Rapid Increase of Molecular Complexity through C–H and C–C Bond Activation

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Department of Chemistry
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Abstract

The activation of carbon-hydrogen (C–H) and carbon-carbon (C–C) bonds by transition metal catalysts is an attractive strategy to streamline organic synthesis. Herein this manuscript, the two main areas of research are described.

Firstly, it was found that a nickel catalyst can promote the insertion of alkynes into the C–C bond of 3-azetidinones and 3-oxetanones to enable quicker access to pyranones and pyridinones in high yields and excellent regioselectivity.

Secondly, a rhodium-catalysed pyridine directed C–H bond activation enables the rearrangement of 1,6-heptadienes into bicyclo[2.2.1]heptanes in good yields. Importantly, three stereogenic centres are created with complete diastereocontrol in this atom-efficient reaction.

In chapter 1, an overview of the literature on transition metal-catalysed C–C bond activation of four membered rings is described. In chapter 2, our efforts to optimise the catalytic conditions and build the scope of the nickel-catalysed reaction are reported. In chapter 3, the results of the mechanistic investigations of the nickel-catalysed reaction are reported.

Finally in chapter 4, a brief overview of the transition metal-catalysed functionalisation of an alkene C–H bond with another alkene is described. Subsequently, the optimisation of the catalytic conditions and the scope of the diastereoselective carbocyclisation of 1,6-heptadienes triggered by rhodium-catalysed activation of an alkene C–H bond are reported.
Acknowledgements

I wish to acknowledge the contributions made to me by my primary supervisor, Doctor Christophe Aïssa. Throughout my PhD, Dr Aïssa has been a consistently a great source of help, guidance and enthusiasm for chemistry. Furthermore, Dr Aïssa gave countless hours of his time and has contributed greatly to my scientific development.

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I am thankful to all of the technical staff in the chemistry department of Liverpool. Particularly to Dr. Jonathan Iggo and Konstantin for their assistance with my many NMR experiments.

I would like to thank all the members of the place of worship in Manchester. I had a really good time with all of you and I have been very lucky to meet each one of you. I thank God for
such an opportunity. I hope the place of worship can grow in the near future. I am really thankful to Zico Liu for being my “bigger” brother. Thank you all for pushing me to keep going, especially when another failed nickel-catalysed reaction had to happen.

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Abbreviations and Definitions

\( \tilde{\nu} \)  
\( \delta \)  
\( ^\circ C \)  
1,2-DCE  
1,2-DME  
BINAP  
Bn  
BnBr  
br  
calcd  
CI  
cod  
coe  
d  
DMAc  
DMAP  
DMI  
DMSO  
DM-SegPHOS  
DPEPHos  
dppe  
dppb  
ee  

wavenumber  
chemical Shift  
Degree Celsius  
1,2-Dichloromethane  
1,2-Dimethoxyethane  
2,2′-bis(diphenylphosphino)-1,1′-binaphthyl  
Benzyl  
Benzyl Bromide  
Broad  
calculated  
Chemical Ionisation  
cyclooctadiene  
cyclooctene  
doublet  
Dimethylacetamide  
4-Dimethylaminopyridine  
1,3-Dimethyl-2-imidazolidinone  
Dimethyl Sulfoxide  
5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole  
(Oxydi-2,1-phenylene)bis(diphenylphosphate)  
1,2-Bis(diphenylphosphino)ethane  
1,2-Bis(diphenylphosphino)butane  
Enantiomeric Excess
equiv  equivalent
ESI  Electrospray Ionisation
EtOAC  Ethyl Acetate
Et<sub>2</sub>O  Diethyl Ether
g  gram
GC  Gas Chromatography
hr  hour
HMBC  Heteronuclear Multiple Bond Correlation
HRMS  High Resolution Mass Spectrometry
HSQC  Heteronuclear Single-Quantum Correlation
Hz  Hertz
IMes  1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IPr  1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR  Infrared Red
J  Coupling Constant
m  Multiplet
M  Molar
LDA  Lithium Diisopropylamide
m.p.  melting point
mg  miligram
MHz  Megahertz
min  minute
ml  millilitre
mmol  millimole
MS  Mass Spectroscopy
MTBE  Methyl tertbutyl ether
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHMDS</td>
<td>Sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>nbd</td>
<td>Norbordiene</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>PE</td>
<td>Petroleum Ether (40/60)</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Part per million</td>
</tr>
<tr>
<td>q</td>
<td>quadruplet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>rac</td>
<td>racemic</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SIPr</td>
<td>1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>T</td>
<td>Temperature</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
</tbody>
</table>
# Table of Contents

Abstract...................................................................................................................... 1

Acknowledgements................................................................................................... 2

Abbreviations and Definitions.................................................................................... 4

Chapter 1  Carbon–Carbon Bond Activation of Four-Membered Rings ...................... 12
  1.1  Introduction ....................................................................................................... 12
  1.2  Transition metal catalysed C–C σ bond cleavage............................................. 15
    1.2.1  Cyclobutanones.......................................................................................... 15
    1.2.2  Cyclobutenones and benzocyclobutenones ............................................... 20
    1.2.3  Cyclobutadienones.................................................................................... 26
    1.2.4  Vinyl-Cyclobutanols and Allenylcyclobutanols.......................................... 28
    1.2.5  Cyclobutenols and benzocyclobutenols.................................................... 32
    1.2.6  Cyclobutanone O-Benzoyloximes ........................................................... 34
    1.2.7  Biphenylenes............................................................................................ 35
    1.2.8  Alkylidenecyclobutanes............................................................................. 37
  1.3  Conclusion and Outlook.................................................................................... 38
  1.4  References...................................................................................................... 44

Chapter 2  Nickel-Catalysed Cycloaddition of 3-Azetinones and 3-Oxetanones with Alkynes. 48
  2.1  Aim and Hypothesis ....................................................................................... 48
  2.2  Optimisation.................................................................................................... 49
  2.3  Scope of the reaction....................................................................................... 58
    2.3.1  Cycloaddition of N-Boc Azetidinone with alkynes .................................... 58
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3.2</td>
<td>Limitations.................................................................70</td>
</tr>
<tr>
<td>2.3.2.1</td>
<td>Terminal Alkynes............................................................70</td>
</tr>
<tr>
<td>2.3.2.2</td>
<td>Alkynyl pyridines...........................................................71</td>
</tr>
<tr>
<td>2.3.2.3</td>
<td>Electron-deficient alkynes................................................72</td>
</tr>
<tr>
<td>2.3.2.4</td>
<td>Alkynyl boronate esters....................................................73</td>
</tr>
<tr>
<td>2.3.2.5</td>
<td>Propargyl ethers..............................................................73</td>
</tr>
<tr>
<td>2.3.2.6</td>
<td>Miscellaneous alkynes........................................................78</td>
</tr>
<tr>
<td>2.3.3</td>
<td>Cycloaddition of $N$-Benzhydryl azetidinone 76 with alkyne 5b ...........79</td>
</tr>
<tr>
<td>2.3.4</td>
<td>Cycloaddition of $N$-Ts Azetidinones with alkynes..........................80</td>
</tr>
<tr>
<td>2.3.5</td>
<td>Aromatisation to pyridinols..................................................84</td>
</tr>
<tr>
<td>2.3.6</td>
<td>Cycloaddition of oxetanones with alkynes....................................85</td>
</tr>
<tr>
<td>2.3.7</td>
<td>Optimisation of the formation of four-membered ring 8..........................88</td>
</tr>
<tr>
<td>2.3.8</td>
<td>Initial attempts of formal [4+2] cycloaddition of azetidinone with alkenes....92</td>
</tr>
<tr>
<td>2.4</td>
<td>Future development of air-stable Ni(II) pre-catalyst........................93</td>
</tr>
<tr>
<td>2.4.1</td>
<td>Introduction and initial optimisation.........................................93</td>
</tr>
<tr>
<td>2.4.2</td>
<td>1,3-Enyne as alkyne surrogate to improve regioselectivity......................97</td>
</tr>
<tr>
<td>2.4.2.1</td>
<td>Regioselectivity issues with alkyne 5k.......................................97</td>
</tr>
<tr>
<td>2.4.2.2</td>
<td>1,3-Enyne as alkyne surrogate................................................99</td>
</tr>
<tr>
<td>2.5</td>
<td>Conclusion..............................................................................105</td>
</tr>
<tr>
<td>2.6</td>
<td>Synthesis of Precursors..........................................................106</td>
</tr>
<tr>
<td>2.6.1</td>
<td>Synthesis of 3-azetidinones....................................................106</td>
</tr>
<tr>
<td>2.6.2</td>
<td>Synthesis of 3-oxetanones......................................................107</td>
</tr>
</tbody>
</table>
2.6.3 Synthesis of alkynes ................................................................. 108

2.7 Experimental Section ........................................................................ 114

2.7.1 Synthesis of 3-azetidinones .......................................................... 114

2.7.2 Synthesis of 3-oxetanones and precursor .................................... 118

2.7.3 Synthesis of alkynes ..................................................................... 119

2.7.4 Nickel(0): Synthesis of pyridinones and pyranones .................... 132

2.7.5 Nickel(II): Synthesis of pyridinones ............................................ 163

2.7.6 Hydrogenation and Aromatisation ................................................ 165

2.8 References ...................................................................................... 169

Chapter 3 Mechanistic Investigations ..................................................... 173

3.1 Introduction ..................................................................................... 173

3.2 Results and Discussion ..................................................................... 183

3.2.1 Re-optimisation of the reaction conditions .................................... 183

3.2.2 Rate law with silylated alkyne 74 .................................................. 185

3.2.2.1 “Initial Burst” Phase .............................................................. 185

3.2.2.2 Kinetic study with silylated alkyne 73 .................................... 193

3.2.2.3 NMR studies ........................................................................ 197

3.3 Revised Mechanism and Conclusion ............................................... 201

3.4 Experimental data ........................................................................... 203

3.4.1 Kinetic study ................................................................................ 203

3.4.1.1 Kinetic study: Ni(cod)2/PPh3 (1:3) ....................................... 203

3.4.1.2 Kinetic Study: Ni(cod)2/PPh3 (1:2) ....................................... 215
3.4.2 NMR studies ........................................................................................................ 224
  3.4.2.1 Product Inhibition ......................................................................................... 224
  3.4.2.2 Competition Experiment ............................................................................. 225
  3.4.2.3 Synthesis of 77 ............................................................................................ 227
  3.4.2.4 Catalytic competency of 77 .......................................................................... 227
  3.4.2.5 Reaction of 77 with excess 73 ...................................................................... 227
  3.4.2.6 Reaction of 77 with excess 79 ...................................................................... 228
  3.4.2.7 Reaction of 77 with 70 ................................................................................ 229

3.5 References .................................................................................................................. 229

Chapter 4 Transition Metal-Catalysed Functionalisation of an Alkene C–H Bond with another Alkene .................................................................................................................. 231

  4.1 Introduction .............................................................................................................. 231
  4.1.1 Formation of a metallacycle intermediate via oxidative cyclisation ............... 233
  4.1.2 In situ formation of metal hydride ................................................................... 235
  4.1.3 C–H bond activation ......................................................................................... 237
    4.1.3.1 Oxidative cross coupling ........................................................................... 237
    4.1.3.2 Group directed C–H activation ................................................................. 240
  4.2 Aims and Hypothesis .............................................................................................. 252
  4.3 Optimisation of the reaction .................................................................................. 253
  4.4 Scope of the reaction ............................................................................................. 270
    4.4.1 Another directing group ................................................................................ 273
  4.5 Mechanistic studies ............................................................................................... 273
4.5.1 Deuterium-labelling experiment ................................................................. 275

4.6 Conclusion ........................................................................................................... 282

4.7 Future work ........................................................................................................ 283

4.8 Synthesis of precursors ..................................................................................... 284

4.9 Experimental ...................................................................................................... 291

4.10 References .......................................................................................................... 322
Chapter 1 Carbon–Carbon Bond

Activation of Four-Membered Rings

1.1 Introduction

Carbon–Carbon (C–C) σ bond activation by transition metals is an attractive atom-economical methodology for organic chemists as it can potentially streamline the synthesis to targets of interest.\(^1\) However, C–C activation is thermodynamically unfavourable as a C–C σ bond (90 kcal mol\(^{-1}\)) is broken to form two weaker metal carbon bonds (20-30 kcal mol\(^{-1}\)).\(^1\) Moreover, by comparison of the orbital alignment of C–C π bonds versus C–C σ bonds (Scheme 1), the C–C σ bond orbitals lie along the bond axis and render them less accessible for a good overlap with the incoming orbitals of the transition metal.\(^2\) Whereas for C–C π bonds, the orbitals are more accessible as they are projected out of the C–C axis.

![Scheme 1 Orbital diagram](image)

To overcome the barriers for C-C σ bond activation, substrates with high strain energy are commonly employed as the release of this energy drives the reaction forward. The orbital alignment of C–C σ bonds in strained systems such as 3- or 4-membered rings generally do not
lie in the plane of the ring but are commonly distorted out of plane which allows for increased orbital interaction with the orbitals of the transition metal.\textsuperscript{3}

Hence, Wiberg reported that orbitals of the C–C bond of cyclobutane are bent out of plane by approximately 7° (Scheme 2).\textsuperscript{4} In cyclohexane, the bond path angles of the C–C bond are closed to ideal. However, the bond path angle in cyclobutane is distorted.

\begin{center}
\begin{tabular}{c c}
<table>
<thead>
<tr>
<th>Bond Path Angle</th>
<th>Value (°)</th>
</tr>
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<tbody>
<tr>
<td>95.7 (89.0)</td>
<td>110.1 (111.4)</td>
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\end{center}

\textbf{Scheme 2} Bond path angles

Experimentally, the C–C–C bond angle in cyclobutane is found to be 89°. This large angle deviation from the ideal contributes to the high angle strain in cyclobutane. Furthermore, many C–H bonds are eclipsing which results in high torsional strain. To minimise the torsional strain, the cyclobutane adopts a puckered conformation to reduce some of the eclipsing interactions. Both angle strain and torsional strain contribute to the high ring strain energy observed in cyclobutane as determined theoretically\textsuperscript{5} and experimentally\textsuperscript{6} (Scheme 3). Therefore, the relief of this high ring strain energy serves as a thermodynamic driving force for the C–C cleavage of cyclobutane. As mentioned earlier, the strength of a typical C–C bond is roughly 90 kcal / mol and it can be seen that the high ring strain of cyclobutane substantially weakens the C–C bond of cyclobutane.

\begin{center}
\begin{tabular}{c c c}
<table>
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<tr>
<th>Ring Strain Energy [kcal/mol]</th>
<th>C–C–C Bond Angle (°)</th>
<th>C–C Bond Strength (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical : 26.7</td>
<td>1.3</td>
<td>90</td>
</tr>
<tr>
<td>Experimental : 26.5</td>
<td>0.0</td>
<td></td>
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\end{tabular}
\end{center}

\textbf{Scheme 3} Ring strain energy in cyclobutane vs cyclohexane
Due to the aforementioned kinetic and thermodynamic factors of four-membered ring systems, these systems are amenable to cleavage of a C–C σ bond by a variety of transition metals. Three of the most common mechanisms for the C–C bond cleavage are direct oxidative insertion, β-C elimination and [1,2]-shift (Scheme 4).\(^1\)

On the one hand, the direct oxidative insertion of a transition-metal complex into a four-membered ring system 1 results in the formation of 5-membered ring metallacycle 2. Metallacycle 2 can then be subjected to a variety of transformations.

On the other hand, transition-metal complexes can activate four-membered ring systems 3 to undergo β-C elimination. β-C elimination is a rearrangement process whereby the relief of ring strain serves as a thermodynamic driving force. The resulting alkyl metal intermediate 4 can then be exploited for further transformations.

Finally, [1,2]-shift is a carbocation rearrangement commonly observed in four-membered ring systems 5. Unlike, oxidative addition and β-C elimination, the metal never comes in direct contact with the C–C bond cleaved in the process. The resulting metal intermediate 6 can then be subjected to further transformations.

**Scheme 4** Three Common C–C bond cleavage processes
1.2 Transition metal catalysed C–C σ bond cleavage

1.2.1 Cyclobutanones

In 1994, Ito and co-workers reported the first catalytic C–C bond activation of cyclobutanone 7 (Scheme 5).\(^7\) It was proposed that oxidative insertion of the rhodium catalyst into the less sterically hindered acyl-carbon bond of 7 would afford pentarhodacycle 8. Under 50 atmospheres of hydrogen, hydrogenolysis of 8 would eventually afford alcohol 9 as product.

\[
\text{Scheme 5 Rhodium-catalysed hydrogenolysis of cyclobutanone}
\]

After this preliminary work, Murakami and co-workers reported a rhodium-catalysed rearrangement of strained spiro-cyclobutanone 10 into cyclohexenone 11 whereby the putative rhodacycle 12 is trapped by another C–C bond cleavage process (Scheme 6).\(^8\) The authors postulated that oxidative insertion of the rhodium catalyst into the acyl-carbon bond of 10 would form the initial pentarhodacycle 12. Ring enlargement by β-C elimination would then afford heptarhodacycle 13, which after reductive elimination and isomerisation of the double bond would afford cyclohexenone 11 as product.
Murakami and co-workers also reported some striking ligand effects on the C–C bond cleavage of cyclobutanone 14 (Scheme 7). With dppe as a ligand, oxidative insertion of the rhodium complex was assumed to be directed by the alkene moiety into bond \( b \) of 14 to form pentarhodacycle 15. Subsequent \( \beta \)-H elimination would afford intermediate 16. Finally, reductive elimination would occur to afford enone 17. However, with dppp as a ligand, the oxidative insertion of the rhodium complex into bond \( a \) of 14 would result in the formation of pentarhodacycle 18, which could then be trapped by intramolecular insertion of the alkene to afford the tricyclic intermediate 19. Finally, reductive elimination would afford the tricyclic ketone 20. Recently, Cramer and co-workers have reported the enantioselective variation of the same sequence of elementary steps.

Murakami and co-workers also reported a change of reactivity of cyclobutanone 14 with a nickel-catalyst (Scheme 7). Oxidative cyclisation of the ketone and alkene moiety by the nickel catalyst would afford nickelapentacycle 21. Afterwards, ring enlargement by \( \beta \)-C elimination would afford intermediate 22. Finally, reductive elimination would afford tricyclic ketone 23 as the product. Later, the same group reported an enantioselective version of this reaction. The different transformations of 14 highlight the ongoing research in C–C activation
to generate a diverse range of structures and the difference in reactivity induced by different catalysts.

Scheme 7 Different catalytic systems

In 2006, Murakami and co-workers extended the reaction to a formal nickel catalysed [4+2+2] cycloaddition to form eight membered rings 26 (Scheme 8).\textsuperscript{13} It is proposed that it would begin by the initial oxidative cyclisation of the diyne 24, the ketone 25 and the nickel catalyst to afford nickelaheptacycle 27. Afterwards, ring enlargement by β-C elimination would give intermediate 28. Finally, reductive elimination would afford cyclooctadienone 26. Symmetrical diynes which processed either internal or terminal alkynes proceeded in good yields. Several modifications to the tether were tolerated under the reaction conditions. Furthermore, non-symmetrical diynes proceeded with excellent regioselectivity under a Ni/IPr catalyst system.
Scheme 8 Nickel-catalysed [4+2+2] cycloaddition of cyclobutanones and diynes

Wender and co-workers reported a rhodium catalysed [6+2] cycloaddition of vinylcyclobutanones 29 to form eight-membered ring systems 30 (Scheme 9). Theoretical studies suggest the formation of rhodacycle 31 happens first. Afterwards, ring opening via β-carbon elimination and concomitant cleavage of bond $b$ would afford rhodacycle 32. Then reductive elimination would occur to afford product 30. Several eight-membered ring ketones were formed in good to excellent yields.
Rhodium-catalysed addition of boronic acids to a carbonyl moiety have been reported to proceed through an organorhodium intermediate which would undergo a 1,2-addition to the carbonyl moiety.\(^\text{16}\) Organorhodium intermediates can also add across an alkyne triple bond to generate an alkenyl rhodium intermediate.\(^\text{17}\) From these work, Murakami and co-workers reported a rhodium-catalysed ring expansion towards seven-membered-ring ketones 33 which involves the exploitation of the initial formation of the alkenyl rhodium intermediate 35 and C–C bond cleavage (Scheme 10).\(^\text{18}\) The initial vinyl rhodium species 35, arising from the regioselective carborhodation of alkyne 33, would undergo an intramolecular 1,2-addition to the ketone which would result in the formation of rhodium alkoxide 36. Subsequent regioselective β-C elimination would afford intermediate 37. Then hydrolysis would afford ketone 34. While several seven-membered ring ketones were synthesised in good to high
yields, the authors found that additional substitution on the cyclobutanone prevented the formation of the desired product.

\[ \text{Scheme 10 Intramolecular 1,2-addition of vinyl rhodium species} \]

### 1.2.2 Cyclobutenones and benzocyclobutenones

Liebeskind and Huffman reported a rhodium-catalysed insertion into cyclobutenone 38 to form eight-membered ring ketones 39 whereby both oxidative insertion and β-C elimination processes had taken place (Scheme 11). Therefore, it was postulated that oxidative insertion of rhodium complex into cyclobutenone 38 would form rhodacycle 40. Subsequent ring enlargement by β-C elimination would then trap rhodacycle 40 and as a result would form
intermediate \( \text{41} \). This would then be followed by reductive elimination to afford cyclooctadiene \( \text{39} \) in a 90\% yield.

![Scheme 11](image)

**Scheme 11** Rhodium-catalysed insertion into cyclobutenone

Liebeskind and Huffman reported a nickel-catalysed annulation of cyclobutenones \( \text{42} \) with alkynes to form phenols \( \text{43} \) (Scheme 12).\(^{20}\) Initial cleavage of the acyl-carbon bond of cyclobutenone \( \text{42} \) would result in the formation of intermediate \( \text{44} \) or \( \text{45} \). Insertion of alkyne would form intermediate \( \text{46} \). Reductive elimination and aromatisation would then afford phenol \( \text{43} \).

Electron-rich substituents on the cyclobutenone were found to be unfavourable under the reaction conditions as decomposition will occur. The insertion of various non-symmetrical internal alkynes proceeded in moderate to good yields. However, the regioselectivity of the alkyne insertion was generally poor. More recently, Harrity and Auvinet reported the nickel-catalysed annulation of cyclobutenones and alkynylboronates which proceeded with excellent regioselectivity.\(^{21}\) In 2007, Kondo and co-workers reported an improved substrate scope to also include electron poor alkenes with a rhodium catalyst.\(^{22}\)
Mitsudo and co-workers reported a rhodium-catalysed transformation of cyclobutenones 47 with alkenes to afford product 51 or 52 depending on the atmosphere (Scheme 13). In the presence of the rhodium-catalyst, either intermediate 48 or 49 would form from the initial acyl-carbon bond cleavage. Insertion of the alkene fragment would form intermediate 50. When the reaction was carried out under an atmosphere of Ar, decarbonylation would then be followed by reductive elimination to afford product 51. However, when the reaction was carried out under 30 atmospheres of CO, the amount of product arising from decarbonylation was reduced and the direct reductive elimination would occur to form mainly product 52.
Scheme 13 Atmosphere dependent rhodium-catalysed transformations of cyclobutenones

In the previous examples, the rhodium catalyst is postulated to undergo oxidative insertion into the acyl –C sp³ bond. In the subsequent examples, the rhodium is postulated to undergo oxidative insertion into the acyl–C sp² bond. Dong and co-workers reported a rhodium-catalysed intramolecular alkene insertion into benzocyclobutenone 53 to form tricyclic ketone 54 (Scheme 14). Interestingly, the major product comes from the rhodium insertion into the C–C sp² bond. To account for their results, the authors proposed that the pendant alkene would direct the oxidative insertion of the rhodium catalyst into the more sterically hindered bond of 53 to form rhodacycle 55 and intramolecular alkene insertion would then form intermediate 56. Finally, reductive elimination would afford product 54. An enantioselective version of this reaction was later reported by the same group. Furthermore, this methodology was used as a key step in the total synthesis of the proposed structure of cycloinumakiol 59 (Scheme 15).
Scheme 14 Rhodium-catalysed intramolecular alkene insertion into cyclobutanone

Scheme 15 Total synthesis of proposed structure of cycloinumakioi

This work was later extended to include alkyne insertion to form either a β-napthol 63 or indene 64 (Scheme 16). It is proposed the tether alkyne would direct the oxidative insertion of the rhodium catalyst into the more sterically hindered bond of 60 would form rhodacycle 61. Intramolecular alkyne insertion would form intermediate 62. Finally, reductive elimination and aromatisation would afford β-napthol 63 when the reaction was carried out in a sealed tube in dioxane at 130°C. However, if the reaction was carried out in xylene under reflux under Argon, decarbonylation of intermediate 62 and then reductive elimination would afford indene 64.
Scheme 16 Rhodium-catalysed intramolecular alkyne insertion into cyclobutane

Liebeskind and co-workers reported experimental evidence of the oxidative insertion of a rhodium complex into the C–C bond of cyclobutenone (Scheme 17) and the C–C bond of benzocyclobutenone (Scheme 18). The insertion into either cyclobutenone or benzocyclobutenone requires high temperatures which is a common requirement for rhodium-catalysed reactions. Furthermore, the oxidative insertion into benzocyclobutenone was shown to happen at both the more and the least sterically hindered acyl–carbon bond and Liebeskind found that the ratio of 69 and 70 is different depending on the time of the reaction. Equilibrium is reached after 5 days, and 69 and 70 were obtained in almost equimolar ratio. This equilibration demonstrates the oxidative insertion is a reversible process. Murakami and co-workers reported the oxidative addition into the least sterically hindered C–C bond of benzocyclobutenone to occur at room temperature which is likely facilitated by the electron rich ligand (Scheme 19).

Scheme 17 Oxidative addition of rhodium into a C–C bond of cyclobutenone
Scheme 18 Oxidative addition of rhodium into a C–C bond of benzocyclobutenone

Scheme 19 Experimental proof of the oxidative addition into the C–C bond

1.2.3 Cyclobutadienones

Mitsudo and co-workers reported a ruthenium-catalysed intermolecular decarbonylative cycloaddition of cyclobutadienone 73 with alkene to form cyclopentenone 74 (Scheme 20). It was necessary to carry the reaction under three atmospheres of CO because external CO was assumed to be required to suppress complete decarbonylation of cyclobutadienone 73 to the corresponding alkyne. Furthermore, 70% scrambling was observed when the reaction was carried out with labelled $^{13}$CO. Therefore, it was proposed the oxidative insertion of the ruthenium catalyst was directed by the alkoxy substituent into bond b over bond a to form pentarhodacycle 75. Subsequent decarbonylation would afford intermediate 76. Afterwards, stereoselective alkene insertion would form intermediate 77. This would then undergo reductive elimination to give product 74. Various substituted cyclobutadienones were tolerated under the reaction conditions. Also, the use of ethene as a coupling partner was effective.
Yamamoto and co-workers reported a rhodium-catalysed intramolecular decarbonylative cycloaddition of cyclobutadienone 78 with pendant alkene to cyclopentenone 79 (Scheme 21).\textsuperscript{21} It was proposed that if X is a heteroatom, it would direct the oxidative insertion of the rhodium complex into bond $a$ of 78 to form pentarhodacycle 80. However, reactivity was still observed when X was methine. Regardless, subsequent decarbonylation would afford intermediate 81. Afterwards, alkene insertion followed by reductive elimination would afford product 79. Unlike the intermolecular decarbonylative decoupling reported by Mitsudo and co-workers, no external CO was necessary.\textsuperscript{30} Various substitution patterns on the alkene system were tolerated. However, gem-disubstituted alkenes were the most reactive. Cyclobutadienone bearing aromatic or alkyl substituents were tolerated. Furthermore, modifications to the tether did not affect the overall reactivity.
Scheme 21 Rhodium-catalysed intramolecular decarbonylative cycloaddition

1.2.4 Vinyl-Cyclobutansols and Allenylcyclobutansols

Uemura and co-workers reported a regioselective oxidative palladium-catalysed ring opening of cyclobutanols 82 to form bicyclic ketones 85 (Scheme 22).\(^{32}\) After the formation of the putative palladium alkoxide 83, ring opening of the least sterically hindered bond \(b\) via \(\beta\)-C elimination would afford alkylpalladium complex 84. An intramolecular Mizoroki-Heck reaction would then occur to give product 85. The presence of base might be vital to facilitate the formation of the palladium alkoxide 83. Conversely, Clark and Thiensathit reported the ring opening of cyclobutanol 82 proceeded in a different manner under another oxidative palladium catalytic system.\(^{33}\) The palladium-catalyst would coordinate to the alkene of 82 to form 86. This would activate the system for ring enlargement by the cleavage of bond \(a\) via [1,2]-shift which would form intermediate 87. Afterwards, \(\beta\)-H elimination and isomerisation of the double bond would afford product 88. Since the report by Clark and Thiensathit, related ring expansions of cyclobutanols have been reported.\(^{34}\)
Cramer and Souillart reported an enantioselective rhodium-catalysed domino reaction of cyclobutanols 89 (Scheme 23). After the formation of putative rhodium alkoxide 91, ring opening via β-C elimination would form intermediate 92. Then intramolecular oxidative addition of 92 would form intermediate 93. Afterwards, insertion of the alkene and then reductive elimination would afford product 90. Various substituents and substitution patterns on the aryl ring were tolerated. Various substituents on the cyclobutanol ring were also tolerated. However, only non-substituted and 1,1-disubstituted alkenes were tolerated under the reaction conditions.
Cramer and Seiser reported a related rhodium-catalysed ring expansion of 1-allenyl cyclobutanols 94 to cyclohexenones 95 (Scheme 24). The mechanism of this reaction is analogous to the rhodium catalysed C–C cleavage of 1-vinyl cyclobutanols. After the formation of the putative rhodium alkoxide 96, ring enlargement via β-C elimination would afford heptarhodacycle 97. Reductive elimination would give 6-membered ring 98 which would then undergo isomerism to give product 95. Various functional groups on the cyclobutanol were tolerated under the reaction conditions. Coordinating groups such as the vinyl and pyridyl group required slightly more forced conditions for full conversion. Cyclic substituted allenes and terminal allenes were tolerated under the reaction condition.
Wender and co-workers reported a rhodium-catalysed [6+1] cycloaddition of allenylcyclobutane ether 99 (Scheme 25). The mechanism of the reaction is now different from 1-allenyl cyclobutanols. Since the oxygen is now protected, the rhodium catalyst will first form a π-complex with the allene to form intermediate 102. It was then proposed that a rhodium-catalysed ring opening of 102 via β-C elimination of the least sterically hindered bond \(a\) would then occur to form intermediate 103. Insertion of CO and then reductive elimination would afford product 100. Occasionally, product 101 arising from the cleavage of the more sterically hindered bond \(b\) was observed.

**Scheme 24** Rhodium catalysed ring expansion of 1-allenyl cyclobutanols
Scheme 25 Rhodium-catalysed [6+1] cycloaddition

1.2.5 Cyclobutenols and benzocyclobutenols

Matsuda and Miura reported a rhodium-catalysed [4+2] annulation of cyclobutenols 105 with alkynes to form tetrasubstituted benzenes 106 (Scheme 26). After the formation of the putative rhodium alkoxide 107, ring opening of 107 by β-C elimination would form alkenylrhodium complex 108. Insertion of alkyne into the rhodium-carbon bond would form rhodium complex 109. Subsequent nucleophilic addition to the ketone would afford cyclohexadiene 110. Protonation would afford alcohol 111. Finally, dehydration would afford tetra-substituted benzene 106. Several tetrasubstituted benzenes were synthesised in a high yield. Silylated alkyne was tolerated and preceded with excellent regioselectivity but poor reactivity. Modification of the reaction conditions improved the yield but slightly diminished the regioselectivity. The insertion of various other non-symmetrical internal alkynes proceeded with good to high regioselectivity.
Murakami and co-workers reported a rhodium-catalysed benzannulation of alkyne and benzocyclobutenols 112 (Scheme 27).\textsuperscript{39} Recent theoretical studies by Morokuma and co-workers reported that after the formation of rhodium alkoxide 114, cleavage of bond $a$ would occur preferentially over bond $b$ because the extra $\pi$-bond interaction of the benzene ring of the substrate with the rhodium catalyst would stabilise the transition state to form intermediate 115.\textsuperscript{40} Afterwards, alkyne insertion would form alkenylrhodium complex 116. Subsequent nucleophilic addition to the ketone and protonation would afford dihydronaphthalene 113. Interestingly, unlike the examples with cyclobutanol as reported by Matsuda and Miura,\textsuperscript{38} the major product is not the aromatised naphthalene.

Various functional groups on the aryl ring were tolerated under the reaction conditions. Alteration of the electronic character of the aryl ring had no significant effect in the reaction outcome. Furthermore, the insertion of non-symmetrical alkynes proceeded with moderate to
excellent regioselectivity. Different functional groups on the alkyne were tolerated but terminal alkynes were not.

**Scheme 27** Rhodium-catalysed benzannulation of benzocyclobutenol and alkyne

1.2.6 Cyclobutanone O-Benzoyloximes

Uemura and co-workers reported ligand effects in the palladium-catalysed ring opening of cyclobutane 117 (Scheme 28). Oxidative insertion into the N–O bond of the oxime would form intermediate 120. With PPFCyA as a ligand, bond \( a \) of intermediate 120 was postulated to be broken via β-C elimination which would form intermediate 121. Intramolecular cyclisation followed by β-H elimination would then afford 118. However, with BINAP as a ligand, bond \( b \) of intermediate 120 was assumed to be preferentially broken via β-C elimination which would form intermediate 122. Subsequent β-H elimination would afford 119.
1.2.7 Biphenylenes

Products resulting from the stoichiometric cleavage of a C–C σ bond of biphenylene 123 by the oxidative insertion of a transition metal complex have been isolated and characterised. However, it wasn’t until 1990 that Vollhardt and co-workers demonstrated the first catalytic C–C σ bond cleavage of biphenylene 123 (Scheme 29). Oxidative insertion of the nickel catalyst into the strained C–C bond of biphenylene 123 would form intermediate 125. Dimerisation of intermediate 125 would form intermediate 126. Subsequent reductive elimination would afford dimer 124.
Jones and co-workers reported a nickel-catalysed [4+2] cycloaddition of biphenylene 123 with alkynes to form phenanthrenes 127 (Scheme 30). Oxidative insertion of the nickel catalyst 128 into 123 would form intermediate 129. Insertion of the alkyne would form intermediate 130. Reductive elimination would afford 127. No cyclotrimerisation was observed. The hemilabile ligand was found to be essential for the catalytic cycle. Interestingly, when dippe (1,2-bis(diisopropylphosphino)ethane) was used as a ligand, 6 mol% of O₂ was required to make the reaction catalytic.\textsuperscript{45}
1.2.8 Alkylidenecyclobutanes

Aissa and co-workers reported a rhodium-catalysed a C–H / C–C bond activation sequence to form 8-membered ring ketones 132 (Scheme 31). Subtle modifications to the catalytic system were required for optimal yields. Mechanistically, initial C–H activation of 131 would give intermediate 133. This would then be followed hydrometalation onto the alkylidenecyclobutane to give intermediate 134. Subsequent ring enlargement by β-C elimination to trap intermediate 134 would give intermediate 135. Afterwards, reductive elimination would afford product 132. Mono-substitution and gem-diphenyl substitution on the cyclobutane ring were tolerated under the reaction conditions. Tetra-substitution on the alkene resulted in no reaction under various rhodium-catalysed conditions. Furthermore, various modifications on the tether were also compatible.
Transition metal catalysed C–C cleavage of four-membered cabocycles is an area of extensive research. This has led to the discovery of many different intermolecular and intramolecular restructuring of the carbon framework. C–C cleavage via oxidative addition, β-C elimination or [1,2] shift are common mechanistic processes used to explain the reaction outcome. However, C–C bond cleavage of small heterocycles had been studied less extensively. The ring strain energy in cyclobutane 136 is similar to the ring strain energy in oxetane 137 and azetidine 138 by both experimental and computational studies (Scheme 32).47
In 2010, Aissa and co-workers reported the first example of a C–C bond cleavage of a small heterocycle 139 (Scheme 33).\textsuperscript{46} Replacing the alkylidenecyclobutane moiety with alkylideneazetidine moiety still resulted in the formation of the desired 8-membered ring 140 in good yields. The mechanistic pathway was proposed to be identical to the all carbon equivalent whereby the C–C bond $a$ of intermediate 142 was broken to eventually afford 8-membered ring ketone 140. Despite the increased loading in catalyst, this work demonstrated the viability of C–C bond cleavage of small heterocycles.

**Scheme 32** Ring strain energies

<table>
<thead>
<tr>
<th></th>
<th>Theoretical (kcal / mol)</th>
<th>Experimental (kcal / mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>136</td>
<td>25.7</td>
<td>26.5</td>
</tr>
<tr>
<td>137</td>
<td>24.9</td>
<td>25.2</td>
</tr>
<tr>
<td>138</td>
<td>25.4</td>
<td>26.2</td>
</tr>
</tbody>
</table>
Afterwards, we became curious about whether or not other small heterocycles can undergo selective C–C cleavage. In 2005, Murakami and co-workers reported the first intermolecular insertion of alkyne into cyclobutanone 144 to afford the corresponding cyclohexenone 145 in a formal [4+2] cycloaddition with a nickel-catalyst (Scheme 34). Therefore it is proposed, the nickel catalyst would coordinate to both the ketone and the alkyne to form intermediate 146. Then oxidative cyclisation would afford nickelapentacycle intermediate 147. Afterwards, ring enlargement by β-C elimination would afford nickelapeptacycle 148. Finally, reductive elimination would afford cyclohexenone 145. Various cyclohexenones were successfully synthesised in moderate to excellent yields. The insertion of non-symmetrical alkynes proceeded with good and consistent regioselectivity regardless of the electronic properties of the alkyne.
Scheme 34 Nickel-catalysed alkyne insertion into cyclobutanone

Drawing inspiration from Murakami’s work, it was of interest to determine if azetidinone 149 could behave like cyclobutanone 144 in a transition-metal catalysed [4+2] cycloaddition with alkyne 150 to generate pyridinone 151 (Scheme 2).

Scheme 35 Hypothesis
Drawing an analogy to the proposed mechanism of the [4+2] cycloaddition of cyclobutanone 144 with an alkyne, it was hypothesised that the nickel-catalyst will first associate azetidinone 149 and alkyne 150 to form intermediate 152. Afterwards, oxidative cyclisation would form nickelapentacycle 153. Ring enlargement by β-C elimination will form nickelahasheptacycle 154. Finally, reductive elimination should afford desired product 151.

This work towards the synthesis of pyridinones 151 would offer an alternative approach to the other methods already published. The approach by ring closing metathesis is generally low yielding as the formation of a tetra-substituted alkene is difficult (Scheme 36). Alternatively, a relay metathesis approach can circumvent this issue but requires a more advanced substrate (Scheme 37).

**Scheme 36** Ring closing metathesis

**Scheme 37** Relay metathesis
Another approach towards pyridinones 164 is by a palladium-catalysed intramolecular Heck-type reaction of oxime 162 as reported by Tong and co-workers (Scheme 38).\textsuperscript{51} After the palladium step, acid hydrolysis of oxime 163 is then carried out to furnish pyridinone 164.

\begin{center}
\includegraphics[width=\textwidth]{scheme38.png}
\end{center}

\textbf{Scheme 38} Palladium catalysed Heck-type reaction

In light of what is known in the literature towards the synthesis of pyridinones 151, the formal [4+2] cycloaddition of azetidinone 149 and alkyne 150 should offer a more direct approach. Furthermore, this method can also be seen as a rapid build-up of molecular complexity. Furthermore, the formal [4+2] cycloaddition is seen as a convergent synthesis rather than a linear synthesis. As a result, the overall steps required to synthesise pyridinones 151 are reduced.

In this context, the initial aims of the work presented herein were to:

a.) To validate the hypothesis of the insertion of an alkyne into the C–C bond of azetidinone to give pyridinones 151

b.) Optimise the reaction

c.) Examine the scope

d.) Investigate the mechanism of the reaction
During the development of the work presented in this thesis, Murakami and co-workers reported an example of C–C cleavage of 3-azetidinol 165 to form tetralone 166 (Scheme 39). After the formation of rhodium alkoxide 167, oxidative addition into the carbon-bromine bond would form rhodacycle 168. C–C cleavage of bond $\alpha$ via $\beta$-C elimination would afford heptarhoacycle 169. Finally, reductive elimination would generate tetralone 166.

Scheme 39 Rhodium catalysed formation of tetralone

1.4 References


Chapter 2 Nickel-Catalysed

Cycloaddition of 3-Azetinones and 3-Oxetanones with Alkynes

2.1 Aim and Hypothesis

As mentioned in the previous section, Aïssa and co-workers reported the first example of C–C bond cleavage of small heterocycles.\(^1\) Afterwards, we became curious about whether or not other small heterocycles can undergo selective C–C cleavage. As discussed in the previous section, Murakami and co-workers reported the nickel-catalysed insertion of alkyne 2 into cyclobutanone 1 to form cyclohexenone 3 (Scheme 1).\(^2\) As a result, a variety of cyclohexenones were synthesised via this methodology.

\[ \text{Scheme 1: Nickel-catalysed insertion of alkyne 2 into cyclobutanone 1} \]

\[ \text{R}^1 = \text{alkyl, aryl} \quad \text{R}^2 = \text{alkyl, aryl} \]
\[ \text{R}^3 = \text{alkyl, aryl} \quad \text{R}^4 = \text{alkyl, aryl} \]
From this work, it was therefore of interest to determine if azetidinone 4 could behave like cyclobutanone 1 in a transition-metal catalysed [4+2] cycloaddition with alkyne 5 to generate pyridinone 6 (Scheme 2).

\[
\begin{align*}
\text{Scheme 2 Hypothesis}
\end{align*}
\]

### 2.2 Optimisation

Using the conditions described by Murakami and co-workers,² treatment of commercially available \(N\)-Boc-Azetidinone 7 with diphenylacetylene 5a in the presence of 10 mol\% Ni(cod)₂ and 20 mol\% PCy₃ in toluene at 100°C gave the expected six-membered ring 6a but also a four-membered ring 8 in a near 1:1 ratio (Scheme 3). Both products were characterised by \(^1\)H and \(^{13}\)C NMR, IR and HRMS.

The formation of the four-membered ring 8 is believed to be a result of a Boc-group directed C–H bond activation to form intermediate 9. Afterwards, hydrometalation onto alkyne 5a would form intermediate 10. Finally, reductive elimination would give four-membered ring 8.
Scheme 3 Initial screen with azetidinone 7 under Murakami’s conditions

A screening of ligands was then carried out to optimise the formation of 6a (Table 1). Phosphines with alkyl groups tend to favour the formation of 8 (Table 1, Entry 1-3). Ligands with ortho substitution (Table 1, Entry 4 and 5) have large cone angles and inhibited the reaction. Ligands with a heteroatom (Table 1, Entry 6 and 7) appear to be somewhat tolerated with electron poor $L_3$ (Table 1, Entry 7) favouring high selectivity towards 6a but with incomplete conversion. Electron poor triphenylphosphite (Table 1, Entry 8) was found to be ineffective. $PPh_3$ (Table 1, Entry 9) had some selectivity towards 6a. Modifying the para substituents on the phenyl ring (Table 1, Entry 10-12) showed that the electronic effects$^4$ had little influence on the formation of 6a or 8 except for $P(p$-ClC$_6$H$_4)_3$ (Table 1, Entry 13) which led to high selectivity towards 6a but with incomplete conversion.
Table 1: Ligand Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (20 mol%)</th>
<th>Conversion (%)</th>
<th>6a/8</th>
<th>$\nu_{CO}$ (cm$^{-1}$)</th>
<th>Cone angle (q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>PCy$_3$</td>
<td>100</td>
<td>50 : 50</td>
<td>2056.4</td>
<td>170</td>
</tr>
<tr>
<td>2.</td>
<td>P'Bu$_3$</td>
<td>95</td>
<td>21 : 79</td>
<td>2056.1</td>
<td>182</td>
</tr>
<tr>
<td>3.</td>
<td>P(Ph$_2$)Me</td>
<td>100</td>
<td>21 : 79</td>
<td>2067.0</td>
<td>136</td>
</tr>
<tr>
<td>4.</td>
<td>L1</td>
<td>55</td>
<td>50 : 50</td>
<td>2066.1</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>P(o-MeC$_6$H$_4$)$_3$</td>
<td>0</td>
<td>0 : 0</td>
<td>2066.6</td>
<td>194</td>
</tr>
<tr>
<td>6.</td>
<td>L2</td>
<td>94</td>
<td>37 : 63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>L3</td>
<td>44</td>
<td>100 : 0</td>
<td>2078.4</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>P(OPh)$_3$</td>
<td>7</td>
<td>100 : 0</td>
<td>2085.3</td>
<td>128</td>
</tr>
<tr>
<td>9.</td>
<td>PPh$_3$</td>
<td>100</td>
<td>59 : 41</td>
<td>2068.9</td>
<td>145</td>
</tr>
<tr>
<td>10.</td>
<td>P(p-MeOC$_6$H$_4$)$_3$</td>
<td>100</td>
<td>71 : 29</td>
<td>2066.1</td>
<td>145</td>
</tr>
<tr>
<td>11.</td>
<td>P(p-MeC$_6$H$_4$)$_3$</td>
<td>100</td>
<td>50 : 50</td>
<td>2066.7</td>
<td>145</td>
</tr>
<tr>
<td>12.</td>
<td>P(p-CF$_3$C$_6$H$_4$)$_3$</td>
<td>&gt;97</td>
<td>61 : 39</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>P(p-ClC$_6$H$_4$)$_3$</td>
<td>50</td>
<td>100 : 0</td>
<td>2072.8</td>
<td>145</td>
</tr>
<tr>
<td>14.</td>
<td>dppe</td>
<td>0</td>
<td>0 : 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>dppb</td>
<td>36</td>
<td>100 : 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Xantphos</td>
<td>&lt;5%</td>
<td>100 : 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>L4</td>
<td>0</td>
<td>0 : 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>IPr</td>
<td>0</td>
<td>0 : 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>SIPr</td>
<td>0</td>
<td>0 : 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] $\nu_{CO}$ (cm$^{-1}$) of Ni(CO)$_3$L in CH$_2$Cl$_2$
Analysis of the various properties of the phosphines revealed there is no correlation between product selectivity and the electronic properties of the ligand (Table 2). Carrying out the reaction with PtBu$_3$ as the ligand gave the same selectivity as PPh$_2$Me despite both ligands being electronically ($\nu$ CO) different. In fact, PPh$_2$Me has similar electronic properties to PPh$_3$ and P(pMeOC$_6$H$_4$)$_3$ but the selectivity obtained with PPh$_2$Me is reversed compared to the latter two phosphines. Furthermore, the selectivity observed with the ligand PtBu$_3$ is the same as with PPh$_2$Me despite the huge difference in cone angle between the two ligands. This illustrates that there is no correlation between the cone angle and product selectivity.

**Table 2 Comparison**

<table>
<thead>
<tr>
<th></th>
<th>PtBu$_3$</th>
<th>PPh$_2$Me</th>
<th>PPh$_3$</th>
<th>P(pMeOC$_6$H$_4$)$_3$[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu$ CO (cm$^{-1}$)</td>
<td>2056.1</td>
<td>2067.0</td>
<td>2068.9</td>
<td>2066.1</td>
</tr>
<tr>
<td>Cone angle ($\theta$)</td>
<td>182</td>
<td>136</td>
<td>145</td>
<td>145[a]</td>
</tr>
<tr>
<td>Conversion (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

[a] assumed that para-substitution will have no effect on the cone angle
Bidentate ligand, dppe (Table 1, Entry 14) proved to be ineffective. However, dppb (Table 1, Entry 15) displayed some reactivity with complete selectivity towards 6a. A much more rigid bidentate ligand, Xantphos (Table 1, Entry 16), was found to be ineffective. Hemi labile ligand, L4 (Table 1, Entry 17) was also ineffective. None of the NHCs tested led to the formation of an active catalyst (Table 1, entry 18 and 19). Despite P(ortho-MeOC₆H₄)₃ and P(ortho-CF₃C₆H₄)₃ displaying slightly better selectivity towards 6a, PPh₃ was chosen for the subsequent solvent screening since it is a much cheaper ligand.

A screening of anhydrous solvents was then carried out with PPh₃ as ligand to optimise the formation of 6a (Table 3). Carrying out the reaction in toluene (Table 3, Entry 1) resulted in little selectivity. However, carrying out the reaction in dioxane (Table 3, Entry 2) increased the selectivity for 6a. However, using MeCN (Table 3, Entry 3) showed better selectivity for 8 and 1, 2-DCE (Table 3, Entry 4) gave no conversion.

Table 3 Initial anhydrous solvent screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion</th>
<th>6a/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Toluene</td>
<td>100%</td>
<td>59 : 41</td>
</tr>
<tr>
<td>2.</td>
<td>Dioxane</td>
<td>93%</td>
<td>91 : 9</td>
</tr>
<tr>
<td>3.</td>
<td>MeCN</td>
<td>100%</td>
<td>33 : 67</td>
</tr>
<tr>
<td>4.</td>
<td>1, 2-DCE</td>
<td>0%</td>
<td>0 : 0</td>
</tr>
</tbody>
</table>

During the study of alkyne insertion into cyclobutanones, Murakami and co-workers reported that 3 equivalents of alkyne were sometimes necessary in order to compensate for alkyne
oligomerisation. Therefore, with dioxane as solvent, a study was commenced to determine the optimal loading of alkyne (Table 4). In our study, lowering the alkyne stoichiometry from 3 equivalents (Table 4, Entry 1) to 1.5 equivalents (Table 4, Entry 2) resulted in only a slight decrease in selectivity for 6a but with a better isolated yield. Reducing the loading of alkyne to 1.1 equivalents (Table 4, Entry 3) resulted in a further slight decrease in selectivity for 6a but with a similar isolated yield. However, a loading of 1.5 equivalents of alkyne was used in further screening as it was a low alkyne loading with good selectivity towards 6a.

**Table 4 Alkyne loading screening in dioxane**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne (eq.)</th>
<th>Conversion</th>
<th>6a/8</th>
<th>Yield of 6a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>96%</td>
<td>91 : 9</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>100%</td>
<td>86 : 14</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>100%</td>
<td>83 : 17</td>
<td>78</td>
</tr>
</tbody>
</table>

Afterwards, the solvent screen was resumed with a loading of 1.5 equivalents of alkyne (Table 5). Using 2-pentanone (Table 5, Entry 1) led to a good selectivity towards 8 but, c-pentanone (Table 5, Entry 2) displayed poor selectivity for either 6a or 8. Both 2-MeTHF (Table 5, Entry 3) and 1,2-DME (Table 5, Entry 4) led to a good selectivity towards 8. However, THF (Table 5, Entry 5) started to re-orientate the selectivity towards 6a. MTBE (Table 5, Entry 6) led to a good selectivity towards 6a. However, no solvent that was screened was able to match or exceed the performance of dioxane in orientating the selectivity towards 6a. It is noteworthy that most of the solvents used in this second screening were used directly from bottles exposed to air and moisture. Hence, it was thought "wet" solvents might display better
selectivity towards 8. When “wet” dioxane (Table 5, Entry 7) was used, lower selectivity towards 6a was observed.

**Table 5** Further solvent screen with 20 mol% PPh₃

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion</th>
<th>6a/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2-pentanone*</td>
<td>&gt;95%</td>
<td>24   : 76</td>
</tr>
<tr>
<td>2.</td>
<td>c-Pentanone*</td>
<td>&gt;95%</td>
<td>40   : 60</td>
</tr>
<tr>
<td>3.</td>
<td>2-MeTHF*</td>
<td>&gt;95%</td>
<td>19   : 81</td>
</tr>
<tr>
<td>4.</td>
<td>1,2-DME*</td>
<td>&gt;95%</td>
<td>29   : 71</td>
</tr>
<tr>
<td>5.</td>
<td>THF</td>
<td>&gt;95%</td>
<td>56   : 44</td>
</tr>
<tr>
<td>6.</td>
<td>MTBE*</td>
<td>&gt;95%</td>
<td>75   : 25</td>
</tr>
<tr>
<td>7.</td>
<td>Dioxane*</td>
<td>&gt;95%</td>
<td>71   : 29</td>
</tr>
</tbody>
</table>

* wet solvents used

A study on the stoichiometry and ratio of Ni(cod)₂/PPh₃ was carried out in anhydrous dioxane (Table 6). Carrying out the reaction with 5 mol% Ni(cod)₂ and 10 mol% PPh₃ (Table 6, Entry 1) or 5 mol% Ni(cod)₂ and 10 mol% PPh₃ (Table 6, Entry 2) gave incomplete conversion. Changing the stoichiometry of PPh₃ with respect to Ni(cod)₂ (Table 6, Entry 3-6) revealed that selectivity for 6a is optimal when the stoichiometry of PPh₃ is greater than 20 mol% with respect to 10 mol% Ni(cod)₂ with isolated yields greater than 69%. As expected, with 10 mol% Ni(cod)₂ and 20 mol% PPh₃, reducing the alkyne loading from 1.5 equivalents to 1.1 equivalents (Table 6, Entry 4 vs 7) reduced the selectivity towards 6a. However, when the loading of PPh₃ was then increased to 30 mol% (Table 6, Entry 8), the selectivity towards 6a is very high with an average
isolated yield of 81%. In the end, further optimisation towards 6a was carried out with 10 mol% Ni(cod) and 30 mol% PPh3.

