Development and Mechanistic Investigations into Metal-Catalysed Cycloisomerisation of Enynamides

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Under the supervision of
Prof Edward Anderson
Development and Mechanistic Investigations into Metal-Catalysed Cycloisomerisation of Enynamides

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Doctor of Philosophy

Michaelmas Term 2017

This thesis reports the work on investigations into the mechanism of palladium-catalysed enynamide cycloisomerisations (with Pd(OAc)$_2$ / bis(benzylidene)ethylenediamine (bbeda) catalyst system in particular). Herein, it has been shown that the mechanism of this catalyst system is likely to proceed via a hydropalladation mechanism. In the course of study, we have uncovered the crucial influences of water, the pre-catalyst, and the ligand (bbeda) in this reaction. One of the key highlights is bbeda itself serves as a source of palladium(II) hydride during the reaction. In addition, kinetic isotope effects obtained from theoretical analysis are consistent with the experimental data. The computational studies also offer enhanced understanding in the stereoselectivity of the reaction.

Apart from the mechanistic study work, we have developed a new bench stable rhodium pre-catalyst from commercially available sources, which is much easier to handle compared to typical catalyst systems. Using this new rhodium complex, various array of alkene substituents has been surveyed, and observed that enynamides with (Z)-alkene geometry give excellent yields and enantioselectivities.
Acknowledgments

There have been several people throughout my DPhil journey whom I would very much like to express my deep gratitude and appreciation to:

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To my mum, dad, and my beloved brother for always being supportive and always to understand. I would not be able to come this far without your support and love.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>APC</td>
<td>allyl palladium chloride dimer</td>
</tr>
<tr>
<td>Ar</td>
<td>generic aryl group</td>
</tr>
<tr>
<td>ArF</td>
<td>3,5-bis(trifluoromethyl)benzene</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>bbeda</td>
<td>N,N'-dibenzylideneethane-1,2-diamine</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>cod</td>
<td>cyclooctadiene</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
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<td>correlation spectroscopy</td>
</tr>
<tr>
<td>Cp*</td>
<td>pentamethycyclopentadiene</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>1,2-DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBALH</td>
<td>diisobutyaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DPPA</td>
<td>diphenylphosphoryl azide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent(s)</td>
</tr>
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<td>Abbreviation</td>
<td>Description</td>
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<td>-------------</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>Fc</td>
<td>ferrocenyl</td>
</tr>
<tr>
<td>Fmoc</td>
<td>fluorenlymethyloxycarbonyl</td>
</tr>
<tr>
<td>H</td>
<td>hour(s)</td>
</tr>
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<td>HMBC</td>
<td>heteronuclear multiple-bond correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple-quantum correlation</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
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<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single-quantum correlation</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IPA</td>
<td>propan-2-ol</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m-</td>
<td>meta</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl, methanesulfonyl</td>
</tr>
<tr>
<td>n.a.</td>
<td>not applicable</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ns</td>
<td>( p )-nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>( o^- )</td>
<td>ortho</td>
</tr>
<tr>
<td>( p^- )</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>R</td>
<td>generic organic group</td>
</tr>
<tr>
<td>( R_f )</td>
<td>retention factor</td>
</tr>
<tr>
<td>RDS</td>
<td>rate determining step</td>
</tr>
<tr>
<td>Red-Al(^\circledast)</td>
<td>sodium bis(2-methoxyethoxy)aluminiumhydride</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>( t_R )</td>
<td>retention time</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>( tert )-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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<tr>
<td>Tol</td>
<td>toluyl</td>
</tr>
<tr>
<td>Ts</td>
<td>( p )-toluenesulfonyl</td>
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<tr>
<td>Wilkinson’s catalyst</td>
<td>( \text{RhCl}(\text{PPh}_3)_3 )</td>
</tr>
<tr>
<td>wt%</td>
<td>weight percent</td>
</tr>
</tbody>
</table>
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Chapter 1: Introduction: Mechanistic Studies on Enyne Cycloisomerisation

Enyne cycloisomerisation – a process whereby 1,\(n\)-enynes undergo an intramolecular Alder-ene reaction to give carbocyclic compounds – is a valuable and fully atom-economic method for ring construction.\(^1\) Since cyclic organic frameworks are common in natural products and biologically active compounds, this method of skeletal reorganisation is a powerful tool for chemists to synthesise such complex molecules.

1.1 History of Enyne Cycloisomerisation

Although the uncatalysed thermal pericyclic cycloisomerisation of enynes has been known for over a century,\(^2\)\(^-\)\(^4\) the high temperatures required (often over 300 °C) severely limited its scope. As a result, it was used relatively little in organic synthesis.\(^5\)

In 1985, Trost and co-workers reported the first metal-catalysed cycloisomerisation of 1,6-enynes through palladium catalysis (Scheme 1.1).\(^6\)

![Scheme 1.1](image)

Since then many other transition metals (\(e.g.\) Rh, Ru, Pt, Au) have been shown to facilitate the cycloisomerisation of 1,\(n\)-enynes (\(n = 4, 5, 6, 7, \text{ etc.}\)). In comparison to the thermal cycloisomerisation, the metal-catalysed transformation can provide 1,3- and/or 1,4-dienes as the products with decent selectivity, while only 1,4-dienes can be obtained from the thermal uncatalysed reactions (Scheme 1.2).\(^7\)
In addition, the metal-catalysed cycloisomerisation usually offers better regiochemical and stereochemical controls compared to the thermal process. As a consequence, cycloisomerisation has become one of the most effective approaches for rapid construction of complex organic cyclic molecules.

The mechanism of a transition metal-catalysed cycloisomerisation depends on the catalyst system and reaction conditions. The following represents some of the possible routes for the cyclisation process to proceed:

*Metal hydride species mediated pathway*

The alkyne undergoes hydrometallation to give a vinyl metal complex 4 (Scheme 1.3). This vinyl species subsequently undergoes carbometallation, and eliminates the β-hydrogen to yield the cyclic dienes.

*Activated η²-metal species mediated pathway*

The metal can complex the alkyne unit to give an electrophilic η²-metal-alkyne intermediate 5, which is prone to nucleophilic cyclisation via either 5-exo-dig or 6-endo-dig pathways with the alkene to form the corresponding cyclopropyl metal carbenes 6, which can participate in further reactions (e.g. skeletal reorganisation) to give the products (Scheme 1.4).
Chapter 1: Introduction: Mechanistic Studies on Enyne Cycloisomerisation

Scheme 1.4

Metallacyclopentene mediated pathway

In this mechanism, the metal simultaneously complexes to both alkene and alkyne units, forming a metallacycle intermediate 7 via an oxidative coupling process (Scheme 1.5). This cyclic metal complex can undergo β-hydride elimination to relieve the ring strain. The cyclic olefin product is obtained by the reductive elimination of metal hydride complex 8.

Scheme 1.5

1.2 Mechanistic Investigations on Enyne Cycloisomerisation

Despite its versatility in organic synthesis, this methodology can still be improved in many aspects, for example, efficiency and robustness of catalysts, scope and selectivity of the reaction, etc. It is challenging to address such issues as the transition metal complex used in most metal-catalysed cycloisomerisation processes is usually in the form of a pre-catalyst, which will subsequently generate the active species.8 This active catalyst can facilitate undesired pathways, leading to the formation of many unwanted products. Indeed, gaining more mechanistic understanding on the metal-catalysed cycloisomerisation will allow chemists not only to suppress side reactions, but also to enhance the catalyst efficiency, and improve selectivity of the reaction.

Herein we focus on the mechanistic studies on the metal-catalysed (mainly palladium and ruthenium) cycloisomerisation of 1,n-enynes that only involves migrations of hydrogen and associated bond
reorganisation with no carbon–carbon bond cleavage. That is, the processes where no carbon skeletal rearrangement takes place (Scheme 1.6).

Season 1.6

1.2.1 Palladium

As noted above, the exploration in palladium-catalysed cycloisomerisation of 1,6-enynes was initiated by Trost and Lautens, who performed carbocyclisation of 1,6-enynes 1 using Pd(OAc)$_2$(PPh$_3$)$_2$ as catalyst; 1,3-dienes 3 were exclusively obtained when the allylic carbon was disubstituted (R$^1$ and R$^2$ ≠ H, Scheme 1.7, left), while (E)-1,4-dienes (E)-2a were formed with high selectivity when the allylic carbon was monosubstituted (R$^1$ = H, Scheme 1.7, right).

Season 1.7

In this early work, Trost et al. considered two mechanisms for this palladium-catalysed cyclisation: 1) allylic C–H insertion, and 2) oxidative cyclopalladation (Scheme 1.8). Since the cycloisomerisation of enyne 1 with a disubstituted allylic group provided 1,3-dienes 3 as sole product, the mechanism for this process cannot proceed via the allylic C–H insertion route. In addition, this mechanism cannot explain some cases where both 1,3- and 1,4 dienes were observed in the reaction, because such a mechanism can only account for the formation of 1,4-dienes.
Interestingly, Trost et al. discovered that when a Pd(0) species such as Pd(PPh₃)₄ was used as catalyst, no reaction was observed after 12 h at reflux in THF (Table 1.1, Entry 1). This suggested that the active species of palladium complex ought to be in the Pd(II) oxidation state. They also found that the effectiveness of the Pd(II) species was connected to the Lewis acidity of the metal centre. For instance, the cyclisation of enyne 9 to give diene 10 in the presence of Pd(CH₃CN)₂Cl₂ was sluggish (16% conversion after 6.5 h at reflux in THF, Entry 2); while Pd(OAc)₂L₂ (L = PPh₃ or P(o-MePh)₃) could effect complete conversion at room temperature or reflux depending on the ligand (Entries 4 and 5).

Table 1.1 Cycloisomerisation of enyne 9 with various palladium sources.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>Temperature (time)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>reflux (12 h)</td>
<td>no conversion</td>
</tr>
<tr>
<td>2</td>
<td>Pd(MeCN)₂Cl₂</td>
<td>reflux (6.5 h)</td>
<td>16%</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>r.t. (n/a)</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂(PPh₃)₂</td>
<td>r.t. (12 h)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂(P(o-MePh)₃)₂</td>
<td>60 °C (1.5 h)</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

This suggested that the mechanistic pathway for 1,ₙ-enzyme cycloisomerisation with the Pd(II) catalysts could be the palladacycle pathway (Scheme 1.8, bottom).
In 1991, Trost and co-workers revised their earlier conclusion on the mechanism of palladium-catalysed enyne cycloisomerisation after more detailed investigations. It was discovered that during the process of preparing enyne 9 using Pd(0)-catalysed alkylation of cyclohexene 11 with alkyne 12, a small amount of 1,4-diene 10 (about 35%) was observed (Scheme 1.9). This unexpected product could have been obtained from a palladium-catalysed cycloisomerisation of enyne 9.

![Scheme 1.9](image)

It was proposed that the Pd(0) catalyst from the coupling reaction could be oxidised by oxygen present in air to give some Pd(II) species, which catalysed the cyclisation of the enyne. The hypothesis was tested by performing the cycloisomerisation of enyne 9 with 5 mol% of Pd(OAc)₂, which indeed gave product 10 with moderate yield at room temperature (Table 1.1, Entry 3). Furthermore, an isotopic labelling study with by cyclohexenyl malonate d₁-9 (>95% D) was conducted (Scheme 1.10); this experiment showed that 1,4 diene (E)-d₁-10 was formed as the major kinetic product at the early stages of the reaction (after 30 min). Later, this product (E)-d₁-10 slowly converted to thermodynamic product (Z)-d₁-10 until an equilibrium was reached. Neither deuterium loss in the substrate and products, nor double bond migration was observed.

![Scheme 1.10](image)

Although H/D exchange of the acetylenic proton is possible, the corresponding protiated substrate 9 was not observed over time. Moreover, NMR spectroscopy showed no signs of products d₂-10 and 10. Hence, the presence of (Z)-d₁-10 in the product mixture was proposed to arise from a side reaction that
was unrelated to the cycloisomerisation. This result is consistent with both the syn-hydropalladation of alkyne pathway (Scheme 1.11), which was at first overlooked, and the oxidative cyclopalladation mechanism.

Scheme 1.11

The Lewis acidity of the Pd(II) source was found to affect the yields, rate of the reaction, and product purity; addition of a Lewis basic nitrogen ligand, for example, \(N,N\)-bis(benzylidene)ethylenediamine (bbeda), together with Pd(OAc)_2 to the reaction substantially improved the yields. Trost proposed that bbeda could not only lead to suitable \(\pi\)-acidity of the Pd(II) complex, but the ligand could also stabilise the putative Pd(IV) palladacyclopentene intermediate (Scheme 1.12).^10

Scheme 1.12

Therefore, it was suggested that the Pd(OAc)_2 / bbeda catalyst system could promote the Pd(II) / Pd(IV) cycle. However, this alone did not rule out the hydropalladation mechanism; to strengthen the feasibility of the oxidative metallacycle mechanism, Trost and Tanoury employed a palladacyclopentene 13 / tri-
o-tolyl phosphine catalyst system to cycloisomerise enyne 14. Pleasingly, this reaction indeed proceeded to give dienes 15 and 16 (Scheme 1.13). This reaction was the first example for the 1,6-enyne cycloisomerisation with a skeletal rearrangement.

![Scheme 1.13](image)

Not long after the first introduction of this palladacycle pre-catalyst, the Trost group reported a new catalyst system: Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH. Trost proposed that this system could generate a Pd(II)–H species \textit{in situ} from oxidative addition, \textit{i.e.} insertion of Pd(0) into the H–O bond of the acid (Scheme 1.14), although, this species was not observed by $^1$H NMR spectroscopy when mixing AcOH and Pd$_2$(dba)$_3$ in CDCl$_3$.

![Scheme 1.14](image)

Intriguingly, the cycloisomerisation of electron deficient enyne 17 with Pd(OAc)$_2$ proceeded smoothly, whereas under Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH conditions, the substrate failed to cyclise to give 18 (Scheme 1.15). This seemed to imply that the two catalyst systems operate \textit{via} different mechanisms: Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH system \textit{via} a Pd(II)–H mediated mechanism, while Pd(OAc)$_2$ \textit{via} a palladacyclopentene mediated pathway.

![Scheme 1.15](image)

Trost \textit{et al.} revealed evidence that supported the hydropalladation mechanism for 1,6-enyne cycloisomerisation using Pd(0) / AcOH. When enyne 19 was cycloisomerised using Pd$_2$(dba)$_3$·CHCl$_3$
as Pd(0) source in the presence of 1 equiv. AcOD, 1,3-diene 20 was obtained with a high level of deuterium scrambling in the products: d$_0$-20 (54%), d$_1$-20 (39%), 1:5 E/Z ratio, and d$_2$-20 (7%) were all formed.$^{15}$ H/D exchange at the terminal alkyne hydrogen of 19, forming d$_1$-19, was also detected. The small amount of d$_2$-20 produced was proposed to arise from deuteriopalladation of the alkyne in starting material d$_1$-19 (Scheme 1.16). The 5:1 Z/E ratio of d$_1$-20 could be explained by the syn-addition of Pd(II)–D to alkyne 19, and the syn-addition of Pd(II)–H to alkyne d$_1$-19, respectively.

Scheme 1.16

While, the hydrometallation mechanism can provide a satisfactory rationale for deuterium scrambling in the products, the Pd(II) / Pd(IV) cycle pathway can also rationalise this. Vinylpalladium hydride species d$_0$-21, formed after β-H elimination, can undergo H/D exchange with AcOD to give corresponding deuteride intermediate d$_1$-21. Reductive elimination of such an intermediate leads to monodeuterated product (Z)-d$_1$-20 (Scheme 1.17). H/D exchange to deuterated substrate d$_1$-19, followed by the same reaction pathway, results in products d$_2$-20 and (E)-d$_1$-20.
A key indication that the hydropalladation mechanism is operative for the Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH was found through interception of the alkylpalladium intermediate. If β-hydride elimination cannot proceed due to no β-hydrogen atom, and the molecule contains another alkene unit, a further syn-carbopalladation can take place to generate additional ring frameworks. To illustrate, dienyne 22 can be cycloisomerised to generate [4.3.3] and [3.3.3] propellanes 24. Such tricyclic propellanes can be then converted into propellenones 25 (Scheme 1.18).\textsuperscript{16}

Mikami and co-workers investigated the mechanism of palladium-catalysed asymmetric cycloisomerisations, and have reported that deuterium incorporation in the product (74% D) was observed during the cycloisomerisation of enyne 26 using Pd(CF$_3$CO$_2$)$_2$ or Pd(MeCN)$_4$(BF$_4$)$_2$ and (R)-BINAP, in the presence of 6 equiv. D$_2$O (Scheme 1.19).\textsuperscript{17}
Chapter 1: Introduction: Mechanistic Studies on Enyne Cycloisomerisation

Scheme 1.19

Mikami proposed that Pd(II)–H species could undergo hydride exchange with D$_2$O to produce Pd(II)–D intermediates, which enter a deuterio-metallation cycle. However, a rationale for how Pd(II)–H species was generated in the first place was not given.

Mikami and Hotano later carried out a detailed mechanistic investigation on oxygen-tethered asymmetric 1,6-ynene cycloisomerisation with a Pd(II) metal precursor and chiral bisphosphine ligand. Mikami et al. first considered three possible pathways for this cyclisation to take place: the η$^2$-metal activated alkyne species mediated pathway, the oxidative enyne coupling via metallacycle intermediate mechanism, and the alkyne hydrometallation route. The study started with the Pd(II)-catalysed cycloisomerisation of enyne 28a to give 1,3-dienes 29a and 1,4-dienes 30a (Scheme 1.20). Since the formation of cyclic exo-diene 31a was not observed, which could have been generated if the π-acid activation mechanism was operating, this mechanism was proposed to be unlikely to be the case.

Scheme 1.20

Next, Mikami et al. aimed to isolate palladacyclopentene 32 from the cyclisation of β-phenyl enyne 28b, as this enyne substrate should lead to a palladacycle species that has no β-hydrogen atom. This was unsuccessful with the reaction instead giving a mixture of dienes 29b (26%) and 30b (55%) (Scheme 1.21). Thus, palladacycle pathway was rejected.
This led to an examination of a hydrometallation mechanism: once again, Pd(II)-catalysed cycloisomerisation of enyne $28a$ was performed, but this time in presence of 6 equiv. D$_2$O (Scheme 1.22). A high percentage of deuterium incorporation was observed in the products at the exocyclic olefin, $\alpha$-position to the ester unit.

Scheme 1.22

This suggested a $syn$-addition of Pd(II)–D across the alkyne, then $syn$-carbopalladation by the vinylpalladium complex with the alkene to give $d_1\cdot33a$. Since this species lacks $\beta$-hydrogens, it can then undergo $syn$-addition / elimination via the cyclopropane intermediate $d_1\cdot34a$ to give 6-membered cyclic $exo$-olefin $d_1\cdot35a$. Elimination of one of the $\beta$-hydrogens produces $d_1\cdot29a$ or $d_1\cdot30a$ as products (Scheme 1.23). Although hydropalladation could thus provide a highly satisfactory explanation for the product distribution and deuterium incorporation, the generation of the active Pd(II)–H species from the Pd(II) precursor was mysterious.
Trost and co-workers also used the Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH catalyst system to isomerise enyne 36 to yield bicyclic dienes 37. Trost discovered that in the absence of acetonitrile, diene isomers 38 and 39 were obtained together with the major product 37. However, in the presence of acetonitrile, the olefin isomerisation was completely suppressed (Scheme 1.24).

This may indicate that decomplexation of the product from the active Pd(II)–H species is promoted by the presence of acetonitrile via a ligand exchange process. On the other hand, without acetonitrile, the 1,4-diene product can still be bound to the Pd(II)–H species, allowing the hydride re-insertion / elimination to take place, resulting in double isomerisation to give products 38 and 39 (Scheme 1.25).
Our group recently reported the use of 1,6-enynamides to investigate the mechanism of cycloisomerisation when using Pd(OAc)$_2$ / bbeda catalyst system. We found that the reaction pathway is unlikely to proceed via the Pd(II) / Pd(IV) catalytic cycle. We reported that the mechanism by which this catalyst system operates is a Pd (II)–H mediated pathway with supporting evidence from $^1$H NMR spectroscopic kinetic profile studies, kinetic isotope effects, and computational analysis. Moreover, we discovered a ground-breaking role of bbeda, which was believed to only act as a ligand. Bbeda in fact is very crucial for the generation of Pd(II)–H species, as it serves as a hydride source for such a process. Equally importantly, we proved that this process also occurs in the enyne cycloisomerisation. The details of this work will be discussed in the later chapters of this thesis.

### 1.2.2 Ruthenium

The first ruthenium-catalysed 1,5- and 1,6- enyne cycloisomerisation (without carbon backbone rearrangement) was reported by Mori and co-workers, who used RuHCl(CO)(PPh$_3$)$_3$ as the ruthenium pre-catalyst for the cycloisomerisation of enyne 40 to give cyclic 1,3-dienes 41 and 42 respectively (Scheme 1.26).
Not long after this work, the Trost\textsuperscript{23-26} and Dixneuf\textsuperscript{27} groups reported another two catalyst systems for enyne cycloisomerisation: CpRu(MeCN)\textsubscript{3}PF\textsubscript{6} and Cp*Ru(cod)Cl / AcOH, respectively. Both Mori and Dixneuf suggested that this reaction proceeds \textit{via} a hydoruthenation mechanism (Dixneuf proposed that the required Ru–H intermediate could be generated from ruthenium insertion into the O–H bond of acetic acid). This was supported by complete stereospecific deuterium incorporation in product 44 when an excess of AcOD was used instead of AcOH (Scheme 1.27)\textsuperscript{27}.

\begin{equation}
\text{Scheme 1.27}
\end{equation}

In addition, the cycloisomerisation of 1,6-enzyme substrates with either the Mori or Dixneuf catalyst systems gives exocyclic 1,3-dienes 46, where R\textsubscript{1} and R\textsubscript{2} are in \textit{trans}-relationships to the new C–C bond (Scheme 1.28)\textsuperscript{21,27}. This again supports the proposed hydrometallation mechanism due to the stereoelectronic requirement for β-hydride elimination.

\begin{equation}
\text{Scheme 1.28}
\end{equation}

On the other hand, the Trost group proposed two different modes of operation for the catalyst system [CpRu(MeCN)\textsubscript{3}]PF\textsubscript{6}, depending on the substrate: 1) ruthenacycle and 2) allylic C–H insertion mechanisms (Scheme 1.29)\textsuperscript{24,25}. The first pathway leads to the formation of 5-membered cyclic 1,4-dienes, while the latter results in 7-membered cyclic 1,4-dienes as the products. When simple enyne 47\textsubscript{a} was subjected to the ruthenium catalyst in acetone at room temperature, 1,4-diene 48 (3:1 \textit{cis}:\textit{trans} ratio) was obtained in 46% yield with no formation of the 1,3-diene that is prevalent with the equivalent palladium-catalysed process. This reaction can proceed \textit{via} a normal ruthenacycle pathway. In contrast,
when similar enyne 47b was reacted under the same conditions, the 7-membered ring product 49 was generated, which was proposed to proceed via a allylic C–H insertion mechanism.

Scheme 1.29

The reason for this dramatic difference in the reaction mechanism could be attributed to steric hindrance in hypothetical enyne-ruthenium complex 51a. When R^1 is OTBDMS and R^3 is Me, disfavoured A₁,₃-strain between R^3 at the quaternary centre and the ester group (R^4) would be very pronounced. Together with severe 1,4-diaxial steric clash between R^1 and R^2 (Me) groups, these steric interactions are likely present the formation of 51a (Scheme 1.30).

Scheme 1.30

The normal ruthenacycle mechanism in which the ruthenacypentene complex could adopt two different conformations: 51b′ and 51b′′. For the first possible conformation, 51b′, the silyl ether group...
(R₃) is placed in a pseudoequatorial position which leads to severe 1,3-allylic strain with the ester group (R⁴). Another possibility is 51b'', the OTBDMS unit (R₃) is in a pseudoequatorial position, resulting in a decrease in 1,3-allylic strain. However, R⁴ group can still create a 1,4-diaxial steric repulsion with the pseudoaxial methyl group (R²). These steric factors lead to the observed diastereoselectivity of the reaction (Scheme 1.31).

![Diastereoselectivity (via ruthenacycle mechanism)](image)

Scheme 1.31

For enyne 47b, the generation of a 7-membered ring product (49) was observed (via allyl-ruthenation of the alkyne). The proposed mechanism was strongly supported by the reaction of deuterated substrate (Z)-d₃-47b, which smoothly produced d₁-49 (with >95%D) as a single regioisotopomer (Scheme 1.32).

![Scheme 1.32](image)

In 2004, Trost and co-workers reported the effect of an allylic silyl ether on the stereoselectivity of the ruthenium-catalysed 1,6- and 1,7-enyne cycloisomerisations. The reaction diastereoselectivity is dependent on the geometry of substrate 52 (E- or Z-isomer). The ruthenacycle mechanism can be used to account for the observed stereoselectivity of the enol silane formation: starting from enyne (E)-52, ruthenacyclopentene 53'' places the silyl ether group in a favourable pseudoequatorial position.
Conformer 53'' (leading to silane \((E)-54\)) is slightly preferred over conformer 53' (leading to silane \((Z)-54\)), as a result the products are obtained with a 2.4:1 \(E:Z\) ratio (Scheme 1.33).

Interestingly, when the Cp group on the ruthenium catalyst is changed to Cp*, the selectivity is reversed, i.e. \((Z)-54\) is the major product \((E:Z\) ratio = 1:5). This is because the difference of steric congestion (with the Cp* ligand) between conformer 55' and 55'' is markedly increased; ruthenium complex 55' is now much more favourable (Scheme 1.34).

In case of the cycloisomerisation of enyne \((Z)-52\), the silyl ether group is now forced to orient in a pseudoaxial position in intermediate 56'. This time, conformer 56'' is much more sterically stable.
compared to $56'$ (Scheme 1.35), and a dramatic increase in $E:Z$ selectivity is observed (from 2.4:1 to 25:1).

**Scheme 1.35**

In 2008, The Trost group reported that ruthenium-catalysed enyne cycloisomerisation could also facilitate the stereoselective formation of bicyclic structures.\(^{29}\) At the beginning, their attempt to cyclise enyne $57a$ was unsuccessful (Scheme 1.36).

**Scheme 1.36**

Trost rationalised that the reaction was initiated by ruthenacyclopentene formation between the alkyne, alkene, and the ruthenium catalyst to form intermediate $58$. Possibly due to the high activation energy for $\beta$-elimination of the hydrogen at the pseudoaxial position in $58$, $\beta$-elimination does not occur, and hence no product was formed.

Using enynes with an electron-deficient alkyne unit, such as $57b$, the reaction proceeds cleanly to afford 1,4 enyne *trans*-59 in a single diastereomer with excellent yield (Scheme 1.37).
This outcome was proposed to arise from an allylic C–H insertion mechanism, which explains the diastereoselectivity of the reaction. The carbonyl group of the ester was proposed to direct the formation of η^3-allyl complex 60, then ligand exchange between the carbonyl and the alkyne groups takes place to form intermediate 61. Carboruthenation, followed by reductive elimination subsequently occur to produce product trans-59 (Scheme 1.38).

Arisawa and co-workers showed that ruthenium hydride complex 62 derived from the second-generation Grubbs catalyst (Grubbs II) could catalyse the cycloisomerisation of silyl enol ether with alkynyl silane 63 to produce indoline 64 (Scheme 1.39).
hydoruthenation of the alkyne. Ruthenium hydride complex 62 coordinates to enyne 63, hydoruthenation at the alkyne subsequently takes place to give the vinylruthenium species. The intermediate then undergoes carbometallation and β-hydride elimination respectively to give product 64 (Scheme 1.40).

Scheme 1.40

1.2.3 Other Metals

1.2.3.1 Gold

Gold (I) complexes are powerful catalysts for the electrophilic activation of alkyne towards nucleophilic attack by various species, including alkenes. Since the [AuL]+ complex is isolobal to H+, it is unlikely to coordinate to the alkene and the alkyne simultaneously. Consequently, unlike Pd(II) or Ru(II) catalysis, the mechanism for Au(I)-catalysed enyne cycloisomerisations usually initiates via the activated η2-metal alkyne complex mediated pathway (Scheme 1.41).31,32

Gold-catalysed enyne cycloisomerisations can proceed through a number of different mechanisms. For instance, the enyne substrate can be transformed via 5-exo-dig cyclisation into cyclopropylcarbenes 66, which then rearrange to form dienes 67 (single cleavage) and/or 68 (double cleavage); such skeletal rearrangements are well known in gold catalysis. On the other hand, 6-endo-dig cyclisation can take place to give alternative carbenes 69 that can lead to non-skeletal rearrangement products 70 via deprotonation / protodeauration. Alternatively, these cyclopropylcarbenes can undergo cyclopropane ring expansion isomerisation to give η2-cyclobutene-gold(I) complexes 71. This intermediate was detected by NMR spectroscopy and has been characterised by X-ray diffraction.33 Isomerisation and decomplexation subsequently takes place to give cyclobutene products 72. Apart from isomerisation,
complex 71 can also undergo gold-catalysed 4π-electrocyclic ring opening, which leads to 67 (Scheme 1.41).

Scheme 1.41

The Echavarren group has conducted mechanistic investigations of gold-catalysed 1,6-enyne cycloisomerisation. 1,6-enyne 73 was cyclised using gold complex 74 to give a mixture of dienes 75 and 76 (Scheme 1.42). 34

Scheme 1.42

Although diene product 75 appears to be the product from traditional Alder-ene isomerisation, the cyclisation of deuterated enyne d1-73 with the same catalyst provided dienes d1-75 and d1-76 in a 1:0.6 ratio. This deuteration pattern is not that expected from the Alder-ene cycloisomerisation, as the classic
cycloisomerisation would lead to d₁-77. The formation of products 75 and 76 can instead be explained by ring opening of cyclopropylcarbene 79 to afford cationic vinylgold complex 80, then deprotonation and protodeauration to give the products (Scheme 1.43).

![Scheme 1.43](image)

**1.2.3.2 Rhodium**

The first rhodium catalyzed 1,6-enyne cycloisomerisation was achieved by Grigg using Wilkinson’s catalyst, whereby enyne 81 was reacted to give cycloisomer 82 (Scheme 1.44).³⁵

![Scheme 1.44](image)

However, this reaction was restricted the use of a terminal alkyne, which is indicative of the insertion of the metal into the C–H bond of the alkyne to generate a Rh(III) hydride intermediate 84. Given that only product 82a was observed (not product 83a), an usual trans-hydorhodation of the alkyne was
proposed, followed by 6-exo-trig carboruthenation to afford cyclohexene 85 β-hydride elimination subsequently occurs to give product 82a (Scheme 1.45).

\[
\text{Scheme 1.45}
\]

It is worth noting that prior to the Grigg’s work Trost and Tour had attempted to use a Ni-Cr-based catalyst to facilitate the cyclisation of similar enynes, but the reaction yield is poor.\(^{36}\) The Zhang group later demonstrated the use of cationic rhodium catalysts with a chiral ligand, such as \((R,R)-\text{Me-DuPhos}\), to perform a highly enantioselective cycloisomerisation of 1,6-oxygen tethered enyne 86 to give 87 (Scheme 1.46).\(^{37}\) This is the first example of asymmetric rhodium-catalysed cycloisomerisation. The mechanism of this rhodium catalysis will be later discussed (see Chapter 4).

\[
\text{Scheme 1.46}
\]

**1.2.3.2 Titanium**

Buchwald reported a rare example of using early transition state metal to catalyse the enyne cycloisomerisation, which involved a highly regioselective cycloisomerisation of enyne 89 to obtain only 1,4-dienes 90 in presence of titanocene catalyst 88 (Scheme 1.47).\(^{38}\)
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The mechanism was proposed to operate via oxidative coupling, β-H elimination, and then CO-driven reductive elimination (Scheme 1.48). This proposed pathway was validated by the preparation of titanocycle 91, which is a key intermediate involved in this mechanism. At high temperature, metalacycle trans-91 decomposes to give the product 90. Interestingly, it was found that this thermal decomposition of the complex can be enhanced by introducing a high pressure of CO.

In addition, cis-91 was prepared and proved to be inactive towards the thermal decomposition, as β-hydride elimination is geometrically unfeasible (Scheme 1.49).
Chapter 2: Mechanistic Insights into Palladium-catalysed Cycloisomerisation—Isotopic Labelling Study and Kinetic Profiling

The remarkable benefits of palladium-catalysed cycloisomerisation in building organic cyclic frameworks have long been long recognised by chemists, especially with the palladium-based catalyst systems developed by the Trost group: Pd(OAc)$_2$/PAR$_3$, Pd(OAc)$_2$/bbeda, and Pd$_2$dba$_3$·CHCl$_3$/AcOH (with or without phosphine ligand or bbeda) (Scheme 2.1).\textsuperscript{9, 14, 39, 40}

Scheme 2.1

In 2013, our group demonstrated the palladium-catalysed cycloisomerisations of enynamides to form pyrrolidine and piperidine enamides (Scheme 2.2).\textsuperscript{20} Such nitrogen heterocyclic compounds are of importance in many fields, such as pharmaceutical and agrochemical industries. In addition, we found that the reaction conditions and time required for enynamide cycloisomerisation are usually milder and shorter compared to that of the regular palladium-catalysed enyne cyclisation.

Scheme 2.2

As discussed in the earlier chapter, some mechanistic studies have been carried out for such catalyst systems. This led to strong support for the system of Pd$_2$dba$_3$·CHCl$_3$/AcOH to operate via the mediation of palladium hydride intermediacy. On the other hand, it is still unclear how the Pd(OAc)$_2$/bbeda catalyst system works during the cycloisomerisation. Trost suggested two possible pathways for
the latter system to proceed: either palladium hydride mediated or palladacycle mediated mechanisms (Scheme 2.3).

For the former (left), the alkyne undergoes syn-hydopalladation resulting in a vinyl palladium complex. This species subsequently undergoes carboxypalladation and β-hydride elimination, producing the cyclic dienes. For the latter (right), palladium simultaneously coordinates to both alkene and alkyne units, forming a palladacyclopentene via oxidative coupling. This cyclic metal complex then undergoes β-hydride elimination. The cyclic olefin products are obtained by reductive elimination of vinyl palladium hydride complex.

Although both mechanisms can account for the formation of 1,3- and 1,4-diene products. The latter route was favoured by Trost, as bbeda was thought to have a capability to stabilise the Pd(IV) intermediate. However, there is no clear evidence for this. As enynamides had been shown to be rapidly cyclised under mild conditions, we elected to use them as substrates for investigating the mechanism of 1,6-enzyme cycloisomerisation with the highly effective catalyst system of Pd(OAc)2 / bbeda.
In our previous work, we reported that the optimised reaction conditions for Pd(OAc)$_2$ / bbeda catalyst system involved the use of 5 mol% of Pd(OAc)$_2$ and 5 mol% of bbeda in toluene (Scheme 2.4). It is also worth noting that the cycloisomerisation of enynamides can also be facilitated by the Pd$_3$dba$_3$·CHCl$_3$ / AcOH / bbeda system, as well as the ruthenium-based catalyst system: Cp*Ru(cod)Cl in MeCN at 60 °C.

![Scheme 2.4](image)

**Conditions:**
- Pd(OAc)$_2$ / bbeda (2.5 mol%), toluene, r.t., 20 min, 85%
- Pd$_3$dba$_3$·CHCl$_3$ / AcOH / bbeda (5 mol%), toluene, 60 °C, 10 min, 53%
- Cp*Ru(cod)Cl (5 mol%), MeCN, 60 °C, 1.5 h, 80%

### 2.1 Deuterium Crossover Experiments

One apparent difference between the two proposed mechanisms in Scheme 2.3 is the way in which the hydride is transferred during the reaction. An intermolecular hydride transfer is involved in the mechanism operating via a palladium hydride species, whilst an intramolecular transfer of hydride supports the palladacycle mechanism. We began our studies with a series of deuterium crossover experiments. In the experiments, deuterated enynamide d$_1$-92 (>98% D) and non-deuterated enynamide 93 were reacted in a 1:1 ratio under the optimised conditions of three different catalyst systems:

- Pd$_3$dba$_3$·CHCl$_3$ / AcOH / bbeda, Cp*Ru(cod)Cl, and Pd(OAc)$_2$ / bbeda.

Deuterated substrate d$_1$-92 was prepared from β-alanine methyl ester hydrochloride salt (Scheme 2.5). First, the salt was converted to sulfonamide 94, which was then reduced to alcohol d$_1$-95 using LiAlD$_4$. The alcohol was subjected to Dess-Martin oxidation to afford the corresponding deuterated aldehyde d$_1$-96. A Wittig olefination of deuterated aldehyde d$_1$-96 gave homoallyl sulfonamide d$_1$-97, which was subsequently converted into deuterated ynamide d$_1$-92 using Hsung copper-catalysed ynamide formation.41
Chapter 2: Mechanistic Insights into Palladium-catalysed Cycloisomerisation

Scheme 2.5

In case of ynamide 93, a Mitsunobu reaction was employed to facilitate the reaction between commercially available alcohol 99 and BocNH2SO2C6H4NO2 to produce Boc-protected \( p \)-nitrosulfonamide 100 (Scheme 2.6). Removal of the Boc group was performed by using a solution of TFA in CH2Cl2, giving sulfonamide 101. The resulting sulfonamide was converted into ynamide 93 using the same ynamide formation strategy.

Scheme 2.6

For Pd\( \text{dba}_3 \cdot \text{CHCl}_3 / \text{AcOH} / \text{bbeda} \), it is believed that an active palladium hydride is generated \textit{in situ}, and subsequently undergoes through a hydropalladation mechanism. Therefore, the result would be expected to observe an intermolecular hydride transfer (Scheme 2.7, left). For the ruthenium system, the catalyst can proceed \textit{via} either allylic C–H insertion or ruthenacyle mechanisms. Since the allylic C–H insertion pathway cannot explain the formation of the 1,3-diene product, the mechanism of this
catalysis is therefore likely to be a ruthenacycle mechanism. Hence, an intramolecular hydride transfer is expected (right).

We were pleased to discover that, with Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH / bbeda, complete crossover of the deuterium label was detected, suggesting that hydride is transferred intermolecularly as we anticipated. In contrast, under ruthenium catalysis, no crossover was observed, and 83% D incorporation was found in product d$_1$-102. This indicates that an intramolecular hydride transfer took place during the reaction course (Scheme 2.8).

For the system of Pd(OAc)$_2$ / bbeda, which we would like to gain some insight of its mechanism, a similar result to that of the system with Pd$_2$(dba)$_3$·CHCl$_3$ / AcOH / bbeda was obtained. That is, products
102 / d₈-102 and 103 / d₈-103 featured nearly equivalent amounts of deuterium incorporation (43 and 44% respectively, determined by ¹H NMR spectroscopy, Figure 2.1). Hence, the result offers support for an intermolecular transfer of hydride via a discrete palladium hydride/deuteride species.

Figure 2.1 ¹H NMR spectrum shows product scrambling when using the Pd(OAc)₂ / bbeda system.
2.2 Timecourse $^1$H NMR Spectroscopic Experiments

2.2.1 Kinetic Profile Comparison

We next exploited timecourse $^1$H NMR spectroscopy, which is a powerful technique to probe reaction mechanisms, to monitor the cycloisomerisation of enynamide 92 under different catalytic conditions. Substrate 92 was obtained in good yield from the similar synthetic strategy to synthesise enynamide 93, BocNHTs was used to react with alcohol 99 instead of BocNSO$_2$C$_6$H$_4$NO$_2$ (Scheme 2.9).

Scheme 2.9
Starting material 92 was submitted to the conditions of Pd$_2$dba$_3$·CHCl$_3$ / AcOH / bbeda. Product 102 was formed immediately after the reaction was initiated (Graph 2.1), indicating that the putative Pd(II)–H species is rapidly generated from the oxidation of Pd$_2$dba$_3$·CHCl$_3$ with AcOH. As a consequence, the formation of product 102 was observed soon after the substrate was mixed with the pre-catalyst. Although the reaction initiated instantaneously, the reaction failed to reach full conversion of starting material. This is perhaps due to the short lifespan of the active palladium species.

![Graph 2.1](image-url)
Similar instantaneous formation of product was also observed from the ruthenium catalysis with Cp*Ru(cod)Cl (Graph 2.2). This is also indicative of the presence of a catalytically reactive species at early stages of the reaction, which is sensible because substrate 92 can easily bind to the ruthenium centre via ligand exchange with the cyclooctadiene (cod) and chloride ion.
Unlike the two previous catalyst systems, the reaction kinetic profile obtained from the system of Pd(OAc)$_2$ / bbeda shows a slight delay in product formation (Graph 2.3), which is suggestive of the generation of an active catalyst species from the Pd(OAc)$_2$ pre-catalyst before cycloisomerisation initiates.

Graph 2.3
Comparison between the product formation profiles of the three catalyst systems illustrates clearly a delay in product formation under Pd(OAc)$_2$ / bbeda conditions (Graph 2.4, green), while the profiles from the other two systems a rapid production formation (red and blue).

In addition to the difference in the kinetic profiles, when d$_1$-92 was cycloisomerised with Pd(OAc)$_2$ / bbeda system to give product d$_1$-102 (Graph 2.5), a significant decrease in the rate of reaction was observed compared to that of the cyclisation of substrate 92. This reflects deuterium isotope effects, which will be discussed in more detail in the next chapter. The kinetic profile of the reaction also shows the extent of product deuteration changed during the reaction. Intriguingly, at the beginning of the reaction (first 5-7 mins), only protiated product 102 was produced (Graph 2.5, red curve), then reaching a plateau after ~ 10 minutes. At later stages of the reaction, deuterated product d$_1$-102 was mainly produced (Graph 2.5, green curve) with incremental increase of corresponding protiated product 102. Thus, deuterium incorporation overall drops from >98% D in the starting material to about 70% in the products.
Such a diminution in deuterium incorporation could be related to the catalyst activation process, for example, with the hydride source being the substrate itself, or it could imply that water plays a role in the product formation. For instance, the loss of deuterium could arise from an exchange process with water present in the reaction solvent. We therefore studied the effect of water on the reaction by comparing the reaction profiles of the cycloisomerisation of enynamide 92 in d₈-toluene with variation of water concentration (Graph 2.6). In order to obtain different concentrations of water in reaction solvent, the deuterated solvents for the NMR experiments were dried by storing freshly-opened bottle d₈-toluene over 3 Å molecular sieves for at least 24 h. The water contents in the solvent were then determined by Karl-Fischer titration. Applying such a drying method, the water content was reduced to ~ 3 ppm (for d₈-toluene). The concentration of water in freshly-opened bottle d₈-toluene was found to be ~ 82 ppm. The water content of water-saturated d₈-toluene was determined to be ~ 480 ppm.
Longer reaction times were observed when performing the cycloisomerisation of enynamide 92 with sieve-dried d$_8$-toluene, compared to the reaction run in ‘bottle’ solvent (Graph 2.6, blue curve). This trend continued to the reaction in water-saturated environment, i.e. a shorter reaction time was required to completely convert substrate to product (Graph 2.6, red curve). These results reveal a positive effect of water on the rate of reaction.

![Chemical reaction diagram]

**Graph 2.6**

- dried d$_8$-toluene (3 ppm)
- ‘bottle’ d$_8$-toluene (82 ppm)
- water-saturated d$_8$-toluene (480 ppm)
Most interestingly, when D\textsubscript{2}O was used to saturate the reaction environment instead of H\textsubscript{2}O (Graph 2.7), a small level of deuterium incorporation was detected in the product obtained from the reaction of protiated substrate 92 (Graph 2.7, green curve). This indicates that D\textsubscript{2}O can serve as a source of deuteride, potentially via H/D exchange of a palladium hydride intermediate.

\[
\text{TsNH} = \text{C} \rightleftharpoons \text{C} \rightleftharpoons \text{H} \quad \text{92} \quad \text{H product} \quad \text{102} \quad \text{D product} \quad \text{d}-\text{102}
\]

\[
\text{5 mol\% Pd(OAc)}_2 / \text{bbeda, D}_2\text{O sat. d}-\text{toluene, 35 °C}
\]

Graph 2.7
Performing equivalent reactions with deuterated substrate \( \text{d}_1\text{-92} \), the formation of protiated product \( \text{102} \) was detected even using sieve-dried solvent, and with no other obvious proton sources (Graph 2.8, top). In addition, a direct correlation between the H\(_2\)O content of the reaction solvent and the amount of protiated product \( \text{102} \) was observed; \( \sim 15\% \) of non-deuterated product \( \text{102} \) was formed in absence of water (Graph 2.8, top left), \( 26\% \) of product \( \text{102} \) was found when ‘bottle’ \( \text{d}_8\)-toluene was used as solvent (Graph 2.8, bottom left), and \( \sim 44\% \) of \( \text{102} \) was detected under water saturated conditions (Graph 2.8, bottom right). In all cases, protiated product \( \text{102} \) was exclusively produced at the early stages of the reaction.

![Graph 2.8](image)

* Substrate \( \text{d}_1\text{-92} \) * H product \( \text{102} \) * D product \( \text{d}_1\text{-102} \) * Total product
2.2.2 The Role of Water

One reason for the observed rate enhancement for substrate 92 with increasing water content could be that water is involved in the initiation process whereby an active (or more reactive) catalyst species is produced. Bedford and co-workers reported that Pd(OAc)$_2$, which is known to exist in a form of trimer 106 in organic solvents, can be hydrolysed by water or alcohols to give complex 107, Pd$_3$(OAc)$_5$OR where R is hydrogen or an alkyl group. The structures of trimeric palladium acetate 106 and the bridging hydroxide complex 107a possess D$_{3h}$ and C$_s$ symmetries, respectively, which can clearly be seen from the X-ray crystal structures (Figure 2.2).

These two species are in equilibrium in organic solvents in the presence of water; with increasing water content, a greater proportion of the bridging hydroxide complex 107 is formed (Scheme 2.10).

It was hypothesised that such a hydroxy bridged complex could serve as a more reactive pre-catalyst. To confirm this hypothesis, complex 107a was prepared as reported by Bedford et al. and used in the cycloisomerisation of enynamide 92 (5 mol% Pd), with an equivalent amount of bbeda (5 mol%) in
sieve-dried d₈-toluene. We were pleased to observe that although an induction period remained, it was diminished compared to Pd₃(OAc)₆, 106 / bbeda in H₂O-saturated d₈-toluene (Graph 2.9).

\[
\begin{align*}
\text{TsN} & \xrightarrow{5 \text{ mol}\% \text{[Pd] / bbeda, d₈-toluene, r.t.}} \text{n-Hex} \\
92 & \xrightarrow{\text{Pd₃(OAc)₆, 106}} \text{n-Hex} \\
\text{TsN} & \xrightarrow{\text{Pd₃(OAc)₆, 107a}} \text{n-Hex}
\end{align*}
\]

This observation on the effect of water on accelerating reaction initiation through the formation of palladium complex 107a suggested that this hydroxy-bridging species could be an intermediate in the formation of monomeric palladium hydride, meaning that hydrolysis of trimeric complex 106 is crucial for initiating the cycloisomerisation. Interestingly, the kinetic profiles of both reactions are similar in the post-initiation phase, implying that these two catalyst systems proceed through common intermediates.

**Graph 2.9**
To our surprise, the equivalent reactions of the deuterated substrate d₁-92 showed a retardation of reaction rate in H₂O-rich environment, compared to the reaction in D₂O-saturated solvent after ~25 mins (Graph 2.10).

This paradoxical role of water was further examined by the reaction of substrate 92 in a solvent more water-miscible than toluene, for which d₈-THF was selected. The cyclisation reaction of 92 in d₈-THF was examined in the presence of increasing amounts of water (from 4Å molecular sieve-dried solvent (~ 23 ppm H₂O) to > ~ 8000 ppm H₂O). Under these conditions, high reactivity was observed until ~ 2300 ppm H₂O; above this point, retardation of the reaction became apparent (Graph 2.11). We suggest that this retardation may result from the off-pathway coordination of water to Pd(II) complexes, which prevents complexation of the alkyne substrate, and thus inhibits the reaction.
2.2.3 The Role of Bbeda

Bbeda has proven to enhance the rate of Pd(OAc)$_2$-catalysed cycloisomerisation. This has also been confirmed by the $^1$H NMR spectroscopic reaction profiles for cycloisomerisation of enynamide 92. The reaction with bbeda could reach completion after ~15 minutes (Graph 2.12, blue curve), while the reaction in the absence of bbeda failed to reach completion after 3 h (Graph 2.12, red curve). In addition, a black suspension was observed over time when the reaction was performed in the absence of bbeda. This is markedly different from the cyclisation with bbeda whereby no or little particulate develops during the reaction. As proposed by Trost, bbeda could act as a ligand that accelerates the catalytic cycle, and / or stabilises off-cycle palladium species (as evidence by the different appearance of the reactions). However, it was discovered that addition of bbeda after ~20 minutes to a bbeda-free reaction did not lead to a rate acceleration (Graph 2.12, green curve). Instead, the rate of reaction was sustained at a slightly higher level compared to the bbeda-free reaction. This supports the idea that bbeda might prevent the aggregation of palladium catalyst.

Graph 2.11
Chapter 2: Mechanistic Insights into Palladium-catalysed Cycloisomerisation

Graph 2.12

For such experimental results, it therefore seemed possible that bbeda could be involved in pre-catalyst deaggregation and/or reaction initiation. To further investigate this, solutions of Pd₃(OAc)₅(OH) and Pd₃(OAc)₆ in anhydrous d₈-toluene were titrated with bbeda (Figure 2.3). A marked spectral change was observed after 0.25 equiv. of bbeda was added to a solution of Pd₃(OAc)₅(OH) in CDCl₃ (Titration A): the authentic ¹H NMR signals of Pd₃(OAc)₅(OH) at δH 1.70, 1.60 and 1.55 ppm shifted to the more deshielded regions (indicated by dash arrows); the signal belonging to trimeric palladium acetate at (⁺, 1.67 ppm), Pd₃(OAc)₆, was also found to have a higher proportion, which reflects an equilibrium between this trimeric species and the hydroxide bridging complex; more interestingly, a new signal showed up at 1.69 ppm (*). When more bbeda was added, the signal of Pd₃(OAc)₆ at 1.67 ppm diminished, suggesting that the trimeric palladium complex turns into an unidentified species in presence of bbeda. We thought that this unknown species might be related to deaggregated complex.

On the other hand, when a solution of Pd₃(OAc)₆ in CDCl₃ was titrated with bbeda (Titration B), a full equivalent of bbeda had to be added to the reaction in order to observe a significant change in the ¹H NMR signals. The heightened reactivity of Pd₃(OAc)₅OH towards bbeda might explain the decrease in
lag time when using Pd$_3$(OAc)$_5$(OH) / bbeda catalyst system for the cycloisomerisation, and equally performing the reaction with Pd(OAc)$_2$ / bbeda in a water saturated environment (Graph 2.9).

Even if reactions were run carefully in an environment devoid of H$_2$O (or other apparent proton source, i.e. >98% deuterated substrate d$_1$-92), a low level of protiated product 102 was consistently observed during the reaction (Graph 2.8, top left and top right, red curve). This perhaps implies that a source of hydride is related to the initiation process, potentially involving the substrate itself. To explore this, various deuterated substrates were prepared.
Deuterated substrate d$_2$-108 was synthesised from aldehyde 96, prepared in the same manner as the corresponding deuterated version (d$_1$-96), but without using deuterated reagents. The aldehyde was reacted with the per-deuterated Wittig salt d$_3$-109 (prepared from the procedure reported by Miyashita et al.) to obtain deuterated sulfonamide d$_2$-110 which was subsequently submitted to Hsung conditions with 1-bromoocytne to afford deuterated enynamide d$_2$-108 (Scheme 2.11).

**Scheme 2.11**

For deuterated ynamide d$_2$-111, β-alanine methyl ester hydrochloride salt was tosylated, and the resulting sulfonamide 94 was deuterated at the α-position to the ester using K$_2$CO$_3$ in CD$_3$OD (91% D). Ester d$_5$-112 was then reduced with DIBALH, and the resulting aldehyde was converted to an alkene using Tebbe reagent, giving deuterated alkenyl sulfonamide d$_2$-113. Copper-catalysed ynamide formation then provided deuterated enynamide d$_2$-111 with 91% D incorporation (Scheme 2.12).

**Scheme 2.12**

The synthesised deuterated substrates (d$_2$-108 and d$_2$-111) were cycloisomerised with Pd(OAc)$_2$/bbeda, no transfer of deuterium was observed (Scheme 2.13), suggesting the substrate is not the source of hydride.
Scheme 2.13

Small amounts of benzaldehyde were consistently observed by $^1$H NMR spectroscopy at the beginning of the non-anhydrous reactions. This observation led us to suspect whether bbeda could be essential for generation of palladium hydride (Scheme 2.14). Bbeda can chelate to Pd(OAc)$_2$ via $\sigma$-donation of the nitrogen atoms, making the imine groups of bbeda more susceptible to an adventitious nucleophile, e.g. water, acetate. In presence of water, hydrolysis of the imine results in the formation of benzaldehyde and primary amine 115, which could undergo $\beta$-hydride elimination to generate palladium hydride. Tautomerisation of the resulting imine 116 gives the corresponding enamine which can then liberate further hydrogen atoms. Under anhydrous conditions, acetate can act as a nucleophile to attack the activated imine to form aminal 117. This species can similarly undergo $\beta$-elimination to afford active palladium hydride species. Unsurprisingly, very small amounts of benzaldehyde were observed when reactions were performed in absence of water.

In presence of water

$$\text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph} \xrightarrow{\text{H}_{2}\text{O}} \text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph}$$

$\beta$-H elimination

$$\text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph}$$

$$\text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph}$$

Under anhydrous conditions

$$\text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph} \xrightarrow{\text{AcO}^{-}} \text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph}$$

$\beta$-H elimination

$$\text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph}$$

$$\text{Ph} = \text{N} \begin{array}{c} \text{N} \text{Pd}^{\text{II}} \text{OAc} \\ \text{Ph} \end{array} \text{Ph}$$

Scheme 2.14
We proved this assumption by preparing \( d_4\)-bbeda from the Gabriel amine synthesis of commercially available \( d_4\)-dibromoethane, followed by hydrazinolysis deprotection, and imine formation with benzaldehyde (Scheme 2.15).\(^{46}\)

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{D} & \quad \text{D} & \quad \text{D} & \quad \text{D} \\
\text{DMF, 95 °C} & \rightarrow & \text{d}_4\text{-118} & \quad 93\% \\
\text{NH}_2\text{NH}_2\text{H}_2\text{O} & \quad \text{CH}_2\text{OH}, \text{reflux} & \text{d}_4\text{-119} & \quad 87\% \\
\text{D} & \quad \text{D} & \quad \text{D} & \quad \text{HCH}_2\text{NH}_2\text{NH}_2\text{HCl} \\
\text{benzaldehyde (2 equiv.),} & \quad 5\% \text{NaOH (aq), rt.} & \text{d}_4\text{-bbeda} & \quad 75\% \\
\text{3 h} & \rightarrow & \\
\Phi & \quad \text{N} & \quad \text{N} & \quad \Phi
\end{align*}
\]

Scheme 2.15
Chapter 2: Mechanistic Insights into Palladium-catalysed Cycloisomerisation

With d₄-bbeda in hand, the cycloisomerisation of d₁-92 in dry toluene using d₄-bbeda was performed. To our delight, deuterated product d₁-102 was obtained as a sole product with >98% deuteration, i.e. no corresponding protiated product 102 produced (Graph 2.13). This strongly supports the proposal that bbeda itself serves as a source of hydride in the initiation pathway, and explains the formation of protiated product 102 in the reaction using deuterated substrate d₁-92 with h₄-bbeda.

![Graph 2.13](image-url)

* Substrate d₁-92  
* H product 102  
* D product d₁-102  
* Total product
The hypothesis was also reinforced by the fact that the reaction of protiated substrate 92 in anhydrous toluene with $d_4$-bbeda and Pd(OAc)$_2$ (5 mol% each), which also produced about 15% of deuterated product $d_1$-102 (Graph 2.14).

![Graph 2.14](image)

Substrate 92  H product 102  D product $d_1$-102  Total product

In addition, we were pleased to see that the product 121 was obtained with 15% D incorporation when enyne 120 was submitted to a solution of $d_4$-bbeda and Pd(OAc)$_2$ (5 mol% each) in anhydrous toluene at 60 °C (87% yield). Therefore, this initiation process appears to be a general mechanism for initiation of enyne cycloisomerisation with the Pd(OAc)$_2$ / bbeda catalyst system (Scheme 2.16).

