Higher-Order Cycloisomerisations of Enynamides

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Robert N. Straker

New College
University of Oxford
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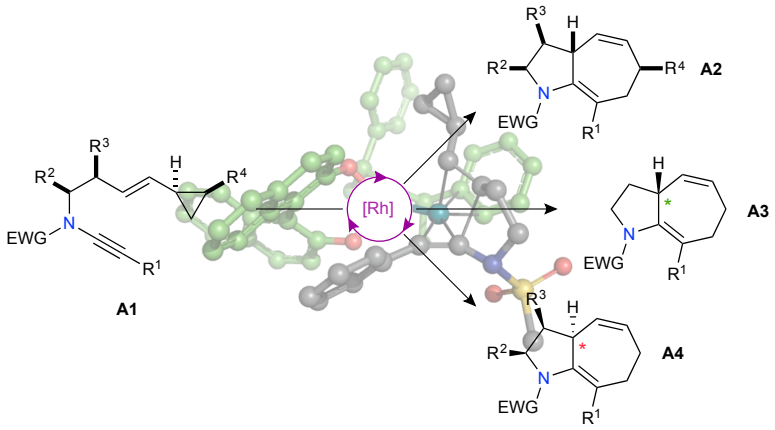
This thesis describes the development of a novel transformation of ynamides, and addresses more general questions of asymmetric cycloisomerisation. The rhodium-catalysed [5+2] cycloisomerisation of ynamide vinylcyclopropanes **A1** to [5.3.0]-heterobicycles **A2** is established (Scheme i). We design a versatile substrate synthesis, which allows the preparation of diversely substituted enynamide substrates. Under achiral rhodium catalysis, the extent of substrate diastereo- and regioselectivity is investigated.



Scheme i. Rhodium-catalysed [5+2] cycloisomerisations of ynamide vinylcyclopropanes.

The reaction is rendered asymmetric with the use of chiral phosphoramidite ligands; where a mechanistic hypothesis for stereoselectivity leads to the development of a powerful catalyst system for the preparation of enantioenriched **A3**. A theoretical reaction analysis elucidates the mechanistic pathway, and gives an energetic rationale for our model of ligand stereoinduction. Our asymmetric catalyst system is applied to the [5+2] cycloisomerisation of chiral substrates in double stereodifferentiating transformations, where it is possible to synthesise previously inaccessible diastereomers of product **A4**.

Acknowledgments

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First and foremost I thank Prof. Edward Anderson for granting me the opportunity to undertake my DPhil in his research group. For all his enthusiasm, support, invaluable advice, and time he has given me.

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Bryony, for making these the best years of my life.

Mum, Dad, and Charlotte for their unwavering care and support.

Abbreviations

Ac_2O	acetic anhydride
Ar^F	3,5-bis(trifluoromethyl)benzene
bbeda	*N*,*N*'-dibenzylideneethane-1,2-diamine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
cod	cyclooctadiene
COSY	correlation spectroscopy
cot	cyclooctatetraene
Cp*	pentamethylcyclopentadiene
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMEDA	*N*,*N*'-dimethylethylenediamine
DPPA	diphenylphosphoryl azide
equiv.	equivalent
ESI	electrospray ionisation
EWG	electron-withdrawing group
Fc	ferrocenyl
Fmoc	fluorenylmethyloxycarbonyl
HMBC	heteronuclear multiple-bond correlation

HMQC	heteronuclear multiple-quantum correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
MEPY	methyl 2-pyrrolidone-5-carboxylate
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	*p*-nitrobenzenesulfonyl
PG	protecting group
PMB	*p*-methoxybenzyl ether
py	pyridine
ppm	parts per million
R_f	retention factor
RDS	rate determining step
Red-Al®	sodium bis(2-methoxyethoxy)aluminiumhydride
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
Wilkinson's catalyst	$RhCl(PPh_3)_3$

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1 Introduction

Cyclic organic scaffolds are present in many biologically active compounds, and as such are key targets for the synthetic community. Of great importance is the ability to construct these systems in an atom economical and stereocontrolled manner.[1,2] In this context, cycloisomerisations represent ideal methods as they enable the generation of one or more rings in a single step from acyclic starting materials. Over the past century, a great deal of attention has been paid to the formation of four-, five- and six-membered rings *via* cycloisomerisation reactions. In stark contrast, the formation of seven-membered rings is underdeveloped, despite their widespread occurrence in nature.[3,4] Among the methods that do exist, an area that has received increased attention over the past couple of decades is the [5+2] cycloisomerisation.[i,5]

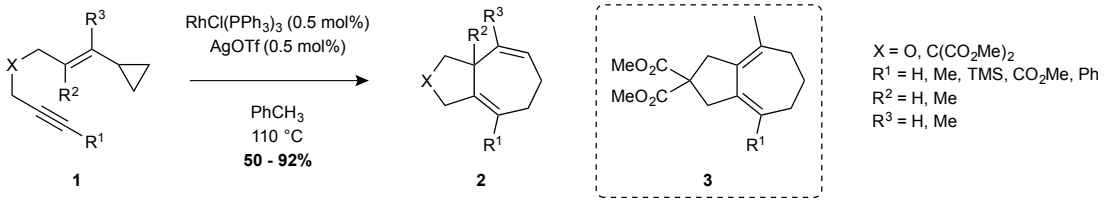
1.1 Vinylcyclopropane [5+2] cycloisomerisations

Vinylcyclopropanes (VCP) represent convenient five-carbon components for the formation of seven-membered rings. Sarel and Breuer were the first to achieve this *via* conjugative 1,5-addition reactions with maleic anhydride.[6] Since then, there have been reports of formal [5+2] cycloisomerisation of VCPs with activated alkenes,[7] but the most attractive method is their use in metal-catalysed [5+2] cycloisomerisation reactions.

[i] For the purposes of this thesis; 'cycloaddition' refers solely to a pericyclic reaction, 'cycloisomerisation' refers to a step-wise cyclisation process, and in the notation [*n*+*n*] '*n*' indicates the number of carbon atoms present in each component.

1.1.1 Rhodium-catalysed [5+2] cycloisomerisations

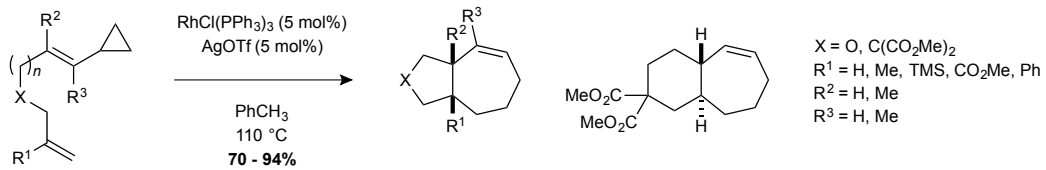
Wender *et al.* first reported the intramolecular [5+2] cycloisomerisation of vinylcyclopropane-alkynes **1**, using Wilkinson's catalyst in combination with silver triflate (Scheme 1.1).[8] The [5.3.0]-bicyclic products **2** were obtained in high yields, and the reaction conditions were tolerant of a number of alkyne substituents. Isomerisation of the products to 1,3-dienes **3** was observed with substrates bearing additional alkene substituents (R^3 = Me), although subsequent work has shown that this problem can be overcome with the use of the dimeric pre-catalyst $[Rh(CO)_2Cl]_2$.[9]



1 **2** **3**

Scheme 1.1. Rhodium-catalysed intramolecular [5+2] cycloisomerisations.

Shortly after their seminal report, the Wender group extended the methodology to vinylcyclopropane-alkenes **4** (Scheme 1.2).[10] These reactions required higher catalyst loadings and extended reaction times compared to those of alkynes. A single diastereomer of the product was obtained in all cases, with the diastereoselectivity observed in the formation of the [5.3.0] product **5** opposite to that of the [5.4.0] **6**.

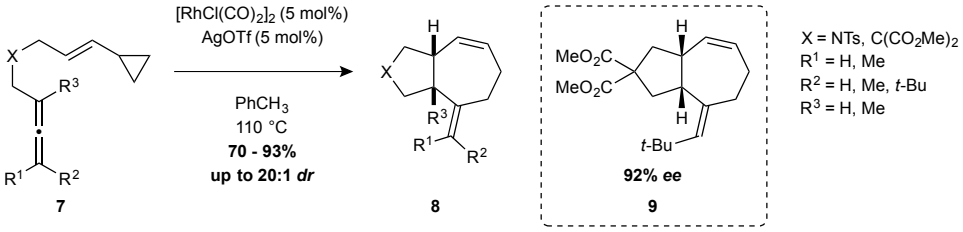


4 ***n*** **= 1** **5** ***n*** **= 2** **6**

Scheme 1.2. Intramolecular [5+2] cycloisomerisation of vinylcyclopropane tethered alkenes.

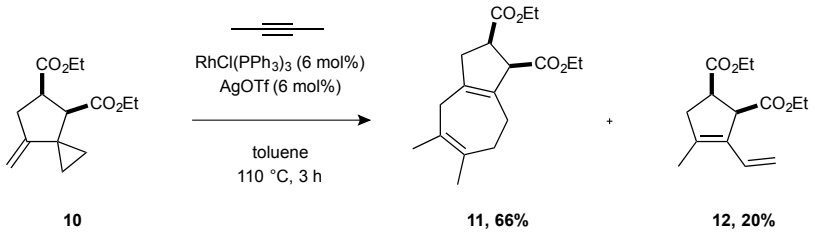
A further extension was in the application to vinylcyclopropane-allenes **7** (Scheme 1.3),[11] where similarly high levels of diastereoselectivity were observed in the formation of

products **8**. The authors discovered that it was possible to transfer chirality from an enantioenriched allene (91% *ee*) to the product **9** with complete retention of stereochemistry (92% *ee*).



Scheme 1.3. Intramolecular [5+2] cycloisomerisation of vinylcyclopropane tethered allenes.

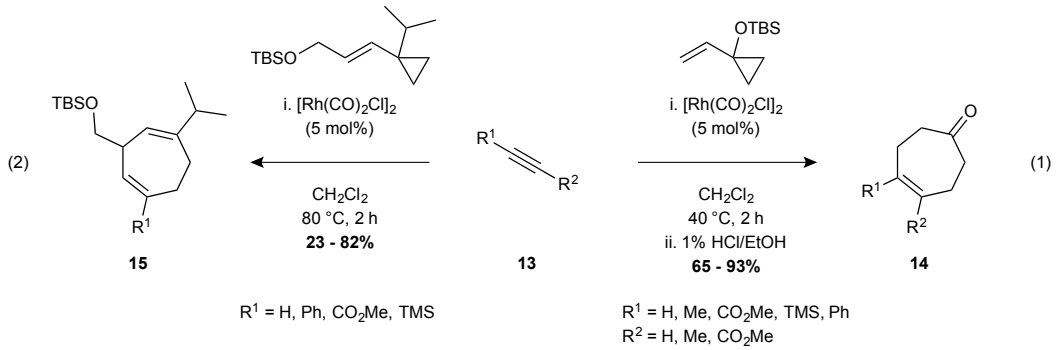
The first, isolated example of an intermolecular [5+2] cycloisomerisation of a vinylcyclopropane and an alkyne was demonstrated by de Meijere *et al.* in an account of cycloisomerisation reactions of vinylcyclopropanes (Scheme 1.4).[12] Under forcing conditions 2-butyne underwent cycloisomerisation with spirocyclic vinylcyclopropane **10** to give the bicyclic product **11** in modest yield, as well as isomerised starting material **12**.



Scheme 1.4. Rhodium-catalysed intermolecular [5+2] cycloisomerisation.

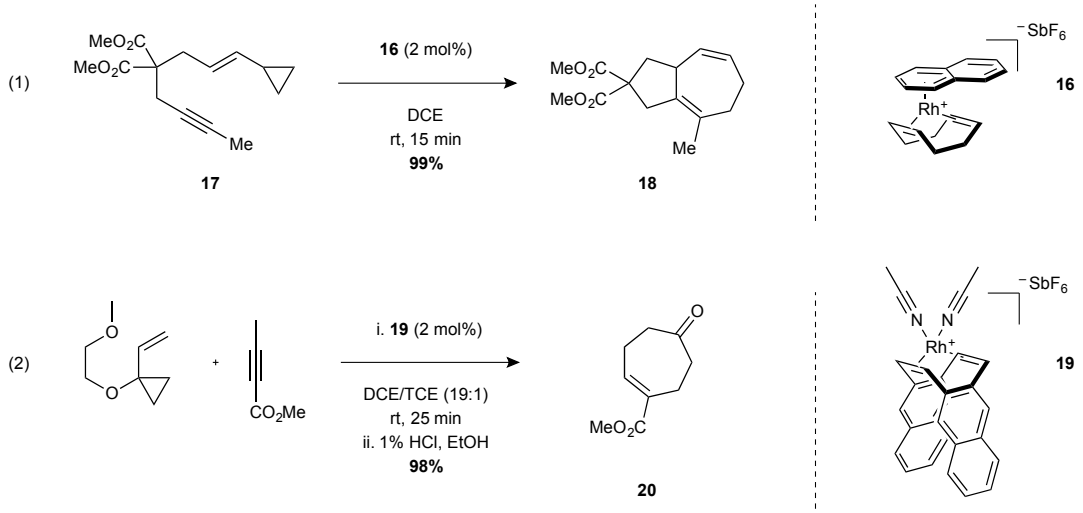
Shortly after, Wender reported a more extensive study using siloxy vinylcyclopropanes, which react under milder conditions (Scheme 1.5, Eq. 1);[13,14] replacement of the cyclopropyl methine proton with a silyloxy group results in a ten-fold increase in rate of reaction. In addition to the electronic contribution of the alkoxy substituent, this could also be a consequence of its conformational influence, through an increase of the population of the reactive conformer. Though the reaction favours one regioisomer with unsymmetrical

alkynes **13**, it is of little consequence as the silyl ethers generated were subsequently deprotected *in situ* to give the ketone products **14**. A further report revealed that simple, unactivated vinylcyclopropanes underwent reaction with terminal alkynes to give the products **15** as single regioisomers (Eq. 2).[15] In this case the reaction was accelerated by bulky cyclopropane substituents, albeit requiring elevated temperatures. Wender has since used these reactions in multi-component syntheses of polycyclic natural products.[16]



Scheme 1.5. Intermolecular [5+2] cycloisomerisation.

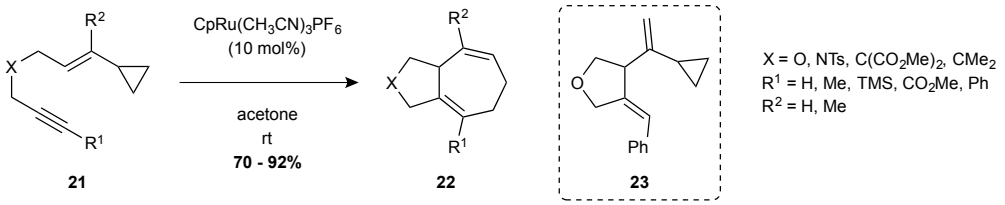
In continued work to improve the rate and yield of the [5+2] reactions, the Wender group have since developed highly active cyclooctadiene (cod) and cyclooctatetraene (cot) catalyst systems (Scheme 1.6). The first of these, an air stable η^6-naphthalene/cyclooctadiene complex of rhodium **16**, was originally reported by Chung *et al.* for [4+2] cycloisomerisation reactions.[17] This system was first found to catalyse the intramolecular [5+2] cycloisomerisation of alkynes **17** at room temperature, with the reactions reaching completion in less than two hours and in high yield (Eq. 1).[18] This catalyst was later applied to the intermolecular reaction with great effect.[19] More recently, dinapthocyclooctatetraene complexes of rhodium **19** were found to be highly effective at catalysing both intra- and intermolecular [5+2] cycloisomerisations, the latter were complete in minutes at room temperature (Eq. 2).[20]



Scheme 1.6. Novel catalyst systems for the [5+2] cycloisomerisation.

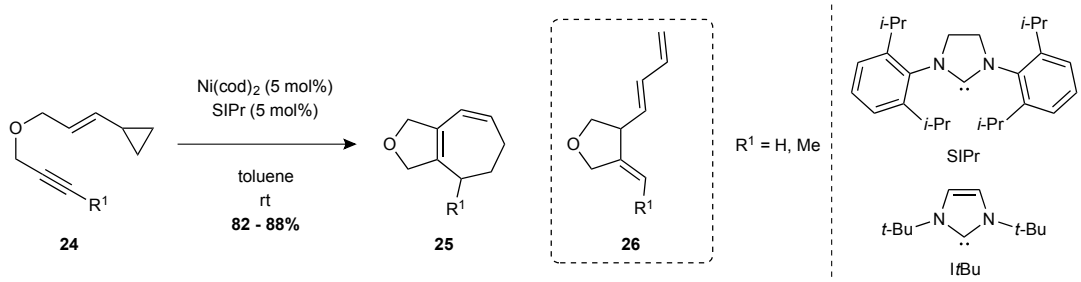
1.1.2 Alternative metal catalysts

Given the potential utility of these transformations, it is perhaps unsurprising that they have since received attention from other research groups. In particular, there have been several attempts to catalyse the reaction with metals other than rhodium, due to its relative expense (for example, the cost of rhodium metal is more than 14 times that of ruthenium). In a comprehensive programme of research, Trost *et al.* have demonstrated the use of ruthenium catalysis in intramolecular [5+2] cycloisomerisation of vinylcyclopropane-alkynes **21** (Scheme 1.7).[21] It was found that a cationic source of ruthenium(II) catalysed the reactions at significantly lower temperatures compared rhodium catalysis, with the products **22** obtained in high yield. Whilst isomerisation of trisubstituted alkene products (R^2 = Me) to 1,3-dienes was not observed, a small amount of β–hydride elimination product **23** was detected (6:1, **22**:**23**). This product was found to be favoured in the cycloisomerisation of a substrate bearing a (*Z*)-alkene (1:14 **22**:**23**).



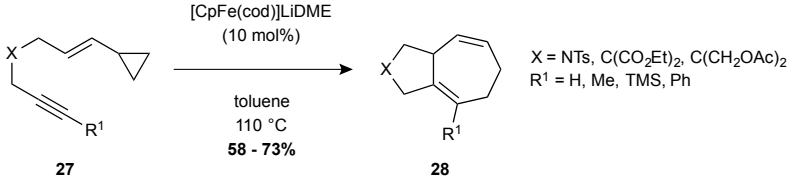
Scheme 1.7. Ruthenium-catalysed intramolecular [5+2] cycloisomerisations.

Louie *et al.* later found that nickel catalysts could be used in combination with NHC ligands in effecting [5+2] cycloisomerisations. However, it was discovered that under the reaction conditions with the SIPr ligand, only 1,3-diene products **25** were obtained (Scheme 1.8).[22] Whilst use of the I*t*Bu ligand led to the selective formation of 1,4,6-triene products **26**.



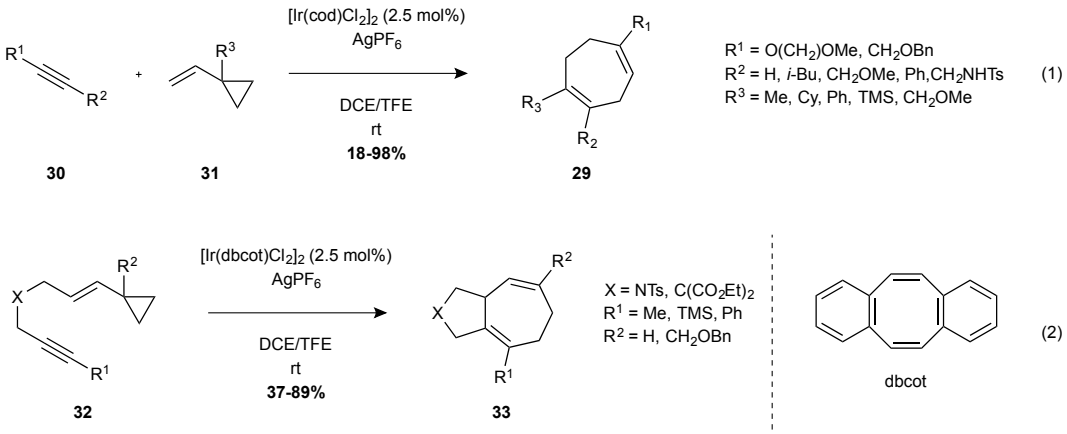
Scheme 1.8. Nickel-catalysed intramolecular [5+2] cycloisomerisation.

In an extended study of iron-catalysed cycloisomerisations, Fürstner applied a bimetallic complex of low-valent iron and lithium to the [5+2] reaction and found that this formed the desired products **28**, albeit requiring elevated temperatures and giving somewhat lower yields (Scheme 1.9).[23]



Scheme 1.9. Iron-catalysed intramolecular [5+2] cycloisomerisation.

Most recently, Strand *et al.* reported inter- and intramolecular [5+2] cycloisomerisations catalysed by cationic iridium(I) complexes (Scheme 1.10).[24] Until this point, the intermolecular reaction had been limited exclusively to rhodium-catalysed examples. These reactions were generally high yielding, with single regioisomers of products **29** obtained from unsymmetrical alkynes **30** (Eq. 1). By direct comparison with equivalent rhodium catalysts, the iridium-catalysed reaction was discovered to be up to 50 times faster, which was rationalised using Density Functional Theory calculations (DFT, see Chapter 4). As was found by Wender for the rhodium-catalysed cycloisomerisation, the dibenzocyclooctatetraene (dbcot) ligand gave an increased rate of reaction compared to that with cyclooctadiene.

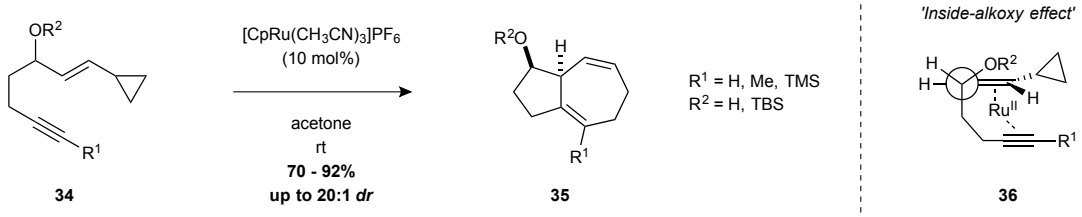


Scheme 1.10. Iridium-catalysed inter- and intramolecular [5+2] cycloisomerisation.

1.1.3 Selectivity in [5+2] cycloisomerisations

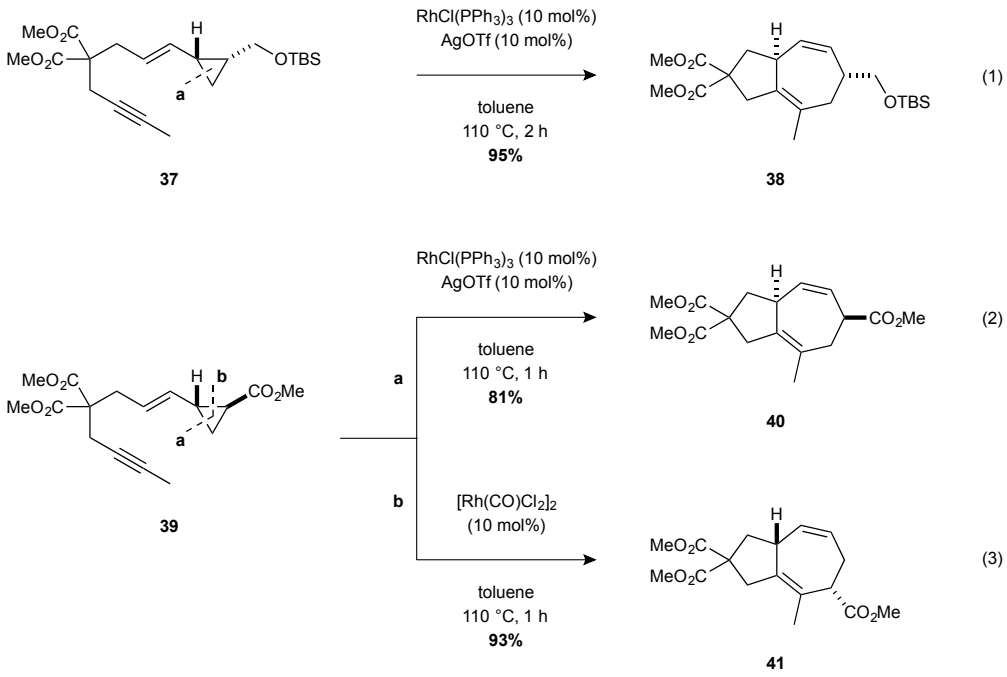
A matter of paramount importance in cycloisomerisation is the control of stereochemistry at the newly formed stereogenic centre – both relative, using substrate stereocontrol; and absolute, using asymmetric catalysis. To this end Trost *et al.* examined the inherent diastereoselectivity of the ruthenium-catalysed reaction, using an array of substrates with substituted tethers **34** (Scheme 1.11).[21,25] High levels of stereoselectivity were observed in

formation of diastereomeric product **35**, which was attributed to the presence of an allylic alkoxy substituent, as explained by the Stork-Houk-Jäger 'inside-alkoxy effect' (**36**).[26]



Scheme 1.11. Diastereoselective [5+2] cycloisomerisation reaction.

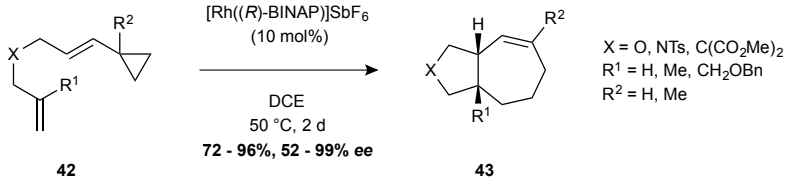
Wender *et al.* explored the effect of substitution on the cyclopropane ring on both the diastereoselectivity in formation of the new stereocentre, and the regioselectivity of the opening event in the rhodium-catalysed reactions (Scheme 1.12). Using Wilkinson's catalyst, substrates bearing *cis*-substituted cyclopropanes **37** underwent cycloisomerisation with cleavage of the least substituted σ-bond (**a**), to form the *trans*-diastereomer of product (**38**, Eq. 1), while *trans*-substituted substrates **39** formed the *cis*-diastereomer **40** of the same regioisomer (Eq. 2).[27]



Scheme 1.12. Regio- and diastereoselective [5+2] cycloisomerisation reactions.

It was found that with the use of an alternative rhodium catalyst ($[Rh(CO)_2Cl]_2$), cleavage of the more substituted σ-bond (**b**) could be achieved, leading to the other regioisomer of product (**41**, Eq. 3).[28] Trost later reported the equivalent ruthenium-catalysed reaction, where *trans*-substituted substrates also proceeded *via* cleavage of the least substituted σ-bond (**a**), but *cis*-substituted substrates reacted *via* the more substituted σ-bond (**b**).[25] It is therefore possible, in theory, to construct any of the four possible diastereomeric regioisomers with judicious choice of substrate and catalyst system.

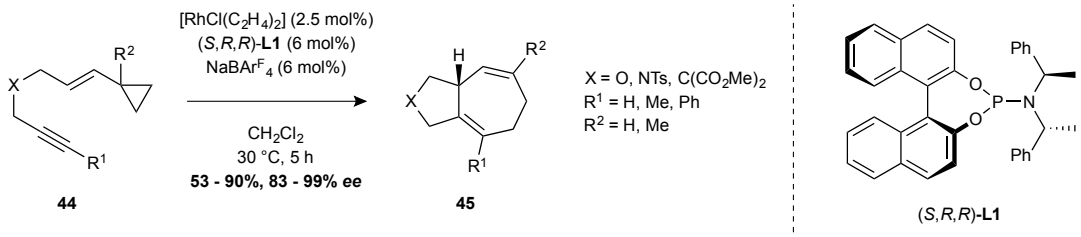
Despite the importance of the control of absolute stereochemistry in ring forming reactions, there have been only two examples of asymmetric [5+2] cycloisomerisations. First, Wender *et al*. achieved high levels of enantioselectivity in the reaction of vinylcyclopropane-alkenes **42** using rhodium-BINAP complexes (Scheme 1.13).[29] The products **43** were obtained in high *ee* and as single diastereomers, after two days at 50 °C. Unfortunately, attempts to apply this methodology to reactions of alkyne substrates were less successful (22-56% *ee*).



42 **43**

Scheme 1.13. Enantioselective [5+2] cycloisomerisation of vinylcyclopropane tethered alkenes.

Hayashi *et al.* were more prosperous in their efforts with vinylcyclopropane-alkynes **44**, achieving high levels of stereocontrol with the use of a rhodium/phosphoramidite (*S*,*R*,*R*)-**L1** complexes (Scheme 1.14).[30] The bicyclic products **45** were obtained in high yield with excellent enantioselectivities, in only hours at ambient temperature. The observed stereochemical outcome was rationalised with an empirical model, based on an X-Ray crystal structure of the catalyst system (see Chapter 3).



Scheme 1.14. Enantioselective [5+2] cycloisomerisation of vinylcyclopropane tethered alkyne.

1.1.4 Mechanism of the [5+2] cycloisomerisation

In their seminal studies of the rhodium-catalysed intramolecular [5+2] cycloisomerisation, Wender *et al.* proposed a reaction mechanism (Fig. 1.1, Pathway **A**),[8] which begins with oxidative coupling of the alkyne and alkene to produce metallacyclopentene intermediate **48**. This is followed by a strain-driven migratory insertion of the metal into the cyclopropane, giving eight-membered metallacycle **49**. Finally, reductive elimination yields the product **50**.

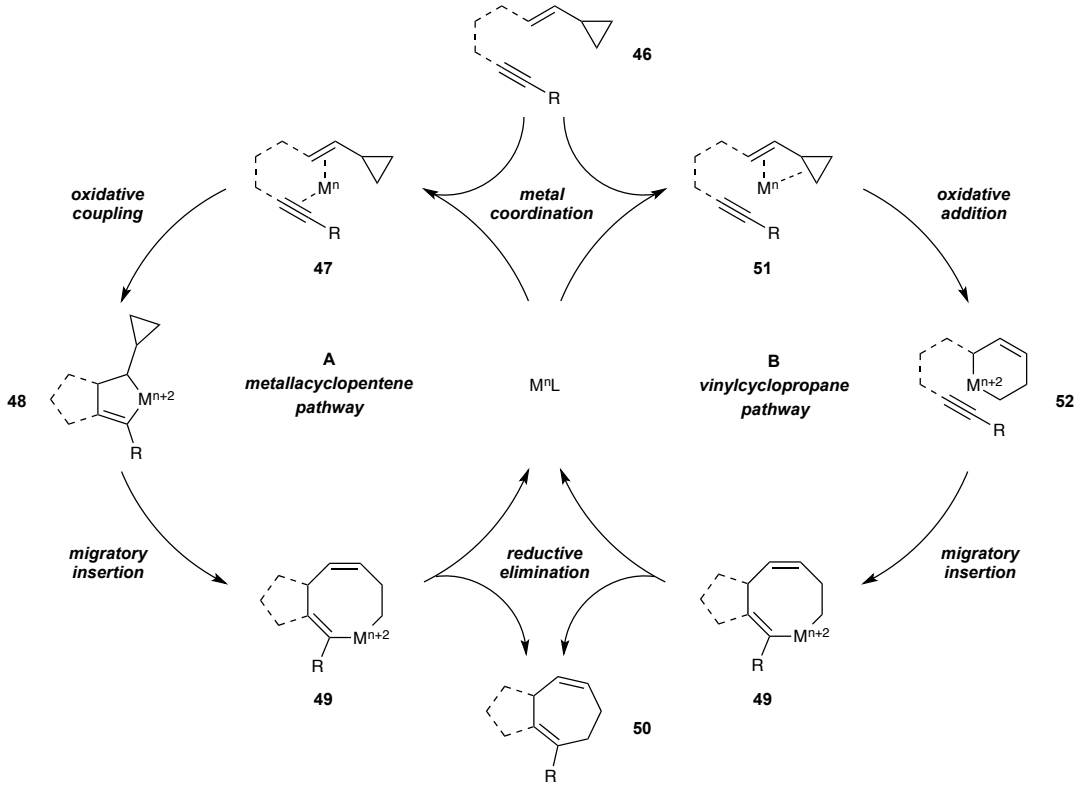
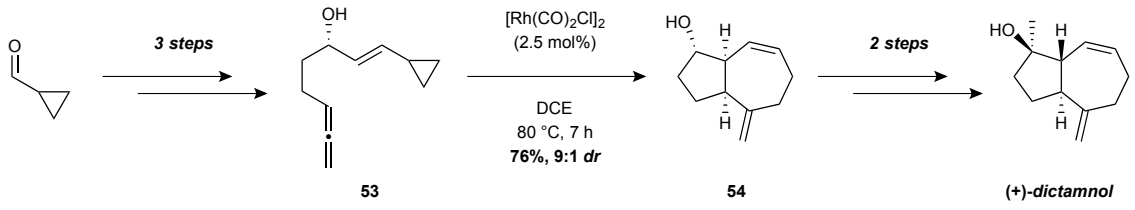


Figure 1.1. Mechanistic pathways of the [5+2] cycloisomerisation reaction.

Trost *et al.* explained their empirical observations of diastereo- and regioselectivity in the equivalent ruthenium-catalysed process with this mechanism.[21] Subsequent reports from the Wender group considered an alternative reaction pathway (Pathway **B**):[10] upon coordination, oxidative addition of the metal into the vinylcyclopropane unit results in metallacyclohexene intermediate **52**. Migratory insertion into the alkyne then gives the same eight-membered intermediate **49** as in the previous catalytic cycle, with reductive elimination giving the product **50**. There have since been a number of computational studies, which ascertain the mechanism by which each metal proceeds (these will be discussed in detail in Chapter 4).

1.1.5 Application in natural product syntheses

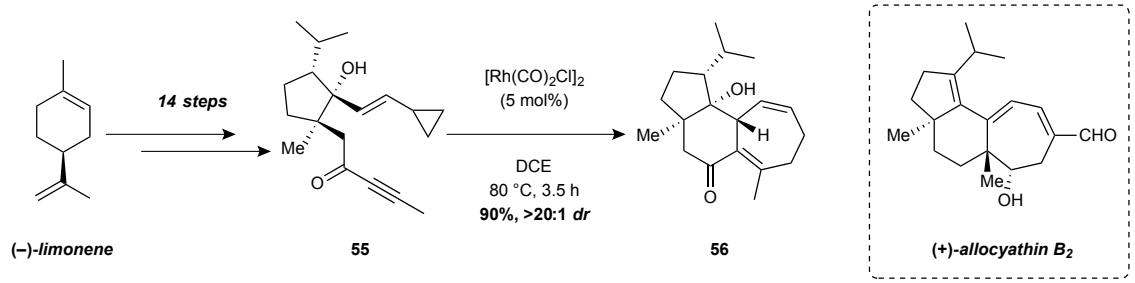
The synthetic utility of these transformations has been realised with their inclusion in the total synthesis of several natural products. Wender *et al.* were the first to apply this chemistry in a six step synthesis of (+)-dictamnol (Scheme 1.15),[31] employing a diastereoselective intramolecular [5+2] cycloisomerisation of a vinylcyclopropane-allene **53**. Unfortunately, the relative stereochemistry of **54** obtained from the cycloisomerisation was the opposite to that of the natural product, and therefore an oxidation/ epimerisation/addition sequence was required to access the desired diastereomer.



Scheme 1.15. Total synthesis of (+)-dictamnol.

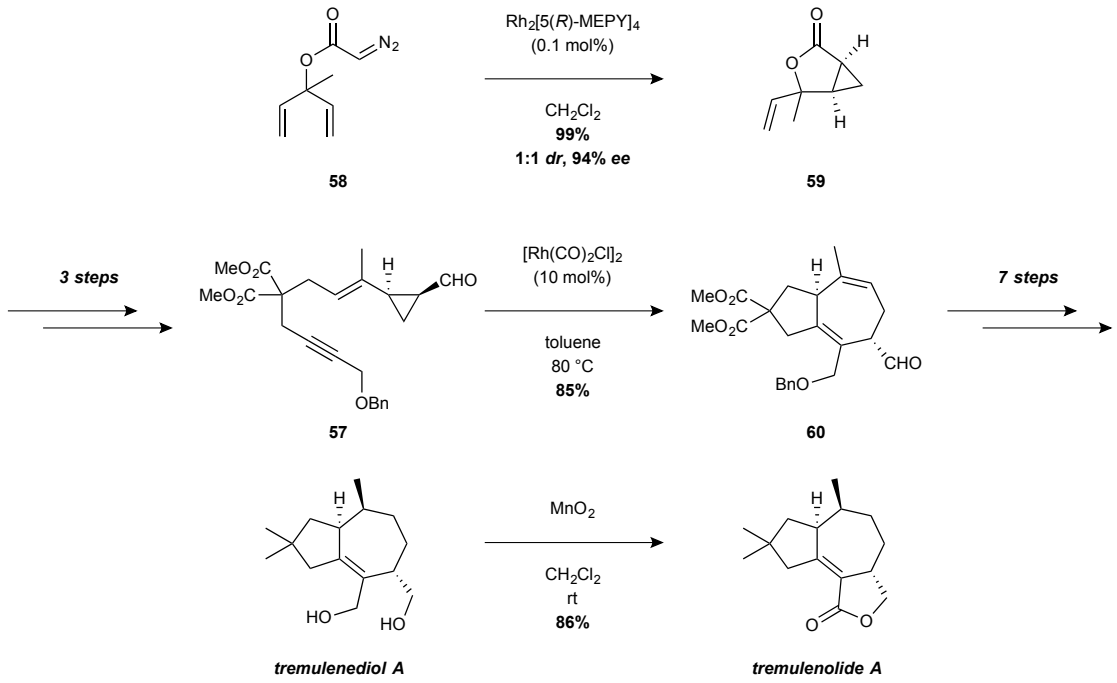
The Wender group also achieved the construction of the tricyclic core of cyathane diterpenes using [5+2] cycloisomerisation of a vinylcyclopropane-alkyne bearing a

cyclopentane unit in the tether. This cycloisomerisation substrate **55** was synthesised in 14 steps from (–)-limonene (Scheme 1.16).[32] Interestingly, reaction of the propargylic alcohol precursor to **55** gave a complex mixture of products, and only the ketone successfully yielded the product **56** as a single regio- and diastereomer.



Scheme 1.16. Construction of the tricyclic core of cyathane diterpines.

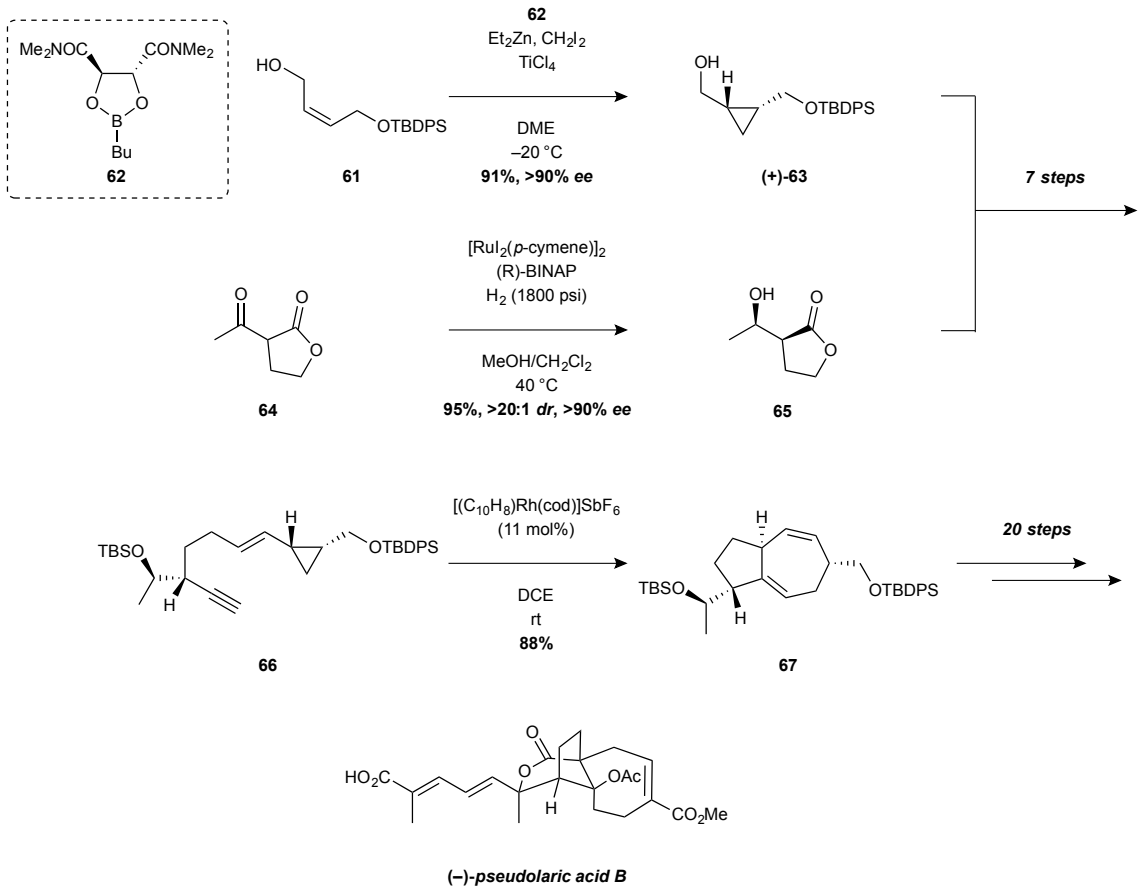
Following these reports, Martin *et al*. made effective use of the tuneable regioselectivity of these processes in the syntheses of tremulenediol A and tremulenolide A (Scheme 1.17).[33]



Scheme 1.17. Total synthesis of tremulenediol A and tremulenolide A.

The cycloisomerisation substrate **57** was generated in 10 steps, involving an elegant rhodium-catalysed enantioselective intramolecular cyclopropanation of **58** as the key step. The *cis*-substituted cyclopropane gave the required diastereo- and regioselectivity in **60**, which was converted in a further 7 steps to tremulenediol A. Selective allylic oxidation with manganese dioxide facilitated lactonisation to tremulenolide A in a total of 17 steps.

Finally, the Trost group took on the ambitious task of a (–)-pseudolaric acid B synthesis (Scheme 1.18).[34,35] With its bridged tricyclic core and four contiguous stereocentres, (–)-pseudolaric acid B is perhaps the most challenging of all the natural products synthesised using the [5+2] methodology.

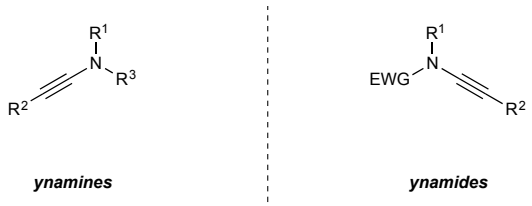


Scheme 1.18. Total synthesis of (–)-pseudolaric acid B.

Enantioselective Simmons-Smith cyclopropanation of **61** introduced asymmetry at an early stage in the synthesis, along with Noyori reduction of ketone **64**. Cycloisomerisation of **66** under ruthenium catalysis was low yielding, and a high proportion of isomerised product was isolated. A switch to the rhodium-catalysed conditions optimised by Wender proved more effective, giving the desired stereochemical outcome of **67** in high yield. The total synthesis of (–)-pseudolaric acid B was achieved in a further 20 steps, involving construction of the quarternary centre, and installation of the diene sidechain.

1.2 Ynamides

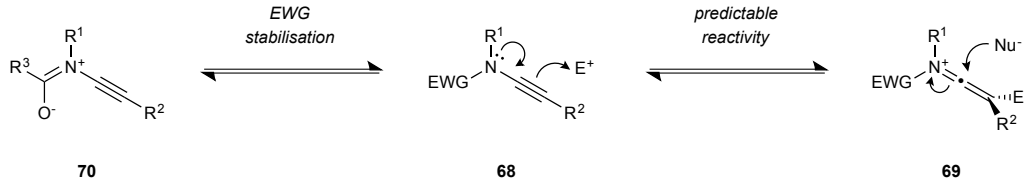
Nitrogen atom substituted alkynes – ynamines (Scheme 1.19) – are particularly useful as they offer the opportunity to exploit the diverse chemistry of alkynes in the introduction of nitrogen-based functionalities into organic molecules. However, due to the exceptionally high reactivity of ynamines, they are inherently unstable towards hydrolysis, and as such have been neglected by the synthetic community. Their instability can be tempered with an electron-withdrawing group (EWG) on the nitrogen atom, which provides the more robust alternative – ynamides.



Scheme 1.19. Nitrogen substituted alkynes.

Ynamides **68** exhibit predictable reactivity due to the polarisation of the C–C triple bond (Scheme 1.20). It is possible to incorporate electrophiles at the β-position in the formation of a ketene iminium ion **69**, which can subsequently be attacked at the α-position by

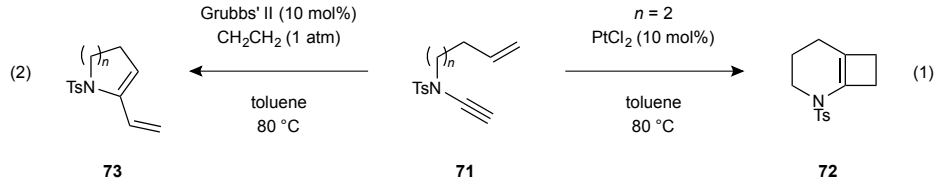
nucleophiles. In addition to the stabilising effect of the EWG (**70**), it may also act as a directing group, or as a chiral auxiliary. Owing to these favourable characteristics, ynamides have received increasing attention over the past two decades.[36,37]



Scheme 1.20. Reactivity of ynamides.

1.2.1 Cycloisomerisations of ynamides

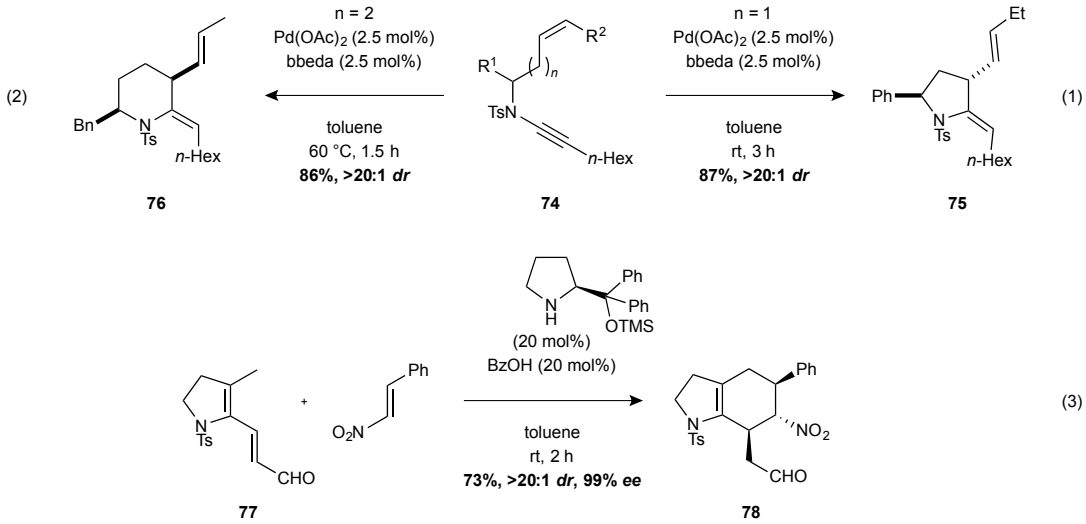
Given the prevalence of azacycles in biologically active compounds, and the breadth of cycloisomerisation substrates, it is surprising that the field of ynamide cycloisomerisation is relatively underdeveloped.[38] Until recently, it was limited to examples of π-acid activation (Scheme 1.21, Eq. 1),[39–41] and ene-yne metathesis (Eq. 2),[42–44] transformations which provide valuable heterocyclic products **72** and **73** respectively, in a single step from acyclic starting materials.



Scheme 1.21. Cycloisomerisations of 1,*n*-enynamides.

A programme of research within the Anderson group has led to the development of a number of unique transformations of ynamides.[45,46] In particular, palladium-catalysed cycloisomerisations of 1,*n*-enynamides **74** and enynhydrazides (Scheme 1.22, Eq. 1 and 2),[47] generate highly functionalised pyrrolidines and pyrazolidines. The products, **75** and **76**, were obtained in high yield and with excellent levels of diastereoselectivity, both in the

double bond geometry and also in the formation of stereocentres. To further illustrate the synthetic utility of these reactions, the 1,3-diene products have since been shown to undergo trienamine-catalysed enantioselective Diels-Alder cycloadditions with a number of dienophiles to form bi- and tricyclic compounds (Eq. 3).[48] Catalysed by the Jørgensen-Hayashi catalyst, reactions of heterocyclic compounds **77** occur with tuneable regio-, diastereo- and enantioselectivity, giving cycloadducts **78** in high yield.

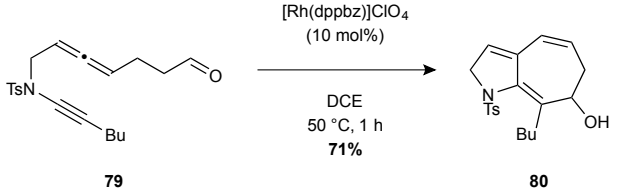


76 **74** **75**

77 **78**

Scheme 1.22. Cycloisomerisation of 1,*n*-enynamides, and derivatisation of their products.

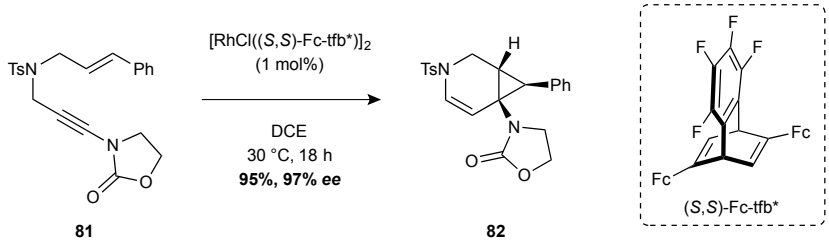
Studies of rhodium-catalysed intramolecular cyclisations of allene-tethered alkynes, to give formal [5+2] products, were reported by Sato *et al.* in 2014.[49] Therein lies an isolated example of an ynamide **79** undergoing this transformation, to give a [5.3.0]-azacycle **80** in good yield (Scheme 1.23).



79 **80**

Scheme 1.23. Isolated example of formal ynamide [5+2] product.

To our knowledge, there is currently only one example of an asymmetric ynamide cycloisomerisation, reported by Hayashi *et al*. (Scheme 1.24).[50] Using a rhodium/chiral diene catalyst, 1,6-enynamides **81** undergo highly enantioselective cycloisomerisation to [4.1.0]-bicyclic products **82** in near quantitative yields.



Scheme 1.24. Asymmetric cycloisomerisation of 1,6-enynamides.

1.3 Thesis summary

First described is development of a synthetic route to cycloisomerisation substrates, which allows us to introduce substituents into the tether in a diastereo- and enantioselectivly controlled fashion. Next the optimisation of the [5+2] cycloisomerisation reaction of an achiral ynamide vinylcyclopropane substrate is discussed, and the scope of ynamide substituents assessed (Chapter 2). With a suitable catalytic manifold in hand, the methodology is applied to a range of racemic substituted substrates in order to evaluate the diastereo- and regioselectivity of the reaction.

In Chapter 3, having established a racemic reaction, we investigate the use of asymmetric catalysis in enantioselective reactions. Ligand optimisation, with the aid of a mechanistic hypothesis, led to a novel catalyst system. Theoretical reaction analysis helped to elucidate the reaction mechanism, and rationalise the empirical results (Chapter 4).

Finally, in Chapter 5 asymmetric reaction conditions are applied to single enantiomer substituted substrates. The power of the catalyst system is tested against the inherent stereochemical preference of the substrate in matched and mismatched settings.

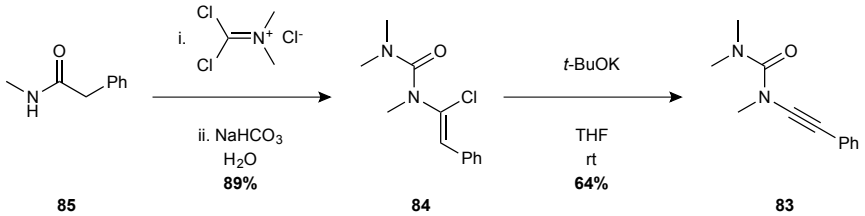
2 Ynamide vinylcyclopropane [5+2] cycloisomerisation

2.1 Introduction

Viehe *et al.* first reported the synthesis and isolation of an ynamide in 1972;[51] however, it was not until the 21st century that the reactivity of this new class of alkyne began to be extensively investigated. Thanks to advances in their preparation, the field of ynamide chemistry has since grown considerably.[36]

2.1.1 Synthesis of ynamides – elimination reactions

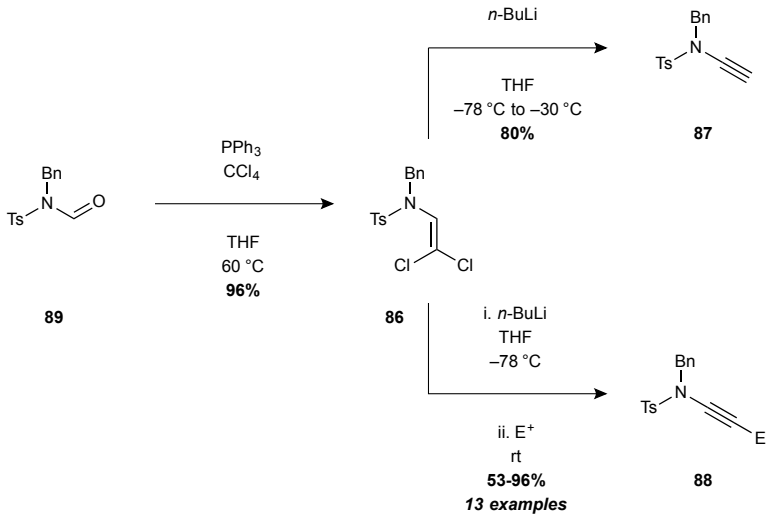
The original synthetic approach towards ynamides **83**, reported by Viehe,[51] involved elimination of HCl from chloroalkenyl ureas **84** with alkoxide base (Scheme 2.1), which were prepared from amide **85** and phosgeneiminium chloride. Though the reaction was used extensively, it suffered from limited substrate scope.



Scheme 2.1. Viehe's seminal synthesis of an ynamide.

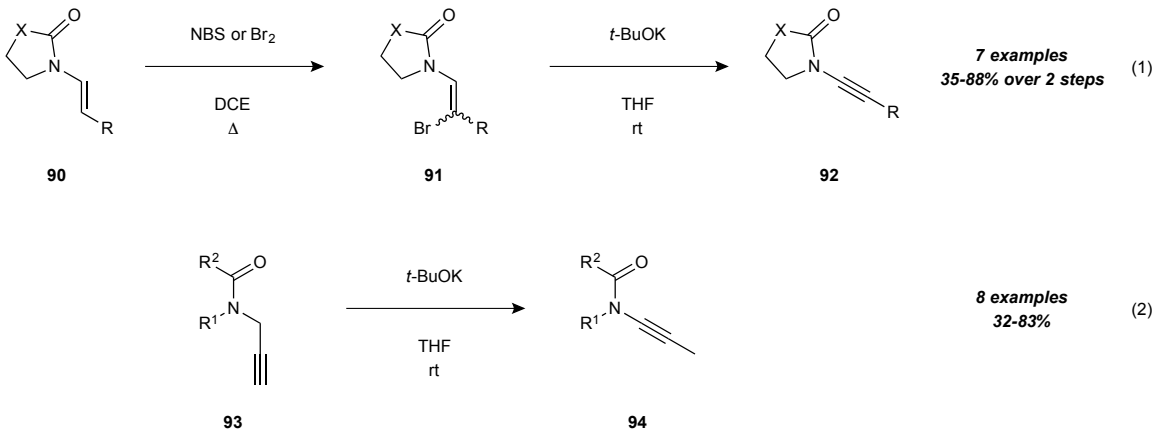
Brückner later reported elimination of 1,1-dichloroalkenyl sulfonamides **86** with BuLi, which produced lithiated ynamides *in situ* (Scheme 2.2).[52] These could either be

protonated to give terminal ynamide **87**, or functionalised by addition to other electrophiles to give internal ynamides **88**. This reaction was not without its limitations, particularly as the preparation of 1,1-dichloroenamides from aldehydes **89** requires excess PPh_3 and CCl_4.



Scheme 2.2. Brückner's elimination–lithiation–addition protocol.

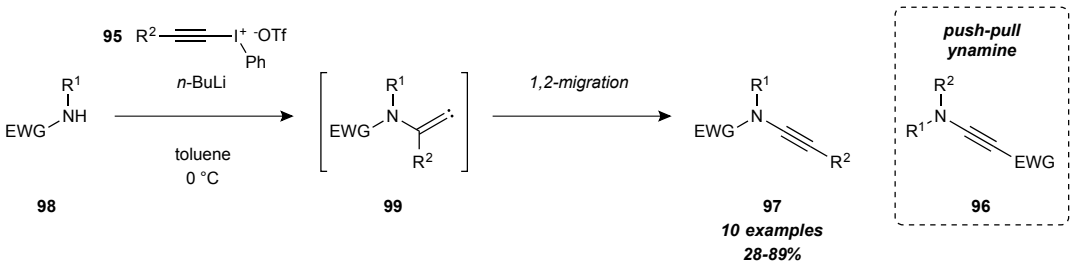
Hsung *et al.* extended Viehe's methodology to the elimination of β-bromoenamides (Scheme 2.3, Eq. 1).[53] Bromination of enamides **90** with either bromine or NBS gave geometric isomer mixtures of bromoenamides **91**. It was found that only the *Z*-isomers of **91** underwent elimination to ynamides **92**, whilst the *E*-isomers were recovered even after 24 hours at reflux.



Scheme 2.3. Hsung's base-promoted ynamide preparation.

This method relies upon the cyclic amide/urea and oxazolidinone motifs for reactivity. In 2002, the authors reported ynamide preparation *via* base-promoted isomerisation of propargyl amides **93** (Eq. 2).[43] Although acyclic amides were tolerated, the reaction is limited to the isomerisation of terminal propargylic amides, and thus only methyl-substituted ynamides **94** could be synthesised.

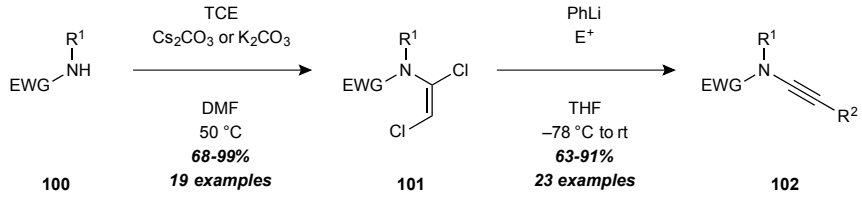
A method for preparing ynamides, which was perhaps the most popular before the era of copper-catalysed reactions, involves hypervalent iodonium salts **95** (Scheme 2.4). The method was originally developed by Stang *et al.* for the preparation of 'push-pull' ynamines **96**,[54] but was later extended to ynamides **97** by Witulski *et al.*[55] Addition of lithiated amide **98** to a hypervalent iodonium ion generates alkylidene carbene intermediate **99**. Subsequent 1,2-migration of the R^2 substituent gives ynamide **97**. The drawbacks to this approach are the availability of the iodonium triflate reagent, and the aptitude of the R^2 substituent towards 1,2-migration, which typically limits the reaction to silyl and, to a lesser extent, aryl alkynes.



Scheme 2.4. Ynamide preparation using hyper-valent iodonium salts.

In order to address some of the shortcomings of these elimination methodologies, the Anderson group has recently developed a robust and modular synthesis of ynamides (Scheme 2.5).[56] Nucleophilic addition of amide **100** to dichloroacetylene, generated *in situ* from trichloroethylene and mild base, generates 1,2-dichloroenamide **101**. This is followed by elimination, lithium-halogen exhange and addition to an electrophile to give **102**. This

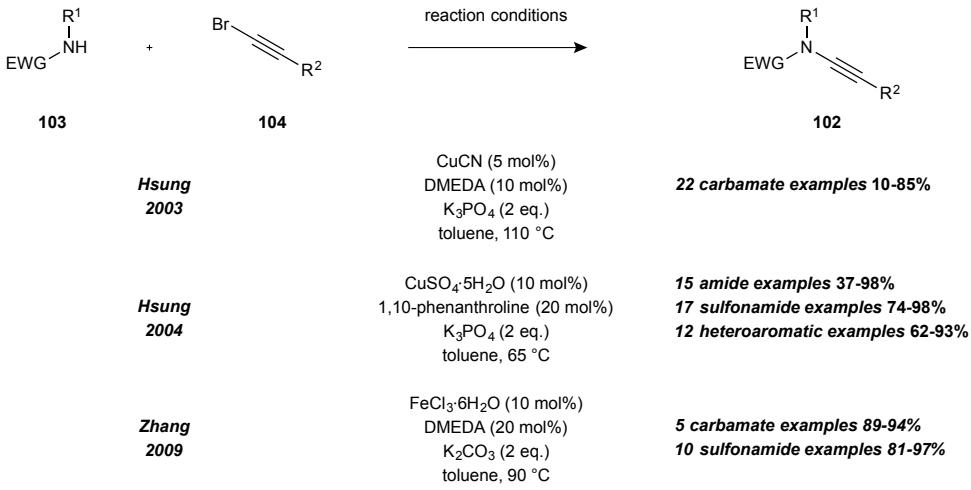
route not only provides a more efficient route to dichloroenamides, but also allows the preparation of previously inaccessible Boc-ynamides, and inclusion of sterically hindered R^1 substituents.



Scheme 2.5. Anderson-Mansfield ynamide synthesis.

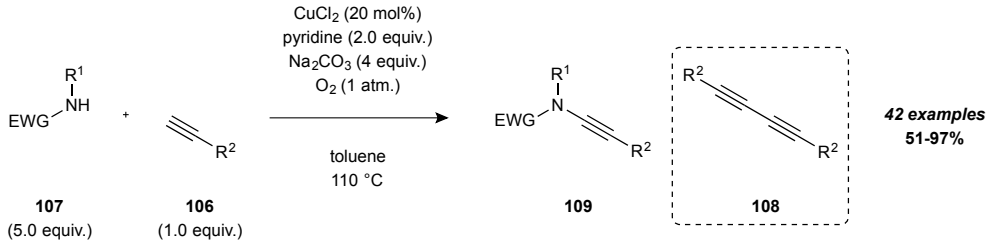
2.1.2 Synthesis of ynamides – cross-coupling reactions

In 2003 Hsung *et al.* reported a significant advancement in the field of ynamide synthesis, with a copper-catalysed coupling of oxazolidinones **103** with bromoalkynes **104** (Scheme 2.6).[57] The scope remained somewhat limited due the strong reliance upon the oxazolidinone functionality; however, a later report using a $CuSO_4$/1,10-phenanthroline catalyst system offered a crucial improvement on this methodology.[58] Under these milder conditions, a wide range of amides, sulfonamides, and heterocycles were tolerated. More recently Zhang *et al.* reported an iron-catalysed variant of this methodology.[59]



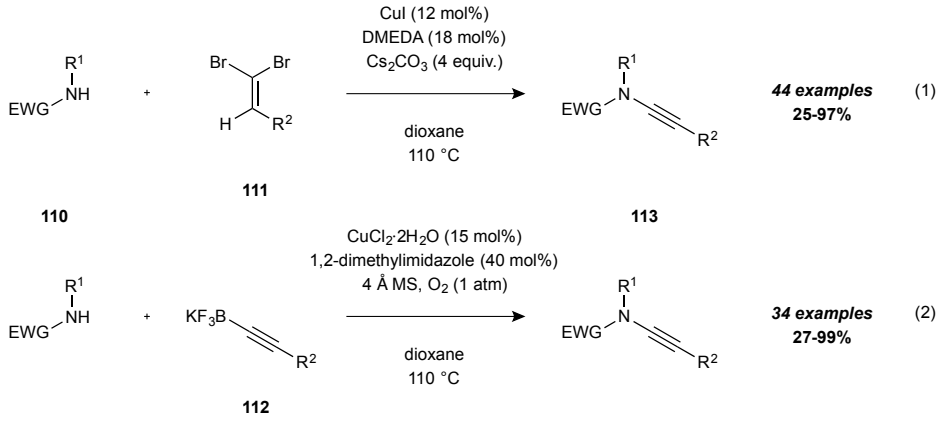
Scheme 2.6. Hsung's copper-catalysed ynamide syntheses.

Stahl *et al.* elegantly bypassed the requirement for bromoalkynes in this transformation with a direct oxidative coupling of terminal alkynes **106** with amides **107**, using oxygen as the terminal oxidant (Scheme 2.7).[60] A problem apparent in these reactions is the Glaser-Hay dimerisation of the alkyne starting materials (**108**). The authors address this by inverting the stoichiometry of amide and alkyne, from typically 1:2 to 5:1 (i.e. excess amide), which clearly has its own synthetic limitations.



Scheme 2.7. Stahl's ynamide synthesis with terminal alkynes.