Table 6 Study on the influence of stoichiometry

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne (eq.)</th>
<th>Ni (mol %)</th>
<th>PPh3 (mol %)</th>
<th>Conversion</th>
<th>6a/8</th>
<th>Yield of 6a (%)[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.5</td>
<td>5</td>
<td>10</td>
<td>18%</td>
<td>100 : 0</td>
<td>100</td>
</tr>
<tr>
<td>2.</td>
<td>1.5</td>
<td>5</td>
<td>15</td>
<td>0%</td>
<td>0 : 0</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>1.5</td>
<td>10</td>
<td>10</td>
<td>93%</td>
<td>81 : 19</td>
<td>81</td>
</tr>
<tr>
<td>4.</td>
<td>1.5</td>
<td>10</td>
<td>20</td>
<td>&gt;95%</td>
<td>83 : 17</td>
<td>83</td>
</tr>
<tr>
<td>5.</td>
<td>1.5</td>
<td>10</td>
<td>30</td>
<td>&gt;95%</td>
<td>87 : 13</td>
<td>87</td>
</tr>
<tr>
<td>6.</td>
<td>1.5</td>
<td>10</td>
<td>40</td>
<td>&gt;95%</td>
<td>91 : 9</td>
<td>91</td>
</tr>
<tr>
<td>7.</td>
<td>1.1</td>
<td>10</td>
<td>20</td>
<td>&gt;95%</td>
<td>78 : 22</td>
<td>78</td>
</tr>
<tr>
<td>8.</td>
<td>1.1</td>
<td>10</td>
<td>30</td>
<td>&gt;95%</td>
<td>90 : 10</td>
<td>90</td>
</tr>
</tbody>
</table>

[^a]Isolated yield of an average of 2-3 runs

Lowering the concentration from 0.22M to 0.1M resulted in incomplete conversion and increasing the concentration had no effect over the timescale of the reaction. Therefore, the concentration used in the subsequent optimisations was kept at 0.22M.

Temperature effects were then studied (Table 7). Increasing the temperature to 120°C gave virtually identical results to that obtained at 100°C (Table 7, Entry 1 vs 2). With dioxane, variable conversions were obtained when the temperature was lowered to 80°C (Table 7, Entry 3 and 4). With 2-pentanone (Table 7, Entry 5 and 6), variable conversions were also obtained but the selectivity towards 6a is much higher suggesting that the formation of 8 is a
higher energy pathway. Carrying out the reaction in dioxane and at 90°C allowed for a high selectivity towards 6a (Table 7, Entry 7 and 8). When 20% of PPh$_3$ was used (Table 7, entry 7), an isolated yield of 84% of 6a was obtained. A 90% isolated yield of 6a was obtained when 30% PPh$_3$ (Table 7, entry 8) was used.

**Table 7** Temperature effects on C–C activation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>5a (eq.)</th>
<th>PPh$_3$ (mol %)</th>
<th>Solvent</th>
<th>Conv.</th>
<th>6a/8</th>
<th>Yield of 6a (%)$^{[a]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>100</td>
<td>1.5</td>
<td>30</td>
<td>Dioxane</td>
<td>&gt;95%</td>
<td>91 : 9</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>120</td>
<td>1.5</td>
<td>30</td>
<td>Dioxane</td>
<td>&gt;95%</td>
<td>91 : 9</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>80</td>
<td>1.5</td>
<td>30</td>
<td>Dioxane</td>
<td>&gt;95%</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>80</td>
<td>1.5</td>
<td>30</td>
<td>Dioxane</td>
<td>63%$^{[b]}$</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>80</td>
<td>1.5</td>
<td>30</td>
<td>2-Pentanone</td>
<td>71%</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>80</td>
<td>1.5</td>
<td>30</td>
<td>2-Pentanone</td>
<td>&gt;95%$^{[b]}$</td>
<td>83 : 17</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>90</td>
<td>1.1</td>
<td>20</td>
<td>Dioxane</td>
<td>&gt;95%</td>
<td>94 : 6</td>
<td>84</td>
</tr>
<tr>
<td>8.</td>
<td>90</td>
<td>1.1</td>
<td>30</td>
<td>Dioxane</td>
<td>&gt;95%</td>
<td>&gt;95 : &lt;5</td>
<td>90</td>
</tr>
</tbody>
</table>

$^{[a]}$ Isolated yield of an average of 2-3 runs; $^{[b]}$ reaction left over the weekend

Attempts to use Ni(PPh$_3$)$_2$Cl$_2$/Zn instead of Ni(cod)$_2$ proved unsuccessful, giving only unreacted starting material or trace formation of 3. Ni(PPh$_3$)$_4$ also failed to give any reaction. Blank tests without Ni(cod)$_2$ and without both Ni(cod)$_2$ and PPh$_3$ resulted in no conversion therefore confirming it is a Ni-catalysed reaction. Therefore, the optimised condition was set at 10 mol% Ni(cod)$_2$, 30 mol% PPh$_3$ in dioxane at 90°C. The azetidinone and alkyne were added sequentially after the formation of the active catalyst.
2.3 Scope of the reaction

2.3.1 Cycloaddition of N-Boc Azetidinone with alkynes

With the optimised reaction condition in hand, the scope of the reaction was examined (Table 8). The insertion of symmetrical alkynes diphenylacetylene 5a and 4-octyne 5b into azetidinone 7 proceeded in high yields to give 6a and 6b respectively. With unsymmetrical alkyne, the insertion of 1-phenyl-1 propyne 5c proceeded with good regioselectivity as determined from isolated yields of 6c and 11c. Furthermore, the isomers were easily separable by standard flash column chromatography. The regioselectivity of insertion of other non-symmetrical alkynes 5d – 5i was good. However, the reactivity of non-symmetrical alkynes 5h and 5i was not initially reproducible. However, the addition of a solution of both azetidinone 7 and the alkyne in dioxane (0.29 mM) gave reproducible results. Furthermore, despite the increase of the steric bulk on the alkyl substituent (Table 8, entries 8 and 9), only a small erosion of the regioselectivity was observed. The regiochemistry of all isomers was determined by NOESY and HMBC experiments (Scheme 4).

\[ \text{Scheme 4 NOESY experiments} \]

The results obtained with alkynes 5e and 5g suggest that electronic differentiation had little influence on the regioselectivity. This was confirmed with the reaction involving 5j. On this substrate, both substituents of the alkyne were differentiated only electronically and displayed identical steric hindrance. The two isomers 6k and 11k were not separable by
column chromatography but from crude NMR, the regioisomers ratio was established as almost equimolar. Comparison of alkynes 5k and 5l, revealed that the increase of steric differentiation between the substituents resulted in improved regioselectivity.

**Table 8 Alkyne scope**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne 5</th>
<th>Major Product 6</th>
<th>Ratio (6/11)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="5a" /></td>
<td><img src="image2" alt="6a" /></td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="5b" /></td>
<td><img src="image4" alt="6b" /></td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="5c" /></td>
<td><img src="image6" alt="6c" /></td>
<td>87 : 13</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="5d" /></td>
<td><img src="image8" alt="6d" /></td>
<td>91 : 9</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="5e" /></td>
<td><img src="image10" alt="6e" /></td>
<td>89 : 11</td>
<td>89</td>
</tr>
</tbody>
</table>
Unless otherwise stated, this ratio was determined from the isolated yields of separated regioisomers 6 and 11. [b] Combined isolated yields of 6 and 11. [c] Alkyne and Azetidinone were premixed. [d] Ratio determined by $^1$H NMR spectroscopy on an inseparable mixture of 6 and 11. [e] Yield of major isomer.
By comparison of the experimental results of nickel-catalysed reductive coupling of simple internal alkynes (alkyl-C≡C-alkyl and alkyl-C≡C-aryl) and aldehydes, the regioselectivities that were obtained followed the same trend as the results we obtained.\textsuperscript{5} Jamison and co-workers reported the nickel-catalysed reductive coupling of alkyne 5c with aldehyde 12 (Scheme 5).\textsuperscript{5f} The coupling proceeded with a similar regioselectivity as the insertion of alkyne 5c into azetidinone 7. Furthermore, the major isomer has the Me group appear nearest to the C(O)–C bond.

![Scheme 5](image)

**Scheme 5** Comparison of our result with the result reported by Jamison

Furthermore, computation studies of nickel-catalysed reductive couplings of simple alkynes and aldehydes revealed the energy of the transition states are affected by the orientation of the alkyne (Scheme 6).\textsuperscript{6} It was calculated that transition state 19a is lower than transition state 19b purely because of steric effects. This study suggests the steric repulsion between the alkyne substituent and the aldehyde is more influential than between the alkyne substituent and the nickel-phosphine catalyst in the oxidative cyclisation step. Due to the greater steric repulsion between the alkyne substituent and the aldehyde, the lowest transition state has the smallest alkyne substituent next to the aldehyde. Therefore, this subtle difference would then explain why some alkynes added onto the aldehyde with good regioselectivity.
Therefore, from the work done on nickel-catalysed reductive couplings of simple internal alkynes and aldehydes, we proposed the regioselectivity of the insertion of alkynes 5c-5l are determined by the steric differentiation between the substituents of the alkyne.

For the mechanism, we propose that prior to the oxidative cyclisation, the alkyne has two orientations whereby the small alkyne substituent in 21 or the large alkyne substituent in 24 can be in proximity to the azetidinone (Scheme 7). For the major regioisomer, the minimisation of the steric interaction between the Boc protective group on the azetidinone and the large alkyne substituent would afford metallacycle 22. Ring enlargement by β-C elimination would then afford nickelahexacycle 23. Finally, reductive elimination would afford product 6.
There appears to be some correlation between regioselectivity and steric differentiation (Scheme 8). A-values are derived from the energy for the interconversion of a monosubstituted cyclohexane ring and these values can be used as a measure of the steric bulk of a substituent.\(^7\) Comparison of the difference in A-value for alkyne 5k, 5c and 5l indicates that the greater the difference, the better the regioselectivity. However, comparison of alkyne 5c and 5h suggests the regioselectivity is not completely influenced by the steric differentiation between the two substituents. Both have a phenyl group conjugated to the alkyne and therefore, the phenyl group could behave as a directing group.

**Scheme 7** Steric differentiation to explain the formation of the regioisomer

**Scheme 8** Correlation between regioselectivity and steric differentiation
Furthermore, insertion of 1,3-enynes into azetidinone 7 proceeded successfully (Table 9). Enyne 5m was found to insert with good regioselectivity which suggests the alkene moiety can behave as a directing group. However, enyne 5n was found to insert with poor regioselectivity which suggests both the alkene and the aryl substituent can complete as a directing group. This could also explain why the insertion of alkynes 5c–5i proceeded with near consistent regioselectivity. Furthermore, both directing groups appear to be able to over-ride or minimise any steric influences.

**Table 9** Insertion of 1,3 enyne

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne 5</th>
<th>Major Product 6</th>
<th>Ratio (6 : 11)[a]</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{5m})</td>
<td>(\text{6m})</td>
<td>88 : 12</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>(\text{5n})</td>
<td>(\text{6n})</td>
<td>60 : 40</td>
<td>86[c]</td>
</tr>
</tbody>
</table>

[a] Unless otherwise stated, this ratio was determined from the isolated yields of separated regioisomers 6 and 11. [b] Combined isolated yields of 6 and 11. [c] Ratio determined by \(^1\)H NMR spectroscopy on an inseparable mixture of 6 and 11.

According to a computational study, the insertion of 1,3-enynes into aldehydes could proceed via one of three pathways (Scheme 9). From the modelled example of the reductive coupling of 1, 3-butynylene and acetaldehyde, the oxidative cyclisation is the rate determining step.
Coupling at the alkene was calculated to have a high activation energy. By comparison, coupling at the alkyne was calculated to be lower in energy. Pathway A is the 1,4 attack to enyne. Pathway B is the 1,2 attack to enyne. Finally, pathway C is the 1,2 attack to enyne to form the minor regioisomer. It is calculated the activation energy to the transition state in pathway A is the lowest out of the three pathways. Furthermore, it is calculated the extra $\eta^3$-allyl/metal interaction in pathway A lowers the energy of the transition state. Interestingly, the authors reported that the activation energy barrier for coupling with 1,3 enynes is lower than coupling with simple alkynes. Therefore, 1,3 enynes should be more reactive as a coupling partner.

**Scheme 9** Theoretical study of the nickel-catalysed reductive coupling of 1,3-enzyme with aldehydes
Therefore, based on the computational study, enyne 5n or 5m will first form complex 27 whereby the alkene or aryl will coordinate to the nickel metal centre (Scheme 10). Then oxidative cyclisation would occur to give metallacycle 28 which subsequently would undergo β-C elimination to give metallacycle 29. Then reductive elimination would afford pyridinone 6 as the major isomer with the vinyl group in the β-position to the carbonyl.

**Scheme 10** Directing group effects to explain the formation of the major regioisomer

Experimental results of the reductive coupling of enynes with aldehydes also proceeded with similar regioselectivities if the other alkyne substituent is an alkyl group. When the other alkyne substituent is an aryl group, the regioselectivity tended to be better rather than worse. To exemplify this, Montgomery and co-workers reported a nickel catalysed reductive coupling of enyne 30 and aldehyde 31 which proceeded in an excellent regioselectivity (Scheme 11) whereas with the nickel-catalysed cycloaddition developed in this thesis, the insertion of 5n into 7 proceeded with poor regioselectivity (Scheme 12).

**Scheme 11** Nickel catalysed reductive couplings of enyne and aldehyde
The reaction of silylated alkynes was unexpected as none worked in the nickel-catalysed insertion into cyclobutanone as reported by Murakami and co-workers. However, insertion of alkyne $5o$ proceeded in a high yield and with excellent regioselectivity. Even with a larger silyl group $5p$, the insertion still proceeded in an excellent yield and regioselectivity. Slightly diminished regioselectivity of the insertion was observed with alkyne $5q$. It appears that if an aryl group is conjugated to the silylated alkyne, the directing group effect of the aryl group and the preference of the silicon being in the $\alpha$-position will make the insertion more regioselective. However, insertion of alkyne $5r$ and $5s$ failed to take place.
Table 10 Silylated alkyne scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne 5</th>
<th>Major Product 6</th>
<th>Ratio 6 / 11&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>Yield 6 (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="5o" /></td>
<td><img src="image2" alt="6o" /></td>
<td>97 : 3</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="5p" /></td>
<td><img src="image4" alt="6p" /></td>
<td>97 : 3</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="5q" /></td>
<td><img src="image6" alt="6q" /></td>
<td>80 : 20&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>78&lt;sup&gt;[d]&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="5r" /></td>
<td><img src="image8" alt="6r" /></td>
<td>n / a</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="5s" /></td>
<td><img src="image10" alt="6s" /></td>
<td>n / a</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Unless otherwise stated, this ratio was determined from the isolated yields of separated regioisomers 6 and 11.  
<sup>[b]</sup> Combined isolated yields of 6 and 11.  
<sup>[c]</sup> Ratio determined by <sup>1</sup>H NMR spectroscopy on an inseparable mixture of 6 and 11.  
<sup>[d]</sup> 1.5 equiv. of alkyne was used.

Furthermore, the nickel-catalysed reductive coupling reactions with silylated alkynes generally proceeded with better regioselectivity when compared to the more simple alkynes. As a
representative example, Jamison and co-workers reported the reductive coupling of alkynes 5 with aldehydes 34 to afford allylic alcohol 35 proceeded with superior regioselectivities when silylated alkynes are used (35b and 35d) compared to when 1-phenyl-1-propyne is used (35a and 35c) (Scheme 13).\textsuperscript{5b}

\textbf{Scheme 13} Comparison of the reductive coupling of silylated and simple alkynes with aldehydes

The principles used to explain the regioselectivity outcome are different with silylated alkynes. By looking at the axial strain values and comparing the outcome between the alkyne insertion of 5k and 5o revealed that steric differentiation was more or less irrelevant with respect to silylated alkynes (Scheme 14). If steric differentiation was important, insertion of alkyne 5k should have proceeded with better regioselectivity than alkyne 5o.

\textbf{Scheme 14} Axial strain values
Therefore, electronic effects are likely to be the prevalent factor in the highly regioselective insertion of silylated alkynes. Nickel-alkynes complexes have been studied extensively.\textsuperscript{10} The \textsuperscript{13}C NMR of a nickel-silylated alkyne complex \textbf{36} shows there is a large chemical shift difference between the two carbons of the coordinated alkyne which reveals the alkyne is significantly polarised. Compared to 1-phenyl-1-propyne, the chemical shift difference between the two coordinated alkyne carbons of complex \textbf{37} is significantly smaller as judged by \textsuperscript{13}C NMR (Scheme 15). The greater polarisation in silylated alkynes might facilitate the proposed oxidative cyclisation step and its direction appears to dictate the regioselectivity.

![Scheme 15 Polarisation exhibited in known nickel alkyne complexes](image)

2.3.2 Limitations

2.3.2.1 Terminal Alkynes

Terminal alkynes \textbf{38} and \textbf{39} were ineffective in the reaction (Scheme 16). It is believed that the cyclotrimerisation pathway is also operating. Regardless, there are examples of nickel-catalysed reactions whereby a terminal alkyne has been successfully incorporated.\textsuperscript{5a,e,h,11} Furthermore, Kumar and Louie reported a successful insertion of \textit{tert}-butylacetylene \textbf{40} into azetidinone \textbf{7} under modified reaction conditions (Scheme 17).\textsuperscript{12} The requirement of an increased loading of alkyne was necessary due to competing co-oligomerisation. Furthermore, slow addition of the alkyne and a reaction temperature of 100°C were necessary. The successful insertion of \textit{tert}-butylacetylene might be imputed to size of the \textit{tert}-butyl substituent...
on the acetylene which makes it harder for another acetylene molecule to coordinate to the metal centre.

Scheme 16 Terminal alkynes attempted

Scheme 17 Kumar and Louie example

2.3.2.2 Alkynyl pyridines

No reaction was observed when an alkyne conjugated to a pyridine was used (Scheme 18). Furthermore, there are examples in the literature of substrates containing heterocyclic moieties which were tolerated in nickel-catalysed reactions (Scheme 19). The success of these reactions suggest that the pyridine on alkyne 43 and 44 makes the alkyne more electron poor and as a result will bind stronger to the nickel centre and render the desired catalytic pathway inactive. Alternatively, the pyridine could coordinate to the nickel-catalyst and render the catalyst inactive.

Scheme 18 Alkynes conjugated to a pyridine attempted
2.3.2.3 Electron-deficient alkynes

Electron deficient alkynes 45 – 47 were then examined (Scheme 20). However, the formation of the desired six-membered ring was never observed. This is likely due to the stronger binding of electron deficient alkynes to the nickel centre. Interestingly, there is a report of a nickel catalysed alkynoate insertion. Montgomery and co-workers reported the reductive coupling of enone 48 and alkynoate 49 which was carried out at room temperature to give ketone 50 as the major regioisomer (Scheme 21). Large excess of 49 was not required nor was careful control of reagent addition necessary. Surprisingly, no homocoupling products were observed.

Scheme 20 Alkyne conjugated to electron withdrawing functional group

Scheme 21 Successful nickel catalysed coupling of enone and alkynoate
2.3.2.4 Alkynyl boronate esters

Alkynyl boronate esters were then studied (Scheme 22). With alkyne 5t, the insertion into 7 took place with 73% conversion. Product 6t that was isolated identified to have had the pinacolborane moiety cleaved off and was isolated in a yield of 44%. Attempts to insert alkyne 5u into azetidinone 7 were unsuccessful.

\[
\text{Scheme 22 Studied of alkynyl boronate esters}
\]

2.3.2.5 Propargyl ethers

Non-symmetrical propargyl ethers were then examined (Table 11). No asymmetrical propargyl alkynes (Table 11, Entry 1-3) were found to successfully insert into azetidinone 7. When the propargyl oxygen atom was replaced with a methine (Table 11, Entry 1 vs 4), there was full conversion with an isolated yield of 72% but with poor regioselectivity. Homologation of the carbon chain between the alkyne and the oxygen (Table 11, Entry 5) resulted in reactivity. Unfortunately, poor regioselectivity was observed. These results suggest oxygen is a poor directing group.
Table 11 Alkynes with a heteroatom

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne 5</th>
<th>Major Product 6</th>
<th>Ratio (6/11)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Alkyne 5" /></td>
<td><img src="#" alt="Major Product 6" /></td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td><img src="#" alt="Alkyne 5" /></td>
<td><img src="#" alt="Major Product 6" /></td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Alkyne 5" /></td>
<td><img src="#" alt="Major Product 6" /></td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td><img src="#" alt="Alkyne 5" /></td>
<td><img src="#" alt="Major Product 6" /></td>
<td>58 : 42</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td><img src="#" alt="Alkyne 5" /></td>
<td><img src="#" alt="Major Product 6" /></td>
<td>55 : 45</td>
<td>91%</td>
</tr>
</tbody>
</table>

However, Jamison and co-workers reported a nickel-catalysed coupling of non-symmetrical propargylic ether 51 with aldehydes 52 to afford allylic alcohol 53 at -25°C (Scheme 23). This result indicates that the ligand or the reaction temperature could be influential factors.
Scheme 23 Nickel-catalysed reductive coupling of aldehyde 52 and propargyl ether 51

A competition experiment was then carried out to determine if the catalytic system is rendered inactive by propargyl ethers (Scheme 24). Previously, the insertion of 4-octyne 6b into 7 proceeded in an excellent yield. However, no reaction occurred when 0.55 equivalent of 4-octyne 5b was added to the nickel catalyst, 7 and 0.55 equivalent of alkyne 5v. Even when the loading of both alkynes were increased to 1.1 equivalent, there was still no reaction. Therefore, propargyl ethers might bind more strongly to the nickel-catalyst than 4-octyne 5b and render the catalyst inactive.

Scheme 24 Competition experiment

Due to the lack of reactivity with propargyl ether 5v, it was of interest to see if another transition metal catalytic system could effect the insertion (Table 12). However, no catalytic systems examined were successful. However, the temperature of the reaction was likely to be too low as there are reports of several rhodium catalysed C–C bond cleavage of four-membered rings which require a higher temperature.14
Table 12 Attempted insertion of alkyne 5v into azetidinone 7

![Chemical Image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Ligand (mol%)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$dba$_3$ (5)</td>
<td>PPh$_3$ (20)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(CO)$_2$Cl]$_2$ (5)</td>
<td>none</td>
<td>Decomp</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(CO)$_2$Cl]$_2$ (5)</td>
<td>PPh$_3$ (20)</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(CO)$_2$Cl]$_2$ (5)</td>
<td>dppp (10)</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)$_2$]BF$_4$ (10)</td>
<td>none</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Out of curiosity, it was of interest to then see if propargylic ether 5w could insert into azetidinone 7 (Table 13). Due to the lack of reactivity with propargylic ether 5v by a nickel catalyst, it was of interest to see if another transition metal could catalyst the insertion of silylated equivalent 5w into 7. However, a brief screen of different catalytic systems revealed no catalytic system could effect successful [4+2] cycloaddition.

Table 13 Attempted insertion of alkyne 5w into azetidinone 7

![Chemical Image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Ligand</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru$<em>3$(CO)$</em>{12}$</td>
<td>none</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Ru$<em>3$(CO)$</em>{12}$</td>
<td>PPh$_3$</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>2xPPh$_3$</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)$_3$</td>
<td>none</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
The insertion of propargylic ethers 5aa into azetidinone 7 was then studied (Scheme 25). Carrying out the reaction with an increased loading of catalyst and at a lower reaction temperature gave rise to a regioselective insertion of alkyne 5aa into azetidinone 7 to form 6aa. Furthermore, another product 54 was formed from the cleavage of the Boc-group.

Attempts to reduce the loading of catalyst were then carried out by Jet-Sing Lee (Table 14). Reattempting the reaction with the increased loading of catalyst (Table 14, Entry 1) reproduced the initial result. When the loading of catalyst was reduced, no formation of the cleaved product 54 was observed. Instead, the other regioisomer 11aa was observed and both isomers were isolated in a ratio of 50:50 (Table 14, Entry 2). With PPh$_3$ (Table 14, Entry 3), the selectivity towards 6aa improved. Changing the solvent to dioxane (Table 14, Entry 4) did make a difference to the outcome. Changing the ligand to 30 mol% of PPh$_2$Cy (Table 14, Entry 5) and carrying the reaction out in dioxane improved the selectivity towards 6aa a little. However, with 30 mol% PPhCy$_2$ as ligand (Table 14, Entry 6) in dioxane slightly reduced the selectivity towards 6aa and suffered from poor reactivity.
Table 14 Catalytic loading screen

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni (mol %)</th>
<th>L (mol %)</th>
<th>Temp (°C)</th>
<th>(6aa/11aa)</th>
<th>Yield (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>Yield 54 (%)&lt;sup&gt;[c]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>PPhCy&lt;sub&gt;2&lt;/sub&gt; (90)</td>
<td>70</td>
<td>100 : 0</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>PPhCy&lt;sub&gt;2&lt;/sub&gt; (30)</td>
<td>70</td>
<td>50 : 50</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt; (30)</td>
<td>60</td>
<td>69 : 31</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>4&lt;sup&gt;[d]&lt;/sup&gt;</td>
<td>10</td>
<td>PPh&lt;sub&gt;3&lt;/sub&gt; (30)</td>
<td>60</td>
<td>68 : 32</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>5&lt;sup&gt;[d]&lt;/sup&gt;</td>
<td>10</td>
<td>PPh&lt;sub&gt;2&lt;/sub&gt;Cy (30)</td>
<td>60</td>
<td>72 : 28</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>6&lt;sup&gt;[d]&lt;/sup&gt;</td>
<td>10</td>
<td>PPhCy&lt;sub&gt;2&lt;/sub&gt; (30)</td>
<td>60</td>
<td>64 : 36</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Ratio determine by <sup>1</sup>H NMR of the crude material; [b] Combined isolated yield of 6aa and 11aa; [c] Isolated yield; [d] in dioxane

2.3.2.6 Miscellaneous alkynes

Several other alkynes were then tested and were found to remain inert or decomposed under the optimised conditions (Scheme 26). Propargyl alcohols 55-58 were ineffective. Ynamides 59 and 60 were unproductive. Alkynol 61 also failed to insert. Halogen directly attached to the alkyne 62 or an alkyne with the halogen further along a tether 63 failed to give rise to the desired 6-membered ring. However, there have been examples in the literature of nickel-catalysed reactions whereby chloro<sup>15</sup>, protected alcohol,<sup>15</sup> mono-protected amines<sup>5f</sup> functional groups are tolerated. An example of this is the report by Liebeskind and Huffman on a nickel-catalysed annulation of cyclobutenones 64 with alkynes 65 to form phenols 66 (Scheme 27).<sup>15</sup>
Scheme 26 Ineffective alkynes

\[
\begin{align*}
&\text{O} \quad \text{AcO} \quad \text{OAc} \quad \text{BnO} \quad \text{OBN} \quad \text{TBSO} \quad \text{OTBS} \\
55 &\quad 56 &\quad 57 &\quad 58 \\
\end{align*}
\]

\[
\begin{align*}
&\text{Ph} \quad \text{N} \quad \text{Ts} \quad \text{Bn} \quad \text{Et} \\
59 &\quad 60 &\quad 61 \\
\end{align*}
\]

\[
\begin{align*}
&\text{MeO} \quad \text{Cl} \\
62 &\quad 63 \\
\end{align*}
\]

**Scheme 26** Ineffective alkynes

\[
\begin{align*}
\text{R}^1 \text{R}^2 &\quad \text{R}^3 \text{R}^4 \\
64 &\quad 65 \\
\text{OH} &\quad \text{OH} \\
66 &\quad 67 \\
\end{align*}
\]

**Scheme 27** Nickel-catalysed reaction that tolerated hetero-functionality on the alkyne

### 2.3.3 Cycloaddition of N-Benzhydryl azetidinone 76 with alkyne 5b

The insertion of alkyne 5b into azetidinone 67 was then examined (Scheme 28). However, no reactivity was observed with our optimised reaction conditions. In 2012, Murakami and co-workers examined this reaction and reported a 82% isolated yield of the desired pyridinone 68 when carried out with 10 mol% Ni(cod)$_2$, 20 mol% PCy$_3$ and in toluene at room temperature.$^{16}$

\[
\begin{align*}
\text{O} &\quad \text{Ph} \quad \text{Ph} \\
67 &\quad 5b \\
\text{OH} &\quad \text{OH} \\
68 &\quad 69 \\
\end{align*}
\]

**Scheme 28** Insertion of azetidinone 67
2.3.4  Cycloaddition of N-Ts Azetidinones with alkynes

Harsher conditions were required when N-Ts-azetidinone 69 was used in the place of N-Boc-Azetidinone 7 for full conversion (Table 15). Insertion of alkyne 5b proceeded in good yields in 1 hour. Insertion of alkyne 5c required a higher catalyst loading and proceeded with a lower regioselectivity. The higher temperature might explain the poorer outcome in regioselectivity.

**Table 15** Screen with N-Ts-azetidinone 69

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Major Product 70</th>
<th>Ratio (70/71)</th>
<th>Yield[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="synonym" alt="5b" /></td>
<td><img src="synonym" alt="70b" /></td>
<td><img src="synonym" alt="73" /></td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td><img src="synonym" alt="5c" /></td>
<td><img src="synonym" alt="70c" /></td>
<td>83 : 17</td>
<td>75[^b]</td>
</tr>
</tbody>
</table>

[^a]: combined isolated yield.  
[^b]: 20 mol% Ni(cod)$_2$, 80 mol% PPh$_3$, 1.5 equiv. of 2b, dioxane, 100°C.

The reaction also worked with α-substituted azetidinones 72 (Table 16). Insertion of symmetrical alkynes 5a and 5b proceeded in excellent yields. In the cycloaddition to form 73b, the enantiomeric purity was slightly eroded with an ee of 97%. Good regioselectivity was observed in the insertion of alkyne 5c. Finally with silylated alkyne 5o, the regioselectivity was high but more decomposition was noted. Notably, the results in the regioselectivity were comparable to the results obtained with N-Boc-Azetidinone 7.
Table 16 α-substituted N-Ts-azetidinone

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Major Product 73[a]</th>
<th>Ratio (73/74)[b]</th>
<th>Yield (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Alkyne 5a" /></td>
<td><img src="image" alt="Product 73a" /></td>
<td>n/a</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Alkyne 5b" /></td>
<td><img src="image" alt="Product 73b" /></td>
<td>n/a</td>
<td>91[c]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Alkyne 5c" /></td>
<td><img src="image" alt="Product 73c" /></td>
<td>93 : 7</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Alkyne 5o" /></td>
<td><img src="image" alt="Product 73o" /></td>
<td>&gt;95 : 5</td>
<td>71[d]</td>
</tr>
</tbody>
</table>

[a] 72 has an ee of >99% as determined by HPLC. [a] Unless otherwise stated, this ratio was determined from the isolated yields of separated regioisomers 73 and 74. [b] Combined isolated yields of 73 and 74. [c] ee of product is 97% as determined by HPLC. [d] Only 73o was isolated.

The principles discussed to explain the regioselectivity of the alkyne insertion into N-Boc-azetidinone 7 appears to be equally applicable here. After the oxidative cyclisation to form intermediate 75, the ring opening proceeded exclusively with the least sterically hindered C–C
bond broken to form intermediate 78 rather than intermediate 77 (Scheme 29). Finally, reductive elimination would afford product 73 as the major isomer.

Scheme 29 C–C cleavage of the least sterically hindered C–C bond

The insertion of 4-octyne 5b into azetidinone 79 proved to be unsuccessful as no reaction was observed. Large α-substitution appears to hinder the reaction. However, Murakami and co-workers reported that after a slight modification to the reaction conditions, the insertion of alkyne 5l into azetidinone 81 proceeded with an isolated yield of 56% of pyridinone 82 (Scheme 31).16

Scheme 30 Failed insertion of alkyne 5b into azetidinone 79
Scheme 31 Insertion of alkyne 5l into azetidinone 81

The insertion of alkyne 5b into azetidinone 83 was then studied (Table 17). With PPh₃ as ligand (Table 17, Entry 1), trace amounts of pyridinone 84 was formed as judged from the ¹H NMR spectra of the crude. Attempts to use nitrogen based ligands (Table 17, Entry 2 and 3) did not give rise to the formation of 84.

Table 17 Attempted insertion of alkyne 5b into azetidinone 83

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>mol %</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃</td>
<td>30</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Phen</td>
<td>15</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Bipy</td>
<td>15</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

![Scheme 31](image-url)
2.3.5 Aromatisation to pyridinols

Several research groups have demonstrated the transformation of pyridinones to the corresponding pyridinols. However, no procedures were reported to deprotect the Boc group and aromatise the deprotected pyridinone to give the corresponding pyridinol. Aromatisation using DDQ as the aromatising agent was ineffective as no reaction occurred even after two nights at rt (Scheme 32). It was found acid hydrolysis of the Boc group of pyridine 6a give a mixture of 85a and 86a (Scheme 33). Complete consumption of 6a always occurs after 18 hrs and usually, mostly 86a is formed but the mixture ratio could never be reproduced. Therefore, it became of interest to force the formation towards 85a. A report on the use of NaNO₂ in the presences of wet SiO₂ as a aromatisation agent of 1,2-dihydroquinolines was reported. Consequently, a procedure was developed to successfully transform pyridinones 6a to the corresponding pyridinols 85 (Scheme 34). Firstly, acid hydrolysis of the Boc group followed by a NaNO₂ mediated aromatisation and subsequent neutralisation with triethylamine furnished the desired pyridinol 92 in a one pot process in good yields. Synthesis of 85d and 85o required another batch of NaNO₂ and allowed to stir for a further hour prior to quenching with Et₃N. For the synthesis of 85f, the solution was diluted with CH₃CN prior to addition of NaNO₂. The role of CH₃CN is currently unclear but it did allow the aromatisation to be carried out within 1 hour. Compounds 85f, 85h and 85o are not fully characterised in this thesis. Nonetheless, the examples given demonstrate the functional group tolerance of this methodology.

Scheme 32 Aromatisation with DDQ
Scheme 33 Initial attempts on aromatisation

Scheme 34 Aromatisation of pyridinones to corresponding pyridinols

2.3.6 Cycloaddition of oxetanones with alkynes

Using the same optimised conditions as those reported with \( N \)-Boc-azetidinone 7 allowed the insertion of alkyne 5 into commercially available 3-oxetanone 87 (Table 18). Insertion of alkyne 5a proceeded in high yields. Insertion of alkyne 5g proceeded with a lower regioselectivity when compared to the insertion of the same alkyne into \( N \)-Boc-azetidinone 7. The poorer regioselectivity might be due to the less steric hindrance of the oxygen of the oxetane when compared to the larger carbamoyl group of then \( N \)-Boc-azetidinone 7. Due to the different behaviour of silylated alkynes, alkyne 5o still proceeded with excellent regioselectivity.
**Table 18** Insertion of alkyne into oxetanone

\[
\text{O} \quad + \quad \text{R}^1 \quad \text{R}^2 \quad \text{Ni(cod), PPh}_3 \quad \text{dioxane, 90°C, 17 h} \quad \text{O} \quad \text{O}
\]

| Entry | Alkyne 5 | Major Product 88 | Ratio (88/89)
\text{[a]} | Yield (%) \text{[b]}
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>88a</td>
<td>n/a</td>
</tr>
<tr>
<td>2[c]</td>
<td>5g</td>
<td>88g</td>
<td>79 : 21</td>
</tr>
<tr>
<td>3</td>
<td>5o</td>
<td>88o</td>
<td>96 : 4</td>
</tr>
</tbody>
</table>

[a] Unless otherwise stated, this ratio was determined from the isolated yields of separated regioisomers 88 and 89.
[b] Combined isolated yields of 88 and 89.
[c] Alkyne and Azetidinone were premixed.

It was found that α-substituted oxetanone 90 underwent the nickel-catalysed cycloaddition, whereby the ring opening of the oxetanone proceeded with less regioselectivity. Products arising from the C–C cleavage of both the least and the most sterically bonds were isolated under the standard reaction conditions. The insertion of 4-octyne 5b into 90 with the optimised reaction condition proceeded to give two isomers 91 and 92 in a 4:1 ratio with 32% recovered starting material (Table 19, entry 1). On increasing the catalytic loading to 20 mol% Ni(cod)₂ and 40 mol% PPh₃, the conversion was complete with an isolated yield of 70% of 91 and 14% yield of 92 (Table 19, entry 2). The insertion of diphenylacetylene 5a into 90 was then
studied with the higher catalyst loading of 20 mol% Ni(cod)$_2$ and 40 mol% PPh$_3$. An isolated yield of 42% of 93 and combined mass recovery of 33% which contained 94 and recovered 90 was achieved (Scheme 35). Due to the difficulty in separating 94 from 90, no characterisation of 94 was carried out. The lower reactivity with 5a might be imputed to the lower reactivity of 5a in general.

**Table 19** Nickel catalysed ring opening of α-substituted oxetanones and 4-octyne

<table>
<thead>
<tr>
<th>Ni(cod)$_2$ (mol %)</th>
<th>PPh$_3$ (mol %)</th>
<th>90 (%)$^b$</th>
<th>91 (%)$^b$</th>
<th>92 (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>30</td>
<td>32</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>n/a$^c$</td>
<td>70</td>
<td>14</td>
</tr>
</tbody>
</table>

[a] recovered starting material. [b] isolated yield. [c] all starting material consumed

**Scheme 35** Nickel catalysed ring opening of α-substituted oxetanones and diphenylacetylene

The ring opening of α-substituted oxetanones proceeded differently when compared to α-substituted azetidinones. Whereas α-substituted azetidinones proceeded with cleavage of only the least sterically hindered bond, α-substituted oxetanones proceeded with the cleavage of preferentially the least sterically hindered bond (Scheme 36). The steric crowding provided
by the protecting group of the azetidinone might contribute to the selective C–C bond cleavage. The mechanistic proposal for the ring opening of oxetanone 90 is as follows. The oxidative cyclisation would form intermediate 95 and then the ring opening could either proceed with the least sterically hindered C–C bond or the more sterically hindered bond broken to form intermediate 96 and 98 respectively. Finally, reductive elimination would then afford product 97 or 99 respectively.

Scheme 36 Mechanistic proposal for the ring opening of α-substituted oxetanones

2.3.7 Optimisation of the formation of four-membered ring 8

During the optimisation of pyridinone 6a, solvent effects were found to be significant in the selectivity between pyridinone 6a and four-membered ring 8. Previously, carrying out the reaction in 2-MeTHF at 100°C gave good selectivity towards 8. However, carrying out the reaction in 2-MeTHF at 90°C resulted in only the formation of 6a (Scheme 37). Therefore, the reaction pathway towards 8 operates at a higher temperature.
A screen of different conditions was then carried out to optimise the selectivity towards four-membered ring 8 (Table 20). Previously, it was noted that alkyl phosphines generally gave good selectivity towards four-membered ring 8. As most alkyl phosphines are liquid and air-sensitive, it was of interest to see if there was a solid alkyl phosphine alternative.

The replacement of one of the phenyl rings of PPh₃ with a cyclohexyl ring (Table 20, Entry 1) gave a slight increase in selectivity towards 8. The replacement of another phenyl ring with a cyclohexyl ring (Table 20, Entry 2) resulted in the selectivity towards 8 becoming comparable to those observed with alkyl phosphines (Table 1, Entry 2 and 3).

Increasing or decreasing the loading of PPhCy₂ (Table 20, Entry 3 and 4) had little effect on the selectivity but with 20 mol% PPhCy₂, the selectivity towards 8 was slightly better. The reduction of alkyne loading (Table 20, Entry 5 – 7) had little detriment in the selectivity towards 8. However, 1.5 equivalent of alkyne was used in further screening as it is a low alkyne loading with good selectivity towards 8.
Table 20 Optimisation Table

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne (equiv.)</th>
<th>Ligand</th>
<th>mol %</th>
<th>Conversion</th>
<th>6a/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Ph₂PCy₂</td>
<td>20</td>
<td>&gt;95%</td>
<td>43 : 57</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>PhPCy₂</td>
<td>20</td>
<td>&gt;95%</td>
<td>19 : 81</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>PhPCy₂</td>
<td>10</td>
<td>&gt;95%</td>
<td>22 : 78</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>PhPCy₂</td>
<td>30</td>
<td>&gt;95%</td>
<td>21 : 79</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>PhPCy₂</td>
<td>20</td>
<td>&gt;95%</td>
<td>20 : 80</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>PhPCy₂</td>
<td>20</td>
<td>&gt;95%</td>
<td>20 : 80</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>PhPCy₂</td>
<td>20</td>
<td>&gt;95%</td>
<td>21 : 79</td>
</tr>
</tbody>
</table>

A screening of different solvents which previously displayed a good selectivity toward the four-membered ring 8 was then carried out (Table 21). Toluene (Table 21, Entry 1) gave good selectivity and reactivity toward 8. Carrying out the reaction in 2-pentanone (Table 21, Entry 2) gave identical selectivity as before (Table 4, Entry 1) but with poorer conversion. 2-MeTHF (Table 21, Entry 3) gave near identical selectivity as before (Table 4, Entry 3) with full conversion and an isolated yield of 63%. Also, 2-pentanone and 2-MeTHF was used directly out of a bottle exposed to air and moisture. Isopropanol (Table 21, Entry 4) gave full conversion but with no selectivity. Increasing the temperature did not enhance the selectivity towards 8. Therefore, the optimised condition for the synthesis of 8 was 10 mol% Ni(cod)₂, 20 mol% PPhCy₂ and in toluene at 100°C.
Table 21 Solvent screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>6a/8</th>
<th>[a] Ratio determined by 1H NMR spectroscopy on a crude mixture of 6 and 11 [b] wet solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>&gt;95</td>
<td>20  : 80</td>
<td></td>
</tr>
<tr>
<td>2[b]</td>
<td>2-pentanone</td>
<td>25</td>
<td>24  : 76</td>
<td></td>
</tr>
<tr>
<td>3[b]</td>
<td>2-MeTHF</td>
<td>&gt;95</td>
<td>18  : 82</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>isopropanol</td>
<td>&gt;95</td>
<td>50  : 50</td>
<td></td>
</tr>
</tbody>
</table>

With the optimised reaction condition in hand, the insertion of symmetrical alkyne 100 was found to proceed with poor selectivity for 102 (Scheme 38). A near 1:1 isolated ratio of 101 and 102 was observed. Furthermore, carrying out the reaction with 4-octyne 5b in toluene resulted in a 62% isolated yield of pyridinone 6b. 1-Phenyl-1-propyne 5c resulted in an 88% conversion to pyridinones 6c and 11c. Neither alkyne 5b nor 5c reacted to form the corresponding four-membered ring. Attempts to incorporate the terminal alkyne phenylacetylene 38 were unsuccessful. Therefore, the methodology towards the four-membered ring appears to be restricted to only bis-aryl alkynes.
Initial attempts of formal [4+2] cycloaddition of azetidinone with alkenes

Jamison and co-workers reported a nickel catalysed coupling of aldehydes 104 with alkenes 103 (Scheme 39). After a screen of different ligands, PPhCy$_2$ was found to give a good selectivity for allylic product 105 over homoallylic product 106.
It was then decided to see if the insertion of alkenes into NBoc-azetidinone 7 was possible with the optimised reaction condition used for the synthesis of four-membered ring 8 (Scheme 40). However, no reactivity took place with ethylacrylate 107. Also, no reactivity took place with alkenes 108 and 109, even when the temperature of the reaction was increased to 120°C.

**Scheme 39** Nickel catalysed coupling of aldehydes with alkenes

**Scheme 40** Alkenes screened

### 2.4 Future development of air-stable Ni(II) pre-catalyst

#### 2.4.1 Introduction and initial optimisation

Ni(cod)$_2$ is an air sensitive complex which is required to be stored cold under an inert atmosphere and is handled inside a glovebox. However, there are many commercially available nickel-catalysts which can be conveniently stored outside of the glovebox. There are reports of commercially air-stable Ni(II) pre-catalysts that can be reduced by a reducing agent *in situ* to become the active Ni(0).\textsuperscript{19} We then became interested to see if we can find a commercially available and air stable Ni(II) pre-catalyst that can do the [4+2] cycloaddition of azetidinone with alkyne. This would primarily allow the reaction to be setup and be carried on
the benchtop which would circumvent the need for a glovebox. Secondly, this method could potentially improve the scope of the methodology.

The commercially available and air stable Ni(PCy₃)₂Cl₂ was chosen as it exhibits better air stability than Ni(PPh₃)₂Cl₂. Zinc was chosen as the reducing agent as it can be stored outside the glovebox. It was found that no activation was necessary and the zinc can be used directly out of a bottle which has been exposed to air and moisture. The initial optimisation with Ni(PCy₃)₂Cl₂ began with 50 mg of azetidinone 7 and 1.1 equivalents of alkyne 5b at 60°C. It was found that the conversion was low when the reaction was carried out in toluene (Table 22, Entry 1). However, THF or iPrOH (Table 22, Entry 2 and 3) gave full conversion in both cases and a 72% isolated yield of pyridinone 6b was obtained with iPrOH. Interestingly, formation of the desired Ni(PPh₃)₂Cl₂ can be achieved by mixing NiCl₂•6H₂O and PPh₃ together in a suitable solvent. Unfortunately, THF and EtOH proved to be poor solvents (Table 22, Entry 4 and 5). On the other hand, iPrOH allowed at least a reasonable conversion to 6b (Table 22, Entry 6). Furthermore, the last 3 entries suggest that the excess water from the NiCl₂•6H₂O is potentially detrimental to the reaction. As a result, the initial formation of Ni(PCy₃)₂Cl₂ from NiCl₂•6H₂O might require better examination.
Table 22 Optimisation with 5b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni cat. (10 mol%)</th>
<th>PCy₃ (mol%)</th>
<th>Solvent</th>
<th>Conv.</th>
<th>Isolated yield of 6b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(PCy₃)₂Cl₂</td>
<td>0</td>
<td>Toluene</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ni(PCy₃)₂Cl₂</td>
<td>0</td>
<td>THF</td>
<td>&gt;95%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ni(PCy₃)₂Cl₂</td>
<td>0</td>
<td>iPrOH</td>
<td>&gt;95%</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂•6H₂O</td>
<td>20</td>
<td>THF</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NiCl₂•6H₂O</td>
<td>20</td>
<td>EtOH</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NiCl₂•6H₂O</td>
<td>20</td>
<td>iPrOH</td>
<td>77%</td>
<td></td>
</tr>
</tbody>
</table>

With these promising results in hand, we became interested to see if the insertion of alkyne 5c could proceed with good regioselectivity. Therefore, the study with 50 mg of azetidinone 7 and 1.1 equivalents of alkyne 5c was carried out (Table 23). However, a mixture of NiCl₂•6H₂O/PCy₃ was ineffective (Table 23, entry 1). Carrying out the reaction with Ni(PCy₃)₂Cl₂ at 80°C was ineffective in either THF or iPrOH (Table 23, entry 1 and 2). Ni(PPh₃)₂Br₂, is a more air-stable nickel pre-catalyst than Ni(PPh₃)₂Cl₂ and can be stored for at least several months outside of the glovebox without loss of activity. Ni(PPh₃)₂Br₂ proved to be an effective pre-catalyst and good conversion towards 6c was observed at 80°C in both THF and iPrOH (Table 23, entry 4 and 5). Furthermore, the insertion of 5c proceeded with good regioselectivity in both solvents. On reducing the temperature to 60°C and the loading of Ni(PPh₃)₂Br₂ to 5 mol%, the reaction proceeded with excellent conversion towards 6c and the regioselectivity was maintained (Table 23, entry 6 and 7). Carrying out the reaction at 40°C in THF gave poorer conversion (Table 23, entry 8). However in iPrOH at 40°C, the regioselectivity remained unchanged and an isolated yield of 84% of 6c was obtained (Table 23, entry 9). Furthermore,
the reaction can be carried out successfully on a 500 mg scale and 7 was isolated in a 83% yield (Table 23, entry 10).

**Table 23** Optimisation with 5c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni. cat.</th>
<th>mol %</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Conv.</th>
<th>Ratio of 6c/11c</th>
<th>6c (%)^[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^[b]</td>
<td>NiCl₂•6H₂O</td>
<td>10</td>
<td>iPrOH</td>
<td>60</td>
<td>trace</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ni(PCy₃)₂Cl₂</td>
<td>10</td>
<td>THF</td>
<td>80</td>
<td>&lt;5%</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ni(PCy₃)₂Cl₂</td>
<td>10</td>
<td>iPrOH</td>
<td>80</td>
<td>20%</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>10</td>
<td>THF</td>
<td>80</td>
<td>85%</td>
<td>88 : 12</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>10</td>
<td>iPrOH</td>
<td>80</td>
<td>82%</td>
<td>86 : 14</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>5</td>
<td>THF</td>
<td>60</td>
<td>92%</td>
<td>90 : 10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>5</td>
<td>iPrOH</td>
<td>60</td>
<td>&gt;95%</td>
<td>89 : 11</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>5</td>
<td>THF</td>
<td>40</td>
<td>60%</td>
<td>91 : 9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>5</td>
<td>iPrOH</td>
<td>40</td>
<td>&gt;95%</td>
<td>89 : 11</td>
<td>84</td>
</tr>
<tr>
<td>10^[c]</td>
<td>Ni(PPh₃)₂Br₂</td>
<td>5</td>
<td>iPrOH</td>
<td>40</td>
<td>&gt;95%</td>
<td>90 : 10</td>
<td>83</td>
</tr>
</tbody>
</table>

^[a] Isolated yield, [b] 20 mol% PCy₃ also used to form the catalyst, [c] carried out on a 500 mg scale
2.4.2 1,3-Enyne as alkyne surrogate to improve regioselectivity

2.4.2.1 Regioselectivity issues with alkyne 5k

Matsubara and co-workers reported a nickel-catalysed reaction involving the insertion of alkyne 5k into 110 which proceeded with a better regioselectivity when compared to the insertion of alkyne 5k into azetidinone 7 with our original optimised reaction conditions (Scheme 41).20

![Scheme 41 Nickel-catalysed insertion of alkyne 5k]

Therefore, a screen was carried out to determine if the regioselectivity of the insertion of alkyne 5k into azetidinone 7 could be improved (Table 24). From entry 2 onwards, the work was carried out by Daniel J. Tetlow and Jet-Sing Lee. On changing the ligand from PPh₃ (Table 24, Entry 1) to PCy₃ (Table 24, Entry 2), the regioselectivity switched but the selectivity remained poor. Any changes to the alkyne equivalents, solvent or temperature did little to influence the regioselectivity (Table 24, Entry 3-6). Using P(OMe)₃ as the ligand reversed the regioselectivity towards 6k with a better selectivity towards 6k than PPh₃ but suffers from a poorer conversion (Table 24, Entry 7 vs 1). However, triphenyl phosphite (Table 24, Entry 8) had no reactivity. Afterwards, several other ligands were screened and a trend was noticed.
With the exception of L1 (Table 24, Entry 9) which proceeded with full conversion and with one of the highest regioselectivities, large phosphines tend to erode the regioselectivity and can actually cause the regioselectivity to reverse (Table 24, Entry 10 – 15).

Table 24 Insertion of alkyne 5k into azetidinone 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne equiv.</th>
<th>Ligand (mol %)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Ratio</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>PPh₃ (30)</td>
<td>Dioxane</td>
<td>90</td>
<td>60 : 40</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>PCy₃ (30)</td>
<td>Dioxane</td>
<td>90</td>
<td>45 : 55</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>PCy₃ (30)</td>
<td>Dioxane</td>
<td>90</td>
<td>43 : 57</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>PCy₃ (30)</td>
<td>Toluene</td>
<td>90</td>
<td>43 : 57</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>PCy₃ (30)</td>
<td>Dioxane</td>
<td>70</td>
<td>44 : 56</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>PCy₃ (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>44 : 56</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>P(OMe)₃ (30)</td>
<td>Dioxane</td>
<td>60</td>
<td>69 : 31</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>P(OPh)₃ (30)</td>
<td>Dioxane</td>
<td>60</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>L1 (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>67 : 33</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>1.1</td>
<td>L2 (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>63 : 37</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>1.1</td>
<td>L3 (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>62 : 38</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>1.1</td>
<td>PPh₃ (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>58 : 42</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>1.1</td>
<td>L₄ (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>55 : 45</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>1.1</td>
<td>L₅ (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>53 : 47</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>1.1</td>
<td>PCy₃ (30)</td>
<td>Dioxane</td>
<td>40</td>
<td>44 : 56</td>
<td>100</td>
</tr>
</tbody>
</table>
2.4.2.2 1,3-Enyne as alkyne surrogate

In 2008, Fagnou and co-workers reported a rhodium-catalysed indole synthesis (Scheme 42).\textsuperscript{21} However, it was found that there is little regiocontrol in the coupling of acetanilide 113 with asymmetrical alkyne 114 to afford unsymmetrical 2,3-aliphatic-substituted indole 115 and 116.

![Scheme 42 Rhodium-catalysed indole synthesis.](image)

In order to circumvent this problem, Fagnou and co-workers reported a highly regioselective coupling of alkyne 118 with acetanilide 117 by a rhodium-catalyst (Scheme 43).\textsuperscript{22} The highly regioselective coupling of alkyne 118 is attributed to the vinyl moiety acting as a directing
group. Afterwards, the vinyl moiety can then be converted by hydrogenation (Scheme 44). As a result, good regiocontrol in the synthesis of various unsymmetrical 2,3-aliphatic-substituted indoles 120 is achieved.

