Synthesis of Diverse Metalloid Scaffolds *via* Transition Metal Catalysis

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This dissertation is submitted for the degree of Doctor of Philosophy

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Department of Chemistry

Declaration

This thesis has not been submitted in support of an application for another degree at this or any other university. It is the result of my own work and includes nothing that is the outcome of work done in collaboration. Many of the ideas presented in this thesis were the outcome of discussion with my supervisor Dr Mark McLaughlin.

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Abstract

The work within this thesis describes developments in platinum catalysed hydrometallation for the synthesis of a range of diverse metalloid scaffolds.

Chapter 1 contains a discussion of the application of organometalloid scaffolds in modern organic chemistry, as well as the widespread application of platinum complexes in the synthesis of said scaffolds. Notable developments in the field are summarised and the generally accepted mechanisms through which these reactions proceed are discussed.

Chapter 2 examines the limitations of previous platinum complexes in catalysing selective hydrosilylations and the reasons for these limitations, as well as discussing the approaches to, and applications of, allylic amines in organic chemistry. The development of a $PtCl_2$Xantphos catalyst to selectively carry out the hydrosilylation of propargylic amines and their derivatives is detailed as well as an investigation of the substrate scope. The synthetic utility of the products is investigated resulting in the development of a remarkably mild aziridination procedure.

Chapter 3 builds on the previous aziridination procedure, demonstrating the applicability of the same sequence to access a range of diverse oxetanes by a hydrosilylation/cyclisation sequence. Previous approaches to oxetanes are discussed, as well as the utility of the scaffold in modern organic and medicinal chemistry. Attempts to expand the methodology to the synthesis of other heterocycles is also discussed.

Chapter 4 details the study of platinum complexes in the context of hydrostannylation chemistry. Previous approaches to the scaffold are discussed, as well as the surprising lack of platinum-based catalyst systems. The effect of ligand denticity on stereoselectivity is reported, with a ligand controlled stereodivergency reported. Using a $PtCl_2(XPhos)_2$ catalyst system, a range of diverse organotin scaffolds are synthesized, and the benefits and limitations of the system in comparison to previous catalysts is discussed. A telescoped

hydrometallation/cross-coupling sequence is developed to minimize the need to handle relatively unstable and toxic stannylated intermediates.

Chapter 5 explores the application of platinum complexes bearing both NHC and phosphine ligands as hydrosilylation catalysts. The synthesis of a broad range of imidazolium salts is presented, alongside the synthesis of several platinum complexes *via* an organosilver intermediate. The efficacy of the complexes towards hydrosilylation is evaluated, and their poor performance rationalized in the context of similar complexes employed in the literature.

Chapter 6 provides overall conclusions from the work presented as well as a discussion of further avenues of study.

Chapter 7 provides bibliographic data for the thesis. Relevant characterisation data for novel compounds or compounds prepared by novel routes can be found at the end of the relevant chapter.

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Firstly, I would like to extend my gratitude to my supervisor, Dr Mark McLaughlin, for his guidance throughout the project, in addition to his significant support in my development as an organic chemist and in achieving my career aspirations. A sincere thank you must also be extended to Dr Thomas Britten as his committed and robust approach to teaching was invaluable to my growth during his time in the group. I would also like to express my appreciation for Dr Andrew Lewis for his frequent encouragement throughout my graduate studies. I would like the extend thanks to my appraisal panel members Dr Julien Doulcet and Dr Michael Peach. I would like to thank Lancaster University for funding my studies. I would also like to acknowledge the various people I have worked with throughout the course of my PhD in Manchester, Lancaster and Belfast.

I would like to thank my parents, Shirley and Mark, for their love and support throughout not only my graduate studies, but my life and career up until this point, and this PhD is as much their achievement as my own. Thank you to my grandparents, Carol, Harold, Sheila & Brian- while sadly not all of them are here to see this completed, their love and support is felt, nonetheless. I would also like to thank Jodie, Darren, Lia, Lexi, Frankie, Hallie and Ronnie for their support throughout. I also would like to thank my partner Hayley for her support throughout the PhD and for tolerating my almost daily chemistry related moaning, and I look forward to life up north as an adopted Scot!