![Scheme 2.16](image)
2.3 Palladium Sources

During our investigations, we also discovered that the batch of Pd(OAc)$_2$ employed as catalyst can influence the stereochemical outcome of enynamide cycloisomerisation of enynamides (Table 2.1). To our surprise however, when the reaction was performed with Pd(OAc)$_2$ from a different supplier (Acros), instead of obtaining the usual Z: E ratio of 97:3 as usual (Entry 1), a ratio of 80:20 was observed (Entry 2). We therefore set about testing various samples of commercially available Pd(OAc)$_2$, with the most extreme being a reversal of stereoselectivity to 38:62 in favour of the (E)-isomer (Entry 3).

### Table 2.1 Changes in diastereoselectivity with different batches of commercial Pd(OAc)$_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Source of Pd(OAc)$_2$</th>
<th>Z</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strem Chemicals</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Acros</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Sigma-Aldrich</td>
<td>38</td>
<td>62</td>
</tr>
</tbody>
</table>

To inspect the discrepancy in diastereoselectivity, a $^1$H NMR spectrum of each bottle of Pd(OAc)$_2$ from the different suppliers (Figure 2.4). Pd(OAc)$_2$ from Strem Chemicals gave a singlet at 1.96 ppm (running and calibrated with CDCl$_3$), which is consistent with pure Pd(OAc)$_2$ existing in a trimeric form with D$_{3h}$ symmetry (red spectrum). In addition to the singlet, there are some minor peaks corresponding to the hydroxide bridging complex 107a (dark blue spectrum). For Pd(OAc)$_2$ from Acros, the $^1$H NMR spectrum shows a singlet of Pd$_3$(OAc)$_5$NO$_2$, 122 was commonly found as impurity in commercial palladium acetate. This is because Pd(OAc)$_2$ is manufactured by the oxidation of freshly formed palladium powder using a mixture of HNO$_3$ and AcOH. The structure of Pd$_3$(OAc)$_5$NO$_2$ is similar to that of trimeric palladium acetate, but one of the κ$_2$-acetate groups is replaced by nitrite. As a result, the D$_{3h}$ symmetry is broken, leading to five acetate singlets of equal intensity, instead of one singlet. Once the authentic spectrum of Pd$_3$(OAc)$_5$NO$_2$ was overlaid with the spectrum of the Acros
sample, the extra peaks of the impurity were found to match well with Pd$_3$(OAc)$_5$NO$_2$. In case of Pd(OAc)$_2$ from Sigma-Aldrich, this sample disappointedly contained solely Pd$_3$(OAc)$_5$NO$_2$.

Although, this contamination of Pd(OAc)$_2$ has been recognised for a long time, many palladium-catalysed reactions are not significantly affected by the nitrite. However, Fairlamb et al. reported that using Pd$_3$(OAc)$_5$NO$_2$ (instead of Pd(OAc)$_2$) in the synthesis of Pd(OAc)$_2$(pip)$_2$ (pip = piperidine), led to a complex mixture of products. For enynamide cycloisomerisation, this does not seem to be the case, and such an extensive impact on the reaction outcome is, to our knowledge, unprecedented.

The synthesis of Pd(OAc)$_2$ by heating Pd$_3$(OPiv)$_6$ in excess acetic acid as reported by Colaco et al. offers high purity palladium acetate (Scheme 2.17), which is equivalent to the original supply (from Strem Chemicals). The purity was confirmed by $^1$H NMR spectroscopic analysis.

![Figure 2.4 $^1$H NMR spectra run in CDCl$_3$ at 500 MHz](image)

Figure 2.4 $^1$H NMR spectra of batches of Pd(OAc)$_2$, and batch-dependent product ratio for cycloisomerisation of 92 (left). X-ray crystal structures of palladium complexes 106 and 122 (right).

Scheme 2.17

When the reaction of enynamide 92 with Pd$_3$(OAc)$_5$NO$_2$ / bbeda was monitored by $^1$H NMR spectroscopy (Scheme 2.15), a slower reaction rate was observed, compared to that of Pd$_3$(OAc)$_6$. In addition, the E/Z isomeric ratio (1:1.8) of enamide products (Z)-102 and (E)-102 remained approximately constant throughout the reaction. Furthermore, no olefin isomerisation was observed on submission of product (Z)-102 to the catalyst, indicating that the formation of these two isomers during the reaction is likely a result of a divergent reaction mechanism, rather than post-cyclisation isomerisation.
Chapter 2: Mechanistic Insights into Palladium-catalysed Cycloisomerisation

A palladium hydride-mediated pathway is likely to be the mechanism of cycloisomerisation using Pd(OAc)$_2$ / bbeda as pre-catalyst, based on the crossover experiments which support the intramolecular hydride transfer type mechanism. Bbeda has been identified as the source of hydride for the generation of a putative palladium hydride intermediate, through a hydrolysis of the bbeda imine / $\beta$-hydride elimination, as demonstrated by the use of d$_4$-bbeda. This process is found to be a general mechanism of initiation in the cycloisomerisation of enyne substrates. In addition to serving as the source of hydride, bbeda also promotes pre-catalyst deaggregation; and also likely stabilises off-pathway Pd(II) species, which prevents catalyst degradation through aggregate formation.

Moreover, water has been shown to play several roles in the reaction. It promotes the equilibration between Pd$_3$(OAc)$_6$ and Pd$_3$(OAc)$_5$OH (which exhibits a reduced induction period compared to Pd$_3$(OAc)$_6$). Water also hydrolyses bbeda as discussed earlier, and thereby increases the rate of generation of palladium hydride species. Additionally, it can serve as a source of hydride as evidenced by reactions performed in solvents of various H$_2$O / D$_2$O contents. Paradoxically, water can also exhibit
an inhibitory effect on the rate of reactions while running cycloisomerisation of deuterated substrate in water-rich environments. This could imply that water could coordinate to active palladium species and prevent the complexation of the alkyne substrate.

The rate and product diastereoselectivity of the cycloisomerisations of enynamides are sensitive towards the purity of palladium precursor Pd₃(OAc)₆. In the presence of Pd₃(OAc)₅NO₂, a common contaminant in commercial palladium acetate, cycloisomerisation processes are retarded and the E/Z ratio of the cyclic enamine product is affected.
Chapter 3: Mechanistic Insights into Palladium-catalysed Cycloisomerisation—Computational Analysis and Kinetic Isotope Effects

With experimental evidence for the intermediacy of palladium hydride species in hand, we also wished to explore the reaction pathway by means of computational modelling to determine whether a hydropalladation reaction mechanism would be energetically feasible. In addition, we hoped to justify the stereoselectivity of the reaction, where substrate control operates in the formation of new stereocentres, and to rationalise the kinetic isotope effects we had observed. This theoretical work was carried out in collaboration with Professor Robert Paton and Dr Almudena Couce-Rios.

3.1 Computational Analysis

3.1.1 Reaction Pathway

A catalytic cycle involving hydropalladation, carbopalladation and β-hydride elimination steps was obtained for a palladium acetate catalyst featuring a single acetate ligand, using model enynamide 123, (which is similar to substrate 92 with the alkyne substituent represented by a methyl group, Figure 3.1). Hydropalladation was found to proceed from Pd(0) acetic acid complex A. The palladium(II) hydride complex F was found to be less stable than the complex A at all levels of theory, by 21.4–33.1 kcal mol\(^{-1}\) (Table 3.1). During hydropalladation to give complex B, the hydrogen atom is transferred to the β-carbon of the enynamide with the aid of an agostic interaction with the metal (TS_{AB}, \Delta G^\ddagger = 7.4 \text{ kcal mol}^{-1}). This suggests that a discrete palladium hydride is unlikely to be generated. Instead, oxidative addition to Pd(0) by acetic acid, and hydropalladation, undergoes as a single concerted irreversible process from the substrate-bound Pd(0)(HOAc) complex A (A \rightarrow B). In addition to offering a new pathway for alkyne hydropalladation, acetic acid complex A also accounts for the facile exchange of H/D when water is present in the reaction solvent, meaning that the exchange can be mediated by acetic acid rather than requiring a specific isotope exchange process at the metal.
Figure 3.1 Energy Profile for the catalytic cycle of the cycloisomerisation.
This may in part account for the failure to detect discrete palladium hydride species by $^1$H NMR spectroscopy. Moreover, the fact that oxidative addition of Pd(0) into acetic acid and hydropalladation take place in a concerted fashion supports the idea that the equilibrium of the oxidative addition process is rapid. The vinylpalladium then undergoes carbopalladation with the alkene unit ($\text{TS}_{\text{BC}}$, $\Delta G^\ddagger = 16.9$ kcal mol$^{-1}$), resulting in alkylpalladium species C, which remains complexed to the enamide alkene. This step is followed by $\beta$-hydride elimination ($\text{TS}_{\text{C'D}}$, $\Delta G^\ddagger = 20.4$ kcal mol$^{-1}$), which is the rate-limiting step. This requires palladium to decomplex from the enamide alkene to enable rotation about the C–C bond in order to align the C–Pd bond $\text{syn}$-coplanar with the C–H bond (C→C$'$). While, this $\beta$-hydride elimination is in theory reversible, the degree of reversibility is likely to be dependent on the facility of product dissociation from the resultant (alkene)Pd(H)(OAc) complex D or (alkene)Pd(HOAc) complex E (and complexation with the next substrate molecule to initiate the next round of the cycle). Experimentally, this depends on the nature of the products formed, because in some
cases the alkene within the products is indeed found to undergo isomerisation. The energy barrier between the product–palladium(II) hydride complex D (form after β-hydride elimination) and the product–Pd(0)(HOAc) complex E was calculated to be just 2.1 kcal mol\(^{-1}\) by M06 calculation. This magnitude of energy is consistent with that of other computational means (1.7 – 4.2 kcal mol\(^{-1}\)) as shown in Table 3.2.

**Table 3.2 Mechanism of product decomplexation.**

<table>
<thead>
<tr>
<th>Method</th>
<th>(E_{activation} ) / kcal mol(^{-1})</th>
<th>(\Delta E ) / kcal mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPSS</td>
<td>4.2</td>
<td>-0.8</td>
</tr>
<tr>
<td>M06</td>
<td>2.1</td>
<td>-14.4</td>
</tr>
<tr>
<td>TPSS-D3</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>PW6B95-D3</td>
<td>1.7</td>
<td>-5.8</td>
</tr>
<tr>
<td>DLPNO-CCSD(T)</td>
<td>3.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

We also are able to locate the transition state for the interconversion between such Pd(II) and Pd(0) species (TS\(_{DE}\)). At this transition state, the \(\kappa^2\)-acetate (from complex D) rotates out of the plane to adopt a \(\kappa^1\)-coordination manner bound *cis*-to the hydride.

In addition to the neutral catalytic cycle with (AcO)Pd(II)–H, we also considered a cationic catalytic cycle involving (bbeda)Pd(II)–H. The reaction pathway was found to be similar to that of the neutral catalytic cycle with (AcO)Pd(II)–H: the three steps (hydropalladation, migratory insertion, and β-
hydride elimination) are feasible, again with $\beta$-hydride elimination showing the highest barrier (Figure 3.2).

Furthermore, the calculations predict a primary KIE for $\beta$-hydride elimination of 2.221 at 35 °C, an inverse secondary KIE of 0.912 for carbopalladation at 35 °C, and a primary KIE for alkyne hydropalladation of 4.665 at 35 °C (12.604 with a parabolic tunnelling correction). The high magnitude of this later KIE may indicate the unique nature of bonding to the hydrogen atom in the hydropalladation transition state $\text{TS}_{\text{AB}}$.

![Energy Profile](image)

**Figure 3.2** Energy Profile for the catalytic cycle with bbeda as a ligand.
3.1.2 Stereoselectivity Explanation

In the course of our investigations into enynamide cycloisomerisations, we observed very high levels of substrate stereocontrol in cycloisomerisations that generate new stereocentres within the product (Table 3.3). Entry 1 reveals the effect of a substituent adjacent to the nitrogen atom of the ynamide, which gave a single regio- and stereoisomer of pyrrolidine enamide 126. Trisubstituted piperidine enamide 128 was yielded with equivalent stereoselectivity, with slight drop in regioselectivity, *i.e.* small amounts of 1,3- and 1,5-diene produced as side products (Entry 2). The production of the 1,5-diene may be indicative of the reversibility of β-hydride elimination of the catalytic pathway; this scenario is often observed in Heck reactions. A syn-α,β-substituted enynamide gave excellent stereoselectivity in the formation of tetrasubstituted pyrrolidine 130 (Entry 3). Trisubstituted enynamides with a phenyl group at α-position provide quaternary stereocentres containing products as single diastereomers (Entries 4 and 5).

**Table 3.3** Diastereoselective cycloisomerizations of enynamides with substituted tethers. *a*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s)</th>
<th>Yield (%)</th>
<th>Ratio / comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 125" /></td>
<td><img src="image" alt="Product 126" /></td>
<td>87</td>
<td>single isomer</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 127" /></td>
<td><img src="image" alt="Product 128" /></td>
<td>86</td>
<td>9:77:14&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 129" /></td>
<td><img src="image" alt="Product 130" /></td>
<td>95</td>
<td>single isomer</td>
</tr>
<tr>
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<td><img src="image" alt="Substrate 131" /></td>
<td><img src="image" alt="Product 132" /></td>
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<td>5</td>
<td><img src="image" alt="Substrate 133" /></td>
<td><img src="image" alt="Product 134" /></td>
<td>78</td>
<td>single isomer</td>
</tr>
</tbody>
</table>

* Reaction conditions: 5 mol% Pd(OAc)2, 5 mol% bbeda, toluene (0.167 M), 60 °C, 30 min; Entry 2 reaction time = 90 min. *b* Isolated yield. *c* Ratio of 1,3:-1,4:-1,5-diienes as determined by 1H NMR spectroscopic analysis of the crude reaction mixture.

The substrates shown in Table 3.3 were prepared as follows. For 125, alcohol 136 was prepared using the opening of epoxide 135 with an alkynyl anion (Scheme 3.1). The corresponding Boc-protected
sulfonamide 137 underwent a Lindlar hydrogenation in order to install the (Z)-double bond. Boc deprotection and ynamide formation then gave the desired enynamide 125 (the route was pioneered by Dr Ross Walker).

![Scheme 3.1](attachment:Scheme3.1.png)

The synthesis of α-benzyl enynamide 127 was implemented by Dr Craig Campbell; and ynamide 129 was synthesised by Dr Venkaiah Chintalapudi.

Substrate 131 was made from sulfonamide 143, which was synthesised from the Ireland-Claisen rearrangement of ester 140, followed by the Curtius rearrangement, Boc deprotection, and tosylation of the resulting amine (Scheme 3.2). 143 was converted to ynamide 131 using ynamide formation method developed by the Hsung group. The work was first undertaken by Dr Ross Walker.
Cyclohexenyl ynamide 133 was prepared from sulfonamide 146 via copper-catalysed alknylation. Sulfonamide 146 was prepared from alcohol 144 by Mitsunobu reaction to produce carbamate 145, then the Boc group was removed using potassium carbonate in refluxing methanol (Scheme 3.3).

Scheme 3.2

Scheme 3.3

The stereoselectivity of the cyclisation of enynamide 125 (Table 3.3, Entry 1) was modelled using substrate 147 in which the alkyne substituent and the group connected to the alkene are represented by a methyl group (Figure 3.3). The carbopalladation substrate resulting from 148 exists in two similar conformations: 148-anti and 148-syn, the transition states (TS-149-anti and TS-149-syn) from the
conformers lead to products $150$-anti (green profile, the observed outcome) and $150$-syn (red profile) respectively. A free energy difference between such transition states ($\Delta \Delta G^\ddagger = 3.4$ kcal mol$^{-1}$) corresponds to a calculated diastereoselectivity of more than 180:1 (assuming that carbopalladation is irreversible and also the diastereodetermining step). This is consistent with the observed reaction stereoselectivity. The energy difference between these transition states can be explained by changes in torsional strain during the carbopalladation step: for TS-$149$-anti, the strain is relieved as carbopalladation proceeds (from the eclipsed C–H bonds to red and green hydrogens in 148-anti). In case of transition state TS-$149$-syn, eclipsing interactions increase the torsional strain as this step proceeds (from the staggered C–H bonds to red and green hydrogens in 148-syn).
Figure 3.3 DFT calculations rationalize the stereochemical outcome of the anti-diastereoselective cycloisomerization of enynamide 147.
Chapter 3: Mechanistic Insights into Palladium-catalysed Cycloisomerisation

3.2 Experiments on Kinetic Isotope Effects

The data obtained from the $^1$H NMR timecourse experiments indicated the occurrence of isotope effects. Such effects cause distinct differences in reaction rate and isotope incorporation during the course of reaction. With the computational prediction of the KIE for the rate-limiting step ($\beta$-hydride elimination) in hand, we aimed to measure the magnitude of the KIE experimentally. The determination of this KIE was carried out by comparing the product distribution from disubstituted alkenyl ynamide ($E$)-151a with that of its deuterated equivalent ($E$)-d$_1$-151a (Scheme 3.4).

\[
\text{Scheme 3.4}
\]

Deuterated substrate ($E$)-d$_1$-151a was prepared as shown in Scheme 3.5. $\beta$-alanine methyl ester hydrochloride salt was converted to sulfonamide 94, then reduced to alcohol d$_2$-95 using LiAlD$_4$. Dess-Martin oxidation gave the corresponding deuterated aldehyde d$_1$-96. Enynamide ($E$)-d$_1$-151a ($E$:Z = <20:1) was synthesised from aldehyde d$_1$-96 using a Wittig reaction with NaHMDS as base, followed by ynamide formation under Hsung's conditions.\(^{41}\)
For the reaction with the deuterated substrate, (E)-d₁-151a, β-deuteride elimination is required to generate 1,3-diene products. The ratio of 1,3-:1,4-dienes was determined by ¹H NMR spectroscopy, and the KIE for β-hydride elimination was determined to have a value of 2.29. This value is consistent with the theoretical value (2.07 at 60 °C; 2.23 at 35 °C for model substrate 123), as well as other reports on β-hydride elimination from alkylpalladium complexes.⁵¹⁻⁵⁴

While the KIE associated with β-hydride elimination is consistent with computation and with literature values, the overall difference in reaction rate between substrates 151a and d₁-151a at 5 mol% catalyst loading is clearly not solely dependent on the KIE for β-hydride elimination. Although KIEs would be expected from the hydropalladation and carbopalladation steps, it was fortunately that the KIE for β-hydride elimination would not be affected by those of the hydropalladation and carbopalladation steps.

As aforementioned, the computation suggested that the reaction pathway with bbeda serving as a ligand for palladium(II) hydride (bbeda·Pd(II)–H) is also feasible. That is, the path from product decomplexation to substrate complexation, and entry to the catalytic cycle via irreversible hydropalladation, perhaps involves a number of 'off-pathway' processes, for example, coordination by bbeda (or its hydrolysé species) to Pd(II)H(OAc) or Pd(0)(HOAc). We therefore speculated whether the catalyst concentration could affect the observed reaction rates of substrate 92, in comparison with
that of deuterated substrate \( \text{d}_1\text{-92} \), such that the concentration of active catalyst species is dependent on the isotope. We were pleased that this was found to be the case as shown by measurement (run in triplicate) of the rates of cycloisomerisation for each substrate at different catalyst loadings (0.5, 1, 2.5, 5 and 10 mol%). The rate constants for both substrates, and their associated errors (one standard deviation) were plotted and tabulated as shown in Graph 3.1. Plateau effects were observed for both substrates at higher catalyst concentrations: for \( \text{92} \), this occurs above 5 mol%, while for \( \text{d}_1\text{-92} \), at or above 2.5 mol%.

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Catalyst loading X (mol%)} & <k_H(\text{obs})> (\text{mmol dm}^{-3} \text{s}^{-1}) & <k_D(\text{obs})> (\text{mmol dm}^{-3} \text{s}^{-1}) & k_H(\text{obs}) / k_D(\text{obs}) \\
\hline
0.5 & 0.58 \pm 0.18 & 0.16 \pm 0.039 & 3.74 \pm 0.40 \\
1 & 1.20 \pm 0.17 & 0.28 \pm 0.12 & 4.20 \pm 0.44 \\
2.5 & 2.04 \pm 0.24 & 0.43 \pm 0.11 & 4.74 \pm 0.28 \\
5 & 2.99 \pm 0.24 & 0.40 \pm 0.17 & 7.45 \pm 0.44 \\
10 & 3.15 \pm 0.16 & 0.40 \pm 0.11 & 7.97 \pm 0.29 \\
\hline
\end{array}
\]

Graph 3.1
This backs up the idea that the difference in energy barriers for hydro- and deuteriopalladation could have an influence on off-cycle equilibrium processes. That is, hydropalladation is much lower in energy than deuteriopalladation. This suggests the impact of the hydropalladation step on entry to the catalytic cycle, as well as illustrating H/D exchange process that can intercept the released Pd(II)–D species *en route* to complexation of the next molecule of substrate.

Moreover, the order of reaction with respect to the metal catalyst can also be determined by these data. Plotting a relationship between \( \ln(k_{\text{obs}}) \) and \( \ln([\text{Pd(OAc)}_2]) \) reveals straight line graph (Graph 3.2), which supports the proposal of a monomeric palladium species as the active catalyst.\(^{55}\) Although the linear with the value of gradient less than 1 reflects the equilibrium between monomeric and dimeric forms of palladium species, the slope magnitude of 0.69 (>0.5) indicates the preference of the monomeric form over the dimeric form.

\[
\text{slope} = 0.69, \ R^2 = 0.98
\]

**Graph 3.2**
In addition, a secondary kinetic isotope effect was observed when comparing the absolute rates of cycloisomerisation of (Z)-151a and (Z)-d1-151a. These substrates gave exclusively 1,4-diene products, i.e., there is no effect β-hydride/deuteride elimination on the rate of reaction.

Deuterated substrate (Z)-d1-151a was prepared as shown in Scheme 3.6. Deuterated aldehyde d1-96 was reacted with Ph3PC3H3Br under basic conditions, followed by the copper-catalysed alkynylation of the sulfonamide to afford the desired ynamide.

Scheme 3.6
The gradients of the cycloisomerisation kinetic profiles were measured in the pseudo-0th order steady state region of the reaction (6-11 minutes), Graph 3.3. A straight-line fit of these linear regions gives two gradients, the ratio of which corresponds to an inverse secondary kinetic isotope effect of 0.87±0.01. The reason for this being secondary KIE is not clear: with the theoretical pathway indicating carbopalladation to be a non-rate limiting step, we suggest that this effect could relate to differences between the two isotopes in agostic interactions, or hyperconjugation effects during the enamide decomplexation / β-hydride elimination steps, or during product decomplexation.

\[
\begin{align*}
\text{(Z)-151a} & \quad \text{Pd(OAc)}_2 (5 \text{ mol%}), \text{bbeda (5 mol%)}, \text{toluene, 35 }^\circ \text{C} \\
\text{(Z)-d}_1\text{-151a} & \rightarrow \text{98}\%\text{D}
\end{align*}
\]

**Graph 3.3**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>(k_H (\text{mmol dm}^{-3} \text{s}^{-1}))</th>
<th>(k_D (\text{mmol dm}^{-3} \text{s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-2.36</td>
<td>-2.73</td>
</tr>
<tr>
<td>2</td>
<td>-2.35</td>
<td>-2.67</td>
</tr>
<tr>
<td>3</td>
<td>-2.37</td>
<td>-2.72</td>
</tr>
<tr>
<td>average</td>
<td>-2.36</td>
<td>-2.71</td>
</tr>
<tr>
<td>SD</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\dot{k}_H(\text{obs}) / \text{mmol dm}^{-3} \text{s}^{-1} &= -2.71 \pm 0.03 \\
\dot{k}_D(\text{obs}) / \text{mmol dm}^{-3} \text{s}^{-1} &= -2.36 \pm 0.01 \\
\frac{\dot{k}_H(\text{obs})}{\dot{k}_D(\text{obs})} &= 0.87 \pm 0.01
\end{align*}
\]
3.3 Conclusions

The reaction mechanism is examined computationally to confirm that a Pd(II)–H mediated pathway is feasible. Modelling of L,Pd(II)H(OAc) and L,Pd(0)(HOAc) complexes (which are in rapid equilibrium) shows that the latter is the active pre-hydopalladation (Pd(0)) complex. Hydropalladation is illustrated to proceed via a novel mechanism in which a hydride transfer from Pd(0)-complexed HOAc to the alkyne is stabilised by an agostic interaction with the metal centre – oxidative hydropalladation type process. This mechanism could have wider implications for other hydrometallation reactions. The rate-limiting step of the reaction is found to be β-hydride elimination, with hydropalladation and carbopalladation both being irreversible.

Exploiting computational analysis, the high stereoselectivity observed from cycloisomerisation of chiral enynamides can be explained. From the calculations, we discovered that torsional strain effects play a crucial role in producing excellent level of diastereoselectivity.

Finally, experimental determination of the KIE for β-hydride elimination correlates well with the theoretical prediction. In addition, we also observed the unexpected KIE, which may indicate an influence of the isotope on the rate of enamide decomplexation / β-hydride elimination (to the 1,4-diene), or on product decomplexation. This combination of experiment and theory therefore provides further support for the palladium hydride mechanism.
Chapter 4: Introduction: Asymmetric Transition Metal-Catalysed 1,6- and 1,7-Enyne Cycloisomerisations

In the previous chapter, the benefits of transition metal-catalysed cycloisomerisation of 1,ₙ-enyne has been demonstrated in accessing various types of cyclic compounds. We now turn our attention to the process in which stereo-defined cyclic 1,3- and 1,4-dienes are produced. Over the past decades, the development of enantioselective enyne cycloisomerisation has attracted significant interests; this chapter will focus on progress in this field using various metals as catalysts.⁵⁶

4.1 Palladium

Enantioselective metal-catalysed enyne cycloisomerisation was first reported by the Trost group.⁴ In this work, chiral carboxylic acids (e.g. Mosher’s acid, (S)-binaphthoic acid) were used in combination with with Pd₂(db₃)$_₃$·CHCl₃ (5 mol%) instead of achiral acid, such as acetic acid (Scheme 4.1). Based on the idea that Pd(0) would undergo oxidative addition across the acid to give H–Pd(II)–O₂CR*, the chiral moiety (R*) of the acid should facilitate stereochemical induction during the cycloisomerisation process. The reaction produced chiral 1,4-diene 3a in moderate yield, but with only modest level of enantioselectivity (up to 33% ee).

![Scheme 4.1](image)

The Trost group later illustrated an improvement in the enantioselectivity by using amidodiphosphane ligand 155 together with a tartrate auxiliary installed on 1,6- and 1,7-enyne substrates 154 (Scheme...
4.2. This enabled a double stereodifferentiating cycloisomerisation to take place, again leading to modest stereoselectivity.

The group discovered that the carboxylic acid group in the substrate is crucial for asymmetric induction, rather than the stereocentres of the tatrate unit. This was supported by the fact that when ethyl and methyl esters, instead of carboxylic acid, were used; poor selectivity (0-6% de) was observed.

In 1996, Ito and co-workers introduced a new ferrocene-based bidentate ligand, (S,S)-(R,R)-Trap, 158.

This ligand enabled palladium-catalysed cycloisomerisation of enynes 157, producing 1,4-dienes 159 as the major product (3.5:1, 159:160) with excellent enantiopurity (95% ee). It is worth noting that the reason for 1,4 dienes being more favoured is that the presence of this ligand reduces the reaction rate; as a result, elimination of H_b (blue) was preferred to the elimination of H_a (green) (Scheme 4.3). Moreover, changing the configuration of the olefin from E to Z led to a reversal the configuration of the stereogenic centre of the product (R to S).
Mikami and co-workers reported that oxygen-tethered enyne 161 could be cycloisomerised using several palladium salts in the presence of chiral bidentate phosphine ligands to give product 162 with up to 99% ee.\(^{17}\) Reaction yields were found to be dependent on the palladium salt. Pd(OCOCF\(_3\))\(_2\) gave the best yield (Scheme 4.4), while others (Pd(OAc)\(_2\) or Pd\(_2\)(dba)\(_3\)·CHCl\(_3\) / AcOH) led to poor reaction yields (< 25%). Interestingly, Mikami observed a marked solvent effect on the stereoselectivity and reaction rates. In DMSO, the cationic palladium species 163 is formed as the CF\(_3\)COO\(^-\) ion can dissociate from Pd, and adopts a square-planar geometry. In non-polar solvents, like benzene, the CF\(_3\)COO\(^-\) ion remains coordinated to the metal centre. As a consequence, a five-coordinate intermediate 164, in which the alkene unit is weakly coordinated (out of plane) to the palladium, is formed. This species leads to a high activation energy, hence a sluggish reaction rate.
Chapter 4: Introduction: Asymmetric Transition Metal-Catalysed Cycloisomerisations

The Mikami group also demonstrated the asymmetric cycloisomerisation of 1,7-enynes (Scheme 4.5).\(^{59}\)
In this work, the cycloisomerisation of enynes 165 and dihydropyranyl alkyne 166 was catalysed by a combination of [Pd(MeCN)\(_2\)]SO\(_4\), (S)-BINAP, and formic acid in DMSO at 100 °C to give quinoline derivatives 167 and spiro products 168, respectively.

**Scheme 4.4**

**Scheme 4.5**
Since Mikami’s conditions were introduced, more recent palladium-based catalyst systems for enantioselective cycloisomerisations have been developed based on such conditions. In 2009, Tanaka et al. showed that a combination of \([\text{Pd(MeCN)}_4](\text{BF}_4)_2\) and (S)-xyl-SEGPHOS could cyclise N-alkenyl arylethynylamides 169 to give axially chiral 4-aryl-2-pyridones 170 with excellent yields and enantiomeric excess (Scheme 4.6). 60

![Scheme 4.6](image)

Although the catalyst system used for this cycloisomerisation very much resembles that of Mikami, the mechanisms of catalysis differ. This reaction is proposed to begin with \(\pi\)-activation of the alkyne via \(\eta^2\)-coordination of palladium, instead of the usual hydrometallation pathway.

Another example of exploiting palladium-catalysed isomerisation to construct axially chiral biaryl compounds is found in work from Uemura et al. 61 This work illustrated that a combination of \([\text{Pd(MeCN)}_4](\text{BF}_4)_2\) and (R)-BINAP could be used to asymmetrically cycloisomerise enynes 171 to give biaryls 172 with decent yields and excellent enantioselectivity (Scheme 4.7).

![Scheme 4.7](image)
Recently, the Andersson group showed that thiazole, imidazole and oxazoline based $N,P$-ligands could be also used to cyclise oxygen-tethered enyne 173 (similar to Mikami’s substrates) to afford chiral tetrahydrofurans 174 in up to 84% yield and 81% ee (Scheme 4.8).62

![Scheme 4.8](image)

The stereochemical outcome of this reaction can be rationalised by the model illustrated in Scheme 4.9. Using DFT calculations, an optimised structure of palladium-ligand complex 175 was obtained. This structure reveals that quadrant 2 and 4 display strong steric crowding resulting from the chiral ligand. When substrate 173 binds to complex 175, intermediate 176 is sterically favourable to be formed (compared to intermediate 177). This species leads to ($S$)-configuration of the product, 174a.
Zhang et al. demonstrated the first asymmetric rhodium-catalysed enyne cycloisomerisation, which employed a cationic rhodium catalyst with chiral diphosphane / diphosphinite ligands in the cyclisation of 1,6-enynes (Z)-178 to give cyclic products (E)-179 (Scheme 4.10).
In addition to 1,6-oxygen/nitrogen tethered enynes, many prototypical substrates with heteroatom tether linkages, such as 180, could also be cycloisomerised with the same catalyst system. It was found that when the ligand was changed to (S)-BINAP, the level of enantioselectivity and reaction reactivity were improved (up to 91% yield and > 99% ee, Scheme 4.11).

Scheme 4.11
Substrate scope for the catalyst system has been expanded by implementing the new experimental protocol, as a result chiral functionalised lactams 183 were yielded with high enantiopurity (Scheme 4.12, top). Moreover, Zhang et al. illustrated the enantioselective synthesis of kainic acid analogues using the same catalyst system (Scheme 4.12, bottom).

Scheme 4.12
In this work, the authors also suggested the possible mechanism for the operation of this catalyst (Scheme 4.13). First, the cationic rhodium catalyst binds to the alkene and alkyne simultaneously. This complex (187) then undergoes oxidative coupling to give rhodacycle 188. Subsequent β-hydride
elimination gives vinyl rhodium complex 189 which then proceeds reductive elimination to give 1,4-diene product \((E)-179\). It is also possible that rhodium complex 188 is in equilibrium with less stable (due to steric clash) complex 192. \(\beta\)-hydride elimination of this complex, followed by reductive elimination can lead to the formation of a \((Z)\)-1,4 diene product, \((Z)-179\). Another possibility is that the hydrogen on the cyclic unit undergoes \(\beta\)-hydride elimination, leading to 1,3-product 191, but this product is not generally observed. However, Zhang et al. reported that this reaction was incompatible with \((E)\)-alkenyl substrates with poor conversion and enantioselectivity observed. This is perhaps due to weaker coordination of \((E)\)-substrate to the rhodium centre.

Scheme 4.13
Zhang and co-workers applied this chemistry a formal synthesis of (+)-pilocarpine with rhodium catalysis as the key synthetic step (Scheme 4.14). It was also shown that chiral γ-lactones 194 could be readily prepared with excellent yields and enantioselectivities (less than 5 min of reaction time).

Scheme 4.14
Not long after reporting the synthesis of (+)-pilocarpine, the Zhang group developed the first highly enantioselective kinetic resolution enyne cycloisomerisation. When 1,6-oxygen tethered enyne 195 was submitted to the catalytic reaction with (S)-BINAP, syn-(±)-195 led to enantiopure (2R, 3S)-196 and syn-(+)-195, while anti-(±)-195 gave >99% ee of (2R, 3S)-196 and anti-(+)-195 with the same ligand (Scheme 4.15). The use of (R)-BINAP with the same isomers gave the opposite hand of the products also with > 99% ee. The limitation of this resolution is that the production of syn-products (196) could not be achieved by performing the mismatched reaction.
In 2009, Muller et al. used Zhang’s catalyst to enantioselectively cyclise allyl alcohols 197 to afford chiral ketones. These ketones can be reduced by NaBH₄ in one-pot fashion to obtain chiral alcohols 198 (Scheme 4.16) with moderate to high yields (38-95%) and excellent enantiomeric excess (>99% ee).

**Scheme 4.15**

During the study towards the total synthesis of platensimycin, Nicolaou et al. reported that the reaction conversion and the level of asymmetric induction improved when [Rh((S)-BINAP)]SbF₆ was used as
catalyst instead of Zhang’s catalyst system. The model substrate used in the study of this asymmetric cycloisomerisation was allyl alcohol 199, which gave chiral aldehyde 200 (Scheme 4.17). The yield and enantioselectivity of the reaction were decent. However, this catalyst must be prepared freshly as a solution in order to obtain good results.

Scheme 4.17

Hayashi reported that chiral diene-phosphine tridentate ligands with rhodium catalyst could facilitate asymmetric cycloisomerisation of 1,6-enynes 201 (Scheme 4.18). In stark contrast, the products obtained from this rhodium catalysis is different from that of Zhang’s or Nicolaou’s catalyst systems: chiral azabicyclo[4.1.0]heptenes 202 instead of chiral pyrrolidine analogues. The results were excellent, high reaction yields and great enantioselectivities were observed. In addition, the bicyclic product, 202a, could be further converted to a highly functionalised cyclopropane 203a.

Scheme 4.18

Hayashi et al. extended their idea of utilising chiral diene ligands to promote the rhodium-catalysed cycloisomerisation. 1,6-Ene-ynamides 204 were cyclised by their rhodium-based catalyst to give enantioenriched bicyclic products 205. The reactions showed good reactivity with excellent levels of
enantiomeric excess. This work also revealed that chiral diene ligands offer much higher reactivity compared with chiral bidentate phosphines, e.g. BINAP (Scheme 4.19). In addition, this is the first example of asymmetric ynamide cycloisomerisation.

Scheme 4.19

The stereoselectivity of this catalytic reaction is proposed to originate from steric hindrance between the ligand and substrate (Scheme 4.20). The cationic rhodium species is coordinated with the alkyne and a carbonyl oxygen of eneamide to give complex 206. The preferred conformation of the coordinated ene-ynamide 207, where the N-tosyl group is placed at a less hindered site, was adopted. The more steric conformation is illustrated as 208. Complex 207 then proceeded via 6-endo-dig cyclisation to give rhodium-carbenoid 209, leading to product 205a.
Tanaka and co-workers demonstrated that a rhodium catalyst with chiral bidentate phosphine ligands could cycloisomerise 1,6-enynes 210 in presence of benzoic acid to give bicyclo[3.1.0]hexanes 211 (Scheme 4.21)\textsuperscript{71}

Scheme 4.21

A mechanistic study with deuterium labelling suggested that this reaction proceeds via a rhodacycle mediated mechanism (Scheme 4.22), because the reaction of deuterated enyne d\textsubscript{2}-212 possessing a dideutered allylic methylene group furnished monodeuterated product d\textsubscript{1}-211a.

Scheme 4.22

The products from this rhodium-catalysed reaction can undergo acid-promoted lactonisation on treatment with TsOH to give bicyclic lactones 214 (Scheme 4.23). The mechanism of lactonisation with TsOH is illustrated in Scheme 4.23, and initiates with alkene protonation, which promotes cyclopropane ring opening.
Recently, the Zhang group reported the first asymmetric cycloisomerisation of \((E)-1,6\) enynes (Scheme 4.24).\(^7\) It was found that common chiral diphosphine ligands, such as BINAP, SEGPHOS, or BIPHEP, were unreactive towards the cyclisation of \((E)\)-substrates. However, when DuanPhos or TangPhos was used with \([\text{Rh(cod)Cl}]_2\), cycloisomerisation of \((E)-1,6\) enynes \(215\) could proceed to give enantoenriched pyrrolidines \(216\). Computational studies suggested that DuanPhos and TangPhos give positive results in cyclising \((E)\)-enynes, because such ligands lead to lower energy of activations throughout the catalysis, compared to common ligands, like BINAP.

### Scheme 4.23

Recently, the Zhang group reported the first asymmetric cycloisomerisation of \((E)-1,6\) enynes (Scheme 4.24).\(^7\) It was found that common chiral diphosphine ligands, such as BINAP, SEGPHOS, or BIPHEP, were unreactive towards the cyclisation of \((E)\)-substrates. However, when DuanPhos or TangPhos was used with \([\text{Rh(cod)Cl}]_2\), cycloisomerisation of \((E)-1,6\) enynes \(215\) could proceed to give enantoenriched pyrrolidines \(216\). Computational studies suggested that DuanPhos and TangPhos give positive results in cyclising \((E)\)-enynes, because such ligands lead to lower energy of activations throughout the catalysis, compared to common ligands, like BINAP.

---

\(20 \text{ mol}\% \ [\text{Rh(cod)Cl}]_2 \cdot \text{BF}_4^-
\)
\(20 \text{ mol}\% \ (S)\)-SEGPHOS
\(40 \text{ mol}\% \text{ BzOH}
\)

1,2-DCE, 80 °C, 16 h

then 1 equiv. TsOH·H₂O, 24 h

\(E = \text{CO}_2\text{Bn}
\)

62%, 80% \(\varepsilon e\)

---

\(2.5 \text{ mol}\% \ [\text{Rh(cod)Cl}]_2, 12 \text{ mol}\%
\)
\(L^* 5 \text{ mol}\% \text{ AgBF}_4
\)

1,2-DCE, r.t.

\(X = \text{NBz, NTS, O, C(CO}_2\text{Me})_2
\)

\(R^1 = \text{Me, Ar, CO}_2\text{Me}
\)

\(R^2 = \text{Me, n-Bu}
\)

72-89%, >99% \(\varepsilon e\)

---

\(L^* =
\)

\((S,c,R)-\text{DuanPhos}
\)

\((S,S,R,R)-\text{TangPhos}
\)
4.3 Other Related Metal-Catalysed Processes

Although palladium and rhodium based catalyst systems can effect cycloisomerisations in excellent yields and enantiomeric excess, some other metals (e.g. platinum, iridium, gold) also show good cycloisomerisation reactivity and stereochemical induction.

In 2004, Genêt et al. reported that chiral monodentate phosphine ((R)-218) with platinum(II) chloride could promote the asymmetric alkoxy carbocyclisation (cycloisomerisation in presence of external nucleophile) of enyne 217 to give enantioenriched chiral carbocycle 219 (Scheme 4.25). The results were satisfying (94% yield and 85% ee).

Scheme 4.25
The Echavarren group demonstrated the first enantioselective gold-catalysed alkoxy carbocyclisation. In this work, enyne 220 in methanol (external nucleophile) was cyclised with a combination of AuCl and (R)-tol-BINAP in 2:1 ratio to afford cyclic product 221. The yield was moderate, but the enantioenrichment of the product was excellent (Scheme 4.26).

Scheme 4.26
In the same year, the first example of asymmetric iridium-catalysed cycloisomerisation of 1,6-enyne was reported. Azabicyclo[4.1.0]heptenes 223 were made from the cycloisomerisation of nitrogen
tethered enynes 222 with the iridium-chiral diphosphine complex, generated from mixing [Ir(cod)Cl]$_2$ and tol-BINAP in presence of AgOTf under a carbon monoxide atmosphere. (Scheme 4.27).\textsuperscript{75}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_4.27.png}
\end{center}

Scheme 4.27

4.4 Conclusions

During the past decades, there have been marvellous advances in the area of metal-catalysed enantioselective cycloisomerisations. A vast variety of compounds can now be readily cyclised to afford chiral products with high enantiopurity. At present, the power of such methodologies has yet to be widely explore in organic synthesis, as asymmetric cycloisomerisations are occasionally used as critical steps in natural product or complex target syntheses.\textsuperscript{76} It is unarguable that such great impacts and applications produced of these cyclisation processes would not reverberate without these pioneering developments.
Chapter 5: Asymmetric Rhodium-Catalysed Cycloisomerisation of Enynamides

In the previous chapter, palladium and rhodium catalyst systems were shown to provide good reactivity and high levels of enantioselectivity in the cycloisomerisations of enynes. In this chapter, we report our investigations to effect asymmetric enynamide cycloisomerisations using palladium and rhodium catalysts.

5.1 Preliminary Study on Asymmetric Cycloisomerisation of Enynamides

5.1.1 Test substrate synthesis

Ynamide (Z)-151a was chosen as the test substrate for our investigations. It was readily prepared from the commercially available alcohol (Z)-224 by Mitsunobu reaction with BocNHTs, followed by Boc-deprotection to afford sulfonamide (Z)-153, and finally coupling with bromoalkyne 98a to give ynamide (Z)-151a in excellent yield (Scheme 5.1).41

Scheme 5.1
5.1.2 Palladium Catalysis

Inspired by the work from the Trost group (see Chapter 4), we attempted to use the system of Pd\(_{2}\)dba\(_3\)-CHCl\(_3\)/PPh\(_3\) in combination with a chiral acid (Table 5.1, Entries 1 and 2). Poor conversions of substrate (Z)-151a to give 1,4-diene products 153a were observed (32%) with 85:15 E/Z ratio. In addition, the ratio between 1,4- and 1,3-diienes (153a and 152a) was found to be 87:13. We next investigated the ability of a variety of chiral ligands to provide stereoselectivity in the reaction using a combination of Pd\(_{2}\)dba\(_3\)-CHCl\(_3\) and chiral ligand with AcOH (Entries 3–7), once again poor cycloisomerisation yields were obtained with 1,4-diienes 153a as major products. The E/Z ratio of product 153a was consistently between 85:15 and 90:10, but disappointingly, all attempts failed to afford any enantioselectivity.

Table 5.1 Catalyst system screening (based on Trost’s conditions) for asymmetric enynamide cycloisomerisation.
Chapter 5: Asymmetric Rhodium-Catalysed Cycloisomerisation of Enynamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system (mol%)</th>
<th>Solvent</th>
<th>T / °C</th>
<th>(E)-153a:(Z)-153a:152a</th>
<th>Yieldb / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / (R,R)-</td>
<td>226 (120) / PPh$_3$ (12)</td>
<td>C$_6$H$_6$</td>
<td>r.t. to 60</td>
<td>74:13:13</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / (S)-CSA</td>
<td>(120) / PPh$_3$ (12)</td>
<td>C$_6$H$_6$</td>
<td>r.t. to 60</td>
<td>69:13:18</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / AcOH</td>
<td>(110) / (R,R)-227 (12)</td>
<td>PhMe</td>
<td>60</td>
<td>77:14:10</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / AcOH</td>
<td>(110) / (R)-BINAP (12)</td>
<td>PhMe</td>
<td>60</td>
<td>76:17:7</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / AcOH</td>
<td>(110) / (R,R)-BOX (12)</td>
<td>PhMe</td>
<td>60</td>
<td>79:9:12</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / AcOH</td>
<td>(110) / (R,R)-228 (12)</td>
<td>PhMe</td>
<td>60</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>Pd$_2$dba·CHCl$_3$ (5) / AcOH</td>
<td>(110) / (R,R)-Josiphos (12)</td>
<td>PhMe</td>
<td>60</td>
<td>71:15:14</td>
</tr>
</tbody>
</table>

a Determined by $^1$H NMR spectroscopy; b Isolated yield; c NMR yield; n/a = not applicable.

According to Mikami’s work,$^{17}$ Pd(OCOCF$_3$)$_2$ or [Pd(MeCN)$_3$](BF$_4$)$_2$ / AcOH with chiral ligands are reported as good conditions for asymmetric cycloisomerisation of enynes. Taking (Z)-151a with Pd(OCOCF$_3$)$_2$ failed to yield any cycloisomerisation, however, [Pd(MeCN)$_3$](BF$_4$)$_2$ / AcOH was found to be effective with 153a/152a isolated in a combined 70% yield (Table 5.2, Entries 1 and 2). Interestingly, the absence of AcOH resulted in an increased yield whilst maintaining isomer ratios. In both cases, though, (R)-BINAP did not induce enantioselectivity in the reaction (Entry 3). When the chiral ligand was changed to (R,R)-BOX or chiral imine (R,R)-227 (Entries 4 and 5), yields dropped slightly to 55–65%; but the product ratio between 1,4-dienes 153a and 1,3-diene 152a (~90:10) was better than that of (R)-BINAP (72:28). Combinations of Pd(OAc)$_2$ with chiral bidentate phosphine ligand provided moderate to good cycloisomerisation yields. To our surprise, when the ligand was (R)-BINAP or (R)-SEGPHOS (Entries 6 and 7), 1,3-diene 152a was formed preferably with 94:6 and 92:8
1,3:1,4-product ratios, respectively. Once palladium complexes 229 and 230 prepared according to the procedure reported by Buchwald et al.\textsuperscript{77} were used with AcOH (Entries 9 and 10), cycloisomerisation underwent with decent yields and regioselectivities: ~90:10 (1,4:1,3-diene ratios) and ~85:15 E/Z ratios for 1,4-diene products. On the contrary, PdCl\(_2\) and either (R)-BINAP or (R)-SEGPHOS together with AgSbF\(_6\) were found to be inactive towards the cycloisomerisation (Entries 11 and 12). None of the catalyst systems gave detectable enantiomeric excess.

**Table 5.2 Further Pd-based catalyst screening**
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system (mol%)</th>
<th>Solvent</th>
<th>T / °C</th>
<th>(E)-153a:(Z)-153a:152a</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OCOCF&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt; (10) / (R)-BINAP</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>80</td>
<td>n/a</td>
<td>n.r</td>
</tr>
<tr>
<td>2</td>
<td><a href="BF%3Csub%3E4%3C/sub%3E">Pd(MeCN)&lt;sub&gt;4&lt;/sub&gt;</a>&lt;sub&gt;2&lt;/sub&gt; (10) / AcOH</td>
<td>(110) / (R)-BINAP (12)</td>
<td>DMSO</td>
<td>100</td>
<td>58:14:28</td>
</tr>
<tr>
<td>3</td>
<td><a href="BF%3Csub%3E4%3C/sub%3E">Pd(MeCN)&lt;sub&gt;4&lt;/sub&gt;</a>&lt;sub&gt;2&lt;/sub&gt; (10) / (R)-BINAP (12)</td>
<td>DMSO</td>
<td>100</td>
<td>58:14:28</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><a href="BF%3Csub%3E4%3C/sub%3E">Pd(MeCN)&lt;sub&gt;4&lt;/sub&gt;</a>&lt;sub&gt;2&lt;/sub&gt; (10) / AcOH</td>
<td>(110) / (R,R)-BOX (12)</td>
<td>DMSO</td>
<td>100</td>
<td>72:18:10</td>
</tr>
<tr>
<td>5</td>
<td><a href="BF%3Csub%3E4%3C/sub%3E">Pd(MeCN)&lt;sub&gt;4&lt;/sub&gt;</a>&lt;sub&gt;2&lt;/sub&gt; (10) / (R,R)-227</td>
<td>(12)</td>
<td>DMSO</td>
<td>100</td>
<td>69:18:13</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10) / (R)-BINAP (12)</td>
<td>PhMe</td>
<td>60</td>
<td>5:1:94</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10) / (R)-SEGPHOS (12)</td>
<td>PhMe</td>
<td>60</td>
<td>7:1:92</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10) / (R,R)-227 (12)</td>
<td>PhMe</td>
<td>60</td>
<td>75:13:12</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt; (10) / (R,R)-BOX (12)</td>
<td>PhMe</td>
<td>60</td>
<td>76:15:9</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>[Pd(R)-BINAP]dba 229 (10) / AcOH (110)</td>
<td>PhMe</td>
<td>r.t. to 60</td>
<td>78:15:7</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>[Pd(R)-SEGPHOS]dba 230 (10) / AcOH (110)</td>
<td>PhMe</td>
<td>r.t. to 60</td>
<td>77:13:10</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt; (10) / (R)-BINAP (12) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (20)</td>
<td>MeCN</td>
<td>40</td>
<td>n/a</td>
<td>n.r.</td>
</tr>
<tr>
<td>12</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt; (10) / (R)-SEGPHOS (12) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (20)</td>
<td>MeCN</td>
<td>40</td>
<td>n/a</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy; <sup>b</sup> Isolated yield; n/a = not applicable; n.r. = no reaction.
Chapter 5: Asymmetric Rhodium-Catalysed Cycloisomerisation of Enynamides

During the course of these studies, we envisaged a Heck-type reaction on \((E)-\alpha\)-haloenamides to perform a cyclisation giving cyclic enamides as products (Scheme 5.2).

![Scheme 5.2](image)

It is worth noting that only \((E)\)-isomer of \(\alpha\)-haloenamides work for the cyclisation to take place. It is difficult for the \((Z)\)-isomer to undergo such a cyclisation, because the carbopalladation step of this isomer is sterically disfavoured (Scheme 5.3).

![Scheme 5.3](image)

We began the study with making \((E)-\alpha\)-haloenamides from our ynamides (Table 5.3). Using Hsung’s method of preparing \((E)-\alpha\)-haloenamides,\(^{76}\) the reaction was highly stereoselective, but required overnight stirring at 55 °C (Entries 1–3). In 2013, Iwasawa et al. demonstrated the regio- and stereospecific synthesis of \((E)-\alpha\)-haloenamide from ynamides in the presence of halotrimethylsilane (TMSX, where X is halide) and \(\text{H}_2\text{O}.\)\(^{77}\) The procedure relies on the in situ generation of hydrogen halide from TMSX. Using this method, \((E)-\alpha\)-haloenamides were prepared as the sole product from the parent ynamides in quantitative yields within 1 h (Entries 4–7). It was found that iodoenamides were prone to be more reactive towards moisture in air, compared to bromoenamides, which could be because iodine is a better leaving group than bromide.
Table 5.3 Preparations of (E)-α-haloenamides from enynamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, R¹</th>
<th>Conditions</th>
<th>time / h</th>
<th>Yield⁰ / %</th>
<th>E/Z ratio⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)-151a, (Z)-Et</td>
<td>MgBr₂·6H₂O (2 equiv.) / 55 °C</td>
<td>12</td>
<td>89</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>(E)-151a, (E)-Et</td>
<td>MgBr₂·6H₂O (2 equiv.) / 55 °C</td>
<td>12</td>
<td>87</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>92, H</td>
<td>MgBr₂·6H₂O (2 equiv.) / 55 °C</td>
<td>15</td>
<td>80</td>
<td>95:5</td>
</tr>
<tr>
<td></td>
<td>then H₂O (20 equiv.) / 0 °C to r.t.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(Z)-151a, (Z)-Et</td>
<td>TMSX, X = Br (2 equiv.) / -78 °C</td>
<td>1</td>
<td>&gt;98</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>then H₂O (20 equiv.) / 0 °C to r.t.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(E)-151a, (E)-Et</td>
<td>TMSX, X = Br (2 equiv.) / -78 °C</td>
<td>1</td>
<td>&gt;98</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>then H₂O (20 equiv.) / 0 °C to r.t.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>92, H</td>
<td>TMSX, X = Br (2 equiv.) / -78 °C</td>
<td>1</td>
<td>&gt;98</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>then H₂O (20 equiv.) / 0 °C to r.t.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>92, H</td>
<td>TMSX, X = I (2 equiv.) / -78 °C</td>
<td>1</td>
<td>&gt;98</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>then H₂O (20 equiv.) / 0 °C to r.t.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ The reactions were conducted in anhydrous CH₂Cl₂; ⁰ Isolated yield; ⁰ The E/Z ratio was determined by ¹H NMR spectroscopy.

With α-haloenamides in hand, asymmetric Heck reactions were performed with the hope to achieve an asymmetric cyclisation of α-haloenamides (Table 5.4). First, the reaction was run under cationic Heck conditions with Ag₂CO₃ as base to accelerate the rate of oxidative addition (Entry 1). This led to moderate reaction yield but promising enantioselectivity (~20% ee). When the reaction was carried out under Heck conditions without a silver salt additive, it was clear that the reaction rate was sluggish (Entry 2). Once Pd(dba)₂ was used as palladium source, no conversion was detected (Entry 3). Allylpalladiumchloride (APC) dimer with (R)-BINAP gave the best reaction yield (80%), as well as good enantiomeric excess of the product (Entry 5). In addition, when enamides 231c and 231c'...
(monosubstituted olefin) were used as substrate, *endo*-1,3-dieneamide 232 was obtained as minor product. However, when the base was changed from heterogeneous inorganic base ($K_2CO_3$) to homogeneous organic base ($NEt_3$), the reaction was failed to proceed. (Entry 6).

**Table 5.4** Condition optimisation for Heck cyclisation of $\alpha$-haloenynamides.

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, $R^1$, X</th>
<th>Catalyst system (mol%)$^a$</th>
<th>time / h</th>
<th>Yield$^b$ / %</th>
<th>(Z)-153a:152a:232$^c$</th>
<th>ee$^d$ / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)-231a, (Z)-Et, Br</td>
<td>$\text{Pd(OAc)}_2$ (10) / (R)-BINAP (15) / $\text{Ag}_2\text{CO}_3$ (200)</td>
<td>2</td>
<td>63</td>
<td>56:10:34:0</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>231c, H, I</td>
<td>$\text{Pd(OAc)}_2$ (10) / (R)-BINAP (15) / $\text{Ag}_2\text{CO}_3$ (200)</td>
<td>20</td>
<td>60</td>
<td>: : :81:19</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>231c, H, Br</td>
<td>$\text{Pd(dba)}_2$ (10) / (R)-BINAP (15) / $\text{Ag}_2\text{CO}_3$ (200)</td>
<td>20</td>
<td>30</td>
<td>n/a</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>231c, H, Br</td>
<td>$\text{APC}$ (5) / (R)-BINAP (15) / $\text{K}_2\text{CO}_3$ (200)</td>
<td>19</td>
<td>72</td>
<td>: : :80:20</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>(Z)-231a, (Z)-Et, Br</td>
<td>$\text{APC}$ (5) / (R)-BINAP (15) / $\text{K}_2\text{CO}_3$ (200)</td>
<td>18</td>
<td>90</td>
<td>56:12:32:0</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>(Z)-231a, (Z)-Et, Br</td>
<td>$\text{APC}$ (5) / (R)-BINAP (15) / $\text{NEt}_3$ (200)</td>
<td>24</td>
<td>n.r.</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

$^a$ Run in PhMe at 80 °C; $^b$ Isolated yield; $^c$ Determined by $^1$H NMR spectroscopy; $^d$ Enantiomeric excess of (E)-153a, which determined by chiral HPLC; n.r. = no reaction; n/a = not applicable; APC = allyl palladium chloride dimer.
Unfortunately, attempts to unify the formation of $\alpha$-halo enamides and the Heck cyclisation to perform ynamide cyclisation in one step were unsuccessful. The key issue arises from the fact that the formation of $\alpha$-halo enamides from ynamides requires acidic conditions; while the Heck cyclisation must be done under basic conditions, since base is required to regenerate the active palladium(0) catalyst from palladium(II) hydride.