Finally, Evano *et al.* reported two novel synthetic routes to ynamides. The first method was a copper-catalysed coupling of amides **110** and vinyl dibromides **111** – useful synthetic equivalents to bromoalkynes (Scheme 2.8, Eq. 1).[61] Whilst the conditions appear to tolerate a range of amides, sulfonamides, and ureas, secondary amides remained troublesome. The second, involved coupling of amides **110** and alkynyl trifluoroborates **112**, was the first base-free, room temperature synthesis of ynamides **113** (Eq. 2).[62]



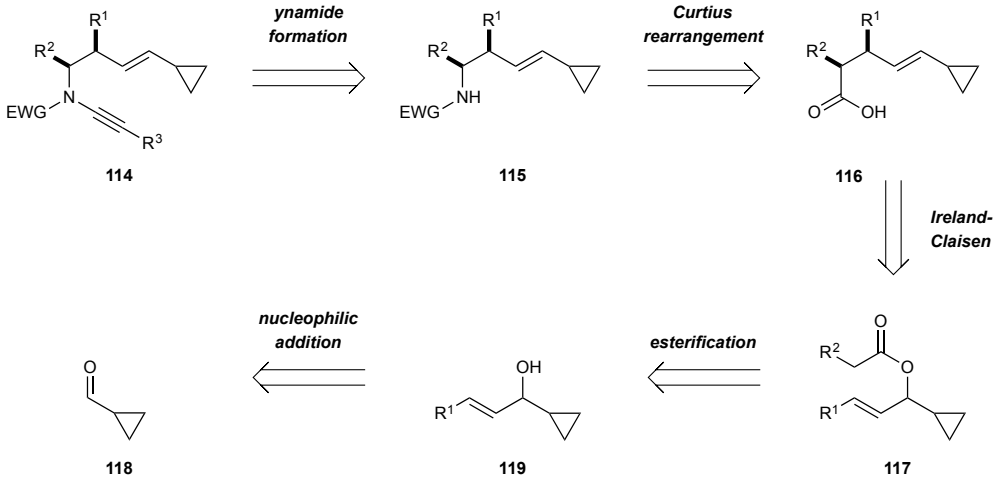
Scheme 2.8. Evano's ynamide syntheses.

2.2 Development of ynamide [5+2] cycloisomerisation methodology

Given the increased attention ynamides have received over the past quarter of a century, it is perhaps surprising that the area of ynamide cycloisomerisation is relatively underdeveloped. In this chapter the development of the first [5+2] cycloisomerisaton of ynamide vinylcyclopropanes, and assessment of the scope and limitations of the reaction, is described.

2.2.1 Retrosynthetic analysis

Our retrosynthetic approach to the target ynamide vinylcyclopropanes **114** relied upon late-stage ynamide formation (Scheme 2.9); with a number of conditions in the literature, and those newly developed in the Anderson group, we were confident in being able to realise this. Formation of amide **115** could be achieved with a Curtius rearrangement of a carboxylic acid **116** and trapping of the isocyanate intermediate with an appropriate nucleophile. When designing a synthetic route to the cycloisomerisation substrates, one of our major considerations was the ability to incorporate a variety of tether substituents in both a diastereo- and enantioselective manner.

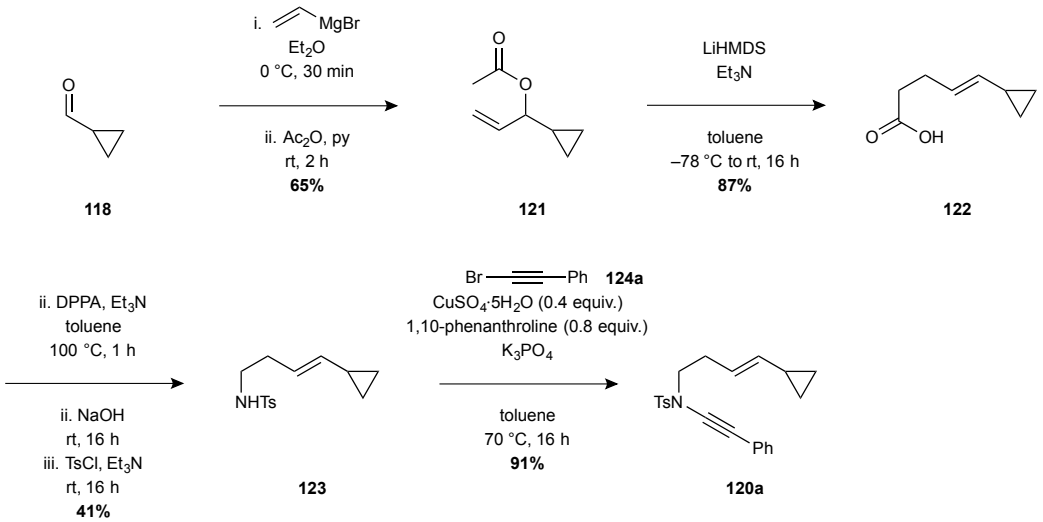


Scheme 2.9. Retrosynthetic analysis of enynamide **114**.

To this end, Ireland-Claisen rearrangement of allylic esters **117** would enable the diastereoselective formation of carboxylic acids **116**. Addition to commercially available aldehyde **118** with a range of nucleophiles, and esterification of the alcohol **119** with a variety of anhydrides would thus allow substitution at every position of the substrate.

2.2.2 Test substrate synthesis

Enynamide **120a** was identified as a test substrate for the [5+2] cycloisomerisation reaction, and was prepared in seven steps (Scheme 2.10). Our initial approach involved vinylmagnesium bromide addition to aldehyde **118** and Johnson-Claisen rearrangement of the resulting alcohol with triethyl orthoacetate. However, due to the forcing conditions required, and the volatility of the alcohol substrate, the process was poor yielding. This issue was circumvented with an alternative strategy; cyclopropylallyl acetate **121** was prepared in one step by vinylmagnesium bromide addition to aldehyde **118**, followed by *in situ* acetylation of the resultant alkoxide.[63] Ireland-Claisen rearrangement of ester **121** gave acid **122** in quantitative yield, and as a single geometric isomer.[64,65]



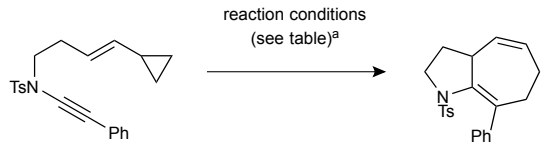
Scheme 2.10. Preparation of [5+2] cycloisomerisation test substrate **120a**.

Conversion of carboxylic acid **122** to the sulfonamide **123** was achieved *via* a three step/one pot process; Curtius rearrangement of the acid **122**, hydrolysis of the isocyanate intermediate, and protection of the amine product with tosyl chloride. Finally, Hsung's copper-catalysed coupling reaction of sulfonamide **123** and bromoalkyne **124a** gave the desired enynamide **120a** in excellent yield.[58,66]

2.2.3 Optimisation of the [5+2] cyclisomerisation reaction conditions

With the test substrate in hand, we began our investigations with a cationic ruthenium catalyst $[CpRu(CH_3CN)_3]PF_6$ developed by Mann *et al.*,[67] and deployed by Trost for alkyne [5+2] cycloisomerisations.[21] However, reaction of enynamide **120a** resulted in a complex mixture of products (Table 2.1, Entry 1). A switch to the rhodium-catalysed conditions reported by Wender *et al.* initially fared no better, with no reaction observed with the use of the dimeric catalyst $[Rh(cod)Cl]_2$ after 20 hours in toluene at reflux (Entry 2).[9] However, Wilkinson's catalyst successfully effected transformation of enynamide **120a** to the heterocyclic product **125a** in respectable yield after 1 hour under the same conditions (Entry 3).[8] Encouraged by this result, the highly active naphthalene/rhodium complex $[(C_{10}H_8)Rh(cod)]SbF_6$ reported by Chung *et al.*,[17] and utilised by Wender for alkyne [5+2] cycloisomerisations,[18] was synthesised from $[Rh(cod)Cl]_2$, $AgSbF_6$ and naphthalene. This catalyst system gave the product **125a** in excellent yield after 1.5 hours at room temperature in either 1,2-dichloroethane or dichloromethane (Entries 4 and 5). It was discovered that lower catalyst loading could be achieved at the expense of longer reaction times; at 5 mol% catalyst loading the reaction was complete within 3 hours, but at 1 mol% the catalyst was no longer active after 3 hours with only 45% conversion achieved (Entries 6 and 7); it is likely that with more rigorous exclusion of air than used at that time, this result could be improved.

Table 2.1. Optimisation of the [5+2] cycloisomerisation reaction.



120a **125a**

Entry	Catalyst	Cat. Loading	Solvent	Temp.	Time	Yield
1	$[CpRu(CH_3CN)_3]PF_6$	10 mol%	acetone	50 °C	20 h	-[b]
2	$[RhCl(cod)]_2$	10 mol%	toluene	110 °C	20 h	-[c]
3	$RhCl(PPh_3)_3$	10 mol%	toluene	110 °C	1 h	72%
4	$[(C_{10}H_8)Rh(cod)]SbF_6$	10 mol%	DCE	rt	1.5 h	92%
5	$[(C_{10}H_8)Rh(cod)]SbF_6$	10 mol%	CH_2Cl_2	rt	1.5 h	94%
6	$[(C_{10}H_8)Rh(cod)]SbF_6$	5 mol%	CH_2Cl_2	rt	3 h	91%
7	$[(C_{10}H_8)Rh(cod)]SbF_6$	1 mol%	CH_2Cl_2	rt	3 h	(45%)[d]

a. Reactions were performed at 0.1 M substrate in the stated solvent. b. Reaction gave a complex mixture of products. c. No reaction observed. d. Conversion determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.

2.3 Scope of the ynamide [5+2] cycloisomerisation

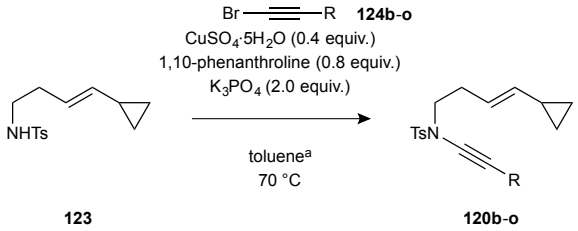
Having established a suitable catalytic manifold for the ynamide [5+2] cycloisomerisation, the scope and limitations of the reaction were explored with a range of enynamide substrates.

2.3.1 Synthesis of enynamide substrates

In order to assess the range of ynamide substituents which could be tolerated in the reaction, sulfonamide **123** was coupled with a series of bromoalkynes **124b-o** (Table 2.2). This delivered an array of enynamides **120a-o** varying in the alkyne substituent in good to

excellent yield. Pleasingly the mild, copper-catalysed coupling conditions tolerated a variety of functional groups including alkyl halides (Entry 2), silyl ethers (Entry 3), and both electron rich and electron poor arenes (Entries 7-14).

Table 2.2. Further ynamide synthesis.

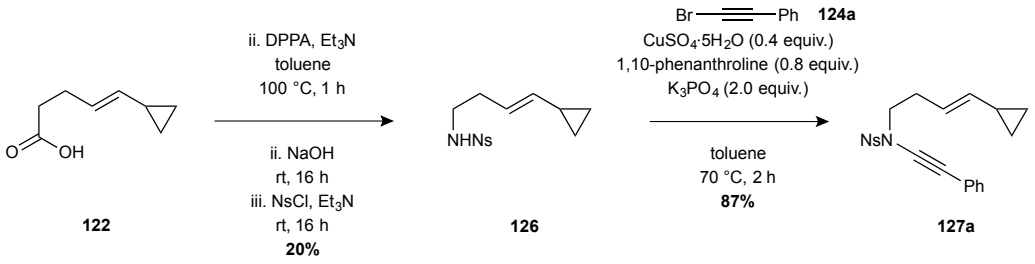


Entry	Substituent		Yield	Entry	Substituent		Yield
1	*n*-Hex	**123b**	62%	8	Me	**123i**	97%
2	Cl	**123c**	81%	9	Ph	**123j**	95%
3	OTBS	**123d**	55%	10	F	**123k**	71%
4	TIPS	**123e**	81%	11	Cl	**123l**	79%
5	NTs	**123f**	61%	12	Cl	**123m**	96%
6	TsN	**123g**	65%	13	CF_3	**123n**	98%
7	OMe	**123h**	65%	14	CN	**123o**	93%

a. Reactions were performed at 0.3 M substrate, with the reaction mixture stirred for 16 h.

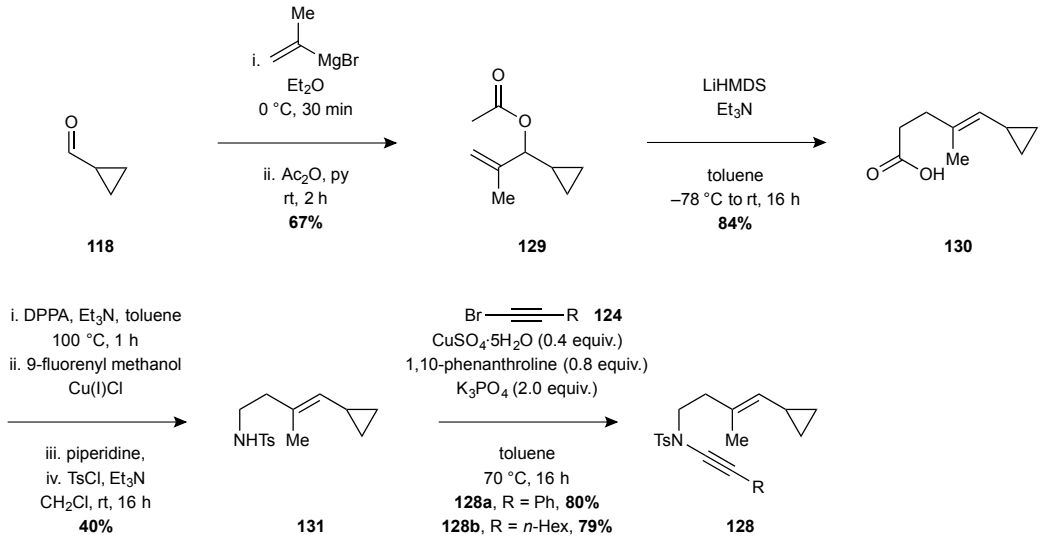
It was possible to vary the ynamide electron-withdrawing substituent *via* use of an alternative sulfonyl chloride reagent in the previous synthetic route (Scheme 2.11). The Curtius rearrangement/hydrolysis amine product was protected with nosyl chloride, giving

sulfonamide **126** in 20% yield over 3 steps. Copper-catalysed Ns-ynamide formation was found to be faster than that of the tosyl equivalent, with **127a** obtained after only 2 h.



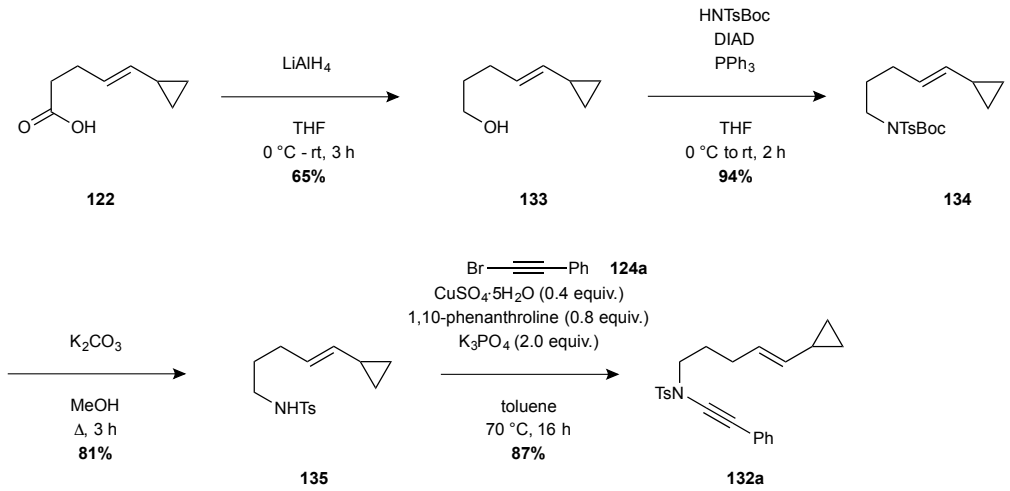
Scheme 2.11. Preparation of nosyl-ynamide **127a**.

With the aim of assessing the tolerance of the reaction to steric hindrance at the forming tertiary centre, enynamides **128a** and **128b** bearing a trisubstituted alkene was prepared using an equivalent synthetic route (Scheme 2.12). Use of isopropenylmagnesium bromide in the formation of the allylic ester **129**, and subsequent Ireland-Claisen rearrangement, introduced a methyl substituent in the vinylcyclopropane of **130** with high *E*:*Z* selectivity (>20:1). Carboxylic acid **130** was submitted to the Curtius rearrangement/hydrolysis/ protection protocol to give sulfonamide **131** in 40% yield over the three steps. Copper-catalysed ynamide formation afforded enynamides **128a** and **128b** in excellent yields.



Scheme 2.12. Synthesis of trisubstituted alkene enynamides **128a** and **128b**.

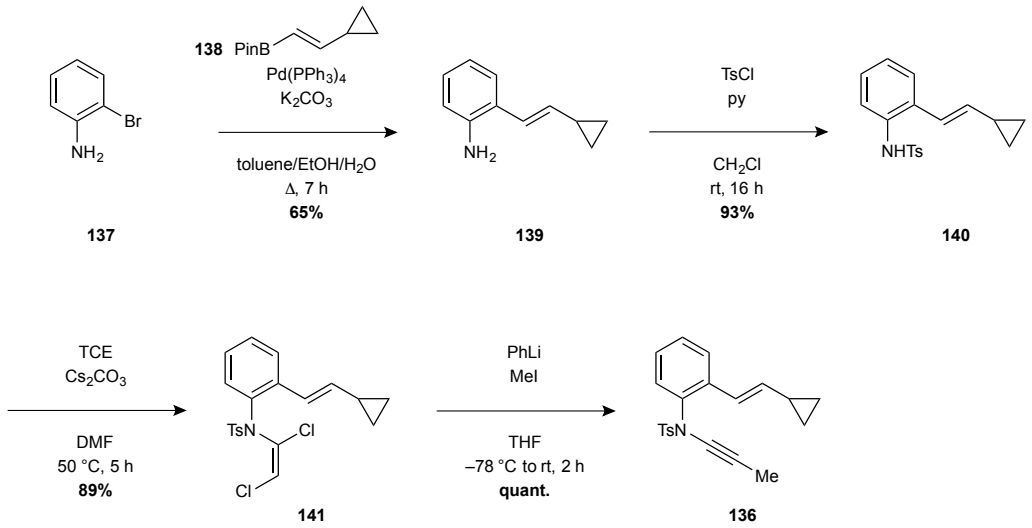
In addition to studying the tolerance of the reaction towards various ynamide substituents, we also wished to examine variation in ring size, through the formation of a [5.4.0] heterocyclic product. The homologous enynamide **132a** was therefore synthesised (Scheme 2.13); a divergence from the previous synthesis at carboxylic acid **122** would allow us to retain the various benefits of this route. Lithium aluminium hydride reduction of the acid gave alcohol **133** in good yield. Mitsunobu reaction of alcohol **133** with BocNHTs gave the protected sulfonamide **134** in excellent yield. It was found that deprotection of the carbamate protecting group was not possible under acidic conditions in the presence of the vinylcyclopropane; however, deprotection proved to be facile using K_2CO_3/MeOH at reflux, which gave sulfonamide **135**. Coupling of **135** with bromoalkyne **124a** yielded the desired enynamide homologue **132a**.



Scheme 2.13. Synthesis of homologous enynamide substrate **132a**.

Finally, the synthesis of a 6,5,7-fused tricyclic scaffold could be achieved with the use of an aryl-tethered enynamide **136**. This cycloisomerisation precursor was accessed in four steps from commercially available amine **137** (Scheme 2.14). Suzuki coupling of unprotected 2-bromoaniline **137** with boronic ester **138** gave **139** in good yield. Protection of the amine functionality with tosyl chloride and triethylamine proved sluggish, and gave

the doubly tosylated product only. However, a switch of the base to pyridine produced the desired sulfonamide **140** exclusively. Due to the poor nucleophilicity of the aniline nitrogen, generation of the ynamide **136** required the dichloroenamide strategy optimised by the Anderson group.[56] Sulfonamide **140** was first converted to the dichloroenamide **141** with trichloroethylene and cesium carbonate, which was then submitted to a one-pot elimination/lithiation/alkylation sequence to give the aryl-tethered enynamide **136** in quantitative yield.



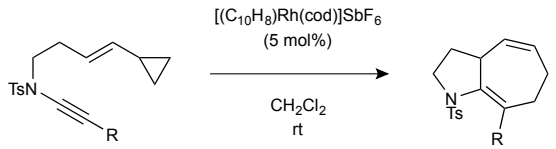
Scheme 2.14. Synthesis of aryl-tethered enynamide **136**.

2.3.2 [5+2] Cycloisomerisation of enynamides

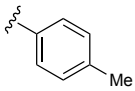
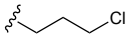
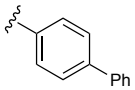
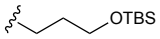
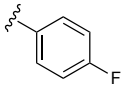
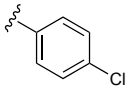
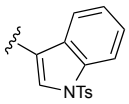
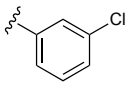
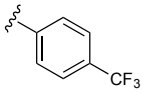
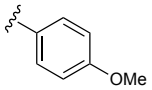
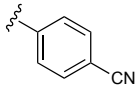
With a range of ynamide vinylcyclopropanes in hand, we set about examining the scope of the reaction. Substrates **120b-o**, possessing various ynamide substituents, were submitted to the optimised reaction conditions, which gave alkyl-substituted heterocyclic products **125b-d** and aromatic- and heteroaromatic-substituted products **125f-n** in good to excellent yields (Table 2.3). We were delighted to find that the reactions were generally complete within 15 minutes at ambient temperature, and at 5 mol% catalyst loading. The reaction conditions were tolerant of a wide variety of functional groups, including aryl and alkyl

ynamide substituents, as well as alkyl halides. Exceptions to this include product **125d** (Entry 3), which was isolated in 60% yield, with an additional 35% of desilylated product.

Table 2.3. Scope of ynamide substituents in the [5+2] cycloisomerisation.



120b-o **125b-o**

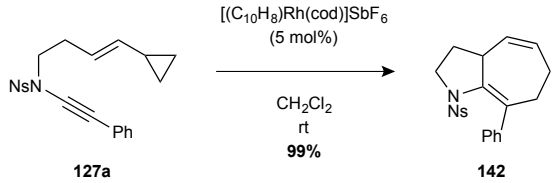
Entry	Substituent		Time	Yield	Entry	Substituent		Time	Yield
1		**125b**	15 min	99%	8		**125i**	20 h	89%
2		**125c**	15 min	99%	9		**125j**	3 h	99%
3		**125d**	15 min	60%	10		**125k**	15 min	99%
4		**125e**	20 h	-[b]	11		**125l**	15 min	56%
5		**125f**	15 min	92%	12		**125m**	15 min	99%
6		**125g**	6 h	87%	13		**125n**	15 min	99%
7		**125h**	20 h	85%	14		**125o**	20 h	-[b]

a. Reactions were performed at 0.1 M substrate. b. No reaction was observed.

Enynamide **120e** was unreactive under the standard conditions or indeed any of the conditions described thus far (Entry 4). This was perhaps due to the sterically encumbering silyl group preventing complexation of the rhodium metal to the ynamide. Removal of the TIPS group and subsequent cycloisomerisation also proved unsuccessful as the terminal ynamide was found to be unstable under the reaction conditions resulting in a complex mixture of products. An interesting effect was observed on variation of the ynamide

electron density; reactions of electron poor ynamides **120k-n** (Entries 10-13) were complete in less than 15 minutes (with the exception of the *p*-cyanophenyl enynamide **120o** which failed to react after 20 hours (Entry 14), perhaps due to ligation of the metal catalyst by the nitrile), whilst electron rich aryl substituted ynamides **120h** and **120i** required extended reaction times (Entries 7 and 8). The observed difference in rate of reaction could be explained by the increased reactivity of electron poor ynamides towards oxidative addition by rhodium.

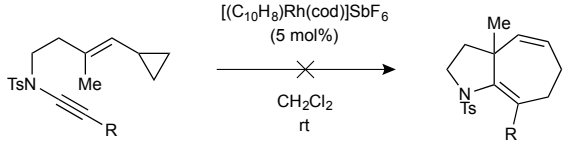
Pleasingly, *p*-nitrobenzenesulfonyl ynamide (**127a**) underwent smooth cycloisomerisation to product **142**, which was obtained after 1 hour in quantitative yield (Scheme 2.15).



127a **142**

Scheme 2.15. Reaction of nosyl ynamide **127a**.

Unfortunately, it was found that formation of a quaternary centre was not tolerated in the reaction, with trisubstituted alkene tethered ynamides **128a** and **128b** both unreactive under the standard reaction conditions (Scheme 2.16). This is perhaps due to increased steric hindrance at the forming stereocentre, or other conformational effects.



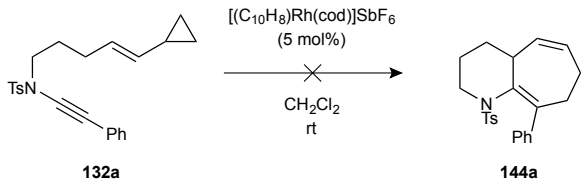
128a, R = Ph
128b, R = *n*-Hex

143a, R = Ph
143b, R = *n*-Hex

Scheme 2.16. Reaction of trisubstituted alkene tethered ynamides **128a** and **128b**.

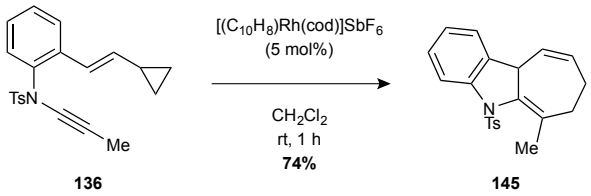
The homologous enynamide **132a** was also found to be unreactive towards [5+2] cycloisomerisation under all conditions attempted, including extended reaction times,

elevated temperatures, and 25% catalyst loading (Scheme 2.17). These results are consistent with Trost's findings in the equivalent alkyne reaction, where no reaction was observed even with the use of stoichiometric ruthenium catalyst.[25]



Scheme 2.17. Unsuccessful synthesis of [5.4.0]-heterocycle **144a**.

Excitingly, under the standard reaction conditions, aryl-tethered enynamide **136** underwent smooth cycloisomerisation to the 6,5,7-fused heterocyclic product **145** in high yield (Scheme 2.18). Surprisingly, isomerisation to the aromatic indole was not observed, which serves to underline the mild nature of the reaction conditions.



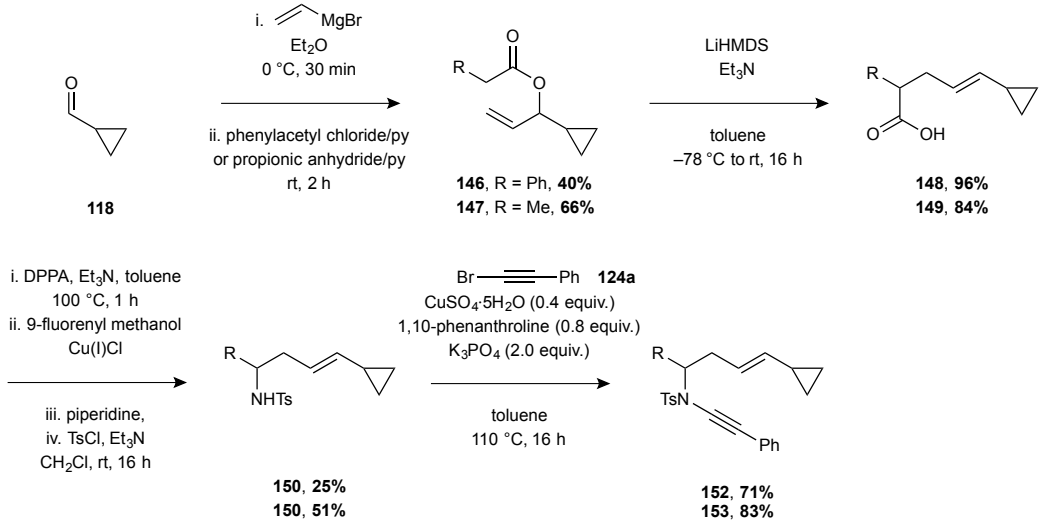
Scheme 2.18. Synthesis of tricyclic product **145**.

2.4 Diastereoselective ynamide [5+2] cycloisomerisation

With the [5+2] cylcoisomerisation of ynamide vinylcyclopropanes established, we turned our attention towards the diastereoselectivity that could be achieved for reactions of enynamides bearing tethered substituents. We planned to examine the dependence of selectivity upon the substituent size and position, and the nature of the catalyst system.

2.4.1 Preparation of substituted ynamide vinylcyclopropanes

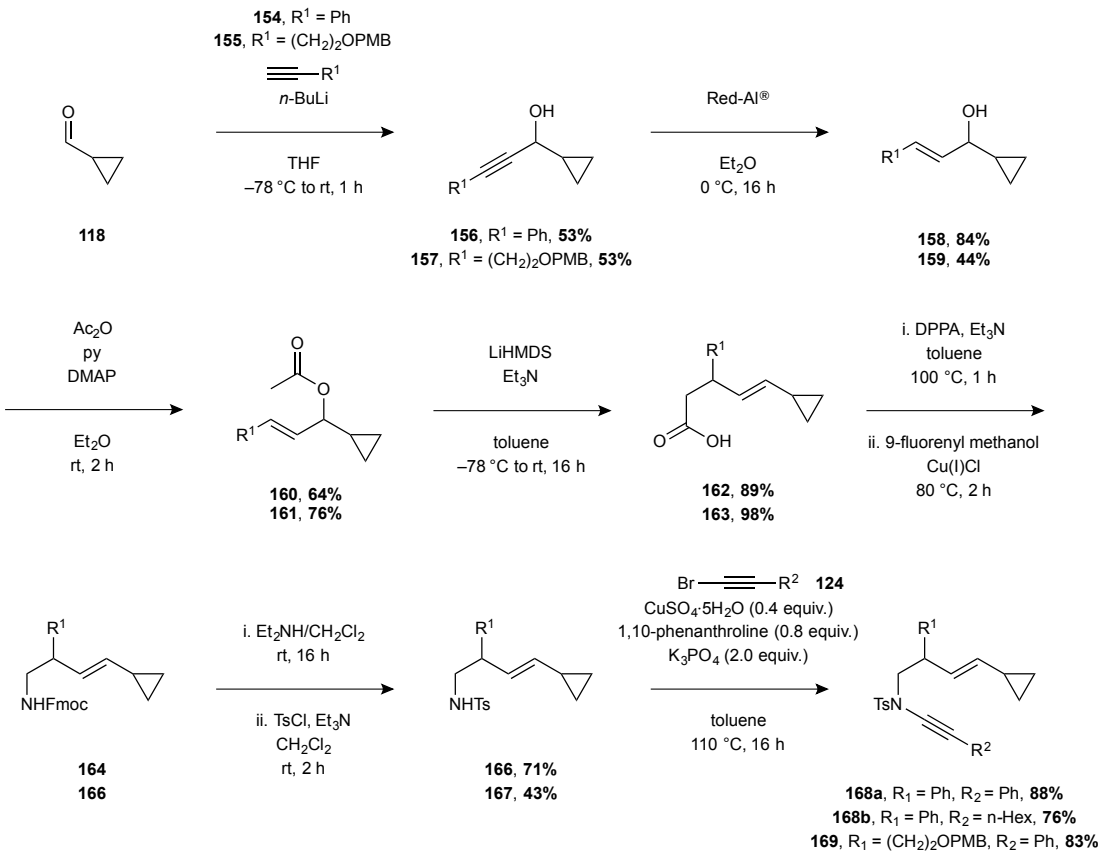
By adopting a similar approach to the synthesis of the unsubstituted substrates, it was possible to introduce substituents at the homo allylic position by modifying the acylating agent, which allowed access to esters **146** and **147** (Scheme 2.19). Ireland-Claisen rearrangement gave carboxylic acids **148** and **149** in reliably high yields. However, initial attempts to convert acid **148** to the sulfonamide **150** using the previously described Curtius rearrangement conditions were unsuccessful. The presence of a homoallylic substituent resulted in slow hydrolysis of the isocyanate intermediate, but rapid decarboxylation of the carbamic acid, resulting in urea formation between the amine product and the isocyanate.



Scheme 2.19. Preparation of homoallylic-substituted enynamides **152** and **153**.

This issue was addressed by trapping the isocyanate as the carbamate with an appropriate alcohol. Mindful of avoiding acidic deprotection conditions due to the acid-sensitivity of the vinylcyclopropane, use of 9-fluorenylmethanol enabled the formation, and then *in situ* deprotection of the Fmoc carbamate under basic conditions. Tosylation of the crude amine gave sulfonamide **150** in 25% yield over the 4 step sequence. Sulfonamide **151** was subsequently prepared in 51% yield *via* this method. Previous research in the Anderson group and by others has shown that couplings of branched sulfonamides under copper-catalysed conditions require elevated temperatures and extended reaction times.[47] As such, it was necessary to conduct the reactions of sulfonamides **150** and **151** at 110 °C to afford substituted enynamides **152** and **153** in excellent yields.

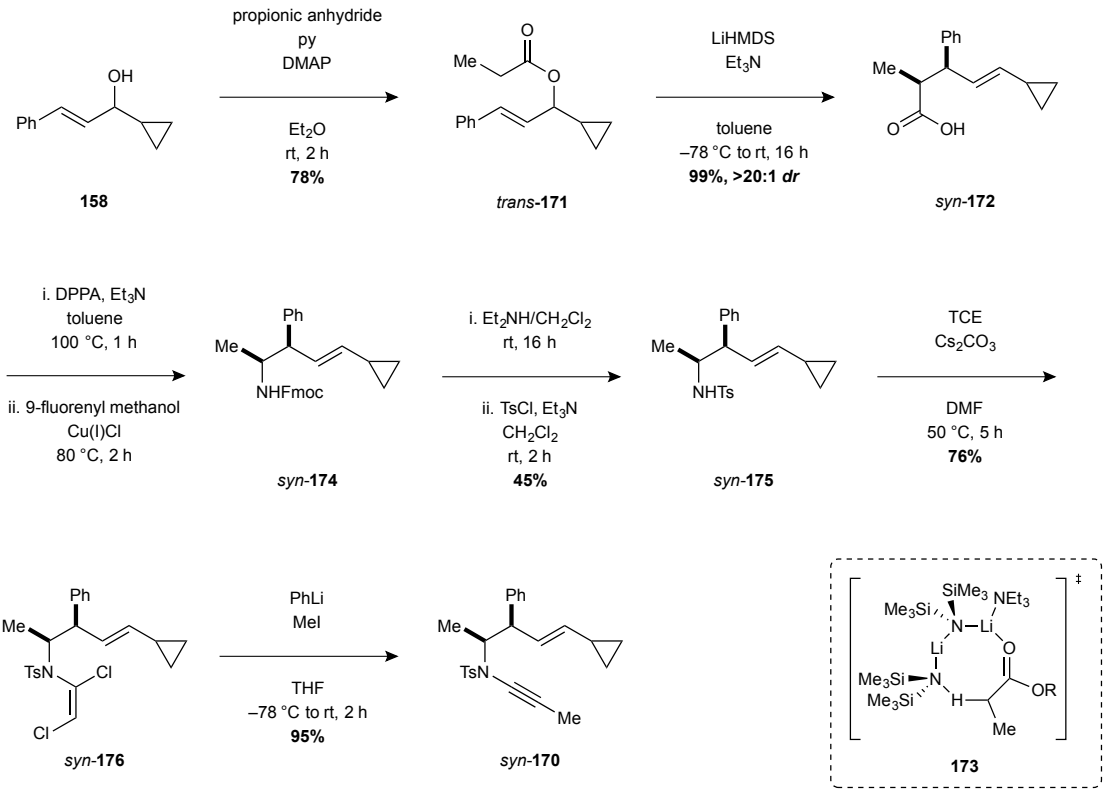
Our ability to vary the nature of the nucleophile in the first step of the synthetic route allowed us to easily introduce allylic substituents on the enynamide tether (Scheme 2.20). Addition of lithium acetylides **154** and **155** to aldehyde **118** gave alcohols **156** and **157** in moderate yields. Reduction of propargylic alcohol **156** with Red-Al gave *trans*-allylic alcohol **158** with perfect diastereoselectivity and high yield. Reduction of **157** under the same conditions gave the desired *trans*-allylic alcohol **159**, but in considerably lower yield. Subsequent acetylation with acetic anhydride gave the allylic esters **160** and **161**, Ireland-Claisen rearrangement of which gave the allylic-substituted carboxylic acids **162** and **163** in excellent yield, which were isolated from the reaction mixture after basic work-up and used without further purification. A similar Curtius rearrangement/Fmoc protection/protecting group switch strategy was employed as with the homo allylic substituted enynamides, to generate sulfonamides **166** and **167**. Ynamide formation gave the allylic-substituted aryl and alkyl enynamides **168a**, **168b** and **169** in high yields.



Scheme 2.20. Preparation of allylic-substituted enynamides **168a**, **168b** and **169**.

It was possible to prepare doubly-substituted enynamide *syn*-**170** (Scheme 2.21), with a divergence at alcohol **158** in the previously discussed synthesis. Esterification with propionic anhydride gave allylic ester *trans*-**171**, which was subjected to the Ireland-Claisen rearrangement conditions. In this case, the amount of triethylamine had a marked influence on the enolate geometry, and thus the diastereoselectivity of the reaction. Initial attempts with 10 equiv. of triethylamine gave a 9:1 ratio of *syn*-**172** to *anti*-**172**. However, the use of 30 equiv. of Et_3N gave the carboxylic acid *syn*-**172** as a single diastereomer (>20:1 *dr*). This effect of Et_3N concentration on enolate geometry was rationalised by Collum *et al.* in the dimeric transition state **173**, which favours formation of the (*E*)-enolate geometry.[65] This species is stabilised by monosolvation of lithium by triethylamine, and is therefore highly dependant upon its concentration. Conversion of the carboxylic acid *syn*-**172** to sulfonamide *syn*-**175** was achieved using the standard protocol.

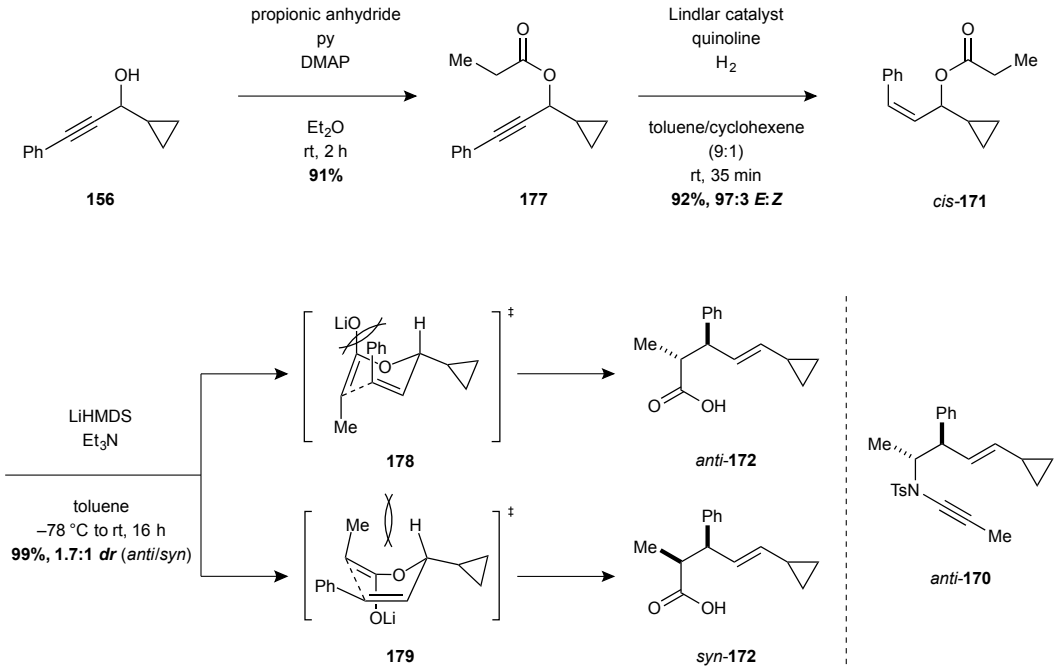
Due to increased steric hindrance, ynamide formation under the copper-catalysed conditions was unsuccessful, even at elevated temperatures, with the starting material recovered after 24 hours. Sulfonamide *syn*-**175** was therefore converted first to the dichloroenamide *syn*-**176** with trichloroethylene, and then to the ynamide *syn*-**170**.[56]



Scheme 2.21. Preparation of doubly substituted enynamide *syn*-**170**.

In order to fully examine the effect of tether substituents on the diastereoselectivity of the reaction, we also aimed to access the *anti*-diastereomer of enynamide **170**. We envisioned construction of carboxylic acid *anti*-**172** *via* Ireland-Claisen rearrangement of allylic ester *cis*-**171** (Scheme 2.22). Esterification of homopropargylic alcohol **156** gave homopropargylic ester **177**, which was submitted to a *cis*-selective semi-reduction. The optimal reduction conditions were found to be Pd/$CaCO_3$ catalyst with 20 mol% quinoline poison, and a toluene/cyclohexene (9:1) solvent mixture, which gave the allylic ester *cis*-**171** in a 97:3 *dr*. Ireland-Claisen rearrangement of ester *cis*-**171**, under the previously

optimised reaction conditions, gave carboxylic acid **172** in quantitative yield, but with an unsatisfactory 1.7:1 *dr* (*anti*:*syn*, inseparable). This may have been due to unfavourable 1,3-diaxial interactions in the six-membered chair transition state **178**. The reaction could therefore proceed *via* a boat-like transition state **179**, which itself suffers from 1,4-flagpole interactions. The synthesis of doubly substituted enynamide *anti*-**170** was abandoned at this point.



Scheme 2.22. Incomplete synthesis of doubly substituted enynamide *anti*-**170**.

2.4.2 [5+2] Cycloisomerisation of substituted enyamides

The substituted enynamides were submitted to the optimised [5+2] cycloisomerisation reaction conditions (Fig. 2.1). Pleasingly, all substrates were found to undergo cycloisomerisation to the desired heterocyclic products **181**-**185** in excellent yields. Allylic aryl and alkyl substituents exhibited a strong diastereoselective influence in the formation of the adjacent ring junction stereocentre, with *syn*-**181a**, *syn*-**181b** and *syn*-**182** obtained in 18:1 to >20:1 *dr*. However, homoallylic substituents were found to show little to no bias

in the formation of the *syn*- or *anti*-diastereomers of products, with *syn*-**183** and *syn*-**184** formed in up to 2:1 *dr*. A substrate containing both allylic and homoallylic substituents showed the highest levels of diastereoselectivity, with *syn*-**185** formed as a single diastereomer in quantitative yield.

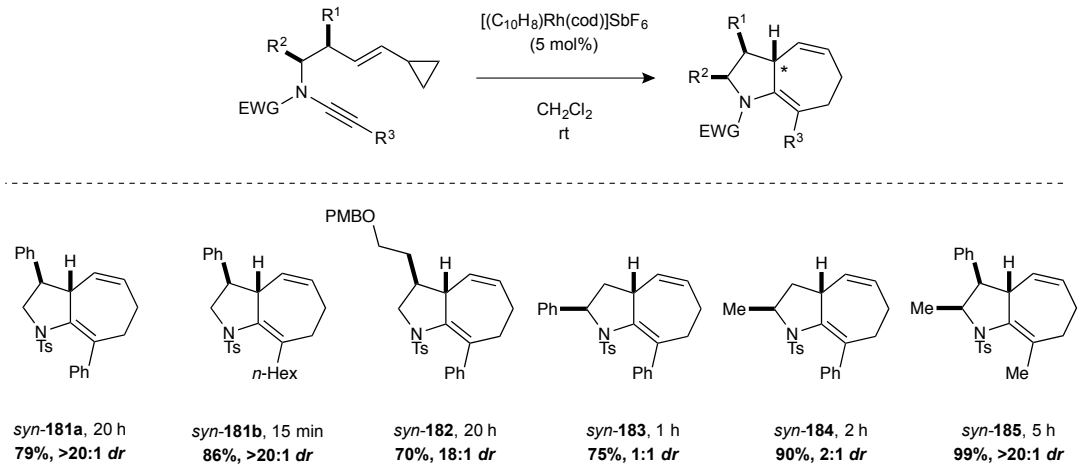


Figure 2.1. Diastereoselectivity of the [5+2] cycloisomerisation reaction.

The relative stereochemistry of **181a** was determined unambiguously as *syn*- by X-Ray crystallographic analysis (Fig 2.2). ^{1}H NMR analysis showed a coupling constant of 11 Hz between the bridgehead proton H3a and the adjacent proton H3. A similar coupling interaction was observed in compounds **181b** and **185**, which were therefore assigned as *syn*- by analogy to **181a**.

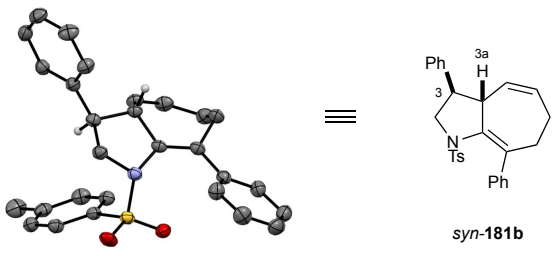


Figure 2.2. Assignment of relative stereochemistry; ORTEP diagram for *syn*-**181a**.

In the case of product **183**, it was possible to separate the two diastereomers, which were subjected to NOESY analysis (Fig. 2.3). In the major diastereomer *syn*-**183**, strong nOe

enhancements were observed between the methyl substituent and H3a (blue), and between H2 and H3α (red), suggesting a *syn* relationship between the methyl group and the bridgehead proton H3a. This assignment was further supported by nOe enhancements between H3β and H3a and the methyl substituent (blue).

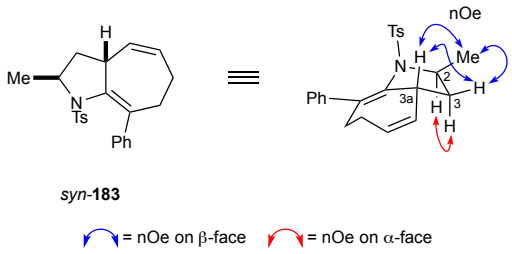
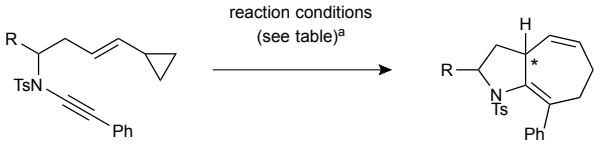


Figure 2.3. Assignment of relative stereochemistry in *syn*-**183**.

In view of the poor diastereoselectivities obtained for homoallylic-substituted enynamides **152** and **153**, we thought it necessary to examine the effect of different catalyst systems on the reaction outcome (Table 2.4). As was found with the unsubstituted reaction, ruthenium catalysed reactions gave a complex mixture of products, and as such a yield was not determined (Entries 3 and 4). However, some product formation was observed, with similar levels of diastereoselectivity to those with the optimised rhodium catalyst. Moderate selectivity was exhibited using Wilkinson's catalyst, with the methyl substituted product *syn*-**184** obtained in a 3:1 ratio of diastereomers (Entry 6). Pleasingly, the selectivity was greatly improved in both cases with the use of dimeric catalyst $[RhCl(cod)]_2$ (Entries 7 and 8), with *syn*-**184** isolated in 12:1 *dr*. Somewhat surprisingly, the methyl substituted enynamide **153** exhibited higher levels of diastereoselectivity than the phenyl analogue **152** with all catalysts tested. Given the marked influence of the catalyst system on the diastereoselectivity of the reaction, we aimed to further optimise these results with dinaphthocyclooctatetraene catalyst systems developed by Wender *et al.*[20] However, owing to the synthetic effort involved other investigations took priority.

Table 2.4. Effect of catalyst on diastereoselectivity.



152, R = Ph
153, R = Me

183, R = Ph
184, R = Me

Entry	R	Catalyst	Solvent	Temp.	Time	Yield	*dr*[b]
1	Ph	$[(C_{10}H_8)Rh(cod)]SbF_6$	DCE	rt	1 h	75%	55:45
2	Me	$[(C_{10}H_8)Rh(cod)]SbF_6$	DCE	rt	2 h	90%	65:35
3	Ph	$[CpRu(CH_3CN)_3]PF_6$	CH_2Cl_2	rt	1 h	n.d.[c]	58:42
4	Me	$[CpRu(CH_3CN)_3]PF_6$	CH_2Cl_2	rt	1 h	n.d.[c]	66:34
5	Ph	$RhCl(PPh_3)_3$	toluene	110 °C	30 min	74%	58:42
6	Me	$RhCl(PPh_3)_3$	toluene	110 °C	1 h	77%	75:25
7	Ph	$[RhCl(cod)]_2$	toluene	110 °C	3 h	92%	75:25
8	Me	$[RhCl(cod)]_2$	toluene	110 °C	3 h	75%	92:8

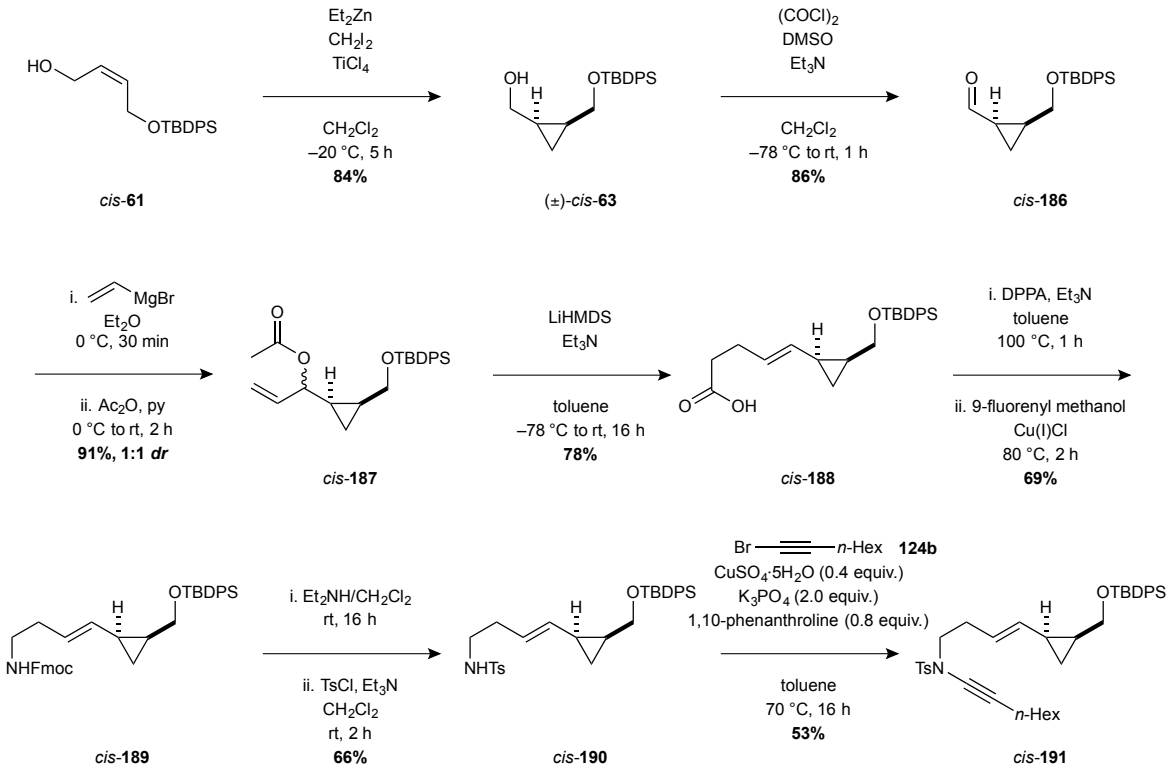
a. Reactions were performed at 0.1 M substrate in the stated solvent with 10 mol% catalyst. b. Diastereomeric ratio determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. c. Reaction gave a complex mixture of products.

2.5 Regioselective ynamide [5+2] cycloisomerisation reaction

The above work had shown that substituted tether ynamide vinylcyclopropanes undergo highly diastereoselective cycloisomerisations. In order to further explore substituent effects, we aimed to investigate the regioselectivity of these transformations using an enynamide bearing a substituted cyclopropane.

2.5.1 Synthesis of substituted cyclopropane enynamide

Using an approach to disubstituted cyclopropane *cis*-**63** optimised by Wender *et al.*,[15] a diastereoselective Simmons-Smith cyclopropanation of mono-TBDPS protected *cis*-but-2-ene-1,4-diol **61** gave *cis*-substituted cyclopropane **63** as a single diastereomer (Scheme 2.23).

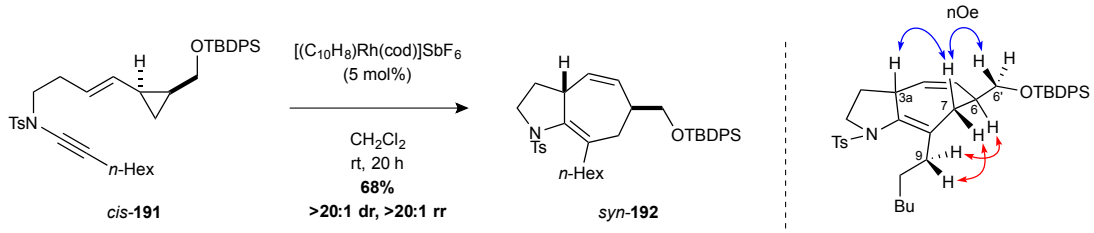


Scheme 2.23. Preparation of substituted cyclopropane eynamide *cis*-**191**.

Swern oxidation of the alcohol *cis*-**63** gave cyclopropyl aldehyde *cis*-**186**, Grignard addition to *cis*-**186**, and *in situ* acetylation of the resultant alkoxide gave allylic ester *cis*-**187** as a 1:1 mixture of diastereomers. Ireland-Claisen rearrangement of this mixture resulted in destruction of the allylic stereocentre, giving carboxylic acid *cis*-**188** as a single diastereomer. The acid was subjected to the standard Curtius rearrangement/ynamide formation protocol to yield enynamide *cis*-**191** in modest yield.

2.5.2 Cycloisomerisation of substituted cyclopropane enynamide

Cycloisomerisation of enynamide *cis*-**191** under the optimised reaction conditions gave heterocycle *syn*-**192** in good yield after 20 hours at ambient temperature (Scheme 2.24). Importantly, the product was obtained as a single diastereomer and regioisomer.



Scheme 2.24. Regioselectivity in [5+2] cycloisomerisation of *cis*-**191**.

The regiochemistry of *syn*-**192** was assigned by HMBC analysis, which necessarily placed the silyloxymethyl sidechain at the C6 position due to mutual 3-bond correlations between H9/C9 and C7/H7. The relative stereochemistry of *syn*-**192** was determined by a NOESY experiment: enhancements were observed on the β-face between bridgehead proton H3a and H7β, and also between H7β and one of H6′. On the α-face, H7α showed an enhancement with one of H9, while the other H9 showed an enhancement with H6. These correlations suggest a *syn* relationship between H3a and the silyloxy methyl sidechain, which is in agreement with Wender and Trost's observations on non-ynamide substrates.[25,34,35]

2.6 Conclusions

The first [5+2] cycloisomerisation of an ynamide vinylcyclopropane has been achieved. These reactions proceed in near quantitative yields under very mild conditions, in most cases are complete in under an hour, and tolerate a broad range of ynamide substituents. In the process of developing the reaction we established a robust and versatile synthetic protocol for substrate synthesis.

We demonstrated that these reactions can occur with extremely high levels of diastereo- and regioselectivity. These results are significant in the wider context of [5+2] cycloisomerisation, where high levels of stereocontrol are normally attributed to an 'inside alkoxy' effect from allylic oxygen substituents, and not due to a general steric-based effect.

Until now we have dealt only with the relative stereochemistry of substituents, and all reactions have resulted in racemic mixtures of products. The next chapter explores asymmetric catalysis, and the possibility for an enantioselective variant of the ynamide [5+2] cycloisomerisation.

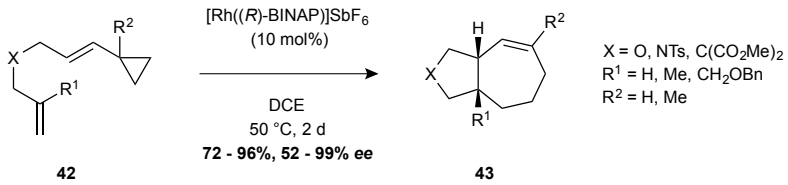
3 Asymmetric [5+2] cycloisomerisation

3.1 Introduction

Metal-catalysed cycloisomerisations represent powerful methods for the formation of multiple C–C bonds. Of particular importance is the generation of a stereogenic centre, and thus two possible enantiomers of product, where asymmetric reagents may control the stereochemical outcome. Given the myriad of cycloisomerisation studies in the literature, it is somewhat surprising that relatively few asymmetric variants of these transformations have been reported.[68–70]

3.1.1 Enantioselective [5+2] cycloisomerisations

An area that has suffered a particular dearth of attention is the enantioselective [5+2] cycloisomerisation (see Chaper 1). In fact, with the exception of chiral auxiliary chemistry, to our knowledge only three reports of this nature exist. Wender *et al.* were the first to demonstrate asymmetry in these transformations with their work on the intramolecular [5+2] cycloisomerisation of vinylcyclopropane-alkenes **42** (Scheme 3.1).[29]

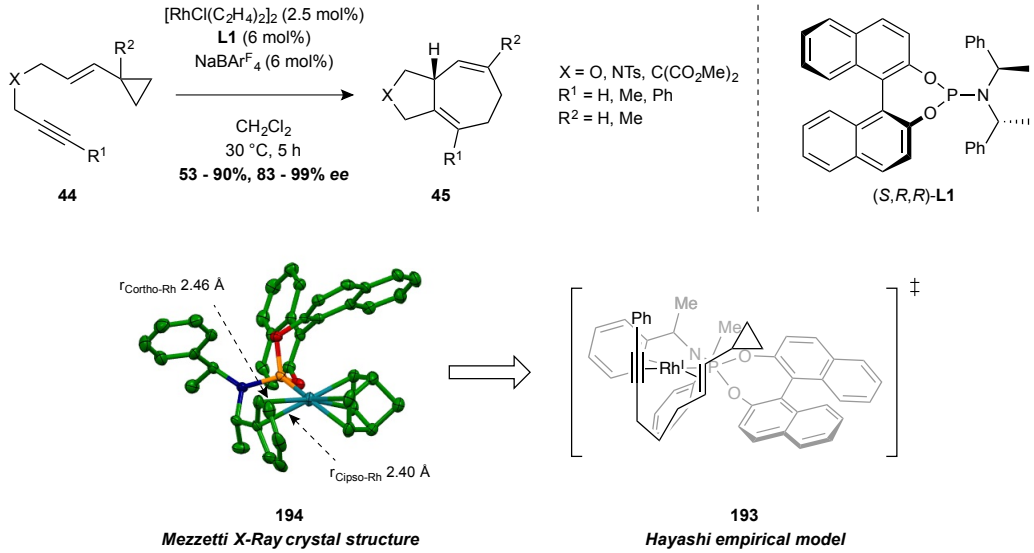


42 **43**

Scheme 3.1. Enantioselective [5+2] cycloisomerisation of vinylcyclopropane tethered alkenes.

They were able to achieve extremely high levels of enantioselectivity, in the construction of **43**, with the use of rhodium/BINAP complexes. However, when applied to reactions of alkynes, much lower levels of selectivity were observed. These findings set the stage for further study.

Hayashi *et al.* later described asymmetric transformations of vinylcyclopropane-alkynes **44** (Scheme 3.2).[30] A range of binaphthyl-derived ligands were screened, which gave low yields and only moderate levels of *ee*. It was found that only the phosphoramidite ligand (*S*,*R*,*R*)-**L1**, developed by the Feringa group,[71] could deliver the products **45** in high yield and with excellent enantioselectivity (88% yield, >99% *ee*). The absolute stereochemistry of products **45** was determined unambiguously by X-ray crystal structure analysis.

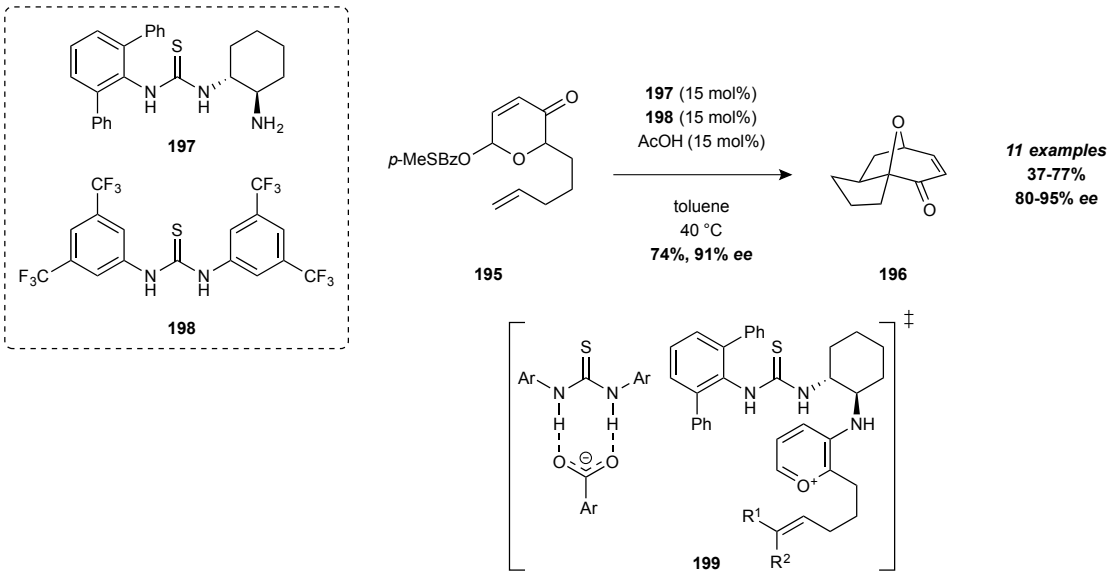


Scheme 3.2. Enantioselective [5+2] cycloisomerisation of alkyne tethered vinylcyclopropanes.

The observed stereoselectivity was rationalised with an empirical model (**193**) of the substrate docked onto the catalyst system. This model was based upon an X-ray crystal structure (**194**) of [Rh(nbd)(*R*,*S*,*S*)-**L1**)] reported by Mezzetti *et al.*,[72] which showed an η^2-complexation of one of the ligand benzylic arene substituents to the metal centre. Replacing the phenyl substituents in (*S*,*R*,*R*)-**L1** with methyl groups resulted in a complete

loss of stereoselectivity (87%, 6% *ee*). Moreover, when the methyl groups of (*S*,*R*,*R*)-**L1** were replaced with phenyl substituents the rate and enantioselectivity were maintained (81%, 99% *ee*). This not only demonstrates the importance of the additional metal-ligand interaction, but also that a chiral amine was not a necessity in achieving stereoinduction.

The last and most recent example, reported by Jacobsen *et al.*,[73] used dual organocatalysis to effect enantioselective oxidopyrilium-based [5+2] cycloaddition of acetoxy pyranones **195** in constructing oxybicyclo [3.2.1] octanes **196** (Scheme 3.3). Condensation of primary aminothiourea **197** with ketone **195** generates a dienamine intermediate. Achiral thiourea **198** then facilitates benzoate abstraction, creating a benzoate•pyrylium ion pair **199**, poised to undergo intramolecular cycloaddition. With this system the authors achieve high levels of stereoinduction, with a wide variety of substrates.

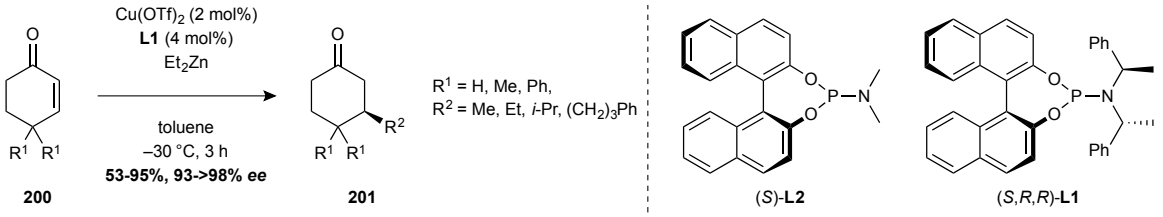


Scheme 3.3. Enantioselective dual catalysis in [5+2] cycloadditions.

For the purposes of the ynamide tethered vinylcyclopropane [5+2] cycloisomerisation, Hayashi's report of rhodium/phosphoramidite catalyst systems is of most relevance and interest, and forms a starting point for our research on the reaction of ynamides.

3.1.2 Phosphoramidite ligands – synthesis and applications

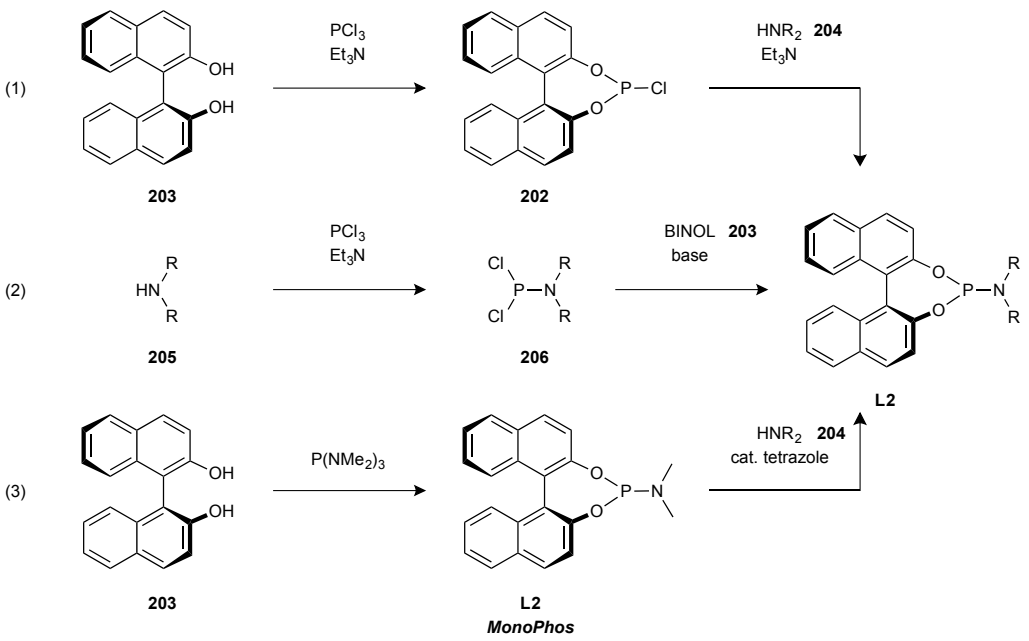
Feringa *et al.* first introduced phosphoramidite ligands in 1994, alongside phosphortriamides, as possible chiral derivatising agents for the ^{31}P NMR spectroscopic determination of *ee*.[74] In the event, they were found to be unreactive with respect to nucleophilic attack by alcohols or amines. However, it was noted that they showed promise as chiral ligands, though the asymmetric catalysis community had long overlooked these species due to their perceived relative instability. The Feringa group later reported a study of enantioselective 1,4-addition reactions of alkylzinc reagents and α,β-unsaturated cyclic ketones **200**, catalysed by copper/phosphoramidite complexes (Scheme 3.4).[71,75] Whilst it was found that phosphoramidite ligands such as (*S*)-**L2** catalysed these reactions with moderate levels of stereoselectivity (55-90% *ee*), it was discovered that phoshoramidite (*S*,*R*,*R*)-**L1** containing two chiral groups, (*R*,*R*)-bis(1-phenylethyl)amine and (*S*)-BINOL, greatly enhanced the level of stereocontrol. The ketone products **201** were obtained in good to high yields and excellent enantioselectivities (93-98% *ee*). This was the first demonstration of the power and potential of these hitherto unexplored monodentate phosphine ligands. In the intervening twenty years, phosphoramidites have become a truly privileged class of ligand.



