-1-yl)(tosyl)carbamate **268** (205 mg, 0.47 mmol) using Procedure 5, except the reaction mixture was stirred at RT for 3 days, to give the title compound as a colourless oil (155 mg, 0.45 mmol, 96%) which was used without further purification; R_f = 0.31 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.57 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.20-7.11 (5H, m, *m*-Ts**H**, Ph**H**), 7.11-7.05 (2H, m, Ph**H**), 5.47-5.39 (1H, m, =C**H**-4), 5.15-5.04 (2H, m, =C**H**-3, N**H**), 4.31 (1H, ap. q, *J*=6.9 Hz, C**H**Ph), 2.54-2.46 (1H, m, C**H**H'-2), 2.46-2.38 (1H, m, CH**H'**-2), 2.36 (3H, s, ArC**H$_3$**), 1.94-1.80 (2H, m, C**HH'**-5), 1.33-1.20 (2H, m, C**HH'**-6), 0.83 (3H, t, *J*=7.4 Hz, C**H$_3$**-7); δ_C (125 MHz, $CDCl_3$) 143.0 (**Ar**), 140.5 (**Ar**), 137.4 (**Ar**), 133.9 (=**C**H-4), 129.3 (Ar**H**), 128.3 (Ar**H**), 127.3 (Ar**H**), 127.1(Ar**H**), 126.6 (Ar**H**), 123.6 (=**C**H-3), 57.7 (**C**HPh), 35.3 (**C**HH'-2), 29.3 (**C**HH'-5), 22.5 (**C**HH'-6), 21.4 (Ar**C**H$_3$), 13.7 (**C**H$_3$-7); IR (thin film) ν_{max}/cm^{-1} 3275 br. w (O-H), 2959 w (C-H), 1324 m (SO_2), 1159 s (SO_2); LRMS *m*/*z* (ESI+) 366.2 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 366.1487; $C_{20}H_{25}NNaO_2S$ requires 366.1498.

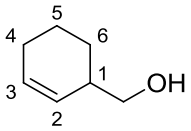
(*Z*)-4-Methyl-*N*-(1-phenyloct-5-en-2-yl)benzenesulfonamide, 277



Scheme 131

Synthesised by Dr. Craig Campbell according to Scheme 131.

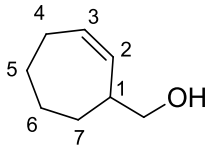
Cyclohex-2-en-1-ylmethanol, 279a



According to the procedure of Clausen and Bols.[170] To a suspension of *t*-BuOK (12.34 g, 95%, 110 mmol, 1.1 eq.) in cyclohexene (75 mL) was added slowly *n*-BuLi (40.0 mL, 2.5 M in hexane, 100 mmol, 1.0 eq.) so that the temperature remained below 40 ºC. The reaction mixture was stirred at RT overnight, heated to 60 ºC and then paraformaldehyde (3.30 g, 110 mmol, 1.1 eq.) added portionwise. The reaction mixture was stirred at 60 ºC for 1 h, allowed to cool and poured into sat. aq. NH_4Cl (30 mL) at 0 ºC. The organic phase was separated and the aqueous layer extracted with DCM (2 × 50 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and carefully concentrated *in vacuo* (≥ 50 mbar at 30 ºC). The resulting crude material was purified by distillation (76-77 ºC/20 mbar) to give the title compound as a colourless oil (8.14 g, 72.6 mmol, 73%); R_f = 0.32 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.83-5.74 (1H, m,

=C**H**-3), 5.57 (1H, dd, *J*=10.1, 2.0 Hz, =C**H**-2), 3.50 (2H, ap. t, *J*=4.9 Hz, C**HH'**OH), 2.33-2.22 (1H, m, C**H**-1), 2.07-1.90 (2H, m, C**HH'**-4), 1.81-1.66 (2H, m, C**H**H'-5, C**H**H'-6), 1.60-1.46 (1H, m, CH**H'**-5), 1.42-1.30 (1H m, CH**H'**-6); δ_C (100 MHz, $CDCl_3$) 129.4 (=**C**H-3), 127.7 (=**C**H-4), 66.9 (**C**HH'OH), 38.1 (**C**H), 25.4 (**C**HH'-6), 25.2 (**C**HH'-4), 20.9 (**C**HH'-5). Data are consistent with literature values.[171]

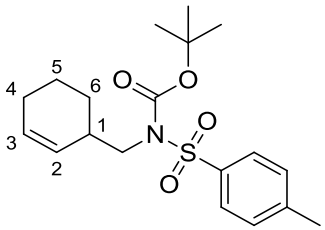
Cyclohept-2-en-1-ylmethanol, 279b



According to the procedure of Clausen and Bols.[170] To a suspension of *t*-BuOK (1.28 g, 11.4 mmol, 1.1 eq.) and cycloheptene (1.50 g, 15.6 mmol, 1.5 eq.) in cyclohexane (2.5 mL) was added slowly *n*-BuLi (4.2 mL, 2.5 M in hexane, 10.4 mmol, 1.0 eq.) so that the temperature remained below 40 ºC. The reaction mixture was stirred at RT overnight, heated to 60 ºC and then paraformaldehyde (343 mg, 11.4 mmol, 1.1 eq.) added portionwise. The reaction mixture was stirred at 60 ºC for 1 h, allowed to cool and poured into sat. aq. NH_4Cl (20 mL) at 0 ºC. The organic phase was separated and the aqueous layer extracted with DCM (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by distillation (95 ºC/20 mbar) to give the title compound as a colourless oil (617 mg, 4.88 mmol, 47%); R_f = 0.26 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.86 (1H, dddd, *J*=11.1, 7.3, 5.1, 2.4 Hz, =C**H**-3), 5.62-5.54 (1H, m, =C**H**-2), 3.60-3.49 (2H, m, C**HH'**OH), 2.45-2.35 (1H, br. m, C**H**-1), 2.22-2.04 (2H, m, C**HH'**-4), 2.02-1.93 (1H, m, C**H**H'-6), 1.75-1.65 (2H, m, C**H**H'-7, C**H**H'-5), 1.63 (1H, br. s, O**H**), 1.61-1.51 (1H, m, CH**H'**-6), 1.32 (1H, ddt, *J*=13.5, 10.6, 2.9 Hz, CH**H'**-5), 1.28-1.19 (1H, m, CH**H'**-7); δ_C (100 MHz, $CDCl_3$) 133.6 (=**C**H-2),

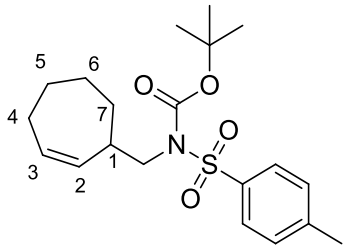
132.8 (=**C**H-3), 67.5 (**C**HH'OH), 42.7 (**C**H-1), 30.2 (**C**HH'-6), 29.9 (**C**HH'-7), 28.8 (**C**HH'-4), 26.9 (**C**HH'-5); IR (thin film) ν_{max}/cm^{-1} 3317 br. m (O-H), 2917 s (C-H).

***tert*-Butyl (cyclohex-2-en-1-ylmethyl)(tosyl)carbamate, 280a**



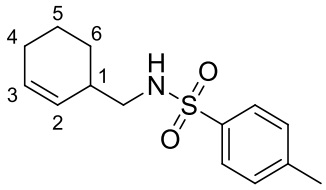
Synthesised from cyclohex-2-en-1-ylmethanol **279a** (6.00 g, 53.5 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 5%→25% Et_2O in pet. ether) to give the title compound as a colourless solid (16.96 g, 46.4 mmol, 87%); m.p. 73-75 °C; R_f = 0.50 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.83-5.74 (1H, m, =C**H**-3), 5.58 (1H, dd, *J*=10.1, 2.3 Hz, =C**H**-2), 3.80-3.74 (2H, m, C**HH'**NTs), 2.69-2.57 (1H, br. m, C**H**-1), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.05-1.96 (2H, br. m, C**HH'**-4), 1.85-1.69 (2H, m, C**H**H'-6, C**H**H'-5), 1.61-1.49 (1H, m, CH**H'**-5), 1.49-1.33 (1H, m, CH**H'**-6), 1.32 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 151.2 (**C**=O), 144.0 (**Ar**CH_3), 137.5 (**Ar**SO_2), 129.2 (*m*-**Ts**H), 129.0 (=**C**H-3), 127.8 (*o*-**Ts**H), 127.6 (=C**H**-2), 84.1 (**C**$(CH_3)_3$), 51.3 (**C**HH'NTs), 35.6 (**C**H-1), 27.8 (C(**C**$H_3)_3$), 26.1 (**C**HH'-6), 25.3 (**C**HH'-4), 21.6 (Ar**C**H_3), 20.4 (**C**HH'-5); IR (thin film) ν_{max}/cm^{-1} 2930 w (C-H), 1719 s (C=O), 1354 m (SO_2), 1135 s (SO_2); LRMS *m*/*z* (ESI+) 753.3 ($[2M+Na]^+$, 100%), 388.1 ($[M+Na]^+$, 83%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 388.1551; $C_{19}H_{27}NNaO_4S$ requires 388.1553.

***tert*-Butyl (cyclohept-2-en-1-ylmethyl)(tosyl)carbamate, 280b**



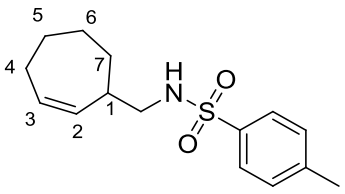
Synthesised from cyclohept-2-en-1-ylmethanol **279b** (300 mg, 2.38 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 9:1, pet. ether:Et_2O) to give the title compound as a colourless solid (740 mg, 1.94 mmol, 82%); m.p. 84-86 °C; R_f = 0.67 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.86 (1H, dddd, *J*=11.2, 7.3, 5.1, 2.2 Hz, =C**H**-3), 5.62-5.56 (1H, m, =C**H**-2), 3.88 (1H, dd, *J*=14.2, 7.8 Hz, C**H**H'NTs), 3.77 (1H, dd, *J*=14.2, 7.9 Hz, CH**H'**NTs), 2.87-2.77 (1H, m, C**H**-1), 2.43 (3H, ArC$\mathbf{H}_3$), 2.23-2.06 (2H, m, C**HH'**-4), 2.05-1.95 (1H, m, C**H**H'-6), 1.74-1.64 (2H, m, C**H**H'-7, C**H**H'-5), 1.64-1.53 (1H, m, CH**H'**-6), 1.39-1.17 (2H, m, CH**H'**-5, CH**H'**-7), 1.31 (9H, s, C(C$\mathbf{H}_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 151.3 (**C**=O), 144.0 (**Ar**CH_3), 137.6 (**Ar**SO_2), 133.2 (=**C**H-2), 132.8 (=**C**H-3), 129.2 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 84.2 (**C**$(CH_3)_3$), 51.6 (**C**HH'NTs), 40.0 (**C**H-1), 30.4 (**C**HH'-7), 30.2 (**C**HH'-6), 28.7 (**C**HH'-4), 27.8 (C(**C**$H_3)_3$), 26.8 (**C**HH'-5), 21.6 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2922 w (C-H), 1724 m (C=O), 1353 m (SO_2), 1152 s (SO_2); LRMS *m*/*z* (ESI+) 781.3 ([2M+Na]$^+$, 100%), 402.2 ([M+Na]$^+$, 77%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 402.1695; $C_{20}H_{29}NNaO_4S^+$ requires 402.1710.

_N_-(Cyclohex-2-en-1-ylmethyl)-4-methylbenzenesulfonamide, 281a



Synthesised from *tert*-butyl (cyclohex-2-en-1-ylmethyl)(tosyl)carbamate **280a** (9.40 g, 25.7 mmol) using Procedure 5 to give the title compound as a colourless solid (6.75 mg, 25.4 mmol, 99%) which was used without further purification; m.p. 43-45 °C; R_f = 0.26 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.78-5.70 (1H, m, =C**H**-3), 5.42 (1H, dd, *J*=10.1, 2.0 Hz, =C**H**-2), 4.88-4.79 (1H, br. m, N**H**), 2.94-2.84 (1H, m, C**H**H'NTs), 2.84-2.75 (1H, m, CH**H'**NTs), 2.41 (3H, s, ArC**H**$_3$), 2.29-2.18 (1H, br. m, C**H**-1), 1.97-1.89 (2H, br. m, C**HH'**-4), 1.76-1.59 (2H, m, C**H**H'-6, C**H**H'-5), 1.52-1.39 (1H, m, CH**H'**-5), 1.33-1.21 (1H, m, **C**HH'-6); δ_C (100 MHz, $CDCl_3$) 143.2 (**Ar**CH_3), 136.9 (**Ar**SO_2), 130.0 (=**C**H-3), 129.6 (*m*-**Ts**H), 127.4 (=**C**H-2), 127.0 (*o*-**Ts**H), 47.8 (**C**HH'NTs), 35.2 (**C**H-1), 26.2 (**C**HH'-6), 25.0 (**C**HH'-4), 21.5 (Ar**C**H_3), 20.7 (**C**HH'-5); IR (thin film) ν_{max}/cm^{-1} 3287 br. w (N-H), 2925 w (C-H), 1719 s (C=O), 1332 m (SO_2), 1159 s (SO_2); LRMS *m*/*z* (ESI+) 553.2 ([2M+Na]$^+$, 100%), 288.1 ([M+Na]$^+$, 93%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 288.1039; $C_{14}H_{19}NNaO_2S$ requires 288.1029.

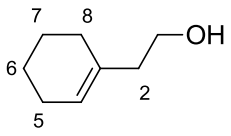
_N_-(Cyclohept-2-en-1-ylmethyl)-4-methylbenzenesulfonamide, 281b



Synthesised from *tert*-butyl (cyclohept-2-en-1-ylmethyl)(tosyl)carbamate **280b** (690 mg, 1.82 mmol) using Procedure 5 to give the title compound as a colourless solid (462 mg, 1.65 mmol, 91%) which was used without further purification; m.p. 71-73 °C; R_f = 0.32 (4:1,

pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.31 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.81 (1H, dddd, *J*=11.1, 7.4, 5.3, 2.4 Hz, =C**H**-3), 5.45-5.38 (1H, m, =C**H**-2), 4.50 (1H, t, *J*=6.1 Hz, N**H**), 2.95-2.85 (2H, m, C**HH'**NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.39-2.30 (1H, br. m, C**H**-1), 2.18-2.08 (1H, m, C**H**H'-4), 2.07-1.97 (1H, m, CH**H'**-4), 1.95-1.86 (1H, m, C**H**H'-6), 1.69-1.55 (2H, m, C**H**H'-5, C**H**H'-7), 1.54-1.42 (1H, m, CH**H'**-6), 1.33-1.16 (2H, m, CH**H'**-5, CH**H'**-7); δ_C (125 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 136.9 (**Ar**SO_2), 133.4 (=**C**H-3), 133.2 (=**C**H-2), 129.7 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 48.5 (**C**HH'NTs), 39.6 (**C**H-1), 30.8 (**C**HH'-7), 29.9 (**C**HH'-6), 28.6 (**C**HH'-4), 26.6 (**C**HH'-5), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3281 br. w (N-H), 2921 w (C-H), 1719 s (C=O), 1325 m (SO_2), 1158 s (SO_2); LRMS *m/z* (ESI+) 581.8 ($[2M+Na]^+$, 87%), 302.1 ($[M+Na]^+$, 71%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 302.1180; $C_{15}H_{21}NNaO_2S$ requires 302.1185.

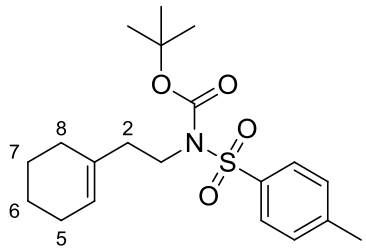
2-(Cyclohex-1-en-1-yl)ethanol, 287



To a suspension of $LiAlH_4$ (183 mg, 4.82 mmol, 1.5 eq.) in dry THF (4 mL) at 0 °C was added a solution of 2-(cyclohex-1-en-1-yl)acetic acid (450 mg, 3.21 mmol, 1.0 eq.) in dry THF (4 mL). The reaction mixture was stirred at RT for 5 h. The solution was cooled to 0 °C, H_2O (0.2 mL) added dropwise, followed by 4 M aq. NaOH (0.2 mL), further H_2O (0.6 mL) and then excess $MgSO_4$. The reaction mixture was stirred at RT for 1 h, filtered through Celite eluting with Et_2O and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (20%→30% EtOAc in pet. ether) to give the title compound as a colourless oil (131 mg, 1.03 mmol, 32%); R_f = 0.38 (7:3, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.49 (1H, br. s, =C**H**), 3.66 (2H, t, *J*=6.3 Hz, C$\mathbf{H_2}$OH), 2.21 (2H, t, *J*=6.3 Hz, C$\mathbf{H_2}$-2), 2.07-1.88 (4H, m, C$\mathbf{H_2}$-5, C$\mathbf{H_2}$-8), 1.70-1.49 (4H, m, C$\mathbf{H_2}$-6, C$\mathbf{H_2}$-7); δ_C (100 MHz, $CDCl_3$)

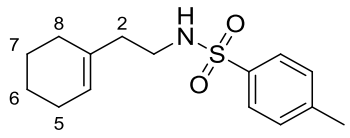
134.0 (=**C**), 124.1 (=**C**H), 60.1 (**C**H_2OH), 41.0 (**C**H_2-2), 27.9 (**C**H_2-(5-8)), 25.2 (**C**H_2-(5-8)), 22.8 (**C**H_2-(5-8)), 22.3 (**C**H_2-(5-8)). Data are consistent with literature values.[172]

***tert*-Butyl (2-(cyclohex-1-en-1-yl)ethyl)(tosyl)carbamate, 288**



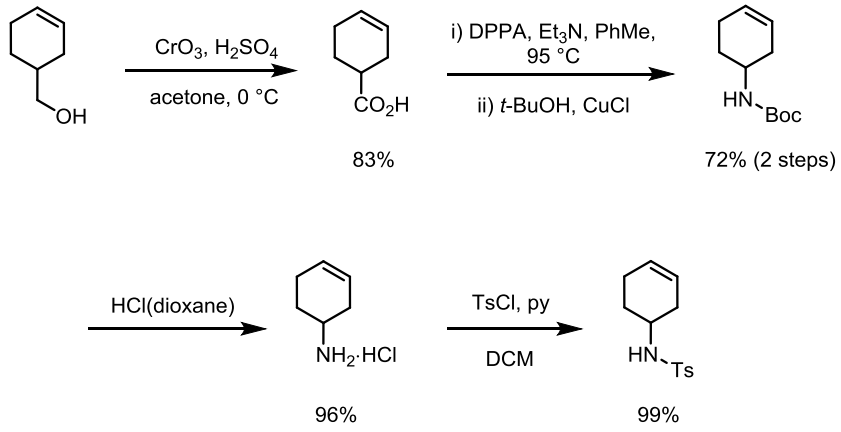
Synthesised from 2-(cyclohex-1-en-1-yl)ethanol **287** (100 mg, 0.79 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 9:1, pet. ether:Et_2O) to give the title compound as a colourless oil (221 mg, 0.58 mmol, 74%); R_f = 0.61 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 5.50 (1H, br. s, =C**H**), 3.91-3.84 (2H, m, C**HH'**NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.35 (2H, t, *J*=7.6 Hz, C$\mathbf{H_2}$-2), 2.04-1.95 (4H, m, C$\mathbf{H_2}$-5, C$\mathbf{H_2}$-8), 1.66-1.51 (4H, m, C$\mathbf{H_2}$-6, C$\mathbf{H_2}$-7), 1.33 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (125 MHz, $CDCl_3$) 150.9 (**C**=O), 143.9 (**C**), 137.7 (**C**), 134.2 (**C**), 129.2 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 123.9 (=**C**H), 83.9 (**C**$(CH_3)_3$), 46.1 (**C**HH'NTs), 38.5 (**C**H_2-2), 28.2 (**C**H_2-(5,8)), 27.9 (C(**C**H_3)$_3$), 25.3 (**C**H_2-(5,8)), 22.9 (**C**H_2-(6,7)), 22.5 (**C**H_2-(6,7)), 21.6 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 1727 m (C=O), 1356 m (SO_2), 1155 s (SO_2); LRMS *m*/*z* (ESI+) 402.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 402.1701; $C_{20}H_{29}NNaO_4S$ requires 402.1710.

N-(2-(Cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide, 289



Synthesised from *tert*-butyl (2-(cyclohex-1-en-1-yl)ethyl)(tosyl)carbamate **288** (200 mg, 0.53 mmol) using Procedure 5 to give the title compound as a colourless oil (141 mg, 0.50 mmol, 95%) which was used without further purification; R_f = 0.45 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.31 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.38 (1H, br. s, =C**H**), 4.35-4.25 (1H, br. m, N**H**), 3.00 (2H, ap. q, *J*=6.4 Hz, C$\mathbf{H_2}$NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.05 (2H, t, *J*=6.4 Hz, C$\mathbf{H_2}$-2), 2.01-1.91 (2H, br. m, C$\mathbf{H_2}$-5), 1.74-1.66 (2H, br. m, C$\mathbf{H_2}$-8), 1.59-1.44 (4H, m, C$\mathbf{H_2}$-6, C$\mathbf{H_2}$-7); δ_C (100 MHz, $CDCl_3$) 143.3 (**C**), 136.7 (**C**), 133.4 (**C**), 129.6 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 124.8 (=**C**H), 40.4 (**C**H_2NTs), 37.3 (**C**H_2-2), 27.4 (**C**H_2-8), 25.1 (**C**H_2-5), 22.6 (**C**H_2-(6,7)), 22.1(**C**H_2-(6,7)), 21.5 (Ar**C**H_3). Data are consistent with literature values.[173]

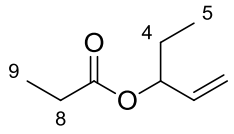
N-(Cyclohex-3-en-1-yl)-4-methylbenzenesulfonamide, 294



Scheme 132

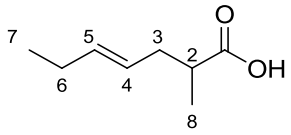
Synthesised by Dr. Craig Campbell according to literature procedure (Scheme 132).[174] Data are consistent with literature values.

Pent-1-en-3-yl propionate, 310a



To a solution of pent-1-en-3-ol (5.13 mL, 50.0 mmol, 1.0 eq.) in DCM (100 mL) at 0 ºC was added pyridine (4.85 mL, 60.0 mmol, 1.2 eq.) followed by propionyl chloride (4.80 mL, 55.0 mmol, 1.1 eq.) dropwise. The reaction mixture was stirred at 0 ºC for 2 h and H_2O (60 mL) added. The organic phase was separated, washed with brine (80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (≥150 mbar at 40 ºC). The resulting crude material was purified by column chromatography (19:1, pentane:Et_2O) to give the title compound as a colourless oil (6.39 g, 44.9 mmol, 90%); R_f = 0.61 (10:1, hexanes:Et_2O); δ_H (500 MHz, $CDCl_3$) 5.76 (1H, ddd, *J*=17.1, 10.6, 6.4 Hz, =C**H**), 5.26-5.12 (3H, m, =C**HH'**, OC**H**), 2.34 (2H, qd, *J*=7.6, 0.7 Hz, C$\mathbf{H_2}$-8), 1.70-1.56 (2H, m, **CHH'**-4), 1.14 (3H, t, *J*=7.6 Hz, C$\mathbf{H_3}$-9), 0.89 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-5); δ_C (125 MHz, $CDCl_3$) 173.8 (**C**=O), 136.4 (=**C**H), 116.5 (=**C**HH'), 75.7 (**C**H), 27.8 (**C**H_2-8), 27.2 (**C**HH'-4), 9.3 (**C**H_3-5), 9.2 (**C**H_3-9); IR (thin film) ν_{max}/cm^{-1} 2924 s (C-H), 1730 m (C=O), 1263 w (C-O), 1087 m (C-O).

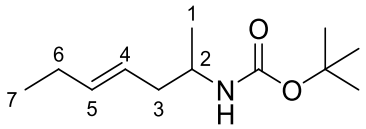
(*E*)-2-Methylhept-4-enoic acid, 311a



Synthesised from pent-1-en-3-yl propionate **310a** (3.00 g, 21 mmol, 1.0 eq.) using Procedure 9 to give the title compound as a pale yellow oil (2.53 g, 17.8 mmol, 84%) which was used without further purification; δ_H (500 MHz, $CDCl_3$) 5.53 (1H, dtt, *J*=15.2, 6.4, 1.0 Hz, =C**H**-5), 5.35 (1H, dtt, *J*=15.2, 7.0, 1.3 Hz, =C**H**-4), 2.50 (1H, ap. sext., *J*=6.9 Hz, C**H**-2), 2.36 (1H, ap. dtd, *J*=13.8, 6.8, 1.0 Hz, C**H**H'-3), 2.14 (1H, ap. dtd, *J*=13.8, 7.1, 1.0 Hz, CH**H'**-3), 2.05-1.96 (2H, m, C$\mathbf{H_2}$-6), 1.16 (3H, d, *J*=7.0 Hz, C$\mathbf{H_3}$-8), 0.96 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz,

$CDCl_3$) 182.8 (**C**=O), 135.1 (=**C**H-5), 125.3 (=**C**H-4), 39.6 (C**H**-2), 36.3 (**C**HH'-3), 25.6 (**C**H_2-6), 16.2 (**C**H_3-8), 13.8 (**C**H_3-9); IR (thin film) ν_{max}/cm^{-1} 2965 br. w (O-H, C-H), 1705 s (C=O); LRMS *m/z* (ESI+) 187.1 ($[M-H+Na+Na]^+$, 45%); LRMS *m/z* (ESI-) 141.1 ($[M-H]^-$, 100%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 165.0889; $C_8H_{14}NaO_2$ requires 165.0886.

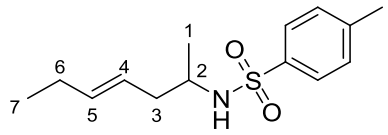
(*E*)-*tert*-Butyl hept-4-en-2-ylcarbamate, 312a



To a mixture of (*E*)-2-methylhept-4-enoic acid **311a** (1.00 g, 7.03 mmol, 1.0 eq.) in toluene (40 mL) was added Et_3N (1.1 mL, 7.74 mmol, 1.1 eq.) followed by DPPA (1.52 mL, 7.03 mmol, 1.0 eq.). The reaction mixture was heated to 60 ºC for 15 min and then heated under reflux for a further 2 h. The reaction mixture was cooled to 50 ºC over 40 min and *t*-BuOH (3.36 mL, 35.2 mmol, 5.0 eq.) was added dropwise followed by CuCl (28 mg, 0.28 mmol, 0.04 eq.). The reaction mixture was heated to 100 ºC for 1 h, cooled to RT, sat. aq. $NaHCO_3$ (20 mL) added and filtered through Celite. The organic layer was separated and the aqueous layer washed with *t*-BuOMe (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10:1, pet. ether:EtOAc) to give the title compound as a colourless oil (938 mg, 4.40 mmol, 63%); R_f = 0.53 (10:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 5.56-5.47 (1H, m, =C**H**-5), 5.35 (1H, dtt, *J*=15.0, 7.2, 1.3 Hz, =C**H**-4), 4.36 (1H, br. s, N**H**), 3.66 (1H, br. s, C**H**-2), 2.15-2.05 (2H, m, C**HH'**-3), 2.05-1.97 (2H, m, C$\mathbf{H_2}$-6), 1.43 (9H, s, C(C$\mathbf{H_3}$)$_3$), 1.09 (3H, d, *J*=6.6 Hz, C$\mathbf{H_3}$-1), 0.96 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 155.3 (**C**=O), 135.5 (=**C**H-5), 124.5 (=**C**H-4), 78.9 (**C**$(CH_3)_3$), 46.2 (**C**H-2), 40.0 (**C**HH'-3), 28.4 (C(**C**H)$_3$), 25.6 (**C**H_2-6), 20.5 (**C**H_3-1), 13.8 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 3340 br. w. (N-H), 2967 m (C-H), 1688 s (C=O), 1173 s; LRMS *m/z* (ESI+) 449.4 ($[2M+Na]^+$, 86%),

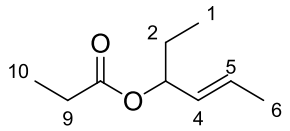
236.2 ([M+Na]$^+$, 71%); HRMS *m/z* (ESI+) found [M+Na]$^+$ 236.1623; $C_{12}H_{23}NNaO_2$ requires 236.1621.

(*E*)-*N*-(Hept-4-en-2-yl)-4-methylbenzenesulfonamide, 313a



To a flask charged with *tert*-butyl but-3-enyl(4-nitrophenylsulfonyl)carbamate **312a** (900 mg, 4.22 mmol, 1.0 eq.) was added 4 M HCl in dioxane (10.5 mL, 42.2 mmol, 10 eq.) and the reaction mixture stirred at RT for 2 h, then concentrated *in vacuo*. To the residue was added DCM (25 mL) and Et_3N (6.72 mL, 50.6 mmol, 12 eq.) followed by *p*-toluenesulfonyl chloride (885 mg, 4.64 mmol, 1.1 eq.) and the reaction mixture stirred at RT for 15 h. The reaction mixture was washed with sat. aq. $NaHCO_3$ (20 mL) and 1 M aq. HCl (20 mL), then the organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, hexanes:*t*-BuOMe) to give the title compound as a pale yellow oil (936 mg, 3.50 mmol, 83%); R_f = 0.38 (4:1, hexanes:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 5.42 (2H, dtt, *J*=15.2, 6.4, 1.0 Hz, =C**H**-5), 5.09 (2H, dtt, *J*=15.2, 7.2, 1.5 Hz, =C**H**-4), 4.58 (1H, br. d, *J*=7.1 Hz, N**H**), 3.33-3.24 (1H, m, C**H**-2), 2.41 (3H, s, ArC**H$_3$**), 2.06-1.99 (2H, m, C**HH'**-3), 1.97-1.87 (2H, m, C**H$_2$**-6), 1.07 (3H, d, *J*=6.6 Hz, C**H$_3$**-1), 0.91 (3H, t, *J*=7.4 Hz, C**H$_3$**-7); δ_C (100 MHz, $CDCl_3$) 143.1 (**Ar**CH_3), 138.0 (**Ar**SO_2), 136.5 (=**C**H-5), 129.5 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 123.5 (=**C**H-4), 49.5 (**C**H-2), 40.0 (**C**HH'-3), 25.5 (**C**H_2-6), 21.4 (Ar**C**H_3), 21.3 (**C**H_3-1), 13.5 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 3278 br. w (N-H), 2964 w (C-H), 1325 m (SO_2), 1159 s (SO_2); HRMS *m/z* (ESI+) found [M+H]$^+$ 268.1375; $C_{14}H_{22}NO_2S$ requires 268.1366.

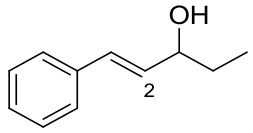
(*E*)-Hex-4-en-3-yl propionate, 310b



To a solution of *trans*-crotonaldehyde (2.49 mL, 30 mmol, 1.0 eq.) in Et_2O (50 mL) at 0 ºC was added dropwise EtMgBr (12.0 mL, 3 M in Et_2O, 36 mmol, 1.2 eq.). The reaction mixture was stirred at 0 ºC for 2 h and then H_2O (15 mL) added. The organic phase was separated, washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (≥250 mbar at 40 ºC) to give a solution of (*E*)-hex-4-en-3-ol **309b** (4.14 g, 55% in Et_2O [determined by ^1H NMR], 22.8 mmol, 76%).

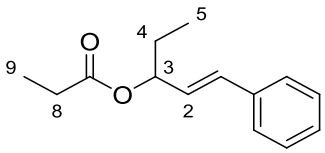
To this solution of (*E*)-hex-4-en-3-ol **309b** (4.14 g, 55% in Et_2O, 22.8 mmol, 1.0 eq.) was added DCM (50 mL), the solution cooled to 0 ºC and pyridine (2.21 mL, 27.3 mmol, 1.2 eq.) followed by propionyl chloride (2.19 mL, 25.0 mmol, 1.1 eq.) added dropwise. The reaction mixture was stirred at 0 ºC for 2 h and H_2O (60 mL) added. The organic phase was separated, washed with brine (80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (≥150 mbar at 40 ºC). The resulting crude material was purified by column chromatography (19:1, pentane:Et_2O) to give the title compound as a colourless oil (3.02 g, 19.3 mmol, 90%); R_f = 0.68 (10:1, hexanes:Et_2O); δ_H (400 MHz, $CDCl_3$) 5.70 (1H, dqd, *J*=15.3, 6.6, 1.0 Hz, =C**H**-5), 5.39 (1H, ddq, *J*=15.3, 7.3, 1.6 Hz, =C**H**-4), 5.11 (1H, ap. br. q, *J*=6.9 Hz, C**H**), 2.30 (2H, q, *J*=7.6 Hz, C$\mathbf{H_2}$-9), 1.68 (3H, br. ddd, *J*=6.6, 1.6, 0.6 Hz, C$\mathbf{H_3}$-6), 1.67-1.50 (2H, m, C**HH'**-2), 1.12 (3H, t, *J*=7.6 Hz, C$\mathbf{H_3}$-10), 0.86 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-1); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**=O), 129.5 (=**C**H-4), 129.0 (=**C**H-5), 75.9 (**C**H), 27.9 (**C**H_2-9), 27.5 (**C**HH'-2), 17.7 (**C**H_3-6), 9.5 (**C**H_3-1), 9.1 (**C**H_3-10); IR (thin film) ν_{max}/cm^{-1} 2926 m (C-H), 1736 s (C=O), 1187 s.

(*E*)-1-Phenylpent-1-en-3-ol, 309c



To a solution of *trans*-cinnamaldehyde (3.78 mL, 30 mmol, 1.0 eq.) in Et_2O (50 mL) at 0 ºC was added dropwise EtMgBr (12.0 mL, 3 M in Et_2O, 36 mmol, 1.2 eq.). The reaction mixture was stirred at 0 ºC for 2 h and then H_2O (15 mL) added. The organic phase was separated, washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10%→30% EtOAc in hexanes) to give the title compound as a colourless oil (1.98 g, 12.2 mmol, 41%); R_f = 0.51 (4:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.37-7.32 (2H, m, *o*-Ph**H**), 7.28 (2H, br. t, *J*=7.6 Hz, *m*-Ph**H**), 7.24-7.19 (1H, m, *p*-Ph**H**), 6.53 (1H, d, *J*=15.9 Hz, =C**H**Ph), 6.18 (1H, dd, *J*=15.9, 6.8 Hz, =C**H**-2), 4.16 (1H, ap. br. q, *J*=6.5 Hz, C**H**), 2.29 (1H, br. s, O**H**), 1.71-1.55 (2H, m, C**HH'**), 0.94 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$); δ_C (125 MHz, $CDCl_3$) 136.7 (**Ph**), 132.2 (=**C**H-2), 130.2 (=**C**HPh), 128.4 (*m*-**Ph**H), 127.5 (*p*-**Ph**H), 126.3 (*o*-**Ph**H), 74.2 (**C**H), 30.1 (**C**HH'), 9.7 (**C**H_3). Data are consistent with literature values.[175]

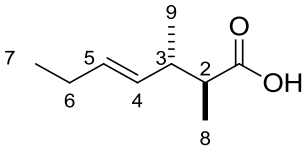
(*E*)-1-Phenylpent-1-en-3-yl propionate, 310c



To this solution of (*E*)-1-phenylpent-1-en-3-ol **309c** (2.80 g, 13.7 mmol, 1.0 eq.) in DCM (40 mL) at 0 ºC was added pyridine (1.38 mL, 17.0 mmol, 1.2 eq.) followed dropwise by propionyl chloride (1.36 mL, 15.6 mmol, 1.1 eq.). The reaction mixture was stirred at 0 ºC for 2 h and H_2O (30 mL) added. The organic phase was separated, washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by

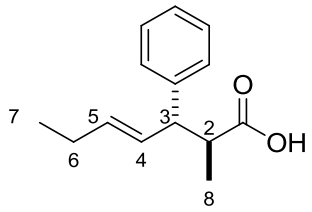
column chromatography (9:1, hexanes:*t*-BuOMe) to give the title compound as a colourless oil (2.34 g, 10.7 mmol, 74%); R_f = 0.34 (10:1, hexanes:Et_2O); δ_H (500 MHz, $CDCl_3$) 7.41-7.35 (2H, m, *o*-Ph**H**), 7.34-7.28 (2H, m, *m*-Ph**H**), 7.27-7.22 (1H, m, *p*-Ph**H**), 6.60 (1H, d, *J*=15.9 Hz, =C**H**Ph), 6.13 (1H, dd, *J*=15.9, 7.3 Hz, =C**H**-2), 5.39-5.32 (1H, m, C**H**-3), 2.36 (2H, qd, *J*=7.6, 1.3 Hz, C$\mathbf{H_2}$-8), 1.82-1.65 (2H, m, C**HH'**-4), 1.16 (3H, t, *J*=7.6 Hz, C$\mathbf{H_3}$-9), 0.94 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-5); δ_C (125 MHz, $CDCl_3$) 173.8 (**C**=O), 136.4 (**Ph**), 132.4 (=**C**HPh), 128.5 (*m*-**Ph**H), 127.8 (*p*-**Ph**H), 127.6 (=**C**H-2), 126.5 (*o*-**Ph**H), 75.7 (**C**H-3), 27.9 (**C**H_2-8), 27.6 (**C**HH'-4), 9.5 (**C**H_2-5), 9.2 (**C**H_3-9); IR (thin film) ν_{max}/cm^{-1} 2972 w (C-H), 1731 s (C=O), 1182 s; LRMS *m*/*z* (ESI+) 241.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 241.1201; $C_{14}H_{18}NNaO_2$ requires 241.1199.