### 5.1.2 Rhodium Catalysis

As discussed in Chapter 4, many research groups have reported conditions for rhodium-catalysed asymmetric enyne cycloisomerisations. In addition to enyne substrates, our group has developed a rhodium catalyst system for a [5+2] cycloisomerisation of vinyl cyclopropane ynamides. In a preliminary examination, a range of Rh-catalysts were screened with enynamide (Z)-151a. We began the investigations with Zhang’s cationic rhodium catalyst system (Table 5.5, Entry 1). Pleasingly, substrate (Z)-151a was cyclised to give product in good yield with very high stereoselectivities. Employing the catalytic conditions reported by Nicolaou et al. (Entry 2), product (E)-153a was exclusively afforded in good yield with 95% ee. In contrast, the catalyst system developed in our group for the [5+2] enynamide cycloisomerisation gave a mixture of products in low yield (28%) after three days (Entry 3). Although Wilkinson’s catalyst has been shown to effect enynamide cycloisomerisation, no conversion was observed with substrate (Z)-151a (Entry 4).
### Table 5.5 Preliminary survey of the rhodium-based catalyst systems for enynamide cycloisomerisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system (mol%)</th>
<th>Time</th>
<th>Yield(^a)/ %</th>
<th>ee(^b)/ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([\text{Rh(cod)}\text{Cl}]_2(5)/ (R)-\text{BINAP}(12)/ \text{AgSbF}_6(10)/ 1,2\text{-DCE}/ \text{r.t.})</td>
<td>75 min</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>([\text{Rh}((R)\text{-BINAP})]<a href="10">\text{SbF}_6</a>/ 1,2\text{-DCE}/ \text{r.t.})</td>
<td>60 min</td>
<td>84</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>([\text{Rh}(\text{C}_2\text{H}_4)\text{Cl}]_2(5)/ (S,R,R)-233(12)/ \text{NaBARf}_4(12)/ \text{r.t. to 40 °C})</td>
<td>3 days</td>
<td>(~28^c)</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Rh(PPh}_3\text{Cl}(10)/ \text{toluene)/ r.t. to 40 °C})</td>
<td>3 h</td>
<td>n.r.</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield; \(^b\) Determined by chiral HPLC; \(^c\) Determined by \(^1\)H NMR spectroscopy (unable to be purified by column chromatography); n/a = not applicable; n.r. = no reaction.

### 5.2 Catalysis System Development

#### 5.2.1 Catalyst System Optimisation

This initial catalyst survey indicated that the Zhang’s and Nicolaou’s conditions are well-suited for enynamide cycloisomerisation. Whilst the specific conditions reported by Nicolaou et al. provided the excellent outcome, we anticipated that tuning of the reaction conditions would be practically difficult to achieve: the catalyst must be prepared freshly each time due to its extreme sensitivity and short life-span. We therefore used Zhang’s catalyst system as a starting point to optimise the cycloisomerisation conditions. We began the optimisation by varying the rhodium source in the reaction (Entries 1–3). No significant differences in reaction yields and stereoselectivities were observed. For the further optimisation, \([\text{Rh(cod)}\text{Cl}]_2\) was then used due to its availability in our lab. Next, we examined the solvent effect on the catalysis. The reaction performed in \(\text{CH}_2\text{Cl}_2\) gave identical results to the reaction running in 1,2-DCE (Entry 4). During the reaction, \(\text{CH}_2\text{Cl}_2\) was inclined to evaporate as the reaction...
proceeded. When the solvent was chloroform (Entry 5), poor reaction conversion was detected leading to low isolated yield, the enantiomeric excess of the product was not therefore determined. No conversion of starting material to product was observed when toluene was used as solvent (Entry 6). Polar solvents, like DMSO (Entry 7), caused a solubility issue of the salts; as a consequence, the substrate remained intact in a reaction mixture.

During the course of our optimisation, we noticed that silver salts also influenced the outcome of the reaction. When the reaction was conducted without AgSbF$_6$ (Entry 8), the reaction did not proceed to give products. This is likely because the phosphine is unable to break apart the dimer into a monomeric rhodium species (will be discussed later). In presence of 5 mol% AgSbF$_6$ (Entry 9), the reaction required 2 h to reach completion, which was significantly slower than the reaction with 10 mol% AgSbF$_6$. In addition, the level of enantiomeric excess was deteriorated to 89%. With 20 mol% of AgSbF$_6$ (Entry 10), reaction proceeded with the similar rate to the reaction with 10 mol% AgSbF$_6$. Interestingly, product 234 was observed (~10% yield) along with major product 153a. Once the reaction was loaded with 50 mol% AgSbF$_6$ (Entry 11), the proportion of 234 increased to 20%, and the rate of reaction was significantly retarded. We then questioned if this unexpected product 234 was derived from the isomerisation of product (E)-153a, whether it was generated from a side pathway. To address this curiosity, the reaction was conducted with the conditions reported in Table 5.6, Entry 1, and allowed to reach completion, then an additional amount of AgSbF$_6$ (10 mol%) was added to the crude reaction mixture, and stirred for another 3 h. The reaction mixture was then examined by $^1$H NMR spectroscopy. Small amount (~10%) of product isomer 234 was detected. This supports our conclusion that compound 234 results from a subsequent isomerisation of 153a in the reaction. However, we cannot yet absolutely confirm that the decrease in enantioselectivity is due to the excess amount of AgSbF$_6$. This is because the silver salt might also interrupt the process of asymmetric induction during catalysis. Further studies are required to prove whether the post-isomerisation of the product results in the deterioration of product’s enantiopurity. Finally, we altered the additive which facilitates the breakdown of the rhodium dimer (Entries 12 and 13). NaBAR$_4$ and AgBF$_4$ failed to drive the reaction forward after 3 h. In the latter case, the reaction mixture turned black, but the starting material could be recovered.
Table 5.6 Optimisation of the Rh-catalysed enynamide cycloisomerisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions (mol%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; / % ee&lt;sup&gt;c&lt;/sup&gt; / %</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / 1,2-DCE</td>
<td>75 min</td>
<td>85 / 95</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / 1,2-DCE</td>
<td>75 min</td>
<td>84 / 94</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(nbd)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / 1,2-DCE</td>
<td>75 min</td>
<td>84 / 95</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>75 min</td>
<td>85 / 95</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; easily evaporated</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2 h</td>
<td>15 / n/a</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / toluene</td>
<td>60 min</td>
<td>n.r. / n/a</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (10) / DMSO</td>
<td>3 h</td>
<td>n.r. / n/a</td>
<td>poor solubility of the salts</td>
</tr>
<tr>
<td>8</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (0) / 1,2-DCE</td>
<td>2 h</td>
<td>n.r. / n/a</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (5) / 1,2-DCE</td>
<td>2 h</td>
<td>80 / 89</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (20) / 1,2-DCE</td>
<td>75 min</td>
<td>77 / 90</td>
<td>product 234 formed, ~10%</td>
</tr>
<tr>
<td>11</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgSbF&lt;sub&gt;6&lt;/sub&gt; (50) / 1,2-DCE</td>
<td>2 h</td>
<td>60 / 90</td>
<td>product 234 formed, ~20%</td>
</tr>
<tr>
<td>12</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / NaBAr&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;4&lt;/sub&gt; (10) / 1,2-DCE</td>
<td>3 h</td>
<td>n.r. / n/a</td>
<td>no precipitation of AgBAr&lt;sub&gt;4&lt;/sub&gt;F&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>13</td>
<td>[Rh(cod)Cl]&lt;sub&gt;2&lt;/sub&gt; (5) / AgBF&lt;sub&gt;4&lt;/sub&gt; (10) / 1,2-DCE</td>
<td>3 h</td>
<td>trace / n/a</td>
<td>reaction turned black after 3 h</td>
</tr>
</tbody>
</table>

<sup>a</sup> With 12 mol% (R)-BINAP at room temperature;  <sup>b</sup> Isolated yield;  <sup>c</sup> Determined by chiral HPLC; n.r. = no reaction; n/a = not applicable.
With these initially optimised conditions in hand (Table 5.7, Entry 1), various chiral ligands were screened to obtain the best enantioselectivity from the reaction. It was found that (R)-tol-BINAP also facilitated an asymmetric cycloisomerisation to give sole product (E)-153a in good yield and ee (Entry 2). However, the reaction took more than 3.5 h to get to obtain full conversion. When the ligand was (R)-SEGPHOS, product (E)-153a was obtained in excellent yield and enantioselectivity within 5 min. Interestingly, a ligand with a similar structure, (R)-SYNPHOS, gave comparable level of enantiomeric excess in the product (Entry 4), but the reaction required longer time to finish (35 min) and the yield is less than the reaction with (R)-SEGPHOS. Moving from chiral binapthyl core to biphenyl core ligands (Entries 5-7), overall reactions were more rapid, with higher yields and enantioselectivities. We found that by far (R)-Cl-OMe-BIPHEP and (R)-OMe-BIPHEP provided the best results. The reaction was also attempted with (S,S)-Me-DuPhos (Entry 8) and (S)-BINAPINE (Entry 9). Unfortunately, no cycloisomerisations were observed; however, starting material could be fully recovered from both conditions. Next, we tried to adjust the temperature of the reaction to see whether even better results could be achieved. Lowering the temperature did not affect the reaction yield and product’s enantiopurity, but the reaction time was slightly prolonged (Entries 10 and 11). In contrast, raising the temperature to 45 °C (Entry 12), the reaction underwent to completion instantaneously, but the enantiomeric excess of the product slightly diminished.
Table 5.7 Ligand and temperature optimisations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand / temperature</th>
<th>Time</th>
<th>Yield(^a) / %</th>
<th>ee(^b) / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP / r.t.</td>
<td>75 min</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>(R)-tol-BINAP / r.t.</td>
<td>&gt; 3.5 h</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>(R)-SEGPHEROS / r.t.</td>
<td>5 min</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>(R)-SYNPHOS / r.t.</td>
<td>35 min</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>(R)-C(_2)-TunePhos / r.t.</td>
<td>15 min</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>(R)-Cl-OMe-BIPHEP / r.t.</td>
<td>&lt;5 min</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>(R)-OMe-BIPHEP / r.t.</td>
<td>&lt;5 min</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>(S,S)-Me-DuPhos / r.t.</td>
<td>10 h</td>
<td>n.r.</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>(S)-BINAPINE / r.t.</td>
<td>10 h</td>
<td>n.r.</td>
<td>n/a</td>
</tr>
<tr>
<td>10</td>
<td>(R)-Cl-OMe-BIPHEP / 0 °C</td>
<td>5 min</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>(R)-Cl-OMe-BIPHEP / -10 °C</td>
<td>10 min</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>(R)-Cl-OMe-BIPHEP / 45 °C</td>
<td>&lt;1 min</td>
<td>97</td>
<td>93</td>
</tr>
</tbody>
</table>

\(^b\) Isolated yield; \(^c\) Determined by chiral HPLC.
5.2.2 The 2\textsuperscript{nd} Generation Catalyst System

The catalyst system used for the optimisation must be prepared and handled under an inert atmosphere such as nitrogen or argon (not as sensitive as Nicolaou’s system). This is due to the fact that the metal centre is exposed to oxidising or nucleophilic species, e.g. oxygen, water, during the preparation of catalyst solution. First, the rhodium dimer \textbf{235} precursor breaks down in presence of AgSbF\textsubscript{6} to give monomeric cationic rhodium species \textbf{236} (Scheme 5.4). This process is rapid and thermodynamically driven by the precipitation of AgCl. Rhodium species \textbf{236} is reactive, as the rhodium centre has two labile coordinating sites, which can allow ligand exchange to take place. In the next step, a chiral diphosphine ligand was introduced to the reaction mixture, followed by hydrogenation to facilitate the decomplexation of cyclooctadiene from the rhodium species. This allows the bidentate phosphine ligand to chelate to the metal centre, giving the rhodium-phosphine complex \textbf{237}. This complex is likely an active catalyst to react with the enynamide substrate.\textsuperscript{84} The reactive cationic rhodium species \textbf{236} and \textbf{237} formed during these steps can readily react with unwanted nucleophilic species, if the reaction environment is not carefully controlled to be free of air and/or moisture.

![Scheme 5.4](image)

To circumvent this procedural issue, we envisaged the preparation of a bench-stable precursor, such as \textbf{239}, for use in these reactions. Various complexes \textbf{239} could be prepared from \textbf{238}, itself commercially available but more conveniently prepared from \textbf{235} by treatment with AgSbF\textsubscript{6} and cyclooctadiene. Rhodium complex \textbf{238} was submitted to a solution of chiral diphosphine ligand in CH\textsubscript{2}Cl\textsubscript{2}. One of the cyclooctadienes is substituted by the phosphine ligand, giving a bench stable rhodium complex \textbf{239}. 

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This perhaps results from the fact that the rhodium centre is bound to both cyclooctadiene and bidentate phosphine, protecting the metal from reacting with external nucleophiles.

![Scheme 5.5](image)

The structure and absolute configuration of complex 239a was determined by single crystal X-ray analysis (Figure 5.1).

![Figure 5.1](image)

With this new pre-catalyst in hand, we set up experiments to compare the performance of this new rhodium complex with the typical catalyst systems (Table 5.8). Gratifyingly, the new pre-catalyst showed that the reactivity and degree of asymmetric induction were comparable to Zhang’s and Nicolaou’s type systems (Entries 1–3). In addition, we discovered that the catalyst loading could be decreased to 5 mol% with respect to rhodium, and still maintained reactivity and selectivity (Entry 4). However, when we pushed the system further to 2.5 mol% catalyst loading, a clear drop in reaction rate

---

1 The X-ray data were collected and processed by Steven J. Mansfield.
was observed as well as the level of enantiomeric excess (Entry 5). This could either result from the fact that the active catalyst is more vulnerable to air and/or moisture as its amount in the reaction mixture decreases, or the catalyst degradation is more pronounced at smaller scale.

**Table 5.8** Comparison between the new catalyst system and conventional systems.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system (mol%)</th>
<th>Time</th>
<th>Yield(^a) / %</th>
<th>ee(^b) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(((R))-Cl-OMe-BIPHEP)(cod)]SbF(_6) (10) then H(_2) (balloon) for 10 min, followed by N(_2) (balloon) for 10 min / 1,2-DCE / r.t.</td>
<td>&lt;5 min</td>
<td>&gt;99</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)Cl(_2)] (5) / (((R))-Cl-OMe-BIPHEP) (12) / AgSbF(_6) (10) / 1,2-DCE / r.t.</td>
<td>&lt;5 min</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>[Rh((((R))-Cl-OMe-BIPHEP))SbF(_6) (10) / 1,2-DCE / r.t.</td>
<td>5 min</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>[Rh((((R))-Cl-OMe-BIPHEP)(cod)]SbF(_6) (5) then H(_2) (balloon) for 10 min, followed by N(_2) (balloon) for 10 min / 1,2-DCE / r.t.</td>
<td>7 min</td>
<td>&gt;99</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>[Rh((((R))-Cl-OMe-BIPHEP)(cod)]SbF(_6) (2.5) then H(_2) (balloon) for 10 min, followed by N(_2) (balloon) for 10 min / 1,2-DCE / r.t.</td>
<td>25 min</td>
<td>96</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield; \(^b\) Determined by chiral HPLC.

Since this new pre-catalyst requires hydrogenation to activate itself, one could argue that the active catalyst is perhaps in the form of rhodium hydride complex, instead of the cationic rhodium species. To prove this is not the case, hydrogenation of rhodium complex 239a was conducted and characterised by \(^{31}\)P\{\(^1\)H\} NMR spectroscopy. It was found that no rhodium hydride species was formed in detectable amounts after hydrogenation (Figure 5.2). Instead, the signals of a rhodium dimer 240 were detected (two signals of double of doublets at 40.9 and 45.2 ppm).
In addition, Imamoto et al. have conducted in-depth studies on the mechanism of asymmetric hydrogenation with rhodium complex 241 as pre-catalyst (Scheme 5.6).\textsuperscript{85} They discovered that even though rhodium hydride species 243a and 243b are in equilibrium with a solvate rhodium complex 242 under a hydrogen atmosphere, to form a fair amount of such hydride species very low temperature (–90 °C) was required (sometimes high pressure of hydrogen is also needed) to facilitate oxidative addition of dihydrogen (H\(_2\)). Imamoto et al. also suggested that bubbling Ar or N\(_2\) through the reaction mixture after hydrogenation could prevent the formation of rhodium hydrides 243. This agrees with Le Chatelier’s principle – removal of H\(_2\) shifts the equilibrium towards 242.
Furthermore, Heller et al. showed that hydrogenation of rhodium-BINAP-diolefin complex 244 at −20 °C or room temperature could facilitate the formation of a solvate cationic rhodium complex 245 and its dimeric form 246, depending on the solvent used in the reaction (Scheme 5.7); and no sign of rhodium hydride species was observed.86

\[
\begin{align*}
\text{Scheme 5.6} \\
\text{[Rh(BINAP)(solvent)]}_2\text{BF}_4 \xrightarrow{e.g. \text{THF at} -20^\circ\text{C}} & \text{Rh(BINAP)(diolefin)BF}_4 + \text{H}_2 \\
\end{align*}
\]

Scheme 5.7

Overall, the experimental evidence we have collected, alongside the observations reported in the literatures, support the involvement of a cationic rhodium species, possibly 247 or 248 (Scheme 5.8), to catalyse the asymmetric enynamide cycloisomerisation. First, the pre-catalyst 239 was activated by hydrogenation leading to an equilibrium between a solvate species 247 and a rhodium dimer 248; the ratio between these two species is depending on solvent. If the solvent is capable of binding to the rhodium centre (e.g. THF), intermediate 247 is produced preferably. If the solvent is a non-coordinating solvent (e.g. CH\textsubscript{2}Cl\textsubscript{2} or 1,2-DCE), rhodium species 248 is majorly formed. Once the substrate (e.g. (Z)-151\textsubscript{a}) was introduced to the reaction mixture, ligand exchange can take place at the rhodium centre, as a result, intermediate 249 is formed. This species can undergo oxidative addition to generate rhodacycle 250, which proceeds via β-hydride elimination to give rhodium hydride 251. The product (E)-153\textsubscript{a} is formed by reductive elimination of species 251, and the active catalyst 247 is regenerated.
5.3 Scope of the Asymmetric Rhodium-Catalysed Cycloisomerisation

5.3.1 Substrate Synthesis

A range of enynamides were prepared in order to examine the substrate scope and limitations of the rhodium catalyst system. The substrates were classified into three categories: disubstituted alkenyl ynamides, trisubstituted alkenyl ynamides, and cycloalkenyl ynamides.

Disubstituted Alkenyl Ynamides
By analogy to the formation of ynamide (Z)-151a from alcohol 224 (Scheme 5.1), a range of ynamides 151b-d were prepared (Scheme 5.9).

\[ \text{Scheme 5.9} \]

Ynamides (Z)-151e were prepared from alcohol 252 in seven steps (Scheme 5.10). After TBS protection, alkyne lithiation and electrophilic trapping with benzyl bromide afforded alkyne 254 in moderate yield. Subsequent Lindlar hydrogenation afforded (Z)-255 in quantitative yield. Upon TBS deprotection and Mitsunobu reaction with HNTsCO₂Me, sulfonamide (Z)-257 was isolated in 67% yield. Decarboxylation with K₂CO₃/MeOH afforded the desired sulfonamide, which was coupled with bromoalkynes 98 to give ynamides (Z)-151e and f.
Trisubstituted Alkenyl Ynamides

For ynamides with a methyl group at position 4, (E)-264a and b (Scheme 5.11), commercially available alkynyl alcohol 252 was reacted with trimethylaluminum and Cp₂ZrCl₂, followed by addition of a solution of I₂ in anhydrous THF. The alcohol unit in the resulting vinyl iodide (E)-259 was protected using TBSCI under basic conditions. (E)-260 was coupled with propylmagnesium bromide by Pd-catalysed Kumada reaction to afford alcohol (E)-261 in 75% yield. The same protocol to covert an alcohol to ynamides was used (Mitsunobu reaction with HNTsCO₂Me, carbamate deprotection, and Hsung ynamide formation), ynamides (E)-264a and b were obtained.
For the preparation of isomeric ynamide (Z)-264a and b (Scheme 5.12), an equivalent synthesis was followed which differed only in the initial step. Reaction of alcohol 252 with trimethylaluminum and Cp₂ZrCl₂ at reflux for 3 days afforded (Z)-259 because of the thermal chelation-controlled isomerisation of the methylalumination product. A solution of I₂ in THF was subsequently added to the reaction mixture to afford vinyl iodide (Z)-259.

Ynamides (E)-269a and b which processes a methyl group at the position 5 were also prepared (Scheme 5.13). First commercially available dihydrofuran 265 was reacted with t-BuLi and 1-iodobutane at −50 °C in anhydrous THF. The functionalised dihydrofuran underwent Kumada cross-coupling with
MeMgBr to give alcohol \((E)-266\).

This alcohol was subjected to the aforementioned series of reactions to afford ynamides \((E)-269a\) and \(b\).

\[ \text{Scheme 5.13} \]

The \((Z)\)-isomers of enyneamides \(269a\) and \(b\) were prepared from commercially available alcohol \(270\). First the alcohol was reacted with trimethylaluminum and titanium(IV) chloride to afford trisubstituted \((E)\)-alkenyl alcohol \((Z)-266\). The same synthetic steps were then followed to convert alcohol \((Z)-266\) to the corresponding ynamides.

\[ \text{Scheme 5.14} \]
Cycloalkenyl Ynamides

Cycloalkenyl ynamides 275 were prepared from commercially available carboxylic acid 271 (Scheme 5.15). Reduction of such an acid with LiAlH₄ gave alcohol 272. Once again, the alcohol was processed using aforementioned procedures to furnish enynamides 275a and b.

Di and trisubstituted Alkenyl Ynamides

Disubstituted alkenyl ynamides 151a-f were submitted to the cycloisomerisation conditions with the hope to produce heterocyclic dienamides (E)-153a-f (Table 5.9). In general, the reactions with (Z)-alkenyl ynamides reached completion within 45 minutes, with the products isolated in good yield and enantioselectivity at room temperature and 5 mol% catalyst loading (Entries 1–4 and 7–8). It was found that variation of the alkynyl substituent did not affect the enantioselectivity of the cycloisomerisation (Entries 1–4), while a slight drop in yield was observed when the group was electron withdrawing. Substrates possessing an (E)-alkene were not converted into product (Entries 5 and 6). Once the group attached to the olefin was benzyl instead of alkyl, the reaction still proceeded with a lower rate of reaction, which could be the effect of steric hindrance caused by the benzyl group (Entries 7 and 8).
However, the yield and enantiopurity remained in good levels. It is worth noting that all reactions produced a single product, a 1,4-dienamide with \((E)\)-geometry at the non-enamide olefin.

**Table 5.10** Cycloisomerisation of disubstituted alkenyl ynamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, Geometry, (R^1, R^2)</th>
<th>Time</th>
<th>Yield(^a)/%</th>
<th>ee(^b)/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((Z)-151a, Z, n)-Hex, Me</td>
<td>5 min</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>((Z)-151b, Z, Ph, Me)</td>
<td>10 min</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>((Z)-151c, Z, p-FC_6H_4, Me)</td>
<td>30 min</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>((Z)-151d, Z, p-O\text{MeC}_6H_4, Me)</td>
<td>5 min</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>5(^c)</td>
<td>((E)-151a, E, n)-Hex, Me</td>
<td>3 h</td>
<td>n.r.(^d)</td>
<td>n/a</td>
</tr>
<tr>
<td>6(^c)</td>
<td>((E)-151b, E, Ph, Me)</td>
<td>3 h</td>
<td>n.r.(^d)</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>((Z)-151e, Z, n)-Hex, Ph</td>
<td>30 min</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>((Z)-151f, Z, Ph, Ph)</td>
<td>45 min</td>
<td>83</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield; \(^b\) Determined by chiral HPLC; \(^c\) The temperature was raised to 40 °C after 1 h; \(^d\) Starting material was fully recovered; n.r. = no reaction; n/a = not applicable.

The structures of the products were confirmed by the analysis of coupling constants of the alkene signals \((J = 15.4 \text{ Hz})\) as well as NOESY experiments, which in all cases showed the relative \(exo\) position of the substituents (Scheme 5.16).
Next, the catalyst system was tested with trisubstituted alkenyl ynamides 264 and 269 (Table 5.11). Similar results were obtained, only substrates with a (Z)-alkene unit underwent cyclisation to give products as (E)-1,4-dienamides (E)-276 (Entries 1–2 and 5–6). The yields and enantiomeric excess are at satisfactory levels. In addition, we were pleased to see that enynamides (Z)-264a and b could also be cycloisomerised to give products (E)-269a and b with a quaternary centre in high degrees of enantioselectivity and moderate yields (Entries 1 and 2). However, when substrates (E)-264 and (E)-269 were submitted to the cycloisomerisation conditions, no reaction progress was observed even at higher temperature; the starting material was fully recovered (Entries 3–4 and 7–8).

**Table 5.11** Cycloisomerisation of trisubstituted alkenyl ynamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, R¹, R², R³, R⁴</th>
<th>Time</th>
<th>Yield² / %</th>
<th>ee³ / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)-264a, n-Hex, n-Pr, H, Me</td>
<td>80 min</td>
<td>61</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>(Z)-264b, Ph, n-Pr, H, Me</td>
<td>105 min</td>
<td>52</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>(E)-264a, n-Hex, H, n-Pr, Me</td>
<td>9 h</td>
<td>n.r. ᵃ</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>(E)-264b, Ph, H, n-Pr, Me</td>
<td>13 h</td>
<td>n.r. ᵃ</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>(Z)-269a, n-Hex, n-Bu, Me, H</td>
<td>45 min</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>(Z)-269b, Ph, n-Bu, Me, H</td>
<td>55 min</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>(E)-269a, n-Hex, Me, n-Bu, H</td>
<td>10 h</td>
<td>n.r. ᵃ</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>(E)-269b, Ph, Me, n-Bu, H</td>
<td>13 h</td>
<td>n.r. ᵃ</td>
<td>n/a</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield; ᵃ Determined by chiral HPLC; ³ The temperature was raised to 40 °C after 3 h; ᵃ Starting material was fully recovered; n.r. = no reaction; n/a = not applicable.
Cycloalkenyl Ynamides

Since we had observed a successful cycloisomerisation of substrates (Z)-264a and b to furnish products (E)-269a and b with a quaternary carbon centre, we questioned if cyclohexenyl ynamides 275 could be cyclised to give spiro compounds 277. Disappointingly, when the reactions were performed with such substrates (Scheme 5.16), it turned out that an unknown compound was obtained. Despite many NMR techniques (1H, 13C, COSY, HSQC, HMBC, DEPTs) were used to characterise the product, we could not define the structure of the products.

Scheme 5.16

5.4 Conclusions

We have successfully prepared a bench stable rhodium pre-catalyst for enynamide cycloisomerisation. As a result, the procedure for performing the cycloisomerisation is much simplified, compared to previous work. Using NMR spectroscopic experiments, our experimental evidence agrees with previous studies and implies that a rhodium hydride species is unlikely to be the active catalyst in our reaction; instead, a solvate cationic rhodium complex 247 or a dimeric complex 248 is formed. The improved catalyst system showed excellent reactivity and enantiomeric excess. We discovered that this catalysis worked well with enynamides with (Z)-geometry olefin, but (E)-alkenyl substrates were found to be inactive. Ynamides containing a cycloalkenyl group afforded either a complex mixture of products or an unidentified by-product.
Chapter 6: Conclusions and Future Work

6.1 Conclusions

Using various NMR spectroscopic techniques together with deuterium labelling, we have uncovered the crucial influences of water, the pre-catalyst, and the ligand (bbeda) in this reaction. Our demonstration that bbeda itself serves as a source of palladium(II) hydride, combined with the computational studies of the reaction pathway correlated with experimental isotope effect, offers a new level of understanding of this classic cyclisation process and allows us to rationalise the substrate stereocontrol under this palladium-catalysed conditions. This work was published in the *Journal of the American Chemical Society* (see Appendix).
In addition to the mechanistic investigations, we also introduced a more robust rhodium-based catalyst system for enynamide cycloisomerisations. Despite, in comparison with the traditional catalyst systems, this new pre-catalyst provides better results, the substrate scope of this catalysis is still limited to enynamides in which the olefin unit is in Z-geometry. Unfortunately, we are still unable to make the catalyst system work with ynamides containing E-alkene or cycloalkenyl group. With some preliminary NMR spectroscopic experiments, we are convinced that the cycloisomerisation proceeds via mediation of a cationic rhodium active catalyst 237. This active species is supposedly derived from hydrogenation of pre-catalyst 239, which subsequently generates either a solvate monomeric rhodium complex 247 or a dimeric rhodium intermediate 248 (Scheme 6.1). We suggest that rhodium hydride species are unlikely to be formed during the hydrogenation, as the complexes could not be detected by $^{31}$P NMR spectroscopy, which is in accordance with precedent literatures.$^{93, 94}$

![Scheme 6.1]
6.2 Future Work: Double Stereodifferentiation in Enynamide Cycloisomerisation

In collaboration with Niels Marien, a visiting PhD student in the Anderson group, the synthesis of a variety of chiral enynamides to be used in examining the double stereodifferentiation of the cycloisomerisation reaction is currently underway (Scheme 6.2)

Scheme 6.2

One type of such enantioenriched enynamides is α-branched enynamides 278, which can be synthesised from the following plan (Scheme 6.3). The route begins with sequential ring-opening of enantiopure epichlorohydrin 282 by a lithiated alkyne, followed by a Grignard reagent to afford chiral secondary alcohol 284. This alkyne is partially hydrogenated with Lindlar catalyst to give Z-alkene 285. The resulting alcohol will then undergo a Mitsunobu reaction with HNTsCO₂Me, generating 286. The carbamate group is subsequently deprotected using a mixture of K₂CO₃ in methanol to reveal sulfonamide 287 which can be converted into the desired enynamide 278 using our ynamide synthesis methodology.
Another class of chiral enynamides is β-branched enynamides 280. To furnish such substrates (Scheme 6.4), the plan is to start with an asymmetric proline-catalysed aldol cyclisation between formaldehyde and aldehyde 289. The hemiacetal product 290 can then undergo Wittig olefination to deliver an enantioenriched alcohol 291. This alcohol is subsequently reacted with HNTsCO₂Me under Mitsunobu conditions to afford carbamate 292. Carbamate deprotection and subsequent Hsung’s ynamide formation will afford β-branched enynamides 280.
With such chiral substrates in hand, we aim to use these single enantiomer enynamides under our rhodium catalyst conditions to investigate the impacts of the chiral catalyst system and the inherent stereochemical control of the substrate in matched and mismatched reactions. The term ‘matched’ implies that the stereocontrols of the catalyst and chiral starting material are reinforcing. On the other hand, ‘mismatched’ refers the case where the stereoinductions of the catalyst and substrate are antagonistic.

### 6.3 Future Work: Kinetic Resolution in Enynamide Cycloisomerisation

Instead of using single enantiomer substrates, this time racemic enynamides will be selected as substrate. These starting materials can be synthesised from racemic epichlorohydrin in the same fashion as the single enantiomer enynamides. Given the strength of the intrinsic substrate stereochemical induction, and thereby the difference between the reaction rate of the matched and mismatched reactions, we can evaluate the feasibility of kinetic resolution in the cycloisomerisation (Scheme 6.5).

**Scheme 6.5**

Another scenario is if each enantiomer of the starting enynamides can undergo cycloisomerisation to deliver a different diastereomeric form of enantioenriched product; we can then examine the diastereodivergence of the cycloisomerisation (Scheme 6.6).

**Scheme 6.6**
Chapter 7: Experimental

7.1 General Experimental

NMR Spectra: $^1$H and $^{13}$C NMR spectra were recorded on Bruker AVII500 (500/125 MHz) or Bruker AV400 (400/100 MHz) spectrometers using TOPSPIN software. Proton and carbon chemical shifts ($\delta_H$, $\delta_C$) are quoted in ppm and referenced to tetramethylsilane with residual protonated solvent as the internal standard. Resonances are described using the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet), br (broad), app (apparent), dd (doublet of doublets) etc. Coupling constants ($J$) are given in Hz and are rounded to the nearest 0.1 Hz. H' and H'' refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry.

Mass Spectra: High resolution mass spectra were recorded by the Mass Spectrometry service of the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (ESI). $m/z$ values are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula, all found values being within a tolerance of 5 ppm.

Infrared Spectra: Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer, equipped with a diamond ATR module. Absorption maxima ($\nu_{\text{max}}$) are quoted in wavenumbers (cm$^{-1}$).

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

Chromatography techniques: TLC was performed on Merck DC-Alufolien 60 F$_{254}$ 0.2 mm pre-coated plates and visualised using basic potassium permanganate, acidic vanillin or ultraviolet light. Retention factors are reported with the solvent system in parentheses. Column chromatography was performed on Merck Keiselgel 60 SiO$_2$ (230-400 mesh) and the solvent system used is recorded in parentheses. Solvents were either used as commercially supplied, or purified by passage through an alumina column solvent dispensing system. Unless otherwise stated, reactions were carried out in oven-dried flasks under an atmosphere of dry argon or nitrogen.
All deuterated solvents for the NMR experiments were dried using the procedure reported by Williams et al.\textsuperscript{42} The water contents in the solvents were determined using Karl-Fischer titration on a 756 KF Coulometer.

7.2 General Experimental Procedures

**Procedure 1: Bromination of primary alkynes using AgNO\textsubscript{3}**

According to the procedure of Anderson et al.\textsuperscript{20} To a suspension of alkyne (1.0 equiv.) in acetone (1 mL/mmol) was added AgNO\textsubscript{3} (2.5 mol%). The reaction mixture was stirred for 5 min and NBS (1.1 equiv.) added. The reaction mixture was stirred at room temperature for 15 h, filtered through a pad of silica (petroleum ether) and concentrated \textit{in vacuo}.

**Procedure 2: Conversion of an alcohol to a sulfonamide**

According to the procedure of Anderson et al.\textsuperscript{20} To a solution of alcohol (1.0 equiv.), triphenylphosphine (2.0 equiv.) and \textit{tert}-butyl tosylcarbamate (1.3 equiv.) in THF (4 mL/mmol of alcohol) at 0 °C was added dropwise DIAD (1.5 equiv.). The reaction mixture was stirred at room temperature overnight, filtered and then concentrated \textit{in vacuo}. The residue was then taken up in Et\textsubscript{2}O:petroleum ether (5 mL:5 mL/mmol of alcohol), sonicated for 5 min and filtered. The filtrate was concentrated \textit{in vacuo} to approximately 15 mL/mmol of alcohol at which point the resulting precipitation was removed by filtration before being concentrated \textit{in vacuo} to dryness.

**Procedure 3: Boc-deprotection using TFA**

To a solution of carbamate (1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (3 mL/mmol of carbamate) was added dropwise TFA (10.0 equiv.). The reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C, quenched with sat. aq. Na\textsubscript{2}CO\textsubscript{3} (3 mL/mmol of carbamate) and transferred to a separating funnel. The organic layer was separated and the aqueous layer extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 2 mL/mmol of carbamate). The combined organic layers were dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}.

**Procedure 4: Boc-deprotection using K\textsubscript{2}CO\textsubscript{3} and MeOH**

To a solution of carbamate (1.0 equiv.) in MeOH (8 mL/mmol carbamate) was added K\textsubscript{2}CO\textsubscript{3} (5.0 equiv.). The reaction mixture was stirred under reflux for 5 h, allowed to cool to room temperature and concentrated \textit{in vacuo} to approx. 5 mL. The mixture was then added to H\textsubscript{2}O (10 mL/mmol carbamate)
and extracted with CH₂Cl₂ (3 × 10 mL/mmol carbamate). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo.

**Procedure 5: Copper(II)-catalyzed ynamide formation**

According to the procedure of Hsung *et al.*,⁴¹ To a mixture of sulfonamide (1.0 equiv.), K₂PO₄ (2.0 equiv.), CuSO₄·5H₂O (0.2 equiv.) and 1,10-phenanthroline (0.4 equiv.) was added a solution of bromoalkyne (1.5 equiv.) in toluene (2 mL/mmol of sulfonamide). The reaction mixture was stirred at 70 °C for 15 h before being allowed to cool to room temperature. The reaction mixture was filtered through Celite® eluting with Et₂O, and the filtrate concentrated in vacuo.

**Procedure 6: Palladium-catalyzed cycloisomerization of alkenyl-ynamides / enynes**

According to the procedure of Anderson *et al.*²⁰ To a solution of ynamide / enyne (1.0 equiv.) in dry toluene (6.5 mL/mmol of ynamide) was added N,N'-bis(benzylidene)ethylenediamine (bbeda, 0.1 equiv.) and Pd(OAc)₂ (0.1 equiv.). The reaction mixture was stirred at the stated temperature (typically room temperature to 60 °C) for the stated time and concentrated in vacuo.

**Procedure 7: Hydrohaloginition of alkenyl-ynamides**

**Method 1** According to the procedure of Hsung *et al.*⁷⁷ To a solution of enynamide (1 equiv.) in wet CH₂Cl₂ (10 mL/mmol enynamide) was added MgX₂·6H₂O (X = Br or I, 1.1 equiv.). The reaction mixture was capped in a glass vial and vigorously stirred at 55 °C for 12 h. The reaction was monitored by TLC analysis. The heterogeneous mixture was washed with (2 × 10 mL/mmol enynamide) with sat. aq. Na₂S₂O₃ solution, dried over MgSO₄, and then dried in vacuo. The crude product was in general very pure and could be used without further purification.

**Method 2** According to the procedure of Iwasawa *et al.*⁷⁶ To a solution of enynamide (1 equiv.) in anhydrous toluene (5 mL/mmol enynamide) at −78 °C was dropwise added 1 M of TMSX (X = Br or I) in dry toluene (1 equiv.) over 5 min. After 15 min stirring, H₂O (20 equiv.) was added, followed by warming to 0 °C over 50 min. The reaction mixture was then stirred for another 10 min. The reaction was quenched with sat. aq. Na₂S₂O₃ solution, dried over MgSO₄, and then dried in vacuo. The crude product was in general very pure and could be used without further purification.
**Procedure 8: Varying water contents in deuterated solvents**

To pre-dried deuterated solvent1 in a flame-dried glass vial sealed with a rubber septum was added the appropriate quantity of H$_2$O or D$_2$O via syringe. The vial was agitated to ensure mixing of the two liquid phases. The solution was then sampled to measure the water content using Karl-Fisher titration on a 756 KF Coulometer. Water content is reported as a mean value of triplicate measurements.

**Procedure 9: NMR timecourse experiments**

**Spectrometer set-up:** To an NMR tube was added a solution of ynamide (0.067 mmol, 1.0 equiv.) and 1,2,4,5-tetrachloronitrobenzene (internal standard) in deuterated solvent (0.4 mL, 0.167 M). This 'dummy' sample was placed in the NMR spectrometer, with a probe temperature of 308 K, for the purposes of pre-optimizing the lock and shim of the reaction sample.

**Timecourse experiment:** To an NMR tube containing ynamide (0.067 mmol, 1.0 equiv.), bbeda (0.0034 mmol, 0.05 equiv.) and 1,2,4,5-tetrachloronitrobenzene (internal standard), was added a solution of palladium catalyst in d$_8$-toluene (0.05 equiv., 0.1 mL), and the total volume adjusted to 0.4 mL (0.167 M). The reaction mixture was briefly mixed on a vortex agitator, then rapidly placed in the NMR machine (at 308K). Timecourse experiment spectra were collected at 34 s intervals (DS = 0, NS = 1, d1 = 20 s (at this relaxation time, the protons in the substrate and product had been independently confirmed to relax fully); 6 s of delay time was added before the initiation of the next acquisition to allow for automated spectrometer processes. This equates to 34 seconds between each acquisition. All experiments were run in triplicate.

The spectra were automatically phased, baseline corrected, and integrated (cross-checked against the internal standard peak) using the TOPSPIN multi_integ3 command. The integration values were plotted using Microsoft Excel as a percentage of the total starting material originally present (proportional to concentration).

**Procedure 10: NMR titration experiments**

**Pd$_3$(OAc)$_5$OH vs bbeda:** To an NMR tube was added a solution of Pd$_3$(OAc)$_5$OH (0.067 mmol, 1.0 equiv.) in pre-dried deuterated solvent (0.4 mL, 0.167 M). The mixture was briefly mixed on a vortex agitator, then placed in the NMR machine (at 308 K). An NMR spectrum of Pd$_3$(OAc)$_5$OH was recorded (with default parameter settings: DS = 2, NS = 16, d1 = 2 s). After the spectrum had been obtained, the
Chapter 7: Experimental

tube was removed from the NMR machine, then bbeda (0.25 equiv.) was added to the tube. The reaction mixture was vigorously agitated, and subsequently resubmitted to the NMR machine to record another spectrum (with identical parameter settings). The titration was repeated until 2.0 equivalents of bbeda were added. The spectra were automatically phased, baseline corrected, and integrated using TOPSPIN software.

\( \text{Pd}_3(\text{OAc})_6 \text{ vs bbeda:} \) To an NMR tube was added a solution of \( \text{Pd}_3(\text{OAc})_5\text{OH} \) (0.067 mmol, 1.0 equiv.) in pre-dried deuterated solvent (0.4 mL, 0.167 M). The mixture was briefly mixed on a vortex agitator, then placed in the NMR machine (at 308 K). An NMR spectrum of \( \text{Pd}_3(\text{OAc})_5\text{OH} \) was recorded (with default parameter settings: \( DS = 2, NS = 16, d1 = 2 \text{ s} \)). After the spectrum had been obtained, the tube was removed from the NMR machine, then bbeda (0.5 equiv.) was added to the tube. The reaction mixture was vigorously agitated, and subsequently resubmitted to the NMR machine to record another spectrum (with identical parameter settings). The titration was repeated until 1.5 equivalents of bbeda were added. The spectra were automatically phased, baseline corrected, and integrated using TOPSPIN software.

**Procedure 11: Asymmetric rhodium-catalysed cycloisomerisation of enynamide**

In a dried glass vial with a rubber septum cap, \([\text{Rh}((R)-\text{Cl}-\text{OMe-BIPHEP})(\text{cod})\text{SbF}_6\) (5 mol\% [Rh]) was dissolved in freshly distilled 1,2-dichloroethane (0.3 mL); the solution was hydrogenated with a hydrogen balloon for 10 min, followed by 5–10 min nitrogen sparging. A solution of substrate (0.03 mmol) in dry 1,2-dichloroethane (0.2 mL) was then introduced into the solution. The resulting mixture was stirred at room temperature. Upon the completion of the reaction indicated by TLC, the reaction mixture was concentrated in vacuo, then directly subjected to column chromatography.
Chapter 7: Experimental

7.3 Characterisation of Compounds

7.3.1 Synthesis of cycloisomerisation substrates

1-Bromooct-1-yne, 98a

Synthesised from oct-1-yne (15.0 mL, 102 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (petroleum ether) to give 98a as a colourless oil (18.4 g, 97.5 mmol, 96%); \( R_f = 0.83 \) (1:1, petroleum ether:EtOAc); \( \delta_H (400 \text{ MHz, CDCl}_3) \) 2.19 (2H, t, \( J = 7.2 \text{ Hz, H3} \)), 1.50 (2H, ap. quin., \( J = 7.2 \text{ Hz, H4} \)), 1.43–1.20 (6H, m, H5–7), 0.89 (3H, t, \( J = 6.9 \text{ Hz, CH}_3 \)); \( \delta_C (100 \text{ MHz, CDCl}_3) \) 80.4, 37.4, 31.3, 28.5, 28.3, 22.5, 19.6, 14.0. Data are consistent with literature values.\(^{100}\)

Methyl 3-((4-methylphenyl)sulfonamido)propanoate, 94

\[ \text{\begin{tikzpicture}
\node (n1) at (0,0) {\text{O}};
\node (n2) at (-1,0) {\text{S}};
\node (n3) at (-2,0) {\text{N}};
\node (n4) at (-3,0) {\text{O}};
\draw (n1) -- (n2) -- (n3) -- (n4);
\end{tikzpicture}} \]

\( \beta \)-alanine methyl ester hydrochloride salt (500 mg, 3.58 mmol, 1.0 equiv.) was stirred in NEt\(_3\) (0.55 mL, 3.94 mmol, 1.1 equiv.) for 1 h under a nitrogen atmosphere. To this solution was added CH\(_2\)Cl\(_2\) (20 mL), pyridine (0.35 mL, 4.30 mmol, 1.2 equiv.) and TsCl (751 mg, 3.94 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature (monitored by TLC). Following completion, the excess solvent was removed \textit{in vacuo}; the resulting crude material was then purified by column chromatography (20%–60% EtOAc / petroleum ether) to afford 94 (681 mg, 2.65 mmol, 74%) as a white solid; \( R_f 0.45 \) (3:2 petroleum ether / EtOAc); \( \delta_H (500 \text{ MHz, CDCl}_3) \) 7.75 (2H, d, \( J = 8.2 \text{ Hz, TS} H \)), 7.32 (2H, d, \( J = 8.2 \text{ Hz, TS} H \)), 5.09 (1H, t, \( J = 6.4 \text{ Hz, NH} \)), 3.67 (3H, s, CH\(_3\)), 3.19 (2H, dt, \( J = 6.4 \text{ and } 5.9 \text{ Hz, CH}_2 \)), 2.54 (2H, t, \( J = 5.9 \text{ Hz, H2} \)), 2.43 (3H, s, CH\(_3\)Ts); \( \delta_C (125 \text{ MHz, CDCl}_3) \) 172.7, 143.7, 137.2, 130.0, 127.2, 52.2, 38.9, 34.0, 21.7. Data are consistent with literature values.\(^{101}\)
Chapter 7: Experimental

N-(3-Hydroxypropyl-3,3-d2)-4-methylbenzenesulfonamide, d2-95

Methyl ester 94 (271 mg, 1.05 mmol, 1.0 equiv.) was dissolved in dry THF (1 mL) under an argon atmosphere, then cooled to –78 °C. This solution was transferred via cannula to a pre-cooled (–78 °C) suspension of LiAlD4 (89 mg, 2.10 mmol, 2.0 equiv.) in dry THF (3 mL). The reaction mixture was stirred for 2 h at –78 °C under argon, then allowed to warm to –40 °C, and then quenched with sodium potassium tartrate (15 mL, sat., aq.). The resulting precipitate was removed by filtration. The filtrate was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO4, filtered, concentrated in vacuo, and purified by column chromatography (30%→60% EtOAc / petroleum ether) to afford d2-95 (238 mg, 1.03 mmol, 98%) as a white solid; m.p. 52–54 °C; Rf 0.18 (3:2 petroleum ether / EtOAc); δH (500 MHz, CDCl3) 7.75 (2H, d, J = 8.3 Hz, TsH), 7.31 (2H, d, J = 8.3 Hz, TsH), 5.00 (1H, t, J = 5.9 Hz, NH), 3.10 (2H, app q, J = 6.2 Hz, H3), 2.43 (3H, s, TsCH3), 1.85–1.53 (1H, br s, OH), 1.69 (2H, t, J = 6.2 Hz, H2); δc (125 MHz, CDCl3) 143.6, 137.0, 130.0, 127.2, 60.7 (quin., J = 21.8 Hz ), 41.2, 31.4, 21.7; IR (thin film) νmax/cm⁻¹ 3497, 3278, 1322, 1158; HRMS m/z (ESI+) found [M+H]+ 232.09718; C10H14D2NO3S+ requires 232.0976.

4-Methyl-N-(3-oxopropyl-3-d)benzenesulfonamide, d1-96

N-(3-hydroxypropyl-3,3-d2)-4-methylbenzenesulfonamide d2-95 (166 mg, 0.72 mmol, 1.0 equiv.) was dissolved in CH2Cl2 (3.6 mL) under an argon atmosphere, then cooled to 0 °C. To the cooled solution was added Dess-Martin periodinane (458 mg, 1.08 mmol, 1.5 equiv.). The reaction mixture was then stirred for 16 h at room temperature, and subsequently filtered through a layer of silica, eluted with EtOAc (3 × 10 mL). The filtrate was concentrated in vacuo. This crude product was used in the next step without purification due to its instability towards storage. Rf 0.31 (3:2 petroleum ether / EtOAc).
Chapter 7: Experimental

**N-(But-3-en-1-yl-3-d)-4-methylbenzenesulfonamide, d\textsubscript{1}-97**

![Chemical structure](image)

According to the procedure of Stone et al.\textsuperscript{102} To a stirred suspension of methyltriphenylphosphonium bromide (247 mg, 0.69 mmol, 1.1 equiv.) in dry THF (2.4 mL), was added t-BuOK (1M in THF, 0.64 mL, 0.64 mmol, 1.1 equiv.). The reaction mixture was stirred for 1 h at room temperature, then cooled to 0 °C. To the cooled solution was added a solution of 4-methyl-N-(3-oxopropyl-3-d)benzenesulfonamide \textsubscript{d1}-96 (140 mg, 0.61 mmol, 1.0 equiv.) in THF (6.9 mL). The reaction mixture was then stirred for 1 h at room temperature, and subsequently quenched with NH\textsubscript{4}Cl (10 mL, sat., aq.). The aqueous phase was extracted with Et\textsubscript{2}O (3 × 10 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, concentrated \textit{in vacuo}, and purified by column chromatography (10→20% EtOAc / petroleum ether) to give \textsubscript{d1}-97 (133 mg, 0.59 mmol, 96%, >98% deuterium incorporation by \textsuperscript{1}H NMR spectroscopy) as a pale yellow oil; \textit{Rf} 0.61 (3:2 petroleum ether / EtOAc); \textit{\delta} \textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.74 (2H, d, \textit{J} = 8.4 Hz, Ts\textsubscript{H}), 7.31 (2H, d, \textit{J} = 8.4 Hz, Ts\textsubscript{H}), 5.05 (1H, m, H\textsubscript{'}), 5.01 (1H, m, H\textquoteright\textsubscript{'}), 4.65 (1H, br s, NH), 3.00 (2H, app q, \textit{J} = 6.6Hz, H4), 2.42 (3H, s, \textit{CH}_3\textsubscript{Ar}), 2.19 (2H, t, \textit{J} = 6.6 Hz, H3); \textit{\delta} \textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 143.6, 137.0, 134.0 (t, \textit{J} = 23.5 Hz), 129.9, 127.2, 118.1, 42.2, 33.6, 21.7; \textbf{IR} (thin film) \textit{\nu}_{max}/\text{cm}^{-1} 2928, 1642, 1354, 1164; \textbf{HRMS} \textit{m/z} (ESI+) found [M+H]\textsuperscript{+} 227.09610; \textit{C}_{11}\textit{H}_{15}\textit{DNO}_{2}\textit{S} requires 227.0965.

**N-(But-3-en-1-yl-3-d)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, d\textsubscript{1}-92**

![Chemical structure](image)

Synthesised from \textit{N}(but-3-en-1-yl-3-d)-4-methylbenzenesulfonamide \textsubscript{d1}-97 (>98% deuterium incorporation by \textsuperscript{1}H NMR spectroscopy) (300 mg, 1.33 mmol) and 1-bromooct-1-yne (301 mg, 1.59 mmol) using \textbf{Procedure 5}. The resulting crude material was purified by column chromatography (petroleum ether→10% Et\textsubscript{2}O in petroleum ether) to afford \textsubscript{d1}-92 (138 mg, 0.36 mmol, 83%, >98%
deuterium incorporation by $^1$H NMR spectroscopy) as a colourless oil; $R_f$ 0.69 (4:1 petroleum ether / EtOAc); δ$_H$ (400 MHz, CDCl$_3$) 7.77 (2H, d, $J = 8.2$ Hz, Ts$H$), 7.32 (2H, d, $J = 8.2$ Hz, Ts$H$), 5.06 (1H, br s, H'), 5.03 (1H, br s, H''), 3.32 (2H, t, $J = 7.3$ Hz, H$_4$), 2.44 (3H, s, CH$_3$Ar), 2.36 (2H, t, $J = 7.3$ Hz, H3), 2.25 (2H, t, $J = 7.0$ Hz, H8), 1.45 (2H, quin, $J = 7.1$ Hz, H9), 1.38–1.24 (6H, m, H10–12), 0.88 (3H, t, $J = 6.8$ Hz, H13); δ$_C$ (100 MHz, CDCl$_3$) 144.2, 134.7, 133.6 (t, $J = 23.5$ Hz), 129.6, 127.6, 117.3, 72.9, 70.6, 50.8, 32.0, 31.3, 28.9, 28.4, 22.6, 21.6, 18.5, 14.0; IR (thin film) ν$_{max}$/cm$^{-1}$ 2930, 2254, 1364, 1168; HRMS m/z (ESI+) found [M+Na]$^+ 357.1709$; C$_{19}$H$_{26}$DNNaO$_2$S$^+$ requires 357.1717.

tert-Butyl 4-nitrophenylsulfonylcarbamate, S1

To a suspension of 4-nitrobenzenesulfonamide (10.0 g, 49.5 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (30 mL) was added triethylamine (7.6 mL, 54.4 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (302 mg, 2.5 mmol, 0.05 equiv.). A solution of di-tert-butyl-dicarbonate (12.5 mL, 54.4 mmol, 1.1 equiv.) in CH$_2$Cl$_2$ (50 mL) was added. The reaction mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. EtOAc (100 mL) and 1M aq. HCl (80 mL) were added and the mixture separated. The organic extract was washed with H$_2$O (60 mL) and brine (600 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Trituration with hot n-hexane (50 mL) gave S1 as a colourless solid (13.91 g, 46.0 mmol, 93%); m.p. 117–122 °C; $R_f = 0.22$ (4:1, petroleum ether:EtOAc); δ$_H$ (500 MHz, CDCl$_3$) 8.42–8.37 (2H, m, Ns$H$), 8.26–8.22 (2H, m, Ns$H$), 7.63 (1H, br. s, NH), 1.40 (9H, s, C(CH$_3$)$_3$); δ$_C$ (125 MHz, CDCl$_3$) 150.7, 148.6, 144.2, 129.7, 124.1, 85.1, 27.8. Data are consistent with literature values.$^{20}$
**Chapter 7: Experimental**

**tert-Butyl but-3-enyl(4-nitrophenylsulfonyl)carbamate. 100**

![Chemical Structure Image]

To a solution of 3-buten-1-ol 99 (1.79 mL, 20.8 mmol, 1.0 equiv.), triphenylphosphine (8.18 g, 31.2, 1.5 equiv.) and S1 (7.55 g, 24.9 mmol, 1.2 equiv.) in THF (80 mL) at 0 °C was added dropwise DIAD (5.32 mL, 27.0 mmol, 1.3 equiv.). The reaction mixture was stirred at room temperature overnight, filtered and then concentrated in vacuo. The residue was then taken up in Et<sub>2</sub>O:petroleum ether (50 mL:50 mL), sonicated for 5 min and filtered. The filtrate was concentrated in vacuo to approximately 15 mL/mmol of alcohol at which point the resulting precipitate was removed by filtration before being concentrated in vacuo to dryness. The resulting crude material was purified by column chromatography (5%→10% t-BuOMe in Hexanes) to give 100 as a brown solid (7.00 g, 19.6 mmol, 94%); m.p. 117–122 °C; R<sub>f</sub> = 0.69 (4:1, Hexanes:EtOAc); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.38–8.33 (2H, m, Ns<sub>H</sub>), 8.15–8.09 (2H, m, Ns<sub>H</sub>), 5.80 (1H, ddt, J = 17.1, 10.2, 7.0 Hz, H'), 5.18–5.07 (2H, m, H'), 3.95–3.87 (H1), 2.51 (2H, ap. br. q, J = 6.6 Hz, H2); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 150.4, 150.3, 145.8, 133.9, 129.3, 123.9, 117.9, 85.2, 46.7, 34.6, 27.9; IR (thin film) ν<sub>max</sub>/cm<sup>-1</sup> 2980, 1732, 1533, 1351, 1151; HRMS m/z (ESI+) found [M+Na]<sup>+</sup> 379.0932; C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>NaO<sub>6</sub>S<sup>+</sup> requires 379.0934.