Clearly, these acknowledgements cannot be finished without mentioning my friends. Karl, Luke, Adam, Matt, Keith, Jack & Dave, you have all helped to no end throughout the course of all of this. I wouldn’t have come this far on my own, and I wouldn’t trade you for the world.

Juggling postgraduate studies with two changes in department and the global COVID-19 pandemic certainly makes for an atypical approach to things, but all things considered, an enjoyable one, and in the end, we got there, even if it was the long way round.

List of Abbreviations

Ac	Acetyl
ADMET	Absorption, Distribution, Metabolism, Excretion & Toxicity
Aq	Aqueous
Ar	Unspecified aryl group
BINAP	[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
bp	Boiling point
Bpin	1,3,2-dioxaborolane
br	Broad
Bu	Butyl
c	Concentration
C	Celcius
COSY	Correlation Spectroscopy
Cy	Cyclohexane
d	doublet
D	Dimensional
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DavePhos	2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPP	1,3-bis(diphenylphosphino)propane
DPPF	1,3-bis(diphenylphosphino)propane
EDG	Electron donating group
ee	Enantiomeric excess
ESI	Electrospray ionization

Et	Ethyl
FTIR	Fourier transform infrared
h	Planck's constant (6.626 x 10^{-34} Js)
HEP	Huynh Electronic Parameter
HMBC	Heteronuclear multiple-bond coherence
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IR	Infrared
ISC	Intersystem crossing
J	Coupling constant
JohnPhos	(Biphenyl)di-tert-butylphosphine
LED	Light-emitting diode
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
M	Molar
m	CPBA *meta*-chloroperoxybenzoic acid
Me	Methyl
Mes	Mesitylene
MIDA	Methyliminodiacetic acid
min	Minutes
mL	Millilitre
mmol	Millimole
Ms	Methanesulfonyl (mesyl)
MS	Mass spectrometry
MTBE	Methyl *tert*-butyl ether
m	Z mass/charge (mass spectrometry)
NBS	*N*-bromosuccinimide
NBS	*N*-chlorosuccinimide
NHC	*N*-Heterocyclic Carbene

NIS	*N*-Iodosuccinimide
NMO	*N*-methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
nOesy	Nuclear overhauser effect spectroscopy
Ph	Phenyl
PMB	*Para*-methoxybenzyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine
q	Quartet
R	Unspecified group
Rf	Retention factor
RT	Room temperature
s	Singlet
SAR	Structure-activity relationship
SCXRD	Single Crystal X-Ray diffraction
SEGPHOS	H,2'H-[4,4'-Bi-1,3-benzodioxole]-5,5'-diyl)bis(diphenylphosphane)
SPhos	Dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-2-yl)phosphane
t	Triplet
TAZY	Triazolin-5-ylidene
tBu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
tBuXPhos	Ditertbutyll[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane
tert	Tertiary
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMDS	Tetramethyldisiloxane
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl

TMVDS	Tetramethylvinyldisiloxane
Ts	Toluenesulfonyl (tosyl)
TT	Thianthrene
UV	Vis ultraviolet-visible
XantPhos	Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)
XPhos	Dicyclohexyl[2’,4’,6’-tris(propan-2-yl)[1,1’-biphenyl]-2-yl]phosphane
°	Degrees
ν	Frequency
Δ	Heat
δ	Chemical shift
‡	Transition State

Chapter 1: Applications and Synthesis of Organometalloid Reagents in Modern Organic Synthesis