![Scheme 43 Rhodium-catalysed indole synthesis.](image)

![Scheme 44 Hydrogenation](image)

Therefore, we became interested to see if enyne 5m can circumvent the low regiocontrol problem observed with non-symmetrical alkyl alkynes. Also, it was of interest if an air-stable nickel pre-catalyst can be used to effect the insertion of alkyne 5m into azetidinone 69 on a 50 mg scale of 69 (Table 25). It was found that 10 mol% of the catalyst and 50 mol% of Zinc at
60°C gave full conversion with a combined isolated yield of 75% and a regioselectivity of 88:12 (Table 25, entry 1). However, reduction of the loading of Ni/Zn reduced the conversion (Table 25, entry 2 and 3). Reducing the Ni/Zn ratio also reduced the conversion which is not too surprising, as the reaction is a suspension (Table 25, entry 4 and 5). When the temperature was increased to 80°C, full conversion was observed but the isolated yield was rather low (Table 25, entry 6). A brief screen of alternative solvents revealed that THF and 2-MeTHF gave slightly better regioselectivities but the difference is not significant (Table 25, entry 7-12). Furthermore, the reaction can be carried out in THF at 40°C but with poorer conversion (Table 25, entry 13). Using a solvent mixture of iPrOH/THF (1:1) at 60°C did not allow the reaction to go to complete conversion but a good regioselectivity was obtained (Table 25, entry 14). When the reaction carried out on a 150 mg scale of 69, the loading of Ni/Zn can be reduced to 1:2 but the regioselectivity decreased (Table 25, entry 15). This result was then reproduced (Table 25, entry 16).
### Table 25 Optimisation with 5m

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni. (mol %)</th>
<th>Zinc (mol %)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Conv.</th>
<th>Yield [a]</th>
<th>Ratio (121/122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>50</td>
<td>iPrOH</td>
<td>60</td>
<td>&gt;95%</td>
<td>75%</td>
<td>88 : 12</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>25</td>
<td>iPrOH</td>
<td>60</td>
<td>88%</td>
<td>53%</td>
<td>88 : 12</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>15</td>
<td>iPrOH</td>
<td>60</td>
<td>34%</td>
<td>21%</td>
<td>87 : 13</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>20</td>
<td>iPrOH</td>
<td>60</td>
<td>86%</td>
<td>50%</td>
<td>88 : 12</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>10</td>
<td>iPrOH</td>
<td>60</td>
<td>45%</td>
<td>30%</td>
<td>86 : 14</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>20</td>
<td>iPrOH</td>
<td>80</td>
<td>&gt;95%</td>
<td>61%</td>
<td>88 : 12</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>20</td>
<td>MeCN</td>
<td>60</td>
<td>50%</td>
<td>21%</td>
<td>88 : 12</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>20</td>
<td>THF</td>
<td>60</td>
<td>&gt;95%</td>
<td>74%</td>
<td>89 : 11</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>20</td>
<td>Acetone</td>
<td>60</td>
<td>44%</td>
<td>33%</td>
<td>88 : 12</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>20</td>
<td>Toluene</td>
<td>60</td>
<td>0%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>20</td>
<td>1,2-DCE</td>
<td>60</td>
<td>&lt;10%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>20</td>
<td>2-MeTHF</td>
<td>60</td>
<td>56%</td>
<td>39%</td>
<td>90 : 10</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>20</td>
<td>THF</td>
<td>40</td>
<td>55%</td>
<td>41%</td>
<td>91 : 9</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>20</td>
<td>iPrOH/THF [b]</td>
<td>60</td>
<td>80%</td>
<td>61%</td>
<td>92:8</td>
</tr>
<tr>
<td>15=c</td>
<td>5</td>
<td>10</td>
<td>THF</td>
<td>60</td>
<td>&gt;95%</td>
<td>79%</td>
<td>83:17</td>
</tr>
<tr>
<td>16=c</td>
<td>5</td>
<td>10</td>
<td>THF</td>
<td>60</td>
<td>&gt;95%</td>
<td>83%</td>
<td>77:23</td>
</tr>
</tbody>
</table>

[a] Combined isolated yield of 121 and 122. [b] 1:1 solvent ratio. [c] On 150 mg scale of 69

Furthermore, the in situ formation of Ni(PPh₃)₂Br₂ can be achieved by the direct mixing of NiBr₂·xH₂O and PPh₃. The insertion of alkyne 5m into azetidinone 69 on a 200 mg scale of 69
was found to proceed to give 121 in 69% yield and 122 on 13% yield (Scheme 45). The experiment was setup without the requirement of a glovebox. Also, this result will allow the screening of ligands to be carried out with ease.

Scheme 45 The in situ formation of Ni(PPh₃)₂Br₂

Akin to the work by Fagnou, hydrogenation of pyridinone 121 formed 123 (Scheme 46). The product of the hydrogenation was shown to be pure as judged by ¹H NMR and used directly in the next reaction. Prolonged hydrogenation led to a variety of unidentified side products. After the filtration to remove the palladium catalyst, 123 was aromatised with potassium tert-butoxide to give pyridinol 124 in a 43% yield over two steps. Therefore, the aromatisation step requires some more optimisation.

Scheme 46 Hydrogenation, deprotection and aromatisation

Therefore, some optimisation of the aromatisation was carried out on model substrate 70b (Table 26). Organic bases Et₃N and imidazole were ineffective regardless of temperature (Table 26, entry 1-4). The aromatisation with 3 equiv. KOtBu in THF without an aqueous workup furnished the desired product in a 58% but the yield could be higher as the column leaked (Table 26, entry 5). Increasing the equivalents of KOtBu to 5 increased the isolated yield to 92% (Table 26, entry 6). However, with 3 equiv. KOtBu in THF that involves initial purification
by standard aqueous workup with a saturated solution of brine resulted in an isolated yield of 42% (Table 26, entry 7). Using a saturated solution of NH₄Cl instead resulted in an isolated yield of 63% (Table 26, entry 8).

**Table 26** Model substrate for aromatisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Workup</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (3)</td>
<td>DCM</td>
<td>rt</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N (3)</td>
<td>DCM</td>
<td>40</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Imidazole (3)</td>
<td>DCM</td>
<td>rt</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Imidazole (3)</td>
<td>DCM</td>
<td>40</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>KOtBu (3)</td>
<td>THF</td>
<td>rt</td>
<td>None</td>
<td>58[a]</td>
</tr>
<tr>
<td>6</td>
<td>KOtBu (5)</td>
<td>THF</td>
<td>rt</td>
<td>None</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>KOtBu (3)</td>
<td>THF</td>
<td>rt</td>
<td>Brine</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>KOtBu (3)</td>
<td>THF</td>
<td>rt</td>
<td>NH₄Cl</td>
<td>63</td>
</tr>
</tbody>
</table>

[a] column leaked

This initial work with the air-stable nickel pre-catalyst demonstrates the reaction can now be set up outside of the glovebox on the benchtop. However, much work remains to optimise the conditions. On the other hand, it is clear that the ligand on the nickel can have a significant influence on the success on the reaction. Furthermore, the regioselectivity of the insertion of non-symmetrical alkynes are in line with those observed when the mixture of air sensitive Ni(cod)₂/PPh₃ was used.
2.5 Conclusion

The [4+2] cycloaddition of four-membered ring heterocycles with alkynes has been successfully developed. This rapid build-up of six-membered heterocycles offers an alternative approach to previous approaches.\(^{23}\) Initially, the choice of ligand and solvent were critical to minimise the formation of the four-membered ring. Upon re-examination, the four-membered ring is found to be both substrate specific and temperature dependent. Furthermore, the reaction towards six-membered ring 127 proceeded smoothly with various azetidinones and oxetanones (Scheme 47). Furthermore, α-substitution on the small heterocycle is tolerated providing the substituent is not too large. The insertion of various alkynes proceeded with good regioselectivity. Moreover, the insertion of silylated alkynes proceeded successfully.

![Scheme 47 Summary of the [4+2] cycloaddition](image.png)

The development of setting up the reaction without the need for a glovebox with an air-stable Ni(II) pre-catalyst is of interest. Furthermore, seeking to improve upon the original scope will be of interest. To determine if the regioselectivity of the alkyne insertion can be improved or even reversed will be of synthetic importance.

As alluded to, since the publication of some of the work which has been presented in this thesis,\(^ {24}\) the groups of Murakami\(^ {16}\) and Louie\(^ {12}\) have published similar results which indicate that small heterocycles are indeed competent partners in C–C activation reactions.
2.6 Synthesis of Precursors

2.6.1 Synthesis of 3-azetidinones

The synthesis of azetidinone 69 was easily achieved in a two-step procedure from 3-hydroxyazetidine hydrochloride S1 (Scheme 48). Compound S2 was obtained by mono-protection with 1 equivalent of tosyl chloride in methanol and three equivalents of triethylamine following a modification to the original reaction procedure. Afterwards, carrying out a standard Swern oxidation afforded azetidinone 69 in 69% yield.

Scheme 48 Synthesis of azetidinone 69

The synthesis of azetidinone 72, 79 and 83 began with the corresponding commercially available amino acid S3, S5 and S8 (Scheme 50 - 49). The protection with tosyl chloride of S5 to give S6 was carried out in a 54% yield. Carboxylic acids S3, S6, S8 were first transformed to the corresponding acyl chloride. All volatiles were removed on the high vacuum line to minimise the inclusion of water. Afterwards, trimethylsilyl diazomethane was added to form diazo S4, S7 and S9 which could be purified by flash column chromatography or used directly in the next step. Then the copper catalysed N–H insertion formed azetidinone 72 in 84% yield from S4, 79 in 48% yield from S7 and 83 in 38% yield over 3 steps from S8.
Scheme 49 Synthesis of α-aryl azetidinone

Scheme 50 Synthesis of α-aryl azetidinone

Scheme 51 Synthesis of α-substituted azetidinone

2.6.2 Synthesis of 3-oxetanones

The gold catalyst S11 was generated by a salt metathesis of the commercially available phosphine gold chloride S9 with silver bis(trifluoromethanesulfonyl)imide in DCM at rt. The silver chloride was separated by filtration and the catalyst was of good quality as judged by $^{31}\text{P}$ NMR. S14 was made by Dr Christophe Aissa and is not described in this thesis. Afterwards, the synthesis of α-substituted oxetanone 90 was carried out by following the procedure described by Zhang and co-workers (Scheme 53).\textsuperscript{27} The synthesis began with the in situ formation of the lithium acetylide. Aldehyde S12 was then added to form propagryl alcohol S13 which was then isolated after workup. Afterwards, the TMS group was cleaved by TBAF to give the terminal alkyne S14. Finally, the gold-catalysed synthesis was carried out to give 90 in a 51% yield.
2.6.3 Synthesis of alkynes

The synthesis of alkynes 5e, 5g-j, 63 and 100 were achieved by a Sonogashira reaction (Table 27). In each case, the palladium-catalysed coupling of an aryl halide with a terminal alkyne in THF proceeded in good to high yields.
## Table 27 Sonogashira reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>X</th>
<th>R²</th>
<th>Alkyne</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO</td>
<td>I</td>
<td>nBu</td>
<td><img src="image" alt="5o" /></td>
<td>Quant</td>
</tr>
<tr>
<td>2ᵃ</td>
<td>CH₃C(O)</td>
<td>Br</td>
<td>nBu</td>
<td><img src="image" alt="5g" /></td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>I</td>
<td>Cy</td>
<td><img src="image" alt="5h" /></td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>I</td>
<td>iBu</td>
<td><img src="image" alt="5i" /></td>
<td>Quant</td>
</tr>
<tr>
<td>5</td>
<td>MeO</td>
<td>I</td>
<td>pCF₃Ph</td>
<td><img src="image" alt="5j" /></td>
<td>Quant</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>I</td>
<td>-CH₂CH₂Br</td>
<td><img src="image" alt="63" /></td>
<td>86%</td>
</tr>
<tr>
<td>7</td>
<td>MeO</td>
<td>I</td>
<td>pMeOPh</td>
<td><img src="image" alt="100" /></td>
<td>70%</td>
</tr>
</tbody>
</table>

[a] 3 mol% Pd(PPh₃)₄ and 3mol% CuI were used

With 2-iodopyridine, the Sonogashira reaction was slightly more difficult (Table 28). Regardless, the desired product was still isolated in moderate to good yields.
Table 28 Sonohashira reaction with 2-iodopyridine

\[
\begin{align*}
\text{S18} & \quad \begin{array}{c}
\text{N} \\
\text{I}
\end{array} & + & \begin{array}{c}
\text{R}
\end{array} & \xrightarrow{5 \text{ mol} \% \text{ PdCl}_2(\text{PPh}_3)_3; 7 \text{ mol} \% \text{ Cu; Et}_3\text{N; THF, r.t.}} & \begin{array}{c}
\text{R}
\end{array} & \begin{array}{c}
\text{N} \\
\text{= - R}
\end{array}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Alkyne</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td><img src="43" alt="Image" /></td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>nButyl</td>
<td><img src="44" alt="Image" /></td>
<td>58%</td>
</tr>
</tbody>
</table>

The syntheses of propargylic alkynes 56 – 58 and 5v were carried out in one step from commercially available starting materials (Scheme 54). Alkyne 57 and 5v were synthesised by benzylation with benzyl bromide S23 as the electrophile. Alkyne 56 was synthesised by acetylation with acetyl chloride S21 as the electrophile. Alkyne 58 was synthesised by silylation with tert-butyldimethylsilyl chloride S22 as the electrophile.

Scheme 54 Synthesis of propargylic alkynes
The synthesis of alkyne 5d began with a modified Ohira-Bestmann using trimethylsilyldiazomethane on aldehyde S25 to form terminal alkyne S26 and was isolated in a 91% yield (Scheme 55). Afterwards, deprotection of alkyne S26 with nBuLi and subsequent trapping with iodomethane afforded desired alkyne 5d in 90% yield. The synthesis of alkyne 5n was a Sonogashira reaction between S26 and 2-bromopropene S27 to form 5n in 86% yield.

**Scheme 55** Synthesis of alkyne 5d

**Scheme 56** Synthesis of alkyne 5n

The syntheses of alkyne 5f, 5p-r, 5y, 61 and 62 were carried out in one step from commercially available alkynes (Table 29). In all cases, treatment of alkyne S28 with nBuLi as the base formed the anion. The anion was then trapped with an electrophile to furnish the desired alkyne. For the synthesis of alkyne 61, an additive was required (Table 28, entry 6).
Table 29 Synthesis of alkyne

<table>
<thead>
<tr>
<th>Entry</th>
<th>S28</th>
<th>Electrophile</th>
<th>Additive</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₂CO≡</td>
<td>MeI</td>
<td>n/a</td>
<td>F₂CO≡</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>SiMe₂PhCl</td>
<td>n/a</td>
<td></td>
<td>Quant.</td>
</tr>
<tr>
<td>3</td>
<td>nOct≡</td>
<td>TMSCl</td>
<td>n/a</td>
<td>nOct≡TMS</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>TMSCl</td>
<td>n/a</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Ph≡</td>
<td>Mel</td>
<td>n/a</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>EIO≡</td>
<td>nC₆H₄Br</td>
<td>HMPA</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>MeO≡</td>
<td>NCS</td>
<td>n/a</td>
<td></td>
<td>76</td>
</tr>
</tbody>
</table>

The synthesis of alkyne 5w and 5z began from the corresponding commercially available alkyne S29 and S31 (Scheme 57). The benzylation of alkyne S29 with benzyll bromide as the electrophile gave terminal alkyne S30 whereby the silyl group was cleaved. Afterwards, the silyl group was reintroduced by trapping the terminal alkyne anion with trimethylsilyl chloride to form alkyne 5w. On the hand, the benzylation of alkyne S31 with benzyl bromide as the electrophile gave terminal alkyne S32. The anion of S32 was generated by treatment with nBuli. Subsequent trapping of the terminal alkyne anion with methyl iodide gave alkyne 5z in 87% yield.
The synthesis of ynamide 59 and 60 started with the silver-catalysed bromination of phenylacetylene 38 (Scheme 58). The bromide S33 was then used directly in the next step without purification by flask column chromatography. Then a copper-catalysed coupling was carried out to form the ynamide. Both ynamides were synthesised by the following the procedure by Liu.29
2.7 Experimental Section

**General.** Otherwise noted, all reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. The solvents were purified with the solvent purification system Pure Solv MD-6 (THF, Et₂O, CH₂Cl₂, benzene, toluene, hexane). Dry dioxane was purchased from Aldrich. All commercially available compounds were used as received. Flash chromatography: Merck silica gel 60 (230-400 mesh) with petroleum ether (PE, 40–60°C) and EtOAc or Et₂O analytical grade. NMR: spectra were recorded on a Bruker DRX 500, Bruker DPX 400, and Bruker AVANCE 400 spectrometers in CDCL₃; chemical shifts (δ) are given in ppm relative to TMS. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl₃: δ_C = 77.0 ppm; residual CHCl₃ in CDCl₃: δ_H = 7.24 ppm). IR: PerkinElmer Spectrum 100 FT-IR spectrometer, wavenumbers (ν) in cm⁻¹. HRMS at the University of Liverpool: VG7070E (Cl), micromass LCT mass spectrometer (ES+). Melting points: Griffin melting point apparatus (not corrected). Elemental analyses: University of Liverpool. Optical rotations were measured on a PerkinElmer 343plus polarimeter.

2.7.1 Synthesis of 3-azetidinones

**Compound 69**

A round-bottom flask was charged with 3-hydroxyazetidine hydrochloride (1000 mg, 9.13 mmol) and suspended in MeOH (9 ml). Triethylamine (1.9 ml, 13.69 mmol) was added dropwise at 0°C and after the addition, the clear solution was allowed to stir at rt for 20 mins. Afterwards, tosyl chloride (1740 mg, 9.13 mmol) and triethylamine (1.9 ml, 13.69 mmol) were
added and allowed to stir at rt overnight. Afterwards, all volatiles were removed and then partitioned between EtOAc and H₂O. Extraction from the aqueous layer was carried out three times with EtOAc. The organic layer was then washed with H₂O, a saturated solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/EtOAc, 1/1→1/2) gave S2 (1.86g, 89%) as a white solid. Under N₂, DMSO (1.5 mL, 21.2 mmol) in CH₂Cl₂ (5 mL) was added to a solution of oxalyl chloride (911 μL, 10.6 mmol) in CH₂Cl₂ (25 mL) at −78°C. After 10 minutes of stirring at −78°C, a solution of S2 (1.86g, 8.16 mmol) in CH₂Cl₂ (10 mL) was added. After 20 minutes of stirring at −78°C, triethylamine (5.7 mL, 40.8 mmol) was added rapidly and the mixture was stirred at room temperature during 10 minutes. A saturated solution of NH₄Cl was added to the reaction mixture which was then extracted three times with EtOAc. The organic layer was washed with H₂O, a saturated solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/EtOAc, 3/1→2/1) gave 69 as a white solid (1.12 g, 61%). This compound is known.³⁰ ¹H NMR (500 MHz, CDCl₃): δ = 7.78 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.61 (s, 4H), 2.45 (s, 3H).

**Compound 72**

![Compound 72](image)

Under N₂, a flame-dried Schlenk flask was charged with N-Ts-(L)-Alanine S3 (300 mg, 1.23 mmol), dry DMF (50 μL) and dry DCM (2.4 ml). At 0 °C, (COCl)₂ (0.12 ml, 1.36 mmol) was then added drop wise. After stirring at room temperature for 1 hour, all volatiles were removed under high vacuum and THF (3 ml) was then added to the pale yellow oil. Then at 0°C, 2.0 M TMSCHN₂ in Et₂O (0.74 ml, 1.48 mmol) was added. After stirring at room temperature for 2 hours, all volatiles were then removed by evaporation and the residue was purified by flash column chromatography (PE/EtOAc, 4/1→2/1) to give S4 (195 mg, 59 %) as a pale yellow solid.
This compound was diluted in benzene (14 ml), and Cu(OAc)$_2$•H$_2$O (14 mg, 0.07 mmol) was added under N$_2$ to this refluxing solution. Immediate evolution of N$_2$ was observed. Completion was reached within 10 minutes stirring at reflux. After evaporation, purification by flash column chromatography (PE/EtOAc, 4/1→2.5/1) gave 69 as a white solid (143 mg, 84%).

Enantiomeric excess > 99%.^ m.p. 75–77 °C [lit.: 78–79 °C];$^{31}$ [$\alpha$]$^D_{20}$ = 76.9 (c = 1 in CHCl$_3$) [lit.: 80 (c = 1 in CHCl$_3$)];$^{31}$ H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.75 (d, $J$ = 8.3 Hz, 2H), 7.36 (d, $J$ = 8.2 Hz, 2H), 4.73 (qd, $J$ = 7.1 Hz, 1.2 Hz, 1H), 4.50–4.41 (m, 2H), 2.43 (s, 3H), 1.42 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 196.7, 145.0, 131.5, 130.0 (2C), 128.4 (2C), 80.9, 69.5, 21.6, 15.7; IR (neat): $\tilde{\nu}$ = 2978 (w), 2930 (w), 2867 (w), 1825 (s), 1597 (w), 1493 (w), 1444 (w), 1419 (w), 1338 (s), 1323 (m), 1299 (m), 1251 (w), 1238 (w), 1182 (w), 1156 (s), 1132 (s), 1101 (s), 1085 (s), 1051 (s), 1013 (s), 973 (s), 848 (w), 822 (m), 812 (s), 803 (m), 778 (m), 731 (s), 708 (m), 668 (s) cm$^{-1}$; MS (Cl): m/z (rel. intensity): 257 (100) [M+NH$_4^+$]+, 240 (7) [M+H]$^+$

^ Determined by chiral HPLC, Chiralpak AD - H Column, iPrOH:hexane = 8/92, 1 mL/min, 230 nm on a Agilent technologies 1200 apparatus

**Compound 79**

A flask was charged with (R)-(−)-2-phenylglycine (1000 mg, 6.62 mmol) and 2M NaOH (8.25 ml). Then TsCl (1.5 g, 7.94 mmol) in Et$_2$O (6.6 ml) was added dropwise. The suspension was then left to stir at rt overnight. Afterwards, conc HCl was added until a pH of 2 was reached. Et$_2$O was added. The precipitate was then collected by filtration and washed with Et$_2$O to give S6 as a white solid (1.1 g, 54%). Under N$_2$, a flame-dried Schlenk flask was charged with S6 (300 mg, 0.98 mmol), dry DMF (2 drops) and dry DCM (2 ml). At 0 °C, (COCl)$_2$ (93 μl, 1.08 mmol) was then added drop wise. After stirring at room temperature for 1 hour, all volatiles were removed under high vacuum and THF (1 ml) was then added to the pale yellow oil. Then at
0°C, 2.0 M TMSCHN$_2$ in Et$_2$O (1 ml, 2 mmol) was added. After stirring at room temperature for 2 hours, all volatiles were then removed by evaporation and the residue was purified by flash column chromatography (PE/EtOAc, 4/1 → 2/1) to give 56 (177 mg, 56 %) as a pale yellow solid. This compound was diluted in toluene (11 ml), and Cu(OAc)$_2$•H$_2$O (11 mg, 0.05 mmol) was added under N$_2$ to this refluxing solution. Immediate evolution of N$_2$ was observed. Completion was reached within 10 minutes stirring at reflux. After evaporation, purification by flash column chromatography (PE/EtOAc, 4/1 → 2.5/1) gave 79 as a white solid (77 mg, 48 %). This compound is known.\textsuperscript{32}  \textsuperscript{1}H NMR (500 MHz, CDCl$_3$): $\delta = 7.80 – 7.75$ (m, 2H), 7.39 – 7.28 (m, 7H), 5.73 (d, $J = 3.9$ Hz, 1H), 4.76 (d, $J = 16.2$ Hz, 1H), 4.61 (dd, $J = 16.2$, 4.0 Hz, 1H), 2.44 (s, 3H)

**Compound 83**

This compound was prepared from N-Ts-(DL)-phenylalanine 58 (500 mg, 1.57 mmol) according to the procedure described for the preparation of 69. This compound is known.\textsuperscript{33} White solid (173 mg, 35%); \textsuperscript{1}H NMR (500 MHz, CDCl$_3$): $\delta = 7.73$ (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.30 – 7.25 (m, 2H), 7.23 – 7.18 (m, 3H), 4.97 – 4.92 (m, 1H), 4.39 (d, $J = 16.1$ Hz, 1H), 4.15 (d, $J = 16.1$, 4.0 Hz, 1H), 3.15 (dd, $J = 14.6$, 6.9 Hz, 1H), 3.09 (dd, $J = 14.4$, 4.3 Hz, 1H), 2.44 (s, 3H)
2.7.2 Synthesis of 3-oxetanones and precursor

**Compound S11**

\[
\text{Ph}_2\text{P}=\text{Au}=\text{NTf}_2
\]

Under N\(_2\), DCM (1 ml) was added to silver bis(trifluoromethanesulfonyl)imide (50 mg, 0.1 mmol) and S9 (39 mg, 0.1 mmol). After 1 hour of stirring at rt, the precipitate was removed by filtration through a celite plug. The plug was washed with DCM. Afterwards, all volatiles were removed to give a S11 as a white solid (71 mg, 94%). This compound has been described.\(^{34}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.60 - 7.42\) ppm (15H); \(^{31}\)P NMR (202 MHz, CDCl\(_3\)): \(\delta = 30.5\)

**Compound 90**

Compound 90 was obtained according to a modified procedure described by Zhang.\(^{27}\) Under N\(_2\), S15 (307 mg, 1.87 mmol) and then MsOH (73\(\mu\)l, 1.12 mmol) were added to a solution of S14 (150 mg, 0.94 ml) in 1,2-DCE (4 ml). Then S11 (35 mg, 0.05 mmol) in 1,2-DCE (4 ml) was added. Left to stir at rt overnight. A saturated solution of NaHCO\(_3\) was added and extracted three times with DCM. Extracts dried over Na\(_2\)SO\(_4\), filtered and concentrated. Purification by flash column chromatography (PE/EtOAc, 19/1 \(\rightarrow\) 9/1) gave 90 as a colourless oil (83 mg, 51%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.31 - 7.25\) (m, 2H), 7.22 - 7.15 (m, 3H), 5.47 - 5.41 (m, 1H), 5.29 (d, \(J = 14.9\) Hz, 1H), 5.24 (dd, \(J = 15.0, 4.2\) Hz, 1H), 2.84 - 2.71 (m, 2H), 2.22 - 2.05 (m, 2H).
2.7.3 Synthesis of alkynes

**Compound S26**

![Structure of S26](image)

Under N₂, a flame-dried RB flask was charged with DIPA (0.5 ml, 3.56 mmol) and THF (10 ml). At 0°C, 2.5M of nBuLi in hexanes (1.3 ml, 3.29 mmol) was added. After 10 mins at 0°C, the vessel was cooled to -78°C and 2M of TMSCHN₂ in Et₂O (1.65 ml, 3.29 mmol) was added. It was then allowed to stir at -78°C for 30 mins. Afterwards, biphenyl-4-carboxaldehyde (500 mg, 2.74 mmol) in THF (5 ml) was cannulated into the flask. Afterwards, the ice-bath was removed and allowed to warm to rt. After 1h, the reaction was complete and a saturated solution of NH₄Cl was added. Then Et₂O was added and the organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/EtOAc, 1/0→60/1) gave S26 as a white solid (452 mg, 91%). This compound has been described.³⁵ **¹H NMR (500 MHz, CDCl₃):** δ = 7.59 – 7.52 (m, 6H), 7.46 – 7.40 (m, 2H), 7.37 – 7.32 (m, 1H), 3.11 (s, 1H).

**Compound 5d**

![Structure of S26](image)

At -20°C, 2.5M of nBuLi was added to a solution of S26 (200 mg, 1.12 mmol) in THF (8 ml). After 40 mins of stirring at -20°C, iodomethane (154 µl, 2.47 mmol) was added. The solution was allowed to stir overnight whilst allowing it to warm to rt. Afterwards, the reaction was quenched with a saturated solution of NH₄Cl. Et₂O was added and the organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/EtOAc, 60/1) gave 5d as a white solid (194 mg, 90%). This is a known compound.³⁵ **¹H NMR (500 MHz, CDCl₃):** δ = 7.57
Compound 5e

Under N₂, a flame-dried round-bottom flask was charged sequentially with PdCl₂ (91 mg, 0.5 mmol), PPh₃ (224 mg, 0.9 mmol), CuI (130 mg, 0.7 mmol) and MeCN (32 ml). The mixture was stirred at rt for 5 mins to give a dark brown solution. 4-Iodoanisole (4 g, 17.1 mmol), 1-hexyne (2.9 ml, 25.6 mmol) and Et₃N (7.2 mL, 51.3 mmol) were then added. The solution was allowed to stir at rt overnight. The crude mixture was then partitioned between water and Et₂O at room temperature. The organic layer washed with a saturated aqueous solution of NH₄Cl, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE) afforded alkyne 5e as an orange oil (3.2 g, quantitative). This is a known compound.³⁶; ¹H NMR (500 MHz, CDCl₃): δ = 7.35 – 7.28 (m, 2H), 6.83 – 6.76 (m, 2H), 3.77 (s, 3H), 2.37 (t, J = 7.0 Hz, 2H), 1.61 – 1.51 (m, 2H), 1.51 – 1.40 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

Compound 5f

This compound was prepared from 4-(trifluoromethoxy)phenylacetylene 57 (300 µl, 1.96 mmol) according to the procedure described for the preparation of 5d. Colourless Oil (251 mg, 64%); ¹H NMR (500 MHz, CDCl₃): δ = 7.40 – 7.35 (m, 2H), 7.13 – 7.08 (m, 2H), 2.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 148.3 (q, J = 1.7 Hz), 132.9, 122.8, 120.8, 120.4 (q, J = 257.6 Hz), 86.8, 78.4, 4.3; IR (neat): ν = 2958 (w), 2922 (w), 2860 (w), 1604 (w), 1507 (m), 1468 (w), 1379
Compound 5g

Under N₂, a flame-dried Schlenk flask was charged with Pd(PPh₃)₄ (697 mg, 0.60 mmol), CuI (115 mg, 0.60 mmol) and para-bromoacetophenone (4 g, 20.1 mmol). THF (84 ml), Et₃N (32 ml) and 1-Hexyne (3.4 ml, 30.1 mmol) were then added in that order. After stirring at 60°C for 18 hours, the crude mixture was partitioned between water and Et₂O at room temperature. The organic layer washed with a saturated aqueous solution of NH₄Cl, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE → PE/Et₂O: 10/1) afforded alkyne 5g as a pale yellow oil (3.68g, 89%). ¹H NMR (500 MHz, CDCl₃): δ = 7.82 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 2.53 (s, 3H), 2.39 (t, J = 7.0 Hz, 2H), 1.55 (quint, 7.5 Hz, 2H), 1.49–1.39 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 197.2, 135.5, 131.5 (2C), 129.1, 128.0 (2C), 94.3, 80.0, 30.5, 26.4, 21.9, 19.1, 13.5; IR (neat): ν = 2958 (w), 2933 (w), 2873 (w), 2229 (w), 1682 (s), 1601 (s), 1555 (w), 1466 (w), 1428 (w), 1403 (m), 1357 (m), 1329 (w), 738 (w) cm⁻¹; MS (Cl): m/z (rel. intensity): 218 (44) [M+NH₄]⁺, 201 (100) [M+H]⁺; elemental analysis (%) calcd for C₁₄H₁₆O: C 83.96, H 8.05; found: C 82.89, H 8.26.

Compound 5h

Under N₂, a flame-dried Schlenk flask was charged sequentially with Pd(PPh₃)₂Cl₂ (37 mg, 0.05 mmol), THF (4 ml), Et₃N (450 μL, 3.2 mmol), CuI (14 mg, 0.07 mmol) and 4-iodoanisole (250 mg, 1.07 mmol). After stirring for 5 minutes, cyclohexylacetylene (181 μL, 1.39 mmol) was
added. After stirring at room temperature for 18 hours, the crude mixture was partitioned between water and Et₂O at room temperature. The organic layer washed with a saturated aqueous solution of NH₄Cl, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE/Et₂O: 200/1) afforded alkyne 5h as an orange oil (188 mg, 81%). This is a known compound.³⁷ ¹H NMR (500 MHz, CDCl₃): δ = 7.34 – 7.29 (m, 2H), 6.81 – 6.76 (m, 2H), 3.77 (s, 3H), 2.59 – 2.49 (m, 1H), 1.91 – 1.81 (m, 2H), 1.79 – 1.68 (m, 2H), 1.57 – 1.45 (m, 3H), 1.38 – 1.26 (m, 3H)

**Compound 5i**

![Compound 5i](image)

This compound was prepared from 4-iodoanisole (250 mg, 1.07 mmol) and 4-methyl-1-pentyne (163 μL, 1.39 mmol) according to the procedure described for the preparation of 5h. Orange oil (204 mg, quantitative). ¹H NMR (500 MHz, CDCl₃): δ = 7.32 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H), 2.26 (d, J = 6.5 Hz, 2H), 1.93–1.80 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃): δ = 158.9, 132.8 (2C), 116.3, 113.8 (2C), 87.7, 81.1, 55.2, 28.6, 28.3, 22.0; IR (neat): ν = 2957 (m), 2932 (w), 2905 (w), 2870 (w), 2836 (w), 1607 (m), 1568 (w), 1507 (s), 1464 (m), 1442 (m), 1385 (w), 1368 (w), 1344 (w), 1282 (m), 1245 (s), 1172 (m), 1105 (w), 1035 (m), 830 (s), 800 (w), 665 (w) cm⁻¹; elemental analysis (%) calcd for C₁₃H₁₆O: C 82.94, H 8.57; found: C 82.17, H 9.01.

**Compound 5j**

![Compound 5j](image)

This compound was prepared from commercially available 4-ethynyl-α,α,α-trifluorotoluene (227 μL, 1.37 mmol) and 4-iodoanisole (250 mg, 1.07 mmol) according to the procedure described for the preparation of 5h. Yellow solid (300 mg, quant). This is a known compound.
\(^{38}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.61 - 7.55\) (m, 4H), 7.47 (d, \(J = 8.8\) Hz, 2H), 6.88 (d, \(J = 8.8\) Hz, 2H), 3.82 (s, 3H).

**Compound 5n**

![Chemical Structure](image)

This compound was prepared from commercially available 4-ethylbiphenyl (150 mg, 0.84 mmol) and 2-bromopropene (112 \(\mu\)L, 1.26 mmol) according to the procedure described for the preparation of 5h. White Solid (160 mg, 86%). m.p. 70–72°C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.59\) (d, \(J = 7.4\) Hz, 2H), 7.55 (d, \(J = 8.2\) Hz, 2H), 7.51 (d, \(J = 8.2\) Hz, 2H), 7.44 (t, \(J = 7.6\) Hz, 2H), 7.35 (t, \(J = 7.3\) Hz, 1H), 5.42 (s, 1H), 5.31 (s, 1H), 2.01 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 140.8, 140.3, 132.0\) (2C), 128.8 (2C), 127.6, 127.0 (2C), 126.93 (2C), 126.86, 122.2, 122.0, 91.2, 88.3, 23.5; IR (neat): \(\tilde{\nu} = 3056\) (w), 3033 (w), 2975 (w), 2920 (w), 2855 (w), 2199 (m), 1671 (m), 1612 (w), 1599 (m), 1581 (w), 1521 (w), 1486 (m), 1448 (m), 1405 (w), 1373 (w), 1316 (m), 1286 (w), 1155 (w), 1113 (m), 1076 (w), 1039 (w), 1006 (m), 976 (w), 893 (m), 840 (s), 761 (s), 721 (m), 692 (s) cm\(^{-1}\); elemental analysis (%) calcd for C\(_{17}\)H\(_{14}\): C 93.54, H 6.46; found: C 92.14, H 6.68.

**Compound 5p**

![Chemical Structure](image)

This compound was prepared from Phenylacetylene 38 (300 \(\mu\)L, 2.7 mmol) and chloro(dimethyl)phenylsilane (688 \(\mu\)L, 4.1 mmol) according to the procedure described for the preparation of 5d. Colourless Oil (660 mg, quantitative); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.71 - 7.65\) (m, 2H), 7.51 - 7.47 (m, 2H), 7.40 - 7.36 (m, 3H), 7.33 - 7.28 (m, 3H), 0.48 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 137.0, 133.7, 132.1, 129.4, 128.7, 128.2, 127.9, 122.9, 106.8, 92.0, -0.8\); IR (neat): \(\tilde{\nu} = 3068\) (w), 3020 (w), 2960 (w), 2158 (m), 1952 (w), 1883 (w), 1817 (w), 1593 (w), 1537 (m), 1486 (m), 1461 (w), 1442 (w), 1408 (w), 1373 (w), 1356 (w), 1337 (w), 1315 (m), 1284 (w), 1183 (w), 1151 (w), 1090 (m), 1039 (w), 953 (m), 892 (m), 867 (m), 765 (s), 721 (m), 692 (s) cm\(^{-1}\); elemental analysis (%) calcd for C\(_{41}\)H\(_{28}\)Si: C 66.72, H 3.68; found: C 66.26, H 3.68.
1574 (w), 1488 (m), 1443 (w), 1428 (w), 1407 (w), 1249 (m), 1219 (w), 1189 (w), 1157 (w), 1118 (m), 1069 (w), 1027 (w), 999 (w), 844 (s), 779 (s), 729 (s), 689 (s), 663 (m) cm⁻¹; HRMS (Cl): calcd for (C_{16}H_{16}Si + NH₄)⁺: 254.1360; found: 254.1358

**Compound 5q**

This compound was prepared from 1-decyne (500 µl, 2.77 mmol) and chlorotrimethylsilane (527 µl, 4.16 mmol) according to the procedure described for the preparation of 5d except at -78°C. This is a known compound.³⁹ Colourless oil (558 mg, 96%).; ¹H NMR (500 MHz, CDCl₃): δ = 2.19 (t, J = 2.19 Hz, 2H), 1.53 – 1.45 (m, 2H), 1.39 – 1.31 (m, 2H), 1.31 – 1.20 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H), 0.12 (s, 9H)

**Compound 5r**

This compound was prepared from cyclohexylacetylene (400 µl, 3.06 mmol) and chlorotrimethylsilane (583 µl, 4.59 mmol) according to the procedure described for the preparation of 5d except at -78°C. This compound is known.⁴⁰ Colourless Oil (505 mg, 91%); ¹H NMR (500 MHz, CDCl₃): δ = 2.41 – 2.30 (m, 1H), 1.82 – 1.72 (m, 2H), 1.72 – 1.63 (m, 2H), 1.52 – 1.35 (m, 3H), 1.33 – 1.19 (m, 3H), 0.12 (s, 9H); HRMS (Cl): calcd for (C_{11}H_{20}Si + NH₄)⁺: 198.1673; found: 198.1675

**Compound 5v**

A flamed dried schlenk was charged with 60% NaH (177mg, 4.4 mmol) and DMF (4 ml). At 0°C, 2-butyn-1-ol (300 µl, 4 mmol) was added dropwise. It was then allowed to stir at 0°C for 30
mins. Then, benzyl bromide (525 µl, 4.4 mmol) was added dropwise. Allowed to stir overnight at rt. Quenched with solution of aqueous NH₄Cl and Et₂O was added. Washed three timed with water, a saturated solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE/EtOAc: 1/0→75/1) afforded alkyne 5v as a colourless oil (579 mg, 90%). This a known compound.₄¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.38 – 7.25 (m, 5H), 4.57 (s, 2H), 4.12 (q, J = 2.3 Hz, 2H), 1.86 (t, J = 2.2 Hz, 3H)

**Compound 5w**

![TMS—O—Bn](attachment:compound5w.png)

A flamed dried Schlenk was charged with 60% NaH (297 mg, 7.42 mmol) and DMF (6.1 ml). At 0°C, 3-(trimethylsilyl)propargyl alcohol (1 ml, 6.77 mmol) was added dropwise. It was then allowed to stir at 0°C for 30 mins. Then, benzyl bromide (900 µl, 7.42 mmol) was added dropwise. Allowed to stir for 2 hours at rt. Quenched with solution of aqueous NH₄Cl and Et₂O was added. Washed three timed with water, a saturated solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE/Et₂O: 40/1→33/1) afforded alkyne S30 as a colourless oil (701 mg, 71%). At -78°C, 1.7M of nBuLi (2.4 ml, 4.10 mmol) was added to a solution of S30 (500 mg, 3.42 mmol) in THF (3.4 ml). After 15 mins of stirring at -78°C, trimethylsilylchloride (651 µl, 5.13 mmol) was added. The solution was allowed to stir for 15 mins at -78°C. Then the ice-bath was removed and allowed to stir at rt for 30 mins. Afterwards, the reaction was quenched with a saturated solution of NH₄Cl. Et₂O was added and the organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/Et₂O, 66/1→50/1) gave 5w as a colourless oil (653 mg, 88%); ¹H NMR (500 MHz, CDCl₃): δ = 7.37 – 7.25 (m, 5H), 4.58 (s, 2H), 4.15 (s,2H), 0.18 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ = 137.4, 128.4, 128.2, 127.9, 101.4, 91.6, 71.5, 57.9, -0.2; IR (neat): ν = 3066 (w), 3031 (w), 2960
Compound 5x

A flame-dried schlenk was charged with TBSCI (244mg, 1.6 mmol) and imidazole (202mg, 3.0 mmol). Then dissolved in DMF (0.85 ml) and 3-(trimethylsilyl)propargyl alcohol (200µl, 1.3 mmol) was added. Allowed to stir at rt overnight. Afterwards, Et₂O was added. Washed three times with water, a saturated solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE/Et₂O: 1/0  100/1) afforded 5x as a colourless oil (191 mg, 58%).; ¹H NMR (500 MHz, CDCl₃): δ = 4.29 (s, 2H), 0.89(s, 9H), 0.14 (s, 9H), 0.10 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ = 104.5, 89.6, 52.3, 25.8, 18.3, -0.3, -5.1; IR (neat): ν = 2957 (w), 2929 (w), 2899 (w), 2332 (w), 2178 (w), 1472 (w), 1463 (w), 1408 (w), 1390 (w), 1362 (w), 1251 (m), 1092 (m), 1003 (m), 939 (w), 831 (s), 776 (m), 759 (m), 722 (w), 699 (w), 668 (w) cm⁻¹; HRMS (Cl): calcd for (C₁₂H₂₆O₃Si₂ + NH₄)⁺: 243.1595; found: 243.1602

Compound 5y

This compound was prepared from 5-phenyl-1-pentyne (200 µl, 1.32 mmol) and iodomethane (123 µl, 1.98 mmol) according to the procedure described for the preparation of 5d except at -78°C. Colourless oil (195 mg, 93%); ¹H NMR (500 MHz, CDCl₃): δ = 7.30 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 2.69 (t, J = 7.6 Hz, 2H), 2.17 – 2.09 (m, 2H), 1.82 – 1.74 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ = 141.8, 128.5, 128.3, 125.8, 78.8, 75.9, 34.8, 30.6, 18.2, 3.5; IR (neat): ν = 3027 (w), 2919 (m), 2859 (m), 1604 (w), 1497 (m), 1454 (m), 1332 (w), 1080 (w), 1031 (w), 744 (m), 699 (s) cm⁻¹
A flamed dried schlenk was charged with 60% NaH (271 mg, 6.77 mmol) and DMF (6.5 ml). At 0°C, 4-pentyne-1-ol (0.6 ml, 6.45 mmol) was added dropwise. It was then allowed to stir at 0°C for 30 mins. Then, benzyl bromide (800 µl, 6.77 mmol) was added dropwise. Allowed to stir for 2 hours at rt. Quenched with solution of aqueous NH₄Cl and Et₂O was added. Washed three timed with water, a saturated solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (PE/Et₂O: 100/1→80/1) afforded alkyne S32 as a colourless oil (552 mg, 49%). At -78°C, 1.7M of nBuLi (0.8 ml, 1.38 mmol) was added to a solution of S32 (200 mg, 1.15 mmol) in THF (1.2 ml). After 15 mins of stirring at -78°C, iodomethane (107 µl, 1.72 mmol) was added. The solution was allowed to stir for 15 mins at -78°C. Then the ice-bath was removed and allowed to stir at rt for 30 mins. Afterwards, the reaction was quenched with a saturated solution of NH₄Cl. Et₂O was added and the aqueous layer was extracted two times with Et₂O. The organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/Et₂O, 50/1) gave 5z as a colourless oil (187 mg, 87%). ¹H NMR (500 MHz, CDCl₃): δ = 7.36 – 7.25 (m, 5H), 4.50 (s, 2H), 3.54 (t, J = 6.2 Hz, 2H), 2.28 – 2.20 (m, 2H), 1.81 – 1.72 (m, 5H); IR (neat): ν = 3064 (w), 3030 (w), 2946 (w), 2919 (w), 2856 (m), 1496 (w), 1454 (m), 1364 (m), 1204 (w), 1102 (s), 1079 (s), 1028 (w), 909 (w), 735 (s), 697 (s) cm⁻¹; HRMS (CI): calcd for (C₁₃H₁₆O + H)⁺: 189.1274; found: 189.1274

Compound 5aaa

This compound was prepared by Jet-Sing Lee. Under N₂, a solution of biphenyl-4-methanol (400 mg, 2.17 mmol) in DMF (5.5 mL) was added NaH (60 wt%, 130 mg, 3.26 mmol) at 0°C. The
mixture was left to stir at r.t. for 1 hour. To this mixture was then added dropwise 1-bromo-2-butyn (300 µL, 3.26 mmol) at 0°C. The mixture was left to stir at r.t. overnight. The golden coloured mixture was quenched with a saturated solution of NH₄Cl at 0°C, diluted with Et₂O and washed with brine. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc, 50:1) to yield 5aa as a white solid (452 mg, 89%). ¹H NMR (500Mz, CDCl₃): 7.64-7.59 (m, 4H), 7.50-7.44 (m, 4H), 7.40-7.35 (m, 1H), 4.66 (s, 2H), 4.21-4.18 (d, J = 2.3 Hz, 2H), 1.92 (t, J = 2.3 Hz, 3H).

**Compound 43**

This compound was prepared from commercially available phenylacetylene (153 µl, 1.39 mmol) and 2-iodopyridine (115 µl, 1.07 mmol) according to the procedure described for the preparation of 5h. White solid (100 mg, 58%). This is a known compound.¹H NMR (500 MHz, CDCl₃): δ = 8.60 (d, J = 4.6 Hz, 1H), 7.65 (apt dt, J = 7.7, 1.3 Hz,1H), 7.61 – 7.55 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.23 – 7.18 (m, 1H)

**Compound 44**

This compound was prepared from commercially available 1-hexyne (160 µl, 1.39 mmol) and 2-iodopyridine (115 µl, 1.07 mmol) according to the procedure described for the preparation of 5h. Colourless oil (142 mg, 73%). This is a known compound.¹H NMR (500 MHz, CDCl₃): δ = 8.51 (d, J = 4.4 Hz, 1H), 7.57 (apt dt, J = 7.7, 1.50 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.14 (dd, J = 7.0, 5.4 Hz, 1H), 2.42 (t, J = 7.1 Hz, 2H), 1.59 (pent, J = 7.4 Hz, 2H), 1.47 (sext, J = 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H)
**Compound 56**

![Chemical Structure](image)

In a flame-dried schlenk, 2-butyne-1,4-diol (200 mg, 2.3 mmol), Et$_3$N (1 ml, 6.97 mmol) and DCM (4.7 ml) were added. At 0°C, acetyl chloride (0.5 ml, 6.97 mmol) was added dropwise over 5 mins. Then allowed to stir overnight at rt. Afterwards, the reaction was quenched with H$_2$O and EtOAc was added. The organic layer was washed with a saturated solution of NaHCO$_3$, water and a saturated solution of brine. Dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (PE/Et$_2$O, 7/1) gave 56 as a colourless oil (328 mg, 83%). This is a known compound. $^{44}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.68 (s, 4H), 2.07 (s, 6H)

**Compound 57**

![Chemical Structure](image)

This compound was prepared from commercially available 2-butyne-1,4-diol (200 mg, 2.3 mmol), benzyl bromide (608 µl, 5.1 mmol) and 60% NaH (205 mg, 5.1 mmol) according to the procedure described for the preparation of 5v. Colourless Oil (401 mg, 65%): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.42 – 7.28$ (m, 10H), 4.62 (s, 4H), 4.25 (s, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 137.3, 128.4, 128.1, 127.9, 82.5, 71.6, 57.4$; IR (neat): $\tilde{\nu} = 3064$ (w), 3031 (w), 2860 (w), 1717 (w), 1603 (w), 1454 (m), 1349 (m), 1264 (w), 1119 (m), 1069 (s), 1026 (m), 908 (w), 739 (s), 698 (s) cm$^{-1}$; HRMS (Cl): calcd for (C$_{18}$H$_{18}$O$_2$ + NH$_4$)$^+$: 284.1645; found: 284.1643

**Compound 58**

![Chemical Structure](image)

This compound was prepared from commercially available 2-butyne-1,4-diol (200 mg, 2.3 mmol), TBSCI (840 mg, 5.6 mmol) and imidazole (840 mg, 10.2 mmol) in DMF (2ml) according
to the procedure described for the preparation of 5x. Colourless oil (768 mg, quantitative). This a known compound.\textsuperscript{45}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta = 4.32 \, (s, \, 4H), \, 0.88 \, (s, \, 18H), \, 0.09 \, (s, \, 12H) \)

**Compound 59**

\[
\text{\begin{center}
\includegraphics[width=1cm]{59.png}
\end{center}}
\]

Compound 59 was obtained using a procedure described by Liu and is fully described within.\textsuperscript{29a} White solid (109 mg, 53%); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta = 7.45 \, – \, 7.39 \, (m, \, 2H), \, 7.31 \, – \, 7.26 \, (m, \, 3H), \, 4.48 \, (a pt, \, J = 8.0 \, Hz, \, 2H), \, 4.00 \, (a pt, \, J = 8.0 \, Hz, \, 2H) \)

**Compound 60**

\[
\text{\begin{center}
\includegraphics[width=1cm]{60.png}
\end{center}}
\]

Compound 59 was obtained using a modified procedure described by Liu.\textsuperscript{29a} This compound is known.\textsuperscript{46} Purple solid (356 mg, 89%); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta = 7.77 \, (d, \, J = 8.2 \, Hz, \, 2H), \, 7.35 \, – \, 7.26 \, (m, \, 7H), \, 7.24 \, – \, 7.19 \, (m, \, 5H), \, 4.56 \, (s, \, 2H), \, 2.43 \, (s, \, 3H) \)

**Compound 61**

\[
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\end{center}}
\]

At -78°C, 1.8M nBuli (0.4 ml, 0.7 mmol) was added to a yellow solution of ethoxyacetylene solution (~40 wt. % in hexanes) \textbf{57} (150 µl, 0.61 mmol) in THF (0.7 ml). The solution was stirred for 15 mins at -78°C. Afterwards, HMPA (212 µl, 1.22 mmol) was added and the solution was stirred for a further ten minutes. Then, 1-bromoocctane (84 µl, 0.49 mmol) was added. The solution was allowed to stir for 15 mins at -78°C. Then the ice-bath was removed and allowed to stir at rt for 90 mins. Afterwards, the reaction was quenched with a saturated solution of
NH₄Cl. Et₂O was added and extracted two times with Et₂O. The organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE) gave 61 as a colourless oil (55 mg, 65%).; ¹H NMR (500 MHz, CDCl₃): δ = 4.00 (q, J = 7.0 Hz, 2H), 2.08 (t, J = 6.9 Hz, 2H), 1.46 – 1.38 (m, 2H), 1.37 – 1.16 (m, 13H), 0.89 – 0.83 (m, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 89.3, 73.8, 37.4, 31.8, 29.7, 29.2, 29.1, 28.8, 22.7, 17.2, 14.4, 14.1; IR (neat): ν = 2952 (w), 2926 (m), 2854 (m), 2271 (m), 1466 (w), 1439 (w), 1379 (w), 1289 (w), 1222 (s), 1089 (w), 1010 (m), 924 (w), 864 (w), 723 (w) cm⁻¹

**Compound 62**

![Chemical structure](image)

This compound was prepared from 4-ethynylanisole (300 µl, 2.3 mmol) and NCS (402mg, 3.0 mmol) according to the procedure described for the preparation of 5d except at -78°C. Yellow Oil (294 mg, 76%); ¹H NMR (500 MHz, CDCl₃): δ = 7.38 – 7.33 (m, 2H), 6.84 – 6.79 (m, 2H), 3.79 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 159.8, 133.4, 114.2, 114.0, 69.3, 66.4, 55.3; IR (neat): ν = 3005 (w), 2934 (w), 2838 (w), 2220 (w), 1606 (m), 1507 (s), 1291 (m), 1248 (s), 1172 (m), 1034 (m), 888 (w), 830 (m) cm⁻¹; HRMS (CI): calcd for (C₉H₇ClO + NH₄)⁺: 184.0524; found: 184.0528

**Compound 63**

![Chemical structure](image)

This compound was prepared from commercially available iodobenzene (120 µl, 1.07 mmol) and 4-bromo-1-butyne (130 µl, 1.39 mmol) according to the procedure described for the preparation of 5h. Colourless oil (192 mg, 86%). This is a known compound; ¹H NMR (500
Compound 100

This compound was prepared from commercially available 4-iodoanisole (250 mg, 1.07 mmol) and 4-ethynylanisole (180 µl, 1.39 mmol) according to the procedure described for the preparation of 5h. Yellow solid (176 mg, 70%). This is a known compound. \(^{48}\); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.45 - 7.40\) (m, 2H), 6.87 – 6.82 (m, 2H), 3.81 (s, 3H)

### 2.7.4 Nickel(0): Synthesis of pyridinones and pyranones

**Procedures**

**Method I.** Inside a glovebox, a Teflon-screw flame-dried Schlenk flask equipped with a small stirrer bar was charged with Ni(cod)$_2$ (8 mg, 0.03 mmol) and taken out of the glovebox. Under N$_2$, PPh$_3$ (23 mg, 0.09 mmol) and dioxane (1.3 ml) were added. The suspension was stirred for 5 minutes and then commercially available azetidinone 7 (49 mg, 0.29 mmol) was added as solid in one portion. After stirring for 5 more minutes, bis-phenylacetylene 5a (57 mg, 0.32 mmol) was added and the flask was sealed and immersed into an oil bath pre-heated at 90 oC. After stirring for 17 hours at that temperature, the mixture was allowed to cool and filtered through a silica plug before evaporation. Purification by flash chromatography (PE/Et2O, 10/1 → 1/1) afforded 6a as white solid (91 mg, 90%).

**Method II.** Used for alkynes which are oils or liquids, the procedure is identical to method I except that Ni(cod)$_2$ and PPh$_3$ were diluted in 1 ml dioxane and that the alkyne was added as a dioxane solution (0.3 ml) under N$_2$.  

132
Method III. Identical to method I except that Ni(cod)$_2$ and PPh$_3$ were diluted in 0.3 mL of dioxane before azetidinone and alkyne were added via canula as a premixed dioxane solution (1 mL).

The NMR spectra of some compounds were recorded at the different temperatures and using a modified delay (d given in s) for the $^{13}$C spectra in order to obtain optimum resolution, which was poor at room temperature due to slow conformer equilibration. Details mentioned after description of the compound.

**Compound 6a**

![Chemical structure of Compound 6a](image)

White solid. (91 mg, 90% using method I): m.p. 127–129°C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.21–7.13 (m, 6H), 7.12–7.06 (m, 2H), 7.00–6.94 (m, 2H), 4.61 (br s, 2H), 4.31 (s, 2H), 1.51 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 192.3, 154.9 (br),$^\text{^1}$ 154.3, 137.0, 135.9, 133.6, 130.8 (2C), 128.7, 128.5 (2C), 128.2 (2C), 127.7 (2C), 127.3, 81.2, 51.8 (br), 48.0 (br), 28.4 (3C); IR (neat): $\tilde{\nu}$ = 3057 (w), 3007 (w), 2974 (w), 2929 (w), 1682 (s), 1619 (w), 1596 (w), 1574 (w), 1492 (w), 1479 (w), 1443 (m), 1421 (s), 1366 (m), 1326 (m), 1250 (m), 1232 (m), 1155 (s), 1194 (s), 1104 (s), 1083 (w), 994 (w), 936 (w), 924 (w), 904 (w), 858 (m), 768 (m), 757 (s), 694 (s) cm$^{-1}$; HRMS (ESI): calcd for (C$_{22}$H$_{23}$NO$_3$ + Na): 372.1576; found: 372.1589; elemental analysis (%) calcd for C$_{22}$H$_{23}$NO$_3$: C 75.62, H 6.63, N 4.01; found: C 75.03, H 6.50, N 3.75.