*N-(But-3-en-1-yl)-4-nitrobenzenesulfonamide, 101*

![Chemical Structure Image]

Synthesised from tert-butyl but-3-enyl(4-nitrophenylsulfonyl)carbamate 100 (6.00 g, 16.8 mmol) using Procedure 4 to give the title compound as an off-white solid (3.10 g, 12.1 mmol, 72%) which was used without further purification; m.p. 74–76 °C; R<sub>f</sub> = 0.20 (4:1, hexanes:EtOAc); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.36 (2H, m, Ns<sub>H</sub>), 8.05 (2H, m, Ns<sub>H</sub>), 5.62 (1H, ddt, J = 17.1, 10.3 and 6.9 Hz, H3), 5.12–5.02 (2H, m, H' and H''), 4.81 (1H, br. t, J = 5.8 Hz, NH), 3.10 (2H, ap. q, J = 6.6 Hz, H1), 2.28–2.20 (2H, m, H2); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 150.1, 145.9, 133.6, 128.3, 124.4, 118.6, 42.2, 33.7; IR (thin film) ν<sub>max</sub>/cm<sup>-1</sup>
Chapter 7: Experimental

1 3292, 3105, 1732, 1527, 1349; HRMS m/z (ESI+) found [M+Na]+ 279.0414; C_{10}H_{12}N_{2}NaO_{4}S requires 279.0410.

\[ \text{N-(But-3-en-1-yl)-4-nitro-N-(oct-1-yn-1-yl)benzenesulfonamide, 93} \]

Synthesised from 101 (384 mg, 1.50 mmol) and 1-bromooc107ty-1-yne 98a (424 mg, 2.24 mmol) using Procedure 5, only the reaction mixture was heated to 105 °C for 24 h. The resulting crude material was purified by column chromatography (10% EtO in in petroleum ether) to give 93 as a yellow oil (412 mg, 1.13 mmol, 75%); Rf = 0.76 (4:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 8.42–8.36 (2H, m, NsH), 8.11–8.05 (2H, m, NsH), 5.70 (1H, ddt, J = 17.1, 10.3, 6.8 Hz, H3), 5.09 (1H, ap. dq, J = 17.1 and 1.5 Hz, H′), 5.05 (1H, ddt, J = 10.3, 1.5, 1.1 Hz, H‴), 3.40 (2H, t, J = 7.2 Hz, H1), 2.45–2.34 (2H, m, H2), 2.27 (2H, t, J = 7.0 Hz, H7), 1.54–1.43 (2H, m, H8), 1.40–1.21 (6H, m, H9–11), 0.89 (3H, t, J = 7.4 Hz, CH3); δC (125 MHz, CDCl3) 150.4, 143.0, 133.3, 128.8, 124.2, 118.0, 71.7, 71.6, 51.2, 32.1, 31.3, 28.8, 28.5, 22.6, 18.4, 14.0; IR (thin film) νmax/cm⁻¹ 3105, 2930, 2859, 2255, 1607, 1531, 1402, 1372, 1174, 854, 738, 684; HRMS m/z (ESI+) found [M+Na]+ 387.1336; C_{18}H_{20}N_{2}NaO_{4}S requires 387.1349.

**tert-Butyl but-3-en-1-yl(tosyl)carbamate, 104**

Synthesised from but-3-en-1-ol 99 (4.00 g, 55.5 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (9:1, petroleum ether:EtO) to give 104 as a colourless oil (17.28 g, 53.1 mmol, 96%); Rf = 0.51 (4:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.78 (2H, d, J = 8.2 Hz, TsH), 7.29 (2H, d, J = 8.2 Hz, TsH), 5.80 (1H, ddt, J = 17.2, 10.2, 6.9 Hz, H3), 5.12 (1H, dd, J = 17.2 and 1.5 Hz, H′), 5.07 (1H, d, J = 10.2 Hz, H‴), 3.88 (2H, dd, J = 8.1 and 6.8 Hz, H1), 2.55–
2.46 (2H, m, H2), 2.43 (3H, s, ArCH3), 1.33 (9H, s, C(CH3)3); δc (100 MHz, CDCl3) 150.9, 144.0, 137.4, 134.4, 129.2, 127.8, 117.4, 84.1, 46.3, 34.5, 27.8, 21.6. Data are consistent with literature values.103

*N-(But-3-en-1-yl)-4-methylbenzenesulfonamide 105*

![N-(But-3-en-1-yl)-4-methylbenzenesulfonamide 105](image)

Synthesised from 104 (16.83 g, 51.7 mmol) using Procedure 3 to give 105 as a colourless oil (11.6 g, 51.6 mmol, 99%) which was used without further purification; Rf = 0.33 (4:1, petroleum ether:EtOAc); δh (400 MHz, CDCl3) 7.74 (2H, d, J = 8.2 Hz, TsH), 7.29 (2H, d, J = 8.2 Hz, TsH), 5.61 (1H, ddt, J = 17.0, 10.3, 6.8 Hz, H3), 5.05–4.97 (2H, m, H′ and H″), 4.84 (1H, br. t, J = 6.1 Hz, NH), 2.99 (2H, ap. q, J = 6.8 Hz, H1), 2.41 (3H, s, ArCH3), 2.18 (2H, ap. q, J = 6.8 Hz, H2); δc (100 MHz, CDCl3) 143.3, 136.8, 134.1, 129.6, 127.0, 117.9, 42.1, 33.5, 21.4. Data are consistent with literature values.104

*N-(But-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide 92*

![N-(But-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide 92](image)

Synthesised from 105 (5.00 g, 22.2 mmol) and 1-bromooct-1-yn 98a (5.04 g, 26.6 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10:1, petroleum ether:Et2O) to give 92 as a colourless oil (7.08 g, 21.2 mmol, 96%); Rf = 0.51 (4:1, petroleum ether:EtOAc); δh (400 MHz, CDCl3) 7.77 (2H, d, J = 8.2 Hz, TsH), 7.32 (2H, d, J = 8.2 Hz, TsH), 5.72 (1H, ddt, J = 17.2, 10.3, 6.7 Hz, H3), 5.07 (1H, dd, J = 17.2 and 1.5 Hz, H′), 5.03 (1H, dd, J = 10.3 and 1.5 Hz, H″), 3.32 (2H, t, J = 7.5 Hz,H1), 2.44 (3H, s, ArCH3), 2.36 (2H, ap. q, J = 7.2 Hz, H2), 2.26 (2H, t, J = 6.9 Hz, H7), 1.51–1.42 (2H, m, H8), 1.39–1.19 (6H, m, H9–11), 0.88 (3H, t, J = 6.8 Hz, CH3); δc (100 MHz, CDCl3) 144.2, 134.6, 133.9, 129.5, 127.6, 117.4, 72.8, 70.5, 50.8, 32.1, 31.3, 28.9, 28.4, 22.6, 21.6, 18.4, 14.0; IR (thin film) νmax/cm−1 2930, 2253, 1364, 1170; HRMS m/z (ESI+) found [M+Na]+ 356.1654; C19H27NNaO2S+ requires 356.1655.
4-Nitro-N-(3-oxopropyl)benzenesulfonamide, 96

To a solution of methyl ester 104 (250 mg, 0.97 mmol, 1.0 equiv.) in dry THF (5 mL) under an argon atmosphere at −78 °C was added DIBAL (1.9 mL, 1 M in Hexanes, 1.9 mmol, 2.0 equiv.) dropwise. The reaction mixture was stirred at −78 °C for 5 h, quenched with sat. aq. Rochelle Salt (10 mL) and diluted with EtOAc (15 mL). The reaction mixture was left to room temperature and stirred for 1 h. The layers were separated, and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo, and purified by column chromatography (5→10% EtOAc / petroleum ether) to afford 96 as a pale yellow oil (143 mg, 0.63 mmol, 65%); R₇ = 0.51 (5:1, petroleum ether:EtOAc); δH (500 MHz, CDCl₃) 9.73 (1H, s), 7.74 (2H, d, J = 8.3 Hz, TsH), 7.32 (2H, d, J = 8.2 Hz, TsH), 5.25 (1H, t, J = 6.2 Hz, NH), 3.21 (2H, q, J = 6.1 Hz, H3), 2.75 (2H, t, J = 5.9 Hz, H2), 2.43 (3H, s, ArCH₃); δc (125 MHz, CDCl₃) 200.9, 143.6, 136.5, 129.7, 126.9, 43.4, 36.7, 21.5; IR (thin film) νmax/cm⁻¹ 3282, 2850, 1720, 1600, 1400, 1320, 1305, 1153, 1090, 1045, 840, 811, 705, 661; HRMS m/z (ESI+) found [M+H]+ 228.0690; C₁₀H₁₄NO₃S+ requires 228.0689.

N-(But-3-en-1-yl-4,4-d₂)-4-methylbenzenesulfonamide, d₂-110

To a stirred suspension of d₂-methyltriphenylphosphonium bromide d₂-109 (250 mg, 0.70 mmol, 1.1 equiv.) in dry THF (2.5 mL), was added t-BuOK (1M in THF, 0.70 mL, 0.70 mmol, 1.1 equiv.). The reaction mixture was stirred for 1 h at room temperature, then cooled to 0 °C. To the cooled solution was added a solution of 4-nitro-N-(3-oxopropyl)benzenesulfonamide 96 (148 mg, 0.65 mmol, 1.0 equiv.) in THF (7 mL). The reaction mixture was then stirred for 1 h at room temperature, and subsequently quenched with NH₄Cl (10 mL, sat., aq.). The aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated in vacuo, and purified by column chromatography (10→20% EtOAc / petroleum ether) to give d₂-110 (135 mg, 0.60 mmol, 92%, >98% deuterium incorporation by ¹H NMR spectroscopy) as a pale yellow oil; R₇ 0.61 (3:2
petroleum ether / EtOAc; δH (400 MHz, CDCl3) 7.74 (2H, d, J = 8.4 Hz, TsH), 7.31 (2H, d, J = 8.4 Hz, TsH), 5.62 (1H, t, J = 6.8 Hz, H1), 4.84 (1H, br. t, J = 6.1 Hz, NH), 2.99 (2H, ap. q, J = 6.8 Hz, H3), 2.41 (3H, s, ArCH3), 2.18 (2H, ap. q, J = 6.8 Hz, H2); δc (100 MHz, CDCl3) 143.3, 136.8, 134.1, 129.6, 127.0, 117.9 (m), 42.1, 33.5, 21.4.; IR (thin film) νmax/cm⁻¹ 2935, 1650 1350, 1162; HRMS m/z (ESI+) found [M+H]+ 228.1030; C₁₁H₁₄D₂NO₂S+ requires 228.1027.

N-(But-3-en-1-yl-4,4-d₃)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, d₃-108

Synthesised from d₃-110 (102 mg, 0.45 mmol) and 1-bromooct-1-yne 98a (129 mg, 0.68 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10:1, petroleum ether:EtO) to give d₃-108 as a colourless oil (137 mg, 0.41 mmol, 91%, >98% deuterium incorporation by ¹H NMR spectroscopy); Rf = 0.51 (4:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.77 (2H, d, J = 8.2 Hz, TsH), 7.32 (2H, d, J = 8.2 Hz, TsH), 5.72 (1H, t, J = 6.7 Hz, H3), 3.32 (2H, t, J = 7.5 Hz, H1), 2.44 (3H, s, ArCH3), 2.36 (2H, ap. q, J = 7.2 Hz, H2), 2.26 (2H, t, J = 6.9 Hz, H7), 1.51–1.42 (2H, m, H8), 1.39–1.19 (6H, m, H9–11), 0.88 (3H, t, J = 6.8 Hz, CH₃); δc (100 MHz, CDCl3) 144.2, 134.6, 133.9, 129.5, 127.6, 117.4 (m), 72.8, 70.5, 50.8, 32.1, 31.3, 28.9, 28.4, 22.6, 21.6, 18.4, 14.0; IR (thin film) νmax/cm⁻¹ 2933, 2253, 1365, 1173; HRMS m/z (ESI+) found [M+H]+ 336.1968; C₁₉H₂₆D₂NO₂S+ requires 336.1966.

Methyl-d₃ 3-((4-methylphenyl)sulfonamido)propanoate-2,2-d₃, d₅-112

To a solution of methyl 3-((4-methylphenyl)sulfonamido)propanoate 104 (100 mg, 0.389 mmol, 1.0 equiv.) in d₅-MeOD (1.0 mL) was added K₂CO₃ (177 mg, 1.28 mmol, 3.3 equiv.). The reaction mixture was stirred at room temperature for 15 h, CH₂Cl₂ (5 mL) and sat. aq. NH₄Cl (5 mL) added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (5 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to give d₅-112 (91% deuterium
incorporation by $^1$H NMR at C2) as a colourless oil (73 mg, 0.38 mmol, 71%) which was used without further purification; $R_f = 0.34$ (1:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.73 (2H, d, $J = 8.2$ Hz, TsH), 7.30 (2H, d, $J = 8.2$ Hz, TsH), 3.16 (2H, s, H1), 2.41 (3H, s, ArC$_3$H$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 172.4, 143.5, 136.8, 129.7, 127.0, (CD$_2$O absent), 38.5, (CD$_2$CO absent), 21.5; IR (thin film) $\nu_{max}$/cm$^{-1}$ 3288, 2926, 1732, 1330, 1155; HRMS $m/z$ (ESI+) found [M+Na]$^+$ 285.0929; C$_{11}$H$_{10}$D$_5$NNaO$_4$S$^+$ requires 285.0928.

**N-(But-3-en-1-yl-2,2-d$_2$)-4-methylbenzenesulfonamide, d$_2$-113**

![Structure of compound](structure.png)

To a solution of d$_5$-112 (91% deuterium incorporation by $^1$H NMR) (227 mg, 0.87 mmol, 1.0 equiv.) in toluene (7 mL) at $-78 \degree$C was added DIBAL (1.73 mL, 1 M in Hexanes, 1.73 mmol, 2.0 equiv.) dropwise. The reaction mixture was stirred at $-78 \degree$C for 5 h, quenched with sat. aq. Rochelle Salt (10 mL) and diluted with EtOAc (15 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The layers were separated and the aqueous layer extracted with EtOAc (15 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was taken up in THF (5.0 mL), added to solution of Cp$_2$TiCH$_2$AlCl(CH$_3$)$_2$ (566 mg 1.99 mmol, 2.3 equiv.) in toluene (2.0 mL) at 0 °C and stirred at room temperature for 15 h. 2 M aq NaOH (0.8 mL), excess MgSO$_4$ and Et$_2$O (20 mL) were added, the mixture stirred at room temperature for 1 h, filtered through Celite® eluting with Et$_2$O and concentrated in vacuo. The resulting crude material was purified by column chromatography (30% Et$_2$O in petroleum ether) to give d$_2$-113 (91% deuterium incorporation by $^1$H NMR) as a colourless oil (38 mg, 0.167 mmol, 19%); $R_f = 0.26$ (4:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.74 (2H, d, $J = 8.3$ Hz, TsH), 7.30 (2H, d, $J = 8.3$ Hz, TsH), 5.61 (1H, dd, $J = 16.9$ and 10.3 Hz, H3), 5.10–4.98 (2H, m, H' and H''), 4.70–4.54 (1H, br. m, NH), 2.99 (2H, d, $J = 6.1$ Hz, H1), 2.42 (3H, s, ArCH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 143.4, 136.9, 134.0, 129.7, 127.1, 118.1, 41.9, (CD$_2$ absent), 21.5; IR (thin film) $\nu_{max}$/cm$^{-1}$ 3280, 2925, 1322, 1155; HRMS $m/z$ (ESI+) found [M+Na]$^+$ 250.0847; C$_{11}$H$_{13}$D$_2$NNaO$_2$S$^+$ requires 250.0841.
N-(But-3-en-1-yl-2,2-d$_2$)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, d$_2$-111

Synthesised from d$_2$-113 (91% deuterium incorporation by $^1$H NMR) (35 mg, 0.154 mmol) and 1-bromooct-1-yne 98a (38 mg, 0.200 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (5% Et$_2$O in petroleum ether) to give d$_2$-111 (91% deuterium incorporation by $^1$H NMR) as a colourless oil (43.5 mg, 0.130 mmol, 84%); $R_y = 0.55$ (4:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.77 (2H, d, $J = 8.2$ Hz, TsH), 7.32 (2H, d, $J = 8.2$ Hz, TsH), 5.71 (1H, dd, $J = 17.1$ and 10.2 Hz, H3), 5.07 (1H, dd, $J = 17.1$ and 1.8 Hz, H'), 5.03 (1H, dd, $J = 10.2$ and 1.8 Hz, H''), 3.30 (2H, s, H1), 2.44 (3H, s, ArC$_3$H), 2.25 (2H, t, $J = 7.0$ Hz, H7), 1.53–1.41 (2H, m, H8), 1.39–1.19 (6H, m, H9–11), 0.88 (3H, t, $J = 7.0$ Hz, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 144.2, 134.6, 133.7, 129.5, 127.6, 117.5, 72.8, 70.5, 50.6, (CD$_2$ absent), 31.3, 28.9, 28.4, 22.6, 21.6, 18.4, 14.0; IR (thin film) $\nu_{max}$/cm$^{-1}$ 2930, 2250, 1363, 1169; HRMS m/z (ESI+) found [M+Na]$^+$ 358.1781; C$_{19}$H$_{25}$D$_2$NNaO$_2$S$^+$ requires 358.1780.

Dimethyl 2-allyl-2-(5-((tert-butyldimethylsilyl)oxy)pent-2-yn-1-yl)malonate, 120

To a suspension of NaH (182 mg, 60% in mineral oil, 7.58 mmol, 1.9 equiv.) in anhydrous THF (8 mL) at 0 °C under a nitrogen atmosphere was added a solution of dimethyl 2-allylmalonate (686 mg, 3.98 mmol, 1.0 equiv.) in THF (8 mL) dropwise. The mixture was stirred for 30 min at 0 °C, then a solution of ((5-bromopent-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane (1.05 g, 3.98 mmol, 1.0 equiv.) in THF (16 mL) was added. The mixture was allowed to warm to room temperature, and was stirred for 16 h. The reaction was quenched with H$_2$O (30 mL), and extracted with Et$_2$O (3 × 15 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography (0→5% EtOAc in petroleum ether) to afford 120 (1.25 g, 3.38 mmol, 85%) as
a colourless oil; $R_f$ 0.29 (20:1 petroleum ether / EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 5.67–5.57 (1H, m, H2), 5.17–5.08 (2H, m, H1), 3.71 (6H, s, 2×CO$_2$CH$_3$), 3.65 (2H, t, $J = 7.2$ Hz, H9), 2.78–2.74 (4 H, m, H3 and H5), 2.35–2.30 (2H, tt, $J = 2.3$ and 7.2 Hz, H8), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.05 (6H, s, 2×SiCH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 170.6, 132.2, 119.8, 80.7, 75.6, 57.4, 52.8, 36.8, 26.0, 23.3, 23.2, 18.5, –5.1; IR (thin film) $\nu_{max}$/cm$^{-1}$ 2940, 1738, 1437, 1290, 1100; HRMS m/z (ESI+) found [M+H]$^+$ 369.2097; C$_{19}$H$_{33}$O$_5$Si$^+$ requires 369.2092.

1-Phenylhept-3-yn-1-ol, 136

![Chemical structure](image)

To a solution of 1-pentyne (0.41 mL, 4.16 mmol, 1.25 equiv.) in dry THF (5.0 mL) at −78 °C was added dropwise $n$–BuLi (1.6 mL, 2.5 M in hexanes, 4.00 mmol, 1.2 equiv.). The reaction mixture was allowed to warm to room temperature and dry DMSO (20 mL) was added over 5 min, followed by a solution of styrene oxide 135 (0.38 mL, 3.33 mmol, 1.0 equiv.) in dry THF (1.0 mL) dropwise. The reaction mixture was stirred at room temperature for 3 h, poured into H$_2$O (15 mL) and extracted with Et$_2$O (4 × 15 mL). The combined organic layers were washed with brine (3 × 40 mL), dried filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (10→15% EtOAc in petroleum ether) to give 136 as a pale yellow oil (154 mg, 1.03 mmol, 32%); $R_f$ = 0.34 (4:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.40–7.23 (5H, m, PhH), 4.84–4.75 (1H, br. m, H1), 2.67–2.48 (3H, m, H2 and OH), 2.18–2.09 (2H, m, H5), 1.50 (2H, ap. sext, $J = 7.3$ Hz, H6), 0.94 (3H, t, $J = 7.3$ Hz, CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 142.8, 128.3, 127.7, 125.7, 83.3, 76.1, 72.6, 30.0, 22.3, 20.7, 13.4; IR (thin film) $\nu_{max}$/cm$^{-1}$ 3377, 2962; HRMS m/z (ESI+) found [M+Na]$^+$ 211.1090; C$_{13}$H$_{16}$NaO$^+$ requires 211.1093.
**Chapter 7: Experimental**

**tert-Butyl (1-phenylhept-3-yn-1-yl)(tosyl)carbamate, 137**

![Chemical Structure](image)

Synthesised from 1-phenylhept-3-yn-1-ol 136 (150 mg, 0.80 mmol) using Procedure 3. The resulting crude material was purified by column chromatography (dry loaded, 5%→10% Et₂O in petroleum ether) to give 137 as a colourless oil (253 mg, 0.57 mmol, 72%); R<sub>f</sub> = 0.40 (4:1, petroleum ether:EtOAc); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.83 (2H, d, J = 8.2 Hz, TsH), 7.60 (2H, d, J = 7.6 Hz, PhH), 7.35–7.30 (2H, m, m PhH), 7.29–7.24 (3H, TsH and PhH), 5.78 (1H, ap. t, J = 7.9 Hz, H1), 3.25 (1H, dtt, J = 8.6, 8.1, 2.3 Hz, H2'), 3.13 (1H, dtt, J = 8.6, 7.6, 2.3 Hz, H2''), 2.43 (3H, s, ArCH₃), 2.02 (2H, ap. tq, J = 7.1 and 2.3 Hz, H5), 1.47–1.37 (2H, m, H6), 1.24 (9H, s, C(CH₃)₃), 0.90 (3H, t, J = 7.3 Hz, CH₃); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 150.6, 143.9, 139.3, 137.3, 129.0, 128.6, 128.2, 127.4, 127.2, 84.2, 83.4, 76.6, 59.9, 27.8, 23.6, 22.2, 21.6, 20.8, 13.5; IR (thin film) <i>ν</i><sub>max</sub>/cm<sup>⁻¹</sup> 2965, 1729, 1358, 1151; HRMS <i>m/z</i> (ESI+) found [M+Na]<sup>+</sup> 464.1856; C₂₅H₃₁NNaO₄S<sup>+</sup> requires 464.1866.

**(Z)-tert-Butyl (1-phenylhept-3-en-1-yl)(tosyl)carbamate, 138**

![Chemical Structure](image)

To a solution of tert-butyl (1-phenylhept-3-yn-1-yl)(tosyl)carbamate 137 (235 mg, 0.53 mmol, 1.0 equiv.) and quinolone (12 µL, 0.11 mmol, 0.2 equiv.) in toluene (5.0 mL) was added Pd on CaCO₃ (57 mg, 5 wt% Pd, 0.027 mmol, 0.05 equiv.). H<sub>2</sub> (balloon, 1 atm) was bubbled through the stirred reaction mixture at room temperature for 1 h. The reaction mixture was stirred for an additional 1 h, filtered through Celite<sup>®</sup> eluting with Et₂O the filtrate concentrated in vacuo. The resulting crude material was purified by column chromatography (15%→20% Et₂O in petroleum ether) to give 138 as a colourless oil (225 mg, 0.51 mmol, 96%); R<sub>f</sub> = 0.47 (4:1, petroleum ether:EtOAc); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.74
(Z)-4-Methyl-N-(1-phenylept-3-en-1-yl)benzenesulfonylamide, 139

Synthesised from (Z)-tert-butyl (1-phenylept-3-en-1-yl)(tosyl)carbamate 138 (205 mg, 0.47 mmol) using Procedure 3, only with the reaction mixture stirred, to give 139 as a colourless oil (155 mg, 0.45 mmol, 96%) which was used without further purification; Rf = 0.31 (4:1, petroleum ether:EtOAc); δH (500 MHz, CDCl3) 7.57 (2H, d, J = 8.2 Hz, TsH), 7.20–7.11 (5H, m, TsH, PhH), 7.11–7.05 (2H, m, PhH), 5.47–5.39 (1H, m, H4), 5.15–5.04 (2H, m, H3, NH), 4.31 (1H, ap. q, J = 6.9 Hz, H1), 2.54–2.46 (1H, m, H2'), 2.46–2.38 (1H, m, H2''), 2.36 (3H, s, ArCH3), 1.94–1.80 (2H, m, H5), 1.33–1.20 (2H, m, H6), 0.83 (3H, t, J = 7.4 Hz, CH3); δc (125 MHz, CDCl3) 143.0, 140.5, 137.4, 133.9, 129.3, 128.3, 127.3, 127.1, 126.6, 123.6, 57.7, 35.3, 29.3, 22.5, 21.4, 13.7; IR (thin film) νmax/cm⁻¹ 3275, 2959, 2914, 1606, 1593, 1478, 1380, 1159; HRMS m/z (ESI+) found [M+Na]+ 366.1487; C20H25NNaO2S+ requires 366.1498.
(Z)-4-Methyl-N-(oct-1-yn-1-yl)-N-(1-phenylhept-3-en-1-yl)benzenesulfonamide, 125

![Chemical Structure](image)

Synthesised from (Z)-4-methyl-N-(1-phenylhept-3-en-1-yl)benzenesulfonamide 139 (105 mg, 0.31 mmol) and 1-bromo-oct-1-yné 98a (87 mg, 0.46 mmol) using Procedure 5, only the reaction mixture was heated to 105 °C for 48 h. The resulting crude material was purified by column chromatography (5%→30% Et₂O in petroleum ether) to give 125 as a colourless oil (72 mg, 0.16 mmol, 52%); \( R_f = 0.63 \) (4:1, petroleum ether:EtoAc); \( \delta_H \) (500 MHz, CDCl₃) 7.53 (2H, d, \( J = 8.2 \) Hz, TsH), 7.30–7.24 (2H, m, PhH), 7.23–7.16 (3H, m, PhH), 7.12 (2H, d, \( J = 8.2 \) Hz, m TsH), 5.40–5.31 (1H, m, H₄), 5.23–5.14 (1H, m, H₃), 4.89 (1H, dd, \( J = 8.5 \) and 7.3 Hz, H1), 2.75–2.66 (1H, m, H₂'), 2.62–2.53 (1H, m, H₂''), 2.36 (3H, s, ArC₃H₃), 2.31 (2H, t, \( J = 6.9 \) Hz, H10), 2.00–1.87 (2H, m, H₅), 1.49 (2H, ap. quin., \( J = 7.3 \) Hz, H11), 1.38–1.20 (8H, m, H₆, and H12–14), 0.88 (3H, t, \( J = 6.9 \) Hz, H15), 0.86 (3H, t, \( J = 7.4 \) Hz, H7); \( \delta_C \) (125 MHz, CDCl₃) 143.7, 139.3, 135.5, 132.7, 129.0, 128.2, 127.8, 127.7, 127.2, 124.6, 73.0, 70.9, 62.9, 31.8, 31.4, 29.5, 28.9, 28.5, 22.6, 21.5, 18.7, 14.1, 13.8; IR (thin film) \( \nu_{max}/\text{cm}^{-1} \) 2929, 2250, 1363, 1168; HRMS \( m/z \) (ESI+) found [M-H]+ 451.2549; C₂₈H₄₇NNaO₂S⁺ requires 451.2545.

(Z)-4-Methyl-N-(oct-1-yn-1-yl)-N-(1-phenyloct-5-en-2-yl)benzenesulfonamide, 127

![Chemical Structure](image)

To a mixture of (Z)-4-methyl-N-(1-phenyloct-5-en-2-yl)benzenesulfonamide [kindly provided by Dr Ross P Walker] (500 mg, 1.40 mmol, 1.0 equiv.), K₂CO₃ (425 mg, 3.07 mmol, 2.2 equiv.), CuSO₄·5H₂O (140 mg, 0.56 mmol, 0.4 equiv.) and 1,10 phenanthroline (202 mg, 1.12 mmol, 0.8 equiv.) was added a solution of 1-bromo-oct-1-yné 98a (529 mg, 2.80 mmol, 2.0 equiv.), in toluene (4.2 mL). The reaction mixture was stirred at 105 °C for 48 h before being allowed to cool to room temperature. The reaction
mixture was filtered through Celite® eluting with Et₂O and the filtrate concentrated in vacuo. The resulting crude material was purified by column chromatography (5%→10% Et₂O in petroleum ether) to give 127 as a pale yellow oil (452 mg, 0.99 mmol, 71%); R_f = 0.55 (9:1, petroleum ether:EtOAc); δ_H (400 MHz, CDCl₃) 7.51 (2H, d, J = 8.3 Hz, Ts_H), 7.24–7.13 (5H, m, ArH), 7.14–7.07 (2H, m, ArH), 5.39–5.30 (1H, m, H5), 5.28–5.19 (1H, m, H4), 4.12 (1H, dddd, J = 9.5, 7.8, 6.9, 4.5 Hz, H1), 2.75 (1H, dd, J = 13.4 and 7.8 Hz, CH'H''Ph), 2.69 (1H, dd, J = 13.4 and 6.9 Hz, CH'H''Ph), 2.39 (3H, s, ArCH₃), 2.34 (2H, t, J = 6.8 Hz, H10), 2.11–2.00 (1H, m, H3'), 1.96 (2H, ap. quin., J = 7.5 Hz, H6), 1.91–1.80 (1H, m, H3''), 1.70–1.58 (1H, m, H2''), 1.56–1.45 (3H, m, H2'' and H11), 1.42–1.23 (6H, m, H12–14), 0.91 (3H, t, J = 7.5 Hz, H7), 0.90 (3H, t, J = 6.8 Hz, H15); δ_C (100 MHz, CDCl₃) 143.6, 138.0, 135.8, 132.4, 129.3, 128.4, 127.6, 127.4, 126.4, 72.8, 69.7, 62.0, 39.8, 32.8, 31.3, 29.0, 28.5, 23.9, 22.6, 21.5, 20.5, 18.6, 14.3, 14.1; IR (thin film) ν_max/cm⁻¹ 2959, 2249, 1363, 1167; HRMS m/z (ESI+) found [M+Na]^+ 488.2601; C₂₉H₃₉NNaO₂S⁺ requires 488.2594.

2-Methylpent-1-en-3-yl 2-phenylacetate, 140

EtMgBr (24.0 mL, 3 M in Et₂O, 72 mmol, 1.2 equiv.) was added dropwise to a solution of methacryl aldehyde (4.95 mL, 60 mmol, 1.0 equiv.) in Et₂O (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then H₂O (30 mL) was added. The organic phase was separated, washed with H₂O (60 mL) and brine (60 mL), dried (MgSO₄), filtered and carefully concentrated in vacuo (≥ 250 mbar at 40 °C) to give a solution of 2-methylpent-1-en-3-ol (6.67 g, 83% in Et₂O [determined by ¹H NMR spectroscopy], 55.3 mmol, 92%).

To a solution of 2-methylpent-1-en-3-ol (2.71 g, 83% in Et₂O, 22.5 mmol, 1.0 equiv.) was added CH₂Cl₂ (50 mL), the solution cooled was to 0 °C, and pyridine (2.13 mL, 27.0 mmol, 1.2 equiv.) was added followed, dropwise, by phenylacetyl chloride (3.81 mL, 24.7 mmol, 1.1 equiv.). The reaction mixture was stirred at 0 °C for 2 h and then H₂O (40 mL) was added. The organic phase was separated, washed with brine (40 mL), dried (MgSO₄), filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (19:1 hexanes/t-BuOMe) to give 140 (4.43 g, 20.3 mmol,
90%) as a colourless oil; $R_f$ 0.70 (9:1, hexanes/EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.36–7.21 (5H, m, PhH), 5.10 (1H, t, $J = 6.6$ Hz, H3), 4.89–4.82 (2H, m, H1), 3.63 (2H, s, CH$_2$Ph), 1.71–1.49 (2H, m, H4), 1.64 (3H, s, H6), 0.82 (3H, t, $J = 7.4$ Hz, H5); $\delta_C$ (100 MHz, CDCl$_3$) 170.8, 142.7, 134.2, 129.2, 128.5, 127.0, 112.8, 78.9, 41.7, 25.5, 18.0, 9.5; IR (thin film) $\nu_{max}/\text{cm}^{-1}$ 2971, 1734. HRMS $m/z$ (ESI+) found [M+Na]$^+$ 241.1200; C$_{14}$H$_{18}$NaO$_2$ requires 241.1204.

**(E)-4-Methyl-2-phenylhept-4-enoic acid, 141**

![Chemical Structure Image]

To a solution of LiHMDS (1M in toluene, 3.0 equiv.) in toluene (22 mL) at $-78$ ºC was added Et$_3$N (30 equiv.), followed by a solution of 2-methylpent-1-en-3-yl 2-phenylacetate 140 (3.93 g, 18.0 mmol, 1.0 equiv.) in toluene (45 mL). The reaction mixture was allowed to warm to room temperature overnight and was then poured into 2 M aq. NaOH (215 mL). The aqueous layer was separated, washed with $t$-BuOMe (44 mL), cooled to 0 ºC, acidified with concentrated HCl and extracted with $t$-BuOMe (3 x 180 mL). These organic washings were combined, dried (MgSO$_4$), filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (10%→30% $t$-BuOMe in hexanes) to give 141 (2.17 g, 9.94 mmol, 55%, >20:1 $E:Z$) as a yellow oil; $\delta_H$ (500 MHz, CDCl$_3$) 7.36–7.20 (5H, m, PhH), 5.14 (1H, br t, $J = 7.1$ Hz, H5), 3.76 (1H, dd, $J = 8.9$ and 6.7 Hz, H2), 2.77 (1H, dd, $J = 13.9$ and 8.9 Hz, H3), 2.39 (1H, dd, $J = 13.9$ and 6.7 Hz, H3), 1.90 (2H, app quin., $J = 7.4$ Hz, H6), 1.58 (3H, s, H8), 0.81 (3H, t, $J = 7.5$ Hz, H7); $\delta_C$ (125 MHz, CDCl$_3$) 179.4, 138.3, 130.6, 129.6, 128.6, 128.1, 127.4, 50.2, 43.1, 21.2, 15.8, 14.0; IR (thin film) $\nu_{max}/\text{cm}^{-1}$ 2961, 1703; HRMS $m/z$ (ESI+) found [M-H+2Na]$^+$ 263.1014; C$_{14}$H$_{17}$NaO$_2$ requires 263.1018.
(E)-tert-Butyl (3-methyl-1-phenylhex-3-en-1-yl)carbamate, 142

To a solution of (E)-4-methyl-2-phenyleth-4-enoic acid 141 (1.00 g, 4.58 mmol, 1.0 equiv.) in t-BuOH (6.4 mL) was added Et₃N (0.77 mL, 5.50 mmol, 1.2 equiv.) and DPPA (1.1 mL, 5.04 mmol, 1.1 equiv.). The reaction mixture was heated to 85 °C for 15 h, then cooled to room temperature and quenched with H₂O (1 mL) and NaHCO₃ (1 mL, sat. aq.). The t-BuOH was evaporated and the residue extracted with t-BuOMe (3 × 10 mL). The combined organic layers were washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (19:1, hexanes/t-BuOMe) to give 142 (462 mg, 1.60 mmol, 35%) as a colourless solid; m.p. 75–77 °C; R_f 0.56 (9:1 hexanes/EtOAc); δ_H (500 MHz, CDCl₃) 7.34–7.18 (5H, m, Ph_H), 5.16 (1H, br t, J = 6.7 Hz, H₄), 4.92–4.47 (2H, br m, H1 and NH), 2.46–2.34 (1H, m, H2), 2.34–2.20 (1H, m, H2), 1.98 (2H, app quin., J = 7.4 Hz, H5), 1.61 (3H, s, H7), 1.50–1.14 (9H, br m, t-Bu), 0.91 (3H, t, J = 7.5 Hz, H6); δ_C (125 MHz, CDCl₃) 155.3, 143.4, 130.6, 130.5, 128.4, 126.9, 126.1, 79.3, 52.8, 47.9, 28.3, 21.2, 15.5, 14.1; IR (thin film) ν_max/cm⁻¹ 3386, 2963, 1683, 1520; HRMS m/z (ESI+) found [M+Na]^+ 312.1937; C₁₈H₂₇NNaO₂ requires 312.1934.

(E)-4-Methyl-N-(3-methyl-1-phenylhex-3-en-1-yl)benzenesulfonamide, 143

To a flask charged with (E)-tert-butyl (3-methyl-1-phenylhex-3-en-1-yl)carbamate 142 (450 mg, 1.55 mmol, 1.0 equiv.) was added 4 M HCl in dioxane (1.94 mL, 7.77 mmol, 5.0 equiv.) and the reaction mixture stirred at room temperature for 2 h, then concentrated in vacuo. To the residue was added CH₂Cl₂ (5 mL) and Et₃N (1.52 mL, 10.9 mmol, 7.0 equiv.) followed by p-toluenesulfonyl chloride (296 mg, 1.55 mmol, 1.0 equiv.) and the reaction mixture stirred at room temperature for 15 h. The reaction mixture was diluted with CH₂Cl₂ (5 mL), washed with NaHCO₃ (5 mL, sat. aq.) and 1 M aq. HCl (5 mL), then the organic phase was dried (MgSO₄), filtered and concentrated in vacuo. The resulting crude
material was purified by column chromatography (17:3 hexanes/t-BuOMe) to give 143 (441 mg, 1.28 mmol, 83%) as a pale yellow oil; \( R_f \) 0.29 (4:1 hexanes/EtOAc); \( \delta_{\text{H}} \) (500 MHz, CDCl\(_3\)) 7.52 (2H, d, \( J = 8.3 \) Hz, TsH), 7.22–7.12 (7H, m, TsH and PhH), 5.18 (1H, br t, \( J = 6.8 \) Hz, H4), 4.69 (1H, br d, \( J = 3.5 \) Hz, N\textsubscript{H}), 4.27 (1H, dt, \( J = 9.5 \) and 4.7 Hz, H1), 2.37 (3H, s, ArCH\(_3\)), 2.30 (1H, dd, \( J = 13.8 \) and 4.9 Hz, H2), 2.20 (1H, dd, \( J = 13.3 \) and 10.1 Hz, H2), 1.96 (1H, app quin., \( J = 7.4 \) Hz, H5), 1.33 (3H, s, H7), 0.93 (3H, t, \( J = 7.5 \) Hz, H6); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\)) 143.0, 141.4, 137.0, 132.1, 130.1, 129.2, 128.2, 127.2, 126.6, 55.3, 48.8, 21.5, 21.2, 15.0, 14.1; IR (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3380, 2961, 1323, 1156; HRMS \( m/z \) (ESI+) found [M+Na]\(^+\) 366.1501; \( C_{20}H_{25}NNaO_2S^+ \) requires 366.1498.

(E)-4-Methyl-N-(3-methyl-1-phenylox-3-en-1-yl)-N-(oct-1-yn-1-yl)benzenesulfonamide, 131

Synthesised from (E)-4-methyl-N-(3-methyl-1-phenylox-3-en-1-yl)benzenesulfonamide 143 (100 mg, 0.29 mmol) and 1-bromooct-1-yne 98a (110 mg, 0.58 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (0%→5% t-BuOMe in hexanes) to give 131 (65 mg, 0.14 mmol, 50%) as a yellow oil; \( R_f \) 0.46 (9:1 hexanes / EtOAc); \( \delta_{\text{H}} \) (500 MHz, CDCl\(_3\)) 7.51 (2H, d, \( J = 8.2 \) Hz, TsH), 7.30–7.23 (2H, m, PhH), 7.21–7.14 (3H, m, PhH), 7.11 (2H, d, \( J = 8.2 \) Hz, TsH), 5.16 (1H, t, \( J = 7.1 \) Hz, H4), 5.08 (1H, dd, \( J = 9.0 \) and 6.2 Hz, H1), 2.70 (1H, dd, \( J = 13.9 \) and 9.1 Hz, H2), 2.43 (1H, dd, \( J = 13.9 \) and 6.1 Hz, H2), 2.35 (3H, s, ArCH\(_3\)), 2.32 (2H, t, \( J = 6.9 \) Hz, H10), 1.95–1.78 (2H, m, H5), 1.58 (3H, s, H7), 1.49 (2H, app quin., \( J = 7.2 \) Hz, H11), 1.40–1.20 (6H, m, H12–14), 0.89 (3H, t, \( J = 7.0 \) Hz, H15), 0.83 (3H, t, \( J = 7.5 \) Hz, H6); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\)) 143.6, 139.6, 135.6, 131.0, 129.1, 129.0, 128.1, 127.6 (2C), 127.2, 73.2, 71.1, 61.2, 44.0, 31.4, 29.0, 28.5, 22.6, 21.5, 21.2, 18.7, 15.7, 14.1, 13.9; IR (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2928, 2254, 1363, 1167; HRMS \( m/z \) (ESI+) found [M+H]\(^+\) 452.2614; \( C_{28}H_{38}NO_2S^+ \) requires 452.2618.
Chapter 7: Experimental

N-(2-(Cyclohex-1-en-1-yl)-1-phenylethyl)-4-methylbenzenesulfonamide, 146

Synthesised from tert-butyl (2-(cyclohex-1-en-1-yl)-1-phenylethyl)(tosyl)carbamate 145 (450 mg, 0.99 mmol, 1.0 equiv.) using Procedure 4. The resulting crude material was purified by column chromatography (20%→30% Et₂O in petroleum ether) to give 146 (267 mg, 0.75 mmol, 76%) as a colourless solid; m.p. 112–114 °C; R_f 0.45 (7:3 petroleum ether/EtOAc); δ_H (400 MHz, CDCl₃) 7.53 (2H, d, J = 8.3 Hz, Ts_H), 7.24–7.11 (7H, m, Ts_H and Ph_H), 5.50–5.43 (1H, br m, H4), 4.70 (1H, br d, J = 3.6 Hz, NH), 4.25 (1H, ddd, J = 9.5, 5.4 and 3.6 Hz, H1), 2.37 (3H, s, ArCH₃), 2.29–2.14 (2H, m, H2), 2.04–1.88 (2H, m, H8), 1.73–1.60 (1H, m, H5), 1.59–1.38 (5H, m, H5–7); δ_C (100 MHz, CDCl₃) 134.0, 141.5, 137.0, 133.4, 129.2, 128.2, 127.2, 127.2, 126.8, 126.5, 55.3, 47.4, 27.4, 25.2, 22.5, 22.0, 21.4; IR (thin film) v_max/cm⁻¹ 3279, 2925, 1323, 1159; HRMS m/z (ESI+) found [M+Na]^+ 378.1498; C₂₁H₂₅NNaO₂S⁺ requires 378.1498.

N-(2-(Cyclohex-1-en-1-yl)-1-phenylethyl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, 133

Synthesised from N-(2-(cyclohex-1-en-1-yl)-1-phenylethyl)-4-methylbenzenesulfonamide 146 (100 mg, 0.29 mmol) and 1-bromoocct-1-yne 98a (103 mg, 0.54 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (17:3, petroleum ether / Et₂O) to give 133 (129 mg, 0.27 mmol, 75%) as a yellow oil; R_f 0.62 (4:1 hexanes/EtOAc); δ_H (400 MHz, C₆D₆) 7.73 (2H, d, J = 8.2 Hz, Ts_H), 7.41 (2H, d, J = 7.1 Hz, Ph_H), 7.09–6.94 (3H, m, 2×Ph_H), 6.66 (2H, d, J = 8.2 Hz, m Ts_H), 5.70–5.64 (1H, br m, H4), 5.47 (1H, dd, J = 9.3 and 6.1 Hz, H1), 2.91 (1H, dd, J = 14.1 and 9.3 Hz, H2'), 2.49 (1H, dd, J = 14.1 and 5.8 Hz, H2''), 2.17–2.03 (1H, m, H5), 2.13 (2H, t, J = 6.8 Hz, H11), 1.99–1.84 (1H, m, H5), 1.81 (3H, s, ArCH₃), 1.65–1.30 (6H, m, H6, H7, H12), 1.30–1.07 (6H,
m, H13–15), 0.86 (3H, J = 7.1 Hz, H16); δC (100 MHz, CDCl3) 143.4, 140.6, 137.0, 133.3, 129.2, 128.5, 128.2, 127.9, 127.7, 125.7, 73.4, 72.4, 61.5, 43.1, 31.7, 29.4, 28.8, 28.5, 25.7, 23.3, 23.0, 22.6, 21.1, 19.0, 14.3; IR (thin film) νmax/cm⁻¹ 2930, 2252, 1364, 1167; HRMS m/z (ESI+) found [M+Na]+ 486.2441; C₂₀H₁₇NNa₂O₂S⁺ requires 486.2437.

(E)-N-(Hex-3-en-1-yl-3-d)-4-methylbenzenesulfonamide, (E)-d₁-154

To a stirred suspension of propyltriphenylphosphonium bromide (1.29 g, 3.35 mmol, 5.1 equiv.) in dry THF (2.2 mL), was added NaHMDS (1 M in THF, 3.3 mL, 3.29 mmol, 5.0 equiv.). The reaction mixture was stirred for 1 h at 0 °C, then cooled to −78 °C. To this cooled solution was added a solution of 4-methyl-N-(3-oxopropyl-3-d)benzenesulfonamide d₁-96 (150 g, 0.66 mmol, 1.0 equiv.) in dry THF (2.2 mL). The reaction mixture was then stirred for 2.5 h at −78 °C, and subsequently quenched with water (10 mL) and warmed to room temperature. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated in vacuo, and purified by column chromatography (3:2 petroleum ether / EtOAc) to give (E)-d₁-154 (121 mg, 0.48 mmol, 64%) as a colourless oil; Rf 0.35 (7:3 petroleum ether / EtOAc); δH (400 MHz, CDCl₃) 7.78 (2H, d, J = 8.2 Hz, TsH), 7.34 (2H, d, J = 8.2 Hz, TsH), 5.48 (1H, t, J = 6.2 Hz, H3), 5.00 (1H, t, J = 6.0 Hz NH), 2.98 (2H, dt, J = 6.1 and 6.8 Hz, H6), 2.45 (3H, s, CH₃Ar), 2.15 (2H, t, J = 6.8 Hz, H5), 1.98 (2H, app quin, J = 7.3 Hz, H2), 0.93 (3H, t, J = 7.6 Hz, H1); δC (100 MHz, CDCl3) 143.3, 137.1, 135.7, 129.7, 127.2, 124.1 (t, J = 23.1 Hz), 42.8, 32.4, 25.5, 21.5, 13.6; IR (thin film) νmax/cm⁻¹ 3275, 3275, 2970, 2920, 1595, 1320; HRMS m/z (ESI+) found [M+Na]+ 277.1088; C₁₃H₁₈DNNa₂O₂S⁺ requires 277.1091.
(E)-N-(Hex-3-en-1-yl-3-d)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, (E)-d1-151a

Synthesised from (E)-N-(hex-3-en-1-yl-3-d)-4-methylbenzenesulfonamide (E)-d1-154 (75 mg, 0.29 mmol) and 1-bromooct-1-yne 98a (67 mg, 0.35 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (9:1 petroleum ether / Et2O) to afford (E)-d1-151a (75 mg, 0.21 mmol, 71%) as a colourless oil; Rf 0.63 (4:1 petroleum ether / Et2O); δH (400 MHz, CDCl3) 7.77 (2H, d, J = 8.1 Hz, TsH), 7.32 (2H, d, J = 8.1 Hz, TsH), 5.50 (1H, m, H3), 3.28 (2H, t, J = 7.4 Hz, H6), 2.44 (3H, s, CH3Ar), 2.30–2.24 (4H, m, H5 and H10), 2.04–1.93 (2H, m, H2), 1.47 (2H, quin, J = 7.3 Hz, H11), 1.36–1.28 (6H, m, H12–14), 0.94 (3H, t, J = 7.4 Hz, H1), 0.88 (3H, t, J = 7.0 Hz, H15); δc (100 MHz, CDCl3) 144.3, 135.3, 135.0, 129.7, 127.8, 123.9 (t, J = 23.1 Hz), 73.1, 70.6, 51.5, 31.5, 31.0, 29.1, 28.6, 25.7, 22.7, 21.8, 18.6, 14.2, 13.8; IR (thin film) νmax/cm⁻¹ 2930, 2253, 1364, 1168; HRMS m/z (ESI+) found [M+Na]+ 385.2027; C21H30DNNaO2S requires 385.2030.

(Z)-N-(Hex-3-en-1-yl-3-d)-4-methylbenzenesulfonamide, (Z)-d1-154

To a stirred suspension of propyltriphenylphosphonium bromide (1.29 g, 3.35 mmol, 5.1 equiv.) in THF (2.2 mL), was added KHMDS (1 M in THF, 3.3 mL, 3.29 mmol, 5.0 equiv.). The reaction mixture was stirred for 1 h at 0 °C, then cooled to −78 °C. To this cooled solution was added a solution of 4-methyl-N-(3-oxopropyl-3-d)benzenesulfonamide d1-96 (150 mg, 0.66 mmol, 1.0 equiv.) in THF (2.2 mL). The reaction mixture was then stirred for 2.5 h at −78 °C, and subsequently quenched with water (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO4, filtered, concentrated in vacuo, and purified by column chromatography (10→20%, EtOAc / petroleum ether) to give (Z)-d1-154 (121 mg, 0.48 mmol, 72%) as a pale yellow oil; Rf = 0.36 (CH2Cl2); δH (400 MHz, CDCl3) 7.74 (2H, d, J = 8.2 Hz, TsH), 7.30 (2H, d, J = 8.2 Hz, TsH), 5.48 (1H,
t, \(J = 7.3\) Hz, H3), 4.50 (1H, \(t, J = 5.9\) Hz NH), 2.96 (2H, dt, \(J = 6.0\) and 6.8 Hz, H6), 2.42 (3H, s, CH\textsubscript{3}Ar), 2.19 (2H, \(t, J = 6.8\) Hz, H5), 1.97 (2H, app quin, \(J = 7.5\) Hz, H2), 0.93 (3H, \(t, J = 7.5\) Hz, H1); \(\delta\text{C (100 MHz, CDCl\textsubscript{3}})\) 143.5, 137.1, 135.5, 129.9, 127.3, 123.8 (t, \(J = 23.6\) Hz), 42.9, 27.4, 21.7, 20.7, 14.3; IR (thin film) \(\nu_{\text{max}}/\text{cm}^{-1}\) 3290, 2963, 2875, 1658, 1440, 1320; HRMS \(m/z\) (ESI+) found [M+H\textsuperscript{+}] 255.12718; C\textsubscript{13}H\textsubscript{19}DNO\textsubscript{2}S\textsuperscript{+} requires 255.1278.  

(Z)-N-(Hex-3-en-1-yl-3-d)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, (Z)-d\textsubscript{1}-151a

\[
\text{Synthesised from (Z)-N-(hex-3-en-1-yl-3-d)-4-methylbenzenesulfonamide (Z)-d\textsubscript{1}-154 (Z:E, 20:1; >98% deuterium incorporation by } ^{1}\text{H NMR spectroscopy) (75 mg, 0.29 mmol) and 1-bromooct-1-yno 98a (67 mg, 0.35 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (9:1 petroleum ether / Et\textsubscript{2}O) to afford (Z)-d\textsubscript{1}-151a (Z:E, 20:1; > 98% deuterium incorporation by } ^{1}\text{H NMR spectroscopy, 80 mg, 0.21 mmol, 76%) as a colourless oil; } R_f 0.63 (4:1 petroleum ether / Et\textsubscript{2}O); \(\delta\text{H (400 MHz, CDCl\textsubscript{3}})\) 7.77 (2H, d, \(J = 8.2\) Hz, TsH), 7.32 (2H, d, \(J = 8.2\) Hz, TsH), 5.46 (1H, \(t, J = 7.2\) Hz, H3), 3.26 (2H, \(t, J = 7.3\) Hz, H6), 2.43 (3H, s, CH\textsubscript{3}Ar), 2.34 (2H, \(t, J = 7.3\) Hz, H10), 2.26 (2H, \(t, J = 7.3\) Hz, H5), 2.00 (2H, app quin, \(J = 7.5\) Hz, H11), 1.47 (app quin, \(J = 7.5\) Hz, H2), 1.38-1.24 (6H, m, H12–14), 0.94 (3H, \(t, J = 7.5\) Hz, H1), 0.88 (3H, \(t, J = 6.9\) Hz, H15); \(\delta\text{C (100 MHz, CDCl\textsubscript{3}})\) 144.2, 134.8, 134.6, 129.6, 127.6, 123.4 (t, \(J = 23.6\) Hz), 72.9, 70.4, 51.2, 31.4, 28.9, 28.5, 25.6, 22.6, 21.6, 20.6, 18.5, 14.2, 14.0; IR (thin film) \(\nu_{\text{max}}/\text{cm}^{-1}\) 2931, 2254, 1364, 1169; HRMS \(m/z\) (ESI+) found [M+Na\textsuperscript{+}] 385.2027; C\textsubscript{21}H\textsubscript{30}DNNaO\textsubscript{2}S\textsuperscript{+} requires 385.2030.
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**tert-Butyl (Z)-hex-3-en-1-yl(tosyl)carbamate, (Z)-225**

\[
\begin{align*}
\text{N} & \text{O} \\
4 & 3 \\
\text{S} & 2 \\
6 & 5 \\
\text{C} & \\
\end{align*}
\]

Synthesised from (Z)-hex-3-en-1-ol (5.00 g, 49.9 mmol) using Procedure 2. The resulting crude material was filtered through a silica pad (slurry packed in CH\textsubscript{2}Cl\textsubscript{2}) using CH\textsubscript{2}Cl\textsubscript{2} (750 mL), concentrated in vacuo to approx. 300 mL, washed with 15% aq. H\textsubscript{2}O\textsubscript{2} (600 mL), sat. aq. Na\textsubscript{2}SO\textsubscript{3} (600 mL) and H\textsubscript{2}O (500 mL). The H\textsubscript{2}O layer was back extracted with CH\textsubscript{2}Cl\textsubscript{2} (200 mL). The combined organic layers were dried (MgSO\textsubscript{4}), concentrated in vacuo to 100 mL, filtered through a silica pad (slurry packed in CH\textsubscript{2}Cl\textsubscript{2}) using CH\textsubscript{2}Cl\textsubscript{2} (300 mL) and then concentrated in vacuo to dryness to give (Z)-225 as a colourless solid (15.20 g, 43.0 mmol, 68%); R\textsubscript{f} = 0.41 (4:1, petroleum ether:EtOAc); \(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.78 (2H, d, \(J = 8.2\) Hz, Ts\textsubscript{H}), 7.28 (2H, d, \(J = 8.2\) Hz, Ts\textsubscript{H}), 5.55–5.46 (1H, m, H\textsubscript{4}), 5.34 (1H, dtt, \(J = 10.7, 7.5, 1.3\) Hz, H\textsubscript{3}), 3.83–3.76 (2H, m, H\textsubscript{1}), 2.48 (2H, ap. q, \(J = 7.5\) Hz, H\textsubscript{2}), 2.42 (3H, s, ArC\textsubscript{H}\textsubscript{3}), 2.08 (2H, ap. quin.d, \(J = 7.5\) and \(1.3\) Hz, H\textsubscript{5}), 1.33 (9H, s, C(C\textsubscript{H}\textsubscript{3})\textsubscript{3}), 0.96 (3H, t, \(J = 7.5\) Hz, CH\textsubscript{3}–6); \(\delta\)\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 150.9, 144.0, 137.5, 134.8, 129.1, 127.8, 124.0, 84.0, 46.5, 28.1, 27.8, 21.5, 20.5, 14.2. Data are consistent with literature values.\textsuperscript{103}

**(Z)-N-(Hex-3-en-1-yl)-4-methylbenzenesulfonamide, (Z)-153**

\[
\begin{align*}
\text{N} & \text{O} \\
4 & 3 \\
\text{S} & 2 \\
6 & 5 \\
\text{C} & \\
\end{align*}
\]

Synthesised from (Z)-tert-butyl hex-3-en-1-yl(tosyl)carbamate (Z)-225 (7.32 g, 20.7 mmol) using Procedure 3 to give (Z)-153 as a pale yellow oil (5.14 g, 20.2 mmol, 98%) which was used without further purification; R\textsubscript{f} = 0.40 (4:1, petroleum ether:EtOAc); \(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.74 (2H, d, \(J = 8.2\) Hz, Ts\textsubscript{H}), 7.29 (2H, d, \(J = 8.2\) Hz, Ts\textsubscript{H}), 5.52–5.42 (1H, m, H\textsubscript{4}), 5.14 (1H, dtt, \(J = 10.9, 7.3, 1.4\) Hz, H\textsubscript{3}), 4.68 (1H, br. s, NH\textsubscript{2}), 2.94 (2H, ap. q, \(J = 6.9\) Hz, H\textsubscript{1}), 2.42 (3H, s, ArCH\textsubscript{3}), 2.19 (2H, ap. q, \(J = 6.8\) Hz, H\textsubscript{2}), 1.95 (2H, ap. quin.d, \(J = 7.5\) and \(1.4\) Hz, H\textsubscript{5}), 0.91 (3H, t, \(J = 7.5\) Hz, CH\textsubscript{3}); \(\delta\)\textsubscript{C} (100 MHz, CDCl\textsubscript{3})...
MHz, CDCl$_3$) 143.3, 136.9, 135.3, 129.6, 127.1, 124.0, 42.7, 27.2, 21.4, 20.5, 14.1. Data are consistent with literature values.$^{105}$

(Z)-N-(Hex-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, (Z)-151a

![Chemical structure](image)

Synthesised from (Z)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonamide (Z)-225 (1.00 g, 3.95 mmol) and 1-bromooct-1-yne 98a (896 mg, 4.74 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→15% Et$_2$O in petroleum ether) to give (Z)-151a as a colourless oil (1.34 g, 3.71 mmol, 94%); $R_f = 0.53$ (5:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.78 (2H, d, $J = 8.2$ Hz, TsH), 7.32 (2H, d, $J = 8.2$ Hz, TsH), 5.45 (1H, dtt, $J = 10.7$, 7.3, 1.4 Hz, H4), 5.27 (1H, dtt, $J = 10.7$, 7.5, 1.5 Hz, H3), 3.29–3.23 (2H, m, H1), 2.44 (3H, s, ArCH$_3$), 2.35 (2H, ap. q, $J = 7.5$ Hz, H2), 2.26 (2H, t, $J = 6.9$ Hz, H9), 2.01 (2H, ap. quin.d, $J = 7.5$ and 1.3 Hz, H5), 1.52–1.42 (2H, m, H10), 1.40–1.20 (6H, m, H11–13), 0.94 (3H, t, $J = 7.6$ Hz, H6), 0.88 (3H, t, $J = 6.9$ Hz, H14); $\delta_C$ (100 MHz, CDCl$_3$) 144.2, 134.8, 129.5, 127.6, 123.7, 72.9, 70.4, 51.1, 31.3, 28.9, 28.5, 25.7, 22.6, 21.6, 20.6, 18.5, 14.2, 14.0; IR (thin film) $v_{\text{max}}$/cm$^{-1}$ 2933, 2254, 1365, 1169; HRMS $m/z$ (ESI+) found [M+Na]$^+$ 384.1955; $C_{21}H_{31}NNaO$_2$S$^+$ requires 384.1968.
N-((E)-1-Bromo-oct-1-en-1-yl)-N-((Z)-hex-3-en-1-yl)-4-methylbenzenesulphonamide, (Z)-231a

Synthesised from (Z)-N-(hex-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulphonamide (Z)-151a (18.0 mg, 0.050 mmol) using Procedure 7.