(2*SR*,3*SR*,*E*)-2,3-Dimethylhept-4-enoic acid, 311b



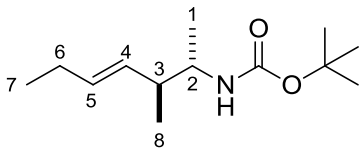
Synthesised from (*E*)-hex-4-en-3-yl propionate **310b** (2.70 g, 17.3 mmol, 1.0 eq.) using Procedure 9 to give the title compound as a yellow oil (2.12 g, 13.6 mmol, 79%) which was used without further purification; δ_H (500 MHz, $CDCl_3$) 5.50 (1H, br. dt, *J*=15.2, 6.5 Hz, =C**H**-5), 5.21 (1H, ddt, *J*=15.2, 8.4, 1.4 Hz, =C**H**-4), 2.45-2.36 (1H, m, C**H**-3), 2.33-2.26 (1H, m, C**H**-2), 2.05-1.96 (2H, m, C$\mathbf{H_2}$-6), 1.11 (3H, d, *J*=7.0 Hz, C$\mathbf{H_3}$-8), 1.04 (3H, d, *J*=6.9 Hz, C$\mathbf{H_3}$-9), 0.96 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 182.0 (**C**=O), 133.2 (=**C**H-5), 130.9 (=**C**H-4), 45.2 (**C**H-2), 39.8 (**C**H-3), 25.6 (**C**H_2-6), 19.0 (**C**H_3-9), 14.4 (**C**H_3-8), 13.9 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2965 br. w (O-H, C-H), 1705 s (C=O); LRMS *m*/*z* (ESI+) 201.1 ([M-H+2Na]$^+$, 85%), 179.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M-H+2Na]$^+$ 201.0855; $C_9H_{15}Na_2O_2$ requires 201.0862.

(2*SR*,3*SR*,*E*)-2-Methyl-3-phenylhept-4-enoic acid, 311c



Synthesised from (*E*)-1-phenylpent-1-en-3-yl propionate **310c** (2.20 g, 10.1 mmol, 1.0 eq.) using Procedure 9 to give the title compound as a yellow oil (1.61 g, 7.39 mmol, 73%) which was used without further purification; δ_H (400 MHz, $CDCl_3$) 7.29 (5H, m, Ph**H**), 5.63-5.44 (2H, m, =C**H**-5, =C**H**-4), 3.46 (1H, ap. t, *J*=9.2 Hz, C**H**-3), 2.77 (1H, dq, *J*=9.2, 6.9 Hz, C**H**-2), 2.06-1.96 (2H, m, C$\mathbf{H_2}$-6), 1.18 (3H, d, *J*=7.0 Hz, C$\mathbf{H_3}$-8), 0.95 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7); δ_C (100 MHz, $CDCl_3$) 181.3 (**C**=O), 142.8 (**Ph**), 134.9 (=**C**H), 128.5 (=**C**H), 128.4 (**Ph**H), 127.6 (**Ph**H), 126.4 (**Ph**H), 51.9 (**C**H-3), 45.1 (**C**H-2), 25.6 (**C**H_2-6), 15.2 (**C**H_3-8). 13.7 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2964 br. w (O-H, C-H), 1705 s (C=O); HRMS *m*/*z* (ESI+) found $[M-H+2Na]^+$ 263.1022; $C_{14}H_{17}Na_2O_2$ requires 263.1018.

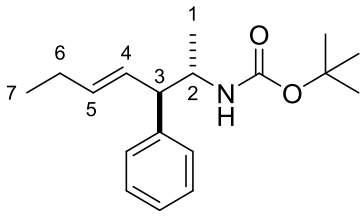
***tert*-Butyl ((2*SR*,3*SR*,*E*)-3-methylhept-4-en-2-yl)carbamate, 312b**



To a mixture of (2*SR*,3*SR*,*E*)-2,3-dimethylhept-4-enoic acid **311b** (500 mg, 3.20 mmol, 1.0 eq.) in toluene (20 mL) was added Et_3N (0.49 mL, 3.52 mmol, 1.1 eq.) followed by DPPA (0.72 mL, 3.36 mmol, 1.0 eq.). The reaction mixture was heated to 60 ºC for 15 min and then heated under reflux for a further 2 h. The reaction mixture was cooled to 50 ºC over 40 min and *t*-BuOH (1.53 mL, 16.0 mmol, 5.0 eq.) was added dropwise followed by CuCl (13 mg, 0.13 mmol, 0.04 eq.). The reaction mixture was heated to 100 ºC for 1 h, cooled to RT, sat. aq. $NaHCO_3$ (10 mL) added and filtered through Celite. The organic layer was separated and the

aqueous layer washed with *t*-BuOMe (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5%→10% *t*-BuOMe in hexanes) to give the title compound as a colourless oil (245 mg, 1.08 mmol, 34%); R_f = 0.56 (9:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 5.48 (1H, dt, *J*=15.2, 6.4 Hz, =C**H**-5), 5.25 (1H, br. dd, *J*=15.2, 8.5 Hz, =C**H**-4), 4.55-4.08 (1H, br. m, N**H**), 3.64-3.30 (1H, br. m, C**H**-2), 2.25-2.13 (1H, br. m, C**H**-3), 2.06-1.97 (2H, m, C$\mathbf{H_2}$-6), 1.43 (9H, s, C(C$\mathbf{H_3}$)$_3$), 1.01 (3H, d, *J*=6.8 Hz, C$\mathbf{H_3}$-1), 0.97 (3H, d, *J*=6.9 Hz, C$\mathbf{H_3}$-8), 0.97 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 155.3 (**C**=O), 133.6 (=**C**H-5), 130.1 (=**C**H-4), 78.8 (**C**(CH$_3$)$_3$), 50.2 (**C**H-2), 42.0 (**C**H-3), 28.4 (C(**C**H$_3$)$_3$), 25.6 (**C**H$_2$-6), 17.4 (**C**H$_3$-8), 16.9 (**C**H$_3$-1), 13.9 (**C**H$_3$-7); IR (thin film) ν_{max}/cm^{-1} 3348 br. w. (N-H), 2966 m (C-H), 1686 s (C=O), 1166 s; HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 250.1768; $C_{13}H_{25}NNaO_2$ requires 250.1778.

***tert*-Butyl ((2*SR*,3*RS*,*E*)-3-phenylhept-4-en-2-yl)carbamate, 312c**

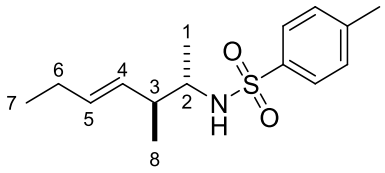


To a mixture of (2*SR*,3*SR*,*E*)-2-methyl-3-phenylhept-4-enoic acid **311c** (698 mg, 3.20 mmol, 1.0 eq.) in toluene (20 mL) was added Et_3N (0.49 mL, 3.52 mmol, 1.1 eq.) followed by DPPA (0.72 mL, 3.36 mmol, 1.0 eq.). The reaction mixture was heated to 60 ºC for 15 min and then heated under reflux for a further 2 h. The reaction mixture was cooled to 50 ºC over 40 min and *t*-BuOH (1.53 mL, 16.0 mmol, 5.0 eq.) was added dropwise followed by CuCl (13 mg, 0.13 mmol, 0.04 eq.). The reaction mixture was heated to 100 ºC for 1 h, cooled to RT, sat. aq. $NaHCO_3$ (10 mL) added and filtered through Celite. The organic layer was separated and the aqueous layer washed with *t*-BuOMe (3 × 20 mL). The combined organic layers were dried

($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (9:1, hexanes:*t*-BuOMe) to give the title compound as a colourless solid (285 mg, 0.98 mmol, 31%); m.p. 61-63 °C; R_f = 0.45 (9:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.34-7.16 (5H, m, Ph**H**), 5.72-5.57 (2H, m, =C**H**-5, =C**H**-4), 4.48-4.16 (1H, br. m, N**H**), 4.07-3.75 (1H, br. m, C**H**-2), 3.35 (1H, ap. br. t, *J*=7.4 Hz, C**H**-3), 2.12-2.03 (2H, m, C$\mathbf{H_2}$-6), 1.38 (9H, br. s, C(C$\mathbf{H_3}$)$_3$), 1.06 (3H, d, *J*=6.7 Hz, C$\mathbf{H_3}$-1), 1.00 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 155.2 (**C**=O), 142.0 (=**C**H), 135.6 (**Ph**), 128.4 (**Ph**H), 128.1 (**Ph**H), (=**C**H absent)*, 126.3 (**Ph**H), (**C**$(CH_3)_3$ absent)*, 54.2 (**C**H-3), 50.1 (**C**H-2), 28.4 (C(**C**H_3)$_3$), 25.7 (**C**H_2-6), 18.0 (**C**H_3-1), 13.7 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 3346 br. w. (N-H), 2968 m (C-H), 1697 s (C=O), 1169 s; HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 312.1937; $C_{18}H_{27}NNaO_2$ requires 312.1934.

*NB Due to the highly rotameric nature of the compound

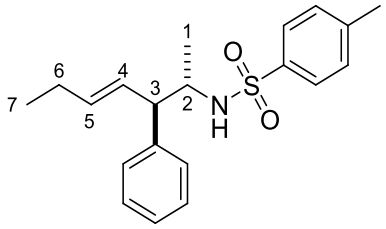
4-Methyl-*N*-((2*SR*,3*SR*,*E*)-3-methylhept-4-en-2-yl)benzenesulfonamide, 313b



To a flask charged with *tert*-butyl ((2*SR*,3*SR*,*E*)-3-methylhept-4-en-2-yl)carbamate **312b** (230 mg, 1.01 mmol, 1.0 eq.) was added 4 M HCl in dioxane (2.53 mL, 10.1 mmol, 10 eq.) and the reaction mixture stirred at RT for 2 h, then concentrated *in vacuo*. To the residue was added DCM (5 mL) and Et_3N (1.60 mL, 12.2 mmol, 12 eq.) followed by *p*-toluenesulfonyl chloride (193 mg, 1.01 mmol, 1.0 eq.) and the reaction mixture stirred at RT for 15 h. The reaction mixture was diluted with DCM (5 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and 1 M aq. HCl (5 mL), then the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10%→20% *t*-BuOMe in hexanes) to give the title compound as a colourless oil (168 mg, 0.60 mmol, 59%);

R_f = 0.59 (4:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.42 (1H, dtd, *J*=15.3, 6.3, 0.6 Hz, =C**H**-5), 5.11 (1H, ddt, *J*=15.3, 8.5, 1.5 Hz, =C**H**-4), 4.31 (1H, br. d, *J*=8.7 Hz, N**H**), 3.28-3.19 (1H, m, C**H**-2), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.14-2.04 (1H, br. m, C**H**-3), 2.01-1.93 (2H, m, C$\mathbf{H_2}$-6), 0.96 (3H, d, *J*=6.8 Hz, C$\mathbf{H_3}$-1), 0.94 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7), 0.90 (3H, d, *J*=7.0 Hz, C$\mathbf{H_3}$-8); δ_C (125 MHz, $CDCl_3$) 143.2 (**Ar**CH_3) 138.4 (**Ar**SO_2), 134.9 (=**C**H-5), 129.6 (*m*-**Ts**H), 128.9 (=**C**H-4), 127.0 (*o*-**Ts**H), 53.6 (**C**H-2), 42.2 (**C**H-3), 25.6 (**C**H_2-6), 21.5 (Ar**C**H_3), 17.4 (**C**H_3-1), 17.1 (**C**H_3-8), 13.8 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 3281 br. w (N-H), 2965 w (C-H), 1324 m (SO_2), 1158 s (SO_2); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 304.1346; $C_{15}H_{23}NNaO_2S$ requires 304.1342.

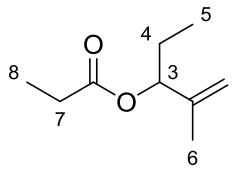
4-Methyl-*N*-((2*SR*,3*RS*,*E*)-3-phenylhept-4-en-2-yl)benzenesulfonamide, 313c



To a flask charged with *tert*-butyl ((2*SR*,3*RS*,*E*)-3-phenylhept-4-en-2-yl)carbamate **312c** (240 mg, 0.83 mmol, 1.0 eq.) was added 4 M HCl in dioxane (2.07 mL, 8.29 mmol, 10 eq.) and the reaction mixture stirred at RT for 2 h, then concentrated *in vacuo*. To the residue was added DCM (5 mL) and Et_3N (1.38 mL, 9.95 mmol, 12 eq.) followed by *p*-toluenesulfonyl chloride (158 mg, 0.83 mmol, 1.0 eq.) and the reaction mixture stirred at RT for 15 h. The reaction mixture was diluted with DCM (5 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and 1 M aq. HCl (5 mL), then the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10%→20% *t*-BuOMe in hexanes) to give the title compound as a pale yellow oil (221 mg, 0.64 mmol, 78%); R_f = 0.55 (4:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.63 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.30-7.15 (5H, m, *m*-Ts**H**, Ph**H**), 7.02-6.97 (2H, m, Ph**H**), 5.59-5.47 (2H, m, =C**H**-5,

=C**H**-4), 4.31 (1H, br. d, *J*=7.7 Hz, N**H**), 3.57-3.48 (1H, m, C**H**-2), 3.16 (1H, dd, *J*=7.9, 6.4 Hz, C**H**-3), 2.43 (3H, s, ArC**H**$_3$), 2.01 (2H, qd, *J*=7.4, 5.0 Hz, C**H**$_2$-6), 1.06 (3H, d, *J*=6.6 Hz, C**H**$_3$-1), 0.95 (3H, t, *J*=7.4 Hz, C**H**$_3$-7); δ_C (125 MHz, $CDCl_3$) 143.2 (**Ar**), 140.9 (**Ar**), 137.7 (**Ar**), 136.6 (=**C**H), 129.6 (*m*-**Ts**H), 128.6 (**Ph**H), 127.8 (**Ph**H), 127.1 (*o*-**Ts**H), 126.7 (**Ph**H), 126.1 (=**C**H), 54.3 (**C**H-3), 53.6 (**C**H-2), 25.6 (**C**H$_2$-6), 21.5 (Ar**C**H$_3$), 18.7 (**C**H$_3$-1), 13.5 (**C**H$_3$-7); IR (thin film) ν_{max}/cm^{-1} 3278 br. w (N-H), 2966 w (C-H), 1327 m (SO_2), 1159 s (SO_2); HRMS *m*/*z* (ESI+) found $[M+H]^+$ 344.1681; $C_{20}H_{26}NO_2S$ requires 344.1679.

2-Methylpent-1-en-3-yl propionate, 310d

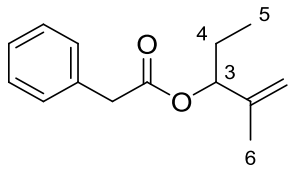


To a solution of methacrylaldehyde (4.95 mL, 60 mmol, 1.0 eq.) in Et_2O (100 mL) at 0 ºC was added dropwise EtMgBr (24.0 mL, 3 M in Et_2O, 72 mmol, 1.2 eq.). The reaction mixture was stirred at 0 ºC for 2 h and then H_2O (30 mL) added. The organic phase was separated, washed with H_2O (60 mL) and brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (≥250 mbar at 40 ºC) to give a solution of 2-methylpent-1-en-3-ol **309d** (6.67 g, 83% in Et_2O [determined by ^{1}H NMR spectroscopy], 55.3 mmol, 92%).

To a solution of 2-methylpent-1-en-3-ol **309d** (2.71 g, 83% in Et_2O, 22.5 mmol, 1.0 eq.) was added DCM (50 mL), the solution cooled to 0 ºC and pyridine (2.13 mL, 27.0 mmol, 1.2 eq.) followed by propionyl chloride (2.16 mL, 24.7 mmol, 1.1 eq.) added dropwise. The reaction mixture was stirred at 0 ºC for 2 h and H_2O (40 mL) added. The organic phase was separated, washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (≥150 mbar at 40 ºC). The resulting crude material was purified by column chromatography (19:1, pentane:Et_2O) to give the title compound as a colourless oil (3.03 g, 19.4 mmol, 86%); R_f = 0.71 (9:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 5.10 (1H, t, *J*=6.7 Hz, C**H**-3), 4.94-4.91

(1H, m, =C**H**H'), 4.89-4.86 (1H, m, =CH**H'**), 2.34 (2H, qd, *J*=7.7, 0.7 Hz, C$\mathbf{H_2}$-7), 1.72-1.69 (3H, m, C$\mathbf{H_3}$-6), 1.68-1.60 (2H, m, C$\mathbf{H_2}$-4), 1.14 (3H, t, *J*=7.6 Hz, C$\mathbf{H_3}$-8), 0.86 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-5); δ_C (125 MHz, $CDCl_3$) 173.8 (**C**=O), 143.0 (=**C**), 112.6 (=**C**HH'), 78.3 (**C**H-3), 27.8 (**C**H_2-7), 25.5 (**C**H_2-4), 18.1 (**C**H_3-6), 9.6 (**C**H_3-5), 9.2 (**C**H_3-8); IR (thin film) ν_{max}/cm^{-1} 2973 m (C-H), 1736 s (C=O), 1183 s.

2-Methylpent-1-en-3-yl 2-phenylacetate, 310e

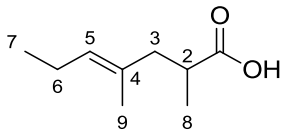


To a solution of methacrylaldehyde (4.95 mL, 60 mmol, 1.0 eq.) in Et_2O (100 mL) at 0 ºC was added dropwise EtMgBr (24.0 mL, 3 M in Et_2O, 72 mmol, 1.2 eq.). The reaction mixture was stirred at 0 ºC for 2 h and then H_2O (30 mL) added. The organic phase was separated, washed with H_2O (60 mL) and brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (≥250 mbar at 40 ºC) to give a solution of 2-methylpent-1-en-3-ol **309d** (6.67 g, 83% in Et_2O [determined by ^{1}H NMR spectroscopy], 55.3 mmol, 92%).

To a solution of 2-methylpent-1-en-3-ol **309d** (2.71 g, 83% in Et_2O, 22.5 mmol, 1.0 eq.) was added DCM (50 mL), the solution cooled to 0 ºC and pyridine (2.13 mL, 27.0 mmol, 1.2 eq.) followed by phenylacetyl chloride (3.81 mL, 24.7 mmol, 1.1 eq.) added dropwise. The reaction mixture was stirred at 0 ºC for 2 h and H_2O (40 mL) added. The organic phase was separated, washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (19:1, hexanes:*t*-BuOMe) to give the title compound as a colourless oil (4.43 g, 20.3 mmol, 90%); R_f = 0.70 (9:1, hexanes:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.36-7.21 (5H, m, Ph**H**), 5.10 (1H, t, *J*=6.6 Hz, C**H**-3), 4.89-4.82 (2H, m, =C**HH'**), 3.63 (2H, s, C$\mathbf{H_2}$Ph), 1.71-1.49 (2H, m, C$\mathbf{H_2}$-4), 1.64 (3H, s, C$\mathbf{H_3}$-6), 0.82 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-5); δ_C (100 MHz, $CDCl_3$) 170.8 (**C**=O), 142.7 (=**C**), 134.2 (**Ph**), 129.2 (**Ph**H),

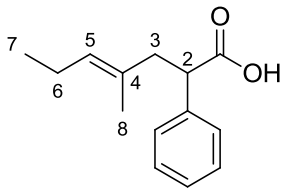
128.5 (**Ph**H), 127.0 (**Ph**H), 112.8 (=**C**HH'), 78.9 (**C**H-3), 41.7 (**C**H_2Ph), 25.5 (**C**H_2-4), 18.0 (**C**H_3-6), 9.5 (**C**H_3-5); IR (thin film) ν_{max}/cm^{-1} 2971 w (C-H), 1734 s (C=O).

(*E*)-2,4-Dimethylhept-4-enoic acid, 311d



Synthesised from 2-methylpent-1-en-3-yl propionate **310d** (2.81 g, 18.0 mmol, 1.0 eq.) using Procedure 9. The resulting crude material was purified by column chromatography (10%→30% *t*-BuOMe in hexanes) to give the title compound as a colourless oil (1.46 g, 9.35 mmol, 52%); δ_H (500 MHz, $CDCl_3$) 5.19 (1H, tq, *J*=7.1, 1.1 Hz, =C**H**), 2.67-2.57 (1H, m, C**H**-2), 2.39 (1H, br. dd, *J*=13.5, 6.9 Hz, C**H**H'-3), 2.04 (1H, dd, *J*=13.5, 8.0 Hz, CH**H'**-3), 2.03-1.95 (2H, m C**H**$_2$-6), 1.59 (3H, s, C**H**$_3$-9), 1.12 (3H, d, *J*=6.9 Hz, C**H**$_3$-8), 0.92 (3H, t, *J*=7.5 Hz, C**H**$_3$-7); δ_C (125 MHz, $CDCl_3$) 182.9 (**C**=O), 131.0 (=**C**-4), 129.4 (=**C**H-5), 43.6 (**C**HH'-3), 37.8 (**C**H-2), 21.2 (**C**H_2-6), 16.2 (**C**H_3-8), 15.4 (**C**H_3-9), 14.2 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2963 br. m (O-H, C-H), 1704 s (C=O); LRMS *m*/*z* (ESI+) 179.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 179.1039; $C_9H_{16}NaO_2$ requires 179.1043.

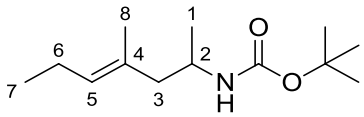
(*E*)-4-Methyl-2-phenylhept-4-enoic acid, 311e



Synthesised from 2-methylpent-1-en-3-yl 2-phenylacetate **310e** (3.93 g, 18.0 mmol, 1.0 eq.) using Procedure 9. The resulting crude material was purified by column chromatography (10%→30% *t*-BuOMe in hexanes) to give the title compound as a yellow oil (2.17 g, 9.94 mmol, 55%); δ_H (500 MHz, $CDCl_3$) 7.36-7.20 (5H, m, Ph**H**), 5.14 (1H, br. t, *J*=7.1 Hz,

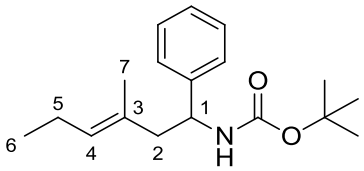
=C**H**-5), 3.76 (1H, dd, *J*=8.9, 6.7 Hz, C**H**-2), 2.77 (1H, dd, *J*=13.9, 8.9 Hz, C**H**H'-3), 2.39 (1H, dd, *J*=13.9, 6.7 Hz, CH**H'**-3), 1.90 (2H, ap. quin., *J*=7.4 Hz, C$\mathbf{H_2}$-6), 1.58 (3H, s, C$\mathbf{H_3}$-8), 0.81 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7), δ_C (125 MHz, $CDCl_3$) 179.4 (**C**=O), 138.3 (**Ph**), 130.6 (=**C**-4), 129.6 (=**C**H-5), 128.6 (**Ph**H), 128.1 (**Ph**H), 127.4 (**Ph**H), 50.2 (**C**H-2), 43.1 (**C**HH'-3), 21.2 (**C**H_2-6), 15.8 (**C**H_3-8), 14.0 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2961 br. m (O-H, C-H), 1703 s (C=O); HRMS *m/z* (ESI+) found $[M-H+2Na]^+$ 263.1014; $C_{14}H_{17}Na_2O_2$ requires 263.1018.

(*E*)-*tert*-Butyl (4-methylhept-4-en-2-yl)carbamate, 312d



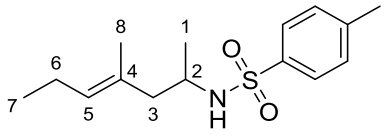
To a solution of (*E*)-2,4-dimethylhept-4-enoic acid **311d** (550 mg, 3.84 mmol, 1.0 eq.) in *t*-BuOH (5.4 mL) was added Et_3N (0.64 mL, 4.61 mmol, 1.2 eq.) and DPPA (0.91 mL, 4.22 mmol, 1.1 eq.). The reaction mixture was heated to 85 ºC for 15 h, cooled to RT and quenched with H_2O (1 mL) and sat. aq. $NaHCO_3$ (1 mL). The *t*-BuOH was evaporated and the residue extracted with *t*-BuOMe (3 × 5 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (19:1, hexanes:*t*-BuOMe) to give the title compound as a colourless oil (248 mg, 1.09 mmol, 28%); R_f = 0.64 (9:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 5.15 (1H, br. t, *J*=6.8 Hz, =C**H**-5), 4.42-4.07 (1H, br. m, N**H**), 3.84-3.51 (1H, br. m, C**H**-2), 2.10 (1H, dd, *J*=13.2, 7.5 Hz, C**H**H'-3), 2.04-1.94 (3H, m, CH**H'**-3, C$\mathbf{H_2}$-6), 1.61 (3H, s, C$\mathbf{H_3}$-8), 1.43 (9H, s, C(**C**$H_3)_3$), 1.08 (3H, d, *J*=6.5 Hz, C$\mathbf{H_3}$-1), 0.93 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 155.4 (**C**=O), 131.3 (=**C**-4), 129.6 (=**C**H-5), 78.8 (**C**$(CH_3)_3$), 47.6 (**C**H-2), 44.6 (**C**HH'-3), 28.4 (C(**C**$H_3)_3$), 21.2 (**C**H_2-6), 21.0 (**C**H_3-1), 15.7 (**C**H_3-8), 14.2 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 3350 br. w (N-H), 2965 m (C-H), 1687 s (C=O), 1503 m; HRMS *m/z* (ESI+) found $[M+Na]^+$ 250.1783; $C_{13}H_{25}NNaO_2$ requires 250.1778.

(*E*)-*tert*-Butyl (3-methyl-1-phenylhex-3-en-1-yl)carbamate, 312e



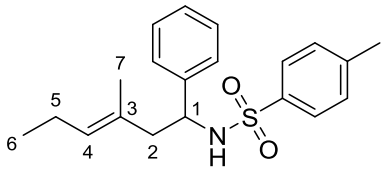
To a solution of (*E*)-4-methyl-2-phenylhept-4-enoic acid **311e** (1.00 g, 4.58 mmol, 1.0 eq.) in *t*-BuOH (6.4 mL) was added Et_3N (0.77 mL, 5.50 mmol, 1.2 eq.) and DPPA (1.1 mL, 5.04 mmol, 1.1 eq.). The reaction mixture was heated to 85 ºC for 15 h, cooled to RT and quenched with H_2O (1 mL) and sat. aq. $NaHCO_3$ (1 mL). The *t*-BuOH was evaporated and the residue extracted with *t*-BuOMe (3 × 10 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (19:1, hexanes:*t*-BuOMe) to give the title compound as a colourless solid (462 mg, 1.60 mmol, 35%); m.p. 75-77 °C; R_f = 0.56 (9:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.34-7.18 (5H, m, Ph**H**), 5.16 (1H, br. t, *J*=6.7 Hz, =C**H**-4), 4.92-4.47 (2H, br. m, C**H**-1, N**H**), 2.46-2.34 (1H, m, C**H**H'-2), 2.34-2.20 (1H, m, CH**H'**-2), 1.98 (2H, ap. quin., *J*=7.4 Hz, C$\mathbf{H_2}$-5), 1.61 (3H, s, C$\mathbf{H_3}$-7), 1.50-1.14 (9H, br. m, C(C$\mathbf{H_3}$)$_3$), 0.91 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (125 MHz, $CDCl_3$) 155.3 (**C**=O), 143.4 (**Ph**), 130.6 (=**C**(H)), 130.5 (=**C**(H)), 128.4 (**Ph**H), 126.9 (**Ph**H), 126.1 (**Ph**H), 79.3 (**C**$(CH_3)_3$), 52.8 (**C**H-1), 47.9 (**C**HH'-2), 28.3 (C(**C**H_3)$_3$), 21.2 (**C**H_2-5), 15.5 (**C**H_3-7), 14.1 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 3386 w (N-H), 2963 w (C-H), 1683 s (C=O), 1520 m; HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 312.1937; $C_{18}H_{27}NNaO_2$ requires 312.1934.

(*E*)-4-Methyl-*N*-(4-methylhept-4-en-2-yl)benzenesulfonamide, 313d



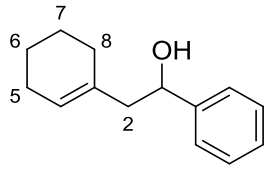
To a flask charged with (*E*)-*tert*-butyl (4-methylhept-4-en-2-yl)carbamate **312d** (240 mg, 1.06 mmol, 1.0 eq.) was added 4 M HCl in dioxane (1.32 mL, 5.23 mmol, 5.0 eq.) and the reaction mixture stirred at RT for 2 h, then concentrated *in vacuo*. To the residue was added DCM (5 mL) and Et_3N (1.03 mL, 7.39 mmol, 7.0 eq.) followed by *p*-toluenesulfonyl chloride (202 mg, 1.06 mmol, 1.0 eq.) and the reaction mixture stirred at RT for 15 h. The reaction mixture was diluted with DCM (5 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and 1 M aq. HCl (5 mL), then the organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, hexanes:*t*-BuOMe) to give the title compound as a pale yellow oil (192 mg, 0.68 mmol, 64%); R_f = 0.31 (4:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.11 (1H, br. t, *J*=7.0 Hz, =C**H**-5), 4.26 (1H, br. d, *J*=4.5 Hz, N**H**), 3.30-3.20 (1H, m, C**H**-2), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.01 (1H, dd, *J*=13.5, 5.5 Hz, C**H**H'-3), 1.98-1.87 (3H, m, CH**H'**-3, C$\mathbf{H_2}$-6), 1.19 (3H, s, C$\mathbf{H_3}$-8), 1.14 (3H, d, *J*=6.4 Hz, C$\mathbf{H_3}$-1), 0.93 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 143.2 (**Ar**CH_3), 137.5 (**Ar**SO_2), 131.1 (=**C**H-5), 130.6 (=**C**-4), 129.5 (*m*-**Ts**H), 127.2 (*o*-**Ts**H), 47.7 (**C**HH'-3), 47.3 (**C**H-2), 22.1 (**C**H_3-1), 21.5 (Ar**C**H_3), 21.2 (**C**H_2-6), 15.1 (**C**H_3-8), 14.1 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 3381 br. w (N-H), 2963 w (C-H), 1320 m (SO_2), 1159 s (SO_2); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 304.1338; $C_{15}H_{23}NNaO_2S$ requires 304.1342.

(*E*)-4-Methyl-*N*-(3-methyl-1-phenylhex-3-en-1-yl)benzenesulfonamide, 313d



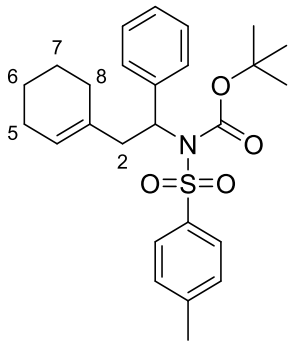
To a flask charged with (*E*)-*tert*-butyl (3-methyl-1-phenylhex-3-en-1-yl)carbamate **312e** (450 mg, 1.55 mmol, 1.0 eq.) was added 4 M HCl in dioxane (1.94 mL, 7.77 mmol, 5.0 eq.) and the reaction mixture stirred at RT for 2 h, then concentrated *in vacuo*. To the residue was added DCM (5 mL) and Et_3N (1.52 mL, 10.9 mmol, 7.0 eq.) followed by *p*-toluenesulfonyl chloride (296 mg, 1.55 mmol, 1.0 eq.) and the reaction mixture stirred at RT for 15 h. The reaction mixture was diluted with DCM (5 mL), washed with sat. aq. $NaHCO_3$ (5 mL) and 1 M aq. HCl (5 mL), then the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, hexanes:*t*-BuOMe) to give the title compound as a pale yellow oil (441 mg, 1.28 mmol, 83%); R_f = 0.29 (4:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.52 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.22-7.12 (7H, m, *m*-Ts**H**, Ph**H**), 5.18 (1H, br. t, *J*=6.8 Hz, =C**H**-4), 4.69 (1H, br. d, *J*=3.5 Hz, N**H**), 4.27 (1H, dt, *J*=9.5, 4.7 Hz, C**H**-1), 2.37 (3H, s, ArC**H**$_3$), 2.30 (1H, dd, *J*=13.8, 4.9 Hz, C**H**H'-2), 2.20 (1H, dd, *J*=13.8, 10.1 Hz, CH**H'**-2), 1.96 (1H, ap. quin., *J*=7.4 Hz, C**H**$_2$-5), 1.33 (3H, s, C**H**$_3$-7), 0.93 (3H, t, *J*=7.5 Hz, C**H**$_3$-6); δ_C (125 MHz, $CDCl_3$) 143.0 (**Ar**), 141.4 (**Ar**), 137.0 (**Ar**), 132.1 (=**C**H-4), 130.1 (=**C**-3), 129.2 (**Ar**H), 128.2 (**Ar**H), 127.2 (**Ar**H), 127.2 (**Ar**H), 126.6 (**Ar**H), 55.3 (**C**H-1), 48.8 (**C**HH'-2), 21.5 (Ar**C**H$_3$), 21.2 (**C**H$_2$-5), 15.0 (**C**H$_3$-7), 14.1 (**C**H$_3$-6); IR (thin film) ν_{max}/cm^{-1} 3380 br. w (N-H), 2961 w (C-H), 1323 m (SO_2), 1156 s (SO_2); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 366.1501; $C_{20}H_{25}NNaO_2S$ requires 366.1498.

2-(Cyclohex-1-en-1-yl)-1-phenylethan-1-ol, 318



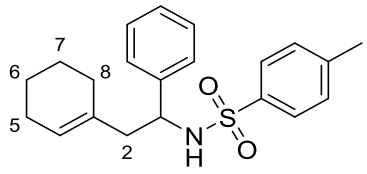
To a solution of benzaldehyde (0.96 mL, 9.5 mmol, 1.0 eq.) in DCM (30 mL) at 0 ºC was added methylenecyclohexane (1.00 g, 10.4 mmol, 1.1 eq) and then Me_2AlCl (15.6 mL, 1.0 M in hexanes, 15.6 mmol, 1.5 eq.). The reaction mixture was stirred at RT for 2 h, followed by the slow addition of sat. aq. NaH_2PO_4 (10 mL) and Et_2O (10 mL). The alumina precipitate was dissolved by dropwise addition of 2 M aq. HCl, the organic layer separated and the aqueous layer washed with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (9:1, pet ether:Et_2O) to give the title compound as a yellow oil (675 mg, 3.34 mmol, 35%); R_f = 0.41 (3:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.41-7.31 (4H, m, Ph**H**), 7.30-7.23 (1H, m, Ph**H**), 5.64-5.57 (1H, br. m, =C**H**), 4.76 (1H, ddd, *J*=9.2, 4.2, 2.0 Hz, C**H**OH), 2.40-2.25 (2H, m, C**HH'**-2), 2.16 (1H, d, *J*=2.0 Hz, O**H**), 2.13-2.00 (3H, m, C**H**H'-5, C**HH'**-8), 1.98-1.85 (1H, m, CH**H'**-5), 1.70-1.53 (4H, m, C**HH'**-6, C**HH'**-7); δ_C (100 MHz, $CDCl_3$) 144.3 (**C**), 134.4 (**C**), 128.3 (**Ph**H), 127.3 (**Ph**H) 125.9 (=**C**H), 125.7 (**Ph**H), 71.2 (**C**HOH), 49.0 (**C**HH'-2), 28.2 (**C**HH'-5), 25.3 (**C**HH'-8), 22.8 (**C**HH'-6), 22.3 (**C**HH'-7).