Scheme 3.4. Enantioselective 1,4-addition.

Three main synthetic routes to phosphoramidites **L3** are in common usage (Scheme 3.5).[76,77] The most frequently used of these involves initial formation of chlorophosphite **202** by reaction of a diol **203** and phosphorous trichloride (Eq. 1), followed by addition of

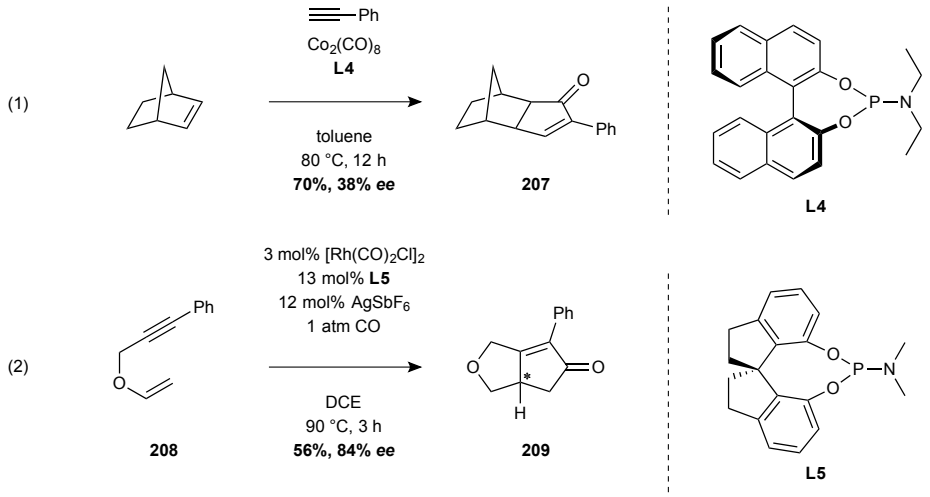
the amine **204** with a base.[71] For more sterically hindered amines **205**, the dichloroamino phosphine **206** is first synthesised with the desired amine **205** and phosphorous trichloride (Eq. 2). The diol **203** is subsequently added to **206** with base.[78] The third pathway begins with formation of commercially available phosphoramidite ligand MonoPhos **L2**, by addition of BINOL **203** to hexamethylphosphorous triamide (Eq. 3).[74] The dimethylamine unit of **L2** can then be substituted with another amine **204**, using tetrazole as a catalyst. The modular nature of phosphoramidite synthesis allows incorporation of a variety of diol and amine moieties. This enables the rapid and facile assembly of ligand libraries, and this has been applied in automated parallel synthesis and screening techniques.[79]



Scheme 3.5. Synthesis of phosphoramidites.

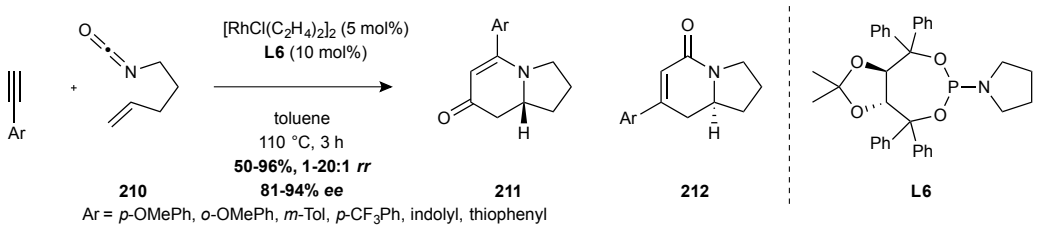
Phosphoramidites have been widely adopted by the synthetic community and are now used in a variety of transformations including allylic substitution, asymmetric hydrogenation, C-H activation, and cross-coupling reactions. However, perhaps the most relevant for our purposes is their use in cycloisomerisation chemistry. The first application in this context was a [2+2+1] Pauson-Khand cycloisomerisation reported by Gimbert *et al.* in 2004

(Scheme 3.6, Eq. 1).[80] The authors used stoichiometric cobalt catalyst [$Co(CO)_8$], in combination with **L4** to effect formation of **207** in good yield but a modest 38% *ee*. Zhou *et al.* followed this in 2005, with a rhodium/phosphoramidite-catalysed variant of the reaction (Eq. 2),[81] where enyne **208** underwent cycloisomerisation using spirocyclic ligand **L5**, giving bicyclic products **209** in modest yield but with high enantioselectivity (56%, 84% *ee*).



Scheme 3.6. Pauson-Khand reactions.

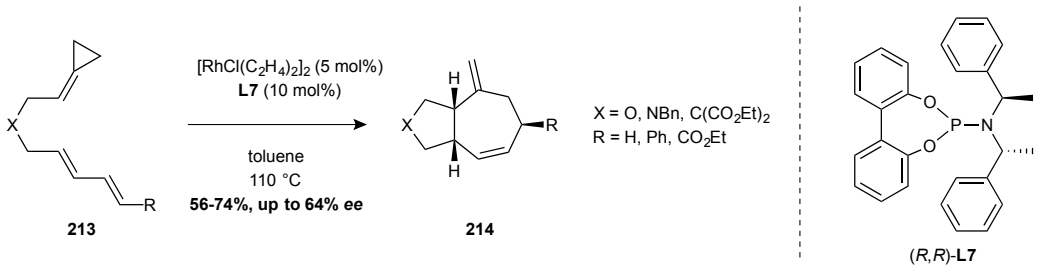
Rovis *et al.* later reported the use of phosphoramidites in forming six-membered heterocycles *via* rhodium-catalysed intermolecular [2+2+2] reactions of alkenyl isocyanates **210** and terminal alkynes (Scheme 3.7).[82] Here, the TADDOL-derived phosphoramidite ligand **L6** effectively catalysed the reaction to give enantioenriched dihydropyridones **211**.



Scheme 3.7. Intermolecular asymmetric [2+2+2] cycloisomerisation.

It was found that electron deficient terminal alkynes gave higher ratios of the lactam products **212**, which were obtained with equally high levels of enantioselectivity, but with the opposite bridgehead stereochemistry.

This was followed by a report of seven-membered ring formation *via* intramolecular [4+3] cycloisomerisation of akylidene cyclopropanes **213** catalysed by palladium/phosphoramidite systems, by Mascareñas *et al.* (Scheme 3.8).[83] The bicyclic products **214** were generally obtained in good yield but with only moderate enantioselectivity, using the biphenyl variant (R_c,R_c)-**L7** of the Feringa ligand (S_a,R_c,R_c)-**L1**. Due to free rotation about the biphenyl C–C bond, the ligand can adopt one of two possible diastereomers in the transition state, which may be the cause of the relatively poor observed enantioselectivity, although these ligands often display high levels of enantioselectivity in other reactions.[78,84]



Scheme 3.8. Enantioselective intramolecular [4+3] cycloisomerisation.

3.2 Enantioselective ynamide [5+2] cycloisomerisation

Ynamide vinylcyclopropanes have been shown to undergo rapid and highly diastereo- and regioselective cycloisomerisation. We were excited by the prospect of rendering this transformation asymmetric, and as such set about exploring the reaction conditions described for alkyne [5+2] cycloisomersation.

3.2.1 Ligand screen

Ynamide vinylcyclopropane **120a** was again chosen as a test substrate for reaction optimisation, using a selection of phosphorous ligands **L1** and **L8-11** under rhodium catalysis (Figure 3.1). Initial investigation with Wender's rhodium/(*S*)-BINAP complex gave no reaction.[29] However, we quickly found reactivity with the rhodium/phosphoramidite catalyst system optimised by Hayashi for the alkyne [5+2] cycloiomerisation.[30] Excitingly, use of the 'Feringa ligand' (*S*,*R*,*R*)-**L1** led to complete reaction in 15 minutes at room temperature, and gave the product (–)-**125a** in quantitative yield and 98% *ee*. The alternative diastereomer of ligand (*R*,*R*,*R*)-**L1** gave the opposite enantiomer of product but with significantly longer reaction time, and lower enantioselectivity (55% *ee*). From this we deduced that for our system (S_a,R_c)- ligands resulted in the 'matched', and (R_a,R_c)- in the 'mismatched' scenario, and also that the BINOL unit was ultimately responsible for stereodiscrimination. This was further evidenced by the use of phosphoramidites possessing achiral amine moieties: the *bis*-benzylamine derived ligand (*S*)-**L8** gave the desired product (–)-**125a** in poor yield after 20 hours, but still exerted a moderate level of enantioselectivity (64% *ee*). Ligand (*S*)-**L9**, developed by the Fletcher group for asymmetric 1,4-addition reactions,[85] gave the product in high yield and excellent enantioselectivity. It was found that the bulkier naphthyl analogue of this ligand (*S*)-**L10** only served to decrease both the rate and selectivity of the

reaction compared to (*S*)-**L9**. Interestingly, the semi-hydrogenated BINOL derived ligand (*S*,*R*,*R*)-**L11** gave almost no stereoselectivity (7% *ee*), which demonstrates the necessity for the fully-unsaturated BINOL unit.

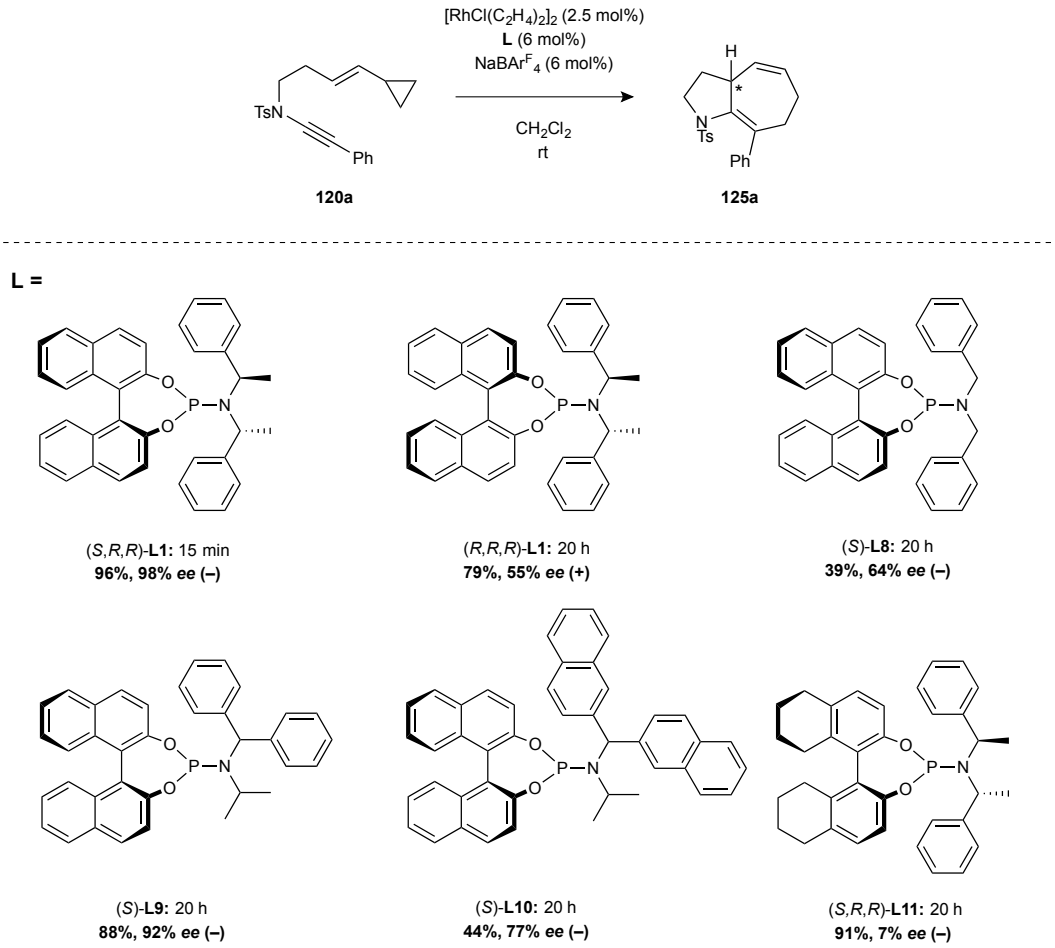


Figure 3.1. Asymmetric [5+2] cycloisomerisation of **120a**: ligand screen.

3.2.2 Ligand optimisation: hypothesis and synthesis

Phosphoramidite ligand (*S*,*R*,*R*)-**L1** had been found to be highly effective in the enantioselective ynamide [5+2] cycloisomerisation of **120a**. However, forays with other substrates suggested that this ligand might not meet our requirements in more challenging settings. We therefore set about designing a novel catalyst system which would be based initially on the Hayashi empirical model (Fig. 3.2).[30] In this model, the rhodium-arene interaction is proposed to be crucial for stereoselectivity.

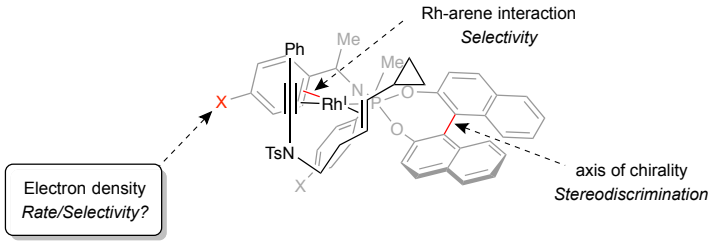


Figure 3.2. Hayashi empirical model for stereoselectivity.

Weller *et al.* recently reported a study of binding affinities of fluorinated benzene ligands in cationic rhodium complexes (Fig. 3.3).[86] It was found that as the number of fluorine substituents on the arene increases, the strength of the metal-arene bond decreases, with C_6H_5F having a binding affinity of 14 kJmol^{-1} (compared to a benzene standard of >25 kJmol^{-1}). We decided to investigate the effect of changes in electron density of the arene substituents, of the amine component, on the strength of the metal-arene bond and thus on the rate and selectivity of the reaction.

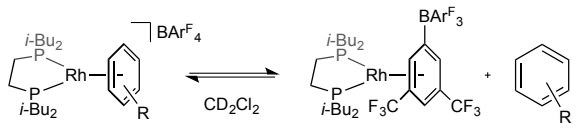
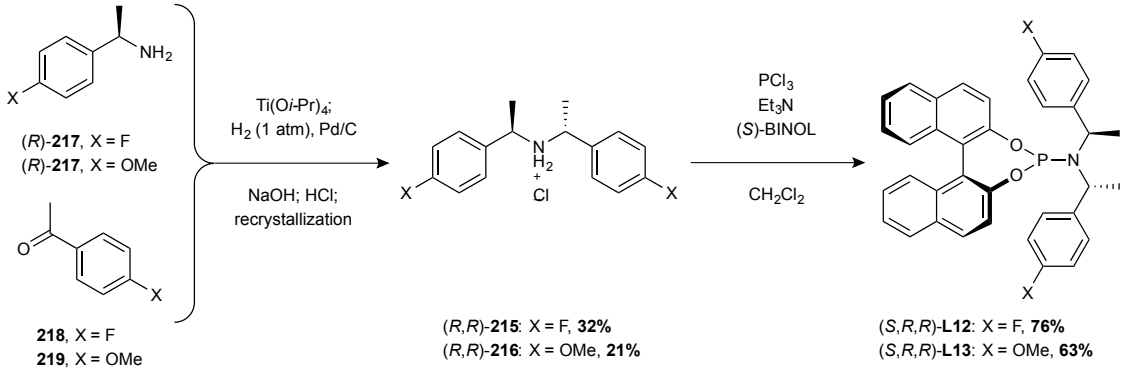


Figure 3.3. Weller rhodium-arene complex equilibrium.

Phosphoramidite ligands (*S*,*R*,*R*)-**L12** (novel) and (*S*,*R*,*R*)-**L13** (known), bearing *p*-fluoro and *p*-methoxy substituted phenyl groups respectively, were thus targeted (Scheme 3.9). Firstly, enantio- and diastereomerically pure amines (*R*,*R*)-**215** and (*R*,*R*)-**216** were prepared *via* a diastereoselective reductive amination with commercially available enantioenriched amines (*R*)-**217** and (*R*)-**218**, and the corresponding ketones **219** and **220**.[87] ^{1}H NMR spectroscopic analysis of the crude reductive amination reaction mixtures showed a 9:1 *dr* in both cases, subsequent recrystallization of the amine hydrochloride salts gave the secondary amines (*R*,*R*)-**215** and (*R*,*R*)-**216** in >99:1 *dr*. Formation of phosphoramidites (*S*,*R*,*R*)-**L12** and (*S*,*R*,*R*)-**L13** was achieved by addition of (*S*)-BINOL to

the dichloroamino phosphines, generated *in situ* from reaction of amines (*R*,*R*)-**215** and (*R*,*R*)-**216** with phosphorous trichloride.[85] Due to product sensitivity with respect to oxidation, rapid filtration and purification on silica was required to obtain (*S*,*R*,*R*)-**L12** and (*S*,*R*,*R*)-**L13** in good yield.

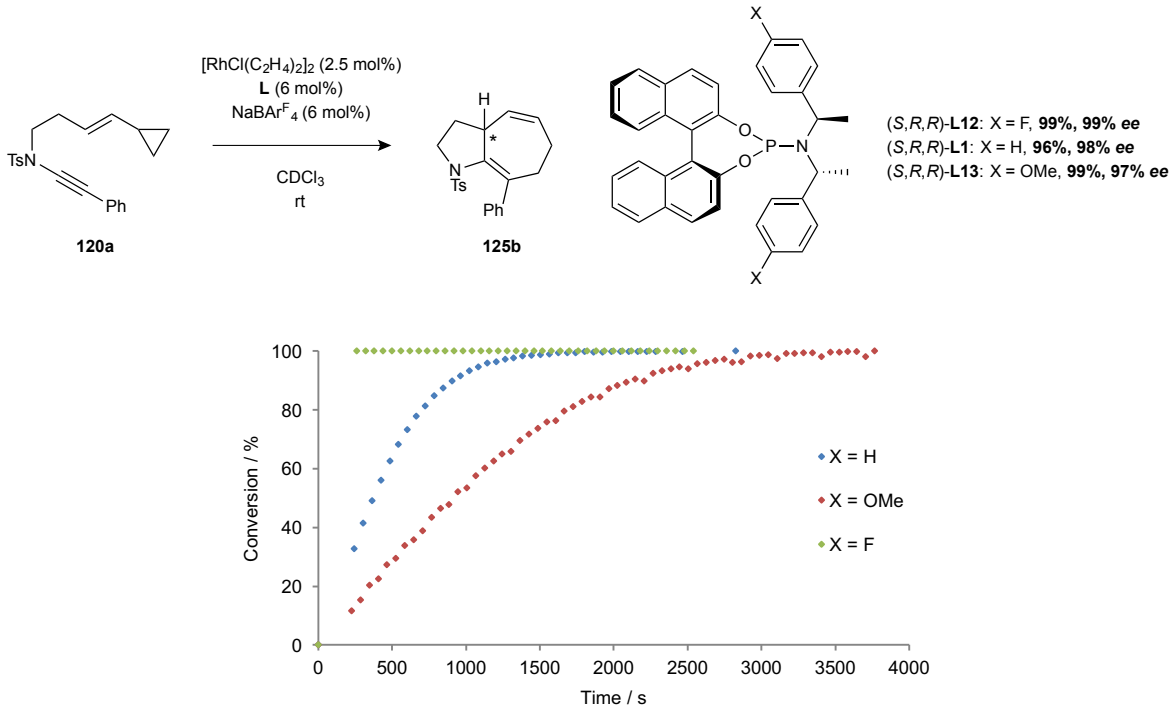


Scheme 3.9. Synthesis of phosphoramidite ligands (*S*,*R*,*R*)-**L12** and (*S*,*R*,*R*)-**L13**.

3.2.3 Ligand optimisation: results

Phosphoramidite ligands (*S*,*R*,*R*)-**L12** and (*S*,*R*,*R*)-**L13** were next tested in the [5+2] cycloisomerisation of enynamide **120a**, in comparison with (*S*,*R*,*R*)–**L1**, with the reaction rates monitored by ^{1}H NMR spectroscopy (Scheme 3.10). To our delight, it was discovered that changes in electron density of the ligand aryl group indeed have a marked influence on both the rate and enantioselectivity of the reaction. The electron poor *p*-fluorinated ligand (*S*,*R*,*R*)-**L12** gave the product in quantitative yield and 99% *ee*, in under four minutes[ii] at room temperature in deuterated chloroform (*cf.* Feringa ligand (*S*,*R*,*R*)-**L1**, 30 minutes, 96% yield, and 98% *ee*). In contrast, the electron rich *p*-methoxy substituted ligand (*S*,*R*,*R*)-**L13** displayed an equal and opposite effect, with the reaction taking one hour to reach completion, and the product obtained in 97% *ee*.

[ii] The reaction reached completion before the first ^{1}H NMR experiment at T = 180 s had finished.

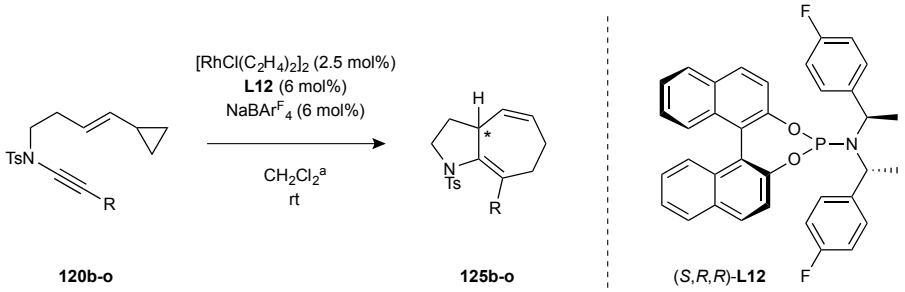


Scheme 3.10. Enantioselective [5+2] cycloisomerissation of **120a**: ligand substituent effect.

3.2.4 Scope of the enantioselective [5+2] cycloisomerisation

With an optimised catalyst system in hand, the scope of the enantioselective reaction could be explored (Table 3.1). A range of ynamide vinylcyclopropanes **120b-o** varying in ynamide substituent, were submitted to the optimised reaction conditions. Much to our delight, the potent activity of ligand (*S*,*R*,*R*)-**L12** extended to a variety of alkyl- and aryl-substituted ynamides. The heterocyclic products **125b-d** and **125h-n** were obtained in all cases in under 30 minutes, in high yields, and with excellent levels of enantioselectivity (94-99% *ee*). Furthermore, synthesis of product **125b** could be achieved on a 1 mmol (374 mg) scale in less than 5 minutes, with 1.25 mol% catalyst loading (Entry 1, see Experimental section for details).

Table 3.1. Scope of the enantioselective ynamide [5+2] cycloisomerisation.

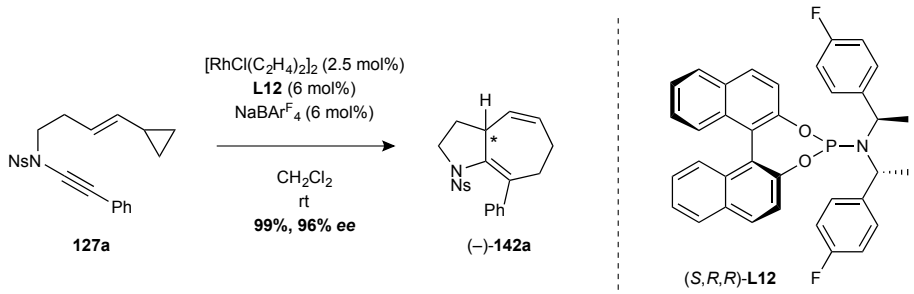


Entry	Substituent		Time	Yield	*ee*	Entry	Substituent		Time	Yield	*ee*
1[b]	*n*-Hex	**125b**	5 min	80%	99%	8	Me	**125i**	5 min	94%	98%
2	Cl	**125c**	15 min	85%	97%	9	Ph	**125j**	5 min	99%	98%
3	OTBS	**125d**	15 min	96%	96%	10	F	**125k**	5 min	98%	99%
4[c]	TIPS	**125e**	20 h	-	-	11	Cl	**125l**	5 min	99%	99%
5	NTs	**125f**	20 h	91%	-[d]	12	Cl	**125m**	5 min	89%	98%
6	TsN	**125g**	7 h	95%	0%	13	CF_3	**125n**	5 min	88%	98%
7	OMe	**125h**	30 min	77%	94%	14[c]	CN	**125o**	20 h	-	-

a. Reactions were performed at 0.1 M substrate. b. Reaction performed on 1 mmol scale with 1.25 mol% $[RhCl(C_2H_4)_2]_2$. c. No reaction was observed. d. Not determined.

The effect of ynamide substituent electron density on the rate of reaction, as observed in the racemic [5+2] cycloisomerisation, was also detected here. Ynamides **120k-n** with electron-withdrawing aryl substituents (Entries 10-13) were found to react significantly faster than those with electron-donating substituents **120h** and **120i** (Entries 7 and 8). In this case this effect was less pronounced as accurate monitoring of reaction rates became difficult below 5 minutes. Enynamides **120e** and **120o** failed to react under the reaction conditions, as in the racemic reaction (Entries 4 and 14). Heterocycle-substituted ynamides

120f and **120g** required extended reaction times, and whilst the enantiomeric excess of **125f** could not be determined (Entry 5),[iii] reaction of **120g** was found to give product **125g** as a racemic mixture (Entry 6). The increased steric encumbrance of the heterocyclic ynamide substituents may have prevented the catalyst system from developing the transition state required to achieve enantioselectivity. Nosyl ynamide **127a** was also found to undergo rapid, enantioselective [5+2] cycloisomerisation to give (–)-**142a** in excellent yield and 99% *ee* (Scheme 3.11).



Scheme 3.11. Asymmetric [5+2] cycloisomerisation of **127a**.

Substrates **128a**, **132a** and **136**, with variations to the tether, were also submitted to the asymmetric reaction conditions (Fig. 3.4). Unsurprisingly, **128a** and **132a**, which were unreactive with the achiral catalyst, were also found to be unreactive under these conditions. Disappointingly, this was also true of aryl-tethered enynamide **136**. This is perhaps due to the rigidity of the arene tether again preventing the substrate from adopting the favoured docking orientation with the catalyst system.

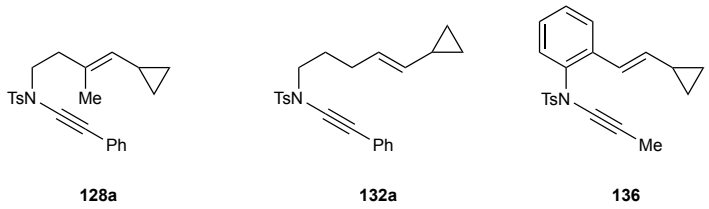


Figure 3.4. Failed asymmetric [5+2] cycloisomerisation substrates.

[iii] The two enantiomers of product could not be separated by HPLC.

3.3 Conclusions

Using rational ligand design, we have developed a highly potent and selective catalyst system for the asymmetric ynamide [5+2] cycloisomerisation. This system has been applied to a broad range of enynamide substrates, giving an array of enantioenriched heterocyclic products.

In the process of ligand optimisation, we discovered an interesting effect of the aryl substituent electronics on the rate and selectivity of the reaction. In order to gain a mechanistic explanation for this relationship, and develop catalyst systems further we undertake a theoretical reaction analysis in Chapter 4.

Given the performance of these ligand systems, and the strength of the substrate preference in the diastereoselective reaction, how would the catalyst fair in a mismatched scenario with an enantioenriched substrate (Chapter 5)?

4 Mechanism of the [5+2] cycloisomersation

4.1 Introduction

Theoretical reaction analysis is a powerful tool for the elucidation of reaction mechanisms. Recent advances in computational methods have led to this approach becoming increasingly popular with the synthetic community.[88] In the context of alkyne vinylcyclopropane [5+2] cycloisomersations, a number of computational studies have been undertaken in an attempt to elucidate the reaction mechanism and explain empirical observations of reactivity and selectivity with a variety of metal catalysts.

4.1.1 [5+2] Cycloisomerisation computational studies

Wender and Trost have proposed two possible mechanistic pathways for the alkyne [5+2] cycloisomerisation, as discussed in Chapter 1 (Figure 4.1). In order to identify the precise mechanisms by which these systems operate, the Houk group have used Density Functional Theory (DFT) calculations to study a number of [5+2] reactions. The first of these was the rhodium-catalysed intermolecular [5+2] cycloisomerisation, in collaboration with the Wender group.[89] The rate-determining step (RDS) in the metallacyclopentene pathway (**A**) was found to be the oxidative coupling of **47** ($\Delta G^{\ddagger}$ = 28.1 kcal mol^{-1}), whilst for the vinylcyclopropane pathway (**B**) it is the migratory insertion of **52** ($\Delta G^{\ddagger}$ = 20.3 kcal mol^{-1}). For this system, it was thus calculated that pathway **B** was preferred by 7.8 kcal

mol^{-1}, which was attributed to the unfavourable orientation of the alkene and alkyne required to achieve oxidative coupling of **47**. In a later study, the Houk group turned their attention to the nickel-catalysed intramolecular reaction. Here the activation barrier to the RDS (oxidative addition) in pathway **B** was discovered to be twofold. In the ground state complex (**51**), both the alkene and alkyne are coordinated to the metal. In order to achieve oxidative addition, the alkyne must first dissociate from the metal, requiring an initial 24.1 kcal mol^{-1}, after which oxidative addition can occur, requiring an additional 13.2 kcal mol^{-1}. In contrast, the activation barrier to oxidative coupling in **A** was found to be only 20.1 kcal mol^{-1}, resulting in an overall preference for pathway **A** of 17.2 kcal mol^{-1}.

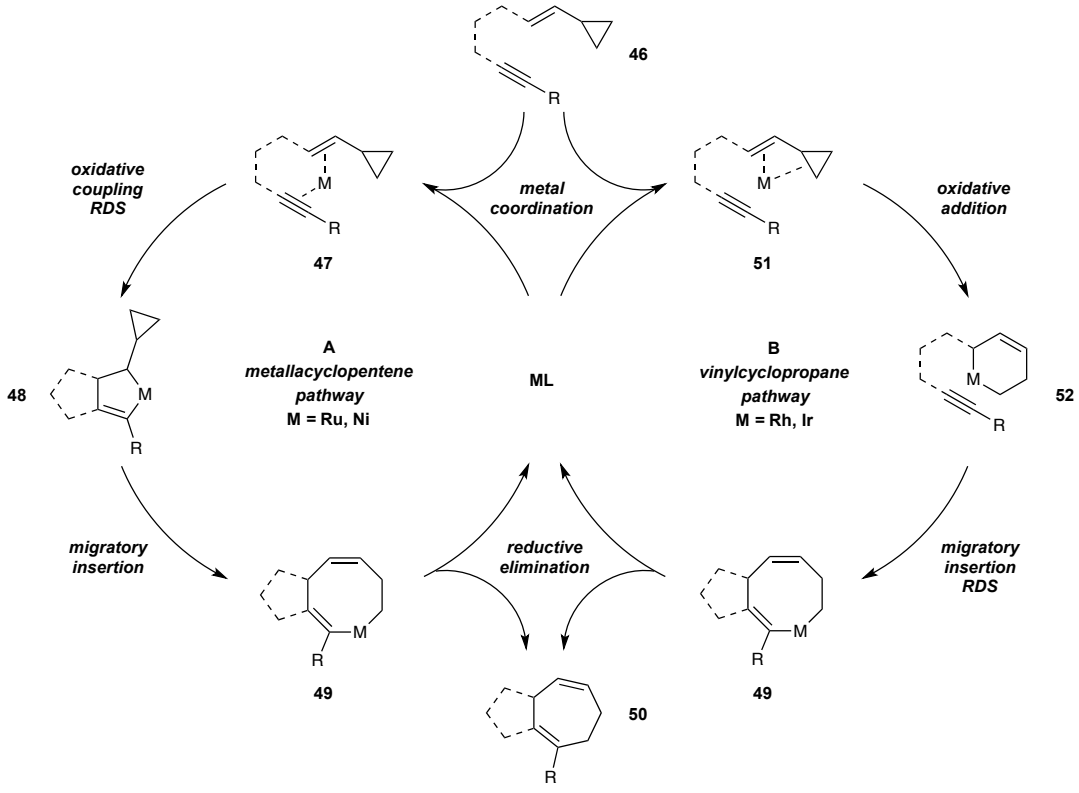


Figure 4.1. Alkyne [5+2] cycloisomerisation catalytic cycles.

Trost and Houk have reported a comprehensive study of the ruthenium-catalysed intramolecular reaction, and the selectivities thereof.[90] Here only a slight preference for the metallacyclopentene pathway (**A**) was calculated. Although the RDSs of these pathways

were in accordance with those of the rhodium-catalysed reaction (oxidative coupling in **A**, and migratory insertion in **B**), the activation energies were found to be almost equivalent ($\Delta G^{\ddagger}_{OC}$ = 13.4 kcal mol^{-1} *vs* $\Delta G^{\ddagger}_{MI}$ = 13.1 kcal mol^{-1}). The preference for pathway **A** was, in fact, due to the relative stabilities of complexes **47** and **52**, the former being 3.4 kcal mol^{-1} lower in energy than the latter.

Most recently Strand *et al.* disclosed the first iridum-catalysed [5+2] cycloisomerisations, and DFT modelling thereof.[24] The authors conducted a direct comparison of [Ir(cod)]$^{+}$ and [Rh(cod)]$^{+}$ complexes in the intermolecular reaction, which showed the iridium-catalysed reaction to be up to 50 times faster. Computational analysis identified pathway **B** to be favoured in the iridium-catalysed reaction due to a prohibitively large activation barrier to oxidative coupling in pathway **A** ($\Delta G^{\ddagger}_{OC}$ = 27.0 kcal mol^{-1} *vs* $\Delta G^{\ddagger}_{MI}$ = 16.0 kcal mol^{-1}). The RDSs for the iridium- and rhodium-catalysed reactions were found to be comparable in energy. The difference in rate of reaction was attributed to a smaller 'free energy span' (δE)[iv] for iridium (16.03 kcal mol^{-1}) compared to that of rhodium (28.2 kcal mol^{-1}).[91]

It is clear from these computational studies that subtle differences in both the substrate and the metal catalyst have profound effects on the reaction mechanism, and can therefore affect its outcome.

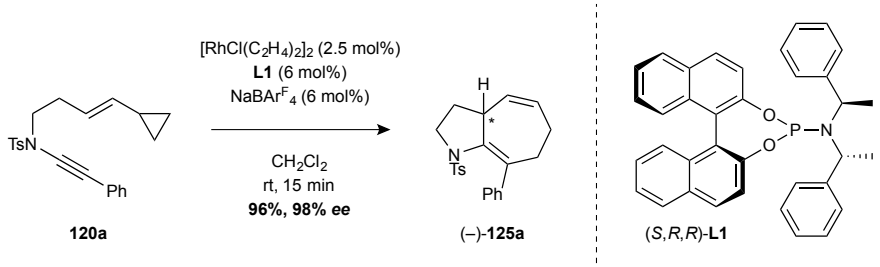
[iv] 'Free energy span' (δE) refers to the free energy difference between the point of lowest energy and that of highest energy along the energetic path of the catalytic sequence.

4.2 Theoretical reaction analysis

In the process of developing the asymmetric [5+2] cycloisomerisation of ynamide vinylcyclopropanes we discovered a powerful effect of ligand electronics on the rate and selectivity of the reaction. We were intrigued by the energetic rationale for this observed effect, and as such undertook a theoretical reaction analysis in collaboration with the Paton group.[v]

4.2.1 Transition state optimisation

We chose to study the [5+2] cycloisomerisation of phenyl substituted vinylcyclopropane **120a** using the 'Feringa ligand' (*S*,*R*,*R*)-**L1** (Scheme 4.1). The first variable considered when calculating the reaction energy profile was the binding orientation of the substrate with the catalyst system. Based upon Hayashi's empirical model (Fig. 4.2, also see Chapter 3), the enynamide substrate can adopt one of four possible orientations relative to the P-(η^2-arene) bidentate phosphoramidite ligand (Table 4.1, **i-iv**). The first of these (**i**) places the alkene proximal to the naphthyl ring, with the ynamide *trans* to the phosphorous atom, and the backbone of the substrate 'down' with respect to the ligand. The second (**ii**) maintains the orientation of the substrate backbone, but switches the position of the alkene to be *trans* to the phosphorous atom.



Scheme 4.1. [5+2] Cycloisomerisation under computational investigation.

[v] All of the computational calculations discussed in this section were performed by Dr Q. Peng.

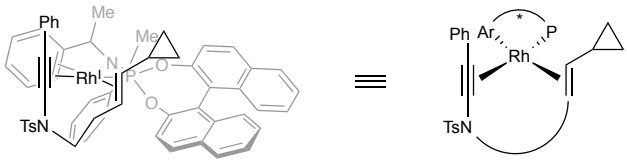
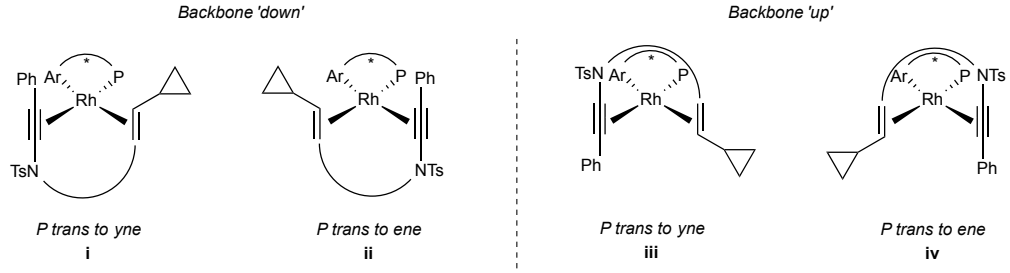


Figure 4.2. Hayashi empirical model binding orientation (**i**).

The final two (**iii** and **iv**) invert the orientation of the substrate backbone, in **i** and **ii**, to be 'up' with respect to the ligand. Each of these four binding modes has two further permutations of vinylcyclopropane position, which correspond to the *Re*- and *Si*-faces. The transition state energies for the rate determining steps in both the metallacyclopentene and vinylcyclopropane pathways were calculated for each of the eight binding orientations.

Table 4.1. Transition state energies of the eight possible binding orientations.[a]



Orientation	Metallacyclopentene pathway		Vinylcyclopropane pathway	
	Re	***Si***	***Re***	***Si***
i	23.6	23.9	29.3	24.5
ii	18.7	31.3	23.0	22.0
iii	23.2	30.7	35.3	41.7
iv	**17.0**	19.7	21.9	24.8

a. Transition state energies (SMD-ωB97XD/6-311+G(d,p)/Lanl2TZ//ωB97XD/6-31G(d)/Lanl2DZ Gibbs free energies) are shown in kcal mol^{-1}, with Q. Peng and R. S. Paton.

In contrast to Hayashi's empirical model (which assumes an enyne orientation as in **i**),[30] the lowest energy orientation (**iv**) was that which placed the backbone of the substrate 'up' with respect to the ligand and the phosphorous *trans*- to the alkene (Fig. 4.3). Notably, in

this orientation the transition states of both pathways favour *Re*-face binding. *Si*-**iv** arises from rotation of the vinylcyclopropane about the C(sp^2)–C(sp^3) bond, resulting in a less favourable backbone conformation. The next lowest energy orientation (**ii**) maintained the binding selectivity of alkene and ynamide, but inverted the backbone position. The two orientations (**i** and **iii**) that placed the ynamide *trans* to the phosphorous were found to be highly unfavourable in both pathways.

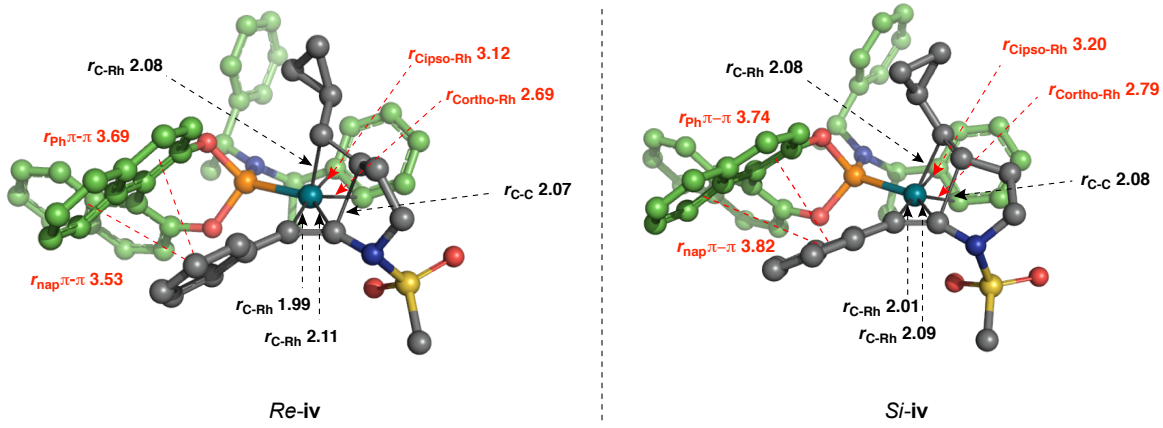


Figure 4.3. Oxidative coupling transtition states (*Re*- and *Si*-**iv**), with Q. Peng and R. S. Paton.

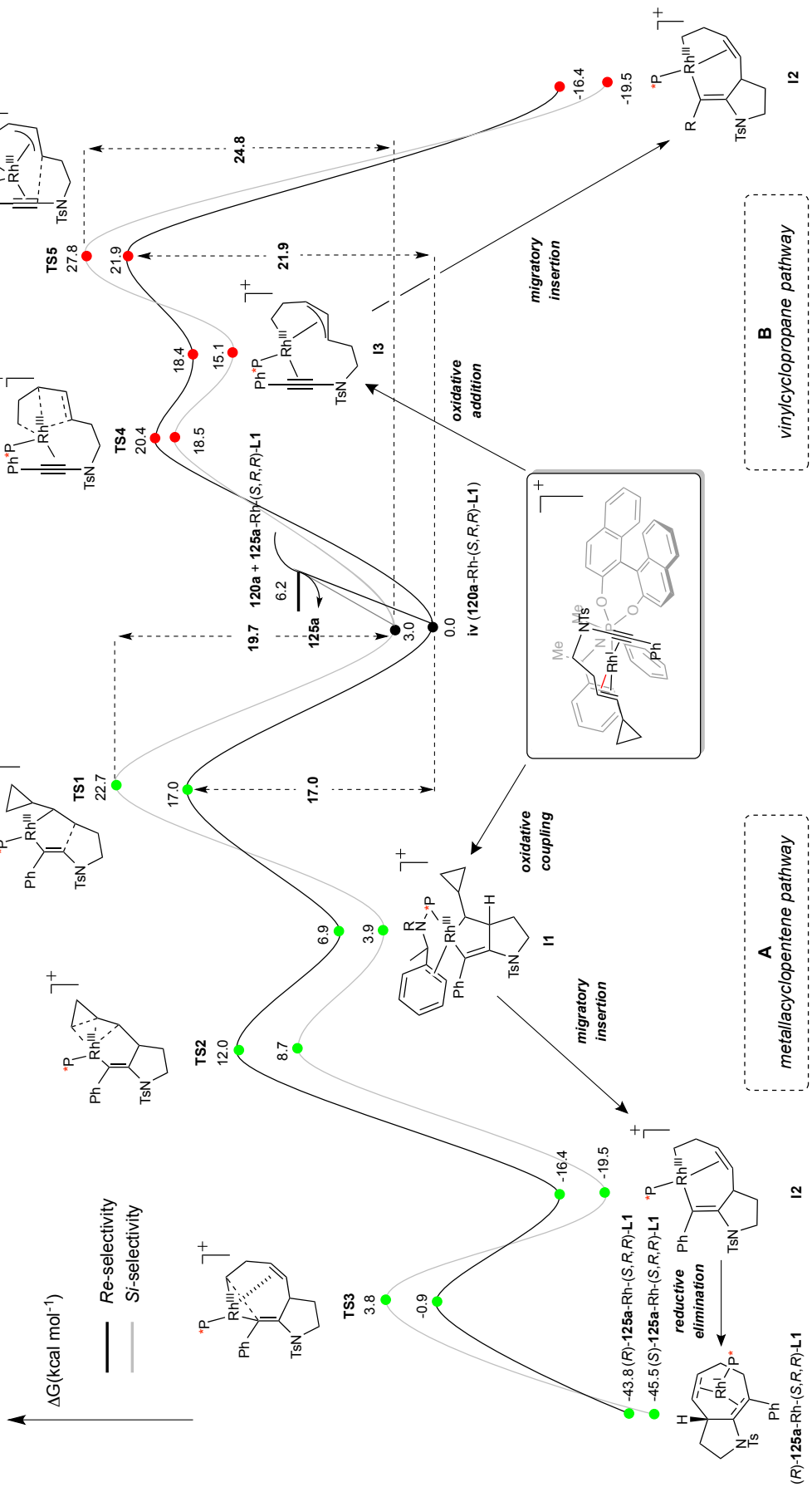
4.2.2 Calculation of reaction energy profile

The two widely accepted mechanistic pathways for the [5+2] cycloisomerisation (see Figure 4.1) were next explored. Using the lowest energy docking orientations (*Re*- and *Si*-**iv**), the energy profiles of the metallacyclopentene (green) and vinylcyclopropane (red) pathways were calculated for the *Re*- (black) and *Si*-selectivities (grey) (Scheme 4.2). The turnover-limiting and stereodetermining step in the metallacyclopentene pathway (**A**) was found to be initial oxidative coupling of the ynamide with the vinylcyclopropane (**iv** to **TS1**, $\Delta G^{\ddagger}_{Re}$ = 17.0 kcal mol^{-1}, $\Delta G^{\ddagger}_{Si}$ = 19.7 kcal mol^{-1}). Migratory insertion of rhodium into the cyclopropane (**I1** to **TS2**), and subsequent reductive elimination (**I2** to **TS3**) gave the product bound to the catalyst complex (**125a**-**Rh**-(*S*,*R*,*R*)-**L1**).

In the vinylcyclopropane pathway, oxidative addition into the vinylcyclopropane (**iv** to **TS4**, $\Delta G^{\ddagger}_{Re}$ = 20.4 kcal mol^{-1}, $\Delta G^{\ddagger}_{Si}$ = 15.5 kcal mol^{-1}) is not rate limiting as the barrier to subsequent migratory insertion is higher in energy still (**I3** to **TS5**, $\Delta G^{\ddagger}_{Re}$ = 21.9 kcal mol^{-1}, $\Delta G^{\ddagger}_{Si}$ = 27.8 kcal mol^{-1}). Reductive elimination of **I2**, *via* the common transition state **TS3**, produced the same complexed product (**125a**-**Rh**-(*S*,*R*,*R*)-**L1**) as in the previous pathway.

Interestingly, *Re*-face binding in the RDS was favoured in both pathways by around 3 kcal mol^{-1} ($\Delta\Delta G^{\ddagger}_{Re/Si}$), giving the product (*R*)-**125a**. When bound to the catalyst system, after reductive elimination, (*R*)-**125a** was found to be 1.7 kcal mol^{-1} higher in energy than (*S*)-**125a**. In addition, the catalyst preferentially binds the substrate **120a** over the product (*R*)-**125a** by 6.2 kcal mol^{-1}. These factors, combined with a free energy profile (**iv** to **125a**-**Rh**-(*S*,*R*,*R*)-**L1**) which is more than 40 kcal mol^{-1} exergonic, support the observed short reaction times at room temperature.

Computational studies of the rhodium-catalysed alkyne [5+2] cycloisomerisation, by Houk and Wender,[89] suggest oxidative addition into the vinylcyclopropane is the first step in the catalytic cycle. Our DFT calculations indicate that, for our system, oxidative coupling of the ynamide and alkene is the preferred reaction pathway by 4-12 kcal mol^{-1} ($\Delta\Delta G^{\ddagger}_{OC/MI}$), depending on the binding orientation. The difference in reaction pathway between the alkyne (Wender) and ynamide (us) may be due to additional stabilisation of the forming Rh(III) intermediate by the electron rich ynamide in the oxidative coupling step.



Scheme 4.2. Theoretical reaction analysis, with Q. Peng and R. S. Paton.

4.2.3 Ligand substituent effect – theory and experiment

Having found the optimal substrate-catalyst docking orientation, and identified the lowest energy reaction pathway, we set about investigating the energetic rationale for the empirical rates and selectivities with different ligand aryl substituents. The oxidative coupling *Re*- and *Si*-face transition state energies with ligands (*S*,*R*,*R*)-**L11-L13** were thus calculated (Fig. 4.4). The *Re*-face selectivity ($\Delta\Delta G^{\ddagger}_{Re/Si}$) for the 'Feringa ligand' (*S*,*R*,*R*)-**L1** was found to be – 2.69 kcal mol^{-1}, which corresponds to a calculated 97.9% *ee*. This was in excellent agreement with the empirical value (98% *ee*, Fig. 4.5). As was observed in the Mezzetti crystal structure,[72] one of the ligand benzyl groups was seen to act as a 2π-electron donor ($r_{\text{Cortho-Rh}}$ = 2.69 Å) to the rhodium metal centre (Fig. 4.3). It was found that the *Re*-face TS with the electron poor *p*-fluoro substituted ligand (*S*,*R*,*R*)-**L12** was lower in energy than that with (*S*,*R*,*R*)-**L1** ($\Delta\Delta G^{\ddagger}_{\mathbf{L12/L1}}$ = – 0.47 kcal mol^{-1}), resulting in a faster rate of reaction. In addition, the *Si*-face TS was higher in energy than that with (*S*,*R*,*R*)-**L1** ($\Delta\Delta G^{\ddagger}_{Re/Si}$ = – 4.56 kcal mol^{-1}), which led to an increased calculated stereoselectivity of 99.9% *ee* (*cf*. expt. 99% *ee*). The opposite effect was observed with the electron rich *p*-methoxy substituted ligand (*S*,*R*,*R*)-**L13** ($\Delta\Delta G^{\ddagger}_{\mathbf{L13/L1}}$ = + 0.76 kcal mol^{-1}, $\Delta\Delta G^{\ddagger}_{Re/Si}$ = – 2.42 kcal mol^{-1}), with a lower calculated rate of reaction and stereoselectivity (96.7% *ee*, *cf*. expt. 97% *ee*).

The calculated and observed trend in reactivity and selectivity (*p*-F-Ph > Ph > *p*-MeO-Ph) was found to be due to electron withdrawing substituents weakening the η^2-arene-rhodium interaction in the TS, as observed by an increased bond length ($r_{\text{Cortho-Rh}}$ = 2.67 Å for (*S*,*R*,*R*)-**L13** *vs* $r_{\text{Cortho-Rh}}$ = 2.70 Å for (*S*,*R*,*R*)-**L12**). This leads to stronger coordination of the substrate alkyne and alkene moieties, which serves to exacerbate unfavourable substrate-complex interactions in the *Si*-face TS for (*S*,*R*,*R*)-**L12**, thus increasing

stereoselectivity. Although tighter substrate binding results in a decrease in the entropy of the system ($\Delta\Delta S^{\ddagger}_{L12/L13}$ = –ve), the overall decrease in TS energy ($\Delta\Delta G^{\ddagger}_{L12/L13}$ = –ve), is a consequence of a much larger decrease in the enthalpy of the system (*i.e.* $\Delta\Delta H^{\ddagger}_{L12/L13}$ is more negative than $\Delta\Delta S^{\ddagger}_{L2/L3}$), due to favourable substrate-complex interactions.

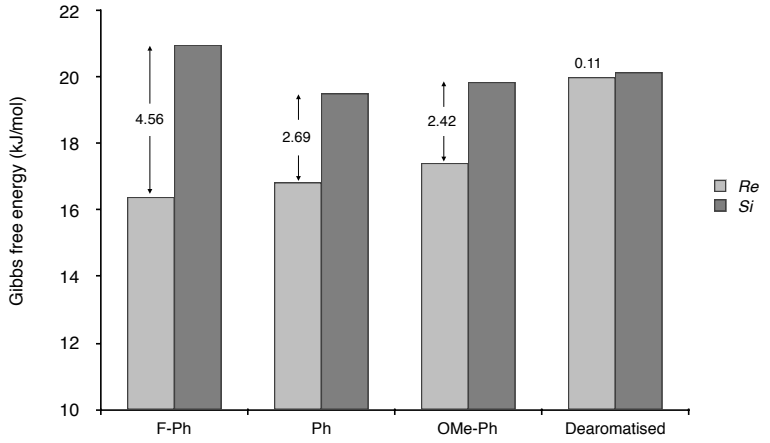


Figure 4.4. Transition state energies with ligand variation, with Q. Peng and R. S. Paton.

The dearomatised-BINOL ligand (*S*,*R*,*R*)-**L11** was calculated to exhibit a significantly lower rate of reaction ($\Delta\Delta G^{\ddagger}_{\mathbf{L11/L1}}$ = + 2.58 kcal mol^{-1}) and stereoselectivity of 9.3% *ee* ($\Delta\Delta G^{\ddagger}_{Re/Si}$ = – 0.11 kcal mol^{-1}), which again correlated well with the experimental values (7% *ee*, 20 hours). This suggests that stabilising dispersive (π-π) interactions between the ligand naphthyl group and the ynamide substituent observed in the (*S*,*R*,*R*)-**L1** TS (r_{nap}π-π = 3.53, r_{Ph}π-π = 3.69) are of high importance.

The excellent correlation between theory and experiment strongly supports our model of stereoinduction. With this in depth knowledge of the relationship between ligand electronics and transition state energies we have a strong basis with which to confidently design further ligand systems.

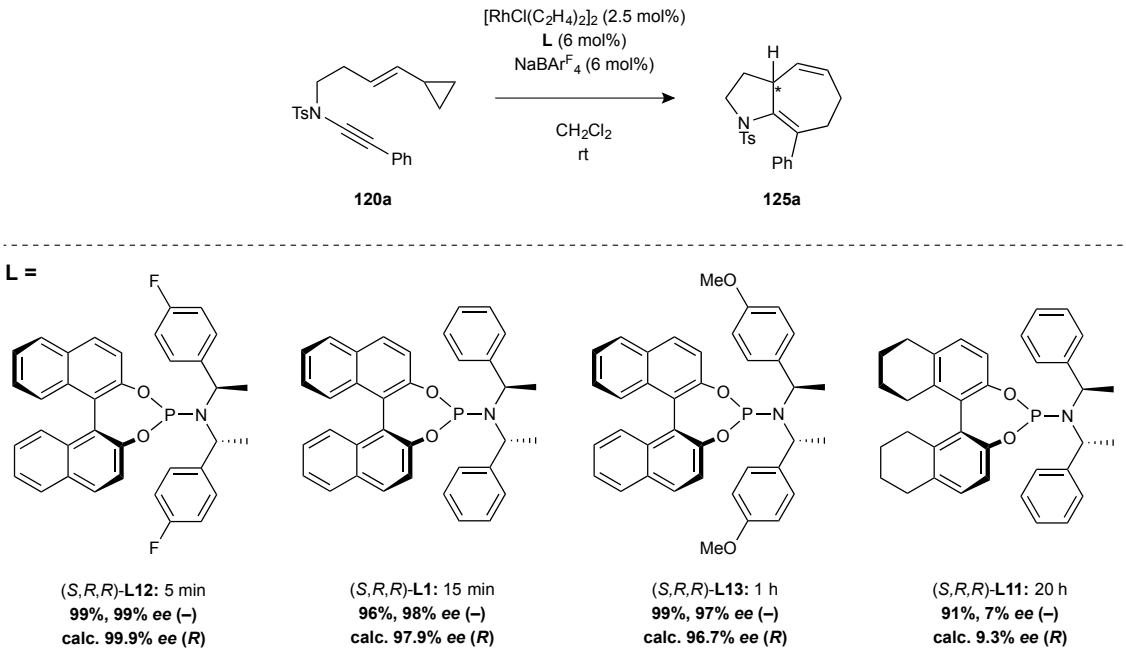


Figure 4.5. Ligand results: calculated *vs* experimental, with Q. Peng and R. S. Paton.

4.3 Conclusions

Using theoretical reaction analysis, we discovered a new mechanistic pathway for rhodium-catalysed [5+2] cycloisomerisations. Ynamides have been found to favour oxidative coupling with the alkene over oxidative addition into the vinylcyclopropane, as is observed in ruthenium-catalysed alkyne [5+2] cycloisomerisations. This allowed the rationalisation of ligand substituent effects on the rate and selectivity of the reaction has been elucidated.

The final goal of the project was to examine the potential of these ligand systems in more challenging settings, where single enantiomer substrates are converted to diastereomeric products in double stereodifferentiating cycloisomerisations (Chapter 5). This raises the question of whether the same principles of ligand design apply, and whether ligands that lead to high enantioselectivity also confer high diastereoselectivity?

5 Double stereodifferentiation in [5+2] cycloisomerisations

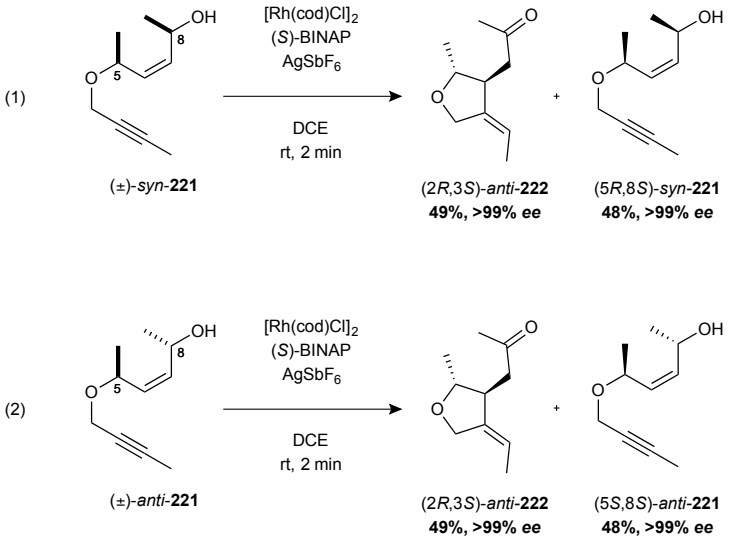
5.1 Introduction

Enantioselective synthesis, the interaction of a chiral reagent with an achiral substrate to yield an enantioenriched product, forms the backbone of modern organic chemistry. Double stereodifferentiation (or 'double asymmetric synthesis'),[92] the process whereby a chiral reagent competes with a chiral substrate in a diastereoselective manner, is an area of particular interest to the asymmetric catalysis community.[93,94] The outcome of these transformations depends not only on the effectiveness of the catalyst system, but also on the strength of the inherent substrate stereocontrol. The term 'matched' refers to the catalyst/substrate combination where their senses of stereoinduction are reinforcing. 'Mismatched' refers to the alternative scenario, where the catalyst and substrate compete with opposing senses of stereoinduction.

5.1.1 Double stereodifferentiating cycloisomerisations

Given the relatively limited number of asymmetric cycloisomerisation examples in the literature,[68–70] it is perhaps unsurprising that there are very few reports of double stereodifferentiation and indeed no examples in [5+2] cycloisomerisations thus far. The first example of double stereodifferentiation in cycloisomerisation was reported by Zhang *et al.*, where substituted 1,6-enynes were converted to diastereomeric tetrahydrofurans (Scheme 5.1).[95] The authors subject a racemic substrate (±)-*syn*-**221** to a single enantiomer

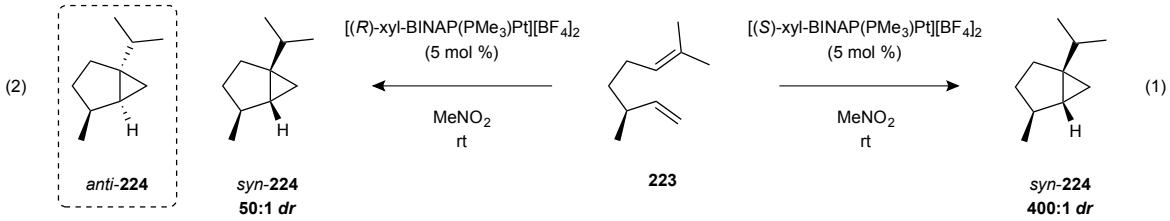
rhodium/BINAP catalyst, achieving a kinetic resolution, and yielding enantiomerically enriched (2*R*,3*S*)-*anti*-**222** and resolved (5*R*,8*S*)-*syn*-**221** (Eq.1). Here the inherent substrate diastereoselectivity is such that the mismatched enantiomer of substrate does not undergo cycloisomerisation, and therefore the resolution is possible. Reaction of the *anti*-diastereomer of substrate (±)-*anti*-**221** also resulted in formation of (2*R*,3*S*)-*anti*-**222**, thus enabling isolation of enatiomerically enriched (5*S*,8*S*)-*anti*-**221**. It is apparent from this that the C-5 stereogenic centre is ultimately stereodetermining. The major limitation here is the inability to perform the mismatched reaction, and thus synthesise the alternative diastereomer of product *syn*-**222**.



Scheme 5.1. Double stereodifferentiation cycloisomerisation: kinetic resolution.

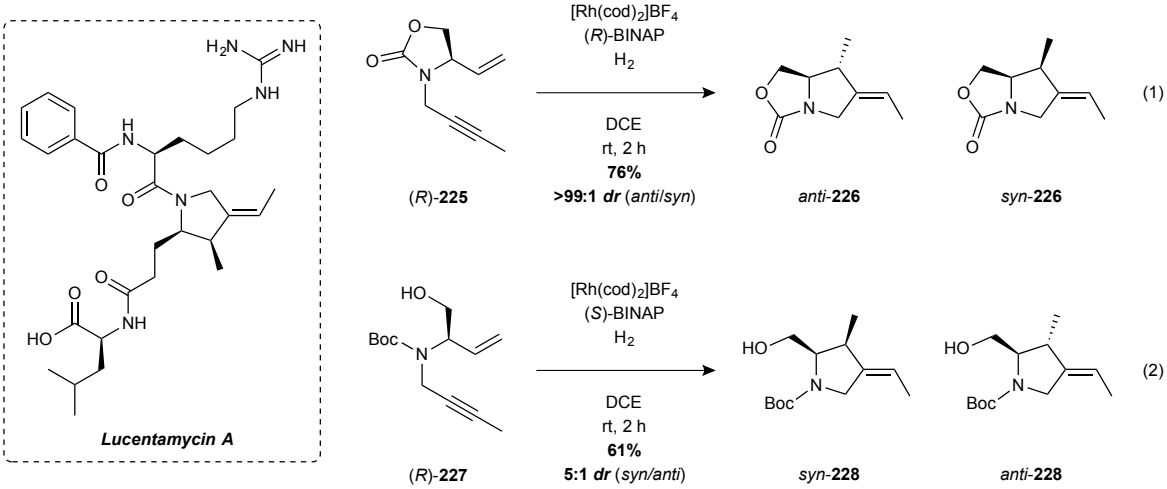
Gagné *et al.* were the first to submit a single enantiomer substrate to both enantiomers of catalyst separately, in their report of 1,6-diene cycloisomerisation (Scheme 5.2).[96] Reaction of enantioenriched **223** with an achiral catalyst gave *syn*-**224** in a 57:1 *dr*, indicating a strong substrate diastereoselectivity. When subjected to the matched/(*S*) enantiomer of platinum(II)/xyl-BINAP catalyst, the substrate preference was reinforced, giving the product *syn*-**224** with 400:1 *dr* (Eq. 1). However, the mismatched/(*R*) enantiomer of

catalyst was unable to override the substrate preference, and only served to reduce the rate of reaction (compared to that with (*S*)-xyl-BINAP) and the *syn*-**224** product *dr* to 50:1 (Eq. 2). It was therefore not possible to form the alternative diastereomer of product (*anti*-**224**).



Scheme 5.2. 1,6-Diene cycloisomerisation: matched vs mismatched.