Method 1

The product (Z)-231a was obtained as a colourless oil (19.2 mg, 0.045 mmol, 89%); \( R_f = 0.44 \) (9:1, petroleum ether:Et\(_2\)O); \( \delta_H \) (400 MHz, C\(_6\)D\(_6\)) 7.83 (2H, d, \( J = 8.2 \) Hz, TsH), 6.77 (2H, d, \( J = 8.2 \) Hz, TsH), 6.09 (1H, t, \( J = 15.3 \) Hz, H8), 5.46 (1H, m, H3), 5.31 (1H, m, H4), 3.73 (1H, m, H1\(^\prime\)), 2.95 (1H, m, H1\(^\prime\)'), 2.41 (2H, m, H2), 2.25 (2H, m, H9), 1.96 (2H, quin, \( J \approx 7.16 \) Hz, H5), 1.87 (3H, s, ArCH\(_3\)), 1.45–1.10 (8H, m, H10–13), 0.93–0.84 (6H, m, H6 and H14); \( \delta_C \) (100 MHz, C\(_6\)D\(_6\)) 144.0, 142.7, 135.9, 135.1, 129.6, 129.0, 125.0, 118.2, 48.8, 32.0, 31.5, 31.4, 29.4, 28.8, 26.0, 23.0, 21.2, 14.3; HRMS \( m/z \) (ESI+) found [M–H]+ 441.1338; C\(_{21}\)H\(_{32}\)NO\(_2\)BrS+ requires 441.1337.

N-((E)-1-Bromo-oct-1-en-1-yl)-N-((E)-hex-3-en-1-yl)-4-methylbenzenesulphonamide, (E)-231a

Synthesised from (E)-N-(hex-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulphonamide (E)-151a (18.0 mg, 0.050 mmol) using Procedure 7.

Method 1

The product (E)-231a was obtained as a colourless oil (18.9 mg, 0.044 mmol, 87%); \( R_f = 0.43 \) (9:1, petroleum ether:Et\(_2\)O); \( \delta_H \) (400 MHz, C\(_6\)D\(_6\)) 7.83 (2H, d, \( J = 8.2 \) Hz, TsH), 6.77 (2H, d, \( J = 8.2 \) Hz, TsH), 6.09 (1H, t, \( J = 15.3 \) Hz, H8), 5.46 (1H, m, H3), 5.31 (1H, m, H4), 3.73 (1H, m, H1\(^\prime\)), 2.95 (1H, m, H1\(^\prime\)'), 2.28 (2H, m, H2), 2.25 (2H, m, H9), 1.90 (2H, p, \( J \approx 7.16 \) Hz, H5), 1.87 (3H, s, ArCH\(_3\)), 1.45–
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1.10 (8H, m, H10–13), 0.93–0.84 (6H, m, H6 and H14); \( \delta_c \) (100 MHz, C\textsubscript{6}D\textsubscript{6}) 144.0, 142.6, 135.9, 135.1, 129.6, 129.0, 125.0, 118.2, 48.8, 32.0, 31.5, 31.4, 29.4, 28.8, 26.0, 23.0, 21.2, 14.3, 13.8; HRMS m/z (ESI+) found [M–H]\(^+\) 441.1339; C\textsubscript{21}H\textsubscript{32}NO\textsubscript{2}BrS\(^+\) requires 441.1337.

**Method 2**

The product \((E)-231a\) was obtained as a colourless oil (21.8 mg, 0.049 mmol, 99%). Data are in accordance with those obtained from **Method 1**.

\((E)-N-(1-Bromooc-t-1-en-1-yl)-N-(but-3-en-1-yl)-4-methylbenzenesulfonamide, 231c\)

![Structure of 231c](image)

Synthesised from \(N\)-(but-3-en-1-yl)-4-methyl-\(N\)-(oct-1-yn-1-yl)benzenesulfonamide 92 (200 mg, 0.60 mmol) using **Procedure 7**.

**Method 1**

The product 231c was obtained as a colourless oil (199 mg, 0.48 mmol, 80%); \( R_f = 0.42 \) (9:1, petroleum ether:Et\(_2\)O); \( \delta_h \) (400 MHz, C\textsubscript{6}D\textsubscript{6}) 7.81 (2H, d, \( J = 8.2 \) Hz, TsH), 6.79 (2H, d, \( J = 8.2 \) Hz, TsH), 6.13 (1H, dt, \( J = 53.9 \) and 7.5 Hz, H6), 5.67 (1H, m, H3), 5.04 (2H, m, H’ and H’’), 3.41 (2H, t, \( J = 6.90 \) Hz H1), 3.33 (2H, ap. q, \( J = 7.2 \) Hz, H2), 2.45–2.09 (4H, m, H7 and H8), 1.87 (3H, s, Ar-CH\(_3\)), 1.38–1.19 (6H, m, H9–11), 0.86 (3H, m, H12); \( \delta_c \) (100 MHz, C\textsubscript{6}D\textsubscript{6}) 137.5, 135.9, 133.8, 129.4, 128.3, 125.9, 116.7, 111.7, 44.1, 31.9, 30.8, 29.3, 28.9, 23.7, 22.7, 21.0, 14.1; HRMS m/z (ESI+) found [M–H]\(^+\) 413.1026; C\textsubscript{19}H\textsubscript{29}NO\textsubscript{2}SBr\(^+\) requires 413.1024
(E)-N-(But-3-en-1-yl)-N-(1-iodooct-1-en-1-yl)-4-methylbenzenesulfonamide, 231c’

Synthesised from N-(but-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide 92 (100 mg, 0.30 mmol) using Procedure 7.

Method 2

The product 231c’ was obtained as a pale yellow oil (135 mg, 0.29 mmol, >98%); \( R_f = 0.41 \) (9:1, petroleum ether:EtO); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.68 (2H, d, \( J = 8.2 \) Hz, TsH), 7.25 (2H, d, \( J = 8.2 \) Hz, TsH), 5.87 (1H, dt, \( J = 17.2 \) and 6.7 Hz, H6), 5.67 (1H, m, H3), 5.04 (2H, m, H’ and H’’), 3.53 (2H, t, \( J = 7.5 \) Hz, H1), 2.58–2.48 (2H, ap. q, \( J = 7.2 \) Hz, H2), 2.43 (3H, s, ArC\(_3\)H3), 1.83–1.78 (2H, t, \( J = 6.9 \) Hz, H7), 1.63–1.54 (2H, m, H8), 1.49–1.18 (6H, m, H9–11), 0.88 (3H, t, \( J = 6.8 \) Hz, H12); \( \delta_C \) (100 MHz, CDCl\(_3\)) 137.4, 135.8, 134.0, 129.4, 128.1, 120.0, 116.5, 96.1, 46.1, 30.9, 29.8, 29.3, 28.9, 25.5, 22.8, 21.3, 14.1; HRMS \( m/z \) (ESI+) found [M–H]\(^+\) 460.0810; \( C_{19}H_{27}INO_2S \) requires 460.0807.

tert-Butyl (E)-hex-3-en-1-yl(tosyl)carbamate, (E)-225

Synthesised from (E)-hex-3-en-1-ol (5.00 g, 49.9 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (dry loaded, 5%–20% Et\(_2\)O in petroleum ether) to give (E)-225 as a colourless solid (15.60 g, 44.1 mmol, 88%); m.p. 61–65 °C; \( R_f = 0.41 \) (4:1, petroleum ether:EtOAc); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.79 (2H, d, \( J = 8.1 \) Hz, TsH), 7.30 (2H, d, \( J = 8.1 \) Hz, m TsH), 5.63–5.53 (1H, m, H4), 5.39 (1H, dt, \( J = 15.4, 6.8, 1.3 \) Hz, H3), 3.88–3.80 (2H, m, H1), 2.48–2.39 (2H, m, H2), 2.44 (3H, s, ArCH3), 2.08 (2H, ap. quin.d, \( J = 7.1, 1.3 \) Hz, H5), 1.34 (9H, s, C(CH\(_3\))\(_3\)), 155.
0.97 (3H, t, J = 7.5 Hz, H6); δc (100 MHz, CDCl3) 150.9, 144.0, 137.6, 135.3, 129.2, 127.8, 124.5, 84.0, 46.9, 33.4, 27.9, 25.6, 21.6, 13.6. Data are consistent with literature values.103

(E)-N-(Hex-3-en-1-yl)-4-methylbenzenesulfonamide, (E)-154

Synthesised from (E)-tert-butyl hex-3-en-1-yl(tosyl)carbamate (E)-225 (15.15 g, 42.9 mmol) using Procedure 3 to give (E)-154 as a colourless oil (10.52 g, 41.5 mmol, 97%) which was used without further purification; Rf = 0.40 (4:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.74 (2H, d, J = 8.2 Hz TsH), 7.29 (2H, d, J = 8.2 Hz, TsH), 5.45 (1H, dt, J = 15.3, 6.3, 1.1 Hz, H4), 5.17 (1H, dt, J = 15.3, 6.8, 1.1 Hz, H3), 4.79–4.71 (1H, br. m, NH), 2.94 (2H, ap. q, J = 6.8 Hz, H1), 2.41 (3H, s, ArCH3), 2.11 (2H, ap. qd, J = 6.8 and 1.1 Hz, H2), 1.94 (2H, ap qdd, J = 7.5, 6.3, 1.3 Hz, H5), 0.91 (3H, t, J = 7.5 Hz, H6); δc (100 MHz, CDCl3) 143.2, 136.9, 135.8, 129.6, 127.0, 124.2, 42.6, 32.3, 25.4, 21.4, 13.5. Data are consistent with literature values.105

(Bromoethynyl)benzene, 98b

Synthesised from phenylacetylene (5.00 mL, 45.5 mmol) using Procedure 1. The resulting crude material was passed through a silica pad (eluting with petroleum ether) to give 98b as a yellow oil (5.99 g, 33.1 mmol, 73%); Rf = 0.68 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.48 (2H, dd, J = 7.7 and 1.9 Hz, 2×PhH), 7.38–7.29 (3H, m, 3×PhH); δc (100 MHz, CDCl3) 132.0, 128.6, 128.3, 122.7, 80.0, 49.7. Data are consistent with literature values.106

1-(Bromoethynyl)-4-fluorobenzene, 98c

Synthesised from 1-ethynyl-4-fluorobenzene (0.24 mL, 2.08 mmol) using Procedure 1. The resulting crude material was passed through a silica pad (eluting with petroleum ether) to give 98c as a pale yellow oil (250 mg, 1.26 mmol, 61%); Rf = 0.38 (5:1, petroleum ether:EtOAc); δH (500 MHz, CDCl3)
7.49–7.37 (2H, m), 7.07–6.92 (2H, m); δC (125 MHz, CDCl₃) 162.8 (d, J = 249 Hz), 134.0 (d, J = 248 Hz), 118.9, (d, J = 3.5 Hz), 115.7, (d, J = 21.7 Hz), 79.0, 49.6; δF (470 MHz, CDCl₃) -115.8. Data are consistent with literature values.¹⁰⁷

**1-(Bromoethynyl)-4-methoxybenzene, 98d**

![Diagram of 1-(Bromoethynyl)-4-methoxybenzene]

Synthesised from 1-1-ethyl-4-methoxybenzene (0.52 mL, 4.0 mmol) using Procedure 1. The resulting crude material was passed through a silica pad (eluting with petroleum ether) to give 98d as a yellow solid (0.68 g, 3.2 mmol, 80%); m.p. = 45–46 °C; Rf = 0.28 (5:1, petroleum ether:EtOAc); δH (500 MHz, CDCl₃) 7.42–7.31 (2H, m), 6.88–6.75 (2H, m), 3.81 (3H, s, OC₃H₃); δC (125 MHz, CDCl₃) 160.0, 133.5, 114.9, 114.0, 80.0, 55.2, 47.9. Data are consistent with literature values.¹⁰⁷

**(E)-N-(Hex-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, (E)-151a**

![Diagram of (E)-N-(Hex-3-en-1-yl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide]

Synthesised from (E)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonamide (E)-154 (1.00 g, 3.95 mmol) and 1-bromooct-1-yne 98a (896 mg, 4.74 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10% Et₂O in petroleum ether) to give (E)-151a as a colourless oil (1.24 g, 3.44 mmol, 87%); Rf = 0.62 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl₃) 7.77 (2H, d, J = 8.2 Hz, TsH), 7.32 (2H, d, J = 8.2 Hz, TsH), 5.51 (1H, dtt, J = 15.3, 6.3, 1.1 Hz, H4), 5.27 (1H, dtt, J = 15.3, 6.8, 1.4 Hz, H3), 3.30–3.24 (2H, m, H1), 2.44 (3H, s, ArCH₃), 2.33–2.25 (2H, m, H2), 2.25 (2H, t, J = 7.1 Hz, H9), 2.01–1.91 (2H, m, H5), 1.52–1.42 (2H, m, H10), 1.39–1.22 (6H, m, H11–13), 0.93 (3H, t, J = 7.5 Hz, H6), 0.88 (3H, t, J = 6.9 Hz, H14); δC (100 MHz, CDCl₃) 144.1, 135.2, 134.7, 129.5, 127.6, 124.0, 72.9, 70.4, 51.3, 31.3, 31.0, 28.9, 28.4, 25.5, 22.6, 21.6, 18.4, 14.0, 13.6; IR (thin film) νmax/cm⁻¹ 2930, 2253, 1364, 1168; HRMS m/z (ESI+) found [M+Na]⁺ 384.1955; C₂₁H₃₁NNaO₂S⁺ requires 384.1968.
(Z)-N-(Hex-3-en-1-yl)-4-methyl-N-(phenylethynyl)benzenesulfonyl amide, (Z)-151b

![Chemical structure of (Z)-151b]

Synthesised from (Z)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonyl amide (Z)-154 (1.00 g, 3.95 mmol) and (bromoethynyl)benzene 98b (1.07 g, 5.92 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→15% Et₂O in petroleum ether) to give (Z)-151b as a yellow oil (1.03 g, 2.91 mmol, 75%); Rᵣ = 0.51 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl₃) 7.84 (2H, d, J = 8.3 Hz, TsH), 7.40–7.33 (4H, m, TsH and PhH), 7.33–7.26 (3H, m, PhH), 5.48 (1H, dtt, J = 10.9, 7.3, 1.3 Hz, H4), 5.27 (1H, dtt, J = 10.9, 7.3, 1.5 Hz, H3), 3.42 (2H, t, J = 7.4 Hz, H1), 2.49–2.40 (2H, m, H2), 2.45 (3H, s, ArC₃H₃), 2.40 (2H, ap. quin.d, J = 7.4 Hz and 1.5 Hz, H5), 0.95 (3H, t, J = 7.5 Hz, H6); δC (100 MHz, CDCl₃) 144.6, 135.0, 134.7, 131.3, 129.7, 128.2, 127.7, 127.6, 123.5, 122.9, 82.2, 70.8, 51.3, 26.0, 21.6, 20.6, 14.2; IR (thin film) νmax/cm⁻¹ 2963, 2234, 1363, 1168; HRMS m/z (ESI⁺) found [M+Na]⁺ 376.1344; C₂₁H₂₃NNaO₂S⁺ requires 376.1342.

(E)-N-(Hex-3-en-1-yl)-4-methyl-N-(phenylethynyl)benzenesulfonyl amide, (E)-151b

![Chemical structure of (E)-151b]

Synthesised from (E)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonyl amide (E)-154 (1.00 g, 3.95 mmol) and (bromoethynyl)benzene 98b (1.07 g, 5.92 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (8→10% Et₂O in petroleum ether) to give (E)-151b as a yellow oil (1.32 g, 3.73 mmol, 95%); Rᵣ = 0.51 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl₃) 7.84 (2H, d, J = 8.3 Hz, TsH), 7.40–7.33 (4H, m, TsH and PhH), 7.33–7.26 (3H, m, PhH), 5.55 (1H, dtt, J = 15.3, 6.3, 1.3 Hz, H4), 5.31 (1H, dtt, J = 15.3, 6.8, 1.3 Hz, H3), 3.43 (2H, ap t, J = 7.4 Hz, H1), 2.45 (3H, s, ArC₃H₃), 2.38 (2H, br. ap. q, J = 7.1 Hz, H2), 1.97 (2H, m, H5), 0.94 (3H, t, J = 7.5 Hz, CH₃); δC (100
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MHz, CDCl$_3$) 144.5, 135.6, 134.7, 131.3, 129.7, 128.2, 127.7, 127.6, 123.8, 122.9, 82.3, 70.8, 51.5, 31.2, 25.6, 21.6, 13.6; IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 2962, 2234, 1364, 1168; HRMS $m/z$ (ESI$^+$) found [M+Na]$^+$ 376.1331; C$_{21}$H$_{23}$NNaO$_2$S$^+$ requires 376.1342.

(Z)-N-((4-Fluorophenyl)ethynyl)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonamide, (Z)-151c

Synthesised from (Z)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonamide (Z)-154 (250 mg, 0.98 mmol) and 1-(bromoethynyl)-4-fluorobenzene 98c (0.27 mg, 5.92 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→20% Et$_2$O in petroleum ether) to give (Z)-151c as a yellow oil (228 mg, 0.62 mmol, 63%); $R_f$ = 0.31 (5:2, petroleum ether:EtOAc); $\delta$H (400 MHz, CDCl$_3$) 7.84 (2H, d, $J = 8.3$ Hz, Ts-H), 7.40–7.33 (4H, m, Ts-H, Ph-H), 7.07–6.93 (2H, m, Ph-H), 5.49 (1H, dtt, $J = 10.9, 7.3, 1.3$ Hz, H4), 5.28 (1H, dtt, $J = 10.9, 7.3, 1.5$ Hz, H3), 3.45 (2H, ap t, $J = 7.4$ Hz, H1), 2.46 (3H, s, ArCH$_3$), 2.44–2.40 (2H, m, H2), 2.05 (2H, ap. quin.d, $J = 7.4$ and $1.5$ Hz, H5), 0.94 (3H, t, $J = 7.5$ Hz, H6); $\delta$C (100 MHz, CDCl$_3$) 162.3 (d, $J = 249.0$ Hz), 144.3, 135.8, 134.3, 133.6 (d, $J = 234.0$ Hz), 129.5, 127.6, 123.0, 119.0 (d, $J = 4.0$ Hz), 115.6 (d, $J = 22.0$ Hz), 82.1, 70.2, 51.3, 31.1, 25.6, 21.3, 13.6; $\delta$F (376 MHz, CDCl$_3$) -115.6; IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 2963, 2230, 1368, 1164 1120; HRMS $m/z$ (ESI$^+$) found [M+Na]$^+$ 394.1250; C$_{21}$H$_{22}$FNNaO$_2$S$^+$ requires 394.1253.

(Z)-N-(Hex-3-en-1-yl)-N-((4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide, (Z)-151d

Synthesised from (Z)-N-(hex-3-en-1-yl)-4-methylbenzenesulfonamide (Z)-154 (250 mg, 0.98 mmol) and 1-(bromoethynyl)-4-methoxybenzene 98d (312 mg, 1.48 mmol) using Procedure 1. The resulting crude material was purified by column chromatography (10→20% Et$_2$O in petroleum ether) to give (Z)-
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151d as a yellow oil (291 mg, 0.76 mmol, 78%); RF = 0.22 (5:2, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.84 (2H, d, J = 8.3 Hz, TsH), 7.35 (2H, d, J = 8.2 Hz, TsH), 7.31 (2H, d, J = 8.5 Hz, PhH), 6.83 (2H, d, J = 8.5 Hz, PhH), 5.53 (1H, dtt, J = 15.3, 6.3, 1.3 Hz, H4), 5.30 (1H, dtt, J = 15.3, 6.8, 1.3 Hz, H3), 3.81 (3H, s, OC6H3), 3.40 (2H, ap t, J = 7.4 Hz, H1), 2.43 (3H, s, ArC6H3), 2.36 (2H, br. ap. q, J = 7.1 Hz, H2), 1.97 (2H, m, H5), 0.93 (3H, t, J = 7.5 Hz, H6); δC (100 MHz, CDCl3) 144.8, 135.2, 134.7, 131.3, 123.0, 128.1, 127.7, 123.8, 122.9, 81.3, 70.9, 51.5, 31.2, 25.6, 21.6, 13.6, 6.9; IR (thin film) νmax/cm⁻¹ 2968, 2231, 1370, 1170; HRMS m/z (ESI+) found [M+Na]+ 406.1452; C22H25NNaO3S⁺ requires 406.1453.

**(But-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane, 253**

![Chemical Structure](image)

To a stirred solution of 3-butyn-1-ol 252 (14.0 g, 200 mmol, 1.0 equiv.) in dry CH2Cl2 (300 mL), TBSCl (45.2 g, 300 mmol, 1.5 equiv.), DMAP (1.20 g, 10 mmol, 0.05 equiv.) and Et3N (42 mL, 300 mmol, 1.5 equiv.) was added. The reaction solution was stirred at room temperature for 8 h, and then sat. aq. NH4Cl was added. The reaction mixture was extracted with CH2Cl2 (3 × 40 mL). The organic layers were combined and dried over MgSO4, concentrated in vacuo to give 253 as a colourless oil (32.1 g, 176 mmol, 88%); RF = 0.83 (petroleum ether); δH (400 MHz, CDCl3) 3.74 (2H, t, J = 4.2 Hz, H1), 2.40 (2H, dt, J = 2.4 and 7.2 Hz, H2), 1.96 (1 H, t, J = 2.4 Hz, H4), 0.90 (9H, s, C(CH3)3), 0.06 (6H, s, 2×CH3); δC (100 MHz, CDCl3) 81.5, 69.3, 61.7, 25.9, 22.8, 18.3, −5.3; IR (thin film) νmax/cm⁻¹ 3310, 2950, 2930, 2857, 1475, 1253, 1100, 915, 830, 771, 635. Data are consistent with literature values.108

**tert-Butyldimethyl((5-phenylpent-3-yn-1-yl)oxy)silane, 254**

![Chemical Structure](image)

A solution of (but-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane 253 (6.70 g, 24.4 mmol, 1.0 equiv.) in dry THF (50 mL) was transferred into a 250 ml flame-dried round-bottom flask. The solution was then cooled to −40 °C and 2.5 M BuLi solution in hexanes (10 mL, 25 mmol, 1.05 equiv.) was added dropwise via syringe. The reaction was allowed to warm up to room temperature, followed by addition
of benzyl bromide (4.18 g, 24.4 mmol, 1.0 equiv.) via syringe. The reaction was left stirred overnight. The reaction mixture was quenched with sat. aq. NH₄Cl (~40 mL). The mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined and dried over MgSO₄, concentrated in vacuo. The crude material was purified by column chromatography (10→30% EtOAc in petroleum ether) to give 254 as a yellow oil (3.53 g, 12.9 mmol, 53%); R_f = 0.62 (1:1, petroleum ether:EtOAc); δ_H (400 MHz, CDCl₃) 7.35–7.21 (5H, m, Ph_H), 3.64 (2H, t, J = 6.2 Hz, H1), 3.61–3.60 (2H, m, H5), 2.23–2.19 (2H, m, H2), 0.90 (9H, s, C(C₃H₃)), 0.06 (6H, s, 2×CH₃); δ_C (100 MHz, CDCl₃) 140.5, 129.4, 128.6, 125.7, 82.3, 75.6, 61.7, 25.9, 23.9, 22.8, 18.5, −5.3. Data are consistent with literature values.¹⁰⁸

(Z)-tert-Butyldimethyl((5-phenylpent-3-en-1-yl)oxy)silane, (Z)-255

A round-bottom flask was charged with Lindlar’s catalyst (500 mg) and purged with nitrogen. tert-butyldimethyl((5-phenylpent-3-yn-1-yl)oxy)silane 254 (1.14 g, 4.11 mmol, 1.0 equiv.) in MeOH (10 mL) was added followed by quinoline (35 µL, 0.27 mmol). The flask was evacuated and refilled with H₂ four times, fitted with a H₂ balloon, and stirred at room temperature under H₂ for 3 h. The reaction was filtered through a plug of silica and concentrated in vacuo. The crude material was purified by column chromatography (0→15% Et₂O in petroleum ether) to give (Z)-255 as a pale yellow oil (1.09 g, 3.95 mmol, 97%); R_f = 0.62 (9:1, petroleum ether:Et₂O); δ_H (500 MHz, CDCl₃) 7.26 (2H, t, J = 7.6 Hz, Ph_H), 7.17 (2H, d, J = 7.6 Hz, Ph_H), 7.16 (H1 t, J = 7.6 Hz, Ph_H), 5.47 (1H, dt, J = 9.6 and 6.9 Hz, H3), 5.38 (1H, dt, J = 9.6 and 6.9 Hz, H4), 3.52 (2H, t, J = 6.9 Hz, H5), 2.64 (2H, t, J = 6.9 Hz, H1), 2.35 (2H, q, J = 6.9 Hz, H2), 0.87 (9H, s, C(CH₃)₃), 0.02 (6H, s, 2×CH₃); δ_C (125 MHz, CDCl₃) 142.0, 130.6, 128.4, 126.4, 125.8, 62.9, 35.9, 31.1, 29.3, 18.4, −5.3. Data are consistent with literature values.¹⁰⁹
(Z)-5-Phenylpent-3-en-1-ol, (Z)-256

\[
\begin{align*}
&\text{To a solution of (Z)-} \text{tert-butyldimethyl((5-phenylpent-3-en-1-yl)oxy)silane (Z)-255 (1.09 g, 3.94 mmol, 1.0 equiv.) in dry THF (7 mL), 1 M tetrabutylammonium fluoride in THF (TBAF, 5.9 mL, 5.9 mmol, 1.5 equiv.) was added, and the mixture was stirred for 4 h at room temperature. The solvent was then} \\
&\text{concentrated in vacuo, and the residue was poured into water. The aqueous phase was extracted with} \\
&\text{Et}_2\text{O (3 \times 15 mL). The organic extract was washed with brine, dried over Na}_2\text{SO}_4 \text{ and concentrated in vacuo. The residue was purified by column chromatography (5→20% EtOAc in petroleum ether) to} \\
&\text{give (Z)-256 as a pale yellow oil (640 mg, 3.60 mmol, 91\%); } R_f = 0.23 \text{ (7:3, petroleum ether:EtOAc);} \\
&\delta_H (500 MHz, CDCl}_3) 7.28–8.31 (2H, m, PhH), 7.18–7.21 (3H, m, PhH), 5.74–5.79 (1H, m, H3), 5.51–5.56 (1H, m, H4), 3.71 (2H, t, } J = 6.6 \text{ Hz, H1), 3.45 (2H, d, } J = 7.3 \text{ Hz, H5, 2.44–2.48 (2H, m, H2),} \\
&1.44 (1H, br s, OH); \delta_C (125 MHz, CDCl}_3 140.9, 131.6, 128.7, 128.5, 128.4, 126.4, 126.2, 62.5, 33.8, 31.0 \text{. Data are consistent with literature values.}\end{align*}
\]

(Z)-N-Acetoxy-4-methyl-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide, (Z)-257

\[
\begin{align*}
&\text{Synthesised from (Z)-5-phenylpent-3-en-1-ol (Z)-256 (217 mg, 1.34 mmol) using Procedure 2. The} \\
&\text{resulting crude material was purified by column chromatography (5→20% EtOAc in petroleum ether) to} \\
&\text{give (Z)-257 as a colourless oil (336 mg, 0.90 mmol, 67\%); } R_f = 0.36 \text{ (4:1, petroleum ether:EtOAc);} \\
&\delta_H (400 MHz, CDCl}_3) 7.79 (2H, d, } J = 8.1 \text{ Hz, TsH), 7.37–7.23 (6H, m, TsH and PhH), 7.20 (1H, t, } J = 7.3 \text{ Hz, PhH), 6.46 (1H, dt, } J = 15.9 \text{ and 7.3 Hz, H4), 6.19 (1 H, dt, } J = 15.9 \text{ and 7.1 Hz, H3),} \\
&3.96 (2H, t, } J = 7.3 \text{ Hz, H1), 3.65 (2H, d, } J = 7.3 \text{ Hz, H5), 2.66 (2H, ap. q, } J = 7.2 \text{ Hz, H2), 2.42} \\
&\text{ (3H, s, ArCH}_3\text{), 1.31 (9H, s, C(CH}_3\text{s)); } \delta_C (100 MHz, CDCl}_3 150.9, 139.0, 137.4, 137.3, 132.6, \\
&129.2, 128.5, 127.9, 127.2, 126.1, 126.0, 84.1, 46.5, 38.7, 33.8, 27.8, 21.6; \text{HRMS } m/z \text{ (ESI+) found} \\
&M–H}^+ 374.1428; \text{C}_{20}\text{H}_{24}\text{NO}_{2}\text{S}^+ \text{ requires 374.1426.}
\end{align*}
\]
(Z)-4-Methyl-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide, (Z)-258

Synthesised from (Z)-N-acetoxy-4-methyl-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide (Z)-257 (300 mg, 0.80 mmol) using Procedure 4. The resulting crude material was purified by column chromatography (5→20% EtOAc in petroleum ether) to give (Z)-258 as a colourless oil (240 mg, 0.76 mmol, 95%); \( R_f \) = 0.37 (4:1, petroleum ether:EtOAc); \( \delta_H \) (400 MHz, CDCl\( _3 \)) 7.74 (2H, d, \( J = 8.3 \) Hz, TsH), 7.35–7.13 (7H, m, TsH and PhH), 6.49 (1H, dt, \( J = 11.6 \) and 7.3 Hz, H4), 5.51 (1H, dt, \( J = 11.6 \) and 7.1 Hz, H3), 4.73–4.56 (1H, br. m, NH), 3.65 (2H, d, \( J = 7.3 \) Hz, H5), 3.09 (2H, ap. q, \( J = 6.5 \) Hz, H1), 2.41 (3H, s, ArC\( _3 \)H), 2.36 (2H, ap. q, \( J = 6.8 \) Hz, H2); \( \delta_C \) (100 MHz, CDCl\( _3 \)) 143.4, 136.9, 136.8, 133.1, 129.7, 128.5, 127.5, 127.1, 126.1, 125.5, 42.5, 38.7, 33.0, 21.5; HRMS m/z (ESI+) found [M–H]\(^+\) 316.1370; \( C_{18}H_{22}NO_2S \) requires 316.1371.

(Z)-4-Methyl-N-(oct-1-yn-1-yl)-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide, (Z)-151e

Synthesised from (Z)-4-methyl-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide (Z)-258 (100 mg, 0.32 mmol) and 1-bromooc-t-1-yn 98a (90 mg, 0.48 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (20% Et\( _2 \)O in petroleum ether) to give (Z)-151e as a colourless oil (97.6 mg, 0.23 mmol, 72%); \( R_f \) = 0.27 (10:1, petroleum ether:Et\( _2 \)O); \( \delta_H \) (400 MHz, CDCl\( _3 \)) 7.76 (2H, d, \( J = 8.1 \) Hz, TsH), 7.36–7.27 (4H, m, TsH and PhH), 7.27–7.20 (3H, m, PhH), 6.50 (1H, dt, \( J = 11.6 \) and 7.3 Hz, H4), 5.59 (1H, dt, \( J = 11.6 \) and 7.2 Hz, H3), 3.62 (2H, d, \( J = 7.3 \) Hz, H5), 3.38 (2H, t, \( J = 7.3 \) Hz, H1), 2.65 (2H, ap. q, \( J = 7.3 \) Hz,H2), 2.44 (3H, s, ArC\( _3 \)H), 2.21 (2H, t, \( J = 6.9 \) Hz, H9), 1.48–1.38 (2H, m, H10), 1.37–1.18 (6H, m, H11–13), 0.88 (3H, t, \( J = 6.7 \) Hz, H14); \( \delta_C \) (100 MHz, CDCl\( _3 \)) 144.2, 137.0, 134.6, 131.4, 129.6, 128.6, 128.2, 127.6, 127.2, 126.8, 72.7,
70.6, 51.1, 36.4, 31.3, 28.8, 28.4, 27.1, 22.5, 21.6, 18.4, 14.0; IR (thin film) ν \text{max}/\text{cm}^{-1} 2929, 2255, 1368, 1160; HRMS m/z (ESI+) found [M+Na]^+ 424.2313; C_{26}H_{33}NNaO_2S requires 424.2310.

(Z)-4-Methyl-N-(phenylethynyl)-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide, (Z)-151f

![Chemical Structure](image)

Synthesised from (Z)-4-methyl-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide (Z)-258 (100 mg, 0.32 mmol) and (bromoethynyl)benzene 98b (90.5 mg, 0.50 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→15% Et\textsubscript{2}O in petroleum ether) to give (Z)-151f as a yellow oil (98.4 mg, 0.24 mmol, 74%); R\text{f} = 0.23 (10:1, petroleum ether:Et\textsubscript{2}O); δ\text{H} (400 MHz, CDCl\textsubscript{3}) 7.76 (2H, d, J = 8.1 Hz, TsH), 7.40–7.28 (6H, m, TsH and PhH), 7.27–7.16 (6H, m, PhH), 6.50 (1H, dt, J = 11.6 and 7.3 Hz, H4), 5.59 (1H, dt, J = 11.6 and 7.2 Hz, H3), 3.62 (2H, d, J = 7.3 Hz, H5), 3.38 (2H, ap. q, J = 7.3 Hz, H1), 2.65 (2H, ap. q, J = 7.3 Hz, H2), 2.44 (3H, s, ArC\textsubscript{H}3); δ\text{C} (100 MHz, CDCl\textsubscript{3}) 144.2, 137.0, 134.6, 131.4, 131.3, 129.6, 128.6, 128.2, 128.1, 127.8, 127.6, 127.2, 126.8, 122.9, 82.7, 70.6, 51.1, 36.4, 27.1, 21.6; IR (thin film) ν \text{max}/\text{cm}^{-1} 2933, 2255, 1363, 1162; HRMS m/z (ESI+) found [M+Na]^+ 438.1508; C_{26}H_{25}NNaO_2S requires 438.1504.

(E)-4-Iodo-3-methylbut-3-en-1-ol, (E)-259

![Chemical Structure](image)

According to the procedure of Spino et al.\textsuperscript{111} To a solution of 3-butyl-1-ol 4 252 (4.52 g, 64.5 mmol, 1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) at 0 °C under argon was added a solution of trimethylaluminium (2M in toluene, 10 mL, 20.0 mmol, 0.3 equiv.) and stirring was continued at the same temperature. To another flask, containing a suspension of ZrC\textsubscript{2}Cl\textsubscript{2} (3.77 g, 12.9 mmol, 0.20 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (240 mL) at –20 °C under argon was added dropwise trimethylaluminium solution (70.5 mL, 141 mmol, 2.2 equiv.) and continued stirring for 15 min. Then H\textsubscript{2}O (1.8 mL, 100.0 mmol, 1.55 equiv.) was added very slowly (Exothermic!), and the resulting yellow slurry was stirred vigorously for 30 min. The mixture of 3-
butyn-1-ol and trimethylaluminium prepared earlier was then cannulated above the slurry at −20 °C, the mixture was allowed to warm to room temperature, and stirred for 3 h. A solution of iodine (19.64 g, 77.4 mmol, 1.2 equiv.) in dry THF (130 mL) was added slowly to the above reaction mixture at −20 °C, and continued stirring at room temperature for 2.5 h. The reaction mixture was decanted into a conical flask containing sat. aq. Rochelle Salt (500 mL) at 0 °C under argon flush. (Exothermic!!) The resulting mixture was stirred for 2 h, filtered through Celite®, washed with Et₂O (100 mL), and the combined organic layers were washed with sat. aq. Na₂S₂O₃, brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by column chromatography (10→20% EtOAc / petroleum ether) to afford (E)-259 as a pale yellow oil. (10.9 g, 51.6 mmol, 80 %); Rₓ = 0.28 (1:1, petroleum ether:EtOAc); δₓH (400 MHz, CDCl₃) 6.02 (1H, d, J = 0.9 Hz, H₄), 3.72 (2H, t, J = 6.3 Hz, H₁), 2.48 (2H, t, J = 6.3 Hz, H₂), 1.88 (3H, d, J = 0.6 Hz, CH₃), 1.41 (1H, br s, OH); δₓC (100 MHz, CDCl₃) 144.6, 76.9, 60.1, 42.3, 23.9 Data are consistent with literature values.¹¹¹

(E)-tert-Butyl((4-iodo-3-methylbut-3-en-1-yl)oxy)dimethylsilane, (E)-260

To an ice-cooled solution of (E)-4-iodo-3-methylbut-3-en-1-ol, (E)-259 (8.3 g, 39.1 mmol, 1.0 equiv.) in CH₂Cl₂ (25 mL) were successively added Et₃N (6.5 mL, 47.0 mmol, 1.2 equiv.), a catalytic amount of DMAP (~ 10 mg.) and TBSCl (6.48 g, 43.0 mmol, 1.1 equiv.). After stirring for 1 h, the reaction mixture was poured into water. The aqueous phase was extracted with CH₂Cl₂ (3 × 25 mL). The organic extract was washed with brine, dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (0→10% Et₂O / petroleum ether) to afford (E)-260 as a colourless oil. (11.6 g, 35.6 mmol, 91 %); Rₓ = 0.47 (5:1, petroleum ether:EtOAc); δₓH (400 MHz, CDCl₃) 5.93 (1H, s, H₄), 3.68 (2H, t, J = 6.8 Hz, H₁), 2.42 (2H, t, J = 6.8 Hz, H₂), 1.84 (3H, s, CH₃), 0.89 (9H, s, C(CH₃)₃), 0.04 (6H, s, 2×CH₃); δₓC (100 MHz, CDCl₃) 147.6, 78.9, 59.1, 45.3, 29.3, 23.9, 18.4, −5.3. Data are consistent with literature values.¹¹¹

111
(E)-3-Methylhept-3-en-1-ol, (E)-261

According to the procedure of Yabuta et al.\textsuperscript{112} A Grignard reagent was prepared in ether from Mg (1.08 g, 45 mmol, 3.0 equiv.) and a catalytic amount of I\textsubscript{2} and 1-bromopropane (6.08 g, 45 mmol, 3.0 equiv.). This solution was added to a solution of (E)-260 (5 g, 15 mmol, 1.0 equiv.) and PdCl\textsubscript{2}(dpff) (3.68 g, 4.5 mmol, 0.3 equiv.) in dry Et\textsubscript{2}O (100 mL) at room temperature. The reaction mixture was stirred for 12 h and then poured into water. The aqueous phase was extracted with Et\textsubscript{2}O (3 × 20 mL), and the organic extract was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The crude residue was dissolved in dry THF (60 mL). To the solution, 1 M tetrabutylammonium fluoride (TBAF, 30 mL, 3 mmol, 0.2 equiv.) was added, and the mixture was stirred for 2 h at room temperature. The solvent was then concentrated \textit{in vacuo}, and the residue was poured into water (80 mL). The aqueous phase was extracted with Et\textsubscript{2}O (3 × 20 mL). The organic extract was washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by column chromatography (0→10% Et\textsubscript{2}O / petroleum ether) to afford (E)-261 as a pale yellow oil. (1.44 g, 11.2 mmol, 75%); \textit{Rf} = 0.24 (5:1, petroleum ether:EtOAc); \textit{\delta}\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 5.23 (1H, t, \textit{J} = 7.3 Hz, H4), 3.64 (2H, t, \textit{J} = 5.8 Hz, H1), 2.26 (2H, t, \textit{J} = 5.8 Hz, H2), 1.99 (2H, dt, \textit{J} = 7.3 and 7.0 Hz, H5), 1.63 (3H, s, CH\textsubscript{3}), 1.37 (2H, sext, \textit{J} = 7.3 Hz, H6), 0.90 (3H, t, \textit{J} = 7.3, H7); \textit{\delta}\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 132.8, 122.4, 58.6, 41.5, 30.1, 23.6, 15.4, 14.9. Data are consistent with literature values.\textsuperscript{112}

Methyl (E)-(3-methylhept-3-en-1-yl)(tosyl)carbamate, (E)-262

Synthesised from (E)-3-methylhept-3-en-1-ol (E)-261 (491 mg, 3.83 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (5→20% Et\textsubscript{2}O in petroleum ether) to
give (E)-262 as a colourless oil (818 mg, 2.41 mmol, 63%); \( R_f = 0.35 \) (9:1, petroleum ether:Et\(_2\)O); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.72–7.70 (2H, m, TsH), 7.33 (2H, d, \( J = 8.2 \) Hz, TsH), 5.22 (1H, t, \( J = 7.3 \) Hz, H4), 3.83 (3H, s, OCH\(_3\)), 3.77 (2H, \( J = 6.4 \) Hz, H1), 2.43 (3H, s, ArCH\(_3\)), 2.30 (2H, ap q, \( J = 7.1 \) Hz, H5), 2.07–1.98 (2H, m, H2), 1.65 (3H, s, CH\(_3\)), 1.44 (2H, m, H6), 0.95 (3H, t, \( J = 7.6 \) Hz, H7); \( \delta_c \) (100 MHz, CDCl\(_3\)) 172.4, 144.6, 134.6, 130.3, 130.0, 129.7, 127.7, 54.4, 51.9, 45.0, 23.6, 21.6, 21.2, 15.7, 14.2; HRMS m/z (ESI+) found [M–H]\(^+\) 340.1580; \( \text{C}_{17}\text{H}_{26}\text{NO}_4\text{S} \) requires 340.1583.

(E)-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide, (E)-263

Synthesised from methyl (E)-(3-methylhept-3-en-1-yl)tosylcarbamate (E)-262 (500 mg, 1.47 mmol) using Procedure 4. The resulting crude material was purified by column chromatography (5→20% EtOAc in petroleum ether) to give (E)-263 as a colourless oil (398 mg, 1.41 mmol, 96%); \( R_f = 0.12 \) (5:1, petroleum ether:EtOAc); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.72 (2H, d, \( J = 8.2 \) Hz, TsH), 7.33 (2H, d, \( J = 8.2 \) Hz, TsH), 5.22 (1H, t, \( J = 7.3 \) Hz, H4), 4.86 (1H, br s, NH), 3.77 (2H, t, \( J = 6.4 \) Hz, H1), 2.43 (3H, s, ArCH\(_3\)), 2.30 (2H, ap q, \( J = 7.1 \) Hz, H5), 2.07–1.98 (2H, m, H2), 1.65 (3H, s, CH\(_3\)), 1.42 (2H, m, H6), 0.93 (3H, t, \( J = 7.6 \) Hz, H7); \( \delta_c \) (100 MHz, CDCl\(_3\)) 144.6, 134.6, 130.3, 130.0, 129.7, 127.7, 46.4, 40.0, 23.6, 21.6, 21.2, 15.7, 14.2; HRMS m/z (ESI+) found [M–H]\(^+\) 281.1450; \( \text{C}_{15}\text{H}_{23}\text{NO}_2\text{S} \) requires 281.1449.

(E)-4-Methyl-N-(3-methylhept-3-en-1-yl)-N-(oct-1-yn-1-yl)benzenesulfonamide, (E)-264a

Synthesised from (E)-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide (E)-263 (150 g, 0.53 mmol) and 1-bromooct-1-yne 98a (202 mg, 1.07 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (20% Et\(_2\)O in petroleum ether) to give (E)-264a as a colourless oil (161 mg, 0.41 mmol, 78%); \( R_f = 0.32 \) (9:1, petroleum ether:EtOAc); \( \delta_H \) (400 MHz,
Chapter 7: Experimental

CDCl$_3$ 7.77 (2H, d, $J = 8.2$ Hz, TsH), 7.32 (2H, d, $J = 8.2$ Hz, TsH), 5.22 (1H, t, $J = 7.3$ Hz, H4), 3.30–3.24 (2H, m, H1), 2.44 (3H, s, ArCH$_3$), 2.42 (2H, ap q, $J = 7.1$ Hz, H5), 2.33–2.25 (2H, m, H2), 2.26 (2H, t, $J = 6.9$ Hz, H10), 2.01–1.98 (2H, m, H6), 1.55 (3H, s, CH$_3$), 1.51–1.42 (2H, m, H11), 1.39–1.19 (6H, m, H12–14), 0.90 (3H, t, $J = 6.8$ Hz, H7), 0.88 (3H, t, $J = 6.8$ Hz, H15); $\delta$C (100 MHz, CDCl$_3$) 144.6, 134.6, 131.3, 130.3, 130.0, 129.7, 127.7, 54.4, 45.0, 31.3, 28.9, 28.4, 23.6, 22.6, 21.6, 21.2, 18.5, 15.7, 14.2, 14.1; IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 2932, 2263, 1361, 1164; HRMS m/z (ESI+) found [M+Na$^+$]+ 412.2285; C$_{23}$H$_{35}$NNaO$_2$S$^+$ requires 412.2286.

(\textit{E})-4-Methyl-N-(3-methylhept-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide, (\textit{E})-264b

![Chemical Structure of (\textit{E})-264b]

Synthesised from (\textit{E})-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide (\textit{E})-263 (150 g, 0.53 mmol) and (bromoethynyl)benzene 98b (163 mg, 0.90 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→15% Et$_2$O in petroleum ether) to give (\textit{E})-264b as a yellow oil (172 mg, 0.45 mmol, 84%); $R_f = 0.48$ (5:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.77 (2H, d, $J = 8.2$ Hz, TsH), 7.40–7.32 (4H, m, TsH and PhH), 7.30–7.26 (3H, m, PhH), 5.23 (1H, t, $J = 7.3$ Hz, H4), 3.30–3.24 (2H, m, H1), 2.44 (3H, s, ArCH$_3$), 2.42 (2H, ap q, $J = 7.1$ Hz, H5), 2.33–2.25 (2H, m, H2), 2.01–1.98 (2H, m, H6), 1.55 (3H, s, CH$_3$), 0.90 (3H, t, $J = 6.8$ Hz, H7); $\delta$C (100 MHz, CDCl$_3$) 144.6, 134.6, 131.3, 130.3, 130.0, 129.7, 127.8, 127.7, 122.8, 82.3, 70.8, 54.4, 45.0, 23.6, 21.6, 21.2, 15.7, 14.2; IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 2933, 2257, 1364; HRMS m/z (ESI+) found [M+Na$^+$]+ 404.1658; C$_{23}$H$_{27}$NNaO$_2$S$^+$ requires 404.1660.
(Z)-4-Iodo-3-methylbut-3-en-1-ol, (Z)-259

According to the procedure of Theodorakis et al.\textsuperscript{113} To a solution of ZrCp\textsubscript{2}Cl\textsubscript{2} (5.00 g, 17.1 mmol, 0.20 equiv.) in 1,2-DCE (140 mL) at 0 °C was added a solution of trimethylaluminum (2M, 107 mL, 214 mmol, 2.5 equiv.) in hexanes dropwise. A solution of but-3-yn-1-ol \textsuperscript{252} (6.49 mL, 86 mmol, 1.0 equiv.) in 1,2-DCE (20 mL) was then added dropwise. The solution was stirred at room temperature overnight. The solution was then heated at reflux for 3 days. The reaction was then cooled to –40 °C and a solution of iodine (43.5 g, 171 mmol, 2 equiv.) in dry THF (100 mL) was added via cannula. The solution was stirred for 30 minutes before allowed to warm up to 0 °C. Sat. aq. K\textsubscript{2}CO\textsubscript{3} was added very slowly (the solution frothed and bubbled) until eventually turning yellow with precipitate. Et\textsubscript{2}O (250 mL) was added and the solution was filtered through Celite\textsuperscript{®}. The mixture was extracted with Et\textsubscript{2}O (200 mL) to remove all unwanted organics. H\textsubscript{2}O (200 mL) was added to the organic phase. The aqueous layer was then extracted with Et\textsubscript{2}O (3× 30 mL). The combined organic layers were washed once with brine, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The resulting crude material was purified by column chromatography (10→20% EtOAc in petroleum ether) to give (Z)-259 as a light brown oil (10.9 g, 51.6 mmol, 60%); \(R_f = 0.31\) (1:1, petroleum ether:EtOAc), \(\delta_H\) (400 MHz, CDCl\textsubscript{3}) 6.01 (1H, d, \(J = 1.4\) Hz, H4), 3.78 (2H, t, \(J = 6.7\) Hz, H1), 2.53 (2H, t, \(J = 6.7\) Hz, H2), 1.94 (3H, d, \(J = 1.5\) Hz, CH\textsubscript{3}), 1.47 (1H, br s, OH); \(\delta_C\) (100 MHz, CDCl\textsubscript{3}) 144.3, 76.3, 60.1, 41.6, 23.8. Data are consistent with literature values.\textsuperscript{113}
To an ice-cooled solution of (Z)-4-iodo-3-methylbut-3-en-1-ol, (Z)-259 (8.0 g, 37.7 mmol, 1.0 equiv.) in CH₂Cl₂ (20 ml) were successively added Et₃N (6.25 mL, 45.2 mmol, 1.2 equiv.), a catalytic amount of DMAP (~10 mg) and TBSCl (6.25 mg, 41.5 mmol, 1.1 equiv.). After stirring for 1 h, the reaction mixture was poured into water. The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The organic extract was washed with brine, dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (10→20% Et₂O / petroleum ether) to afford (Z)-260 as a colourless oil. (11.9 g, 36.6 mmol, 97%); Rₛ = 0.52 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl₃) 5.93 (1H, s, H₄), 3.68 (2H, t, J = 6.4 Hz, H₁), 2.41 (2H, t, J = 6.4 Hz, H₂), 1.85 (H₃, s, C(CH₃)), 0.88 (9H, s, C(CH₃)₃); δC (100 MHz, CDCl₃) 146.9, 83.9, 60.1, 45.3, 29.3, 23.9, 18.4, -5.3. Data are consistent with literature values.¹¹²

(Z)-3-Methylhept-3-en-1-ol, (Z)-261

According to the procedure of Yabuta et al.¹¹² A Grignard reagent was prepared in dry Et₂O from Mg (1.08 g, 45 mmol, 3.0 equiv.) and a catalytic amount of I₂ and 1-bromopropane (6.08 g, 45 mmol, 3.0 equiv.). This solution was added to a solution of (Z)-260 (5 g, 15 mmol, 1.0 equiv.) and PdCl₂(dppf) (3.68 g, 4.5 mmol, 0.3 equiv.) in dry Et₂O (100 mL) at room temperature. The reaction mixture was stirred for 12 h and then poured into water. The aqueous phase was extracted with Et₂O (3 × 20 mL), and the organic extract was dried over Na₂SO₄ and concentrated in vacuo. The crude residue was dissolved in dry THF (60 mL). To the solution, 1 M tetrabutylammonium fluoride (TBAF, 30 mL, 3 mmol, 0.2 equiv.) was added, and the mixture was stirred for 2 h at room temperature. The solvent was then concentrated in vacuo, and the residue was poured into water (80 mL). The aqueous phase was
extracted with Et₂O (3 × 20 mL). The organic extract was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (0→10% Et₂O / petroleum ether) to afford (Z)-261 as a pale yellow oil. (1.57 g, 12.2 mmol, 82%); R_f = 0.21 (5:1, petroleum ether:EtOAc); δ_H (400 MHz, CDCl₃) 5.34 (1H, t, J = 7.3 Hz, H₄), 3.65 (2H, t, J = 6.3 Hz, H₁), 2.30 (2H, t, J = 6.3 Hz, H₂), 2.00 (2H, dt, J = 7.3 and 7.0 Hz, H₅), 1.71 (3H, s, CH₃), 1.36 (2H, sext, J = 7.3 Hz, H₆), 0.90 (3H, t, J = 7.3, H₇);
δ_C (100 MHz, CDCl₃) 130.6, 121.6, 58.4, 41.3, 30.2, 23.6, 15.4, 14.9. Data are consistent with literature values.¹¹²

Methyl (Z)-(3-methylhept-3-en-1-yl)(tosyl)carbamate, (Z)-262

Synthesised from (Z)-3-methylhept-3-en-1-ol (Z)-261 (490 g, 3.82 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (5→20% Et₂O in petroleum ether) to give (Z)-262 as a colourless oil (869 mg, 2.56 mmol, 67%); R_f = 0.38 (9:1, petroleum ether:Et₂O); δ_H (400 MHz, CDCl₃) 7.72–7.70 (2H, m, TsH), 7.33 (2H, d, J = 8.2 Hz, TsH), 5.35 (1H, t, J = 7.3, Hz, H₄), 3.82 (3H, s, OCH₃), 3.75 (2H, t, J = 6.4 Hz, H₁), 2.46 (3H, s, ArCH₃), 2.33 (2H, ap q, J = 7.1 Hz, H₅), 2.07–1.98 (2H, m, H₂), 1.75 (3H, s, CH₃), 1.44 (2H, m, H₆), 0.95 (3H, t, J = 7.6 Hz, H₇); δ_C (100 MHz, CDCl₃) 172.4, 144.6, 134.6, 130.3, 130.0, 129.7, 127.7, 54.6, 53.9, 42.0, 23.1, 21.5, 21.2, 15.7, 14.2; HRMS m/z (ESI+) found [M–H]⁺ 340.1581; C₁₇H₂₆NO₄S⁺ requires 340.1583.