***tert*-Butyl (2-(cyclohex-1-en-1-yl)-1-phenylethyl)(tosyl)carbamate, 319**



Synthesised from 2-(cyclohex-1-en-1-yl)-1-phenylethan-1-ol **318** (400 mg, 1.98 mmol) using Procedure 3, except the reaction mixture was stirred at 50 ºC for 24 h. The resulting crude material was purified by column chromatography (dry loaded, 5%→20% Et_2O in pet. ether) to give the title compound as a colourless oil (485 mg, 1.06 mmol, 54%); R_f = 0.45 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.49-7.44 (2H, m, Ph**H**), 7.36-7.24 (3H, m, Ph**H**), 7.22 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.83 (1H, dd, *J*=9.8, 5.7 Hz, C**H**Ph), 5.62-5.57 (1H, br. m, =C**H**), 3.18 (1H, dd, *J*=13.9, 9.8 Hz C**H**H'-2), 2.77 (1H, dd, *J*=13.8, 5.7 Hz, CH**H'**-2), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.32-2.21 (1H, m, C**H**H'-5), 2.08-1.90 (3H, m, C**HH'**-8, CH**H'**-5), 1.77-1.49 (4H, m, C**HH'**-6, C**HH'**-7), 1.21 (9H, s, C(C$\mathbf{H_3}$)$_3$); δ_C (100 MHz, $CDCl_3$) 150.8 (**C**=O), 143.7 (**C**), 140.3 (**C**), 137.7 (**C**), 134.1 (**C**), 129.0 (*m*-**Ts**H), 128.2 (*o*-**Ts**H), 128.1 (**Ph**H), 128.0 (**Ph**H), 127.2 (**Ph**H), 125.6 (=**C**H), 83.9 (**C**$(CH_3)_3$), 58.7 (**C**HPh), 40.7 (**C**HH'-2), 28.2 (**C**HH'-5), 27.8 (C(**C**$H_3)_3$), 25.4 (**C**HH'-8), 22.8 (**C**HH'-6), 22.2 (**C**HH'-7), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2930 w (C-H), 1725 s (C=O), 1348 m, 1150 s; LRMS *m*/*z* (ESI+) 478.2 ([M+Na]$^+$, 54%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 478.2025; $C_{26}H_{33}NNaO_4S^+$ requires 478.2023.

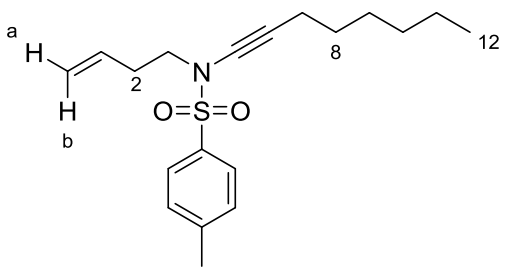
_N_-(2-(Cyclohex-1-en-1-yl)-1-phenylethyl)-4-methylbenzenesulfonamide, 320



Synthesised from *tert*-butyl (2-(cyclohex-1-en-1-yl)-1-phenylethyl)(tosyl)carbamate **319** (450 mg, 0.99 mmol) using Procedure 5, except the reaction mixture was stirred under reflux for 3 days. The resulting crude material was purified by column chromatography (20%→30% Et_2O in pet. ether) to give the title compound as a colourless solid (267 mg, 0.75 mmol, 76%); m.p. 112-114 °C; R_f = 0.45 (7:3, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.24-7.11 (7H, m, Ph**H**, *m*-Ts**H**), 5.50-5.43 (1H, br. m, =C**H**), 4.70 (1H, br. d, *J*=3.6 Hz, N**H**), 4.25 (1H, ddd, *J*=9.5, 5.4, 3.6 Hz, C**H**Ph), 2.37 (3H, s, ArC$\mathbf{H_3}$), 2.29-2.14 (2H, m, C**HH'**-2), 2.04-1.88 (2H, m, C**HH'**-8), 1.73-1.60 (1H, m, C**H**H'-5), 1.59-1.38 (5H, m, CH**H'**-5, C**HH'**-6, C**HH'**-7); δ_C (100 MHz, $CDCl_3$) 134.0 (**C**), 141.5 (**C**), 137.0 (**C**), 133.4 (**C**), 129.2 (*m*-Ts**H**), 128.2 (**Ph**H), 127.2 (*o*-**Ts**H), 127.2 (**Ph**H), 126.8 (=**C**H), 126.5 (**Ph**H), 55.3 (**C**HPh), 47.4 (**C**HH'-2), 27.4 (**C**HH'-5), 25.2 (**C**HH'-8), 22.5 (**C**HH'-7), 22.0 (**C**HH'-6), 21.4 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3279 br. w (N-H), 2925 w (C-H), 1323 m (SO_2), 1159 s (SO_2); LRMS *m*/*z* (ESI+) 378.1 ($[M+Na]^+$, 100%), 733.3 ($[2M+Na]^+$, 67%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 378.1498; $C_{21}H_{25}NNaO_2S^+$ requires 378.1498.

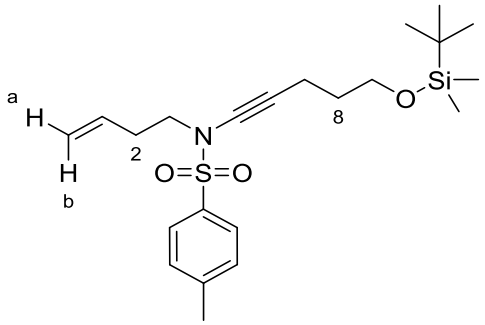
6.3.3 Enynamides

_N_-(But-3-en-1-yl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 195a



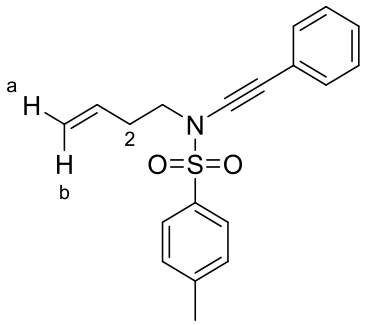
Synthesised from *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **240a** (5.00 g, 22.2 mmol) and 1-bromooct-1-yne (5.04 g, 26.6 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10:1, pet. ether:Et_2O) to give the title compound as a colourless oil (7.08 g, 21.2 mmol, 96%); R_f = 0.51 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.72 (1H, ddt, *J*=17.2, 10.3, 6.7 Hz, =C**H**), 5.07 (1H, dd, *J*=17.2, 1.5 Hz, =CH^a**H^b**), 5.03 (1H, dd, *J*=10.3, 1.5 Hz, =C**H^a**H^b), 3.32 (2H, t, *J*=7.5 Hz, C**H$_2$**NTs), 2.44 (3H, s, ArC**H$_3$**), 2.36 (2H, ap. q, *J*=7.2 Hz, C**H$_2$**-2), 2.26 (2H, t, *J*=6.9 Hz, ≡CC**H$_2$**), 1.51-1.42 (2H, m, C**H$_2$**-8), 1.39-1.19 (6H, m, C**H$_2$**-(9-11)), 0.88 (3H, t, *J*=6.8 Hz, C**H$_3$**-12); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 134.6 (**Ar**SO_2), 133.9 (=**C**H), 129.5 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 117.4 (=**C**H^{a}H^b), 72.8 (≡**C**), 70.5 (≡**C**), 50.8 (**C**H_2NTs), 32.1 (**C**H_2-2), 31.3 (**C**H_2-(9-11)), 28.9 (**C**H_2-8), 28.4 (**C**H_2-(9-11)), 22.6 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 18.4 (≡C**C**H_2), 14.0 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2930 m (C-H), 2253 w (C≡C), 1364 m (SO_2), 1170 s (SO_2); LRMS *m*/*z* (ESI+) 689.4 ([2M+Na]$^+$, 100%), 356.2 ([M+Na]$^+$, 74%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 356.1654; $C_{19}H_{27}NNaO_2S^+$ requires 356.1655.

_N_-(But-3-en-1-yl)-_N_-(5-((_tert_-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methylbenzenesulfonamide, 195b



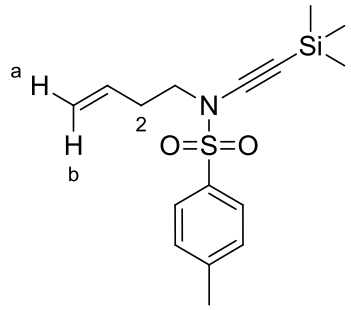
Synthesised from *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **240a** (500 mg, 2.22 mmol) and ((5-bromopent-4-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (923 mg, 3.33 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10:1, pet. ether:Et_2O) to give the title compound as a colourless oil (728 mg, 1.73 mmol, 78%); R_f = 0.56 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.71 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz, =C**H**), 5.12-5.00 (2H, m, =C**H**$^{\mathbf{a}}$**H**$^{\mathbf{b}}$), 3.64 (2H, t, *J*=6.1 Hz, C$\mathbf{H_2}$O), 3.31 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.40-2.31 (4H, m, C$\mathbf{H_2}$-2, ≡CC$\mathbf{H_2}$), 1.68 (2H, ap. quin., *J*=6.6 Hz, C$\mathbf{H_2}$-8), 0.88 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.03 (6H, s, Si(C$\mathbf{H_3}$)$_2$; δ_C (100 MHz, $CDCl_3$) 144.3 (**Ar**CH_3), 134.6 (**Ar**SO_2), 133.8 (=**C**H), 129.6 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 117.5 (=**C**H^{a}H^{b}), 72.9 (≡**C**), 70.0 (≡**C**), 61.5 (**C**H_2O), 50.7 (**C**H_2NTs), 32.1 (**C**H_2-2), 32.0 (**C**H_2-8), 25.9 (SiC(**C**H_3)$_3$), 21.6 (Ar**C**H_3), 18.3 (Si**C**$(CH_3)_3$), 14.9 (≡C**C**H_2), 5.4 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 2928 w (C-H), 2254 w (C≡C), 1365 m (SO_2), 1170 s (SO_2); LRMS *m*/*z* (ESI+) 865.4 ([2M+Na]$^+$, 100%), 444.2 ([M+Na]$^+$, 83%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 444.1996; $C_{22}H_{35}NNaO_3SSi^+$ requires 444.1999.

_N_-(But-3-en-1-yl)-4-methyl-_N_-(phenylethynyl)benzenesulfonamide, 195c



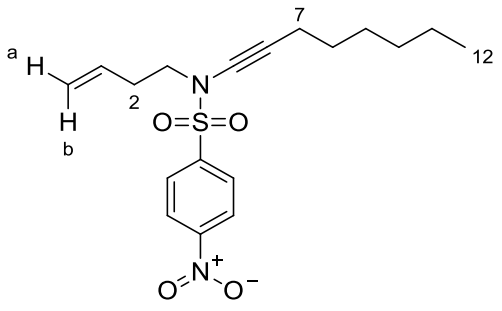
Synthesised from *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **240a** (500 mg, 2.22 mmol) and (bromoethynyl)benzene (602 mg, 3.32 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether) to give the title compound as a yellow oil (694 mg, 2.13 mmol, 96%); R_f = 0.56 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.40-7.33 (4H, m, *o*-Ph**H,** *m*-Ts**H**), 7.33-7.27 (3H, m, *m*-Ph**H**, *p*-Ph**H**), 5.76 (1H, ddt, *J*=17.1, 10.3, 6.7 Hz, =C**H**), 5.12 (1H, dd, *J*=17.1, 1.4 Hz, =CH^a**H^b**), 5.07 (1H, dd, *J*=10.3, 1.4 Hz, =C**H^a**H^b), 3.47 (2H, t, *J*=7.5 Hz, C**H$_2$**NTs), 2.50-2.42 (2H, m, **CH$_2$**-2), 2.45 (3H, s, ArC**H$_3$**); δ_C (100 MHz, $CDCl_3$) 144.6 (**Ar**CH_3), 134.6 (**Ar**SO_2), 133.6 (=**C**H), 131.3 (*o*-**Ph**H), 129.7 (*m*-**Ts**H), 128.2 (*m*-**Ph**H), 127.8 (*p*-**Ph**H), 127.7 (*o*-**Ts**H), 122.8 (**Ph**), 117.7 (=**C**H^{a}H^b), 82.1 (≡**C**NTs), 70.9 (≡**C**Ph), 50.9 (**C**H_2NTs), 32.3 (**C**H_2-2), 21.6 (Ar**C**H_3). Data are consistent with literature values.[35]

_N_-(But-3-en-1-yl)-4-methyl-_N_-((trimethylsilyl)ethynyl)benzenesulfonamide, 195d



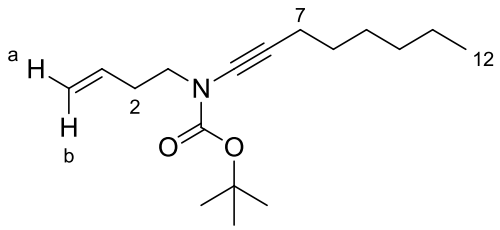
According to the procedure of Sato.[176] To a mixture of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **240a** (200 mg, 0.89 mmol, 1.0 eq.), K_3PO_4 (377 mg, 1.78 mmol, 2.0 eq.) and CuI (8.5 mg, 0.044 mmol, 0.05 eq.) in toluene (2.5 mL) was added a solution of (bromoethynyl)trimethylsilane (236 mg, 1.33 mmol, 1.5 eq.) in toluene (7.5 mL) followed by *N*,*N*′-dimethylethane-1,2-diamine (19 μL, 0.178 mmol, 0.2 eq.). The reaction mixture was stirred under reflux for 15 h, allowed to cool to RT, filtered through a silica pad (EtOAc) and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound as a colourless solid (132 mg, 0.411 mmol, 46%); m.p. 47-50 ºC (lit. m.p. 53-55 ºC)[30]; R_f = 0.52 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.34 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.70 (1H, ddt, *J*=17.2, 10.2, 6.8 Hz, =C**H**), 5.08 (1H, ap. dq, *J*=17.2, 1.5 Hz, =CH^a**H**^{b}), 5.03 (1H, ap. dq, *J*=10.2, 1.4 Hz, =C**H**^{a}H^b), 3.36 (2H, t, *J*=7.4 Hz, C**H**$_2$NTs), 2.45 (3H, s, Ar**C**H_3), 2.40-2.33 (2H, m, C**H**$_2$-2), 0.16 (9H, s, Si(C**H**$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 144.6 (**Ar**CH_3), 134.5 (**Ar**SO_2), 133.7 (=**C**H), 129.6 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 117.7 (=**C**H^{a}H^b), 94.8 (≡**C**), 73.5 (≡**C**), 50.6 (**C**H_2NTs), 32.1 (**C**H_2-2), 21.6 (Ar**C**H_3), 0.1 (Si(**C**H_3)$_3$). Elemental Anal. calculated for $C_{16}H_{23}NO_2SSi$: C 59.8, H 7.2, N 4.4; found: C 59.9, H 7.3, N 4.3. Data are consistent with literature values.[30]

_N_-(But-3-en-1-yl)-4-nitro-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 195e



Synthesised from *N*-(but-3-en-1-yl)-4-nitrobenzenesulfonamide **240b** (195 mg, 0.761 mmol) and 1-bromo-1-octyne (288 mg, 1.52 mmol) using Procedure 6, except the reaction mixture was heated to 100 °C for 24 h. The resulting crude material was purified by column chromatography (19:1, pet. ether:Et_2O) to give the title compound as a yellow oil (200 mg, 0.562 mmol, 72%); R_f = 0.29 (9:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 8.42-8.36 (2H, m, Ns**H**), 8.11-8.05 (2H, m, Ns**H**), 5.70 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz, =C**H**), 5.09 (1H, ap. dq, *J*=17.1, 1.5 Hz, =CH^{a}**H**^{b}), 5.05 (1H, ddt, *J*=10.3, 1.5, 1.1 Hz, =C**H**^{a}H^{b}), 3.40 (2H, t, *J*=7.2 Hz, C**H**$_2$NNs), 2.45-2.34 (2H, m, C**H**$_2$-2), 2.27 (2H, t, *J*=7.0 Hz, C**H**$_2$-7), 1.54-1.43 (2H, m, C**H**$_2$-8), 1.40-1.21 (6H, m, C**H**$_2$-(9-11)), 0.89 (3H, t, *J*=7.4 Hz, C**H**$_3$-12); δ_C (125 MHz, $CDCl_3$) 150.4 (**Ns**), 143.0 (**Ns**), 133.3 (=**C**H), 128.8 (**Ns**H), 124.2 (**Ns**H), 118.0 (=**C**H^{a}H^{b}), 71.7 (≡**C**), 71.6 (≡**C**), 51.2 (**C**H$_2$NNs), 32.1 (**C**H$_2$-2), 31.3 (**C**H$_2$-(9-11)), 28.8 (**C**H$_2$-8), 28.5 (**C**H$_2$-(9-11)), 22.6 (**C**H$_2$-(9-11)), 18.4 (**C**H$_2$-7), 14.0 (**C**H$_3$-12); IR (thin film) ν_{max}/cm^{-1} 3105 w (C-H), 2930 m (C-H), 2859 m (C-H), 2255 w (C≡C), 1607 w (C=C), 1531 s (NO_2), 1402 s (SO_2/NO_2), 1372 s (SO_2/NO_2), 1174 s (SO_2); LRMS *m*/*z* (ESI+) 365.2 ([M+H]$^+$, 100%), 387.1 ([M+Na]$^+$, 95%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 387.1336; $C_{18}H_{24}N_2NaO_4S$ requires 387.1349.

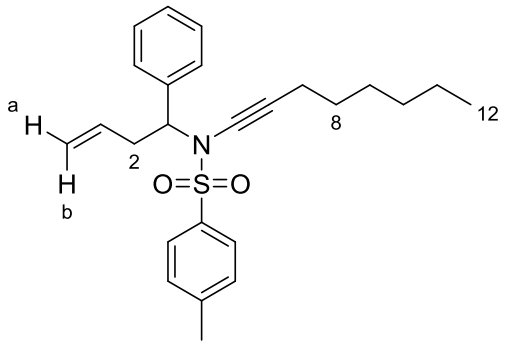
***tert*-Butyl but-3-en-1-yl(oct-1-yn-1-yl)carbamate*, 195f**



***Reaction carried out by Dr. Craig Campbell.**

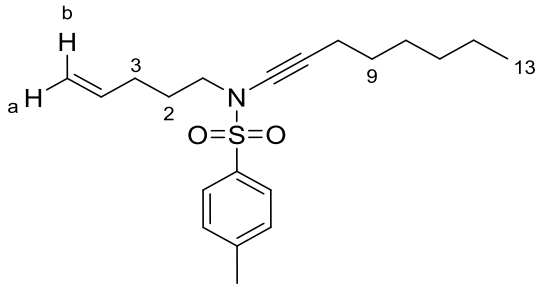
Synthesised from *N*-(but-3-en-1-yl)carbamate **242** (400 mg, 2.34 mmol) and 1-bromo-1-octyne (1.33 g, 7.01 mmol) using modified form of Procedure 6 at 110 °C for 10 d. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound as a colourless oil (45.7 mg, 0.164 mmol, 7%); R_f = 0.25 (9:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 5.77 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz, =C**H**), 5.10 (1H, ap. dq, *J*=17.1, 1.4 Hz, =CH^a**H**^{b}), 5.03 (1H, br. d, *J*=10.3 Hz, =C**H**^{a}H^b), 3.43 (2H, t, *J*=7.3 Hz, C**H**$_2$N), 2.38 (2H, ap. q, *J*=6.9 Hz, C**H**$_2$-2), 2.28 (2H, t, *J*=6.8 Hz, C**H**$_2$-7), 1.55-1.44 (2H, m, C**H**$_2$-8), 1.47 (9H, s, C(C**H**$_3$)$_3$), 1.44-1.21 (6H, m, C**H**$_2$-(9-11)), 0.88 (3H, t, *J*=6.7 Hz, C**H**$_3$-12); δ_C (100 MHz, $CDCl_3$) 154.7 (**C**=O), 134.6 (=**C**H), 116.9 (=**C**H^{a}H^b), 81.7 (**C**), 74.2 (**C**), 69.4 (**C**), 48.3 (**C**H$_2$N), 32.1 (**C**H$_2$-2), 31.4 (**C**H$_2$-(9-11)), 29.0 (**C**H$_2$-8), 28.5 (**C**H$_2$-(9-11)), 28.0 (C(**C**H$_3$)$_3$), 22.6 (**C**H$_2$-(9-11)), 18.5 (**C**H$_2$-7), 14.0 (**C**H$_3$-12); IR (thin film) ν_{max}/cm^{-1} 2932 m (C-H), 2263 w (C≡C), 1718 s (C=O); LRMS *m*/*z* (ESI+) 581.5 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 302.2082; $C_{17}H_{29}NNaO_2$ requires 302.2091.

4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide, 195g



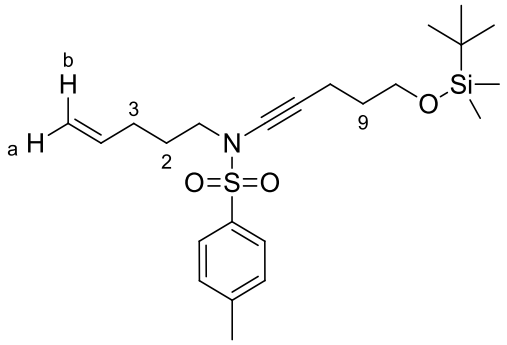
Synthesised from 4-methyl-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide **240c** (50.0 mg, 0.166 mmol) using Procedure 6, except the reaction mixture was heated to 110 °C for 24 h. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound as a yellow oil (38.0 mg, 0.093 mmol, 55% (85% brsm)); R_f = 0.58 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.53 (2H, d, *J*=8.4 Hz, *o*-Ts**H**), 7.30-7.25 (2H, m, *m*-Ph**H**), 7.24-7.18 (3H, m, *o*-Ph**H**, *p*-Ph**H**), 7.13 (2H, d, *J*=8.4 Hz, *m*-Ts**H**), 5.63 (1H, ddt, *J*=17.1, 10.2, 6.8 Hz, =C**H**), 5.09 (1H, dd, *J*=17.1, 1.4 Hz, =C**H**^{a}H^b), 5.01-5.94 (2H, m, =CH^a**H**^{b}, C**H**Ph), 2.80-2.72 (1H, m, C**H**H'-2), 2.62-2.53 (1H, m, CH**H'**-2), 2.38 (3H, s, ArC**H**$_3$), 2.32 (2H, t, *J*=6.9 Hz, ≡CC**H**$_2$), 1.54-1.45 (2H, m, C**H**$_2$-8), 1.39-1.23 (6H, m, C**H**$_2$-(9-11)), 0.90 (3H, t, *J*=6.9 Hz, C**H**$_3$-15); δ_C (125 MHz, $CDCl_3$) 143.7 (**Ph**), 139.0 (Ar**C**H$_3$), 135.4 (**Ar**SO$_2$), 133.8 (=**C**H), 129.0 (*m*-**Ts**H), 128.2 (*o*-**Ph**H), 127.9 (*p*-**Ph**H), 127.7 (*o*-**Ts**H), 127.1 (*m*-**Ph**H), 118.0 (=**C**H^{a}H^b), 73.1 (≡**C**), 70.8 (≡**C**), 62.6 (**C**HPh), 38.2 (**C**HH'-2), 31.3 (**C**H$_2$-(9-11)), 28.9 (**C**H$_2$-8), 28.5 (**C**H$_2$-(9-11)), 22.6 (**C**H$_2$-(9-11)), 21.5 (Ar**C**H$_3$), 18.7 (≡C**C**H$_2$), 14.0 (**C**H$_3$-12); IR (thin film) ν_{max}/cm^{-1} 2956 w (C-H), 2252 w (C≡C), 1362 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 841.5 ([2M+Na]$^+$, 100%), 432.2 ([M+Na]$^+$, 15%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 432.1965; $C_{25}H_{31}NNaO_2S^+$ requires 432.1968.

4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(pent-4-en-1-yl)benzenesulfonamide, 195h



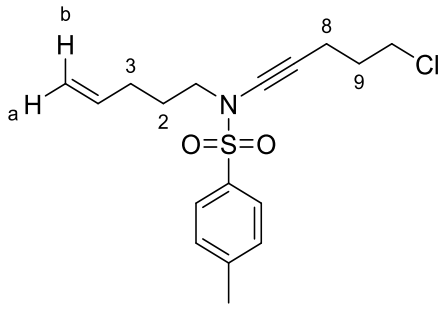
Synthesised from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **240d** (700 mg, 2.92 mmol) and 1-bromooct-1-yne (830 mg, 4.39 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10:1, pet. ether:Et_2O) to give the title compound as a colourless oil (893 mg, 2.56 mmol, 89%); R_f = 0.78 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.76 (1H, ddt, *J*=17.0, 10.3, 6.6 Hz), 5.06-4.95 (2H, m, =C**H**^{a}**H**^{b}), 3.26 (2H, t, *J*=7.1 Hz, C**H**$_2$NTs), 2.44 (3H, s, ArC**H**$_3$), 2.25 (2H, t, *J*=6.9 Hz, ≡CC**H**$_2$), 2.12-2.04 (2H, m, C**H**$_2$-3), 1.72 (2H, ap. quin., *J*=7.3 Hz, C**H**$_2$-2), 1.51-1.42 (2H, m, C**H**$_2$-9), 1.39-1.17 (6H, m, C**H**$_2$-(10-12)), 0.88 (3H, t, *J*=6.9 Hz, C**H**$_3$-13); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 137.2 (=**C**H), 134.6 (**Ar**SO_2), 129.6 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 115.4 (=**C**H^{a}H^b), 73.0 (≡**C**), 70.2 (≡**C**), 50.9 (**C**H_2NTs), 31.3 (**C**H_2-(10-12)), 30.3 (**C**H_2-3), 28.9 (**C**H_2-9), 28.4 (**C**H_2-(10-12)), 27.0 (**C**H_2-2), 22.6 (**C**H_2-(10-12)), 21.6 (Ar**C**H_3), 18.4 (≡C**C**H_2), 14.0 (**C**H_3-13); IR (thin film) ν_{max}/cm^{-1} 2931 m (C-H), 2254 w (C≡C), 1364 m (SO_2), 1170 s (SO_2); LRMS *m*/*z* (ESI+) 717.4 ([2M+Na]$^+$, 100%), 370.2 ([M+Na]$^+$, 30%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 370.1814; $C_{20}H_{29}NNaO_2S^+$ requires 370.1811.

_N_-(5-((_tert_-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methyl-_N_-(pent-4-en-1-yl)benzenesulfonamide, 195i



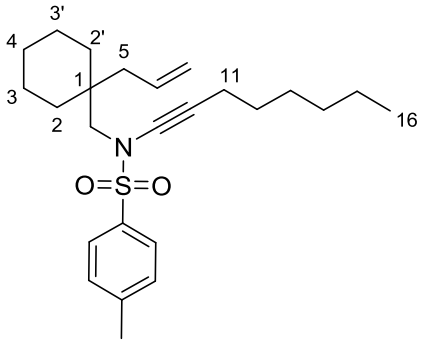
Synthesised from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **240d** (500 mg, 2.09 mmol) and ((5-bromopent-4-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (696 mg, 2.51 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether) to give the title compound as a colourless oil (688 mg, 1.58 mmol, 76%); R_f = 0.55 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.76 (1H, ddt, *J*=17.1, 10.3, 6.7 Hz, =C**H**), 5.06-4.94 (2H, m, =C**H**$^{\mathbf{a}}$**H**$^{\mathbf{b}}$), 3.64 (2H, t, *J*=6.1 Hz, C**H**$_2$O), 3.25 (2H, t, *J*=7.2 Hz, C**H**$_2$NTs), 2.44 (ArC**H**$_3$), 2.34 (2H, t, *J*=7.1 Hz ≡CC**H**$_2$), 2.08 (2H, ap. q, *J*=6.9 Hz C**H**$_2$-3), 1.71-1.63 (4H, m, C**H**$_2$-2, C**H**$_2$-9), 0.88 (9H, s, SiC(C**H**$_3$)$_3$), 0.33 (6H, s, Si(C**H**$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 137.1 (=**C**H) 134.5 (**Ar**SO_2), 129.6 (*m*-**Ts**H), 127.5 (*o*-**Ts**H), 115.4 (=**C**H^{a}H^{b}), 73.0 (≡**C**), 69.7 (≡**C**), 61.5 (**C**H_2O), 50.8 (**C**H_2NTs), 32.0 (**C**H_2-9), 30.2 (**C**H_2-3), 26.9 (**C**H_2-2) 25.9 (SiC(**C**H_3)$_3$), 21.6 (Ar**C**H_3), 18.3 (Si**C**$(CH_3)_3$), 14.9 (≡C**C**H_2), 5.4 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 2253 w (C≡C), 1363 m (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 893.4 ([2M+Na]$^+$, 100%), 458.2 ([M+Na]$^+$, 98%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 458.2147; $C_{23}H_{37}NNaO_3SSi^+$ requires 458.2156; Elemental Anal. calculated for $C_{23}H_{37}NO_3SSi$: C 63.4, H 8.6, N 3.2; found: C 63.3, H 8.5, N 3.2.

_N_-(5-Chloropent-1-yn-1-yl)-4-methyl-_N_-(pent-4-en-1-yl)benzenesulfonamide, 195j



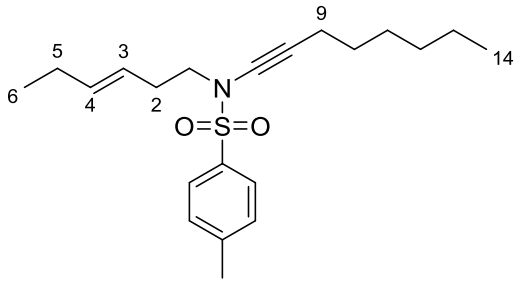
Synthesised from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **240d** (318 mg, 1.33 mmol) and 1-bromo-5-chloropent-1-yne (313 mg, 1.73 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (5%→15% Et_2O in pet. ether) to give the title compound as a colourless oil (367 mg, 1.08 mmol, 81%); R_f = 0.45 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.34 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.76 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz, =C**H**), 5.02 (1H, ap. dq, *J*=17.1, 1.7 Hz, =CH^a**H**^{b}), 4.99 (1H, ap. dq, *J*=10.3, 1.5 Hz, =C**H**^{a}H^b), 3.60 (2H, t, *J*=6.5 Hz, C**H**$_2$Cl), 3.27 (2H, t, *J*=7.2 Hz, C**H**$_2$NTs), 2.47 (2H, t, *J*=6.5 Hz, C**H**$_2$-8), 2.45 (3H, s, ArC**H**$_3$), 2.12-2.04 (2H, m, C**H**$_2$-3), 1.92 (2H, quin., *J*=6.5 Hz, C**H**$_2$-9), 1.72 (2H, quin., *J*=7.3 Hz, C**H**$_2$-2); δ_C (100 MHz, $CDCl_3$) 144.4 (**Ar**CH_3), 137.1 (=**C**H), 143.5 (**Ar**SO_2), 129.7 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 115.5 (=**C**H^{a}H^b), 74.1 (≡**C**), 68.2 (≡**C**), 50.8 (**C**H_2NTs), 43.6 (**C**H_2Cl), 31.5 (**C**H_2-9), 30.2 (**C**H_2-3), 27.0 (**C**H_2-2), 21.6 (Ar**C**H_3), 15.9 (**C**H_2-8); IR (thin film) ν_{max}/cm^{-1} 2924 s (C-H), 2257 w (C≡C), 1364 m (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 362.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 362.0963; $C_{17}H_{22}{}^{35}ClNNaO_2S^+$ requires 362.0952.

_N_-((1-Allylcyclohexyl)methyl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 195k



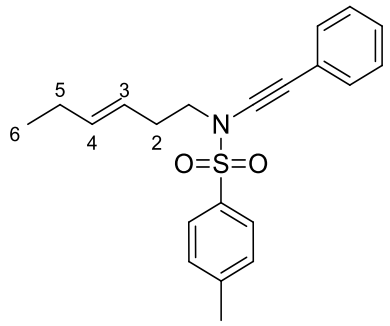
Synthesised from *N*-((1-allylcyclohexyl)methyl)-4-methylbenzenesulfonamide **245** (200 mg, 0.65 mmol) and 1-bromooct-1-yne (148 mg, 0.78 mmol) using Procedure 6, except the reaction mixture was stirred at 100 ºC for 48 h. The resulting crude material was purified by column chromatography (0%→5% Et_2O in pet. ether) to give the title compound as a colourless oil (160 mg, 0.38 mmol, 59%); R_f = 0.54 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.89-5.78 (1H, m, =C**H**), 5.07-5.01 (2H, m, =C**HH'**), 3.14 (2H, s, C$\mathbf{H_2}$NTs), 2.45 (3H, s, ArC$\mathbf{H_3}$), 2.25 (2H, d, *J*=7.3 Hz, C$\mathbf{H_2}$-5), 2.20 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-11), 1.54-1.18 (18H, m, C**HH'**-(2-4), C$\mathbf{H_2}$-(12-15)), 0.88 (3H, t, *J*=7.1 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 144.1 (**Ar**CH_3), 134.4 (**Ar**SO_2), 134.4 (=**C**H), 129.5 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 117.6 (=**C**HH'), 76.1 (≡**C**), 69.1 (≡**C**), 59.1 (**C**H_2NTs), 39.2 (**C**H_2-5), 37.8 (**C**-1), 33.1 (**C**H_2-(2-4, 12-15)), 31.3 (**C**H_2-(2-4, 12-15)), 28.7 (**C**H_2-(2-4, 12-15)), 28.5 (**C**H_2-(2-4, 12-15)), 25.9 (**C**H_2-(2-4, 12-15)), 22.6 (**C**H_2-(2-4, 12-15)), 21.6 (Ar**C**H_3), 21.3 (**C**H_2-(2-4, 12-15)), 18.4 (**C**H_2-11), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2927 m (C-H), 2252 w (C≡C), 1365 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 416.2 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 438.2436; $C_{25}H_{37}NNaO_2S$ requires 438.2437.

(*E*)-*N*-(Hex-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 195l



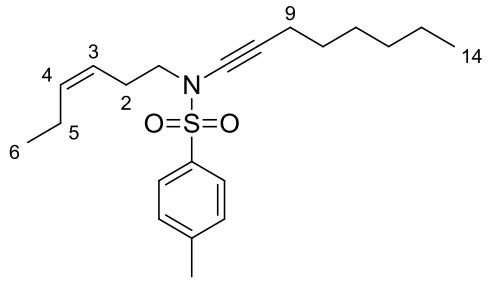
Synthesised from (*E*)-*N*-(hex-3-en-1-yl)-4-methylbenzenesulfonamide **252a** (1.00 g, 3.95 mmol) and 1-bromooct-1-yne (896 mg, 4.74 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound as a colourless oil (1.24 g, 3.44 mmol, 87%); R_f = 0.62 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.51 (1H, dtt, *J*=15.3, 6.3, 1.1 Hz, =C**H**-4), 5.27 (1H, dtt, *J*=15.3, 6.8, 1.4 Hz, =C**H**-3), 3.30-3.24 (2H, m, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.33-2.25 (2H, m, C$\mathbf{H_2}$-2), 2.25 (2H, t, *J*=7.1 Hz, C$\mathbf{H_2}$-9), 2.01-1.91 (2H, m, C$\mathbf{H_2}$-5), 1.52-1.42 (2H, m, C$\mathbf{H_2}$-10), 1.39-1.22 (6H, m, C$\mathbf{H_2}$-(11-13)), 0.93 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6), 0.88 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-14); δ_C (100 MHz, $CDCl_3$) 144.1 (**Ar**CH_3), 135.2 (=**C**H-4), 134.7 (**Ar**SO_2), 129.5 (*m*-**Ts**H), 127.6 (*o*-Ts**H**), 124.0 (=**C**H-3), 72.9 (≡**C**), 70.4 (≡**C**), 51.3 (**C**H_2NTs), 31.3 (C$\mathbf{H_2}$-(11-13)), 31.0 (**C**H_2-2), 28.9 (**C**H_2-10), 28.4 (C$\mathbf{H_2}$-(11-13)), 25.5 (**C**H_2-5), 22.6 (C$\mathbf{H_2}$-(11-13)), 21.6 (Ar**C**H_3), 18.4 (C$\mathbf{H_2}$-9), 14.0 (C$\mathbf{H_3}$-14), 13.6 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 2930 w (C-H), 2253 w (C≡C), 1364 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 384.2 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 384.1955; $C_{21}H_{31}NNaO_2S^+$ requires 384.1968.