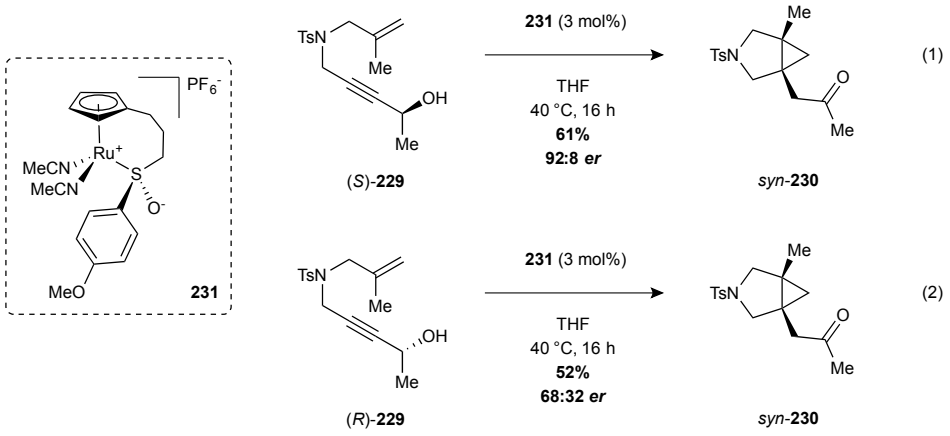
More recently, Sim *et al.* reported the synthesis of lucentamycin A and its stereoisomers using double stereodifferentiating reductive cyclisations of 1,6-enynes (Scheme 5.3).[97] The authors found it was possible to synthesise all four stereoisomers of product with judicious choice of substrate and catalyst. In the cyclic form, substrate (*R*)-**225** exhibited a strong preference for the *anti*-**226** product using (*R*)-BINAP (Eq. 1), while reaction with (*S*)-BINAP to form *syn*-**226** did not proceed. However, it was discovered that the acyclic 1,6-enyne (*R*)-**227** had little to no substrate diastereoselective preference; reaction with racemic BINAP catalyst gave a 1:1 mixture of *syn*-**228** and *anti*-**228** products.



Scheme 5.3. Reductive cyclisation of 1,6-enynes.

The *syn*-**228** product could therefore be synthesised from (*R*)-**227** using (*S*)-BINAP, albeit with a modest 5:1 *dr*. The enantiomers of *anti*-**226** and *syn*-**228** were also synthesised, using (*S*)-**225** and (*S*)-**227** and the corresponding antipodes of catalyst.

The most recent report, by Trost *et al.*, concerns asymmetric redox cycloisomerisation of 1,6-enynes **229** to [3.1.0]-bicycles *syn*-**230** using a ruthenium/chiral sulfoxide catalyst **231** (Scheme 5.4).[98] When performed in acetone, racemic propargyl alcohol *rac*-**229** underwent highly stereoselective cycloisomerisation, to give bicyclic product *syn*-**230** with a high enantiomeric ratio (94:6 *er*). However, mechanistic studies showed that a significant matched/mismatched effect was exhibited by single enantiomer substrates when the reactions were performed in THF. Reaction of (*S*)-**229** gave *syn*-**230** with 92:8 *er*, whilst (*R*)-**229** gave the same product with only 68:32 *er*. Notably in this case, the stereocontrolling stereogenic centre is destroyed during the cyclisation.



Scheme 5.4. Asymmetric redox cycloisomerisation of 1,6-enynes.

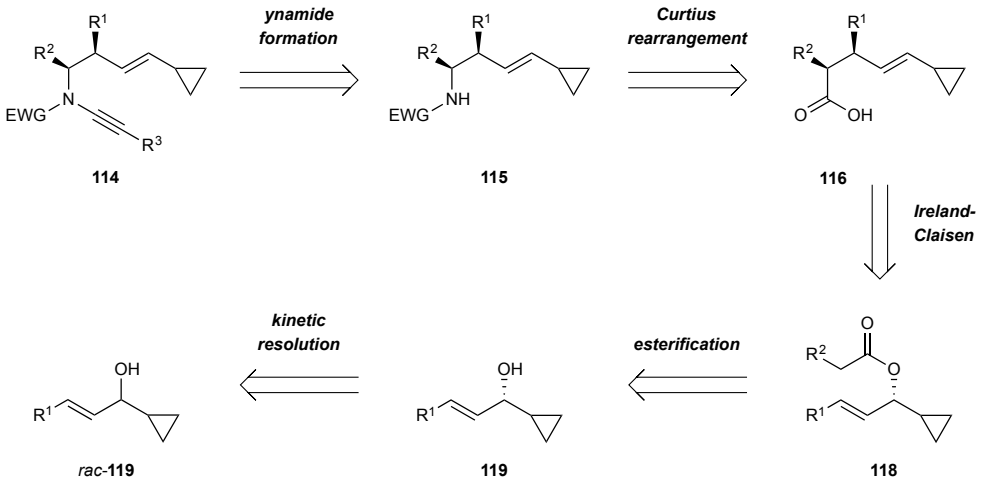
Although these examples begin to address the concept of double stereodifferentiation in cycloisomerisation, there has not yet been a report where a chiral catalyst succeeds in overriding a strong substrate diastereoselectivity preference in an enantiospecific and diastereoselective process.

5.2 Double stereodifferentiation in ynamide [5+2] cycloisomerisation

Given the ability of our novel catalyst system to effect enantioselective ynamide [5+2] cycloisomerisations, we were excited to discover how it would fare in a double stereodifferentiating setting. We envisioned the use of single enantiomer enynamides, which bore substituents at various positions in the tether, in order to assess the effect of differing inherent substrate diastereoselectivity on the outcome of the reaction.

5.2.1 Synthesis of enantioenriched substrates

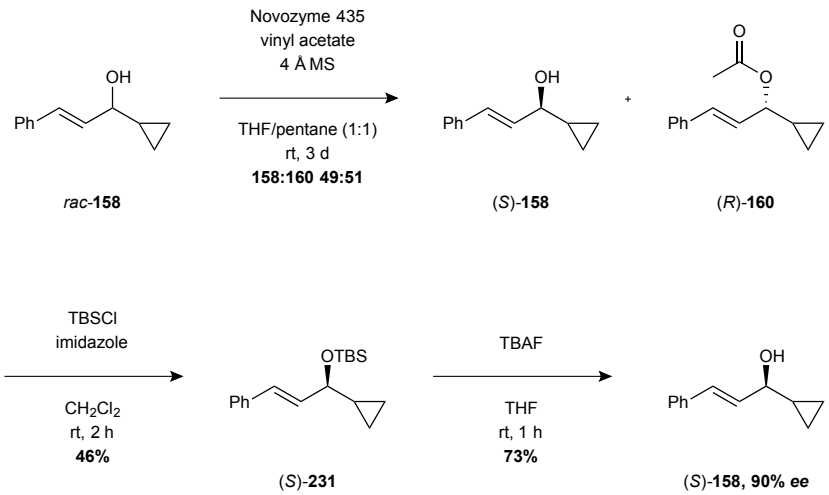
A synthetic route to our enantioenriched enynamide substrates (**114**) was designed (Scheme 5.5). It was envisioned that the incorporation of a kinetic resolution of allylic alcohols **119** in the previous synthetic route (see Chapter 2) would allow the introduction of a range of substituents in the enynamide tether, in an enantio- and diastereostereoselective manner.



Scheme 5.5. Retrosynthetic route to enantioenriched enynamides.

Alcohol *rac*-**158** was therefore submitted to an enzymatic resolution, using Novozyme 435 and vinyl acetate (Scheme 5.6). The reaction was followed by ^{1}H NMR spectroscopic

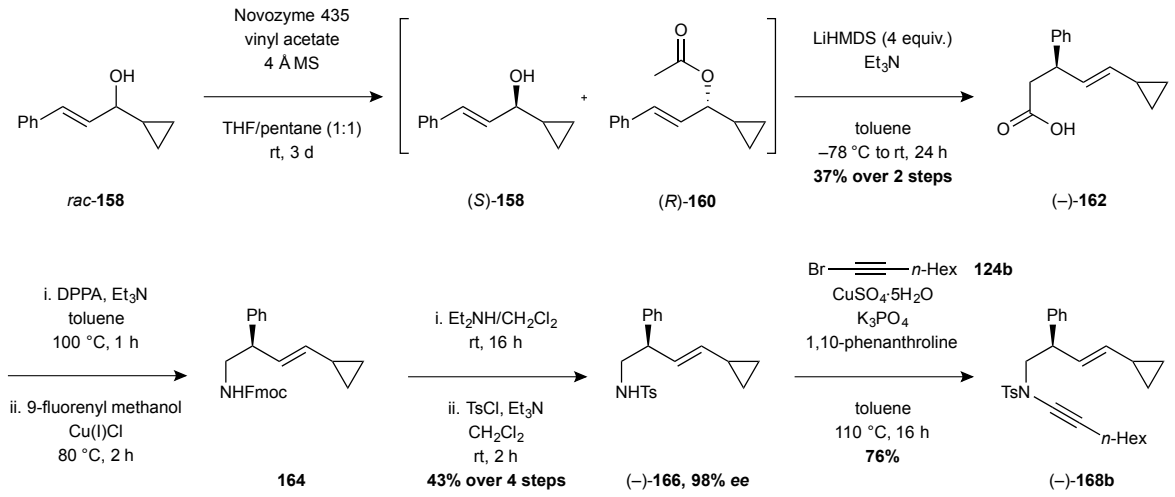
analysis of the crude reaction mixture. After 72 hours the reaction had reached 51% conversion (determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture), and HPLC analysis of the crude reaction mixture showed a 96% *ee* of the remaining starting material. To our surprise, upon purification on silica gel, the optical purity of (*S*)-**158** decreased to 70% *ee*. This was rationalised by a silica-promoted S_N1 deacetoxylation of the enantioenriched product ((*R*)-**160**). In an attempt to circumvent this issue, the crude alcohol was protected as the silyl ether ((*S*)-**231**), and subsequently separated from the allylic ester (*R*)-**160** *via* column chromatography. Deprotection of (*S*)-**231** with TBAF, and purification on silica gave allylic alcohol (*S*)-**158** in 90% *ee*, which suggested that the alcohol was also epimerising on silica. Though this was a high level of optical purity, it would not be sufficient for accurate examination of diastereoselectivity in the [5+2] cycloisomerisation.



Scheme 5.6. Enzymatic resolution of allylic alcohol.

An alternative strategy was to halt the enzymatic resolution of *rac*-**158** below 50% conversion, and submit the crude enantioenriched allylic ester (*R*)-**160** to Ireland-Claisen rearrangment (Scheme 5.7). However, this involved a level of risk, as HPLC analysis of the crude resolution reaction mixture showed the ester (**160**) to be a racemic mixture! We

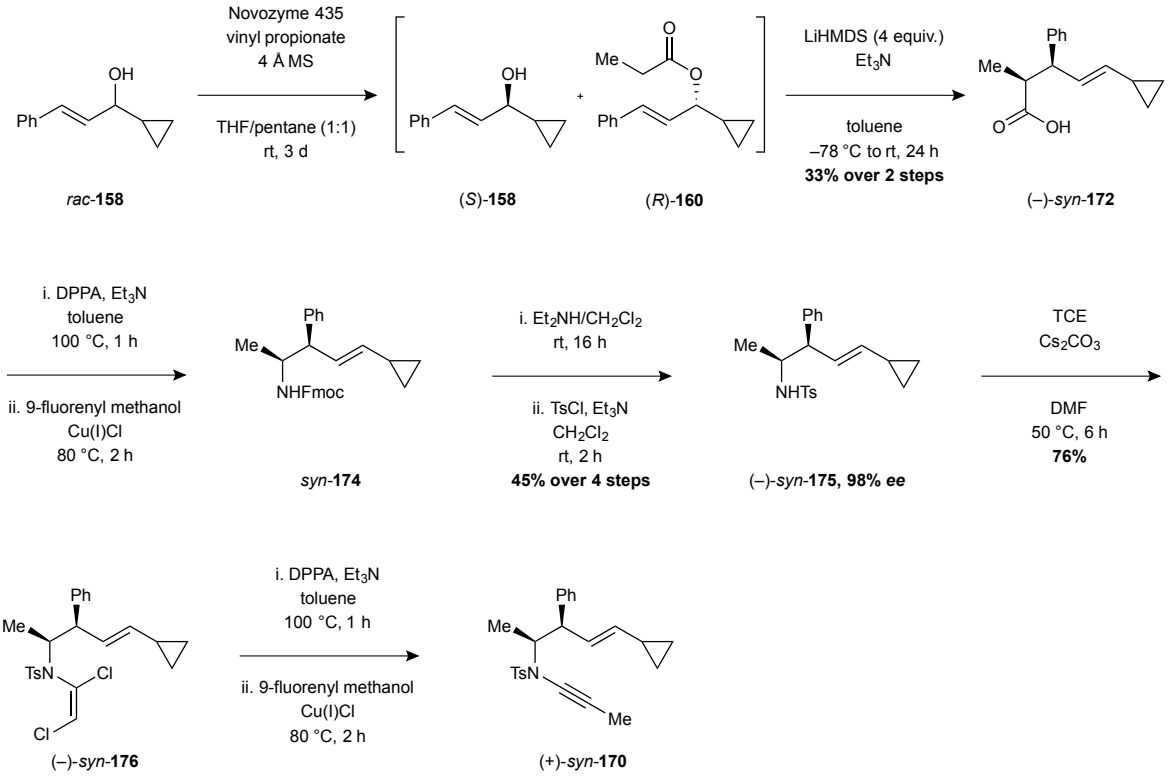
hypothesised that this was due to racemisation of ester (*R*)-**160** on the HPLC silica, and that it would in fact remain at high optical purity provided it was used without purification. Enzymatic resolution of *rac*-**158** was performed on a 2 g scale, and after 3 days (43% conversion) was halted *via* filtration through celite. The concentrated crude material was immediately submitted to Ireland-Claisen rearrangment, using an additional equivalent of LiHMDS in order to account for residual alcohol (*S*)-**158**. Carboxylic acid (–)-**162** was obtained in 37% yield over 2 steps, and was found to remain optically active. Acid **162** was converted to sulfonamide **166**, *via* a Curtius rearrangement/Fmoc trapping/protecting group switch protocol, in 43% yield over 4 steps. To our delight, HPLC analysis revealed the *ee* of sulfonamide (–)-**166** to be 98%. Finally, copper-catalysed ynamide formation gave the desired enantioenriched allylic-substituted enynamide (–)-**168b** in good yield.



Scheme 5.7. Synthesis of enantioenriched allylic-substituted eynamide (–)-**168b**.

Our success in the two-step enzymatic resolution/Ireland-Claisen sequence gave us confidence in forming the enantioenriched disubstituted enynamide (+)-*syn*-**170** (Scheme 5.8). Enzymatic resolution of *rac*-**158** was repeated using vinyl propionate, and again the reaction was halted after 3 days. The crude reaction mixture was submitted to the Ireland-Claisen conditions and stirred for 24 hours, giving the optically active carboxylic acid (–)-

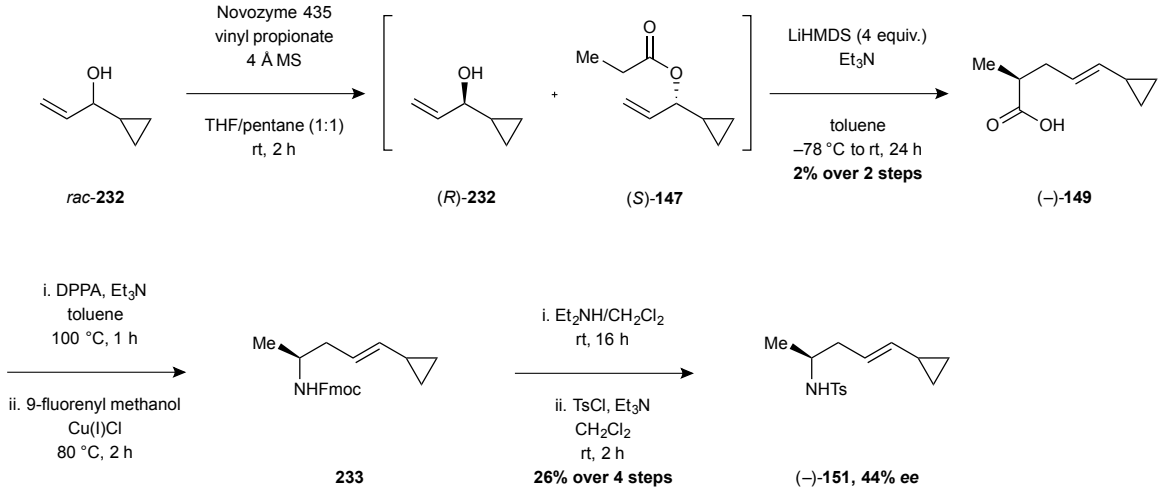
syn-**172** as a single diastereomer (>20:1 *dr*). The acid was converted to sulfonamide (–)-*syn*-**175** in 45% yield, using the previously described Curtius rearrangement protocol. The presence of a homoallylic substituent necessitated two step ynamide formation *via* dichloroenamide (–)-*syn*-**176**.[56] An elimination/lithiation/alkylation sequence gave enantioenriched disubstituted enynamide (+)-*syn*-**170** in 95% yield.



Scheme 5.8. Synthesis of enantioenriched disubstitued enynamide (+)-*syn*-**170**.

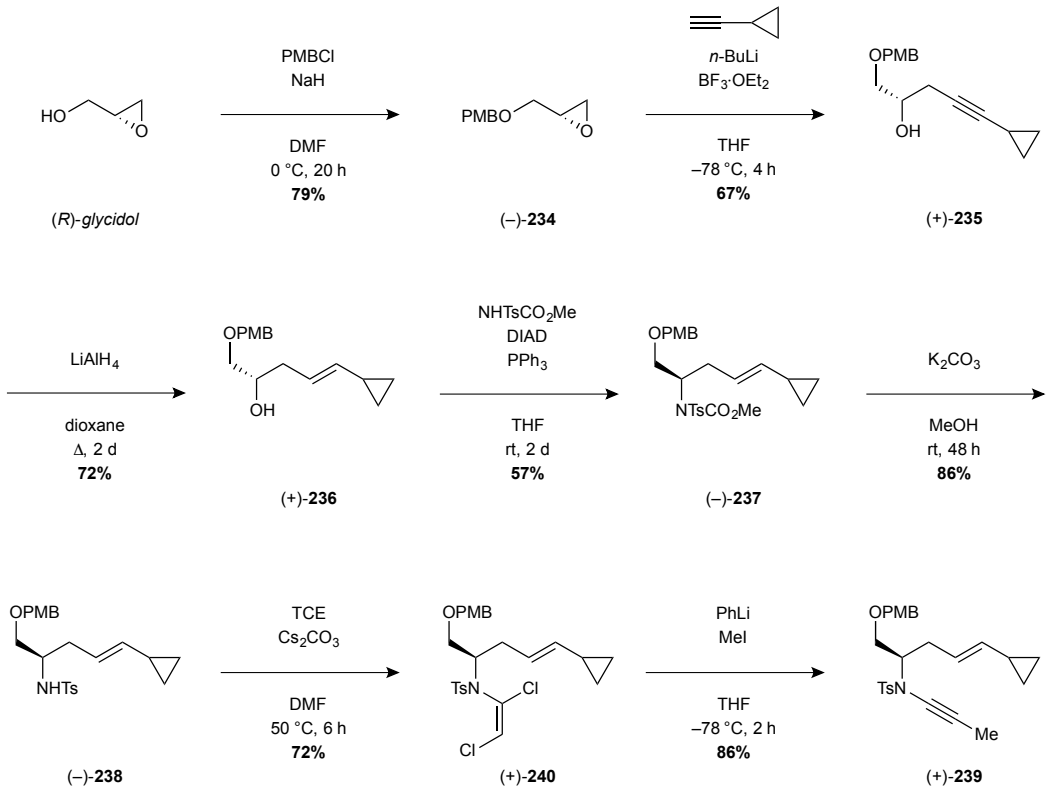
Unfortunately, access to enantioenriched singly-substituted homoallylic enynamides was rather more troublesome (Scheme 5.9). Terminal allylic alcohol *rac*-**232** was submitted to the enzymatic resolution conditions described above, and was found to react significantly faster than the phenyl substituted analogue *rac*-**158** (Scheme 5.9), with the reaction having reached 44% conversion after just 8 hours. Ireland-Claisen of the crude ester gave only trace amounts of carboxylic acid (–)-**149**. However, it was possible to isolate sufficient material to persevere with formation of sulfonamide (–)-**151**, at which point it was

discovered that the product had only 44% *ee*. It was clear that enzymatic resolution of *rac*-**232** had not been successful, perhaps due to the similarity in size between the terminal alkene and cyclopropane unit.



Scheme 5.9. Failed synthesis of enantioenriched homoallylic substituted enynamide.

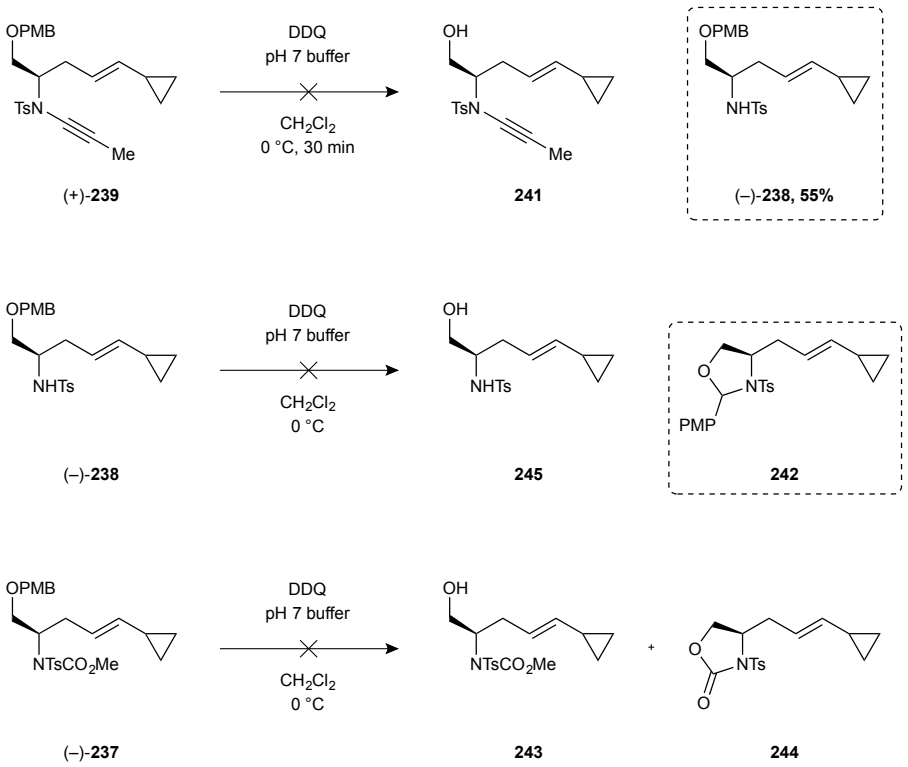
An alternative strategy was required to access enantioenriched homoallylic-substituted enynamides. Until this point we had relied upon a kinetic resolution and had not yet explored the use of chiral pool starting materials. We chose to start with (*R*)-glycidol (Scheme 5.10), a cheap and commercially available chiral epoxide, which was protected, and subsequently opened with cyclopropylacetylide to give homopropargylic alcohol (+)-**235** in good yield. Initial attempts to reduce the alkyne with Red-Al® were unsuccessful, even at elevated temperatures. It was found that $LiAlH_4$ in dioxane at reflux was required to effect transformation of homopropargylic alcohol (+)-**235** to homoallylic alcohol (+)-**236**. Misunobu reaction (and stereochemical inversion) of alcohol (+)-**236** gave methyl carbamate-protected sulfonamide (–)-**237**, and facile deprotection with potassium carbonate in methanol at room temperature gave sulfonamide (–)-**238** in high yield. Formation of ynamide (+)-**239** from (–)-**238** was achieved in two steps and 62% yield, *via* dichloroenamide (+)-**240**, as described above.



Scheme 5.10. Preparation of enantioenriched homoallylic substituted enynamide.

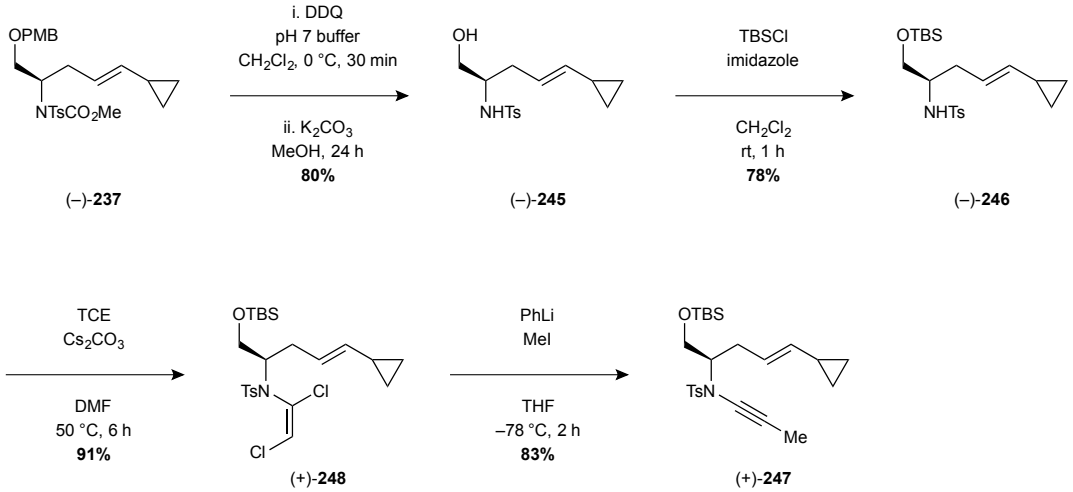
Although a PMB ether had been tolerated in the racemic [5+2] cycloisomerisation (*cf.* syn-**182**, Chapter 2, Fig. 2.1), preliminary results in the asymmetric [5+2] cycloisomerisation of enynamide (+)-**239** unfortunately suggested that an alternative protecting group would be required (see Section 5.2.2). We therefore attempted to carry out a protecting group switch at various points during the synthetic route (Scheme 5.11). This began with removal of the PMB ether of enynamide (+)-**239**, with DDQ and a pH 7 phosphate buffer. However, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed cleavage of the ynamide, and sole presence of sulfonamide (–)-**238** (55%). We next submitted sulfonamide (–)-**238** to the deprotection conditions and discovered, from ^{1}H NMR spectroscopic analysis of the crude reaction mixture, that on oxidation of the PMB ether an intramolecular cyclisation of the nitrogen atom onto the oxonium had occurred, giving oxazolidine **242**. To avoid this issue we treated the precursor carbamate (–)-**237** with the

oxidant, which to our delight gave the free alcohol **243**. However, upon purification on silica gel the oxygen atom partially cyclised onto the carbamate, generating oxazolidinone **244**.



Scheme 5.11. Attempts to cleave PMB group.

This issue was circumvented by submitting the crude oxidative deprotection reaction mixture to potassium carbonate in methanol (Scheme 5.12), which cleaved the methyl carbamate and gave sulfonamide (–)-**245** in 80% yield over two steps. The alcohol was protected with TBSCl, as we were confident that the silyl ether ((–)-**246**) would be tolerated in the asymmetric [5+2] cycloisomerisation (*cf.* **120d**, Chapter 3, Table 3.1). Finally, formation of ynamide (+)-**247** was achieved in two steps and 76% yield.



Scheme 5.12. Preparation of homoallylic-substituted enynamide (+)-**247**.

5.2.2 [5+2] Cycloisomerisation of enantioenriched substrates

Before embarking upon investigations of double stereodifferentiation, the inherent diastereoselectivity of each of the substrates with an achiral catalyst was first assessed (Fig. 5.1). Allylic substituted enynamide **168b**, and doubly substituted enynamide *syn*-**170** were already known to exhibit very strong diastereoselective preferences in the formation of the new stereocentre, both giving the *syn*-diastereomers of products **181b** and **185** in >20:1 *dr* (see Chapter 2, Fig. 2.1).

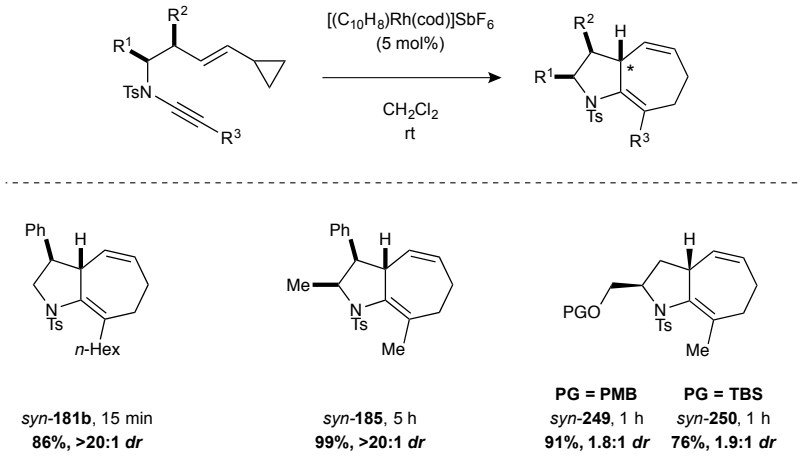


Figure 5.1. Diastereoselective [5+2] cycloisomerisation.

Conversely, the newly synthesised homoallylic-substituted enynamides (+)-**239** and (+)-**247** showed poor diastereoselectivities, with products *syn*-**249** and *syn*-**250** both obtained in a 2:1 *dr* (*syn*:*anti*).

We now set about investigation of the double stereodifferentiating [5+2] cycloisomerisations (Fig. 5.2, Matched). The various substrates were first subjected to the optimised asymmetric reaction conditions with the 'matched' enantiomer of ligand (the ligand (*S*,*R*,*R*)-**L12** which, in theory, promotes formation of the (*R*)-stereocentre, and thus the *syn*-diastereomer of product). Pleasingly, enynamides (–)-**168b**, (+)-*syn*-**170** and (+)-**247** were all found to undergo rapid cycloisomerisation to the *syn*-diastereomers of products (–)-**181b**, (–)-**185**, and (–)-**250** in near quantitative yields.

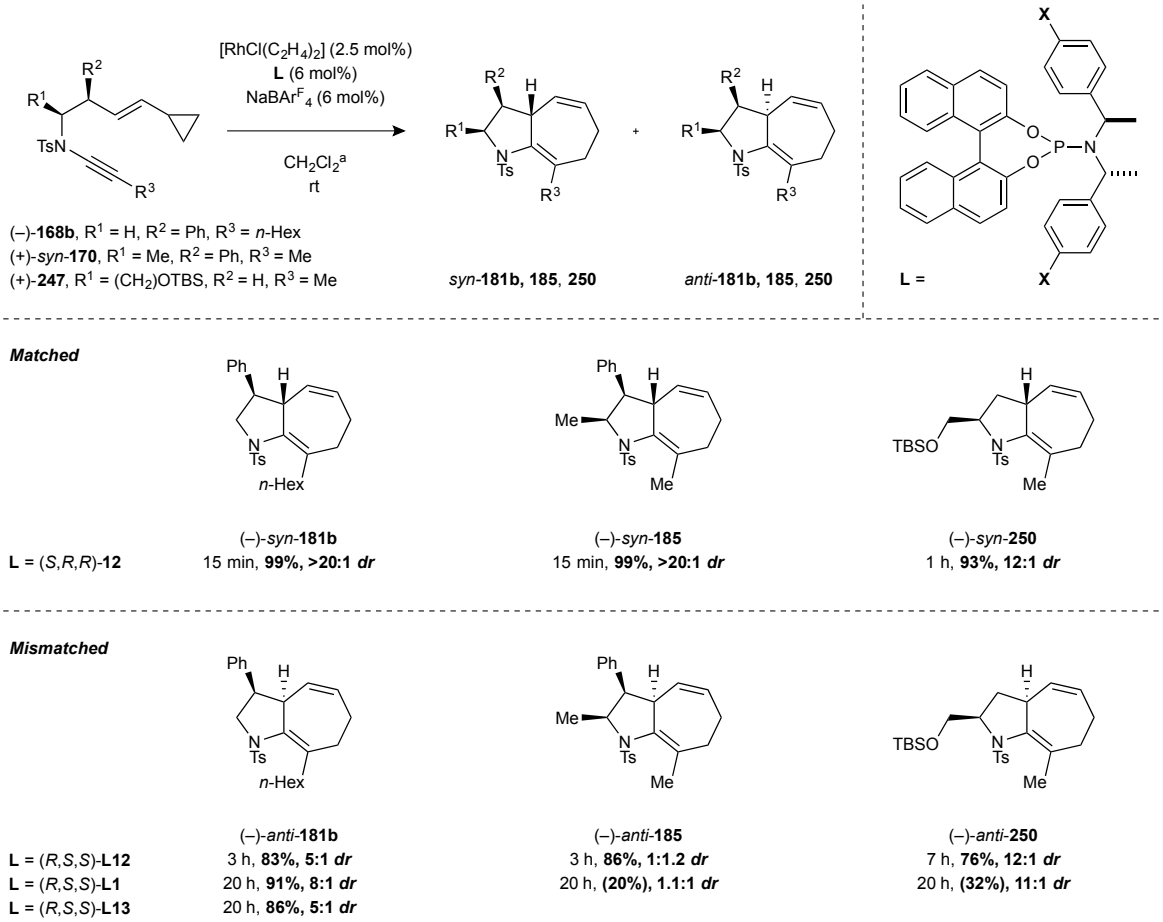


Figure 5.2. Doublestereodifferentiating [5+2] cycloisomerisations: matched *vs* mismatched.

In the case of (–)-**168b** and (+)-*syn*-**170**, which exhibited very strong substrate selectivities for the *syn*-products in the achiral reaction, perfect diastereoselectivites were observed in formation of products (–)-*syn*-**181b** and (–)-*syn*-**185** (>20:1 *dr*). Reaction of enynamide (+)-**247**, which showed only a weak substrate preference for the *syn*-product in the substrate stereocontrolled reaction, gave (–)-*syn*-**250** in a significantly enhanced 12:1 *dr*. Enynamide (+)-**239**, bearing a PMB ether group, was found to be unreactive under the asymmetric reaction conditions. This was perhaps due to the electron-rich *p*-methoxyphenyl group outcompeting the electron-poor *p*-fluorophenyl ligand substituent in coordination of rhodium, thus disrupting the favoured oxidative coupling transition state.

Finally, the enantioenriched substrates were subjected to the asymmetric reaction conditions with the 'mismatched' enantiomer of ligand ((*R*,*S*,*S*)-**L12**, prepared using the synthesis described in Chapter 3, Scheme 3.9). Pleasingly, reaction with the homoallylic-substituted enynamide (+)-**247** gave the desired (–)-*anti*-**250** with an equal and opposite *dr* of 12:1 (Fig. 5.2, Mismatched). Despite the inherent substrate selectivity of (+)-**247** being poor, a mismatched effect was still observed, with the reaction taking 7 hours as opposed to 1 hour for the matched case. In the reaction of (–)-**168b**, we were delighted to find that the catalyst system was able to entirely overturn the strong substrate stereoselectivity, to give (–)-*anti*-**181b** in a 5:1 *dr*. The strength of the catalyst system was truly tested in the reaction of (+)-*syn*-**170**, where the substrate preference was equalled, resulting in a 1:1.1 (*anti*:*syn*) mixture of diastereomers of product **185**, thus demonstrating that the additional tether substituent serves to reinforce the substrate preference.

Given the marked effect of ligand substituents on the rate and selectivity of the enantioselective reactions, we were intrigued by how they might also affect the outcome of these diastereoselective reactions. We therefore submitted (–)-**168b** to the mismatched

reaction conditions with the unsubstituted 'Feringa ligand' (*R*,*S*,*S*)-**L1**. Interestingly, this reaction gave (–)-*anti*-**181b** in excellent yield and an increased *dr* of 8:1, but suffered from a significantly lower rate of reaction than with the *p*-fluoro substituted (*R*,*S*,*S*)-**L12**. In the matched reaction, in order to achieve the *syn*-diastereomer of product **181b,** the phenyl tether substituent likely adopts a pseudo-equatorial position in the transition state (Fig. 5.3, (–)-**168b**-Rh-(*S*,*R*,*R*)-**L12**). In the mismatched reaction, in order to maintain the favoured substrate backbone orientation in formation of the *anti*-diastereomer of product **181b**, the phenyl substituent is required to adopt an unfavourable pseudo-axial position ((–)-**168b**-Rh-(*R*,*S*,*S*)-**L12**). Although it is possible in this case for the substituent to achieve a pseudo-equitorial position, this would lead to a disruption of the optimal substrate-catalyst interaction and likely further increase the energy of the transition state.

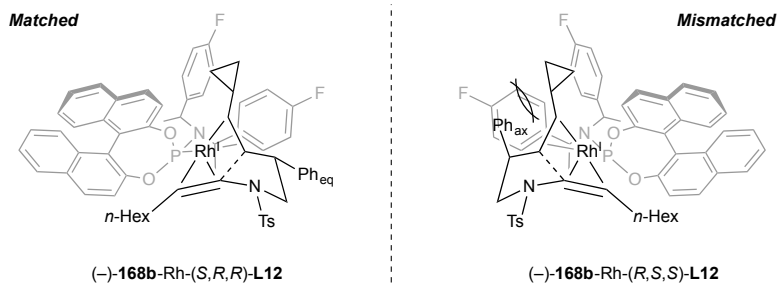


Figure 5.3. Double stereodifferentiation: oxidative coupling transition states.

The decreased diastereoselectivity observed with (*R*,*S*,*S*)-**L12** compared to (*R*,*S*,*S*)-**L1** may be a result of stronger substrate-Rh complexation, which increases rate and stereoselectivity in the enantioselective reaction, but exacerbates unfavourable steric interactions in the mismatched transition state.

5.2.3 Assignment of relative and absolute stereochemistry

The relative stereochemistry of (–)-*syn*-**181b** had previously been assigned by analogy to that of *syn*-**181a**, which was determined unambiguously by X-Ray crystallographic

analysis (see Chapter 2, Fig. 2.2). In order to determine the relative stereochemistry of newly synthesised product (–)-*anti*-**181b**, NOESY experiments were performed on both *syn*- and *anti*-**181b** diastereomers (Fig. 5.4). In *syn*-**181b** strong nOe enhancements were observed between H2β and H3a, and between both of these and the *ortho*-H of the phenyl substituent, which suggested a *syn*-relationship between them. In addition, a strong enhancement was observed between H3 and H2α. No enhancement was observed between H2α and the phenyl substituent. In *anti*-**181b** a strong nOe enhancement was observed between H2β and the phenyl substituent. However, in this case, no enhancement was observed between H3a and H2β. Crucially, an enhancement was observed between H3a and H2α, albeit weak. These observations, taken together with our assignment of *syn*-**181a** and syn-**181b**, indicate a different and therefore *anti*-relationship between H3a and H3 in *anti*-**181b**.

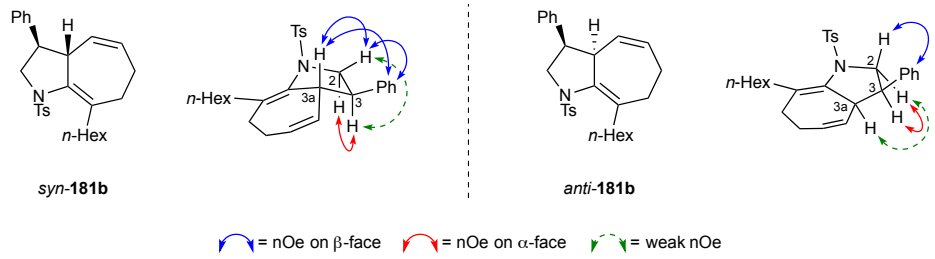


Figure 5.4. Assignment of relative stereochemistry of **181b**.

Assignment of the relative stereochemistry of (–)-*syn*-**250** and (–)-*anti*-**250** was based upon nOe enhancements measured using NOESY experiments (Fig. 5.5). In *syn*-**250** a strong nOe enhancement was observed between H2 and H3α, the latter of which did not show enhancement with either of the H2' protons or H3a, which suggested that H3a and H2 were on opposite faces. A strong enhancement observed between H3β and one of the H2' protons further supports this assignment. The NOESY spectrum for *anti*-**250** showed strong nOe enhancements between both H2' protons and H3β. In addition, complementary

enhancements were observed between H3α and H3a and H2, which suggests H3a and H2 to be on the same face.

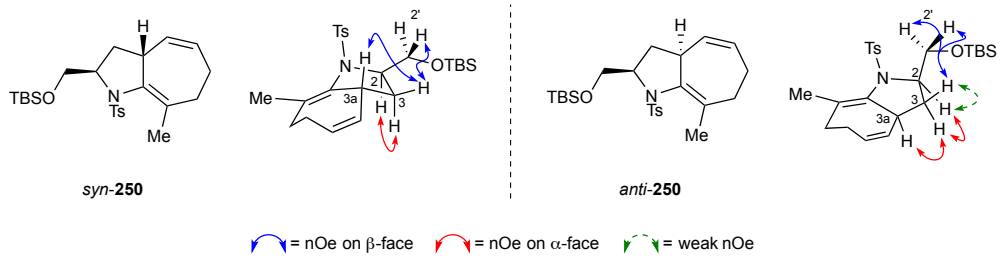


Figure 5.5. Assignment of relative and absolute stereochemistry of **250**.

Having synthesised (+)-**247** as a single enantiomer from a known chiral pool starting material ((*R*)-glycidol), and unequivocally assigned the relative stereochemistry of both *syn*-**250** and *anti*-**250**, we were confident in assigning the absolute stereochemistry of their newly formed C3a stereogenic centres as (*R*) and (*S*) respectively. From this we could infer that in the enantioselective reaction, the (*S*,*R*,*R*)-catalyst system indeed induces (*R*) stereochemistry, which we had not been able to definitively assign up to this point (for example by X-Ray crystallographic analysis). This is further supported by our findings in the theoretical reaction analysis (see Chapter 4).

5.3 Conclusions

We have demonstrated the first successful example of an enantiospecific diastereoselective transition metal-catalysed cycloisomerisation reaction, where the catalyst system outcompetes a strong substrate stereoselectivity to form a previously inaccessible diastereomer of product. This far exceeds the state of the art in the area of double stereodifferentiating cycloisomerisations.

In the process of this investigation, we designed a synthetic route to single enantiomer ynamide vinylcyclopropanes, which therefore allows the assembly of a diverse array of poly-substituted ring systems with fully tuneable stereoselectivity.

6 Conclusions and future work

The first ynamide vinylcyclopropane [5+2] cycloisomerisation has been developed using rhodium catalysis. These processes were found to occur with high substrate diastereo- and regioselectivity, and tolerate a wide range of ynamide substituents. We next achieved enantioselective ynamide [5+2] cycloisomerisation; a mechanistic hypothesis, based on key empirical metal-ligand interactions, led to the development of a novel catalyst system which demonstrated superior reactivity and selectivity to that of the state of the art. Theoretical reaction analysis revealed a new mechanism for the rhodium-catalysed reaction, and gave support to our working hypothesis of ligand design. Finally, we applied our catalyst system to reactions of single enantiomer substrates, and achieved the first double stereodifferentiating [5+2] cycloisomerisation, where the catalyst system was capable of overcoming strong substrate stereoselectivity to form previously inaccessible diasteromers of product. Our results in this area were published in *Nature Communications* (see Appendix).[99]

6.1 Ligand structure/activity relationship

Together with M. Wong and G. Chaubet in the Anderson group, further investigation of novel ligands for the asymmetric [5+2] cycloisomerisation is underway. Our aim is to elucidate the exact origins of stereoselectivity *via* logical alterations to ligand substituents. Through this we hope to rationally design a catalyst system that further improves the

diastereoselectivity of the mismatched reaction with substituted enynamides. In addition, we intend to simplify ligand preparation, as the current ligand synthesis requires expensive chiral amine starting materials, and recrystallisation of the diastereomeric secondary amines (see Chapter 3, Scheme 3.9). To that end, a range of phosphoramidite ligands **L14-19** have been synthesised, and tested in the reaction of enynamide **120a** (Figure 6.1).

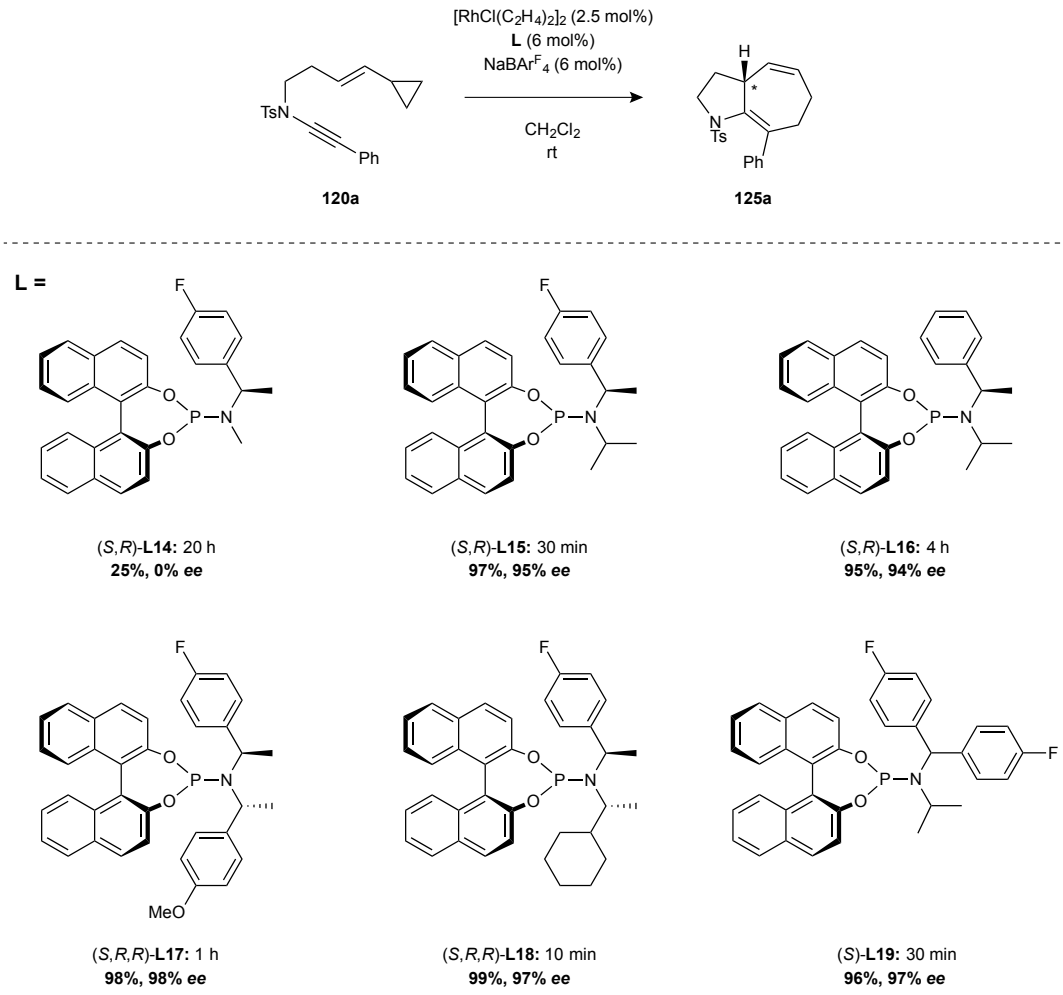


Figure 6.1. Further ligand synthesis; with M. Wong and G. Chaubet.

Firstly, we assessed the effect of amine substituent size on the reaction. Methyl substituted ligand (*S*,*R*)-**14** gave the product **125a** in poor yield and as a racemic mixture (20 hours, 25%, 0% *ee*), whilst reaction with the isopropyl analogue (*S*,*R*)-**15** gave the product (*R*)-**125a** in near quantitative yield and with high enantioselectivity (30 min, 97%, 95% *ee*). It

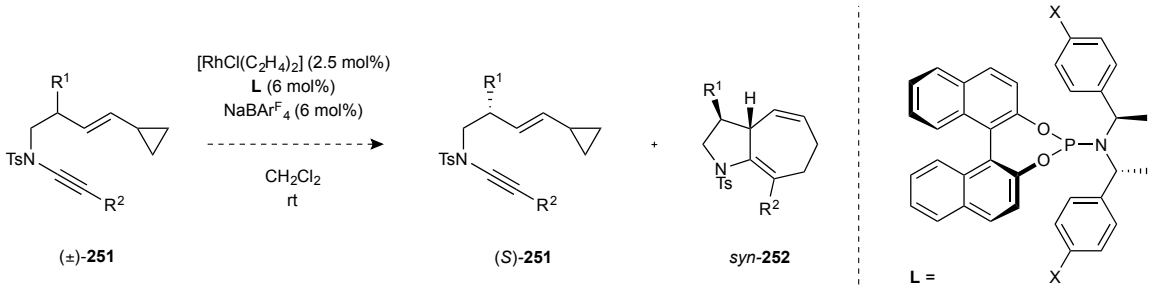
was immediately apparent from this that a sterically encumbering substituent is required for both reactivity and selectivity. We next varied the electronics of the two amine substituents with ligand (*S*,*R*,*R*)-**17**, which possesses both a strongly binding aryl group (*p*-MeO-Ph) and a weakly binding aryl group (*p*-F-Ph), in the hope that the more reactive arene would dominate. Disappointingly, this was found to exhibit reactivity and selectivity between the two corresponding symmetrical ligands (*S*,*R*,*R*)-**L12** and (*S*,*R*,*R*)-**L13**. Excitingly, achiral amine bearing ligand (*S*)-**L19**[100] exhibited very high reactivity and selectivity, with the product obtained in under 30 minutes and in 97% *ee* (*cf.* Fletcher ligand (*S*)-**L9**, 20 h and 92% *ee*).[85] This further demonstrates the powerful effect of electron withdrawing arene substituents on rate of this reaction, and that chiral amine moieties are not necessarily required for stereoinduction.

This research is ongoing; we are currently examining the limitations of bulk and electronics, and the effect of BINOL substituents on enantioselectivity. Ultimately, our aim is to apply these ligands in a double stereodifferentiating setting, and to other asymmetric transformations.

6.2 [5+2] Cycloisomerisation kinetic resolution

Given the strength of the inherent substrate stereocontrol, and thus the difference in rate between the matched and mismatched reactions, we envision the possibility of the first [5+2] cycloisomerisation kinetic resolution (Scheme 6.1). Subjecting racemic substituted enynamides (**251**) to the asymmetric reaction conditions with a single enantiomer of ligand (*S*,*R*,*R*)-**L** will result in a matched scenario for one enantiomer of substrate, and a mismatched scenario for the other. Preliminary results, with Kai Ma, suggest that a kinetic resolution is indeed possible, with (*R*)-**251** being rapidly converted to *syn*-**252** with high

ee, and (*S*)-**251** remaining unreacted. However, the present rate of consumption of (*S*)-**251** is such that in order to achieve high *ee* the reaction must be run to beyond 50% conversion, thus lowering the yield.



Scheme 6.1. [5+2] Cycloisomerisation kinetic resolution, with Kai Ma.

We have observed an interesting effect of ligand electronics on the outcome of the reaction, which has lead to further computational collaboration. Our aim is to design a catalyst system that is not only able to achieve an efficient resolution, but that is also capable of a highly selective diastereo-divergent synthesis of single enantiomer diastereomers.

During the course of our research we have discovered a number of exciting results with respect to the reactivity of ynamides, the factors affecting catalyst stereoinduction, and the differences in catalyst control in enantioselective and diastereoselective cycloisomerisations. These studies set the stage for the development of further rationally designed ligand systems, and double stereodifferentiating reactions.

7 Experimental

7.1 General experimental considerations

Nuclear Magnetic Resonance: ^{1}H NMR spectra were obtained on a Bruker AVII500 (500 MHz) or AVIII400 (400 MHz) spectrometer and were referenced to residual non-deuterated solvent peaks in $CDCl_3$ (δ = 7.26) or C_6D_6 (δ = 7.16). Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sept), octet (oct), nonet (non) and multiplet (m). Coupling constants (*J* values) are measured to the nearest 0.5 Hz and are presented as observed. ^{13}C NMR spectra were obtained on a Bruker AVII500 with cryoprobe (126 MHz) or AVIII400 (101 MHz) spectrometer and were referenced to solvent peaks in $CDCl_3$ (δ = 77.16) and C_6D_6 (δ = 128.06).

Mass spectrometry: Low-resolution mass spectra (*m/z*) were recorded on a Waters LCT Premier EX mass spectrometer, using electrospray ionization (ESI). High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Bruker MicroTOF (resolution = 5000 FWHM) using electrospray (ESI). The parent ion $[M]^+$, $[M+H]^+$ or $[M+Na]^+$ is calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Infra-red spectra: Absorption spectra were obtained in $CHCl_3$ as solvent on a Bruker Tensor 27 FT-IR spectrometer. The sample was prepared as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Wavelengths of maximum absorbance (ν_{max}) are quoted in wavenumbers (cm^{-1}). Only selected, characteristic IR absorption data are provided for each compound.

Polarimetry: Optical rotations were recorded on a Perkin Elmer 241 or 341 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). $[\alpha]_D$ are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are reported in g/100 mL. Temperatures are reported in °C.

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

Chromatography: Column chromatography refers to normal layer column chromatography and was performed on silica gel (35-70 mm). Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet light (254 nm) and/or heating the plate after staining with vanillin. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 Series running in normal layer under UV detection using a ZORBAX RX-SIL (150 mm x 4.6 mm ID) as the analytic column. Chiral analysis was carried out using a DAICEL CHIRALPAK-IA or IB (250 mm x 4.6 mm ID).

Materials: Unless otherwise stated, all reactions were carried out in oven-dried glassware under an atmosphere of argon. Diethyl ether, dichloromethane, THF and toluene were

dried over activated alumina beads before use. All other commercially available reagents and solvents, where appropriate, were dried and purified before use using standard procedures. Petrol refers to the fraction of light petroleum ether boiling at 40-60 °C. Bromoalkynes **124a-g** and **124k** and **124l** were given as gifts by A. Mekareeya and Dr P. R. Walker. Phosphoramidite ligands **L8-11** were given as gifts by Dr P. Roth from the Prof. S. P. Fletcher group. Achiral catalyst $[(C_{10}H_8)Rh(cod)]SbF_6$ was prepared according to a literature procedure.

7.2 General experimental procedures

General Procedure A: *Ester formation*

According to the procedure of Echavarren et al.[63] To a solution of Grignard reagent (1.05 equiv.) at 0 °C was added a solution of cyclopropanecarboxaldehyde (1.0 equiv.) in diethyl ether (10 mL/mmol of aldehyde) and the reaction mixture stirred for 30 min. A mixture of pyridine (1.25 equiv.) and anhydride (1.25 equiv.) was added and the solution warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with methanol (0.1 mL/mmol of anhydride) and diluted with diethyl ether (10 mL/mmol of aldehyde) and water (10 mL/mmol of aldehyde). The aqueous layer was extracted with diethyl ether (3 x 10 mL/mmol of aldehyde) and the combined organic extracts washed with 1 M *aq.* hydrochloric acid (2 x 20 mL/mmol of aldehyde), brine (1 x 20mL/mmol of aldehyde), dried over magnesium sulfate and concentrated carefully *in vacuo*.

General Procedure B: *Ireland-Claisen rearrangement*

According to the procedure of Collum et al.[65] To a solution of lithium hexamethyldisilazide (1 M in toluene, 3.0 equiv.) and triethylamine (10 equiv.) in toluene (10 mL/mmol of ester) at –78 °C was added a solution of ester (1.0 equiv.) in toluene (1 mL/mmol of ester) dropwise and the reaction mixture stirred for 30 min before being allowed to reach room temperature and stirred for a further 5 h. 1 M *aq.* sodium hydroxide (10 mL/mmol of ester) was added and the solution stirred for 30 min. The aqueous layer was separated, washed with diethyl ether (2 x 10 mL/mmol of ester) and acidified with 1 M *aq.* citric acid to pH ~ 4. The aqueous layer was extracted with diethyl ether (3 x 10 mL/mmol of ester) and the combined organic extracts washed with brine (10 mL/mmol of ester), dried over magnesium sulfate and concentrated *in vacuo*.

General Procedure C: Curtius rearrangement

To a stirred solution of carboxylic acid (1.0 equiv.) and triethylamine (1.1 equiv.) in anhydrous toluene (3 mL/mmol of acid) at 0 °C was added diphenyl phosphoryl azide (1.1 equiv.) dropwise and the reaction mixture heated to 100 °C for 1 h. 9-fluorenemethanol (1.0 equiv.) and copper(I) chloride (0.033 equiv.) were added and the solution stirred for 16 h. To the reaction mixture was added piperidine (2.0 equiv.) and the solution stirred for a further 24 h. The reaction mixture was diluted with diethyl ether (10 mL/mmol of acid) and 1 M *aq.* citric acid (10 mL/mmol of acid) and the aqueous layer separated. The aqueous layer was washed with diethyl ether (2 x 10 mL/mmol of acid), basified to pH ~ 11 with 2 M *aq.* sodium hydroxide and extracted with diethyl ether (3 x 20 mL/mmol of acid). The combined organic extracts were washed with brine (50 mL/mmol of acid), dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (10 mL/mmol of acid), tosyl chloride (1.0 equiv.) and triethylamine (1.0 equiv.) were added and the solution stirred for 4 h at room temperature. To the solution was added sat. *aq.* ammonium chloride (10 mL/mmol) and the aqueous layer extracted with dichloromethane (3 x 10 mL/mmol of acid). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*.

General Procedure D: *Bromination of terminal alkynes using $AgNO_3$*

To a suspension of alkyne (1.0 equiv.) in acetone (1 mL/mmol) was added $AgNO_3$ (10 mol%). The reaction mixture was stirred for 5 min and NBS (1.1 equiv.) added. The reaction mixture was stirred at room temperature for 16 h, filtered through a pad of silica (pentane) and concentrated *in vacuo*.

General Procedure E: *Copper(II)-catalysed ynamide formation*

According to the procedure of Hsung et al.[58] To a mixture of sulfonamide (1.0 equiv.), K_3PO_4 (2.0 equiv.), $CuSO_4 \cdot 5H_2O$ (0.4 equiv.) and 1,10-phenanthroline (0.8 equiv.) was added a solution of bromoalkyne (1.5 equiv.) in toluene (3 mL/mmol of sulfonamide). The reaction mixture was stirred at 70 °C for the stated time and then cooled to room temperature. The reaction mixture was filtered through Celite eluting with diethyl ether and the filtrate concentrated *in vacuo*.

General Procedure F: *Cs_2CO_3 promoted synthesis of dichloroenamides*

According to the procedure of Anderson et al.[56] To a suspension of amide (1.0 equiv.) and Cs_2CO_3 (3.0 equiv.) in DMF (0.75 ml/mmol amide), at 50 °C, was added trichloroethylene (3.0 equiv.) dropwise over ten minutes. The resulting mixture was stirred at 50 °C for the stated time. Upon cooling to room temperature, the mixture was partitioned between ethyl acetate (10 mL/mmol) and water (10 mL/mmol), the organic layer separated and further washed with water (3 x 10 mL/mmol). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*.

General Procedure G: *Synthesis of ynamides using phenyllithium*

According to the procedure of Anderson et al.[56] To a solution of 1,2-dichloroenamide (1.0 equiv.) in THF (10 ml/mmol of enamide), at –78 °C, was added phenyllithium solution (2.0 M in dibutyl ether, 2.2 equiv.) dropwise over 10 minutes. The reaction mixture was stirred at –78 °C for 1 h, after which time the electrophile (1.2 equiv.) was added. The solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with water (10 mL/mmol) and the aqueous layer extracted with

diethyl ether (3 x 10 mL/mmol). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*.

General Procedure H: *Racemic [5+2] Cycloisomerisation*

According to the procedure of Wender et al.[18] To an oven-dried vial containing the ynamide vinylcyclopropane (1.0 equiv.) under Ar was added a solution of $[(C_{10}H_8)Rh(cod)]SbF_6$ (5 mol%) in degassed dichloromethane (10 mL/mmol of ynamide). The reaction mixture was stirred at room temperature under Ar until consumption of the ynamide was observed by TLC.

General Procedure I: *Asymmetric [5+2] cycloisomerisation*

According to the procedure of Hayashi et al.[30] A solution of $[RhCl(C_2H_4)_2]_2$ (2.5 mol%), $NaBAr^F_4$ (6 mol%) and phosphoramidite ligand (6 mol%) in degassed dichloromethane (10 mL/mmol of ynamide) was stirred for 20 min under Ar. The solution was filtered (through a PTFE filter-tipped syringe) into an oven-dried vial containing ynamide vinylcyclopropane (1.0 equiv.) under Ar. The reaction mixture was stirred at room temperature under Ar until consumption of the ynamide was observed by TLC.

General Procedure J: *Synthesis of amines*

According to the procedure of Alexakis et al.[87] To a solution of amine (1.0 equiv.) in $Ti(O\textit{i}\text{-}Pr)_4$ (3.0 equiv.) was added ketone (1.0 equiv.) and the reaction mixture stirred for 1 h. Pd/C (10 wt%) was added and the resulting suspension was stirred under H_2 (1 atm, balloon) for 16 h. To the reaction mixture was added 3M *aq.* sodium hydroxide (1.5 mL/mmol of amine) and ethyl acetate (3 mL/mmol of amine), and the solution was stirred for 1 h. The organic layer was separated and a further two rounds of this extraction process

were carried out on the resulting (and subsequent) aqueous layer. The combined organic extracts were dried over sodium sulfate, filtered through a pad of celite, and concentrated *in vacuo*. The residue was taken up in ethyl acetate (5 mL) and conc. hydrochloric acid (1 mL), and the resulting solution was azeotroped with ethyl acetate until a white solid (the amine hydrochloride salt) was obtained.

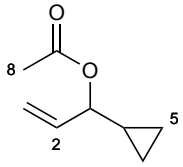
General Procedure K: *Synthesis of phosphoramidites*

According to the procedure of Fletcher et al.[85] To a solution of PCl_3 (1.0 equiv.) in dichloromethane (10 mL/mmol of amine) at 0 °C was added triethylamine (6.0 equiv.) dropwise. The solution was allowed to reach room temperature, then the amine (1.0 equiv.) was added and the reaction mixture stirred for 5 h. To the stirred solution was added BINOL (1.0 equiv.) and the subsequent mixture stirred for a further 16 h. The reaction mixture was filtered through a pad of silica (5 mm) and celite (5 mm), washed with dichloromethane and the solvent removed *in vacuo*.

7.3 Characterisation of compounds

7.3.1 Synthesis of cycloisomerisation substrates

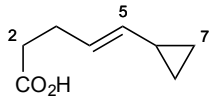
1-Cyclopropylallyl acetate, 121



Prepared by General Procedure A using vinylmagnesium bromide (1 M in THF, 42.2 mL, 42.2 mmol, 1.05 equiv.), cyclopropanecarboxaldehyde **118** (3.0 mL, 40.1 mmol, 1.0 equiv.) and acetic anhydride (4.7 mL, 50.2 mmol, 1.25 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **121** as a colourless oil (3.7 g, 26.1 mmol, 65%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.85 (1H, ddd, *J* = 17.0, 10.5 and 6.0 Hz, H2), 5.27 (1H, dt, *J* = 17.0 and 1.5 Hz, H3), 5.17 (1H, dt, *J* = 10.5 and 1.5 Hz, H3), 4.71 (1H, dt, *J* = 8.5 and 6.0 Hz, H1), 2.09 (3H, s, H8), 1.11-1.02 (1H, m, H4), 0.62-0.51 (2H, m, H5), 0.45-0.23 (2H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.4, 135.6, 116.5, 78.6, 21.3, 14.6, 3.5, 2.5.

The spectroscopic data was found to be in agreement with that reported by Ashe *et al.*[101]

(*E*)-5-Cyclopropylpent-4-enoic acid, 122

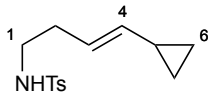


Prepared by General Procedure B using ester **121** (1.0 g, 7.1 mmol, 1.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1) + 1% acetic acid) to give **122** as a colourless oil (0.87 g, 6.2 mmol, 87%); $\mathbf{R_f}$

0.29 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3082, 3006, 2918, 1707, 1412, 1297, 1213, 1098; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.51 (1H, dt, *J* = 15.0 and 6.5 Hz, H4), 5.03 (1H, dd, *J* = 15.0 and 8.5 Hz, H5), 2.42 (2H, t, *J* = 7.0 Hz, H2), 2.31 (2H, dt, *J* = 7.0 and 6.5 Hz, H3), 1.39-1.30 (1H, m, H6), 0.71-0.63 (2H, m, H7), 0.39-0.27 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 179.8, 135.5, 125.3, 34.2, 27.5, 13.5, 6.5; **HRMS** (ESI–) calc. for $C_8H_{11}O_2$ $[M-H]^-$ 139.0765, found 139.0771.

The physical and spectroscopic data were found to be in agreement with that reported by Crich *et al.*[102]

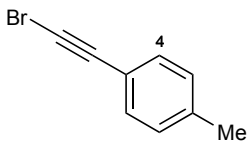
(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 123



To a stirred solution of carboxylic acid **122** (0.50 g, 3.57 mmol, 1.0 equiv.) and triethylamine (0.55 mL, 3.92 mmol, 1.1 equiv.) in toluene (11 mL) at 0 °C was added diphenyl phosphoryl azide (0.85 mL, 3.92 mmol, 1.1 equiv.) dropwise and the reaction mixture heated to 100 °C for 1 h. The solution was allowed to cool to room temperature, 2 M *aq.* sodium hydroxide (3.57 mL, 7.14 mmol, 2.0 equiv.) was added and the biphasic mixture stirred for 16 h. The reaction mixture was diluted with diethyl ether (20 mL) and citric acid (20 mL) and the aqueous layer separated. The aqueous layer was washed with diethyl ether (2 x 20 mL), basified to pH ~ 11 with 2 M *aq.* sodium hydroxide and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL), tosyl chloride (0.68 g, 3.57 mmol, 1.0 equiv.) and triethylamine (0.50 mL, 3.57 mmol, 1.0 equiv.) were added and the solution stirred for 4 h at room temperature. To the solution was added sat. *aq.* ammonium chloride (20 mL) and

the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **123** as a colourless oil (0.39 g, 1.47 mmol, 41%); $\mathbf{R_f}$ 0.17 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3282, 3081, 3004, 2926, 1598, 1324, 1157, 1094, 964; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.36 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 4.96 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.49 (1H, br. t, *J* = 6.0 Hz, N*H*), 2.97 (2H, app. q, *J* = 6.5 Hz, H1), 2.43 (3H, s, TsCH_3), 2.12 (2H, app. q, *J* = 6.5 Hz, H2), 1.34-1.27 (1H, m, H5), 0.69-0.65 (2H, m, H6), 0.32-0.29 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.3, 138.0, 137.0, 129.7, 127.1, 122.8, 42.6, 32.3, 21.5, 13.5, 6.6; **HRMS** (ESI+) calc. for $C_{14}H_{19}NNaO_2S$ $[M+Na]^+$ 288.1029, found 288.1039.