(Z)-4-Methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide, (Z)-263

Synthesised from methyl (Z)-(3-methylhept-3-en-1-yl)(tosyl)carbamate (Z)-262 (500 mg, 1.47 mmol) using Procedure 4. The resulting crude material was purified by column chromatography (5→20% EtOAc in petroleum ether) to give (Z)-263 as a colourless oil (405 mg, 1.44 mmol, 98%); R_f = 0.15
(5:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.72 (2H, d, $J = 8.2$ Hz, TsH), 7.33 (2H, d, $J = 8.2$ Hz, TsH), 5.35 (1H, t, $J = 7.3$ Hz, H4), 4.63 (1H, br s, NH), 3.77 (2H, t, $J = 6.4$ Hz, H1), 2.43 (3H, s, ArCH$_3$), 2.30 (2H, ap q, $J = 7.1$ Hz, H5), 2.07–1.98 (2H, m, H2), 1.73 (3H, s, CH$_3$), 1.42 (2H, m, H6), 0.93 (3H, t, $J = 7.6$ Hz, H7); $\delta_C$ (100 MHz, CDCl$_3$) 144.6, 134.6, 130.3, 130.0, 129.7, 127.7, 46.4, 41.5, 22.8, 21.6, 21.2, 15.7, 14.2; HRMS $m/z$ (ESI+) found [M–H]+ 281.1451; C$_{15}$H$_{23}$NO$_2$S+ requires 281.1449.

(Z)-4-Methyl-N-(3-methylhept-3-en-1-yl)-N-(oct-1-yn-1-yl)benzenesulfonamide, (Z)-264a

![Chemical Structure](image)

Synthesised from (Z)-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide (Z)-263 (150 g, 0.53 mmol) and 1-bromo-oct-1-ylene 98a (202 mg, 1.07 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (20% Et$_2$O in petroleum ether) to give (Z)-264a as a colourless oil (173 mg, 0.44 mmol, 83%); $R_f = 0.33$ (9:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 7.78 (2H, d, $J = 8.2$ Hz, TsH), 7.32 (2H, d, $J = 8.2$ Hz, TsH), 5.34 (1H, t, $J = 7.3$ Hz, H4), 3.30–3.24 (2H, m, H1), 2.44 (3H, s, ArCH$_3$), 2.42 (2H, ap q, $J = 7.1$ Hz, H5), 2.33–2.25 (2H, m, H2), 2.26 (2H, t, $J = 6.9$ Hz, H10), 2.01–1.98 (2H, m, H6), 1.55 (3H, s, CH$_3$), 1.51–1.42 (2H, m, H11), 1.39–1.19 (6H, m, H12–14), 0.89 (3H, t, $J = 6.8$ Hz, H7), 0.87 (3H, t, $J = 6.8$ Hz, H15); $\delta_C$ (100 MHz, CDCl$_3$) 144.6, 134.6, 130.3, 130.0, 129.7, 127.7, 54.4, 46.4, 41.3, 28.9, 28.4, 23.6, 22.6, 21.6, 21.2, 18.5, 15.7, 14.2, 14.1; IR (thin film) $\nu_{max}$/cm$^{-1}$ 2938, 2243, 1360, 1166; HRMS $m/z$ (ESI+) found [M+Na]$^+$ 412.2285; C$_{23}$H$_{35}$NNaO$_2$S+ requires 412.2286.
(Z)-4-Methyl-N-(3-methylhept-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide, (Z)-264b

![Chemical Structure](image)

Synthesised from (Z)-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide (Z)-263 (150 g, 0.53 mmol) and (bromoethynyl)benzene 98b (164 mg, 0.91 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→15% Et₂O in petroleum ether) to give (Z)-264b as a yellow oil (176 mg, 0.46 mmol, 87%); \( R_f = 0.47 \) (petroleum ether:EtOAc); \( \delta_H \) (400 MHz, CDCl₃) 7.78 (2H, d, \( J = 8.2 \) Hz, Ts\( \mathbf{H} \)), 7.40–7.32 (4H, m, Ts\( \mathbf{H} \) and Ph\( \mathbf{H} \)), 7.31–7.05 (3H, m, Ph\( \mathbf{H} \)), 5.34 (1H, t, \( J = 7.3 \) Hz, H4), 3.30–3.24 (2H, m, H1), 2.44 (3H, s, ArC\( \mathbf{H} \)), 2.42 (2H, ap q, \( J = 7.1 \) Hz, H5), 2.33–2.25 (2H, m, H2), 2.01–1.98 (2H, m, H6), 1.55 (3H, s, CH₃), 0.89 (3H, t, \( J = 6.8 \) Hz, H7); \( \delta_C \) (100 MHz, CDCl₃) 144.6, 134.6, 131.3, 130.3, 130.0, 129.7, 128.2, 127.8, 127.7, 122.8, 82.3, 70.9, 46.4, 41.3, 23.6, 21.6, 21.2, 15.7, 14.2; \( \text{IR (thin film)} \ v_{\text{max}}/\text{cm}^{-1} \) 2936, 2247, 1362, 1159; \( \text{HRMS m/z (ESI+) found } [\text{M+Na}]^+ \) 404.1658; \( C_{23}H_{27}NNaO_{2}S^+ \) requires 404.1660.

(E)-4-Methyloct-3-en-1-ol, (E)-266

![Chemical Structure](image)

According to the procedure of Takacs et al.\(^\text{114}\) 2,3-dihydrofuran 265 (3.0 g, 43 mmol, 1.8 equiv.) was dissolved in dry THF (20 mL) with subsequent cooling (–50 °C). \( \text{t-Butyllithium (1.7 M solution in pentanes, 16.7 mL, 28.3 mmol, 1.2 equiv.) was then added dropwise over 2 h. The mixture was allowed to slowly warm to –5 °C, and then was cooled to –20 °C, followed by the addition of 1-iodobutane (4.35 g, 23.7 mmol, 1.0 equiv.) over 1 h at the same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was then cooled to 0 °C, and poured into sat. aq. NH₄Cl (100 mL) and Et₂O (100 mL). The aqueous was extracted with Et₂O (3 x 100 mL), and the combined organic layers were dried over MgSO₄ followed by concentration in vacuo. The resulting oil
(crude 2,3-dihydro-5-butylfuran) was used for the next step without purification. To a solution of NiCl₂(PPh₃)₂ (1.95 g, 3.0 mmol) in dry benzene (43 mL) was added methylmagnesium bromide (4.85 mL, 3 M solution in Et₂O, 14.5 mmol, 0.61 equiv.) at room temperature. After stirring for 1 h, more methylmagnesium bromide (20 mL of 3 M solution in Et₂O, 60 mmol, 2.5 equiv.) was added before the excess solvent was removed in vacuo. The residue was taken up in benzene (60 mL) and transferred to a three-neck round bottom flask equipped with a condenser. A solution of 2,3-dihydro-5-butylfuran in benzene (6 mL) was added and the resulting mixture was heated to reflux for 3 h. The mixture was cooled to 0 °C and poured as a steady, slow stream into pre-cooled sat. aq. NH₄Cl (100 mL). The stirring was continued for 30 min, followed by separation of the organic layer and aqueous extract with Et₂O (3 x 100 mL). The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The resulting crude material was purified by column chromatography (15→20% EtOAc in petroleum ether) to give (E)-266 as a pale yellow oil (2.43 g, 17.1 mmol, 72%); Rᶠ = 0.50 (4:1, petroleum ether:EtOAc); δ_H (400 MHz, CDCl₃) 5.21–5.13 (1H, m, H₃), 3.63 (2H, t, J = 6.8 Hz, H₁), 2.36–2.25 (2H, m, H₂), 2.00 (2H, t, J = 7.2 Hz, H₅), 1.66 (3H, s, CH₃), 1.46–1.33 (2H, m, H₆), 1.35–1.25 (2H, m, H₇), 0.91 (3H, t, J = 7.2 Hz, H₈); δ_C (100 MHz, CDCl₃) 139.2, 119.5, 62.5, 39.6, 31.5, 30.2, 22.4, 16.0, 13.9; IR (thin film) ν_max/cm⁻¹ 3335, 2950, 1456, 1370, 1050; HRMS m/z (ESI+) found [M+Na⁺] 165.1250; C₉H₁₈NaO⁺ requires 165.1255.

**Methyl (E)-(4-methyloct-3-en-1-yl)(tosyl)carbamate, (E)-267**

![](image)

Synthesised from (E)-4-methyloct-3-en-1-ol (E)-266 (1.00 g, 7.03 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (5→20% Et₂O in petroleum ether) to give (E)-267 as a colourless oil (1.76 g, 5.00 mmol, 71%); Rᶠ = 0.56 (4:1, petroleum ether:EtO); δ_H (400 MHz, CDCl₃) 7.77 (2H, d, J = 8.2 Hz, TsH), 7.33 (2H, d, J = 8.2 Hz, TsH), 5.29 (t, J = 5.1 Hz, H₃), 3.84 (3H, s, OCH₃), 3.60 (2H, t, J = 7.1 Hz, H₁), 2.51 (2H, ap q, J = 7.0 Hz, H₂), 1.95 (2H, t, J =
7.0 Hz, H5), 1.59 (3H, s, CH3), 1.48–1.28 (4H, m, H6 and H7), 0.92 (3H, t, J = 7.2 Hz, H8); \(\delta_c\) (100 MHz, CDCl3) 173.3, 142.7, 136.4, 136.2, 131.0, 129.3, 123.1, 53.2, 43.9, 39.9, 29.8, 26.8, 26.3, 23.4, 20.5, 14.6; HRMS m/z (ESI+) found [M–H]+ 354.1740; \(\text{C}_{18}\text{H}_{28}\text{NO}_{4}\text{S}\) requires 354.1739.

\((E)-4\)-Methyl-N-\((4\)-methyl-3-en-1-yl\)benzenesulfonamide, \((E)-268\)

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

Synthesised from methyl \((E)-(4\)-methyl-3-en-1-yl\)-(tosyl)carbamate \((E)-267\) (1.00 g, 2.83 mmol) using Procedure 4. The resulting crude material was purified by column chromatography (5→20% EtOAc in petroleum ether) to give \((E)-268\) as a colourless oil (835 mg, 2.82 mmol, 99%); \(R_f = 0.21\) (4:1, petroleum ether:EtOAc); \(\delta_H\) (400 MHz, CDCl3) 7.77 (2H, d, \(J = 8.2\) Hz, TsH), 7.33 (2H, d, \(J = 8.2\) Hz, TsH), 5.43 (t, \(J = 6.4\) Hz, H3), 4.84 (1H, br s, NH), 3.10 (2H, t, \(J = 7.0\) Hz, H1), 2.41 (2H, ap q, \(J = 6.9\) Hz, H2), 2.15 (2H, t, \(J = 7.0\) Hz, H5), 1.59 (3H, s, CH3), 1.48–1.28 (4H, m, H6 and H7), 0.92 (3H, t, \(J = 7.2\) Hz, H8); \(\delta_c\) (100 MHz, CDCl3) 142.8, 138.0, 135.6, 130.4, 127.2, 123.1, 44.6, 40.5, 29.8, 27.8, 26.0, 23.1, 21.6, 14.4; HRMS m/z (ESI+) found [M–H]+ 296.1682; \(\text{C}_{16}\text{H}_{26}\text{NO}_{2}\text{S}\) requires 296.1684.

\((E)-4\)-Methyl-N-\((4\)-methyl-3-en-1-yl\)-\(N\)-(oct-1-yn-1-yl)benzenesulfonamide, \((E)-269a\)

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

Synthesised from \((E)-4\)-methyl-N-\((4\)-methyl-3-en-1-yl\)benzenesulfonamide \((E)-268\) (200 mg, 0.68 mmol) and 1-bromooct-1-yne \(98a\) (205 mg, 1.08 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (20% Et\(_2\)O in petroleum ether) to give \((E)-269a\) as a colourless oil (214 mg, 0.53 mmol, 78%); \(R_f = 0.39\) (9:1, petroleum ether:EtOAc); \(\delta_H\) (400 MHz, CDCl3) 7.75 (2H, d, \(J = 8.1\) Hz, TsH), 7.42 (2H, d, \(J = 8.1\) Hz, TsH), 5.27 (1H, t, \(J = 7.0\) Hz, H3), 3.34
(2H, t, J = 5.9 Hz, H1), 2.45 (2H, ap q, J = 6.0 Hz, H2), 2.43 (3H, s, ArCH₃), 2.25 (2H, t, J = 6.1 Hz, H11), 1.92 (2H, t, J = 7.0 Hz, H5), 1.59 (3H, s, CH₃), 1.55–1.37 (4H, m, H6 and H12), 1.37–1.23 (8H, m, H7 and H13–15), 0.90 (6H, m, H8 and H16); δc (100 MHz, CDCl₃) 143.9, 137.8, 129.6, 128.1, 123.3, 76.1, 58.6, 51.0, 35.5, 31.1, 29.8, 28.9, 28.5, 27.6, 26.1, 22.7, 18.6, 16.1, 14.9, 14.0; IR (thin film) νmax/cm⁻¹ 2932, 2255, 1363, 1161; HRMS m/z (ESI+) found [M+Na]⁺ 426.2440; C₁₉H₃₇NNaO₂S⁺ requires 426.2443.

(E)-4-Methyl-N-(4-methyloct-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide, (E)-269b

Synthesised from (E)-4-methyl-N-(4-methyloct-3-en-1-yl)benzenesulfonamide (E)-268 (150 g, 0.51 mmol) and (bromoethynyl)benzene 98b (157 mg, 0.87 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (5→20% Et₂O in petroleum ether) to give (E)-269b as a yellow oil (163 mg, 0.41 mmol, 81%); Rf = 0.34 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl₃) 7.75 (2H, d, J = 8.1 Hz, TsH), 7.42–7.31 (4H, m, TsH and PhH), 7.30–7.22 (3H, m, PhH), 5.27 (1H, t, J = 7.0 Hz, H3), 3.34 (2H, t, J = 5.9 Hz, H1), 2.45 (2H, ap q, J = 6.0 Hz, H2), 2.43 (3H, s, ArCH₃), 2.01 (2H, t, J = 7.0 Hz, H5), 1.59 (3H, s, CH₃), 1.45–1.37 (2H, m, H6), 1.35–1.32 (2H, m, H7), 0.90 (3H, t, J= 7.2 Hz, H8); δc (100 MHz, CDCl₃) 144.1, 136.6, 131.1, 130.0, 129.6, 128.3, 127.1, 125.7, 123.3, 81.8, 69.0, 50.9, 39.9, 29.4, 27.6, 22.5, 21.7, 16.1, 14.3; IR (thin film) νmax/cm⁻¹ 2932, 2253, 1361, 1162; HRMS m/z (ESI+) found [M+Na]⁺ 418.1821; C₂₁H₂₉NNaO₂S⁺ requires 418.1817.

(Z)-4-Methyloct-3-en-1-ol, (Z)-266

According to the procedure of Sigman et al.¹¹⁵ (A1Me₃)₂ (6.3 mL, 66 mmol, 2.2 equiv.) was transferred via syringe into CH₂Cl₂ (100 mL) contained in a three-necked round-bottom flask equipped with a gas inlet, rubber septa, and a magnetic stirring bar. The solution was cooled to 0 °C and oct-3-yn-1-ol 270
(3.7 mL, 30 mmol, 1.0 equiv.) was added slowly via syringe through a septum. The liberated methane was vented through the gas. The solution was then cooled to –78 °C, and neat TiCl₄ (3.6 mL, 33 mmol, 1.1 equiv.) was added dropwise to the reaction. The reaction mixture was stirred at –45 °C for 1 h, and then quenched via syringe addition of pre-cooled (0 °C) MeOH (30 mL). Aq. 3 N HCl sat. with NaCl (200 mL) was then added. The reaction mixture was allowed to warm to room temperature and stirred for 45 min. The combined organic layers were washed with H₂O and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (5→15% EtOAc in petroleum ether) to give (Z)-266 as a pale yellow oil (2.35 g, 16.5 mmol, 55%); RF = 0.53 (4:1, petroleum ether:EtOAc); δH (500 MHz, CDCl₃) 5.21–5.13 (1H, m, H₃), 3.63 (2H, t, J = 6.8 Hz, H₁), 2.36–2.25 (2H, m, H₂), 2.00 (2H, t, J = 7.2 Hz, H₅), 1.66 (3H, s, CH₃), 1.46–1.33 (2H, m, H₆), 1.35–1.25 (2H, m, H₇), 0.91 (3H, t, J = 7.2 Hz, H₈); δC (125 MHz, CDCl₃) 139.4, 120.2, 62.6, 31.6, 31.3, 30.3, 23.5, 22.7, 14.0; IR (thin film) νmax/cm⁻¹ 3315, 2960, 2930, 2857, 14551 1381, 1050, 842; HRMS m/z (ESI+) found [M+Na⁺] 165.1250; C₉H₁₈NO⁺ requires 165.1255.

Methyl (Z)-(4-methyloct-3-en-1-yl)(tosyl)carbamate, (Z)-267

![Structure of (Z)-267](image)

Synthesised from (Z)-3-methylhept-3-en-1-ol (Z)-266 (1.00 g, 7.03 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (5→20% Et₂O in petroleum ether) to give (Z)-267 as a colourless oil (1.63 g, 4.64 mmol, 66%); RF = 0.54 (4:1, petroleum ether:Et₂O); δH (400 MHz, CDCl₃) 7.77 (2H, d, J = 8.2 Hz, TsH), 7.33 (2H, d, J = 8.2 Hz, TsH), 5.35 (t, J = 6.2 Hz, H₃), 3.84 (3H, s, OCH₃), 3.77 (2H, t, J = 7.1 Hz, H₁), 2.41 (2H, ap q, J = 7.0 Hz, H₂), 1.95 (2H, t, J = 7.0 Hz, H₅), 1.59 (3H, s, CH₃), 1.48–1.28 (4H, m, H₆ and H₇), 0.92 (3H, t, J = 7.2 Hz, H₈); δC (100 MHz, CDCl₃) 173.3, 142.8, 136.8, 136.1, 130.8, 129.3, 123.0, 53.2, 43.9, 37.5, 29.8, 26.8, 26.4, 23.4, 20.5, 14.6; HRMS m/z (ESI+) found [M–H]⁻ 354.1741; C₁₉H₂₈NO₄S⁻ requires 354.1739.
(Z)-4-Methyl-N-(4-methyloct-3-en-1-yl)benzenesulfonamide, (Z)-268

\[
\begin{align*}
\text{H} & \quad \text{O=S=O} \\
\text{O} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\end{align*}
\]

Synthesised from methyl (Z)-(4-methyloct-3-en-1-yl)(tosyl)carbamate (Z)-267 (1.00 g, 2.83 mmol) using Procedure 4. The resulting crude material was purified by column chromatography (5→20% EtOAc in petroleum ether) to give (Z)-268 as a colourless oil (833 mg, 2.81 mmol, 98%); \( R_f = 0.25 \) (4:1, petroleum ether:EtOAc); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.77 (2H, d, \( J = 8.2 \) Hz, TsH), 7.33 (2H, d, \( J = 8.2 \) Hz, TsH), 5.28 (1H, t, \( J = 6.8 \) Hz, H3), 4.84 (1H, br s, NH), 3.60 (2H, t, \( J = 7.0 \) Hz, H1), 3.21 (2H, ap q, \( J = 6.9 \) Hz, H2), 2.15 (2H, t, \( J = 7.0 \) Hz, H5), 1.59 (3H, s, CH\(_3\)), 1.48–1.28 (4H, m, H6 and H7), 0.92 (3H, t, \( J = 6.9 \) Hz, H8); \( \delta_c \) (100 MHz, CDCl\(_3\)) 142.8, 137.9, 135.6, 130.1, 127.2, 123.1, 44.6, 37.5, 29.8, 27.7, 26.0, 23.1, 21.6, 14.3; HRMS m/z (ESI+) found [M–H]\(^+\) 296.1682; C\(_{16}\)H\(_{26}\)NO\(_2\)S\(^+\) requires 296.1684.

(Z)-4-Methyl-N-(4-methyloct-3-en-1-yl)-N-(oct-1-yn-1-yl)benzenesulfonamide, (Z)-269a

\[
\begin{align*}
\text{H} & \quad \text{O=S=O} \\
\text{O} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\end{align*}
\]

Synthesised from (Z)-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide (Z)-268 (200 mg, 0.68 mmol) and 1-bromooct-1-yne 98a (206 mg, 1.09 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (20% Et\(_2\)O in petroleum ether) to give (Z)-269a as a colourless oil (206 mg, 0.51 mmol, 75%); \( R_f = 0.37 \) (9:1, petroleum ether:EtOAc); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.77 (2H, d, \( J = 8.1 \) Hz, TsH), 7.42 (2H, d, \( J = 8.1 \) Hz, TsH), 5.37 (1H, t, \( J = 6.4 \) Hz, H3), 3.34 (2H, t, \( J = 5.9 \) Hz, H1), 2.45 (2H, ap q, \( J = 6.0 \) Hz, H2), 2.43 (3H, s, ArCH\(_3\)), 2.25 (2H, t, \( J = 6.1 \) Hz,
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H11), 1.92 (2H, t, J = 7.0 Hz, H5), 1.64 (3H, s, CH3), 1.55–1.37 (4H, m, H6 and H12), 1.37–1.23 (8H, m, H7 and H13–15), 0.95–0.84 (6H, m, H8 and H16); δC (100 MHz, CDCl3) 144.1, 136.8, 129.6, 128.1, 123.3, 76.1, 58.6, 51.0, 35.5, 31.1, 29.8, 28.9, 28.5, 26.6, 26.1, 22.3, 22.1, 21.6, 18.5, 14.9, 14.1; IR (thin film) νmax/cm⁻¹ 2931, 2252, 1367, 1161; HRMS m/z (ESI+) found [M+Na]+ 426.2441; C24H37NNaO2S+ requires 426.2443.

(Z)-4-Methyl-N-(4-methloct-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide, (Z)-269b

Synthesised from (Z)-4-methyl-N-(3-methylhept-3-en-1-yl)benzenesulfonamide (Z)-268 (150 g, 0.51 mmol) and (bromoethynyl)benzene 98b (160 mg, 0.89 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (10→15% Et2O in petroleum ether) to give (Z)-269b as a yellow oil (165 mg, 0.42 mmol, 82%); Rf = 0.35 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 7.7 (2H, d, J = 8.1 Hz, TsH), 7.42–7.31 (4H, m, TsH and PhH), 7.30–7.22 (3H, m, PhH), 5.35 (1H, t, J = 6.5 Hz, H3), 3.34 (2H, t, J = 5.9 Hz, H1), 2.45 (2H, ap q, J = 6.0 Hz, H2), 2.42 (3H, s, ArCH3), 2.01 (2H, t, J = 7.0 Hz, H5), 1.59 (3H, s, CH3), 1.45–1.37 (2H, m, H6), 1.35–1.32 (2H, m, H7), 0.90 (3H, t, J = 7.2 Hz, H8); δc (100 MHz, CDCl3) 144.2, 136.8, 131.0, 129.9, 129.5, 128.3, 127.1, 125.7, 123.3, 81.8, 69.0, 50.9, 36.9, 29.4, 26.6, 26.1, 22.5, 20.1, 14.3; IR (thin film) νmax/cm⁻¹ 2936, 2242, 1359, 1163; HRMS m/z (ESI+) found [M+Na]+ 418.1821; C24H29NNaO2S+ requires 418.1817.

2-(Cyclohex-1-en-1-yl)ethan-1-ol, 272

To a suspension of LiAlH4 (183 mg, 4.82 mmol, 1.5 equiv.) in dry THF (4 mL) at 0 °C was added a solution of 2-(cyclohex-1-en-1-yl)acetic acid 271 (450 mg, 3.21 mmol, 1.0 equiv.) in dry THF (4 mL). The reaction mixture was stirred at room temperature for 5 h. The solution was cooled to 0 °C, H2O (1
mL/g LiAlH₄) added dropwise, followed by 4M aq. NaOH (1 mL/g LiAlH₄), further H₂O (3 mL/g LiAlH₄) and then excess MgSO₄. The reaction mixture was stirred at room temperature for 1 h, filtered through Celite® eluting with Et₂O and concentrated in vacuo. The resulting crude material was purified by column chromatography (20→30% EtOAc in petroleum ether) to give 272 as a colourless oil (138 mg, 1.15 mmol, 36%); R_f = 0.38 (7:3, petroleum ether:EtOAc); δ_H (400 MHz, CDCl₃) 5.49 (1H, br. s, H₄), 3.66 (2H, t, J = 6.3 Hz, H₁), 2.21 (2H, t, J = 6.3 Hz, H₂), 2.07–1.88 (4H, m, H₅ and H₈), 1.70–1.49 (4H, m, H₆ and H₇); δ_C (100 MHz, CDCl₃) 134.0, 124.1, 60.1, 41.0, 27.9, 25.2, 22.8, 22.3. Data are consistent with literature values.¹¹⁶

**tert-Butyl (2-(cyclohex-1-en-1-yl)ethyl)(tosyl)carbamate, 273**

![Chemical structure of 273]

Synthesised from 2-(cyclohex-1-en-1-yl)ethanol 272 (100 mg, 0.79 mmol) using Procedure 2. The resulting crude material was purified by column chromatography (dry loaded, 10% Et₂O in petroleum ether) to give 273 as a colourless oil (221 mg, 0.58 mmol, 74%); R_f = 0.61 (4:1, petroleum ether:EtOAc); δ_H (500 MHz, CDCl₃) 7.78 (2H, d, J = 8.3 Hz, TsH), 7.29 (2H, d, J = 8.3 Hz, TsH), 5.50 (1H, br. s, H₄), 3.91–3.84 (2H, m, H₁), 2.43 (3H, s, ArCH₃), 2.35 (2H, t, J = 7.6 Hz, H₂), 2.04–1.95 (4H, m, H₅ and H₈), 1.66–1.51 (4H, m, H₆ and H₇), 1.33 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 150.9, 143.9, 137.7, 134.2, 129.2, 127.8, 123.9, 83.9, 46.1, 38.5, 28.2, 27.9, 25.3, 22.9, 22.5, 21.6; IR (thin film) ν_max/cm⁻¹ 2929, 1727, 1356, 1155; HRMS m/z (ESI+) found [M+Na]+ 402.1701; C₂₀H₂₉NNaO₅S⁺ requires 402.1710.

**N-(2-(Cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide, 274**

![Chemical structure of 274]

Synthesised from tert-butyl (2-(cyclohex-1-en-1-yl)ethyl)(tosyl)carbamate 273 (200 mg, 0.53 mmol) using Procedure 3 to give 274 as a colourless oil (141 mg, 0.50 mmol, 95%) which was used without further purification; R_f = 0.45 (4:1, petroleum ether:EtOAc); δ_H (400 MHz, CDCl₃) 7.74 (2H, d, J =
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8.1 Hz, TsH), 7.31 (2H, d, J = 8.1 Hz, TsH), 5.38 (1H, br. s, H4), 4.35–4.25 (1H, br. m, NH), 3.00 (2H, ap. q, J = 6.4 Hz, H1), 2.43 (3H, s, ArCH3), 2.05 (2H, t, J = 6.4 Hz, H2), 2.01–1.91 (2H, br. m, H5), 1.74–1.66 (2H, br. m, H8), 1.59–1.44 (4H, m, H6 and H7); δC (100 MHz, CDCl3) 143.3, 136.7, 133.4, 129.6, 127.1, 124.8, 40.4, 37.3, 27.4, 25.1, 22.6, 21.5. Data are consistent with literature values.20

N-(2-(Cyclohex-1-en-1-yl)ethyl)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, 275a

Synthesised from N-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide 274 (120 mg, 0.43 mmol) and 1-bromooct-1-yne 98a (97 mg, 0.52 mmol) using Procedure 5. The resulting crude material was purified by column chromatography (0→5% Et2O in petroleum ether) to give 275a as a pale yellow oil (138 mg, 0.36 mmol, 83%); Rf = 0.72 (4:1, petroleum ether:EtOAc); δH (500 MHz, CDCl3) 7.78 (2H, d, J = 8.2 Hz, TsH), 7.32 (2H, d, J = 8.2 Hz, TsH), 5.45–5.40 (1H, br. m, H4), 3.36–3.29 (2H, m, H1), 2.44 (3H, s, ArCH3), 2.29–2.18 (4H, m, H11 and H2), 1.99–1.93 (2H, m, H5), 1.93–1.86 (2H, m, H8), 1.64–1.41 (6H, m, H7, H6 and H12), 1.39–1.19 (6H, m, H13–15), 0.89 (3H, t, J = 7.1 Hz, CH3); δC (125 MHz, CDCl3) 144.1, 134.9, 133.6, 129.5, 127.8, 123.9, 73.0, 70.3, 50.2, 36.2, 31.3, 28.9, 28.4, 28.2, 25.2, 22.8, 22.6, 22.2, 21.6, 18.5, 14.1; IR (thin film) νmax/cm−1 2928, 2252, 1364, 1169; HRMS m/z (ESI+) found [M+Na]+ 410.2109; C23H33NNaO2S+ requires 410.2124.

N-(2-(Cyclohex-1-en-1-yl)ethyl)-4-methyl-N-(phenylethynyl)benzenesulfonamide, 275b

Synthesised from N-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide 274 (100 mg, 0.36 mmol) and (bromoethynyl)benzene 98b (104 mg, 0.57mmol) using Procedure 5. The resulting crude material was purified by column chromatography (0→5% Et2O in petroleum ether) to give 275b as a
pale yellow oil (88.8 mg, 0.23 mmol, 65%); Rf = 0.72 (4:1, petroleum ether:EtOAc); δH (500 MHz, CDCl3) 7.78 (2H, d, J = 8.2 Hz, TsH), 7.40–7.32 (4H, m, TsH and PhH), 7.30–7.26 (3H, m, PhH), 5.45–5.40 (1H, br. m, H4), 3.36–3.29 (2H, m, H1), 2.44 (3H, s, ArC\_H\_3), 2.23 (2H, t, \( J = 7.3 \) Hz, H2), 1.99–1.93 (2H, m, H5), 1.93–1.86 (2H, m, H8), 1.54–1.37 (4H, m, H7 and H6); δC (125 MHz, CDCl3) 144.1, 134.9, 133.6, 131.3, 129.5, 127.8, 127.7, 123.9, 122.8, 73.0, 70.3, 50.2, 36.2, 28.2, 25.2, 22.8, 22.2, 21.6; IR (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2933, 2251, 1367, 1164; HRMS m/z (ESI+) found [M+Na]+ 402.1507; \( \text{C}_{23}\text{H}_{25}\text{NNaO}_{2}\text{S}^{+} \) requires 402.1504.

### 7.3.2 Ligands / Catalysts / Pre-catalysts

**N,N’-(Ethane-1,2-diyl)bis(1-phenylmethanimine), bbeda**

According to the procedure of Fontecave *et al.* To a stirred solution of benzaldehyde (3.05 mL, 30.0 mmol, 2.0 equiv.) in MeOH (40 mL) was added ethylenediamine (1.0 mL, 15.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred at room temperature for 1 h and then concentrated *in vacuo* to give bbeda as a colourless solid (3.32 g, 126 mmol, 84%) which was used without further purification; m.p. 43-46 °C; Rf = 0.27 (5:1, petroleum ether:EtOAc); δH (400 MHz, CDCl3) 8.29 (2H, s, CH=N), 7.73–7.67 (4H, m, o-PhH), 7.43–7.35 (6H, m, m-PhH, p-PhH), 2.17 (4H, s, CH\_2); δC (100 MHz, CDCl3) 162.6, 136.1, 130.6, 128.5, 128.0, 61.6. Data are consistent with literature values.117

**2,2’-(Ethane-1,2-diyl-d\_4) bis(isoindoline-1,3-dione), d\_r-118**

According to the procedure of Bonnesen *et al.* Potassium phthalimide (4.25 g, 22.0 mol, 2.2 equiv.) was added to a solution of d\_r-1,2-dibromoethane (2.00 g, 10.4 mol, 1.0 equiv.) in dry DMF (30 mL). The mixture was stirred at 95 °C overnight, then cooled to room temperature. Water (50 mL) was added...
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to form a white precipitate, which was stirred for another 30 min. The solid was collected by filtration, and washed with water (3 × 20 mL), then dried under vacuum to afford d₄-118 (3.14 g, 9.7 mol, 93%) as a white solid; m.p. 235-236 °C; δ_H (400 MHz, CDCl₃) 7.79–7.76 (4H, m, Ar_H), 7.70–7.67 (4H, m, Ar_H); δ_C (100 MHz, CDCl₃) 168.4, 134.2, 132.2, 123.5, 36.6 (t, J = 22.9 Hz). Data are consistent with literature values.⁴⁶

Ethane-d₄-1,2-diamine dihydrogen chloride, d₄-119

Diphthalimide d₄-118 (2.00 g, 6.17 mmol, 1.0 equiv.) was dissolved in methanol (12 mL), then heated to reflux. Hydrazine monohydrate (680 mg, 13.6 mmol, 2.2 equiv.) was added to the solution. The solution was refluxed overnight, during which time a white precipitate formed. The mixture was allowed to cool to room temperature, and the precipitate was filtered off and washed with methanol (3 × 10 mL). The combined filtrate was acidified to pH 2 using 6 M hydrochloric acid, resulting in a formation of white precipitate. The solid was collected by filtration, then dried under vacuum to afford d₄-119 (735 mg, 5.36 mmol, 87%) as a white crystalline powder.

(1E,1′E)-N,N′-(Ethane-1,2-diyl-d₄)bis(1-phenylmethanimine), d₄-bbeda

To a stirred solution of benzaldehyde (637 mL, 6.01 mmol, 2.0 equiv.) in MeOH (30 mL) was added ethane-d₄-1,2-diamine dihydrogen chloride d₄-119 (700 mg, 3.0 mmol, 1.0 equiv.) dropwise. A solution of 5% NaOH (40 mL, aq.) was subsequently added to the stirred solution. The reaction mixture was stirred at room temperature for 3 h, and then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting crude material was washed with 1:3 toluene / petroleum ether, to give d₄-bbeda (1.00 g, 2.25 mmol, 75%) as a white crystalline powder; m.p. 49 °C; δ_H (400 MHz, CDCl₃) 8.29 (2H, s, CH=N), 7.71–7.68 (4H, m, Ph_H), 7.41–7.37 (6H, m, Ph_H); δ_C (100 MHz, CDCl₃) 162.9, 136.3, 130.8, 128.7, 128.3, 61.6 (weak m); IR
(thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2845, 2199, 2079, 1640, 1370, 1156; **HRMS** $m/z$ (ESI+) found [M+H]$^+$ 241.16345; $\text{C}_{16}\text{H}_{13}\text{D}_4\text{N}_2^+$ requires 241.1643.

**Trimeric palladium acetate, Pd$_3$(OAc)$_6$ (as also known as palladium acetate)**

According to the procedure of Colacot *et al.*$^{49}$ A round-bottom flask equipped with a magnetic stirrer bar was charged with Pd$_3$(OPiv)$_6$ (247 mg, 0.80 mmol) and acetic acid (0.93 mL, 16.2 mmol). The flask was heated to 100 ºC and stirred for 5 hours. The reaction mixture was then cooled to room temperature and filtered under gravity, followed by dying *in vacuo* to afford the tiled product as a brick red solid (155 mg, 0.69 mmol, 86%); $\delta_H$ (400 MHz, C$_6$D$_6$) 1.76 (18H, s). Data are consistent with literature values.$^{49}$

**[Pd$_3$(μ²-OH)(OAc)$_4$], 107a**

According to the procedure of Bedford *et al.*$^{43}$ A solution of Pd(OAc)$_2$ (50 mg, 0.0743 mmol, 1.0 equiv.) and H$_2$O (40 µL, 2.29 mmol, 30 equiv.) were stirred in acetone (5 mL) for 30 min. Nitrogen gas was bubbled through the solution, while $n$-hexane was slowly added to maintain the total volume of solution for 10 min, resulting in a formation of brown precipitate. The solid was then washed with $n$-hexane (2 $\times$ 5 mL) and dried *in vacuo* to obtain 107a (48 mg, 0.0428 mmol, 86%) as a brown powder; $\delta_H$ (400 MHz, CDCl$_3$) 2.03 (6H, s, C$_3$H$_3$), 1.97 (3H, s, C$_3$H$_3$), 1.89 (6H, s, CH$_3$), −1.04 (1H, br s, OH); $\delta_C$ (100 MHz, CDCl$_3$) 190.1, 189.7, 186.1, 23.4, 22.7, 22.1. Data are consistent with literature values.$^{43}$

**[Pd(R)-BINAP](dba), 229**

According to the procedure of Buchwald *et al.*$^{118}$ A solution of Pd$_3$(dba)$_3$ (72 mg, 0.08 mmol, 1.0 equiv.) and (R)-BINAP (100 mg, 0.16 mmol, 2.0 equiv.) in benzene (5 mL) was stirred at room temperature for 3 h. The resulting orange solution was filtered through Celite® and concentrated *in vacuo* to give an oily residue that was dissolved in dry Et$_2$O (5 mL). The precipitate that formed overnight was collected,
washed with dry Et$_2$O, and dried in vacuo to afford 229 (110 mg, 70%) as an orange solid: $\delta_H$ (400 MHz, CDCl$_3$) 7.83 (t, $J = 8.3$ Hz), 7.70 (br), 7.56 (br), 7.50 (m), 7.38 (t, $J = 8.5$ Hz), 7.20 (q, $J = 7.6$ Hz), 7.10 (m), 7.0–6.7 (br, m), 6.61 (t, $J = 7.4$ Hz), 6.46 (t, $J = 6.8$ Hz), 6.31 (t, $J = 6.8$ Hz); $\delta_F$ $^1$H (120 MHz, CDCl$_3$) 25.8, 24.6; IR (thin film) $\nu_{max}$/cm$^{-1}$ 3041, 1645, 1585, 1501, 1472, 1430, 1330, 1210, 1095, 741, 690. Data are consistent with literature values.$^{118}$

$N,N'$-((1$R$,2$R$)-cyclohexane-1,2-diyl)bis(1-phenylmethanimine), 227

![Diagram of 227]

To a vigorously stirred mixture of (1$R$,2$R$)-trans-cyclohexane-1,2-diammonium $L$-Tartrate (1.00 g, 3.78 mmol, 1.0 equiv.), K$_2$CO$_3$ (1.04 g, 7.56 mmol, 2.0 equiv.) and H$_2$O (5 mL) was added EtOH (20 mL). The mixture was heated to reflux and a solution of benzaldehyde (0.77 mL, 7.56 mmol, 2.0 equiv.) in EtOH (8 mL) added over 10 mins. The reaction mixture was heated under reflux for 2 h, allowed to cool to room temperature, concentrated in vacuo and the residue diluted with H$_2$O. The resulting mixture was stirred at 0 ºC for 1 h and the precipitate was filtered to give the crude imine. The residue was dissolved in CH$_2$Cl$_2$ (15 mL), washed with H$_2$O (2 × 10 mL) and brine (10 mL), dried (NaSO$_4$), filtered and concentrated in vacuo to give 227 as a colourless solid (1.030 g, 3.55 mmol, 94%); m.p. 61–65 ºC; $R_f = 0.41$ (4:1, petroleum ether:EtOAc); $\delta_H$ (400 MHz, CDCl$_3$) 8.21 (2H, s, =CHPh), 7.63–7.53 (4H, m, PhH), 7.36–7.27 (6H, m, PhH), 3.48–3.36 (2H, m, CH-N), 1.95 1.72 (6H, m, H1',H1'', H4', H4'' H2', H3''), 1.58–1.41 (2H, m, H2'' and H3''); $\delta_C$ (100 MHz, CDCl$_3$) 161.0, 136.4 , 130.2, 128.4, 127.9, 73.8, 33.0, 24.5. Data are consistent with literature values.$^{119}$
[Rh((R)-Cl-OMe-biphep)(cod)]SbF$_6$, 239a

[Rh(cod)$_2$]SbF$_6$ (10 mg, 0.018 mmol, 1.0 equiv.) and (R)-Cl-OMe-BIPHEP (11.7 mg, 0.018 mmol, 1.0 equiv.) were dissolved in anhydrous CH$_2$Cl$_2$ (0.5 mL), and stirred at room temperature for 1 h. The solvent was removed *in vacuo* to afford a bright orange solid. The crude solid was purified by recrystallisation (vapour diffusion of $n$-pentane), the product 239a was obtained as a bright orange crystal (14.3 mg, 0.013 mmol, 72%); $\delta$$_H$ (400 MHz, CDCl$_3$) 7.76 (4H, m, ArH), 7.60–7.14 (20H, m, PhH), 4.50 (2H, m, =CH), 4.69 (2H, m, =CH), 3.50 (2H, m, OCH$_3$), 2.68 (2H, m, OCH$_3$), 2.44 (2H, m, CH$_2$), 2.22 (2H, m, CH$_2$), 2.06 (2H, m, CH$_2$); $\delta$$_p$ {1$^H$} (162 MHz, CDCl$_3$) 24.7 (d, $J$ = 146.1 Hz, P–Rh).

This rhodium complex was also characterised by X-ray crystallography (see X-Ray Crystallographic Data section).

### 7.3.3 Palladium-catalysed cycloisomerisation products

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

Synthesised from $N$-(but-3-en-1-yl)-4-methyl-$N$-(oct-1-yn-1-yl)benzenesulfonamide 92 (50 mg, 0.150 mmol) using Procedure 6, with the reaction mixture stirred for 10 min. The resulting crude material was purified by column chromatography (10% Et$_2$O in petroleum ether) to give 102 as a pale yellow oil (41 mg, 0.123 mmol, 82%); $R_f$ = 0.49 (5:1, petroleum ether:EtOAc); $\delta$$_H$ (500 MHz, CDCl$_3$) 7.68 (2H, d, $J$ = 8.2 Hz, TsH), 7.23 (2H, d, $J$ = 8.2 Hz, TsH), 5.87 (1H, t, $J$ = 7.4 Hz, H4), 5.20 (1H, t, $J$ = 2.3 Hz, H$''$), 4.64 (1H, t, $J$ = 2.3 Hz, H$''$), 3.53 (2H, t, $J$ = 7.4 Hz, H3), 2.53 (2H, q, $J$ = 7.6 Hz, H7), 2.42 (2H, s, ArCH$_3$), 1.83 (2H, tt, $J$ = 7.4 and 2.3 Hz, H4), 1.48–1.23 (8H, m, H8–11), 0.89 (3H, t, $J$ =...
6.9 Hz, \( \text{CH}_3 \)); \( \delta \text{C} \) (125 MHz, CDCl\(_3\)) 143.8, 143.2, 136.5, 136.0, 129.5, 127.7, 122.1, 103.5, 48.5, 31.7, 29.7, 29.5, 29.1, 29.0, 22.7, 21.6, 14.1. Data are consistent with literature values.\(^{20}\)

(Z)-2-(Heptylidene-1-d)-3-methylene-1-tosylpyrrolidine, \( \text{di}-92 \)

![Chemical structure](image)

Synthesised from \( N \)-(but-3-en-1-yl)-4-methyl-\( N \)-(oct-1-yn-1-yl)benzenesulphonamide \( \text{di}-92 \) (1.00 g, 3.00 mmol), \( \text{di}-\text{bbeda} \) (7.1 mg, 0.030 mmol) and Pd(OAc)\(_2\) (6.7 mg, 0.030 mmol) using Procedure 6. The reaction mixture was stirred at 60 °C for 2.5 h, and then concentrated \textit{in vacuo}. The resulting crude material was purified by column chromatography (10% EtOAc in petroleum ether) to give \( \text{di}-102 \) (830 mg, 2.49 mmol, 83%) as a colourless oil; \( R_f 0.49 \) (5:1 petroleum ether / EtOAc); \( \delta \text{H} \) (500 MHz, CDCl\(_3\)) 7.68 (2H, d, \( J = 8.2 \) Hz, Ts\( \text{H} \)), 7.23 (2H, d, \( J = 8.2 \) Hz, Ts\( \text{H} \)), 5.21 (1H, t, \( J = 2.3 \) Hz, H'), 4.64 (1H, t, \( J = 2.3 \) Hz, H''), 3.53 (2H, t, \( J = 7.4 \) Hz, H5), 2.53 (2H, t, \( J = 7.4 \) Hz, H7), 2.41 (3H, s, Ar\( \text{C} \text{H}_3 \)), 1.83 (2H, tt, \( J = 2.1 \) and 7.4 Hz, H4), 1.44–1.24 (8H, m, H8–H11), 0.89 (3H, t, \( J = 6.8 \) Hz, H12); \( \delta \text{C} \) (125 MHz, CDCl\(_3\)) 143.9, 143.4, 136.6, 136.1, 129.7, 127.9, 122.3 (t, \( J = 23.8 \) Hz), 103.7, 48.9, 31.9, 29.9, 29.7, 29.3, 29.2, 22.8, 21.8, 14.3; IR (thin film) \( \nu_{\text{max}} / \text{cm}^{-1} \) 2925, 1166, 1091, 801, 415; HRMS \( m/z \) (ESI+) found [M+Na]+ 357.1719; \( \text{C}_{19}\text{H}_{26}\text{DNNaO}_2\text{S}^+ \) requires 357.1723.

(Z)-2-Heptylidene-3-methylene-1-(4-nitrophenylsulfonyl)pyrrolidine, 103

![Chemical structure](image)

Synthesised from \( N \)-(but-3-en-1-yl)-4-nitro-\( N \)-(oct-1-yn-1-yl)benzenesulphonamide 93 (50 mg, 0.137 mmol) using Procedure 6 (0.333 M; 2.5 mol% cat.), with the reaction mixture stirred for 20 mins. The resulting crude material was purified by column chromatography (10→15% EtO in petroleum ether) to give 103 as a pale yellow oil (42 mg, 0.115 mmol, 84%); \( R_f = 0.28 \) (9:1, petroleum ether:EtoAc); \( \delta \text{H} \)
(500 MHz, CDCl$_3$) 8.33–8.26 (2H, m, NsH), 8.02–7.96 (2H, m, NsH), 5.92 (1H, t, $J = 7.4$ Hz, H6), 5.23 (1H, t, $J = 2.4$ Hz, H'), 4.67 (1H, t, $J = 2.0$ Hz, H''), 3.61 (2H, t, $J = 2.0$ Hz, H'), 3.53 (2H, t, $J = 2.0$ Hz, H''), 2.52 (2H, ap. q, $J = 7.5$ Hz, H7), 1.94–1.85 (2H, m, H4), 1.51–1.41 (2H, m, H8), 1.40–1.24 (6H, m, H9–11), 0.89 (3H, t, $J = 7.4$ Hz, C$_3$H$_3$); $\delta$C (125 MHz, CDCl$_3$) 150.3, 144.5, 142.0, 135.7, 129.0, 124.0, 123.2, 104.7, 48.6, 31.7, 29.7, 29.1, 28.8, 22.6, 14.1; IR (thin film) $\nu_{max}$/cm$^{-1}$ 2926, 1531, 1349, 1170; HRMS m/z (ESI+) found [M+Na]$^+$ 387.1340; C$_{18}$H$_{24}$N$_2$NaO$_4$S requires 387.1349.

(Z)-2-Heptylidene-3-(methylene-d$_2$)-1-tosylpyrrolidine, d$_2$-113

Synthesised from N-(but-3-en-1-yl-4,4-d$_2$)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonylamide, d$_2$-111 (15 mg, 0.045 mmol) using Procedure 6, with the reaction mixture stirred for 10 min. The resulting crude material was purified by column chromatography (10% Et$_2$O in petroleum ether) to give d$_2$-113 as a colourless oil (13 mg, 0.040 mmol, 89%, >98% deuterium incorporation); RF = 0.49 (5:1, petroleum ether:EtOAc); $\delta$H (500 MHz, CDCl$_3$) 7.68 (2H, d, $J = 8.2$ Hz, TsH), 7.23 (2H, d, $J = 8.2$ Hz, TsH), 5.87 (1H, t, $J = 7.4$ Hz, H4), 3.53 (2H, t, $J = 7.4$ Hz, H3), 2.53 (2H, q, $J = 7.6$ Hz, H7), 2.42 (2H, s, ArCH$_3$), 1.83 (2H, tt, $J = 7.4$ and 2.3 Hz, H4), 1.48–1.23 (8H, m, H8–11), 0.89 (3H, t, $J = 6.9$ Hz, CH$_3$); $\delta$C (125 MHz, CDCl$_3$) 143.8, 143.2, 136.5, 136.0, 129.5, 127.7, 122.1, 103.5 (m), 48.5, 31.7, 29.7, 29.5, 29.1, 29.0, 22.7, 21.6, 14.1; HRMS m/z (ESI+) found [M+Na]$^+$ 358.4919; C$_{18}$H$_{24}$D$_2$NaO$_4$S$^+$ requires 358.4920.
Dimethyl (E)-3-(3-((tert-butyldimethylsilyloxy)propylidene-1-d)-4-methylenecyclopentane-1,1-dicarboxylate, 121/d1-121

Synthesised from dimethyl 2-allyl-2-(5-((tert-butyldimethylsilyloxy)pent-2-yn-1-yl)malonate 120 (50 mg, 0.136 mmol, 1.0 equiv.), d4-bbeda (1.62 mg, 0.007 mmol, 0.05 equiv.) and Pd(OAc)2 (1.52 mg, 0.007 mmol, 0.05 equiv.) using Procedure 6. The reaction mixture was stirred at 60 °C for 31 h, and then concentrated in vacuo. The resulting crude material was purified by column chromatography (10% EtOAc in petroleum ether) to give d1-121 (43.6 mg, 0.118 mmol, 87%, 15% deuterium incorporation by 1H NMR spectroscopy) as a colourless oil. Data for deuterated compound d1-121; Rf 0.44 (7:3 petroleum ether / EtOAc); δH (400 MHz, CDCl3) 5.26–5.25 (1H, m, H'), 4.84 (1H, ap. s, H'''), 3.73 (6H, s, 2×CO2CH3), 3.65 (2H, t, J = 6.8 Hz, H9), 3.01–3.00 (4 H, m, H3 and H5), 2.32 (2H, q, J = 6.8 Hz, H8), 0.89 (9H, s, SiC(CH3)3), 0.05 (6H, s, 2×SiCH3); δc (100 MHz, CDCl3) 172.0, 145.2, 137.8, 118.8 (t, J = 19.5 Hz), 103.4, 62.6, 57.8, 53.0, 41.7, 38.0, 33.5, 26.1, 18.6, −5.1; IR (thin film) νmax/cm−1 2954, 1737,1434,1288, 1095; HRMS m/z (ESI+) found [M+H]+ 370.2153; C19H32DO5Si+ requires 370.2160.

(3RS,5RS,Z)-3-((E)-But-1-en-1-yl)-2-heptylidene-5-phenyl-1-tosylpyrrolidine, 126

Synthesised from (Z)-4-methyl-N-(oct-1-yn-1-yl)-N-(1-phenylhept-3-en-1-yl)benzenesulfonamide 125 (20 mg, 0.044 mmol) using Procedure 8, only with the reaction mixture stirred at room temperature for 3 h. The resulting crude material was purified by column chromatography (5→10% EtO in petroleum ether) to give 126 as a colourless oil (17.4 mg, 0.040 mmol, 87%); Rf = 0.47 (4:1, petroleum ether:EtOAc); δH (500 MHz, CDCl3) 7.69 (2H, d, J = 8.2 Hz, TsH), 7.32–7.19 (7H, m, TsH and PhH),
5.34 (1H, dt, J = 15.0 and 6.2 Hz, H7), 5.17 (1H, dd, J = 7.6 and 3.8 Hz, H3), 5.13 (1H, ddd, J = 9.4, 4.8, 1.0 Hz, H10), 4.63 (1H, ddt, J = 15.0, 8.4, 1.5 Hz, H6), 3.02 (1H, ap. br. q, J = 7.7 Hz, H5), 2.61–2.51 (1H, m, H11'), 2.49–2.38 (1H, m, H11''), 2.42 (3H, s, ArCH3), 1.92–1.82 (3H, m, H4', H8' and H8''), 1.52–1.44 (2H, m, H4'' and H12''), 1.39–1.22 (7H, m, H12' and H13–15), 0.90 (3H, t, J = 7.4 Hz, H9), 0.89 (3H, t, J = 6.9 Hz, H16); δc (125 MHz, CDCl3) 143.7, 141.7, 139.5, 136.3, 132.8, 129.7, 129.4, 128.4, 128.0, 127.1, 125.9, 122.0, 64.5, 46.6, 38.0, 31.8, 29.9, 29.8, 29.1, 25.3, 22.7, 21.5, 14.1, 13.5; IR (thin film) νmax/cm⁻¹ 2926, 1357, 1167; HRMS m/z (ESI+) found [M+Na]^+ 474.2421; C28H37NNaO2S⁺ requires 474.2437.

(3R,5R,Z)-2-Heptylidene-3-methyl-5-phenyl-3-((E)-prop-1-en-1-yl)-1-tosylpyrrolidine, 132

Synthesised from (E)-4-methyl-N-(3-methyl-1-phenylhex-3-en-1-yl)-N-(oct-1-yn-1-yl)benzenesulfonamide 131 (34 mg, 0.075 mmol) using Procedure 8 (0.167 M; 10 mol% cat.), with the reaction mixture stirred for 30 min at 60 °C. The resulting crude material was purified by column chromatography (9:1 hexanes / t-BuOMe) to give 132 (28.5 mg, 0.063 mmol, 84%) as a pale yellow oil; Rf 0.31 (10:1 hexanes / EtOAc); δH (500 MHz, CDCl3) 7.44 (2H, d, J = 8.2 Hz, TsH), 7.31–7.18 (5H, m, PhH), 7.10 (2H, d, J = 8.2 Hz, TsH), 5.46 (1H, dq, J = 15.4 and 6.4 Hz, H7), 5.08–5.01 (1H, m, H6), 5.01–4.94 (2H, m, H5 and H10), 2.39–2.32 (2H, m, H11), 2.35 (3H, s, ArCH3), 2.28 (1H, dd, J = 12.5 and 7.4 Hz, H4), 1.58 (1H, dd, J = 12.5 and 8.9 Hz, H4), 1.55–1.45 (4H, m, H8 and H12), 1.42–1.20 (7H, m, H12 and H13–15), 1.10 (3H, s, H9), 0.89 (3H, t, J = 6.8 Hz, H16); δc (125 MHz, CDCl3) 144.5, 143.2, 143.1, 136.8, 135.0, 128.9, 128.4, 128.0, 127.2, 126.4, 123.2, 116.9, 62.9, 47.5, 47.1, 31.7, 29.8, 29.4, 29.0, 25.6, 22.7, 21.4, 18.0, 14.1; IR (thin film) νmax/cm⁻¹ 2925, 1347, 1166; HRMS m/z (ESI+) found [M+H]^+ 452.2623; C28H38NO2S⁺ requires 452.2618.
Conformational Analysis

Assignment of stereochemistry of 132 is based on interpretation of 1D $^1$H NMR nOe data ($C_6D_6$). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between the alkene sidechain (H6), the benzylic proton (H5), and H4α. Complementary enhancements are seen between the methyl group and H4β, and from the Ph (ortho-protons) to H4β.

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(3RS,5RS,Z)-1-\text{heptylidene-3-phenyl-2-tosyl-2-azaspiro[4.5]dec-6-ene, 134}
\]

Synthesised from $N$-(2-(cyclohex-1-en-1-yl)-1-phenylethyl)-4-methyl-$N$-(oct-1-yn-1-yl)benzenesulfonamide 133 (35 mg, 0.075 mmol) using Procedure 8 (0.167 M; 5 mol% cat.), with the reaction mixture stirred at 60 °C for 30 min. The resulting crude material was purified by column chromatography (5→10% Et$_2$O in petroleum ether) to give 134 ($\geq$ 98:2 d.r., 27.5 mg, 0.059 mmol, 78%) as a pale yellow oil; R$_f$ 0.65 (4:1 hexanes/EtOAc); $\delta$H (500 MHz, $C_6D_6$) 7.70 (2H, d, $J = 8.1$ Hz, TsH), 7.28 (2H, d, $J = 7.3$ Hz, PhH), 7.12 (2H, app t, $J = 7.6$ Hz, PhH), 7.06–7.00 (1H, m, PhH), 6.68 (2H, d, $J = 8.1$ Hz, TsH), 5.62 (1H, br d, $J = 10.0$ Hz, H6), 5.48 (1H, dt, $J = 10.0$ and 3.6 Hz, H7), 5.42 (1H, dd, $J = 6.1$ and 7.9 Hz, H3), 5.22 (1H, dd, $J = 9.0$ and 4.9 Hz, H11), 2.78–2.61 (2H, m, H12), 2.00 (1H, dd, $J = 12.4$ and 7.9 Hz, H4), 1.82–1.76 (2H, m, H8), 1.62 (1H, dd, $J = 12.4$ and 6.1 Hz, H4), 1.61–1.53 (2H, m, H10 and H13), 1.50–1.40 (2H, m, H9 and H13), 1.40–1.20 (8H, m, H14–16, H9 and H10), 0.88 (3H, t, $J = 6.9$ Hz, H17); $\delta$C (125 MHz, $C_6D_6$) 145.5, 143.5, 143.1, 138.3, 132.3, 129.3, 128.7, (o-TsH obscured by solvent peak), 127.3, 126.6, 125.9, 118.6, 63.1, 47.9, 47.2.
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35.2, 32.2, 30.5, 30.3, 29.6, 25.1, 23.1, 21.1, 20.6, 14.4; IR (thin film) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2927, 1361, 1167; HRMS \( m/z \) (ESI+) found [M+Na]\(^+\) 486.2444; C\(_{29}\)H\(_{37}\)NNaO\(_2\)S\(^+\) requires 486.2437.