(*E*)-*N*-(Hex-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 195m



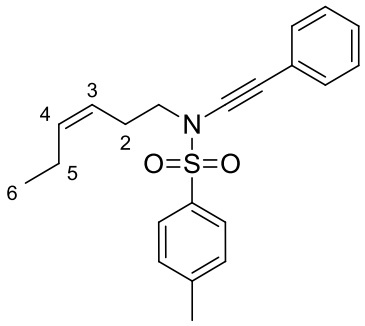
Synthesised from (*E*)-*N*-(hex-3-en-1-yl)-4-methylbenzenesulfonamide **252a** (1.00 g, 3.95 mmol) and (bromoethynyl)benzene (1.07 g, 5.92 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (8%→10% Et_2O in pet. ether) to give the title compound as a yellow oil (1.32 g, 3.73 mmol, 95%); R_f = 0.51 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.40-7.33 (4H, m, *m*-Ts**H**, Ph**H**), 7.33-7.26 (3H, m, Ph**H**), 5.55 (1H, dtt, *J*=15.3, 6.3, 1.3 Hz, =C**H**-4), 5.31 (1H, dtt, *J*=15.3, 6.8, 1.3 Hz, =C**H**-3), 3.43 (2H, ap. t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 2.45 (3H, s, ArC$\mathbf{H_3}$), 2.38 (2H, br. ap. q, *J*=7.1 Hz, C$\mathbf{H_2}$-2), 1.97 (2H, m, C$\mathbf{H_2}$-5), 0.94 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 144.5 (**Ar**CH_3) 135.6 (=**C**H-4), 134.7 (**Ar**SO_2), 131.3 (**Ar**H), 129.7 (**Ar**H), 128.2 (**Ar**H), 127.7 (**Ar**H), 127.7 (**Ar**H), 123.8 (=**C**H-3), 122.9 (**Ph**), 82.3 (≡**C**NTs), 70.8 (≡**C**Ph), 51.5 (**C**H_2NTs), 31.2 (**C**H_2-2), 25.6 (**C**H_2-5), 21.6 (Ar**C**H_3), 13.6 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 2962 w (C-H), 2234 w (C≡C), 1364 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 729.3 ($[2M+Na]^+$, 100%), 354.1 ($[M+H]^+$, 17%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 376.1331; $C_{21}H_{23}NNaO_2S^+$ requires 376.1342.

(*Z*)-*N*-(Hex-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 195n



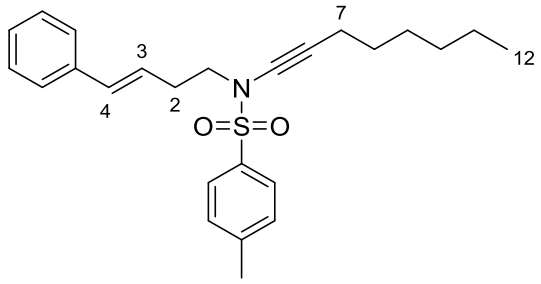
Synthesised from (*Z*)-*N*-(hex-3-en-1-yl)-4-methylbenzenesulfonamide **252b** (1.00 g, 3.95 mmol) and 1-bromooct-1-yne (896 mg, 4.74 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether) to give the title compound as a colourless oil (1.34 g, 3.71 mmol, 94%); R_f = 0.53 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**),7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.45 (1H, dtt, *J*=10.7, 7.3, 1.4 Hz, =C**H**-4), 5.27 (1H, dtt, *J*=10.7, 7.5, 1.5 Hz, =C**H**-3), 3.29-3.23 (2H, m, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.35 (2H, ap. q, *J*=7.5 Hz, C$\mathbf{H_2}$-2), 2.26 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-9), 2.01 (2H, ap. quin.d, *J*=7.5, 1.3 Hz, C$\mathbf{H_2}$-5), 1.52-1.42 (2H, m, C$\mathbf{H_2}$-10), 1.40-1.20 (6H, m, C$\mathbf{H_2}$-(11-13)), 0.94 (3H, t, *J*=7.6 Hz, C$\mathbf{H_3}$-6), 0.88 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-14); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 134.8 (=**C**H-4, **Ar**SO_2), 129.5 (*m*-**Ts**H), 127.6 (*o*-Ts**H**), 123.7 (=**C**H-3), 72.9 (≡**C**), 70.4 (≡**C**), 51.1 (**C**H_2NTs), 31.3 (**C**H_2-(11-13)), 28.9 (**C**H_2-10), 28.5 (**C**H_2-(11-13)), 25.7 (**C**H_2-2), 22.6 (**C**H_2-(11-13)), 21.6 (Ar**C**H_3), 20.6 (**C**H_2-5), 18.5 (C$\mathbf{H_2}$-9), 14.2 (**C**H_3-6), 14.0 (**C**H_3-14); IR (thin film) ν_{max}/cm^{-1} 2933 w (C-H), 2254 w (C≡C), 1365 m (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 384.3 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 384.1955; $C_{21}H_{31}NNaO_2S^+$ requires 384.1968.

(*Z*)-*N*-(Hex-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 195o



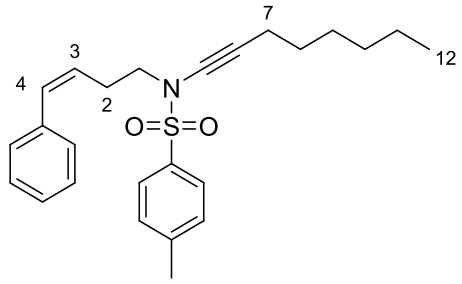
Synthesised from (*Z*)-*N*-(hex-3-en-1-yl)-4-methylbenzenesulfonamide **252b** (1.00 g, 3.95 mmol) and (bromoethynyl)benzene (1.07 g, 5.92 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether) to give the title compound as a yellow oil (1.03 g, 2.91 mmol, 74%); R_f = 0.51 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.40-7.33 (4H, m, *m*-Ts**H**, Ph**H**), 7.33-7.26 (3H, m, Ph**H**), 5.48 (1H, dtt, *J*=10.9, 7.3, 1.3 Hz, =C**H**-4), 5.27 (1H, dtt, *J*=10.9, 7.3, 1.5 Hz, =C**H**-3), 3.42 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 2.49-2.40 (2H, m, C$\mathbf{H_2}$-2), 2.45 (3H, s, ArC$\mathbf{H_3}$), 2.04 (2H, ap. quin.d, *J*=7.4, 1.5 Hz, C$\mathbf{H_2}$-5), 0.95 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 144.6 (**Ar**CH_3), 135.0 (=**C**H-4), 134.7 (**Ar**SO_2), 131.3 (**Ar**H), 129.7 (**Ar**H), 128.2 (**Ar**H), 127.7 (**Ar**H), 127.7 (**Ar**H), 123.5 (=**C**H-3), 122.9 (**Ph**), 82.2 (≡**C**NTs), 70.8 (≡**C**Ph), 51.3 (**C**H_2NTs), 26.0 (**C**H_2-2), 21.6 (Ar**C**H_3), 20.6 (**C**H_2-5), 14.2 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 2963 w (C-H), 2234 w (C≡C), 1363 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 729.3 ($[2M+Na]^+$, 100%), 354.1 ($[M+H]^+$, 21%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 376.1344; $C_{21}H_{23}NNaO_2S^+$ requires 376.1342.

(*E*)-4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide, 195p



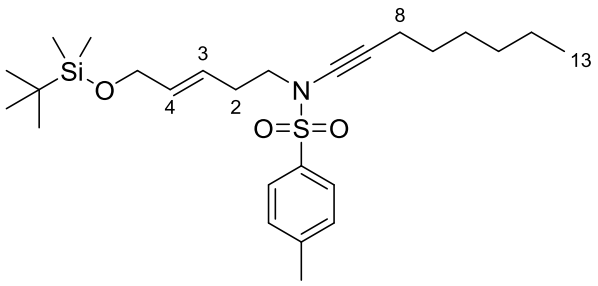
Synthesised from (*E*)-4-methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide **252c** (100 mg, 0.33 mmol) and 1-bromooct-1-yne (75 mg, 0.40 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (5%→20% Et_2O in pet. ether) to give the title compound as a colourless oil (109 mg, 0.27 mmol, 81%); R_f = 0.57 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32-7.17 (7H, m, *m*-Ts**H**, Ph**H**), 6.39 (2H, d, *J*=15.8 Hz, =C**H**-4), 6.07 (1H, dt, *J*=15.8, 7.1 Hz, =C**H**-3), 3.42 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.53 (2H, ap. qd, *J*=7.1, 1.3 Hz, C$\mathbf{H_2}$-2), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.27 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-7), 1.48 (2H, quin., *J*=7.2 Hz, C$\mathbf{H_2}$-8), 1.40-1.21 (6H, m, C$\mathbf{H_2}$-(9-11)), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-12); δ_C (125 MHz, $CDCl_3$) 144.2 (**Ar**), 137.1 (**Ar**), 134.7 (**Ar**), 132.6 (=**C**-4), 129.6 (**Ar**H), 128.5 (**Ar**H), 127.6 (*o*-**Ts**H), 127.3 (**Ar**H), 126.1 (**Ar**H), 125.5 (=**C**-3), 72.9 (≡**C**), 70.7 (≡**C**), 51.1 (**C**H_2NTs), 31.6 (**C**H_2-2), 31.3 (**C**H_2-(9-11)), 28.9 (**C**H_2-8), 28.5 (**C**H_2-(9-11)), 22.6 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 18.5 (**C**H_2-7), 14.1 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 2253 w (C≡C), 1364 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 432.1 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 432.1961; $C_{25}H_{31}NNaO_2S$ requires 432.1968.

(*Z*)-4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide, 195q



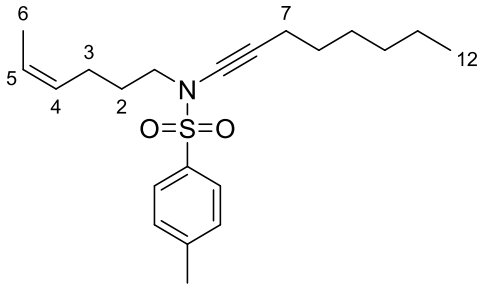
Synthesised from (*Z*)-4-methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide **252d** (200 mg, 0.66 mmol) and 1-bromooct-1-yne (151 mg, 0.80 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (10%→20% Et_2O in pet. ether) to give the title compound as a colourless oil (250 mg, 0.61 mmol, 92%); R_f = 0.54 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.36-7.27 (4H, m, *m*-Ts**H,** Ph**H**), 7.27-7.20 (3H, m, Ph**H**), 6.50 (1H, d, *J*=11.6 Hz, =C**H**-4), 5.59 (1H, dt, *J*=11.6, 7.2 Hz, =C**H**-3), 3.38 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.65 (2H, ap. q, *J*=7.3 Hz, C$\mathbf{H_2}$-2), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.21 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-7), 1.48-1.38 (2H, m, C$\mathbf{H_2}$-8), 1.37-1.18 (6H, m, C$\mathbf{H_2}$-(9-11)), 0.88 (3H, t, *J*=6.7 Hz, C$\mathbf{H_3}$-12); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**), 137.0 (**Ar**), 134.6 (**Ar**), 131.4 (=**C**H-4), 129.6 (*m*-**Ts**H), 128.6 (**Ph**H), 128.2 (**Ph**H), 127.6 (*o*-**Ts**H), 127.2 (**=C**H-3), 126.8 (**Ph**H), 72.7 (≡**C**), 70.6 (≡**C**), 51.1 (**C**H_2NTs), 31.3 (**C**H_2-(9-11)), 28.8 (**C**H_2-8), 28.4 (**C**H_2-(9-11)), 27.1 (**C**H_2-2), 22.5 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 18.4 (**C**H_2-7), 14.0 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 2254 w (C≡C), 1364 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 432.2 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 432.1957; $C_{25}H_{31}NNaO_2S$ requires 432.1968.

(*E*)-*N*-(5-((*tert*-Butyldimethylsilyl)oxy)pent-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 195r



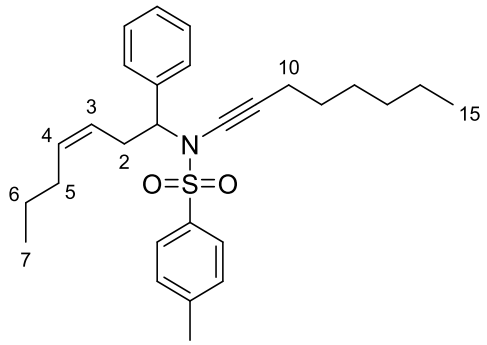
Synthesised from (*E*)-*N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)-4-methylbenzenesulfonamide **259** (72 mg, 0.19 mmol) and 1-bromooct-1-yne (44 mg, 0.23 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (19:1, pet. ether:Et_2O) to give the title compound as a colourless oil (82 mg, 0.17 mmol, 90%); R_f = 0.58 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.65-5.48 (2H, m, =C**H**-4, =C**H**-3), 4.08 (2H, dd, *J*=4.5, 0.9 Hz, C$\mathbf{H_2}$O), 3.33-3.26 (2H, m, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.35 (2H, br. q, *J*=6.8 Hz, C$\mathbf{H_2}$-2), 2.25 (2H, t, *J*=7.0 Hz, C$\mathbf{H_2}$-8), 1.47 (2H, ap. quin., *J*=7.2 Hz, C$\mathbf{H_2}$-9), 1.39-1.20 (6H, m, C$\mathbf{H_2}$-(10-12)), 0.92-0.85 (3H, m, C$\mathbf{H_3}$-13), 0.90 (9H, s, C(C$\mathbf{H_3}$)$_3$), 0.06 (6H, s, Si(C$\mathbf{H_3}$)$_2$); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 134.6 (**Ar**SO_2), 132.3 (=**C**H-4), 129.5 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 125.8 (=**C**H-3), 72.8 (≡**C**), 70.5 (≡**C**), 63.6 (**C**H_2O), 50.9 (**C**H_2NTs), 31.3 (**C**H_2-(10-12)), 30.6 (**C**H_2-2), 28.9 (**C**H_2-9), 28.4 (**C**H_2-(10-12)), 25.9 (C(**C**H_3)$_3$), 22.6 (**C**H_2-(10-12)), 21.6 (Ar**C**H_3), 18.5 (**C**H_2-8), 18.4 (**C**$(CH_3)_3$), 14.0 (**C**H_3-13), -5.2 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 2926 s (C-H), 2254 w (C≡C), 1365 m (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 500.3 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 500.2625; $C_{26}H_{43}NNaO_3SSi^+$ requires 500.2625.

(*Z*)-*N*-(Hex-4-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 195s



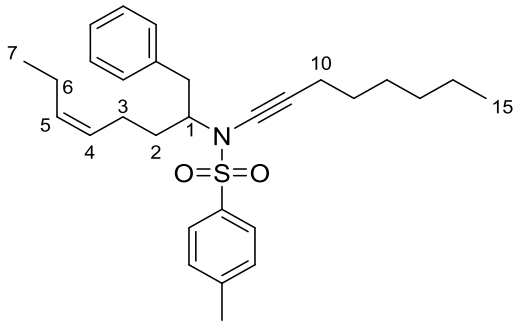
Synthesised from (*Z*)-*N*-(hex-4-en-1-yl)-4-methylbenzenesulfonamide **252e** (1.00 g, 3.92 mmol) and 1-bromooct-1-yne (888 mg, 4.70 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (5%→15% Et_2O in pet. ether) to give the title compound as a colourless oil (1.35 g, 3.73 mmol, 95%); R_f = 0.59 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.47 (1H, dqt, 11.0, 6.7, 1.2 Hz, =C**H**-5), (1H, dtq, *J*=11.0, 7.3, 1.6 Hz, =C**H**-4), 3.25 (2H, t, *J*=7.2 Hz, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.25 (2H, t, *J*=7.0 Hz, C$\mathbf{H_2}$-7), 2.06 (2H, q, *J*=7.3 Hz, C$\mathbf{H_2}$-3), 1.67 (2H, quin., *J*=7.3 Hz, C$\mathbf{H_2}$-2), 1.58 (3H, dd, *J*=6.7, 1.2 Hz, C$\mathbf{H_3}$-6), 1.51-1.41 (2H, m, C$\mathbf{H_2}$-8), 1.39-1.18 (6H, m, C$\mathbf{H_2}$-(9-11)), 0.88 (3H, t, *J*=6.8 Hz, C$\mathbf{H_3}$-12); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 134.5 (**Ar**SO_2), 129.5 (*m*-**Ts**H), 128.9 (=**C**H-4) 127.6 (*o*-**Ts**H), 125.0 (=**C**H-5), 72.9 (≡**C**), 70.2 (≡**C**), 50.9 (**C**H_2NTs), 31.3 (**C**H_2-(9-11)), 28.9 (**C**H_2-8), 28.4 (**C**H_2-(9-11)), 27.6 (**C**H_2-2), 23.6 (**C**H_2-3), 22.6 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 18.5 (**C**H_2-7), 14.0 (**C**H_3-12), 12.8 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 2253 w (C≡C), 1363 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 362.2 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 384.1958; $C_{21}H_{31}NNaO_2S^+$ requires 384.1968.

(*Z*)-4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(1-phenylhept-3-en-1-yl)benzenesulfonamide, 195t



Synthesised from (*Z*)-4-methyl-*N*-(1-phenylhept-3-en-1-yl)benzenesulfonamide **269** (105 mg, 0.31 mmol) and 1-bromooct-1-yne (87 mg, 0.46 mmol) using Procedure 6, except the reaction mixture was heated to 110 °C for 24 h. The resulting crude material was purified by column chromatography (5%→30% Et_2O in pet. ether) to give the title compound as a colourless oil (72 mg, 0.16 mmol, 52% (77% brsm)); R_f = 0.63 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.53 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30-7.24 (2H, m, Ph**H**), 7.23-7.16 (3H, m, Ph**H**), 7.12 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.40-5.31 (1H, m, =C**H**-4), 5.23-5.14 (1H, m, =C**H**-3), 4.89 (1H, dd, *J*=8.5, 7.3 Hz, C**H**Ph), 2.75-2.66 (1H, m, C**H**H'-2), 2.62-2.53 (1H, m, CH**H'**-2), 2.36 (3H, s, ArC$\mathbf{H_3}$), 2.31 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-10), 2.00-1.87 (2H, m, C**HH'**-5), 1.49 (2H, ap. quin., *J*=7.3 Hz, C$\mathbf{H_2}$-11), 1.38-1.20 (8H, m, C**HH'**-6, C$\mathbf{H_2}$-(12-14)), 0.88 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-15), 0.86 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-7); δ_C (125 MHz, $CDCl_3$) 143.7 (**Ar**), 139.3 (**Ar**), 135.5 (**Ar**), 132.7 (=**C**H-4), 129.0 (*m*-**Ts**H), 128.2 (**Ph**H), 127.8 (**Ph**H), 127.7 (*o*-**Ts**H), 127.2 (**Ph**H), 124.6 (=**C**H-3), 73.0 (≡**C**), 70.9 (≡**C**), 62.9 (**C**HPh), 31.8 (**C**HH'-2), 31.4 (**C**H_2-(12-14)), 29.5 (**C**HH'-5), 28.9 (**C**H_2-11), 28.5 (**C**H_2-(12-14)), 22.6 (**C**HH'-6, **C**H_2-(12-14)), 21.5 (Ar**C**H_3), 18.7 (**C**H_2-10), 14.1 (**C**H_3-15), 13.8 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 2250 w (C≡C) 1363 m (SO_2), 1168 s (SO_2); HRMS *m*/*z* (FI) found [M] 451.2549; $C_{28}H_{37}NNaO_2S$ requires 451.2545.

(*Z*)-4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(1-phenyloct-5-en-2-yl)benzenesulfonamide*, 195u

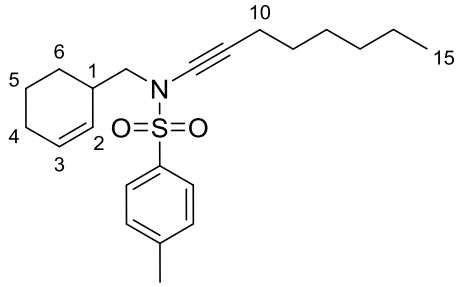


***Reaction carried out by Dr. Craig Campbell.**

To a mixture of (*Z*)-4-methyl-*N*-(1-phenyloct-5-en-2-yl)benzenesulfonamide **277** (500 mg, 1.40 mmol, 1.0 eq.), K_2CO_3 (425 mg, 3.07 mmol, 2.2 eq.), $CuSO_4$•$5H_2O$ (140 mg, 0.56 mmol, 0.4 eq.) and 1,10-phenanthroline (202 mg, 1.12 mmol, 0.8 eq.) was added a solution of 1-bromooct-1-yne (529 mg, 2.80 mmol, 2.0 eq.), in toluene (4.2 mL). The reaction mixture was stirred at 105 °C for 48 h before being allowed to cool to RT. The reaction mixture was filtered through Celite eluting with Et_2O and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5%→10% Et_2O in pet. ether) to give the title compound as a pale yellow oil (452 mg, 0.99 mmol, 71%); R_f = 0.55 (9:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.51 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.24-7.13 (5H, m, Ar**H**), 7.14-7.07 (2H, m, Ar**H**), 5.39-5.30 (1H, m, =C**H**-5), 5.28-5.19 (1H, m, =C**H**-4), 4.12 (1H, dddd, *J*=9.5, 7.8, 6.9, 4.5 Hz, C**H**-1), 2.75 (1H, dd, *J*=13.4, 7.8 Hz, C**H**H'Ph), 2.69 (1H, dd, *J*=13.4, 6.9 Hz, CH**H'**Ph), 2.39 (3H, s, ArC$\mathbf{H_3}$), 2.34 (2H, t, *J*=6.8 Hz, C$\mathbf{H_2}$-10), 2.11-2.00 (1H, m, C**H**H'-3), 1.96 (2H, ap. quin., *J*=7.5 Hz, C$\mathbf{H_2}$-6), 1.91-1.80 (1H, m, CH**H'**-3), 1.70-1.58 (1H, m, C**H**H'-2), 1.56-1.45 (3H, m, CH**H'**-2, C$\mathbf{H_2}$-11), 1.42-1.23 (6H, m, C$\mathbf{H_2}$-(12-14)), 0.91 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7), 0.90 (3H, t, *J*=6.8 Hz, C$\mathbf{H_3}$-15); δ_C (100 MHz, $CDCl_3$) 143.6 (**Ar**), 138.0 (**Ar**), 135.8 (**Ar**), 132.4 (=**C**H-5), 129.3 (**Ar**H×2), 128.4 (**Ar**H), 127.6 (=**C**H-4), 127.4 (**Ar**H), 126.4 (**Ar**H), 72.8 (≡**C**), 69.7 (≡**C**), 62.0 (**C**H-1), 39.8 (**C**HH'Ph), 32.8 (**C**HH'-2), 31.3 (**C**H_2-(12-14)), 29.0 (**C**H_2-11), 28.5 (**C**H_2-(12-14)), 23.9 (**C**HH'-3), 22.6

(**C**H_2-(12-14)), 21.5 (Ar**C**H_3), 20.5 (**C**H_2-6), 18.6 (**C**H_2-10), 14.3 (**C**H_3-7), 14.1 (**C**H_3-15); IR (thin film) ν_{max}/cm^{-1} 2959 m (C-H), 2249 w (C≡C), 1363 m (SO_2), 1167 s (SO_2); LRMS *m*/*z* (ESI+) 466.3 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 488.2601; $C_{29}H_{39}NNaO_2S^+$ requires 488.2594.

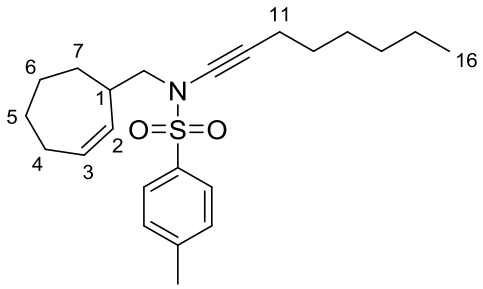
_N_-(Cyclohex-2-en-1-ylmethyl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 282a



Synthesised from *N*-(cyclohex-2-en-1-ylmethyl)-4-methylbenzenesulfonamide **281a** (2.00 g, 7.54 mmol) and 1-bromooct-1-yne (1.71 g, 9.04 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (5%→10% Et_2O in pet. ether) to give the title compound as a colourless solid (2.50 g, 6.68 mmol, 89%); m.p. 28-30 °C; R_f = 0.61 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.80-5.73 (1H, m, =C**H**-3), 5.52 (1H, dq, *J*=10.0, 2.1 Hz, =C**H**-2), 3.16 (1H, dd, *J*=12.3, 8.8 Hz, C**H**H'NTs), 3.09 (1H, dd, *J*=12.3, 6.3 Hz, CH**H'**NTs); 2.58-2.48 (1H, m, C**H**-1), 2.44 (3H, s, ArC**H**$_3$), 2.25 (2H, t, *J*=6.9 Hz, C**H**$_2$-10), 2.03-1.96 (2H, br. m, C**HH'**-4), 1.81-1.74 (1H, m, C**H**H'-6), 1.74-1.66 (1H, m, C**H**H'-5), 1.59-1.42 (3H, m, CH**H'**-5, C**H**$_2$-11), 1.40-1.20 (7H, CH**H'**-6, C**H**$_2$-(12-14)), 0.88 (3H, t, *J*=7.1 Hz, C**H**$_3$-15); δ_C (100 MHz, $CDCl_3$) 144.1 (**Ar**CH_3), 134.6 (**Ar**SO_2), 129.5 (*o*-**Ts**H), 129.4 (=**C**H-3), 127.6 (*m*-**Ts**H), 127.2 (=**C**H-2), 73.3 (≡**C**NTs), 70.2 (≡**C**CH_2), 56.0 (**C**HH'NTs), 33.9 (**C**H-1), 31.3 (**C**H_2-(12-14)), 28.9 (**C**H_2-11), 28.4 (**C**H_2-(12-14)), 26.0 (**C**HH'-5), 25.3 (**C**HH'-4), 22.6 (**C**H_2-(12-14)), 21.6 (Ar**C**H_3), 20.4 (**C**HH'-5), 18.5 (**C**H_2-10), 14.0 (**C**H_3-15); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 2252 w (C≡C), 1357 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 769.4

([2M+Na]$^+$, 100%), 396.2 ([M+Na]$^+$, 62%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 396.1962; $C_{22}H_{31}NNaO_2S^+$ requires 396.1968; Elemental Anal. calculated for $C_{22}H_{31}NO_2S$: C 70.7, H 8.4, N 3.8; found: C 70.6, H 8.5, N 3.7.

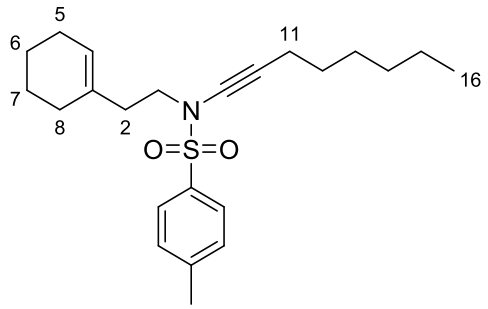
_N_-(Cyclohept-2-en-1-ylmethyl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 282b



Synthesised from *N*-(cyclohept-2-en-1-ylmethyl)-4-methylbenzenesulfonamide **281b** (190 mg, 0.68 mmol) and 1-bromooct-1-yne (154 mg, 0.82 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (2%→10% Et_2O in pet. ether) to give the title compound as a colourless oil (373 mg, 0.10 mmol, 88%); R_f = 0.52 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.33 (2H, d, *J*=8.2, *m*-Ts**H**), 5.83 (1H, dddd, *J*=11.1, 7.3, 5.2, 2.2 Hz, =C**H**-3), 5.55-5.49 (1H, m, =C**H**-2), 3.21-3.11 (2H, m, C**HH'**NTs), 2.70-2.60 (1H, br. m, C**H**-1), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.25 (2H, t, *J*=6.9 Hz, ≡CC$\mathbf{H_2}$), 2.21-2.12 (1H, m, C**H**H'-4), 2.12-2.03 (1H, m, CH**H'**-4), 2.00-1.91 (1H, m, C**H**H'-6), 1.74-1.62 (2H, m, C**H**H'-7, C**H**H'-5), 1.60-1.42 (3H, m, CH**H'**-6, C$\mathbf{H_2}$-12), 1.39-1.19 (8H, m, CH**H'**-5, CH**H'**-7, C$\mathbf{H_2}$-(13-15)), 0.88 (3H, t, *J*=7.1 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 134.5 (**Ar**SO_2), 132.9 (=**C**H-2), 132.9 (=**C**H-3), 129.5 (*m*-**Ts**H), 127.7 (*o*-**Ts**H), 73.2 (≡**C**NTs), 70.4 (≡**C**CH_2), 56.1 (**C**HH'NTs), 38.2 (**C**H-1), 31.3 (**C**H_2-(13-15)), 30.2 (**C**HH'-7), 29.9 (**C**HH'-6), 28.9 (**C**H_2-12), 28.7 (**C**HH'-4), 28.4 (**C**H_2-(13-15)), 26.8 (**C**HH'-5), 22.6 (**C**H_2-(13-15)), 21.6 (Ar**C**H_3), 18.5 (≡C**C**H_2), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2924 m (C-H), 2257 w (C≡C), 1357 m (SO_2), 1165 s (SO_2);

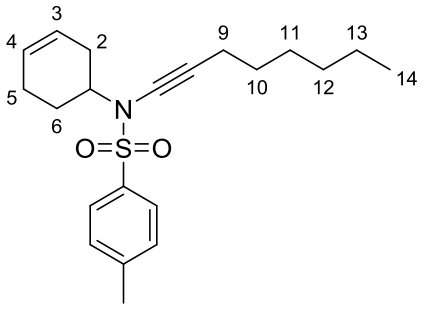
LRMS m/z (ESI+) 388.2 ($[M+H]^+$, 91%); HRMS m/z (ESI+) found $[M+H]^+$ 388.2300; $C_{23}H_{34}NO_2S^+$ requires 388.2305.

_N_-(2-(Cyclohex-1-en-1-yl)ethyl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 282c



Synthesised from *N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide **289** (120 mg, 0.43 mmol) and 1-bromooct-1-yne (97 mg, 0.52 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (0%→5% Et_2O in pet. ether) to give the title compound as a pale yellow oil (138 mg, 0.36 mmol, 83%); R_f = 0.72 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.45-5.40 (1H, br. m, =C**H**), 3.36-3.29 (2H, m, C**HH'**NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.29-2.18 (4H, m, C$\mathbf{H_2}$-11, C$\mathbf{H_2}$-2), 1.99-1.93 (2H, m, C$\mathbf{H_2}$-5), 1.93-1.86 (2H, m, C$\mathbf{H_2}$-8), 1.64-1.41 (6H, m, C$\mathbf{H_2}$-7, C$\mathbf{H_2}$-6, C$\mathbf{H_2}$-12), 1.39-1.19 (6H, m, C$\mathbf{H_2}$-(13-15)), 0.89 (3H, t, *J*=7.1 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 144.1 (**C**), 134.9 (**C**), 133.6 (**C**), 129.5 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 123.9 (=**C**H), 73.0 (≡**C**), 70.3 (≡**C**), 50.2 (**C**HH'NTs), 36.2 (**C**H_2-2), 31.3 (**C**H_2-(13-15)), 28.9 (**C**H_2-12), 28.4 (**C**H_2-(13-15)), 28.2 (**C**H_2-8), 25.2 (**C**H_2-5), 22.8 (**C**H_2-7), 22.6 (**C**H_2-(13-15)), 22.2 (**C**H_2-6), 21.6 (Ar**C**H_3), 18.5 (C$\mathbf{H_2}$-11), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2928 m (C-H), 2252 w (C≡C), 1364 m (SO_2), 1169 s (SO_2); LRMS m/z (ESI+) 410.1 ($[M+Na]^+$, 100%); HRMS m/z (ESI+) found $[M+Na]^+$ 410.2109; $C_{23}H_{33}NNaO_2S$ requires 410.2124.

_N_-(Cyclohex-3-en-1-yl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide*, 282d

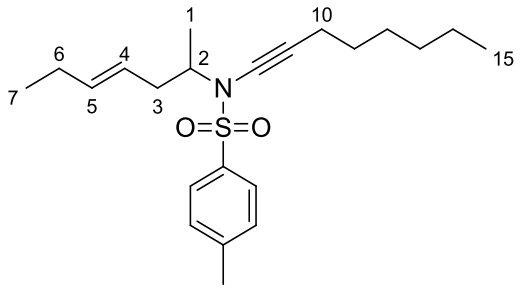


***Reaction carried out by Dr. Craig Campbell.**

To a mixture of *N*-(cyclohex-3-en-1-yl)-4-methylbenzenesulfonamide **294** (948 mg, 3.77 mmol, 1.0 eq.), K_3PO_4 (1.60 g, 7.54 mmol, 2.0 eq.), $CuSO_4 \bullet 5H_2O$ (376 mg, 1.51 mmol, 0.4 eq.) and 1,10-phenanthroline (544 mg, 3.02 mg, 0.8 eq.) was added a solution of 1-bromooct-1-yne (1.43 mg, 7.54 mmol, 2.0 eq.), in toluene (11 mL). The reaction mixture was stirred at 105 °C for 15 h before being allowed to cool to RT. The reaction mixture was filtered through Celite eluting with Et_2O and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5%→10% EtOAc in pet. ether) to give the title compound as a colourless oil (969 mg, 2.70 mmol, 71% (88% brsm)); R_f = 0.28 (11:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.83-7.78 (2H, m, *o*-Ts**H**), 7.31 (2H, d, *J*=8.0 Hz, *m*-Ts**H**), 5.62-5.55 (1H, m, =C**H**-4), 5.55-5.48 (1H, m, =C**H**-3), 4.07-3.95 (1H, m, C**H**NTs), 2.43 (3H, s, ArC**H**$_3$), 2.27 (2H, t, *J*=6.9 Hz, C**H**$_2$-9), 2.25-2.17 (1H, m, C**H**H'-2), 2.17-2.08 (2H, m, C**H**H'-5), 2.02-1.91 (1H, m, CH**H'**-2), 1.77-1.59 (2H, m, C**HH'**-6), 1.53-1.43 (2H, m, C**H**$_2$-10), 1.39-1.20 (6H, m, C**H**$_2$-(11-13)), 0.87 (3H, t, *J*=6.8 Hz, C**H**$_3$-14); δ_C (125 MHz, $CDCl_3$) 144.0 (**Ar**CH_3), 136.3 (**Ar**SO_2), 129.6 (*m*-**Ts**H), 127.3 (*o*-**Ts**H), 126.3 (=**C**H-4), 124.6 (=**C**H-3), 71.8 (≡**C**), 70.2 (≡**C**), 55.6 (**C**H_2NTs), 31.3 (**C**H_2-(11-13)), 29.3 (**C**HH'-2), 28.9 (**C**H_2-10), 28.4 (**C**H_2-(11-13)), 27.1 (**C**HH'-6), 25.3 (**C**HH'-5), 22.5 (**C**H_2-(11-13)), 21.6 (Ar**C**H_3), 18.5 (**C**H_2-9), 14.0 (**C**H_3-14); IR (thin film) ν_{max}/cm^{-1} 2929 m (C-H), 2253 m (C≡C), 1598 m (C=C), 1362 m (SO_2), 1166 s (SO_2); LRMS *m*/*z* (ESI+) 360.3

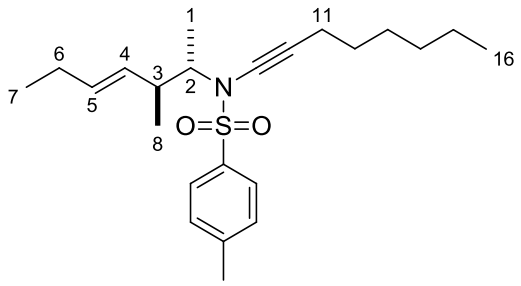
([M+H]$^+$, 80%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 382.1803; $C_{21}H_{29}NNaO_2S^+$ requires 382.1811.

(*E*)-*N*-(Hept-4-en-2-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 306a



Synthesised from (*E*)-*N*-(hept-4-en-2-yl)-4-methylbenzenesulfonamide **313a** (400 mg, 1.50 mmol) and 1-bromooct-1-yne (424 mg, 2.24 mmol) using Procedure 6, except the reaction mixture was stirred at 100 ºC for 24 h. The resulting crude material was purified by column chromatography (19:1, hexanes:*t*-BuOMe) to give the title compound as a yellow oil (441 mg, 1.17 mmol, 78%); R_f = 0.79 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.44 (1H, br. dt, *J*=15.2, 6.3 Hz, =C**H**-5), 5.20-5.10 (1H, m, =C**H**-4), 3.94 (1H, ap. sext., *J*=6.8 Hz, C**H**-2), 2.43 (3H, s, ArC**H$_3$**), 2.29 (2H, t, *J*=7.1 Hz, C**H$_2$**-10), 2.25-2.15 (1H, m, C**H**H'-3), 2.09-2.00 (1H, m, CH**H'**-3), 1.89 (2H, ap. quin., *J*=7.1 Hz, C**H$_2$**-6), 1.49 (2H, quin., *J*=7.1 Hz, C**H$_2$**-11), 1.41-1.21 (6H, m, C**H$_2$**-(12-14)), 1.05 (3H, d, *J*=6.6 Hz, C**H$_3$**-1), 0.90 (3H, t, *J*=7.4 Hz, C**H$_3$**-7), 0.88 (3H, t, *J*=6.9 Hz, C**H$_3$**-15); δ_C (125 MHz, $CDCl_3$) 143.9 (**Ar**CH_3), 136.3 (**Ar**SO_2), 135.3 (=**C**H-5), 129.4 (*m*-**Ts**H), 127.4 (*o*-**Ts**H), 124.4 (=**C**H-4), 72.1 (≡**C**), 69.8 (≡**C**), 56.3 (**C**H-2), 38.0 (**C**HH'-3), 31.3 (**C**H_2-(12-14)), 29.0 (**C**H_2-11), 28.4 (**C**H_2-(12-14)), 25.5 (**C**H_2-6), 22.6 (**C**H_2-(12-14)), 21.6 (Ar**C**H_3), 18.6 (**C**H_2-10), 18.4 (**C**H_3-1), 14.0 (**C**H_3-15), 13.6 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2931 m (C-H), 2253 m (C≡C), 1361 m (SO_2), 1169 s (SO_2); HRMS *m*/*z* (ESI+) found [M+H]$^+$ 376.2308; $C_{22}H_{34}NO_2S^+$ requires 376.2305.