$^\text{^1}$ Carbon appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{13}$C APT NMR spectrum. Similar observation was made on related Boc-protected compounds.$^{49}$

($^{13}$C APT NMR (d = 2) and $^{13}$C CPD NMR (d = 4): 40°C)
Compound 8

Colourless oil isolated in 30% yield following conditions of table 1, entry 1. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.95–7.51 (br s, 1H), 7.39 (d, $J$ = 7.7 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 2H), 7.29–7.14 (m, 6H), 4.57 (d, $J$ = 1.6 Hz, 1H), 4.20 (d, $J$ = 18.9 Hz, 1H), 3.95 (dd, $J$ = 18.8 Hz, 2.1 Hz, 1H), 1.53 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 201.7, 151.9 (br), 137.7, 135.7, 129.3 (2C), 128.6 (2C), 127.9, 127.7 (2C), 127.0, 125.3 (2C + 1C), 116.0, 82.5, 56.0 (br), 50.2 (br), 28.3 (3C); IR (neat): $\tilde{\nu}$ = 3058 (w), 2978 (w), 2930 (w), 1759 (m), 1702 (s), 1599 (w), 1492 (w), 1448 (w), 1394 (w), 1369 (m), 1316 (w), 1239 (s), 1149 (s), 1117 (m), 1072 (w), 1026 (w), 852 (w), 764 (m), 698 (s) cm$^{-1}$; HRMS (ESI): calcd for (C$_{22}$H$_{23}$NO$_3$ + Na): 372.1576; found: 372.1581.

($^{13}$C APT NMR (d = 2): 50°C, $^{13}$C CPD NMR (d = 4): 50°C)

Compound 6b

Colourless oil (65 mg, 88% using method I); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.09 (br s, 2H), 4.00 (s, 2H), 2.22 (dt, $J$ = 7.2 Hz, 4H), 1.52 (sext, $J$ = 7.6 Hz, 2H), 1.43 (s, 9H), 1.32 (sext, $J$ = 7.6Hz, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H), 0.88 (t, $J$ = 7.3Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 193.1, 154.2, 155.8, 134.3, 80.6, 51.4, 46.1, 34.2, 28.3, 26.6, 22.4, 21.4, 14.1, 14.1; IR (neat): $\tilde{\nu}$ = 2962 (m), 2032 (w), 2873 (w), 1700 (s), 1672 (s), 1633 (m), 1417 (m), 1366 (s), 1281 (m), 1240 (m), 1164 (s), 1130 (s), 1095 (m), 1032 (w), 978 (w), 904 (m), 861 (w), 766 (m), 737 (w) cm$^{-1}$; MS (ESI): calcd for (C$_{16}$H$_{27}$NO$_3$ + Na): 304.1889; found: 304.1895; elemental analysis (%) calcd for C$_{16}$H$_{27}$NO$_3$: C 68.29, H 9.67, N 4.98; found: C 66.50, H 9.53, N 4.98.
^ Carbon is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation

**Compound 6c**

![Compound 6c](image)

Colourless oil (64 mg, 80% from 48 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.46$–7.33 (m, 3H), 7.29–7.22 (m, 2H), 4.39 (br s, 2H), 4.17 (s, 2H), 1.75 (s, 3H), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 193.9, 154.1, 153.6$ (br), $^\wedge 137.3, 130.6, 128.8, 128.6$ (2C), 127.6 (2C), 80.8, 51.2 (br), 47.8 (br), 28.3 (3C), 11.9; IR (neat): $\tilde{\nu} = 3053$ (w), 2977 (w), 2929 (w), 1694 (s), 1675 (s), 1632 (w), 1575 (w), 1476 (w), 1416 (m), 1383 (m), 1381 (m), 1364 (s), 1326 (m), 1281 (m), 1244 (s), 1230 (s), 1163 (s), 1116 (s), 1068 (w), 1032 (w), 1003 (w), 994 (w), 896 (w), 861 (w), 763 (m), 701 (s) cm$^{-1}$; HRMS (ESI): calcd for (C$_{17}$H$_{21}$NO$_3$ + Na): 310.1419; found: 310.1432; elemental analysis (%) calcd for C$_{17}$H$_{21}$NO$_3$: C 71.06, H 7.37, N 4.87; found: C 70.74, H 7.51, N 4.92.

^ Carbon appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{13}$C APT NMR spectrum.

($^{13}$C APT NMR (d = 2): 40°C)

**Compound 11c**

White solid (10 mg, 12% from 48 mg of 7 using method II): m.p.: 104–106°C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.37$ (t, $J = 7.3$ Hz, 2H), 7.33–7.28 (m, 1H), 7.07 (d, $J = 7.4$ Hz, 2H), 4.28 (br s, 2H), 4.20 (s, 2H), 1.84 (s, 3H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 191.6, 154.6$,
154.2, 136.3, 133.8, 129.9 (2C), 128.2 (2C), 127.7, 81.0, 51.4 (br), 47.7 (br), 28.4 (3C), 19.5; IR (neat): $\tilde{\nu}$ = 2977 (w), 2931 (w), 1695 (s), 1677 (s), 1636 (w), 1600 (w), 1495 (w), 1479 (w), 1417 (m), 1393 (w), 1365 (m), 1323 (w), 1285 (w), 1243 (s), 1217 (w), 1157 (s), 1107 (m), 1075 (w), 1047 (w), 977 (w), 946 (w), 895 (m), 857 (w), 763 (m), 701 (w); HRMS (ESI): calcd for (C$_{17}$H$_{21}$NO$_3$ + Na): 310.1419; found: 310.1422.

$^{13}$C APT NMR (d = 2): 45°C

^ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets.

**Compound 6c**

White foam (86 mg, 83% from 49 mg of 7 using method I): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.64 (d, $J$ = 8.2 Hz, 2H), 7.62–7.57 (m, 2H), 7.47–7.41 (m, 2H), 7.38–7.32 (m, 3H), 4.43 (br s, 2H), 4.19 (s, 2H), 1.82 (t, $J$ = 1.8 Hz, 3H), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 193.9, 154.2, {153.8},^ 141.9, 140.2, 136.1, 130.8, 128.9 (2C), 128.2 (2C), 127.8, 127.3 (2C), 127.1 (2C), 80.9, 51.4, 47.8, 28.4 (3C), 12.1; IR (neat): $\tilde{\nu}$ = 2975 (w), 2926 (w), 1698 (s), 1676 (s), 1629 (w), 1488 (w), 1419 (m), 1401 (m), 1380 (m), 1364 (m), 1283 (w), 1240 (m), 1232 (m), 1165 (s), 1119 (m), 1071 (w), 1007 (w), 898 (w), 861 (w), 841 (w), 766 (m), 735 (w), 698 (w) cm$^{-1}$; MS (ESI): calcd for (C$_{23}$H$_{25}$NO$_3$ + Na): 386.1732; found: 386.1745; elemental analysis (%) calcd for C$_{23}$H$_{25}$NO$_3$: C 76.01, H 6.93, N 3.85; found: C 75.08, H 7.04, N 3.71.

$^{13}$C APT NMR (d = 2): 40°C

^ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets.
**Compound 11d**

![Compound 11d](image)

Colourless oil (8 mg, 8% from 49 mg of 7 using method I): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.63–7.56 (m, 4H), 7.45–7.39 (m, 2H), 7.36–7.29 (m, 1H), 7.15 (d, $J$ = 8.1 Hz, 2H), 4.30 (br s, 2H), 4.20 (s, 2H), 1.90 (s, 3H), 1.50 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 191.6, (155.2),^ 154.1, 140.9, 140.6, 136.0, 132.7, 130.3 (2C), 128.7 (2C), 127.3, 127.1 (2C), 126.9 (2C), 81.0, 51.5, 47.7, 28.4 (2C), 19.6; IR (neat): $\tilde{\nu}$ = 3029 (w), 2977 (w), 2933 (w), 1696 (s), 1678 (s), 1636 (w), 1601 (w), 1487 (w), 1417 (w), 1366 (m), 1325 (w), 1284 (w), 1243 (m), 1220 (w), 1157 (s), 1108 (w), 1040 (w), 1008 (w), 977 (w), 938 (w), 895 (w), 837 (w), 766 (m), 732 (m), 698 (m) cm$^{-1}$; HRMS (ESI): calcd for (C$_{23}$H$_{25}$NO$_3$ + Na): 386.1732; found: 386.1733.

($^{13}$C APT NMR (d = 2): 40°C)

^ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets.

**Compound 6e**

![Compound 6e](image)

Yellow oil (80 mg, 79% from 48 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.18 (d, $J$ = 8.4 Hz, 2H), 6.92 (d, $J$ = 8.6 Hz, 2H), 4.32 (br s, 2H), 4.12 (s, 2H), 3.82 (s, 3H), 2.24–2.14 (m, 2H), 1.46 (s, 9H), 1.30–1.20 (m, 2H), 1.14 (sext, $J$ = 7.3 Hz, 2H), 0.74 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 193.7, 160.0, 154.3, 153.7 (br),^ 135.2, 129.7, 128.8 (2C), 114.1 (2C), 80.8, 55.3, 51.7 (br), 48.3 (br), 31.4, 28.3 (2C), 25.6, 22.6, 13.6; IR (neat): $\tilde{\nu}$ = 2960 (w),
2931 (w), 2861 (w), 1699 (m), 1675 (s), 1607 (m), 1412 (m), 1366 (m), 1287 (w), 1246 (s), 1163 (s), 1124 (s), 1040 (m), 1028 (m), 945 (w), 900 (w), 861 (w), 732 (s), 767 (m), 731 (m) cm⁻¹; HRMS (ESI): calcd for (C₂₁H₂₉NO₄ + Na): 382.1994; found: 382.1985; elemental analysis (%) calcd for C₂₁H₂₉NO₄: C 70.17, H 8.13, N 3.90; found: C 69.19, H 8.41, N 3.64.

(¹³C APT NMR (d = 2): 40°C and ¹³C CPD NMR (d = 4): 45°C)

Carbon marked with an asterisk appears as a very broad peak in ¹³C CPD NMR spectrum and is not visible in the ¹³C APT NMR spectrum. However, HMBC correlations are visible which confirms the ¹³C CPD NMR.

**Compound 11e**

![Compound 11e](image)

Colourless oil (10 mg, 10% from 48 mg of 7 using method II): ¹H NMR (500 MHz, CDCl₃): δ = 6.97 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.28 (br s, 2H), 4.17 (s, 2H), 3.80 (s, 3H), 2.19–2.11 (m, 2H), 1.48 (s, 9H), 1.46–1.36 (m, 2H), 1.25–1.14 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 192.5, 159.1, 158.1 (br),¹ 154.3, 135.9, 131.0 (2C), 126.0, 113.8 (2C), 80.9, 55.2, 51.7 (br), 46.1 (br), 33.0, 30.2, 28.4 (3C), 22.7, 13.6; IR (neat): ν = 2959 (w), 2930 (w), 2862 (m), 1698 (m), 1676 (s), 1606 (m), 1510 (m), 1416 (m), 1366 (m), 1329 (w), 1287 (m), 1243 (s), 1154 (s), 1107 (m), 1033 (m), 989 (w), 927 (w), 896 (w), 858 (w), 828 (m), 798 (w), 766 (w) cm⁻¹; HRMS (ESI): calcd for (C₂₁H₂₉NO₄ + Na): 382.1994; found: 382.1996.

(¹³C APT NMR (d = 2) and ¹³C CPD NMR (d = 4): 45°C)

Carbon marked with an asterisk appears as a very broad peak in ¹³C CPD NMR spectrum and is not visible in the ¹³C APT NMR spectrum. However, HMBC correlations are visible which confirms the ¹³C CPD NMR.
**Compound 6f**

Colourless oil (72 mg, 69% from 48 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.33 – 7.24 (m, 4H), 4.35 (br s, 2H), 4.16 (s, 2H), 1.77 – 1.71 (m, 3H), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 193.6, 154.1, 152.0, $^*$149.5 (m), 135.9, 131.3, 129.3, 120.5 (q, 257.9 Hz), 121.0, 81.1, 51.4, 47.8, 28.3, 12.0; IR (neat): $\tilde{\nu} =$ 2984 (w), 2922 (w), 1692 (m), 1677 (m), 1625 (w), 1507 (w), 1420 (w), 1363 (w), 1209 (s), 1152 (s), 1114 (s), 1016 (w), 1001 (w), 897 (w), 834 (m), 762 (w), 685 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{18}$H$_{20}$NO$_4$F$_3$ + Na): 394.1242; found: 394.1258

($^{13}$C APT NMR (d = 2) and $^{13}$C CPD NMR (d = 4): 45°C)

$^*$Carbon marked with an asterisk appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{12}$C APT NMR spectrum. However, HMBC correlations are visible which confirms the $^{13}$C CPD NMR.

**Compound 6g**

Yellow oil (91 mg, 88% from 48 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.98 (d, $J =$ 7.4 Hz, 2H), 7.32 (d, $J =$ 7.4 Hz, 2H), 4.32 (br s, 2H), 4.14 (s, 2H), 2.60 (s, 3H), 2.20–2.05 (m, 2H), 1.44 (s, 9H), 1.28–1.18 (m, 2H), 1.15–1.03 (m, 2H), 0.70 (t, $J =$ 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 197.1, 193.2, 154.2, {152.8}, $^*$146.6, 142.1, 137.2, 135.9, 128.6 (2C), 127.6 (2C), 82.1, 51.6 (br), 48.0 (br), 31.3, 28.3 (2C), 26.4, 25.6, 22.5, 13.6; IR (neat): $\tilde{\nu} =$ 2960 (w), 2931 (w), 2872 (w), 1680 (s), 1604 (m), 1560 (w), 1401 (m), 1365 (s), 1264 (s), 1162 (s),
1128 (s), 1076 (w), 1037 (w), 1015 (w), 958 (m), 910 (w), 835 (m), 769 (w), 732 (m) cm\(^{-1}\); HRMS (ESI): calcd for (C\(_{22}\)H\(_{29}\)NO\(_4\) + Na): 394.1994; found: 394.2001.

(13C APT NMR (d = 2): 40°C)

^ Carbon marked with an asterisk is not visible in the \(^{13}\)C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets

**Compound 11g**

![Chemical structure of Compound 11g]

Colourless oil (12 mg, 11% from 48 mg of 7 using method II): \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.95 (d, J = 8.1 \text{ Hz}, 2\text{H}), 7.16 (d, J = 8.2 \text{ Hz}, 2\text{H}), 4.31 (\text{br s}, 2\text{H}), 4.18 (s, 2\text{H}), 2.59 (s, 3\text{H}), 2.19–2.09 (m, 2\text{H}), 1.49 (s, 9\text{H}), 1.47–1.36 (m, 2\text{H}), 1.26–1.14 (m, 2\text{H}), 0.78 (t, J = 7.4 \text{ Hz}, 3\text{H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 197.6, 191.8, \{158.8\},^\wedge 154.2, 139.2, 136.6, 135.6, 130.2 (2\text{C}), 128.2 (2\text{C}), 81.2, 51.7 (\text{br}), 46.1 (\text{br}), 33.0, 30.2, 28.4 (3\text{C}), 26.5, 22.7, 13.6; IR (neat): \(\tilde{\nu} = 2961 \text{ (w), 2932 (w), 2872 (w), 1683 (s), 1628 (w), 1604 (w), 1430 (w), 1403 (w), 1366 (w), 1324 (w), 1265 (w), 1244 (w), 1159 (m), 1110 (w), 958 (w), 897 (w), 830 (w) cm\(^{-1}\); MS (ESI): calcd for (C\(_{22}\)H\(_{29}\)NO\(_4\) + Na): 394.1994; found: 394.2000.

(\(^1\)H NMR: 45°C, \(^{13}\)C APT NMR (d = 2): 45°C)

^ Carbon marked with an asterisk is not visible in the \(^{13}\)C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets
Compound 6h

Colorless oil (88 mg, 76% from 51 mg of 7 using method III); ¹H NMR (500 MHz, CDCl₃): δ = 7.20–7.11 (m, 2H), 6.92 (d, J = 8.0 Hz, 2H), 4.27 (br s, 2H), 4.05 (s, 2H), 3.83 (s, 3H), 2.25 (t, J = 11.3 Hz, 1H), 1.90 (qd, J = 12.6 Hz, 2.8 Hz, 2H), 1.63 (d, J = 12.7 Hz, 2H), 1.55–1.48 (m, 1H), 1.46 (s, 9H), 1.38 (d, J = 12.4 Hz, 2H), 1.26–1.11 (m, 2H), 1.06–0.93 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 193.8, 160.0, 154.3, 154.0 (br), 138.7, 130.1, 128.8 (2C), 114.1 (2C), 80.7, 55.3, 52.5 (br), 48.9 (br), 40.1, 30.6, 28.4 (3C), 26.9, 25.8; IR (neat): ν = 2972 (w), 2926 (m), 1698 (s), 1572 (w), 1509 (m), 1442 (w), 1413 (w), 1393 (w), 1366 (s), 1328 (w), 1307 (m), 1287 (m), 1244 (s), 1166 (s), 1129 (s), 1088 (w), 1031 (w), 996 (w), 926 (w), 890 (w), 870 (w), 832 (m), 791 (w), 772 (m), 741 (w) cm⁻¹; HRMS (ESI): calcd for (C₂₃H₃₁NO₄ + Na): 408.2151; found: 408.2145; elemental analysis (%) calcd for C₂₃H₃₁NO₄: C 71.66, H 8.11, N 3.63; found: C 70.08, H 8.18, N 3.39.

¹³C APT NMR (d = 2) and ¹³C CPD NMR (d = 4): 45°C

Carbon appears as a very broad peak in ¹³C CPD NMR spectrum and is not visible in the ¹³C APT NMR spectrum.

Compound 11h

Colourless oil (14 mg, 12% from 51 mg of 7 using method III); ¹H NMR (500 MHz, CDCl₃): δ = 6.95 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.28 (br s, 2H), 4.14 (s, 2H), 3.81 (s, 3H), 2.40 (tt, J = 12.1 Hz, 3.1 Hz, 1H), 1.77–1.67 (m, 2H), 1.66–1.55 (m, 3H), 1.49 (s, 9H), 1.46–1.32 (m, 3H),
1.18–0.99 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 193.0, 162.1$ (br),$^\wedge$ 159.1, 154.3, 134.9, 130.7 (2C), 126.2, 113.8 (2C), 80.9, 55.2, 52.0 (br), 43.1 (br), 42.4, 30.7, 28.4 (3C), 25.9, 25.7; IR (neat): $\tilde{\nu} = 2967$ (w), 2929 (m), 2854 (w), 1698 (s), 1678 (s), 1605 (m), 1510 (s), 1445 (m), 1422 (m), 1393 (w), 1366 (m), 1324 (w), 1286 (m), 1243 (s), 1158 (s), 1107 (w), 1034 (w), 1002 (w), 903 (w), 858 (w), 828 (m), 801 (w), 766 (w), 731 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{23}$H$_{31}$NO$_4$ + Na): 408.2151; found: 408.2157.

($^{13}$C APT NMR (d = 2) and $^{13}$C CPD NMR (d = 4): 45°C)

$^\wedge$ Carbon appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{13}$C APT NMR spectrum.

**Compound 6i**

![Compound 6i](image)

Colourless oil (76 mg, 76% from 47 mg of 7 using method III): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.19$–7.13 (m, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 4.32 (br s, 2H), 4.13 (s, 2H), 3.82 (s, 3H), 2.17 (d, $J = 7.4$ Hz, 2H), 1.65–1.56 (m, 1H), 1.47 (s, 9H), 0.64 (d, $J = 6.7$, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 194.0, 159.9, \{155.8\}$,$^\wedge$ 154.4, 134.4, 129.7, 129.1 (2C), 114.1 (2C), 80.8, 55.2, 51.8 (br), 48.8 (br), 34.1, 28.3 (3C), 27.6, 22.2; IR (neat): $\tilde{\nu} = 2957$ (m), 2932 (w), 2869 (w), 1698 (s), 1674 (s), 1608 (m), 1573 (w), 1510 (m), 1464 (m), 1440 (m), 1412 (m), 1394 (m), 1365 (s), 1323 (m), 1306 (w), 1282 (m), 1242 (s), 1162 (s), 1124 (s), 1070 (m), 1042 (m), 1027 (m), 981 (w), 917 (w), 880 (m), 858 (w), 832 (s), 769 (m), 733 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{21}$H$_{29}$NO$_4$ + Na): 382.1994; found: 382.2002; elemental analysis (%) calcd for C$_{23}$H$_{29}$NO$_4$: C 70.17, H 8.13, N 3.90; found: C 69.56, H 8.22, N 3.84.

($^{13}$C APT NMR (d = 2): 45°C);
^ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets

**Compound 11i**

![Structure of Compound 11i]

Colourless oil (15 mg, 15% from 47 mg of 7 using method III): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 6.95 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H), 4.25 (br s, 2H), 4.17 (s, 2H), 3.80 (s, 3H), 2.10 (d, $J$ = 7.4 Hz, 2H), 1.87–1.75 (m, 1H), 1.47 (s, 9H), 0.78 (d, $J$ = 6.1 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 192.6, 159.1, {157.7}, $^\wedge$ 154.2, 136.8, 131.2 (2C), 126.1, 113.8 (2C), 81.0, 55.2, 51.8 (br), 46.4 (br), 42.2, 28.4 (3C), 27.2, 22.5; IR (neat): $\tilde{\nu}$ = 2958 (m), 2932 (w), 2870 (w), 2837 (w), 1697 (s), 1677 (s), 1606 (m), 1577 (w), 1510 (s), 1420 (m), 1393 (m), 1366 (s), 1322 (w), 1287 (m), 1241 (s), 1154 (s), 1106 (m), 1034 (m), 990 (w), 926 (w), 900 (w), 856 (w), 828 (m), 810 (w), 797 (w), 766 (w), 730 (w), 675 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{21}$H$_{29}$NO$_4$ + Na): 382.1994; found: 382.2000.

($^{13}$C APT NMR (d = 4); 45°C);

^ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets

**Compound 6j and 11j**

![Structure of Compounds 6j and 11j]

After purification by flash chromatography, a 55:45 mixture of regioisomers was obtained as white solid (102 mg, 82% from 47 mg of 7 using method I). However, solubilisation of this
material in 1 mL CH$_2$Cl$_2$ and adding a layer of PE (3 mL) induced precipitation of a solid which was filtered and washed with PE and dried. This solid was an enriched mixture ($6j/11j = 6:1$) and evaporation of the filtrate gave a mixture enriched in the other regioisomer ($6j/11j = 1:4$). This facilitated the interpretation of the NMR spectra. $^1$H NMR (400 MHz, CDCl$_3$): ($6j$) $\delta = 7.44$ (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.01 (d, $J = 8.0$ Hz, 2H), 6.71 (d, $J = 8.0$ Hz, 2H), 4.62 (br s, 2H), 4.29 (s, 2H), 3.74 (s, 3H), 1.51 (s, 9H); ($11j$) $\delta = 7.46$ (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 4.58 (br s, 2H), 4.30 (s, 2H), 3.73 (s, 3H), 1.51 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): ($6j$) $\delta = 191.9$, 159.2, (156.4), 154.2, 138.1, 134.0, 131.4 (2C), 130.3 (2C), 129.3 (q, $J = 32.7$ Hz), 124.7 (q, $J = 3.7$ Hz, 2C), 124.2 (q, $J = 272.2$ Hz), 114.0 (2C), 81.3, 55.2, 51.9, 47.8, 28.4 (3C); ($11j$) $\delta = 192.4$, 160.5, 154.2, 153.1, 141.0, 136.3, 132.0 (2C), 130.6, (q, $J = 32.7$ Hz), 128.9 (2C), 125.3 (q, $J = 3.7$ Hz, 2C), 123.7 (q, $J = 272.3$ Hz), 113.6 (2C), 81.4, 55.1, 51.9, 47.8, 28.4 (3C); IR (neat): $\tilde{\nu} = 2978$ (w), 2935 (w), 2840 (w), 1677 (s), 1605 (m), 1571 (w), 1509 (m), 1408 (m), 1366 (m), 1322 (s), 1293 (m), 1247 (s), 1156 (s), 1122 (s), 1109 (s), 1066 (s), 1029 (m), 1019 (m), 991 (w), 909 (m), 868 (w), 828 (s), 766 (w), 729 (s), 692 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{24}$H$_{24}$NO$_4$F$_3$ + Na): 470.1555; found: 470.1574.

($^1$H NMR: 45°C, $^{13}$C APT NMR (d = 2): 45°C);

^ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets

**Compound 6k and 11k**

![Compound 6k and 11k](image)

Colourless oil (67 mg, 90% from 50 mg of 1 using method II), mixture of regioisomers ($6k/11k = 60:40$): $^1$H NMR (500 MHz, CDCl$_3$): ($6k$) $\delta = 4.09$ (br s, 2H), 3.98 (s, 2H), 2.95 (sept, $J = 7.0$ Hz, 1H), 1.76 (t, $J = 1.7$ Hz, 3H), 1.41 (s, 9H), 1.08 (d, $J = 7.0$ Hz, 6H); ($11k$) $\delta = 4.01$ (br s, 2H), 3.91
(s, 2H), 2.90 (sept, \( J = 7.1 \) Hz, 1H), 1.90 (s, 3H), 1.41 (s, 9H), 1.13 (d, \( J = 7.3 \) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): (6k) \( \delta = 193.7, 160.9 \) (br),\(^\Delta 154.2, 128.4, 80.6, 51.3 \) (br), 42.0 (br), 30.6, 28.3 (3C), 19.7 (2C), 9.4; (11k) \( \delta = 192.5, 154.0, 151.7 \) (br),\(^\Delta 138.8, 80.6, 51.8 \) (br), 48.0 (br), 28.3 (3C), 27.0, 20.2 (2C), 17.8; IR (neat): \( \tilde{\nu} = 2971 \) (m), 2932 (w), 2874 (w), 1697 (s), 1671 (s), 1628 (m), 1419 (m), 1392 (m), 1382 (m), 1364 (s), 1318 (m), 1281 (m), 1242 (s), 1205 (w), 1159 (s), 1125 (s), 1061 (w), 970 (w), 926 (w), 899 (m), 859 (w), 766 (m), 684 (w) cm\(^{-1}\); HRMS (ESI): calcd for (C\(_{14}\)H\(_{23}\)NO\(_3\) + Na): 276.1576; found: 276.1575.

(\(^1\)H NMR: 47°C; \(^{13}\)C APT NMR (d = 2) and \(^{13}\)C CPD NMR (d = 4): 45°C);

\(^\Delta \) Carbon marked with an asterisk appears as a very broad peak in \(^{13}\)C CPD NMR spectrum and is not visible in the \(^{13}\)C APT NMR spectrum. However, HMBC correlations are visible which confirms the \(^{13}\)C CPD NMR.

**Compound 6l**

![Compound 6l](image)

Colourless oil (64 mg, 87% from 47 mg of 7 using method II): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 4.20 \) (br s, 2H), 4.00 (s, 2H), 1.95 (t, \( J = 1.7 \) Hz, 3H), 1.44 (s, 9H), 1.26 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 194.9, \{162.4\},\(^\Delta 154.2, 130.4, 80.7, 50.9 \) (br), 44.9 (br), 36.9, 29.1 (3C), 28.3 (3C), 13.2; IR (neat): \( \tilde{\nu} = 2974 \) (w), 1698 (s), 1676 (s), 1606 (w), 1477 (w), 1421 (m), 1367 (m), 1288 (w), 1249 (m), 1234 (w), 1167 (s), 1124 (m), 1072 (w), 1039 (w), 1020 (w), 972 (w), 901 (w), 858 (w), 766 (w) cm\(^{-1}\); HRMS (ESI): calcd for (C\(_{15}\)H\(_{25}\)NO\(_3\) + Na): 290.1732; found: 290.1740; elemental analysis (%) calcd for C\(_{15}\)H\(_{25}\)NO\(_3\): C 67.38, H 9.42, N 5.24; found: C 66.86, H 9.70, N 4.78.

(\(^{13}\)C APT NMR (d = 10): 32°C)
Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets.

**Compound 6m**

![Structure of Compound 6m]

Colourless oil (56 mg, 77% from 47 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 5.10 (s, 1H), 4.84 (br s, 1H), 4.12 (s, 2H), 4.02 (s, 2H), 2.26 (q, $J = 7.4$ Hz, 2H), 1.91 (s, 3H), 1.44 (s, 9H), 0.95 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 193.4, 156.5 (br), $^\wedge$ 154.2, 141.4, 134.7, 115.2, 80.8, 51.5 (br), 46.1 (br), 28.3 (3C), 21.8, 19.4, 14.2; IR (neat): $\tilde{\nu} =$ 2976 (w), 2935 (w), 1699 (s), 1679 (s), 1620 (w), 1477 (w), 1416 (m), 1394 (m), 1366 (s), 1336 (w), 1276 (w), 1237 (s), 1166 (s), 1132 (s), 1085 (w), 1056 (w), 1011 (w), 981 (w), 905 (m), 865 (w), 768 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{15}$H$_{23}$NO$_3$ + Na): 288.1576; found: 288.1582; elemental analysis (%) calcd for C$_{15}$H$_{23}$NO$_3$: C 67.90, H 8.74, N 5.28; found: C 67.66, H 8.83, N 5.27.

($^1$H NMR: 45°C, $^{13}$C APT NMR (d = 2): 45°C)

Carbon marked with an asterisk appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{13}$C APT NMR spectrum. However, HMBC correlations are visible which confirms the $^{13}$C CPD NMR.

**Compound 11m**

![Structure of Compound 11m]

Colourless oil (8 mg, 11% from 50 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 5.19 (s, 1H), 4.72 (s, 1H), 4.18 (br s, 2H), 4.05 (s, 2H), 2.31 (q, $J = 7.6$ Hz, 2H), 1.84 (s, 3H), 1.47 (s, 9H), 1.12 (t, $J = 7.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 192.1, (157.9),$^\wedge$ 154.2, 139.4, 137.5,
116.6, 80.9, 51.5 (br), 45.3 (br), 28.4 (3C), 26.1, 23.3, 13.0; IR (neat): \( \bar{\nu} = 2976 \) (w), \( 1699 \) (s), \( 1678 \) (s), \( 1419 \) (m), \( 1367 \) (m), \( 1326 \) (w), \( 1244 \) (m), \( 1163 \) (s), \( 1115 \) (w), \( 1018 \) (w), \( 888 \) (w), \( 768 \) (w) cm\(^{-1}\); HRMS (ESI): calcd for \((\text{C}_{25}\text{H}_{27}\text{NO}_3 + \text{Na})\): 412.1889; found: 412.1880.

\(^1\)H NMR: 47°C; \(^{13}\)C APT NMR (d = 2): 45°C

\(^\wedge\) Carbon marked with an asterisk is not visible in the \(^{13}\)C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets.

**Compound 6n and 11n**

Yellow oil (69 mg, 86% from 35 mg of 7 using method II), inseparable mixture of regioisomers (6n/11n = 60:40): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.62 - 7.56 \) (m, 6H), \( 7.54 \) (d, \( J = 8.2 \) Hz, 2H), \( 7.46 - 7.28 \) (m, 8H), \( 7.23 \) (m, 1.5H), \( 5.12 - 5.07 \) (m, 1.7H), \( 5.05 \) (s, 0.7H), \( 4.71 \) (s, 1H), \( 4.49 \) (br s, 2H), \( 4.40 \) (br s, 1.3H), \( 4.23 \) (s, 1.3H), \( 4.20 \) (s, 2H), \( 1.77 \) (s, 3H), \( 1.62 \) (s, 2H), \( 1.53 - 1.48 \) (m, 17H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)):\(^\sim\) \( \delta = 192.4, 192.2, 157.0 \) (br),\(^\wedge 154.2, 153.2 \) (br),\(^\wedge 141.8, 141.7, 140.8, 140.6, 140.1, 138.4, 138.0, 136.3, 134.2, 133.0, 130.4, 128.8, 128.7, 128.0, 127.7, 127.3, 127.04, 127.01, 126.97, 126.5, 119.2, 118.6, 81.1, 51.7 \) (br), \( 47.7 \) (br), \( 47.0 \) (br), \( 28.4 \) (3C), \( 23.3, 21.8; IR (neat): \( \bar{\nu} = 3031 \) (w), \( 2977 \) (w), \( 2932 \) (w), \( 2251 \) (w), \( 1677 \) (s), \( 1601 \) (w), \( 1553 \) (w), \( 1519 \) (w), \( 1487 \) (w), \( 1393 \) (m), \( 1365 \) (s), \( 1323 \) (m), \( 1283 \) (w), \( 1240 \) (m), \( 1156 \) (s), \( 1113 \) (m), \( 1072 \) (w), \( 1029 \) (w), \( 1008 \) (w), \( 996 \) (w), \( 908 \) (m), \( 866 \) (w), \( 836 \) (m), \( 765 \) (s), \( 729 \) (s), \( 696 \) (s) cm\(^{-1}\); HRMS (ESI): calcd for \((\text{C}_{25}\text{H}_{27}\text{NO}_3 + \text{Na})\): 412.1889; found: 412.1880.

\(^1\)H NMR: 47°C; \(^{13}\)C APT NMR (d = 2) and \(^{13}\)C CPD NMR (d = 4): 45°C

\(^\sim\)Peaks common to 6n and 11n are underlined, peaks attributed to 11n are indicated in italic.

\(^\wedge\) Carbon appears as a very broad peak in \(^{13}\)C CPD NMR spectrum and is not visible in the \(^{13}\)C APT NMR spectrum.
**Compound 60**

![Compound 60](image)

Colourless oil (183 mg, 91% from 100 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.42–7.34 (m, 3H), 7.27–7.20 (m, 2H), 4.29 (br s, 2H), 4.07 (s, 2H), 1.48 (s, 9H), -0.15 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 197.7, 168.0 (br), 154.2, 139.3, 137.5, 129.3, 128.4 (2C), 127.8 (2C), 80.8, 51.3 (br), 49.3 (br), 28.3 (3C), 0.3; IR (neat): $\tilde{\nu} =$ 3053 (w), 2977 (w), 2897 (w), 1697 (s), 1665 (s), 1604 (w), 1582 (m), 1477 (w), 1408 (m), 1365 (m), 1242 (s), 1223 (m), 1160 (s), 1077 (w), 1024 (w), 999 (w), 940 (w), 927 (w), 905 (m), 842 (s), 759 (s), 700 (s) cm$^{-1}$; MS (ESI): calcd for (C$_{19}$H$_{27}$NO$_3$Si + Na): 368.1658; found: 368.1662; elemental analysis (%): calcd for C$_{19}$H$_{27}$NO$_3$Si: C 66.05, H 7.88, N 4.05; found: C 65.82, H 7.96, N 3.86.

($^{13}$C APT NMR (d = 2): 40°C);

$^\wedge$ Carbon marked with an asterisk appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{13}$C APT NMR spectrum. However, HMBC correlations are visible which confirms the $^{13}$C CPD NMR.

**Compound 110**

![Compound 110](image)

Colourless oil (5 mg, 3% using method I): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.35–7.31 (m, 3H), 7.08–7.04 (m, 2H), 4.35 (br s, 2H), 4.19 (s, 2H), 1.48 (s, 9H), -0.12 (s, 9H); IR (neat): $\tilde{\nu} =$ 2976 (w), 1686 (s), 1477 (w), 1412 (m), 1366 (m), 1307 (w), 1250 (m), 1160 (s), 1109 (w), 1062 (w), 927 (w), 841 (m), 759 (m), 701 (m) cm$^{-1}$; MS (ESI): calcd for (C$_{19}$H$_{27}$NO$_3$Si + Na): 368.1658; found: 368.1660
Compound 6p

Colourless oil (108 mg, 91% from 48 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.50 – 7.43 (m, 2H), 7.38 – 7.31 (m, 1H), 7.31 – 7.24 (m, 5H), 7.20 – 7.08 (m, 2H), 4.32 (br s, 2H), 4.09 (s, 2H), 1.49 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 197.5, 169.0 (br),$^*$ 154.3, 139.0, 138.9, 136.4, 133.9, 129.4, 128.6, 128.3, 128.0, 127.5, 80.9, 51.5, 49.5, 28.4, -1.0; IR (neat): $\tilde{\nu} =$ cm$^{-1}$; HRMS (ESI): calcd for (C$_{24}$H$_{29}$NO$_3$Si + Na)$^+$: 430.1814; found: 430.1813

$^*$ Carbon marked with an asterisk appears as a very broad peak in $^{13}$C CPD NMR spectrum and is not visible in the $^{13}$C APT NMR spectrum. However, HMBC correlations are visible which confirms the $^{13}$C CPD NMR.

Compound 11p

Colourless oil (6 mg, 5% from 48 mg of 7 using method II): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.40 – 7.20 (m, 8H), 6.97 (d, $J =$ 7.0 Hz, 2H), 4.28 (br s, 2H), 4.16 (s, 2H), 1.45 (s, 9H), 0.08 (s, 6H); IR (neat): $\tilde{\nu} =$ 2976 (w), 1685 (s), 1491 (w), 1477 (w), 1427 (m), 1365 (m), 1242 (m), 1157 (s), 1110 (m), 1061 (m), 925 (w), 846 (m), 831 (m), 808 (m), 779 (m), 736 (w), 699 (s) cm$^{-1}$; HRMS (ESI): calcd for (C$_{24}$H$_{29}$NO$_3$Si + Na)$^+$: 430.1814; found: 430.1808
**Compound 6q and 11q**

Colourless oil (55 mg, 80% from 30 mg of 7 following method II except that 1.5 equiv of alkyne was used), inseparable mixture of regioisomers (6q/11q = 80:20): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.16 (br s, 0.33H), 4.05 (br s, 1.6H), 4.00 (s, 0.33H), 3.92 (s, 1.6H), 2.35–2.27 (m, 2H), 1.54–1.41 (m, 1H), 1.45 (s, 9H), 1.39–1.19 (m, 11H), 0.90–0.82 (m, 3H), 0.24 (s, 1.6H), 0.21 (s, 7.4H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $^*$ $\delta$ = 197.5, 192.6, 154.3, {170.4}, $^\dagger$ 155.2, $^\dagger$ 154.2, 146.0, 135.1, 80.67, 80.65, 51.9 (br), 51.3 (br), 47.1 (br), 46.5 (br), 35.6, 31.83, 31.77, 30.1, 30.0, 29.9, 29.8, 29.5, 29.4, 29.2, 29.1, 28.4 (3C), 22.6, 14.0, 1.3 (3C), -0.5 (3C); IR (neat): $\tilde{\nu}$ = 2954 (m), 2928 (s), 2856 (m), 1702 (s), 1665 (m), 1612 (w), 1412 (w), 1368 (m), 1248 (s), 1159 (s), 904 (w), 844 (s), 768 (w) cm$^{-1}$; MS (ESI): calcd for (C$_{21}$H$_{39}$NO$_3$Si + Na): 404.2597; found: 404.2601.

($^1$H NMR: 47°C; $^{13}$C APT NMR (d = 2) and $^{13}$C CPD NMR (d = 4); 45°C)

* Peaks common to 6q and 11q are underlined, peaks attributed to 6l are indicated in italic.

$^\dagger$ Carbon marked with an asterisk is not visible in the $^{13}$C APT NMR spectrum but its chemical shift could be determined by HMBC correlation and is indicated in brackets.

**Compounds 6t**

Colourless oil (21 mg, 44% from 49 mg of 7 using method II): This compound has not been fully characterised but the assignment of the isolated isomer is based on the proton of 2-cyclohexen-1-one.; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 5.97 (s, 1H), 4.09 (br s, 2H), 4.01 (s, 2H), 2.21 (t, $J$ = 7.4 Hz, 2H), 1.56 (sext, $J$ = 7.4 Hz, 2H), 1.44 (s, 9H), 0.94 (t, $J$ = 7.3 Hz, 3H)
Compounds 6y and 11y

Colourless oil (43 mg, 75% from 30 mg of 7 following method II), inseparable mixture of regioisomers (6y/11y = 58:42), this compound has not been fully characterised but the assignment of the two isomers is based on the proton of 6k/11k: ¹H NMR (500 MHz, CDCl₃): (6y) δ = 7.35 – 7.16 (m, 5H), 4.15 (br s, 2H), 4.07 (s, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.34 – 2.27 (m, 2H), 1.87 (pent, J = 7.9 Hz, 2H), 1.78 (s, 3H), 1.49 (s, 9H); (11y) δ = 7.35 – 7.16 (m, 5H), 4.12 (br s, 2H), 4.06 (s, 2H), 2.66 (t, J = 7.8 Hz, 2H), 2.41 – 2.34 (m, 2H), 1.91 (s, 3H), 1.69 (pent, J = 7.9 Hz, 2H), 1.49 (s, 9H)

Compounds 6z and 11z

Colourless oil (57 mg, 91% from 30 mg of 7 following method II), inseparable mixture of regioisomers (6z/11z = 55:45): ¹H NMR (500 MHz, CDCl₃): (6z) δ = 7.36 – 7.20 (m, 5H), 4.48 (s, 2H), 4.12 (br s, 2H), 4.01 (s, 2H), 3.48 (t, J = 6.0 Hz, 2H), 2.44 – 2.34 (m, 2H), 1.86 – 1.75 (m, 5H), 1.45 (s, 9H); (11z) δ = 7.36 – 7.20 (m, 5H), 4.46 (s, 2H), 4.08 (s, 2H), 3.44 (t, J = 6.2 Hz, 2H), 2.44 – 2.34 (m, 2H), 1.94 (s, 3H), 1.71 – 1.61 (m, 2H), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 193.3, 192.5, 154.1, 138.7, 138.3, 134.0, 130.1, 128.4, 128.3, 127.6, 127.6, 127.5, 127.4, 80.7, 80.7, 73.0, 72.8, 70.0, 69.4, 51.1, 47.7, 46.3, 29.3, 28.7, 28.3, 27.7, 21.5, 18.0, 9.9; IR (neat): ʋ = 2976 (w), 1930 (w), 2860 (w), 1698 (s), 1673 (s), 1641 (m), 1496 (w), 1454 (m), 1420 (s), 1365 (m), 1328 (w), 1282 (w), 1242 (m), 1168 (m), 1134 (m), 1102 (m), 1029 (w), 899 (w), 738 (m), 698 (m) cm⁻¹; MS (ESI): calcd for (C₂₁H₂₉NO₄ + Na): 382.1994; found: 382.2004.

(¹H NMR and ¹³C APT NMR (d = 2): 40°C)
**Compound 6aa**

![Structure of Compound 6aa](image)

This product was made by Jet-Sing Lee: ¹H NMR (400Mz, CDCl₃): δ = 7.60-7.54 (m, 5H), 7.45-7.37 (m, 5H), 7.36-7.31 (m, 1H), 4.58 (s, 2H), 4.33 (s, 2H), 4.29 (s, 2H), 4.08 (s, 2H), 1.79 (s, 3H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 193.3, 154.1, 141.0, 140.7, 130.4, 128.7, 128.1, 127.3, 127.2, 127.0 80.7, 72.9, 68.2, 44.4, 28.3 (3C), 9.8; HRMS (ES+): calcd for (C₂₉H₂₅NO₄ + Na): 430.5; found: 430.2.

**Compound 11aa**

![Structure of Compound 11aa](image)

This product was made and characterised by Jet-Sing Lee. ¹H NMR (400Mz, CDCl₃): δ = 7.63-7.58 (m, 4H), 7.48-7.42 (m, 4H), 7.38-7.33 (m, 1H), 4.60 (s, 2H), 4.35 (s, 2H), 4.20 (s, 2H), 4.11 (s, 2H), 2.10 (s, 3H), 1.50 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 191.8, 140.9, 140.7, 137.2, 128.7 (2C), 128.4 (2C), 127.2, 127.1 (2C), 127.1 (2C), 81.0, 72.8, 61.5, 29.7, 28.3 (3C), 18.2; HRMS (ES+): calcd for (C₂₉H₂₅NO₄ + Na): 430.5; found: 430.2.

**Compound 54**

![Structure of Compound 54](image)

Colourless oil (6 mg, 49% from 10 mg of 7 using method I except with 30 mol% Ni(cod)₂ and 90 mol% PPhCy₂): ¹H NMR (500 MHz, CDCl₃): δ = 7.60 – 7.54 (m, 4H), 7.46 – 7.39 (m, 4H), 7.36 – 7.31 (m, 1H), 5.12 (s, 2H), 1.49 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 153.5, 141.3, 140.7,
134.6, 128.8, 128.7, 127.4, 127.3, 127.1, 82.3, 68.4, 27.8; HRMS (ESI): calcd for (C_{18}H_{20}O_{3} + Na): 307.1310; found: 307.1305

**Compound 70b**

White solid (21 mg, 73% from 69 (19 mg, 0.09 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 110 °C): m.p: 51–55 °C; \(^1^H\) NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.62\) (d, \(J = 8.0\) Hz, 2H), 7.30 (d, \(J = 8.0\) Hz, 2H), 3.83 (s, 2H), 3.70 (s, 2H), 2.40 (s, 3H), 2.19–2.13 (m, 2H), 2.12–2.07 (m, 2H), 1.51–1.40 (m, 2H), 1.20–1.08 (m, 2H), 0.94 (t, \(J = 7.5\) Hz, 3H), 0.82 (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 191.2, 153.8, 144.2, 134.7, 132.8, 130.0\) (2C), 129.7 (2C), 52.5, 47.8, 34.4, 26.5, 22.4, 21.5, 21.3, 14.3, 14.2; IR (neat): \(\tilde{\nu} = 2961\) (m), 2872 (w), 1675 (s), 1630 (w), 1598 (w), 1447 (w), 1350 (s), 1244 (w), 1165 (s), 1138 (w), 1090 (m), 1038 (w), 1010 (w), 964 (m), 815 (w), 672 (m) cm\(^{-1}\); HRMS (ESI): calcd for (C_{18}H_{25}NO_{3}S + Na): 358.1453; found: 358.1456; elemental analysis (%) calcd for C_{18}H_{25}NO_{3}S: C 64.45, H 7.51, N 4.18; found: C 64.02, H 7.60, N 3.93.

**Compound 70c**

Colourless oil (23 mg, 62% from 69 (25 mg, 0.11 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 100 °C); \(^1^H\) NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.65\) (d, \(J = 8.0\) Hz, 2H), 7.44 – 7.36 (m, 3H), 7.31 (d, \(J = 8.1\) Hz, 2H), 7.19 – 7.15 (m, 2H), 4.12 (s, 2H), 3.86 (s, 2H), 2.40 (s, 3H), 1.60 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 192.1, 151.4, 144.3, 136.5, 132.7, 131.1, 130.0\) (2C), 129.2, 128.7 (2C), 127.7 (2C), 127.6 (2C), 52.5,
Compound 71c

![Structure of compound 71c]

Colourless oil (5 mg, 13% from 69 (25 mg, 0.11 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 100 °C); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.69$ (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.34–7.26 (m, 3H), 6.85–6.77 (m, 2H), 4.05 (s, 2H), 3.93 (s, 2H), 2.44 (s, 3H), 1.77 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 189.8$, 152.0, 144.4, 136.6, 133.3, 132.8, 130.1 (2C), 129.6 (2C), 128.1 (2C), 127.8, 127.7 (2C), 52.7, 49.4, 21.5, 19.7; IR (neat): $\tilde{\nu} = 2924$ (w), 1677 (m), 1634 (w), 1598 (w), 1495 (w), 1443 (w), 1380 (w), 1349 (m), 1307 (w), 1187 (w), 1162 (s), 1092 (w), 1030 (w), 954 (w), 933 (w), 836 (w), 816 (w), 787 (w), 762 (w), 688 (w), 671 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{19}$H$_{19}$NO$_3$S + Na): 364.0983; found: 364.0986.

Compound 73a

![Structure of compound 73a]

Colourless oil (32 mg, 92% from 72 (20 mg, 0.08 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 110 °C); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.71$ (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.2$ Hz, 2H), 7.22–7.13 (m, 3H), 7.10–7.00 (m,
3H), 6.93 – 6.88 (m, 2H), 6.43 (d, J = 6.9 Hz, 2H), 4.87 (d, J = 20.4 Hz, 1H), 4.72 (q, J = 7.3 Hz, 1H), 4.40 (d, J = 20.4 Hz, 1H), 2.38 (s, 3H), 1.53 (d, J = 1.53 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 194.0, 150.9, 144.1, 136.5, 136.0, 134.5, 132.9, 130.4, 130.1, 129.0, 128.3, 128.2, 127.5, 127.3, 127.1, 57.0, 45.2, 21.4, 15.8; IR (neat): $\tilde{\nu}$ = 3057 (w), 2983 (w), 1673 (s), 1624 (w), 1597 (w), 1491 (w), 1375 (s), 1351 (m), 1335 (s), 1241 (w), 1157 (s), 1086 (m), 1043 (m), 985 (w), 921 (w), 867 (w), 819 (m), 769 (m), 757 (m), 738 (m) cm$^{-1}$

**Compound 73b**

![Compound 73b](image)

Colourless oil (32 mg, 91% from 72 (25mg, 0.10 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 110°C); enantiomeric excess = 97%. $^{50}$ $^\alpha$$_D$ = 59.1 (c = 2.7 in CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.57 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.43 (q, J = 7.2 Hz, 1H), 4.30 (d, J = 19.8 Hz, 1H), 3.94 (d, J = 19.8 Hz, 1H), 2.35 (s, 3H), 2.12 (ddd, J = 10.0 Hz, 9.3 Hz, 6.0 Hz, 1H), 2.07–2.01 (m, 1H), 2.00–1.88 (m, 2H), 1.51–1.40 (m, 1H), 1.39–1.30 (m, 1H), 1.25 (d, J = 7.3 Hz, 3H), 1.03–0.92 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H), 0.90–0.82 (m, 1H), 0.73 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 194.8, 152.2, 143.7, 136.5, 133.1, 129.8 (2C), 127.0 (2C), 56.5, 43.7, 33.9, 26.4, 22.4, 21.4, 15.7, 14.3, 14.1; IR (neat): $\tilde{\nu}$ = 2961 (m), 2932 (w), 2872 (w), 1671 (s), 1630 (w), 1598 (w), 1457 (w), 1380 (w), 1350 (m), 1335 (m), 1240 (w), 1206 (w), 1161 (s), 1092 (m), 1037 (w), 1011 (w), 912 (m), 815 (w), 708 (w), 666 (m) cm$^{-1}$; HRMS (ESI): calcd for (C$_{19}$H$_{27}$NO$_3$S + Na): 372.1609; found: 372.1618.
Compound 73c

Colourless oil (27 mg, 93% from 72 (20 mg, 0.08 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 100 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.65$ (d, $J = 8.2$ Hz, 2H), 7.43 – 7.35 (m, 3H), 7.28 – 7.22 (m, 2H), 7.13 – 7.07 (m, 2H), 4.65 – 4.52 (m, 2H), 4.22 – 4.12 (m, 1H), 2.37 (s, 3H), 1.44 (s, 3H), 1.36 (d, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 195.6$, 150.1, 143.8, 136.4, 136.4, 129.8, 129.4, 129.1, 128.7, 127.4, 127.1, 56.7, 45.2, 21.5, 15.5, 11.9; IR (neat): $\tilde{\nu} = 3058$ (w), 2926 (w), 1673 (s), 1597 (w), 1442 (m), 1351 (m), 1332 (s), 1187 (w), 1162 (s), 1091 (w), 1028 (m), 1002 (m), 906 (w), 815 (w), 764 (m), 702 (m) cm$^{-1}$

Compound 74c

Colourless oil (1.9 mg, 7% from 72 (20 mg, 0.08 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 100 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.66$ (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.26 – 7.20 (m, 3H), 6.59 – 6.52 (m, 2H), 4.59 (q, $J = 7.3$ Hz, 1H), 4.45 (d, $J = 20.0$ Hz, 1H), 4.14 (d, $J = 20.1$ Hz, 1H), 2.42 (s, 3H), 1.67 (s, 3H), 1.42 (d, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 193.2$, 150.3, 144.0, 136.9, 135.2, 133.3, 130.1, 129.6, 128.0, 127.7, 127.1, 57.0, 45.4, 21.4, 19.1, 15.8; IR (neat): $\tilde{\nu} = 2984$ (w), 2932 (w), 1675 (m), 1663 (w), 1597 (w), 1495 (w), 1443 (w), 1381 (w), 1353 (m), 1333 (m), 1160 (s), 1104 (m), 1059 (m), 1004 (m), 877 (w), 702 (w), 687 (w), 665 (m) cm$^{-1}$; HRMS (ESI): calcd for (C$_{20}$H$_{21}$NO$_3$S + Na)$^+$: 378.1140; found: 378.1154
Compound 73o

Colourless oil (25 mg, 71% from 72 (20 mg, 0.18 mmol) using method I, except that 1.5 equiv of alkyne was used and that the oil bath temperature was set at 110 °C); 1H NMR (500 MHz, CDCl₃): δ = 7.68 (d, J = 8.3 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.26 (d, J = 8.1 Hz, 2H), 7.12 – 7.07 (m, 2H), 4.59 (d, J = 20.6 Hz, 1H), 4.46 (q, J = 7.2 Hz, 1H), 4.06 (d, J = 20.6 Hz, 1H), 2.36 (s, 3H), 1.36 (d, J = 7.3 Hz, 3H), -0.38 (s, 9H); 13C NMR (125 MHz, CDCl₃): δ = 198.8, 164.4, 143.9, 138.4, 136.5, 136.4, 130.0, 129.5, 128.5, 127.6, 127.1, 56.5, 46.7, 21.4, 15.8, 0.1; IR (neat): ν = 3060 (w), 2954 (w), 2897 (w), 1662 (m), 1581 (w), 1490 (w), 1429 (w), 1351 (m), 1325 (w), 1247 (m), 1161 (s), 1105 (w), 1042 (w), 990 (w), 902 (w), 838 (s), 773 (m), 700 (m), 667 (s) cm⁻¹; MS (ESI): calcd for (C₂₂H₂₇NO₃SiS)⁺ Na: 436.1379; found: 436.1378.