1.1 Applications of and Synthetic Approaches Towards Organometalloid Reagents

In recent years, transition metal catalysed cross-coupling reactions between aryl halides and organometalloid compounds have underpinned the development and synthesis of medicinally relevant compounds.[1-3] The prevalence of these types of reactions in drug discovery can be seen in the increase in utility of the Suzuki reaction in 2014 versus 1984 (**Figure 1**).[4] The widespread utility of cross-coupling reactions in modern synthetic chemistry can be rationalised predominantly by the commercial availability of aryl halides which allows for the rapid diversification of a compound to afford a library of derivatives. While aryl halides are widely commercially available, the commercial availability of compounds featuring a Csp^2-M bond (where M=B, Si, Sn…) is much lower and as such the cost of these types of reagents is generally significantly higher. For example, comparison of the price between bromobenzene and (pinacolboryl)benzene from Sigma Aldrich shows the cost of the boronic ester per mole is approximately 155 times the cost of the halide even for a relatively simple borylated building block.

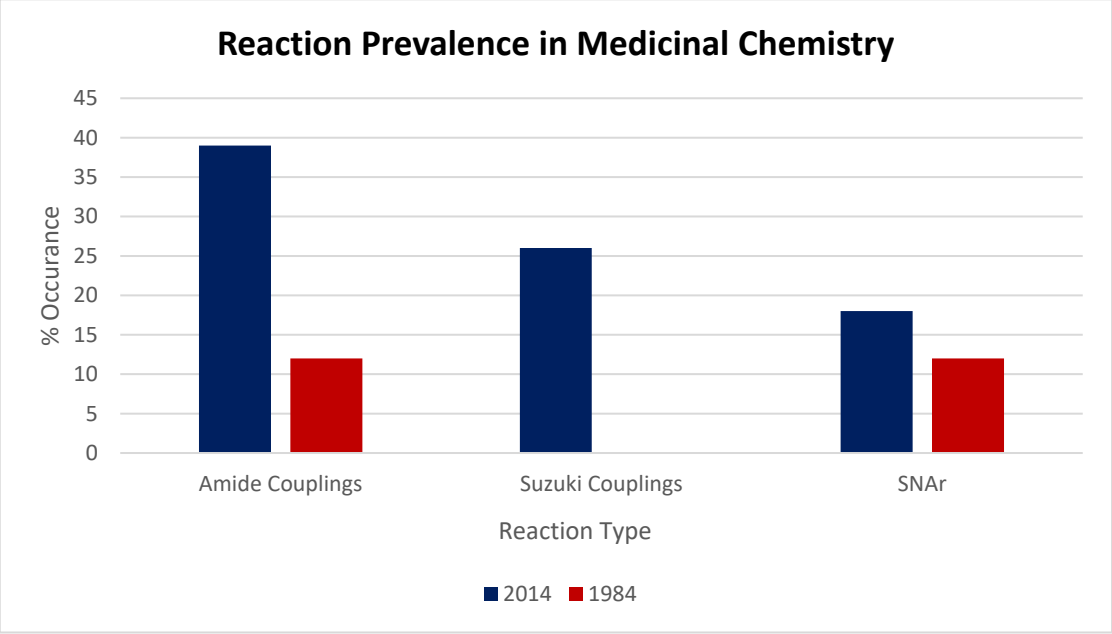
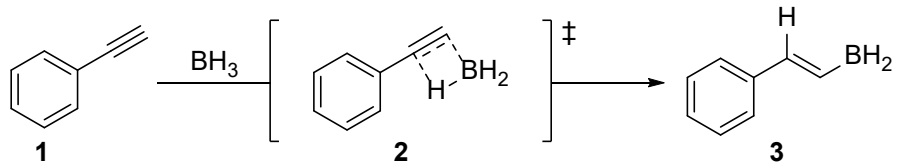


Figure 1 Reaction prevalence in medicinal chemistry as defined by percentage of manuscripts (n=125) featuring said reaction type. Adapted from literature sources.[4]