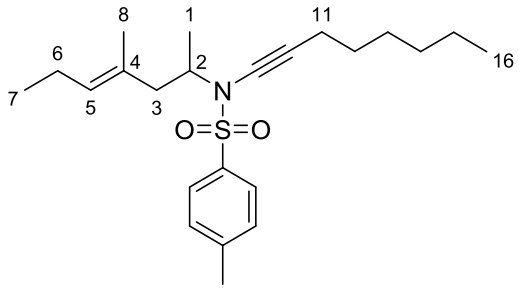
4-Methyl-*N*-((2*SR*,3*SR*,*E*)-3-methylhept-4-en-2-yl)-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 306b



To a mixture of 4-methyl-*N*-((2*SR*,3*SR*,*E*)-3-methylhept-4-en-2-yl)benzenesulfonamide **313b** (150 mg, 0.53 mmol, 1.0 eq.), K_3PO_4 (225 mg, 1.06 mmol, 2.0 eq.), $CuSO_4 \bullet 5H_2O$ (67 mg, 0.27 mmol, 0.5 eq.) and 1,10-phenanthroline (96 mg, 0.53 mg, 1.0 eq.) was added a solution of 1-bromooct-1-yne (200 mg, 1.06 mmol, 2.0 eq.) in toluene (1.5 mL). The reaction mixture was stirred at 110 °C for 48 h before being allowed to cool to RT. The reaction mixture was filtered through Celite eluting with *t*-BuOMe and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5%→20% *t*-BuOMe in hexanes) to give the title compound as a pale yellow oil (27.5 mg, 0.071 mmol, 13% (37% brsm)); R_f = 0.70 (4:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.78 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.47 (1H, dt, *J*=15.2, 6.3 Hz, =C**H**-5), 5.18 (1H, ddt, *J*=15.2, 8.7, 1.4 Hz, =C**H**-4), 3.64 (1H, dq, *J*=9.7, 6.7 Hz, C**H**-2), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.29 (2H, t, *J*=6.8 Hz, C$\mathbf{H_2}$-11), 2.29-2.15 (1H, m, **C**H-3), 2.08 (2H, qdd, *J*=7.5, 6.3, 1.4 Hz, C$\mathbf{H_2}$-6), 1.55-1.43 (2H, m, C$\mathbf{H_2}$-12), 1.42-1.20 (6H, m, C$\mathbf{H_2}$-(13-15)), 0.96 (3H, d, *J*=6.7 Hz, C$\mathbf{H_3}$-1), 0.95 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7), 0.94 (3H, d, *J*=6.9 Hz, C$\mathbf{H_3}$-8), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 143.9 (**Ar**CH_3), 136.2 (**Ar**SO_2), 133.4 (=**C**H-5), 130.9 (=**C**H-4), 129.5 (*m*-**Ts**H), 127.5 (*o*-**Ts**H), 71.9 (≡**C**), 70.0 (≡**C**), 60.4 (**C**H-2), 41.8 (**C**H-3), 31.3 (**C**H_2-(13-15)), 29.0 (**C**H_2-12), 28.4 (**C**H_2-(13-15)), 25.6 (**C**H_2-6), 22.6 (**C**H_2-(13-15)), 21.6 (Ar**C**H_3), 18.6 (**C**H_2-11), 18.5 (**C**H_3-1), 16.8 (**C**H_3-8), 14.0 (**C**H_3-16), 13.7 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1}

2925 m (C-H), 2248 w (C≡C), 1362 m (SO_2), 1169 s (SO_2); HRMS *m/z* (ESI+) found $[M+H]^+$ 390.2458; $C_{23}H_{36}NO_2S$ requires 390.2461.

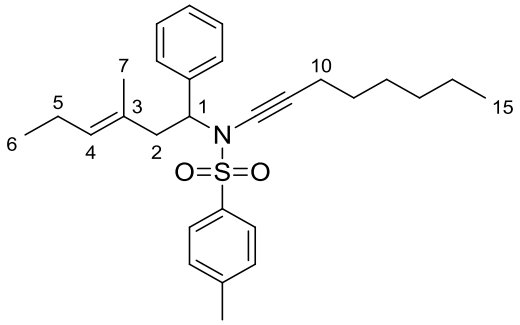
(*E*)-4-Methyl-*N*-(4-methylhept-4-en-2-yl)-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 306d



To a mixture of (*E*)-4-methyl-*N*-(4-methylhept-4-en-2-yl)benzenesulfonamide **313d** (180 mg, 0.64 mmol, 1.0 eq.), K_3PO_4 (272 mg, 1.28 mmol, 2.0 eq.), $CuSO_4•5H_2O$ (80 mg, 0.32 mmol, 0.5 eq.) and 1,10-phenanthroline (115 mg, 0.64 mmol, 1.0 eq.) was added a solution of 1-bromooct-1-yne (242 mg, 1.26 mmol, 2.0 eq.) in toluene (1.3 mL). The reaction mixture was stirred at 110 °C for 48 h before being allowed to cool to RT. The reaction mixture was filtered through Celite eluting with *t*-BuOMe and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (0%→20% *t*-BuOMe in hexanes) to give the title compound as a yellow oil (89 mg, 0.23 mmol, 36% (57% brsm)); R_f = 0.53 (4:1, hexanes:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.78-7.74 (2H, m, *o*-Ts**H**), 7.32-7.27 (2H, m, *m*-Ts**H**), 5.19-5.11 (1H, m, =C**H**-5), 4.11 (1H, ap. sext., *J*=6.9 Hz, C**H**-2), 2.43 (2H, s, ArC$\mathbf{H_3}$), 2.30 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-11), 2.17 (1H, dd, *J*=13.3, 7.7 Hz, C**H**H'-3), 1.99 (1H, dd, *J*=13.3, 7.0 Hz, CH**H'**-3), 1.97-1.85 (2H, m, C$\mathbf{H_2}$-6), 1.55 (3H, s, C$\mathbf{H_3}$-8), 1.54-1.45 (2H, m, C$\mathbf{H_2}$-12), 1.42-1.21 (6H, m, C$\mathbf{H_2}$-(13-15)), 1.02 (3H, d, *J*=6.6 Hz, C$\mathbf{H_3}$-1), 0.90 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 143.8 (**Ar**CH_3), 136.4 (**Ar**SO_2), 130.3 (=**C**H-5), 130.0 (=**C**-4), 129.4 (*m*-**Ts**H), 127.4 (*o*-**Ts**H), 72.3 (≡**C**), 69.8 (≡**C**), 54.4 (**C**H-2), 45.0 (**C**HH'-3), 31.3 (**C**H_2-(13-15)), 29.0 (**C**H_2-12), 28.5 (**C**H_2-(13-15)), 22.6 (**C**H_2-(13-15)), 21.6 (Ar**C**H_3), 21.2 (**C**H_2-6), 18.6 (**C**H_2-11), 18.2 (**C**H_3-1), 15.7 (**C**H_3-8), 14.1

(**C**H_3-7, **C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2929 m (C-H), 2248 w (C≡C), 1360 m (SO_2), 1167 s (SO_2); HRMS *m/z* (ESI+) found $[M+Na]^+$ 390.2457; $C_{23}H_{36}NO_2S$ requires 390.2461.

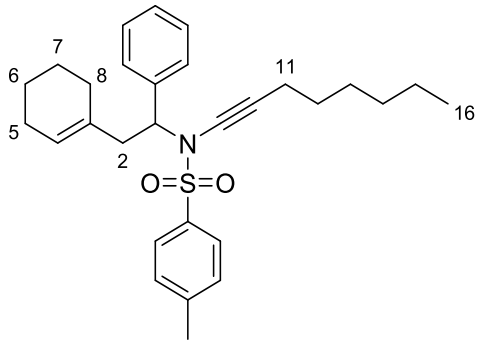
(*E*)-4-Methyl-*N*-(3-methyl-1-phenylhex-3-en-1-yl)-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 306e



To a mixture of (*E*)-4-methyl-*N*-(3-methyl-1-phenylhex-3-en-1-yl)benzenesulfonamide **313e** (100 mg, 0.29 mmol, 1.0 eq.), K_3PO_4 (135 mg, 0.64 mmol, 2.2 eq.), $CuSO_4•5H_2O$ (36 mg, 0.15 mmol, 0.5 eq.) and 1,10-phenanthroline (52 mg, 0.29 mg, 1.0 eq.) was added a solution of 1-bromooct-1-yne (110 mg, 0.58 mmol, 2.0 eq.) in toluene (0.6 mL). The reaction mixture was heated to 150 ºC in the microwave for 2 h (71% conversion by ^{1}H NMR spectroscopy). The reaction mixture was filtered through Celite eluting with *t*-BuOMe and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (0%→5% *t*-BuOMe in hexanes) to give the title compound as a yellow oil (65 mg, 0.14 mmol, 50%); R_f = 0.46 (9:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.51 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30-7.23 (2H, m, Ph**H**), 7.21-7.14 (3H, m, Ph**H**), 7.11 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.16 (1H, t, *J*=7.1 Hz, =C**H**-4), 5.08 (1H, dd, *J*=9.0, 6.2 Hz, C**H**-1), 2.70 (1H, dd, *J*=13.9, 9.1 Hz, C**H**H'-2), 2.43 (1H, dd, *J*=13.9, 6.1 Hz, CH**H'**-2), 2.35 (3H, s, ArC$\mathbf{H_3}$), 2.32 (2H, t, *J*=6.9 Hz, C$\mathbf{H_2}$-10), 1.95-1.78 (2H, m, C**HH'**-5), 1.58 (3H, s, C$\mathbf{H_3}$-7), 1.49 (2H, ap. quin., *J*=7.2 Hz, C$\mathbf{H_2}$-11), 1.40-1.20 (6H, m, C$\mathbf{H_2}$-(12-14)), 0.89 (3H, t, *J*=7.0 Hz, C$\mathbf{H_3}$-15), 0.83 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (125 MHz, $CDCl_3$) 143.6 (**C**), 139.6 (**C**), 135.6 (**C**), 131.0 (=**C**H-4), 129.1 (**C**), 129.0 (*m*-**Ts**H), 128.1 (**Ph**H), 127.6 (*o*-**Ts**H, **Ph**H), 127.2 (**Ph**H), 73.2 (≡**C**), 71.1 (≡**C**),

61.2 (**C**H-1), 44.0 (**C**HH'-2), 31.4 (**C**H_2-(12-14)), 29.0 (**C**H_2-11), 28.5 (**C**H_2-(12-14)), 22.6 (**C**H_2-(12-14)), 21.5 (Ar**C**H_3), 21.2 (**C**HH'-5), 18.7 (**C**H_2-10), 15.7 (**C**H_3-7), 14.1 (**C**H_3-16), 13.9 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 2928 m (C-H), 2254 w (C≡C), 1363 m (SO_2), 1167 s (SO_2); HRMS *m/z* (ESI+) found $[M+H]^+$ 452.2614; $C_{28}H_{38}NO_2S$ requires 452.2618.

_N_-(2-(Cyclohex-1-en-1-yl)-1-phenylethyl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 321

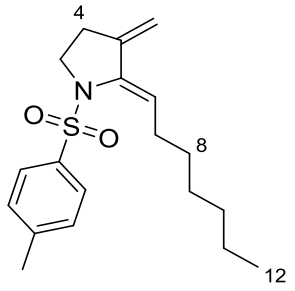


To a mixture of *N*-(2-(cyclohex-1-en-1-yl)-1-phenylethyl)-4-methylbenzenesulfonamide **320** (130 mg, 0.37 mmol, 1.0 eq.), K_2CO_3 (101 mg, 0.73 mmol, 2.0 eq.), $CuSO_4$•$5H_2O$ (46 mg, 0.18 mmol, 0.5 eq.) and 1,10-phenanthroline (66 mg, 0.37 mg, 1.0 eq.) was added a solution of 1-bromooct-1-yne (103 mg, 0.54 mmol, 1.5 eq.) in toluene (1.0 mL). The reaction mixture was stirred at 110 °C for 48 h before being allowed to cool to RT. The reaction mixture was filtered through Celite eluting with Et_2O and the filtrate concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, pet. ether:Et_2O) to give the title compound as a yellow oil (129 mg, 0.27 mmol, 75%); R_f = 0.62 (4:1, hexanes:EtOAc); δ_H (400 MHz, C_6D_6) 7.73 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.41 (2H, d, *J*=7.1 Hz, *o*-Ph**H**), 7.09-6.94 (3H, m, *m*-Ph**H**, *p*-Ph**H**), 6.66 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.70-5.64 (1H, br. m, =C**H**), 5.47 (1H, dd, *J*=9.3, 6.1 Hz, C**H**Ph), 2.91 (1H, dd, *J*=14.1, 9.3 Hz C**H**H'-2), 2.49 (1H, dd, *J*=14.1, 5.8 Hz, CH**H'**-2), 2.17-2.03 (1H, m, C**H**H'-5), 2.13 (2H, t, *J*=6.8 Hz, C$\mathbf{H_2}$-11), 1.99-1.84 (1H, m, CH**H'**-5), 1.81 (3H, s, ArC$\mathbf{H_3}$), 1.65-1.30 (6H, m, C**HH'**-6, C**HH'**-7, C**HH'**-12),

1.30-1.07 (6H, m, C**H**$_2$-(13-15)), 0.86 (3H, t, *J*=7.1 Hz, C**H**$_3$-16); δ_C (100 MHz, $CDCl_3$) 143.4 (**C**), 140.6 (**C**), 137.0 (**C**), 133.3 (**C**), 129.2 (*m*-**Ts**H), 128.5 (*m*-**Ph**H), 128.2 (*o*-**Ts**H), 127.9 (*p*-**Ph**H), 127.7 (*o*-**Ph**H), 125.7 (=**C**H), 73.4 (≡**C**), 72.4 (≡**C**), 61.5 (**C**HPh), 43.1 (**C**HH'-2), 31.7 (**C**H_2-(13-15)), 29.4 (C**H**$_2$-12), 28.8 (**C**H_2-(13-15)), 28.5 (**C**HH'-5), 25.7 (**C**HH'-8), 23.3 (**C**HH'-6), 23.0 (**C**H_2-(13-15)), 22.6 (**C**HH'-7), 21.1 (Ar**C**H_3), 19.0 (**C**HH'-11), 14.3 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2930 m (C-H), 2252 w (C≡C), 1364 m (SO_2), 1167 s (SO_2); LRMS *m*/*z* (ESI+) 464.3 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 486.2441; $C_{29}H_{37}NNaO_2S$ requires 486.2437.

6.3.4 Cycloisomerisation products

(*Z*)-2-Heptylidene-3-methylene-1-tosylpyrrolidine, 102a



Method A

See reactions of cyclic dienamides.

Method B

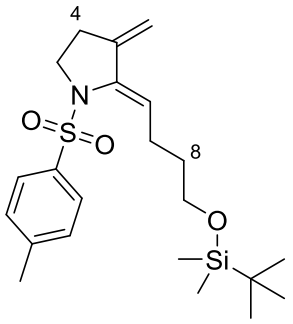
To a solution of *N*-(but-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195a** (1.00 g, 3.00 mmol, 1.0 eq.) in dry toluene (0.4 mL) was added *N*,*N*′-bis(benzylidene)ethylenediamine (7.1 mg, 0.030 mmol, 0.01 eq.) and $Pd(OAc)_2$ (6.7 mg, 0.030 mmol, 0.01 eq.). The reaction mixture was stirred at 60 °C for 2.5 h and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10:1, pet. ether:EtOAc + 1% Et_3N) to give the title compound as a colourless oil (830 mg, 2.49 mmol,

83%). R_f = 0.49 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.68 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.23 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.87 (1H, t, *J*=7.4 Hz, =C**H**CH_2), 5.20 (1H, t, *J*=2.3 Hz, =C**H**H'), 4.64 (1H, t, *J*=2.3 Hz, =CH**H'**), 3.53 (2H, t, *J*=7.4 Hz, C**H**$_2$NTs), 2.53 (2H, q, *J*=7.6 Hz, =CHC**H**$_2$), 2.42 (2H, s, ArC**H**$_3$), 1.83 (2H, tt, *J*=7.4, 2.3 Hz, C**H**$_2$-4), 1.48-1.23 (8H, m, C**H**$_2$-(8-11)), 0.89 (3H, t, *J*=6.9 Hz, C**H**$_3$-12); δ_C (125 MHz, $CDCl_3$) 143.8 (**Ar**CH_3), 143.2 (=**C**), 136.5 (=**C**), 136.0 (**Ar**SO_2), 129.5 (*m*-**Ts**H), 127.7 (*o*-**Ts**H), 122.1 (=**C**HCH_2), 103.5 (=**C**HH'), 48.5 (**C**H_2NTs), 31.7 (**C**H_2-(8-11)), 29.7 (=CH**C**H_2), 29.5 (**C**H_2-(8-11)), 29.1 (**C**H_2-(8-11)), 29.0 (**C**H_2-4), 22.7 (**C**H_2-(8-11)), 21.6 (Ar**C**H_3), 14.1 (**C**H_3-12). Data are consistent with literature values.[48]

Method C

To a solution of *N*-(but-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195a** (50 mg, 0.150 mmol, 1.0 eq.) in MeCN (0.5 mL) was added Cp*RuCl(cod) (3 mg, 0.0075 mmol, 0.05 eq.). The reaction mixture was stirred at 60 °C for 1.5 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10:1, pet ether:EtOAc) to give the title compound as a colourless oil (30 mg, 0.090 mmol, 60%). Data are in accordance with Method B.

(*Z*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)butylidene)-3-methylene-1-tosylpyrrolidine, 102b



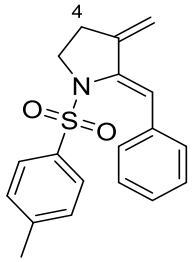
Method A

Synthesised from *N*-(but-3-en-1-yl)-*N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methylbenzenesulfonamide **195b** (32 mg, 0.076 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (28.5 mg, 0.068 mmol, 90%); R_f = 0.48 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.22 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.89 (1H, t, *J*=7.4 Hz, =C**H**CH_2), 5.20 (1H, t, *J*=2.4 Hz, =C**H**H'), 4.64 (1H, t, *J*=2.2 Hz, =CH**H'**), 3.67 (2H, t, *J*=6.8 Hz, C$\mathbf{H_2}$O), 3.52 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 2.57 (2H, ap. q, *J*=7.6 Hz, =CHC$\mathbf{H_2}$), 2.40 (3H, s, ArC$\mathbf{H_3}$), 1.82 (2H, ap. tt, *J*=7.4, 2.0 Hz, C$\mathbf{H_2}$-4), 1.70 (2H, ap. quin., *J*=7.1 Hz, C$\mathbf{H_2}$-8), 0.90 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.06 (6H, s, Si(C$\mathbf{H_3}$)$_2$); δ_C (100 MHz, $CDCl_3$) 143.8 (**C**), 134.1 (**C**), 136.7 (**C**), 135.9 (**C**), 129.4 (*m*-**Ts**H), 127.7 (*o*-**Ts**H), 121.3 (=**C**CH_2), 103.6 (=C**HH'**), 63.1 (**C**H_2O), 48.5 (**C**H_2NTs), 32.6 (**C**H_2-8), 29.0 (**C**H_2-4), 26.3 (=CH**C**H_2), 26.0 (SiC(**C**H_3)$_3$, 21.6 (Ar**C**H_3), 18.3 (Si**C**$(CH_3)_3$), 5.3 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 1332 m (SO_2), 1159 s (SO_2); LRMS *m*/*z* (ESI+) 444.2 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 444.1989; $C_{22}H_{35}NNaO_3SSi^+$ requires 444.1999; Elemental Anal. calculated for $C_{22}H_{35}NO_3SSi$: C 62.7, H 8.4, N 3.3; found: C 62.7, H 8.4, N 3.3.

Method B

To a solution of *N*-(but-3-en-1-yl)-*N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methylbenzenesulfonamide **195b** (50 mg, 0.119 mmol, 1.0 eq.) in MeCN (0.5 mL) was added Cp*RuCl(cod) (2.3 mg, 5.9 μmol, 0.05 eq.). The reaction mixture was stirred at 60 °C for 1 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (41 mg, 0.097 mmol, 82%). Data are in accordance with Method A.

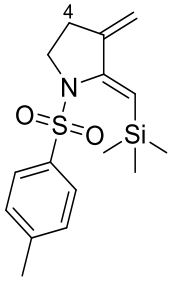
(Z)-2-Benzylidene-3-methylene-1-tosylpyrrolidine, 102b



Synthesised from *N*-(but-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **195c** (24.0 mg, 0.074 mmol) using Procedure 8 (0.167M; 5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (4:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a pale yellow oil (19.0 mg, 0.058 mmol, 79%); R_f = 0.58 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J*=7.8 Hz, *o*-Ph**H**), 7.68 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.37-7.30 (2H, m, *m*-Ph**H**), 7.28-7.20 (3H, m, *m*-Ts**H**, *p*-Ph**H**), 6.72 (1H, s, =C**H**Ph), 5.43 (1H, t, *J*=2.5 Hz, =C**H**H'), 4.84 (1H, t, *J*=2.3 Hz, =CH**H'**), 3.67 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.42 (3H, s, ArC$\mathbf{H_3}$), 1.87 (2H, tdd, *J*=7.3, 2.5, 2.3 Hz, C$\mathbf{H_2}$-4); δ_C (100 MHz, $CDCl_3$) 144.2 (=**C**), 144.0 (=**C**), 136.0 (**Ar**), 135.7 (**Ar**), 135.5 (**Ar**), 129.5 (*m*-**Ts**H), 129.5 (*o*-**Ph**H), 127.9 (*o*-**Ts**H), 127.9 (*m*-**Ph**H), 127.6 (*p*-**Ph**H), 117.7 (=**C**HPh), 104.9 (=**C**HH'), 48.6 (**C**H_2NTs), 28.7 (**C**H_2-4), 21.6 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2924 w (C-H), 1355 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 673.2 ($[2M+Na]^+$,

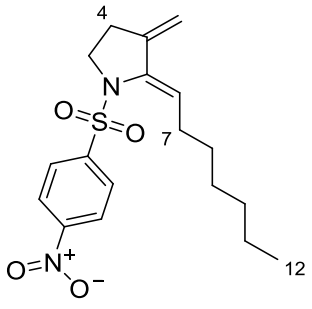
100%), 348.1 ([M+Na]$^+$, 94%); HRMS m/z (ESI+) found [M+Na]$^+$ 348.1027; $C_{19}H_{19}NNaO_2S^+$ requires 348.1029.

(*Z*)-3-Methylene-1-tosyl-2-((trimethylsilyl)methylene)pyrrolidine, 102d



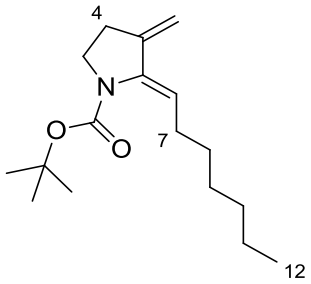
Synthesised from *N*-(but-3-en-1-yl)-4-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide **195d** (50.0 mg, 0.156 mmol) using Procedure 8 (0.167M; 10 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (31.5 mg, 0.098 mmol, 63%); R_f = 0.48 (4:1, pet. ether:EtOAc); δ_H (500 MHz, C_6D_6) 7.66 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 6.67 (2H, d, *J*=7.9 Hz, *m*-Ts**H**), 5.92 (1H, s, =C**H**), 5.23 (1H, t, *J*=2.5 Hz, =C**H**H'), 4.49 (1H, t, *J*=2.2 Hz, =C**H**H'), 3.27 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 1.80 (3H, s, ArC$\mathbf{H_3}$), 1.36 (2H, ap. tt, *J*=7.3, 2.4 Hz, C$\mathbf{H_2}$-4), 0.58 (9H, s, Si(C$\mathbf{H_3}$)$_3$); δ_C (125 MHz, C_6D_6) 148.8 (**C**), 144.8 (**C**), 143.4 (**C**), 137.1 (**C**), 129.5 (*m*-**Ts**H), 127.9 (*o*-**Ts**H), 115.1 (=**C**H), 106.4 (=**C**HH'), 48.0 (**C**H_2NTs), 28.6 (**C**H_2-4), 21.1 (Ar**C**H_3), 0.5 (Si(**C**H_3)$_3$); IR (thin film) ν_{max}/cm^{-1} 2926 w (C-H), 1355 m (SO_2), 1164 s (SO_2); LRMS m/z (ESI+) 344.1 ([M+Na]$^+$, 100%); HRMS m/z (ESI+) found [M+Na]$^+$ 344.1118; $C_{16}H_{23}NNaO_2SSi$ requires 344.1111.

(*Z*)-2-Heptylidene-3-methylene-1-(4-nitrophenylsulfonyl)pyrrolidine, 102e



Synthesised from *N*-(but-3-en-1-yl)-4-nitro-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195e** (50.0 mg, 0.137 mmol) using Procedure 8 (0.333 M; 2.5 mol% cat.), with the reaction mixture stirred for 20 min. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether) to give the title compound as a pale yellow oil (42 mg, 0.115 mmol, 84%); R_f = 0.28 (9:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 8.33-8.26 (2H, m, Ns**H**), 8.02-7.96 (2H, m, Ns**H**), 5.92 (1H, t, *J*=7.4 Hz, =C**H**), 5.23 (1H, t, *J*=2.4 Hz, =C**H**H'), 4.67 (1H, t, *J*=2.0 Hz, =CH**H'**), 3.61 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NNs), 2.52 (2H, ap. q, *J*=7.5 Hz, C$\mathbf{H_2}$-7), 1.94-1.85 (2H, m, C$\mathbf{H_2}$-4), 1.51-1.41 (2H, m, C$\mathbf{H_2}$-8), 1.40-1.24 (6H, m, C$\mathbf{H_2}$-(9-11)), 0.89 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-12); δ_C (125 MHz, $CDCl_3$) 150.3 (**C**), 144.5 (**C**), 142.0 (**C**), 135.7 (**C**), 129.0 (**Ns**H), 124.0 (**Ns**H), 123.2 (=**C**H), 104.7 (=**C**HH'), 48.6 (**C**H_2NNs), 31.7 (**C**H_2-(9-11)), 29.7 (**C**H_2-7), 29.4 (**C**H_2-8), 29.1 (**C**H_2-(9-11)), 28.8 (**C**H_2-4), 22.6 (**C**H_2-(9-11)), 14.1 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2926 m (C-H), 1531 s (N-O), 1349 s (SO_2), 1170 s (SO_2); LRMS *m*/*z* (ESI+) 387.1 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 387.1340; $C_{18}H_{24}N_2NaO_4S$ requires 387.1349.

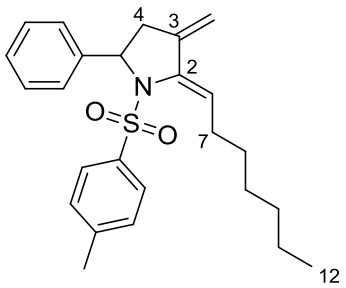
(*Z*)-*tert*-Butyl 2-heptylidene-3-methylenepyrrolidine-1-carboxylate*, 102f



***Reaction carried out by Dr. Craig Campbell.**

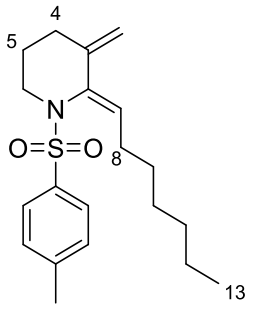
Synthesised from *tert*-butyl but-3-enyl(oct-1-ynyl)carbamate **195f** (30.0 mg, 0.107 mmol) using Procedure 8 (0.167 M; 5 mol% cat.), with the reaction mixture stirred for 60 min. The resulting crude material was purified by column chromatography (97:3, pet. ether:Et_2O) to give the title compound as a colourless oil (20.0 mg, 0.072 mmol, 67%); R_f = 0.42 (9:1, pet. ether:Et_2O); δ_H (400 MHz, $CDCl_3$) 5.43 (1H, t, *J*=7.1 Hz, =C**H**), 5.28 (1H, t, *J*=2.4 Hz, =C**H**H'), 4.82 (1H, t, *J*=2.2 Hz, =CH**H'**), 3.62 (2H, t, *J*=7.2 Hz, C$\mathbf{H_2}$N), 2.50 (2H, ap. tt, *J*=7.3, 2.2 Hz, C$\mathbf{H_2}$-4), 2.09 (2H, q, *J*=7.3 Hz, C$\mathbf{H_2}$-7), 1.49 (9H, s, C(C$\mathbf{H_3}$)$_3$), 1.45-1.20 (8H, m, C$\mathbf{H_2}$-(8-11)), 0.87 (3H, t, *J*=7.3 Hz, C$\mathbf{H_3}$-12); δ_C (100 MHz, $CDCl_3$) 153.0 (**C**), 144.2 (**C**), 125.4 (**C**), 112.4 (=**C**H), 102.7 (=**C**HH'), 80.3 (**C**(CH$_3$)$_3$), 46.6 (**C**H$_2$N), 31.8 (**C**H$_2$-(8-11)), 29.8 (**C**H$_2$-4), 29.6 (**C**H$_2$-7), 29.4 (**C**H$_2$-(8-11)), 29.2 (**C**H$_2$-(8-11)), 28.4 (C(**C**H$_3$)$_3$), 22.6 (**C**H$_2$-(8-11)), 14.1 (**C**H$_3$-12); IR (thin film) ν_{max}/cm^{-1} 2925 m (C-H), 1716 s (C=O), 1695 s (C=O); LRMS *m*/*z* (ESI+) 581.5 ([2M+Na]$^+$, 33%) 280.3 ([M+H]$^+$, 39%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 302.2086; $C_{17}H_{29}NNaO_2$ requires 302.2091.

(*Z*)-2-Heptylidene-3-methylene-5-phenyl-1-tosylpyrrolidine, 102g



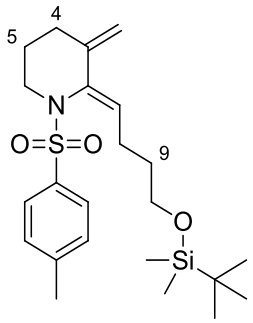
Synthesised from 4-methyl-*N*-(oct-1-yn-1-yl)-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide **195g** (31 mg, 0.076 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 1 h. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether + 1% Et_3N) to give the title compound as a colourless oil (*Z*:*E* enamides; 92:8) (27.0 mg, 0.066 mmol, 88%); Data reported for the major isomer; R_f = 0.46 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.31-7.19 (7H, m, *m*-Ts**H**, Ph**H**), 5.91 (1H, dd, *J*=9.6, 5.2 Hz, =C**H**), 5.22 (1H, br. s, =C**H**H'), 5.07 (1H, d, *J*=8.5 Hz, C**H**Ph), 4.67 (1H, br. s, =CH**H'**), 2.70-2.59 (1H, m, C**H**H'-7), 2.59-2.49 (1H, m, CH**H'**-7), 2.43 (3H, s, ArC**H**$_3$), 2.37 (1H, dd, *J*=16.4, 1.6 Hz, C**H**H'-4), 2.10 (1H, ddt, *J*=16.4, 8.5, 3.0 Hz, CH**H'**-4), 1.55-1.44 (1H, m, C**H**H'-8), 1.42-1.21 (7H, m, CH**H'**-8, C**H**$_2$-(9-11)), 0.88 (3H, t, *J*=6.8 Hz, C**H**$_3$-12); δ_C (125 MHz, $CDCl_3$) 143.8 (**Ar**CH_3), 142.7 (=**C**-2), 141.4 (**Ph**), 136.0 (**Ar**SO_2), 135.9 (=**C**-3), 129.6 (**Ar**H), 128.4 (**Ar**H), 127.7 (*o*-Ts**H**), 127.3 (**Ar**H), 126.1 (**Ar**H), 122.8 (=**C**H), 103.8 (=**C**HH'), 61.8 (**C**HPh), 36.7 (**C**HH'-4), 31.8 (**C**H_2-(9-11)), 30.0 (**C**HH'-7), 29.5 (**C**HH'-8), 29.1 (**C**H_2-(9-11)), 22.6 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 14.1 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2925 m (C-H), 1355 m (SO_2), 1166 s (SO_2); LRMS *m*/*z* (ESI+) 841.4 ([2M+Na]$^+$, 100%), 432.2 ([M+Na]$^+$, 65%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 432.1959; $C_{25}H_{31}NNaO_2S^+$ requires 432.1968.

(*Z*)-2-Heptylidene-3-methylene-1-tosylpiperidine, 102h



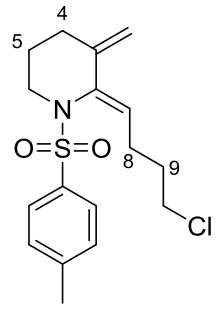
Synthesised from 4-methyl-*N*-(oct-1-yn-1-yl)-*N*-(pent-4-en-1-yl)benzenesulfonamide **195h** (26 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a pale yellow oil (21.0 mg, 0.060 mmol, 81%); R_f = 0.46 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.23 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.85 (1H, t, *J*=7.2 Hz, =C**H**), 4.99 (1H, d, *J*=1.2 Hz, =C**H**H'), 4.57 (1H, d, *J*=1.5 Hz, =CH**H'**), 3.58-3.50 (2H, br. m, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.35 (2H, ap. q, *J*=7.3 Hz, C$\mathbf{H_2}$-8), 2.02 (2H, t, *J*=6.2 Hz, C$\mathbf{H_2}$-4), 1.45-1.36 (2H, m, C$\mathbf{H_2}$-9), 1.36-1.18 (8H, m, C$\mathbf{H_2}$-5, C$\mathbf{H_2}$-(10-12)), 0.88 (3H, t, *J*=6.8 Hz, C$\mathbf{H_3}$-13); δ_C (100 MHz, $CDCl_3$) 143.6 (=**C**), 143.1 (=**C**), 137.6 (**Ar**CH_3), 135.6 (**Ar**SO_2), 132.6 (=**C**H), 129.3 (*m*-**Ts**H), 128.0 (*o*-**Ts**H), 109.8 (=**C**HH'), 47.7 (**C**H_2NTs), 32.0 (**C**H_2-4), 31.7 (**C**H_2-(10-12)), 29.0 (**C**H_2-9), 28.6 (**C**H_2-(10-12)), 22.8 (**C**H_2-(10-12)), 22.6 (**C**H_2-5), 21.5 (Ar**C**H_3), 14.1 (**C**H_3-13); IR (thin film) ν_{max}/cm^{-1} 2926 m (C-H), 1348 m, (SO_2), 1160 s (SO_2); LRMS *m*/*z* (ESI+) 717.4 ($[2M+Na]^+$, 100%), 448.2 ($[M+H]^+$, 22%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 348.1984; $C_{20}H_{30}NO_2S^+$ requires 348.1992.