Compound 88a

White solid (64 mg, 82% from commercially available 87 (20 μL, 0.31 mmol) using method I); m.p. 100 – 103 °C; 1H NMR (500 MHz, CDCl₃): δ = 7.22 – 7.15 (m, 6H), 7.09 – 6.99 (m, 4H), 4.76 (s, 2H), 4.38 (s, 2H); 13C NMR (125 MHz, CDCl₃): δ = 193.3, 155.3, 135.4, 134.6, 132.7, 130.7 (2C), 128.9, 128.4 (2C), 128.3 (2C), 127.4 (2C), 127.4, 71.2, 69.5; IR (neat): ν = 3056 (w), 3023 (w), 2969 (w), 2853 (w), 2816 (w), 1678 (s), 1613 (w), 1596 (w), 1573 (w), 1491 (w), 1443 (w), 1380 (w), 1327 (m), 1280 (w), 1250 (w), 1195 (w), 1141 (m), 1080 (w), 1052 (w), 1038 (w), 1027 (w), 1001 (w), 967 (w), 932 (w), 912 (w), 868 (w), 755 (m), 720 (w), 696 (s) cm⁻¹; HRMS (ESI): calcd
for \((C_{17}H_{34}O_2 + Na)\): 273.0891; found: 273.0890; elemental analysis (%) calcd for \(C_{17}H_{34}O_2\): C 81.58, H 5.64; found: C 80.98, H 5.73.

**Compound 88g**

![Compound 88g](image)

Colourless oil (93 mg, 73% from commercially available 87 (20 μL, 0.47 mmol) using method II); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.98 (d, J = 8.4 \text{ Hz}, 2H), 7.30 (d, J = 8.4 \text{ Hz}, 2H), 4.47 (s, 2H), 4.20 (s, 2H), 2.59 (s, 3H), 2.22–2.13 (m, 2H), 1.34 – 1.21 (m, 2H), 1.13 (sext, \(J = 7.3 \text{ Hz}, 2H\), 0.71 (t, \(J = 7.2 \text{ Hz}, 3H\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 197.3, 194.3, 153.3, 140.5, 137.0, 135.0, 128.6 (2C), 127.6 (2C), 71.9, 69.3, 31.3, 26.6, 24.9, 22.5, 13.6; IR (neat): \(\tilde{\nu} = 2958 \text{ (w)}, 2932 \text{ (w)}, 2860 \text{ (w)}, 1683 \text{ (s)}, 1604 \text{ (w)}, 1440 \text{ (w)}, 1403 \text{ (w)}, 1380 \text{ (w)}, 1359 \text{ (w)}, 1338 \text{ (w)}, 1266 \text{ (w)}, 1206 \text{ (w)}, 1151 \text{ (w)}, 1119 \text{ (w)}, 1014 \text{ (w)}, 960 \text{ (w)}, 922 \text{ (w)}, 833 \text{ (w)} \text{ cm}^{-1}; \) HRMS (ESI): calcd for \((C_{17}H_{20}O_3 + Na)\): 295.1310; found: 295.1311; elemental analysis (%) calcd for \(C_{17}H_{20}O_3\): C 74.97, H 7.40; found: C 74.95, H 7.75.

**Compound 89g**

![Compound 89g](image)

Colourless oil (25 mg, 19% from commercially available 87 (30 μL, 0.47 mmol) using method II); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.96 (d, J = 8.2 \text{ Hz}, 2H), 7.20 (d, J = 8.2 \text{ Hz}, 2H), 4.46 (s, 2H), 4.24 (s, 2H), 2.59 (s, 3H), 2.14–2.07 (m, 2H), 1.41–1.32 (m, 2H), 1.19 (sext, \(J = 7.4 \text{ Hz}, 2H\), 0.77 (t, \(J = 7.3 \text{ Hz}, 3H\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 197.8, 192.7, 159.7, 138.1, 136.3, 134.4, 130.0 (2C), 128.2 (2C), 72.0, 68.1, 31.5, 30.0, 26.6, 22.6, 13.6; IR (neat): \(\tilde{\nu} = 2958 \text{ (w)}, 2931 \text{ (w)},\)}
2862 (w), 2819 (w), 1678 (s), 1626 (w), 1603 (m), 1560 (w), 1466 (w), 1438 (w), 1403 (w), 1384 (w), 1358 (w), 1330 (w), 1265 (s), 1184 (w), 1126 (m), 1088 (w), 1017 (w), 960 (m), 830 (w), 762 (w), 701 (w) cm\(^{-1}\); HRMS (ESI): calcd for (C\(_{17}\)H\(_{20}\)O\(_3\) + Na): 295.1310; found: 295.1313; elemental analysis (%): calcd for C\(_{17}\)H\(_{20}\)O\(_3\): C 74.97, H 7.40; found: C 74.74, H 7.42.

**Compound 88o**

![Image](image_url)

White solid (73 mg, 95% from commercially available 87 (20 μL, 0.31 mmol) using method II); m.p. 39–41 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.43–7.34\) (m, 3H), 7.24–7.18 (m, 2H), 4.41 (s, 2H), 4.13 (s, 2H), -0.13 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 198.1, 169.0, 137.8, 136.2, 129.4, 128.4\) (2C), 127.9 (2C), 71.4, 70.3, 0.2 (3C); IR (neat): \(\nu = 3059\) (w), 2952 (w), 2897 (w), 2850 (w), 2812 (w), 1665 (s), 1603 (w), 1581 (w), 1567 (w), 1490 (w), 1443 (w), 1433 (w), 1372 (w), 1288 (m), 1275 (m), 1244 (s), 1216 (w), 1137 (m), 1077 (w), 1053 (w), 1033 (w), 1016 (w), 969 (w), 937 (m), 835 (s), 756 (s), 699 (s), 682 (m) cm\(^{-1}\); HRMS (ESI): calcd for (C\(_{14}\)H\(_{18}\)O\(_2\)Si + Na): 269.0974; found: 269.0975; elemental analysis (%): calcd for C\(_{14}\)H\(_{18}\)O\(_2\)Si: C 68.25, H 7.36; found: C 68.10, H 7.42.

**Compound 89o**

![Image](image_url)

Yellow oil (3 mg, 4% from commercially available 87 using method II); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.35–7.29\) (m, 3H), 7.15–7.05 (m, 2H), 4.53 (s, 2H), 4.25 (s, 2H), -0.13 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 192.4, 159.9, 145.2, 135.7, 130.0\) (2C), 128.2, 127.9 (2C), 72.4, 69.1, -1.2 (3C); IR (neat): \(\nu = 3048\) (w), 3028 (w), 2956 (w), 2896 (w), 2851 (w), 2810 (w), 1685 (s), 159
1492 (w), 1444 (w), 1374 (w), 1312 (m), 1251 (w), 1192 (w), 1138 (m), 1033 (w), 952 (w), 869 (s), 840 (s), 755 (w), 701 (w) cm$^{-1}$; MS (Cl): $m/z$ (rel. intensity): 264 (100) [M+NH$_4^+$], 247 (55) [M+H]$^+$; HRMS (ESI): calcd for (C$_{14}$H$_{18}$O$_2$Si + Na): 269.0974; found: 269.0967.

**Compound 91**

![Compound 91 structure]

Colourless oil (14 mg, 44% from 90 (20 mg, 0.11 mmol) using method I); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.29 – 7.23$ (m, 2H), 7.22 – 7.13 (m, 3H), 4.30 (apt q, $J = 17.5$ Hz, 2H), 3.85 – 3.79 (m, 1H), 2.82 – 2.64 (m, 2H), 2.30 – 2.08 (m, 5H), 2.01 – 1.91 (m, 1H), 1.49 (sext, $J = 7.5$ Hz, 2H), 1.33 (sext, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.3$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 196.0, 155.9, 141.6, 133.2, 128.6, 128.3, 125.8, 78.9, 66.9, 32.6, 31.7, 31.3, 26.3, 22.5, 21.4, 14.3, 14.2$; MS (ESI): calcd for (C$_{19}$H$_{26}$O$_2$ + Na): 309.1831; found: 309.1827.

**Compound 92**

![Compound 92 structure]

Colourless oil (4 mg, 11% from 90 (20 mg, 0.11 mmol) using method I); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.31 – 7.26$ (m, 2H), 7.22 – 7.16 (m, 3H), 4.26 (d, $J = 16.6$ Hz, 1H), 4.21 (d, $J = 10.0$ Hz, 1H), 4.05 (d, $J = 17.0$ Hz, 1H), 2.90 – 2.81 (m, 1H), 2.81 – 2.68 (m, 1H), 2.35 – 2.27 (m, 1H), 2.27 – 2.16 (m, 2H), 2.09 – 1.86 (m, 3H), 1.52 – 1.42 (m, 1H), 1.40 – 1.29 (m, 3H), 0.96 – 0.86 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 194.5, 159.6, 141.4, 133.6, 128.5, 128.5, 126.1, 74.6, 67.8, 32.7, 32.5, 32.3, 26.4, 22.6, 21.8, 14.4, 14.2$. Further analytical data was not obtained.
**Compound 93**

Colourless oil (17 mg, 42% from 90 (20 mg, 0.11 mmol) using method I); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.32 – 7.23 (m, 4H), 7.22 – 7.14 (m, 7H), 7.07 (m, 2H), 7.01 – 6.96 (m, 2H), 4.86 (d, $J$ = 18.0 Hz, 1H), 4.70 (dd, $J$ = 17.9, 1.3 Hz, 1H), 4.15 – 4.09 (m, 1H), 2.93 – 2.76 (m, 2H), 2.41 – 2.30 (m, 1H), 2.17 – 2.06 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 195.0, 154.7, 141.4, 135.5, 134.4, 133.2, 130.8, 128.8, 128.7, 128.5, 128.4, 128.3, 127.8, 127.3, 126.0, 79.2, 68.4, 31.6, 31.2; IR (neat): $\tilde{\nu}$ = 3059 (w), 3026 (w), 2927 (w), 2861 (w), 2810 (w), 1677 (s), 1598 (w), 1494 (w), 1444 (w), 1327 (m), 1135 (m), 1030 (w), 1002 (w), 945 (w), 756 (m), 697 (s) cm$^{-1}$; MS (ESI): calcd for (C$_{25}$H$_{22}$O$_2$ + Na): 377.1517; found: 377.1521.

**Compound 101**

Colourless oil (48 mg, 41% from 7 (49 mg, 0.29 mmol) using method I, except that 1.5 equiv of alkyne and 20 mol% of PhCy$_3$P were used. The reaction was also carried out in toluene and that the oil bath temperature was set at 100 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.05 (d, $J$ = 8.7 Hz, 2H), 6.92 (d, $J$ = 8.7 Hz, 2H), 6.75 – 6.68 (m, 4H), 5.58 (s, 2H), 4.26 (s, 2H), 3.75 – 3.72 (m, 6H), 1.51 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 192.7, 160.0, 158.8, 154.3, 153.9, 132.1, 130.3, 134.6, 129.3, 126.3, 113.8, 113.5, 82.1, 55.2, 55.1, 51.9, 47.8, 28.4; IR (neat): $\tilde{\nu}$ = 2975 (w), 2935 (w), 2837 (w), 1694 (m), 1675 (s), 1605 (m), 1508 (s), 1440 (w), 1366 (m), 1289 (m), 161
1245 (s), 1157 (s), 1110 (m), 938 (w), 827 (m) cm\(^{-1}\); MS (ESI): calcd for (C\(_{24}\)H\(_{27}\)NO\(_5\)S + Na): 432.1787; found: 432.1778.

\(^{\dagger}\) Carbon marked with an asterisk appears as a very broad peak in \(^{13}\)C CPD NMR spectrum and is not visible in the \(^{13}\)C APT NMR spectrum. However, HMBC correlations are visible which confirms the \(^{13}\)C CPD NMR.

(\(^{13}\)C APT NMR (d = 2): 40\(^\circ\)C, \(^{13}\)C CPD NMR (d = 4): 40\(^\circ\)C)

**Compound 102**

Orange oil (57 mg, 49% from 7 (49 mg, 0.29 mmol) using method I, except that 1.5 equiv of alkyne and 20 mol% of PhCy\(_2\)P were used. The reaction was also carried out in toluene and that the oil bath temperature was set at 100 °C)\(^{\dagger}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.77 – 7.33\) (br m, 1H), 7.27 (d, \(J = 8.6\) Hz, 2H), 7.18 (d, \(J = 8.7\) Hz, 2H), 6.87 – 6.81 (m, 2H), 6.78 (d, \(J = 8.7\) Hz, 2H), 4.44 (d, \(J = 1.8\) Hz, 1H), 4.18 (br d, \(J = 18.2\) Hz, 1H), 3.91 (dd, \(J = 18.8, 2.0\) Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 1.52 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 202.1, 159.5, 159.0, 152.0, 130.2, 128.8, 127.6, 126.4, 123.7, 114.7, 114.2, 82.2, 77.3, 55.5, 55.3, 50.3, 49.6, 28.3\); IR (neat): \(\tilde{\nu} = 2976\) (w), 2933 (w), 2837 (w), 1702 (s), 1647 (m), 1607 (m), 1507 (s), 1441 (m), 1370 (s), 1294 (s), 1246 (s), 1152 (s), 1111 (m), 1034 (s), 946 (w), 827 (m), 765 (w) cm\(^{-1}\); MS (ESI): calcd for (C\(_{24}\)H\(_{27}\)NO\(_5\) + Na): 432.1787; found: 432.1779.

(\(^{13}\)C APT NMR (d = 2): 40\(^\circ\)C, \(^{13}\)C CPD NMR (d = 2): 40\(^\circ\)C)
2.7.5 **Nickel(II): Synthesis of pyridinones**

Method I. Inside a glovebox, a Teflon-screw flame-dried Schlenk flask equipped with a small stirrer bar was charged with NiCl$_2$(PCy$_3$)$_2$ (8.1 mg, 0.0.1 mmol) and zinc (16 mg, 0.58 mmol) and taken out of the glovebox. Under N$_2$, azetidinone 7 (20 mg, 0.12 mmol) and alkyne 5b (19 μl, 0.73 mmol) were then added. Afterwards, iPrOH (0.6 ml) was then added and the flask was sealed and immersed into an oil bath pre-heated at 60°C. After stirring for 17 hours at that temperature, the mixture was allowed to cool and filtered through a silica plug before evaporation. Purification by flash chromatography (PE/EtOAc, 9/1) gave 6b as colourless oil (23 mg, 72%).

Method II. On the bench top, under N$_2$, a flame-dried Schlenk flask equipped with a small stirrer bar was charged with NiBr$_2$•xH$_2$O (38.8 mg, 0.18 mmol) and PPh$_3$ (93 mg, 0.36 mmol) and iPrOH (3.6 ml). The suspension was stirred at 60°C for 10 minutes and was then cooled back down to rt. Afterwards, zinc (58 mg, 0.89 mmol), azetidinone 69 (200 mg, 0.89 mmol) and alkyne 5m (121 μl, 0.98 mmol) were then added. Afterwards, the schlenk was immersed into an oil bath pre-heated at 60°C. After stirring for 17 hours at that temperature, the mixture was allowed to cool and filtered through a silica plug before evaporation. The crude ratio of 120:121 is 86:14 as judged by $^1$H NMR analysis. Purification by flash chromatography (PE/EtOAc, 8/1 → 4/1) afforded 120 as a white solid (196 mg, 69%) and 121 as white solid (36 mg, 13%).

**Compound 6b**

Colourless oil (23 mg, 72%) using method I; Full characterisation reported earlier.
Compound 6c

Colourless oil (696 mg, 83% from 500 mg of 6c using method I), except 5 mol% NiBr$_2$(PPh$_3$)$_2$ and 50 mol% zinc were used and the oil bath was set at 40°C: Full characterisation reported earlier.

Compound 121

White solid (196 mg, 69%) from 69 (200 mg, 0.89 mmol) using method II; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.63$ (d, $J = 8.3$ Hz, 2H), 7.32 – 7.28 (m, 2H), 5.10 – 5.08 (m, 1H), 4.76 – 4.73 (m, 1H), 3.92 (s, 2H), 3.80 (s, 2H), 2.40 (s, 3H), 2.11 (q, $J = 7.5$ Hz, 2H), 1.87 – 1.85 (m, 3H), 0.75 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 191.5, 153.8, 144.3, 140.7, 135.2, 133.3, 130.0, 127.7, 115.7, 52.6, 47.6, 21.8, 21.5, 19.2, 14.0; IR (neat): $\tilde{\nu} =$ 2969 (w), 2928 (w), 2871 (w), 1679 (s), 1618 (w), 1598 (w), 1494 (w), 1444 (w), 1350 (s), 1253 (w), 1163 (s), 1121 (w), 1090 (w), 1029 (w), 960 (w), 910 (w), 815 (w) 785 (w), 768 (w), 662 (w) cm$^{-1}$; MS (ESI): calcd for (C$_{17}$H$_{21}$NO$_3$S + Na): 342.1140; found: 342.1135.

Compound 122

Colourless oil (36 mg, 13% from 69 (200 mg, 0.89 mmol) using method II); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.64$ (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 5.10 – 5.06 (m, 1H), 4.45 – 4.41 (m,
$^1$H, 3.95 (s, 2H), 3.81 (s, 2H), 2.40 (s, 3H), 2.20 (q, $J = 7.6$ Hz, 2H), 1.66 (s, 3H), 1.04 (t, $J = 7.6$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 190.2, 155.4, 144.3, 138.6, 137.7, 133.3, 130.0, 127.6, 113.7, 52.7, 47.0, 26.0, 23.0, 21.4, 12.8; IR (neat): $\tilde{\nu} =$ 2974 (w), 2937 (w), 2923 (w), 2878 (w), 1677 (m), 1620 (w), 1598 (w), 1444 (w), 1350 (m), 1308 (w), 1241 (w), 1185 (w), 1163 (s), 1089 (w), 1046 (w), 998 (w), 957 (w), 906 (w), 830 (w), 816 (w), 707 (w), 681 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{17}$H$_{21}$NO$_3$S + Na)$^+$: 342.1140; found: 342.1129

2.7.6 Hydrogenation and Aromatisation

**Compound 85a**

Under air, a suspension of 6a (50 mg, 0.14 mmol), SiO$_2$ (50 mg) and TFA (0.15 ml) in dichloromethane (0.5 ml) was stirred at room temperature for 10 minutes. NaNO$_2$ (15 mg, 0.21 mmol) was then added and the suspension was stirred at room temperature for 30 minutes. Afterwards, Et$_3$N (0.5 ml) was added and the suspension was stirred for another 30 minutes. Afterwards, SiO$_2$ was added and all volatiles were removed *in vacuo*. The residue was loaded on a column and purified by flash chromatography (PE/EtAOc, 3/1 $\rightarrow$ 2/3) to give 85a as a white solid (33 mg, 83%): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 8.44 (s, 1H), 8.21 (s, 1H), 8.06 (br s, OH), 7.35 – 7.25 (m, 3H), 7.21 – 7.13 (m, 5H), 7.09 – 7.03 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 150.6, 141.9, 137.2, 137.1, 136.6, 134.8, 133.0, 129.7, 128.8, 128.0, 127.3; IR (neat): $\tilde{\nu} =$ 3028 (w), 2590 (br w), 1696 (w), 1578 w/1543 (w), 1491 (w), 1443 (w), 1415 (s), 1319 (w), 1287 (m), 1195 (w), 1117 (m), 1073 (w), 999 (w), 910 (w), 763 (s), 696 (s) cm$^{-1}$; HRMS (ESI): calcd for (C$_{17}$H$_{14}$NO + Na): 248.1075; found: 248.1071; elemental analysis (%) calcd for C$_{17}$H$_{14}$NO: C 82.56, H 5.30, N 5.67; found: C 82.27, H 5.31, N 5.63.
Compound 85d

Under air, a suspension of 6d (30 mg, 0.08 mmol), SiO\textsubscript{2} (25 mg) and TFA (0.1 ml) in dichloromethane (0.25 ml) was stirred at room temperature for 1 hour. NaNO\textsubscript{2} (8.5 mg, 0.12 mmol) was then added and the suspension was stirred at room temperature for 1 hour before adding another batch of NaNO\textsubscript{2} (8.5 mg, 0.12 mmol). After 1 hour stirring for 1 hour, Et\textsubscript{3}N (0.25 ml) was added and the suspension was stirred for another 30 minutes. Afterwards, SiO\textsubscript{2} was added and all volatiles were removed \textit{in vacuo}. The residue was loaded on a column and purified by flash chromatography (PE/Et\textsubscript{2}O, 2/1 \(\rightarrow\) 1/9) to give 85d as a white solid (13 mg, 68\%): m.p. 158–163 \(^\circ\)C (decomposition); \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 8.37\) (s, 1H), 8.06 (s, 1H), 7.68 (d, \(J = 8.1\) Hz, 2H), 7.64 (d, \(J = 7.5\) Hz, 2H), 7.46 (t, \(J = 7.6\) Hz, 2H), 7.42 (d, \(J = 8.1\) Hz, 2H), 7.37 (t, \(J = 7.3\) Hz, 1H), 2.31 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta = 154.4, 140.7, 140.5, 139.3, 138.8, 136.1, 134.9, 132.8, 129.8\) (2C), 128.9 (2C), 127.5, 127.2 (2C), 127.1 (2C), 13.3; IR (neat): \(\bar{\nu} = 3030\) (m), 2962 (w), 2916 (w), 2841 (w), 2618 (br and m), 1596 (w), 1569 (m), 1486 (s), 1422 (s), 1320 (m), 1293 (m), 1223 (w), 1142 (s), 1000 (m), 843 (m), 767 (s), 732 (w), 696 (m) cm\(^{-1}\); HRMS (ESI): calcd for (C\textsubscript{18}H\textsubscript{16}NO + Na): 262.1232; found: 262.1236.

Compound 85f

Under air, a suspension of 6f (24 mg, 0.07 mmol) in dichloromethane (0.2 ml) was added TFA (0.2 ml) and was then stirred at room temperature for 1 hour. CH\textsubscript{3}CN (0.6 ml) was then added
and then NaNO₂ (7 mg, 0.10 mmol) was added and the suspension was stirred at room temperature for 1 hour. Afterwards, SiO₂ was added and all volatiles were removed in vacuo. The residue was loaded on a column and purified by flash chromatography (PE/EtAOc, 1/2) to give 85f as a white solid (14 mg, 81%): ¹H NMR (500 MHz, CD₃COCD₃): δ = 8.68 (s, 1H), 8.35 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 2.36 (s, 3H); ¹³C NMR (125 MHz, CD₃COCD₃): δ = 155.2, 149.3, 141.2, 139.6, 134.6, 133.7, 131.4, 128.1, 121.3, 120.5 (q, J = 255.6 Hz), 13.2; HRMS (ESI): calcd for (C₁₃H₁₁NO₂F₃ + Na): 270.0742; found: 270.0752

Compound 85h

This compound was prepared from 6h (50 mg, 0.14 mmol) according to the procedure described for the preparation of 85a, except a second batch of NaNO₂ (1.5 equiv.) was added and allowed to stir for 1 hour before quenching with Et₃N. Yellow solid (25 mg, 66%): ¹H NMR (500 MHz, CDCl₃): δ = 8.31 (s, 1H), 7.91 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 2.71 (t, J = 11.9 Hz, 1H), 2.31 – 2.16 (m, 2H), 1.69 (d, J = 12.6 Hz, 2H), 1.63 – 1.47 (m, 3H), 1.25 – 1.03 (m, 3H). Further analytical data was not obtained.

Compound 85o

This compound was prepared from 6o (70 mg, 0.20 mmol) according to the procedure described for the preparation of 85a. White solid (27 mg, 53%): ¹H NMR (500 MHz, CDCl₃): δ = 8.28 (s, 1H), 7.95 (s, 1H), 7.40 – 7.34 (m, 3H), 7.28 – 7.22 (m, 2H), 0.00 (s, 9H); ¹³C NMR (125
Compound 124

A vial was charged with 121 (63 mg, 0.20 ml), Pd/C (6 mg) and suspended in EtOAC (2 ml). The vial was quickly evacuated and backfilled with H₂. Kept under 1 atm of H₂ with a H₂ balloon and stirred vigorously for 4 hours. Afterwards, the Pd/C was filtered off and concentrated. The residue was re-dissolved in THF (2 ml) and KOtBu (66 mg, 0.59 mmol) was added. After completion within 30 mins as judged by TLC, all volatiles were removed and the residue was loaded on top of a silica column. Purification by flash chromatography (PE/EtAOc, 1/1 → 1/5) afforded 124 as a white solid (14 mg, 43%): ¹H NMR (500 MHz, CDCl₃): δ = 8.16 (s, 1H), 8.00 (s, 1H), 3.16 (sept, J = 6.9 Hz, 1H), 2.77 (q, J = 7.5 Hz, 2H), 1.27 (d, J = 6.9 Hz, 6H), 1.18 (t, J =7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 153.2, 143.3, 139.1, 137.1, 132.9, 27.6, 23.8, 18.6, 13.8; IR (neat): v = 2965 (w), 2933 (w), 2873 (w), 2596 (w), 1727 (w), 1678 (w), 1596 (w), 1569 (w), 1511 (w), 1464 (w), 1429 (s), 1389 (w), 1301 (s), 1194 (w), 1168 (w), 1154 (w), 1084 (w), 1052 (w), 953 (w), 869 (w) cm⁻¹; HRMS (Cl): calcd for (C₁₀H₁₅NØ + H)⁺: 166.1226; found: 166.1233

Compound 125

Compound 70b (40mg, 0.12 mmol) was dissolved in THF (1.2 ml) and KOtBu (67 mg, 0.60 mmol) was added. After allowing it to stir at rt overnight, all volatiles were removed and the
residue was loaded on top of a silica column. Purification by flash chromatography (PE/EtAOc, 1/1 \rightarrow 1/5) afforded 125 as a white solid (10 mg, 92%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.68$ (s, 1H), 7.77 (s, 1H), 2.82-2.75 (m, 2H), 2.72 – 2.65 (m, 2H), 1.70 – 1.54 (m, 4H), 1.06 – 0.97 (m, 6H). Further analytical data was not obtained.

### 2.8 References


50.) Determined by chiral HPLC Chiralcel OJ - H Column, iPrOH:hexane = 5/95, 1 mL/min, 230 nm on an Agilent technologies 1200 apparatus.
Chapter 3 Mechanistic Investigations

3.1 Introduction

At the outset of this work, we postulated that the mechanism of the [4+2] cycloaddition would begin with the nickel-catalyst associating both azetidinone 1 and alkyne 2 to form intermediate 4 (Scheme 1). Afterwards, oxidative cyclisation would form oxanickelacyclopentene 5. Ring enlargement by β-C elimination will form seven-membered nickelacycle intermediate 6. Finally, reductive elimination would afford pyridinone 3.

Scheme 1 Original mechanistic proposal

In 1997, Oblinger and Montgomery reported a nickel-catalysed alkylative cyclisation of ynal 7 to form allylic alcohols 9 (Scheme 3). The authors proposed the formation of oxanickelacyclopentene 8 as an intermediate of the reaction. If a Ni(cod)₂/PtBu₃ (1:4 ratio of Ni to phosphine) catalytic system was employed, a reductive cyclisation of ynals 10 will form
allylic alcohols 11 (Scheme 3). The formation of an oxanickelacyclopentene 8 is postulated to occur.

\[
\begin{align*}
\text{O} & \quad \text{X} & \quad \text{H} \\
\text{7} & \quad \text{R}^1 & \quad \text{R}^2 \\
\text{X} &= \text{CH}_2, \text{NCO} \text{Ph} \\
\text{R}^1 &= \text{H, CH}_3, \text{Ph} \\
\text{R}^2 &= \text{CH}_3, \text{Et, } n\text{Bu}, \text{Ph}
\end{align*}
\]

2.5 - 3.0 equiv. ZnR$_2$
5 - 20 mol% Ni(cod)$_2$
THF, 62 - 76 %

\[
\begin{align*}
\text{L} & \quad \text{R}^1 \\
\text{8} \\
\text{HO} & \quad \text{R}^2 & \quad \text{H} \\
\text{9} & \quad \text{R}^1 \\
\end{align*}
\]

Scheme 2 Alkylative cyclisation

\[
\begin{align*}
\text{O} & \quad \text{X} & \quad \text{H} \\
\text{10} & \quad \text{R}^1 & \quad \text{R}^2 \\
\text{X} &= \text{CH}_2, \text{NCO} \text{Ph} \\
\text{R}^1 &= \text{H, CH}_3, \text{Ph} \\
\text{R}^2 &= \text{CH}_3, \text{Et, } n\text{Bu, Ph}
\end{align*}
\]

2.5 - 3.5 equiv. ZnEt$_2$
5 - 20 mol% Ni(cod)$_2$
20 - 80 mol% Pd(cod)$_2$
THF, 62 - 74 %

\[
\begin{align*}
\text{L} & \quad \text{R}^1 \\
\text{8} \\
\text{HO} & \quad \text{R}^2 & \quad \text{H} \\
\text{11} & \quad \text{R}^1 \\
\end{align*}
\]

Scheme 3 Reductive cyclisation

In the same paper, the authors reported a nickel-catalysed three-component coupling to form allyl alcohols 15 whereby the formation of oxanickelacyclopentene 14 is postulated to occur (Scheme 4). Jamison and co-workers reported a nickel-catalysed intermolecular reductive coupling of aldehydes 16 and alkynes 17 to form allylic alcohols 18 but no mechanism was proposed (Scheme 5). Regardless, oxanickelacyclopentene 14 can be invoked. Furthermore, theoretical studies support the formation of 14.

\[
\begin{align*}
\text{O} & \quad \text{R}^1 \\
\text{12} & \quad \text{R}^2 \\
\text{R}^1 &= \text{iPr, Ph} \\
\text{R}^2 &= \text{C}_6\text{H}_{13}, \text{Ph} \\
\text{R}^3 &= \text{Me, } n\text{Bu}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{R}^1 \\
\text{13} & \quad \text{R}^2 \\
\text{R}^1 &= \text{H} \\
\text{R}^2 &= \text{Pr, Ph} \\
\text{R}^3 &= \text{C}_6\text{H}_{13}, \text{Ph} \\
\text{R}^4 &= \text{Me, } n\text{Bu}
\end{align*}
\]

\[
\begin{align*}
\text{L} & \quad \text{R}^1 \\
\text{14} \\
\text{OH} & \quad \text{R}^2 & \quad \text{H} \\
\text{15} & \quad \text{R}^1 & \quad \text{R}^3 \\
\end{align*}
\]

Scheme 4 Nickel-catalysed three-component coupling
Baxter and Montgomery carried out a mechanistic study of the nickel-catalysed intramolecular reductive cyclisation of ynal 19 to form silyl ether 20 (Scheme 6).\textsuperscript{4} It is postulated that the formation of oxanickelacyclopentene 21 is most likely. However, intermediates 22 - 24 could lead to the formation of 20. Therefore, a mechanistic study was commenced to gain mechanistic insight into the operative pathway.

Scheme 5 Nickel-catalysed intermolecular reductive coupling

Scheme 6 Nickel-catalysed reductive cyclisation

Kinetic studies by \textit{in situ} IR monitoring allowed for real-time monitoring of the reaction. A first-order dependence of the reaction rate on ynal 19, first-order dependence of the reaction rate on catalyst and zero-order dependence of the reaction rate on Et\textsubscript{3}SiH were observed. Kinetic isotopic effect studies revealed that Et\textsubscript{3}SiH and Et\textsubscript{3}SiD have no significant kinetic isotopic effect and crossover studies revealed little crossover (Scheme 7).
Afterwards, *in situ* IR monitoring of the addition of a solution of 1.0 equiv of the catalyst derived from Ni(cod)$_2$ and PCy$_3$ to a solution of Et$_3$SiH resulted in no change to the silicon hydride stretch (2100 cm$^{-1}$) which along with the other mechanistic data rules out intermediate 22. Interestingly, the addition of a solution of 1.0 equiv of the same catalyst to a solution of Et$_3$SiH and hydrocinnamaldehyde resulted in no change to the silicon hydride stretch which rules out intermediate 23. Furthermore, the addition of a solution 1.0 equiv of the same catalyst to a solution of Et$_3$SiH and phenyl propyne resulted in no change to the silicon hydride stretch which rules out intermediate 24. Finally, the addition of a solution of 1.0 equiv of the same catalyst to a solution of Et$_3$SiH and ynal 19 resulted in conversion to 20, which along with the previous mechanistic data support the intermediacy of 21.

Ogoshi and co-workers reported a AlMe$_3$-promoted oxidative cyclisation between an alkene, a ketone and nickel(0) to give oxanickelacyclopentene 28 (Scheme 8). The reaction of Ni(cod)$_2$ and PCy$_3$ with ketone 26 gave complex 27. Complex 27 was isolated in a 86% and the X-ray structure confirmed that C=O and C=C bonds both coordinate to the nickel centre in $\eta^2$-fashion. After the formation of 27, heating to 60°C or the addition of Me$_3$SiOTf did not induce the transformation to oxanickelacyclopentene 28. Reaction of 27 with AlMe$_3$ in C$_6$D$_6$ then afforded 28 in a quantitative yield. The structure of 28 was confirmed by X-ray diffraction analysis. However, no further reaction was observed in C$_6$D$_6$. 

**Scheme 7** Kinetic isotopic effect study and crossover study
Scheme 8 Oxidative cyclisation to form pentanickelacycle

The addition of THF to oxanickelacyclopentene 28 generated complex 31 (Scheme 9). The authors proposed the initial transmetallation was followed by methane elimination to afford intermediate 29. Oxidation addition into the C–O bond would afford intermediate 30. Finally, transmetallation would afford complex 31 in a 56% yield. Interestingly, when catalytic amount of Ni(cod)$_2$ and PCy$_3$ were employed, rapid cycloisomerisation of ketone 26 formed allylic alcohol 32 after protonation in an 86% yield (Scheme 10).

Scheme 9 Generation of complex 31

Scheme 10 Cycloisomerisation of ketone 26 to form allylic alcohol 32

Ogoshi and co-workers reported a nickel-catalysed transformation of aldehyde 33 to form ketone 34 (Scheme 11). Stoichiometric reactions were then carried out to gain insight into the mechanism. The treatment of 34 with Ni(cod)$_2$ and iPrBu resulted in the quick formation of
complex 35 and was isolated in a 83% yield. Complex 35 slowly dimerised to form a mixture of syn-36 and anti-36 over 33 days and the mixture was isolated together in a 84% yield. Furthermore, the structure of anti-35 was confirmed by X-ray diffraction analysis. It is assumed the dimerisation goes through monomeric intermediate 37 but 37 is never observed over the course of the reaction as judged by NMR analysis. The conversion of 36 into 34 was very slow. When 2.5 mol% of 36 was used, the transformation of 33 into 34 took place within 5 hours and a yield of 101% (maximum 105%) was obtained. Therefore it is concluded that under the reaction conditions, monomeric 37 is part of the catalytic cycle and 37 is in equilibrium with 36.

Scheme 11 Mechanistic study on the nickel-catalysed transformation of 33 into 34

Ogoshi and co-workers reported the formation of nickeladihydrofuran 40 from the reaction of benzaldehyde 38, butyne 39, Ni(cod)$_2$ and PCy$_3$ (Scheme 12). Furthermore, 40 was isolated in a 40% yield and the structure was confirmed by X-ray diffraction analysis. Also, the nickel centre exhibits a square planar geometry. 40 decomposed in THF to form enone 42 and was
isolated in a 70% yield. It is postulated that β-H elimination from 40 would afford 41. Subsequent reductive elimination would then afford 42. This result demonstrates that 40 can be a key intermediate in a nickel-catalysed reaction.

Scheme 12 Formation of nickeladihydrofuran 40 and its decomposition

The postulated mechanism for the [4+2] cycloaddition relied on the formation of an oxanickelacyclopentene via oxidative cyclisation. Overall, all experimental and theoretical studies discussed above are in support of this mechanistic proposal.

In contrast, Li and Lin recently reported a theoretical study on the nickel-catalysed cycloaddition of 3-azetidinones with alkynes. After modelling the insertion of 2-butyne with the proposed model (Scheme 1), the barrier calculated for the β-C elimination step from oxanickelacyclopentene 43 was calculated to be 46.7 kcal/mol and is therefore inaccessible. Alternatively, a ligand could ligate to form oxanickelacyclopentene 45 but the barrier calculated for the subsequent β-C elimination step is still inaccessible (46.5 kcal/mol). Therefore, these calculations rule out the initial formation of oxanickelacyclopentene 43 or 45 (Scheme 13).
Scheme 13 The β-C elimination pathway, L = PMe₃ and R = Boc

As a result, the authors proposed that the oxidative insertion of the nickel complex 50 into azetidinone 51 will occur instead (Scheme 14). The oxidative insertion of 50 into 51 is calculated to be the rate determining step with a barrier of 26.8 kcal/mol. Furthermore, this energy barrier is far lower than the energy barrier calculated for the β-C elimination step. Importantly, the authors’ new mechanistic proposal is very different from the mechanism proposed for the [4+2] cycloaddition.⁹
Scheme 14 Oxidative insertion pathway, L = PMe$_3$ and R = Boc

Furthermore, the theoretical study also looked at the nature of the insertion of 1-(trimethylsilyl)propyne (Scheme 15). The oxidative insertion of the nickel-complex 57 into 51 has the same energy barrier regardless of the orientation of the alkyne. The TMS group is a strong π acceptor and will decrease the electron density at the carbon atom of the alkyne which is substituted with the methyl group. This therefore makes it more difficult for the carbon atom of the alkyne which is substituted with the methyl group to attack the metal bonded C=O carbon centre. This is reflected in the higher energy requirements to reach transition states 61 and 66. Therefore, the authors proposed the insertion of the silylated alkyne into the Ni–C bond occurs instead. Furthermore, the calculations revealed that the orientation of the alkyne have a significant effect on the transition state. The authors proposed that since the carbon atom of the alkyne which is substituted with the methyl group is π electron poor, it will couple with the Ni-bonded carbon better. Also, the carbon atom of the alkyne which is substituted with the methyl group is less sterically hindered than the carbon atom of the alkyne which is substituted with the TMS group. This is reflected in the lower energy requirements to reach transition state 67 when compared to 60. Interestingly,
the predicted regioselectivity of the insertion is in good agreement with the experimental observation. \(^9\)

Scheme 15 Insertion of 1-(trimethylsilyl)propyne

The mechanism of the nickel-catalysed cycloaddition of 3-azetidinones with alkynes has yet to be studied experimentally. From the theoretical work of Li and Lin, the β-C elimination step is not a feasible step due to the high energy barrier but proposed the insertion of nickel into the acyl–carbon bond of azetidinone to account for the C–C bond cleavage step. On the other
hand, experimental work by Ogoshi and co-workers demonstrated that oxanickelacyclopentene are real intermediates which could be potentially present in the nickel-catalysed [4+2] cycloaddition. Therefore, our efforts towards the understanding of the mechanism of the nickel-catalysed cycloaddition of 3-azetidinones with alkynes are described.

### 3.2 Results and Discussion

#### 3.2.1 Re-optimisation of the reaction conditions

Before commencing the kinetic study, it was of interest to re-optimise the reaction conditions in light of different conditions reported by Louie and Murakami (Table 1).\(^\text{10}\) Furthermore, the reaction had to be sufficiently slow for meaningful kinetic data to be obtained. Moreover, it was of interest to see if the kinetic study can be carried out in toluene. This will allow the possibility of NMR experiments to be carried out in d\(_8\)-toluene which will be far more economical than using d\(_8\)-dioxane. It was found that the reaction is complete in 10 minutes when carried out at 90°C in toluene (Table 1, entry 1). Lowering the temperature of the reaction to 70°C and 60°C resulted in the reaction being over within 30 minutes (Table 1, entry 2 and 3). Lowering the temperature of the reaction to 40°C resulted in 50% conversion after 30 minutes (Table 1, entry 4). However, the rate of the reaction became too slow when the reaction was carried out at rt (Table 1, entry 5).
**Table 1** Re-optimisation of the reaction conditions in toluene

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (mins)</th>
<th>Conversion[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>10</td>
<td>Full</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>60</td>
<td>Full</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>30</td>
<td>Full</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>30</td>
<td>~50%</td>
</tr>
<tr>
<td>5</td>
<td>rt</td>
<td>30</td>
<td>~10%</td>
</tr>
</tbody>
</table>

[a] Conversion determined from the ratio of 70 and 72 by ^1^H NMR

The progress of the reaction for the kinetic study is monitored by the appearance of product by taking aliquots from the reaction vessel at specific times. However, there was an issue with the mass balance and it was found that either 70 could azeotrope with the solvent during evaporation or decompose over silica. However, when the reaction of 1 equiv. of 70 and 1.1 equiv. of 71 is monitored until >95% conversion as judged by integration of 72 against 1 equiv. of triphenylethylene as an internal standard, no unexpected disappearance of 72 was observed (Scheme 16). This therefore validates the initial rate method used in the subsequent kinetic study.
3.2.2 Rate law with silylated alkyne 74

3.2.2.1 “Initial Burst” Phase

A systematic study was then commenced to determine the rate law to gain insight into the mechanism. Initial rates were monitored by taking aliquots from the reaction mixture periodically and analysed by $^1$H NMR. It was of interest to carry out a kinetic study of the cycloaddition of azetidinone 70 with silylated alkyne 74 using the re-optimised conditions (Scheme 17).
On the initial attempt with 10 mol% Ni(cod)$_2$, 30 mol% PPh$_3$ in toluene at 40°C with 1 equivalent of 70 and 1.1 equivalents of 73, it was discovered the trend line would not give a good fit if passed through the intercept at 0 (Scheme 18). Therefore, this initial burst phase in the reaction was looked into with more detail. Attempts to maintain the “initial burst” phase by slow dropwise addition of either the alkyne or a solution of alkyne and azetidinone at 40°C proved to be unfruitful. Therefore, a more detailed study of the “initial burst” phase was carried out.

![Graph showing concentration over time](image)

**Scheme 18** Initial discovery of the initial “burst” phase

Temperature effects on the initial “burst” phase were then studied (Table 2). When the first point was taken at 10 minutes at 40°C, there was 32% conversion to 74 (Table 2, entry 1). On prolonging the reaction to 60 minutes, the conversion to 74 was at 54% (Table 2, entry 2). Interestingly, upon lowering the reaction temperature to rt, there was 21% conversion (Table 2, entry 3). At the 30 minute mark, the conversion increased slightly to 23 % (Table 2, entry 4). Analysis of the aliquot taken at the 60 minute mark revealed only 30% conversion to 74 and some decomposition of the starting material was observed (Table 2, entry 5). These results tell us that they are two phases in the reaction; an initial “burst” phase at the start of the reaction and the steady state phase. The steady state phase appears to be the more energetically
demanding of the two phases of the reaction as a high temperature was required for a reasonable rate.

**Table 2** Temperature effects on the “initial burst”

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (mins)</th>
<th>Conv. (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>r.t.</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>r.t.</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>r.t.</td>
<td>60</td>
<td>30</td>
</tr>
</tbody>
</table>

[a] Conversion against triphenylethylene as internal standard

However, there were some issues, as different batches of commercially available azetidinone 70 gave slightly different results despite being from the same supplier but the conclusions remain the same (Table 3). The first batch of azetidinone was purified by flash column chromatography and stored inside the glove box. Furthermore, this batch was used in the examples of the previous table. The second batch of azetidinone was a separate purification by flash column chromatography and also stored inside the glove box. As azetidinone 70 is known to be hygroscopic, the varying time required for the solvent evaporation might have influenced how much water was absorbed by the azetidinone. Regardless, both <sup>1</sup>H NMRs of the purified material were identical.

The conversion after 10 minutes under the standard conditions with batch 1 is 32% (Table 3, entry 1). Interestingly, the conversion after 10 seconds was 17% (Table 3, entry 2). A 20 mol%
PPh₃ resulted in 14% conversion to 74 at 10 seconds (Table 3, entry 3). Interestingly, when the experiment was repeated with batch 2 of azetidinone, the conversion at 10 minutes with 30% PPh₃ averaged out at 23% over two runs (22% and 24%) (Table 3, entry 4). Furthermore, the conversion at 10 minutes is lower with batch 2 when compared with batch 1 (Table 3, entry 4 vs 1). The conversion at 10 seconds with 30 mol% PPh₃ averaged out at 13% over two runs (12% and 13%) (Table 3, entry 5). These results confirmed the reproducibility of the reaction when 70 is stored correctly. The conversion at 10 seconds with 20 mol% PPh₃ is 11% (Table 3, entry 6). On the other hand, with 10 mol% PPh₃, the conversion at 10 seconds is 5% and 12% at 10 minutes (Table 3, entry 7 and 8). Regardless of the two batches, the results reveal the initial “burst” phase is extremely fast and does not appear to go much past the 10% conversion mark which suggests the initial “burst” phase is stoichiometric in the active metal complex which promotes it. The little difference in the conversion in the initial “burst” phase between 20 and 30 mol% PPh₃ suggests 20 mol% PPh₃ is sufficient for the reaction. The big difference in the conversion between the two batches suggests trace water could indeed have a negative impact on the reaction. Then it was of interest to see if the initial “burst” was indeed promoted by a nickel-phosphine complex. Elimination of either or both Ni(cod)₂ and PPh₃ resulted in no reaction (Table 3, entry 9-11).
Table 3 A study on the initial burst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni(cod)$_2$ (mol %)</th>
<th>PPh$_3$ (mol %)</th>
<th>Azetidinone</th>
<th>Time</th>
<th>Conv (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>30</td>
<td>Batch 1</td>
<td>10 min</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>30</td>
<td>Batch 1</td>
<td>10 sec</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>20</td>
<td>Batch 1</td>
<td>10 sec</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>30</td>
<td>Batch 2</td>
<td>10 min</td>
<td>23$^a$</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>30</td>
<td>Batch 2</td>
<td>10 sec</td>
<td>13$^a$</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>20</td>
<td>Batch 2</td>
<td>10 sec</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>10</td>
<td>Batch 2</td>
<td>10 sec</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>10</td>
<td>Batch 2</td>
<td>10 min</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>Batch 2</td>
<td>10 min</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>30</td>
<td>Batch 2</td>
<td>10 min</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>0</td>
<td>Batch 2</td>
<td>10 min</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] average of two runs

It was then proposed that the formation of the nickel-alkyne complex was responsible for the suppression of the initial “burst” phase. Therefore, a study on the effect of the alkyne loading on the initial “burst” phase was then commenced (Table 4). After the generation of the nickel-phosphine catalyst, a precise amount of alkyne was then added and after another 5 minutes, azetidinone and the remaining alkyne (to make it a total of 1.1 equiv.) were then added. An initial addition of 5 mol% of alkyne gave a 13% conversion after 10 seconds (Table 4, entry 1) and 25% conversion at 10 minutes (Table 4, entry 2). On increasing the loading of initial alkyne to 10 mol%, the conversion was reduced to 9% at 10 seconds (Table 4, entry 3) and 15%
at 10 minutes (Table 4, entry 4). When 20 mol% PPh$_3$ was used, the conversion at 10 seconds was worst with 5% (Table 4, entry 5). On increasing the alkyne loading further to 20 mol%, the conversion was reduced further to 5% at 10 seconds and 13% at 10 minutes (Table 4, entry 6 and 7). The conversion with 20 mol% PPh$_3$ at 10 seconds is now minimal (Table 4, entry 8). If all of the alkyne was added first before the azetidinone, the conversion at 10 seconds is barely noticeable (Table 4, entry 9) and the conversion at 10 minutes stands at 10% (Table 4, entry 10). This result is reproducible (Table 4, entry 11). Furthermore, carrying out the same reaction with 20 mol% PPh$_3$ gave 15% conversion at 10 minutes (Table 4, entry 12).

As noted, there is a trend linking increased initial alkyne loading with decreased levels of conversion. Furthermore, these results confirmed the nickel-alkyne complex is not the active catalyst for the initial burst. It does appear that the higher loading of phosphine gave better conversion for the burst phase (Table 4, entry 3 vs 5). Perhaps, the extra phosphine prevents the formation of a less active Ni-alkyne complex. Furthermore, after the formation of the nickel-alkyne complex, the lower loading of phosphine is more effective as it displayed a higher reactivity (Table 4, entry 12 vs 10). Also, in the steady state, the extra phosphine will compete for binding with the reactants and the binding is reversible. However, the role of the extra phosphine in the initial “burst” phase remains speculative.
Table 4  Effects on the concentration of alkyne on the initial “burst” phase.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PPh₃ (mol %)</th>
<th>Initial alkyne (mol %)</th>
<th>Time</th>
<th>Conv (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>5</td>
<td>10 sec</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>5</td>
<td>10 min</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>10</td>
<td>10 sec</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>10</td>
<td>10 min</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>10</td>
<td>10 sec</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>20</td>
<td>10 sec</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>20</td>
<td>10 min</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>20</td>
<td>10 sec</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>30</td>
<td>110</td>
<td>10 sec</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>110</td>
<td>10 min</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>110</td>
<td>10 min</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>110</td>
<td>10 min</td>
<td>15</td>
</tr>
</tbody>
</table>

Afterwards, a study on the stoichiometry and ratio of Ni(cod)₂ and PPh₃ were carried out in anhydrous toluene. The conversion at 10 seconds was then analysed in all cases. As mentioned earlier, with 10 mol% Ni(cod)₂, the conversion was 12% when 30 mol% PPh₃ was used (Table 5, entry 1) and 11% when 20 mol% PPh₃ was used (Table 5, entry 2). On reducing the loading of Ni(cod)₂ to 7.5 mol%, the conversion was reduced to 8% with 22.5 mol% PPh₃ (Table 5, entry 3) and 7% with 15 mol% PPh₃ (Table 5, entry 4). On reducing the loading of Ni(cod)₂ further to 5 mol%, the conversion was reduced more to 6% with 15 mol% PPh₃ (Table 5, entry 5) and 4% with 10 mol% PPh₃ (Table 5, entry 6).
Table 5 A study on the stoichiometry and ratio of Ni(cod)$_2$ and PPh$_3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni(cod)$_2$ (mol %)</th>
<th>PPh$_3$ (mol %)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>22.5</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>7.5</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Then it was of interest to see if the initial burst was suppressed by the product when 30 mol% PPh$_3$ was used (Table 6). Therefore, the reaction was carried out whereby a known amount of pyridinone 74 is added after the formation of the active catalyst. Then after five minutes, the remaining reactants were then added. If the reaction was started with 20 mol% 74, the conversion at 10 minutes is 22% (Table 6, entry 1) which is the virtually the same as the reaction that was carried out without 20 mol% 74 (Table 3, entry 4). Even with a lower loading of 10 mol% 74, the conversion at 10 minutes remained unaffected (Table 6, entry 2). Even the initial “burst” phase is not affected by 74 as the conversion is 12% (Table 6, entry 3) which is virtually the same as the reaction that was carried without the inclusion of the product (Table 3, entry 5). Therefore, it can be concluded that the product does not inhibit the catalyst that allows for the initial “burst” phase.
Table 6 A study on the effect of product on the initial burst

<table>
<thead>
<tr>
<th>Entry</th>
<th>74 (mol %)</th>
<th>Time</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>10 mins</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10 mins</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>10 secs</td>
<td>12</td>
</tr>
</tbody>
</table>

3.2.2.2 Kinetic study with silylated alkyne 73

The kinetic study was carried out with the method of initial rate. The kinetic study was carried out in a round-bottom flask under an atmosphere of Argon with triphenylethylene as an internal standard. Aliquots were taken from the reaction vessel at specific times, filtered over a plug of silica, rinsed, all volatiles removed and analysed by $^1$H NMR to allow the monitoring of the reaction. To gain the order dependence in each reactant, the appearance of product is plotted vs the time as the concentration of each reactant is varied. The kinetic study was first carried out with a Ni(cod)$_2$ and PPh$_3$ ratio of 1:3 (Scheme 19).

Scheme 19 The reaction to be studied
Firstly, the concentration of the azetidinone was varied while the concentration of the other reactants remains constant. The concentration of azetidinone varied from 0.12 – 0.24 M. After obtaining the rate with each concentration of azetidinone, by plotting the log(initial rate) against log(M), first order dependence on the azetidinone was found (Figure 1).

![Order in Azetidinone and Alkyne](image1)

\[ y = 1.3132x - 0.8731, \ R^2 = 0.9472 \]
\[ y = -0.6566x - 2.1843, \ R^2 = 0.9243 \]

Secondly, the concentration of the alkyne was varied while the concentration of the other reactants remains constant. The concentration of alkyne was varied from 0.10 – 0.30 M. After obtaining the rate with each concentration of alkyne, by plotting the log(initial rate) against log(M), first order dependence on the alkyne was found (Figure 1).

![Order in Catalyst and Eyring Plot](image2)

\[ y = 0.9092x - 0.2133, \ R^2 = 0.9434 \]
\[ y = -6842x + 9.274, \ R^2 = 0.9789 \]

**Figure 1** Ni(cod)₂ and PPh₃ ratio of 1:3

194
log(M), negative first order dependence on the alkyne was found. Finally, the concentration of the Ni(cod)$_2$ and PPh$_3$ were varied but the ratio of 1:3 was kept while the concentration of the other reactants remains constant. The concentration of Ni(cod)$_2$ was varied from 0.005 – 0.025M. The concentration of PPh$_3$ was varied from 0.015 – 0.075M. After obtaining the rate with each concentration of the catalyst, by plotting the log(initial rate) against log(M), first order dependence in the catalyst was found. As a result, the rate law can be formulated by the following:

$$\text{Rate} = k_{\text{obs}}[\text{Azetidinone}]^{1.3}[\text{Alkyne}]^{-0.7}[\text{Catalyst}]^{0.9}$$

An Eyring plot was then plotted to elucidate the nature of the transition state of the rate determining step. From the Eyring plot an equation of \( y = -6842x + 9.274 \) was obtained. \( \Delta H \) is obtained from the following equation whereby \( R \) is gas constant (8.314 J K$^{-1}$ mol$^{-1}$):

$$\Delta H = mR$$

As a result, \( \Delta H \) is calculated to be 56.9 kJ mol$^{-1}$. \( \Delta S \) is obtained from the following equation whereby \( h \) is the Planck constant (6.626 x $10^{-34}$ J$\cdot$s) and \( k_B \) is the Boltzmann’s constant (1.38 x $10^{-23}$ J K$^{-1}$):

$$y(x = 0) = \ln \frac{h}{k_B} + \frac{\Delta S}{R}$$

As a result, \( \Delta S \) is calculated to be -120.4 J mol$^{-1}$. Finally, the \( \Delta G \) is obtained from the following equation:

$$\Delta G = \Delta H - T\Delta S$$

As a result, \( \Delta G \) is calculated to be 94.6 kJ mol$^{-1}$ at 40°C. These data demonstrate the high pre-organisation that exists in the transition state. From the experimental rate law, both the azetidinone and the catalyst are present at the rate determining step. However, a negative order dependence on the alkyne revealed the alkyne competes for binding to the catalyst with the azetidinone.
Before postulating a mechanism, the role of the extra phosphine was studied. The cycloaddition of azetidinone 70 with silylated alkyne 73 was studied using the modified optimised conditions of 10 mol% Ni(cod)$_2$ and 20 mol% PPh$_3$.