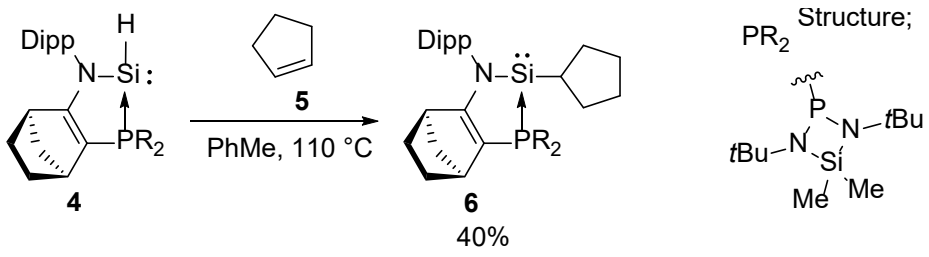
As such, a variety of methodologies have been developed to allow for facile access to metalated building blocks. These developed methodologies range from relatively intuitive approaches, such as lithiation of an aryl or vinyl halide and subsequent trapping with a suitable metalloid electrophile to more modern catalytic approaches.[5] Of note is the recent development of catalyst C-H metalation approaches, such as those reported by Buchwald, Grubbs and Johnson.[6-8]

Much more commonplace for the introduction of metalloid moieties into organic substrates is the hydrometallation of unsaturated substrates, a method frequently employed in the reduction of carbonyl compounds and their derivatives due to the relative ease of cleavage of X-M bonds (X=O, N M=B, Si, Sn).[9] When the same methodology is applied to the reduction of alkenes or alkynes by hydrometallation, the resultant organometalloid species is generally stable enough to allow for isolation and subsequent synthetic manipulation of the metalloid moiety. While these reactions can be carried out *via* radical chemistry, more typically a transition metal or Lewis acid catalyst is employed to facilitate a higher yielding and more selective process with regards to regioselectivity and stereoselectivity.[10,11] Notably, the hydroboration of olefins and alkynes using simple borane adducts is able to proceed under catalyst free conditions, albeit with diminished selectivity, *via* the concerted mechanism shown in **Scheme 1**. This type of reactivity is frequently employed in the Brown hydroboration-oxidation sequence to achieve the *anti*-Markovnikov hydration of olefins, providing complimentary selectivity to the analogous acid mediated approach.