(*Z*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)butylidene)-3-methylene-1-tosylpiperidine, 102i



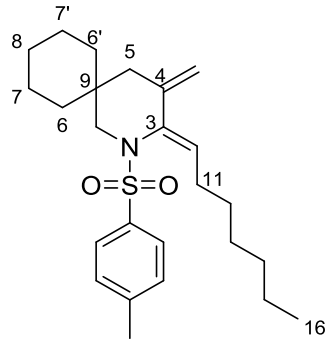
Synthesised from *N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **195i** (33.0 mg, 0.076 mmol) using Procedure 8 (0.167M; 5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (28.0 mg, 0.064 mmol, 85%); R_f = 0.42 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.23 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.88 (2H, t, *J*=7.3 Hz, =C**H**CH_2), 4.98 (1H, s, =C**H**H'), 4.57 (1H, d, *J*=1.3 Hz, =CH**H'**), 3.65 (2H, t, *J*=6.8 Hz, C$\mathbf{H_2}$O), 3.59-3.49 (2H, br. m, C$\mathbf{H_2}$NTs), 2.45-2.35 (2H, m, =CHC$\mathbf{H_2}$), 2.40 (3H, s, ArC$\mathbf{H_3}$), 2.02 (2H, t, *J*=6.2 Hz, C$\mathbf{H_2}$-4), 1.66 (2H, ap. quin., *J*=7.1 Hz, C$\mathbf{H_2}$-9), 1.24 (2H, ap. quin., *J*=6.1 Hz, C$\mathbf{H_2}$-5), 0.90 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.06 (6H, s, Si(C$\mathbf{H_3}$)$_2$); δ_C (100 MHz, $CDCl_3$) 143.5 (**C**), 143.2 (**C**), 137.6 (**C**), 135.9(**C**), 131.9 (=**C**HCH_2), 129.3 (*m*-**Ts**H), 128.1 (*o*-**Ts**H), 109.9 (=**C**HH'), 63.0 (**C**H_2O), 47.7 (**C**H_2NTs), 32.3 (**C**H_2-9), 32.0 (**C**H_2-4), 26.0 (SiC(**C**H_3)$_3$), 25.1 (=CH**C**H_2), 22.7 (**C**H_2-5), 21.5 (Ar**C**H_3), 18.3 (Si**C**$(CH_3)_3$), -5.3 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 2929 w (C-H), 1350 m (SO_2), 1161 s (SO_2); LRMS *m*/*z* (ESI+) 893.4 ([2M+Na]$^+$, 84%), 458.2 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 458.2160; $C_{23}H_{37}NNaO_3SSi^+$ requires 458.2156.

(*Z*)-2-(4-Chlorobutylidene)-3-methylene-1-tosylpiperidine, 102j



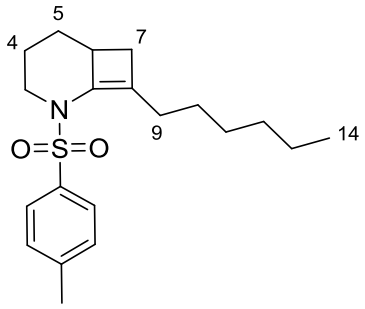
Synthesised from *N*-(5-chloropent-1-yn-1-yl)-4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **195j** (26.0 mg, 0.075 mmol) using Procedure 8 (0.167M; 5 mol% cat.), with the reaction mixture stirred for 20 min. The resulting crude material was purified by column chromatography (15%→20% Et_2O in pet. ether) to give the title compound as a colourless oil (20.0 mg, 0.059 mmol, 77%); R_f = 0.37 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.24 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.82 (1H, t, *J*=7.3 Hz, =C**H**), 4.99 (1H, d, *J*=1.3 Hz, =C**H**H'), 4.59 (1H, d, *J*=1.6 Hz, =CH**H'**), 3.60-3.51 (4H, m, C$\mathbf{H_2}$Cl, C$\mathbf{H_2}$NTs), 2.52 (2H, q, *J*=7.2 Hz, C$\mathbf{H_2}$-8), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.03 (2H, br. t, *J*=6.3 Hz, C$\mathbf{H_2}$-4), 1.93 (2H, ap. quin., *J*=7.1 Hz, C$\mathbf{H_2}$-9), 1.25 (2H, ap. quin., *J*=6.1 Hz, C$\mathbf{H_2}$-5) δ_C (100 MHz, $CDCl_3$) 143.4 (**C**), 143.3 (**C**), 137.4 (**C**), 137.0 (**C**), 130.2, (=**C**H) 129.4 (*m*-**Ts**H), 128.1 (*o*-**Ts**H), 110.2 (=**C**HH'), 47.8 (**C**H_2NTs), 44.6 (**C**H_2Cl), 32.0 (**C**H_2-4, **C**H_2-9), 26.1 (**C**H_2-8), 22.7 (**C**H_2-5), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2948 w (C-H), 1347 m (SO_2), 1159 s (SO_2); LRMS *m*/*z* (ESI+) 340.1 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 362.0938; $C_{17}H_{22}{}^{35}ClNNaO_2S^+$ requires 362.0952.

(*Z*)-3-Heptylidene-4-methylene-2-tosyl-2-azaspiro[5.5]undecane, 102k



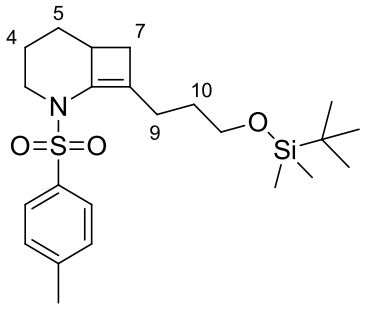
Synthesised from *N*-((1-allylcyclohexyl)methyl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195k** (31.0 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 1 h. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (25.5 mg, 0.061 mmol, 82%); R_f = 0.75 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.68 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.23 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.96 (1H, t, *J*=7.4 Hz, =C**H**CH_2), 5.14 (1H, d, *J*=0.9 Hz, =C**H**H'), 4.56 (1H, d, *J*=1.3 Hz, =CH**H'**), 3.32 (2H, s, C$\mathbf{H_2}$NTs), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.29 (2H, q, *J*=7.5 Hz, C$\mathbf{H_2}$-11), 1.61 (2H, s, C$\mathbf{H_2}$-5), 1.46-1.07 (18H, m, C**HH'**-(6-8), C$\mathbf{H_2}$-(12-15)), 0.88 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 143.1 (**C**), 141.8 (**C**), 137.4 (**C**), 133.9 (**C**), 131.1 (=**C**HCH_2), 19.2 (*m*-**Ts**H), 127.5 (*o*-**Ts**H), 108.6 (=**C**HH'), 56.6 (**C**H_2NTs), 40.8 (**C**H_2-5), 36.4 (**C**H_2-(6-8, 12-15)), 33.4 (**C**-9), 31.6 (**C**H_2-(6-8, 12-15)), 29.1 (**C**H_2-(6-8, 12-15)), 29.0 (**C**H_2-(6-8, 12-15)), 29.0 (**C**H_2-11), 25.8 (**C**H_2-(6-8, 12-15)), 22.6 (**C**H_2-(6-8, 12-15)), 21.7 (**C**H_2-(6-8, 12-15)), 21.5 (Ar**C**H_3), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2925 s (C-H), 1350 m (SO_2), 1162 s (SO_2); LRMS *m*/*z* (ESI+) 416.3 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 438.2430; $C_{25}H_{37}NNaO_2S$ requires 438.2437.

8-Hexyl-2-tosyl-2-azabicyclo[4.2.0]oct-1(8)-ene, 295a



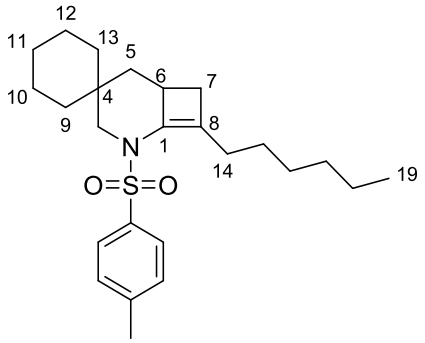
To a solution of 4-methyl-*N*-(oct-1-yn-1-yl)-*N*-(pent-4-en-1-yl)benzenesulfonamide **195h** (100 mg, 0.29 mmol, 1.0 eq.) in MeCN (1.0 mL) was added Cp*RuCl(cod) (5 mg, 0.014 mmol, 0.05 eq.). The reaction mixture was stirred at 85 °C for 2.5 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10:1, pet ether:Et_2O + 1% Et_3N) to give the title compound in >95% purity (~4% dienamide) as a colourless oil (90 mg, 0.25 mmol, 90%); R_f = 0.59 (10:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 3.75 (1H, dt, *J*=12.7, 3.5 Hz, C**H**H'NTs), 3.03 (1H, td, *J*=12.7, 2.9 Hz, CH**H'**NTs), 2.42 (3H, s, ArC**H**$_3$), 2.33 (1H, dd, *J*=12.3, 4.1 Hz, C**H**H'-7), 2.21-2.10 (3H, m, C**H**$_2$-9, C**H**), 1.90-1.80 (2H, m, CH**H'**-7, C**H**H'-5), 1.59-1.51 (1H, m, C**H**H'-4), 1.44-1.35 (2H, m, C**H**$_2$-10), 1.35-1.23 (6H, m, C**H**$_2$-(11-13)), 1.23-1.16 (1H, m, CH**H'**-4), 1.16-1.04 (1H, m, C**H**H'-5), 0.89 (3H, t, *J*=6.7 Hz, C**H**$_3$-14); δ_C (125 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 137.5 (**Ar**SO_2), 134.5 (=**C**), 130.6 (=**C**), 129.6 (*m*-**Ts**H), 127.2 (*o*-**Ts**H), 47.8 (**C**HH'NTs), 36.3 (**C**H), 33.8 (**C**HH'-7), 31.7 (**C**H_2-(11-13)), 29.4 (**C**HH'-5), 29.2 (**C**H_2-(11-13)), 27.8 (**C**H_2-9), 27.1 (C**H**$_2$-10), 24.3 (**C**HH'-4), 22.7 (**C**H_2-(11-13)), 21.5 (Ar**C**H_3), 14.1 (**C**H_3-14); IR (thin film) ν_{max}/cm^{-1} 2926 m (C-H), 1350 m (SO_2), 1161 s (SO_2); LRMS *m*/*z* (ESI+) 717.4 ([2M+Na]$^+$, 100%), 370.2 ([M+Na]$^+$, 14%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 370.1808; $C_{20}H_{29}NNaO_2S^+$ requires 370.1811.

8-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-2-tosyl-2-azabicyclo[4.2.0]oct-1(8)-ene, 295b



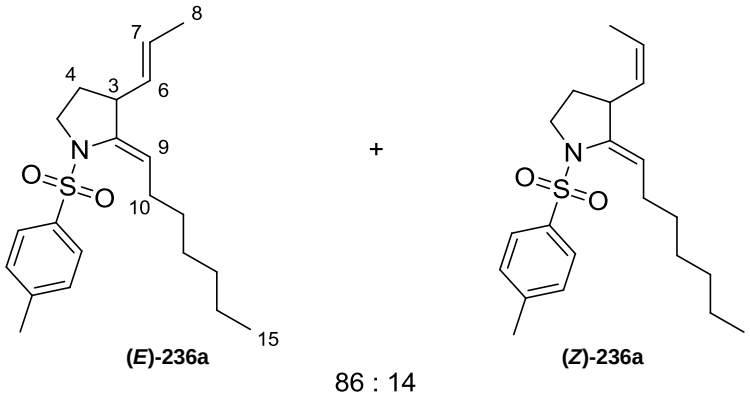
To a solution of *N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-4-methyl-*N*-(pent-4-en-1 yl)benzenesulfonamide **195i** (50.0 mg, 0.115 mmol, 1.0 eq.) in MeCN (0.4 mL) was added Cp*RuCl(cod) (2.2 mg, 5.7 μmol, 0.05 eq.). The reaction mixture was stirred at 60 °C for 1.5 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, pet. ether:Et_2O + 1% Et_3N) to give the title compound (~5% dienamide) as a colourless oil (35.5 mg, 0.081 mmol, 71%); R_f = 0.45 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 3.73 (1H, dt, *J*=12.7, 3.1 Hz, C**H**H'NTs), 3.62 (2H, t, *J*=6.8 Hz, C$\mathbf{H_2}$O) 3.02 (1H, td, *J*=12.7, 2.8 Hz, CH**H'**NTs), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.35 (1H, dd, *J*=12.3, 4.1 Hz, C**H**H'-7), 2.23 (2H, t, *J*=7.6 Hz, C$\mathbf{H_2}$-9), 2.18-2.10 (1H, m, C**H**), 1.88 (1H, d, *J*=12.3 Hz, CH**H'**-7), 1.88-1.80 (1H, m, C**H**H'-5), 1.72-1.61 (2H, m, C$\mathbf{H_2}$-10), 1.55 (1H, dt, *J*=13.8, 3.1 Hz, C**H**H'-4), 1.24-1.14 (1H, m, CH**H'**-4), 1.16-1.05 (1H, m, C**H**H'-5), 0.90 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.05 (6H, s, Si(C$\mathbf{H_3}$)$_2$); δ_C (125 MHz, $CDCl_3$) 143.3 (**Ar**CH_3), 137.4 (**Ar**SO_2), 133.5 (=**C**), 130.9 (=**C**), 129.6 (*m*-**Ts**H), 127.2 (*o*-**Ts**H), 63.1 (**C**H_2O), 47.8 (**C**HH'NTs), 36.4 (**C**H), 33.9 (**C**HH'-7), 30.4 (**C**H_2-10), 29.2 (**C**HH'-5), 26.0 (SiC(**C**H_3)$_3$), 24.3 (**C**H_2-9, **C**HH'-4), 21.5 (Ar**C**H_3), 18.4 (Si**C**$(CH_3)_3$), -5.3 (Si(**C**H_3)$_2$); IR (thin film) ν_{max}/cm^{-1} 2929 m (C-H), 1352 m (SO_2), 1161 s (SO_2); LRMS *m*/*z* (ESI+) 458.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 458.2149; $C_{23}H_{37}NNaO_3SSi^+$ requires 458.2156.

8-Hexyl-2-tosyl-2-azaspiro[bicyclo[4.2.0]oct[1(8)]ene-4,1'-cyclohexane], 295c



To a solution of *N*-((1-allylcyclohexyl)methyl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195k** (25.0 mg, 0.060 mmol, 1.0 eq.) in MeCN (0.2 mL) was added Cp*RuCl(cod) (1.1 mg, 6.0 μmol, 0.05 eq.). The reaction mixture was stirred at RT for 1 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (19:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound in >95% purity (~2% dienamide) as a colourless oil (23.0 mg, 0.055 mmol, 92%); R_f = 0.76 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.27 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 3.50 (1H, d, *J*=12.0 Hz, C**H**H'NTs), 2.73 (1H, d, *J*=12.0 Hz, CH**H'**NTs), 2.49-2.38 (1H, m, C**H**-6), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.35 (1H, dd, *J*=12.0, 4.1 Hz, C**H**H'-7), 2.15 (2H, t, *J*=7.1 Hz, C$\mathbf{H_2}$-14), 1.85-1.77 (2H, m, C**H**H'-7, C**H**H'-5), 1.47-1.10 (18H, m, C**HH'**-(9-13), C$\mathbf{H_2}$-(15-18)), 0.96-0.84 (4H, m, CH**H'**-5, C$\mathbf{H_3}$-19); δ_C (125 MHz, $CDCl_3$) 143.2 (**Ar**CH_3), 137.3 (**Ar**SO_2), 130.3 (=**C**), 130.1 (=**C**), 129.4 (*m*-**Ts**H), 127.2 (*o*-**Ts**H), 56.0 (**C**H_2NTs), 40.3 (**C**HH'-5), 37.6 (**C**HH'-(9-13)), 35.5 (**C**-4), 33.4 (**C**HH'-7), 32.9 (**C**H-6), 31.9 (**C**HH'-(9-13)), 31.7 (**C**HH'-(15-18)), 29.2 (**C**H_2-(15-18)), 28.0 (**C**H_2-12), 27.3 (**C**H_2-(15-18)), 26.3 (**C**H_2-(9-13)), 22.7 (**C**H_2-(15-18)), 21.5 (**C**H_2-(9-13)), 21.5 (Ar**C**H_3), 21.4 (**C**H_2-(9-13)), 14.1 (**C**H_3-17); IR (thin film) ν_{max}/cm^{-1} 2925 s (C-H), 1349 m (SO_2), 1160 s (SO_2); LRMS *m/z* (ESI+) 416.3 ($[M+H]^+$, 100%); HRMS m/z (ESI+) found $[M+Na]^+$ 438.2428; $C_{25}H_{37}NNaO_2S$ requires 438.2437.

(*Z*)-2-Heptylidene-3-((*E*)-prop-1-en-1-yl)-1-tosylpyrrolidine, (*E*)-236a



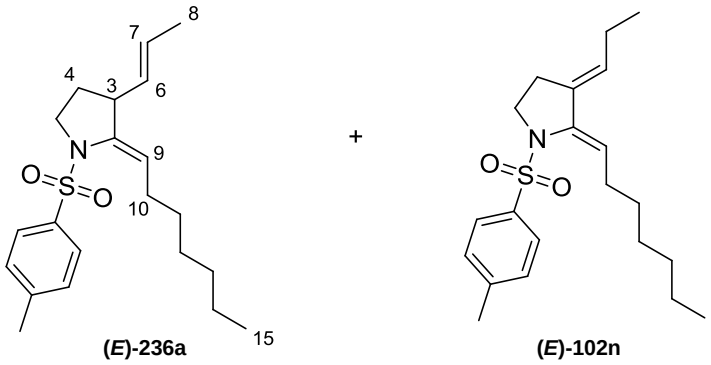
(*E*)-236a 86 : 14 (*Z*)-236a

Method A

Synthesised from (*Z*)-*N*-(hex-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195n** (27.0 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), except the reaction mixture was stirred at RT for 1.5 h. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (**(*E*)-236a:(*Z*)-236a**; 86:14) (23.5 mg, 0.065 mmol, 87%); Data reported for the major isomer; R_f = 0.62 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H d, *J*=8.1 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.27 (1H, dq, *J*=15.1, 6.5 Hz, =C**H**-7), 5.02-4.92 (2H, m, =C**H**-6, =C**H**-9), 3.54 (1H, ddd, *J*=11.4, 8.6, 3.0 Hz, C**H**H'NTs), 3.38 (1H, ddd, *J*=11.4, 9.2, 7.9 Hz, CH**H'**NTs), 2.49-2.34 (2H, m, C$\mathbf{H_2}$-10), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.24 (1H, br. ap. q, *J*=8.5 Hz, C**H**-3), 1.69 (1H, dddd, *J*=12.0, 8.0, 7.9, 3.0 Hz, C**H**H'-4), 1.62 (3H, dd, *J*=6.6, 1.6 Hz, C$\mathbf{H_3}$-8), 1.45-1.24 (9H, m, CH**H'**-4, C$\mathbf{H_2}$-(11-14)), 0.88 (3H, t, *J*=6.9 Hz, **C**H_3-15); δ_C (125 MHz, $CDCl_3$) 143.6 (**Ar**CH_3), 139.9 (=**C**), 134.8 (**Ar**SO_2), 130.4 (=**C**H-6), 129.4 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 127.5 (=**C**H-7), 121.2 (=**C**H-9), 49.1 (**C**HH'NTs), 45.6 (**C**H-3), 31.7 (**C**H_2-(11-14)), 29.8 (**C**H_2-(11-14)), 29.3 (**C**HH'-4), 29.0 (**C**H_2-(11-14)), 29.0 (**C**H_2-10), 22.7 (**C**H_2-(11-14)), 21.6 (Ar**C**H_3), 17.8 (**C**H_3-8), 14.1 (**C**H_3-15); IR (thin film) ν_{max}/cm^{-1} 2923 w (C-H), 1355 m (SO_2), 1165 s (SO_2); LRMS *m*/*z* (ESI+) 745.4 ($[2M+Na]^+$, 100%), 362.2 ($[M+H]^+$, 29%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 384.1964; $C_{21}H_{31}NNaO_2S^+$ requires

384.1968; Elemental Anal. calculated for $C_{21}H_{31}NO_2S$: C 69.8, H 8.6, N 3.9; found: C 69.9, H 8.6, N 3.8.

Method B

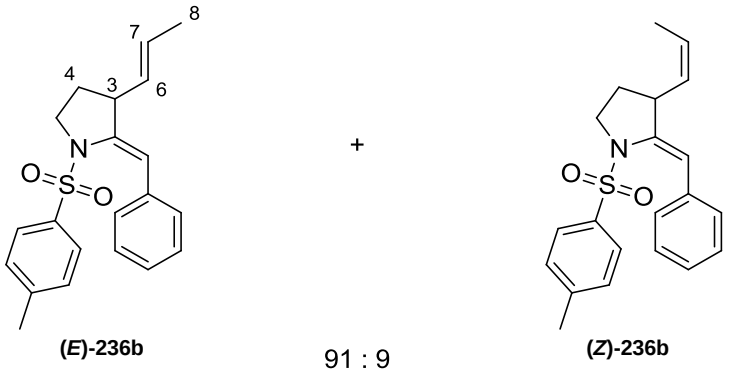


(*E*)-236a **(*E*)-102n**

78 : 22

Synthesised from (*E*)-*N*-(hex-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195l** (27.0 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give an inseparable mixture of **(*E*)-236a:(*E*)-102n**; 78:22 as a colourless oil (21.5 mg, 0.059 mmol, 80%); Data for major isomer in accordance with Method A.

(*Z*)-2-Benzylidene-3-((*E*)-prop-1-en-1-yl)-1-tosylpyrrolidine, (*E*)-236b

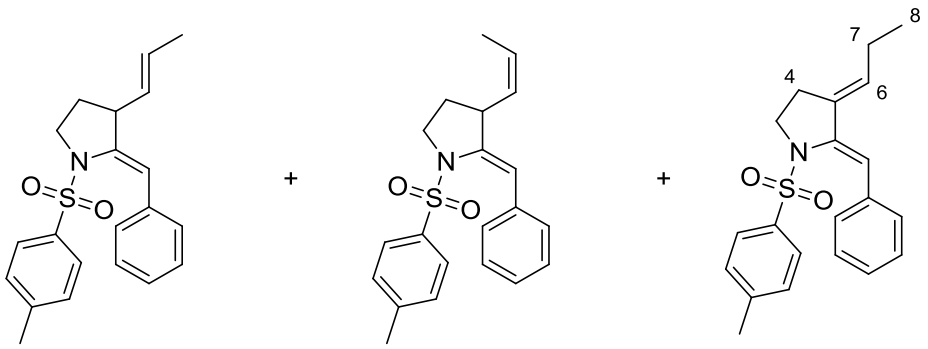


(*E*)-236b 91 : 9 (*Z*)-236b

Method A

Synthesised from (*Z*)-*N*-(hex-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **195o** (27.0 mg, 0.076 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (4:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a pale yellow oil (**(*E*)-236b**:**(*Z*)-236b**; 91:9) (22.0 mg, 0.062 mmol, 81%); Data reported for the major isomer; R_f = 0.32 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.66 (2H, d, *J*=8.5 Hz, *o*-Ts**H**), 7.62 (2H, d, *J*=7.6 Hz, *o*-Ph**H**), 7.32-7.24 (4H, m, *m*-Ts**H**, *m*-Ph**H**), 7.18 (1H, br. t, *J*=7.4 Hz, *p*-Ph**H**), 5.93 (1H, d, *J*=1.9 Hz, =C**H**Ph), 5.40 (1H, dq, *J*=15.1, 6.3 Hz, =C**H**-7), 5.10 (1H, ddd, *J*=15.1, 8.3, 1.6 Hz, =C**H**-6), 3.69 (1H, ddd, *J*=11.4, 8.7, 3.2 Hz, C**H**H'NTs), 3.52 (1H, ddd, *J*=11.4, 9.1, 7.6 Hz, CH**H'**NTs), 2.52 (1H, dddd, *J*=10.5, 8.3, 8.0, 1.9 Hz, C**H**-3), 2.43 (3H, s, ArC$\mathbf{H_3}$), 1.80 (1H, dddd, *J*=12.0, 8.0, 7.6, 3.2 Hz, C**H**H'-4), 1.68 (3H, dd, *J*=6.3, 1.6 Hz, C$\mathbf{H_3}$-8), 1.42 (1H, dddd, *J*=12.0, 10.5, 9.1, 8.7 Hz, CH**H'**-4); δ_C (125 MHz, $CDCl_3$) 143.9 (**Ar**CH_3), 141.0 (=**C**), 136.5 (**Ph**), 134.5 (**Ar**SO_2), 130.1 (=**C**H-6), 129.4 (*m*-**Ts**H), 128.8 (*o*-**Ph**H), 128.3 (=**C**H-7), 128.0 (*o*-**Ts**H), 127.7 (*m*-**Ph**H), 126.7 (*p*-**Ph**H), 118.5 (=**C**HPh), 49.1 (**C**HH'NTs), 46.7 (**C**H-3), 28.9 (**C**HH'-4), 21.6 (Ar**C**H_3), 17.9 (**C**H_3-8); ν_{max}/cm^{-1} 2968 w (C-H), 1358 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 729.2 ($[2M+Na]^+$, 100%), 376.1 ($[M+Na]^+$, 32%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 376.1343; $C_{21}H_{23}NNaO_2S^+$ requires 376.1342.

Method B

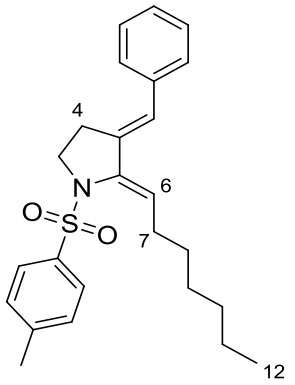


(*E*)-236b **(*Z*)-236b** **S5**

70 : 3 : 27

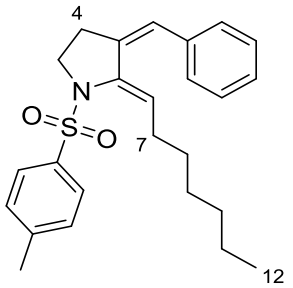
Synthesised from (*E*)-*N*-(hex-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **195m** (27.0 mg, 0.076 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (4:1, pet. ether:Et_2O + 1% Et_3N) to give an inseparable mixture of **(*E*)-236b**:**(*Z*)-236b:S5**; 70:3:27 as a yellow oil (22.5 mg, 0.064 mmol, 83%); Data for major isomer **(*E*)-236b** in accordance with Method A. Data for minor isomer **S5**: R_f = 0.32 (5:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.79 (2H, d, *J*=7.8 Hz, Ar**H**), 7.70-7.58 (2H, m, Ar**H**), 7.34-7.22 (2H, m, Ar**H**), 7.22-7.13 (3H, m, Ar**H**), 6.59 (1H, s, C**H**Ph), 5.84 (1H, tt, *J*=7.6, 2.6 Hz, =C**H**-6), 3.67 (2H, t, *J*=7.4 Hz, C$\mathbf{H_2}$NTs), 2.39 (3H, s, ArC$\mathbf{H_3}$), 1.85 (2H, quin., *J*=7.6 Hz, C$\mathbf{H_2}$-7), 1.78-1.72 (2H, m, C$\mathbf{H_2}$-4), 0.87 (3H, t, *J*=7.6 Hz, C$\mathbf{H_3}$-8); δ_C (125 MHz, $CDCl_3$) 143.9 (**C**), 136.8 (**C**), 135.9 (**C**), 135.4 (**C**), 135.3 (**C**), 129.3 (**Ar**H), 129.3 (**Ar**H), 128.0 (**Ar**H), 127.9 (**Ar**H), 127.2 (**Ar**H), 123.5 (=**C**H-6), 116.5 (=**C**HPh), 48.5 (**C**H_2NTs), 25.2 (**C**H_2-4), 23.2 (**C**H_2-7), 21.5 (Ar**C**H_3), 13.2 (**C**H_3-8).

(2*Z*,3*E*)-3-Benzylidene-2-heptylidene-1-tosylpyrrolidine, (*E*)-102l



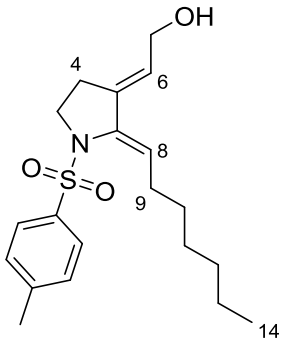
Synthesised from (*E*)-4-methyl-*N*-(oct-1-yn-1-yl)-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide **195p** (31.0 mg, 0.076 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 4 h. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give the title compound as a colourless oil (25.0 mg, 0.061 mmol, 82%); R_f = 0.48 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.70 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30-7.23 (2H, m, *m*-Ph**H**), 7.20-7.14 (3H, m, *m*-Ts**H**, *p*-Ph**H**), 7.06 (2H, d, *J*=7.3 Hz, *o*-Ph**H**), 6.62 (1H, br. t, *J*=2.4 Hz, =C**H**Ph), 5.99 (1H, t, *J*=7.5 Hz, =C**H**-6), 3.62 (2H, t, *J*=7.2 Hz, C$\mathbf{H_2}$NTs), 2.60 (2H, ap. q, *J*=7.4 Hz, C$\mathbf{H_2}$-7), 2.31 (3H, s, ArC$\mathbf{H_3}$), 2.07 (2H, td, *J*=7.2, 2.4 Hz, C$\mathbf{H_2}$-4), 1.53-1.45 (2H, m, C$\mathbf{H_2}$-8), 1.44-1.28 (6H, m, C$\mathbf{H_2}$-(9-11)), 0.90 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-12); δ_C (125 MHz, $CDCl_3$) 143.9 (**C**), 138.3 (**C**), 137.2 (**C**), 136.2 (**C**), 135.6 (**C**), 129.4 (*m*-**Ts**H), 128.3 (*m*-**Ph**H), 128.2 (*o*-**Ph**H), 127.8 (*o*-**Ts**H), 126.7 (*p*-**Ph**H), 122.0 (=**C**H-6), 119.6 (=**C**HPh), 48.8 (**C**H_2NTs), 31.8 (**C**H_2-(9-11)), 29.9 (**C**H_2-7), 29.6 (**C**H_2-8), 29.1 (**C**H_2-(9-11)), 28.1 (**C**H_2-4), 22.7 (**C**H_2-(9-11)), 21.5 (Ar**C**H_3), 14.1 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2925 w (C-H), 1353 m (SO_2), 1165 s (SO_2); LRMS *m*/*z* (ESI+) 432.2 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 432.1959; $C_{25}H_{31}NNaO_2S$ requires 432.1968.

(2*Z*,3*Z*)-3-Benzylidene-2-heptylidene-1-tosylpyrrolidine, (*Z*)-102l



Synthesised from (*Z*)-4-methyl-*N*-(oct-1-yn-1-yl)-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide **195q** (31.0 mg, 0.076 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 15 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound as a colourless oil (26.0 mg, 0.060 mmol, 84%); R_f = 0.41 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.81 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.37-7.18 (7H, m, *m*-Ts**H**, Ph**H**), 6.09 (1H, ap. s, =C**H**Ph), 5.86 (1H, t, *J*=7.4 Hz, =C**H**CH_2), 3.56 (2H, t, *J*=7.5 Hz, C$\mathbf{H_2}$NTs), 2.46-2.35 (2H, m, C$\mathbf{H_2}$-7), 2.40 (3H, s, ArC$\mathbf{H_3}$), 2.06 (2H, td, *J*=7.5, 2.2 Hz, C$\mathbf{H_2}$-4), 1.40-1.15 (8H, m, C$\mathbf{H_2}$-(8-11)), 0.85 (3H, t, *J*=7.0 Hz, C$\mathbf{H_3}$-12)); δ_C (125 MHz, $CDCl_3$) 143.9 (**C**), 137.0 (**C**), 135.8 (**C**), 135.1 (**C**), 134.6 (**C**), 129.5 (*m*-**Ts**H), 128.9 (=**C**HCH_3), 128.5 (**Ph**H), 128.1 (**Ph**H), 127.8 (*o*-**Ts**H), 127.0 (**Ph**H), 121.6 (=**C**HPh), 47.4 (**C**H_2NTs), 31.6 (**C**H_2-(8-11)), 30.7 (**C**H_2-4), 29.6 (**C**H_2-7), 28.9 (**C**H_2-(8-11), **C**H_2-(8-11)), 22.6 (**C**H_2-(8-11)), 21.6 (Ar**C**H_3), 14.1 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2924 w (C-H), 1352 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 432.2 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 432.1953; $C_{25}H_{31}NNaO_2S$ requires 432.1968.

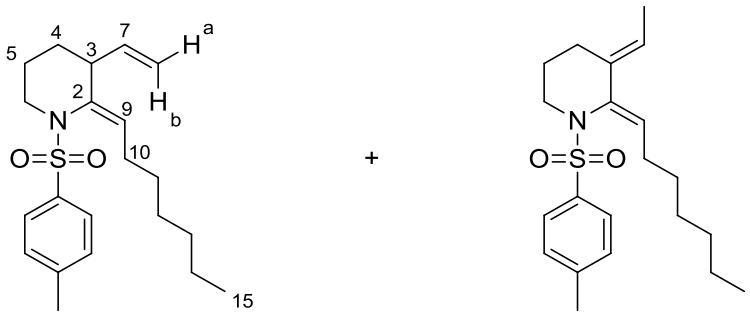
(*E*)-2-((*Z*)-2-Heptylidene-1-tosylpyrrolidin-3-ylidene)ethan-1-ol, (*E*)-102m



To a solution of (*E*)-*N*-(5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195r** (36.0 mg, 0.075, 1.0 eq.) in dry toluene (0.5 mL) was added *N*,*N*′-bis(benzylidene)ethylenediamine (0.9 mg, 3.8 μmol, 0.05 eq.) and $Pd(OAc)_2$ (0.8 mg, 3.8 μmol, 0.05 eq.). The reaction mixture was stirred at 60 °C for 20 min (ratio of 1,3-diene:1,4-diene; 67:33 by ^{1}H NMR spectroscopy), cooled to 0 °C and TBAF (0.15 mL, 1 M in THF, 0.150 mmol, 2.0 eq.) added. The reaction mixture was stirred at RT for 15 h, sat. aq. NH_4Cl (1 mL) added and the mixture transferred to a separating funnel. Further sat. aq. NH_4Cl (4 mL) and Et_2O (5 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (1:1, pet. ether:EtOAc) to give the title compound as a colourless oil (14.5 mg, 0.040 mmol, 53%); R_f = 0.22 (1:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.67 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.23 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.85 (1H, t, *J*=7.3 Hz, =C**H**-8), 5.80 (1H, tt, *J*=6.9, 2.5 Hz, =C**H**-6), 3.93 (2H, d, *J*=6.9 Hz, C$\mathbf{H_2}$OH), 3.56 (2H, t, *J*=7.3 Hz, C$\mathbf{H_2}$NTs), 2.52 (2H, ap. q, *J*=7.5 Hz, C$\mathbf{H_2}$-9), 2.41 (3H, s, ArC$\mathbf{H_3}$), 1.82 (2H, br. t, *J*=6.1 Hz, C$\mathbf{H_2}$-4), 1.48-1.39 (2H, m, C$\mathbf{H_2}$-10), 1.39-1.23 (6H, m, C$\mathbf{H_2}$-(11-13)), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-14); δ_C (125 MHz, $CDCl_3$) 143.9 (**C**), 137.9 (**C**), 136.5 (**C**), 135.8 (**C**), 129.4 (*m*-**Ts**H), 127.9 (*o*-**Ts**H), 122.7 (=**C**H-8), 118.0 (=**C**H-6), 60.6 (**C**H_2OH), 48.4 (**C**H_2NTs), 31.7 (**C**H_2-(11-13)), 29.6 (**C**H_2-9), 29.4 (**C**H_2-10), 29.1 (**C**H_2-(11-13)), 25.7 (**C**H_2-4), 22.7 (**C**H_2-(11-13)), 21.6 (Ar**C**H_3), 14.1

(**C**H_3-14); IR (thin film) ν_{max}/cm^{-1} 3536 br. w (O-H), 2925 m (C-H), 1350 m (SO_2), 1164 s (SO_2); LRMS *m*/*z* (ESI+) 364.2 ([M+H]$^+$, 80%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 386.1767; $C_{20}H_{29}NNaO_3S^+$ requires 386.1760.

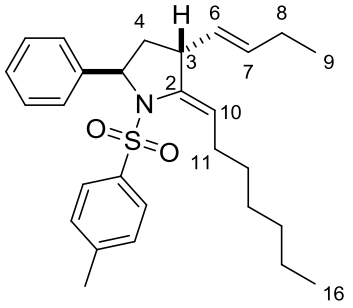
(*Z*)-2-Heptylidene-1-tosyl-3-vinylpiperidine, 236c



Synthesised from (*Z*)-*N*-(hex-4-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **195s** (54.0 mg, 0.150 mmol) using Procedure 8 (0.167M; 5 mol% cat.), with the reaction mixture stirred for 20 min. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O + 1% Et_3N) to give an inseparable mixture of **236c:S6**; 91:9 as a colourless oil (39.0 mg, 0.108 mmol, 72%); Data reported for the major isomer; R_f = 0.56 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.75 (1H, ddd, *J*=17.4, 10.3, 7.6 Hz, =C**H**-7), 5.37 (1H, ddd, *J*=8.6, 5.6, 1.5, =C**H**-9), 5.05 (1H, dd, *J*=10.3, 1.1 Hz, =C**H**^{a}H^b), 4.96 (1H, d, *J*=17.4 Hz, =CH^a**H**^{b}), 4.15-3.92 (1H, br. m, C**H**H'NTs), 3.10-2.91 (1H, m, CH**H'**NTs), 2.54-2.39 (1H, m, C**H**-3), 2.43 (3H, s, ArC**H**$_3$), 2.31-2.18 (1H, m, C**H**H'-10), 2.13-1.96 (1H, m, CH**H'**-10), 1.76-1.65 (1H, m, C**H**H'-4), 1.54-1.13 (11H, m, CH**H'**-4, C**HH'**-5, C**H**$_2$-(11-14)), 0.87 (3H, t, *J*=6.8 Hz, C**H**$_3$-15); δ_C (100 MHz, $CDCl_3$) 143.2 (**Ar**CH_3), 138.9 (=**C**H-7), 138.6 (**Ar**SO_2), 129.9 (**C**H-9), 129.6 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 115.5 (=**C**H^{a}H^b), 49.1 (**C**HH'NTs), 44.4 (**C**H-3), 32.4 (**C**HH'-4), 31.6 (**C**H$_2$-(11-14)), 29.1 (**C**H$_2$-(11-14)), 29.0 (**C**H$_2$-(11-14)), 27.9 (**C**HH'-10), 23.4 (**C**HH'-5), 22.6 (**C**H$_2$-(11-14)), 21.5 (Ar**C**H_3), 14.1 (**C**H_3-15); IR (thin film) ν_{max}/cm^{-1} 2925 m (C-H), 1353 m

(SO_2), 1342 m (SO_2) 1159 s (SO_2); LRMS m/z (ESI+) 362.2 ($[M+H]^+$, 100%), 745.3 ($[2M+Na]^+$, 75%); HRMS m/z (ESI+) found $[M+Na]^+$ 384.1969; $C_{21}H_{31}NNaO_2S^+$ requires 384.1968.