Firstly, the concentration of the azetidinone was varied while the concentration of the other reactants remains constant. The concentration of azetidinone varied from 0.12 – 3.0M. After obtaining the rate with each concentration of azetidinone, by plotting the log(initial rate) against log(M), first order dependence on the azetidinone was found (Figure 2).

**Order in Azetidinone**

\[ y = 1.0998x - 0.9897, \quad R^2 = 0.7419 \]

**Order in Alkyne**

\[ y = -0.7672x - 2.1317, \quad R^2 = 0.9989 \]

**Order in catalyst**

\[ y = 0.7346x - 0.3768, \quad R^2 = 0.9982 \]

**Eyring Plot**

\[ y = -7287 + 10.981, \quad R^2 = 0.9988 \]

**Figure 2** Ni(cod)$_2$ and PPh$_3$ ratio of 1:2
Secondly, the concentration of the alkyne was varied while the concentration of the other reactants remain constant. The concentration of alkyne varied from 0.10 – 0.30M. After obtaining the rate with each concentration of alkyne, by plotting the log(initial rate) against log(M), negative first order dependence on the alkyne was found. Finally, the concentration of the Ni(cod)$_2$ and PPh$_3$ were varied but the ratio of 1:2 was kept while the concentration of the other reactants remained constant. The concentration of Ni(cod)$_2$ was varied from 0.008 – 0.025M. The concentration of PPh$_3$ was varied from 0.016 – 0.050M. After obtaining the rate with each concentration of catalyst, by plotting the log(initial rate) against log(M), first order dependence on the catalyst was found. As a result, the rate law can be formulated by the following:

\[
\text{Rate} = k_{\text{obs}}[\text{Azetidinone}]^{1.1}[\text{Alkyne}]^{-0.8}[\text{Catalyst}]^{0.7}
\]

An Eyring plot was then plotted to elucidate the nature of the transition state of the rate determining step. A $\Delta H$ of 60.6 kJ mol$^{-1}$, $\Delta S$ -106.3 J mol K$^{-1}$ and $\Delta G$ 93.8 kJ mol$^{-1}$ at 40°C were obtained.

### 3.2.2.3 NMR studies

A NMR study in a J-Young NMR tube was then carried out to determine if there was any complexation of pyridinone 74 to the catalyst (Scheme 20). Treatment of 1 equiv of Ni(cod)$_2$ and 3 equiv of PPh$_3$ in d$_8$-toluene resulted in the rapid formation of a dark-red solution assumed to be PPh$_3$-nickel-complex 75. Afterwards, 74 was added and then NMR measurements were taken. Analysis of the $^1$H and $^{31}$P NMR spectra showed peaks which are characteristic of 74 and 75. 75 has two PPh$_3$ and a cod ligand attached to the nickel centre which is formed from the displacement of the first cod ligand. In the spectra, there is a second peak which is assumed to be either Ni(PPh$_3$)$_3$ or O=PPh$_3$. However, no formation of nickel-product complex 76 was observed as confirmed by analysis of the $^1$H NMR spectra which
suggests that the remaining cod ligand is not readily displaced by 74. Furthermore, this reveals that inhibition of the catalyst by 74 is unlikely as there is no complexation of 74 to the catalyst.

Scheme 20 Attempted study on the complexation of 74 to the catalyst

A competition study between alkyne 73 and product 74 was then carried out (Scheme 21). After 5 minutes of stirring to form phosphine-nickel complex 75 in d₈-toluene, 74 and then 73 were added. Observation by ³¹P NMR showed new peaks. The peak attributed to 75 was completely consumed and two new peaks (40.5 ppm, d, J = 31.7 Hz and 37.9 ppm, d, J = 31.7Hz) were there instead. Since the nickel-alkyne complex 77 is described,¹¹ we are confident complex 77 is indeed formed and the product remains uncoordinated. Furthermore, ¹H NMR peaks of 74 matched with the example given above which indicates that 74 is likely to be uncoordinated. Furthermore, this study revealed that the displacement of the alkyne with 74 is a very difficult process.

Scheme 21 Competition study between product and alkyne
The synthesis of complex 77 began with the addition of 73 to a pre-mixed solution of Ni(cod)$_2$ in PPh$_3$ in toluene (Scheme 22). After stirring for 1 hour, the suspension was filtered and all the volatiles were removed and washed with hexane to give 77 in a yield of 97%. 77 is also catalytically competent as full conversion to 74 was observed under the modified standard reaction conditions (Scheme 23).

![Scheme 22 Synthesis of complex 77](image)

Scheme 22 Synthesis of complex 77

A NMR study was then commenced to see if complex 77 is the active catalyst. In the kinetic study, a negative first order dependence in alkyne 73 was found. Therefore, 77 could lose an alkyne to give the active catalyst or 77 is the active catalyst which came from bis-alkyne nickel-complex 78. To test which of the two pathways were most plausible, an attempt to force the formation of the bis-alkyne complex 78 by addition of 5 equivalents of 73 was made (Scheme 24). However, no new peaks were observed in either the $^{31}$P or $^1$H spectra. As a result of the difficulty in forcing the formation of 78, the active catalyst is most likely formed by the loss of alkyne 73 at the rate determining step.
Furthermore, mixing complex 78 and alkyne 79 in d₆-toluene resulted in the formation of complex 80 and 73 as determined by ³¹P NMR (Scheme 25). It is likely there is an equilibration between 77 and 80. However, no other peaks were observed in the ³¹P or ¹H NMR spectra. Therefore, this shows the exchange of alkyne occurs faster than the “NMR timescale”.

The formation of the oxanickelacyclopentene 81 was attempted by mixing complex 77 with 1 equiv. of azetidinone 70 in d₆-toluene (Scheme 26). However, no formation of 81 was detected by ¹H or ³¹P NMR. On the other hand, there was a slow appearance of product 74. Heating the solution to 40°C did not significantly improve the conversion to 74.
3.3 Revised Mechanism and Conclusion

In light of the kinetic study and various NMR investigations, a mechanism is proposed (Scheme 27). Nickel-complex 77 is a resting state of the reaction and is observed experimentally. From the kinetic study, a negative first order dependence on the alkyne, a first order dependence on the azetidinone and a first order dependence on the catalyst were observed. Furthermore, the formation of oxanickelacyclopentene 81 and bis-alkyne complex 78 were not possible. Therefore, a revised mechanism was hypothesised (Scheme 26). This revealed that 77 is an inactive resting state and is therefore off cycle because an alkyne has to be lost. Therefore, complex 83 is the active catalyst which will participate in the oxidative addition in the RDS which will account for the first order dependence on catalyst. The addition of azetidinone at the RDS will account for the first order dependence on azetidinone. Finally, the loss of an alkyne will account for the negative first order dependence on alkyne.

**Scheme 27 Revised mechanism**

Based on the revised mechanism, the following equation gives the rate of the reaction which depends on the concentration of intermediate 83 and azetidinone 70:
Intermediate 83 is formed by the loss of an alkyne 73 from complex 77. However, 83 is depleted by the reverse reaction with 83 and 73. Also, 83 is depleted in the reaction with 70. Therefore, the concentration of 83 will change as a function of time:

\[
\frac{d[83]}{dt} = k_1[77] - k_{-1}[73][83] - k_2[83][70] = 0
\]

Equation 2

By carrying out a steady state approximation whereby the concentration of 83 does not change with time, upon rearrangement of the previous equation, the following equation is attained:

\[
[83] = \frac{k_1[77]}{k_{-1}[73] + k_2[70]}
\]

Equation 3

Substitution of the expression for [83] into equation 1 will arrive at the following equation:

\[
\frac{d[84]}{dt} = \frac{k_1 k_2[77][70]}{k_{-1}[73] + k_2[70]}
\]

Equation 4

To fit the observed order dependence of each reactant, $k_2[Azetidinone] \ll k_1[Alkyne]$. This isn’t surprising as 77 is observed as a resting state by NMR. As a result, the kinetic expression is simplified to:

\[
\frac{d[84]}{dt} = \frac{k_1 k_2[77][70]}{k_{-1}[70]}
\]

Equation 5

Therefore the $k_{obs}$ is:

\[k_{obs} = \frac{k_1 k_2}{k_{-1}}\]
From the kinetic studies, an alkyne is lost at the rate determining step which is different from what is predicted theoretically by Li and Lin. Furthermore, the original proposed mechanism is now in doubt. As judged by NMR studies, a nickel-complex 77 is the resting state in the catalytic cycle and no other intermediates are observed over the course of the reaction. Also, the 77 is catalytically competent. However, further tests will be necessary to determine if the insertion of the catalyst into the azetidinone to form 84 is a reality.

3.4 Experimental data

3.4.1 Kinetic study

General procedure for all kinetic studies: Kinetic experiments were run inside an argon filled glovebox. Reactions were run up to about 6 – 63% conversion and the data (% product versus time) was analysed using the initial rates method.

3.4.1.1 Kinetic study: Ni(cod)2/PPh3 (1:3)

Order in azetidinone 70: The order in 70 was determined by studying the initial rate of reactions with different [70]: Inside a glovebox, a round bottom flask was charged with the Ni(cod)2 (6.4 mg, 0.02 mmol) and PPh3 (18.4 mg, 0.07 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (0.14 – 0.28 mmol), alkyne (51 μl, 0.26 mmol) and triphenylethylene (59.9 mg, 0.24 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath set at 40°C. Aliquots were taken out with a syringe from the reaction vessel at specific
times and immediately filtered through a plug of SiO$_2$ and washing with Et$_2$O. After all the volatiles were removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.

![Diagram of chemical reaction](image)

### 0.14 mmol of 70

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[a] Integration of $^1$H NMR

### 0.14 mmol of 70

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[a] Integration of $^1$H NMR
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[a] Integration of $^1$H NMR

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[a] Integration of $^1$H NMR

### 0.24 mmol of 70

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[a] Integration of $^1$H NMR
Order in alkyne 73: The order in 73 was determined by studying the initial rate of reactions with different [73]: Inside a glovebox, a round bottom flask was charged with the Ni(cod)₂ (6.4 mg, 0.02 mmol) and PPh₃ (18.4 mg, 0.07 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (40 mg, 0.23 mmol), alkyne (0.12 – 0.35 mmol) and triphenylethylene (59.9 mg, 0.13 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath set at 40°C. Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO₂ and washing with Et₂O. After all the volatiles were
removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.

![Chemical reaction diagram](image)

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[a] Integration of $^1$H NMR

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[a] Integration of $^1$H NMR
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[a] Integration of $^1$H NMR

### 0.26 mmol of 73

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[a] Integration of $^1$H NMR

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0.35 mmol of 73

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[a] Integration of $^1$H NMR

Order in catalyst: The order in catalyst was determined by studying the initial rate of reactions with different loadings of catalyst: Inside a glovebox, a round bottom flask was charged with the Ni(cod)$_2$ (0.006 – 0.029 mmol) and PPh$_3$ (0.018 – 0.088 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (40 mg, 0.23 mmol), alkyne (51 μl, 0.26 mmol) and triphenylethylene (59.9 mg, 0.23 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath set at 40°C. Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO$_2$ and washing with Et$_2$O. After all the volatiles were removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.
0.006 mmol of Ni(cod)$_2$ and 0.018 mmol of PPh$_3$

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$^a$ Integration of $^1$H NMR

0.009 mmol of Ni(cod)$_2$ and 0.028 mmol of PPh$_3$

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$^a$ Integration of $^1$H NMR
0.012 mmol of Ni(cod)$_2$ and 0.035 mmol of PPh$_3$

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[a] Integration of $^1$H NMR

0.018 mmol of Ni(cod)$_2$ and 0.053 mmol of PPh$_3$

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[a] Integration of $^1$H NMR

0.023 mmol of Ni(cod)$_2$ and 0.070 mmol of PPh$_3$

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[a] Integration of $^1$H NMR
0.023 mmol of Ni(cod)$_2$ and 0.070 mmol of PPh$_3$

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[a] Integration of $^1$H NMR

0.029 mmol of Ni(cod)$_2$ and 0.088 mmol of PPh$_3$

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<td>1.4143</td>
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</table>

[a] Integration of $^1$H NMR

Eyring plot: The Eyring plot was determined by studying the initial rate of reactions at different temperatures: Inside a glovebox, a round bottom flask was charged with the Ni(cod)$_2$ (6.4 mg, 0.02 mmol) and PPh$_3$ (18.4 mg, 0.07 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (40 mg, 0.23 mmol), alkyne (51 μl, 0.26 mmol) and triphenylethylene (59.8 mg, 0.23 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath (35 – 60°C). Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO$_2$ and washing with Et$_2$O. After all the volatiles were
removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.

$$\text{Boc} \quad 0.23 \text{ mmol} \quad 70$$

$$\text{TMS} \quad 0.26 \text{ mmol} \quad 73$$

$\xrightarrow{10 \text{ mol%Ni(cod)$_2$,} \ 30 \text{ mol%PPh$_3$,} \ \text{toluene (0.2 M), 35-80°C,} \ \text{time}}$ $\xrightarrow{10 \text{ mol%Ni(cod)$_2$,} \ 30 \text{ mol%PPh$_3$,} \ \text{toluene (0.2 M), 35-80°C,} \ \text{time}}$

$$\text{Boc} \quad \text{TMS} \quad 74$$

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<th>$\textbf{74}^{[b]}$</th>
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[a] Integration of $^1$H NMR

At 40°C

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[a] Integration of $^1$H NMR
At 40°C

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[a] Integration of $^1$H NMR

At 50°C

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[a] Integration of $^1$H NMR

At 60°C

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[a] Integration of $^1$H NMR
3.4.1.2 Kinetic Study: Ni(cod)2/PPh3 (1:2)

Order in azetidinone 70: The order in 70 was determined by studying the initial rate of reactions with different [70]: Inside a glovebox, a round bottom flask was charged with the Ni(cod)2 (6.4 mg, 0.02 mmol) and PPh3 (12.3 mg, 0.05 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (0.14 – 0.35 mmol), alkyne (51 μl, 0.26 mmol) and triphenylethylene (59.8 mg, 0.23 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath set at 40°C. Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO2 and washing with Et2O. After all the volatiles were removed, product yield from the corresponding reaction was monitored by 1H NMR analysis using triphenylethylene as internal standard.

![Chemical reaction diagram]

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<tr>
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[a] Integration of 1H NMR
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[^a] Integration of \(^1^H\) NMR

<table>
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<th>74 (M)</th>
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</thead>
<tbody>
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<td>0.9166</td>
<td>0.04575</td>
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<tr>
<td>10</td>
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<td>1</td>
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<td>0.059945</td>
</tr>
<tr>
<td>20</td>
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[^a] Integration of \(^1^H\) NMR

<table>
<thead>
<tr>
<th>Time (min)</th>
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[^a] Integration of \(^1^H\) NMR
Order in alkyne 73: The order in 73 was determined by studying the initial rate of reactions with different [73]: Inside a glovebox, a round bottom flask was charged with the Ni(cod)$_2$ (6.4 mg, 0.02 mmol) and PPh$_3$ (12.3 mg, 0.05 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (40 mg, 0.23 mmol), alkyne (0.12 – 0.35 mmol) and triphenylethylene (59.8 mg, 0.23 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath set at 40°C. Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO$_2$ and washing with Et$_2$O. After all the volatiles were
removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.

![Chemical reaction structure]

<table>
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[a] Integration of $^1$H NMR

<table>
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<th>74 (M)</th>
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[a] Integration of $^1$H NMR
### 0.21 mmol of **73**

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[a] Integration of $^1$H NMR

### 0.26 mmol of **73**

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<tr>
<td>5</td>
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<td>0.04575</td>
</tr>
<tr>
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<td>1</td>
<td>1.0727</td>
<td>0.053541</td>
</tr>
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<td>20</td>
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[a] Integration of $^1$H NMR

### 0.35 mmol of **73**

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[a] Integration of $^1$H NMR

Order in catalyst: The order in catalyst was determined by studying the initial rate of reactions with different loadings of catalyst: Inside a glovebox, a round bottom flask was charged with
the Ni(cod)$_2$ (0.009 – 0.29 mmol) and PPh$_3$ (0.018 – 0.58 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (40 mg, 0.23 mmol), alkyne (51 μl, 0.26 mmol) and triphenylethylene (59.8 mg, 0.23 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath set at 40°C. Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO$_2$ and washing with Et$_2$O. After all the volatiles were removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.

![Reaction Scheme](image)

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$^{[a]}$ Integration of $^1$H NMR
0.012 mmol of Ni(cod)$_2$ and 0.023 mmol of PPh$_3$

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<th>$74$ (M)</th>
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[a] Integration of $^1$H NMR

0.018 mmol of Ni(cod)$_2$ and 0.036 mmol of PPh$_3$

<table>
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<tr>
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<tr>
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[a] Integration of $^1$H NMR

0.023 mmol of Ni(cod)$_2$ and 0.047 mmol of PPh$_3$

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<td>0.04575</td>
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<td>1</td>
<td>1.0727</td>
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<tr>
<td>20</td>
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<td>0.066888</td>
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[a] Integration of $^1$H NMR
0.029 mmol of Ni(cod)$_2$ and 0.058 mmol of PPh$_3$

<table>
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<td>1</td>
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$^{[a]}$ Integration of $^1$H NMR

Eyring plot: The Eyring plot was determined by studying the initial rate of reactions at different temperatures: Inside a glovebox, a round bottom flask was charged with the Ni(cod)$_2$ (6.4 mg, 0.02 mmol) and PPh$_3$ (12.3 mg, 0.05 mmol). A rubber septa was used to seal the round bottom flask and taken out of the glovebox. Immediately, an argon balloon was used to keep the round bottom flask under inert atmosphere. Toluene (0.37 ml) was then added via syringe. After 5 mins of stirring at rt, a solution of azetidinone (40 mg, 0.23 mmol), alkyne (51 μl, 0.26 mmol) and triphenylethylene (59.8 mg, 0.23 mmol) in toluene (0.80 ml) was added via syringe. Immediately, the round bottom flask was transferred to a pre-heated oil bath (35 – 60°C). Aliquots were taken out with a syringe from the reaction vessel at specific times and immediately filtered through a plug of SiO$_2$ and washing with Et$_2$O. After all the volatiles were removed, product yield from the corresponding reaction was monitored by $^1$H NMR analysis using triphenylethylene as internal standard.
At 35°C

<table>
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<td>40</td>
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\(^{[a]}\) Integration of \(^1\)H NMR

At 40°C

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[a] Integration of 1H NMR

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[a] Integration of 1H NMR

3.4.2 NMR studies

All solvents used were stored in a schlenk or in a glovebox. All solvents were degasses prior to use by standard techniques.

3.4.2.1 Product Inhibition

Procedure: In the glovebox, a J-Young NMR tube is charged with Ni(cod)₂ (3.2mg, 0.01 mmol) and taken out. Under Ar, dissolved in d₈-toluene (0.1 ml) and a solution of PPh₃ (9.2 mg, 0.04 mmol) in d₈-toluene (0.15 ml) was added. Afterwards, the contents were mixed gently. Finally, under Ar, a solution of 74 (8 mg, 0.2 mmol) in d₈-toluene (0.3 ml) was added. Again, the contents were mixed gently and the NMR study was carried out at rt and 40°C. At rt: Complex 75: ³¹P NMR (162 MHz, d₈-tol): δ = 39.4. Ni(PPh₃)₃ or O=PPh₃: ³¹P NMR (162 MHz, d₈-tol): δ =
24.4. At 40°C: Complex 75; \(^{31}\text{P}\) NMR (162 MHz, \(d_8\)-tol): \(\delta = 39.1\). \(\text{Ni}(\text{PPh}_3)_3\) or \(\text{O=PPh}_3\); \(^{31}\text{P}\) NMR (162 MHz, \(d_8\)-tol): \(\delta = 24.2\).

3.4.2.2 Competition Experiment

Procedure: In the glovebox, a J-Young NMR tube is charged with \(\text{Ni(cod)}_2\) (3.2 mg, 0.01 mmol) and taken out. Under Ar, dissolved in \(d_8\)-toluene (0.1 ml) and a solution of \(\text{PPh}_3\) (9.2 mg, 0.04 mmol) in \(d_8\)-toluene (0.15 ml) was added. Afterwards, the contents were mixed gently. Finally, under Ar, a solution of 74 (8 mg, 0.2 mmol) in \(d_8\)-toluene (0.3 ml) was added. Then, alkyne 73 (25 \(\mu\)l, 0.13 mmol) was added. Again, the contents were mixed gently and the NMR study was
carried out at rt and 40°C. At rt: Complex 77; $^{31}$P NMR (162 MHz, d$_8$-tol): $\delta = 40.5$ (d, $J = 31.4$ Hz), 37.9 (d, $J = 31.3$ Hz). Ni(PPh$_3$)$_3$ or O=PPh$_3$; $^{31}$P NMR (162 MHz, d$_8$-tol): $\delta = 24.4$. At 40°C: Complex 77; $^{31}$P NMR (162 MHz, d$_8$-tol): $\delta = 40.5$ (d, $J = 31.3$ Hz), 37.9 (d, $J = 31.2$ Hz). Ni(PPh$_3$)$_3$ or O=PPh$_3$; $^{31}$P NMR (162 MHz, d$_8$-tol): $\delta = 24.2$. 

$^{31}$P at rt

$^{31}$P at 40°C
3.4.2.3 Synthesis of 77

Inside a glovebox, toluene (2.4 ml) was added to a flask containing Ni(cod)$_2$ (100 mg, 0.36 mmol) and PPh$_3$ (191 mg, 0.73 mmol). After allowing the deep red solution to stir for 10 minutes, 73 (72 μl, 0.36 mmol) was added dropwise. Allowed to stir at rt for 1 hour whereupon the solution became dark brown. Afterwards, all volatiles were removed. The orange solid was washed with hexanes (3 x 5 ml) to give a golden yellow solid (269 mg, 97%). This is a known compound.$^{11}$; $^1$H NMR (500 MHz, C$_7$D$_8$): $\delta$ = 7.64 – 7.55 (m, 6H), 7.39 (apt t, $J = 8.5$ Hz, 6H), 7.04 – 6.90 (m, 11H), 6.90 – 6.83 (m, 3H), 6.82 – 6.74 (m, 9H), -0.04 (s, 9H); $^{31}$P NMR (202 MHz, C$_7$D$_8$): $\delta$ = 40.5 (d, $J = 31.5$ Hz), 37.9 (d, $J = 30.6$ Hz)

3.4.2.4 Catalytic competency of 77

Inside a glovebox, 77 (8.8 mg, 0.01 mmol) was dissolved in d$_8$-toluene (0.58 ml). After 5 minutes, 70 (20 mg, 0.12 mmol), 73 (25 μl, 0.13 mmol) and 3,5-dimethoxytoluene (19.6 mg, 0.12 mmol) were added. After 5 minutes of stirring, the contents were transferred to a J-Young NMR tube. Taken out of the glovebox and heated at 40°C for 15 hours. NMR integration of the product against 3,5-dimethoxytoluene as an internal standard revealed full conversion.

3.4.2.5 Reaction of 77 with excess 73

Inside a glovebox, 77 (8.8 mg, 0.01 mmol) was dissolved in d$_8$-toluene (0.58 ml). Afterwards, 73 (11.5 μl, 0.06 mmol) was added. After 5 minutes of stirring, the contents were transferred to a J-Young NMR tube. No change in the $^1$H and $^{31}$P NMR spectra was observed between rt and 40°C.
3.4.2.6 Reaction of 77 with excess 79

Inside a glovebox, 77 (8.8 mg, 0.01 mmol) was dissolved in d<sub>8</sub>-toluene (0.58 ml). Afterwards, 73 (10.4 mg, 0.06 mmol) was added. After 5 minutes of stirring, the contents were transferred to a J-Young NMR tube. From the $^{31}$P NMR spectra, the appearance of 80 is found at rt and at 40°C. Complex 80 is a known compound.$^{11}$ At rt: Complex 77; $^{31}$P NMR (202 MHz, d<sub>8</sub>-tol): $\delta = 40.5$ (d, $J = 30.9$ Hz), 37.9 (d, $J = 30.4$ Hz). Complex 80; $^{31}$P NMR (202 MHz, d<sub>8</sub>-tol): $\delta = 39.8$. At 40°C: Complex 77; $^{31}$P NMR (202 MHz, d<sub>8</sub>-tol): $\delta = 40.5$ (d, $J = 31.1$ Hz), 37.9 (d, $J = 31.6$ Hz). Complex 80; $^{31}$P NMR (202 MHz, d<sub>8</sub>-tol): $\delta = 39.8$. 

![31P NMR spectra at rt](image1.png)

$^{31}$P at rt

![31P NMR spectra at 40°C](image2.png)

$^{31}$P at 40°C
3.4.2.7 Reaction of 77 with 70

Inside a glovebox, 77 (8.8 mg, 0.01 mmol) was dissolved in d$_8$-toluene (0.58 ml). Afterwards, 70 (4.5 mg, 0.03 mmol) was added. After 5 minutes of stirring, the contents were transferred to a J-Young NMR tube. No change was observed in the $^{31}$P NMR. By $^1$H NMR spectra, the appearance of 74 is found at rt and at 40°C but trace conversion was found after 1 hour at 40°C.

3.5 References


Chapter 4 Transition Metal-Catalysed Functionalisation of an Alkene C–H Bond with another Alkene

4.1 Introduction

Transition metal-catalysed activation and subsequent transformation of aromatic C–H bonds is an area of research which has experienced a rapid rate of growth.\textsuperscript{1} Hydrovinylation reactions using ethylene to functionalised alkene C–H bonds have been well documented and won’t be covered in this review.\textsuperscript{2} Furthermore, homo co-dimerisation of alkenes will not be covered.\textsuperscript{3} However, transition metal-catalysed C–H functionalisation of an alkene with another different alkene has been less studied. Regardless, several modes of C–H functionalisation of an alkene with another different alkene by a transition metal have been postulated to occur to account for the products observed. Oxidative cyclisation, \textit{in situ} generation of the metal hydride and C–H bond activation are three modes of C–H functionalisation commonly postulated.

For example, Mitsudo and co-workers reported a ruthenium-catalysed codimerisation of norbornenes 1 with various Michael acceptors 2 to give products 3 and 4.\textsuperscript{1} The reaction generally proceeded in a \textit{trans}-selective manner. The authors then proposed three pathways to account for the results of the reaction. Path A is the oxidative cyclisation which would form ruthenacycle 5. Then β-H elimination would form intermediate 6. Afterwards, reductive elimination would give mainly 3.
Path B is the addition of the *in situ* generated ruthenium hydride across the alkene of norbornene 1 which would form intermediate 7. Insertion of alkene 2 would form intermediate 8. Finally reductive elimination would afford product 3.

Lastly, path C is the carbonyl-directed C–H activation pathway which would form intermediate 9. Hydrometallation across the alkene of norbornene 1 would afford intermediate 10. Finally, reductive elimination would afford product 4. However, path C was postulated to be unlikely as products of the C–H activation pathway would have been predominantly *cis*-products 4. This methodology allowed the codimerisation of various norbornenes with various Michael acceptors to proceed in good to high yields with good to excellent *trans*-selectivity.

Scheme 1 Ruthenium catalysed codimerisation of norbornenes with various Michael acceptors
4.1.1 Formation of a metallacycle intermediate via oxidative cyclisation

Hirano and co-workers reported a ruthenium-catalysed asymmetric codimerisation of methyl methacrylate 11 with various alkenes.\(^5\) It was observed that the codimerisation of methyl methacrylate 11 with alkene 12 proceeded to give 13 in high yields and with high enantioselectivity (Scheme 2). Furthermore, three other products 14-16 were also identified. To account for the formation of the four products, the authors proposed that the initial oxidative cyclisation would form intermediate 17. Then the major product 13 would then come about from the endo β-H elimination which would form intermediate 18. Reductive elimination would then afford product 13. However, exo β-H elimination from the methyl group would form intermediate 19. Reductive elimination would then afford product 14. Alternatively, β-H elimination from the tetrahydrofuran core would result in the formation of intermediate 20. Finally, reductive elimination would then afford product 15. However, the formation of 16 is currently speculative.
Scheme 2 Ruthenium catalysed asymmetric codimerisation of methyl methacrylate with various alkenes

Ogoshi and co-workers reported a nickel-catalysed direct conjugate addition of simple alkenes 22 to enones 21 to form product 23 (Scheme 3). The nickel catalyst would pre-organise alkene 22 and enone 21 to form intermediate 24. Afterwards, oxidative cyclisation would afford intermediate 25. β-H elimination would afford intermediate 26. Finally, reductive elimination would then afford product 23. This methodology allowed the synthesis of various conjugate addition products in good to high yields. Furthermore, potentially isomerisable alkenes were employed successfully.
Nickel-catalysed direct conjugate addition of simple alkenes to enones

**Scheme 3** Nickel-catalysed direct conjugate addition of simple alkenes to enones

4.1.2 *In situ* formation of metal hydride

Kondo and co-workers reported a ruthenium-catalysed codimerisation reaction of alkenes 28 with N-vinylamides 27 (Scheme 4). After the *in situ* formation of the putative ruthenium hydride, it would then add across alkene 28 to form intermediate 30. The chelation assisted insertion of N-vinylamide 27 would form intermediate 31. Then β-H elimination would proceed to give product 29. Electron deficient alkenes dimerised with N-vinylamide in good to high yields with excellent E-selectivity. However, norbornene or ethene dimerised with N-vinylamide in poor yields (33% and 16% respectively) but with excellent E-selectivity.
Zhou and co-workers reported a ruthenium-catalysed dimerisation of \(N\)-acetyl \(\alpha\)-arylenamines \(32\) with acrylates \(33\) to form product \(34\) (Scheme 5).\(^8\) Though there was no mechanistic proposal by the authors, \(N\)-acetyl \(\alpha\)-arylenamine \(32\) could direct the ruthenium hydride in a regioselective manner to form intermediate \(35\). The coordination of alkene \(33\) to the metal centre would then form intermediate \(36\). Afterwards, migratory insertion would form intermediate \(37\). Finally, reductive elimination would occur to give product \(34\). Various \(N\)-acetyl \(\alpha\)-arylenamines with different functional groups on the phenyl ring dimerised with various acrylates in usually high yields with excellent \(E\)-selectivity.

Scheme 4 Ruthe...
Scheme 5 Ruthenium catalysed dimerisation of N-acetyl α-arylenamines with acrylates

4.1.3   C–H bond activation

4.1.3.1 Oxidative cross coupling

Ishii and co-workers reported a palladium-catalysed oxidative cross coupling of acrylates 38 with enol acetate 39 to form diene 40. It is postulated the palladium catalyst would react with enol acetate 39 to form intermediate 41 with concomitant loss of acetic acid. As a comparison, C–H bond activation with a Pd(0) catalyst would form a palladium hydride complex. Acrylate 38 would then insert itself into the Pd–C bond of intermediate 41 to give intermediate 42. Finally, β-H elimination would afford product 40. The oxidative cross coupling between a variety of acrylates and a variety of enol acetates proceeded in good yields but usually with poor E/Z selectivity.
Loh and co-workers demonstrated the first example of a direct cross coupling reaction between simple alkenes 43 and acrylates 44 (Scheme 7).\(^\text{10}\) Palladium-catalysed C–H activation of simple alkene 43 would form intermediate 46. Acrylate 44 would then insert itself into the Pd–C bond of intermediate 46 to give intermediate 47. Finally, β-H elimination would afford product 45. A wide range of 2-substituted alkenes 43 were compatible. Generally, the reaction was selective for the E-isomer but non-styrene type alkenes were not as stereoselective. Later, the same group expanded the scope of the palladium catalysed direct cross coupling of indenes with various electron deficient alkenes.\(^\text{11}\)
Miura and co-workers reported a rhodium-catalysed oxidative cross-dimerisation of acrylic acids 48 with acrylates 49 to form butenolide 50 (Scheme 8). It was proposed the carboxylic acid of 48 would direct the rhodium catalyst for β C–H activation to form rhodacycle 51. Subsequent alkene insertion would form intermediate 52. This would then be followed by β-H elimination to give intermediate 53. This intermediate would then undergo nucleophilic cyclisation to afford butenolide 50. A variety of butenolides 50 were synthesised in generally good yields. However, in certain cases a slight modification of reaction conditions was required for higher yields.

Scheme 7 Palladium catalysed cross coupling between simple alkenes and acrylates
4.1.3.2 Group directed C–H activation

In the 1970s, Yamamoto and co-workers reported the first experimental evidence of an oxidative addition of ruthenium complex 54 into the C–H of alkene 55 to generate ruthenium complex 56 (Scheme 9). Complex 56 was fully characterised and an X-Ray crystal structure was obtained. The X-Ray revealed the coordination of the carbonyl moiety to the ruthenium complex which could suggest that the carbonyl moiety directed ruthenium complex 63 into the cis-C–H alkene bond.
In 1995, Trost and co-workers reported the first catalytic functionalisation of an alkene C–H bond with another alkene via group directed C–H bond activation (Scheme 10).\textsuperscript{14} It is remarkable that methyl benzoate failed to couple with an alkene under the optimised reaction condition. In an attempt to elucidate the mechanism, the resting state of the catalyst was found to have no hydrogen as deduced by NMR. Furthermore, carrying the reaction under an atmosphere of CO inhibited the reaction which suggests no CO is likely to be ligated onto the active catalyst. Furthermore, if the β-C-H bond is trans to the carbonyl group, no reaction was observed.

Therefore, it was proposed that the conjugated carbonyl moiety of 57 would direct the catalyst into the syn-C–H alkene bond to give intermediate 60. Afterwards, 60 would coordinate to alkene 58 to form intermediate 61. Migratory insertion of the alkene would form intermediate 62. Finally, reductive elimination would afford product 59. It was demonstrated that the ester functional group is a better directing group than a ketone. Furthermore, various functional groups on the ester were tolerated under the reaction conditions. Independently, Murai and co-workers reported similar observations\textsuperscript{15} and later demonstrated that an aldehyde can behave as a directing group\textsuperscript{16}.
Since then, several groups have reported examples whereby group directed C–H bond activation is postulated to occur. For example, Darses and co-workers reported a ruthenium-catalysed functionalisation of the syn C–H bond of Michael acceptors 63 with vinyl silanes 64 to form either 65 or 66 (Scheme 11). For the synthesis of 65, it was proposed that the carbonyl moiety of 63 would direct the ruthenium catalyst into the cis-C–H alkene bond to give intermediate 67. Afterwards, 67 would hydrometallate onto alkene 64 to form intermediate 68. Finally, reductive elimination and dissociation of the ruthenium catalyst would occur to afford product 65. For the synthesis of 66, after the formation of putative intermediate 68, conjugate addition of the alkyl silane moiety would form intermediate 69. Then β-H elimination would happen to form intermediate 70. Afterwards, reductive elimination and keto-enol tautomerism would then occur to afford product 66. While most substrates couple in a similar manner to the examples observed by Trost and Murai to form silane 65, crotyl
substrates 63 would couple with vinyl silanes 64 to give rise to products 66 with a stereodefined trisubstituted allyl silanes (E/Z > 97 : 3 in all examples).

\[ R^1-EWG + \text{Si}R_3 \xrightarrow{2.5 \text{ mol\% } [\text{RuCl}_2(\phi-\text{cym})_2] \text{ and } 15 \text{ mol\% } R(\phi\text{CF}_2\text{CF}_2\text{H})_3} \text{cat. NaHCO}_3 \text{, dioxane, 100 °C} \rightarrow R^1-\text{Si}R_3 + R^1-\text{Si}R_3 \]

\[ \text{selected products} \]

\[ \begin{align*}
\text{Si(OEt)}_3 & \quad \text{Si(OEt)}_3 & \quad \text{Si(OEt)}_3 & \quad \text{Si(OEt)}_3 \\
\text{Me} & \quad \text{Ph} & \quad \text{NHfBu} & \quad \text{OMe} \\
99\% & \quad 80\% & \quad 69\% & \quad 50\%
\end{align*} \]

**Scheme 11** Ruthenium catalysed functionalisation of an alkene C–H bond with another alkene with differing reactivity

Another way to direct the functionalisation of the cis-C–H bond of Michael acceptors is through temporary chelation assistance. Jun and co-workers reported a rhodium-catalysed chelation assisted C–H bond activation of Michael acceptors 71 for β-alkylation (Scheme 12).\(^{18}\) Control experiments supported the presence of dienamine 75 for the chelation assisted C–H bond activation. Therefore it is proposed that after the formation of the putative dienamine 75, the nitrogen would direct the rhodium catalyst for C–H bond activation to form
intermediate 76. Afterwards, migratory insertion of the alkene would form intermediate 77. Finally reductive elimination would afford intermediate 78 which would equilibrate with intermediate 79. Finally, acid hydrolysis would afford a mixture of products 73 and 74. Furthermore, the deconjugation likely happened during the rhodium catalysis step rather than at the hydrolysis step. Various \( \beta \) alkylation products were synthesised in good to high yields with moderate to high selectivity for the deconjugated product.

**Scheme 12** Rhodium catalysed chelation assisted C–H bond activation

Bergman and co-workers reported a rhodium-catalysed reaction whereby an imine can behave as a directing group (Scheme 13).\(^{19}\) It was found that \( \alpha,\beta \)-unsaturated imines 80 can be alkylated with simple alkenes 81 via C–H activation in a highly stereoselective manner when both a rhodium catalyst and an electron-donating ligand were used. Therefore, it is proposed that the imine would direct the rhodium catalyst into the alkene C–H bond to form
intermediate 84. Afterwards, migratory insertion of the alkene would form intermediate 85.

Finally, reductive elimination and hydrolysis would afford products 82 and 83. While the β-alkylation is initially Z-selective, the hydrolysis resulted in some isomerisation of the double bond. Nonetheless, the process is generally high yielding whereby even alkenes with β-Hs can be incorporated successfully. Furthermore, the same group later applied the methodology as a key step in the total synthesis of (-)-Incarvillateine 89.20

Scheme 13 Rhodium catalysed β alkylation
Scheme 14 Synthesis of (−)-Incarvillateine with C–H bond as the key step

In contrast to chelation assisted C–H bond activation for β-alkylation as mentioned previously, Dong and Mo reported a rhodium-catalysed chelation assisted C–H bond activation for α-alkylation (Scheme 15). After the formation of the putative enamine, group directed C–H activation would afford intermediate 92. Afterwards, the coordination of an alkene would form intermediate 93. Next, migratory insertion of the alkene would afford intermediate 94. Reductive elimination and hydrolysis would afford product 91. The α-alkylation proceeded in good yields and a wide range of functional groups substituted on the cyclopentanone were tolerated.
Scheme 15 Rhodium catalysed chelation assisted C–H bond activation for α alkylation.

Another directing group used to direct the transition metal into the cis-C–H bond of the alkene is pyridine. Kim and co-workers reported a rhodium-catalysed pyridine directed C–H activation. Alkylation of vinyl pyridines 95 is believed to be Z-selective but under the reaction conditions, some isomerisation took place which suggests another reaction pathway could be taking place (Scheme 16). Pyridine directed C–H activation would afford intermediate 98. After the initial alkene coordination which would form intermediate 99, migratory insertion would form intermediate 100. Finally, reductive elimination would afford product 97. The alkylation proceeded with a variety of alkenes in generally excellent yields and with moderate to good trans-selectivity. Furthermore, this methodology was extended to functionalisation of the vinyl pyridine with norbornene and allyl ethers.
Lim and co-workers reported striking ligand effects in the rhodium-catalysed reaction of 2-vinylpyridines 101 with 1,5-hexadiene 102 (Scheme 17).\(^{25}\) Carrying out the reaction with the Wilkinson’s catalyst gave a mixture of three products. Switching the catalyst source to [Rh(coe)_2Cl]_2 and 20 mol% PPh_3 did not alter the selectivity of the reaction. On exchanging the ligand to 20 mol% PCy_3, selective formation of functionalised alkene 105 was observed. Furthermore, it was found that other ligands altered the selectivity of the reaction. The small electron poor phosphine, P(OMe)_3, gave mostly product 106 whereby the alkylation occurs on the same side as the pyridine (Scheme 18). Furthermore, P(nBu)_3 gave mostly product 107 whereby the alkylation occurs predominantly on the same side as the pyridine (Scheme 19).
Murai and co-workers reported a rhodium-catalysed intramolecular pyridine directed C–H activation with concomitant alkene insertion to form cyclic structures. A three carbon unit tether 108 resulted in the non-selective formation of six-membered ring 109 and five-membered ring 110 (Scheme 20). It was postulated that the pyridine directed C–H bond activation would form intermediate 111 and then the insertion of the alkene could then proceed to give heptarhodacycle 112. Then reductive elimination would give product 109.
Alternatively, the insertion of the alkene could proceed to give hexarhodacycle 113 which would then undergo reductive elimination to give product 110.

A two carbon tether 114 resulted in the selective formation of five-membered ring 115 (Scheme 21). It was proposed that the pyridine directed C–H bond activation would occur to form intermediate 116. Afterwards, the insertion of the alkene would then proceed to give hexarhodacycle 117. Subsequently, reductive elimination would then occur to give product 115. The formation of various five-membered rings were synthesised in good to high yields. Furthermore, various substitutions on the alkene were tolerated.

Scheme 20 Rhodium catalysed intramolecular C–H activation with concomitant alkene insertion
Aïssa and Fürstner reported a rhodium-catalysed C–H / C–C bond activation sequence to form seven-membered rings 119 (Scheme 22). Initial C–H activation with a neutral rhodium catalyst would form intermediate 120. Hydrometalation onto an ACP would form pentarhodacycle 121. Subsequently, the C–C bond cleavage of the cyclopropane would result in a ring enlarged metallacycle 122. Finally, reductive elimination would furnish product 119. While the yields were generally moderate to good, it offered a proof of concept of a tandem catalytic C–H / C–C bond activation sequence.
4.2 Aims and Hypothesis

Transition metal-catalysed C–H functionalisation of an alkene with another alkene is an area of increasing research. This had to lead to the discovery of various modes of activation. Though C–H activation by a directing group has been studied extensively, oxidative cyclisation and exploitation of in situ generated metal hydrides have contributed to the diversity of products generated.

As mentioned earlier, Aïssa and Fürstner reported a rhodium-catalysed C–H / C–C bond activation sequence to form seven-membered rings whereby C–C bond activation is used to trap the intermediate formed by the reversible hydrometallation (Scheme 22). 27
Therefore, it was of interest to determine if there was another way to trap the intermediate formed by the reversible hydrometalation. With that in mind, it was postulated a tethered alkene could trap the proposed intermediate and to form bicyclo[2.2.1]heptane 125 (Scheme 23).

Scheme 23 Hypothesis

In this context, the aim of the work presented herein is to:

a.) Synthesise a substrate of type 123
b.) Optimise the reaction and determine the scope
c.) Investigate the mechanism of the reaction

4.3 Optimisation of the reaction

Vinyl pyridine 126 was used as a model substrate to test the hypothesis (Table 1). Treating 126 with 5 mol% [Rh(cod)Cl]2 in THF at 90°C for 17 hours did not proceed to give the desired product 127 but with 33% conversion to the five-membered ring 128. However, when 10 mol% P(pOMePh)3 was used as a ligand, the formation of 127 was observed despite incomplete conversion. When the loading of ligand was increased to 20 mol%, full consumption of the 126 was observed with improved selectivity towards 127. However, the two products were not separable by standard flash column chromatography. This necessitated a need to optimise the reaction to achieve a selectivity to 127 of >95:5.
The alkene geometry of starting material 127 was discovered to affect product selectivity. When 126 was synthesised by the Wittig method, a variable cis/trans mixture of 126 was observed (91:9). Using the cis/trans mixture of 126 resulted in the formation of 127 and 128 in ratio of 83:17 under the rhodium catalysis. On the other hand, when 126 was synthesised by another method (see synthesis of precursor) to give selectively the E-isomer, improved selectivity towards 127 was observed. However, the increase in phosphine loading did not improve the selectivity towards 127. Therefore, the method that gave pure E-126 was used in the subsequent screenings.

Table 1 Initial optimisation

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</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by ^1^H NMR spectroscopy. [b] Ratio determined by ^1^H NMR spectroscopy

Afterwards, it was of interest to see if other rhodium catalysts could provide better selectivity towards 126 (Table 2). With 10 mol% [Rh(cod)]_2BF_4 and 10 mol% P(pMeOC_6H_4)_3 (Table 2, Entry 1), the starting material was completely consumed but the selectivity between the 127 and
128 was the same as with 5 mol% [Rh(cod)Cl]$_2$ and 20 mol% $P(p$MeOC$_6$H$_4$)$_3$. Increasing the phosphine loading to 20 mol% (Table 2, entry 2) improved the selectivity towards 127 slightly but the overall conversion was reduced. Increasing the phosphine loading to 30 mol% (Table 2, entry 3) eroded the selectivity when compared to with 20 mol% phosphine and the overall conversion was barely improved. Furthermore, the catalytic system of 5 mol% [Rh(CO)$_2$Cl]$_2$ and 10 mol% $P(p$MeOC$_6$H$_4$)$_3$ (Table 2, Entry 4) was completely ineffective and no conversion was observed. Carrying out the reaction with an increased phosphine loading of 20 mol% $P(p$MeOC$_6$H$_4$)$_3$ (Table 2, entry 5) or 30 mol% $P(p$MeOC$_6$H$_4$)$_3$ (Table 2, entry 6) were equally ineffective as both conditions resulted in no conversion of the starting material.

**Table 2 Rhodium catalyst**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh. cat.</th>
<th>mol %</th>
<th>Ligand (mol %)</th>
<th>Conv.</th>
<th>Ratio (127:128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)$_2$]BF$_4$</td>
<td>10</td>
<td>10</td>
<td>&gt;95%</td>
<td>88:12</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)$_2$]BF$_4$</td>
<td>10</td>
<td>20</td>
<td>88%</td>
<td>91:9</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)$_2$]BF$_4$</td>
<td>10</td>
<td>30</td>
<td>91%</td>
<td>88:12</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(CO)$_2$Cl]$_2$</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(CO)$_2$Cl]$_2$</td>
<td>5</td>
<td>20</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(CO)$_2$Cl]$_2$</td>
<td>5</td>
<td>30</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by $^1$H NMR spectroscopy. [b] Ratio determined by $^1$H NMR spectroscopy.
A study on the temperature effects on the selectivity of \textbf{127} and \textbf{128} with 5 mol\% [Rh(cod)Cl]$_2$ and varying mol\% of P(pMeOC$_6$H$_4$)$_3$ was then commenced (Table 3). When the reaction was carried out with 10 mol\% P(pMeOC$_6$H$_4$)$_3$ at 110°C (Table 3, entry 1), the selectivity towards \textbf{127} is significantly eroded. This erosion was remedied by increasing the phosphine loading to 20 mol\% P(pMeOC$_6$H$_4$)$_3$ (Table 3, entry 2) which improved the selectivity towards \textbf{127}, albeit the selectivity remained slightly poorer than in the case of the reaction carried out at 90°C (Table 1, entry 4). However, when the temperature of the reaction was reduced to 70°C (Table 3, entry 3), the conversion dropped significantly and the five-membered ring \textbf{128} is formed with high selectivity.

### Table 3 Temperature effects

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (mol %)</th>
<th>Temp (°C)</th>
<th>Conv.[a]</th>
<th>Ratio (127:128)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>110</td>
<td>&gt;95%</td>
<td>65:35</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>110</td>
<td>&gt;95%</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>70</td>
<td>18%</td>
<td>5:&gt;95</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of \textbf{126} against the combined ratio of \textbf{127:128} as determined by \textsuperscript{1}H NMR spectroscopy. [b] Ratio determined by \textsuperscript{1}H NMR spectroscopy

Intrigued by the sudden drop of reactivity when the reaction was carried out at 70°C, it was assumed the rhodium concentration was simply too low. Therefore, the concentration of the reaction was increased to 100mM from 50mM and a screening of different temperatures was carried out (Table 4). Carrying the reaction out at 90°C gave complete conversion with good
selectivity of 89:11 for 127 (Table 4, entry 1). When the temperature was reduced to 70°C, the conversion vastly improved from 18% to 91% (Table 3, entry 3 vs Table 4, entry 2 and the selectivity towards 127 improved to 92:8. Lowering the temperature further to 60°C lowered the conversion but the selectivity towards 127 is fractionally better (Table 4, entry 3).

Table 4 Temperature effects at 100mM

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Conv.</th>
<th>Ratio (127:128)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>&gt;95%</td>
<td>89:11</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>91%</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>55%</td>
<td>93:7</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by 1H NMR spectroscopy. [b] Ratio determined by 1H NMR spectroscopy

A screen of different ligands was then carried out to see if the selectivity towards 127 could be increased further (Table 5). Furthermore, as the conversion at 60°C was very low, the screen was carried out at 70°C. When the reaction was carried out with 20 mol% PPh₃, there was full conversion and the selectivity was found to be 90:10. Modifications of the phenyl ring which made the phosphine more electron deficient resulted in the reaction to proceed with lower conversion but the selectivity remained unaffected (Table 5, entry 2 and 3). However, electron deficient P(2-furyl)$_3$ (Table 5, Entry 4) proved to be an exception with full conversion and slightly improved selectivity towards 127 of 91:9. On the other hand, modification of the phenyl ring which made the phosphine more electron rich resulted in the reaction to proceed
with excellent to full conversion and with a selectivity of 91:9 (Table 5, entry 5 and 6). It was
noted that a phosphine with a large cone angle is an ineffective ligand (Table 5, entry 7).
Substitution of a phenyl ring with a cyclohexyl group gave poor conversion and reduced the
selectivity towards 127 (Table 5, entry 8). Replacement of another phenyl ring with a
cyclohexyl group gave poor conversion and the reaction is now more or less non-selective
(Table 5, entry 9). These last two results suggest that incremental increase in the cone angle is
detrimental to the rate of reaction and selectivity for 127. Electron poor triphenyl phosphite is
an ineffective ligand (Table 5, entry 10). Furthermore, hemi-lable ligand JohnPhos is also an
ineffective ligand (Table 5, entry 11).
Table 5 Ligand Screen

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>mol %</th>
<th>Conv.(^{[a]})</th>
<th>Ratio (127:128)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh(_3)</td>
<td>20</td>
<td>&gt;95%</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>P(pCF(_3)Ph)(_3)</td>
<td>20</td>
<td>80%</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>P(pClPh)(_3)</td>
<td>20</td>
<td>68%</td>
<td>91:9</td>
</tr>
<tr>
<td>4</td>
<td>P(2-furyl)(_3)</td>
<td>20</td>
<td>&gt;95%</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>P(3, 5-xylyl)(_3)</td>
<td>20</td>
<td>&gt;95%</td>
<td>91:9</td>
</tr>
<tr>
<td>6</td>
<td>P(p-tol)(_3)</td>
<td>20</td>
<td>93%</td>
<td>91:9</td>
</tr>
<tr>
<td>7</td>
<td>P(o-tol)(_3)</td>
<td>20</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>PPh(_2)Cy</td>
<td>20</td>
<td>32%</td>
<td>68:32</td>
</tr>
<tr>
<td>9</td>
<td>PPhCy(_2)</td>
<td>20</td>
<td>40%</td>
<td>55:45</td>
</tr>
<tr>
<td>10</td>
<td>P(OPh)(_3)</td>
<td>20</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>11</td>
<td>JohnPhos</td>
<td>10</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by \(^1\)H NMR spectroscopy. [b] Ratio determined by \(^1\)H NMR spectroscopy.
After the identification of ligands which displayed excellent conversion and selectivity, they were then tested with the temperature of the reaction reduced to 60°C (Table 6). It was previously found that 20 mol% P(μMeOC₆H₄)₃ at 60°C resulted in a conversion of 55% and with a selectivity of 93:7. Interestingly, carrying out the reaction with PPh₃ gave 87% conversion and a selectivity of 91:9 (Table 6, Entry 1). P(3, 5-xylyl)₃ is an effective ligand with excellent conversion and with an even better selectivity of 93:7 (Table 6, Entry 2). The electron poor P(2-fur)₂ also proved to be an effective ligand with excellent conversion and with a selectivity of 92:8 (Table 6, Entry 3). However, P(ptol)₃ proved to be ineffective at 60°C as the conversion was reduced from 93% at 70°C to 29%. Furthermore, the selectivity dropped from 91:9 to 65:35 (Table 6, Entry 4). This result appears to indicate if the rate of formation of 127 is slowed down, then the formation of five-membered ring 128 becomes more noticeable.

Table 6 Selected ligands at 60°C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv.[a]</th>
<th>Ratio (127:128)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃</td>
<td>87%</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>P(3, 5-xylyl)₃</td>
<td>92%</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>P(2-furyl)₃</td>
<td>91%</td>
<td>92:8</td>
</tr>
<tr>
<td>4</td>
<td>P(ptol)₃</td>
<td>29%</td>
<td>65:35</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by ¹H NMR spectroscopy. [b] Ratio determined by ¹H NMR spectroscopy.
A change of model substrate to 129 was then decided and was used to continue the optimisation as we became interested if 126 was the optimal substrate for the methodology. Phosphines P(3, 5-xylyl)$_3$ and P(2-furyl)$_3$ were chosen because both ligands gave excellent conversion and good selectivity for 127 at 60°C (Table 7). However, carrying out the reaction with 5 mol% [Rh(cod)Cl]$_2$ and 20 mol% P(3, 5-xylyl)$_3$ gave poor conversion and poor selectivity which appears to confirm that the new substrate might be more challenging than the original substrate (Table 7, entry 1). Using 20 mol% P(2-furyl)$_3$ gave even worst conversion and the selectivity of the reaction becomes in favour of 130 (Table 7, entry 2). On changing the source of rhodium catalyst to 5 mol% [Rh(coe)$_2$Cl]$_2$ and with 20 mol% P(3, 5-xylyl)$_3$ gave a much improved conversion of 86% but the selectivity remains poor (Table 7, entry 3). Using 20 mol% P(2-furyl)$_3$ did not improve the conversion and the reaction becomes non-selective (Table 7, entry 4).