Scheme 1 Generalised concerted hydroboration mechanism

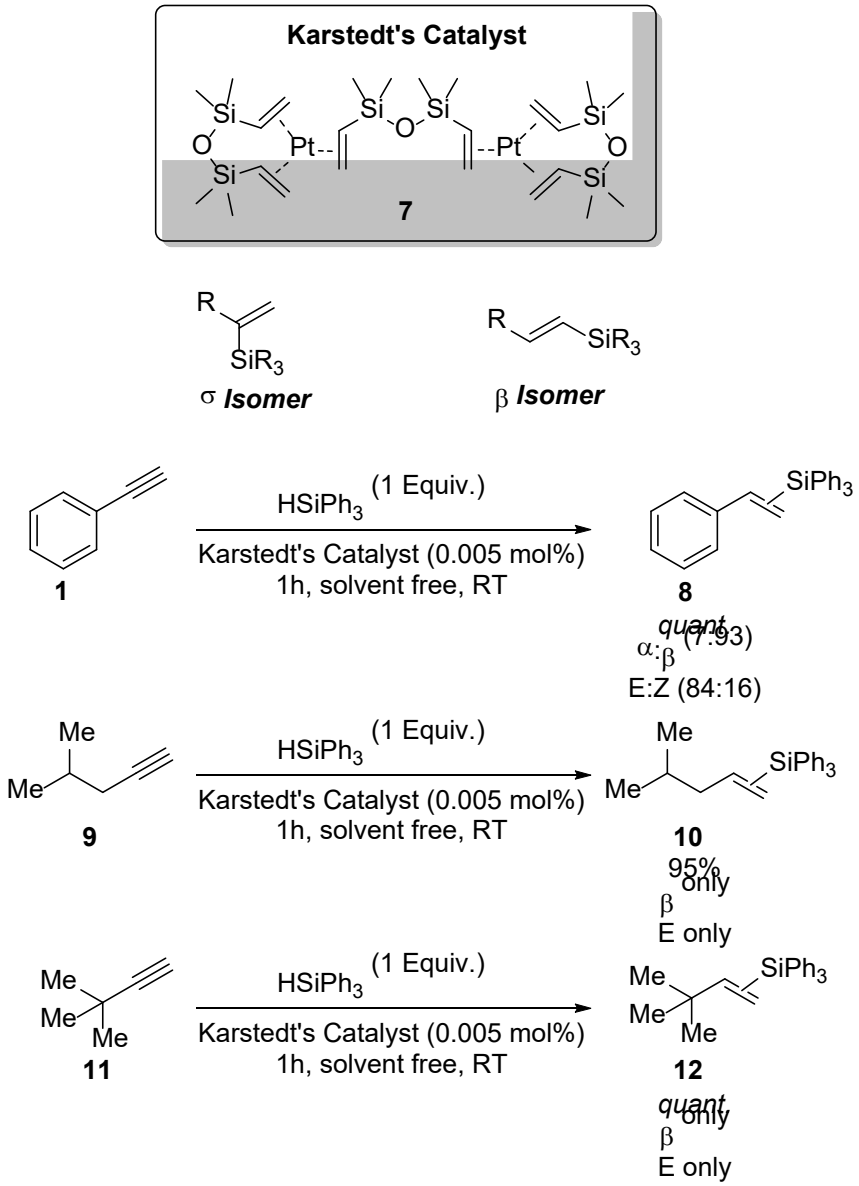
Conversely, this is seldom true for other hydrometallations, with the first example of a catalyst-free hydrosilylation reported in 2011 by Rodriguez *et al* using the Si(II) silylene **4** for the hydrosilylation of **5** as shown in **Scheme 2**.[12] As previously noted, much of the recent work in the field of hydrometallation of unsaturated carbon-carbon bonds has employed transition metal catalysts to realise a more selective transformation. As will be discussed in **Chapter 1.2**, platinum-based catalysts are ubiquitous in the field of hydrosilylation chemistry although a wide range of transition metal complexes have been utilised as hydrometallation complexes. While many complexes used for this purpose employ a precious metal (Rh, Ru, Pd, Ir) centre, recent developments have shifted towards the development of processes catalysed by more earth abundant base metals or avoiding the necessity for transition metals entirely.[13-16]



Scheme 2 First reported example of a catalyst free hydrosilylation

1.2 Synthesis of Organometalloid Reagents *via* Platinum Catalysed Hydrosilylation

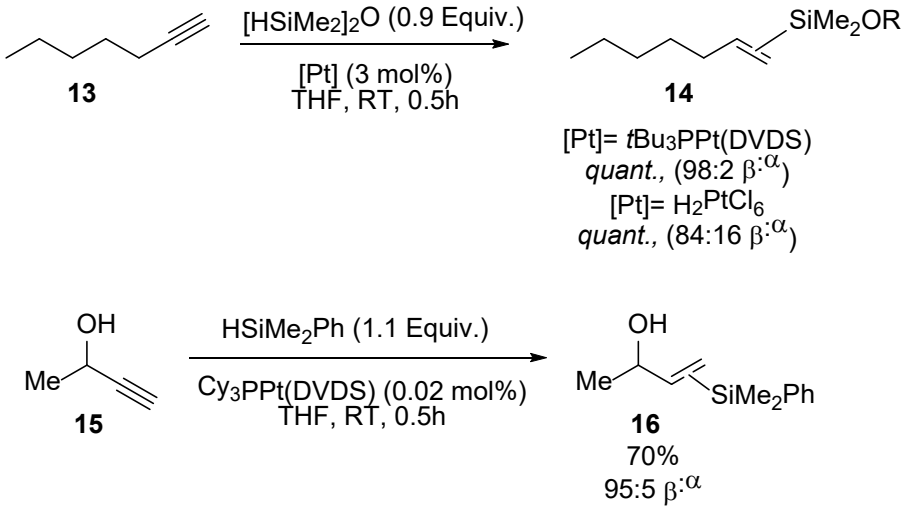
The first application of platinum based complexes for hydrosilylation catalysts was reported in 1956 by Speier and co-workers who demonstrated the high conversion of a range of olefins into the corresponding silicon adducts when treated with a H_2PtCl_6 and $HSiCl_2Me$, resulting in the salt being dubbed Speier's catalyst.[17] Further developments in the field would subsequently be made, with the 1970 patent by Karstedt detailing the use of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane **7** as a hydrosilylation catalyst with increased activity and selectivity in comparison to Speier's catalyst (**Scheme 3**).[18] For clarity, α and β nomenclature refers to the placement of the metalloid post-hydrometallation, with the α-isomer referring to the branched derivative and the β-isomer referring the linear variant as shown in **Scheme 3**.