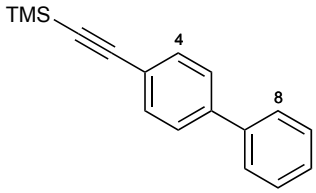
1-(Bromoethynyl)-4-methylbenzene, 124i



Prepared by General Procedure D using 4-ethynyltoluene (1.0 g, 8.60 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give **124i** as a colourless solid (1.36 g, 6.97 mmol, 81%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (2H, d, *J* = 8.0 Hz, H4), 7.12 (2H, d, *J* = 8.0 Hz, H5), 2.35 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.0, 132.0, 129.2, 119.8, 80.3, 48.9, 21.7.

The spectroscopic data was found to be in agreement with that reported by Xu *et al.*[103]

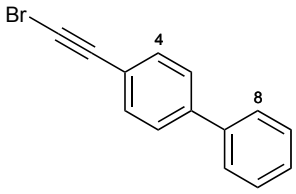
([1,1'-Biphenyl]-4-ylethynyl)trimethylsilane, S1



To a solution of 4-bromo-1,1'-biphenyl (0.93 g, 3.99 mmol, 1.0 equiv.), ethynyltrimethylsilane (1.13 mL, 7.98 mmol, 2.0 equiv.), Cu(I)I (76 mg, 0.40 mmol, 0.1 equiv.) and PPh_3 (209 mg, 0.80 mmol, 0.2 equiv.) in piperidine (20 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol, 0.05 equiv.) and the reaction mixture heated to reflux and stirred for 20 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was taken up in pentane and sat. *aq.* sodium bicarbonate (50 mL), and the aqueous layer extracted with pentane (2 x 50 mL). The combined organic extracts were washed with water (150 mL) and brine (150 mL), and filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (pentane) to give **S1** as a colourless solid (598 mg, 2.39 mmol, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.59 (2H, d, J = 7.5 Hz, H8), 7.55 (4H, s, H4 and H5), 7.45 (2H, t, J = 7.5 Hz, H9), 7.36 (1H, t, J = 7.5 Hz, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.2, 140.5, 132.3, 129.0, 127.9, 127.1, 127.0, 122.1, 105.3, 95.0, 0.1.

The spectroscopic data was found to be in agreement with that reported by Chen *et al.*[104]

4-(Bromoethynyl)-1,1'-biphenyl, 124j

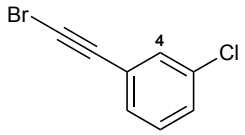


Prepared by General Procedure D using **S1** (500 mg, 2.00 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to

give **124j** as a colourless solid (209 mg, 0.82 mmol, 41%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58 (2H, d, *J* = 8.0 Hz, H8), 7.55 (2H, d, *J* = 8.0 Hz, H4), 7.52 (2H, d, *J* = 8.0 Hz, H5), 7.45 (2H, app. t, *J* = 8.0 Hz, H9), 7.36 (1H, t, *J* = 7.5 Hz, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.6, 140.3, 132.5, 129.0, 127.9, 127.3, 127.1, 121.7, 80.0, 50.4.

The spectroscopic data was found to be in agreement with that reported by Sun *et al.*[105]

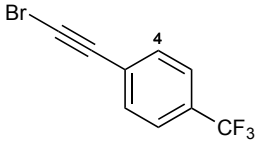
1-(Bromoethynyl)-3-chlorobenzene, 124m



Prepared by General Procedure D using 3-chlorophenyl acetylene (0.95 g, 6.96 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give **124m** as a colourless solid (1.28 g, 5.92 mmol, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.42 (1H, m, H4), 7.33-7.30 (2H, m, H6 and H8), 7.25-7.21 (1H, m, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.3, 132.0, 130.2, 129.7, 129.2, 124.5, 78.9, 51.7.

The spectroscopic data was found to be in agreement with that reported by Jiang *et al.*[106]

1-(Bromoethynyl)-4-(trifluoromethyl)benzene, 124n

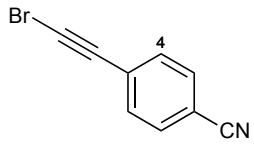


Prepared by General Procedure D using 4-ethynyl-α,α,α-trifluorotoluene (1.0 g, 5.88 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give **124n** as a colourless solid (1.33 g, 5.35 mmol, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58 (2H, d, *J* = 8.5 Hz, H4), 7.54 (2H, d, *J* = 8.5 Hz, H5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 132.4, 130.6 (q, J = 33.0 Hz), 126.7 (q, J = 1.5 Hz), 125.0 (q, J = 4.0 Hz), 124.0 (q, J = 272.0 Hz), 79.0, 53.1.

The spectroscopic data was found to be in agreement with that reported by Xu *et al.*[103]

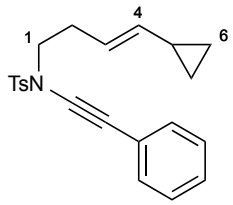
4-(Bromoethynyl)benzonitrile, 124o



Prepared by General Procedure D using 4-ethynylbenzonitrile (1.0 g, 7.86 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give **124o** as a colourless solid (1.36 g, 6.60 mmol, 84%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, J = 8.5 Hz, H4), 7.52 (2H, d, J = 8.5 Hz, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 132.5, 132.1, 127.4, 118.2, 112.1, 78.6, 55.2.

The spectroscopic data was found to be in agreement with that reported by Witulski *et al.*[107]

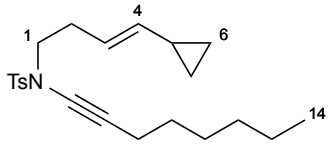
(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 120a



Prepared by General Procedure E using sulfonamide **123** (200 mg, 0.75 mmol, 1.0 equiv.) and bromoalkyne **124a** (205 mg, 1.13 mmol, 1.5 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120a** as a colourless oil (250 mg, 0.68 mmol, 91%); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (9:1));

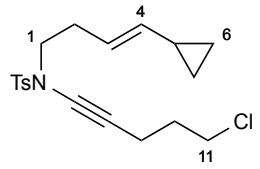
IR (thin film, ν_{max}/cm^{-1}) 3004, 2925, 2234, 1666, 1364, 1167, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.85 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.39-7.28 (7H, m, Ts*H* and Ph*H*), 5.40 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 5.05 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 3.43 (2H, t, *J* = 7.5 Hz, H1), 2.46 (3H, s, TsCH_3), 2.38 (2H, app. q, *J* = 7.5 Hz, H2), 1.35-1.28 (1H, m, H5), 0.68-0.64 (2H, m, H6), 0.33-0.30 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.8, 137.7, 135.0, 131.6, 130.0, 128.5, 128.0, 128.0, 123.2, 122.8, 82.6, 71.2, 51.8, 31.5, 21.9, 13.9, 6.8; **HRMS** (ESI+) calc. for $C_{22}H_{23}NNaO_2S$ $[M+Na]^+$ 388.1342, found 388.1327.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 120b



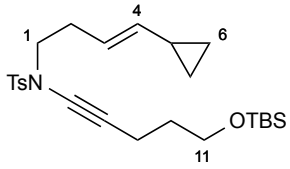
Prepared by General Procedure E using sulfonamide **123** (100 mg, 0.38 mmol, 1.0 equiv.) and bromoalkyne **124b** (107 mg, 0.57 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120b** as a colourless oil (87 mg, 0.23 mmol, 62%); $\mathbf{R_f}$ 0.55 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2929, 2858, 2252, 1456, 1364, 1167, 1092; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.36 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.00 (1H, dd, *J* = 15.5 and 8.0 Hz, H4), 3.27 (2H, t, *J* = 7.5 Hz, H1), 2.44 (3H, s, TsCH_3), 2.30-2.24 (4H, m, H2 and 9), 1.49-1.44 (2H, m, H10), 1.36-1.23 (7H, m, H5, 11, 12 and 13), 0.88 (3H, t, *J* = 7.0 Hz, H14), 0.67-0.63 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.1, 137.1, 134.7, 129.5, 127.6, 122.7, 72.9, 70.4, 51.3, 31.3, 31.0, 28.9, 28.5, 22.6, 21.6, 18.5, 14.1, 13.6, 6.4; **HRMS** (ESI+) calc. for $C_{22}H_{31}NNaO_2S$ $[M+Na]^+$ 396.1968, found 396.1958.

(*E*)-*N*-(5-Chloropent-1-yn-1-yl)-*N*-(4-cyclopropylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 120c



Prepared by General Procedure E using sulfonamide **123** (100 mg, 0.38 mmol, 1.0 equiv.) and bromoalkyne **124c** (103 mg, 0.57 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120c** as a colourless oil (112 mg, 0.31 mmol, 81%); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3081, 3003, 2926, 2253, 1597, 1363, 1166, 1120; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.35 (1H, dt, *J* = 15.5 and 7.5 Hz, H3), 5.00 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.60 (2H, t, *J* = 6.5 Hz, H11), 3.28 (2H, t, *J* = 7.5 Hz, H1), 2.46 (2 H, t, *J* = 6.5 Hz, H9), 2.44 (3H, s, TsCH_3), 2.28 (2H, q, *J* = 7.5 Hz, H2), 1.92 (2H, quin, *J* = 6.5 Hz, H10), 1.33-1.26 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.4, 137.3, 134.6, 129.6, 127.6, 122.6, 74.1, 68.4, 51.3, 43.6, 31.5, 31.0, 21.6, 15.9, 13.6, 6.5; **HRMS** (ESI+) calc. for $C_{19}H_{24}ClNNaO_2S$ $[M+Na]^+$ 388.1108, found 388.1093.

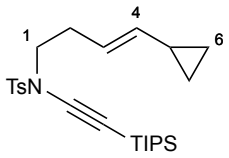
(*E*)-*N*-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)-*N*-(4-cyclopropylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 120d



Prepared by General Procedure E using sulfonamide **123** (100 mg, 0.38 mmol, 1.0 equiv.) and bromoalkyne **120d** (157 mg, 0.57 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120d** as a

colourless oil (96 mg, 0.21 mmol, 55%); $\mathbf{R_f}$ 0.58 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2953, 2923, 2857, 2254, 1363, 1254, 1168, 1097; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.35 (1H, dt, *J* = 15.5 and 7.5 Hz, H3), 5.00 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.64 (2H, t, *J* = 6.5 Hz, H11), 3.26 (2H, t, *J* = 7.5 Hz, H1), 2.44 (3H, s, TsCH_3), 2.34 (2H, t, *J* = 6.5 Hz, H9), 2.28 (2H, q, *J* = 7.5 Hz, H2), 1.68 (2H, quin, *J* = 6.5 Hz, H10), 1.33-1.26 (1H, m, H5), 0.88 (9H, s, SiC(CH_3)$_3$), 0.67-0.63 (2H, m, H6), 0.32-0.28 (2H, m, H6), 0.03 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.1, 137.1, 134.8, 129.5, 127.6, 122.7, 73.0, 70.0, 61.6, 51.4, 32.1, 31.0, 25.9, 21.7, 18.4, 14.9, 13.6, 6.5, –5.4; **HRMS** (ESI+) calc. for $C_{25}H_{39}NNaO_3SSi$ $[M+Na]^+$ 484.2312, found 484.2299.

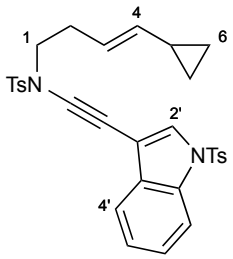
(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide, 120e



Prepared by General Procedure E using sulfonamide **123** (100 mg, 0.38 mmol, 1.0 equiv.) and bromoalkyne **124e** (148 mg, 0.57 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120e** as a colourless solid (136 mg, 0.31 mmol, 81%); $\mathbf{R_f}$ 0.59 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2941, 2865, 2160, 1494, 1370, 1169, 1119; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.36 (1H, dt, *J* = 15.5 and 7.5 Hz, H3), 4.99 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.34 (2H, t, *J* = 7.5 Hz, H1), 2.44 (3H, s, TsCH_3), 2.31 (2H, app. q, *J* = 7.5 Hz, H2), 1.32-1.25 (1H, m, H5), 1.04 (21H, s, Si(C*H*(CH_3)$_2$)$_3$), 0.66-0.62 (2H, m, H6), 0.30-0.27 (2H, m, H6); **^{13}C NMR**

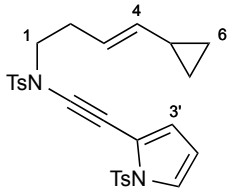
(125 MHz, C_6D_6) δ_C 144.4, 137.4, 134.7, 129.6, 127.8, 122.6, 96.2, 69.5, 51.2, 30.9, 21.6, 18.6, 13.6, 11.4, 6.4; **HRMS** (ESI+) calc. for $C_{25}H_{39}NNaO_2SSi$ $[M+Na]^+$ 468.2363, found 468.2359.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-((1-tosyl-1*H*-indol-3-yl)ethynyl)benzenesulfonamide, 120f



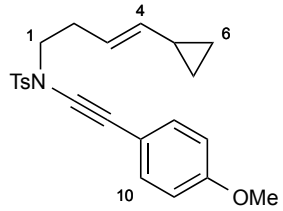
Prepared by General Procedure E using sulfonamide **123** (50 mg, 0.19 mmol, 1.0 equiv.) and bromoalkyne **124f** (85 mg, 0.23 mmol, 1.2 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **120f** as an orange oil (64 mg, 0.11 mmol, 61%); $\mathbf{R}_f$ 0.16 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3004, 2925, 2241, 1447, 1369, 1169, 1130, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.96 (1H, d, *J* = 8.5 Hz, H4′), 7.84 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.78 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.67 (1H, s, H2′), 7.49 (1H, d, *J* = 8.0 Hz, H7′), 7.36-7.33 (3H, m, H6′ and Ts*H*), 7.28-7.24 (3H, m, H5′ and Ts*H*), 5.39 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.45 (2H, t, *J* = 7.5 Hz, H1), 2.47 (3H, s, TsCH_3), 2.40-2.36 (5H, m, H2 and TsCH_3), 1.33-1.26 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.4, 144.7, 137.6, 134.9, 134.7, 134.2, 131.2, 130.0, 129.8, 128.9, 127.7, 127.0, 125.4, 123.6, 122.4, 120.5, 113.5, 104.6, 86.0, 61.8, 51.6, 31.2, 21.7, 21.6, 13.6, 6.5; **HRMS** (ESI+) calc. for $C_{31}H_{30}N_2NaO_4S_2$ $[M+Na]^+$ 581.1539, found 581.1532.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-((1-tosyl-1*H*-pyrrol-2-yl)ethynyl)benzenesulfonamide, 120g



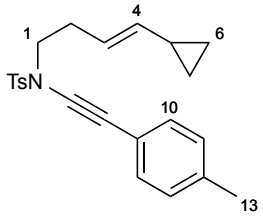
Prepared by General Procedure E using sulfonamide **123** (93 mg, 0.35 mmol, 1.0 equiv.) and bromoalkyne **124g** (228 mg, 0.70 mmol, 2.0 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (9:1)) to give **120g** as a colourless oil (114 mg, 0.23 mmol, 65%): $\mathbf{R}_f$ 0.34 (petroleum ether/diethyl ether (5:2)); **IR** (thin film, ν_{max}/ cm^{-1}) 2999, 2916, 2338, 2227, 1661, 1437, 1047, 1363, 1313, 1172, 1019; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.86-7.84 (4H, m, Ts*H*), 7.36-7.33 (3H, m, Ts*H* and H5′), 7.29-7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.45 (1H, dd, *J* = 3.5 and 1.5 Hz, H3′), 6.19 (1H, t, *J* = 3.5 Hz, H4′), 5.35 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.04 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.38 (2H, t, *J* = 7.5 Hz, H1), 2.45 (3H, s, TsCH_3), 2.40 (3H, s, TsCH_3), 2.33 (2H, app. q, *J* = 7.5 Hz, H2), 1.33-1.27 (1H, m, H5), 0.66-0.62 (2H, m, H6), 0.30-0.28 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.3, 144.8, 137.7, 135.6, 135.1, 130.1, 130.0, 128.0, 127.9, 123.8, 122.6 (2C), 115.1, 111.7, 87.1, 61.6, 51.8, 31.2, 21.8 (2C), 13.8, 6.7; **HRMS** (ESI+) calc. for $C_{27}H_{28}N_2NaO_4S_2$ $[M+Na]^+$ 531.1383, found 531.1382.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-*N*-((4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide, 120h



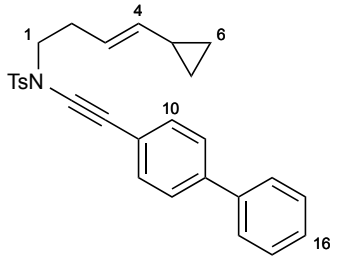
Prepared by General Procedure E using sulfonamide **123** (175 mg, 0.66 mmol, 1.0 equiv.) and bromoalkyne **124h** (278 mg, 1.32 mmol, 2.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (9:1)) to give **120h** as a yellow oil (170 mg, 0.43 mmol, 65%): $\mathbf{R}_f$ 0.14 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/ cm^{-1}) 3003, 2934, 2237, 1605, 1568, 1512, 1457, 1363, 1288, 1248, 1167, 1091, 1030; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.35 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.5 Hz, H10), 6.82 (2H, d, *J* = 8.5 Hz, H11), 5.39 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.81 (3H, s, OCH_3), 3.40 (2H, t, *J* = 7.5 Hz, H1), 2.45 (3H, s, TsCH_3), 2.36 (2H, td, *J* = 7.5 and 7.0 Hz, H2), 1.33-1.27 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.9, 144.8, 137.8, 135.2, 133.8, 130.1, 128.1, 123.1, 115.3, 114.3, 81.2, 70.9, 55.7, 52.0, 31.6, 22.1, 14.0, 6.9; **HRMS** (ESI+) calc. for $C_{23}H_{25}NNaO_3S$ $[M+Na]^+$ 418.1453, found 418.1458.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-(*p*-tolylethynyl)benzenesulfonamide, 120i



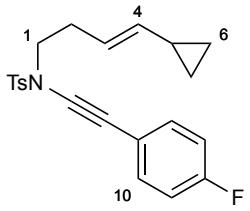
Prepared by General Procedure E using sulfonamide **123** (150 mg, 0.57 mmol, 1.0 equiv.) and bromoalkyne **124i** (165 mg, 0.85 mmol, 2.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120i** as a colourless oil (208 mg, 0.55 mmol, 97%); $\mathbf{R}_f$ 0.44 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}), 3003, 2923, 2235, 1666, 1512, 1364, 1166, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.26 (2H, d, *J* = 8.0 Hz, H10), 7.10 (2H, d, *J* = 8.0 Hz, H11), 5.39 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 15.5 and 9.0 Hz, H4), 3.41 (2H, t, *J* = 8.0 Hz, H1), 2.45 (3H, s, TsCH_3), 2.37 (2H, app. q, *J* = 7.5 Hz, H2), 2.34 (3H, s, H13), 1.34-1.27 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.32-0.29 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.6, 138.1, 137.5, 134.8, 131.6, 129.8, 129.1, 127.8, 122.7, 119.9, 81.6, 70.9, 51.6, 31.3, 21.8, 21.6, 13.7, 6.6; **HRMS** (ESI+) calc. for $C_{23}H_{25}O_2NNaS$ $[M+Na]^+$ 402.1498, found 402.1507.

(*E*)-*N*-([1,1'-Biphenyl]-4-ylethynyl)-*N*-(4-cyclopropylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 120j



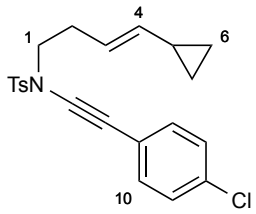
Prepared by General Procedure E using sulfonamide **123** (150 mg, 0.57 mmol, 1.0 equiv.) and bromoalkyne **124j** (145 mg, 0.85 mmol, 2.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120j** as a colourless oil (238 mg, 0.54 mmol, 95%); $\mathbf{R}_f$ 0.30 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3003, 2925, 2233, 1597, 1487, 1364, 1167, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.86 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.59 (2H, d, *J* = 8.0 Hz, H14), 7.54 (2H, d, *J* = 8.5 Hz, H11), 7.46-7.43 (4H, m, H10 and H15), 7.37-7.34 (3H, m, Ts*H* and H16), 5.41 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 5.05 (1H, dd, *J* = 15.0 and 9.0 Hz, H4), 3.44 (2H, t, *J* = 7.5 Hz, H1), 2.46 (3H, s, TsCH_3), 2.40 (2H, app. q, *J* = 7.5 Hz, H2), 1.35-1.28 (1H, m, H5), 0.68-0.64 (2H, m, H6), 0.33-0.30 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.7, 140.6, 140.5, 137.6, 134.8, 131.9, 129.9, 128.9, 127.8, 127.7, 127.1, 127.1, 122.6, 122.0, 83.1, 70.9, 51.7, 31.3, 21.8, 13.7, 6.6; **HRMS** (ESI+) calc. for $C_{28}H_{27}O_2NNaS$ $[M+Na]^+$ 464.1655, found 464.1655.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-*N*-((4-fluorophenyl)ethynyl)-4-methylbenzenesulfonamide, 120k



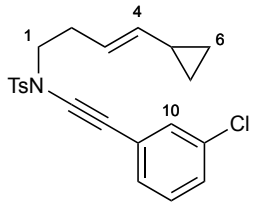
Prepared by General Procedure E using sulfonamide **123** (175 mg, 0.66 mmol, 1.0 equiv.) and bromoalkyne **124k** (263 mg, 1.32 mmol, 2.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (9:1)) to give **120k** as a yellow oil (180 mg, 0.47 mmol, 71%): $\mathbf{R_f}$ 0.24 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/ cm^{-1}) 3075, 3004, 2924, 2273,1599, 1510, 1354, 1225, 1161, 1089; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.84-7.81 (2H, m, Ts*H*), 7.36-7.31 (4H, m, Ts*H* and H10), 7.01-6.95 (2H, m, H11), 5.38 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.02 (1H, ddt, *J* = 15.5, 8.5 and 1.0 Hz, H4), 3.40 (2H, t, *J* = 7.5 Hz, H1), 2.45 (3H, s, TsCH_3), 2.36 (2H, app. q, *J* = 7.0, H2), 1.33-1.25 (1H, m, H5), 0.67-0.61 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 162.3 (d, *J* = 249.0 Hz), 144.7, 137.6, 134.8, 133.6 (d, *J* = 234.0 Hz), 129.9, 127.8, 122.6, 119.0 (d, *J* = 4.0 Hz), 115.6 (d, *J* = 22.0 Hz), 82.0, 69.9, 51.6, 31.3, 21.8, 13.8, 6.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F −115.6; **HRMS** (ESI+) calc. for $C_{22}H_{22}FNNaO_2S$ $[M+Na]^+$ 406.1253, found 406.1256.

(*E*)-*N*-((4-Chlorophenyl)ethynyl)-*N*-(4-cyclopropylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 120l



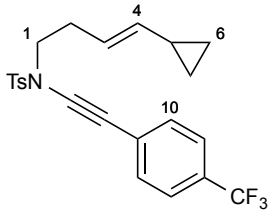
Prepared by General Procedure E using sulfonamide **123** (130 mg, 0.49 mmol, 1.0 equiv.) and bromoalkyne **124l** (210 mg, 0.98 mmol, 2.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (9:1)) to give **120l** as a yellow oil (153 mg, 0.38 mmol, 79%): $\mathbf{R}_f$ 0.28 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/ cm^{-1}) 3004, 2928, 2236, 1596, 1366, 1168, 1090, 1014; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.35 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.29-7.24 (4H, m, H10 and H11), 5.38 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 3.41 (2H, t, *J* = 7.5 Hz, H1), 2.45 (3H, s, TsCH_3), 2.36 (2H, td, *J* = 7.5 and 7.0 Hz, H2), 1.34-1.26 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.32-0.28 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.7, 137.5, 134.7, 133.7, 132.5, 129.8, 128.6, 127.7, 122.4, 121.5, 83.3, 70.0, 51.5, 31.2, 21.7, 13.6, 6.5; **HRMS** (ESI+) calc. for $C_{22}H_{22}ClNNaO_2S$ $[M+Na]^+$ 422.0957, found 442.0960.

(*E*)-*N*-((3-Chlorophenyl)ethynyl)-*N*-(4-cyclopropylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 120m



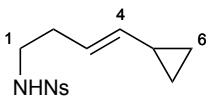
Prepared by General Procedure E using sulfonamide **123** (150 mg, 0.57 mmol, 1.0 equiv.) and bromoalkyne **124m** (183 mg, 0.85 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120m** as a colourless oil (217 mg, 0.54 mmol, 96%); $\mathbf{R}_f$ 0.47 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3003, 2927, 2234, 1594, 1365, 1167, 1089; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.36 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.33-7.32 (1H, m, H10), 7.26-7.20 (3H, m, H12-14), 5.38 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 3.42 (2H, t, *J* = 7.5 Hz, H1), 2.45 (3H, s, TsCH_3), 2.36 (2H, app. q, *J* = 7.5 Hz), 1.33-1.26 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.32-0.29 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.9, 137.7, 134.8, 134.2, 131.1, 129.9, 129.6, 129.4, 128.0, 127.8, 124.9, 122.5, 83.7, 70.0, 51.6, 31.3, 21.8, 13.7, 6.6; **HRMS** (ESI+) calc. for $C_{22}H_{22}O_2NClNaS$ $[M+Na]^+$ 422.0952, found 422.0949.

(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-methyl-*N*-((4-(trifluoromethyl)phenyl)ethynyl)benzenesulfonamide, 120n



Prepared by General Procedure E using sulfonamide **123** (150 mg, 0.57 mmol, 1.0 equiv.) and bromoalkyne **124n** (211 mg, 0.85 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **120n** as a colourless oil (239 mg, 0.55 mmol, 98%); $\mathbf{R}_f$ 0.49 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3004, 2929, 2233, 1667, 1368, 1320, 1165, 1119, 1065; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.54 (2H, d, *J* = 8.5 Hz, H11), 7.43 (2H, d, *J* = 8.5 Hz, H10), 7.36 (2H, d, *J* = 8.0, Ts*H*), 5.38 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 8.5, H4), 3.44 (2H, t, *J* = 7.5 Hz, H1), 2.45 (3H, s, TsCH_3), 2.37 (2H, app. q, *J* = 7.5 Hz, H2), 1.33-1.26 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.0, 137.8, 134.8, 131.1, 130.0, 129.3 (q, *J* = 32.5 Hz), 127.8, 127.1, 125.3 (q, *J* = 3.5 Hz), 124.2 (q, *J* = 270.0 Hz), 122.4, 85.1, 70.4, 51.6, 31.4, 21.8, 13.7, 6.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F –62.7; **HRMS** (ESI+) calc. for $C_{23}H_{22}O_2NF_3NaS$ $[M+Na]^+$ 456.1216, found 456.0981.

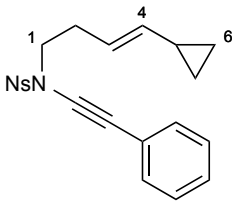
(*E*)-4-((4-Cyclopropylbut-3-en-1-yl)amino)-3-nitrobenzenesulfonic acid, 126



Prepared by General Procedure C using acid **122** (0.50 g, 3.57 mmol, 1.0 equiv.) and nosyl chloride (0.79 g, 3.57 mmol, 1.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **126** as a yellow oil

(0.22 g, 0.73 mmol, 20%); $\mathbf{R}_f$ 0.43 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3294, 3106, 3004, 2937, 1528, 1348, 1309, 1161, 1093; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.36 (2H, d, *J* = 9.0 Hz, Ns*H*), 8.05 (2H, d, *J* = 9.0 Hz, Ns*H*), 5.24 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 4.98 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.70 (1H, t, *J* = 6.0 Hz, N*H*), 3.04 (2H, dt, *J* = 6.5 and 6.0 Hz, H1), 2.15 (2H, dt, *J* = 7.0 and 6.5 Hz, H2), 1.32-1.24 (1H, m, H5), 0.70-0.65 (2H, m, H6), 0.32-0.28 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 150.1, 146.0, 138.7, 128.4, 124.4, 122.4, 42.9, 32.5, 13.7, 6.7; **HRMS** (ESI–) calc. for $C_{13}H_{15}O_4N_2S$ $[M-H]^-$ 295.0758, found 295.0755.

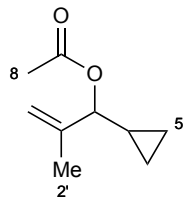
(*E*)-*N*-(4-Cyclopropylbut-3-en-1-yl)-4-nitro-*N*-(phenylethynyl)benzenesulfonamide, 127a



Prepared by General Procedure E using sulfonamide **126** (100 mg, 0.34 mmol, 1.0 equiv.) and bromoalkyne **124a** (92 mg, 0.51 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **127a** as a colourless oil (116 mg, 0.29 mmol, 87%); $\mathbf{R}_f$ 0.36 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3105, 3004, 2238, 1530, 1371, 1348, 1172, 1070; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.41 (2H, d, *J* = 9.0 Hz, Ns*H*), 8.14 (2H, d, *J* = 9.0 Hz, Ns*H*), 7.38-7.36 (2H, m, Ph*H*), 7.32-7.30 (3H, m, Ph*H*), 5.34 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 5.03 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 3.50 (2H, t, *J* = 7.5 Hz, H1), 2.39 (2H, td, *J* = 7.5 and 7.0 Hz, H2), 1.29-1.23 (1H, m, H5), 0.67-0.63 (2H, m, H6), 0.30-0.27 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 150.6, 143.1, 138.1, 131.6, 128.9, 128.5, 128.4, 124.4, 122.1, 122.0, 80.8, 71.6, 52.0,

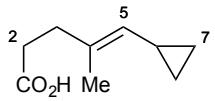
31.2, 13.7, 6.6; **HRMS** (ESI+) calc. for $C_{21}H_{20}O_4N_2NaS$ $[M+Na]^+$ 419.1036, found 419.1030.

1-Cyclopropyl-2-methylallyl acetate, 129



Prepared by General Procedure A using isopropenylmagnesium bromide (0.5 M in THF, 31.4 mL, 15.7 mmol, 1.1 equiv.) and acetic anhydride (1.62 mL, 17.1 mmol, 1.2 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **129** as a colourless oil (1.47 g, 9.5 mmol, 67%); $\mathbf{R}_f$ 0.39 (petroleum ether/diethyl ether (95:5)); **IR** (thin film, ν_{max}/cm^{-1}) 3085, 2963, 2923, 1738, 1433, 1371, 1240; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.97 (1H, s, H3), 4.87 (1H, s, H3), 4.55 (1H, d, *J* = 9.0 Hz, H1), 2.08 (3H, s, H8), 1.80 (3H, s, H2´), 1.12-1.05 (1H, m, H4), 0.62-052 (2H, m, H5), 0.45-0.40 (1H, m, H5), 0.33-0.28 (1H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.4, 143.6, 112.1, 81.3, 21.3, 18.9, 14.2, 3.7, 3.4; **HRMS** not found.

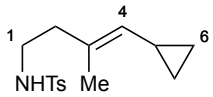
(*E*)-5-Cyclopropyl-4-methylpent-4-enoic acid, 130



Prepared by General Procedure B using ester **129** (1.2 g, 7.78 mmol, 1.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1) + 1% acetic acid) to give **130** as a colourless oil (1.0 g, 6.48 mmol, 84%); $\mathbf{R}_f$ 0.35 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3081, 3003, 2916, 2670, 1705, 1412, 1297, 1212, 1046; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.58 (1H, d,

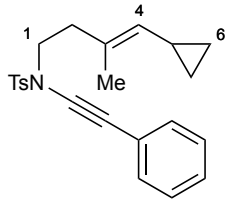
J = 9.5 Hz, H5), 2.44 (2H, t, *J* = 8.5 Hz, H2), 2.29 (2H, t, *J* = 8.5 Hz, H3), 1.7 (3H, s, H4′), 1.47-1.40 (1H, m, H6), 0.71-0.67 (2H, m, H7), 0.28-0.25 (2H, m, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 179.8, 131.8, 129.7, 34.2, 32.9, 16.3, 10.0, 6.7; **HRMS** (ESI+) calc. for $C_9H_{14}NaO_2$ $[M+Na]^+$ 177.0886, found 177.0880.

(*E*)-*N*-(4-Cyclopropyl-3-methylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 131



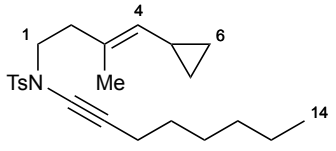
Prepared by General Procedure C using carboxylic acid **130** (1.0 g, 6.48 mmol, 1.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **131** as a colourless oil (0.72 g, 4.67 mmol, 40%); $\mathbf{R_f}$ 0.17 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3281, 3080, 3001, 2924, 1670, 1427, 1306, 1156, 1094; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.5 Hz, Ts*H*), 4.48 (1H, d, *J* = 9.5 Hz, H5), 4,34 (1H, t, *J* = 5.5 Hz, N*H*), 3.00 (2H, q, *J* = 6.5 Hz, H2), 2.43 (3H, s, TsCH_3), 2.07 (2H, t, *J* = 6.5 Hz, H3), 1.56 (3H, s, H4′), 1.42-1.35 (1H, m, H6), 0.72-0.68 (2H, m, H7), 0.28-0.25 (2H, m, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.4, 136.9, 132.5, 129.7, 129.1, 127.2, 40.6, 38.8, 21.5, 15.6, 10.0, 6.8; **HRMS** (ESI+) calc. for $C_{15}H_{21}NNaO_2S$ $[M+Na]^+$ 302.1185, found 302.1188.

(*E*)-*N*-(4-Cyclopropyl-3-methylbut-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 128a



Prepared by General Procedure E using sulfonamide **131** (100 mg, 0.36 mmol, 1.0 equiv.) and 1-bromo-2-phenylacetylene **124a** (97 mg, 0.54 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **128a** as a colourless oil (108 mg, 0.28 mmol, 80%); $\mathbf{R_f}$ 0.38 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3080, 3001, 2927, 2234, 1598, 1307, 1140, 1070, 1019; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.84 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.37-7.28 (7H, m, Ts*H* and Ph*H*), 4.56 (1H, d, *J* = 9.5 Hz, H5), 3.48 (2H, t, *J* = 7.5 Hz, H2), 2.45 (3H, s, TsCH_3), 2.33 (2H, t, *J* = 7.5 Hz, H3), 1.74 (3H, s, H4′), 1.44-1.36 (1H, m, H6), 0.70-0.65 (2H, m, H7), 0.26-0.23 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.5, 134.8, 132.0, 131.4, 129.8, 129.1, 128.3, 127.8, 123.0, 82.4, 70.8, 50.4, 37.9 21.7, 16.3, 10.1, 6.7; **HRMS** (ESI+) calc. for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$ 402.1498, found 402.1501.

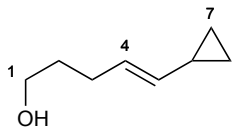
(*E*)-*N*-(4-Cyclopropyl-3-methylbut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 128b



Prepared by General Procedure E using sulfonamide **131** (100 mg, 0.36 mmol, 1.0 equiv.) and 1-bromooct-1-yne **124b** (102 mg, 0.54 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **128b** as a

colourless oil (109 mg, 0.28 mmol, 79%); $\mathbf{R_f}$ 0.52 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3080, 3001, 2929, 2858, 2254, 1597, 1495, 1363, 1167, 1093; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.5 Hz, Ts*H*), 4.54 (1H, d, *J* = 9.5 Hz, H5), 3.32 (2H, t, *J* = 8.0 Hz, H2), 2.44 (3H, s, TsCH_3), 2.27-2.22 (4H, m, H4 and H10), 1.71 (3H, s, H4′), 1.50-1.20 (9H, m, H6 and H11-14), 0.88 (3H, t, *J* = 7.0 Hz, H15), 0.70-0.65 (2H, m, H7), 0.27-0.23 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.1, 134.9, 131.6, 129.5, 129.4, 127.7, 73.0, 70.4, 50.3, 37.7, 31.4, 28.9, 28.5, 22.6, 21.7, 18.5, 16.3, 14.1, 10.1, 6.7; **HRMS** (ESI+) calc. for $C_{23}H_{33}NNaO_2S$ $[M+Na]^+$ 410.2124, found 410.2126.

(*E*)-5-Cyclopropylpent-4-en-1-ol, 133

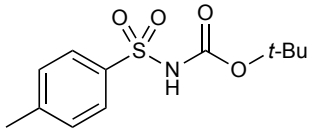


According to the procedure of Paolucci et al.[108] To a solution of carboxylic acid **122** (500 mg, 3.6 mmol, 1.0 equiv.) in anhydrous THF (18 mL) at 0 °C was added lithium aluminium hydride (4 M in diethyl ether, 0.9 mL, 3.7 mmol, 1.05 equiv.). The solution was allowed to reach room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C and water (0.14 mL), 2 M sodium hydroxide (0.28 mL) and water (0.42 mL) were added sequentially. To the solution was added magnesium sulfate and the resulting suspension stirred for 30 min, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/diethyl ether (9:1)) to give **133** as a colourless oil (293 mg, 2.3 mmol, 65%); $\mathbf{R_f}$ 0.22 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3331, 3081, 3005, 2933, 2867, 1430, 1057, 1045, 959; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.52 (1H, dt, *J* = 15.0 and 7.0 Hz, H4), 5.01 (1H, dd, *J* = 15.0 and 8.0 Hz, H5), 3.65 (2H, t, *J* = 6.5 Hz, H1), 2.08 (2H, app. q, *J* = 7.0 Hz, H3), 1.63 (2H,

quin, J = 7.0 Hz, H2), 1.48 (1H, s, O*H*), 1.39-1.30 (1H, m, H6), 0.68-0.63 (2H, m, H7), 0.33-0.30 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 134.6, 127.3, 62.6, 32.5, 28.8, 13.5, 6.4.

The physical and spectroscopic data were found to be in agreement with that reported by Paolucci *et al*.[108]

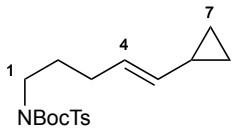
tert-Butyl tosylcarbamate, S2



According to the procedure of White et al.[109] To a solution of *tert*-butanol (23.1 mL, 241 mmol, 1.0 equiv.) in dichloromethane (400 mL) at 0 °C was added *p*-toluenesulfonyl isocyanate (50.0 g, 254 mmol, 1.05 equiv.) and the reaction mixture allowed to warm to room temperature. After 2 h the solution was concentrated *in vacuo* and the solid recrystallised (diethyl ether/dichloromethane (5:1)) to give **S2** as a colourless crystalline solid (55.73 g, 205 mmol, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, J = 8.5 Hz, Ts*H*), 7.42 (1H, s, N*H*), 7.26 (2H, d, J = 8.5 Hz, Ts*H*), 2.38 (3H, s, TsCH_3), 1.31 (9H, s, Boc*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.2, 144.7, 136.0, 129.5, 128.2, 84.1, 27.9, 21.7.

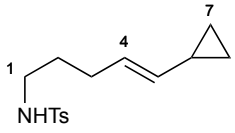
The spectroscopic data was found to be in agreement with that reported by Hanson *et al*.[110]

(*E*)-*tert*-Butyl (5-cyclopropylpent-4-en-1-yl)(tosyl)carbamate, 134



To a solution of alcohol **133** (100 mg, 0.79 mmol, 1.0 equiv.), triphenylphosphine (270 mg, 1.03 mmol, 1.3 equiv.), tosylcarbamate **S2** (237 mg, 0.87 mmol, 1.1 equiv.) in anhydrous THF (8 mL) at 0 °C was added diisopropyl azodicarboxylate (0.19 mL, 0.95 mmol, 1.2 equiv.) dropwise and the solution allowed to reach room temperature and stirred for 2 h. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **134** as a colourless oil (280 mg, 0.73 mmol, 94%); $\mathbf{R}_f$ 0.44 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2981, 2921, 1724, 1354, 1285, 1154, 1088, 1019; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.52 (1H, dt, *J* = 15.5 and 7.0 Hz, H4), 5.01 (1H, dd, *J* = 15.5 and 8.5 Hz, H5), 3.83-3.79 (2H, m, H1), 2.44 (3H, s, TsCH_3), 2.05 (2H, q, *J* = 7.0 Hz, H3), 1.82 (2H, quin., *J* = 7.0 Hz, H2), 1.39-1.31 (10H, m, H6 and Boc*H*), 0.68-0.64 (2H, m, H7), 0.34-0.31 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.0, 144.0, 137.6, 134.8, 129.2, 127.8, 126.6, 84.0, 46.9, 30.0, 29.6, 27.9, 21.7, 13.5, 6.4; **HRMS** (ESI+) calc. for $C_{20}H_{29}NNaO_4S$ $[M+Na]^+$ 402.1710, found 402.1707.

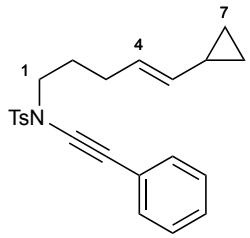
(*E*)-*N*-(5-Cyclopropylpent-4-en-1-yl)-4-methylbenzenesulfonamide, 135



To a solution of sulfonamide **134** (100 mg, 0.26 mmol, 1.0 equiv.) in anhydrous methanol (2.6 mL) was added potassium carbonate (182 mg, 1.32 mmol, 5.0 equiv.) and the reaction mixture heated to 65 °C for 3h. The solution was concentrated *in vacuo* and the residue

partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **135** as a colourless oil (60 mg, 0.21 mmol, 81%); $\mathbf{R}_f$ 0.17 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3282, 3080, 3003, 2926, 2867, 1425, 1324, 1157, 1094, 962; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.32 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.37 (1H, dt, *J* = 15.5 and 7.0 Hz, H4), 4.92 (1H, dd, *J* = 15.5 and 8.5 Hz, H5), 4.46 (1H, t, *J* = 6.0 Hz, N*H*), 2.94 (2H, app. q, *J* = 7.0 Hz, H1), 2.44 (3H, s, TsCH_3), 1.97 (2H, q, *J* = 7.0 Hz, H3), 1.52 (2H, quin, *J* = 7.0 Hz, H2), 1.34-1.27 (1H, m, H6), 0.67-0.63 (2H, m, H7), 0.30-0.27 (2H, m, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.3, 137.0, 135.2, 129.7, 127.1, 126.2, 42.6, 29.4, 29.3, 21.5, 13.4, 6.4; **HRMS** (ESI+) calc. for $C_{15}H_{21}NNaO_2S$ $[M+Na]^+$ 302.1185, found 302.1184.

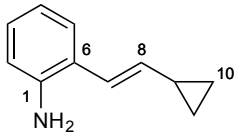
(*E*)-*N*-(5-Cyclopropylpent-4-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 132a



Prepared by General Procedure E using sulfonamide **135** (50 mg, 0.18 mmol, 1.0 equiv.) and bromoalkyne **124a** (65 mg, 0.36 mmol, 2.0 equiv.), with the reaction mixture stirred for 3 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **132a** as a colourless oil (60 mg, 0.16 mmol, 87%); $\mathbf{R}_f$ 0.50 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3080, 3003, 2927, 2235,

1696, 1598, 1365, 1168, 1091, 963; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.85 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.38-7.28 (7H, m, Ts*H* and Ph*H*), 5.46 (1H, dt, *J* = 15.0 and 7.0 Hz, H4), 5.00 (1H, dd, *J* = 15.0 and 8.5 Hz, H5), 3.40 (2H, t, *J* = 7.0 Hz, H1), 2.46 (3H, s, TsCH_3), 2.06 (2H, q, *J* = 7.0 Hz, H3), 1.77 (2H, quin, *J* = 7.0 Hz, H2), 1.37-1.30 (1H, m, H6), 0.68-0.64 (2H, m, H7), 0.33-0.30 (2H, m, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.5, 135.3, 134.6, 131.3, 129.7, 128.2, 127.7, 127.7, 126.1, 122.9, 82.4, 70.6, 51.0, 29.1, 27.9, 21.6, 13.5, 6.4; **HRMS** (ESI+) calc. for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$ 402.1498, found 402.1488.

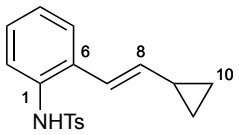
(*E*)-2-(2-Cyclopropylvinyl)aniline, 139



According to the procedure of Driver et al.[111] To a solution of (*trans*)-2-cyclopropylvinylboronic acid pinacol ester **138** (0.18 mL, 0.87 mmol, 1.5 equiv.), $Pd(PPh_3)_4$ (67 mg, 0.06 mmol, 0.1 equiv.) and K_2CO_3 (321 mg, 2.33 mmol, 4.0 equiv.) in a mixture of toluene/ethanol/water (5/2/1, 8 mL) was added 2-bromoaniline **137** (100 mg, 0.58 mmol, 1.0 equiv.). The reaction mixture was heated to reflux for 7 h. The mixture was allowed to cool to room temperature and diluted with water (20 mL) and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **139** as a brown oil (57 mg, 0.36 mmol, 61%); $\mathbf{R}_f$ 0.33 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3446, 3370, 3078, 3004, 1617, 1492, 1456; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.19 (1H, dd, *J* = 7.5 and 1.5 Hz, H5), 7.03 (1H, td, *J* = 7.5 and 1.5 Hz, H3), 6.74 (1H, td, *J* = 7.5 and 1.0 Hz, H4), 6.67 (1H, dd, *J* = 7.5 and 1.5 Hz, H2), 6.50 (1H, d, *J* = 15.5 Hz, H7), 5.59 (1H, dd, *J* = 15.5 and 9.0 Hz, H8), 3.71 (2H, s, NH_2), 1.63-1.55 (1H, m, H9), 0.85-0.81

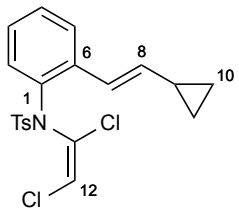
(2H, m, H10), 0.53-0.49 (2H, m, H10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.2, 136.9, 127.7, 127.7, 124.4, 122.8, 119.0, 115.9, 14.9, 7.3; **HRMS** (ESI+) calc. for $C_{11}H_{14}N$ $[M+H]^+$ 160.1121, found 160.1121.

(*E*)-*N*-(2-(2-Cyclopropylvinyl)phenyl)-4-methylbenzenesulfonamide, 140



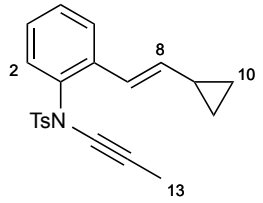
To a solution of **139** (160 mg, 1.00 mmol, 1.0 equiv.) and pyridine (0.24 mL, 3.01 mmol, 3.0 equiv.) in dichloromethane (2 ml) was added tosyl chloride (230 mg, 1.21 mmol, 1.2 equiv.) and the reaction mixture stirred for 16 h. The reaction mixture was diluted with *aq.* citric acid (1.0 M, 20 mL) and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo.* The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **140** as a colourless solid (282 mg, 0.90 mmol, 90%); $\mathbf{R_f}$ 0.22 (petroleum ether/ethy acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3269, 3005, 1645, 1598, 1487, 1399, 1329, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34 (1H, dd, *J* = 8.0 and 1.5 Hz, H5), 7.21 (3H, m, H2 and Ts*H*), 7.15 (1H, td, *J* = 8.0 and 1.5 Hz, H4), 7.09 (1H, td, *J* = 7.5 and 1.5 Hz, H3), 6.49 (1H, s, N*H*), 6.15 (1H, d, *J* = 15.5 Hz, H7), 5.39 (1H, dd, *J* = 15.5 and 9.0 Hz, H8), 2.39 (3H, s, TsCH_3), 1.47-1.39 (1H, m, H9), 0.82-0.77 (2H, m, H10), 0.43-0.39 (2H, m, H10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.9, 139.8, 136.7, 132.7, 129.7, 127.7, 127.3, 126.4, 124.8, 121.3, 21.6, 14.9, 7.5; **HRMS** (ESI+) calc. for $C_{18}H_{19}O_2NNaS$ $[M+Na]^+$ 336.1029, found 336.1021.

_N_-(2-((_E_)-2-Cyclopropylvinyl)phenyl)-_N_-((_E_)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, 141



Prepared by General Procedure F using sulfonamide **140** (280 mg, 0.89 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give **141** as a colourless oil (308 mg, 0.76 mmol, 84%); $\mathbf{R}_f$ 0.49 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3084, 3006, 2923, 2852, 1645, 1597, 1402, 1168; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.49 (1H, d, *J* = 8.0 Hz, H5), 7.29 (1H, dd, *J* = 8.0 and 7.5 Hz, H4), 7.26 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.23 (1H, d, *J* = 8.0 Hz, H2), 7.10 (1H, dd, *J* = 8.0 and 7.5 Hz, H3), 6.93 (1H, d, *J* = 16.0 Hz, H7), 6.43 (1H, s, H12), 5.62 (1H, dd, *J* = 16.0 and 9.0 Hz, H8), 2.44 (3H, s, TsCH_3), 1.52-1.43 (1H, m, H9), 0.81-0.76 (2H, m, H10), 0.47-0.43 (2H, m, H10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.8, 138.9, 137.4, 135.7, 133.6, 131.9, 130.9, 129.8, 129.6, 129.1, 126.7, 126.1, 123.6, 119.2, 21.9, 14.9, 7.5; **HRMS** (ESI+) calc. for $C_{20}H_{19}O_2N_{35}Cl_2NaS$ $[M+Na]^+$ 430.0406, found 430.0399.

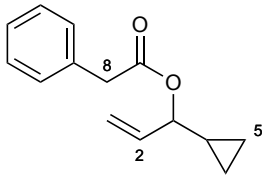
(_E_)-_N_-(2-(2-Cyclopropylvinyl)phenyl)-4-methyl-_N_-(prop-1-yn-1-yl)benzenesulfonamide, 136



Prepared by General Procedure G using dichloroenamide **141** (250 mg, 0.61 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum

ether/ethyl acetate (95:5)) to give **136** as a colourless oil (216 mg, 0.61 mmol, >99%); $\mathbf{R_f}$ 0.36 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3004, 2919, 2257, 1645, 1597, 1483, 1449, 1366, 1171; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.50 (1H, d, *J* = 8.0 Hz, H5), 7.33 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.26 (1H, dd, *J* = 8.0 and 7.5 Hz, H4), 7.10 (1H, dd, *J* = 8.0 and 7.5 Hz, H3), 6.93 (1H, d, *J* = 8.0 Hz, H2), 6.57 (1H, d, *J* = 16.0 Hz, H7), 5.71 (1H, dd, *J* = 16.0 and 9.0 Hz, H8), 2.47 (3H, s, H13), 1.91 (3H, s, TsCH_3), 1.52-1.45 (1H, m, H9), 0.83-0.79 (2H, m, H10), 0.49-0.46 (2H, m, H10); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.7, 137.7, 136.9, 135.6, 134.5, 129.6, 129.3, 128.9, 128.5, 127.2, 125.9, 122.2, 73.5, 64.8, 21.9, 15.0, 7.7, 3.5; **HRMS** (ESI+) calc. for $C_{21}H_{21}O_2NNaS$ $[M+Na]^+$ 374.1185, found 374.1179.

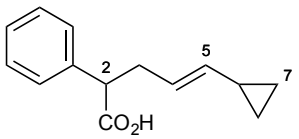
1-Cyclopropylallyl 2-phenylacetate, 146



Prepared by General Procedure A using vinylmagnesium bromide (1 M in THF, 13.4 mL, 13.4 mmol, 1.0 equiv.), cyclopropanecarboxaldehyde **118** (1.07 mL, 13.4 mmol, 1.0 equiv.) and phenylacetyl chloride (2.21 mL, 16.7 mmol, 1.25 equiv.). The residue was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **146** as a colourless oil (1.15 g, 5.3 mmol, 40%); $\mathbf{R_f}$ 0.68 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3087, 3011, 1731, 1645, 1604, 1497, 1428, 1346, 1252, 1156, 967; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27-7.17 (5H, m, Ph*H*), 5.76 (1H, ddd, *J* = 17.0, 10.0 and 6.0 Hz, H2), 5.13 (1H, dt, *J* = 17.0 and 1.5 Hz, H3), 5.05 (1H, dt, *J* = 10.0 and 1.5 Hz, H3), 4.67 (1H, dd, *J* = 8.5 and 6.0 Hz, H1), 3.58 (2H, s, H8), 1.03-0.94 (1H, m, H4), 0.52-0.40 (2H, m, H5), 0.34-0.18 (2H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.5, 133.0, 131.8,

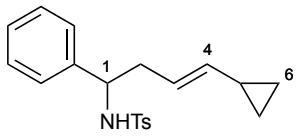
126.8, 126.1, 124.6, 114.1, 76.4, 39.2, 12.1, 0.9, 0.0; **HRMS** (ESI+) calc. for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239.1043, found 239.1046.

(*E*)-5-Cyclopropyl-2-phenylpent-4-enoic acid, 148



Prepared by General Procedure B using ester **146** (0.5 g, 2.3 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1) + 1% acetic acid) to give **148** as a colourless oil (0.48 g, 2.2 mmol, 96%); $\mathbf{R}_f$ 0.30 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3082, 3005, 2919, 1704, 1601, 1496, 1414, 1283, 1246, 1205, 1020; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.36-7.27 (5H, m, Ph*H*), 5.42 (1H, dt, *J* = 15.0 and 7.0 Hz, H4), 5.04 (1H, dd, *J* = 15.0 and 8.5 Hz, H5), 3.60 (1H, dd, *J* = 7.0 and 8.5 Hz, H2), 2.76 (1H, app. dt, *J* = 14.0 and 7.0 Hz, H3), 2.46 (1H, app. dt, *J* = 14.0 and 7.0 Hz, H3), 1.34-1.27 (1H, m, H6), 0.66-0.62 (2H, m, H7), 0.30-0.27 (2H, m, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 179.8, 138.1, 137.0, 128.6, 128.1, 127.5, 123.7, 52.1, 36.1, 13.5, 6.5; **HRMS** (ESI+) calc. for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239.1043, found 239.1035.

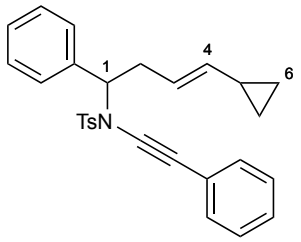
(*E*)-*N*-(4-Cyclopropyl-1-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 150



To a stirred solution of carboxylic acid **148** (400 g, 1.85 mmol, 1.0 equiv.) and triethylamine (0.26 mL, 1.85 mmol, 1.0 equiv.) in anhydrous toluene (10 mL) at 0 °C was added diphenyl phosphoryl azide (0.40 mL, 1.85 mmol, 1.0 equiv.) dropwise and the

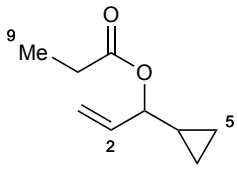
reaction mixture heated to 100 °C for 1 h. 9-fluorenemethanol (363 g, 1.85 mmol, 1.0 equiv.) and copper chloride (6 mg, 0.06 mmol, 0.033 equiv.) were added and the solution stirred for a further 48 h. The reaction mixture was diluted with diethyl ether (30 mL) and 1 M *aq.* citric acid (30 mL) and the aqueous layer separated. The aqueous layer was washed with diethyl ether (3 x 30 mL), basified to pH ~ 11 with 2 M *aq.* sodium hydroxide and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL), tosyl chloride (353 mg, 1.85 mmol, 1.0 equiv.) and triethylamine (0.26 mL, 1.85 mmol, 1.0 equiv.) were added and the solution stirred for 4 h at room temperature. To the solution was added sat. *aq.* ammonium chloride (20 mL) and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **150** as a colourless oil (160 mg, 0.47 mmol, 25%); $\mathbf{R}_f$ 0.16 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3278, 3065, 3004, 2925, 1665, 1495, 1455, 1324, 1156, 1093; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.57 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.20-7.09 (7H, m, Ph*H* and Ts*H*), 5.12 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 4.98 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 4.86 (1H, m, N*H*), 4.30 (1H, dt, *J* = 7.0 and 6.5 Hz, H1), 2.38 (3H, s, TsCH_3), 2.36-2.33 (2H, m, H2), 1.30-1.21 (1H, m, H5), 0.70-0.65 (2H, m, H6), 0.32-0.28 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.1, 140.8, 139.3, 137.4, 129.3, 128.3, 127.3, 127.2, 126.6, 121.7, 57.3, 40.8, 21.5, 13.6, 6.7; **HRMS** (ESI+) calc. for $C_{20}H_{23}NNaO_2S$ $[M+Na]^+$ 364.1342, found 364.1340.

(*E*)-*N*-(4-Cyclopropyl-1-phenylbut-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzene-sulfonamide, 152



Prepared by General Procedure E using sulfonamide **150** (135 mg, 0.40 mmol, 1.0 equiv.) and bromoalkyne **124a** (143 mg, 0.79 mmol, 2.0 equiv.), with the reaction mixture stirred at 105 °C for 16 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **152** as a colourless oil (125 mg, 0.28 mmol, 71%); $\mathbf{R_f}$ 0.30 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3063, 3031, 3005, 2925, 2233, 1694, 1598, 1495, 1362, 1168, 1089; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.63 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.38-7.24 (10H, m, Ph*H*), 7.18 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.28 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.05 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 5.00 (1H, dd, *J* = 9.5 and 6.0 Hz, H1), 2.79 (1H, m, H2), 2.56 (1H, m, H2), 2.39 (3H, s, TsCH_3), 1.24-1.17 (1H, m, H5), 0.66-0.60 (2H, m, H6), 0.30-0.22 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.0, 139.2, 138.0, 135.3, 131.1, 129.2, 128.4, 128.3, 128.0, 127.7, 127.6, 127.1, 123.2, 122.4, 80.6, 73.4, 63.4, 37.3, 21.6, 13.6, 6.5; **HRMS** (ESI+) calc. for $C_{28}H_{27}NNaO_2S$ $[M+Na]^+$ 464.1655, found 464.1641.

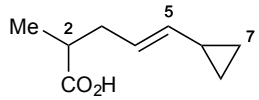
1-Cyclopropylallyl propionate, 147



Prepared by General Procedure A using vinylmagnesium bromide (1 M in THF, 13.4 mL, 13.4 mmol, 1.05 equiv.), cyclopropanecarboxaldehyde **118** (1.0 mL, 13.4 mmol,

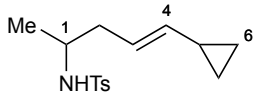
1.0 equiv.) and propionic anhydride (2.06 mL, 16.1 mmol, 1.25 equiv.). The residue was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **147** as a colourless oil (1.35 g, 8.75 mmol, 66%); $\mathbf{R}_f$ 0.69 (petroleum ether/ethyl acetate (9:1); **IR** (thin film, ν_{max}/cm^{-1}) 3086, 2984, 2943, 1734, 1463, 1426, 1360, 1182, 1080, 1024; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.85 (1H, ddd, *J* = 17.0, 10.5 and 6.0 Hz, H2), 5.27 (1H, dt, *J* = 17.0 and 1.5 Hz, H3), 5.16 (1H, dt, *J* = 10.5 and 1.5 Hz, H3), 4.73 (1H, ddt, *J* = 8.5, 6.0 and 1.5 Hz, H1), 2.36 (2H, q, *J* = 7.5 Hz, H8), 1.16 (3H, t, *J* = 7.5 Hz, H9), 1.10-1.02 (1H, m, H4), 0.61-0.50 (2H, m, H5), 0.44-0.28 (2H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.0, 135.9, 116.5, 78.4, 28.0, 14.7, 9.3, 3.5, 2.6; **HRMS** not found.

(*E*)-5-Cyclopropyl-2-methylpent-4-enoic acid, 149



Prepared by General Procedure B using ester **147** (0.50 g, 3.2 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1) + 1% acetic acid) to give **149** as a colourless oil (0.38 g, 2.5 mmol, 77%); $\mathbf{R}_f$ 0.28 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3082, 3005, 2978, 2937, 1703, 1463, 1417, 1291, 1240, 961; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.46 (1H, dt, *J* = 15.5 and 7.0 Hz, H4), 5.05 (1H, dd, *J* = 15.0 and 8.5 Hz, H5), 2.50 (1H, sext, *J* = 7.0 Hz, H2), 2.37 (1H, dt, *J* = 14.0 and 7.0 Hz, H3), 2.13 (1H, dt, *J* = 14.0 and 7.0 Hz, H3), 1.39-1.32 (1H, m, H6), 1.17 (3H, d, *J* = 7.0 Hz, H8), 0.68-0.65 (2H, m, H7), 0.34-0.31 (2H, m, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 182.7, 136.9, 124.0, 39.7, 36.2, 16.2, 13.5, 6.5; **HRMS** (ESI+) calc. for $C_9H_{14}NaO_2$ $[M+Na]^+$ 177.0886, found 177.0882.

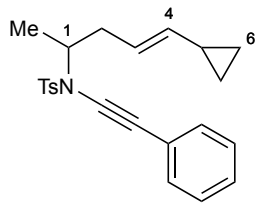
(*E*)-*N*-(5-Cyclopropylpent-4-en-2-yl)-4-methylbenzenesulfonamide, 151



To a stirred solution of carboxylic acid **149** (0.40 g, 2.60 mmol, 1.0 equiv.) and triethylamine (0.40 mL, 2.85 mmol, 1.1 equiv.) in anhydrous toluene (15 mL) at 0 °C was added diphenyl phosphoryl azide (0.62 mL, 2.85 mmol, 1.1 equiv.) dropwise and the reaction mixture heated to 100 °C for 1 h. 9-fluorenemethanol (0.61 g, 3.11 mmol, 1.1 equiv.) and copper chloride (9 mg, 0.09 mmol, 0.033 equiv.) were added and the solution stirred for a further 48 h. The reaction mixture was diluted with diethyl ether (30 mL) and 1 M *aq.* citric acid (30 mL) and the aqueous layer separated. The aqueous layer was washed with diethyl ether (3 x 30 mL), basified to pH ~ 11 with 2 M *aq.* sodium hydroxide and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (40 mL), tosyl chloride (0.77 g, 4.02 mmol, 1.0 equiv.) and triethylamine (0.56 mL, 4.02 mmol, 1.0 equiv.) were added and the solution stirred for 4 h at room temperature. To the solution was added sat. *aq.* ammonium chloride (40 mL) and the aqueous layer extracted with dichloromethane (3 x 40 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **151** as a colourless oil (0.37 g, 1.3 mmol, 51%); $\mathbf{R}_f$ 0.36 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3280, 3082, 3003, 2977, 2928, 1599, 1455, 1325, 1159, 1094, 1021; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.30 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.17 (1H, dt, *J* = 15.0 and 7.5 Hz, H3), 4.92 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.47 (1H, d, *J* = 7.0 Hz, N*H*), 3.29 (1H, sept, *J* = 7.0 Hz, H1), 2.43 (3H, s, TsCH_3), 2.07-1.98 (2H, m, H2), 1.29-1.22 (1H, m, H5), 1.09

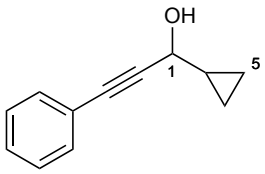
(3H, d, *J* = 7.0 Hz, H7), 0.68-0.64 (2H, m, H6), 0.31-0.28 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.2, 138.6, 138.0, 129.6, 127.1, 122.1, 49.5, 40.0, 21.5, 21.3, 13.6, 6.5; **HRMS** (ESI+) calc. for $C_{15}H_{21}NNaO_2S$ $[M+Na]^+$ 302.1185, found 302.1180.

(*E*)-*N*-(5-Cyclopropylpent-4-en-2-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 153



Prepared by General Procedure E using (*E*)-*N*-(5-cyclopropylpent-4-en-2-yl)-4-methylbenzenesulfonamide **151** (100 mg, 0.36 mmol, 1.0 equiv.) and 1-bromo-2-phenylacetylene (130 mg, 0.72 mmol, 2.0 equiv.), with the reaction mixture stirred at 115 °C for 16 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **153** as a colourless oil (113 mg, 0.30 mmol, 83%); $\mathbf{R_f}$ 0.72 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3081, 3003, 2981, 2929, 2233, 1598, 1363, 1169, 1091, 972; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.84 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.39-7.25 (7H, m, Ph*H* and Ts*H*), 5.25 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 4.98 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.05 (1H, sext, *J* = 7.0 Hz, H1), 2.44 (3H, s, TsCH_3), 2.29 (1H, dt, *J* = 14.0 and 7.0 Hz, H2), 2.13 (1H, dt, *J* = 14.0 and 7.0 Hz, H2), 1.24-1.18 (1H, m, H5), 1.16 (3H, d, *J* = 7.0 Hz, H1'), 0.66-0.60 (2H, m, H6), 0.30-0.23 (2H, m, H6); **^{13}C NMR** (500 MHz, $CDCl_3$) δ_C 144.4, 137.7, 136.1, 131.4, 129.8, 128.4, 127.7, 127.7, 123.4, 122.9, 79.7, 72.9, 57.1, 38.3, 21.8, 18.9, 13.7, 6.6, 6.6; **HRMS** (ESI+) calc. for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$ 402.1498, found 402.1500.

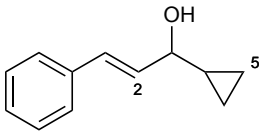
1-Cyclopropyl-3-phenylprop-2-yn-1-ol, 156



According to the procedure of Shair et al.[112] To a solution of phenylacetylene (1.91 mL, 17.4 mmol, 1.0 equiv.) in THF (8.7 mL) at –78 °C was added *n*-butyllithium (2.5 M in hexanes, 7.9 mL, 17.4 mmol, 1.0 equiv.) and the solution stirred for 15 min. To the reaction mixture was added cyclopropanecarboxaldehyde **118** (1.3 mL, 17.4 mmol, 1.0 equiv.), the solution was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with sat. *aq.* ammonium chloride and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (8:2)) to give **156** as a colourless oil (1.59 g, 9.2 mmol, 53%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.41 (2H, m, Ph*H*), 7.33-7.29 (3H, m, Ph*H*), 4.44 (1H, t, *J* = 6.0 Hz, H1), 2.02 (1H, d, *J* = 6.0 Hz, O*H*), 1.38-1.30 (1H, m, H4), 0.65-0.48 (4H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 130.1, 126.8, 126.7, 120.9, 86.2, 83.4, 64.6, 15.6, 1.7, 0.0.