(3*RS*,5*RS*,*Z*)-3-((*E*)-But-1-en-1-yl)-2-heptylidene-5-phenyl-1-tosylpyrrolidine, (*E*)-236d

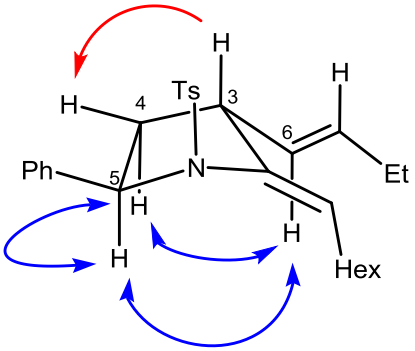


Synthesised from (*Z*)-4-methyl-*N*-(oct-1-yn-1-yl)-N-(1-phenylhept-3-en-1-yl)benzenesulfonamide **195t** (34.0 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), except the reaction mixture was stirred at RT for 3 h. The resulting crude material was purified by column chromatography (5%→10% Et_2O in pet. ether + 1% Et_3N) to give the title compound as a colourless oil (28.0 mg, 0.062 mmol, 82%); R_f = 0.47 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32-7.19 (7H, m, *m*-Ts**H**, Ph**H**), 5.34 (1H, dt, *J*=15.0, 6.2 Hz, =C**H**-7), 5.17 (1H, dd, *J*=7.6, 3.8 Hz, C**H**Ph), 5.13 (1H, ddd, *J*=9.4, 4.8, 1.0 Hz, =C**H**-10), 4.63 (1H, ddt, *J*=15.0, 8.4, 1.5 Hz, =C**H**-6), 3.02 (1H, ap. br. q, *J*=7.7 Hz, C**H**-3), 2.61-2.51 (1H, m, C**H**H'-11), 2.49-2.38 (1H, m, CH**H'**-11), 2.42 (3H, s, ArC$\mathbf{H_3}$), 1.92-1.82 (3H, m, C**H**H'-4, C**HH'**-8), 1.52-1.44 (2H, m, CH**H'**-4, C**H**H'-12), 1.39-1.22 (7H, m, CH**H'**-12, C$\mathbf{H_2}$-(13-15)), 0.90 (3H, t, *J*=7.4 Hz, C$\mathbf{H_3}$-9), 0.89 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 143.7 (**C**), 141.7 (**C**), 139.5 (**C**), 136.3 (**C**), 132.8 (=**C**H-7), 129.7 (=**C**-6), 129.4 (**Ar**H), 128.4 (**Ar**H), 128.0 (**Ar**H), 127.1 (**Ar**H), 125.9 (**Ar**H), 122.0 (=**C**H-10), 64.5 (**C**HPh), 46.6 (**C**H-3), 38.0 (**C**HH'-4), 31.8 (**C**H_2-(13-15)), 29.9 (**C**HH'-11), 29.8 (**C**HH'-12), 29.1 (**C**H_2-(13-15)), 25.3 (**C**HH'-8), 22.7 (**C**H_2-(13-15)), 21.5 (Ar**C**H_3), 14.1 (**C**H_3-16), 13.5 (**C**H_3-9); IR (thin film) ν_{max}/cm^{-1} 2926 w (C-H), 1357 m (SO_2),

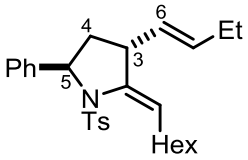
1167 s (SO_2); LRMS *m/z* (ESI+) 474.3 ($[M+Na]^+$, 100%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 474.2421; $C_{28}H_{37}NNaO_2S$ requires 474.2437.

Conformational Analysis

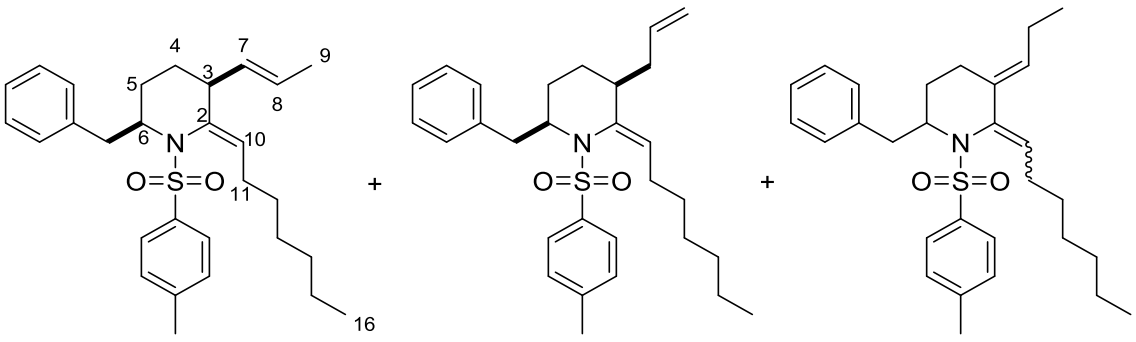
Assignment of stereochemistry of **(*E*)-236d** as *anti* is based on interpretation of 1D ^{1}H NMR nOe data ($CDCl_3$). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between the alkene sidechain (H6), the benzylic proton (H5), and H4α. Complementary enhancement is seen between H3 and H4β.



(*E*)-236d



(3*SR*,6*RS*,*Z*)-6-Benzyl-2-heptylidene-3-((*E*)-prop-1-en-1-yl)-1-tosylpiperidine, (*E*)-236e



(E)-236e **296** **S7**

77 : 14 : 9

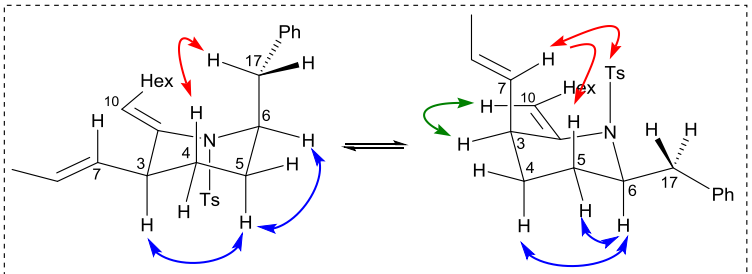
Synthesised from (*Z*)-4-methyl-*N*-(oct-1-yn-1-yl)-*N*-(1-phenyloct-5-en-2-yl)benzenesulfonamide **195u** (50.0 mg, 0.107 mmol) using Procedure 8 (0.167M; 5 mol% cat.), with the reaction mixture stirred for 1.5 h. The resulting crude material was purified by

column chromatography (19:1, pet. ether:Et_2O) to give a mixture of **(*E*)-236e**:**296**:**S7**; 77:14:19 as a pale yellow oil (43.0 mg, 0.092 mmol, 86%). A small amount of major isomer **(*E*)-236e** was isolated by semi-preparative HPLC for characterisation purposes (2.5% Et_2O in hexane, 5.5 mL/min, t_R = 25.3 min): R_f = 0.38 (9:1, pet. ether:Et_2O); δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30-7.16 (5H, m, Ar**H**), 7.15-7.10 (2H, m, Ar**H**), 5.57 (1H, dd, *J*=9.3, 4.6 Hz, =C**H**-10), 5.46 (1H, dqd, *J*=15.4, 6.4, 1.0 Hz, =C**H**-8), 5.30 (1H, ddq, *J*=15.4, 6.8, 1.5 Hz, =C**H**-7), 4.07-3.95 (1H, m, C**H**-6), 3.00 (1H, dd, *J*=13.2, 4.6 Hz, C**H**H'Ph), 2.95-2.87 (1H, br. m, C**H**-3), 2.75 (1H, dd, *J*=13.2, 10.8 Hz, CH**H'**Ph), 2.41 (3H, s, ArC$\mathbf{H_3}$), 2.41-2.17 (2H, m, C**HH'**-11), 1.92-1.79 (1H, m, C**H**H'-4), 1.62 (3H, d, *J*=6.3 Hz, C$\mathbf{H_3}$-9), 1.54-1.41 (2H, m, C**H**H'-5, C**H**H'-12), 1.41-1.20 (8H, m, CH**H'**-12, C**HH'**-(13-15), CH**H'**-4), 1.15-1.04 (1H, m, CH**H'**-5), 0.88 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-16);); δ_C (125 MHz, $CDCl_3$) 142.9 (**C**), 138.4 (**C**), 137.9 (**C**), 133.3 (**C**), 132.5 (=**C**H-7), 132.2 (=**C**H-10), 129.2 (**Ar**H), 129.2 (**Ar**H), 128.5 (**Ar**H), 128.0 (**Ar**H), 126.3 (**Ar**H), 125.2 (=**C**H-8), 57.7 (**C**H-6), 44.8 (**C**H-3), 39.2 (**C**HH'Ph), 31.8 (**C**HH'-(13-15)), 29.5 ((**C**HH'-12), 29.3 (**C**HH'-(13-15)), 29.0 (**C**HH'-11), 25.7 (**C**HH'-4), 22.7 (C**H**H'-(13-15)), 22.0 (**C**HH'-5), 21.5 (Ar**C**H_3), 18.0 (**C**H_3-9), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2927 m (C-H), 1344 m (SO_2), 1159 s (SO_2); LRMS *m*/*z* (ESI+) 953.5 ($[2M+Na]^+$, 74%), 488.3 ($[M+Na]^+$, 65%), 466.3 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 488.2583; $C_{29}H_{39}NNaO_2S$ requires 488.2594.

Conformational Analysis

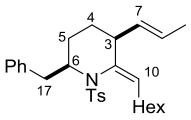
Assignment of stereochemistry of **(*E*)-236e** as *syn* is also based on interpretation of 1D ^1H NMR nOe data. Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between protons H6, H5α, H4α, and H3 which suggest these protons to be on the same face of the molecule. Complementary enhancements are seen between the benzyl sidechain (H17a), H4β, H5β, the alkene sidechain H7, and Ts (*ortho*-protons). The enhancements can be explained by considering an interconverting mixture of conformers. For

conformers **297** and **298** the enhancements H17a–H4β and H7–H5β indicate the sidechains must both be on the same face of the molecule, i.e. 1,4-*syn*-substitution. These enhancements are inconsistent with the alternative *anti*-isomer with both sidechains equatorial (conformer **299**), assuming that *bis*-axial conformer **300** is significantly less-populated.

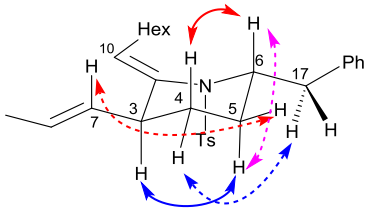


297 **298**

Consistent:
Key nOes on alpha face: H3–H5α, H5α–H6, H4α–H6
Key nOes on beta face: H17a–H4β, H7–H5β, H7–Ts

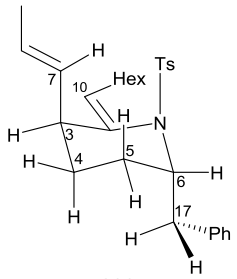


(*E*)-236e



299

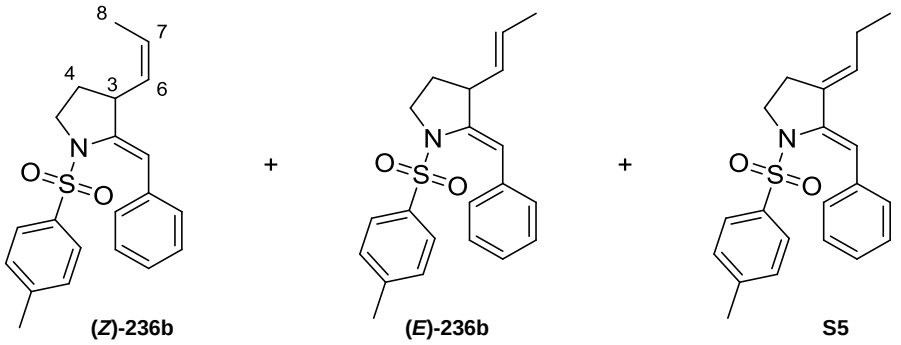
Inconsistent:
nOe is observed from H17a to H4α
nOe is observed from H7 to H5β
nOe is observed from H6 to H5α



300

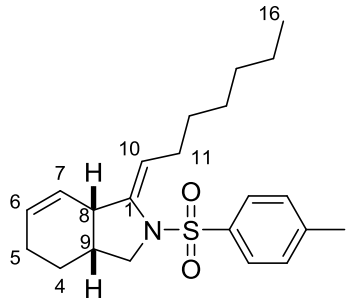
Inconsistent: Not populated as all substituents axial

(*Z*)-2-Benzylidene-3-((*Z*)-prop-1-en-1-yl)-1-tosylpyrrolidine, (*Z*)-236b



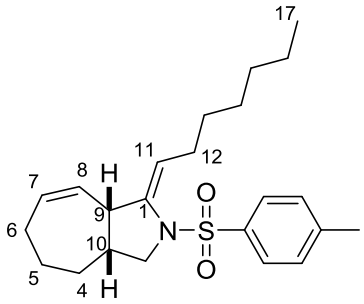
To a solution of (*E*)-*N*-(Hex-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide **195m** (50.0 mg, 0.141 mmol, 1.0 eq.) in MeCN (0.5 mL) was added Cp*RuCl(cod) (2.7 mg, 7.1 μmol, 0.05 eq.). The reaction mixture was stirred at 60 °C for 1 h and then concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, pet. ether:Et_2O + 1% Et_3N) to give an inseparable mixture of **(*Z*)-236b**:**(*E*)-236b**:**S5**; 58:9:33 as a pale yellow oil (42.0 mg, 0.119 mmol, 84%); Data reported for major isomer **(*Z*)-236b**; R_f = 0.33 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.71-7.60 (4H, m, *o*-Ts**H**, *o*-Ph**H**), 7.35-7.24 (4H, m, *m*-Ts**H**, *m*-Ph**H**), 7.23-7.15 (1H, *p*-Ph**H**), 5.88 (1H, d, *J*=2.2 Hz, C**H**Ph), 5.62 (1H, dqd, *J*=10.7, 6.9, 0.8 Hz, =C**H**-7), 5.13-5.05 (1H, m, =C**H**-6), 3.72 (1H, ddd, *J*=11.5, 8.8, 2.2 Hz, C**H**H'NTs), 3.54 (1H, ddd, *J*=11.5, 9.5, 7.6 Hz, CH**H'**NTs), 2.73-2.63 (1H, m, C**H**-3), 2.42 (3H, s, ArC**H$_3$**), 1.87-1.77 (1H, m, C**H**H'-4), 1.48 (2H, dd, *J*=6.8, 1.7 Hz, C**H$_3$**-8), 1.45-1.34 (1H, m, CH**H'**-4); δ_C (125 MHz, $CDCl_3$) 143.9 (**Ar**CH_3), 140.2 (**C**), 136.3 (**C**), 134.3 (**C**), 129.4 (**C**), 129.3 (=**C**H-6), 128.9 (**Ar**H), 128.0 (**Ar**H), 127.7 (**Ar**H), 127.0 (**Ar**H), 126.8 (=**C**H-7) 118.4 (=**C**HPh), 49.0 (**C**HH'NTs), 40.6 (**C**H-3), 28.9 (**C**HH'-4), 21.5 (Ar**C**H_3), 12.9 (**C**H_3-8); ν_{max}/cm^{-1} 2963 w (C-H), 1356 m (SO_2), 1163 s (SO_2); LRMS *m*/*z* (ESI+) 376.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 376.1338; $C_{21}H_{23}NNaO_2S^+$ requires 376.1342.

(3a*RS*,7a*SR*,*Z*)-1-Heptylidene-2-tosyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindole, 301a



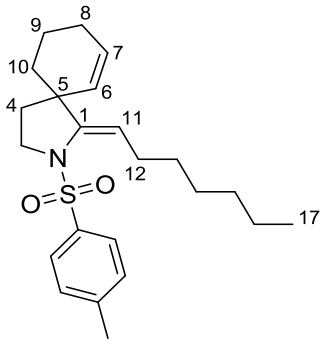
Synthesised from *N*-(cyclohex-2-en-1-ylmethyl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **282a** (28.0 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), except the reaction mixture was stirred for 2.5 h at RT. The resulting crude material was purified by column chromatography (10%→15% Et_2O in pet. ether) to give the title compound as a colourless solid (*Z*:*E* enamides; 96:4) (25.0 mg, 0.067 mmol, 89%); m.p. 88-90 °C; Data reported for the major isomer; R_f = 0.57 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.27 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.65-5.58 (1H, m, =C**H**-6), 5.44 (1H, ddt, *J*=10.0, 4.3, 1.9 Hz, =C**H**-7), 4.95 (1H, ddd, *J*=8.5, 5.7, 1.6 Hz, =C**H**-10), 3.65 (1H, dd, *J*=11.2, 7.6 Hz, C**H**H'NTs), 3.17 (1H, dd, *J*=11.2, 3.5 Hz, CH**H'**NTs), 2.53-2.32 (2H, m, C**HH'**-11), 2.41 (3H, s, ArC**H**$_3$), 2.13 (1H, br. s, C**H**-8), 2.00 (1H, dtt, *J*=11.2, 7.6, 3.5 Hz, C**H**-9), 1.94-1.82 (2H, m, C**HH'**-5), 1.52-1.20 (10H, m, C**HH'**-4, C**H**$_2$-(12-15)), 0.87 (3H, t, *J*=6.8 Hz, C**H**$_3$-16); δ_C (125 MHz, $CDCl_3$) 143.5 (**Ar**CH_3), 139.6, (=**C**-1), 134.8 (**Ar**SO_2), 129.4 (*m*-**Ts**H), 128.9 (=**C**H-6), 127.8 (*o*-**Ts**H), 124.6 (=**C**H-7), 122.9 (=**C**H-10), 54.0 (**C**HH'NTs), 41.6 (**C**H-8), 32.7(**C**H-9), 31.7 (**C**H_2-(11-15)), 29.8 (**C**H_2-(11-15)), 29.0 (**C**H_2-(11-15)), 28.9 (**C**HH'-11), 23.9 (**C**HH'-5), 23.9 (**C**HH'-4), 22.7 (**C**H_2-(11-15)), 21.6 (Ar**C**H_3), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2918 w (C-H), 1344 s (SO_2), 1156 s (SO_2); LRMS *m*/*z* (ESI+) 769.4 ([2M+Na]$^+$, 74%), 396.2 ([M+Na]$^+$, 24%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 396.1969; $C_{22}H_{31}NNaO_2S^+$ requires 396.1968.

(3a*RS*,8a*SR*,*Z*)-1-Heptylidene-2-tosyl-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[c]pyrrole, 301b



Synthesised from *N*-(cyclohept-2-en-1-ylmethyl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **282b** (29.0 mg, 0.075 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), except the reaction mixture was stirred for 2.5 h at RT. The resulting crude material was purified by column chromatography (2.5%→10% Et_2O in pet. ether) to give the title compound as a colourless solid (5,7-*cis*:5,7-*trans* fused rings; 90:10) (26.5 mg, 0.068 mmol, 91%); m.p. 62-64 °C; Data reported for the major isomer; R_f = 0.53 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.77 (1H, ddd, *J*=11.7, 7.4, 3.9 Hz, =C**H**-7), 5.28 (1H, ddd, *J*=11.7, 6.1, 1.7 Hz, =C**H**-8), 5.07-5.01 (1H, m, =C**H**-11), 3.52 (1H, dd, *J*=11.0, 6.9 Hz, C**H**H'NTs), 3.10 (1H, dd, *J*=11.0, 2.8 Hz, CH**H'**NTs), 2.59-2.48 (1H, m, C**H**H'-12), 2.42 (3H, s, ArC**H**$_3$), 2.40-2.29 (2H, m, C**H**-9, CH**H'**-12), 2.18-2.07 (1H, m, C**H**H'-6), 1.94-1.81 (2H, m, C**H**-10, CH**H'**-6), 1.68-1.60 (1H, m, C**H**H'-5), 1.60-1.52 (1H, m, C**H**H'-4), 1.49-1.15 (10H, m, CH**H'**-4, C**H**$_2$-(13-16), CH**H'**-5), 0.88 (3H, t, *J*=6.8 Hz, C**H**$_3$-17); δ_C (125 MHz, $CDCl_3$) 143.6 (**Ar**CH_3), 137.9 (=**C**-1), 134.5 (**Ar**SO_2), 132.9 (=**C**H-7), 129.4 (*m*-**Ts**H), 127.8 (*o*-**Ts**H), 126.5 (=**C**H-8), 121.5 (=**C**H-11), 56.3 (**C**HH'NTs), 46.6 (**C**H-9), 38.0 (**C**H-10), 31.7 (**C**H_2-(13-16)), 31.5 (**C**HH'-4), 29.9 (**C**H_2-(13-16)), 29.3 (**C**HH'-6), 29.0 (**C**H_2-(13-16)), 28.7 (**C**HH'-12), 24.9 (**C**HH'-5), 22.7 (**C**H_2-(13-16)), 21.6 (Ar**C**H_3), 14.1 (**C**H_3-17); IR (thin film) ν_{max}/cm^{-1} 2923 m (C-H), 1356 m (SO_2), 1167 s (SO_2); LRMS *m*/*z* (ESI+) 797.4 ([2M+Na]$^+$, 100%), 388.2 ([M+H]$^+$, 68%); HRMS *m*/*z* (ESI+) found [M+H]$^+$ 388.2302; $C_{23}H_{34}NO_2S^+$ requires 388.2305.

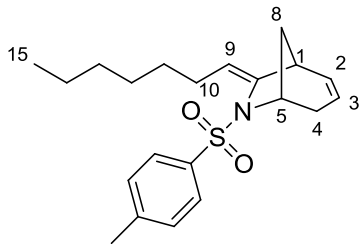
(*Z*)-1-Heptylidene-2-tosyl-2-azaspiro[4.5]dec-6-ene, 301c



Synthesised from *N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **282c** (30 mg, 0.077 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), with the reaction mixture stirred for 1 h. The resulting crude material was purified by column chromatography (19:1, pet. ether:Et_2O) to give the title compound as a colourless oil (1,4-diene:1,5-diene; 93:7) (24.5 mg, 0.063 mmol, 82%); Data reported for the major isomer; R_f = 0.54 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.72 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.73 (1H, dt, *J*=9.9, 3.7 Hz, =C**H**-7), 5.15 (1H, br. d, *J*=9.9 Hz, =C**H**-6), 4.84 (1H, dd, *J*=7.7, 6.1 Hz, =C**H**-11), 3.61-3.54 (1H, m, C**H**H'NTs), 3.49 (1H, td, *J*=9.9, 8.2 Hz, CH**H'**NTs), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.39-2.31 (2H, m, C**HH'**-12), 2.02-1.78 (2H, m, C**HH'**-8), 1.60-1.54 (2H, m, C**HH'**-4), 1.44-1.18 (10H, m, C**HH'**-9, C$\mathbf{H_2}$-(13-16)), 0.94 (1H, ddd, *J*=12.9, 10.1, 2.8 Hz, C**H**H'-10), 0.90-0.80 (1H, m, CH**H'**-10), 0.88 (3H, t, *J*=6.9 Hz, C$\mathbf{H_3}$-17); δ_C (125 MHz, $CDCl_3$) 143.5 (**C**), 142.6 (**C**), 135.8 (**C**), 132.5 (=**C**H-6), 129.3 (*m*-**Ts**H), 128.6 (=**C**H-7), 127.7 (*o*-**Ts**H), 119.7 (=**C**H-11), 48.2 (**C**HH'NTs), 46.6 (**C**-5), 36.5 (**C**HH'-4), 31.7 (**C**HH'-10), **C**H_2-(13-16)), 30.1 (**C**H_2-(13-16)), 29.4 (**C**HH'-12), 29.0 (**C**H_2-(13-16)), 25.0 (**C**HH'-8), 22.7 (**C**H_2-(13-16)), 21.5 (Ar**C**H_3), 19.2 (**C**HH'-9), 14.1 (**C**H_3-17); IR (thin film) ν_{max}/cm^{-1} 2926 m (C-H), 1358 m (SO_2), 1165 s (SO_2); LRMS *m/z*

(ESI+) 410.1 ([M+Na]$^+$, 100%); HRMS m/z (ESI+) found [M+Na]$^+$ 410.2113; $C_{23}H_{33}NNaO_2S$ requires 410.2124.

(1*SR*,5*SR*,*Z*)-7-Heptylidene-6-tosyl-6-azabicyclo[3.2.1]oct-2-ene*, 301d

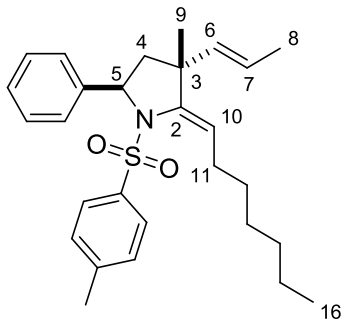


***Reaction carried out by Dr. Craig Campbell.**

Synthesised from *N*-(cyclohex-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **282d** (25.0 mg, 0.070 mmol) using Procedure 8 (0.333M; 2.5 mol% cat.), except the reaction mixture was stirred at 35 °C for 5 h. The resulting crude material was purified by column chromatography (19:1, pet. ether:EtOAc) to give the title compound as a colourless oil (*Z*:*E* enamides; 91:9) (20.0 mg, 0.059 mmol, 77%); Data reported for the major isomer; R_f = 0.22 (11:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$); 7.69-7.64 (2H, m, *o*-Ts**H**), 7.27 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 6.02-5.92 (1H, m, =C**H**-2), 5.50-5.40 (1H, m, =C**H**-3), 4.69-4.62 (1H, br. m, C**H**-5), 4.49 (1H, t, *J*=7.1 Hz, =C**H**-9), 2.85 (1H, br. t, *J*=5.4 Hz, C**H**-1), 2.70-2.59 (1H, m, C**H**H'-4), 2.41 (3H, s, ArC**H$_3$**), 2.41-2.34 (1H, m, CH**H'**-4), 2.11-2.01 (2H, m, C**H$_2$**-10), 1.79-1.65 (2H, m, C**HH'**-8), 1.35-1.15 (2H, m, C**H$_2$**-11), 1.16-1.04 (6H, m, C**H$_2$**-(12-14)), 0.84 (3H, t, *J*=7.2 Hz, C**H$_3$**-15); δ_C (125 MHz, $CDCl_3$) 143.1 (**C**), 141.1 (**C**), 138.5 (**C**), 132.4 (=**C**H-2), 129.5 (*m*-**Ts**H), 126.6 (*o*-**Ts**H), 123.1 (=**C**H-3), 107.0 (=**C**H-9), 61.9 (**C**H-5), 43.4 (**C**H-1), 33.9 (**C**HH'-4), 32.8 (**C**HH'-8), 31.6 (**C**H$_2$-(12-14)), 30.3 (**C**H$_2$-(12-14)), 28.8 (**C**H$_2$-(12-14)), 28.1 (**C**H$_2$-10), 22.6 (**C**H$_2$-11), 21.5 (Ar**C**H$_3$), 14.1 (**C**H$_3$-15); IR (thin film) ν_{max}/cm^{-1} 3033 m (C-H), 2954 m (C-H), 2918 m (C-H), 1708 s (C=C), 1599 m (C=C), 1327 m (SO_2), 1160 s (SO_2); LRMS *m*/*z* (ESI+) 360.3 ([M+H]$^+$, 22%), 378.1 ([M+H$_2$O+H]$^+$, 39%),

400.2 ([M+H_2O+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 382.1805; $C_{21}H_{29}NNaO_2S^+$ requires 382.1811.

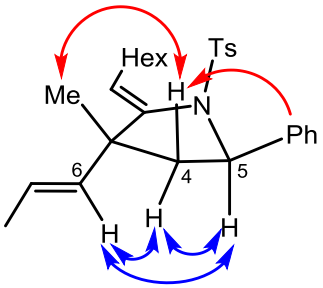
(3*RS*,5*RS*,*Z*)-2-Heptylidene-3-methyl-5-phenyl-3-((*E*)-prop-1-en-1-yl)-1-tosylpyrrolidin, (*E*)-307d



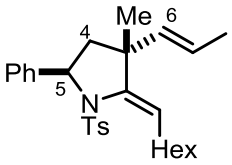
Synthesised from (*E*)-4-methyl-*N*-(3-methyl-1-phenylhex-3-en-1-yl)-*N*-(oct-1-yn-1-yl)benzenesulfonamide **306e** (34 mg, 0.075 mmol) using Procedure 8 (0.167M; 10 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (9:1, hexanes:*t*-BuOMe) to give the title compound as a pale yellow oil (28.5 mg, 0.063 mmol, 84%); R_f = 0.31 (10:1, hexanes:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.44 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.31-7.18 (5H, m, Ph**H**), 7.10 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.46 (1H, dq, *J*=15.4, 6.4 Hz, =C**H**-7), 5.08-5.01 (1H, m, =C**H**-6), 5.01-4.94 (2H, m, C**H**-5, =C**H**-10), 2.39-2.32 (2H, m, C**HH'**-11), 2.35 (3H, s, ArC$\mathbf{H_3}$), 2.28 (1H, dd, *J*=12.5, 7.4 Hz, C**H**H'-4), 1.58 (1H, dd, *J*=12.5, 8.9 Hz, CH**H'**-4), 1.55-1.45 (4H, m, C$\mathbf{H_3}$-8, C**H**H'-12), 1.42-1.20 (7H, m, CH**H'**-12, C$\mathbf{H_2}$-(13-15)), 1.10 (3H, s, C$\mathbf{H_3}$-9), 0.89 (3H, t, *J*=6.8 Hz, C$\mathbf{H_3}$-16); δ_C (125 MHz, $CDCl_3$) 144.5 (**C**), 143.2 (**C**), 143.1 (**C**), 136.8 (**C**), 135.0 (=**C**H-6), 128.9 (*m*-**Ts**H), 128.4 (**Ph**H), 128.0 (*o*-**Ts**H), 127.2 (**Ph**H), 126.4 (**Ph**H), 123.2 (=**C**H-7), 116.9 (=**C**H-10), 62.9 (**C**H-5), 47.5 (**C**-3), 47.1 (**C**HH'-4), 31.7 (**C**H_2-(13-15)), 29.8 (**C**HH'-12), 29.4 (**C**HH'-11), 29.0 (**C**H_2-(13-15)), 25.6 (**C**H_3-9), 22.7 (**C**H_2-(13-15)), 21.4 (Ar**C**H_3), 18.0 (**C**H_3-8), 14.1 (**C**H_3-16); IR (thin film) ν_{max}/cm^{-1} 2925 m (C-H), 1347 m (SO_2), 1166 s (SO_2); HRMS *m*/*z* (ESI+) found [M+H]$^+$452.2623; $C_{28}H_{38}NO_2S$ requires 452.2618.

Conformational Analysis

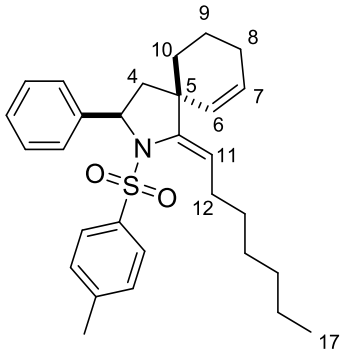
Assignment of stereochemistry of **(*E*)-307d** is based on interpretation of 1D ^{1}H NMR nOe data (C_6D_6). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between the alkene sidechain (H6), the benzylic proton (H5), and H4α. Complementary enhancement is seen between the methyl group and H4β, as well as from the Ph (*ortho*-protons) to H4β.



(*E*)-307d



(3*RS*,5*RS*,*Z*)-1-Heptylidene-3-phenyl-2-tosyl-2-azaspiro[4.5]dec-6-ene, 322

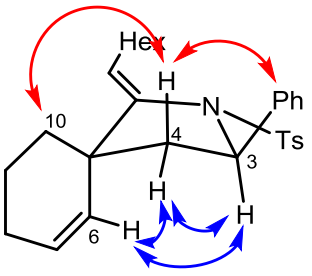


Synthesised from *N*-(2-(cyclohex-1-en-1-yl)-1-phenylethyl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **321** (35 mg, 0.075 mmol) using Procedure 8 (0.167M; 5 mol% cat.), with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (5%→10% Et_2O in pet. ether) to give the title compound as a pale yellow oil (≥98:2 d.r.) (27.5 mg, 0.059 mmol, 79%); R_f = 0.65 (4:1, hexanes:EtOAc); δ_H (500 MHz, C_6D_6) 7.70 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.28 (2H, d, *J*=7.3 Hz, *o*-Ph**H**), 7.12 (2H, ap.

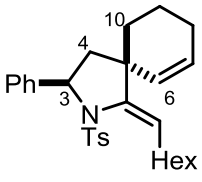
t, *J*=7.6 Hz, *m*-Ph**H**), 7.06-7.00 (1H, m, *p*-Ph**H**), 6.68 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.62 (1H, br. d, *J*=10.0 Hz, =C**H**-6), 5.48 (1H, dt, *J*=10.0, 3.6 Hz, =C**H**-7), 5.42 (1H, dd, *J*=6.1, 7.9 Hz, C**H**Ph), 5.22 (1H, dd, *J*=9.0 4.9 Hz, =C**H**-11), 2.78-2.61 (2H, m, C**HH'**-12), 2.00 (1H, dd, *J*=12.4, 7.9 Hz, C**H**H'-4), 1.82 (3H, s, ArC**H**$_3$), 1.82-1.67 (2H, m, C**HH'**-8), 1.62 (1H, dd, *J*=12.4, 6.1 Hz, CH**H'**-4), 1.61-1.53 (2H, m, C**H**H'-10, C**H**H'-13), 1.50-1.40 (2H, m, C**H**H'-9, CH**H'**-13), 1.40-1.20 (8H, m, C**H**$_2$-(14-16), CH**H'**-9, CH**H'**-10), 0.88 (3H, t, *J*=6.9 Hz, C**H**$_3$-17); δ_C (125 MHz, C_6D_6) 145.5 (**C**), 143.5 (**C**), 143.1(**C**), 138.3 (**C**), 132.3 (=**C**H-6), 129.3 (*m*-**Ts**H), 128.7 (*m*-**Ph**H), (*o*-**Ts**H obscured by solvent peak), 127.3 (*p*-**Ph**H), 126.6 (*o*-**Ph**H), 125.9 (=**C**H-7), 118.6 (=**C**H-11), 63.1 (**C**HPh), 47.9 (**C**HH'-4), 47.2 (**C**-5), 35.2 (**C**HH'-10), 32.2 (**C**H$_2$-(14-16)), 30.5 (**C**HH'-12), 30.3 (**C**HH'-13), 29.6 (**C**H$_2$-(14-16)), 25.1 (**C**HH'-8), 23.1 (**C**H$_2$-(14-16)), 21.1 (Ar**C**H$_3$), 20.6 (**C**HH'-9), 14.4 (**C**H$_3$-17); IR (thin film) ν_{max}/cm^{-1} 2927 m (C-H), 1361 m (SO_2), 1167 s (SO_2); LRMS *m*/*z* (ESI+) 464.3 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 486.2444; $C_{29}H_{37}NNaO_2S$ requires 486.2437.

Conformational Analysis

Assignment of stereochemistry of **322** is based on interpretation of 1D ^{1}H NMR nOe data ($CDCl_3$). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between the alkene moiety of the cyclohexenyl substituent (H6), the benzylic proton (H3), and H4α. Complementary enhancement is seen between CH_2-10 and H4β, as well as between the Ph (*ortho*-protons) and H4β.