**Conformational Analysis:** Assignment of stereochemistry of 134 is based on interpretation of 1D \(^1\)H NMR nOe data (CDCl\(_3\)). Enhancements are seen between protons on the alpha face of the molecule (as depicted below) between the alkene moiety of the cyclohexenyl substituent (H\(_6\)), the benzylic proton (H\(_3\)), and H\(_{4\alpha}\). Complementary enhancement is seen between CH\(_2\)-10 and H\(_{4\beta}\), as well as between the Ph (ortho-protons) and H\(_{4\beta}\).

![Conformational analysis diagram](attachment:conformational_analysis.png)

**(Z)-2-(Heptylidene-1-d)-3-((E)-prop-1-en-1-yl)-1-tosylpyrrolidine, d\(_1\)-153a**

![Molecular structure](attachment:molecular_structure.png)

Synthesised from (E)-N-(hex-3-en-1-yl-3-d)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, (E)-d\(_1\)-151a, (20 mg, 0.055 mmol, 1.0 equiv.) using Procedure 6. The crude material was passed through a silica plug with Et\(_2\)O as eluent, and then concentrated in vacuo to give an inseparable mixture of 152a, (E)-d\(_1\)-153a and (Z)-d\(_1\)-153a (11:87:2) as a pale yellow oil (16.8 mg). NOTE: Up to 11% deuterium incorporation at the enamide proton is expected across these products, arising from 11% formation of 4b. For clarity, products (E)-d\(_1\)-153a and (Z)-d\(_1\)-153a are represented as singly-deuterated compounds. Data are reported for the major isomer ((E)-d\(_1\)-153a); \( \delta_H \) (500 MHz, CDCl\(_3\)) 7.69 (2H, d, \( J = 8.1 \) Hz, Ts\(_H\)), 7.28 (2H, d, \( J = 8.1 \) Hz, Ts\(_H\)), 5.27 (1H, dq, \( J = 15.1 \) and 6.5 Hz, H\(_7\)), 4.99 (1H, m, H\(_6\)), 3.54 (1H, ddd, \( J = 11.4, 8.6 \) and 3.0 Hz, H\(_5'\)), 3.38 (ddd, \( J = 11.4, 9.2 \) and 7.9 Hz, H\(_5''\)), 2.50 (2H, m, H\(_{10}\)),
2.43 (3H, s, CH₃Ar), 2.24 (1H, m, H3), 1.71–1.65 (1H, m, H4'), 1.61 (3H, dd, J = 6.6 and 1.6 Hz, H8), 1.45–1.24 (9H, m, H4'' and H11–14), 0.88 (3H, t, J = 6.9 Hz, H15). δC (125 MHz, CDCl₃) 143.8, 140.1, 134.9, 130.5, 129.6, 128.0, 127.7, 121.4 (t, J = 19.2 Hz), 49.3, 45.8, 31.9, 30.0, 29.5, 29.3, 29.2, 22.9, 21.8, 18.0, 14.3.

(Z)-2-Heptylidene-3-((E)-prop-1-en-1-yl)-1-tosylpyrrolidine-3-d, d₁-153a

Synthesised from (Z)-N-(hex-3-en-1-yl-3-d)-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide, (Z)-d₁-151a, (20 mg, 0.055 mmol, 1.0 equiv.), Pd(OAc)₂ (0.6 mg, 0.0028 mmol, 0.05 equiv.), and bbeda (0.7 mg, 0.0028 mmol, 0.05 equiv.) using Procedure 6. The resulting crude material was passed through a silica plug with Et₂O as eluent, and then concentrated in vacuo to afford an inseparable mixture of (E)-d₁-153a and (Z)-d₁-153a (86:16) as a pale yellow oil (18.5 mg). Data reported for the major isomer: δH (500 MHz, CDCl₃) 7.69 (2H, d, J = 8.1 Hz, TsH), 7.28 (2H, d, J = 8.1 Hz, TsH), 5.27 (1H, dq, J = 15.1 and 6.5 Hz, H7), 5.00–4.92 (2H, m, H6 and H9), 3.54 (1H, ddd, J = 11.4, 8.6 and 3.0 Hz, H5'), 3.38 (ddd, J = 11.4, 9.2 and 7.9 Hz, H5''), 2.43 (3H, s, CH₃Ar), 2.40 (2H, m, H10), 1.69 (1H, dt, J = 7.4 and 2.4 Hz, H4'), 1.62 (3H, dd, J = 6.6 and 1.6 Hz, H8), 1.45–1.24 (9H, m, H4'' and H11–14), 0.88 (3H, t, J = 6.9 Hz, H15). δC (125 MHz, CDCl₃) 143.8, 140.1, 135.0, 130.6, 129.6, 128.0, 127.7, 121.4, 49.3, 45.6 (t, J = 21.7 Hz), 31.9, 30.0, 29.5, 29.2, 29.0, 22.8, 21.8, 18.0, 14.3.
7.3.4 Rhodium-catalysed cycloisomerisation products

\((\rightarrow)-(Z)-2\)-Heptylidene-3-\(((E)-\text{prop-1-en-1-yl})-1\)-tosylpyrrolidine, \((E)-153a\)

Synthesised from \((Z)-N\)-(hex-3-en-1-yl)-4-methyl-\(N\)-(oct-1-yn-1-yl)benzenesulfonylamide \((Z)-151a\) (20 mg, 0.055 mmol) using Procedure 11, with the reaction mixture stirred at room temperature for 5 min. The resulting crude material was purified by column chromatography (10% Et₂O in petroleum ether) to give \((E)-153a\) as a colourless oil (19.8 mg, 0.054 mmol, 98%); \([\alpha]_D^{25} -67.3 \ (c = 1.0, \text{CHCl}_3)\); 97% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, \(t_R\) major – 18.26 min, minor – 19.87 min); \(R_f = 0.62\) (4:1, petroleum ether:EtOAc); \(\delta_h\) (500 MHz, CDCl₃) 7.69 (2H d, \(J = 8.1\) Hz, TsH), 7.28 (2H, d, \(J = 8.1\) Hz, TsH), 5.27 (1H, dq, \(J = 15.1, 6.5\) Hz, H7), 5.02–4.92 (2H, m, H6 and H9), 3.54 (1H, dq, \(J = 15.1, 6.5\) Hz, H7), 3.38 (1H, ddd, \(J = 11.4, 9.2, 7.9\) Hz, H3”a), 2.49–2.34 (2H, m, H10), 2.43 (3H, s, ArC₃H₃), 2.24 (1H, br. ap. q, \(J = 8.5\) Hz, H3), 1.69 (1H, dddd, \(J = 12.0, 8.0, 7.9, 3.0\) Hz, H4”), 1.62 (3H, dd, \(J = 6.6, 1.6\) Hz, H8), 1.45–1.24 (9H, m, H4” and H11–14), 0.88 (3H, t, \(J = 6.9\) Hz, H15); \(\delta_c\) (125 MHz, CDCl₃) 143.6, 139.9, 134.8, 130.4, 129.4, 127.8, 127.5, 121.2, 49.1, 45.6, 31.7, 29.8, 29.3, 29.0, 29.0, 22.7, 21.6, 17.8, 14.1; IR (thin film) \(\nu_{\text{max}}/\text{cm}^{-1}\) 2923, 1355, 1165; HRMS \(m/z\) (ESI+) found \([M+Na]^+\) 384.1964; \(C_{21}H_{31}NNaO_2S^+\) requires 384.1968.

\((\rightarrow)-2-((Z)-\text{Hexylidene})-3-((E)-\text{prop-1-en-1-yl})-1\)-tosylpyrrolidine, \((E)-153b\)

Synthesised from \((Z)-N\)-(hex-3-en-1-yl)-4-methyl-\(N\)-(phenylethynyl)benzenesulfonylamide \((Z)-151b\) (10 mg, 0.028 mmol) using Procedure 11, with the reaction mixture stirred for 10 min. The resulting crude
material was purified by column chromatography (25% Et₂O in petroleum ether) to give (E)-153b as a pale yellow oil (9.4 mg, 0.026 mmol, 93%); [α]_D^{25} = -38.1 (c = 1.0, CHCl₃); 96% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, tᵣ major – 20.56 min, minor – 22.84 min); Rₓ = 0.32 (5:1, petroleum ether:EtOAc); δₓ (500 MHz, CDCl₃) 7.66 (2H, d, J = 8.5 Hz, TsH), 7.62 (2H, d, J = 7.6 Hz, PhH), 7.32–7.24 (4H, m, TsH and PhH), 7.18 (1H, br. t, J = 7.4 Hz, PhH), 5.93 (1H, d, J = 1.9 Hz, =CHPh), 5.40 (1H, dq, J = 15.1 and 6.3 Hz, H7), 5.10 (1H, ddd, J = 15.1, 8.3, 1.6 Hz, H6), 3.69 (1H, ddd, J = 11.4, 8.7, 3.2 Hz, H3'), 3.52 (1H, ddd, J = 11.4, 9.1, 7.6 Hz, H3''), 2.52 (1H, dddd, J = 10.5, 8.3, 8.0, 1.9 Hz, H3), 2.43 (3H, s, ArCH₃), 1.80 (1H, dddd, J = 12.0, 8.0, 7.6, 3.2 Hz, H4'), 1.68 (3H, dd, J = 6.3 and 1.6 Hz, CH₂), 1.42 (1H, dddd, J = 12.0, 10.5, 9.1, 8.7 Hz, H4''); δₓ (125 MHz, CDCl₃) 143.9, 141.0, 136.5, 134.5, 130.1, 129.4, 128.8, 128.3, 128.0, 127.7, 126.7, 118.5, 49.1, 46.7, 28.9, 21.6, 17.9; IR (thin film) ν_max/cm⁻¹ 2968, 1358, 1164; HRMS m/z (ESI+) found [M+Na]⁺ 376.1343; C₂₁H₂₃NNaO₂S⁺ requires 376.1342.

(--)-2-((Z)-4-Fluorobenzylidene)-3-((E)-prop-1-en-1-yl)-1-tosylpyrrolidine, (E)-153c

Synthesised from (Z)-N-((4-fluorophenyl)ethynyl)-N-(hex-3-en-1-yl)-4-methylbenzenesulphonamide (Z)-151c (10 mg, 0.027 mmol) using Procedure 11, with the reaction mixture stirred for 30 min. The resulting crude material was purified by column chromatography (25% Et₂O in petroleum ether) to give (E)-153c as a pale yellow oil (9.5 mg, 0.026 mmol, 95%); [α]_D^{25} = -23.5 (c = 1.0, CHCl₃); 94% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, tᵣ major – 20.48 min, minor – 22.35 min); Rₓ = 0.28 (5:1, petroleum ether:EtOAc); δₓ (500 MHz, CDCl₃) 7.77 (2H, d, J = 8.5 Hz, TsH), 7.61 (2H, d, J = 7.6 Hz, PhH), 7.32–7.24 (4H, m, TsH and PhH), 5.97 (1H, d, J = 1.9 Hz, =CHPh), 5.40 (1H, dq, J = 15.1 and 6.3 Hz, H7), 5.10 (1H, ddd, J = 15.1, 8.3, 1.6 Hz, H6), 3.69 (1H, ddd, J = 11.4, 8.7, 3.2 Hz, H3'), 3.52 (1H, ddd, J = 11.4, 9.1, 7.6 Hz, H3''), 2.52 (1H, dddd, J = 10.5, 8.3, 8.0, 1.9 Hz, H3), 2.43 (3H, s, ArCH₃), 1.80 (1H, dddd, J = 12.0, 8.0, 7.6, 3.2 Hz, H4'), 1.68 (3H, dd, J = 6.3 and 1.6 Hz, CH₂).
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1.42 (1H, dddd, J = 12.0, 10.5, 9.1, 8.7 Hz, H4’’); δC (125 MHz, CDCl3) 160.1 (d, J = 249.0 Hz), 146.3, 143.8, 136.0, 133.6 (d, J = 234.0 Hz), 129.8, 129.7, 129.6, 129.5, 128.3, 128.0, 127.4, 115.1 (d, J = 22.0 Hz), 49.7, 47.3, 32.6, 21.7, 17.8; δF (470 MHz, CDCl3) –116.3; IR (thin film) νmax/cm⁻¹ 3067, 2920, 1594, 1503, 1357, 1225, 1162; HRMS m/z (ESI+) found [M+Na]+ 394.1250; C21H22FNNaO2S+ requires 394.1253.

(−)-2-((Z)-4-Methoxybenzylidene)-3-((E)-prop-1-en-1-yl)-1-tosylpyrrolidine, (E)-153d

Synthesised from (Z)-N-(hex-3-en-1-yl)-N-((4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide (Z)-151d (10 mg, 0.026 mmol) using Procedure 11, with the reaction mixture stirred for 5 min. The resulting crude material was purified by column chromatography (25% Et₂O in petroleum ether) to give (E)-153d as a pale yellow oil (8.7 mg, 0.023 mmol, 87%); [α]D²⁵ −53.5 (c = 1.0, CHCl₃); 95% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, tR major – 26.81 min, minor – 28.02 min); Rf = 0.22 (5:1, petroleum ether:EtOAc); δH (500 MHz, CDCl₃) 7.77 (2H, d, J = 8.5 Hz, TsH), 7.43 (2H, d, J = 7.6 Hz, PhH), 7.32–7.21 (4H, m, TsH and PhH), 5.37 (1H, d, J = 1.5 Hz, –CHPh), 5.40 (1H, dq, J = 15.1 and 6.3 Hz, H7), 5.10 (1H, ddd, J = 15.1, 8.3, 1.6 Hz, H6), 3.69 (1H, ddd, J = 11.4, 8.7, 3.2 Hz, H3’), 3.57 (3H, s, OCH₃), 3.52 (1H, ddd, J = 11.4, 9.1, 7.6 Hz, H3’’), 2.52 (1H, dddd, J = 10.5, 8.3, 8.0, 1.9 Hz, H3), 2.43 (3H, s, ArCH₃), 1.80 (1H, dddd, J = 12.0, 8.0, 7.6, 3.2 Hz, H4’), 1.68 (3H, dd, J = 6.3 and 1.6 Hz, CH₃), 1.42 (1H, dddd, J = 12.0, 10.5, 9.1, 8.7 Hz, H4’’); δC (125 MHz, CDCl₃) 161.0, 146.1, 143.8, 136.1, 130.1, 129.8, 129.7, 129.2, 128.2, 128.0, 127.4, 113.3, 55.4, 49.7, 47.0, 32.7, 21.6, 17.6; IR (thin film) νmax/cm⁻¹ 3012, 2950, 2835, 1609, 1513, 1352, 1242, 1161; HRMS m/z (ESI+) found [M+Na]+ 406.1451; C₂₂H₂₅NNaO₃S+ requires 406.1453.
(--)(Z)-2-Heptylidene-3-((E)-styryl)-1-tosylpyrrolidine, (E)-153e

Synthesised from (Z)-4-methyl-N-(oct-1-yn-1-yl)-N-(5-phenylpent-3-en-1-yl)benzenesulfonamide (Z)-151e (10 mg, 0.024 mmol) using Procedure 11, with the reaction mixture stirred at room temperature for 30 min. The resulting crude material was purified by column chromatography (20% Et₂O in petroleum ether) to give (E)-153e as a colourless oil (9.1 mg, 0.022 mmol, 93%); [α]⁺₂⁵ –125.5 (c = 1.0, CHCl₃); 93% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, tₖ major – 19.18 min, minor – 21.43 min); Rₛ = 0.50 (4:1, petroleum ether:EtOAc); δH (500 MHz, CDCl₃) 7.78 (2H d, J = 8.1 Hz, TsH), 7.43–7.25 (6H, m, TsH and PhH), 7.22–7.19(1H, m, PhH), 6.40–6.27 (2H, m, H6 and H7), 5.02 (1H, dt, J = 6.9 and 1.8 Hz, H9), 3.54 (1H, ddd, J = 11.4, 8.6, 3.0 Hz, H5'), 3.38 (1H, ddd, J = 11.4, 9.2, 7.9 Hz, H5‘‘), 2.49–2.34 (2H, m, H10), 2.43 (3H, s, ArCH₃), 2.24 (1H, br. ap. q, J = 8.5 Hz, H3), 1.69 (1H, dddd, J = 12.0, 8.0, 7.9, 3.0 Hz, H4'), 1.62 (3H, dd, J = 6.6, 1.6 Hz, H8), 1.45–1.24 (9H, m, H4″ and H11–14), 0.88 (3H, t, J = 6.9 Hz, H15); δC (125 MHz, CDCl₃) 143.7, 140.2, 137.3, 136.0, 130.7, 129.7, 129.4, 128.6, 128.3, 128.2, 126.1, 117.7, 48.5, 47.4, 32.8, 31.7, 28.90, 28.4, 25.3, 22.7, 21.5, 14.1; IR (thin film) νmax/cm⁻¹ 2934, 2257, 1358, 1167; HRMS m/z (ESI⁺) found [M+Na]⁺ 424.2313; C₂₆H₃₃NNaO₂S⁺ requires 424.2310.
(−)-2-((Z)-Benzyldiene)-3-((E)-prop-1-en-1-yl)-1-tosylpyrrolidine, (E)-153f

Synthesised from (Z)-4-methyl-N-(phenylethynyl)-N-(5-phenylpent-3-en-1-yl)benzenesulfonylamide (Z)-151f (10 mg, 0.024 mmol) using Procedure 11, with the reaction mixture stirred for 45 min. The resulting crude material was purified by column chromatography (25% Et₂O in petroleum ether) to give (E)-153f as a pale yellow oil (8.4 mg, 0.020 mmol, 83%); [α]$_D^{25}$ $-83.5$ (c = 1.0, CHCl₃); 94% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, $t_R$ major – 19.76 min, minor – 21.43 min); $R_f$ = 0.41 (5:1, petroleum ether:EtOAc); $\delta$H (500 MHz, CDCl₃) 7.78 (2H, d, $J = 8.5$ Hz, TsH), 7.35–7.18 (12H, m, TsH and PhH), 5.93 (1H, d, $J = 1.9$ Hz, $=CH$Ph), 5.40 (1H, dq, $J = 15.1$ and 6.3 Hz, H7), 5.10 (1H, ddd, $J = 15.1$, 8.3, 1.6 Hz, H6), 3.69 (1H, ddd, $J = 11.4$, 8.7, 3.2 Hz, H5′), 3.52 (1H, ddd, $J = 11.4$, 9.1, 7.6 Hz, H5″), 2.52 (1H, dddd, $J = 10.5$, 8.3, 8.0, 1.9 Hz, H3), 2.43 (3H, s, ArCH₃), 1.80 (1H, dddd, $J = 12.0$, 8.0, 7.6, 3.2 Hz, H4′), 1.68 (3H, dd, $J = 6.3$ and 1.6 Hz, CH₃), 1.42 (1H, dddd, $J = 12.0$, 10.5, 9.1, 8.7 Hz, H4″); $\delta$C (125 MHz, CDCl₃) 146.1, 144.1, 136.8, 136.0, 134.4, 131.0, 129.8, 129.5, 129.0, 128.6, 128.4, 128.2, 128.1, 128.0, 127.72, 126.5, 50.7, 47.2, 32.4, 21.5; IR (thin film) ν$_{max}$/cm$^{-1}$ 2938, 2254, 1350, 1159; HRMS m/z (ESI+) found [M+Na]$^+$ 438.1508; C$_{26}$H$_{25}$NNaO$_2$S$^+$ requires 438.1504.
(−)-(Z)-3-((E)-But-1-en-1-yl)-2-heptylidene-3-methyl-1-tosylpyrrolidine, (E)-276a

Synthesised from (Z)-4-methyl-\(N\)-(3-methylhept-3-en-1-yl)-\(N\)-(oct-1-yn-1-yl)benzenesulfonamide (Z)-264a (10 mg, 0.025 mmol) using Procedure 11, with the reaction mixture stirred for 80 min. The resulting crude material was purified by column chromatography (25% Et\(_2\)O in petroleum ether) to give (E)-276a as a pale yellow oil (6.2 mg, 0.015 mmol, 61%); \([\alpha]_{D}^{25}\) −53.5 (c = 1.0, CHCl\(_3\)); 94% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, \(t_R\) major − 16.26 min, minor − 18.19 min); \(R_f\) = 0.53 (5:1, petroleum ether:EtOAc); \(\delta_H\) (500 MHz, CDCl\(_3\)) 7.70 (2H d, \(J = 8.1\) Hz, Ts\(H\)), 7.28 (2H, d, \(J = 8.1\) Hz, Ts\(H\)), 5.27 (1H, dt, \(J = 15.1, 6.5\) Hz, H7), 5.02–4.92 (2H, m, H6 and H10), 3.54 (1H, ddd, \(J = 11.4, 8.6, 3.0\) Hz, H5'), 3.38 (1H, ddd, \(J = 11.4, 9.2, 7.9\) Hz, H5''), 2.49–2.34 (2H, m, H11), 2.43 (3H, s, Ar\(C_H\)), 1.99 (2H, m, H8), 1.69 (1H, ddd, \(J = 12.0, 7.9, 3.0\) Hz, H4'), 1.45–1.24 (9H, m, H4'' and H12–15), 1.18 (3H, s, CH\(_3\)), 0.95 (3H, t, \(J = 7.0\) Hz, H9), 0.88 (3H, t, \(J = 6.9\) Hz, H16); \(\delta_C\) (125 MHz, CDCl\(_3\)) 146.0, 143.8, 136.6, 135.8, 129.8, 128.3, 111.3, 53.7, 46.8, 40.3, 31.2, 28.9, 28.1, 26.3, 26.2, 25.3, 22.5, 21.7, 14.1, 13.9; \(\text{IR (thin film)}\ v_{\text{max/cm}}^{-1}\) 2924, 1357, 1163; \(\text{HRMS } m/z\) (ESI+) found [M+Na]\(^+\) 412.2285; C\(_{23}\)H\(_{33}\)NNaO\(_2\)S\(^+\) requires 412.2286.
(−)-2-((Z)-Benzylidene)-3-((E)-but-1-en-1-yl)-3-methyl-1-tosylpyrrolidine, (E)-276b

Synthesised from (Z)-4-methyl-N-(3-methylhept-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide (Z)-264b (10 mg, 0.026 mmol) using Procedure 11, with the reaction mixture stirred for 105 min. The resulting crude material was purified by column chromatography (25% Et₂O in petroleum ether) to give (E)-276b as a pale yellow oil (5.2 mg, 0.014 mmol, 52%); \([\alpha]^{25}_D\) −31.7 (c = 1.0, CHCl₃); 92% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, \(t_R\) major = 23.41 min, minor = 24.77 min); \(R_f\) = 0.33 (5:1, petroleum ether:EtOAc); \(\delta_H\) (500 MHz, CDCl₃) 7.70 (2H d, \(J = 8.1\) Hz, TsH), 7.43–7.16 (4H, m, TsH and PhH), 7.03 (1H, m, PhH), 5.27 (1H, dt, \(J = 15.1, 6.5\) Hz, H7), 5.02–4.92 (2H, m, H6 and H10), 3.54 (1H, ddd, \(J = 11.4, 8.6, 3.0\) Hz, H5'), 3.38 (1H, ddd, \(J = 11.4, 9.2, 7.9\) Hz, H5''), 2.43 (3H, s, ArC₃H₃), 1.99 (2H, m, H8), 1.69 (1H, ddd, \(J = 12.0, 8.0, 3.0\) Hz, H4'), 1.45–1.24 (1H, m, H4'') 1.18 (3H, s, CH₃), 0.95 (3H, t, \(J = 7.0,\) H9); \(\delta_C\) (125 MHz, CDCl₃) 148.4, 143.8, 136.7, 135.9, 135.6, 132.1, 130.1, 129.1, 128.4, 128.1, 127.8, 126.1, 54.5, 43.9, 40.4, 26.1, 25.4, 21.3, 14.3; IR (thin film) \(\nu_{max}/cm^{-1}\) 2963, 1352, 1162; HRMS m/z (ESI+) found [M+Na]+ 404.1658; \(C_{23}H_{27}NNaO_2S\) requires 404.1660.

(−)-(Z)-2-Heptylidene-3-((E)-pent-2-en-2-yl)-1-tosylpyrrolidine, (E)-276c

Synthesised from (Z)-4-methyl-N-(4-methyloct-3-en-1-yl)-N-(oct-1-yn-1-yl)benzenesulfonamide (Z)-269a (10 mg, 0.025 mmol) using Procedure 11, with the reaction mixture stirred at room temperature for 45 min. The resulting crude material was purified by column chromatography (10% Et₂O in
petroleum ether) to give (E)-276c as a colourless oil (9.4 mg, 0.024 mmol, 95%); [α]$_D^{25}$ = –63.5 (c = 1.0, CHCl$_3$); 93% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, $t_R$ major – 18.86 min, minor – 21.25 min); $R_f$ = 0.54 (4:1, petroleum ether:EtOAc); $\delta$$_H$ (500 MHz, CDCl$_3$) 7.70 (2H d, $J$ = 8.1 Hz, TsH), 7.28 (2H, d, $J$ = 8.1 Hz, TsH), 5.27 (1H, t, $J$ = 7.0 Hz, H7), 5.05 (1H, m, H10), 3.54 (1H, ddd, $J$ = 11.4, 8.6, 3.0 Hz, H5'), 3.38 (1H, ddd, $J$ = 11.4, 9.2, 7.9 Hz, H5"'), 2.49–2.34 (2H, m, H11), 2.43 (3H, s, ArCH$_3$), 2.24 (1H, br. t, $J$ = 8.5 Hz, H3), 1.69 (1H, dddd, $J$ = 12.0, 8.0, 3.0 Hz, H4"'), 1.62 (3H, d, $J$ = 6.6, 1.6 Hz, H8), 1.57 (3H, s, CH$_3$), 1.45–1.24 (9H, m, H4'' and H12–15), 0.90 (3H, t, $J$ = 7.0 Hz, H9), 0.88 (3H, t, $J$ = 6.9 Hz, H16); $\delta$C (125 MHz, CDCl$_3$) 143.5, 140.0, 136.1, 132.7, 133.0, 129.8, 127.3, 113.1, 51.3, 47.8, 32.4, 31.8, 28.9, 28.1, 25.6, 22.6, 21.3, 20.4, 16.0, 14.2, 14.0; IR (thin film) $\nu_{max}$/cm$^{-1}$ 12930, 1345, 1164; HRMS m/z (ESI+) found [M+Na]$^+$ = 426.2441; C$_{24}$H$_{37}$NNaO$_2$S$^+$ requires 426.2443.

Synthesised from (Z)-4-methyl-N-(4-methyloct-3-en-1-yl)-N-(phenylethynyl)benzenesulfonamide (Z)-269b (10 mg, 0.025 mmol) using Procedure 11, with the reaction mixture stirred for 55 min. The resulting crude material was purified by column chromatography (25% Et$_2$O in petroleum ether) to give (E)-276d as a pale yellow oil (9.4 mg, 0.023 mmol, 92%); [α]$_D^{25}$ = –23.5 (c = 1.0, CHCl$_3$); 94% ee (CHIRALPAK IC, 40% IPA/hexane, 0.3 mL/min, $t_R$ major – 24.86 min, minor – 25.71 min); $R_f$ = 0.33 (5:1, petroleum ether:EtOAc); $\delta$$_H$ (500 MHz, CDCl$_3$) 7.70 (2H d, $J$ = 8.1 Hz, TsH), 7.40–7.28 (4H, m, TsH and PhH), 5.27 (1H, t, $J$ = 7.0 Hz, H7), 5.05 (1H, m, H10), 3.54 (1H, ddd, $J$ = 11.4, 8.6, 3.0 Hz, H5"'), 3.38 (1H, ddd, $J$ = 11.4, 9.2, 7.9 Hz, H5"'), 2.43 (3H, s, ArCH$_3$), 2.25 (1H, br. t, $J$ = 8.5 Hz, H3), 1.69 (1H, dddd, $J$ = 11.9, 7.9, 8.0, 3.0 Hz, H4"'), 1.62 (3H, dq, $J$ = 6.6, 1.6 Hz, H8), 1.57 (3H, s, CH$_3$), 1.45–1.24 (1H, dddd, $J$ = 12.0, 7.9, 8.0, 2.8 Hz, H4"'), 0.90 (3H, t, $J$ = 7.0 Hz, H9); $\delta$C (125 MHz, CDCl$_3$) 144.2, 143.0, 136.1, 135.1, 132.8, 132.7, 132.4, 129.9, 129.2, 128.5, 128.3, 128.0,
54.3, 48.1, 32.3, 21.6, 21.3, 16.1, 14.1; IR (thin film) $\nu_{\text{max}}$/cm$^{-1}$ 2927, 1355, 1164; HRMS m/z (ESI+) found [M+Na]$^+$ 418.1821; $C_{24}H_{20}NNaO_2S^+$ requires 418.1817.
Chapter 7: Experimental

7.4 X-Ray Crystallographic Data

Low temperature\textsuperscript{120} single crystal X-ray diffraction data were collected using I19-1 at the Diamond Light Source\textsuperscript{121} at 100 K. Data were reduced using CrysAlisPro. All structures were solved ab initio using SuperFlip\textsuperscript{123} and the structures were refined using CRYSTALS.\textsuperscript{124}

Structure DIA0293 (239a) contained large solvent accessible voids comprising weak, diffuse electron density. The discrete Fourier transforms of the void regions were treated as contributions to the A and B parts of the calculated structure factors using PLATON/SQUEEZE\textsuperscript{125} integrated within the CRYSTALS software.

Table 7.1 Summary of X-ray crystallographic data

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>239a (DIA0293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moiety Formula</td>
<td>RhSbF$_6$Cl$_2$O$<em>2$P$<em>2$C$</em>{46}$H$</em>{64}$</td>
</tr>
<tr>
<td>CCDC</td>
<td>n/a</td>
</tr>
<tr>
<td>Space Group</td>
<td>P 6$_5$</td>
</tr>
<tr>
<td>a [Å]</td>
<td>11.45500(10)</td>
</tr>
<tr>
<td>b [Å]</td>
<td>11.45500(10)</td>
</tr>
<tr>
<td>c [Å]</td>
<td>57.6292(5)</td>
</tr>
<tr>
<td>α [°]</td>
<td>90</td>
</tr>
<tr>
<td>β [°]</td>
<td>90</td>
</tr>
<tr>
<td>γ [°]</td>
<td>120</td>
</tr>
<tr>
<td>V [Å$^3$]</td>
<td>6548.82(12)</td>
</tr>
<tr>
<td>Z</td>
<td>6</td>
</tr>
<tr>
<td>T [K]</td>
<td>100</td>
</tr>
<tr>
<td>Total Reflections</td>
<td>133295</td>
</tr>
<tr>
<td>$R_{int}$</td>
<td>0.1128</td>
</tr>
<tr>
<td>Reflections, Restraints, Parameters (I&gt;3.0/σ(I))</td>
<td>21721, 1, 542</td>
</tr>
<tr>
<td>Min. and Max. Residual Density, [eÅ$^{-3}$]</td>
<td>-1.69, 1.77</td>
</tr>
<tr>
<td>$R_1$ (I&gt;2σ(I))</td>
<td>0.0453</td>
</tr>
<tr>
<td>$wR_2$</td>
<td>0.1065</td>
</tr>
</tbody>
</table>

\textsuperscript{1} The X-ray data were collected and processed by Steven J. Mansfield.
Figure 7.1: Solid state structure of 239a. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms are omitted for clarity.
Chapter 8: References


Chapter 9: Appendix

9.1 Publications during DPhil research

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


2. Mechanistic Study of Arylsilane Oxidation through $^{19}$F NMR Spectroscopy


3. Mechanistic Insight into Palladium-Catalyzed Cycloisomerization: A Combined Experimental and Theoretical Study


4. Copper-Catalyzed Synthesis and Applications of Yndiamides

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

R.N. Straker1, Q. Peng1, A. Mekareeya1, R.S. Paton1 & E.A. Anderson1

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.

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Demands for higher efficiency, economy and selectivity in the synthesis of novel molecular scaffolds drives organic chemistry. In this context, cycloisomerizations represent ideal methods for the formation of cyclic organic molecules, as they can fulfill all of these criteria. Despite much research into transition metal-catalyzed cycloisomerization, and reports where high enantioselectivity is achieved for the cyclization of prochiral substrates to enantioenriched products, 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, the development of this process using ynamides—or indeed any asymmetric cycloisomerization of ynamide-tethered enynes—has not been explored either experimentally or theoretically. 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. Intrinsically, these studies is a combined theoretical and experimental approach to optimize catalyst design, 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-lead 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, or via formation of an intermediate dichloremamine. Initial screening of ruthenium and rhodium catalyst systems (Table 1) revealed that only the latter afforded high yields of azabicycle 7a from ynamide 1a, using \(\text{[Rh(cod)naphthalene]SbF}_6\) (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 11–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. Cyclization of substrates containing homoallylic stereocenters proved less selective; however, good stereocontrol (\(d_r = 12:1\)) could be achieved using \(\text{[Rh(cod)Cl]_2}\). 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 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[CpRu(MeCN)3]PF6 (10)</td>
<td>acetone</td>
<td>50</td>
<td>20</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>2</td>
<td>[RhCl(cod)]2 (10)</td>
<td>toluene</td>
<td>110</td>
<td>20</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>RhCl(PPh3)3 (10)</td>
<td>toluene</td>
<td>110</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>[(C5H5)Rh(cod)3]BF4 (10)</td>
<td>1,2-dichloroethane</td>
<td>rt</td>
<td>1.5</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>[(C5H5)Rh(cod)3]BF4 (10)</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>1.5</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>[(C5H5)Rh(cod)3]BF4 (5)</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>3</td>
<td>91</td>
</tr>
</tbody>
</table>

*aReactions performed at 0.1 M substrate in the solvent stated.  bReaction 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 alkene-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]BF4 reported by Mezetti (8) (ref. 42), which reveals an η2-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 alkyn coordinates trans to the phosphorous atom of the phosphoramidite ligand, and the vinylcyclopropane coordinates trans to the η2-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 catalysis32. Our theoretical work first explored eight possibilities for the binding of ynamide-vinylcyclopropane 1a to the [Rh(L1)]
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 pathway17,21, our DFT calculations...
(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] cycloisomerization17. 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 ($\Delta G^\ddagger_{Re/Si} = -2.69$ kcal mol$^{-1}$), which is in excellent agreement with the experimental value (R, 98% ee). The calculated enantioselectivity for phosphoramidite L4 (9.3% ee, $\Delta G^\ddagger_{Re/Si} = -0.11$ 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...
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)\(^{12}\), one of the ligand benzylamine groups acts as 2π-electron donor (2.6–2.7 Å) in these transition states.

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

<table>
<thead>
<tr>
<th>Orientation</th>
<th>Metallacyclopentene Pathway</th>
<th>Vinylvyclopropane pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Re-selectivity (R)</td>
<td>Si-selectivity (S)</td>
</tr>
<tr>
<td>1</td>
<td>18.7</td>
<td>31.3</td>
</tr>
<tr>
<td>2</td>
<td>17.0</td>
<td>19.7</td>
</tr>
<tr>
<td>3</td>
<td>23.6</td>
<td>23.9</td>
</tr>
<tr>
<td>4</td>
<td>23.2</td>
<td>30.7</td>
</tr>
</tbody>
</table>

Transition state energies (SMD-ωB97X/D/6-311 + G(d,p)/Lanl2TZ//ωB97X/D/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-ωB97X/D/6-311 + G(d,p)/Lanl2TZ//ωB97X/D/6-31G(d)/Lanl2DZ Gibbs free energies are shown in kcal mol\(^{-1}\).
We hypothesized that variation of the electronic character of this \( \pi^2 \)-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 \( \text{para} \) 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 (\( \Delta G^0_{\text{L5-L1}} = -0.47 \text{ kcal mol}^{-1} \)) and enantioselectivity (\( \Delta G^0_{\text{Re/Si}} = -4.56 \text{ kcal mol}^{-1}, 99.9\% \text{ ee} \)), while an electron-donating substituent (p-MeO, L6) would have the opposite effect (\( \Delta G^0_{\text{L5-L1}} = +0.76 \text{ kcal mol}^{-1}, \Delta G^0_{\text{Re/Si}} = -2.42 \text{ kcal mol}^{-1}, 96.7\% \text{ ee} \)). This computed trend in reactivity and enantioselectivity, namely \( \text{L5} > \text{L1} > \text{L6} \), 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.

**Figure 6 | Enantioselective and double stereodifferentiating, ynamide \([5 \cdot 2]\) 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) \( \text{H}^1 \text{NMR spectroscopic monitoring of reaction progress emphasizes the rate enhancement between ligands L6, L1 and L5.} \) 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 \( \text{H}^1 \text{NMR spectroscopic analysis.} \)

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 poten reaction 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 1H NMR spectroscopy (in CDCl3, 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 d.r., respectively when cyclized using [Rh(cod)naphthalene]SbF6 (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 ((S,R,S)-L1) successfully overturned this powerful substrate stereoselectivity, giving 14l in up to 1:8 d.r. Interestingly, it was ligand 1l—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/enantiomERIC[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

Reaction [5 + 2] cycloisomerization. To an oven-dried vial containing the ynamide vinylcyclopropane (1.0 equiv.) under Ar was added a solution of [(C6H5)2Rh(cod)]SbF6 (5 mol%) in degassed CH2Cl2 (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 (SiO2, petroleum ether/ethyl acetate eluent) (Fig. 3).

Asymmetric [5 + 2] cycloisomerization. A solution of [RhCl(C6H5)2]2 (2.5 mol%), NaBArF4 (6 mol%) and phosphoramidite ligand (6 mol%) in degassed CH2Cl2 (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 (SiO2, 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-correctedωB97X-D functional46 without symmetry constraints. The effective core potentials (ECPs) of Hay and Wadt47 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(B31G). 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 (LANL2TZ48) for Rh (B32) by single-point calculations, in implicit solvent CH2Cl2 treated with the SMD universal solvation model49. The structures of the ynamide substrate and a series of phosphoramidite ligands were computed in full, while the toluenesulfonylamine 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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Mechanistic Study of Arylsilane Oxidation through $^{19}$F NMR Spectroscopy

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ABSTRACT: The mechanism of the oxidation of arylsilanes to phenols has been investigated using $^{19}$F NMR spectroscopy. The formation of silanols in these reactions results from a rapid background equilibrium between silanol and alkoxysilane; the relative rates of reaction of these species was evaluated by modeling of concentration profiles obtained through $^{19}$F NMR spectroscopic reaction monitoring. Combining these results with a study of initial rates of phenol formation, and of substituent electronic effects, a mechanistic picture involving rapid and reversible formation of a pentavalent peroxide ate complex, prior to rate-limiting aryl migration, has evolved.

INTRODUCTION

Arylsilanes are highly versatile intermediates in organic synthesis, with a number of methods having recently been disclosed for both their preparation1 and transformations.2 Among these, the oxidation of arylsilanes to phenols is relatively underexploited compared to the equivalent conversion of alkyl and alkenylsilanes into aliphatic alcohols and ketones, respectively.3,4 and has only recently been developed as an efficient and general methodology.5,6 Despite the demonstrated synthetic utility of this oxidation, mechanistic explorations of this phenol synthesis are limited to a study of arylfluorosilane oxidation by Tamao and co-workers,3h and theoretical investigations on the oxidation of alkylfluorosilanes,8, and alkylalkoxysilanes (and mixed alkoxyfluorosilane derivatives)9 by Mader and Norrby. Here we describe an experimental study of the mechanism of the H$_2$O$_2$-mediated oxidation of arylalkoxysilanes, a reaction that proceeds in the presence or absence10 of fluoride. In addition to shedding new light on the dynamic behavior of alkoxysilanes, this work explores the effects of low concentrations of fluoride ion on the oxidation, which can be rationalized by consideration of the relative reactivity of different organosilane intermediates.

The Tamao group’s seminal mechanistic studies on the hydrogen peroxide-mediated oxidation of fluorosilanes (and their corresponding fluoride ate complexes) led to their proposal (Scheme 1a) of a rate-limiting addition of hydrogen peroxide or hydroperoxide anion, under neutral or basic conditions respectively, to pentacoordinate ate complex 1 (formed by rapid and reversible addition of fluoride ion to 2).3h This peroxide association step was proposed to be rate-limiting, as the reaction was found to be first order with respect to H$_2$O$_2$. Each pathway leads to a hexacoordinate species (3 or 4), and then to pentacoordinate aryloxysilane 5 via aryl migration; a concerted peroxide association/migration was not excluded. Tamao found that aryl groups migrate in preference to alkyl...
groups, and proposed that the addition of fluoride ion is necessary for the oxidation to proceed.

Mader and Norrby subsequently calculated (Scheme 1b) that anionic substitution of anionic pentavalent silicates (e.g., 6) is rapid, and that hydroperoxide anion is more likely to attack pentacoordinate silicon (6) than the neutral species (7). They also proposed that addition of fluoride ions is not essential for the oxidation to proceed, but increases the rate of hydroperoxide attack at silicon via formation of a greater proportion of pentavalent trifluorosilicate species, which are more reactive toward substitution of F⁻ by HOO⁻ than neutral tetravalent difluorosilanes. Importantly, these authors concluded that alkyl migration from conformer 3 (Scheme 1c) had shown that the oxidation of arylhydrosilanes is the rate-limiting step. Our own experimental work (Scheme 1c) had shown that the oxidation of arylhydrosilanes, and arylalkoxysilanes, proceeds under fluoride-promoted or fluoride-free conditions, thus supporting the notion that fluoride ion is a nonessential (but generally beneficial) component of the reaction.

Several points arise from this previous work. First, there is a general acceptance that stoichiometric amounts of fluoride are required for successful oxidation (albeit that fluoride ion may not be coordinated to silicon in the migration step itself), and that fluoride is sequestered in the course of the reaction by liberated silanes. Second, the peroxide-mediated oxidation of silanes featuring only one, or even no electronegative substituents, has not been studied from a mechanistic perspective. Third, no experimental correlation of Mader and Norrby’s calculations on alkoxysilane oxidation has been achieved. Finally, the observation of silanols and disiloxanes, as intermediates or byproducts, has not been considered in detail. In this work, we disclose investigations of arylsilane oxidation which unite the various experimental and computational studies in the field, and provide a comprehensive picture of the equilibria that are at play during oxidation, as well as the influence of fluoride.

## RESULTS AND DISCUSSION

In earlier work, we had found that the addition of a fluoride source was not essential to achieve full conversion of arylsilanes to phenols, but that even substoichiometric amounts increase the overall efficiency of oxidation. This observation is mirrored in studies by Phillips and co-workers on the deprotection of silyl ethers using catalytic amounts of TBAF (0.1 equiv), which also demonstrate that fluoride ion can be recycled from fluoroethers byproducts (that fluoroethers are formed irreversibly is an understandable assumption based on the strength of the Si-F bond, ~135 kcal mol⁻¹). Phillips found the protection of arylsilyl ethers to be especially rapid, underlining that these ethers are particularly susceptible to nucleophilic attack, and thus potentially more amenable to fluoride recycling as is also required in a fluoride-catalyzed oxidation manifold. Both our group and the Phillips group found the predominant fate of the organosilane to be the formation of a silanol (rather than fluoroethers, alkoxysilane, or disiloxane), again supporting the release of fluoride at some point after silyl ether cleavage. With these observations in mind, we set out to study the processes at play during the oxidation of arylhydrosilanes and arylalkoxysilanes, under fluoride-free and fluoride-catalyzed reaction conditions.

### Oxidation of Arylhydrosilanes in THF/MeOH.

We began this work by examining the oxidation of arylhydrosilanes (ArMe₂SiH), substrates which do not contain an electronegative substituent as has previously been thought to be crucial for Tamao oxidation. The conversion of 4-(dimethylsilyl)benzonitrile 9a, a substrate we had found to be among the more reactive toward oxidation, was monitored by ¹H NMR spectroscopy (Figure 1). To reproduce “standard” Tamao oxidation conditions, this experiment was performed in a mixed deuterated solvent system of d₄-MeOD/d₆-THF (1:1), with 6.0 equiv H₂O₂ (30% aq.) and 1.6 equiv KHCO₃. Although monitoring of the reaction was complicated by a broad water peak at 3.5−5.5 ppm, two regions of the spectrum proved informative (Figure 1a): the aromatic region (~6.5 ppm), where oxidation is characterized by an upfield shift of the aromatic protons; and the silane region (~0.5 ppm), where the silane substituents are characterized by their multiplicity (the methyl signals appear as a doublet in the hydrosilane, but as a singlet in compounds that do not contain Si-H). The profile of this reaction is shown in Figure 1b. This revealed a smooth consumption of hydrosilane 9a, and the formation of a nonoxidized arylsilane species assigned as silanol 11a, which was converted to phenol 12a as the reaction proceeded. The identity of 11a was confirmed through independent synthesis, and submission of a mixture of authentic 11a and hydrosilane 9a to the oxidation. Identical chemical shifts and a similar reaction profile were observed for this mixture as had been seen in the first oxidation, which confirmed the identity of 11a in the mixed NMR solvent system.

We questioned whether the silanol observed in this oxidation was a necessary intermediate, or if direct hydrosilane oxidation could compete. Due to the limitations of observing the oxidation by ¹H NMR spectroscopy, we turned to p-fluorodimethylsilane (9b, Figure 2), which enabled reaction...
monitoring by $^{19}$F NMR spectroscopy, 9b is significantly less reactive than benzonitril silane 9a, but nonetheless revealed a similar trend of reactivity (Graph a), and allowed us to observe subtle details of the early phase of the oxidation, where a significant lag in the production of phenol was apparent until appreciable quantities of silanol had formed. This supports the intermediacy of the silanol in the oxidation, rather than a direct oxidation of the hydrosilane (i.e., migration of H is favored over Ar in the initial oxidation).

Interestingly, small amounts of methoxysilane 10b were observed throughout the reaction. As expected, the equivalent oxidation of 9b under fluoride-promoted conditions proceeded more rapidly (0.1 equiv TBAF, Graph b), although a delay in the production of phenol was again observed, with silanol 11b being produced alongside small amounts of methoxysilane 10b throughout the reaction. This suggests that an equivalent (but accelerated) reaction pathway operates in the presence of fluoride.

Oxidation of Silanols and Methoxysilanes in THF/MeOH. Although silanols were clearly intermediates in the oxidation of arylhydrosilanes under either fluoride-free or fluoride-promoted conditions, their reactivity relative to methoxysilanes, and the importance of exchange between these two species, was as yet unclear. To probe this, the fluoride-free oxidations of (4-fluorophenyl)dimethylsilanol 11b and (4-fluorophenyl) methoxydimethylsilane 10b were studied (Figure 3). We immediately noticed that oxidation of silanol 11b (Figure 3a) proceeded at a much reduced rate compared to methoxysilane 10b (Figure 3b), and that the latter oxidation featured significant quantities of silanol. Oxidation of 10b under fluoride-promoted conditions (0.1 equiv TBAF, Figure 3c) proceeded at an overall rate broadly similar to that of the fluoride-free reaction. However, the composition of the various reaction intermediates was rather different, with silanol 11b produced to a much greater extent, in addition to small amounts of a further silicon-containing species which was identified as disiloxane 13b.

While both the methoxysilane and silanol could potentially serve as substrates for oxidation, it was not clear whether both indeed did, given that these two components likely exist in equilibrium. To study this, methoxysilane 10b was subjected to basic conditions (KHCO$_3$) in deuterated THF/MeOH (1:1, plus a volume of water equivalent to that of the 30% aq. H$_2$O$_2$ used in the oxidations), in the presence and absence of TBAF. Under fluoride- and peroxide-free conditions (Figure 4, Graph a), an equilibrium between 10b and 11b was established over ~48 h, which stabilized with an equilibrium constant of $K_{eq} = 2.48$ (in favor of silanol 11b). The addition of TBAF greatly increased the rate at which equilibrium was reached, but not its position (Graph b, $K_{eq} = 2.57$; see the Supporting Information (SI) for further details on this equilibrium and the negligible effect of fluoride ion concentration). In both experiments, significant amounts of disiloxane 13b were formed at the expense of the equilibrium mixture of silanol and methoxysilane; this side-reaction, which is to the detriment of oxidation, was clearly promoted by fluoride. Under “true” oxidation conditions, the rate of equilibration could also be
affected by the nucleophilic hydroperoxide anion, particularly in the case of fluoride-free Graph 4a.

This suggested that under both sets of oxidation conditions, a dynamic equilibrium between the silanol and methoxysilane operates alongside the oxidation of either or both species, which is consistent with the exchange of ligands between different ate complexes. To elucidate the relative rates of these various processes, we modeled the timecourse kinetic data of the oxidation of methoxysilane 10b in THF/MeOH using Berkeley Madonna software, based on the reaction scheme in Figure 5a. Graph b illustrates the experimental and modeled data for the fluoride-free oxidation of 10b, and Graph c illustrates the data for fluoride-promoted oxidation.21 Best-fit correlations of the experimental data with the illustrated reaction scheme were obtained, which led to the relative rate coefficients depicted in the Table (Figure 5).22

The modeling led to an excellent fit between experiment and theory, suggesting that the reaction scheme adopted is a valid depiction of the processes at play during the oxidation. Both models correlate with the equilibrium constants obtained experimentally \( K_{eq} \approx 2.5 \), c.f. Figure 4), and give a qualitative indication that the rate of methoxysilane oxidation is around 10-fold that of silanol oxidation \( \text{i.e., } k_2 \gg k_1 \). This may reflect the propensity of the silanol to form hydrogen bonds with methanol (Si–O–H···O(H)Me), which could increase electron density at the silicon atom and therefore deactivate it toward attack by hydroperoxide anion.23 In the absence of TBAF, the rate of methoxysilane oxidation appears significantly faster than substitution at silicon by water/hydroxide \( k_2 > k_1 > k_{\text{sub}} \). Although hydroperoxide presumably serves as a highly competent nucleophile for ate complex formation (as evidenced by the more rapid interconversion of methoxysilane and silanol in its presence compared to the peroxide-free equilibrium experiment in Figure 4a), the peroxide ate complex formed from the methoxysilane seems more prone to undergo (unimolecular) oxidation than (bimolecular) substitution. Equilibrium between methoxysilane and silanol is not reached until \(~5\) h reaction time (Figure 3b), such that a greater proportion of more reactive methoxysilane is present in the reaction before this time point. However, in the presence of TBAF (Figure 3c), the rate of substitution at silicon (i.e., the interconversion of methoxysilane and silanol) is increased to such an extent that it now outpaces the rate of oxidation \( k_1 > k_{\text{sub}} \). This suggests a bifurcation to the interconversion of the methoxysilane and silanol to benefit significantly from fluoride (c.f. Figure 4b), and the rapid establishment of this equilibrium is to the detriment of methoxysilane oxidation.8,9

The culmination of these effects is that fluoride-free and fluoride-promoted methoxysilane oxidations proceed at similar overall rates, but by different compositions of intermediates.

Attempts to fit reaction parameters to the slower oxidation of the silanol (i.e., Figure 3a) proved more challenging; although these oxidations gave reproducible trends in 1:1 THF/MeOH, they did not afford reproducible relative rates of reaction, which prevented reliable parameter fitting. The reactions were found to be highly susceptible to agitation, with a momentary effervescence being observed which coincided with a marked “spike” (increase) in the rate of reaction. We surmised that this corresponded to release of carbon dioxide (from KHCO₃/ H₂CO₃ decomposition), the evolution of which would have a dramatic effect on the acid–base equilibria of the reaction system and therefore presumably on the concentration of peroxide (or other) anions. This could be circumvented to an extent by purging the reaction mixture with argon, which displaced solubilized CO₂. However, the most significant improvement was gained through the use of methanol alone as solvent, which now gave reproducible kinetic profiles.24

The oxidations of the methoxysilane 10b and silanol 11b were monitored under these modified conditions (Figure 6), and the profiles modeled using Berkeley Madonna.21 Considering the fluoride-free oxidations of 10b (Graph a) and 11b (Graph b), it was immediately apparent that the rate of nucleophilic substitution at silicon was significantly enhanced in pure MeOH compared to MeOH/THF mixtures: after initial rapid equilibration of silanol and methoxysilane (perhaps promoted by the higher solubility of KHCO₃ in MeOH), the two reaction profiles were very similar. Due to the high reproducibility of the reactions,24 we were able to fit identical rate coefficients to the oxidation of both the silanol and methoxysilane, indicating that these oxidations operate under a Curtin–Hammel situation where rapid interconversion of 10b and 11b precedes rate-limiting oxidation—in other words, near identical reaction pathways operate from both arylsilanol and arylmethoxysilane substrates. The oxidation rate coefficients evaluated in the modeling suggest that although the silanol predominates at equilibrium, the vast majority of oxidation proceeds via the methoxysilane (i.e., \( k_1 > k_{\text{sub}} \)).

The reaction profile of the fluoride-catalyzed oxidation of methoxysilane 10b (0.1 equiv TBAF, Graph c) also revealed broadly similar kinetics, with a rapid equilibration of methoxysilane and silanol compared to methoxysilane oxidation. TBAF might be expected to further enhance the rate of methoxysilane—silanol exchange, but no accompanying acceleration of oxidation was apparent. The reason for this was soon to become clear.

**Influence of Reagent Concentration on Initial Rate of Reaction.** The influence of the concentration of the various reagents was evaluated by measurement of initial rates of

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**Figure 5.** Modeling of kinetic data for oxidations of methoxysilane 10b, as shown in Figure 3, using Berkeley Madonna. The model is based on experimental data up to 50% conversion (data points shown). (a) Modeled reaction pathways; (b) model for fluoride-free oxidation. (c) model for fluoride-promoted oxidation (0.1 equiv TBAF). Values are normalized relative to \( k_1 \). Experimental data obtained at 0.1 M substrate, 0.6 M H₂O₂, 1.8 equiv KHCO₃ in d₄-MeOH/d₄-THF (1:1). Relative rate coefficients were obtained by best fit of parameters to the reaction profile a.
phenol formation in MeOH (Figure 7, experiments run in triplicate for each data point). Graph a shows the variation in initial rate of phenol formation with hydrogen peroxide concentration. As expected, the reaction shows a linear relationship to [H₂O₂], but at higher concentrations a plateau effect is seen. We propose that this arises from the limiting concentration of KHCO₃ present in the reaction, which in turn limits the maximum concentration of active hydroperoxide anion. Similar results were obtained when the concentration of KHCO₃ was varied (Graph b): an increase in rate can again be seen with increasing concentration of base, with plateauing observed as the reaction mixture approaches a limit of base solubility at 0.3 equiv. KHCO₃ (i.e., 0.03 M).

The effect of TBAF concentration was next examined. Here we were surprised to observe an overall inhibitory effect of fluoride in the initial rate profiles (Graph c). Fluoride ions increase the rate of nucleophilic substitution around tetravalent silicon by increasing the electrophilicity of the silicon center in a pentavalent silicon-fluoride ate complex, where negative charge is dispersed onto the electronegative apical ligands; nucleophilic attack at pentavalent silicon can be up to 150 times faster than at tetravalent silicon. However, in the oxidation reaction, we suggest that this effect is offset by an increased rate of interconversion of the various tetracoordinate and pentacoordinate silicon species, including the possibility that fluoride could retard the overall rate of oxidation by competitive displacement of hydroperoxide from preoxidation ate complexes, thereby decreasing the overall rate of reaction. Finally, the effect of water present in the reaction was examined, as this would likely also affect the concentration of the two silane species, and hence the rate of oxidation. Figure 8 illustrates the influence of water on the methoxysilane–silanol equilibrium constant. Not only is there a clear correlation between Kₑqₑ and the concentration of water, but also with the nature of the cosolvent, with a higher proportion of silanol being observed in THF/MeOH mixtures (Series A) compared

Figure 6. ¹⁹F NMR spectroscopic observation, and modeled reaction parameters, for oxidations in MeOH. (a) Fluoride-free oxidation of methoxysilane 10b; (b) fluoride-free oxidation of silanol 11b; and (c) fluoride-promoted oxidation of 10b. Experimental data obtained under the conditions indicated in d₄-MeOH. Relative rate coefficients were obtained by best fit of parameters to the illustrated reaction profiles.