The spectroscopic data was found to be in agreement with that reported by Chan *et al*.[113]

(*E*)-1-Cyclopropyl-3-phenylprop-2-en-1-ol, 158

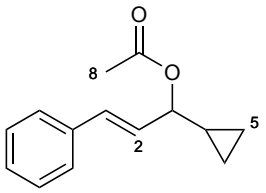


According to the procedure of Shair et al.[112] To a solution of Red-Al (65% in toluene, 5.2 mL, 17.4 mmol, 1.5 equiv.) in diethyl ether (5.2 mL) at 0 °C was added a solution of alcohol **156** (2.0 g, 11.6 mmol, 1.0 equiv.) in diethyl ether (6.4 mL). The reaction mixture

was warmed to warm temperature and stirred for 16 h. The reaction mixture was diluted with 1 N hydrochloric acid (50 mL) and diethyl ether (50 mL). The organic layer was separated, washed with 1 N hydrochloric acid (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (8:2)) to give **158** as a colourless oil (1.69 g, 9.7 mmol, 84%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.41-7.39 (2H, m, Ph*H*), 7.34-7.30 (2H, m, Ph*H*), 7.26-7.22 (1H, m, Ph*H*), 6.61 (1H, d, *J* = 16.0 Hz, H3), 6.32 (1H, dd, *J* = 16.0 and 6.0 Hz, H4), 3.68 (1H, m, H1), 1.78 (1H, d, *J* = 3.5 Hz, O*H*), 1.13-1.05 (1H, m, H4), 0.64-0.54 (2H, m, H5), 0.45-0.40 (1H, m, H5), 0.36-0.30 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.9, 131.1, 130.2, 128.7, 127.8, 126.6, 77.2, 17.8, 3.3, 2.4.

The spectroscopic data was found to be in agreement with that reported by Shair *et al*.[112]

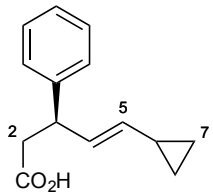
(*E*)-1-Cyclopropyl-3-phenylallyl acetate, 160



To a solution of alcohol **158** (1.5 g, 8.6 mmol, 1.0 equiv.) in diethyl ether (8.6 mL) at room temperature was added acetic anhydride (1.02 mL, 10.8 mmol, 1.25 equiv.), pyridine (0.87 mL, 10.8 mmol, 1.25 equiv.) and *N*,*N*-dimethylpyridin-4-amine (11 mg, 0.09 mmol, 0.01 equiv.) and the solution stirred for 2 h. The reaction mixture was quenched with methanol (1 mL) and diluted with diethyl ether (50 mL) and 1 N hydrochloric acid (50 mL). The organic layer was washed with 1 N hydrochloric acid (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **160** as a colourless oil (1.18 g, 5.5 mmol, 64%); $\mathbf{R}_f$ 0.26 (petroleum ether/diethyl ether (95:5)); **IR** (thin film,

ν_{max}/cm^{-1}) 3083, 3009, 1731, 1369, 1236, 1068; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.38 (2H, m, Ph*H*), 7.34-7.29 (2H, m, Ph*H*), 7.27-7.22 (1H, m, Ph*H*), 6.62 (1H, d, *J* = 16.0 Hz, H3), 6.21 (1H, dd, *J* = 16.0 and 6.5 Hz, H2), 4.91-4.86 (1H, m, H1), 2.11 (3H, s, H7), 1.23-1.13 (1H, m, H4), 0.65-0.56 (2H, m, H5), 0.50-0.45 (1H, m, H5), 0.40-0.34 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.5, 136.4, 132.1, 128.6, 128.0, 126.9, 126.7, 78.6, 21.4, 15.0, 3.7, 2.7; **HRMS** (ESI+) calc. for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239.1043, found 239.1043.

(*E*)-5-Cyclopropyl-3-phenylpent-4-enoic acid, 162



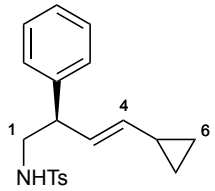
Method A: Prepared by General Procedure B using ester **160** (1.0 g, 4.62 mmol, 1.0 equiv.) to give **162** as a colourless oil (0.89 g, 4.12 mmol, 89%).

Method B: To a mixture of **158** (2.0 g, 11.5 mmol, 2.0 equiv.), Novozyme 435 (200 mg, 10 wt%) and 4 Å molecular sieves (crushed, 1 g, 50 wt%) in THF/pentane (1:1, 60 mL) was added vinyl acetate (3.2 mL, 34.4 mmol, 3.0 equiv.) and the reaction mixture stirred for 6 days. The suspension was filtered through a pad of celite and concentrated *in vacuo*. The crude residue was immediately dissolved in toluene (6 mL) and added dropwise to a solution of lithium hexamethyldisilazide (1.0 M in toluene, 23.0 mL, 23.0 mmol, 3.0 equiv.) and triethylamine (32.0 mL, 230 mmol, 30 equiv.) in toluene (153 mL) at –78 °C. The solution was allowed to reach room temperature and stirred for 16 h. The reaction mixture was quenched with 1 M *aq.* sodium hydroxide (153 mL) and the layers separated. The aqueous layer was washed with diethyl ether (2 x 150 ml), acidified to pH ~ 4 with 1 M *aq.* citric acid (150 mL), and extracted with dichloromethane (3 x 150 mL).

The combined organic extracts were washed with brine (450 mL), dried over magnesium sulfate and concentrated *in vacuo* to give (–)-**162** as a colourless oil (0.90 g, 4.16 mmol, 73%).

$[\alpha]_D^{25}$ –30.7 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.15 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3082, 3027, 3005, 2673, 1706, 1494, 1411, 1288; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32-7.29 (2H, m, Ph*H*), 7.23-7.20 (3H, m, Ph*H*), 5.65 (1H, dd, *J* = 15.5 and 7.5 Hz, H4), 5.01 (1H, dd, *J* = 15.5 and 9.0 Hz, H5), 3.78 (1H, q, *J* = 8.0 Hz, H3), 2.73 (2H, d, *J* = 8.0 Hz, H2), 1.39-1.30 (1H, m, H6), 0.70-0.62 (2H, m, H7), 0.35-0.27 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 177.7, 143.0, 135.0, 129.2, 128.6, 127.4, 126.6, 44.3, 40.7, 13.6, 6.7, 6.6; **HRMS** (ESI+) calc. for $C_{14}H_{16}NaO_2$ $[M+Na]^+$ 239.1043, found 239.1048.

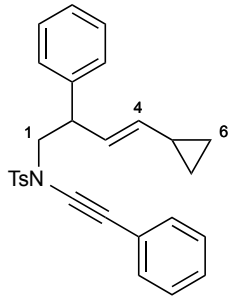
(*E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 166



To a solution of **162** (0.85 g, 3.93 mmol, 1.0 equiv.) and triethylamine (0.66 mL, 4.72 mmol, 1.2 equiv.) in toluene (12 mL) at room temperature was added diphenylphosphoryl azide (1.02 mL, 4.72 mmol, 1.2 equiv.). The reaction mixture was heated to 100 °C and stirred for 2 h. The solution was cooled to room temperature, and 9-fluorenylmethanol (0.93 g, 4.72 mmol, 1.2 equiv.) and copper(I) chloride (13 mg, 0.13 mmol, 0.033 equiv.) were added. The solution was heated to 80 °C and stirred for 1 h. The reaction mixture was quenched with sat. *aq.* ammonium chloride (40 mL) and the aqueous layer extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (120 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to

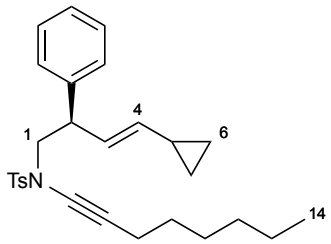
give a colourless solid (0.87 g, 2.12 mmol, 54%). The pure material was immediately dissolved in dichloromethane/diethylamine (1:1, 20 mL) and the reaction mixture stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in dichloromethane (20 mL). To the solution was added tosyl chloride (372 mg, 1.95 mmol, 1.0 equiv.) and triethylamine (0.27 mL, 1.95 mmol, 1.0 equiv.), and the solution stirred for 2 h. The reaction mixture was quenched with 1 M *aq*. citric acid (20 mL) and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (60 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (–)-**166** as a colourless oil (0.49 g, 1.43 mmol, 79%); $[\alpha]_D^{25}$ –30.6 (*c* = 1.0, $CHCl_3$); 96% *ee* (CHIRALPAK IB, 5% IPA/hexane, 1.3 mL/min, t_R major – 8.48 min, minor – 9.83 min); $\mathbf{R}_f$ 0.16 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3283, 3063, 3027, 2926, 2871, 1599, 1495, 1326, 1158, 1094; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.32-7.7.20 (5H, m, Ph*H*), 7.06 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.49 (1H, dd, *J* = 15.0 and 8.0 Hz, H4), 4.97 (1H, dd, *J* = 15.0 and 9.0 Hz, H5), 4.35 (1H, s, N*H*), 3.32 (1H, q, *J* = 8.0 Hz, H3), 3.22-3.12 (2H, m, H2), 2.44 (3H, s, TsCH_3), 1.37-1.29 (1H, m, H6), 0.73-0.63 (2H, m, H7), 0.37-0.27 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.5, 140.9, 137.4, 136.9, 129.7, 128.9, 127.5, 127.2, 127.1, 126.9, 48.3, 47.7, 21.6, 13.7, 6.8, 6.8; **HRMS** (ESI+) calc. for $C_{20}H_{23}NNaO_2S$ $[M+Na]^+$ 364.1342, found 364.1343.

(*E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 168a



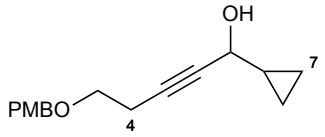
Prepared by General Procedure E using sulfonamide *rac*-**166** (100 mg, 0.29 mmol, 1.0 equiv.) and bromoalkyne **124a** (80 mg, 0.44 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **168a** as a colourless oil (113 mg, 0.26 mmol, 88%); $\mathbf{R_f}$ 0.31 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3062, 3028, 2926, 2235, 1598, 1443, 1307, 1168, 1020; **^{1}H NMR** (700 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.34-7.28 (9H, m, Ph*H*), 7.23-7.20 (3H, m, Ph*H* and Ts*H*), 5.65 (1H, dd, *J* = 15.5 and 8.0 Hz, H3), 5.05 (1H, dd, *J* = 15.5 and 9.0 Hz, H4), 3.75 (1H, q, *J* = 8.0 Hz, H2), 3.68-3.64 (2H, m, H1), 2.43 (3H, s, TsCH_3), 1.36-1.31 (1H, m, H5), 0.67-0.62 (2H, m, H6), 0.34-0.29 (2H, m, H6); **^{13}C NMR** (176 MHz, $CDCl_3$) δ_C 144.5, 141.1, 137.0, 134.7, 131.4, 129.7, 128.7, 128.3, 127.9, 127.8, 127.7, 126.9, 126.8, 123.0, 82.5, 71.2, 56.2, 47.5, 21.7, 13.8, 6.7, 6.6; **HRMS** (ESI+) calc. for $C_{28}H_{27}NNaO_2S$ $[M+Na]^+$ 464.1655, found 464.1663.

(*R, E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 168b



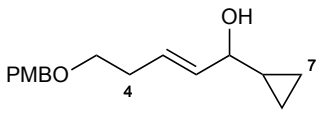
Prepared by General Procedure E using sulfonamide (–)-**166** (100 mg, 0.29 mmol, 1.0 equiv.) and bromoalkyne **124b** (90 mg, 0.44 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (–)-**168b** as a colourless oil (103 mg, 0.22 mmol, 76%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –19.5 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.46 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3064, 3028, 2955, 2858, 2253, 1598, 1365, 1168, 1092; **^{1}H NMR** (700 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.29-7.25 (4H, m, Ph*H*), 7.21 (1H, t, *J* = 7.0 Hz, Ph*H*), 7.18 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.62 (1H, dd, *J* = 15.5 and 8.0 Hz, H3), 5.02 (1H, dd, *J* = 15.5 and 9.0 Hz, H4), 3.67 (1H, q, *J* = 8.0 Hz, H2), 3.53 (1H, dd, *J* = 13.0 and 8.5 Hz, H1), 3.48 (1H, dd, *J* = 13.0 and 7.5 Hz, H1), 2.42 (3H, s, TsCH_3), 2.24 (2H, t, *J* = 7.0 Hz, H9), 1.48-1.43 (2H, m, H10), 1.36-1.24 (7H, m, H5 and H11-13), 0.90 (3H, t, *J* = 7.5 Hz, H14), 0.68-0.63 (2H, m, H6), 0.34-0.28 (2H, m, H6); **^{13}C NMR** (176 MHz, $CDCl_3$) δ_C 144.0, 141.3, 136.7, 134.8, 129.5, 128.6, 128.0, 127.7, 127.0, 126.8, 73.0, 70.9, 55.9, 47.1, 31.4, 29.0, 28.5, 22.6, 21.6, 18.5, 14.1, 13.8, 6.7, 6.6; **HRMS** (ESI+) calc. for $C_{28}H_{35}NNaO_2S$ $[M+Na]^+$ 472.2281, found 472.2281.

1-Cyclopropyl-5-((4-methoxybenzyl)oxy)pent-2-yn-1-ol, 157



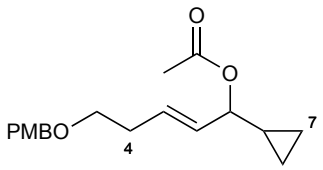
To a solution of 1-((but-3-yn-1-yloxy)methyl)-4-methoxybenzene (2.19 g, 11.5 mmol, 1.0 equiv.) in THF (11.5 mL) at –78 °C was added *n*-butyllithium (2.5 M in hexanes, 4.6 mL, 11.5 mmol, 1.0 equiv.) and the solution stirred for 15 min. To the reaction mixture was added cyclopropanecarboxaldehyde **118** (0.86 mL, 11.5 mmol, 1.0 equiv.), the solution was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with sat. *aq*. ammonium chloride and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (8:2)) to give **157** as a colourless oil (1.58 g, 6.07 mmol, 53%); $\mathbf{R}_f$ 0.22 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3404, 3081, 3005, 2910, 2863, 1612, 1513, 1246, 1175, 1094, 1028; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.88 (2H, d, *J* = 8.5 Hz, PMB*H*), 4.47 (2H, s, PMBCH_2), 4.18 (1H, t, *J* = 6.0 Hz, H1), 3.81 (3H, s, PMBCH_3), 3.55 (2H, t, *J* = 7.0 Hz, H5), 2.51 (2H, td, *J* = 7.0 and 2.0 Hz, H4), 2.04 (1H, d, *J* = 6.0 Hz, O*H*), 1.25-1.17 (1H, m, H6), 0.57-0.38 (4H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 157.8, 128.7, 127.9, 112.4, 80.9, 78.6, 71.2, 66.6, 64.4, 53.8, 18.6, 15.8, 1.7, 0.0; **HRMS** (ESI+) calc. for $C_{16}H_{20}NaO_3$ $[M+Na]^+$ 283.1305, found 283.1308.

(*E*)-1-Cyclopropyl-5-((4-methoxybenzyl)oxy)pent-2-en-1-ol, 159



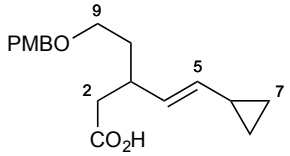
To a solution of Red-Al (65% in toluene, 2.4 mL, 8.64 mmol, 1.5 equiv.) in diethyl ether (2.4 mL) at 0 °C was added a solution of alcohol **157** (1.5 g, 5.76 mmol, 1.0 equiv.) in diethyl ether (3.4 mL). The reaction mixture was warmed to warm temperature and stirred for 16 h. The reaction mixture was diluted with 1 N hydrochloric acid (50 mL) and diethyl ether (50 mL). The organic layer was separated, washed with 1 N hydrochloric acid (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (8:2)) to give **159** as a colourless oil (0.66 g, 2.52 mmol, 44%); $\mathbf{R}_f$ 0.21 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3416, 3078, 3003, 2934, 2907, 2856, 1612, 1513, 1247, 1092, 1032; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.87 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.72-5.60 (2H, m, H2 and 3), 4.44 (2H, s, PMBCH_2), 3.80 (3H, s, PMBCH_3), 3.49 (2H, t, *J* = 6.5 Hz, H5), 3.46-3.42 (1H, m, H1), 2.36 (2H, q, *J* = 6.5 Hz, H4), 1.68-1.66 (1H, m, O*H*), 1.02-0.93 (1H, m, H6), 0.57-0.46 (2H, m, H7), 0.36-0.20 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 157.1, 131.3, 128.5, 127.3, 125.9, 111.7, 74.9, 70.5, 67.4, 53.3, 30.7, 15.5, 1.0, 0.0; **HRMS** (ESI+) calc. for $C_{16}H_{22}NaO_3$ $[M+Na]^+$ 285.1461, found 285.1463.

(*E*)-1-Cyclopropyl-5-((4-methoxybenzyl)oxy)pent-2-en-1-yl acetate, 161



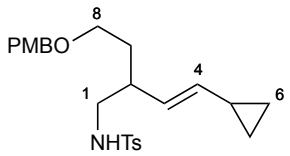
To a solution of alcohol **159** (0.63 g, 2.41 mmol, 1.0 equiv.) in diethyl ether (24 mL) at room temperature was added acetic anhydride (0.28 mL, 3.01 mmol, 1.25 equiv.), pyridine (0.24 mL, 3.01 mmol, 1.25 equiv.) and *N*,*N*-dimethylpyridin-4-amine (3 mg, 0.02 mmol, 0.01 equiv.) and the solution stirred for 2 h. The reaction mixture was quenched with methanol (1 mL) and diluted with diethyl ether (50 mL) and 1 N hydrochloric acid (50 mL). The organic layer was washed with 1 N hydrochloric acid (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **161** as a colourless oil (0.55 g, 1.81 mmol, 76%); $\mathbf{R}_f$ 0.30 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3007, 2935, 2856, 1729, 1613, 1513, 1368, 1238, 1095, 1029; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.87 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.73 (1H, dt, *J* = 15.5 and 6.5 Hz, H3), 5.54 (1H, dd, *J* = 15.5 and 7.0 Hz, H2), 4.70 (1H, t, *J* = 7.0 Hz, H1), 4.44 (2H, s, PMBCH_2), 3.80 (3H, s, PMBCH_3), 3.48 (2H, t, *J* = 7.0 Hz, H5), 2.35 (2H, q, *J* = 7.0 Hz, H4), 2.06 (3H, s, H9), 1.09-1.01 (1H, m, H6), 0.58-0.48 (2H, m, H7), 0.42-0.25 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.5, 159.2, 130.6, 130.1, 129.3, 129.2, 113.8, 78.4, 72.6, 69.2, 55.3, 32.8, 21.4, 14.9, 3.5, 2.6; **HRMS** (ESI+) calc. for $C_{18}H_{24}NaO_4$ $[M+Na]^+$ 327.1567, found 327.1568.

(*E*)-5-Cyclopropyl-3-(2-((4-methoxybenzyl)oxy)ethyl)pent-4-enoic acid, 163



Prepared by General Procedure B using ester **161** (0.50 g, 1.64 mmol, 1.0 equiv.) to give **163** as a colourless oil (0.49 g, 1.61 mmol, 98%); $\mathbf{R}_f$ 0.22 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3079, 3003, 2933, 2861, 1706, 1612, 1247, 1174, 1150; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.87 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.28 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 4.99 (1H, dd, *J* = 15.5 and 8.5 Hz, H5), 4.43 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.38 (1H, d, *J* = 11.5 Hz, PMBCH_2), 3.81 (3H, s, PMBCH_3), 3.49-3.39 (2H, m, H9), 2.68-2.58 (1H, m, H3), 2.40 (1H, dd, *J* = 15.0 and 6.0 Hz, H2), 2.30 (1H, dd, *J* = 15.0 and 8.0 Hz, H2), 1.79-1.71 (1H, m, H8), 1.60-1.52 (1H, m, H8), 1.35-1.25 (1H, m, H6), 0.66 (2H, m, H7), 0.30-0.26 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.0, 159.2, 135.6, 130.5, 129.4, 129.1, 113.8, 72.6, 67.7, 55.3, 40.4, 36.2, 34.6, 13.5, 6.6, 6.5; **HRMS** (ESI+) calc. for $C_{18}H_{24}NaO_4$ $[M+Na]^+$ 327.1567, found 327.1569.

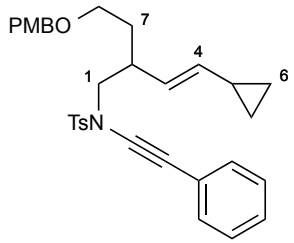
(*E*)-*N*-(4-Cyclopropyl-2-(2-((4-methoxybenzyl)oxy)ethyl)but-3-en-1-yl)-4-methylbenzenesulfonamide, 167



Prepared by General Procedure C using carboxylic acid **163** (0.40 g, 1.31 mmol, 1.0 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **167** as a colourless oil (0.12 g, 0.27 mmol, 21%); $\mathbf{R}_f$ 0.27 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3283, 3002,

2931, 2861, 1664, 1586, 1327, 1246, 1159, 1092, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.21 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.87 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.05 (1H, dd, *J* = 15.5 and 9.0 Hz, H3), 4.89 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 4.67 (1H, dd, *J* = 7.5 and 4.5 Hz, N*H*), 4.38 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.33 (1H, d, *J* = 11.5 Hz, PMBCH_2), 3.81 (3H, s, PMBCH_3), 3.44-3.32 (2H, m, H8), 3.00-2.94 (1H, m, H1), 2.74-2.68 (1H, m, H1), 2.41 (3H, s, Ts*H*), 2.27-2.18 (1H, m, H2), 1.65-1.57 (1H, m, H7), 1.50-1.41 (1H, m, H7), 1.32-1.23 (1H, m, H5), 0.71-0.62 (2H, m, H6), 0.32-0.24 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.23, 143.2, 137.7, 137.1, 130.4, 129.7, 129.4, 127.6, 127.1, 113.8, 72.7, 67.4, 55.3, 47.1, 39.9, 32.7, 21.5, 13.6, 6.9, 6.7; **HRMS** (ESI+) calc. for $C_{24}H_{31}NNaO_4S$ $[M+Na]^+$ 452.1866, found 452.1865.

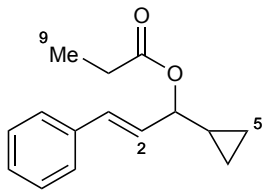
(*E*)-*N*-(4-Cyclopropyl-2-(2-((4-methoxybenzyl)oxy)ethyl)but-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 169



Prepared by General Procedure E using sulfonamide **167** (100 mg, 0.23 mmol, 1.0 equiv.) and bromoalkyne **124a** (63 mg, 0.35 mmol, 1.5 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **169** as a colourless oil (102 mg, 0.19 mmol, 83%); $\mathbf{R}_f$ 0.54 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3002, 2930, 2860, 2235, 1612, 1513, 1364, 1247, 1168, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.35-7.32 (4H, m, Ts*H* and Ph*H*), 7.29-7.26 (3H, m, Ph*H*), 7.23 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.82 (2H, d, *J* = 8.5 Hz, PMB*H*),

5.20 (1H, dd, *J* = 15.5 and 9.0 Hz, H3), 4.96 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 4.43 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.35 (1H, d, *J* = 11.5 Hz, PMBCH_2), 3.78 (3H, s, PMBCH_3), 3.52-3.42 (2H, m, H8), 3.37 (1H, dd, *J* = 12.5 and 7.0 Hz, H1), 3.29 (1H, dd, *J* = 12.5 and 8.0 Hz, H1), 2.70-2.62 (1H, m, H2), 2.44 (3H, s, TsCH_3), 1.89-1.83 (1H, m, H7), 1.51-1.44 (1H, m, H7), 1.31-1.24 (1H, m, H5), 0.66-0.59 (2H, m, H6), 0.29-0.24 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.1, 144.5, 137.4, 134.8, 131.4, 130.7, 129.7, 129.3, 128.3, 127.8, 127.7, 127.0, 123.1, 113.7, 82.8, 72.4, 70.9, 67.4, 56.0, 55.3, 38.7, 32.0, 21.7, 13.6, 6.6; **HRMS** (ESI+) calc. for $C_{32}H_{36}O_4NS$ $[M+H]^+$ 530.2360, found 530.2350.

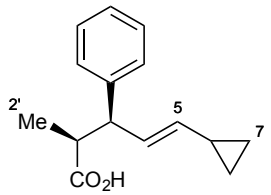
(*E*)-1-Cyclopropyl-3-phenylallyl propionate, 171



To a solution of alcohol *rac*-**158** (1.0 g, 5.74 mmol, 1.0 equiv.) in diethyl ether (5.74 mL) at room temperature was added propionic anhydride (0.92 mL, 7.17 mmol, 1.25 equiv.), pyridine (0.58 mL, 7.17 mmol, 1.25 equiv.) and *N*,*N*-dimethylpyridin-4-amine (7 mg, 0.06 mmol, 0.01 equiv.) and the solution stirred for 2 h. The reaction mixture was quenched with methanol (1 mL) and diluted with diethyl ether (50 mL) and 1 N hydrochloric acid (50 mL). The organic layer was washed with 1 N hydrochloric acid (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **171** as a colourless oil (1.03 g, 4.48 mmol, 78%); $\mathbf{R}_f$ 0.30 (petroleum ether/diethyl ether (95:5)); **IR** (thin film, ν_{max}/cm^{-1}) 3083, 3008, 2942, 1730, 1360, 1180, 1080; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33-7.30 (2H, m, Ph*H*), 7.26-7.22 (2H, m, Ph*H*), 7.19-7.15 (1H, m, Ph*H*), 6.54 (1H, d, *J* = 16.0 Hz, H3), 6.14 (1H, dd, *J* = 16.0 and 7.0 Hz, H2), 4.83

(1H, dd, *J* = 8.0 and 7.0 Hz, H1), 2.43-2.28 (2H, m, H8), 1.14-1.05 (4H, m, H4 and H9), 0.57-0.48 (2H, m, H5), 0.43-0.37 (1H, m, H5), 0.32-0.27 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.0, 136.5, 132.1, 128.7, 128.0, 127.1, 126.7, 78.3, 28.0, 15.1, 9.3, 3.7, 2.8; **HRMS** (ESI+) calc. for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1199, found 253.1204.

(2*S*,3*S*,*E*)-5-Cyclopropyl-2-methyl-3-phenylpent-4-enoic acid, *syn*-**172**

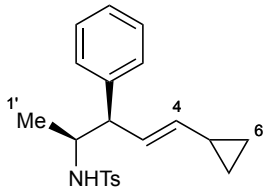


Method A: Prepared by General Procedure B using ester **171** (650 mg, 2.80 mmol, 1.0 equiv.) and triethylamine (11.8 mL, 84.7 mmol, 30 equiv.) to give *syn*-**172** as a colourless oil (644 mg, 2.77 mmol, 99%).

Method B: To a mixture of alcohol *rac*-**158** (2.0 g, 11.5 mmol, 1.0 equiv.), Novozyme 435 (200 mg, 10 wt%) and 4 Å molecular sieves (crushed, 1 g, 50 wt%) in THF/pentane (1:1, 60 mL) was added vinyl propionate (0.38 mL, 34.4 mmol, 3.0 equiv.) and the reaction mixture stirred for 3 days. The suspension was filtered through a pad of celite and concentrated *in vacuo*. The crude residue was immediately dissolved in toluene (6 mL) and added dropwise to a solution of lithium hexamethyldisilazide (1.0 M in toluene, 23.0 mL, 23.0 mmol, 3.0 equiv.) and triethylamine (32 mL, 230 mmol, 30 equiv.) in toluene (153 mL) at –78 °C. The solution was allowed to reach room temperature and stirred for 16 h. The reaction mixture was quenched with 1 M *aq.* sodium hydroxide (153 mL) and the layers separated. The aqueous layer was washed with diethyl ether (2 x 150 ml), acidified to pH ~ 4 with 1 M *aq.* citric acid (150 mL), and extracted with dichloromethane (3 x 150 mL). The combined organic extracts were washed with brine (450 mL), dried over magnesium sulfate and concentrated *in vacuo* to give (–)-*syn*-**172** as a colourless oil

(0.44 g, 1.90 mmol, 33%); $[\alpha]_D^{25}$ –61.5 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.22 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3083, 3028, 2936, 2646, 1704, 1454, 1288; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29-7.25 (2H, m, Ph*H*), 7.21-7.16 (3H, m, Ph*H*), 5.59 (1H, dd, *J* = 15.0 and 9.5 Hz, H4), 5.07 (1H, dd, *J* = 15.0 and 8.5 Hz, H5), 3.44 (1H, t, *J* = 9.5 Hz, H3), 2.77 (1H, dq, *J* = 9.5 and 7.0 Hz, H2), 1.40-1.31 (1H, m, H6), 1.20 (3H, d, *J* = 7.0 Hz, H2'), 0.71-0.61 (2H, m, H7), 0.36-0.27 (2H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 181.4, 142.8, 136.9, 128.5, 127.6, 127.1, 126.5, 51.8, 45.2, 15.3, 13.7, 6.7; **HRMS** (ESI+) calc. for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1199, found 253.1201.

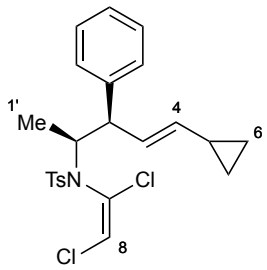
***N*-((2*S*,3*R*,*E*)-5-Cyclopropyl-3-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide, *syn*-175**



To a solution of (–)-*syn*-**172** (0.37 g, 1.61 mmol, 1.0 equiv.) and triethylamine (0.27 mL, 1.93 mmol, 1.2 equiv.) in toluene (5 mL) at room temperature was added diphenylphosphoryl azide (0.42 mL, 1.93 mmol, 1.2 equiv.). The reaction mixture was heated to 100 °C and stirred for 2 h. The solution was cooled to room temperature, and 9-fluorenylmethanol (0.38 g, 1.93 mmol, 1.2 equiv.) and copper(I) chloride (5 mg, 0.05 mmol, 0.033 equiv.) were added. The solution was heated to 80 °C and stirred for 1 h. The reaction mixture was quenched with sat. *aq.* ammonium chloride (5 mL) and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give a white solid (0.39 g, 0.93 mmol, 58%). The pure material was immediately

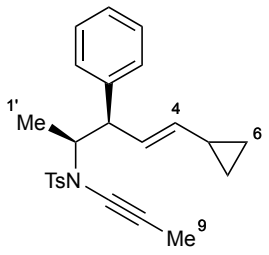
dissolved in dichloromethane/diethylamine (1:1, 10 mL) and the reaction mixture stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in dichloromethane (10 mL). To the solution was added tosyl chloride (177 mg, 0.93 mmol, 1.0 equiv.) and triethylamine (0.13 mL, 0.93 mmol, 1.0 equiv.), and the solution stirred for 2 h. The reaction mixture was quenched with 1 M *aq*. citric acid (10 mL) and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (–)-*syn*-**175** as a colourless oil (0.22 g, 0.63 mmol, 77%); $[\alpha]_D^{25}$ –33.3 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.20 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3280, 3062, 3027, 2931, 1326, 1158, 1046; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31-7.16 (5H, m, Ph*H*), 7.01 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.63 (1H, dd, *J* = 15.0 and 9.5 Hz, H3), 4.96 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.37 (1H, d, *J* = 8.0 Hz, N*H*), 3.58 (1H, m, H1), 3.16 (1H, dd, *J* = 9.5 and 6.0 Hz, H2), 2.42 (3H, s, TsCH_3), 1.39-1.30 (1H, m, H5), 1.05 (3H, d, *J* = 7.0 Hz, H1'), 0.73-0.62 (2H, m, H6), 0.37-0.25 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.3, 141.0, 138.9, 138.0, 129.7, 128.8, 128.0, 127.2, 126.9, 124.5, 54.3, 53.9, 21.6, 18.6, 13.9, 7.0; **HRMS** (ESI+) calc. for $C_{21}H_{25}O_2NNaS$ $[M+Na]^+$ 378.1498, found 378.1485.

_N_-((2_S_,3_R_,_E_)-5-Cyclopropyl-3-phenylpent-4-en-2-yl)-_N_-((_E_)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, ***syn*-176**



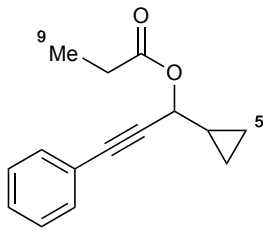
Prepared by General Procedure F using sulfonamide (–)-*syn*-**175** (200 mg, 0.56 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give (–)-*syn*-**176** as a colourless oil (192 mg, 0.43 mmol, 76%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ – 63.0 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.45 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3084, 3002, 1598, 1494, 1451, 1356, 1165, 1090, 1020; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.85-7.75 (2H, m, Ts*H*), 7.31-7.10 (7H, m, Ph*H* and Ts*H*), 6.54-6.42 (1H, m, H8), 5.63 (1H, dd, *J* = 15.0 and 10.0 Hz, H3), 5.13-5.01 (0.5H, m, H4), 4.81-4.67 (0.5H, m, H4), 4.33-4.26 (1H, m, H1), 3.85-3.70 (1H, m, H2), 2.43 (3H, s, TsCH_3), 1.38-1.13 (4H, m, H1′ and H5), 0.68-0.57 (2H, m, H6), 0.34-0.19 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.5, 144.3, 143.0, 137.9, 137.4, 136.6, 129.7, 128.7, 128.6, 128.2, 126.5, 125.0, 124.7, 123.2, 122.9, 63.7, 60.8, 53.4, 51.9, 21.8, 15.9, 15.5, 13.9, 6.6, 6.5; **HRMS** (ESI+) calc. for $C_{23}H_{25}O_2NCl_2NaS$ $[M+Na]^+$ 472.0875, found 472.0874.

_N_-((2_S_,3_R_,_E_)-5-Cyclopropyl-3-phenylpent-4-en-2-yl)-4-methyl-_N_-(prop-1-yn-1-yl)benzenesulfonamide, ***syn*-170**



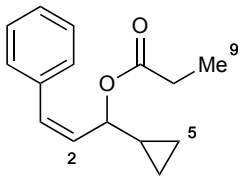
Prepared by General Procedure G using dichloroenamide (–)-*syn*-**176** (50 mg, 0.11 mmol, 1.0 equiv.) and iodomethane (8 μL, 0.24 mmol, 1.2 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (–)-*syn*-**170** as a colourless oil (42 mg, 0.11 mmol, 95%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +22.50 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.36 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3003, 2920, 2249, 1663, 1495, 1356, 1166, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.32 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.24-7.21 (2H, m, Ph*H*), 7.19-7.17 (3H, m, Ph*H*), 7.11 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.62 (1H, dd, *J* = 15.0 and 9.5 Hz, H3), 5.03 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.30 (1H, dq, *J* = 10.0 and 6.5 Hz, H1), 3.35 (1H, dd, *J* = 10.0 and 9.5 Hz, H2), 2.38 (3H, s, H9), 1.92 (3H, s, TsCH_3), 1.37-1.30 (1H, m, H5), 1.22 (3H, d, *J* = 6.5 Hz, H1′), 0.69-0.60 (2H, m, H6), 0.35-0.24 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.7, 142.4, 137.1, 135.8, 129.4, 128.5, 127.9, 127.6, 127.1, 126.5, 69.1, 68.3, 59.5, 54.2, 21.7, 17.6, 13.8, 6.7, 6.6, 3.6; **HRMS** (ESI+) calc. for $C_{24}H_{27}O_2NNaS$ $[M+Na]^+$ 416.1655, found 416.1652.

1-Cyclopropyl-3-phenylprop-2-yn-1-yl propionate, 177



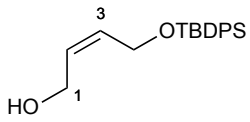
To a solution of propargylic alcohol **156** (0.50 g, 2.90 mmol, 1.0 equiv.) in diethyl ether (2.90 mL) at room temperature was added propionic anhydride (0.47 mL, 3.63 mmol, 1.25 equiv.), pyridine (0.29 mL, 3.63 mmol, 1.25 equiv.) and *N*,*N*-dimethylpyridin-4-amine (3 mg, 0.03 mmol, 0.01 equiv.) and the solution stirred for 2 h. The reaction mixture was quenched with methanol (1 mL) and diluted with diethyl ether (20 mL) and 1 N hydrochloric acid (20 mL). The organic layer was washed with 1 N hydrochloric acid (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give **177** as a colourless oil (604 mg, 2.65 mmol, 91%); $\mathbf{R}_f$ 0.26 (petroleum ether/diethyl ether (95:5)); **IR** (thin film, ν_{max}/cm^{-1}) 3085, 2983, 2943, 2243, 1736, 1490 1358, 1171; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45-7.42 (2H, m, Ph*H*), 7.32-7.27 (3H, m, Ph*H*), 5.49 (1H, d, J = 7.0 Hz, H1), 2.41 (2H, q, J = 7.5 Hz, H8), 1.40-1.32 (1H, m, H4), 1.18 (3H, t, J = 7.5 Hz, H9), 0.66-0.52 (4H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.7, 132.0, 128.7, 128.4, 122.3, 85.3, 84.8, 67.8, 27.8, 14.8, 9.2, 3.6, 2.4; **HRMS** (ESI+) calc. for $C_{15}H_{16}O_2Na$ $[M+Na]^+$ 251.1043, found 251.1043.

(*Z*)-1-Cyclopropyl-3-phenylallyl propionate, *cis*-171



To a solution of ester **177** (100 mg, 0.44 mmol, 1.0 equiv.) and quinoline (10 μL, 0.09 mmol, 0.2 equiv.) in toluene/cyclohexane (4.4 mL, 9:1) at room temperature, was added Pd/$CaCO_3$ (47 mg, 0.44 mmol, 1.0 equiv.). The reaction flask was purged with H_2 gas and stirred for 35 min. The mixture was filtered through a pad of celite and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/Diethyl ether (98:2)) to give *cis*-**171** as a colourless oil (93 mg, 0.40 mmol, 92%); $\mathbf{R}_f$ 0.30 (petroleum ether/diethyl ether (95:5)); **IR** (thin film, ν_{max}/cm^{-1}) 3084, 3012, 2942, 1731, 1359, 1181; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36-7.16 (5H, m, Ph*H*), 6.56 (1H, d, *J* = 11.5 Hz, H3), 5.61 (1H, dd, *J* = 11.5 and 9.5 Hz, H2), 5.46 (1H, dd, *J* = 9.5 and 7.5 Hz, H1), 2.35-2.28 (2H, m, H8), 1.22-1.14 (1H, m, H4), 1.13 (3H, t, *J* = 7.5 Hz, H9), 0.56-0.38 (3H, m, H5), 0.27-0.20 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.9, 132.0, 128.7, 128.5, 128.6, 127.5, 126.0, 73.8, 28.0, 15.3, 9.3, 3.5, 2.0; **HRMS** not found.

(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)but-2-en-1-ol, *cis*-61

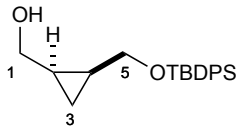


According to the procedure of Toste et al.[114] To a suspension of sodium hydride (60 wt%, 1.46 g, 36.4 mmol, 1.0 equiv.) in THF (72.8 mL) at room temperature was added (*Z*)-but-2-ene-1,4-diol (2.99 mL, 36.4 mmol, 1.0 equiv.) and the mixture stirred for 1 h. To the mixture was added TBDPSCl (9.46 mL, 36.4 mmol, 1.0 equiv.) and the mixture stirred for

a further 1 h. The reaction mixture was quenched with water (5 mL) and the solvent removed *in vacuo*. The residue was dissolved in ether (200 mL), washed with brine (200 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (8:2)) to give *cis*-**61** as a colourless oil (7.42 g, 22.7 mmol, 62%); **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 7.70-7.68 (4H, m, Ph*H*), 7.45-7.38 (6H, m, Ph*H*), 5.75-5.61 (2H, m, H2 and H3), 4.26 (2H, d, *J* = 6.0 Hz, H4), 4.01 (2H, d, *J* = 6.0 Hz, H1), 1.55 (1H, s, O*H*), 1.05 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 135.6, 133.4, 131.0, 129.9, 129.8, 127.7, 60.3, 58.8, 26.8, 19.1.

The spectroscopic data was found to be in agreement with that reported by Deslongchamps *et al.*[115]

2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)methanol, *cis*-63

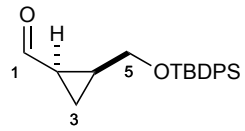


According to the procedure of Toste et al.[114] To a solution of diiodomethane (2.96 mL, 36.8 mmol, 4.0 equiv.) in dichloromethane (92 mL) at 0 °C was added diethyl zinc solution (1.0 M in hexane, 18.4 mL, 18.4 mmol, 2.0 equiv.), the resulting suspension was stirred for 15 min and then cooled to –78 °C. To the suspension was added alcohol *cis*-**61** (3.0 g, 9.2 mmol, 1.0 equiv.) and the solution stirred for 15 min, after which time titanium tetrachloride (10 μL, 0.09 mmol, 0.01 equiv.) was added and the reaction mixture warmed to –20 °C and stirred for 5 h. The reaction was poured onto sat. *aq.* ammonium chloride (90 mL), and the aqueous layer separated and extracted with dichloromethane (2 x 90 mL). The combined organic extracts were washed with sat. *aq.* ammonium chloride (100 mL)

and brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (8:2)) to give *cis*-**63** as a colourless oil (2.62 g, 7.69 mmol, 84%); **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 7.74-7.67 (4H, m, Ph*H*), 7.47-7.38 (6H, m, Ph*H*), 4.09 (1H, dd, *J* = 12.0 and 5.5, H1), 4.02 (1H, dd, *J* = 12.0 and 5.5 Hz, H1), 3.35 (1H, d, *J* = 11.5 Hz, H5), 3.32 (1H, d, *J* = 11.5 Hz, H5), 1.49-1.39 (1H, m, H2), 1.28-1.19 (1H, m, H4), 1.06 (9H, s, C(CH_3)$_3$), 0.74-0.68 (1H, m, H3), 0.16-0.19 (1H, m, H3); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 135.7, 135.6, 133.0, 129.9, 129.8, 127.9, 127.8, 65.0, 63.3, 26.8, 19.1, 18.4, 17.2, 8.3.

The spectroscopic data was found to be in agreement with that reported by Charette *et al*.[116]

(1*R*,2*S*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropane-1-carbaldehyde, *cis*-186

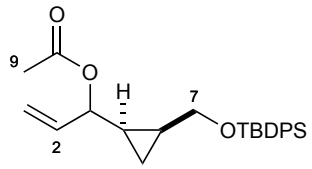


According to the procedure of Toste et al.[114] To a solution of oxalyl chloride (1.12 mL, 13.2 mmol, 1.5 equiv.) in dichloromethane (35 mL) at –78 °C was added DMSO (1.88 mL, 26.4 mmol, 3.0 equiv.) dropwise and the solution stirred for 30 min. To the solution was added alcohol *cis*-**63** (3.0 g, 8.81 mmol, 1.0 equiv.) in dichloromethane (9 mL) dropwise and the reaction mixture stirred for 30 min. To the solution was added triethylamine (7.37 mL, 52.9 mmol, 6.0 equiv.) and the mixture warmed to room temperature. Water (44 mL) was added, and the aqueous layer separated and extracted with dichloromethane (2 x 44 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give *cis*-**186** as a colourless oil (2.57 g, 7.59 mmol, 86%); **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 9.37 (1H, d, *J* = 5.5 Hz, H1),

7.68-7.62 (4H, m, Ph*H*), 7.46-7.37 (6H, m, Ph*H*), 4.01 (1H, dd, *J* = 11.5 and 5.5 Hz, H5), 3.66 (1H, dd, *J* = 11.5 and 8.0 Hz, H5), 1.99-1.92 (1H, m, H2), 1.82-1.72 (1H, m, H4), 1.30-1.26 (1H, m, H3), 1.22-1.17 (1H, m, H3), 1.03 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 200.8, 135.6, 133.5, 133.3, 129.8, 129.7, 127.8, 127.7, 62.1, 27.5, 26.8, 25.9, 19.2, 12.2.

The spectroscopic data was found to be in agreement with that reported by Kazuta *et al*.[117]

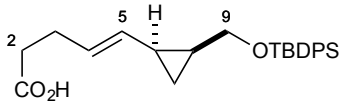
(*R*)-1-((1*R*,2*S*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)allyl acetate, ***cis*-187**



Prepared by General Procedure A using vinylmagnesium bromide (1 M in THF, 8.12 mL, 8.12 mmol, 1.1 equiv.), aldehyde *cis*-**186** (2.50 g, 7.38 mmol, 1.0 equiv.) and acetic anhydride (0.84 mL, 8.86 mmol, 1.2 equiv.). The resulting crude material was purified by column chromatography (petroleum ether/diethyl ether (95:5)) to give *cis*-**187** as an inseparable mixture of diastereomers (1:1), a colourless oil (2.75 g, 6.73 mmol, 91%); $\mathbf{R_f}$ 0.50 (petroleum ether/ethyl acetate (95:5)); **IR** (thin film, ν_{max}/cm^{-1}) 3072, 2958, 2858, 1735, 1472, 1428, 1368, 1237, 1110, 1071, 1017; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.72-7.66 (8H, m, Ph*H*), 7.45-7.37 (12H, m, Ph*H*), 6.08 (1H, ddd, *J* = 17.5, 10.5 and 5.0 Hz, H2), 5.89 (1H, ddd, *J* = 17.5, 10.5 and 6.0 Hz, H2), 5.28 (1H, d, *J* = 17.5 Hz, H3), 5.23 (1H, d, *J* = 17.5 Hz, H3), 5.16-5.13 (2H, m, H3), 5.10-5.06 (1H, m, H1), 4.89-4.85 (1H, m, H1), 3.84 (1H, dd, *J* = 11.5 and 6.0 Hz, H7), 3.75-3.63 (3H, m, H7), 2.09 (3H, s, H9), 1.99 (3H, s, H9), 1.31-1.12 (4H, m, H4 and H6), (18H, s, $C(CH_3)_3$), 0.81-0.70 (2H, m, H5), 0.41-0.37 (1H, m, H5), 0.19-0.14 (1H, m, H5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.4,

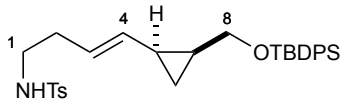
169.9, 136.9, 136.6, 135.7, 135.6, 134.0, 133.9, 133.8, 129.7, 129.6, 127.7, 127.6, 127.5, 116.0, 115.3, 75.0, 74.9, 63.7, 63.5, 26.9, 26.8, 21.3, 21.2, 19.9, 19.6, 19.3, 19.2, 18.8, 18.7, 8.0, 7.7; **HRMS** (ESI+) calc. for $C_{25}H_{32}O_3NaSi$ $[M+Na]^+$ 431.2013, found 431.2000.

(*E*)-5-((1*S*,2*S*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)pent-4-enoic acid, *syn*-188



Prepared by General Procedure B using ester *cis*-**187** (2.5 g, 6.12 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1) + 1% acetic acid) to give *syn*-**188** as a colourless oil (1.94 g, 4.75 mmol, 78%); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3071, 2957, 2930, 2858, 1708, 1428, 1391, 1110, 1077; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.70-7.67 (4H, m, Ph*H*), 7.44-7.36 (6H, m, Ph*H*), 5.49 (1H, dt, *J* = 15.0 and 6.5 Hz, H4), 5.26 (1H, dd, *J* = 15.0 and 8.0 Hz, H5), 3.73 (1H, dd, *J* = 11.0 and 6.5 Hz, H9), 3.58 (1H, dd, *J* = 11.0 and 8.0 Hz, H9), 2.38-2.27 (4H, m, H2 and H3), 1.56-1.48 (1H, m, H6), 1.31-1.21 (1H, m, H8), 1.06 (9H, s, C(C*H*$_3$)$_3$), 0.84-0.79 (1H, m, H7), 0.30-0.26 (1H, m, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.9, 135.7, 135.6, 134.1, 134.0, 130.5, 129.6, 128.2, 127.6, 127.5, 64.0, 34.0, 27.6, 26.9, 20.3, 19.2, 18.5, 10.2; **HRMS** (ESI–) calc. for $C_{25}H_{31}O_3Si$ $[M-H]^-$ 407.2048, found 407.2045.

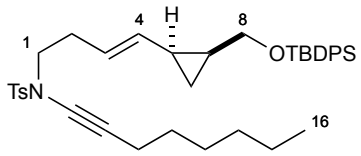
(*E*)-*N*-(4-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)but-3-en-1-yl)-4-methylbenzenesulfonamide, *syn*-190



To a solution of acid *syn*-**188** (0.50 g, 1.22 mmol, 1.0 equiv.) and triethylamine (0.19 mL, 1.35 mmol, 1.2 equiv.) in toluene (4 mL) at room temperature was added diphenylphosphoryl azide (0.29 mL, 1.35 mmol, 1.2 equiv.). The reaction mixture was heated to 100 °C and stirred for 2 h. The solution was cooled to room temperature, and 9-fluorenylmethanol (0.26 g, 1.35 mmol, 1.2 equiv.) and copper(I) chloride (4 mg, 0.04 mmol, 0.033 equiv.) were added. The solution was heated to 80 °C and stirred for 1 h. The reaction mixture was quenched with sat. *aq*. ammonium chloride (5 mL) and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give a colourless solid (0.51 g, 0.85 mmol, 69%). The pure material was immediately dissolved in dichloromethane/diethylamine (1:1, 9 mL) and the reaction mixture stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in dichloromethane (9 mL). To the solution was added tosyl chloride (158 mg, 0.85 mmol, 1.0 equiv.) and triethylamine (0.12 mL, 0.85 mmol, 1.0 equiv.), and the solution stirred for 2 h. The reaction mixture was quenched with 1 M *aq*. citric acid (9 mL) and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**190** as a colourless oil (0.29 g, 0.54 mmol, 66%); $\mathbf{R}_f$ 0.24 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3279, 2930,

2857, 1428, 1326, 1158, 1108, 1073; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.68-7.64 (4H, m, Ph*H*), 7.44-7.34 (6H, m, Ph*H*), 7.26 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.27 (1H, dt, *J* = 15.5 and 6.5 Hz, H3), 5.19 (1H, dd, *J* = 15.5 and 7.5 Hz, H4), 4.44 (1H, t, *J* = 6.0 Hz, N*H*), 3.71 (1H, dd, *J* = 11.0 and 6.0 Hz, H8), 3.53 (1H, dd, *J* = 11.0 and 8.0 Hz, H8), 2.97-2.89 (2H, m, H1), 2.40 (3H, s, TsCH_3), 2.14-2.06 (2H, m, H2), 1.50-1.43 (1H, m, H5), 1.29-1.20 (1H, m, H7), 1.02 (9H, s, C(CH_3)$_3$), 0.83-0.78 (1H, m, H6), 0.28-0.24 (1H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.3, 137.1, 135.6, 134.1, 133.9, 133.1, 129.7, 127.6, 127.1, 125.7, 64.0, 42.8, 32.7, 26.9, 21.5, 20.5, 19.3, 18.6, 10.5; **HRMS** (ESI+) calc. for $C_{31}H_{39}O_3NNaSSi$ $[M+Na]^+$ 556.2312, found 556.2294.

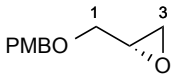
_N_-((_E_)-4-((1_S_*,2_S_*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)but-3-en-1-yl)-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, *syn*-**191**



Prepared by General Procedure E using sulfonamide *syn*-**190** (100 mg, 0.19 mmol, 1.0 equiv.) and 1-bromooct-1-yne (71 mg, 0.37 mmol, 2.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**191** as a colourless oil (63 mg, 0.10 mmol, 53%); $\mathbf{R}_f$ 0.55 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3070, 2955, 2857, 2253, 1494, 1404, 1185, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.69-7.65 (4H, m, Ph*H*), 7.43-7.35 (6H, m, Ph*H*), 7.30 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.36 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.24 (1H, dd, *J* = 15.5 and 8.0 Hz, H4), 3.71 (1H, dd, *J* = 11.0 and 6.0 Hz, H8), 3.54 (1H, dd, *J* = 11.0 and 8.0 Hz, H8), 3.23 (2H, t, *J* = 8.0 Hz, H1), 2.42 (3H, s, TsCH_3), 2.30-2.27 (2H, m, H2), 2.25 (2H, t, *J* = 7.0 Hz, H11), 1.50-1.44 (3H, m, H5 and H12), 1.36-1.23 (7H, m,

H7 and H13-15), 1.04 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, t, *J* = 7.5 Hz, H16), 0.82-0.78 (1H, m, H6), 0.28-0.25 (1H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.3, 135.7, 135.7, 134.9, 134.2, 134.1, 132.3, 129.7, 129.7, 127.8, 127.7, 127.7, 125.6, 73.1, 70.6, 64.0, 51.5, 31.5, 31.4, 29.1, 28.6, 27.0, 22.7, 21.7, 20.5, 19.3, 18.8, 18.6, 14.2, 10.4; **HRMS** (ESI+) calc. for $C_{39}H_{51}O_3NNaSSi$ $[M+Na]^+$ 664.3251, found 664.3234.

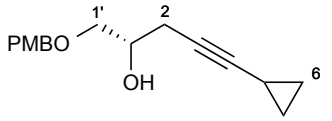
(*S*)-2-(((4-Methoxybenzyl)oxy)methyl)oxirane, (–)-**234**



According to the procedure of White et al.[118] To a stirred solution of NaH (60% dispersion in mineral oil, 0.91 g, 22.7 mmol, 1.1 equiv.) in DMF (41 mL) at 0 °C was added *p*-methoxybenzyl chloride (3.1 mL, 22.7 mmol, 1.1 equiv.) dropwise. After 25 min, (*R*)-glycidol (1.37 mL, 20.6 mmol, 1.0 equiv.) was added dropwise *via* syringe pump over 45 min. The mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was partitioned between sat. *aq*. ammonium chloride (20 mL) and ethyl acetate (40 mL). The organic layer was washed with 10% *aq*. sodium bicarbonate (20 mL) and water (40 mL), and the combined aqueous layers extracted with ethyl acetate (20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1 – 4:1)) to give (–)-**234** as a colourless oil (3.15 g, 16.2 mmol, 79%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –3.7 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.29 (petroleum ether/ethyl acetate (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.88 (2H, d, *J* = 8.5 Hz, PMB*H*), 4.54 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.48 (1H, d, *J* = 11.5 Hz, PMBCH_2), 3.80 (3H, s, PMBCH_3), 3.73 (1H, dd, *J* = 11.5 and 3.0 Hz, H1), 3.41 (1H, dd, *J* = 11.5 and 6.0 Hz, H1), 3.20-3.15 (1H, m, H2), 2.79 (1H, dd, *J* = 5.0 and 4.0 Hz, H3), 2.61 (1H, dd, *J* = 5.0 and 2.5 Hz, H3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.4, 130.1, 129.5, 113.9, 73.1, 70.6, 55.4, 51.0, 44.5.

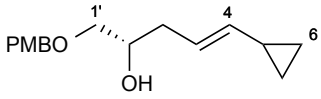
The spectroscopic data was found to be in agreement with that reported by White *et al*.[118]

(*S*)-5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-yn-2-ol, (+)-**235**



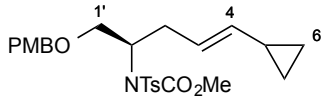
To a solution of cyclopropylacetylene (1.0 mL, 12.4 mmol, 1.2 equiv.) in THF (31 mL) at –78 °C was added *n*-butyllithium (2.5 M in hexanes, 4.5 mL, 11.3 mmol, 1.1. equiv.) dropwise and the solution stirred for 30 min. To the mixture was added (–)-**234** (2.0 g, 10.3 mmol, 1.0 equiv.) and $BF_3{\cdot}OEt_2$ (1.5 mL, 12.4 mmol, 1.2 equiv.), and the mixture stirred at –78 °C for 3 h. The reaction mixture was quenched at –78 °C with sat. *aq*. ammonium chloride (5 mL) and warmed to room temperature. The biphasic mixture was partitioned between sat. *aq*. ammonium chloride (50 mL) and ethyl acetate (50 mL), and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1 – 4:1)) to give (+)-**235** as a colourless oil (1.79 g, 6.9 mmol, 67%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +13.6 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.18 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3434, 3007, 2909, 2862, 1612, 1513, 1247, 1096; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.88 (2H, d, *J* = 8.5 Hz, PMB*H*), 4.49 (2H, s, PMBCH_2), 3.91-3.85 (1H, m, H1), 3.80 (3H, s, PMBCH_3), 3.55 (1H, dd, *J* = 9.5 and 4.0 Hz, H1′), 3.43 (1H, dd, *J* = 9.5 and 6.5 Hz, H1′), 2.42-2.31 (3H, m, H2 and O*H*), 1.23-1.15 (1H, m, H5), 0.73-0.67 (2H, m, H6), 0.63-0.57 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.8, 130.5, 129.9, 114.3, 86.3, 73.5, 73.2, 71.4, 69.6, 55.8, 24.4, 8.5, 0.0; **HRMS** (ESI+) calc. for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1305, found 283.1305.

(*S*,*E*)-5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-ol, (+)-**236**



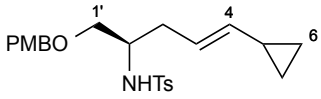
To a solution of (+)-**235** (1.5 g, 5.8 mmol, 1.0 equiv.) in 1,4-dioxane (58 mL) at room temperature was added $LiAlH_4$ (4.0 M in diethyl ether, 1.4 mL, 5.8 mmol, 1.0 equiv.) dropwise. The solution was heated to reflux and stirred for 48 h, after which time the reaction mixture was allowed to cool to room temperature and quenched with saturated *aq.* sodium bicarbonate (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1 – 4:1)) to give (+)-**236** as a colourless oil (1.1 g, 4.2 mmol, 72%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +2.4 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.28 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3454, 3003, 2907, 2860, 2837, 1666, 1513, 1248, 1097; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.89 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.48 (1H, dt, *J* = 15.5 and 7.0 Hz, H3), 5.04 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 4.48 (2H, s, PMBCH_2), 3.83-3.77 (1H, m, H1), 3.81 (3H, s, PMBCH_3), 3.47 (1H, dd, *J* = 9.5 and 3.5 Hz, H1´), 3.33 (1H, dd, *J* = 9.5 and 7.5 Hz, H1´), 2.19-2.16 (3H, m, H2 and O*H*), 1.40-1.31 (1H, m, H5), 0.72-0.60 (2H, m, H6), 0.38-0.27 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.3, 137.5, 130.2, 129.4, 122.9, 113.9, 73.6, 73.0, 70.1, 55.3, 36.7, 13.6, 6.6, 6.5; **HRMS** (ESI+) calc. for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1461, found 285.1460.

Methyl (*R*,*E*)-(5-cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)(tosyl)carbamate, (–)-**237**



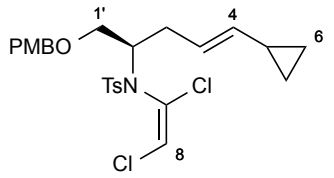
To a solution of (+)-**236** (0.80 g, 3.0 mmol, 1.0 equiv.), triphenylphosphine (1.04 g, 4.0 mmol, 1.3 equiv.) and methyl tosylcarbamate (0.77 g, 3.4 mmol, 1.1 equiv.) in THF (30 mL) at 0 °C was added DIAD (0.72 mL, 3.7 mmol, 1.2 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 48 h, after which time the solvent was removed *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (–)-**237** as a colourless oil (0.82 g, 1.7 mmol, 57%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –6.7 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.36 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3003, 2956, 2863, 1732, 1356, 1275, 1248, 1165; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.86 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.18-7.13 (4H, m, Ts*H* and PMB*H*), 6.84 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.41 (1H, dt, *J* = 15.0 and 7.5 Hz, H3), 5.03 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.82-4.75 (1H, m, H1), 4.49 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.37 (1H, d, *J* = 11.5 Hz, PMBCH_2), 3.86 (1H, app. t, *J* = 9.5 Hz, H1´), 3.80 (3H, s, PMBCH_3), 3.60 (3H, s, CO_2CH_3), 3.57 (1H, dd, *J* = 9.5 and 5.5 Hz, H1´), 2.54 (1H, dt, *J* = 14.0 and 8.5 Hz, H2), 2.41 (1H, dd, *J* = 14.0 and 7.0 Hz, H2), 2.38 (3H, s, TsCH_3), 1.35-1.26 (1H, m, H5), 0.69-0.59 (2H, m, H6), 0.35-0.25 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.3, 152.6, 143.9, 137.7, 137.1, 130.2, 129.4, 128.9, 128.8, 123.2, 113.7, 72.5, 69.6, 58.9, 55.3, 53.2, 33.6, 21.6, 13.5, 6.5; **HRMS** (ESI+) calc. for $C_{25}H_{31}O_6NNaS$ $[M+Na]^+$ 496.1764, found 496.1760.

(*R*,*E*)-*N*-(5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)-4-methylbenzenesulfonamide, (–)-**238**



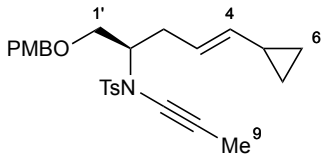
To a solution of (–)-**237** (600 mg, 1.27 mmol, 1.0 equiv.) in methanol (13 mL) at room temperature was added K_2CO_3 (876 mg, 6.33 mmol, 5.0 equiv.) and the suspension stirred for 48 h. The reaction mixture was partitioned between water (50 mL) and dichloromethane (50 mL), and the aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate ((4:1)) to give (–)-**238** as a colourless oil (457 mg, 1.10 mmol, 86%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –8.8 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.31 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3286, 3079, 3003, 2911, 2862, 1513, 1330, 1248, 1160, 1093; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.25 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.16 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.86 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.13 (1H, dt, *J* = 15.5 and 7.5 Hz, H3), 4.89 (1H, dd, *J* = 15.5 and 8.5 Hz, H4), 4.73 (1H, d, *J* = 7.5 Hz, N*H*), 4.33 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.30 (1H, d, *J* = 11.5 Hz, PMBCH_2), 3.81 (3H, s, PMBCH_3), 3.40 (1H, dd, *J* = 9.0 and 3.5 Hz, H1´), 3.34-3.27 (1H, m, H1), 3.24 (1H, dd, *J* = 9.0 and 5.0 Hz, H1´), 2.41 (3H, s, TsCH_3), 2.22-2.09 (2H, m, H2), 1.25-1.17 (1H, m, H5), 0.67-0.59 (2H, m, H6), 0.28-0.21 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.3, 143.2, 138.2, 137.9, 130.0, 129.6, 129.3, 127.2, 122.3, 113.8, 72.8, 70.4, 55.3, 53.2, 35.3, 21.5, 13.6, 6.6, 6.5; **HRMS** (ESI+) calc. for $C_{23}H_{29}O_4NNaS$ $[M+Na]^+$ 438.1710, found 438.1710.

_N_-((_R_,_E_)-5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)-_N_-((_E_)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, (+)-**240**



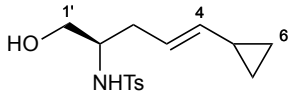
Prepared by General Procedure F using sulfonamide (–)-**238** (200 mg, 0.48 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (+)-**240** as a colourless oil (176 mg, 0.34 mmol, 72%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +14.4 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.27 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3082, 3004, 2934, 2863, 1664, 1514, 1357, 1248, 1165, 1091; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.87-7.80 (2H, m, Ts*H*), 7.28-7.09 (4H, m, Ts*H* and PMB*H*), 6.87-6.82 (2H, m, PMB*H*), 6.61-6.58 (1H, m, H8), 5.42-5.35 (0.5H, m, H3), 5.11-4.97 (1H, m, H3 and 4), 4.86-4.80 (0.5H, m, H4), 4.42-4.32 (1H, m, PMBCH_2), 4.26-4.16 (1H, PMBCH_2), 4.02-3.91 (1H, m, H1), 3.81 (3H, s, PMBCH_3), 3.65-3.55 (1H, m, H1´), 3.46-3.44 (1H, m, H1´), 2.49-2.31 (4.5H, m, TsCH_3 and H2), 2.18-2.11 (0.5H, m, H2), 1.29-1.09 (1H, m, H5), 0.65-0.61 (2H, m, H6), 0.28-0.21 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.1, 144.3, 137.4, 137.3, 136.6, 129.6, 129.4, 129.3, 129.2, 128.6, 128.5, 123.3, 123.1, 113.7, 72.8, 72.6, 70.5, 69.3, 61.9, 55.2, 34.5, 32.9, 21.7, 13.5, 6.5; **HRMS** (ESI+) calc. for $C_{25}H_{29}O_4NCl_2NaS$ $[M+Na]^+$ 532.1087, found 532.1086.

(*R*,*E*)-*N*-(5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)-4-methyl-*N*-(prop-1-yn-1-yl)benzenesulfonamide, (+)-**239**



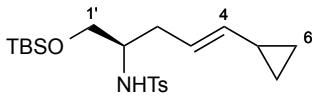
Prepared by General Procedure G using dichloroenamide (+)-**240** (120 mg, 0.24 mmol, 1.0 equiv.) and iodomethane (18 μL, 0.28 mmol, 1.2 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (+)-**239** as a colourless oil (93 mg, 0.21 mmol, 86%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +18.7 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.19 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3003, 2918, 2256, 1613, 1513, 1357, 1248, 1166, 1092; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.22 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.13 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.84 (2H, d, *J* = 8.5 Hz, PMB*H*), 5.21 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 4.97 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.36 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.28 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.10-4.04 (1H, m, H1), 3.81 (3H, s, PMBCH_3), 3.45 (1H, dd, *J* = 10.0 and 8.5 Hz, H1′), 3.36 (1H, dd, *J* = 10.0 and 5.0 Hz, H1′), 2.39 (3H, s, TsCH_3), 2.19-2.16 (2H, m, H2), 1.88 (3H, s, H9), 1.23-1.16 (1H, m, H5), 0.66-0.59 (2H, m, H6), 0.30-0.23 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.2, 143.8, 137.6, 136.2, 130.3, 129.4, 129.3, 128.1, 122.6, 113.7, 72.6, 69.9, 68.8, 67.8, 59.8, 55.4, 33.3, 21.8, 13.7, 6.6, 6.6, 3.7; **HRMS** (ESI+) calc. for $C_{26}H_{31}O_4NNaS$ $[M+Na]^+$ 476.1866, found 476.1858.