**Table 7 Rhodium and Phosphine screen**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh cat.</th>
<th>Ligand</th>
<th>Conv. $^a$</th>
<th>Ratio (130:131)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)Cl]$_2$</td>
<td>P(3, 5-xylyl)$_3$</td>
<td>35%</td>
<td>56:44</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)Cl]$_2$</td>
<td>P(2-furyl)$_3$</td>
<td>16%</td>
<td>37:63</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(coe)$_2$Cl]$_2$</td>
<td>P(3, 5-xylyl)$_3$</td>
<td>86%</td>
<td>56:44</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(coe)$_2$Cl]$_2$</td>
<td>P(2-furyl)$_3$</td>
<td>64%</td>
<td>48:52</td>
</tr>
</tbody>
</table>

$^a$ Conversion based on ratio of 129 against the combined ratio of 130:131 as determined by $^1$H NMR spectroscopy. $^b$ Ratio determined by $^1$H NMR spectroscopy.
After the identification of \( \text{P(3, 5-xylyl)}_3 \) as the ideal ligand, a screen of different solvents was carried out to determine if the selectivity towards 130 could be improved further (Table 8). Non-polar toluene gave a conversion of 82% but there was almost no selectivity (Table 8, entry 1). Polar acetone gave a conversion of 79% but, there was no selectivity (Table 8, entry 2). The more polar MeCN gave no conversion which could be because of the increased coordinating capability of MeCN which could render the catalyst inactive (Table 8, entry 3). The polar and protic iPrOH gave full conversion and with a selectivity for 130 of 75:25 (Table 8, entry 4). Interestingly, if HPLC grade iPrOH was used, full conversion was observed and the selectivity towards 130 improved slightly to 78:22 (Table 8, Entry 5). Using EtOH which came from a bottle exposed to air and moisture gave a conversion of 85% but the selectivity towards 130 improved further to 82:18 (Table 8, Entry 6). Using MeOH which came from a bottle exposed to air and moisture gave only a conversion of 52% but the selectivity towards 130 increased to 84:16 (Table 8, Entry 7). Interestingly, when dry methanol was used instead, the conversion lowered to 29% and the selectivity towards 130 dropped to 73:27 (Table 8, Entry 8). This suggests that trace water or air is actually beneficial to the selectivity towards 130.
Table 8 Solvent Screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conv.[a]</th>
<th>Ratio (130:131)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>82%</td>
<td>45:55</td>
</tr>
<tr>
<td>2</td>
<td>Acetone</td>
<td>79%</td>
<td>47:53</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>iPrOH</td>
<td>&gt;95%</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>iPrOH (HPLC)</td>
<td>&gt;95%</td>
<td>78:22</td>
</tr>
<tr>
<td>6</td>
<td>EtOH (GPR grade)</td>
<td>85%</td>
<td>82:18</td>
</tr>
<tr>
<td>7</td>
<td>MeOH (GPR grade)</td>
<td>52%</td>
<td>84:16</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>29%</td>
<td>73:27</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 129 against the combined ratio of 130:131 as determined by $^1$H NMR spectroscopy. [b] Ratio determined by $^1$H NMR spectroscopy.

Due to the lack of selectivity towards 130 with model substrate 129, full characterisation of 130 was not carried out. Furthermore, 130 and 131 could not be separated by flash column chromatography. As a result, a screen of different solvents with the original substrate 126 was then investigated (Table 9). Therefore with 5 mol% [Rh(coe)$_2$Cl]$_2$ and 20 mol% P(3, 5-xylyl)$_3$ in dried methanol, the reaction proceeded with an improved conversion of 83% and a selectivity of 83:17 (Table 9, entry 1). As suspected earlier of the positive influence of water, doping the reaction with water resulted in an increase conversion from 83% to 88% and a slightly improved selectivity of 87:13 (Table 9, entry 2). However, when MeOH was used directly out of a bottle that has been exposed to air and moisture, the reaction proceeded with poorer...
conversion of 68% and with an even poorer selectivity towards 127 of 67:33 (Table 9, entry 3).

A mixed solvent system of MeOH and THF in a 1:1 ratio gave excellent conversion and selectivity towards 127 of 94:6 (Table 9, entry 4).

**Table 9** Solvent screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conv.</th>
<th>Ratio (127:128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>83%</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>MeOH/H$_2$O (5:1)</td>
<td>88%</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (bottle)</td>
<td>69%</td>
<td>67:33</td>
</tr>
<tr>
<td>4</td>
<td>MeOH/THF (1:1)</td>
<td>94%</td>
<td>94:6</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by $^1$H NMR spectroscopy. [b] Ratio determined by $^1$H NMR spectroscopy

Afterwards, a screening of other ligands and different solvent ratios was then commenced (Table 10). Sterically demanding NHC IPr is an ineffective ligand (Table 10, Entry 1). However, the electron poor P(2-furyl)$_3$ improved the selectivity towards 127 and gave full conversion (Table 10, Entry 2). Then it was decided to retest P($\rho$MeOC$_6$H$_4$)$_3$ and the reaction proceeded with an excellent selectivity towards 127 of 97:3 and with full conversion (Table 10, Entry 3). Then the solvent ratio was modified but it was found that increasing the ratio in favour of THF had no effect on both the selectivity and conversion (Table 10, Entry 4-6). Except, the THF/MeOH solvent ratio of 9:1 reduced the conversion and decreased the selectivity towards 127 (Table 10, entry 6).
Table 10 A screening of other ligands and different solvent ratios

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conv.</th>
<th>Ratio (127:128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ipr</td>
<td>MeOH/THF (1:1)</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>P(2-furyl)$_3$</td>
<td>MeOH/THF (1:1)</td>
<td>&gt;95%</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>P(pMeOC$_6$H$_4$)$_3$</td>
<td>MeOH/THF (1:1)</td>
<td>&gt;95%</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>P(pMeOC$_6$H$_4$)$_3$</td>
<td>MeOH/THF (1:2)</td>
<td>&gt;95%</td>
<td>96:4</td>
</tr>
<tr>
<td>5</td>
<td>P(pMeOC$_6$H$_4$)$_3$</td>
<td>MeOH/THF (1:4)</td>
<td>&gt;95%</td>
<td>96:4</td>
</tr>
<tr>
<td>6</td>
<td>P(pMeOC$_6$H$_4$)$_3$</td>
<td>MeOH/THF (1:9)</td>
<td>83%</td>
<td>88:12</td>
</tr>
</tbody>
</table>

[a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by $^1$H NMR spectroscopy. [b] Ratio determined by $^1$H NMR spectroscopy.

Then other bidentate ligands were tested to see if the selectivity towards 127 could be improved (Table 11). The solvent system of MeOH/THF in a 1:2 ratio was used as it was more practical than 1:4. However, all bidentate ligands that were examined led to no conversion (Table 11, entry 1-6).
It was then thought that a cationic rhodium complex would be more active. Freeing up a coordination site on the rhodium centre might allow the second alkene to coordinate more readily to the rhodium centre and thus improve the selectivity towards 127. A common

### Table 11 Screening of other ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv.(^{[a]})</th>
<th>Ratio (127:128)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DPePhos</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>DM-BINAP</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>R-Segphos</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>XantPhos</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>DPPF</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>XPhos</td>
<td>0%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by \(^{1}\text{H}\) NMR spectroscopy. \(^{[b]}\) Ratio determined by \(^{1}\text{H}\) NMR spectroscopy.
method used to make a neutral complex cationic is by halide abstraction with a silver salt (Table 12). Pleasingly, the halide abstraction with AgBF$_4$ gave complete conversion and with excellent selectivity towards 127 (Table 12, entry 1). A quick re-examination with different bidentate ligands gave no conversion despite the use of a silver salt (Table 12, entry 2 and 3). Abstraction of the halide with AgSbF$_6$ also proceeded with full conversion and with excellent selectivity towards 127 (Table 12, entry 4). However, halide abstraction with AgOBz or AgOTs proceeded with full conversion but the selectivity towards 127 was a little lower in both cases (Table 12, entry 5 and 6). The lower selectivity could be imputed to the greater coordinating ability of the OBz and OTs anion. It was assumed MeOH could complex to the cationic rhodium and as a result, diminished the selectivity towards 127. Finally, carrying out the reaction in THF with AgBF$_4$ gave a selectivity of 98:2 with an isolated yield of 89% and further optimisation was halted (Table 12, entry 7). Therefore, the condition to be used for the subsequent screening is 5 mol% [Rh(coe)$_2$Cl]$_2$, 20 mol% P($p$MeO$_6$H$_4$)$_3$, 10 mol% AgBF$_4$ in 100mM THF at 60°C for 17 hours.
Table 12 Screening of ligands and silver cation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>mol %</th>
<th>AgX</th>
<th>Solvent</th>
<th>Conv.</th>
<th>Ratio (127:128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(ρ MeOC₆H₄)₃</td>
<td>20</td>
<td>AgBF₄</td>
<td>THF/MeOH (2:1)</td>
<td>&gt;95%</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>DM-BINAP (S)</td>
<td>10</td>
<td>AgBF₄</td>
<td>THF/MeOH (2:1)</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>Segphos (R)</td>
<td>10</td>
<td>AgBF₄</td>
<td>THF/MeOH (2:1)</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>P(ρ MeOC₆H₄)₃</td>
<td>20</td>
<td>AgSbF₆</td>
<td>THF/MeOH (2:1)</td>
<td>&gt;95%</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>P(ρ MeOC₆H₄)₃</td>
<td>20</td>
<td>AgOBz</td>
<td>THF/MeOH (2:1)</td>
<td>&gt;95%</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>P(ρ MeOC₆H₄)₃</td>
<td>20</td>
<td>AgOTs</td>
<td>THF/MeOH (2:1)</td>
<td>&gt;95%</td>
<td>93:7</td>
</tr>
<tr>
<td>7</td>
<td>P(ρ MeOC₆H₄)₃</td>
<td>20</td>
<td>AgBF₄</td>
<td>THF</td>
<td>&gt;95%</td>
<td>98:2</td>
</tr>
</tbody>
</table>

| [a] Conversion based on ratio of 126 against the combined ratio of 127:128 as determined by ¹H NMR spectroscopy. [b] Ratio determined by ¹H NMR spectroscopy. [c] Isolated yield of 89%

127 was fully characterised by ¹H, ¹³C NMR, 2D NMR, IR and HRMS analysis. NOESY was used to ascertain the stereochemistry and revealed the bridgehead hydrogen 1 and one of the hydrogens of the *exo*-methyl 2 are *syn* in space (Scheme 24). Furthermore, *endo*-hydrogen 3 has a NOESY correlation with *endo*-hydrogen 4. Furthermore, only one diastereoisomer is formed. It was then of interest to get an X-Ray to confirm the stereochemistry of 127. As 127 is an oil, the hydrochloride salt was made which allowed crystals of sufficient X-ray quality to be grown (Scheme 25). The X-ray structure confirmed the stereochemistry of product 127 by analogy.
**Scheme 24** NOESY experiments

**Scheme 25** X-Ray of Pyridinium Salt of 127
4.4 Scope of the reaction

With the optimised conditions in hand, the scope of the reaction was examined (Table 13). All products were fully characterised by $^1$H, $^{13}$C NMR, 2D NMR, IR and HRMS analysis. In all cases whereby 133 is formed, 133 is isolated as a single diastereoisomer. Unfortunately in all cases, 133 and five-membered ring 134 were inseparable by flash column chromatography. As a result, the ratio described is the crude ratio of 133 and 134 as judged by $^1$H NMR. Furthermore, the yield mentioned is the combined isolated yield of 133 and 134.

The starting materials 132a-d, f and g were prepared and subjected to the corresponding rhodium-catalysed reaction by Daniel J. Tetlow and are not described in this thesis. It is found that the selectivity for 133 over 134 is greater when R is large. Vinylpyridines 132a – c, with R = aryl, gave high selectivity towards 133 in good to high yields (Table 13, Entry 1-3). Modulation of the electronic properties of the aryl ring did not have a significant effect on the selectivity between the corresponding 133 and 134. However, small erosion in selectivity is observed when a vinyl pyridine that contains an electron rich substituent was tested (Table 13, Entry 3). Interestingly, vinylpyridine 132d with R = benzofuran gave poorer selectivity towards 133d (Table 13, Entry 4). It was then of interest to determine what other functional groups are tolerated under the reaction conditions.

Vinylpyridines 132e-g (Table 13, Entry 5-7), whereby R is a large group, gave excellent selectivity towards the corresponding 133e-g. Vinylpyridine 132h gave good selectivity towards 133h when the loading of phosphine was reduced to 15 mol% (Table 13, Entry 8). Vinylpyridines 132i and 132j (Table 13, Entry 9 and 10), whereby R is a small group, gave moderate selectivity towards the 133i and 133j respectively.
Table 13 Reaction scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Start Material 132</th>
<th>Major Product</th>
<th>Ratio</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td><img src="image" alt="132a" /></td>
<td><img src="image" alt="133a" /></td>
<td>96 : 4</td>
<td>97%</td>
</tr>
<tr>
<td>2[a]</td>
<td><img src="image" alt="132b" /></td>
<td><img src="image" alt="133b" /></td>
<td>96 : 4</td>
<td>81%</td>
</tr>
<tr>
<td>3[a]</td>
<td><img src="image" alt="132c" /></td>
<td><img src="image" alt="133c" /></td>
<td>95 : 5</td>
<td>76%</td>
</tr>
<tr>
<td>4[a]</td>
<td><img src="image" alt="132d" /></td>
<td><img src="image" alt="133d" /></td>
<td>85 : 15</td>
<td>84%</td>
</tr>
</tbody>
</table>

\[ \text{Ratio} = (133:134)^{[b]} \]
<table>
<thead>
<tr>
<th></th>
<th><img src="image1" alt="Molecule 132e" /></th>
<th><img src="image2" alt="Molecule 133e" /></th>
<th>97 : 3</th>
<th>88%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image3" alt="Molecule 132f" /></td>
<td><img src="image4" alt="Molecule 133f" /></td>
<td>95 : 5</td>
<td>76%</td>
</tr>
<tr>
<td>6[a]</td>
<td><img src="image5" alt="Molecule 132g" /></td>
<td><img src="image6" alt="Molecule 133g" /></td>
<td>96 : 4</td>
<td>75%</td>
</tr>
<tr>
<td>7[a]</td>
<td><img src="image7" alt="Molecule 132h" /></td>
<td><img src="image8" alt="Molecule 133h" /></td>
<td>95 : 5[b]</td>
<td>83%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image9" alt="Molecule 132i" /></td>
<td><img src="image10" alt="Molecule 133i" /></td>
<td>67 : 33</td>
<td>71%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image11" alt="Molecule 132j" /></td>
<td><img src="image12" alt="Molecule 133j" /></td>
<td>75 : 25</td>
<td>72%</td>
</tr>
</tbody>
</table>

[a] Synthesis of substrate and Rh-catalysed cyclisation were carried out by Daniel J. Tetlow. [b] Ratio determined by $^1$H NMR spectroscopy. [c] Rh : L (1:1.5)
4.4.1 Another directing group

Other directing groups have been successfully employed in C–H bond activation. It was of interest to see if the selectivity towards bicyclo[2.2.1]heptanes could be improved by a change in directing group. It was thought an imidazole directing group would be more effective as it is more basic. However, under the optimised conditions, no reaction was observed with vinyl imidazole 135 (Scheme 26).

\[ \begin{align*}
5 \text{ mol}\% \text{[Rh(cod)Cl]$_2$} \\
20 \text{ mol}\% \text{(pMeOC$_2$)$_2$Rh} \\
\text{THF (100 mM), 60°C, 17 h}
\end{align*} \]

\[ \text{135} \rightarrow \text{136} \]

Scheme 26 Imidazole directing group

4.5 Mechanistic studies

Daniel J. Tetlow then studied the conversion of 132f by monitoring the reaction by $^1$H NMR. Over the course of the reaction, an extra set of signals were observed which would gradually build up and then disappear when the reaction was over. Monitoring the reaction by TLC revealed a new spot would form but would disappear by the end of the reaction. Therefore, the reaction was quenched after 30 mins and the intermediate 137 was isolated in a 33% yield (Scheme 27). Characterisation of the intermediate by $^1$H, $^{13}$C NMR, 2D NMR, IR and HRMS revealed the structure of the intermediate to be four-membered ring 137. NOESY experiments allowed the assignment of the relative configuration at the stereocentres. Furthermore, the stereochemistry of 137 is inverted when compared to 133f.
Scheme 27 Formation of the four-membered ring as judged by $^1$H NMR

Therefore, it was then of interest to see if the four-membered ring intermediate could be isolated with substrate 126. A kinetic profile using the standard reaction condition of the transformation of 126 was carried out by taking aliquots from the reaction and analysing the aliquot by $^1$H NMR (Scheme 28). As expected, an extra set of signals would gradually build up and would then disappear by the end of the reaction. These extra set of signals were assumed to the four-membered ring 138. To confirm this, attempts were made to isolate 138 because isolation of 138 would allow the stereochemistry to be assigned. Furthermore, this would also allow the relative configuration of 138 and bicyclic 127 to be compared. However, 138 could not be separated from 127 by flash column chromatography as they co-elute together.
To obtain more mechanistic information, a deuterium labelling study of 139 was then carried out (Scheme 29). Subjecting a deuterium labelled 139 to the standard reaction conditions furnished bicyclic 140 and 141 in a combined 90% yield with a ratio of 60:40 as confirmed by $^2$H NMR (Scheme 30). Furthermore, there was complete transfer of the deuterium to the indicated positions. 140 has the deuterium on the exo-methyl carbon. 141 has the deuterium on the carbon $\alpha$ to the vinyl pyridine. Also, the deuterium on 141 is equally distributed on the exo- and endo- position.

**Scheme 28** Formation of the four-membered ring

**4.5.1 Deuterium-labelling experiment**

To obtain more mechanistic information, a deuterium labelling study of 139 was then carried out (Scheme 29). Subjecting a deuterium labelled 139 to the standard reaction conditions furnished bicyclic 140 and 141 in a combined 90% yield with a ratio of 60:40 as confirmed by $^2$H NMR (Scheme 30). Furthermore, there was complete transfer of the deuterium to the indicated positions. 140 has the deuterium on the exo-methyl carbon. 141 has the deuterium on the carbon $\alpha$ to the vinyl pyridine. Also, the deuterium on 141 is equally distributed on the exo- and endo- position.
Before determining the kinetic isotopic effect, it was of interest to understand a little bit more why the deuterium was scrambled over two carbons. In the study of the rhodium-catalysed intramolecular cyclisation of 1,5-diene 142, Murai and co-workers reported the C–H activation and hydrometalation steps occur reversibly at room temperature with the deuterium atom scrambled over three positions (Scheme 31). Furthermore, the hydrometalation of the alkene preferentially occurs in the 2,1-fashion.
To account for the non-statistical distribution of the deuterium atom, Murai and co-workers then subjected the labelled compound 142 to the standard reaction conditions (Scheme 32). Analysis of the product 144 revealed a near statistical distribution of the deuterium atom which suggests the equilibration is far faster than the alkene migratory insertion.

Scheme 32 Labelled compound 142 to the standard reaction conditions

From these experiments, a mechanism was formulated by Murai and co-workers (Scheme 33). After the pyridine directed C–H bond activation to form intermediate 145, hydrometalation of the alkene can occur in the 1,2- or 2,1-fasion. From the deuterium scrambling studies, the hydrometalation onto the alkene in the 2,1-fashion is fast and reversible. On the other hand, the hydrometalation onto the alkene in the 1,2- fashion is slow but, when it does occur, irreversible reductive elimination would furnish five membered ring 144.

Scheme 33 Proposed mechanism
Therefore, it was of interest to see if this phenomenon exists in our system. Subjecting deuterium labelled 139 to the standard reaction condition resulted in the deuterium remaining in the original position or being incorporated to the external alkene double bond 148 (Scheme 34). Interestingly, the alternative product 149 was not observed (Scheme 35).

This is similar to the observations by Murai, whereby in our system, the deuterium atom is scrambled over two carbons. Like Murai’s example, the 1,2-hydrometallation is a slow process and the deuterium incorporation at C2 is very small. On the other hand, the 2,1-hydrometallation is much faster as reflected in the deuterium incorporation into the alkene C1 being noticeably higher. No formation of the five-membered ring or 140 or 141 were observed after 1 hr. This therefore demonstrates that the C–H cleavage process is facile at room temperature. Also, the migratory insertion of the first alkene is reversible and happens much faster than the subsequent steps of the catalytic cycle.

<table>
<thead>
<tr>
<th>Time</th>
<th>Ratio (139:148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>52 : 48</td>
</tr>
<tr>
<td>60 min</td>
<td>26 : 74</td>
</tr>
</tbody>
</table>

Scheme 34 Scrambling at r.t.
Then a study on the kinetic isotopic effect was commenced to gain insight into the mechanism. If the C–H activation step is indeed the rate determining step, this would be reflected in the rate of reaction between 126 and deuterated 139. Therefore, parallel completion experiments of 126 and 139 were carried out (Scheme 36). By comparing the rate of the reaction between 126 and 139, an average kinetic isotopic effect of $k_{126}/k_{139}$ of 1.2 was obtained. Furthermore, the ratio of 126 and 139 does not change with time. This result demonstrated the C–H bond activation is not the rate determining step and a normal secondary kinetic isotopic effect is observed. Also, the formation of 127 is not reversible.
Crossover experiment was then carried out to determine if the reaction is an intra- or intermolecular process (Scheme 37). The rhodium-catalysed reaction was carried out with both substrate 139 and substrate 132f in the same reaction vessel. However, at the end of the reaction substrate 132f was isolated in 89% yield with no deuterium incorporation. Furthermore, product 140 and 141 were isolated in a combined 95% yield with a ratio of 64:36. Moreover, there was complete transfer of the deuterium to the indicated positions. 140 has the deuterium atom on the exo-methyl carbon. 141 has the deuterium atom on the carbon α to the vinyl pyridine. Also, the deuterium atom on 141 is equally distributed between the exo- and endo- position. The lack of crossover confirmed that the reaction is purely intramolecular.

Scheme 37 Crossover experiment

The deuterium scrambling studies revealed the C–H bond activation step and hydrometalation is reversible and both steps happen a lot faster than the subsequent steps. The crossover experiment confirms it is an intramolecular reaction. From the optimisation, the formation of five-membered ring 128 occurs faster at higher temperature than the formation of 127. The stereocentres found in the four-membered ring side 137 is inverted when compared to
stereocenters of 133f. Furthermore, the four-membered ring is not seen if the reaction is allowed to proceed to completion. The formation of the bicyclo[2.2.1]heptane is completely diastereoselective.

To account for all these observations, a potential mechanism have been postulated (Scheme 38). After the pyridine directed C–H bond activation to form intermediate 150, hydrometalation onto the alkene can occur in the 1,2- or 2,1-fashion. The hydrometalation onto the alkene in the 1,2-fashion to form 152 is slow as determined by deuterium labelling studies. However, when it does occur, irreversible reductive elimination furnishes five-membered ring 134.

From the deuterium-labelling studies, hydrometalation onto the alkene in the 2,1-fashion is considerably faster and reversible but it is also clear that the hydrometalation is not completely stereoselective. If the hydrometalation proceeds to give intermediate 153 whereby the exo-methyl group and the allyl group are anti, reductive elimination can occur to give four-membered ring 154. From the time profile studies, four membered ring 154 is not observed at the end of the reaction and therefore is reversibly formed.

The formation of 133 occurs when hydrometalation onto the alkene occurs in the 2,1-fashion to give intermediate 151 whereby the exo-methyl group and the allyl group are syn. After the formation of 151, the migratory insertion of the pendant alkene occurs to furnish the seven-membered rhodacycle 155. Finally, reductive elimination occurs to furnish 133.
The generation of bicyclo[2.2.1]heptane 133 from vinyl pyridines 132 by a rhodium catalyst have been accomplished (Scheme 39). Interestingly, 133 was formed as a single diastereoisomer in all cases whereby the bridgehead carbon and the exo-methyl carbon are syn in space. However, the 133 is always contaminated with 132 to varying degrees as neither could be separated by flash column chromatography. It has been noted that a large Thorpe-Ingold effect influences the selectivity in favour of 133. Furthermore, this work could be further enhanced by carrying out the reaction enantioselectively.

Scheme 38 Postulated mechanism

4.6 Conclusion

The generation of bicyclo[2.2.1]heptane 133 from vinyl pyridines 132 by a rhodium catalyst have been accomplished (Scheme 39). Interestingly, 133 was formed as a single diastereoisomer in all cases whereby the bridgehead carbon and the exo-methyl carbon are syn in space. However, the 133 is always contaminated with 132 to varying degrees as neither could be separated by flash column chromatography. It has been noted that a large Thorpe-Ingold effect influences the selectivity in favour of 133. Furthermore, this work could be further enhanced by carrying out the reaction enantioselectively.
The generation of bicyclo[2.2.1]heptane 133 from vinyl pyridines 132 proceeded in a diastereoselective manner. Therefore, a further extension to this methodology would be an enantioselective synthesis of 133 (Scheme 40). This would make the methodology extremely attractive as there would be potentially complete stereocontrol on the formation of all 3 chiral centres of 133 despite starting from prochiral 132.

Employing a chiral ligand should enable a catalytic enantioselective synthesis of 133. As there is a large library of different chiral bidentate phosphine ligands available, chiral bidentate phosphines would be a good starting point to find conditions for the enantioselective synthesis of 133. However, during the optimisation of this reaction, it became clear that bidentate ligands were ineffective.
On the other hand, chiral monodentate phosphine ligands have been recognised as effective ligands for many enantioselective transition-catalysed reactions. Therefore, a suitable chiral monodentate phosphine ligand could potentially enable an enantioselective synthesis of 133.

4.8 Synthesis of precursors

The synthesis of aldehyde S5 started from commercially available ester S1 (Scheme 41). The first allylation with allyl bromide afforded the mono-allylated ester S2 in 97% yield. The allylation was then repeated with allyl bromide with TBAI to afford the bis-allylated ester S3 in 97% yield. Reduction with LiAlH₄ gave alcohol S4 in 97% yield. Finally, oxidation to aldehyde S5 was achieved by Swern oxidation which was then used directly in the next step.

Scheme 41 Synthesis of aldehyde S5

The synthesis of vinyl pyridine 126 via the Wittig olefination was achieved (Scheme 44). However, Wittig olefination with triphenyl(2-pyridylmethyl)phosphonium chloride hydrochloride generally proceeded with E-selectivities of roughly 91:9. Attempts to vary the reaction conditions did not drastically improve the selectivity for E-126. Therefore, a new method was devised which gave a E-selectivity of >95:5.
The synthesis of vinyl pyridine 126 with an $E$-selectivity of >95:5 was achieved by E2 elimination with a strong base (Scheme 44). Aldehyde S5 was added to the vinyl pyridine anion at -78°C. After purification by aqueous workup to form secondary alcohol S7, mesylation with mesyl chloride in DCM was then carried out. After purification by aqueous workup, the mesylated product was used directly in the next step. To the crude mesylate, E2 elimination was carried out with NaHMDS as base to afford vinyl pyridine 126 in 55% yield over four steps from S4 with a $E/Z$ ratio of >95:5.

The synthesis of vinyl pyridine 132e started from the commercially available $\beta$-ketoester S8 (Scheme 44). One pot double allylation of $\beta$-ketoester S8 with NaH as base afforded $\beta$-ketoester S9 in 96% yield. The protection of ketone with ethylene glycol and then reduction with LiAlH$_4$ afforded S10 in 52% over 2 steps. Afterwards, a Swern oxidation$^{30}$ was carried out. After a quick purification by filtration over a silica plug, the aldehyde was added to the vinyl
pyridine anion at -78°C to form the secondary alcohol. Finally, mesylation and E2 elimination with NaHMDS afforded vinyl pyridine 132e in 52% yield over the four steps from S10.

**Scheme 44 Synthesis of vinyl pyridine 132e**

The synthesis of vinyl pyridine 132h started from the commercially available malonate S11 (Scheme 45). Benzylation of malonate S11 with NaH as base afforded malonate S12. Krapcho decarboxylation using lithium chloride in DMSO under reflux gave monoester S13. Now, allyllation of malonate S13 with LDA as base afforded malonate S14 in quantitative yield. Afterwards, reduction with LiAlH₄ followed by the oxidation of the alcohol by the Swern oxidation afforded the aldehyde. After a quick filtration over a silica plug, the crude material was of sufficient purity as judged by ¹HMR to be used directly in the next step. Then, the aldehyde was added to the vinyl pyridine anion at -78°C to form the secondary alcohol. Finally, mesylation and E2 elimination with NaHMDS afforded vinyl pyridine 132h in 64% yield over 4 steps.
The synthesis of diol S17 started from the bis-allylation of the commercially available malonate S17. The synthesis of 129 and 132i began with the mono-protection of diol S17 using either tert-butyldimethylsilyl chloride or benzylbromide or as the electrophile which proceeded in a 84% and 69% yield respectively (Scheme 46). The resulting mono-protected alcohols were then subjected to Swern oxidation to afford aldehydes. After a quick filtration over a silica plug, the crude material was of sufficient purity as judged by $^1$HMR to be used directly in the next step. Then, vinyl pyridine was deprotonated by nBuLi at -78°C and the crude aldehyde was added. After an aqueous workup, the secondary alcohol was mesylated with mesyl chloride. After another aqueous workup, a E2 elimination was carried out with NaHMDS as base to give vinyl pyridine 129 and 132i in a 55% and 57% overall yield respectively from the corresponding mono-protected alcohols.

Scheme 45 Synthesis of vinyl pyridine 132h
The synthesis of $S_22$ began with the one-pot bis-allylation of malonate $S_20$ to form bis-allylated malonate $S_21$ (Scheme 47). Afterwards, Krapcho decarboxylation using lithium chloride in DMSO at 160°C gave monoester $S_22$.

From the mono-ester $S_22$, the synthesis of vinyl pyridine $132j$ was achieved (Scheme 48). Due to the volatility of the subsequent intermediates, no attempts on their isolation were made. Therefore, the crude material after the aqueous workup was used directly in the next step until the formation of the secondary alcohol $S_23$. The synthesis of secondary $S_23$ began with the methylation of $S_22$. Afterwards, LiAlH$_4$ reduction followed by the Swern oxidation afforded the aldehyde. After a quick filtration over a silica plug, the crude material was of
sufficient purity as judged by \( ^1 \)HMR to be used directly in the next step. Then, the aldehyde was added to the vinyl pyridine anion at -78°C to form the secondary alcohol \( S_{23} \). \( S_{23} \) was isolated in a 42% yield over four steps and fully characterised. Finally, mesylation and E2 elimination with NaHMDS as base afforded vinyl pyridine \( 132j \) in 68% yield over two steps.

**Scheme 48** Synthesis of vinyl pyridine \( 132j \)

The synthesis of vinyl-imidazole \( 135 \) with a \( E \)-selectivity of >95:1 was achieved by E2 elimination with a strong base (Scheme 49). Swern oxidation\(^{30}\) of \( S_4 \) afforded the aldehyde. After a quick filtration over a silica plug, the crude material was of sufficient purity as judged by \( ^1 \)HMR to be used directly in the next step. Aldehyde was added to the vinyl-imidazole anion at -78°C. After purification by aqueous workup to form secondary alcohol \( S_{24} \) which was isolated in a 86% yield over two steps. Afterwards, mesylation with mesyl chloride in DCM was then carried out. After purification by aqueous workup, the mesylated product was used directly in the next step. To the crude mesylate, E2 elimination was carried out with NaHMDS as base to afford vinyl-imidazole \( 135 \) in 58% yield over the two steps.
Deuterium labelled vinyl pyridine 139 was synthesised from ester S3 (Scheme 50). Reduction of the ester with LiAlD₄ afforded alcohol S25 in 94% yield. Afterwards, the Swern oxidation was carried out and was purified by filtration over a small plug of silica. Then the aldehyde was added to the vinyl pyridine anion at -78°C to form the secondary alcohol. Finally, mesylation and E2 elimination with NaHMDS as base afforded vinyl pyridine 139 in 71% yield over four steps.
4.9 Experimental

**General.** Otherwise noted, all reactions were carried out in flame-dried glassware under dry nitrogen atmosphere. The solvents were purified with the solvent purification system Pure Solv MD-6 (THF, Et₂O, CH₂Cl₂, benzene, toluene, hexane) except otherwise noted. Flash chromatography: Merck silica gel 60 (230-400 mesh). NMR: Spectra were recorded on a Bruker DRX 500 and a Bruker DPX 400 spectrometers in CDCl₃; chemical shifts (δ) are given in ppm. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl₃: δ_C = 77.0 ppm; residual CHCl₃ in CDCl₃: δ_H = 7.24 ppm). IR: PerkinElmer Spectrum 100 FT-IR spectrometer, wavenumbers (ʋ) in cm⁻¹. HRMS at the University of Liverpool: micromass LCT mass spectrometer (ES+) and Trio-1000 or Agilent QTOF 7200 mass spectrometers (CI). Melting points: Griffin melting point apparatus (not corrected). Elemental analyses: University of Liverpool. X-Ray crystallography: Bruker D8 Venture Photon 100 Dual Microsource diffractometer. All commercially available compounds were used as received.

**Compound S3**

At 0°C, 2.5M of Buli in hexane (11.1 ml, 27.9 mmol) was added to a stirred solution of DIPA (4.3 ml, 30.3 mmol) in THF (36 ml). It was allowed to stir at 0°C for 10 mins. Cooled to -78°C, methyl phenylacetate S1 (3.5 ml, 24.2 mmol) in THF (70 ml) was added. It was then allowed to stir at -78°C for 40 mins. Afterwards, allyl bromide (2.7 ml, 21.5 mmol) was added. It was then allowed to stir at rt overnight. Afterwards, the reaction was quenched with a saturated solution of NH₄Cl. Et₂O was added and extracted two times with Et₂O. The organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and
concentrated. Purification by flash column chromatography (PE/DE, 50/1→30/1) gave S2 as a colourless oil (4.45 g, 97%). At 0°C, 2.5 M of Buli in hexane (10.8 ml, 26.9 mmol) was added to a stirred solution of DIPA (4.2 ml, 26.2 mmol) in THF (36 ml). It was allowed to stir at 0°C for 10 mins. Cooled to -78°C, S2 (4.45 g, 23.4 mmol) in THF (73 ml) was added. It was then allowed to stir at -78°C for 40 mins. Afterwards, allyl bromide (2.7 ml, 30.4 mmol) and TBAI (864 mg, 2.34 mmol) were added. It was then allowed to stir at rt overnight. Afterwards, the reaction was quenched with a saturated solution of NH₄Cl. Et₂O was added and extracted three times with Et₂O. The organic layer was washed with water and a saturated solution of brine. Dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (PE/DE, 40/1→30/1) gave S3 as a colourless oil (5.24 g, 97%). This is a known compound. ¹H NMR (500 MHz, CDCl₃): δ = 7.35 – 7.28 (m, 2H), 7.26 – 7.18 (m, 3H), 5.56 – 5.44 (m, 2H), 5.09 – 4.99 (m, 4H), 3.63 (s, 3H), 2.83 – 2.69 (m, 4H)

**Compound S9**

NaH (927 mg, 23.17 mmol, 60% dispersion in mineral oil) and allyl bromide (2 ml, 23.17 mmol) were added to ester S8 (1 ml, 9.27 mmol) in DMF (19 mL) at 0°C under N₂. Then the reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was re-cooled to 0°C, diluted with Et₂O and quenched carefully with H₂O (initially via dropwise addition). The organic layer was separated and washed repeatedly with H₂O to remove excess DMF. The organic phase was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was used in the next step without further purification. Pale yellow oil (1.72 g, 96%); ¹H NMR (500 MHz, CDCl₃): δ = 5.62 – 5.51 (m, 2H), 5.11 – 5.05 (m, 4H), 3.70 (s, 3H), 2.62 (ddt, J = 14.6, 7.4, 1.1 Hz, 2H), 2.56 (ddt, J = 14.4, 7.5, 1.1 Hz, 2H), 2.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 203.9, 172.0, 132.1 (2C), 119.2 (2C), 63.4, 52.3, 36.0 (2C), 292
27.0; IR (neat): $\tilde{\nu} = 3080$ (w), 2981 (w), 2953 (w), 1744 (m), 1711 (s), 1641 (w), 1435 (m), 1357 (w), 1321 (w), 1279 (m), 1250 (w), 1179 (m), 1141 (m), 1052 (w), 993 (m), 919 (s), 871 (w), 844 (w), 794 (w), 750 (w), 697 (w) cm$^{-1}$; MS (Cl(CH$_4$)): 197 (24) [M + H], 165 (28), 137 (97), 123 (100), 95 (21); HRMS (Cl(CH$_4$)) calcd for (C$_{11}$H$_{16}$O$_3$ + H): 197.1172; found: 197.1170

**Compound S12**

![Structure of Compound S12](image)

Obtained from dimethyl allylmalonate (1 ml, 6.22 mmol) following the representative procedure except with benzyl bromide (1.1 ml, 9.33 mmol). Colourless oil (1.45 g, 89%). This compound is known. $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.27 - 7.18$ (m, 3H), 7.07 (d, $J = 7.1$ Hz), 5.79 – 5.68 (m, 1H), 5.17 – 5.09 (m, 2H), 3.69 (s, 6H), 3.22 (s, 2H), 2.54 (d, $J = 7.3$ Hz, 2H).

**Compound S13**

![Structure of Compound S13](image)

Lithium chloride (231 mg, 5.45 mmol) was added to a solution of S12 (650 mg, 2.48 mmol) in DMSO (17 mL). Water (15 drops) was added and then the mixture was stirred at 160°C (oil bath temperature) overnight. At room temperature, the mixture was then partitioned between H$_2$O (10 mL) and Et$_2$O. The organic layer was washed with H$_2$O (2 x 20 mL), then brine, and dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc : 20/1) gave S13 as a colourless oil (348 mg, 72%): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.28-7.23$ (m, 1H), 7.21–7.16 (m, 1H), 7.15–7.12 (m, 2H), 5.73 (ddt, $J = 17.1$, 10.2, 7.0, 1H), 5.08–5.00 (m, 2H), 3.58 (s, 3H), 2.97–2.88 (m, 1H), 2.80–2.69 (m, 2H), 2.40–2.31 (m, 1H), 2.29–2.21 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 175.3, 139.1, 135.1, 128.9, 128.4,$
126.4, 117.1, 51.4, 47.2, 37.7, 36.0; IR (neat): $\tilde{\nu}$ = 3065 (w), 3028 (w), 2950 (w), 1733 (s), 1642 (w), 1604 (w), 1584 (w), 1495 (w), 1455 (w), 1370 (w), 1262 (w), 1230 (m), 1195 (m), 1161 (s), 1116 (w), 1077 (w), 1031 (w), 994 (w), 915 (m), 832 (w), 762 (w), 743 (m), 698 (s), 656 (w) cm$^{-1}$; MS (Cl(CH$_4$)): 205 (11) [M + H], 173 (11), 145 (100), 91 (25); HRMS (Cl(CH$_4$)): calcd for (C$_{13}$H$_{16}$O$_2$ + H): 205.1229; found: 205.1224.

**Compound S14**

![Structure of Compound S14](image)

Under N$_2$, a solution of S13 (150 mg, 0.73 mmol) in THF (0.6 mL) was added to a solution of LDA (0.95 mmol) at -78°C {LDA prepared from 0.38 mL of a 2.5 M of nBuLi and 0.14 mL of diisopropylamine in THF (1.4 mL) at 0°C}. The resulting solution was stirred at -78°C for 1.5 hour then allyl bromide (89 µL, 1.03 mmol) was slowly added. The mixture was allowed to warm to room temperature overnight before being quenched with few drops of a saturated solution of NH$_4$Cl. The mixture was diluted with H$_2$O and extracted three times with diethyl ether. The organic layer was then washed with H$_2$O and brine and dried over Na$_2$SO$_4$, then filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc: 25/1) afforded S14 as a colourless oil (179 mg, quant.): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.26–7.16 (m, 3H), 7.11–7.06 (m, 2H), 5.78 (ddt, $J$ = 16.6, 10.6, 7.3 Hz, 2H), 5.14–5.07 (m, 4H), 3.63 (s, 3H), 2.88 (s, 2H), 2.38 (dd, $J$ = 14.3, 7.2 Hz, 2H), 2.27 (dd, $J$ = 14.3, 7.4 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 175.8, 137.3, 133.6 (2C), 130.0 (2C), 128.1 (2C), 126.5, 118.6 (2C), 51.5, 50.9, 41.4, 38.2 (2C); IR (neat): $\tilde{\nu}$ = 3077(w), 3030 (w), 2980 (w), 2949 (w), 1727 (s), 1639 (w), 1605 (w), 1496 (w), 1435 (m), 1347 (w), 1274 (w), 1200 (m), 1179 (m), 1155 (m), 1079 (w), 1032 (w), 994 (w), 994 (m), 972 (w), 914 (s), 851 (w), 814 (w), 777 (w), 740 (m), 700 (s) cm$^{-1}$; elemental analysis (%) calcd for C$_{16}$H$_{20}$O$_2$: C 78.65, H 8.25; found: C 79.17, H 8.36.
Compound S21

Obtained from dimethyl malonate (2.5 ml, 21.9 mmol) following the representative procedure. Colourless oil (3.2 g, 68%). This compound is known. $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 5.68 – 5.56$ (m, 2H), 5.13 – 5.04 (m, 4H), 3.70 (s, 6H), 2.62 (d, $J = 7.4$ Hz, 4H).

Compound S22

Obtained from S21 (1.92 mmol, 0.40 mL) following the procedure described for the preparation of S13. Colourless oil (155 mg, 52 %): $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 5.71$ (ddt, $J = 17.1$, 10.1, 7.0 Hz, 2H), 5.04 (dt, $J = 17.1$, 1.6 Hz, 2H), 5.03–4.98 (m, 2H), 3.64 (s, 3H), 2.51 (tt, $J = 8.1$, 6.1 Hz, 1H), 2.39–2.30 (m, 2H), 2.28–2.19 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 135.2$ (2C), 117.0 (2C), 51.4, 44.9, 35.8 (2C); IR (neat): $\tilde{\nu} = 3080$ (w), 2981 (w), 2951 (w), 2846 (w), 1736 (s), 1642 (w), 1437 (m), 1369 (w), 1266 (w), 1236 (m), 1193 (m), 1168 (s), 1139 (m), 994 (m), 914 (s), 862 (w), 833 (w), 763 (w), 702 (w) cm$^{-1}$; elemental analysis (%) calcd for C$_9$H$_{14}$O$_2$: C 70.10, H 9.15; found: C 70.18, H 9.28

Representative procedure for the reduction of esters into alcohols – A solution of ester S3 (7.38 mmol, 1.7g) in Et$_2$O (12 mL) was added under N$_2$ to a suspension of LiAlH$_4$ (4.05 mmol, 150 mg) in Et$_2$O (24 mL) at 0°C. After stirring at room temperature for 30 minutes, another portion of LiAlH$_4$ (4.05 mmol, 150 mg) was added. After stirring for 30 minutes, the reaction mixture was quenched carefully at 0°C with a saturated aqueous solution of Na$_2$SO$_4$. After filtration over Celite to remove the white precipitate, the solvent was evaporated under
reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc = 10:1) to afford S4 as colourless oil (1.42 g, 95%).

**Compound S4**

![Chemical structure of S4]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.36$–7.31 (m, 4H), 7.24–7.19 (m, 1H), 5.62 (ddt, $J = 17.1$, 10.1, 7.2 Hz, 2H), 5.11–4.99 (m, 4H), 3.78 (d, $J = 6.6$ Hz, 2H), 2.53 (dd, $J = 13.9$, 7.2 Hz, 2H), 2.45 (dd, $J = 14.1$, 7.2 Hz, 2H), 1.26 (t, $J = 6.6$ Hz, 1H(OH)); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 143.4$, 134.3 (2C), 128.4 (2C), 126.8 (2C), 126.2, 117.8 (2C), 67.8, 45.8, 39.5 (2C); IR (neat): $\tilde{\nu} = 3410$ (br), 3074 (w), 3006 (w), 2978 (w), 2925 (w), 1638 (w), 1600 (w), 1581 (w), 1498 (m), 1445 (m), 1415 (w), 1385 (w), 1326 (w), 1294 (w), 1218 (w), 1143 (w), 1046 (m), 997 (m), 911 (s), 859 (w), 768 (m), 744 (w), 698 (s), 672 (m) cm$^{-1}$; elemental analysis (%) calcd for C$_{14}$H$_{18}$O: C 83.12, H 8.97; found: C 83.25, H 9.04.

**Compound S10**

![Chemical structure of S10]

Under N$_2$, TsOH•H$_2$O (49 mg, 0.25 mmol) was added to a solution of S9 (508 mg, 2.59 mmol), diethylene glycol (0.567 mmol, 10.19 mmol) and trimethyl orthoformate (0.56 mL, 5.10 mmol) at room temperature. After stirring overnight, the mixture was quenched with a saturated solution of NaHCO$_3$ and extracted with Et$_2$O (3 x 5 mL). The organic layer was washed with H$_2$O and then a saturated solution of brine. It was then dried over Na$_2$SO$_4$, filtered and concentrated to give 622 mg of an oil which was dissolved in Et$_2$O (3 mL) under N$_2$ and added by cannula to a suspension of LiAlH$_4$ (53.0 mg, 1.40 mmol) in Et$_2$O (10 mL) at 0 °C. After 10
mins at 0 °C, another portion of LiAlH₄ (53.0 mg, 1.40 mmol) was added. After 2 hours of stirring at room temperature, the reaction mixture was quenched carefully at 0°C with a saturated aqueous solution of Na₂SO₄ which will cause a white precipitate to form. After filtration over Celite to remove the white precipitate, the solvent was evaporated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc: 4/1) to afford **S9** as a colourless oil (284 mg, 52 % over 2 steps). ¹H NMR (500 MHz, CDCl₃): δ = 5.92 (ddt, J = 17.1, 10.0, 7.3 Hz, 2H), 5.05 (d, J = 17.4 Hz, 2H), 5.04 (d, J = 10.0 Hz, 2H), 3.99–3.89 (m, 4H), 3.51 (d, J = 5.9 Hz, 2H), 3.08 (t, J = 5.9 Hz, 1H(OH)), 2.22 (dd, J = 14.4, 7.0 Hz, 2H), 2.15 (dd, J = 14.3, 7.6 Hz, 2H), 1.31 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 135.0 (2C), 117.3 (2C), 114.7, 66.0, 64.4 (2C), 47.9, 34.9 (2C), 20.0; IR (neat): ʋ = 3526 (br), 3074 (w), 2980 (w), 2941 (w), 2888 (m), 1638 (w), 1471 (w), 1436 (w), 1413 (w), 1377 (w), 1334 (w), 1204 (m), 1095 (m), 1038 (s), 998 (m), 950 (m), 912 (s), 874 (m), 765 (w), 693 (w) cm⁻¹; HRMS (Cl(NH₃)): calcd for (C₁₂H₂₀O₃ + H): 213.1485; found: 213.1490

**Compound S15**

![Structure of S15](image)

Obtained from **S14** (1.23 mmol, 300 mg) following the representative procedure. Colourless oil (246 mg, 93%): ¹H NMR (500 MHz, CDCl₃): δ = 7.29–7.23 (m, 2H), 7.23–7.17 (m, 3H), 5.98–5.87 (m, 2H), 5.15–5.06 (m, 4H), 3.36 (d, J = 6.0 Hz, 2H), 2.63 (s, 2H), 2.04 (d, J = 7.4 Hz, 4H), 1.33, (t, J = 6.1 Hz, 1H(OH)); ¹³C NMR (125 MHz, CDCl₃): δ = 138.1, 134.6, 130.6, 128.0, 126.1, 118.0, 66.8, 42.1, 40.4, 38.6; IR (neat): ʋ = 3413 (br), 3075 (w), 3029 (w), 2977 (w), 2923 (m), 1638 (m), 1604 (w), 1496 (w), 1441 (m), 1415 (w), 1328 (w), 1230 (w), 1156 (w), 1048 (m), 1031 (m), 1016 (m), 995 (m), 911 (s), 861 (w), 812 (w), 783 (w), 740 (m), 702 (s), 665 (w) cm⁻¹; elemental analysis (%) calcd for C₁₅H₂₀O: C 83.28, H 9.32; found: C 83.37, H 9.35.
Compound S17

Obtained from diethyl diallylmalonate (2 mL, 8.27 mmol) following the procedure for the synthesis of S10. Clear Oil (1.19 g, 92%): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 5.83 (ddt, $J =$ 16.8, 10.3, 7.5 Hz, 2H), 5.13 – 5.06 (m, 4H), 3.58 (d, $J =$ 4.8 Hz, 4H), 2.08 (dt, $J =$ 7.5, 1.1 Hz, 4H), 2.05 – 1.98 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 133.8, 118.1, 68.1, 42.0, 36.0; IR (neat): $\tilde{\nu} =$ 3343 (br m), 3076 (w), 3006 (w), 2979 (w), 2924 (w), 1836 (w), 1639 (w), 1465 (w), 1440 (m), 1416 (w), 1333 (w), 1223 (w), 1146 (w), 1057 (m), 1021 (s), 996 (s), 910 (s), 862 (w), 807 (w), 684 (w) cm$^{-1}$; elemental analysis (%) calcd for C$_9$H$_{16}$O$_2$: C 69.19, H 10.32; found: C 69.02, H 10.33

Compound S18

At 0°C, 60 % of NaH (187 mg, 1.24 mmol) was added to a solution of S17 (194 mg, 1.24 mmol) in THF (12 mL). The ice bath was removed and allowed to stir at rt for 2 hours. The suspension was cooled back down to 0°C and TBSCI (187 mg, 1.24 mmol) was added. The resulting mixture was stirred at rt overnight. The mixture was quenched with a saturated solution of NH$_4$Cl and extracted three times with diethyl ether. The organic layer was washed with a saturated aqueous solution of brine, dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc : 9/1) gave S18 as a clear oil (284 mg, 84%): $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 5.84 – 5.74 (m, 2H), 5.10 – 5.03 (m, 4H), 3.53 – 3.47 (m, 4H), 2.65 (t, $J =$ 2.65 Hz, OH), 2.07 (dd, $J =$ 13.9, 7.4 Hz, 2H), 2.02 (dd, $J =$ 13.9, 7.7 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 134.0, 117.9, 68.9, 68.6, 41.9, 36.0, 25.8, 18.1, -5.7
Compound S19

At 0°C, 60% of NaH (58 mg, 1.44 mmol) was added to a solution of S17 in THF (6 mL). The ice bath was removed and allowed to stir at rt for 1 hour. The suspension was cooled back down to 0°C and benzyl bromide (172 µL, 1.44 mmol) was added. The resulting mixture was stirred at rt overnight. The mixture was quenched with a saturated solution of NH₄Cl and extracted three times with diethyl ether. The organic layer was washed with a saturated aqueous solution of brine, dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc : 9/1) gave S19 as a light yellow oil (244 mg, 69%): ¹H NMR (500 MHz, CDCl₃): δ = 7.38 – 7.25 (m, 5H), 5.85 – 5.72 (m, 2H), 5.12 – 5.00 (m, 4H), 4.48 (s, 2H), 3.52 (d, J = 5.4 Hz, 2H), 3.37 (s, 2H), 2.56 (br s, 1H), 2.15 – 2.03 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 137.9, 133.9, 128.4, 127.7, 127.5, 118.0, 75.9, 73.6, 68.4, 41.7, 36.2; IR (neat): ν = 3437 (br w), 3074 (w), 3031 (w), 3005 (w), 2977 (w), 2861 (m), 1639 (m), 1497 (m), 1415 (w), 1363 (w), 1330 (w), 1251 (w), 1206 (w), 1096 (s), 1075 (m), 1029 (m), 999 (m), 910 (s), 876 (w), 736 (m), 697 (s) cm⁻¹; elemental analysis (%) calcd for C₁₆H₂₂O₂: C 78.01, H 9.00; found: C 78.16, H 8.99

Compound S25

Obtained from S3 (1.23 mmol, 283 mg) following the representative procedure but using LiAlD₄. Colourless oil (237 mg, 94%); ¹H NMR (500 MHz, CDCl₃): δ = 7.38 – 7.29 (m, 4H), 7.24 – 7.18 (m, 1H), 5.62 (ddt, J = 17.2, 10.0, 7.3 Hz, 2H), 5.11–5.04 (m, 2H), 5.04–4.99 (m, 2H), 2.53 (dd, J = 14.1, 7.2 Hz, 2H), 2.45 (dd, J = 13.9, 7.4 Hz, 2H), 1.25 (s, 1H(OH)); ¹³C NMR (125 MHz, CDCl₃): δ = 143.3, 134.3 (2C), 128.4 (2C), 126.8 (2C), 126.2, 117.8 (2C), 67.0 (pent, J = 21.8 Hz), 299
45.6, 39.5 (2C); IR (neat): \( \bar{\nu} = 3399 \text{ (br)}, 3074 \text{ (w)}, 3006 \text{ (w)}, 2978 \text{ (w)}, 2923 \text{ (w)}, 2207 \text{ (w)}, 2101 \text{ (w)}, 1638 \text{ (w)}, 1600 \text{ (w)}, 1580 \text{ (w)}, 1497 \text{ (w)}, 1445 \text{ (m)}, 1415 \text{ (w)}, 1292 \text{ (w)}, 1193 \text{ (w)}, 1158 \text{ (w)}, 1102 \text{ (m)}, 1030 \text{ (w)}, 998 \text{ (m)}, 975 \text{ (m)}, 910 \text{ (s)}, 838 \text{ (w)}, 807 \text{ (w)}, 759 \text{ (m)}, 733 \text{ (w)}, 697 \text{ (s)}, 665 \text{ (w)} \text{ cm}^{-1}; \) MS (Cl(NH\(_3\)): \( m/z \) (rel. intensity): 222 (100) [M + NH\(_4\)]; HRMS (Cl(NH\(_3\))) calcd for (C\(_{14}\)H\(_{16}\)D\(_2\)O + NH\(_4\)): 222.1821; found: 222.1824.