Figure 7. Order of reaction for the oxidation of methoxysilane 10b with respect to reagents. Reactions run 0.1 M in substrate, in MeOH. Variation of concentration of (a) H₂O₂ (0.1 equiv TBAF, 0.1 equiv KHCO₃); (b) KHCO₃ (0.1 equiv TBAF, 6.0 equiv H₂O₂); (c) TBAF (0.1 equiv KHCO₃, 6.0 equiv H₂O₂). Data points represent the mean rate coefficient of three reactions. Error bars indicate one standard deviation from the mean. See the SI for raw data sets.

Figure 8. Effect of water on the methoxysilane/silanol equilibrium. All experiments employed 0.05 mmol 10b and 0.1 equiv KHCO₃. Series A: THF/MeOH (1:1). Series B: MeOH. Series C: MeOH, 1 equiv TBAF.
to MeOH alone (Series B, C). It is again notable in the latter solvent that fluoride does not affect the position of equilibrium. These results suggest that increasing amounts of water are likely to inhibit oxidation, albeit the inorganic base will be better solubilized.

**Aryldimethylfluorosilane Intermediacy.** The importance of fluoride ions in silicon chemistry merited a search for fluorosilanes intermediates, which we expected would likely be present during the oxidation. To study this, we prepared the p-fluorophenyl dimethylfluorosilane (4-FC₆H₄SiMe₂F), and recorded its ¹⁹F NMR spectrum, which showed two signals at −113.5 (C−F) and −165.1 (Si−F) ppm (in MeOH, Figure 9a).²⁹ Close inspection of the reaction profiles of the oxidation of methoxysilane 10b in MeOH, using 0.1 equiv TBAF and 3 or 6 equiv of H₂O₂ revealed a small amount of this fluorosilane to be rapidly formed in these reactions (Figure 9b, 6 equiv H₂O₂). The proportion of fluorosilane observed was inversely proportional to the concentration of H₂O₂ and the fluorosilane peak completely disappeared in the reaction using 6 equiv of H₂O₂ once this reaction reached completion (Figure 9c).²⁹ These observations substantiate the notion that fluorosilane formation is indeed influential on reaction progress, and that fluoride ion can be recycled from silane intermediates.

**Charge Development in the Rate-Limiting Step.** The experimental data obtained supports a rapid exchange of electronegative ligands around silicon (methoxide, hydroxide, hydroperoxide, and fluoride) as a prelude to a slower, rate-determining migration. In methanol, the rate of ligand exchange approaches a Curtin−Hammett straight line fit, with reaction constants of ρ = +0.60 and ρ = +0.45 for Graphs a and b, respectively. Mindful that mesomeric effects might play a limited role during a rate-limiting migration step, we also explored Swain−Lupton plots of these data;³⁰ Graph c shows the Swain−Lupton plot in 1:1 d₅-THF/d₅-MeOH, and Graph d in MeOH (δₛₛ = 0.77). Of great intrigue is the balance of Swain−Lupton sensitivity factors f (field/inductive) and r (resonance), which were obtained using Dual Obligation Vector Evaluation (DOVE) as reported by Swain et al.³¹ In MeOH/THF, f = 0.491, r = 0.509; while in MeOH, f = 0.459, r = 0.541. These values show that mesomeric and inductive effects play an equal role in the rate-determining step of the oxidation.

Despite a significant change in the rates of nucleophilic substitution at silicon when the solvent system is changed from

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**Figure 9.** ¹⁹F NMR spectra of 4-FC₆H₄SiMe₂F, and oxidation of 10b in MeOH. (a) Authentic sample of fluorosilane. (b) Oxidation of 10b after 4 h reaction time. (c) Spectrum of reaction mixture of oxidation of 10b at completion (36 h), showing consumption of the fluorosilane.

**Figure 10.** LFER plots for the oxidations of p-substituted ArSiMe₂OMe. (a) Hammett plot in 1:1 d₅-THF/d₅-MeOH; (b) Hammett plot in d₅-MeOH; (c) Swain−Lupton plot in 1:1 d₅-THF/d₅-MeOH; (d) Swain−Lupton plot in d₅-MeOH. All reactions run in competition with 4-FC₆H₄SiMe₂OMe. kₛₛ = [p-XC₆H₄OH]/[p-FC₆H₄OH], as determined by ¹H NMR spectroscopic analysis of each reaction. Error bars show one standard deviation from the mean.
THF/MeOH to pure MeOH (Compare Figures 4 and 6, respectively), the somewhat similar \( \rho \) values observed for these two reactions under both Hammett and Swain–Lupton analyses further argues against nucleophilic attack of hydrogen peroxide at silicon being rate-determining, albeit \( \text{H}_2\text{O}_2 \) concentration clearly has a rate-influencing effect. These values are, nonetheless, indicative of modest negative charge development in the transition state of the rate-limiting step, which may reflect a positioning of the migrating group in the (charge dense) apical position around pentacoordinate silicon prior to/ during the migration step itself. The balance of inductive and mesomeric effects is harder to interpret, as these could affect both migration, or \( \text{HOO}^- \) coordination to the silane, but provide an additional interesting insight into the electronic characteristics of the RDS. The effect of the solvent on the extent of negative charge development adjacent to the arene in the RDS may reflect a change in the position of the transition state. For instance, it seems reasonable to suppose that \( \text{O} \cdots \text{O} \) bond breaking may be more advanced in MeOH due to better solvation of the hydroxide leaving group.

Finally, we note that these reaction constants are similar in magnitude to the results of an intramolecular competition study of aryl migration conducted by the Tamao group (Scheme 2, eq 1), which was attributed to electronic effects on aryl migration alone, but lower than a related intermolecular competition (eq 2) which Tamao concluded implied a rate-limiting attack of peroxide at silicon.

**CONCLUSIONS**

By observing the oxidation of arylsilanes using \( ^{19}\text{F} \) NMR spectroscopy, the major reaction components of the oxidation have been identified and the reaction profiles characterized. A significant formation of silanol during the oxidations was revealed, as well as a sensitivity of the oxidation to solvent effects. The rapid rate of nucleophilic substitution at silicon in MeOH compared to THF/MeOH, but the similarity between the LFER reaction parameters for the oxidation in MeOH and THF/MeOH mixtures, indicates that hydrogen peroxide coordination is not a rate-limiting process. Instead, aryl migration is proposed to be the rate limiting step, supporting the conclusions of previous theoretical work. The results of these studies offer new insight into organosilane reactivity for the design of silicon-based organic reactions.

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oxidation, which masks the expected lag.

higher rate of silanol-methoxysilane equilibration, and methoxysilane intermediates through comparison with authentic materials.

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silanols and methoxysilanes, see: Kno

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(18) See the SI for details of the identification of various key reaction intermediates through comparison with authentic materials.

(19) We suggest that the lack of an observable lag in product formation from the p-CN hydrosilane (Figure 1) is due to a much higher rate of silanol-methoxysilane equilibration, and methoxysilane oxidation, which masks the expected lag.

(20) Aryldisiloxanes are poor substrates for oxidation, see ref 5a.

(21) Modelling is based on the first 50% conversion, with the concentration of H2O2 assumed constant. See the SI for details.

(22) Relative rate coefficients have been normalized with respect to silanol oxidation (krel = 1 s-1). Relative second order rate coefficients for the formation of the disiloxane 13b were also modeled. The relative rate coefficient for formation of 13b from 10b and 11b was kii = 2.02 s-1 mol-1 dm3. The relative rate coefficient for the formation of 13b from two molecules of 11b was 4.1 × 10-2 s-1 mol-1 dm3. The concentration of H2O2 is assumed constant in these calculations.

(23) The extreme of this interaction in a basic medium would be deprotonation of the silanol; however, the presence of silanolate ions was not detected spectroscopically.

(24) These experiments were run in triplicate. See the SI for reaction profiles, which gave identical rate data. For example, the oxidation of the methoxysilane under fluoride-free conditions in d4-MeOD using a standardized degassing procedure gave three initial rate coefficients of 5.316 × 10-6 s-1 and 5.312 × 10-6 mol dm-3 s-1, with r2 values of 0.92, 0.99, and 0.99 respectively; %RSD (relative standard deviation) = 0.082.

(25) For this reason, reactions in MeOH were run at increased dilution (0.1M). See the SI for details of the optimization of conditions, and consistency of kinetic data.


(28) The Si–F 19F NMR peak at ~165.1 ppm is masked when using hexafluorobenzene as internal standard. These NMR spectra are run in the absence of this internal standard.

(29) Reaction using 3 equiv of H2O2 did not reach completion after 24 h, and fluorosilane remained after this time. We note that the fluorosilane could arise from a number of reaction pathways, including breakdown of fluoride-peroxide ate complexes.


(31) We suggest that the reduced susceptibility of the diarylsilane to electronic effects could reflect the difference in reactivity effects for this substrate class, as opposed to an arylmethyilsilane.
Mechanistic Insight into Palladium-Catalyzed Cycloisomerization: A Combined Experimental and Theoretical Study

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Supporting Information

ABSTRACT: The cycloisomerization of enynes catalyzed by Pd(OAc)2 and bis-benzylidene ethylenediamine (bbeda) is a landmark methodology in transition-metal-catalyzed cycloisomerization. However, the mechanistic pathway by which this reaction proceeds has remained unclear for several decades. Here we describe mechanistic investigations into this reaction using enynamides, which deliver azacycles with high regio- and stereocontrol. Extensive 1H NMR spectroscopic studies and isotope effects support a palladium(II) hydride-mediated pathway and reveal crucial roles of bbeda, water, and the precise nature of the Pd(OAc)2 pre-catalyst. Computational studies support these mechanistic findings and lead to a clear picture of the origins of the high stereocontrol that can be achieved in this transformation, as well as suggesting a novel mechanism by which hydrometalation proceeds.

INTRODUCTION

Transition-metal-catalyzed cycloisomerizations are among the most atom-efficient methods to access organic ring systems. The appeal of these skeletal reorganizations lies in both the importance of ring synthesis in organic chemistry and the diversity of products that can arise from a single substrate, depending on the mechanistic pathway taken. Among the many transition metals that have been used for enyne cycloisomerization, palladium catalysts have seen widespread use, with extensive work from Trost and co-workers demonstrating the versatility of this metal in three particularly robust catalyst systems (Scheme 1, eq 1): Pd(OAc)2/triarylphosphine, Pd(OAc)2/bis-benzylidene ethylenediamine (bbeda), and Pd(db)3·CHCl/AcOH (with or without a phosphine ligand or bbeda). Since these pioneering studies, palladium-catalyzed cycloisomerization has been widely exploited in methodology and synthesis contexts. Our group has shown that Pd(OAc)2/bbeda is particularly effective in catalyzing the cycloisomerization of enynamides to pyrrolidine and piperidine enamides (Scheme 1, eq 2), useful heterocycles that can undergo a variety of further ring-forming transformations.

Despite this rich history, the mechanism by which the Pd(OAc)2/bbeda catalysis system operates is far from clear. Under Pd2dba3 catalysis, it is widely accepted that reaction of Pd(0) with acetic acid generates a palladium(II) hydride species (Scheme 2, Path A), which effects cycloisomerization by alkyne hydropalladation (1 → 2), alkene carbopalladation (3), and β-hydride elimination (8) and then reductive elimination—a route believed to proceed through a palladacyclopentene intermediate (7).

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operate for other transition metals such as ruthenium and rhodium. However, despite the proposal of Pd(IV) palladacycles in other palladium-catalyzed processes, no direct evidence for palladacyclopentenes has been reported. Other support for this pathway includes high selectivity for β-hydride elimination “away” from the newly formed ring (leading to a 1,4-diene), which would be favored on geometric grounds as the C–Pd and bridgehead C–H bonds cannot easily adopt a syn-coplanar orientation in palladacycle 7, and also through the observation of different product distributions between the various palladium catalyst systems. In light of this continuing uncertainty, both mechanistic explanations have been routinely adopted.

On the basis of our own experimental observations, we questioned whether enynamide cyclizations could offer new insight into this mechanistic puzzle, and a deeper understanding of the high stereoselectivity that can be achieved in the palladacycle 7, and also through the observation of different product distributions between the various palladium catalyst systems. In light of this continuing uncertainty, both mechanistic explanations have been routinely adopted.

**RESULTS AND DISCUSSION**

**Reaction Optimization and Regio-/Stereoselectivity Observations.** A screen of palladium-catalyzed enyne cycloisomerization conditions had revealed that cyclization of enynamide 1a to amidodiene 4a (Scheme 3a) could best be effected using Pd(II) precatalysts, with Pd(OAc)2/bbeda offering superior reactivity. Pd2dba3·CHCl3/AcOH systems gave poor conversion unless employed in combination with bbeda, which effected rapid conversion of 1a to 4a, albeit at higher temperature. Cyclization of enynamide 1a under Ru catalysis (5 mol% Cp*Ru(cod)Cl in MeCN) provided a useful reference point of a reaction widely recognized to proceed through a metallacyclic intermediate.

Under the Pd(OAc)2/bbeda catalytic manifold, we found that the cycloisomerization of 1,2-disubstituted alkenes occurs with high stereo- and regioselectivity: enynamides (E)-1b/c gave predominantly the (E)-1,4-dienes 5b and 5c, with minor amounts of 1,3-diene and only traces of (Z)-1,4-diene, while reaction of enynamides (Z)-1b/c also afforded 5b and 5c as the major products, but now with minor amounts of (Z)-1,4-diene and only traces of 1,3-diene. The equivalent cyclization of (Z)-1c under ruthenium catalysis led to a contrasting product ratio, with (Z)-1,4-diene 6c being the major product. As this latter cyclization likely proceeds through a ruthenacyclic intermediate, differing selectivity already seemed suggestive of distinct mechanistic pathways.

We also observed very high levels of substrate stereocentrality in cycloisomerizations that generate new stereocenters (Table 1). Entry 1 shows the influence of a substituent adjacent to the amidodiene nitrogen atom, which gave a single regio- and stereoisomer of pyrrolidine 3 (Scheme 3a). Entries 4 and 5 depict cyclizations that generate quaternary stereocenters with remarkable stereocentrality, with pyrrolidines 5g and 5h formed as single isomers. The exquisite stereoselectivity imparted in these cyclizations can be rationalized by a theoretical analysis of the reaction pathway (see below), in which the irreversible cyclization step operates with very high levels of stereocentrality.

**Deuterium Crossover Experiments**

Under the Pd(OAc)2/bbeda catalytic manifold, we found that the cycloisomerization of 1,2-disubstituted alkenes occurs with high stereo- and regioselectivity: enynamides (E)-1b/c gave predominantly the (E)-1,4-dienes 5b and 5c, with minor amounts of 1,3-diene and only traces of (Z)-1,4-diene, while reaction of enynamides (Z)-1b/c also afforded 5b and 5c as the major products, but now with minor amounts of (Z)-1,4-diene and only traces of 1,3-diene. The equivalent cyclization of (Z)-1c under ruthenium catalysis led to a contrasting product ratio, with (Z)-1,4-diene 6c being the major product. As this latter cyclization likely proceeds through a ruthenacyclic intermediate, differing selectivity already seemed suggestive of distinct mechanistic pathways.

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**Deuterium Crossover Experiments**

Deuterium crossover experiments could offer insight as to whether an inter- or intramolecular hydride transfer takes place; the former would suggest involvement of a discrete palladium hydride species, while the
latter would be more consistent with a metallacycle pathway. To explore this, deuterated toluenesulfonyl enynamide D-1a (>98% D)\(^{18}\) and non-deuterated p-nitrobenzenesulfonyl enynamide 1i were reacted in a 1:1 ratio using each of the catalyst systems (Scheme 4). With Pd\(_{2}\text{dba}_3\cdot\text{CHCl}_3/\text{AcOH}/\text{bbeda}, complete crossover of the deuterium label was observed. In contrast, under ruthenium catalysis, no crossover occurred and D-4a was isolated with 83% D incorporation (supporting an intramolecular hydride transfer pathway). Finally, products 4a and 4i arising from the equivalent Pd(OAc)\(_2/\text{bbeda} \) experiment also featured nearly equivalent amounts of deuterium incorporation (43 and 44% respectively), thus supporting intermolecular transfer of hydride via a discrete Pd–H/D intermediate under both palladium-catalyzed reaction conditions.

To compare the three reaction manifolds in more detail, we next monitored the cyclizations of 1a using \(^1\)H NMR spectroscopy. Under Pd\(_{2}\text{dba}_3\cdot\text{CHCl}_3/\text{AcOH}/\text{bbeda} \) or Cp\(^*\)Ru(cod)Cl catalysis (Figure 1, graphs a and b), immediate conversion of starting material to product was observed, suggesting that a catalytically competent species is present, or rapidly formed, at the start of the reaction.\(^{19}\) In the case of Pd\(_{2}\text{dba}_3\cdot\text{CHCl}_3, \) this is presumably a palladium(II) hydride species, formed through oxidative addition of Pd(0) with acetic acid,\(^{3b,6,20}\) whereas the ruthenium-catalyzed reaction likely only requires ligand exchange of cyclooctadiene and the substrate in the Cp\(^*\)Ru(I)(L)\(_2\) complex. A marked difference in reaction profile was observed with Pd(OAc)\(_2/\text{bbeda} \) (graph c): despite this being a superior catalyst system (compared to the other catalysts) in terms of conversion and scope, this reaction exhibited a distinct induction period that presumably relates to the generation of an active catalyst species from Pd(OAc)\(_2\). The conversion of D-1a to the deuterated product D-4a was also monitored (graph d): this reaction required a much extended reaction time to reach full conversion compared with non-deuterated 1a, revealing significant deuterium isotope effects (vide infra). Of greater intrigue was the observation that the extent of product deuteriation changed during the reaction. At early stages, only protiated product was produced (red curve), whereas at later stages, the deuterated product was formed almost exclusively (green curve)—in this case leading to a drop of deuterium incorporation from 100% D in the starting material D-1a, to ∼70% in the product D-4a.

This result led us to speculate that water has a crucial impact on reaction progress and product formation, with deuterium loss arising from an exchange process with water present in the NMR reaction solvent. We therefore set about comparing the reaction profiles of 1a and deuterated enynamide D-1a using d\(_8\)-toluene containing varying concentrations of water (determined by Karl Fischer titration); the results of these collected experiments are illustrated in Figure 2. Non-deuterated 1a was first tested using pre-dried d\(_8\)-toluene as solvent (dried for several days over 4 Å molecular sieves, 3 ppm H\(_2\)O).\(^{22}\) We found that a somewhat extended reaction time was required to reach completion (Figure 2, graph HA) compared to the reaction using “bottle” d\(_8\)-toluene (82 ppm of H\(_2\)O, graph HB), indicating a beneficial effect of water on reaction rate. This trend extended to water-saturated d\(_8\)-toluene (480 ppm, graph

### Table 1. Diastereoselective Cycloisomerizations of Enynamides with Substituted Tethers\(^{22}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s)</th>
<th>Yield (%)(^{b})</th>
<th>Ratio / comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph TnSn—n-Hex</td>
<td>1d</td>
<td>87</td>
<td>single isomer</td>
</tr>
<tr>
<td>2</td>
<td>Ph TnSn—n-Hex</td>
<td>1e</td>
<td>86</td>
<td>9:77:14</td>
</tr>
<tr>
<td>3</td>
<td>Ph TnSn—OTBS</td>
<td>1f</td>
<td>95</td>
<td>single isomer</td>
</tr>
<tr>
<td>4</td>
<td>Ph TnSn—n-Hex</td>
<td>1g</td>
<td>84</td>
<td>single isomer</td>
</tr>
<tr>
<td>5</td>
<td>Ph TnSn—n-Hex</td>
<td>1h</td>
<td>78</td>
<td>single isomer</td>
</tr>
</tbody>
</table>

\(^{a}\)Reaction conditions: 5 mol% Pd(OAc)\(_2\), 5 mol% bbeda, toluene (0.167 M), 60 °C, 30 min; entry 2 reaction time = 90 min. \(^{b}\)Isolated yield. \(^{c}\)Ratio of 1,3-:1,4-:1,5-dienes as determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture.
HC), where a further acceleration was observed; a summary of this effect is illustrated in Figure 2b. Interestingly, running the reaction in d₈-toluene saturated with D₂O led to the incorporation of a small amount of deuterium into the product (graph HD), thus confirming that adventitious water can indeed serve as a source of “hydride”. The equivalent reactions of the deuterated substrate D-1a (graphs DA-DD) showed that as the water (H₂O) content of the reaction solvent increases, so does the proportion of protiated product 4a (red curves in graphs DA-DC), which is consistently and exclusively produced at the start of all reactions. Notably, around 15% of protiated product was produced in both reactions DA and DD, despite the use of 100% deuterated substrate and a reaction medium devoid of H₂O. This observation was later to be rationalized through discovery of the pathway for reaction initiation.23

The Role of Water. We hypothesized that water could accelerate the reaction through involvement in the initiation process. Bedford et al.24 recently characterized the influence of water on Pd(OAc)₂, which in organic solutions exists as a trimeric complex [Pd₃(OAc)₆], a structure with D₃h symmetry featuring bridging acetate ligands.25 In the presence of water, this trimer is in equilibrium with the [Pd₃(OAc)₅OH] (Figure 3a), in which one of the bridging acetate ligands has been replaced by a bridging hydroxide ion.24 In increasingly water-rich environments, a greater proportion of this complex is formed, and we questioned whether this could act as a more reactive pre-catalyst. To test this, [Pd₃(OAc)₅OH] was prepared as reported by Bedford.24 Reaction of 1a with [Pd₃(OAc)₅OH]/bbeda in pre-dried d₈-toluene indeed showed a reduced induction period (Figure 3a, red curve), compared to [Pd₃(OAc)₆]/bbeda in H₂O-saturated d₈-toluene (blue curve), suggesting that hydrolysis of [Pd₃(OAc)₆] is an important process in reaction initiation. Interestingly, the post-initiation rate of these reactions was similar, which may imply that a common catalytic species forms from both pre-catalysts.

The Role of bbeda. Although Pd(OAc)₂-catalyzed cycloisomerizations can operate in the absence of bbeda, reactions in which it is present reach completion more rapidly.1H NMR spectroscopic reaction profiles for the cycloisomerization of 1a showed that bbeda-free reactions fail to reach completion after >3 h (Figure 4, red curve), compared to ∼15 min in its presence (blue curve). The appearance of these reactions also differs markedly: in the absence of bbeda, black particulates develop over time, as opposed to a consistent yellow color (and
little or no particulate formation) in reactions containing the imine. Possible roles of bbeda include that of a ligand which accelerates the catalytic cycle, or a stabilizing component for off-cycle palladium species. Interestingly, addition of bbeda after 20 min reaction time to a bbeda-free reaction did not lead to a marked acceleration (Figure 4, green curve) but did result in a somewhat higher rate of reaction being sustained compared to the bbeda-free reaction. Although these two reactions may well operate by different pathways, this could indicate that bbeda inhibits catalyst aggregation.

From these experiments, it also seemed possible that bbeda might also be involved in precatalyst deaggregation and/or reaction initiation. To explore this, we titrated solutions of [Pd₃(OAc)₅(OH)] and [Pd₃(OAc)₆] in anhydrous d₈-toluene with bbeda (Figure 5). A dramatic effect was seen on addition of even 0.25 equiv of bbeda to [Pd₃(OAc)₅(OH)] (titration a): the ¹H NMR signals corresponding to this complex at δ 1.70, 1.60, and 1.55 ppm shifted downfield (dashed arrows), and a significant new signal appeared at 1.69 ppm (*). The proportion of [Pd₃(OAc)₆] (†, 1.67 ppm) appeared to increase; with addition of further bbeda, this peak was consumed. Under these conditions, it thus seems that these two complexes are in facile equilibrium, and that [Pd₃(OAc)₅(OH)] is converted by bbeda to an unidentified species, which we suggest to be a deaggregated complex. In contrast, a solution of pure [Pd₃(OAc)₆] was barely affected by bbeda until 1.0−1.5 equiv of ligand was added (titration b). The greater susceptibility of [Pd₃(OAc)₅(OH)] to the action of bbeda may explain the decreased induction period observed when using this complex, or [Pd₃(OAc)₆] in water-rich reactions (see Figure 3); however, the dramatically enhanced rate of reactions run in the presence of bbeda (Figure 4) yet remained unexplained.

**Initiation Pathway.** Although we had now identified a number of different factors that influenced the rate of initiation, the source of the putative palladium(II) hydride remained a mystery, particularly given the consistent low levels of protiated product observed under anhydrous/protium-free reactions of D-1a (graphs DA and DD, Figure 2). The reactions of a number of other substrates deuterated at various positions did not lead to any deuteration of the enamide alkene, suggesting the substrate is not the origin of hydride. This left bbeda itself—and a key observation of the production of small amounts of benzaldehyde at early stages of our NMR experiments. This aldehyde could arise from Lewis acid (i.e., Pd(II)) promoted hydrolysis of bbeda by water in the reaction solvent, a process that would release a primary amine (9, Figure 6a), which could then undergo β-hydride elimination to generate palladium(II) hydride. Tautomerization of the resulting imine 10 to the corresponding enamine could then release further hydrogen atoms. For water-free reactions (where only traces of benzaldehyde were observed), nucleophilic activation via addition of acetate to Pd(II)-complexed bbeda could lead to an aminal (11) that could also be susceptible to β-hydride elimination.

To test this, d₄-bbeda was prepared by reaction of d₄-ethylenediamine with benzaldehyde. To our delight, cycloisomerization of D-1a in dry toluene with d₄-bbeda afforded D-4a with >98% deuteration (Figure 5), thus supporting the proposal that bbeda itself is the source of hydride in the initiation pathway, and explaining the formation of protiated product in experiments using D-4a and H₄-bbeda. Furthermore, reaction of the protiated substrate 1a in dry toluene with d₄-bbeda (5 mol %) led to a low level of product deuteration (15%),

![Figure 5](image)

**Figure 5.** Effect of bbeda on (a) [Pd₃(OAc)₅(OH)] and (b) [Pd₃(OAc)₆]. Titrations performed in dry d₈-toluene at room temperature.

![Figure 6](image)

**Figure 6.** Bbeda as a source of hydride. (a) Proposed mechanism for the formation of Pd(II)−H from bbeda. (b) Use of d₄-bbeda leads to complete deuteration of D-4a from D-1a. (c) Use of d₄-bbeda leads to partial deuteration of 4a from 1a. (d) Use of d₄-bbeda with enyne 12 also leads to partial deuteration of 13.
reinforcing this hypothesis (Figure 6c). Equally importantly, we also observed deuterium incorporation (15%) using enyne 12 (87% yield), thus supporting this process as a general mechanism for initiation of enyne cycloisomerization using Pd(OAc)$_2$/bbeda (Figure 6d).

**Batch Dependency.** During these investigations, we also uncovered a critical dependence of the stereochemical outcome of the reaction on the batch of Pd(OAc)$_2$ employed as catalyst. This discovery was made through the chance purchase of Pd(OAc)$_2$ from a different supplier, which led to an unexpected ratio of enamide alkene geometries ((Z):(E)-4a = 80:20), rather than the typical ratio of ~97:3. The screening of further samples of Pd(OAc)$_2$ gave variable results, the most extreme being a reversal of stereoselectivity to 40:60 in favor of the (E)-isomer. This batch-dependency was soon explained upon acquisition of $^1$H NMR spectra of the various catalysts: while our original bottle of Pd(OAc)$_2$ exhibited a $^1$H NMR spectrum (in CDCl$_3$) characteristic of pure Pd(OAc)$_2$ (Figure 7, batch 1), catalyst did not result in alkene isomerization, suggesting that the two isomers arise during the cycloisomerization as a consequence of a divergent reaction mechanism, rather than through product isomerization. While the mechanistic origin of this isomer mixture remains unknown, recent studies on alkny semireduction using Pd([PEt$_3$]$_4$) and formic acid suggest that isomerization of alkenylpalladium complexes formed through hydropalladation can be facile.

**Computational Analysis of the Reaction Pathway.** With significant experimental evidence for the intermediacy of palladium(II) hydride species in hand, we set out to explore the reaction pathway from a theoretical perspective to establish whether a hydropalladation reaction mechanism would prove energetically feasible. In addition, we hoped to rationalize the stereoselectivity of the reaction, and to gain insight into the observed kinetic isotope effects. Density functional theory (DFT) and local coupled cluster calculations were performed with Gaussian09 rev D.01 and with Orca v4. The meta-generalized gradient approximation (meta-GGA) TPSS exchange-correlation functional was used for all geometry optimizations with density fitting for Coulomb integrals (RI-J), a fine integration grid and the Karlsruhe def2-TZVP basis set for all elements. A quasi-harmonic approximation was used for conversion of $^1$H NMR spectroscopic reaction profile for conversion of 1a to (Z)-4a and (E)-4a catalyzed by [Pd$_3$(OAc)$_5$(NO$_2$)]/bbeda, in pre-dried d$_6$-toluene, 35 °C, and X-ray crystal structure of Pd$_3$(OAc)$_5$NO$_2$ $^{25a}$

![Figure 8. $^1$H NMR spectroscopic reaction profile for conversion of 1a to (Z)-4a and (E)-4a catalyzed by [Pd$_3$(OAc)$_5$(NO$_2$)]/bbeda, in pre-dried d$_6$-toluene, 35 °C, and X-ray crystal structure of Pd$_3$(OAc)$_5$NO$_2$.](image)

A singulet corresponding to the D$_{5h}$-symmetric [Pd$_3$(OAc)$_5$] trimer, minor peaks arise from [Pd$_3$(OAc)$_5$(OH)]$^{25a}$ other samples showed increasing amounts of an impurity (batches 2 and 3), with the worst product ratio arising from samples devoid of [Pd$_3$(OAc)$_5$]. This latter batch in fact consisted solely of [Pd$_3$(OAc)$_5$(NO$_2$)], an impurity common in Pd(OAc)$_2$ that arises from its method of production, as previously characterized by Cotton and Murillo. The ability of this “impurity” to mediate palladium-catalyzed reactions has been documented, albeit in many cases its presence does not affect the reaction outcome; the observation of such a significant overturning of product selection is, to our knowledge, unprecedented. The synthesis of pure Pd(OAc)$_2$ from Pd(NO$_2$)$_2$ and NaOAc as reported by Stolyarov and co-workers offers a convenient solution to this problem, and delivers palladium(II) acetate of purity equivalent to the original supply; $^1$H NMR spectroscopic analysis of subsequent commercial batches of Pd(OAc)$_2$ gave reassurance that these would behave as expected. Interestingly, monitoring of the reaction of 1a with [Pd$_3$(OAc)$_5$(NO$_2$)]/bbeda (Figure 8) revealed that reactions with this catalyst proceeded at a somewhat lower rate than pure Pd(OAc)$_2$/bbeda, and that the isomeric ratio of enamide products remained consistent throughout the reaction. Submission of pure (Z)-4a to this
be significantly less stable at all levels of theory, by 21.4−33.1 kcal mol$^{-1}$. As hydropalladation takes place to give B, transfer of the hydrogen atom to the $\beta$-carbon of the ynamide is facilitated by an agostic interaction with the metal (TS$_{AB}$, $\Delta G^\ddagger = 7.4$ kcal mol$^{-1}$), suggesting that a discrete palladium(II) hydride is not formed, or is not located as an energy minimum on the potential energy surface; in effect, oxidative addition to Pd(0) by acetic acid, and hydropalladation, take place as a single concerted process from the favored substrate-bound Pd(0)(HOAc) complex. As well as representing a new pathway for alkyne hydrometalation, complex A also accounts for the facile exchange of H/D with water in the reaction solvent (and with hydrolyzed bbeda) which can thus be mediated by acetic acid rather than requiring a specific isotope exchange process at the metal. It also accounts for the difficulty in detecting elusive palladium(II) hydride species by $^1$H NMR spectroscopy, and is consistent with the notion that oxidative addition of Pd(0) into acetic acid is rapid and reversible. Subsequent to this irreversible hydrometalation to give B, the metal then effects carbopalladation of the alkene (TS$_{BC}$, $\Delta G^\ddagger = 16.9$ kcal mol$^{-1}$), which rationalizes the stereochemical outcome of the anti-diastereoselective cycloisomerization of enynamide 1k.
mol\(^{-1}\)), leading to an alkylpalladium species C that remains complexed to the enamide alkene. Carbopalladation is also irreversible at all levels of theory considered, and is followed by rate-limiting \(\beta\)-hydride elimination (TS\(_{C-D}\), \(\Delta G^f = 20.4\) kcal mol\(^{-1}\)), a process that first requires endothermic enamide decomplexation and C–C bond rotation in order to position the C–Pd bond syn-coplanar with the C–H bond (C \(\rightarrow\) C'). The degree of reversibility of \(\beta\)-hydride elimination is challenging to assess, as it depends on the kinetics of product dissociation from the resultant (alkene)Pd(H)(OAc) complex (D or E), and complexation with the next molecule of substrate. This is in part likely to be product dependent, as only in certain cases is alkenic isomerization observed in the product.

Formation of product-bound Pd(0)(HOAc) complex \(E\) from D is facile, with a barrier of 2.1 kcal/mol. This is true across all levels of theory, where the barrier for this step ranges from 1.7–4.2 kcal/mol. In TS\(_{DE}\) the \(k^2\)-acetate rotates out of the plane to adopt a \(k^1\)-coordination mode bound cis to the hydride (see the SI for full details).

The calculated energy profile of 1j is consistent with room temperature reactivity: \(^{35}\) the energetic span of the computed catalytic cycle (20.4 kcal mol\(^{-1}\)) is commensurate with a \(1/2\) of 3 min. To compute the KIEs we applied the Biegelsen–Mayer equation with a parabolic tunneling correction based on scaled TPSS/de2-TZVP harmonic frequencies at 35 °C. \(^{44}\) Our calculations predict a primary KIE for \(\beta\)-hydride elimination of 2.225, \(^{45}\) an inverse secondary KIE of 0.916 for carbopalladation, and a primary KIE for alkyne hydro-palladation of 4.689 (12.671 with a parabolic tunneling correction). The latter value may reflect the trifurcated nature of bonding to the hydrogen atom in the hydropalladation transition state TS\(_{AB}\). \(^{46}\)

The stereoselectivity of the cyclization of enynamide 1e (see Table 1, entry 1) was next modeled using substrate 1k (Figure 10). The carbopalladation substrate derived from 1k exists in two energetically similar conformations: 14-anti and 14-syn, the diastereomeric transition states from which (TS-15-anti and TS-15-syn) lead to products anti-16 (the observed outcome) and syn-16 respectively. A free energy difference between these transition states of \(\Delta G^f = 3.4\) kcal mol\(^{-1}\) corresponds to a calculated diastereoselectivity of \(>180:1\), \(^{47}\) which is consistent with the observed reaction outcome. The energy difference between these transition states (consistent with M06 and DLPNO-CCSD(T), as discussed in the SI) can be rationalized by changes in torsional strain upon carbopalladation of the alkene by the alkenylpalladium complex: in the case of transition state TS-15-anti, this strain is relieved as carbopalladation proceeds from the eclipsed C–H bonds to red and green hydrogens in 14-anti. For the alternative transition state TS-15-syn, eclipsing interactions increase during this step (from the staggered C–H bonds to red and green hydrogens in 14-syn). \(^{48}\)

**Experimental Observations on Isotope Effects.** \(^{49}\) The data collected in the time course experiments indicate the influence of several isotope effects, resulting in marked differences in reaction rate and isotope incorporation as the reaction proceeds. We now turned to correlation of our computational work with these experimental observations, in particular the KIE for the rate-determining \(\beta\)-hydride elimination. This was achieved by comparison of the product distribution from disubstituted alkene (E)-1b with that of its deuterated equivalent (E)-D-1b (Scheme S, >98% D, E.Z > 20:1), where \(\beta\)-deuteride elimination is required for the latter to generate 1,3-diene products. The ratio of 1,3:1,4-dienes (4b: D-5b/D-6b, as determined by integration of appropriate peaks in the \(^1H\) NMR spectrum) \(^{50}\) was found to be 8.09, compared to a ratio of 3.54 for (E)-1b, which gives an experimental KIE for \(\beta\)-hydride elimination of 2.29. This value is consistent with other reports on \(\beta\)-hydride elimination from alkylpalladium complexes, and with the computed value (2.07 at 60 °C; 2.23 at 35 °C for model substrate 1j). \(^{45,49,51}\)

While the isotope effect associated with \(\beta\)-hydride elimination is consistent with computation and with literature values, the overall difference in reaction rate between substrates 1a and D-1a at typical catalyst loadings of 5 mol% is not explained by \(\beta\)-hydride elimination alone. Although negligible KIEs would be expected from the hydropalladation and carbopalladation steps, it seemed possible that off-cycle equilibrium processes might be affected by the difference in activation energies between hydro- and deuteriopalladation. The path from product decomplexation to substrate association (and subsequent irreversible hydropalladation) could involve complexation of palladium by bbeda, or its hydrolysis product, or catalyst re-aggregation (to dimeric or trimeric complexes). These processes would be expected to depend on catalyst concentration, \(^{52}\) with hydropalladation perturbing the equilibria by effectively sequestering monomeric “active” Pd(0)(AcOH).

This indeed turned out to be the case. The relative rates of reaction of substrates 1a and D-1a were compared at various catalyst concentrations (by observation of the post-induction regions of reactions such as HA and DA, see Figure 2, once the production of protiated product has plateaued in reactions involving D-1a). The rates of cyclization of each substrate were measured at five different catalyst loadings (0.5, 1, 2.5, 5, and 10 mol%, Figure 11a), with each experiment run in triplicate. The rate constants for both substrates, and their associated errors (one standard deviation) are shown in the table in Figure 11. Plateau effects were observed for both substrates at higher catalyst concentrations: \(^{52}\) for 1a, this occurs at or above 5 mol %, while for D-1a, at or above 2.5 mol%. We speculate this may be related to the difference in energy barriers for hydro- vs deuteriopalladation, which in the latter case could increase the extent of off-cycle catalyst sequestration, compared to substrate complexation and entry to the catalytic cycle. The dominance of hydropalladation at early reaction stages using D-1a adds support to the influence of this step on entry to the catalytic cycle. In addition, this data allowed us to determine the order of reaction with respect to the metal catalyst. A plot of \(\ln(k_{\text{obs}})\) against \(\ln([\text{Pd(OAc)}_2])\) showed a linear relationship (Figure 11b), supporting the proposal of a monomeric palladium species as the active catalyst. \(^{53}\)

Alongside this, we were intrigued to observe that the rate of cycloisomerization of (Z)-D-1b exceeded that of (Z)-1b
Figure 11. Dependence of reaction rate on catalyst concentration. \( k_H \) and \( k_D \) are given in units of \( 10^4 \) mol dm\(^{-3}\) s\(^{-1}\). Errors of one standard deviation are shown. (a) \( k_H(\text{obs}) \) and \( k_D(\text{obs}) \) at different catalyst concentrations; table shows values and ratios of observed rate constants. (b) Plot of \( \ln(k_H(\text{obs})) \) against \( \ln[\text{Pd(OAc)}_2] \) shows first-order dependence with respect to the catalyst. See the SI for further details.

Figure 12. Isotope effect from alkene deuteration.\(^{21}\)

The reason for this secondary KIE is not clear: with the theoretical pathway indicating carbopalladation to be non-rate-determining, we suggest that this effect could relate to differences between the two isotopes in agostic interactions, or hyperconjugation effects during the enamide decomplexation/\( \beta \)-hydride elimination steps, or during product decomplexation.

**DISCUSSION**

The above experimental and theoretical studies provide strong support for a hydropalladation mechanism for \( \text{Pd(OAc)}_2 / \text{bbeda} \)-catalyzed enamide cycloisomerization. A full outline of the proposed reaction pathway is illustrated in Scheme 6. Reaction initiation entails a number of processes, commencing with a water-promoted \( \text{Pd}_3(\text{OAc})_6 \) equilibrium with \( [\text{Pd}_2(\text{OAc})_6(\text{OH})] \), the latter of which undergoes bbeda-assisted deaggregation, presumably to give a monomeric \([\text{bbeda}]\text{Pd(OAc)}_2\) complex. Partial hydrolysis of this complex liberates benzaldehyde and amine complex 17, which undergoes \( \beta \)-hydride elimination to form \( \text{Pd(II)} - \text{H} \) complex 18a (this process could also be promoted by addition of acetate, see Scheme 6a). Throughout the reaction, additional bbeda (or the derived amine ligand) could stabilize off-cycle \( \text{Pd(II)} \) species (19), thereby prolonging catalyst lifetime. The resultant \( \text{L}_2\text{Pd(II)} - \text{H(OAc)} \) complex 18a is in equilibrium with \( \text{L}_2\text{Pd(0)}(\kappa^2-\text{HOAc}) \) 18b, with the latter form predicted computationally to be favored on binding the enamide substrate (A), and required for hydropalladation.\(^{54}\) Notably, acetic acid complex 18b also explains the facile exchange of H/D with water. The substrate-complexed \( \text{Pd(0)} \) catalyst (A) then effects an irreversible “oxidative hydropalladation” of the alkyne component (to give B), followed by irreversible carbopalladation with a pseudo-axially oriented alkene group. The resulting alkylpalladium(II) species (C) offers a possible resting state of the catalyst; further reaction requires an endergonic decomplexation of the enamide from the metal, C–C bond rotation, and agostic coordination of the bridgehead hydrogen atom (C’). \( \beta \)-Hydride elimination then proceeds rapidly and potentially reversibly, delivering a \( \text{Pd(II)} - \text{H(OAc)}(\text{alkene}) \) complex (D) that is in equilibrium with \( \text{Pd(0)}(\text{AcOH}) \) (E). Finally, we note that although original proposals for different reaction pathways using \( \text{Pd(II)} \) or \( \text{Pd(0)} \) precatalysts were based on observed differences in reaction outcomes or product distributions, we suggest that these may relate more to the influence of the specific ligand environment around the metal center, rather than the cycloisomerization pathway itself.

![Scheme 6. Pd-Catalyzed Cycloisomerization: Overview](image)
Palladium-catalyzed enyne cycloisomerization is a fundamentally important reaction manifold in this field of ring synthesis. Despite the utility of the Pd(OAc)$_2$/bbeda catalyst system, mechanistic understanding has remained elusive. Through extensive NMR studies with deuterated substrates, we have uncovered the crucial influences of water, the precatalyst, and the ligand itself in this reaction. Our demonstration that bbeda itself serves as a source of Pd(II)−H, combined with theoretical analysis of the reaction pathway correlated with experimental isotope effects, offers a new level of understanding of this classic cyclization process, and offers enhanced understanding for the design of applications of this chemistry in stereoselective synthesis.

ASSOCIATED CONTENT

* Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jacs.7b05436.

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Notes
The authors declare no competing financial interest.

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Reactions catalyzed by Pd,dba₂-CHCl₃/AcOH/bbeda proved capricious, particularly when run as NMR experiments, and often failed to reach completion for enynamide substrates.

Experiments were run at 0.167 M, 35 °C using 5 mol% Pd catalyst/ligand, with 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard, in triplicate. See the SI for full details of NMR time course experiments.

In contrast to 1, the reactions of D-1a appear to show a retardation effect as the concentration of water increases. This may reflect an off-cycle complexation of water to the metal, which is discussed in further detail in the SI.

We suggest that 15% product deuterium arises from the release of additional deuterium through inime/examine tautomerization of 10.


Irreversible C–C bond formation ensures carbopalladation is diastereodetermining and product selectivity may be computed applying TST assuming Curtin–Hammett-type behavior. See: Peng, Q.; Duarte, F.; Paton, R. S. Chem. Soc. Rev. 2016, 45, 6093–6107.

See the SI for rationalization of the stereoselective cycloisomerizations of 1b and of an (E)-enamide.


We believe that bidentate coordination of the substrate to the metal is required, as only 1,6- and 1,7-enynamides undergo successful cyclosomeration. This alkene-coordination effect was also noted by Trost; see ref 5c.

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Copper-Catalyzed Synthesis and Applications of Yndiamides

Steven J. Mansfield, Kirsten E. Christensen, Amber L. Thompson, Kai Ma, Michael W. Jones, Aroonroj Mekareeya, and Edward A. Anderson*

Abstract: The first synthetic route to yndiamides, a novel class of double aza-substituted alkene, has been established by the copper(I)-catalyzed cross-coupling of 1,1-dibromoamides with nitrogen nucleophiles. The utility of these compounds is demonstrated in a range of transition-metal-catalyzed and acid-catalyzed transformations to afford a wide variety of 1,2-diamide functionalized products.

Ynamides (1, Figure 1) are extremely versatile building blocks in organic synthesis. Their rich chemistry can in part be attributed to the conjugation and polarization effects afforded by the amide group, which leads to heightened reactivity and regioselectivity in their reactions. In contrast, the synthesis and chemistry of yndiamides (2), acetylenes that feature two amido substituents, is unknown. This class of alkyne would be of considerable interest as a synthetic building block—as well as introducing an additional nitrogen substituent, yndiamides could exhibit distinct reactivity compared to ynamides. Herein, we report the first method for the preparation of yndiamides, and an exploration of their unique reactivity, which reveals them to be valuable components in azacycle synthesis.

Exploration of potential yndiamide precursors revealed the copper-catalyzed coupling of 1,1-dibromoamidamides 3a with sulfonamide 4a to be most promising (Table 1). Although the conditions developed for dibromoalkene–amide coupling (CuI, dmeda, Cs₂CO₃) led mainly to decomposition of 3a (entry 1), conditions more usually applied to bromoalkynes (CuSO₄·5H₂O, 1,10-phenanthroline, K₂PO₄) delivered appreciable amounts of yndiamide 2a, along with the byproduct bromoketene aminal 5a (entries 2 and 3).

Table 1: Selected optimization of yndiamide formation.

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<th>[Cu]/L (equiv)</th>
<th>Base (equiv)</th>
<th>T [°C]</th>
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<td>8</td>
<td>Cu (0.2)/terpy (0.4)</td>
<td>Cs₂CO₃ (2.5)</td>
<td>85</td>
<td>THF</td>
<td>6:8:80:6</td>
</tr>
<tr>
<td>9</td>
<td>Cu (0.2)/1,10-phen (0.4)</td>
<td>Cs₂CO₃ (2.5)</td>
<td>60</td>
<td>THF</td>
<td>9:0:2:89:83</td>
</tr>
</tbody>
</table>

a) Ratios were determined by 'H NMR spectroscopic analysis of the crude reaction mixture after 18 h. Isolated yields in parentheses. b) Sealed tube. Tdramatically improved the proportion of yndiamide formed, with 2a isolated in 83% yield (entry 9).

A variety of amide nucleophiles 4 were screened using the optimized conditions described above. Sulfonamides and phosphoramidates underwent smooth coupling with 3a, giving yndiamides 2b–s in high yields (Figure 2a). A wide

Figure 1. Comparison between ynamides and yndiamides. EWG = electron-withdrawing group.
range of functionality was tolerated on the amide, including alkenes and alkynes (2g–m, 2o), esters (2p), acetals (2p, 2q), silyl ethers (2r), and heterocycles (2s). Evaluation of dibromoenamide scope (Figure 2b) showed that sulfonamide-based enamides were required for effective coupling, with amides or carbamates proving to be unreactive. The sidechain of the sulfonamide was readily varied, leading to the election of difunctionalized yndiamides (2j, 2t–bb). The flexibility of this approach to unsymmetrical yndiamides is emphasized by compounds 2j and 2x, which could be produced from either of their respective sulfonamide/enam ide partners in comparable yields (2j: 78/79%, 2x: 72/79%). Efficiency was maintained on larger scales, with >3 g of yndiamide 2j prepared by using 10 mmol (5 g) of 3a (61%). The yndiamides were found to be bench-stable compounds (see inset in Figure 2b) that can be routinely purified by silica-gel chromatography.

Single-crystal X-ray analysis[9] revealed that yndiamides possess highly twisted conformations,[11] with C-N-C dihedral angles generally between 60–100° (Figure 3). The amide substituents adopt near trigonal planar arrangements, and alkyne bond lengths were found to range from 1.17–1.19 Å (“typical” alkyne ≈ 1.20 Å). This behavior was also manifested in solution, with 1H NMR spectra of 2o and 2p showing the diastereotopic nature of the benzylic protons, despite being rather remote from the stereocenter(s), thus implying restricted rotation of the axially chiral yndiamide. This conformational effect was found to derive from stereo-electronic factors: DFT calculations (B3LYP/6-31G(d,p))[9] showed partial conjugation of the lone pairs of both nitrogen atoms with each of the alkyne p-systems (to different extents, according to the dihedral angles between the N lone pair and the Cp -orbitals). This results in two near-degenerate alkyne-centered HOMOs for the yndiamide, compared to HOMOs of rather different energy for a ynamide. Interestingly, the LUMO of the yndiamide also extends across the whole N-C-C-N structure, encompassing both N-S σ∗ orbitals, and is thus lower in energy compared to that of an ynamide.

Yndiamides proved to be excellent substrates for a variety of transformations. Palladium-catalyzed cycloisomerizations using Pd(OAc)2/N,N’-bis(benzylidene)ethylene diamine (bbeda; Table 2, entries 1–6)[12] proceeded at reduced rates compared to those of the equivalent ynamides,[12a,b] but afforded 1,3-diene 6a and various 1,4-dienes, including spirocycle 6d, in good yields (72–79%, entries 1–4).[13] High levels of substrate stereocontrol were observed in the reaction of vinylcyclopropane 2o, which gave triene 6e as a single diastereomer at the newly formed stereocenter (66%, entry 5). In contrast to ynamides, bbeda was an essential component in these cyclizations; in its absence, the reaction of 2j resulted in the surprising formation of imine 6f (63%, entry 6) following initial rapid formation of diene 6a. It is
Table 2: Transition-metal-catalyzed and acid-catalyzed reactions of enyndiamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions (t)</th>
<th>Product</th>
<th>Yield [%][f]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>A (40 min)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>6a 73</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>A (25 min)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>79[4]</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>A (90 min)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>6c 72</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>A (30 min)</td>
<td><img src="image4.png" alt="Image" /></td>
<td>73[4]</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>A (60 min)</td>
<td><img src="image5.png" alt="Image" /></td>
<td>6e 66</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>B (35 min)</td>
<td><img src="image6.png" alt="Image" /></td>
<td>6l 63[4]</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>C (16 h)</td>
<td><img src="image7.png" alt="Image" /></td>
<td>7 58</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>D (2 h)</td>
<td><img src="image8.png" alt="Image" /></td>
<td>8a R = Me, 96 R = Ph, 91</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>D (8 h)</td>
<td><img src="image9.png" alt="Image" /></td>
<td>8b R = Ph</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>E (5 h)</td>
<td><img src="image10.png" alt="Image" /></td>
<td>5 88</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>F (8 h)</td>
<td><img src="image11.png" alt="Image" /></td>
<td>10 51</td>
</tr>
<tr>
<td>12</td>
<td>1l</td>
<td>G (10 min)</td>
<td><img src="image12.png" alt="Image" /></td>
<td>11 78</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>H (10 min)</td>
<td><img src="image13.png" alt="Image" /></td>
<td>12 86</td>
</tr>
<tr>
<td>14</td>
<td>1n</td>
<td>I (24 h)</td>
<td><img src="image14.png" alt="Image" /></td>
<td>13 63</td>
</tr>
</tbody>
</table>

[a] Conditions A: Pd(OAc)$_2$/N,N,N-bis(benzylidene)ethylene diamine (bbeda) (10 mol%), PhMe, 60°C; B: Pd(OAc)$_2$ (10 mol%), PhMe, 60°C, C: [(C$_5$H$_5$)Rh(cod)SbF$_5$] (5 mol%), 1,2-dichloroethane, 80°C; D: RhCl(PPh$_3$)$_2$ (10 mol%), PhMe, 50°C; E: Co$_2$(CO)$_8$ (1.1 equiv), PhMe, 110°C; F: AuCl(PPh$_3$)$_2$/AgSbF$_6$ (30 mol%), CH$_2$Cl$_2$; G: TFOH (2.0 equiv), CH$_2$Cl$_2$, 0°C; H: CF$_3$CO$_2$H (2.0 equiv), silica gel, CH$_2$Cl$_2$, 0°C; I: HCl (1.8 equiv), dioxane, CH$_2$Cl$_2$.
[b] Isolated yields;

Table 2: Transition-metal-catalyzed and acid-catalyzed reactions of enyndiamides.

Yndiamide activation could also be achieved by using Brønsted acids. Treatment of 2a with triflic acid gave dihydroisouquinoline 11 (78%, entry 12), whereas the use of trifluoroacetic acid led to amide 12 (via the enol trifluoroacetate, entry 13). These reactions reveal the potent reactivity of yndiamides towards Brønsted acids, and in the former case represent the first test of 5-versus 6-membered ring formation in keteniminium ion cyclizations.[10] Finally, reaction of 2q with HCl resulted in smooth conversion to enone 13 (entry 14), presumably by means of 1.5-hydrate transfer onto an intermediate keteniminium ion.[11,19]

Further transformations of dienamide 6a (Scheme 1) underline the utility of yndiamides. Diels–Alder reactions with N-phenylmaleimide, dimethylacetylene dicarboxylate, and 4-phenyl-1,2,4-trizolane-3,5-dione (PTAD) afforded cycloadducts 14a–c in high yields (65–85%). Dihydropyran 14d was formed as a single regio- and diastereoisomer through the Lewis acid catalyzed reaction of 6a with 4-bromobenzaldehyde, a result that shows the powerful electron-donating effect of the exocyclic enamide compared to the pyrrolidine nitrogen atom.[20] Similarly, acidic hydrolysis afforded enal 15 exclusively. Oxidation of 6a with 1.5 equivalents of 3-chloroperbenzoic acid (m-CPBA) gave dihydrofuran 16, which underwent possible that bbeda suppresses further reaction of 6a by promoting decomplexation of palladium from the product.

Rh-catalyzed [5+2] cycloisomerization of vinylcyclopropane yndiamide (–)–2o yielded a single diastereomer of the 5,7-fused bicyclic 7 (entry 7),[14] again requiring more forcing conditions compared to the equivalent ynamides. However, cyclization of triyenes 2y and 2z by using Wilkinson’s catalyst[15] proceeded more rapidly than with the related ynamides, giving pyrrolineolindoles 8a and 8b in excellent yields (96 and 91%, respectively, entries 8 and 9).[14b] The Pauson–Khand reaction of 2j afforded the amidocyclopentone 9 (88%, entry 10), whereas Au-catalyzed cyclization led to cyclobutenamide 10 (entry 11), an outcome that is again distinct from that of the equivalent ynamide chemistry, which affords ring-opened products.[17]
further oxidation using excess m-CPBA to give keto-ester 17 (94%). Reduction/hydrolysis of 17 led to a single diastereomer of the unusual, highly functionalized aminosugar 18 (72%).

In considering possible mechanisms for yndiamide formation, bromoyndiamine 19 (Scheme 2) is an attractive intermediate. This intermediate is also the likely source of bromoketene aminal 5 (the near exclusive product in the absence of copper catalyst), and could arise from elimination of HBr by the amide anion. Efforts to prepare 19 by using lithium hexamethyldisilazide (LiHMDS) led only to isolation of the formal bromoyndiamine dimer 20.bl Attemptsed conversion of the ketene aminal 5 to the yndiamide failed under a variety of conditions, likely ruling out a vinylidene carbene rearrangement pathway (also supported by a [13C labelling experiment as shown in Scheme 2, in which a single labelled yndiamide was formed).bl If the yndiamide is indeed a reaction intermediate, formation of a copper acetylides, such as 21, could offer a feasible route for C–N bond formation. Circumstantial evidence for the formation of 21 was found in the isolation of byproduct diyndiamide 22 in reactions with hindered amide coupling partners. Alternative routes, such as amido-cupration of 19 followed by β-elimination of bromide, or direct amination of the dibromoyndiamine (23) followed by elimination of HBr, cannot be ruled out at this stage.

In conclusion, we report the first route to yndiamides—novel, bench-stable alkynyl derivatives that are readily prepared from simple precursors. Yndiamides are highly versatile, and provide access to a range of nitrogen-substituted frameworks by using transition-metal-catalyzed or acid-catalyzed processes. Yndiamides have a unique reactivity profile, which both mirrors and contrasts that of ynamides, suggesting significant potential for future applications.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: copper catalysis · cycloisomerization · heterocycles · ynamides · yndiamides

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[4] Other substrates, such as terminal ynamides or chloroynamides, proved to be ineffective. See the Supporting Information for full details.


1.3- and 1,5-dienes were observed as minor products in Table 2, entries 2–4, which is consistent with related ynamide processes, see Ref. [11a].