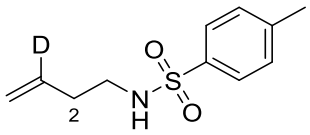


322



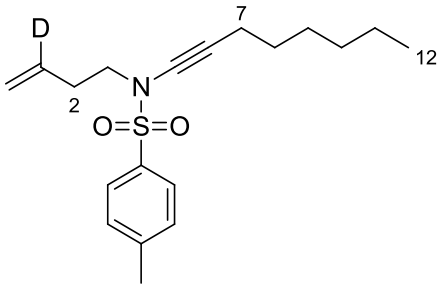
6.3.5 Deuterated substrates

_N_-(But-3-en-1-yl-3-_d_)-4-methylbenzenesulfonamide, 376



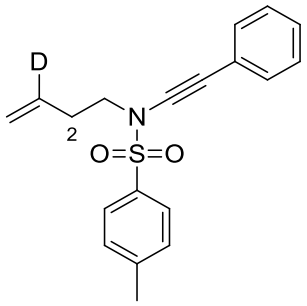
According to the procedure of Hoveyda and co-workers.[127] $Ni(dppp)Cl_2$ (81 mg, 0.15 mmol, 0.03 eq.) was placed in an oven-dried flask and the flask purged with argon for 10 min. THF (5 mL) was added followed by the dropwise addition of DIBALH (11.5 mL, 1M in hexanes, 11.5 mmol, 2.3 eq.) at RT. The resulting black solution was cooled to 0 ºC and a solution of *N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (1.12 g, 5.0 mmol, 1.0 eq.) in THF (5 mL) was added over 5 min (exothermic). The resulting black solution was stirred at RT for 2 h and then cooled to 0 ºC. D_2O (0.3 mL) was added dropwise and the reaction mixture stirred at 0 ºC for 30 min. 4M aq. NaOH (0.3 mL) and H_2O (1 mL) were added followed by excess $MgSO_4$ and Et_2O (20 mL). The resulting mixture was stirred at RT for 1 h, filtered through Celite eluting with Et_2O and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (3:2, pet. ether:Et_2O) to give the title compound (90% deuterium incorporation by ^1H NMR spectroscopy) as a colourless oil (748 mg, 3.30 mmol, 66%); R_f = 0.50 (3:2, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.31 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.09-4.98 (2H, m, =C**HH'**), 4.65-4.48 (1H, m, N**H**), 3.01 (2H, ap. q, *J*=6.4 Hz, C$\mathbf{H_2}$NH), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.19 (2H, br. t, *J*=6.6 Hz, **C**H_2-2); δ_C (100 MHz, $CDCl_3$) 143.4 (**Ar**CH_3), 136.9 (**Ar**SO_2), 133.8 (weak t, =**C**D) 129.7 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 118.0 (=**C**HH'), 42.0 (**C**H_2NH), 33.4 (**C**H_2-2), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3378 br. w (N-H), 2925 w (C-H), 1320 m (SO_2), 1154 s (SO_2); LRMS *m*/*z* (ESI+) 475.2 ([2M+Na], 100%), 249.1 ($[M+Na]^+$, 33%), 227.1 ($[M+H]^+$, 33%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 249.0784; $C_{11}H_{14}DNNaO_2S$ requires 249.0778.

_N_-(But-3-en-1-yl-3-_d_)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 377a



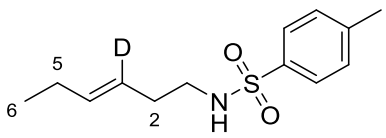
Synthesised from *N*-(but-3-en-1-yl-3-*d*)-4-methylbenzenesulfonamide **376** (90% deuterium incorporation by ^{1}H NMR spectroscopy) (300 mg, 1.33 mmol) and 1-bromooct-1-yne **125a** (301 mg, 1.59 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (0%→10% Et_2O in pet. ether) to give the title compound (90% deuterium incorporation by ^{1}H NMR spectroscopy) as a colourless oil (138 mg, 0.36 mmol, 83%); R_f = 0.69 (4:1, pet. ether:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.10-5.00 (2H, m, =C**HH'**), 3.35-3.28 (2H, m, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.36 (2H, br. t, *J*=7.3 Hz, C$\mathbf{H_2}$-2), 2.25 (2H, t, *J*=7.0 Hz, C$\mathbf{H_2}$-7), 1.52-1.42 (2H, m, C$\mathbf{H_2}$-8), 1.39-1.20 (6H, m, C$\mathbf{H_2}$-(9-11)), 0.88 (3H, t, *J*=6.8 Hz, C$\mathbf{H_3}$-12); δ_C (100 MHz, $CDCl_3$) 144.1 (**Ar**CH_3), 134.6 (**Ar**SO_2), 133.5 (weak t, =**C**D) 129.5 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 117.3 (=**C**HH'), 72.8 (≡**C**), 70.5 (≡**C**), 50.8 (**C**H_2NH), 32.0 (**C**H_2-2), 31.3 (**C**H_2-(9-11)), 28.9 (**C**H_2-8), 28.4 (**C**H_2-(9-11)), 22.6 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 18.4 (**C**H_2-7), 14.0 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2930 w (C-H), 2254 w (C≡C), 1364 m (SO_2), 1168 s (SO_2); LRMS *m*/*z* (ESI+) 335.2 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 357.1709; $C_{19}H_{26}DNNaO_2S$ requires 357.1717.

_N_-(But-3-en-1-yl-3-_d_)-4-methyl-_N_-(phenylethynyl)benzenesulfonamide, 377b



Synthesised from *N*-(but-3-en-1-yl-3-*d*)-4-methylbenzenesulfonamide **376** (90% deuterium incorporation by ^{1}H NMR spectroscopy) (100 mg, 0.44 mmol) and (bromoethynyl)benzene **125b** (96 mg, 0.53 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound (90% deuterium incorporation by ^{1}H NMR spectroscopy) as a pale yellow oil (107 mg, 0.33 mmol, 74%); R_f = 0.47 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.40-7.33 (4H, m, Ph**H**, *m*-Ts**H**), 7.32-7.27 (3H, m, Ph**H**), 5.14-5.03 (2H, m, =C**HH'**), 3.49-3.44 (2H, m, C$\mathbf{H_2}$NTs), 2.49-2.41 (5H, m, C$\mathbf{H_2}$-2, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 144.6 (**Ar**CH_3), 134.6 (**Ar**SO_2), (=**C**D absent), 131.4 (**Ph**H), 129.8 (*m*-Ts**H**), 128.3 (**Ph**H), 127.8 (**Ph**H), 127.7 (*o*-Ts**H**), 122.8 (**Ph**), 117.6 (=**C**HH'), 82.1 (≡**C**), 70.9 (≡**C**), 50.9 (C$\mathbf{H_2}$NTs), 32.2 (**C**H_2-2), 21.7 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 2926 w (C-H), 2235 w (C≡C), 1365 s (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 327.2 ([M+H]$^+$, 100%), 349.1 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 349.1093; $C_{19}H_{18}DNNaO_2S$ requires 349.1091.

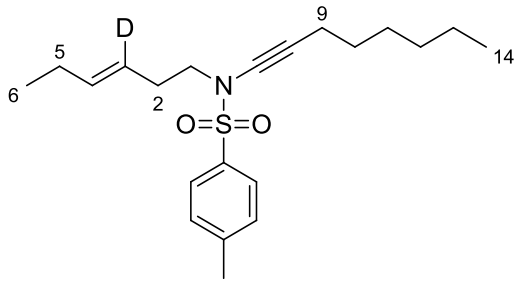
(_E_)-_N_-(Hex-3-en-1-yl-3-_d_)-4-methylbenzenesulfonamide, 381



To an oven-dried vial containing Hoveyda-Grubbs II Catalyst (8 mg, 0.013 mmol, 0.03 eq.) was added a solution of *N*-(but-3-en-1-yl-3-*d*)-4-methylbenzenesulfonamide **376** (90%

deuterium incorporation by ^{1}H NMR spectroscopy) (100 mg, 0.44 mmol, 1.0 eq.) in DCM (2.5 mL), followed by *trans*-3-hexene (0.33 mL, 2.65 mmol, 6.0 eq.). The reaction mixture was stirred under reflux for 48 h and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (20%→30% Et_2O in pet. ether) to give the title compound (*E*:*Z,* 85:15; 90% deuterium incorporation by ^{1}H NMR spectroscopy) as a colourless oil (81 mg, 0.32 mmol, 72%); R_f = 0.35 (7:3, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.31 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.53-5.41 (1H, br. m, =C**H**), 4.48-4.33 (1H, br. m, N**H**), 2.97 (2H, ap. q, *J*=6.4 Hz, C$\mathbf{H_2}$NTs), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.12 (2H, t, *J*=6.5 Hz, C$\mathbf{H_2}$-2), 1.97 (2H, ap. quin., *J*=7.2 Hz, C$\mathbf{H_2}$-5), 0.94 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6); δ_C (100 MHz, $CDCl_3$) 143.4 (**Ar**CH_3), 137.0 (**Ar**SO_2), 136.1 (=**C**H), 129.7 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 42.5 (**C**H_2NTs), 32.3 (**C**H_2-2), 25.4 (**C**H_2-5), 21.5 (Ar**C**H_3), 13.6 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 3272 br. w (N-H), 2964 w (C-H), 1325 m (SO_2), 1161 s (SO_2); LRMS *m*/*z* (ESI+) 531.3 ([2M+Na], 100%), 277.1 ([M+Na]$^+$, 75%), 255.1 ([M+H]$^+$, 75%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 277.1088; $C_{13}H_{18}DNNaO_2S$ requires 277.1091.

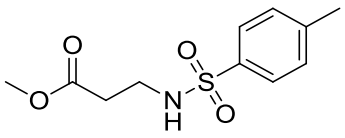
(*E*)-*N*-(Hex-3-en-1-yl-3-*d*)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 382



Synthesised from (*E*)-*N*-(hex-3-en-1-yl-3-*d*)-4-methylbenzenesulfonamide **381** (*E*:*Z,* 85:15; 90% deuterium incorporation by ^{1}H NMR spectroscopy) (75 mg, 0.29 mmol) and 1-bromooct-1-yne **125a** (67 mg, 0.35 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (9:1, pet. ether:Et_2O) to give the title compound (*E*:*Z,* 85:15; 90% deuterium incorporation by ^{1}H NMR spectroscopy) as a colourless oil

(75 mg, 0.21 mmol, 71%); R_f = 0.63 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.55-5.45 (1H, m, =C**H**), 3.30-3.24 (2H, m, C$\mathbf{H_2}$NTs), 2.44 (3H, s, ArC$\mathbf{H_3}$), 2.32-2.22 (4H, m, C$\mathbf{H_2}$-2, C$\mathbf{H_2}$-9), 2.04-1.90 (2H, m, C$\mathbf{H_2}$-5), 1.52-1.42 (2H, m, C$\mathbf{H_2}$-10), 1.39-1.20 (6H, m, C$\mathbf{H_2}$-(11-13)), 0.93 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-6), 0.88 (3H, t, *J*=7.0 Hz, C$\mathbf{H_3}$-14); δ_C (100 MHz, $CDCl_3$) 144.1 (**Ar**CH_3), 135.1 (=**C**H), 134.8 (**Ar**SO_2), 129.5 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 72.9 (≡**C**), 70.4 (≡**C**), 51.3 (C$\mathbf{H_2}$NTs), 31.3 (**C**H_2-(11-13)), 30.9 (C$\mathbf{H_2}$-2), 28.9 (**C**H_2-10), 28.4 (**C**H_2-(11-13)), 25.5 (**C**H_2-5), 22.6 (**C**H_2-(11-13)), 21.6 (Ar**C**H_3), 18.5 (**C**H_2-9), 14.0 (**C**H_3-14), 13.6 (**C**H_3-6); IR (thin film) ν_{max}/cm^{-1} 2931 w (C-H), 2254 w (C≡C), 1364 m (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 363.2 ($[M+H]^+$, 100%); HRMS *m*/*z* (ESI+) found $[M+Na]^+$ 385.2027; $C_{21}H_{30}DNNaO_2S$ requires 385.2030.

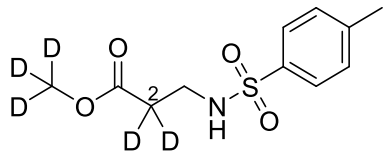
Methyl 3-(4-methylphenylsulfonamido)propanoate, 391



To a solution of *β*-alanine methyl ester hydrochloride (2.79 g, 20 mmol, 1.0 eq.) in DCM (120 mL) at 0 ºC was added Et_3N (6.97 mL, 50 mL, 2.5 eq.). The reaction mixture was stirred at 0 ºC for 10 min and *p*-toluenesulfonyl chloride (3.81 g, 20.0 mmol, 1.0 eq.) added. The reaction mixture was allowed to warm to RT and sat. aq. NH_4Cl (100 mL) added. The organic layer was separated and the aqueous layer washed with DCM (2 × 100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a pale yellow oil (5.02 g, 19.4 mmol, 97%) which was used without further purification; R_f = 0.34 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.1 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.1 Hz, *m*-Ts**H**), 5.37-5.23 (1H, br. m, N**H**), 3.64 (3H, s, C$\mathbf{H_3}$O), 3.17 (2H, ap. q, *J*=6.1 Hz C$\mathbf{H_2}$NH), 2.52 (2H, t, *J*=6.1 Hz,

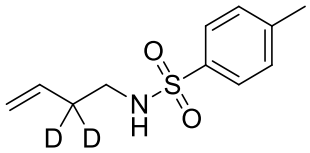
C**H**$_2$CO), 2.41 (3H, s, ArC**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.4 (**C**=O), 143.4 (**Ar**CH_3), 136.8 (**Ar**SO_2), 129.7 (*m*-**Ts**H), 127.0 (*o*-**Ts**H), 51.9 (C**H**$_3$O), 38.7 (C**H**$_2$NH), 33.8 (**C**H_2CO), 21.5 (Ar**C**H_3); Data are consistent with literature values.[177]

Methyl-*d*$_3$ 3-((4-methylphenyl)sulfonamido)propanoate-2,2-*d*$_2$, 392



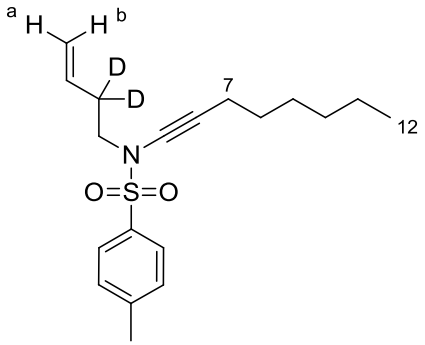
To a solution of methyl 3-(4-methylphenylsulfonamido)propanoate **391** (100 mg, 0.389 mmol, 1.0 eq.) in MeOD-d_4 (1.0 mL) was added K_2CO_3 (177 mg, 1.28 mmol, 3.3 eq.). The reaction mixture was stirred at RT for 15 h, DCM (5 mL) and sat. aq. NH_4Cl (5 mL) added and the layers separated. The aqueous layer was extracted with DCM (5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (91% deuterium incorporation by ^{1}H NMR at C-2) as a colourless oil (73 mg, 0.38 mmol, 71%) which was used without further purification; R_f = 0.34 (1:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.30 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 3.16 (2H, s, C**H**$_2$NH), 2.41 (3H, s, ArC**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.4 (**C**=O), 143.5 (**Ar**CH_3), 136.8 (**Ar**SO_2), 129.7 (*m*-**Ts**H), 127.0 (*o*-**Ts**H), (C**D**$_3$O absent), 38.5 (C**H**$_2$NH), (**C**D_2CO absent), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3288 br. w (N-H), 2926 m (C-H), 1732 m (C=O), 1330 s (SO_2), 1155 s (SO_2); LRMS *m*/*z* (ESI+) 547.2 ([2M+Na]$^+$, 100%), 285.1 ([M+Na]$^+$, 85%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 285.0929; $C_{11}H_{10}D_5NNaO_4S$ requires 285.0928.

_N_-(But-3-en-1-yl-2,2-d_2)-4-methylbenzenesulfonamide, 393



To a solution of methyl-d_3 3-((4-methylphenyl)sulfonamido)propanoate-2,2-d_2 **392** (91% deuterium incorporation by ^{1}H NMR spectroscopy) (227 mg, 0.87 mmol, 1.0 eq.) in toluene (7 mL) at -78 ºC was added DIBALH (1.73 mL, 1 M in hexanes, 1.73 mmol, 2.0 eq.) dropwise. The reaction mixture was stirred at -78 ºC for 5 h, quenched with sat. aq. Rochelle Salt (10 mL) and diluted with EtOAc (15 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h. The layers were separated and the aqueous layer extracted with EtOAc (15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was taken up in THF (5.0 mL), added to a solution of $Cp_2TiCH_2AlCl(CH_3)_2$ (566 mg 1.99 mmol, 2.3 eq.) in toluene (2.0 mL) at 0 °C and stirred at RT for 15 h. 2 M aq. NaOH (0.8 mL), excess $MgSO_4$ and Et_2O (20 mL) were added, the mixture stirred at RT for 1 h, filtered through Celite eluting with Et_2O and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (7:3, pet. ether:Et_2O) to give the title compound (91% deuterium incorporation by ^{1}H NMR spectroscopy) as a colourless oil (38 mg, 0.167 mmol, 19%); R_f = 0.26 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.74 (2H, d, *J*=8.3 Hz, *o*-Ts**H**), 7.30 (2H, d, *J*=8.3 Hz, *m*-Ts**H**), 5.61 (1H, dd, *J*=16.9, 10.3 Hz, =C**H**), 5.10-4.98 (2H, m, =C**HH'**), 4.70-4.54 (1H, br. m, N**H**), 2.99 (2H, d, *J*=6.1 Hz, C$\mathbf{H_2}$NTs), 2.42 (3H, s, ArC$\mathbf{H_3}$); δ_C (100 MHz, $CDCl_3$) 143.4 (**Ar**CH_3), 136.9 (**Ar**SO_2), 134.0 (=**C**H), 129.7 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 118.1 (=**C**HH'), 41.9 (**C**H_2NTs), (**C**D_2 absent), 21.5 (Ar**C**H_3); IR (thin film) ν_{max}/cm^{-1} 3280 br. w (N-H), 2925 w (C-H), 1322 m (SO_2), 1155 s (SO_2); LRMS *m*/*z* (ESI+) 477.2 ([2M+Na]$^+$, 100%), 228.1 ([M+H]$^+$, 22%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 250.0847; $C_{11}H_{13}D_2NNaO_2S$ requires 250.0841.

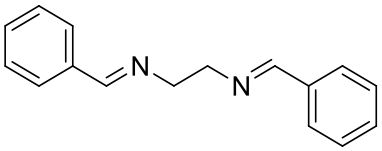
_N_-(But-3-en-1-yl-2,2-d_2)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 394



Synthesised from *N*-(but-3-en-1-yl-2,2-d_2)-4-methylbenzenesulfonamide **393** (91% deuterium incorporation by ^{1}H NMR spectroscopy) (35 mg, 0.154 mmol) and 1-bromooct-1-yne (38 mg, 0.200 mmol) using Procedure 6. The resulting crude material was purified by column chromatography (19:1, pet. ether:Et_2O) to give the title compound (91% deuterium incorporation by ^{1}H NMR spectroscopy) as a colourless oil (43.5 mg, 0.130 mmol, 84%); R_f = 0.55 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.32 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.71 (1H, dd, *J*=17.1, 10.2 Hz, =C**H**), 5.07 (1H, dd, *J*=17.1, 1.8 Hz, =CH^a**H^b**), 5.03 (1H, dd, *J*=10.2, 1.8 Hz, =C**H^a**H^b), 3.30 (2H, s, C**H$_2$**NTs), 2.44 (3H, s, ArC**H$_3$**), 2.25 (2H, t, *J*=7.0 Hz, C**H$_2$**-7), 1.53-1.41 (2H, m, C**H$_2$**-8), 1.39-1.19 (6H, m, C**H$_2$**-(9-11)), 0.88 (3H, t, *J*=7.0 Hz, C**H$_3$**-12); δ_C (100 MHz, $CDCl_3$) 144.2 (**Ar**CH_3), 134.6 (**Ar**SO_2), 133.7 (=**C**H), 129.5 (*m*-**Ts**H), 127.6 (*o*-**Ts**H), 117.5 (=**C**H^{a}H^b), 72.8 (≡**C**), 70.5 (≡**C**), 50.6 (**C**H_2NTs), (**C**D_2 absent), 31.3 (**C**H_2-(9-11)), 28.9 (**C**H_2-8), 28.4 (**C**H_2-(9-11)), 22.6 (**C**H_2-(9-11)), 21.6 (Ar**C**H_3), 18.4 (**C**H_2-7), 14.0 (**C**H_3-12); IR (thin film) ν_{max}/cm^{-1} 2930 w (C-H), 2250 w (C≡C), 1363 s (SO_2), 1169 s (SO_2); LRMS *m*/*z* (ESI+) 336.3 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+) found [M+Na]$^+$ 358.1781; $C_{19}H_{25}D_2NNaO_2S$ requires 358.1780.

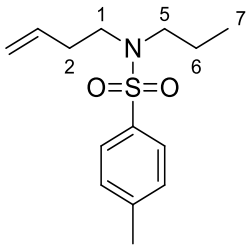
6.3.6 Miscellaneous

_N_,_N_′-Bis(benzylidene)ethylenediamine



According to the procedure of Fontecave and co-workers.[178] To a stirred solution of benzaldehyde (3.05 mL, 30.0 mmol, 2.0 eq.) in MeOH (40 mL) was added ethylenediamine (1.0 mL, 15.0 mmol, 1.0 eq.) dropwise. The reaction mixture was stirred at RT for 1 h and then concentrated *in vacuo* to give the title compound as a colourless solid (3.32 g, 126 mmol, 84%) which was used without further purification; m.p. 43-46 °C; R_f = 0.27 (5:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 8.29 (2H, s, C**H**=N), 7.73-7.67 (4H, m, *o*-Ph**H**), 7.43-7.35 (6H, m, *m*-Ph**H**, *p*-Ph**H**), 2.17 (4H, s, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 162.6 (**C**H=N), 136.1 (**Ph**), 130.6 (*p*-**Ph**H), 128.5 (*m*-**Ph**H), 128.0 (*o*-**Ph**H), 61.6 (**C**H_2). Data are consistent with literature values.[179]

_N_-(But-3-en-1-yl)-4-methyl-_N_-propylbenzenesulfonamide, 371



To a rapidly stirred biphasic mixture of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **240a** (338 mg, 1.50 mmol, 1.0 eq.), TBAI (11 mg, 0.3 mmol, 0.2 eq.) and $TBAHSO_4$ (102 mg, 0.3 mmol, 0.2 eq.) in 25% aq. NaOH (15 mL) and toluene (15 mL) was added 1-iodopropane (0.18 mL, 1.8 mmol, 1.2 eq.). The reaction mixture was stirred at RT for 15 h then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and

concentrated *in vacuo*. The resulting crude material was purified by column chromatography (17:3, pet. ether:Et_2O) to give the title compound as a colourless oil (333 mg, 1.25 mmol, 83%); R_f = 0.50 (4:1, pet. ether:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.2 Hz, *o*-Ts**H**), 7.29 (2H, d, *J*=8.2 Hz, *m*-Ts**H**), 5.71 (1H, ddt, *J*=17.1, 10.3, 6.7 Hz, =C**H**), 5.10-4.98 (2H, m, =C**HH'**), 3.20-3.13 (2H, m, C$\mathbf{H_2}$-1), 3.11-3.04 (2H, m, C$\mathbf{H_2}$-5), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.33-2.24 (2H, m, C$\mathbf{H_2}$-2), 1.55 (2H, ap. sext., *J*=7.5 Hz, C$\mathbf{H_2}$-6), 0.87 (3H, t, *J*=7.5 Hz, C$\mathbf{H_3}$-7); δ_C (100 MHz, $CDCl_3$) 143.0 (**Ar**CH_3), 137.1 (**Ar**SO_2), 134.7 (=**C**H), 129.6 (*m*-**Ts**H), 127.1 (*o*-**Ts**H), 116.9 (=**C**HH'), 50.1 (**C**H_2-5), 47.6 (**C**H_2-1), 33.3 (**C**H_2-2), 21.9 (**C**H_2-6), 21.5 (Ar**C**H_3), 11.2 (**C**H_3-7); IR (thin film) ν_{max}/cm^{-1} 2967 w (C-H), 1338 m (SO_2), 1153 s (SO_2); LRMS *m/z* (ESI+) 268.2 ($[M+H]^+$, 100%), 557.3 ([2M+Na], 90%); HRMS *m/z* (ESI+) found $[M+Na]^+$ 290.1185; $C_{14}H_{21}NNaO_2S$ requires 290.1185.

7. References

1. DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064-5106.

2. Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840-2859.

3. Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 917-918.

4. Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459-466.

5. Brückner, D. *Synlett* **2000**, 3809-3814.

6. Brückner, D. *Tetrahedron* **2006**, *62*, 3809-3814.

7. Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209-2212.

8. Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905-910.

9. Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Tetrahedron* **2006**, *62*, 3843-3855.

10. Rodríguez, D.; Martínez-Esperón, F. M.; Castedo, L.; Saá, C. *Synlett* **2007**, 1963-1965.

11. Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417-2420.

12. Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489-492.

13. Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037-2039.

14. Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927-10966.

15. Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368-2369.

16. Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011-4014.

17. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151-1154.

18. Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170-4177.

19. Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630-4633.

20. Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833-835.

21. Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381-4385.

22. Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272-3275.

23. Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

24. Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371-384.

25. Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884-4908.

26. Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509-1511.

27. Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345-9353.

28. Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047-1050.

29. Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726-6730.

30. Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron* **2009**, *65*, 1809-1832.

31. Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672-6678.

32. Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059-5062.

33. Garcia, P.; Harrak, Y.; Diab, L.; Cordier, P.; Ollivier, C.; Gandon, V.; Malacria, M.; Fensterbank, L.; Aubert, C. *Org. Lett.* **2011**, *13*, 2952-2955.

34. Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803-805.

35. Mori, M.; Wakamatsu, H.; Saito, N.; Sato, Y.; Narita, R.; Sato, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 3872-3881.

36. Wakamatsu, H.; Sakagami, M.; Hanata, M.; Takeshita, M.; Mori, M. *Macromol. Symp.* **2010**, *293*, 5-9.

37. Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606-5607.

38. Mori, M.; Tanaka, D.; Saito, N.; Sato, Y. *Organometallics* **2008**, *27*, 6313-6320.

39. Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 2426-2430.

40. Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Commun.* **2000**, 1965-1966.

41. Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281-3284.

42. Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730-7731.

43. Saito, N.; Ichimaru, T.; Sato, Y. *Org. Lett.* **2012**, *14*, 1914-1917.

44. Garcia, P.; Moulin, S.; Miclo, Y.; Leboeuf, D.; Gandon, V.; Aubert, C.; Malacria, M. *Chem. Eur. J.* **2009**, *15*, 2129-2139.

45. Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. *Org. Lett.* **2013**, *15*, 1938-1941.

46. Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323-2326.

47. Greenaway, R. L.; Campbell, C. D.; Holton, O. T.; Russell, C. A.; Anderson, E. A. *Chem. Eur. J.* **2011**, *17*, 14366-14370.

48. Greenaway, R. L.; Campbell, C. D.; Chapman, H. A.; Anderson, E. A. *Adv. Synth. Catal.* **2012**, *354*, 3187-3194.

49. Dake, G. *Tetrahedron* **2006**, *62*, 3467-3492.

50. Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403-4404.

51. Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336-10337.

52. Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172-174.

53. Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551-2651.

54. Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

55. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743.

56. Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2254-2257.

57. Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565-5567.

58. Husmann, R.; Sugiono, E.; Mersmann, S.; Raabe, G.; Rueping, M.; Bolm, C. *Org. Lett.* **2011**, *13*, 1044-1047.

59. Bodnar, B. S.; Miller, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2-20.

60. Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031-2043.

61. Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192-5200.

62. Dubey, S. K.; Knaus, E. E. *J. Org. Chem.* **1985**, *50*, 2080-2086.

63. Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368-2371.

64. Calvet, G.; Blanchard, N.; Kouklovsky, C. *Synthesis* **2005**, 3346-3354.

65. Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perk. Trans. 1* **1985**, 1401-1406.

66. Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351-3354.

67. Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885-888.

68. Li, F.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 8836-8841.

69. Reiter, M.; Torssell, S.; Lee, S.; MacMillan, D. W. C. *Chem. Sci.* **2010**, *1*, 37-42.

70. Becker, Y.; Eisenstadt, A.; Shvo, Y. *Tetrahedron* **1974**, *30*, 839-847.

71. Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755-11772.

72. Shireman, B. T.; Miller, M. J.; Jonas, M.; Wiest, O. *J. Org. Chem.* **2001**, *66*, 6046-6056.

73. Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365-5367.

74. Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476-486.

75. Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34-42.

76. Trost, B. M. *Chem. Eur. J.* **1998**, *4*, 2405-2412.

77. Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781-1783.

78. Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586-4588.

79. Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265-272.

80. Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887-4890.

81. Trost, B. M.; Jebaratnam, D. J. *Tetrahedron Lett.* **1987**, *28*, 1611-1613.

82. Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636-644.

83. Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255-4267.

84. Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483-3484.

85. Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1502-1504.

86. Trost, B. M.; Hipskind, P. A. *Tetrahedron Lett.* **1992**, *33*, 4541-4544.

87. Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651-654.

88. Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268-4278.

89. Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625-6633.

90. Le Paih, J.; Cuervo Rodríguez, D.; Dérien, S.; Dixneuf, P. H. *Synlett* **2000**, 95-97.

91. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714-715.

92. Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379-2380.

93. Saito, N.; Saito, K.; Shiro, M.; Sato, Y. *Org. Lett.* **2011**, *13*, 2718-2721.

94. Saito, N.; Tanaka, D.; Mori, M.; Sato, Y. *Chem. Rec.* **2011**, *11*, 186-198.

95. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373-6374.

96. Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925-928.

97. Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078-9081.

98. Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett.* **2013**, *15*, 3122-3125.

99. Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801-3804.

100. Furstner, A.; Schlecker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277-4279.

101. Saito, N.; Tanaka, Y.; Sato, Y. *Org. Lett.* **2009**, *11*, 4124-4126.

102. Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010**, *12*, 3780-3783.

103. Schotes, C.; Mezzetti, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3072-3074.

104. Smith, D. L.; Chidipudi, S. R.; Goundry, W. R.; Lam, H. W. *Org. Lett.* **2012**, *14*, 4934-4937.

105. Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9206-9218.

106. Hatano, M.; Mikami, K. *Org. Biomol. Chem.* **2003**, *1*, 3871-3873.

107. Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704-4705.

108. Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588-2595.

109. Washburn, D. G.; Heidebrecht, R. W.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523-3525.

110. Godenschwager, P. F.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 8726-8732.

111. Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65-72.

112. Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636-1638.

113. Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753-4755.

114. Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294-5295.

115. Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712-733.

116. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421-9438.

117. Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161-3163.

118. Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255-7258.

119. Trost, B. M.; Edstrom, E. D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 520-522.

120. Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146-5147.

121. Yamada, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 3027-3030.

122. Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735-4738.

123. Bakhmutov, V. I.; Berry, J. F.; Cotton, F. A.; Ibragimov, S.; Murillo, C. A. *Dalton Trans.* **2005**, 1989-1992.

124. Stolyarov, I.; Demina, L.; Cherkashina, N. *Russ. J. Inorg. Chem.* **2011**, *56*, 1532-1537.

125. Bajwa, S. E.; Storr, T. E.; Hatcher, L. E.; Williams, T. J.; Baumann, C. G.; Whitwood, A. C.; Allan, D. R.; Teat, S. J.; Raithby, P. R.; Fairlamb, I. J. S. *Chem. Sci.* **2012**, *3*, 1656-1661.

126. Hrobárik, P.; Hrobáriková, V.; Meier, F.; Repiský, M.; Komorovský, S.; Kaupp, M. *J. Phys. Chem. A* **2011**, *115*, 5654-5659.

127. Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961-10963.

128. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613.

129. Johnson, J. R.; McEwen, W. L. *Org. Syn.* **1941**, *Coll. Vol. 1*, 521.

130. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501-4504.

131. Lespieau, R.; Bourgel, M. *Org. Syn.* **1941**, *Col. Vol. 1*, 209.

132. Greenaway, R. L. *DPhil Thesis, University of Oxford* **2013**.

133. Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621-1626.

134. Johnson II, D. C.; Widlanski, T. S. *Tetrahedron Lett.* **2004**, *45*, 8483-8487.

135. Neustadt, B. R. *Tetrahedron. Lett.* **1994**, *35*, 379-380.

136. Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820-1821.

137. Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901-8905.

138. Jawalekar, A. M.; Reubsaet, E.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Commun.* **2011**, *47*, 3198-3200.

139. Hania, M. M. *E-J. Chem.* **2009**, *6*, 629-632.

140. Wang, J.-R.; Fu, Y.; Zhang, B.-B.; Cui, X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2006**, *47*, 8293-8297.

141. Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108-1113.

142. Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 4650-4653.

143. Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238-1240.

144. Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 8914-8918.

145. Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941-2958.

146. Millot, N.; Piazza, C.; Avolio, S.; Knochel, P. *Synthesis* **2000**, 941-948.

147. Baeza, A.; Pfaltz, A. *Chem. Eur. J.* **2010**, *16*, 4003-4009.

148. Selander, N.; Willy, B.; Szabó, K. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4051-4053.

149. Griffiths, J.; Murphy, J. A. *Tetrahedron* **1992**, *48*, 5543-5556.

150. de Meijere, A.; Limbach, M.; Janssen, A.; Lygin, A.; Korotkov, V. S. *Eur. J. Org. Chem.* **2010**, 3665-3671.

151. Vilaivan, T. *Tetrahedron Lett.* **2006**, *47*, 6739-6742.

152. Yoshida, M.; Komatsuzaki, Y.; Ihara, M. *Org. Lett.* **2008**, *10*, 2083-2086.

153. Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023-5026.

154. Ito, H.; Omodera, K.; Takigawa, Y.; Taguchi, T. *Org. Lett.* **2002**, *4*, 1499-1501.

155. Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839-2844.

156. Tsui, G. C.; Menard, F.; Lautens, M. *Org. Lett.* **2010**, *12*, 2456-2459.

157. Fan, R.; Pu, D.; Wen, F.; Ye, Y.; Wang, X. *J. Org. Chem.* **2008**, *73*, 3623-3625.

158. Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474-1475.

159. Usanov, D. L.; Yamamoto, H. *J. Am. Chem. Soc.* **2011**, *133*, 1286-1289.

160. Sabitha, G.; Reddy, S.; Srihari, P.; Yadav, J. S. *Synthesis* **2003**, 2699-2704.

161. Combettes, L. E.; Schuler, M.; Patel, R.; Bonillo, B.; Odell, B.; Thompson, A. L.; Claridge, T. D. W.; Gouverneur, V. *Chem. Eur. J.* **2012**, *18*, 13126-13132.

162. Nath, D.; Fleming, F. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 11790-11793.

163. Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221-2223.

164. Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948-12949.

165. Spivey, A. C.; Laraia, L.; Bayly, A. R.; Rzepa, H. S.; White, A. J. P. *Org. Lett.* **2010**, *12*, 900-903.

166. Kim, I. S.; Dong, G. R.; Jung, Y. H. *J. Org. Chem.* **2007**, *72*, 5424-5426.

167. Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182-1203.

168. Rao, W.; Chan, P. W. H. *Chem. Eur. J.* **2008**, *14*, 10486-10495.

169. Walker, S. M.; Williams, J. T.; Russell, A. G.; Kariuki, B. M.; Snaith, J. S. *Org. Biomol. Chem.* **2007**, *5*, 2925-2931.

170. Clausen, R. P.; Bols, M. *J. Org. Chem.* **2000**, *65*, 2797-2801.

171. Lin, M.-H.; Lin, L.-Z.; Chuang, T.-H. *Synlett* **2011**, 1871-1874.

172. Kamata, K.; Hirano, T.; Kuzuya, S.; Mizuno, N. *J. Am. Chem. Soc.* **2009**, *131*, 6997-7004.

173. Marcotullio, M. C.; Campagna, V.; Sternativo, S.; Costantino, F.; Curini, M. *Synthesis* **2006**, 2760-2766.

174. Marco-Contelles, J.; Gómez-Sánchez, E.; Samadi, A.; Soriano, E.; Valderas, C.; Álvarez-Pérez, M.; Carreiras, M. *Arkivoc* **2010**, 56-73.

175. Hou, J.; Feng, C.; Li, Z.; Fang, Q.; Wang, H.; Gu, G.; Shi, Y.; Liu, P.; Xu, F.; Yin, Z.; Shen, J.; Wang, P. *Eur. J. Med. Chem.* **2011**, *46*, 3190–3200.

176. Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727-729.

177. Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006-10010.

178. Ménage, S.; Galey, J.-B.; Dumats, J.; Hussler, G.; Seité, M.; Luneau, I. G.; Chottard, G.; Fontecave, M. *J. Am. Chem. Soc.* **1998**, *120*, 13370-13382.

179. Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980-3992.