(*R*,*E*)-*N*-(5-Cyclopropyl-1-hydroxypent-4-en-2-yl)-4-methylbenzenesulfonamide, (–)-**245**



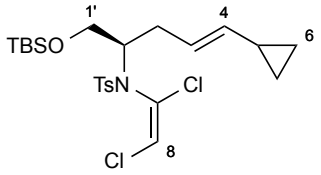
To a solution of (–)-**257** (112 mg, 0.24 mmol, 1.0 equiv.) in dichloromethane/pH 7 phosphate buffer (9:1 v/v, 2.4 mL) was added DDQ (107 mg, 0.47 mmol, 2.0 equiv.) and the mixture stirred for 4 h at 0 °C. The reaction mixture was diluted with water (10 mL) and the aqueous layer extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was dissolved in methanol (2.4 mL), and K_2CO_3 (163 mg, 1.20 mmol, 5.0 equiv.) was added. The suspension was stirred for 30 min, after which time the reaction mixture was diluted with water (10 mL) and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (–)-**245** as a colourless oil (57 mg, 0.19 mmol, 80%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –80.0 (*c* = 0.2, $CHCl_3$); $\mathbf{R}_f$ 0.19 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3506, 3281, 3003, 2925, 1495, 1323, 1157, 1093; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.04 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 4.92 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.81 (1H, d, *J* = 7.0 Hz, N*H*), 3.60 (1H, dd, *J* = 11.5 and 4.0 Hz, H1′), 3.53 (1H, dd, *J* = 11.5 and 5.5 Hz, H1′), 3.24-3.15 (1H, m, H1), 2.43 (3H, s, TsCH_3), 2.24-2.01 (3H, m, H2 and O*H*), 1.24-1.15 (1H, m, H5), 0.69-0.61 (2H, m, H6), 0.31-0.24 (2H, m, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.7, 138.9, 137.4, 129.8, 127.4, 122.0, 64.8, 55.4, 34.9, 21.7, 13.7, 6.7, 6.7; **HRMS** (ESI+) calc. for $C_{15}H_{22}O_3NS$ $[M+H]^+$ 296.1315, found 296.1315.

(*R*,*E*)-*N*-(1-((*tert*-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-4-methylbenzenesulfonamide, (–)-**246**



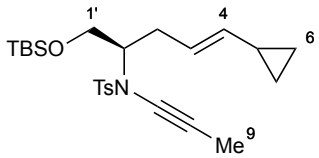
To a solution of (–)-**245** (57 mg, 0.19 mmol, 1.0 equiv.) in dichloromethane (1.0 mL) was added TBSCl (35 mg, 0.23 mmol, 1.2 equiv.) and imidazole (26 mg, 0.39 mmol, 2.0 equiv.) and the resulting suspension stirred for 30 min at room temperature. The reaction mixture was quenched with sat. *aq*. ammonium chloride (5 mL) and the aqueous layer extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give (–)-**246** as a colourless oil (62 mg, 0.15 mmol, 78%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –5.0 (*c* = 0.2, $CHCl_3$); $\mathbf{R}_f$ 0.44 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3283, 2953, 2929, 2857, 1332, 1161, 1094; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.17 (1H, dt, *J* = 15.0 and 7.5 Hz, H3), 4.91 (1H, dd, *J* = 15.0 and 8.5 Hz, H4), 4.69 (1H, d, *J* = 7.5 Hz, N*H*), 3.53 (1H, dd, *J* = 10.0 and 3.5 Hz, H1′), 3.35 (1H, dd, *J* = 10.0 and 5.0 Hz, H1′), 3.23-3.16 (1H, m, H1), 2.42 (3H, s, TsCH_3), 2.20-2.08 (2H, m, H2), 1.28-1.19 (1H, m, H5), 0.84 (9H, s, SiC(CH_3)$_3$), 0.67-0.62 (2H, m, H6), 0.29-0.25 (2H, m, H6), –0.02 (3H, s, SiCH_3), –0.03 (3H, s, SiCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.3, 138.2, 138.1, 129.7, 127.3, 122.7, 63.8, 54.8, 35.0, 26.0, 21.6, 18.4, 13.7, 6.6, 6.6, –5.4, –5.4; **HRMS** (ESI+) calc. for $C_{21}H_{35}O_3NNaSSi$ $[M+Na]^+$ 432.1999, found 432.1993.

_N_-((_R_,_E_)-1-((*tert*-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-_N_-((_E_)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, (+)-**248**



Prepared by General Procedure F using sulfonamide (–)-**246** (62 mg, 0.15 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give (+)-**248** as a colourless oil (69 mg, 0.14 mmol, 91%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +25.0 (*c* = 0.2, $CHCl_3$); $\mathbf{R}_f$ 0.47 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3084, 2954, 2928, 2885, 2856, 1598, 1495, 1359, 1254, 1166; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.86 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.57-6.52 (1H, m, H8), 5.45-5.34 (0.5H, m, H3), 5.11-4.96 (1H, m, H3 and 4), 4.86-4.80 (0.5H, m, H4), 3.85-3.73 (2.5H, m, H1 and H1′), 3.67-3.52 (0.5H, m, H1′), 2.59-2.30 (4.5H, m, H2 and TsCH_3), 2.06-1.96 (0.5H, m, H2), 1.32-1.10 (1H, m, H5), 0.89-0.80 (9H, m, SiC(CH_3)$_3$), 0.66-0.59 (2H, m, H6), 0.29-0.20 (2H, m, H6), 0.05–0.10 (6H, m, Si(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.4, 137.3, 136.8, 129.7, 128.6, 123.7, 123.0, 123.0, 63.9, 63.8, 32.1, 25.9, 21.8, 18.3, 13.7, 6.5, 6.5, –5.4, –5.6; **HRMS** (ESI+) calc. for $C_{23}H_{35}O_3NCl_2NaSSi$ $[M+Na]^+$ 526.1376, found 526.1379.

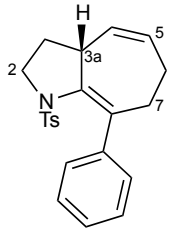
(*R*,*E*)-*N*-(1-((*tert*-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-4-methyl-*N*-(prop-1-yn-1-yl)benzenesulfonamide, (+)-**247**



Prepared by General Procedure G using dichloroenamide (+)-**248** (69 mg, 0.14 mmol, 1.0 equiv.) and iodomethane (10 μL, 0.16 mmol, 1.2 equiv.). The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give (+)-**247** as a colourless oil (51 mg, 0.11 mmol, 83%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +7.5 (*c* = 0.4, $CHCl_3$); $\mathbf{R}_f$ 0.42 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2954, 2928, 2856, 2256, 1598, 1471, 1436, 1253, 1168, 1120, 1093; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.12 (1H, dt, *J* = 15.0 and 7.0 Hz, H3), 4.93 (1H, d, *J* = 15.0 and 8.5 Hz, H4), 3.84 (1H, dq, *J* = 9.0 and 6.0 Hz, H1), 3.62 (1H, dd, *J* = 10.5 and 6.0 Hz, H1′), 3.54 (1H, dd, *J* = 10.5 and 6.0 Hz, H1′), 2.41 (3H, s, TsCH_3), 2.29-2.22 (1H, m, H2), 2.16-2.10 (1H, m, H2), 1.90 (3H, s, H9), 1.13 (1H, m, H5), 0.85 (9H, s, SiC(CH_3)$_3$), 0.64-0.56 (2H, m, H6), 0.28-0.20 (2H, m, H6), 0.00 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.9, 137.3, 136.4, 129.6, 127.8, 123.0, 69.2, 67.4, 63.9, 61.8, 32.7, 25.9, 21.8, 18.4, 13.7, 6.6, 6.6, 3.6, –5.4, –5.4; **HRMS** (ESI+) calc. for $C_{24}H_{37}O_3NNaSSi$ $[M+Na]^+$ 470.2156, found 470.2153.

7.3.2 [5+2] Cycloisomerisation products

(*R*)-8-Phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125a



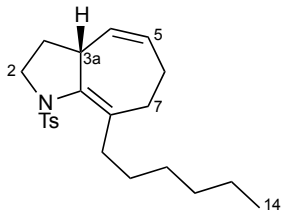
Method A: Prepared by General Procedure H using ynamide **120a** (20 mg, 55 μmol, 1.0 equiv.), with a reaction time of 3 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *rac*-**125a** as a colourless oil (18 mg, 50 μmol, 91%).

Method B: Prepared by General Procedure I using ynamide **120a** (20 mg, 55 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125a** as a colourless oil (15 mg, 41 μmol, 75%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –93.5 (*c* = 1.0, $CHCl_3$); 99% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 11.86 min, minor – 12.71 min); $\mathbf{R}_f$ 0.30 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2954, 2891, 1598, 1357, 1163, 1091; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.50 (2H, d, *J* = 7.5 Hz, Ph*H*), 7.47 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.23 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.10 (1H, t, *J* = 7.5 Hz, Ph*H*), 6.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.45-5.40 (1H, m, H5), 5.03 (1H, d, *J* = 11.0 Hz, H4), 3.51-3.45 (1H, m, H3a), 3.41 (1H, ddd, *J* = 12.5, 7.0 and 5.5 Hz, H2), 3.18 (1H, dt, *J* = 12.5 and 7.5 Hz, H2), 2.86 (1H, m, H7), 2.35 (1H, m, H7), 2.24-2.19 (1H, m, H6), 2.08-2.01 (1H, m, H6), 1.87 (3H, s, TsCH_3), 1.55-1.48 (1H, m, H3), 0.98-0.91 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.5, 142.7, 139.5, 137.9, 132.3, 130.9, 130.3, 129.2, 128.9, 128.6, 128.1, 126.5, 49.6, 40.4, 33.3, 32.3, 26.8, 21.1; **HRMS** (ESI+)

calc. for $C_{22}H_{24}NO_2S$ $[M+H]^+$ 366.1522, found 366.1507; **EA** calc. for $C_{22}H_{23}NO_2S$: C, 72.3; H, 6.3; N, 3.8. Found: C, 72.4; H, 6.5; N, 3.8.

(*R*)-8-Hexyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125b



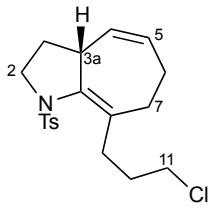
Method A: Prepared by General Procedure H using ynamide **120b** (20 mg, 54 μmol, 1.0 equiv.), with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give *rac*-**125b** as a colourless oil (20 mg, 54 μmol, 99%).

Method B: Prepared by General Procedure I using ynamide **120b** (20 mg, 54 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give (*R*)-**125b** as a colourless oil (16 mg, 43 μmol, 80%).

Method C (1 mmol scale reaction): To a stirred solution of ynamide **120b** (374 mg, 1 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added a solution of $[RhCl(C_2H_4)_2]_2$ (5 mg, 13 μmol, 0.0125 equiv.), $NaBAr^F{}_4$ (22 mg, 25 μmol, 0.025 equiv.) and phosphoramide (*S*,*R*,*R*)-**L12** (14 mg, 25 μmol, 0.025 equiv.) in dichloromethane (5 mL). The reaction mixture was stirred for 5 min, after which time water (20 mL) was added. The aqueous layer was extracted with dichloromethane (2 x 20 mL) and the combined organic extracts dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give (*R*)-**125b** as a colourless oil (300 mg, 0.80 mmol, 80% yield).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –24.0 (*c* = 1.0, $CHCl_3$); 99% *ee* (CHIRALPAK IA, 2% IPA/hexane, 1.3 mL/min, t_R minor – 6.89 min, major – 7.42 min); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2954, 2927, 2856, 1719, 1456, 1350, 1161, 1089; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.74 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.41-5.37 (1H, m, H5), 4.87 (1H, d, *J* = 11.0 Hz, H4), 3.49 (1H, ddd, *J* = 12.5, 7.5 and 4.5 Hz, H2), 3.19 (1H, m, H3a), 3.14 (1H, ddd, *J* = 12.5, 8.5 and 7.0 Hz, H2), 3.01-2.95 (1H, m, H9), 2.70 (1H, m, H9), 2.52-2.45 (1H, m, H7), 2.09-2.01 (3H, m, H7 and 6), 1.87 (3H, s, TsCH_3), 1.76-1.59 (2H, m, H10), 1.48-1.30 (6H, m, H11, 12 and 13), 1.17-1.11 (1H, m, H3), 0.92 (3H, t, *J* = 7.0 Hz, H14), 0.59-0.52 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.1, 137.8, 137.6, 134.8, 131.1, 130.0, 129.5, 128.5, 49.8, 39.7, 35.9, 32.4, 31.5, 30.1, 30.0, 28.0, 27.0, 23.2, 21.2, 14.5; **HRMS** (ESI+) calc. for $C_{22}H_{31}NNaO_2S$ $[M+Na]^+$ 396.1968, found 396.1956.

(*R*)-8-(3-Chloropropyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125c

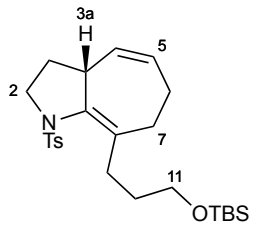


Method A: Prepared by General Procedure H using ynamide **120c** (20 mg, 55 μmol, 1.0 equiv.), with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *rac*-**125c** as a colourless oil (19 mg, 51 μmol, 93%).

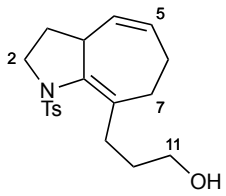
Method B: Prepared by General Procedure I using ynamide **120c** (20 mg, 55 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125c** as a colourless oil (17 mg, 47 μmol, 85%).

$[\alpha]_D^{25}$ –30.3 (*c* = 1.0, $CHCl_3$); 97% *ee* (CHIRALPAK IB, 1% IPA/hexane, 1.3 mL/min, t_R minor – 10.51 min, major – 11.03 min); $\mathbf{R}_f$ 0.27 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2956, 2893, 1652, 1445, 1349, 1163, 1090; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.70 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.35-5.31 (1H, m, H5), 4.81 (1H, dq, *J* = 11.0 and 2.0 Hz, H4), 3.43 (1H, ddd, *J* = 13.0, 7.5 and 4.5 Hz, H2), 3.39-3.29 (2H, m, H11), 3.15-3.09 (1H, m, H3a), 3.07 (1H, ddd, *J* = 13.0, 8.5 and 7.0 Hz, H2), 2.87-2.81 (1H, m, H9), 2.61-2.55 (1H, m, H9), 2.39-2.33 (1H, m, H7), 2.07 (4H, m, H6 and 10), 1.88 (3H, s, TsCH_3), 1.85-1.80 (1H, m, H7), 1.16-1.11 (1H, m, H3), 0.56-0.48 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.3, 138.7, 137.4, 132.9, 130.9, 129.9, 129.5, 128.4, 49.7, 45.3, 39.8, 33.3, 31.4, 31.2, 29.8, 26.7, 21.2; **HRMS** (ESI+) calc. for $C_{19}H_{24}ClNNaO_2S$ $[M+Na]^+$ 388.1108, found 388.1093.

(*R*)-8-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125d and 3-(1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[b]pyrrol-8-yl)pr*o*pan-1-ol, S3



125d



S3

Method A: Prepared by General Procedure H using ynamide **120d** (20 mg, 43 μmol, 1.0 equiv.), with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *rac*-**125d** (12 mg, 26 μmol, 60%) and *rac*-**S3** (5 mg, 14 μmol, 35%).

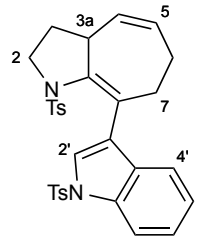
Method B: Prepared by General Procedure I using ynamide **120d** (20 mg, 43 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 15 min. The crude material was

purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125d** as a colourless oil (19 mg, 41 μmol, 96%).

For *(R)*-**125d**: $[\alpha]_D^{25}$ –24.1 (*c* = 1.0, $CHCl_3$); 96% *ee* (CHIRALPAK IB, 1% IPA/hexane, 1.3 mL/min, t_R minor – 5.65 min, major – 6.08 min); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2953, 2929, 2893, 2856, 1353, 1254, 1164, 1092; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.73 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.37-5.33 (1H, m, H5), 4.85 (1H, dq, *J* = 11.0 and 2.0 Hz, H4), 3.79-3.71 (2H, m, H11), 3.47 (1H, ddd, *J* = 13.0, 7.5 and 4.5 Hz, H2), 3.20-3.14 (1H, m, H3a), 3.12 (1H, ddd, *J* = 13.0, 8.5 and 7.0 Hz, H2), 3.02-2.96 (1H, m, H9), 2.73-2.67 (1H, m, H9), 2.51-2.44 (1H, m, H7), 2.09-1.94 (5H, m, H6, 7 and 10), 1.88 (3H, s, TsCH_3), 1.16 (1H, m, H3), 1.03 (9H, s, SiC(CH_3)$_3$), 0.58-0.52 (1H, m, H3), 0.12 (6H, s, Si(CH_3)$_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.1, 138.1, 137.6, 134.3, 131.0, 130.0, 129.4, 128.5, 63.9, 49.8, 39.8, 32.3, 31.5, 31.4, 30.0, 26.8, 26.3, 21.2, 18.6, –5.0, –5.1; **HRMS** (ESI+) calc. for $C_{25}H_{39}NNaO_3SSi$ $[M+Na]^+$ 484.2312, found 484.2299.

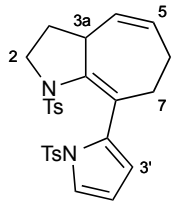
For **S3**: $\mathbf{R}_f$ 0.20 (petroleum ether/ethyl acetate (8:2)); **IR** (thin film, ν_{max}/cm^{-1}) 2961, 2925, 1597, 1452, 1348, 1161, 1089, 1057; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.74 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.74 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.37-5.33 (1H, m, H5), 4.84 (1H, d, *J* = 11.0 Hz, H4), 3.58 (2H, t, *J* = 6.5 Hz, H11), 3.47-3.42 (1H, m, H2), 3.20-3.14 (1H, m, H3a), 3.11-3.05 (1H, m, H2), 2.95-2.89 (1H, m, H9), 2.66-2.60 (1H, m, H9), 2.45-2.40 (1H, m, H7), 2.02-1.98 (2H, m, H6), 1.96-1.92 (1H, m, H7), 1.87 (3H, s, TsCH_3), 1.85-1.75 (2H, m, H10), 1.22 (1H, s, O*H*), 1.19-1.13 (1H, m, H3), 0.61-0.54 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 141.8, 136.7, 136.1, 132.8, 129.6, 128.6, 128.1, 127.1, 61.5, 48.4, 38.4, 30.6, 30.1, 29.6, 28.6, 25.4, 19.8; **HRMS** (ESI+) calc. for $C_{19}H_{25}NNaO_3S$ $[M+Na]^+$ 370.1447, found 370.1435.

1-Tosyl-8-(1-tosyl-1*H*-indol-3-yl)-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125f



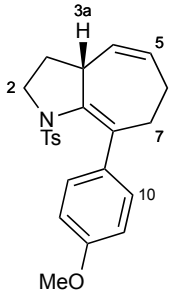
Prepared by General Procedure H using ynamide **120f** (20 mg, 36 μmol, 1.0 equiv.), with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **125f** as a colourless oil (19 mg, 33 μmol, 93%); $\mathbf{R}_f$ 0.12 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3011, 2952, 2889, 2280, 1597, 1447, 1358, 1167; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 8.19 (1H, d, *J* = 8.0 Hz, H4′), 7.90 (1H, s, H2′), 7.82 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.42 (1H, d, *J* = 8.0 Hz, H7′), 7.27 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.13 (1H, dd, *J* = 8.0 and 7.5 Hz, H6′), 7.06 (1H, dd, *J* = 8.0 and 7.5 Hz, H5′), 6.61-6.59 (4H, m, Ts*H*), 5.47-5.42 (1H, m, H5), 5.06 (1H, dq, *J* = 11.5 and 2.0 Hz, H4), 3.53-3.47 (1H, m, H3a), 3.37-3.32 (1H, m, H2), 3.24-3.19 (1H, m, H2), 2.83-2.77 (1H, m, H7), 2.24-2.19 (1H, m, H7), 2.15-2.07 (1H, m, H6), 2.04-1.96 (1H, m, H6), 1.90 (3H, s, TsCH_3), 1.57-1.50 (4H, m, H3 and TsCH_3), 1.01-0.94 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 144.3, 142.9, 141.7, 137.4, 136.3, 135.6, 130.7, 130.5, 130.3, 129.9, 129.2, 127.7, 127.1, 125.5, 125.0, 124.5, 123.5, 123.2, 121.6, 114.1, 49.7, 40.6, 33.2, 32.2, 26.6, 21.2, 20.9; **HRMS** (ESI+) calc. for $C_{31}H_{30}N_2NaO_4S_2$ $[M+Na]^+$ 581.1539, found 581.1519.

1-Tosyl-8-(1-tosyl-1*H*-pyrrol-2-yl)-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125g



Prepared by General Procedure H using ynamide **120g** (20 mg, 39 μmol, 1.0 equiv.), with a reaction time of 6 h. The crude material was purified by column chromatography (petroleum ether/diethyl ether (5:2)) to give **125g** as a colourless oil (17 mg, 34 μmol, 86%); $\mathbf{R}_f$ 0.28 (petroleum ether/diethyl ether) (5:2)); **IR** (thin film, ν_{max}/cm^{-1}) 2955, 2919, 2893, 1597, 1357, 1332, 1166, 1150, 1091; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.95-7.75 (4H, m, Ts*H*), 7.10-6.99 (1H, m, H5′), 6.79 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.63 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.36-6.33 (1H, m, H3′), 6.06 (1H, t, *J* = 3.5 Hz, H4′), 5.53-5.34 (1H, m, H5), 5.11-4.96 (1H, m, H4), 3.62-3.38 (3H, m, H2 and H3a), 3.09-2.93 (1H, m, H7), 2.50-2.34 (1H, m, H7), 2.26-2.08 (1H, m, H6), 1.93-1.82 (4H, m, H6 and TsCH_3), 1.76 (3H, s, TsCH_3), 1.26-1.14 (1H, m, H3), 1.08-0.94 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.1, 142.6, 141.6, 137.2, 136.6, 129.8, 129.0, 128.5, 128.3, 126.8, 121.4, 112.7, 111.4, 49.3, 39.8, 32.9, 30.7, 29.0, 25.1, 19.9, 19.7; **HRMS** (ESI+) calc. for $C_{27}H_{28}O_4N_2NaS_2$ $[M+Na]^+$ 531.1383, found 531.1382.

(*R*)-8-(4-Methoxyphenyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125h

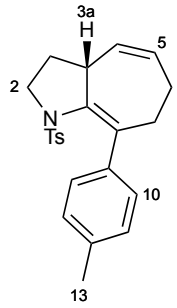


Method A: Prepared by General Procedure H using ynamide **120h** (20 mg, 51 μmol, 1.0 equiv.), with a reaction time of 20 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **125h** as a colourless oil (17 mg, 43 μmol, 85%).

Method B: Prepared by General Procedure I using ynamide **120h** (20 mg, 51 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 30 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (*R*)-**125h** as a colourless oil (15 mg, 38 μmol, 75%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –79.3 (*c* = 1.0, $CHCl_3$); 94% *ee* (CHIRALPAK IC, 30% IPA/hexane, 1.0 mL/min, t_R major – 38.45 min, minor – 51.01 min); $\mathbf{R}_f$ 0.17 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3010, 2953, 2835, 1607, 1510, 1353, 1246, 1161; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.53 (2H, d, *J* = 8.0 Hz, H11), 7.44 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.82 (2H, d, *J* = 8.5 Hz, Ts*H*), 6.69 (2H, d, *J* = 8.0 Hz, H10), 5.47-5.42 (1H, m, H5), 5.04 (1H, d, *J* = 11.5 Hz, H4), 3.52-3.44 (2H, m, H2 and H3a), 3.34 (3H, s, OCH_3), 3.29-3.20 (1H, m, H2), 2.91-2.85 (1H, m, H7), 2.40-2.35 (1H, m, H7), 2.27-2.18 (1H, m, H6), 2.11-2.05 (1H, m, H6), 1.88 (3H, s, TsCH_3), 1.55-1.48 (1H, m, H3), 0.98-0.91 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 158.9, 142.8, 139.1, 138.2, 135.8, 132.1, 131.2, 130.5, 130.2, 129.3, 128.3, 114.0, 54.9, 49.9, 40.7, 33.5, 32.6, 27.0, 21.3; **HRMS** (ESI+) calc. for $C_{23}H_{25}O_3NNaS$ $[M+Na]^+$ 418.1447, found 418.1442.

(*R*)-8-(*p*-Tolyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125i

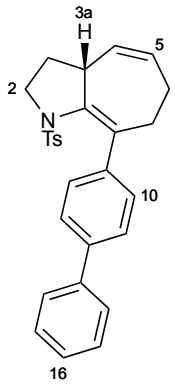


Method A: Prepared by General Procedure H using ynamide **120i** (20 mg, 53 μmol, 1.0 equiv.), with the reaction mixture stirred for 20 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **125i** as a colourless oil (18 mg, 47 μmol, 89%).

Method B: Prepared by General Procedure I using ynamide **120i** (20 mg, 53 μmol, 1.0 equiv.), and (*S*,*R*,*R*)-**L12**, with a reaction time of 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125i** as a colourless oil (19 mg, 49 μmol, 94%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –73.7 (*c* = 1.0, $CHCl_3$); 98% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 11.0 min, minor – 12.8 min); $\mathbf{R}_f$ 0.24 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3017, 2921, 1356, 1336, 1161, 1106; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.51 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.45 (2H, d, *J* = 8.0 Hz, H10), 7.05 (2H, d, *J* = 8.0 Hz, H11), 6.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.46-5.41 (1H, m, H5), 5.03 (1H, dq, *J* = 11.0 and 2.0 Hz, H4), 3.51-3.43 (2H, m, H3a and H2), 3.22 (1H, ddd, *J* = 12.5, 7.5 and 7.0 Hz, H2), 2.88 (1H, ddd, *J* = 15.0, 13.0 and 3.0 Hz, H7), 2.42-2.37 (1H, m, H7), 2.27-2.19 (1H, m, H6), 2.16 (3H, s, H13), 2.11-2.03 (1H, m, H7), 1.88 (3H, s, TsCH_3), 1.53-1.46 (1H, m, H3), 0.96-0.89 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 142.6, 140.5, 139.3, 138.1, 135.9, 132.2, 131.0, 130.3, 129.2, 129.0, 128.8, 128.1, 49.7, 40.4, 33.3, 32.3, 26.8, 21.3, 21.2; **HRMS** (ESI+) calc. for $C_{23}H_{26}O_2NS$ $[M+H]^+$ 380.1679, found 380.1678.

(*R*)-8-([1,1'-Biphenyl]-4-yl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125j



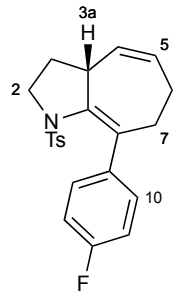
Method A: Prepared by General Procedure H using ynamide **120j** (20 mg, 45 μmol, 1.0 equiv.), with the reaction mixture stirred for 3 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **125j** as a colourless oil (20 mg, 45 μmol, >99%).

Method B: Prepared by General Procedure I using ynamide **120j** (20 mg, 45 μmol, 1.0 equiv.), and (*S*,*R*,*R*)-**L12**, with a reaction time of 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125j** as a colourless oil (20 mg, 45 μmol, >99%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –103.3 (*c* = 1.0, $CHCl_3$); 98% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 16.1 min, minor – 18.1 min); $\mathbf{R}_f$ 0.18 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3027, 2887, 1598, 1486, 1356, 1335, 1159, 1091; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.52-7.50 (4H, m, H10 and H14), 7.48-7.45 (4H, m, H11 and Ts*H*), 7.24 (2H, t, *J* = 8.0 Hz, H15), 7.17-7.13 (1H, m, H16), 6.65 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.49-5.45 (1H, m, H5), 5.09 (1H, dq, *J* = 11.0 and 2.0 Hz, H4), 3.58-3.52 (1H, m, H3a), 3.48 (1H, ddd, *J* = 12.0, 7.0 and 5.5 Hz, H2), 3.28 (1H, app. dt, *J* = 12.0 and 7.0 Hz, H2), 2.91 (1H, ddd, *J* = 14.5, 10.5 and 3.0 Hz, H7), 2.41-2.37 (1H, m, H7), 2.28-2.20 (1H, m, H6), 2.13-2.06 (1H, m, H6), 1.81 (3H, s, TsCH_3), 1.63-1.56 (1H, m, H3), 1.07-1.00 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 142.7, 142.4, 141.6, 140.0, 139.4, 138.3, 131.5, 130.9,

130.3, 129.4, 129.2, 129.0, 127.4, 127.3, 126.9, 127.9, 49.8, 40.5, 33.1, 32.6, 26.8, 21.1; **HRMS** (ESI+) calc. for $C_{28}H_{28}O_2NS$ $[M+H]^+$ 442.1835, found 442.1831.

(*R*)-8-(4-Fluorophenyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125k



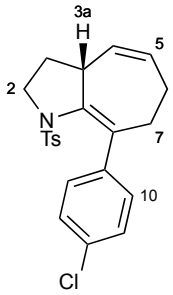
Method A: Prepared by General Procedure H using ynamide **120k** (20 mg, 52 μmol, 1.0 equiv.), with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give **125k** as a colourless oil (20 mg, 52 μmol, >99%).

Method B: Prepared by General Procedure I using ynamide **120k** (20 mg, 52 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (*R*)-**125k** as a colourless oil (20 mg, 51 μmol, 98%).

$[\alpha]_D^{25}$ –44.3 (*c* = 1.0, $CHCl_3$); 99% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 10.22 min, minor – 11.29 min); $\mathbf{R}_f$ 0.26 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3065, 2923, 1599, 1508, 1352, 1227, 1162; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.46 (2H, d, *J* = 8.5 Hz, Ts*H*), *7*.27 (2H, dd, J_{HH} = 9.0 Hz and J_{HF} = 5.5 Hz, H10), 6.86 (2H, dd, J_{HH} = 9.0 Hz and J_{HF} = 9.0 Hz, H11), 6.69 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.44-5.39 (1H, m, H5), 5.00 (1H, d, *J* = 11.5 Hz, H4), 3.46-3.38 (2H, m, H2 and H3a), 3.17 (1H, ddd, *J* = 12.5, 8.0 and 7.0 Hz, H2), 2.82-2.76 (1H, m, H7), 2.23-2.18 (1H, m, H7), 2.17-2.09 (1H, m, H6), 2.06-1.98 (1H, m, H6), 1.88 (3H, s, TsCH_3), 1.51-1.45 (1H, m, H3), 0.95-0.87 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 162.0 (d, J_{CF} = 245.0 Hz),

143.0, 139.8, 139.3 (d, J_{CF} = 3.5 Hz), 137.9, 131.0, 130.8, 130.5 (d, J_{CF} = 8.0 Hz), 130.2, 129.3, 128.0, 115.1 (d, J_{CF} = 21.5 Hz,), 49.7, 40.4, 33.2, 32.3, 26.7, 21.1; **^{19}F NMR** (470 MHz, C_6D_6) δ_F –116.0; **HRMS** (ESI+) calc. for $C_{22}H_{22}O_2NFNaS$ $[M+Na]^+$ 406.1248, found 406.1242.

(*R*)-8-(4-Chlorophenyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125l



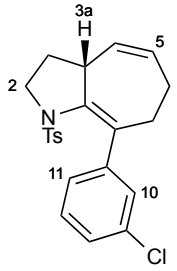
Method A: Prepared by General Procedure H using ynamide **120l** (20 mg, 50 μmol, 1.0 equiv.), with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **125l** as a colourless oil (11 mg, 28 μmol, 56%).

Method B: Prepared by General Procedure I using ynamide **120l** (20 mg, 50 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125l** as a colourless oil (20 mg, 50 μmol, 99%).

$[\alpha]_D^{25}$ –24.3 (*c* = 1.0, $CHCl_3$); 99% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 10.46 min, minor – 12.20 min); $\mathbf{R}_f$ 0.23 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3011, 2954, 2889, 1597, 1490, 1162, 1091; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.42 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.18 (2H, d, *J* = 8.5 Hz, H11), 7.12 (2H, d, *J* = 8.5 Hz, H10), 6.70 (1H, d, *J* = 8.0 Hz, Ts*H*), 5.44-5.39 (1H, m, H5), 5.01 (1H, d, *J* = 11.0 Hz, H4), 3.46-3.38 (2H, m, H3a and H2), 3.18 (1H, ddd, *J* = 12.5, 7.5 and 7.0 Hz, H2), 2.80-2.74 (1H, m, H7), 2.18-2.13 (1H, m, H7), 2.11-2.06 (1H, m, H6), 2.04-1.97 (1H,

m, H6), 1.91 (3H, s, TsCH_3), 1.54-1.47 (1H, m, H3), 0.97-0.90 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.0, 141.7, 140.3, 138.0, 132.2, 130.7, 130.5, 130.3, 130.2, 129.3, 128.4, 127.8, 49.8, 40.5, 32.9, 32.4, 26.6, 21.2; **HRMS** (ESI+) calc. for $C_{22}H_{23}O_2NClS$ $[M+H]^+$ 400.1133, found 400.1135.

(*R*)-8-(3-Chlorophenyl)-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125m



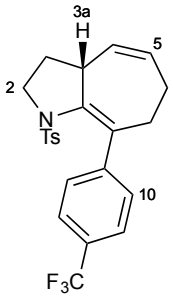
Method A: Prepared by General Procedure H using ynamide **120m** (20 mg, 50 μmol, 1.0 equiv.), with the reaction mixture stirred for 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **125m** as a colourless oil (20 mg, 50 μmol, >99%).

Method B: Prepared by General Procedure I using ynamide **120m** (20 mg, 50 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12** with the reaction mixture stirred for 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125m** as a colourless oil (18 mg, 44 μmol, 89%).

$[\alpha]_D^{25}$ –60.1 (*c* = 1.0, $CHCl_3$); 98% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 11.0 min, minor – 14.4 min); $\mathbf{R}_f$ 0.20 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3064, 3011, 2952, 2889, 2828, 1594, 1356, 1333, 1159, 1091; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.51 (1H, t, *J* = 2.0 Hz, H10), 7.46 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.28 (1H, dt, *J* = 8.0 and 2.0 Hz, H12), 7.05 (1H, ddd, *J* = 8.0, 2.0 and 1.0 Hz, H14), 6.93 (1H, t, *J* = 8.0 Hz, H13), 6.71 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.41-5.36 (1H, m, H5), 4.99 (1H, dq, *J* = 11.5 and 2.0 Hz, H4), 3.45-3.39 (1H, m, H3a), 3.34 (1H, ddd, *J* = 12.5, 7.0 and

5.5 Hz, H2), 3.09 (1H, ddd, *J* = 12.5, 7.5 and 5.0 Hz, H2), 2.74 (1H, ddd, *J* = 14.5, 13.0 and 3.0 Hz, H7), 2.19-2.14 (1H, m, H7), 2.11-2.03 (1H, m, H6), 1.99-1.92 (1H, m, H6), 1.89 (3H, s, TsCH_3), 1.52-1.46 (1H, m, H3), 0.97-0.90 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 145.4, 143.1, 140.6, 137.7, 134.0, 130.6, 130.4, 130.2, 129.6, 129.4, 128.9, 127.9, 127.2, 126.6, 49.7, 40.5, 32.8, 32.2, 26.6, 21.2; **HRMS** (ESI+) calc. for $C_{22}H_{23}O_2NClS$ $[M+H]^+$ 400.1133, found 400.1131.

(*R*)-1-Tosyl-8-(4-(trifluoromethyl)phenyl)-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, 125n



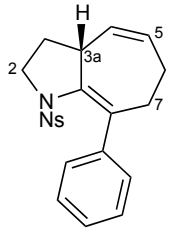
Method A: Prepared by General Procedure H using ynamide **120n** (20 mg, 46 μmol, 1.0 equiv.), with the reaction mixture stirred for 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **125n** as a colourless oil (20 mg, 46 μmol, >99%).

Method B: Prepared by General Procedure I using ynamide **120n** (20 mg, 46 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12** with the reaction mixture stirred for 5 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**125n** as a colourless oil (18 mg, 41 μmol, 88%).

$[\alpha]_D^{25}$ –83.8 (*c* = 1.0, $CHCl_3$); 98% *ee* (CHIRALPAK IA, 5% IPA/hexane, 1.3 mL/min, t_R major – 7.7 min, minor – 8.7 min); $\mathbf{R}_f$ 0.24 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3012, 2925, 1651, 1357, 1324, 1160, 1119, 1105; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.35 (2H, d, *J* = 8.5 Hz, H10), 7.33 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.27 (2H, d,

J = 8.5 Hz, H11), 6.68 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.45-5.40 (1H, m, H5), 5.03 (1H, dq, *J* = 11.5 and 2.0 Hz, 3.49-3.43 (1H, m, H3a), 3.39 (1H, ddd, *J* = 12.0, 7.0 and 5.5 Hz, H2), 3.19 (1H, ddd, *J* = 12.0, 7.5 and 7.0 Hz, H2), 2.77 (1H, ddd, *J* = 15.0, 13.0 and 3.0 Hz, H7), 2.16-2.11 (1H, m, H7), 2.10-2.05 (1H, m, H6), 2.04-1.97 (1H, m, H6), 1.89 (3H, s, TsCH_3), 1.59-1.52 (1H, m, H3), 1.02-1.09 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 147.1, 143.1, 141.1, 137.9, 130.6, 130.2, 130.1, 129.3, 129.2, 128.2, 127.6, 125.3 (q, *J* = 272.5 Hz), 125.1 (q, *J* = 4.0 Hz), 49.8, 40.5, 32.8, 32.4, 26.6, 21.1; **^{19}F NMR** (376 MHz, C_6D_6) δ_F –61.7; **HRMS** (ESI+) calc. for $C_{23}H_{23}O_2NF_3S$ $[M+H]^+$ 434.1396, found 434.1398.

(*R*)-1-((4-Nitrophenyl)sulfonyl)-8-phenyl-1,2,3,3a,6,7-hexahydrocyclohepta[b]pyrrole, 127a

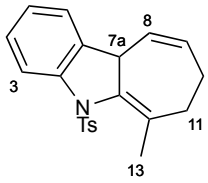


Method A: Prepared by General Procedure H using ynamide **127a** (20 mg, 54 μmol, 1.0 equiv.), with a reaction time of 1 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *rac*-**142a** as a yellow oil (20 mg, 54 μmol, >99%).

Method B: Prepared by General Procedure I using ynamide **127a** (20 mg, 54 μmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 10 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (*R*)-**142a** as a yellow oil (20 mg, 54 μmol, >99%).

$[\alpha]_D^{25}$ –149.0 (*c* = 1.0, $CHCl_3$); 96% *ee* (CHIRALPAK IB, 10% IPA/hexane, 1.3 mL/min, t_R minor – 12.5 min, major – 14.5 min); $\mathbf{R_f}$ 0.28 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3104, 2953, 1605, 1523, 1349, 1309, 1169, 1107; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.51 (2H, d, *J* = 9.0 Hz, Ns*H*), 7.18-7.12 (4H, m, Ns*H* and Ph*H*), 6.99-6.96 (2H, m, Ph*H*), 6.93-6.89 (1H, m, Ph*H*), 5.38-5.34 (1H, m, H5), 4.97 (1H, d, *J* = 11.0 Hz, H4), 3.47-3.41 (1H, m, H3a), 3.34 (1H, ddd, *J* = 12.0, 7.0 and 5.5, H2), 3.12 (1H, ddd, *J* = 12.0, 7.5 and 7.0, H2), 2.79-2.73 (1H, m, H7), 2.21-2.16 (1H, m, H7), 2.12-2.03 (1H, m, H6), 2.02-1.94 (1H, m, H6), 1.61-1.54 (1H, m, H3), 1.00-0.94 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 148.5, 144.6, 141.5, 137.8, 131.2, 129.3, 129.2, 127.5, 127.2, 127.1, 125.6, 122.3, 48.7, 38.9, 31.9, 31.7, 25.4; **HRMS** (ESI+) calc. for $C_{21}H_{20}O_4N_2NaS$ $[M+Na]^+$ 419.1036, found 419.1030.

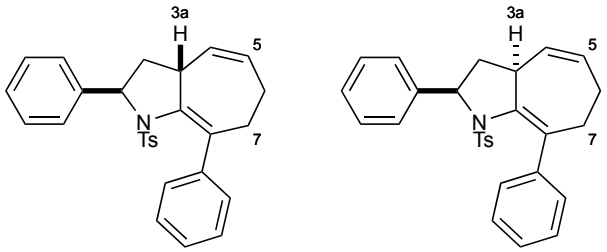
6-Methyl-5-tosyl-5,7,8,10a-tetrahydrocyclohepta[*b*]indole, 145



Prepared by General Procedure H using ynamide **136** (20 mg, 57 μmol, 1.0 equiv.), with a reaction time of 1 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give **145** as a colourless oil (15 mg, 42 μmol, 74%); $\mathbf{R_f}$ 0.34 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3032, 2910, 1656, 1493, 1358, 1170; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.98 (1H, d, *J* = 8.0 Hz, H6), 7.40 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.00 (1H, t, *J* = 8.0 and 7.5 Hz, H5), 6.85 (1H, t, *J* = 7.5 Hz, H4), 6.67 (1H, d, *J* = 7.5 Hz, H3), 6.50 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.53-5.48 (1H, m, H9), 5.34 (1H, d, *J* = 11.0 Hz, H8), 3.90-3.85 (1H, m, H7a), 2.35-2.28 (4H, m, H11 and 13), 2.09-2.02 (1H, m, H10), 1.87-1.80 (2H, m, H10 and 11), 1.70 (3H, s, TsCH_3); **^{13}C NMR**

(125 MHz, C_6D_6) δ_C 143.6, 143.4, 138.0, 136.6, 135.0, 133.0, 131.7, 129.7, 129.0, 128.6, 127.7, 126.4, 123.1, 121.4, 43.1, 33.1, 25.6, 23.1, 21.1; **HRMS** (ESI+) calc. for $C_{21}H_{22}O_2NS$ $[M+H]^+$ 352.1366, found 352.1360.

(2*R,3a*R**)-2,8-Diphenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole,** ***syn*-183 and (2*R**,3a*S**)-2,8-diphenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole,** ***anti*-183**

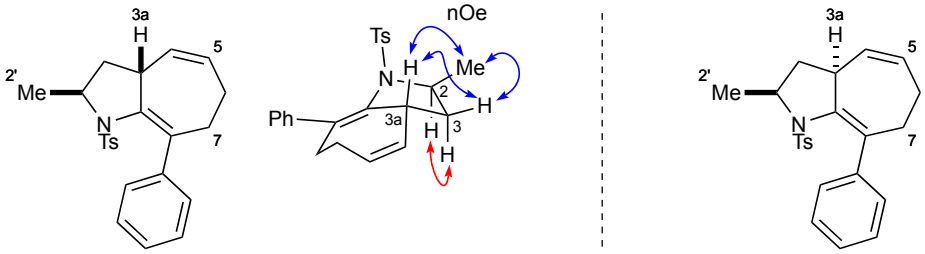


syn-**183** *anti*-**183**

Prepared by General Procedure H using ynamide **152** (20 mg, 45 μmol, 1.0 equiv.), with the reaction mixture stirred for 1 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *syn*-**183** and *anti*-**183** in a 55:45 ratio respectively (15 mg, 34 μmol, 75%); $\mathbf{R}_f$ 0.30 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2961, 2925, 2852, 1649, 1494, 1358, 1164, 1090, 1003; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.59 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.49 (2H, d, *J* = 8.0 Hz, Ph*H*), 7.40-7.34 (8H, m, Ph*H*, Ph′*H* and Ts′*H*), 7.22-7.13 (8H, m, Ph*H* and Ph′*H*), 7.09-7.03 (4H, m, Ph*H* and Ph′*H*), 5.56-5.49 (1H, m, H5′), 5.48-5.42 (1H, m, H5), 5.29 (3H, m, H2, H2′ and H4′), 4.98 (1H, d, *J* = 11.5 Hz, H4), 3.80-3.72 (1H, m, H3a), 3.59 (1H, m, H3a′), 2.90-2.83 (1H, m, H7′), 2.78-2.70 (1H, m, H7), 2.46-2.27 (3H, m, H6, H7 and H7′), 2.23-2.15 (1H, m, H3′), 2.14-1.92 (4H, m, H3, H6 and H6′), 1.88 (3H, s, TsC*H*3), 1.84 (3H, s, Ts′CH_3), 1.66 (1H, m, H3′), 1.23 (1H, m, H3); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 143.5, 143.4, 142.6, 142.5, 142.1, 140.8, 140.7, 138.3, 137.5, 137.3, 134.2, 131.8, 130.9, 130.6,

129.6, 129.5, 129.3, 129.0, 128.9, 128.6, 128.3, 128.2, 127.9, 127.3, 126.8, 126.4, 126.3, 63.6, 63.5, 41.4, 40.2, 38.4, 35.8, 34.2, 33.1, 27.3, 26.1, 20.9, 20.8; **HRMS** (ESI+) calc for $C_{28}H_{27}NNaO_2S$ $[M+Na]^+$ 464.1655, found 464.1646.

(2*S,3a*R**)-2-Methyl-8-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *syn*-184 and (2*S**,3a*S**)-2-methyl-8-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *anti*-184**



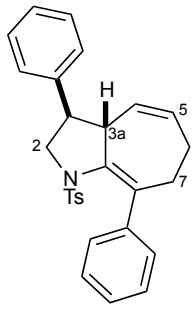
syn-184 *anti*-184

Prepared by General Procedure H using ynamide **153** (20 mg, 53 μmol, 1.0 equiv.), with a reaction time of 2 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *syn*-**184** and *anti*-**184** as an inseparable mixture in a 2:1 ratio as a colourless oil (18 mg, 48 μmol, 90%).

For *syn*-**184**: $\mathbf{R}_f$ 0.35 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3018, 2958, 1651, 1494, 1444, 1355, 1164, 1087, 1035; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.59-7.56 (4H, m, Ts*H* and Ph*H*), 7.27 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.11 (1 H, t, *J* = 7.5, Ph*H*), 6.7 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.45 (1H, m, H5), 4.91 (1H, d, *J* = 11.5 Hz, H4), 4.16 (1H, quin, *J* = 7.0 Hz, H2), 3.66-3.59 (1H, m, H3a), 2.90-2.84 (1H, m, H7), 2.46-2.38 (2H, m, H6), 2.16-2.09 (1H, m, H6), 1.88 (3H, s, TsCH_3), 1.23-1.19 (1H, m, H3β), 1.00-0.94 (4H, m, H2′ and 3α); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.8, 142.6, 138.2, 137.8, 132.5, 130.0, 129.6, 129.1, 128.4, 128.4, 128.3, 126.6, 57.0, 39.5, 37.8, 33.1, 27.7, 21.1, 20.5; **HRMS** (ESI+) calc. for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$ 402.1498, found 402.1491.

For *anti*-**184**: $\mathbf{R}_f$ 0.41 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3019, 2962, 1652, 1492, 1451, 1355, 1165, 1087, 1032; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.51 (2H, d, *J* = 8.0 Hz, Ph*H*), 7.45 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.25 (2H, t, *J* = 8.0 Hz, Ph*H*), 7.11 (1H, t, *J* = 8.0 Hz, Ph*H*), 6.68 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.47-5.42 (1H, m, H5), 5.21 (1H, d, *J* = 11.5 Hz, H4), 4.06 (1H, quin d, *J* = 7.0 and 2.5 Hz, H2), 3.54-3.48 (1H, m, H3a), 2.95-2.89 (1H, m, H7), 2.39-2.34 (1H, m, H7), 2.03-1.98 (2H, m, H6), 1.86 (3H, s, TsCH_3), 1.84-1.78 (1H, m, H3α), 1.09 (3H, d, *J* = 7.0 Hz, H2′), 0.92-0.88 (1H, m, H3β); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.4, 142.7, 138.3, 137.9, 134.8, 132.8, 130.1, 129.6, 129.2, 128.3, 127.9, 126.5, 57.2, 40.5, 38.8, 33.9, 26.0, 21.6, 21.1; **HRMS** (ESI+) calc. for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$ 402.1498, found 402.1490.

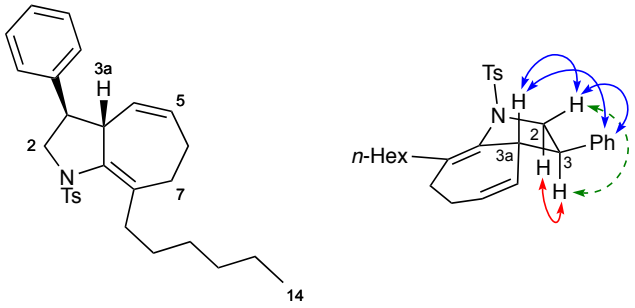
(3*R,3a*S**)-3,8-Diphenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole,** *syn*-**181a**



Prepared by General Procedure H using ynamide *rac*-**168a** (20 mg, 45 μmol, 1.0 equiv.), with a reaction time of 16 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**181a** as a colourless oil (16 mg, 36 μmol, 79%); $\mathbf{R}_f$ 0.23 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3027, 2970, 2947, 1739, 1598, 1493, 1360, 1165, 1074; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.57 (2H, d, *J* = 8.0 Hz, Ph*H*), 7.50 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.26 (2H, t, *J* = 8.0 Hz, Ph*H*), 7.13 (1H, t, *J* = 8.0 Hz, Ph*H*), 7.09-7.03 (3H, m, Ph*H*), 6.85 (2H, d, *J* = 7.5 Hz, Ph*H*), 6.71 (2H, d,

J = 8.0 Hz, Ts*H*), 5.51-5.47 (1H, m, H5), 5.19 (1H, d, *J* = 11.0 Hz, H4), 4.00 (1H, dd, *J* = 12.0 and 7.5 Hz, H2), 3.67 (1H, br d, *J* = 11.0 Hz, H3a), 3.18 (1H, t, *J* = 12.0, H2), 2.83 (1H, t, *J* = 13.5 Hz, H7), 2.66 (1H, td, *J* = 11.0 and 7.5 Hz, H3), 2.43-2.33 (2H, m, H6 and 7), 2.16-2.11 (1H, m, H6), 1.88 (3H, s, TsCH_3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.8, 142.9, 139.9, 138.6, 137.7, 132.5, 130.5, 129.3, 129.0, 128.8, 128.4, 128.3, 128.1, 128.0, 127.4, 126.6, 56.0, 51.4, 49.4, 33.4, 27.4, 21.2; **HRMS** (ESI+) calc. for $C_{28}H_{27}NNaO_2S$ $[M+Na]^+$ 464.1655, found 464.1660.

(3*R*,3a*S*)-8-Hexyl-3-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, ***syn*-181b**



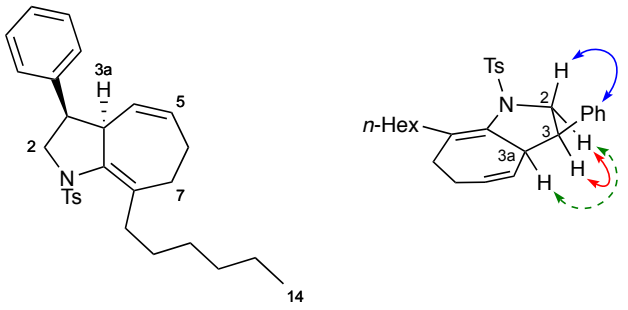
Method A: Prepared by General Procedure H using ynamide *rac*-**168b** (20 mg, 44 µmol, 1.0 equiv.), with a reaction time of 16 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**181b** as a colourless oil (17 mg, 38 µmol, 86%).

Method B: Prepared by General Procedure I using ynamide (–)-**168b** (20 mg, 44 µmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with a reaction time of 15 min. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give (–)-*syn*-**181b** as a colourless oil (20 mg, 44 µmol, >99%).

$[\alpha]_D^{25}$ –44.9 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3028, 2954, 2925, 2855, 1598, 1496, 1353, 1163; **^{1}H NMR** (500 MHz, C_6D_6) δ_H

7.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.02-6.98 (3H, m, Ph*H* and Ts*H*), 6.79 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.67-6.65 (2H, m, Ph*H*), 5.42-5.37 (1H, m, H5), 4.98 (1H, d, *J* = 11.0 Hz, H4), 4.01 (1H, dd, *J* = 12.5 and 7.5 Hz, H2), 3.42 (1H, br d, *J* = 10.5 Hz, H3a), 3.17 (1H, t, *J* = 12.5 Hz, H2), 3.13-3.07 (1H, m, H9), 2.68-2.62 (1H, m, H9), 2.49-2.43 (1H, m, H6), 2.20-2.06 (4H, m, H3, 6 and 2 x H7), 1.90 (3H, s, TsCH_3), 1.89-1.81 (1H, m, H10), 1.63-1.33 (7H, m, H10 and H11-13), 0.94 (3H, s, H14); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 142.13, 138.6, 136.0, 135.9, 134.1, 129.1, 128.3, 127.7, 127.6, 127.3, 127.1, 126.1, 55.0, 49.2, 47.2, 35.0, 31.1, 29.1, 29.0, 26.8, 25.9, 22.0, 20.0, 13.2; **HRMS** (ESI+) calc. for $C_{28}H_{35}NNaO_2S$ $[M+Na]^+$ 472.2281, found 472.2284.

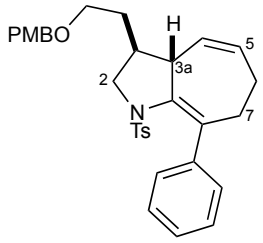
(3*R*,3a*R*)-8-Hexyl-3-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, ***anti*-181b**



Prepared by General Procedure I using ynamide (–)-**168b** (20 mg, 44 µmol, 1.0 equiv.) and (*R*,*S*,*S*)-**L12**, with a reaction time of 3 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (–)-*anti*-**181b** as a colourless oil (17 mg, 38 µmol, 83%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –48.9 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2926, 2856, 1456, 1354, 1165, 1090; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.83 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.07 (2H, t, *J* = 7.5 Hz, Ph*H*), 7.00 (1H, t, *J* = 7.5 Hz, Ph*H*), 6.83 (2H, d, *J* = 7.5 Hz, Ph*H*), 6.79 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.43-5.38 (1H, m, H5), 4.98 (1H, d, *J* = 11.5 Hz, H4), 3.91 (1H, dd, *J* = 12.0 and 7.5 Hz,

H2), 3.53 (1H, dd, *J* = 12.0 and 6.0 Hz, H2), 3.16-3.10 (2H, m, H3a and 9), 2.76-2.69 (2H, m, H3 and 9), 2.37-2.31 (1H, m, H7), 2.11-2.03 (2H, m, H6 and 7), 1.88 (3H, s, TsCH_3), 1.84-1.73 (2H, m, H6 and 10), 1.53-1.32 (7H, m, H10 and 11-13), 0.94 (3H, t, *J* = 7.0 Hz, H14); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.4, 140.7, 136.7, 136.6, 135.1, 131.6, 129.6, 128.9, 128.5, 128.4, 127.6, 127.0, 54.8, 45.8, 45.5, 37.0, 32.5, 30.8, 30.3, 28.0, 26.8, 23.2, 21.2, 14.5; **HRMS** (ESI+) calc. for $C_{28}H_{35}O_2NNaS$ $[M+Na]^+$ 472.2281, found 472.2268.

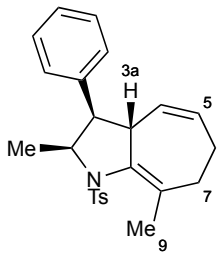
(3*S,3a*S**)-3-(2-((4-Methoxybenzyl)oxy)ethyl)-8-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole,** ***syn*-182**



Prepared by General Procedure H using ynamide **169** (20 mg, 38 μmol, 1.0 equiv.), with a reaction time of 20 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**182** as a colourless oil (14 mg, 26 μmol, 70%); $\mathbf{R}_f$ 0.40 (petroleum ether/ethyl acetate (4:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3057, 2917, 2857, 1612, 1513, 1356, 1248, 1162, 1090, 1033; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.55-7.52 (4H, m, Ts*H* and Ph*H*), 7.25-7.21 (4H, m, PMB*H* and Ph*H*), 7.10 (1H, t, *J* = 7.5 Hz, Ph*H*), 6.86 (2H, d, *J* = 8.5 Hz, PMB*H*), 6.69 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.48-5.43 (1H, m, H5), 5.06 (1H, app. dq, *J* = 11.5 and 2.0 Hz, H4), 4.24 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.20 (1H, d, *J* = 11.5 Hz, PMBCH_2), 4.08 (1H, dd, *J* = 12.5 and 7.0 Hz, H2), 3.33 (3H, s, PMBCH_3), 3.16-3.07 (3H, m, H3a and H9), 2.82 (1H, dd, *J* = 12.5 and 11.0 Hz, H2) 2.81 (1H, ddd, *J* = 15.0, 13.5 and 2.0 Hz, H7), 2.41-2.32 (2H, m, H6 and H7), 2.16-2.09 (1H, m, H6), 1.87 (3H, s, TsCH_3), 1.63-1.57 (1H, m, H3), 1.51-1.44 (1H, m, H8), 1.30-1.23 (1H,

m, H8); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 158.6, 142.6, 141.5, 138.0, 136.7, 130.4, 129.8, 128.8, 128.3, 128.2, 128.0, 127.4, 127.4, 127.1, 125.3, 113.0, 71.7, 67.3, 54.0, 53.7, 46.3, 42.1, 32.0, 31.6, 26.3, 20.0; **HRMS** (ESI+) calc. for $C_{32}H_{36}O_4NS$ $[M+H]^+$ 530.2360, found 530.2355.

(2*S*,3*R*,3a*S*)-2,8-Dimethyl-3-phenyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *syn*-185



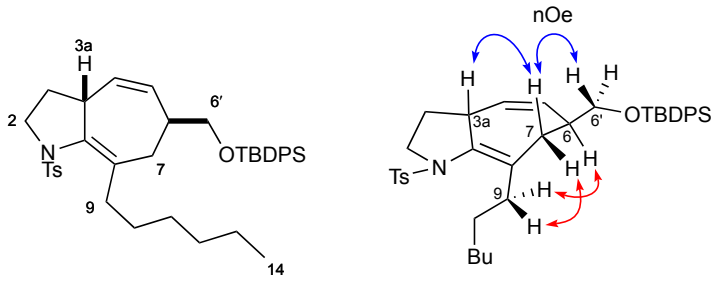
Method A: Prepared by General Procedure H using ynamide *rac-syn*-**170** (20 mg, 51 μmol, 1.0 equiv.), with the reaction mixture stirred for 5 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give *syn*-**185** as a colourless oil (20 mg, 51 μmol, >99%).

Method B: Prepared by General Procedure I using ynamide (+)-*syn*-**170** (20 mg, 51 μmol, 1.0 equiv.), and (*S*,*R*,*R*)-**L12** with the reaction mixture stirred for 1 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (95:5)) to give (–)-*syn*-**185** as a colourless oil (20 mg, 51 μmol, >99%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –42.30 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.44 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3062, 2977, 2850, 1598, 1451, 1349, 1165, 1088; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.88 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.05-6.97 (3H, m, Ph*H*), 6.82-6.79 (4H, m, Ph*H* and Ts*H*), 5.37-5.33 (1H, m, H5), 4.83 (1H, d, *J* = 11.0 Hz, H4), 4.35 (1H, app. quin, *J* = 7.0, H2), 3.90 (1H, d, *J* = 12 Hz, H3a), 2.71 (1H, td, *J* = 14.0 and 2.5 Hz, H7), 2.33 (3H, d, *J* = 1.5 Hz, H9), 2.31 (1H, dd, *J* = 12.0 and 7.0 Hz, H3), 2.21-2.11 (1H, m, H6), 2.03-1.96

(1H, m, H6), 1.87-1.81 (1H, m, H7), 1.86 (3H, s, TsCH_3), 0.79 (3H, d, J = 7.0 Hz, CH_3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.3, 137.7, 137.7, 136.3, 132.0, 130.2, 129.5, 128.8, 128.7, 128.7, 128.6, 127.1, 60.9, 52.9, 41.8, 32.8, 26.6, 23.2, 21.2, 15.7; **HRMS** (ESI+) calc. for $C_{24}H_{28}O_2NS$ $[M+H]^+$ 394.1835, found 394.1835.

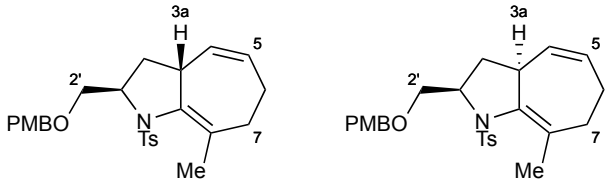
(3a*R,6*S**)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-8-hexyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *syn*-192**



Prepared by General Procedure H using ynamide *cis*-**186** (20 mg, 31 µmol, 1.0 equiv.), with a reaction time of 20 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**192** as a colourless oil (14 mg, 22 µmol, 68%); **R_f** 0.43 (petroleum ether/ethyl acetate (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3070, 2956, 2929, 2857, 1471, 1354, 1164, 1111; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.81-7.79 (4H, m, PhH), 7.76 (2H, d, J = 8.0 Hz, TsH), 7.28-7.23 (6H, m, PhH), 6.74 (2H, d, J = 8.0 Hz, TsH), 5.30 (1H, d, J = 12.0, H5), 4.90 (1H, d, J = 12.0 Hz, H4), 3.64 (1H, dd, J = 10.0 and 6.0 Hz, H6'), 3.56-3.50 (2H, m, H2 and 6'), 3.21-3.11 (2H, m, H2 and 3a), 3.08-3.02 (1H, m, H9), 2.76-2.69 (1H, m, H9), 2.59-2.52 (1H, m, H6), 2.51-2.46 (1H, m, H7), 2.43-2.37 (1H, m, H7), 1.88 (3H, s, TsCH_3), 1.86-1.77 (2H, m, H10), 1.54-1.47 (2H, m, H11), 1.45-1.34 (4H, m, H12 and 13), 1.22 (9H, s, SiC(CH_3)$_3$), 1.20-1.11 (1H, m, H3), 0.93 (3H, t, J = 7.0 Hz, H14), 0.59-0.51 (1H, m, H3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 143.1, 138.3, 137.8, 136.1, 134.1, 134.1, 133.2, 132.1, 131.0, 130.1, 129.5, 128.5, 68.7, 50.1, 40.5, 40.1,

36.0, 33.2, 32.4, 31.6, 30.3, 28.0, 27.2, 23.2, 21.2, 19.6, 14.5; **HRMS** (ESI+) calc. for $C_{39}H_{51}O_3NNaSSi$ $[M+Na]^+$ 664.3251, found 664.3241.

(2*R*,3a*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-8-methyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *syn*-249 and (2*R*,3a*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-methyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *anti*-249

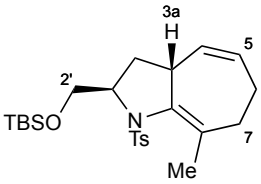


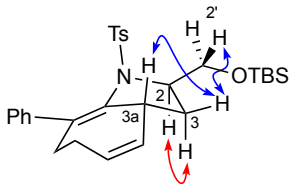
syn-**249** *anti*-**249**

Prepared by General Procedure H using ynamide (+)-**239** (20 mg, 44 μmol, 1.0 equiv.), with the reaction mixture stirred for 1 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (9:1)) to give *syn*-**249** and *anti*-**249** in a 1.8:1 ratio as a colourless oil (18 mg, 40 μmol, 91%); $\mathbf{R}_f$ 0.30 (petroleum ether/ethyl acetate (8:2)); **IR** (thin film, ν_{max}/cm^{-1}) 3007, 2934, 2905, 2853, 1613, 1513, 1351, 1247, 1165, 1091; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.77-7.74 (4H, m, Ts*H* of *syn*-**249** and *anti*-**249**), 7.19-7.16 (4H, m, PMB*H* of *syn*-**249** and *anti*-**249**), 6.80-6.72 (8H, m, Ts*H* and PMB*H* of *syn*-**249** and *anti*-**249**), 5.53-5.48 (1H, m, H5 of *anti*-**249**), 5.30-5.25 (1H, m, H5 of *syn*-**249**), 5.16 (1H, d, *J* = 11.0 Hz, H4 of *anti*-**249**), 4.75 (1H, d, *J* = 11.0 Hz, H4 of *syn*-**249**), 4.39-4.19 (6H, m, PMBCH_2 and H1 of *syn*-**249** and *anti*-**249**), 3.86 (1H, dd, *J* = 9.0 and 5.0 Hz, H2′ of *anti*-**249**), 3.59-3.53 (1H, m, H3a of *syn*-**249**), 3.49 (1H, dd, *J* = 9.5 and 5.0 Hz, H2′ of *syn*-**249**), 3.34 (1H, dd, *J* = 9.0 and 9.0 Hz, H2′ of *anti*-**249**), 3.30 (3H, s, PMBCH_3 of *syn*-**249**), 3.29 (3H, s, PMBCH_3 of *anti*-**249**), 3.21 (1H, dd, *J* = 9.5 and 7.5 Hz, H2′ of *syn*-**249**), 2.82-2.76 (1H, m, H3a of *anti*-**249**), 2.60-2.54 (1H, m,

H7 of *syn*-**249**), 2.32-2.26 (4H, m, H9 of *syn*-**249**, and H7 of *anti*-**249**), 2.10 (3H, d, J = 2.0 Hz, H9 of *anti*-**249**), 2.13-2.05 (2H, m, H6 of *syn*-**249** and *anti*-**249**), 1.97-1.82 (9H, m, H6 and TsCH_3 of *syn*-**249**, and H6, H7 and TsCH_3 of *anti*-**249**), 1.79 (1H, dd, J = 12.5 and 9.0 Hz, H3 of *syn*-**249**), 1.76-1.72 (1H, m, H7 of *syn*-**249**), 1.64-1.58 (1H, m, H3 of *anti*-**249**), 1.40-1.35 (1H, m, H3 of *anti*-**249**), 0.65-0.59 (1H, m, H3 of *syn*-**249**); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 159.4, 142.9, 142.7, 137.8, 136.8, 136.3, 135.1, 131.9, 131.9, 130.6, 130.6, 130.4, 130.4, 129.5, 129.2, 129.0, 128.9, 128.8, 128.4, 128.0, 113.8, 113.7, 72.8, 72.8, 72.7, 71.2, 60.7, 59.1, 54.4, 39.6, 38.6, 34.6, 33.1, 32.9, 32.3, 26.1, 25.5, 23.4, 22.8, 20.8, 20.8; **HRMS** (ESI+) calc. for $C_{26}H_{31}O_4NNaS$ $[M+Na]^+$ 476.1866, found 476.1854.