**Representative procedure for the Swern oxidation** – Under N\(_2\), DMSO (87 \( \mu \text{L}, 1.20 \text{ mmol}) in CH\(_2\)Cl\(_2\) (0.8 mL) was added to a solution of oxalyl chloride (53 \( \mu \text{L}, 0.61 \text{ mmol}) in CH\(_2\)Cl\(_2\) (3.9 mL) at –78°C. After 10 minutes stirring at –78°C, a solution of the S4 (95 mg, 0.47 mmol) in CH\(_2\)Cl\(_2\) (0.8 mL) was added. After 20 minutes stirring at –78°C, triethylamine (0.32 mL, 2.34 mmol) was added rapidly and the mixture was stirred at room temperature during 20 minutes. A saturated solution of NH\(_4\)Cl was added to the reaction mixture which was then extracted three times with diethyl ether. The organic layer was washed with H\(_2\)O and a saturated solution of brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated to give 93 mg of aldehyde which was used without further purification in the next step. Under N\(_2\), nBuLi (0.32 mL, 0.55 mmol, 1.7 M in hexanes) was added to a –78°C solution of 2-Methylpyridine (59 \( \mu \text{L}, 0.60 \text{ mmol}) in THF (2.5 mL). After 10 minutes of stirring at –78°C, a solution of the aldehyde (93 mg, 0.46 mmol) in THF (0.8 mL) was added by cannula. After stirring for 10 minutes at –78°C, the reaction was quenched with enough MeOH to turn the deep red solution to yellow and was then allowed to warm to room temperature. The crude mixture was then partitioned between a saturated aqueous solution of NaHCO\(_3\), water and Et\(_2\)O. After three extractions with Et\(_2\)O (5 mL), the combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated. Purification by flash column chromatography (petroleum ether/EtOAc: 7/1 \( \rightarrow \) 6/1) afforded 133 mg of a clear oil which was dissolved in CH\(_2\)Cl\(_2\) (0.4 mL) under N\(_2\) and cooled to –40°C. Et\(_3\)N (193 \( \mu \text{L}, 1.36 \text{ mmol}) and methanesulfonyl chloride (53 \( \mu \text{L}, 0.68 \text{ mmol}) were added dropwise. After stirring overnight at room temperature, the precipitate thus formed was then filtered off over Celite,
washed with EtOAc, and the filtrate was concentrated under reduce pressure. Under N₂, the residue was dissolved in THF (2.4 mL) under N₂. At –20°C, NaHMDS (0.6 mL, 0.61 mmol, 1M in THF) was added. After stirring at room temperature for 1 hour, the reaction mixture was quenched with a saturated solution of NaHCO₃ and partitioned between water and EtOAc. After three extractions with Et₂O (5 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (petroleum ether/Et₂O: 9/1 → 8/1) afforded **126** as a white solid (56 mg, 55% over four steps)

**Compound E-126**

mp.: 27–28°C; ¹H NMR (500 MHz, CDCl₃): δ = 8.53 (d, J = 4.6 Hz, 1H), 7.62–7.56 (m, 1H), 7.35–7.26 (m, 5H), 7.22–7.16 (m, 1H), 7.12–7.07 (m, 1H), 6.85 (d, J = 16.4 Hz, m1H), 6.53 (d, J = 16.2 Hz, 1H), 5.61 (ddt, J = 17.2, 10.0, 7.1 Hz, 2H), 5.08–4.97 (m, 4H), 2.68 (d, J = 7.1 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 156.0, 149.5, 144.8, 141.8, 136.4, 134.4 (2C), 128.7, 128.1, 127.4, 126.2, 121.8, 121.0, 117.8 (2C), 46.8, 41.9 (2C); IR (neat): υ = 3059 (w), 3034 (w), 3007 (w), 2922 (w), 2902 (w), 2841 (w), 1953 (w), 1892 (w), 1836 (w), 1650 (m), 1640 (m), 1598 (w), 1585 (m), 1563 (m), 1493 (m), 1469 (m), 1444 (m), 1429 (m), 1322 (w), 1302 (w), 1262 (w), 1243 (w), 1189 (w), 1150 (w), 1127 (w), 1097 (w), 1089 (w), 1049 (w), 1030 (w), 1009 (w), 990 (m), 979 (m), 943 (m), 935 (m), 915 (s), 889 (m), 856 (m), 779 (m), 766 (m), 749 (s), 701 (s), 671 (w), 654 (w) cm⁻¹; HRMS (ESI): calcd for (C₂₀H₂₁N + Na): 276.1752; found: 276.1750; elemental analysis (%): calcd for C₂₀H₂₁N: C 87.23, H 7.69, N 5.09; found: C 87.71, H 7.69, N 4.87.
Compound E/Z-126

2.5M of nBuli in hexane (0.4 ml, 1 mmol) was added to a schlenk containing triphenyl(2-pyridylmethyl)phosphonium chloride hydrochloride (213 mg, 0.50 mmol) in THF (0.1 ml) at -78°C. The mixture was stirred at 35°C for 2 hours. Then, S5 in THF (0.2 ml) was added at rt. It was then allowed to stir overnight at rt. The reaction was quenched with a saturated solution of NaHCO₃. The crude material was partitioned between H₂O and EtOAc. The aqueous layer was then extracted three times with EtOAc. Extracts dried over Na₂SO₄ and filtered. Silica was then added, all volatiles were removed and the dry deposit was loaded on to the top of a column. Purification by flash column chromatography (petroleum ether/Et₂O: 9/1) afforded 126 as a white solid (29 mg, 43%) with a E/Z ratio of 91:9 as judged from the ¹H NMR spectra; Key peaks of Z-126, ¹H NMR (500 MHz, CDCl₃): δ = 8.36 – 8.33 (m, 1H), 6.63 (d, J = 13.0 Hz, 1H), 5.97 (d, J = 13.0 Hz, 1H).

Compound 139

Obtained from S25 (1.03 mmol, 211 mg) following the representative procedure. Colourless oil (202 mg, 71% over four steps); ¹H NMR (500 MHz, CDCl₃): δ = 8.53 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 7.59 (dt, J = 7.7, 1.8 Hz, 1H), 7.35–7.26 (m, 5H), 7.21–7.16 (m, 1H), 7.09 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 6.52 (s, 1H), 5.61 (ddt, J = 17.2, 10.1, 7.1 Hz, 2H), 5.07–4.97 (m, 4H), 2.70 – 2.66 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 156.0, 149.5, 144.8, 141.4 (t, J = 22.5 Hz), 136.4, 134.4 (2C), 128.6, 128.1 (2C), 127.4 (2C), 126.2, 121.8, 121.0, 117.8 (2C), 46.7, 41.9 (2C); IR (neat): $\nu =$
3075 (w), 3003 (w), 2978 (w), 2930 (w), 1638 (m), 1586 (s), 1562 (w), 1494 (w), 1469 (m), 1445 (m), 1429 (m), 1149 (w), 1033 (w), 996 (m), 910 (s), 753 (m), 700 (s) cm⁻¹; HRMS (Cl(NH₃)): calcd for (C₂₀H₂₀DN + H): 277.1815; found: 277.1808.

**Compound 132e**

![Compound 132e](image)

Obtained from **S10** (0.56 mmol, 119 mg) following the representative procedure. Colourless oil (86 mg, 52% over four steps); ¹H NMR (500 MHz, CDCl₃): δ = 8.53 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H), 7.58 (dt, J = 7.7, 1.8 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.07 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 6.82 (d, J = 16.5 Hz, 1H), 6.50 (d, J = 16.5 Hz, 1H), 5.94–5.84 (m, 2H), 5.04 (dt, J = 17.1, 1.5 Hz, 2H), 5.00 (dt, J = 10.2, 1.1 Hz, 2H), 3.97–3.88 (m, 4H), 2.49 (dd, J = 14.4, 7.7 Hz, 2H), 2.44 (dd, J = 14.4, 6.8 Hz, 2H), 1.28 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 156.1, 149.4, 139.2, 136.3, 135.5 (2C), 130.1, 121.7, 120.9, 116.5 (2C), 113.1, 64.8 (2C), 50.6, 36.6 (2C), 21.1; IR (neat): ν = 3073 (w), 2979 (m), 2939 (w), 2883 (w), 1638 (w), 1586 (s), 1563 (m), 1469 (m), 1430 (m), 1373 (m), 1304 (w), 1266 (w), 1198 (s), 1149 (m), 1127 (m), 1100 (m), 1083 (m), 1036 (s), 991 (s), 950 (m), 910 (s), 852 (w), 765 (m), 742 (w) cm⁻¹; MS (Cl(CH₄)): m/z (rel. intensity): 286 (100) [M + H]; HRMS (Cl(CH₄)): calcd for (C₁₈H₂₃NO₂ + H): 286.1802; found: 286.1804; elemental analysis (%) calcd for C₁₈H₂₃NO₂: C 75.76, H 8.12, N 4.91; found: C 76.44, H 8.33, N 4.93.
**Compound 132f**

Compound prepared by Daniel J. Tetlow. Yellow oil (320 mg, 60% over four steps); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.50$ (d, $J = 4.6$ Hz, 1H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.60 (td, $J = 7.7$, 1.5 Hz, 1H), 7.21–7.15 (m, 3H), 7.11 (dd, $J = 7.4$, 4.9 Hz, 1H), 6.58 (d, $J = 16.3$ Hz, 1H), 6.44 (d, $J = 16.3$ Hz, 1H), 5.72 (ddt, $J = 17.1$, 10.1 and 7.0 Hz, 2H), 5.10 (d, $J = 16.2$ Hz, 2H), 5.09 (d, $J = 9.7$ Hz, 2H), 2.97 (s, 3H), 2.81 (dd, $J = 14.2$, 7.5 Hz, 2H), 2.64 (dd, $J = 14.2$, 6.4 Hz, 2H), 2.37 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 154.9$, 149.4, 142.7, 139.8, 136.5, 136.4, 133.0 (2C), 130.0, 129.3 (2C), 127.2 (2C), 122.3, 121.6, 118.9 (2C), 66.3, 40.1 (2C), 33.4, 21.4; IR (neat): $\bar{\nu} = 3075$ (w), 2977 (w), 2925 (w), 1584 (m), 1564 (w), 1494 (w), 1469 (m), 1430 (m), 1337 (s), 1304 (m), 1255 (w), 1211 (w), 1153 (s), 1117 (m), 1088 (s), 1049 (w), 1018 (w), 981 (s), 915 (s), 813 (s), 770 (m), 743 (m), 720 (s), 657 (s) cm$^{-1}$; MS (ESI): $m/z$ (rel. intensity): 421 (10) [M + K], 405 (72) [M + Na], 383 (100) [M + H]; HRMS (ESI) calcd for (C$_{22}$H$_{27}$N$_2$O$_2$S + Na): 383.1793; found: 383.1786.

**Compound 132h**

Obtained from S15 (1.23 mmol, 300 mg) following the representative procedure. Yellow oil (199 mg, 64% over four steps); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.56–8.51$ (m, 1H), 7.58 (dt, $J = 7.7$, 1.8 Hz, 1H), 7.23–7.12 (m, 6H), 7.09 (ddd, $J = 7.4$, 4.9, 1.0 Hz, 1H), 6.69 (d, $J = 16.2$ Hz, 1H), 6.28 (d, $J = 16.2$ Hz, 1H), 5.92–5.82 (m, 2H), 5.13–5.05 (m, 4H), 2.78 (s, 2H), 2.31–2.20 (m, 4H);...
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 155.9, 149.4, 141.6, 137.8, 136.4, 134.5$ (2C), $130.8$ (2C), 128.6, 127.7 (2C), 126.1, 121.7, 121.0, 117.9 (2C), 44.5, 43.0, 40.6 (2C); IR (neat): $\tilde{\nu} = 3074$ (w), 3029 9 (w), 3005 (w), 2977 (w), 2922 (w), 2852 (w), 1638 (w) m 1603 (w), 1584 (m), 1563 (w), 1495 (w), 1469 (w), 1454 (w), 1429 (m), 1334 (w), 1304 (w), 1262 (w), 1149 (w), 1088 (w), 1049 (w), 1031 (w), 991 (m), 911 (s), 849 (w), 795 (w), 767 (m), 743 (s), 701 (s), 667 (w) cm$^{-1}$; elemental analysis (%) calcd for C$_{21}$H$_{23}$N: C 87.15, H 8.01, N 4.84; found: C 86.98, H 8.20, N 4.75.

Compound 132i

![Compound 132i](image)

Obtained from S19 (0.80 mmol, 197 mg) following the representative procedure. Yellow oil (146 mg, 57% over four steps); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.54$–8.50 (m, 1H), 7.58 (dt, $J = 7.7, 1.8$ Hz, 1H), 7.34 – 7.28 (m, 4H), 7.28 – 7.22 (m, 2H), 7.08 (ddd, $J = 7.4, 4.9, 1.0$ Hz, 1H), 6.67 (d, $J = 16.3$ Hz, 1H), 6.42 (d, $J = 16.3$ Hz, 1H), 5.77 (ddt, $J = 17.1, 10.0, 7.3$ Hz, 2H), 5.09–4.99 (m, 4H), 4.50 (s, 2H), 3.41 (s, 2H), 2.38–2.27 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 156.0, 149.4, 139.4, 138.7, 136.3, 134.4$ (2C), 128.9, 128.3, 127.5 (2C), 127.4 (2C), 121.7, 121.1, 117.7 (2C), 74.1, 73.3, 43.5, 40.0 (2C); IR (neat): $\tilde{\nu} = 3074$ (w), 3004 (w), 2911 (w), 2857 (m), 1649 (w), 1639 (w), 1585 (s), 1564 (m), 1497 (w), 1470 (m), 1454 (m), 1430 (m), 1363 (w), 1305 (w), 1206 (w), 1095 (s), 1029 (w), 992 (m), 976 (s), 914 (s), 767 (s), 739 (s), 698 (s) cm$^{-1}$; elemental analysis (%) calcd for C$_{22}$H$_{25}$NO: C 82.72, H 7.89, N 4.38; found: C 83.06, H 7.92, N 4.34.
Compound 129

Obtained from S18 (500mg, 1.85 mmol) following the representative procedure. Colourless oil (347 mg, 55% over four steps); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.51\) (d, \(J = 4.2\) Hz, 1H), 7.57 (appt, \(J = 7.7, 1.8\) Hz, 1H), 7.26 – 7.21 (m, 1H), 7.08 – 7.04 (m, 1H), 6.62 (d, \(J = 16.5\) Hz, 1H), 6.40 (d, \(J = 16.5\) Hz, 1H), 5.78 (ddt, \(J = 15.2, 9.9, 7.3\) Hz, 2H), 5.09 – 4.97 (m, 4H), 3.52 (s, 2H), 2.30 (dd, \(J = 13.8, 7.5\) Hz, 2H), 2.25 (dd, \(J = 13.8, 7.2\) Hz, 2H), 0.87 (s, 9H), 0.01 (s, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 156.1, 149.4, 139.3, 136.3, 134.6, 129.0, 121.6, 120.8, 117.5, 66.4, 44.1, 39.5, 25.8, 18.2, -5.6\); IR (neat): \(\tilde{\nu} = 3075\) (w), 3005 (w), 2954 (m), 2928 (m), 2897 (m), 2856 (m), 1639 (w), 1585 (m), 1564 (w), 1470 (m), 1430 (w), 1388 (w), 1361 (w), 1304 (w), 1250 (m), 1147 (w), 1096 (s), 992 (m), 978 (m), 913 (m), 834 (s), 774 (s), 671 (w) cm\(^{-1}\); elemental analysis (%) calcd for C\(_{21}\)H\(_{33}\)NO\(_2\)Si: C 73.41, H 9.68, N 4.08; found: C 73.68, H 7.71, N 4.03.

Compound S23

Under N\(_2\), a solution of LDA (1.41 mmol) (prepared from 0.67 mL of a 2.5 M of nBuLi and 0.20 mL of diisopropylamine in THF (1.8 mL)) at 0 °C, was added to a solution of S22 (155 mg, 1.00 mmol) in THF (0.7 mL) at -78°C. The resulting solution was stirred at -78°C for 1.5 hour then methyl iodide (94 \(\mu\)L, 1.51 mmol) was slowly added. The mixture was allowed to warm to room temperature overnight before being quenched with few drops of a saturated aqueous solution of NH\(_4\)Cl. The mixture was diluted with H\(_2\)O and extracted three times with Et\(_2\)O (5 mL). The organic layer was then washed with H\(_2\)O and a saturated aqueous solution of brine,
dried over Na₂SO₄, filtered and concentrated. Purification by flash chromatography (petroleum ether/ Et₂O: 99/1) afforded 148 mg of a colourless oil which was dissolved in Et₂O (0.8 mL) and added by cannula to a suspension of LiAlH₄ (19 mg, 0.49 mmol) in Et₂O (1.6 mL) at 0°C. After 10 minutes at 0°C another portion of LiAlH₄ (19 mg, 0.49 mmol) was added. After stirring for 1 hour at room temperature, the reaction mixture was quenched carefully at 0°C with a saturated aqueous solution of Na₂SO₄ which resulted in the formation of a white precipitate. After filtration over Celite to remove the white precipitate, the solvent was evaporated under reduced pressure to give 107 mg of alcohol.

Under N₂, DMSO (145 μL, 2.04 mmol) in CH₂Cl₂ (0.8 mL) was added to a solution of oxalyl chloride (88 μL, 1.02 mmol) in CH₂Cl₂ (3.9 mL) at −78°C. After 10 minutes stirring at −78°C, a solution of the alcohol (107 mg, 0.78 mmol) in CH₂Cl₂ (0.8 mL) was added. After 20 minutes stirring at −78°C, triethylamine (0.55 mL, 3.92 mmol) was added rapidly and the mixture was stirred at room temperature during 20 minutes. A saturated solution of NH₄Cl was added to the reaction mixture which was then extracted three times with diethyl ether. The organic layer was washed with H₂O and a saturated solution of aqueous brine, dried over Na₂SO₄, filtered, and concentrated to give 96 mg of aldehyde.

Under N₂, nBuLi (0.39 mL, 0.81 mmol, 2.1 M in hexanes) was added to a -78°C solution of 2-methylpyridine (80 μL, 0.81 mmol) in THF (2.0 mL). After 10 minutes of stirring at -78°C, a solution of aldehyde (82 mg, 0.60 mmol) in THF (1 mL) was added by cannula. After stirring for 15 minutes at -78°C, the reaction was quenched with enough MeOH to turn the deep red solution to yellow and then allowed to warm to room temperature. The crude mixture was then partitioned between a saturated solution of NaHCO₃, water and ethyl acetate and then extracted three times with ethyl acetate (5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (petroleum ether/EtOAc: 5/1) afforded S23 as a clear oil (98 mg, 42% over four steps): ¹H NMR (500 MHz, CDCl₃): δ = 8.48–8.43 (m, 1H), 7.59 (dt, J = 7.6, 1.8 Hz, 1H), 7.15–7.09 (m, 2H), 5.95–5.82 (m, 2H), 5.10–5.00 (m, 4H + 1H(OH)), 3.80 (dd, J = 10.5, 1.7 Hz,
1H), 2.90 (dd, J = 14.6, 1.7 Hz, 1H), 2.80 (d, J = 14.5, 10.4 Hz, 1H), 2.33–2.23 (m, 2H), 2.14 (dd, J = 13.9, 7.5 Hz, 1H), 2.03 (dd, J = 13.7, 7.8 Hz, 1H), 0.94 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 161.0, 148.6, 136.8, 135.4, 135.2, 123.7, 121.4, 117.24, 117.19, 75.7, 40.6, 40.4, 40.2, 37.7, 20.5; IR (neat): $\tilde{\nu}$ = 3351 (br w), 3074 (m), 2975 (m), 2917 (m), 1638 (m), 1597 (s), 1570 (m), 1475 (m), 1438 (s), 1375 (w), 1317 (w), 1145 (w), 1097 (w), 1049 (m), 999 (m), 912 (s), 756 (s) cm$^{-1}$; elemental analysis (%) calcd for C$_{13}$H$_{21}$NO: C 77.88, H 9.15, N 6.05; found: C 77.79, H 9.17, N 5.88.

**Compound 132j**

At 0°C, methanesulfonyl chloride (30 μL, 0.39 mmol) was added dropwise to a solution of S23 (75 mg, 0.32 mmol) and Et$_3$N (68 μL, 0.49 mmol) in CH$_2$Cl$_2$ (0.64 mL). After stirring at room temperature overnight, the crude mixture was partitioned between a saturated solution of NaHCO$_3$ and ethyl acetate, and extracted three times with ethyl acetate (5 mL). The combined organic layers were washed with water, then a saturated aqueous solution of brine, then dried over Na$_2$SO$_4$, filtered and concentrated. Under N$_2$, the residue was dissolved in THF (0.32 mL). At 0 °C, NaHMDS (0.5 mL, 0.49 mmol, 1M in THF) was added. After stirring for 2 hours at room temperature, the reaction mixture was quenched with a saturated solution of NaHCO$_3$ and extracted three times with ethyl acetate and the combined extracts were washed with water, followed by a saturated aqueous solution of brine, then dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (petroleum ether/Et2O: 6/1 \(\rightarrow\) 4/1) afforded 132j as a clear oil (47 mg, 68 %): $^1$H NMR (500 MHz, CDCl$_3$): δ = 8.52 (ddd, J = 4.9, 1.7, 0.8 Hz, 1H), 7.59 (dt, J = 7.7, 1.8 Hz, 1H), 7.27–7.22 (m, 1H), 7.08 (ddd, J = 7.5, 4.9, 1.0 Hz,
1H), 6.69 (d, J = 16.2 Hz, 1H), 6.37 (d, J = 16.1 Hz, 1H), 5.82 – 5.72 (m, 2H), 5.06 – 4.99 (m, 4H),
2.22 (dd, J = 13.7, 7.0 Hz, 2H), 2.15 (dd, J = 13.7, 7.7 Hz, 2H), 1.08 (s, 3H); $^{13}$C NMR (125 MHz,
CDCl$_3$): δ = 156.1, 149.4, 143.0, 136.4, 134.8 (2C), 127.6, 121.6, 121.1, 117.4 (2C), 45.0 (2C),
39.3, 23.3; IR (neat): $\tilde{\nu} = 3075$ (m), 3004 (w), 2976 (m), 2915 (m), 1640 (m), 1585 (s), 1564 (m),
1471 (m), 1430 (s), 1377 (w), 1321 (w), 1149 (w), 992 (m) 913 (s), 766 (m), 742 (w) cm$^{-1}$;
 elemental analysis (%) calcd for C$_{15}$H$_{19}$N: C 84.46, H 8.98, N 6.57; found: C 84.17, H 9.11, N
6.13.

**Compound 135**

![Compound 135](image)

Obtained from S4 (200mg, 0.99 mmol) following the representative procedure, except using
1,2-dimethylimidazole and S24 was isolated as a yellow oil (254 mg, 86%). Afterwards,
methanesulfonyl chloride (37 µL, 0.47 mmol) was added dropwise to a 0°C solution of S24
(71mg, 0.24 mmol) and triethylamine (66 µL, 0.47 mmol) in DCM (0.50 mL). Afterwards, it was
allowed to stir at r.t. for 2 hours. Afterwards, the crude mixture was partitioned between a
saturated solution of NaHCO$_3$ and ethyl acetate. Extracted three times with ethyl acetate and
the combined extracts was washed with H$_2$O, a saturated solution of brine, dried over Na$_2$SO$_4$,
filtered and concentrated. Under N$_2$, the residue was dissolved in THF (0.5 mL). Cooled to 0°C,
NaHMDS (65 mg, 0.35 mmol) was added. It was then allowed to stir overnight at r.t. The
reaction mixture was quenched with a saturated solution of NaHCO$_3$. The crude mixture was
partitioned between water and ethyl acetate. Extracted three times with ethyl acetate and the
combined extracts was washed with H$_2$O, a saturated solution of brine, dried over Na$_2$SO$_4$,
filtered and concentrated. Purification by flash column chromatography (PE/EA : 1/1) afforded
compound 135 as a clear oil (39 mg, 58 %): $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.35 – 7.26 (m, 4H),

309
7.21 – 7.15 (m, 1H), 7.00 (s, 1H), 6.86 (d, J = 16.2 Hz, 1H), 6.81 (s, 1H), 6.25 (d, J = 16.1 Hz, 1H),
5.61 (ddt, J = 17.1, 10.1, 7.1 Hz, 2H), 5.08 – 4.98 (m, 4H), 3.59 (s, 3H), 2.66 (d, J = 7.1 Hz, 1H);
13C NMR (125 MHz, CDCl3): δ = 145.5, 144.5, 141.7, 134.3, 128.3, 128.0, 127.4, 126.1, 121.0, 117.8, 114.9, 46.9, 42.2, 32.7; IR (neat): ṽ = 3346 (br w), 3073 (w), 3006 (w), 2977 (w), 1638 (w), 1598 (w), 1515 (w), 1483 (m), 1444 (m), 1410 (s), 1284 (m), 1187 (w), 1135 (w), 1082 (w), 1033 (w), 996 (m), 975 (m), 912 (s), 843 (w), 826 (w), 769 (m), 734 (m), 698 (s), 657 (w) cm⁻¹; MS (Cl): calcd for (C₁₉H₂₂N₂ + H): 279.1856; found: 279.1854

Preparation³² of [Rh(coe)₂Cl]₂ – To a 3-neck round-bottomed flask containing RhCl₃•3H₂O (175 mg, 0.84 mmol) were sequentially added degassed water (1 mL), degassed iPrOH (4 mL) and cyclooctene (0.56 mL, 4.30 mmol). The resulting dark red solution was heated under reflux for 2 hours. Afterwards, the resulting orange suspension was cooled to room temperature. The precipitate was collected by filtration, washed with cold ethanol, washed with petroleum ether and dried in vacuo to give [Rh(coe)₂Cl]₂ (165 mg, 28 %) as yellow solid. The purity of each batch of this pre-catalyst was assessed by elemental analysis (%) calcd for C₃₂H₅₀Cl₂Rh₂: C 53.57, H 7.87; found: C 52.23, H 7.62.

Representative procedure for the rhodium-catalysed carbocyclisation of 1,6-dienes – [Rh(coe)₂Cl]₂ (2.6 mg, 0.0036 mmol) and P(μMeOC₆H₄)₃ (5.1 mg, 0.0145 mmol) were added to a flame-dried J-Young Schlenk flask under N₂. THF (0.17 mL) was added and the red solution stirred at room temperature for 5 minutes. AgBF₄ (1.4 mg, 0.0073 mmol) in THF (0.1 mL) was added and stirred for 5 minutes. Then, under N₂, 126 (20 mg, 0.0726 mmol) in THF (0.4 mL) was added via cannula, the tube sealed and the reaction heated at 60°C for 17 hours. The reaction mixture was cooled to room temperature, filtered through a small plug of silica (using CH₂Cl₂ to rinse) and the solvent was removed under reduced pressure. Purification by flash
column chromatography (petroleum ether/Et2O, 25:1 → 20:1) afforded 127 as colourless oil (17.7 mg, 89%, 127/128 = 98:2).

**Compound 127**

![Chemical structure of Compound 127]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.48 (ddd, $J = 4.8, 1.7, 0.8$ Hz, 1H), 7.50 (dt, $J = 7.8, 1.8$ Hz, 1H), 7.36–7.31 (m, 4H), 7.25–7.21 (m, 1H), 7.10 (d, $J = 8.1$ Hz, 1H), 6.96 (ddd, $J = 7.4, 4.9, 0.9$ Hz, 1H), 5.75 (t, $J = 2.3$ Hz, 1H), 2.86 (dt, $J = 17.2, 3.5$ Hz, 1H), 2.67 (dt, $J = 17.2, 2.5$ Hz, 1H), 2.23 (d, $J = 4.2$ Hz, 1H), 2.19 (ddd, $J = 11.6, 8.5, 2.5$ Hz, 1H), 1.97 (ddt, $J = 9.8, 2.1, 1.0$ Hz, 1H), 1.93–1.84 (m, 1H), 1.82 (ddd, $J = 9.7, 3.3, 1.7$ Hz, 1H), 1.54 (dd, $J = 11.8, 4.8$ Hz, 1H), 1.02 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 158.2, 157.6, 149.1, 142.8, 135.7, 128.19 (2C), 128.15 (2C), 126.3, 122.7, 120.1, 119.7, 59.6, 43.5, 42.6, 41.2, 40.9, 36.4, 22.3; IR (neat): $\tilde{\nu}$ = 3057 (w), 2951 (m), 2866 (w), 1655 (w), 1585 (s), 1559 (w), 1497 (w), 1471 (m), 1445 (w), 1427 (m), 1375 (w), 1346 (w), 1317 (w), 1260 (w), 1236 (w), 1220 (w), 1184 (w), 1148 (w), 1081 (w), 1061 (w), 1035 (w), 991 (w), 961 (w), 920 (w), 894 (w), 864 (w), 778 (w), 758 (m), 741 (m), 699 (s), 659 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{20}$H$_{21}$N + H): 276.1755; found: 276.1752.

**Compound 128**

![Chemical structure of Compound 128]

This compound could be isolated by preparative TLC during the optimisation study. Colourless oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.60 (ddd, $J = 4.8, 1.7, 0.8$ Hz, 1H), 7.61 (dt, $J = 7.7, 1.8$ Hz, 1H), 7.43–7.38 (m, 2H), 7.30–7.25 (m, 3H), 7.19–7.14 (m, 1H), 7.06 (ddd, $J = 7.4, 4.9, 0.8$ Hz, 1H), 6.98 (ddd, $J = 8.1, 3.5, 0.8$ Hz, 1H), 5.77 (t, $J = 2.3$ Hz, 1H), 2.86 (dt, $J = 17.2, 3.5$ Hz, 1H), 2.67 (dt, $J = 17.2, 2.5$ Hz, 1H), 2.23 (d, $J = 4.2$ Hz, 1H), 2.19 (ddd, $J = 11.6, 8.5, 2.5$ Hz, 1H), 1.97 (ddt, $J = 9.8, 2.1, 1.0$ Hz, 1H), 1.93–1.84 (m, 1H), 1.82 (ddd, $J = 9.7, 3.3, 1.7$ Hz, 1H), 1.54 (dd, $J = 11.8, 4.8$ Hz, 1H), 1.02 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 158.2, 157.6, 149.1, 142.8, 135.7, 128.19 (2C), 128.15 (2C), 126.3, 122.7, 120.1, 119.7, 59.6, 43.5, 42.6, 41.2, 40.9, 36.4, 22.3; IR (neat): $\tilde{\nu}$ = 3057 (w), 2951 (m), 2866 (w), 1655 (w), 1585 (s), 1559 (w), 1497 (w), 1471 (m), 1445 (w), 1427 (m), 1375 (w), 1346 (w), 1317 (w), 1260 (w), 1236 (w), 1220 (w), 1184 (w), 1148 (w), 1081 (w), 1061 (w), 1035 (w), 991 (w), 961 (w), 920 (w), 894 (w), 864 (w), 778 (w), 758 (m), 741 (m), 699 (s), 659 (w) cm$^{-1}$; HRMS (ESI): calcd for (C$_{20}$H$_{21}$N + H): 276.1755; found: 276.1752.
1H), 6.44 (t, J = 2.5 Hz, 1H), 5.80–5.69 (m, 1H), 5.04 (ddt, J = 17.1, 1.9, 1.4 Hz, 1H), 5.00 (ddt, J = 10.2, 2.1, 1.0 Hz, 1H), 2.89–2.82 (m, 2H), 2.75 (ddt, J = 14.2, 7.4, 1.0 Hz, 1H), 2.64 (ddt, J = 14.2, 6.6, 1.3 Hz, 1H), 2.21 (ddd, J = 12.6, 6.5, 3.6 Hz, 1H), 1.87 (ddd, J = 12.7, 10.1, 7.1 Hz, 1H), 1.80–1.70 (m, 1H), 1.64–1.50 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ = 157.2, 156.1, 149.2, 146.1, 135.9, 135.6, 128.1 (2C), 127.1 (2C), 125.9, 123.5, 123.4, 120.5, 117.2, 55.8, 44.9, 37.7, 32.3, 22.1; HRMS (ESI): calcd for (C\(_{20}\)H\(_{21}\)N + H): 276.1752; found: 276.1751.

**Compound 140 and 141**

![Compound 140 and 141](image)

Obtained from **139** (0.071 mmol, 19.6 mg) following the representative procedure. Colourless oil (19.6 mg, quantitative); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ = 8.48 (ddd, J = 4.8, 1.6, 0.7 Hz, 1H), 7.51 (dt, J = 7.8, 1.8 Hz, 1H), 7.37–7.31 (m, 4H), 7.26–7.21 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.96 (ddd, J = 7.4, 4.8, 0.9 Hz, 1H), 5.77–5.74 (m, 1H), 2.86 (dt, J = 17.3, 3.4 Hz, 0.8H), 2.67 (dt, J = 17.3, 2.5 Hz, 0.8H), 2.25–2.21 (m, 1H), 2.18 (ddd, J = 11.6, 8.5, 2.5 Hz, 1H), 1.99–1.94 (m, 1H), 1.93–1.84 (m, 1H), 1.82 (ddd, J = 9.7, 3.1, 1.5 Hz, 1H), 1.54 (dd, J = 11.8, 4.9 Hz, 1H), 1.05–0.98 (m, 2.4H); \(^2\)D NMR (77 MHz, CDCl\(_3\)): δ = 2.86 (s, 0.2D), 2.78 (s, 0.2D), 1.04 (s, 0.6D); \(^{13}\)C NMR (125 MHz, CDCl\(_3\))\(\uparrow\): δ = 158.20, [158.16], 157.6, 149.1, 142.7, 135.7, 128.17 (2C), 128.14 (2C), 126.3, 122.6, 120.1, [119.71], 119.66, 59.6, [43.47], 43.43, 42.51, [42.45], 41.2, 40.9, [40.5 (t, J = 20.3 Hz)], [36.32], 36.26, [22.3], 22.0 (t, J = 19.2 Hz); IR (neat): \(\tilde{\nu}\) = 3057 (w), 3002 (w), 2949 (s), 2866 (w), 2165 (w), 1655 (m), 1602 (w), 1585 (s), 1559 (w), 1497 (w), 1471 (m), 1446 (w), 1427 (s), 1375 (w), 1318 (w), 1257 (w), 1234 (w), 1220 (w), 1148 (w), 1086 (w), 1060 (w), 1036 (w), 990 (w), 958 (w), 890 (w), 864 (w), 776 (w), 758 (s), 741 (m), 699 (s) cm\(^{-1}\); MS (Cl(CH\(_3\))):
$m/z$ (rel. intensity): 277 (70) [M + H], 169 (100); HRMS (Cl(CH$_4$)): calcd for (C$_{20}$H$_{20}$DN + H): 277.1815; found: 277.1805.

^ As easily established by comparison of $^{13}$C NMR APT, HSQC and HMBC NMR of 127 and the mixture of 140 and 141, the chemical shifts in brackets correspond to the mono-deuterated isomer for which the deuterium atom is incorporated at the position indicated by a star.

**Hydrochloride salt of compound 127**

127 (20 mg, 0.073 mmol) was dissolved in Et$_2$O (0.2 mL). Then 3 drops of conc. HCl solution were added to give a white suspension. After mixing vigorously for 5 minutes, all volatiles were removed. The residue was dissolved in a vial with CH$_2$Cl$_2$ (1 mL) and then petroleum ether (5 mL) so that the two layers do not mix. All volatiles evaporated slowly at room temperature at atmospheric pressure to give brown crystals which were washed with diethyl ether to give brown crystals which were suitable for X-ray crystallography (15 mg, 66 %). mp.: 167–174°C (decomposition); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.71–8.54 (m, 1H), 8.19–8.06 (m, 1H), 7.67–7.56 (m, 1H), 7.53–7.44 (m, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.4 Hz, 3H), 6.37–6.29 (m, 1H), 2.94 (d, J = 16.1 Hz, 1H), 2.66 (d, J = 16.1 Hz, 1H), 2.34 (s, 1H), 2.28–2.19 (m, 1H), 2.06 (d, J = 9.7 Hz, 1H), 1.97–1.86 (m, 2H), 1.61 (dd, J = 12.0, 4.5 Hz, 1H), 1.05 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 170.3, 151.6, 144.2, 141.5 (br), 140.1, 128.7 (2C), 128.0 (2C), 127.3, 124.8, 122.7, 111.9, 61.0, 43.3, 42.2, 41.3, 41.1, 35.9, 22.0; IR (neat): $\tilde{\nu}$ = 3086 (w), 3040 (w), 2958 (w), 2916 (w), 2862 (w), 2266 (m), 2209 (m), 2041 (m), 1980 (m), 1933 (m), 1650 (m), 1608 (s), 1528 (m), 1496 (m), 1456 (m), 1444 (m), 1399 (w), 1371 (m), 1323 (w), 1290 (m), 1251 (w), 1233 (w), 1155 (m), 1141 (w), 1096 (w), 1064 (w), 1038 (w), 1025 (w), 988 (m), 961 (w), 950 (w), 923 (w), 896 (w), 882 (w), 871 (w), 847 (w), 827
(w), 814 (w), 772 (s), 763 (s), 702 (s), 659 (w) cm\(^{-1}\); elemental analysis (%) calcd for C\(_{20}\)H\(_{22}\)ClN: C 77.03, H 7.11, N 4.49; found: C 76.49, H 7.06, N 4.41.

**Compound 133e**

Obtained from 132e (0.070 mmol, 20 mg) following the representative procedure. Colourless oil (18 mg, 88%); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.54\) (ddd, \(J = 4.8, 1.8, 0.8\) Hz, 1H), 7.55 (dt, \(J = 7.7, 1.9\) Hz, 1H), 7.22 (d, \(J = 8.1\) Hz, 1H), 6.98 (ddd, \(J = 7.4, 4.9, 1.0\) Hz, 1H), 6.79 (t, \(J = 2.3\) Hz, 1H), 4.07–3.88 (m, 4H), 2.71 (dt, \(J = 17.1, 3.4\) Hz, 1H), 2.61 (dt, \(J = 17.1, 2.5\) Hz, 1H), 2.04 (d, \(J = 3.9\) Hz, 1H), 1.74 (ddd, \(J = 9.6, 3.4, 1.8\) Hz, 1H), 1.73–1.67 (m, 1H), 1.62 (ddd, \(J = 11.4, 8.4, 2.4\) Hz, 1H), 1.45 (s, 3H), 1.44–1.38 (m, 2H), 0.97 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 158.1, 152.8, 149.0, 135.7, 123.1, 120.2, 120.0, 110.9, 65.2, 64.5, 63.0, 42.3, 42.0, 38.9, 38.6, 35.8, 22.2, 21.7\); IR (neat): \(\tilde{\nu} = 3052\) (w), 2950 (s), 2871 (m), 1650 (m), 1585 (s), 1558 (w), 1470 (m), 1428 (s), 1371 (m), 1321 (w), 1287 (w), 1264 (m), 1239 (w), 1216 (w), 1198 (s), 1161 (s), 1111 (m), 1090 (m), 1075 (w), 1063 (m), 1040 (s), 992 (w), 943 (w), 920 (w), 899 (m), 870 (m), 812 (w), 779 (m), 761 (w), 741 (m), 658 (w) cm\(^{-1}\); HRMS (Cl(CH\(_4\))): calcd for (C\(_{18}\)H\(_{23}\)NO\(_2\) + H): 286.1802; found: 286.1000.
Compound 133f

Compound prepared by Daniel J. Tetlow. Obtained from 132f (0.146 mmol, 56 mg) following the representative procedure. Colourless gum (43 mg, 76%);\(^\text{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.54\ (dd, J = 4.8\ and\ 1.0\ Hz,\ 1\ H),\ 7.73\ (d, J = 8.1\ Hz,\ 2\ H),\ 7.55\ (td, J = 7.8, 1.8\ Hz,\ 1\ H),\ 7.26\ (d, J = 8.1\ Hz,\ 2\ H),\ 7.13\ (d, J = 7.9\ Hz,\ 1\ H),\ 7.02\ (ddd, J = 7.3, 4.8, 0.6\ Hz,\ 1\ H),\ 6.38\ (t, J = 2.2\ Hz,\ 1\ H),\ 3.11\ (s, 3\ H),\ 2.77–2.62\ (m,\ 2\ H),\ 2.39\ (s, 3\ H),\ 2.19\ (ddd, J = 11.2, 8.4, 2.4\ Hz,\ 1\ H),\ 1.97\ (d, J = 2.6\ Hz,\ 1\ H),\ 1.86\ (d, J = 9.5\ Hz,\ 1\ H),\ 1.81–1.72\ (m,\ 1\ H),\ 1.58\ (dd, J = 8.8, 5.0\ Hz,\ 1\ H),\ 1.57–1.53\ (m,\ 1\ H),\ 0.88\ (d, J = 6.9\ Hz,\ 3\ H);\ ^{13}\text{C}\ NMR\ (125\ MHz,\ CDCl_3):\ \delta = 159.9,\ 149.7,\ 149.0,\ 142.8,\ 139.5,\ 135.9,\ 129.5\ (2\ C),\ 126.8\ (2\ C),\ 123.6,\ 120.4,\ 118.4,\ 74.9,\ 43.2,\ 39.81,\ 39.76,\ 38.9,\ 35.7,\ 35.4, 22.1,\ 21.4;\ IR\ (neat):\ \tilde{\nu} = 2954\ (w),\ 2923\ (w),\ 2868\ (w),\ 1666\ (w),\ 1585\ (m),\ 1560\ (w),\ 1494\ (w),\ 1470\ (m),\ 1428\ (m),\ 1377\ (w),\ 1336\ (s),\ 1306\ (s),\ 1280\ (w),\ 1225\ (w),\ 1151\ (s),\ 1119\ (w),\ 1089\ (s),\ 1042\ (s),\ 1016\ (w),\ 982\ (w),\ 902\ (m),\ 842\ (s),\ 812\ (s),\ 778\ (m),\ 759\ (w),\ 741\ (m),\ 706\ (w),\ 661\ (s)\ cm^{−1};\ HRMS\ (ESI):\ \text{calcd\ for\ (C}_{22}\text{H}_{27}\text{N}_{2}\text{O}_{2}\text{S}\ +\ H):\ 383.1793;\ \text{found:}\ 383.1783.

\(^\text{1}\)Over time, we observed a small doublet appearing at 2.64 ppm (\(J = 5.4\ Hz\)) in \(^{1}\text{H}\) NMR which could correspond to the Me-N of a minor impurity where the tosyl group is cleaved. A small peak (ESI) with the expected \(m/z = 228\ [M – Ts + H]\) also confirms this analysis.
Obtained from 132h (0.070 mmol, 20.3 mg) following the representative procedure, except that P(pMeOC₆H₄)₃ (3.6 mg, 0.0101 mmol) was used. Colourless oil. (17 mg, 83%, 133h/134h = 95:5); ¹H NMR (500 MHz, CDCl₃): δ = 8.55 (ddd, J = 4.9, 1.7, 0.8 Hz, 1H), 7.59 (dt, J = 7.7, 1.9 Hz, 1H), 7.29–7.24 (m, 3H), 7.21–7.16 (m, 3H), 7.02 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 6.44–6.40 (m, 1H), 3.05 (d, J = 13.4 Hz, 1H), 2.99 (d, J = 13.4 Hz, 1H), 2.67 (dt, J = 17.1, 3.4 Hz, 1H), 2.57 (dt, J = 16.9, 2.5 Hz, 1H), 1.98 (d, J = 4.1 Hz, 1H), 1.72–1.62 (m, 1H), 1.50 (ddd, J = 11.7, 8.5, 2.5 Hz, 1H), 1.33 (ddd, J = 9.8, 3.1, 1.7 Hz, 1H), 1.26–1.21 (m, 1H), 1.06 (dd, J = 11.8, 4.9 Hz, 1H), 0.77 (d, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 157.7, 156.9, 149.2, 139.7, 135.8, 131.0 (2C), 127.8 (2C), 125.8, 122.5, 120.2, 117.7, 55.3, 42.7, 41.8, 41.7, 39.3, 38.2, 36.0, 22.0; IR (neat): ν = 3061 (w), 3027 (w), 3002 (w), 2950 (m), 2866 (w), 1655 (m), 1603 (w), 1585 (s), 1559 (w), 1496 (w), 1471 (m), 1454 (w), 1428 (m), 1375 (w), 1346 (w), 1308 (w), 1276 (w), 1221 (w), 1149 (w), 1096 (w), 1062 (w), 1031 (w), 991 (w), 889 (w), 858 (w), 804 (w), 771 (w), 754 (m), 741 (w), 702 (s), 658 (w) cm⁻¹; HRMS (ESI): calcd for (C₂₁H₂₄N + H): 290.1911; found: 290.1909; elemental analysis (%) calcd for C₂₁H₂₃N: C 87.15, H 8.01, N 4.84; found: C 86.55, H 8.13, N 4.63.
Compound 133i

Obtained from 132i (0.070 mmol, 22.4 mg) following the representative procedure (15.9 mg, 71%, 133i/134i = 2:1). Isomers 133i and 134i could be separated by preparative TLC (petroleum ether/EtOAc = 14:1). Colourless oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.54–8.49 (m, 1H), 7.56 (dt, $J$ = 7.7, 1.8 Hz, 1H), 7.38–7.30 (m, 4H), 7.29–7.24 (m, 1H), 7.21 (d, $J$ = 8.0 Hz, 1H), 6.99 (ddd, $J$ = 7.4, 4.9, 0.7 Hz, 1H), 6.25–6.23 (m, 1H), 4.60 (s, 2H), 3.77 (d, $J$ = 9.6 Hz, 1H), 3.73 (d, $J$ = 9.6 Hz, 1H), 2.68 (dt, $J$ = 17.1, 3.5 Hz, 1H), 2.53 (dt, $J$ = 17.1, 2.5 Hz, 1H), 2.08 (d, $J$ = 4.1 Hz, 1H), 1.77–1.68 (m, 1H), 1.64 (ddd, $J$ = 9.7, 3.2, 1.6 Hz, 1H), 1.56 (ddd, $J$ = 11.9, 8.5, 2.4 Hz, 1H), 1.41–1.36 (m, 1H), 1.26 (dd, $J$ = 11.9, 4.9 Hz, 1H), 0.98 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 157.6, 154.1, 149.1, 138.8, 135.8, 128.3 (2C), 127.5 (2C), 127.4, 122.5, 120.2, 117.7, 73.4, 71.2, 55.3, 42.5, 41.4, 41.2, 38.8, 36.0, 22.2; IR (neat): $\tilde{\nu}$ = 3058 (w), 303 (w), 3002 (w), 2950 (s), 2864 (m), 1720 (w), 1658 (m), 1585 (s), 1559 (w), 1495 (w), 1470 (m), 1454 (m), 1428 (s), 1364 (w), 1271 (w), 1205 (w), 1148 (w), 1093 (s), 1028 (w), 927 (w), 889 (w), 857 (w), 739 (s), 697 (m); MS (ESI): calcd for (C22H25NO + H): 320.2014; found: 320.2013.

Compound 134i

Colourless oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.55 (ddd, $J$ = 4.7, 1.6, 0.8 Hz, 1H), 7.58 (dt, $J$ = 7.8, 1.8 Hz, 1H), 7.33–7.28 (m, 4H), 7.27–7.20 (m, 2H), 7.02 (ddd, $J$ = 7.5, 4.8, 1.0 Hz, 1H), 6.37 (t, $J$ = 2.4 Hz, 1H), 5.85–5.73 (m, 1H), 5.08–4.97 (m, 2H), 4.53 (d, $J$ = 12.4 Hz, 1H), 4.49 (d, $J$ =
12.4 Hz, 1H), 3.36 (s, 2H), 2.90–2.81 (m, 1H), 2.80–2.70 (m, 1H), 2.47 (dd, \( J = 13.8, 8.0 \) Hz, 1H), 2.35 (dd, \( J = 13.8, 6.6 \) Hz, 1H), 1.84–1.62 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 157.5, 155.2, 149.1, 138.8, 135.4, 128.3 (2C), 127.4 (2C), 127.3, 123.2, 122.0, 120.4, 117.3, 76.4, 73.3, 51.5, 41.5, 33.5, 33.4, 23.5; \) IR (neat): \( \tilde{\nu} = 3065 \) (w), 2020 (w), 3004 (w), 2951 (w), 2856 (w), 1647 (w), 1584 (m), 1559 (w), 1496 (w), 1471 (m), 1454 (w), 1427 (m), 1360 (w), 1287 (w), 1218 (w), 1204 (w), 1148 (w), 1094 (s), 1028 (w), 991 (w), 911 (m), 890 (w), 864 (w), 818 (w), 775 (w), 736 (s), 696 (s) \( \text{cm}^{-1} \); elemental analysis (%): calcd for C\(_{22}\)H\(_{25}\)NO: C 82.72, H 7.89, N 4.38; found: C 82.64, H 7.99, N 4.12.

**Compound 133j**

![](image)

Obtained from 132j (0.080 mmol, 17.1 mg) following the representative procedure, except that P(pMeOC\(_6\)H\(_4\))\(_3\) (3.6 mg, 0.0101 mmol) was used. Colourless oil (12.3 mg, 72%, 133j/134j = 3:1, not separable); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 8.53–8.50 \) (m, 1H), 7.56 (dt, \( J = 7.8, 1.8 \) Hz, 1H), 7.27–7.22 (m, 1H), 6.98 (ddd, \( J = 7.4, 4.9, 0.9 \) Hz, 1H), 6.27–6.24 (m, 1H), 2.64 (dt, \( J = 17.1, 3.5 \) Hz, 1H), 2.50 (dt, \( J = 17.1, 2.5 \) Hz, 1H), 2.04 (d, \( J = 4.2 \) Hz, 1H), 1.76–1.62 (m, 1H), 1.57 (ddd, \( J = 11.8, 8.5, 2.5 \) Hz, 1H), 1.52 (ddd, \( J = 9.6, 3.1, 1.5 \) Hz, 1H), 1.31 (s, 3H), 1.27–1.22 (m, 1H), 1.04 (dd, \( J = 11.9, 4.9 \) Hz, 1H), 0.96 (d, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 157.8, 157.5, 149.1, 135.8, 122.3, 120.0, 117.0, 51.0, 46.0, 42.7, 42.6, 41.0, 36.8, 22.3, 18.1; \) IR (neat): \( \tilde{\nu} = 3073 \) (w), 3003 (s), 2868 (w), 1731 (w), 1657 (m), 1585 (s), 1559 (w), 1471 (m), 1463 (m), 1427 (s), 1375 (w), 1316 (w), 1279 (w), 1265 (w), 1227 (w), 1149 (w), 1088 (w), 1061 (w), 989 (w), 966 (w), 912 (w), 887 (w), 858 (w), 823 (w), 775 (m), 740 (m) \( \text{cm}^{-1} \); \) HRMS (Cl(CH\(_4\))): calcd for (C\(_{15}\)H\(_{19}\)N + H): 214.1590; found: 214.1594.

\(^{1}\)IR recorded and HRMS recorded on the 133j/134j mixture

318
**Compound 134j**

![Compound 134j](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.57–8.53$ (m, 1H), 7.61 – 7.54 (m, 1H), 7.27 – 7.22 (m, 1H), 7.00 (ddd, $J = 7.5$, 5.0, 0.9 Hz, 1H), 6.29 (t, $J = 2.4$ Hz, 1H), 5.84–5.73 (m, 1H), 5.06–4.98 (m, 2H), 2.92–2.82 (m, 1H), 2.80–2.69 (m, 1H), 2.26 – 2.15 (m, 2H), 1.80–1.63 (m, 3H), 1.48–1.41 (m, 1H), 1.13 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 159.3$, 157.7, 149.1, 135.8, 135.6, 122.9, 120.5, 120.2, 116.9, 47.1, 45.4, 38.0, 32.6, 26.6, 23.0.

**Compound 137**

![Compound 137](image)

Compound prepared by Daniel J. Tetlow. Obtained from 132f (0.117 mmol, 45 mg) using the representative procedure for the Rh(I)-catalysed cycloisomerisation, except that the reaction was stopped after 30 minutes heating. Purification by flash column chromatography (petroleum ether/EtOAc, 10:1) yielded the title compound as colourless oil (15 mg, 33%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.53$ (ddd, $J = 4.7$, 1.6 and 0.7 Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.59 (td, $J = 7.7$, 1.6 Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 7.8$ Hz, 1H), 7.06 (ddd, $J = 7.5$, 4.7, 0.8 Hz, 1H), 6.50 (d, $J = 2.2$ Hz, 1H), 5.90–5.79 (m, 1H), 5.18–5.12 (m, 1H), 5.09 (dt, $J = 10.2$, 0.8 Hz, 1H), 3.26–3.15 (m, 1H), 2.92 (s, 3H), 2.94–2.86 (m, 1H), 2.77 (dd, $J = 13.9$, 8.5 Hz, 1H), 2.55 (dd, $J = 12.8$, 9.0 Hz, 1H), 2.38 (s, 3H), 2.27 (dd, $J = 12.8$, 5.3 Hz, 1H), 1.12 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 155.2$, 152.0, 149.5, 143.0, 138.6, 136.1, 133.8, 129.4 (2C), 127.3 (2C), 127.1, 123.0, 121.4, 118.9, 68.6, 42.5, 37.0, 34.6, 33.6, 21.5, 18.5; IR (neat) $\tilde{\nu} = 3074$ (w),
2958 (w), 2869 (w), 1665 (w), 1638 (w), 1584 (m), 1563 (w), 1494 (w), 1469 (m), 1430 (m), 1329 (s), 1304 (m), 1289 (m), 1270 (w), 1214 (w), 1184 (w), 1150 (s), 1086 (s), 1018 (w), 993 (w), 893 (s), 846 (m), 813 (s), 743 (s), 707 (m), 688 (w), 658 (s) cm⁻¹; MS (ESI): m/z (rel. intensity): 421 (12) [M + K], 405 (27) [M + Na], 383 (100) [M + H]; HRMS (ESI) calcd for (C₂₂H₂₆N₂O₂S + H): 383.1793, found: 383.1792.
Table 14 Crystal data and structure refinement for Hydrochloride salt of 127

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<th>Property</th>
<th>Value</th>
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<td>Final R indexes [all data]</td>
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4.10 References