(2*R*,3a*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-8-methyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, *syn*-250



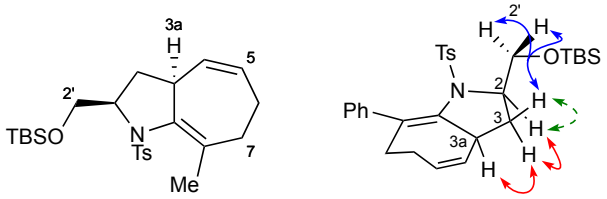


Method A: Prepared by General Procedure H using ynamide (+)-**247** (20 mg, 45 µmol, 1.0 equiv.), with the reaction mixture stirred for 1 h. The crude material was purified by column chromatography (petroleum ether/ethyl acetate (98:2)) to give *syn*-**250** and *anti*-**250** in a 1.9:1 ratio as a colourless oil (15 mg, 34 µmol, 76%).

Method B: Prepared by General Procedure I using ynamide (+)-**247** (15 mg, 34 µmol, 1.0 equiv.) and (*S*,*R*,*R*)-**L12**, with the reaction mixture stirred for 1 h. The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give (–)-*syn*-**250** as a colourless oil (14 mg, 32 µmol, 93%).

$[\alpha]_D^{25}$ –78.8 (*c* = 1.0, $CHCl_3$); **R**$_f$ 0.37 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2929, 2903, 2856, 1354, 1166, 1116, 1093; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.76 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.31-5.27 (1H, m, H5), 4.79 (1H, d, *J* = 11.0 Hz, H4), 4.24 (1H, td, *J* = 7.5 and 5.0 Hz, H2), 3.69-3.63 (2H, m, H2′ and H3a), 3.44 (1H, dd, *J* = 10.0 and 7.5 Hz, H2′), 2.62 (1H, td, *J* = 14.0 and 3.0 Hz, H7), 2.31 (3H, d, *J* = 1.5 Hz, H9), 2.13-2.05 (1H, m, H6), 2.00-1.93 (1H, m, H6), 1.90 (3H, s, TsCH_3), 1.87-1.83 (1H, m, H7), 1.79-1.74 (1H, m, H3), 0.91 (9H, s, SiC(CH_3)$_3$), 0.69-0.63 (1H, m, H3), 0.01 (3H, s, SiCH_3), –0.02 (3H, s, SiCH_3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 141.8, 137.3, 136.0, 130.0, 128.2, 128.1, 127.9, 127.6, 64.2, 61.7, 38.0, 31.6, 31.6, 25.3, 24.8, 22.1, 20.0, 17.2, –6.6, –6.6; **HRMS** (ESI+) calc. for $C_{24}H_{37}O_3NNaSSi$ $[M+Na]^+$ 470.2156, found 470.2153.

(2*R*,3a*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-8-methyl-1-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*b*]pyrrole, ***anti*-250**

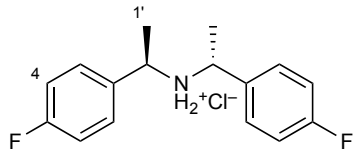


Prepared by General Procedure I using ynamide (+)-**247** (15 mg, 34 μmol, 1.0 equiv.) and (*R*,*S*,*S*)-**L12** with the reaction mixture stirred for 7 h. The crude material was purified by column chromatography (petroleum ether/diethyl ether (98:2)) to give (–)-*anti*-**250** as a colourless oil (11 mg, 25 μmol, 76%); $[\alpha]_D^{25}$ –64.9 (*c* = 1.0, $CHCl_3$); **R**$_f$ 0.37 (petroleum ether/diethyl ether (9:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2953, 2930, 2856, 1598, 1471, 1355, 1255, 1167, 1119, 1092; **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.75 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.71 (2H, d, *J* = 8.0 Hz, Ts*H*), 5.56-5.51 (1H, m, H5), 5.22 (1H, d, *J* = 11.0 Hz, H4), 4.12-4.07 (1H, m, H2), 4.04 (1H, dd, *J* = 10.0 and 5.0 Hz, H2′), 3.55 (1H, dd, *J* = 10.0 and 8.0 Hz,

H2′), 2.83-2.77 (1H, m, H3a), 2.33-2.27 (1H, m, H7), 2.24 (3H, d, J = 2.0 Hz, H9), 2.16-2.08 (1H, m, H6), 1.94-1.87 (2H, m, H6 and H7), 1.85 (3H, s, TsCH_3), 1.60 (1H, ddd, J = 12.5, 10.0 and 8.0, H3), 1.41 (1H, ddd, J = 12.5, 8.0 and 5.0, H3), 0.94 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 142.1, 135.5, 134.4, 131.0, 130.9, 129.6, 128.3, 127.1, 65.2, 60.1, 38.9, 33.2, 32.3, 24.9, 24.7, 22.7, 20.0, 17.3, –6.4, –6.5; **HRMS** (ESI+) calc. for $C_{24}H_{37}O_3NNaSSi$ $[M+Na]^+$ 470.2156, found 470.2154.

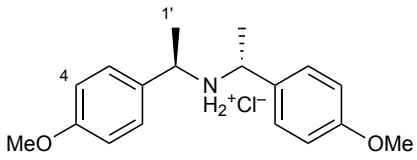
7.3.3 Synthesis of ligands

(*R*)-bis((*R*)-1-(4-Fluorophenyl)ethyl)ammonium chloride, (*R*,*R*)-**215**



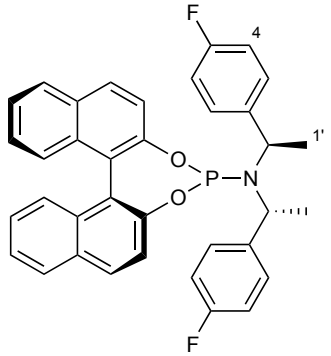
Prepared by General Procedure J using (*R*)-1-(4-fluorophenyl)ethan-1-amine (*R*)-**217** (0.97 mL, 7.19 mmol, 1.0 equiv.) and 1-(4-fluorophenyl)ethan-1-one (0.87 mL, 7.19 mmol, 1.0 equiv.). The crude material was recrystallised from hot ethyl acetate and methanol to give (*R*,*R*)-**215** as colourless crystals (604 mg, 2.29 mmol, 32%); **m.p.** 185–187 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –16.70 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.31 (petroleum ether/ethyl acetate (8:2)); **IR** (thin film, ν_{max}/cm^{-1}) 3044, 2755, 2494, 1584, 1514, 1229, 1165; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.51 (2H, s, NH_2), 7.53 (4H, dd, J_{HH} = 8.5 Hz and J_{HF} = 5.0 Hz, H3), 7.13 (4H, app. t, J = 8.5 Hz, H4), 3.88-3.80 (2H, m, H1), 1.89 (6H, s, H1'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 163.2 (d, J_{CF} = 250.5 Hz), 132.1 (d, J_{CF} = 3.5 Hz), 130.2 (d, J_{CF} = 8.5 Hz), 116.5 (d, J_{CF} = 22.0 Hz), 56.5, 21.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F –111.7; **HRMS** (ESI+) calc. for $C_{16}H_{18}NF_2$ $[M+H]^+$ 262.1402, found 262.1401.

(*R*)-bis((*R*)-1-(4-Methoxyphenyl)ethyl)ammonium chloride, (*R*,*R*)-**216**



Prepared by General Procedure J using (*R*)-1-(4-methoxyphenyl)ethan-1-amine (*R*)-**218** (0.98 mL, 6.61 mmol, 1.0 equiv.) and 1-(4-methoxyphenyl)ethan-1-one (0.99 g, 6.61 mmol, 1.0 equiv.). The crude material was recrystallised from hot ethyl acetate and methanol to give (*R*,*R*)-**216** as colourless crystals (395 mg, 1.38 mmol, 21%); **m.p.** 209–211 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –119.50 (c = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.22 (petroleum ether/ethyl acetate (2:1)); **IR** (thin film, ν_{max}/cm^{-1}) 2954, 2704, 2493, 1612, 1581, 1516, 1250, 1182; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.28 (2H, s, NH_2), 7.48 (4H, d, *J* = 8.5 Hz, H3), 6.94 (4H, d, *J* = 8.5 Hz, H4), 3.85-378 (2H, m, H1), 3.83 (6H, s, OCH_3), 1.87 (6H, d, *J* = 7.0 Hz, H1'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 160.1, 129.8, 128.5, 114.6, 56.6, 55.5, 21.7; **HRMS** (ESI+) calc. for $C_{18}H_{24}O_2N$ $[M+H]^+$ 286.1802, found 286.1802.

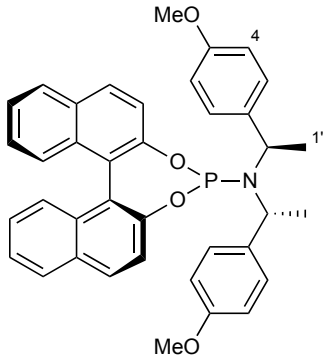
(11b*S*)-*N*,*N*-bis((*R*)-1-(4-Fluorophenyl)ethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine, (*S*,*R*,*R*)-**L12**



Prepared by General Procedure K using amine (*R*,*R*)-**215** (243 mg, 0.87 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/dichloromethane (8:2)) to give (*S*,*R*,*R*)-**L12** as a colourless crystalline solid (380 mg,

0.66 mmol, 76%); $[\alpha]_D^{25}$ –468.00 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.19 (petroleum ether/dichloromethane (8:2)); **IR** (thin film, ν_{max}/cm^{-1}) 3060, 2973, 1603, 1509, 1230; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.99-7.90 (4H, m, BINOL*H*), 7.58 (1H, d, *J* = 9.0 Hz, BINOL*H*), 7.45 (1H, d, *J* = 9.0 Hz, BINOL*H*), 7.42-7.39 (3H, m, BINOL*H*), 7.30-7.22 (3H, m, BINOL*H*), 7.06-7.03 (4H, m, H3), 6.83 (4H, dd, J_{HH} = 8.5 Hz and J_{HF} = 8.5 Hz, H4), 4.48-4.42 (2H, m, H1), 1.71 (6H, d, *J* = 7.0 Hz, H1'); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 161.6 (2C, d, J_{CF} = 245.5 Hz), 149.9 (d, J_{CP} = 7.5 Hz), 149.4, 138.7 (2C), 132.8 (2C), 131.5, 130.5, 130.5, 129.6, 129.5 (4C, d, J_{CF} = 8.0 Hz), 128.4, 128.2, 127.2, 127.1, 126.1, 126.1, 124.9, 124.6, 124.1 (d, J_{CP} = 5.5 Hz), 122.3, 122.2, 121.8 (d, J_{CP} = 2.5 Hz), 114.5 (4C, d, J_{CF} = 21.0 Hz), 51.7 (2C, d, J_{CP} = 12.0 Hz), 22.2 (2C); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F –116.1; **^{31}P NMR** (202 MHz, $CDCl_3$) δ_P 145.5; **HRMS** (ESI+) calc. for $C_{36}H_{29}O_2NF_2P$ $[M+H]^+$ 576.1899, found 576.1897.

11b*S*)-*N*,*N*-bis((*R*)-1-(4-Methoxyphenyl)ethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine, (*S*,*R*,*R*)-**L13**



Prepared by General Procedure K using amine (*R*,*R*)-**216** (268 mg, 0.83 mmol, 1.0 equiv.). The crude material was purified by column chromatography (petroleum ether/dichloromethane (3:1)) to give (*S*,*R*,*R*)-**L13** as a colourless crystalline solid (316 mg, 0.53 mmol, 63%); $[\alpha]_D^{25}$ –492.40 (*c* = 1.0, $CHCl_3$); $\mathbf{R}_f$ 0.36 (petroleum ether/dichloromethane (1:1)); **IR** (thin film, ν_{max}/cm^{-1}) 3060, 2969, 2835, 1611, 1590, 1511,

1249, 1232; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.94 (2H, d, *J* = 9.0 Hz, BINOL*H*), 7.91-7.88 (2H, m, BINOL*H*), 7.58 (1H, d, *J* = 9.0 Hz, BINOL*H*), 7.42 (1H, d, *J* = 8.5 Hz, BINOL*H*), 7.40-7.37 (3H, m, BINOL*H*), 7.28 (1H, d, *J* = 8.5 Hz, BINOL*H*), 7.26-7.21 (2H, m, BINOL*H*), 7.04-7.02 (4H, m, H3), 6.70 (4H, d, *J* = 9.0 Hz, H4), 4.48-4.41 (2H, m, H1), 3.76 (6H, s, OCH_3), 1.70 (6H, d, *J* = 6.5 Hz, H1'); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 158.3 (2C), 150.2 (d, J_{CP} = 7.0 Hz), 149.6, 135.2 (2C), 132.8 (2C), 131.4, 130.5, 130.2, 129.4, 129.1 (4C), 128.3, 128.2, 127.2, 127.1, 126.0, 125.9, 124.7, 124.4, 124.0 (d, J_{CP} = 5.5 Hz), 122.5, 122.5, 121.8 (d, J_{CP} = 2.5 Hz), 113.1 (4C), 55.3 (2C), 51.5 (2C, d, J_{CP} = 12.5 Hz), 22.3 (2C); **^{31}P NMR** (202 MHz, $CDCl_3$) δ_P 147.4; **HRMS** (ESI+) calc. for $C_{38}H_{35}O_4NP$ $[M+H]^+$ 600.2298, found 600.2298.

7.4 X-Ray crystallographic information

Single crystal X-ray diffraction data was obtained for compound *syn*-**181a**. In this case, a typical crystal was mounted using the oil drop technique, in perfluoropolyether oil at 150(2) K using a Cryostream N open-flow cooling device.[119] Diffraction data was collected using graphite monochromatic Mo-K_α radiation (λ = 0.71073 Å) on a Nonius Kappa CCD diffractometer. For data collection, a series of ω-scans was performed in such a way as to collect a complete data set to a maximum resolution of 0.77 Å. Data reduction including unit cell refinement and inter-frame scaling was carried out using DENZO-SMN/SCALEPACK.[120] Intensity data was processed and corrected for absorption effects by the multi-scan method, based on repeat measurements of identical and Laue equivalent reflections. Structure solution was carried out with direct methods using the program SIR92[121] within the CRYSTALS software suite.[122] Coordinates and anisotropic displacement parameters of all non-hydrogen atoms were refined freely. Hydrogen atoms were generally visible in the difference map and refined with soft restraints prior to inclusion in the final refinement using a riding model.[123] X-ray crystallographic data is provided below (Tables 7.1-7.2), and an ORTEP depiction of the single crystal X-ray structure follows (Fig. 7.1).

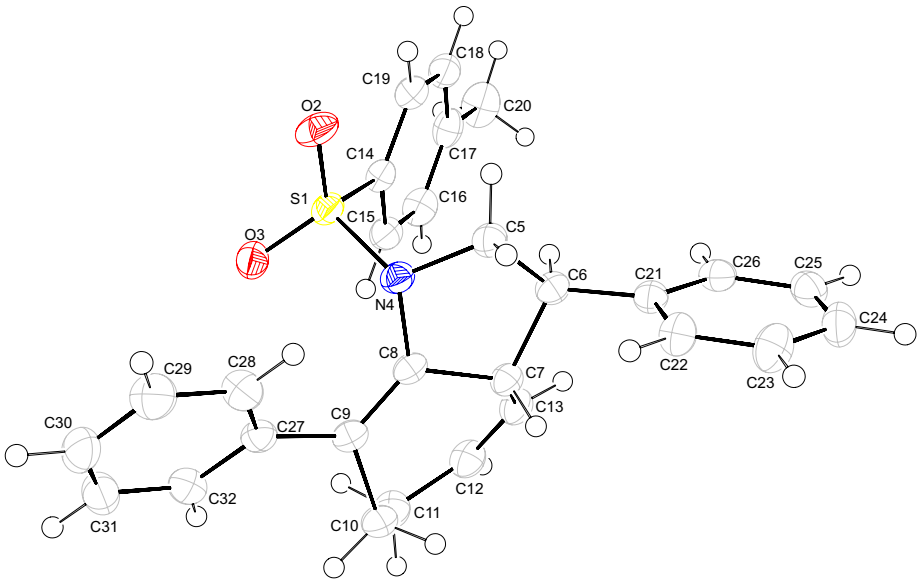
Table 7.1. Crystal data and structure refinement for **181a**.

Empirical formula	C28 H27 N1 O2 S1	
Formula weight	441.59	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 7.90860(10) Å	α = 90°.
	b = 15.9469(2) Å	β = 100.5837(7)°.
	c = 18.2748(3) Å	γ = 90°.
Volume	2265.57(5) $Å^3$	
Z	4	
Density (calculated)	1.295 Mg/m^3	
Absorption coefficient	0.169 mm^{-1}	
F(000)	936	
Crystal size	0.52 x 0.44 x 0.25 mm^3	
Theta range for data collection	5.114 to 27.509°.	
Index ranges	-10 < = h < = 10, -20 < = k < = 20, -23 < = l < = 23	
Reflections collected	9949	
Independent reflections	5170 [R(int) = 0.024]	
Completeness to theta = 26.959°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.96 and 0.96	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5167 / 0 / 289	
Goodness-of-fit on F^2	0.9997	
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.0993	
R indices (all data)	R1 = 0.0513, wR2 = 0.1058	
Largest diff. peak and hole	0.32 and -0.39 e.$Å^{-3}$	

Table 7.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **181a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-1087(1)	5719(1)	1471(1)	26
O(2)	-2468(1)	5348(1)	955(1)	34
O(3)	-1129(1)	6587(1)	1654(1)	33
N(4)	664(2)	5566(1)	1111(1)	26
C(5)	1087(2)	4683(1)	962(1)	28
C(6)	2677(2)	4471(1)	1552(1)	26
C(7)	3610(2)	5328(1)	1712(1)	25
C(8)	2253(2)	5983(1)	1413(1)	24
C(9)	2584(2)	6801(1)	1364(1)	26
C(10)	4350(2)	7091(1)	1758(1)	32
C(11)	4648(2)	7008(1)	2604(1)	37
C(12)	4853(2)	6127(1)	2896(1)	34
C(13)	4445(2)	5423(1)	2520(1)	31
C(14)	-858(2)	5141(1)	2306(1)	26
C(15)	244(2)	5446(1)	2932(1)	30
C(16)	359(2)	5017(1)	3600(1)	35
C(17)	-606(2)	4300(1)	3658(1)	33
C(18)	-1683(2)	4004(1)	3019(1)	32
C(19)	-1807(2)	4415(1)	2341(1)	29
C(20)	-473(3)	3853(1)	4389(1)	46
C(21)	3829(2)	3797(1)	1328(1)	26
C(22)	4395(2)	3841(1)	651(1)	32
C(23)	5520(2)	3250(1)	462(1)	39
C(24)	6123(2)	2607(1)	949(1)	38
C(25)	5591(2)	2557(1)	1624(1)	34
C(26)	4442(2)	3144(1)	1812(1)	29
C(27)	1444(2)	7436(1)	926(1)	27
C(28)	424(2)	7234(1)	241(1)	34
C(29)	-525(2)	7839(1)	-198(1)	42
C(30)	-481(2)	8664(1)	39(1)	42
C(31)	502(2)	8876(1)	719(1)	38
C(32)	1463(2)	8270(1)	1157(1)	32

Fig 7.1. ORTEP representation of the X-Ray crystal structure of **181a** with thermal elipsoids at 50% probability.



8 Appendix

8.1 Publication arising from DPhil research

nature COMMUNICATIONS

ARTICLE

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Computational ligand design in enantio- and diastereoselective ynamide [5 + 2] cycloisomerization

R.N. Straker[1], Q. Peng[1], A. Mekareeya[1], R.S. Paton[1] & E.A. Anderson[1]

Transition metals can catalyse the stereoselective synthesis of cyclic organic molecules in a highly atom-efficient process called cycloisomerization. Many diastereoselective (substrate stereocontrol), and enantioselective (catalyst stereocontrol) cycloisomerizations have been developed. However, asymmetric cycloisomerizations where a chiral catalyst specifies the stereochemical outcome of the cyclization of a single enantiomer substrate—regardless of its inherent preference—are unknown. Here we show how a combined theoretical and experimental approach enables the design of a highly reactive rhodium catalyst for the stereoselective cycloisomerization of ynamide-vinylcyclopropanes to [5.3.0]-azabicycles. We first establish highly diastereoselective cycloisomerizations using an achiral catalyst, and then explore phosphoramidite-complexed rhodium catalysts in the enantioselective variant, where theoretical investigations uncover an unexpected reaction pathway in which the electronic structure of the phosphoramidite dramatically influences reaction rate and enantioselectivity. A marked enhancement of both is observed using the optimal theory-designed ligand, which enables double stereodifferentiating cycloisomerizations in both matched and mismatched catalyst–substrate settings.

[1] Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK. Correspondence and requests for materials should be addressed to E.A.A. (email: edward.anderson@chem.ox.ac.uk) or to R.S.P. (email: robert.paton@chem.ox.ac.uk) or to Q.P. (email: qian.peng@chem.ox.ac.uk).

Demand for higher efficiency, economy and selectivity in the synthesis of novel molecular scaffolds drives organic chemistry[1,2]. In this context, cycloisomerizations represent ideal methods for the formation of cyclic organic molecules, as they can fulfil all of these criteria. Despite much research into transition metal-catalysed cycloisomerization[3,4], and reports where high enantioselectivity is achieved for the cyclization of prochiral substrates to enantioenriched products[5,6], this important field of synthetic methodology has neglected the development of enantiospecific diastereoselective transformations, where single enantiomer starting materials are subjected to asymmetric cycloisomerization to give specific diastereomer products (that is, double stereodifferentiation, where catalyst and substrate stereocontrol compete)[7–10]. In an age where absolute control of molecular substitution and stereochemistry is paramount for applications, the realization of such processes would represent a major advance in the sustainable synthesis of precision-manufactured target molecules.

Here we describe rationally designed cycloisomerization catalysts that address these challenges. The reaction selected for this study was the [5+2] cycloisomerization of ynamide-vinylcyclopropanes to [5.3.0] azabicycles (**1**→**2**, **3**, Fig. 1). Although [5+2] processes have a rich history in the field of alkyne-vinylcyclopropanes[11–22], the development of this process using ynamides—or indeed any asymmetric cycloisomerization of ynamide-tethered enynes—has not been explored either experimentally or theoretically[23–27]. More generally, we question whether a catalyst system optimized to achieve an enantioselective cyclization (**1**→**2**, Fig. 1b) can translate to a double stereodifferentiating setting (**1**→**3** or ***epi*-3**, Fig. 1c), particularly should the catalyst be required to overcome powerful substrate stereocontrol. Intrinsic to these studies is a combined theoretical and experimental approach to optimize catalyst design[28–30], which in the event reveals an unexpected mechanistic pathway for rhodium-catalysed [5+2] carbocyclizations (Fig. 1a). This work demonstrates the powerful role of density functional level of theory (DFT) computations in understanding asymmetric catalysis, leading to quantitative computational-led design of new, highly selective ligands.

Results

Substrate synthesis and reaction optimization. A selection of ynamide cycloisomerization substrates **1** were readily accessed from allylic esters **4** (Fig. 2) by an Ireland-Claisen/Curtius rearrangement/ynamide formation sequence. Substituents could be introduced at one or both of the carbon atoms on the ene-ynamide backbone, and by incorporating an enzymatic resolution into this synthesis, enantioenriched ynamides could be prepared. Ynamide formation (**6**→**1**) was achieved using copper-catalysed coupling of the sulfonamide with a bromoalkyne[32], or via formation of an intermediate dichloroenamide[33]. Initial screening of ruthenium[14] and rhodium[20,34] catalyst systems (Table 1) revealed that only the latter afforded high yields of azabicycle **7a** from ynamide **1a**; using [Rh(cod)naphthalene]SbF_6 (5 mol%) as the catalyst[35,36], the cycloisomerization could be effected within 3 h at room temperature, giving **7a** in 91% yield (Entry 6).

Substrate scope. A variety of ynamides **1a–s** were now examined in the cycloisomerization using these optimized conditions (Fig. 3). Aryl-substituted ynamides **1b–d** reacted with high efficiency, and revealed a clear electronic effect on the reaction rate, with electron-deficient ynamides **1b** and **1c** showing reduced reaction times. Alkyl-substituted ynamides **1e–g** also displayed enhanced reactivity compared with phenyl ynamide **1a**, affording the corresponding [5.3.0]-azabicycles **7e–g** in excellent yields within 15 min at ambient temperature. Similar efficient reactivity was observed for the cyclization of the heteroaryl-substituted ynamides **1h** and **1i** to the indolyl- and pyrrolyl-substituted products **7h** and **7i**. The mild conditions of the reaction are emphasized by the cyclization of the aniline-derived ynamide **1j**, which led to tricycle **7j** in 74% yield—notably, this 1,4-diene did not undergo *in situ* isomerization to the indole.

Of clear interest was the level of substrate stereocontrol that might be achieved using ynamides **1l–s**. Excellent levels of substrate stereoinduction were observed, with products **7l–s** afforded in high yield and as single diastereomers for substrates featuring an allylic stereocenter; and, for **7s**, as a single regioisomer as well as diastereoisomer[14]. Cyclization of substrates containing homoallylic stereocenters proved less selective; however, good stereoselectivity ($dr = 12{:}1$) could be achieved using $[Rh(cod)Cl]_2$. These collected results are significant in the wider context of [5+2] cycloisomerization, where high levels of substrate stereocontrol have previously been generally interpreted to arise from an 'inside alkoxy effect' from oxygen-bearing stereocenters allylic to the vinylcyclopropane[37,38]. In this work, it is apparent that such stereoelectronic effects are not a prerequisite for high stereoselectivity.

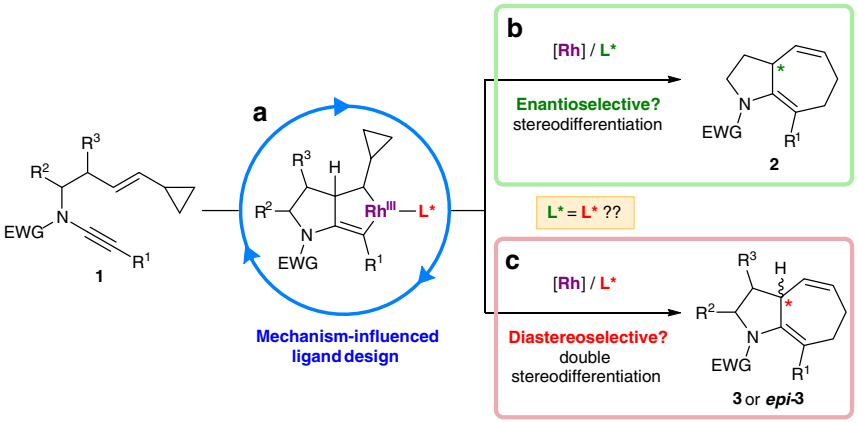


Figure 1 | A reaction blueprint for enantioselective and/or double stereodifferentiating diastereoselective ynamide-vinylcyclopropane cycloisomerization. (**a**) We show that mechanistic calculations are crucial in the design of an enantioselective cycloisomerization catalyst. (**b**) Enantioselective higher order ynamide cycloisomerization is realized. (**c**) Despite high levels of substrate stereocontrol, the computationally designed catalyst is able to define product stereochemistry.

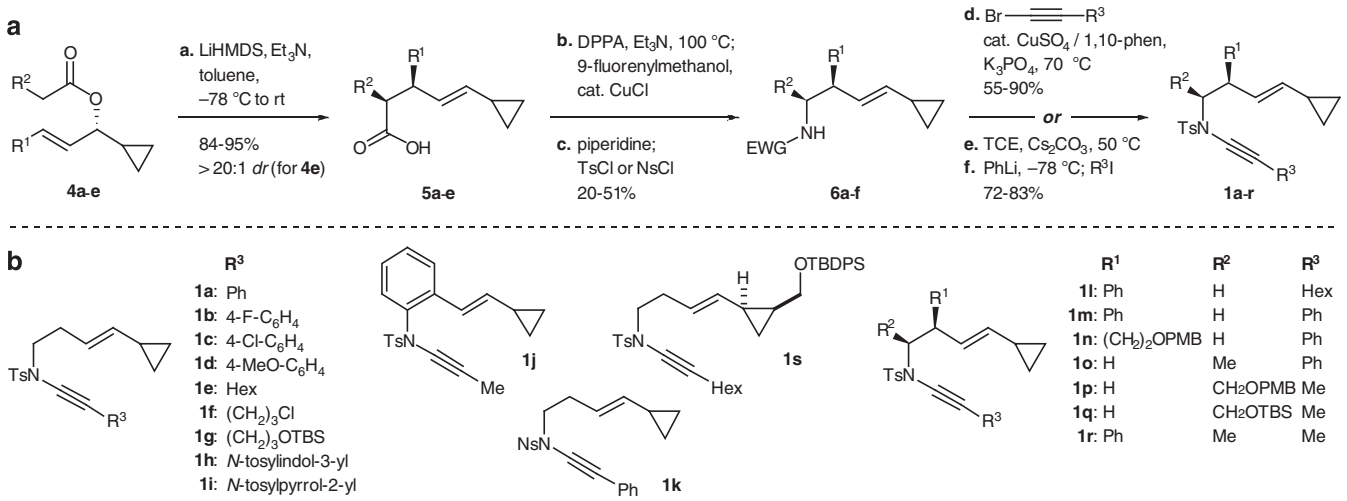
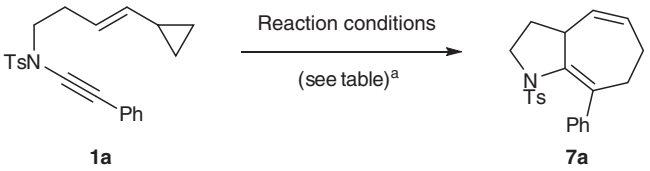


Figure 2 | Synthesis of ynamide-vinylcyclopropanes 1. (**a**) The synthetic route employed uses an Ireland-Claisen rearrangement of esters **4a–e** to construct the vinylcyclopropane and install up to two backbone substituents; subsequent Curtius rearrangement / sulfonylation converts the carboxylic acids **5** to sulfonamides **6**; ynamide formation is then achieved using copper-catalysed coupling with a bromoalkyne or, for hindered or aniline-derived ynamides, a two step route via a dichloroenamide. For the preparation of enantioenriched esters **4b**, **4d** and **4e**, and ynamides **1q** and **1s**, see Supplementary Fig. 4. (**b**) Ynamide-vinylcyclopropanes prepared using this strategy.

Table 1 | Optimization of the [5 + 2] cycloisomerization reaction.



Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	$[CpRu(MeCN)_3]PF_6$ (10)	acetone	50	20	– [b]
2	$[RhCl(cod)]_2$ (10)	toluene	110	20	– [b]
3	$RhCl(PPh_3)_3$ (10)	toluene	110	1	72
4	$[(C_{10}H_8)Rh(cod)]SbF_6$ (10)	1,2-dichloroethane	rt	1.5	92
5	$[(C_{10}H_8)Rh(cod)]SbF_6$ (10)	CH_2Cl_2	rt	1.5	94
6	$[(C_{10}H_8)Rh(cod)]SbF_6$ (5)	CH_2Cl_2	rt	3	91

[a]Reactions performed at 0.1 M substrate in the solvent stated. [b]Reaction gave a complex mixture of products.

Enantioselective cycloisomerization. In targeting an asymmetric version of the cyclization, we were mindful of the excellent asymmetric [5 + 2] Rh-catalysed cycloisomerization of alkyne-vinylcyclopropanes described by Shintani *et al.*[39,40], which employed the versatile phosphoramidite ligand **L1** (Fig. 4a)[41]. A preliminary screen of a range of phosphoramidite ligands **L1**–**L4** revealed that **L1** indeed seemed optimal for the enantioselective cycloisomerization of ynamide-vinylcyclopropane **1a**, delivering product (–)-**7a** in excellent yield and enantioselectivity (96%, 98% *ee*) after just 15 min at room temperature (see Supplementary Information for assignment of absolute stereochemistry). However, forays with other substrates suggested that this ligand might not meet our expectations in more challenging settings, and we realized that any further advance would require a combined theoretical and experimental design approach.

To this end, we conducted a computational exploration of the reaction pathway, which began with investigation of the empirical model adopted by Shintani *et al.* to explain the enantioselectivity of vinylcyclopropane-alkyne cycloisomerization. This model (Fig. 4b) is based on an X-ray crystal structure of [Rh(**L1**) norbornadiene]BF_4 reported by Mezetti (**8**) (ref. 42), which reveals an η^2-complexation of one of the α-methylbenzylamine arenes to the rhodium cation—the phosphoramidite thus acting as a bidentate ligand. The Shintani–Hayashi model docks the vinylcyclopropane-alkyne onto this ligated rhodium framework as in structure **9**, such that the alkyne coordinates *trans* to the phosphorous atom of the phosphoramidite ligand, and the vinylcyclopropane coordinates *trans* to the η^2-complexed arene, with an orientation that minimizes steric interactions between the cyclopropane ring and naphthyl group.

Computational study and ligand optimization. Computation, particularly at the DFT level, has emerged as a powerful tool for assessing the feasibility of mechanistic steps involved in catalysis[43]. Our theoretical work first explored eight possibilities for the binding of ynamide-vinylcyclopropane **1a** to the [Rh(**L1**)]

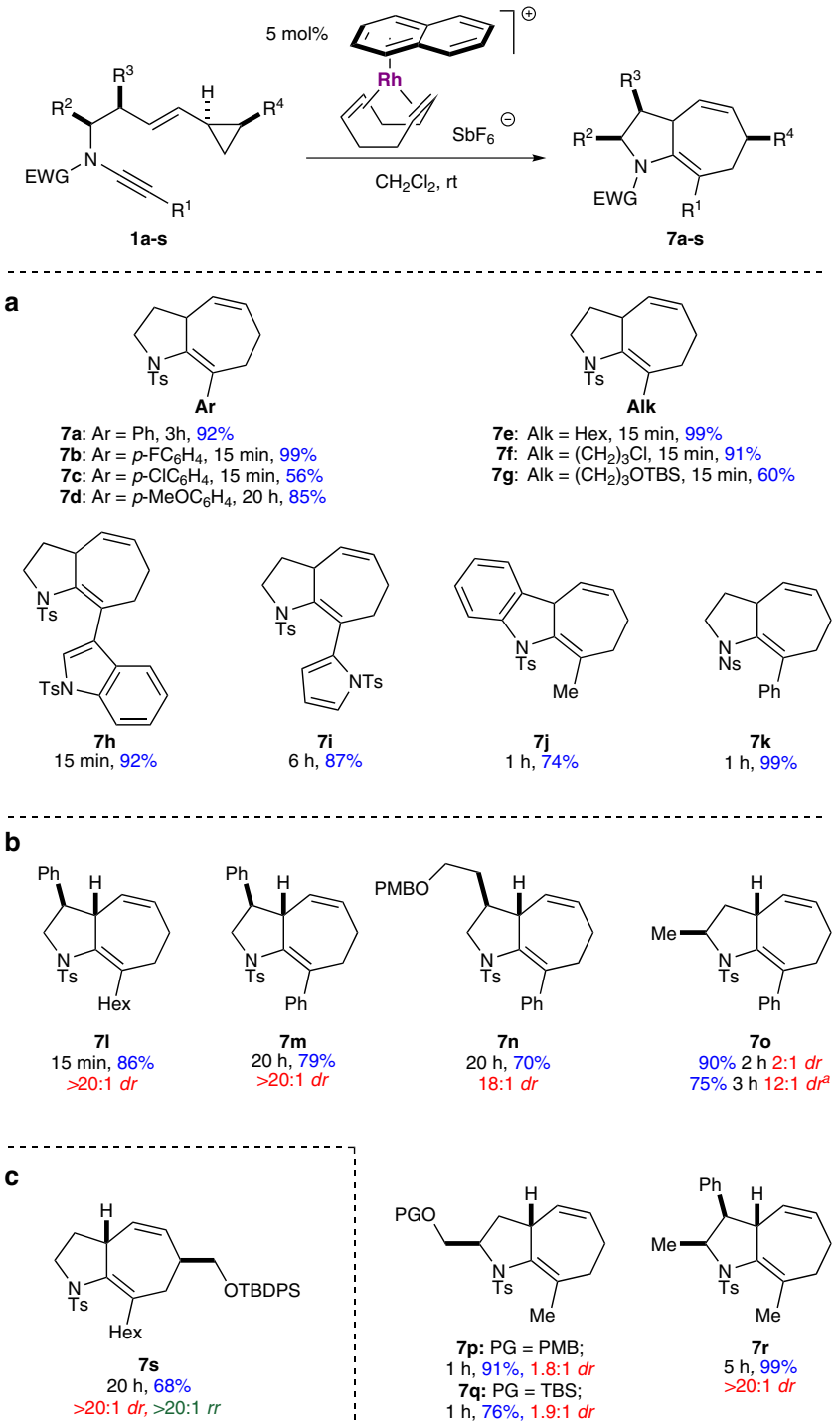


Figure 3 | Rhodium-catalysed ynamide [5 + 2] cycloisomerization. (**a**) Ynamide substituent scope. (**b**) Diastereoselective cycloisomerization proceeds with high levels of substrate stereoinduction. (**c**) High regioselectivity and diastereoselectivity is observed with a substituted cyclopropane. [a]Reaction performed using $[Rh(cod)Cl]_2$ (10 mol%), toluene, 110 °C.

cation (Table 2). In contrast to the Shintani–Hayashi model, this suggested that the lowest energy complex of [Rh(**L1**)**1a**] positions the ynamide proximal to the naphthyl ring and *trans*- to the arene ligand, and the vinylcyclopropane *trans*- to the phosphorous atom (**10**, Fig. 5, P-*trans*-ene/Up). The next lowest energy structure maintains this positional selectivity of substrate binding, but inverts its orientation (that is, P-*trans*-ene/Down). Next, calculations were carried out to explore the two widely accepted mechanisms for [5 + 2] cycloisomerization, which initiate either with an oxidative addition into the vinylcyclopropane, followed by alkyne insertion into the resultant σ/π-allyl rhodium(III) complex **11** to give eight-membered rhodacycle **12** (vinylcyclopropane pathway), or via oxidative cycloaddition of Rh(I) with the alkyne and alkene to give rhodacyclopentene **13**, followed by ring expansion into the cyclopropane to give the same intermediate **12** (metallacyclopentene pathway). Where investigations by Yu, Houk and Wender on Rh-catalysed [5 + 2] cycloisomerizations suggest that oxidative addition into the vinylcyclopropane is the first step on the catalytic pathway[17,21], our DFT calculations

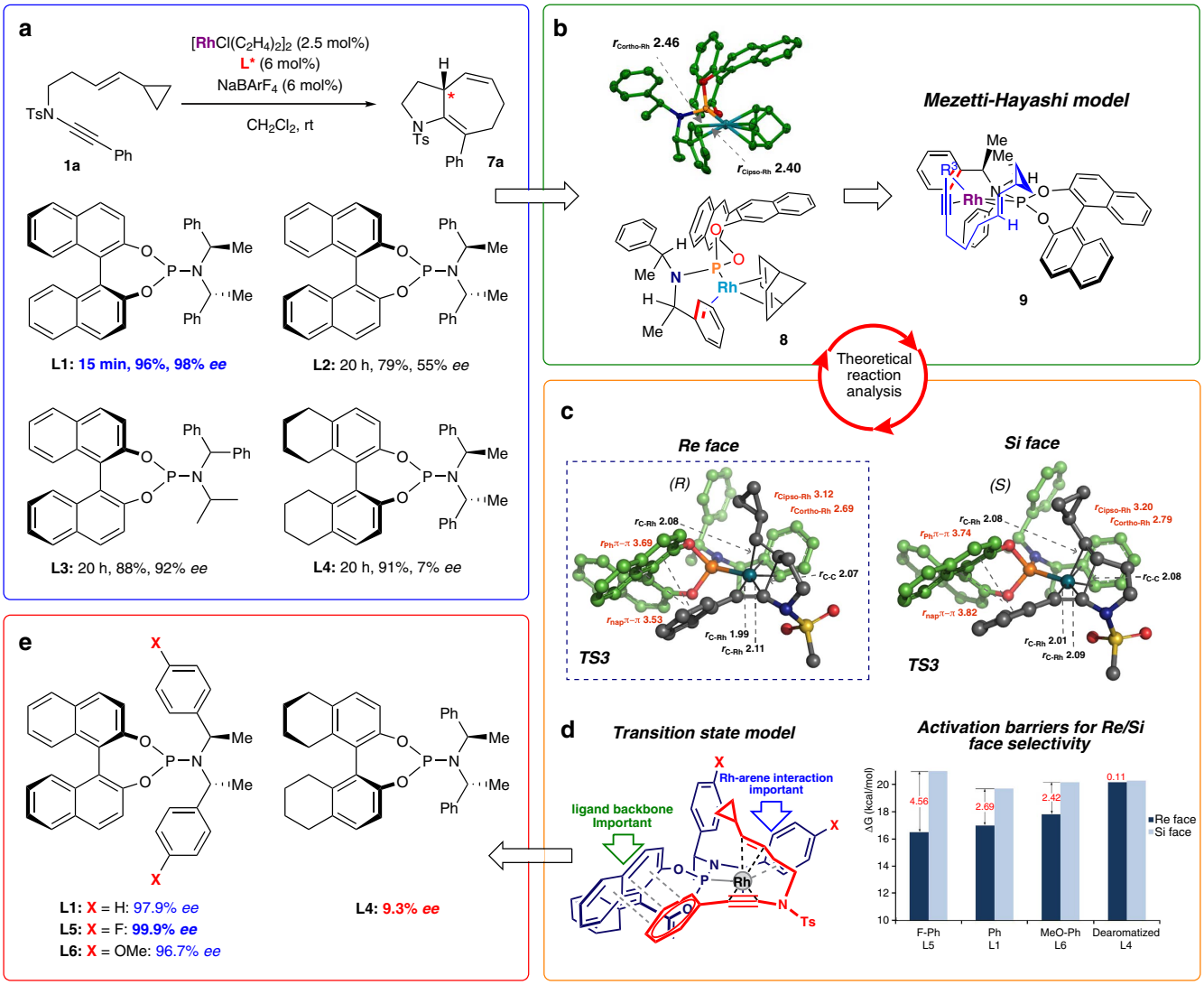
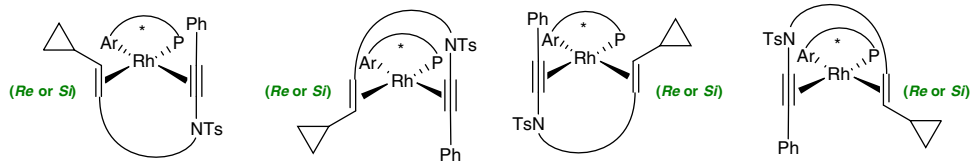


Figure 4 | Exploration of asymmetric ynamide [5 + 2] cycloisomerization inspires a computation-guided ligand design. (**a**) A selection of phosphoramidite ligands screened reveals a strong dependence of enantioselectivity and reaction rate on amine and BINOL components' structure and chirality, with **L1** giving superior results. (**b**) The Shintani–Hayashi model for enantioselectivity is based on a crystal structure of [**L1** Rh(norbornadiene)]$^+$. (**c**) Our calculations (Fig. 5) support an alternative mode of binding of the ynamide, and an alternative reaction pathway that initiates with rhodacyclopentene formation. *Re* face binding of the vinylcyclopropane is favoured, with calculated structures, and activation barriers (kcal mol^{-1})/selectivities depicted (distances in Å). (**d**) A transition state model is shown that identifies key ligand design parameters. (**e**) Variation of the electronic character of the η^2-bound arene of the phosphoramidite leads to predicted enantioselectivies for **L5** (*p*-F) and **L6** (*p*-OMe), and an excellent correlation of experiment and theory for **L1** and **L4**.

(Fig. 5) suggest that oxidative coupling of the alkene-ynamide to form metallacyclopentene **13** appears to be the preferred reaction pathway for an ynamide-vinylcyclopropane to give **12**, followed by ring expansion of the cyclopropane. Notably, this mechanism has also been calculated to be the preferred pathway in ruthenium-catalysed [5 + 2] cycloisomerization[17]. The preference for this pathway over vinylcyclopropane oxidative addition is in the range of 4–12 kcal mol^{-1}, depending on the orientation with which **1a** binds to the [Rh(**L1**)] cation; notably, the transition states for both pathways favour *Re*-face binding of the alkene in a P-*trans*-ene/Down orientation. This sequence of steps is favoured in this intramolecular reaction due to additional stabilization of the forming Rh(III) intermediate in the oxidative coupling step by the electron-rich ynamide. The free energy profile for the catalytic cycle is exergonic by more than 40 kcal mol^{-1}, and product inhibition is predicted to be minimal, since the reactant preferentially binds to the catalyst by 6.2 kcal mol^{-1}; taken together with a turnover and selectivity determining barrier of 17.0 kcal mol^{-1} for the metallacyclopentene pathway, our computations are consistent with the short reaction times observed at room temperature for the conversion of **1a**–**7a** using **L1**.

The lowest energy transition state for the oxidative coupling of this metallacyclopentene pathway (TS3) is illustrated in Fig. 4c. This transition state leads to a calculated enantioselectivity for cyclization with ligand **L1** of 97.9% *ee* ($\Delta\Delta G^{\ddagger}_{Re/Si} = -2.69$ kcal mol^{-1}), which is in excellent agreement with the experimental value (*R*, 98% *ee*). The calculated enantioselectivity for phosphoramidite **L4** (9.3% *ee*, $\Delta\Delta G^{\ddagger}_{Re/Si} = -0.11$ kcal mol^{-1}) also correlates well with the poor selectivity we had already observed experimentally with this ligand (7% *ee*), supporting the mechanistic model, and implying that the naphthyl ring plays a crucial role—likely related (for aryl ynamides) to a stabilizing dispersive ($\pi - \pi$) interaction between

Table 2 | Eight possible orientations of enynamide docking onto the L1-Rh cation are explored.



Orientation 1: P *trans* to **ene** Backbone of substrate **Down** to Ar-Rh-P

Orientation 2: P *trans* to **ene** Backbone of substrate **Up** to Ar-Rh-P

Orientation 3: P *trans* to **yne** Backbone of substrate **Down** to Ar-Rh-P

Orientation 4: P *trans* to **yne** Backbone of substrate **Up** to Ar-Rh-P

Orientation	Metallacyclopentene Pathway		Vinylcyclopropane pathway	
	***Re*-selectivity (*R*)**	***Si*-selectivity (*S*)**	***Re*-selectivity (*R*)**	***Si*-selectivity (*S*)**
1	18.7	31.3	23.0	22.0
2	**17.0**	19.7	21.9	24.8
3	23.6	23.9	29.3	24.5
4	23.2	30.7	35.3	41.7

Transition state energies (SMD-ωB97XD/6-311+G(d,p)/Lanl2TZ//ωB97XD/6-31G(d)/Lanl2DZ Gibbs free energies, shown in kcal mol^{-1}) associated with each mode of binding are tabulated.

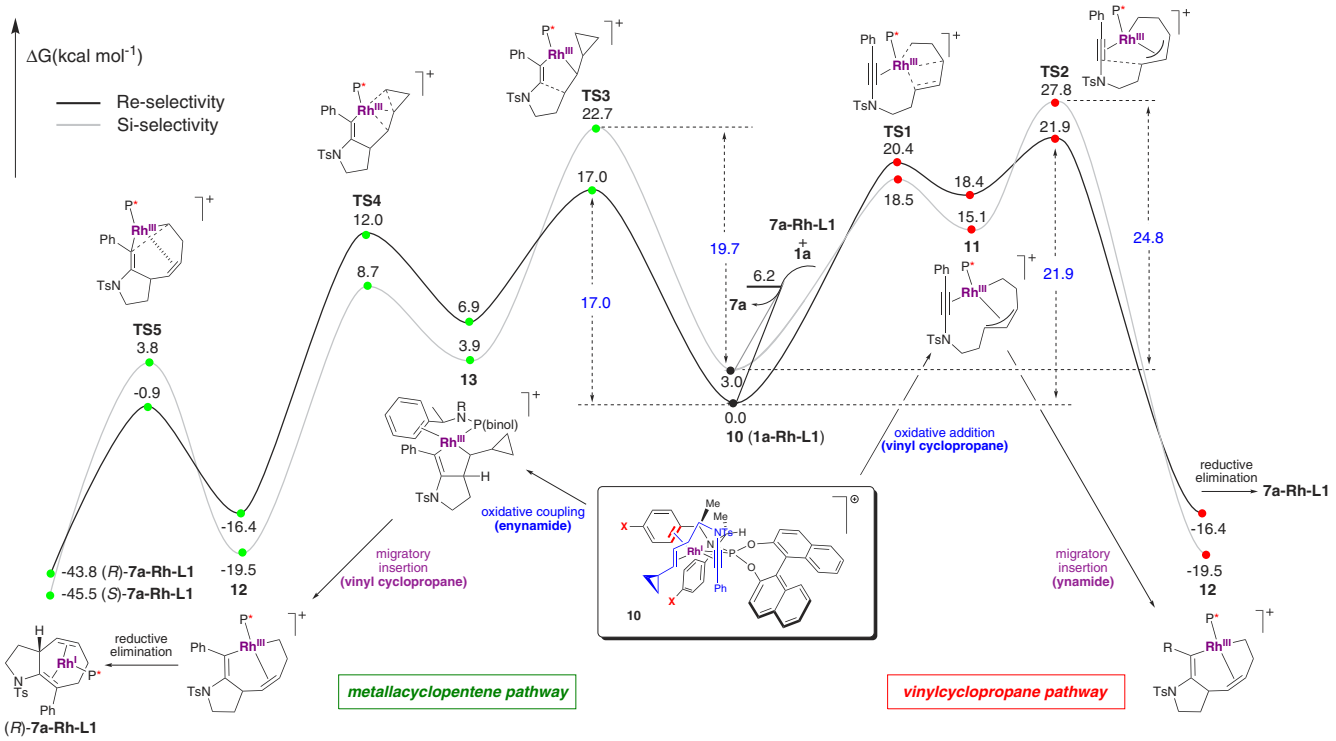


Figure 5 | Theoretical reaction analysis. Complex **10** (*Re* face binding) is found to be the lowest energy ground state for ynamide complexation, and transition state for oxidative coupling (metallacyclopentene pathway, see Table 2). The calculated energy profiles of the cycloisomerization for Re-face (black, bold) and Si-face (grey) substrate association via pathways initiating with metallacyclopentene formation (left), or vinylcyclopropane insertion (right) are illustrated; the former is favoured. SMD-ωB97XD/6-311+G(d,p)/Lanl2TZ//ωB97XD/6-31G(d)/Lanl2DZ Gibbs free energies are shown in kcal mol^{-1}.

the ynamide substituent and the naphthyl group in TS3. Although partial saturation of the naphthyl backbone (that is, in **L4**) leads to higher activation barriers, it is notable that the erosion of enantioselectivity for this ligand results from a greater increase (by 2.58 kcal mol^{-1}) to the activation barrier for *Re*-face addition compared with *Si*-face addition; this supports the existence, and importance, of stabilizing non-bonding (dispersion) interactions because of the aromatic backbone of **L1** in favouring the major enantiomer. Alkyl substituents are expected to experience similar attractive non-bonding interactions (CH–π); these interactions are further evident from an analysis of the computed non-covalent interaction index (Supplementary Fig. 68).

The oxidative coupling (TS3) is the rate-limiting and enantioselectivity determining step in this rhodacyclopentene mechanism. As observed in the Mezetti norbornene crystal structure (Fig. 4b)[42], one of the ligand benzylamine groups acts as 2π-electron donor (2.6–2.7 Å) in these transition states.

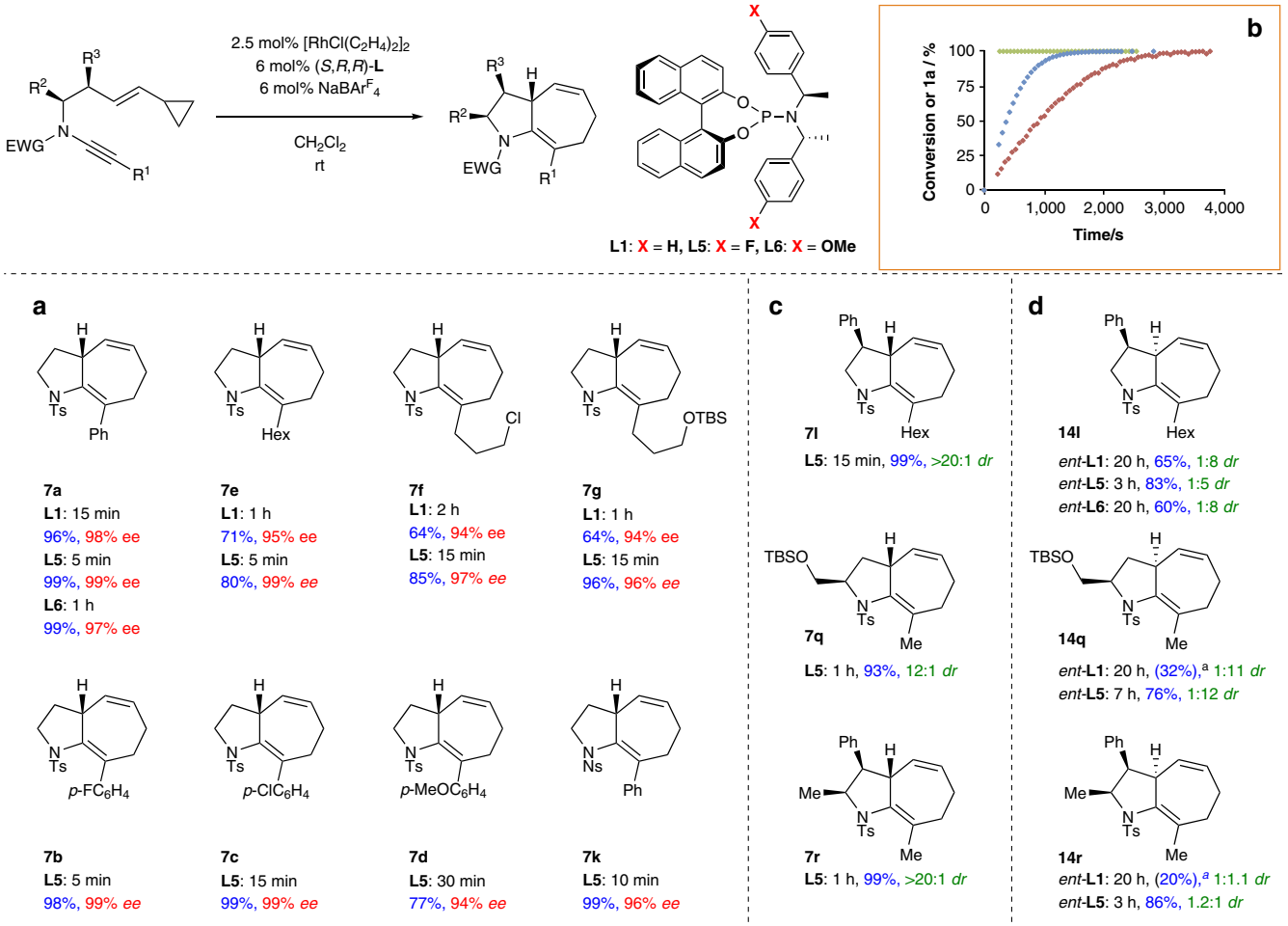


Figure 6 | Enantioselective and double stereodifferentiating, ynamide [5 + 2] cycloisomerizations. (**a**) Enantioselective cyclization is tested against a range of ynamide-vinylcyclopropanes, showing an excellent correlation of computation and experiment for the theory-designed ligands **L5** and **L6**. The synthesis of **7e** was performed on 1 mmol scale (1.25 mol% catalyst). (**b**) ^{1}H NMR spectroscopic monitoring of reaction progress emphasizes the rate enhancement between ligands **L6**, **L1** and **L5**, also predicted theoretically. (**c**) Matched double stereodifferentiating cycloisomerizations proceed with high selectivity and rate. (**d**) Mismatched double stereodifferentiating cycloisomerizations proceed successfully under catalyst stereocontrol using the enantiomers of ligands **L1**, **L5** and **L6** (that is, (*R,S,S*)-**L** stereochemistry); the major diastereomer is shown. The [a] signifies reaction conversion, as judged by ^{1}H NMR spectroscopic analysis.

We hypothesized that variation of the electronic character of this η^2-complexed arene could dramatically influence both the rate, and selectivity, of the reaction. Calculations on the effect of electronically-biasing methoxy and fluoro groups at the *para* position of these arenes suggested that decreasing the electron density on the arene (*p*-F, **L5**, Fig. 4d,e) would lead to an increase in reaction rate ($\Delta\Delta G^{\ddagger}_{\mathbf{L5/L1}} = -0.47$ kcal mol^{-1}) and enantioselectivity ($\Delta\Delta G^{\ddagger}_{\mathrm{Re/Si}} = -4.56$ kcal mol^{-1}, 99.9% *ee*), while an electron-donating substituent (*p*-MeO, **L6**) would have the opposite effect ($\Delta\Delta G^{\ddagger}_{\mathbf{L6/L1}} = +0.76$ kcal mol^{-1}, $\Delta\Delta G^{\ddagger}_{\mathrm{Re/Si}} = -2.42$ kcal mol^{-1}, 96.7% *ee*). This computed trend in reactivity and enantioselectivity, namely **L5** > **L1** > **L6**, results from a weakened metal-arene interaction in the TS leading to the major enantiomer, which is compensated for through stronger coordination of the alkynyl and alkenyl groups (see Supplementary Information for further details and discussion). These ligand structural modifications also modulate the Lewis basicity at phosphorus, however preferential stabilization of the major enantiomeric pathway confirms that the predominant effect is not inductive in nature, but rather depends on through-space interactions involving the Rh-coordinating aryl group.

Substrate scope in the asymmetric cycloisomerization. While phosphoramidite **L6** is known, (ref. 44) **L5** is not, but could be readily synthesized using standard methods[45]. Both were evaluated in the enantioselective cyclization alongside **L1** (Fig. 6a). To our delight, experiment correlated well with the predicted outcomes of these cyclizations; the *p*-fluorobenzyl ligand **L5** indeed showed a dramatic enhancement of rate and selectivity in the cyclization of **1a** compared with the parent ligand **L1**, affording **7a** in under 5 min with 99% *ee* (calc. 99.9% *ee*), while the *p*-methoxybenzyl ligand **L6** exhibited a much reduced rate of reaction, and also lower enantioselectivity (1 h, 97% *ee*, calc. 96.7% *ee*). The cyclization of alkyl-substituted ynamides **1e–g** to give enantioenriched azabicycles **7e–g** also showed a rate and selectivity enhancement between **L1** and **L5**. The potent reactivity of the latter ligand was extended to a variety of aryl-substituted ynamides, where the marked rate difference between electron-poor (**1b**) and electron-rich (**1d**) ynamides supports the hypothesis that the ynamide is intimately involved in the rate-determining step (that is, a metallacyclopentene pathway). In all cases using ligand **L5**, these reactions proceeded in under 30 min with excellent levels of enantioselectivity (94–99% *ee*); furthermore, the synthesis of **7e**

could be achieved on a 1 mmol scale in less than 5 min with 1.25 mol% catalyst loading. Monitoring of reaction conversion by ^{1}H NMR spectroscopy (in $CDCl_3$, Fig. 6b) emphasizes the dramatic rate difference between these three ligands, with the reaction using **L5** complete in under 4 min, compared with the slower cyclizations with **L1** and **L6** (addition of the catalyst solution to the substrate followed by NMR spectroscopic analysis necessitated a four minute delay between reaction initiation and acquisition of the first NMR spectrum. The reaction catalysed by [L5Rh] was complete by this time).

Finally, the performance of these ligands was tested against the challenge of cyclizations that proceed with high levels of substrate stereocontrol, to address the question of how a high enantioselectivity-inducing catalyst would cope with mismatched substrate-catalyst diastereoselective cycloisomerization scenarios. Three substrates were chosen for this challenge: ynamides **1l**, **1q** and **1r**, which gave >20:1, 1.8:1 and >20:1 *dr*, respectively when cyclized using [Rh(cod)naphthalene]SbF_6 (Fig. 3). As expected, these single enantiomer substrates cyclized rapidly, and with high efficiency and selectivity, with the matched substrate-catalyst combination (that is, (*S,R,R*)-**L5**, Fig. 6c). To our delight, we found that cycloisomerization of substrate **1l** using the enantiomeric catalyst system ((*R,S,S*)-**L1**) successfully overturned this powerful substrate stereoselectivity, giving **14l** in up to 1:8 *dr*. Interestingly, it was ligand **L1**—and not **L5**—which performed optimally in this challenging situation, albeit requiring an extended reaction time. In the case of **1q**, the catalyst (with either **L1** or **L5**) was able to achieve an equivalent (reversed) level of selectivity to that achieved in the matched sense—in this instance, a modest level of inherent substrate stereocontrol being completely overturned. Finally, the most challenging setting of the reinforcing substituents in **1r** proved a hurdle that could also be partly overcome, again demonstrating significant catalyst influence.

These observations may suggest that tighter substrate-Rh complexation in the case of **L5** (a consequence of a slightly weaker ligand-metal interaction observed in our calculations (see Supplementary Information for details), which improves rate and enantioselectivity), enhances unfavourable (that is, mismatched) steric effects in a double stereodifferentiating setting such that it effectively increases the stereocontrolling influence of the substrate relative to that of the ligand. The most reactive/selective catalysts for enantioselective cyclizations could thus suffer from higher than expected transition state energies in diastereoselective cyclizations, where such steric effects are enhanced compared with 'less enantioselective' catalysts (looser substrate binding); and that different considerations are therefore needed in the development of double stereodifferentiating reactions, with more 'promiscuous' catalysts potentially giving superior selectivity.

Discussion

In summary, the first example of an enantioselective ynamide-tethered cycloisomerization has been achieved, with a series of highly enantio- and diastereoselective cyclizations giving a range of substituted/enantioenriched [5.3.0] azabicycles. Theoretical reaction analysis crucially influenced ligand design, leading to a catalyst system that displayed enhanced rate and enantioselectivity in the cycloisomerization. The demonstration of the first successful examples of enantiospecific diastereoselective transition metal-catalysed cycloisomerizations in a significantly mismatched substrate-catalyst environment illustrates that cycloisomerization can assemble functionalized ring systems with tuneable selectivity. These studies set the stage for the development of further computationally guided catalyst systems.

Methods

Racemic [5 + 2] cycloisomerization. To an oven-dried vial containing the ynamide vinylcyclopropane (1.0 equiv.) under Ar was added a solution of [($C_{10}H_8$)Rh(cod)]SbF_6 (5 mol%) in degassed CH_2Cl_2 (10 ml mmol^{-1} of ynamide). The reaction mixture was stirred at room temperature under Ar until consumption of the ynamide was observed by thin layer chromatography (see Fig. 3 for reaction times). The reaction mixture was then concentrated, and the resulting material was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate eluent) (Fig. 3).

Asymmetric [5 + 2] cycloisomerization. A solution of [RhCl(C_2H_4)$_2$]$_2$ (2.5 mol%), $NaBAr^F_4$ (6 mol%) and phosphoramidite ligand (6 mol%) in degassed CH_2Cl_2 (10 ml mmol^{-1} of ynamide) was stirred for 20 min under Ar. The solution was filtered (through a PTFE filter-tipped syringe) into an oven-dried vial containing ynamide vinylcyclopropane (1.0 equiv.) under Ar. The reaction mixture was stirred at room temperature under Ar until consumption of the ynamide was observed by thin layer chromatography (see Fig. 6 for reaction times). The reaction mixture was then concentrated, and the resulting material was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate eluent) (Fig. 6).

Computational methods. Molecular geometries were fully optimized at the DFT theory level in Gaussian 09 (rev. D.01), using the dispersion-corrected ω-B97XD functional[46] without symmetry constraints. The effective core potentials (ECPs) of Hay and Wadt[47] with a double-ζ basis set (LanL2DZ) were used for Rh, S and P, and the 6-31G(d) basis set was used for H, C, N and O(BS1). The energies were further estimated using a larger basis set (6-311 + G (d, p) basis set for H, C, N, O, S and P) and triple-ζ basis set (LanL2TZ)[48] for Rh (BS2) by single-point calculations, in implicit solvent CH_2Cl_2 treated with the SMD universal solvation models[49]. The structures of the ynamide substrate and a series of phosphoramidite ligands were computed in full, while the toluenesulfonamide *p*-tolyl group was modelled as a methyl group in the interests of computational tractability. See Supplementary Methods for further details.

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Author contributions

E.A.A. and R.N.S. conceived of the synthetic methodology. R.N.S. carried out the experimental work, with the aid of A.M. Q.P. and R.S.P. carried out the theoretical calculations. R.N.S., E.A.A., Q.P. and R.S.P. analysed the collected results. E.A.A., R.N.S., Q.P. and R.S.P. wrote the manuscript.

Additional information

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