Scheme 3 Effect of substrate bulk on regioselectivity

While the high activity of **7** has resulted in its widespread application in industrial synthesis of organosilanes, its ability to afford high levels of regiocontrol is limited as shown by the work of Lewis *et al* who studied the selectivity of the hydrosilylation of a range of simple alkynes using **7**. While the reaction almost exclusively forms products derived from a *syn*-delivery of the silyl hydride, the regioselectivity of the reaction is largely dictated by the steric bulk of the alkyne as can be seen in the selectivity for the hydrosilylation of alkynes **1**, **9** and **11**. As the steric bulk of the alkyne substituent is increased, the propensity of the silyl group to be delivered to the α position of the alkyne is decreased, resulting in a more regioselective reaction.[19]

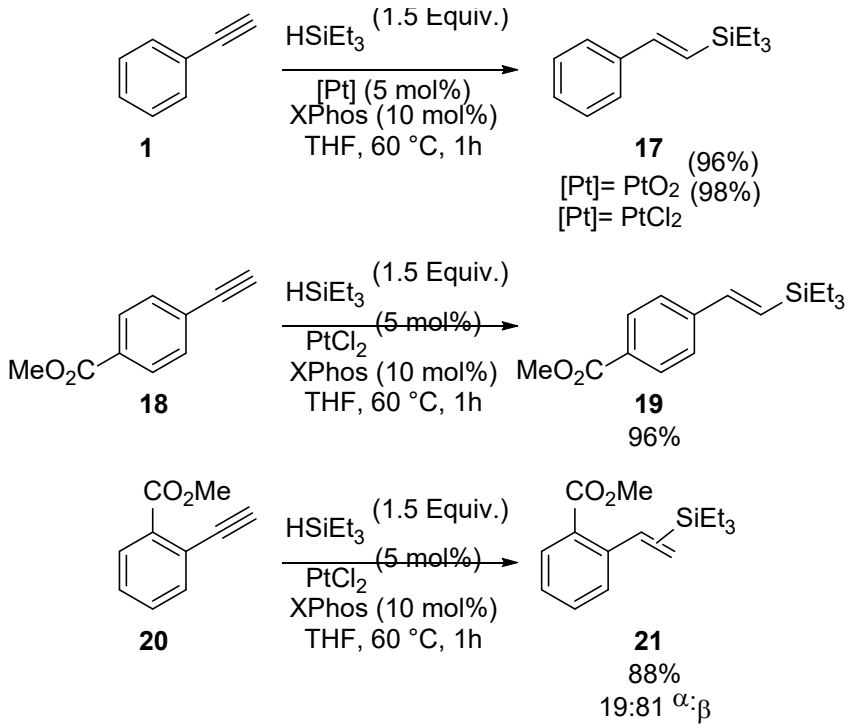
Later work reported by the Denmark and Procter groups respectively would detail the dramatic increase in selectivity which could be achieved in this transformation through the application of bulky phosphine ligands. Denmark showed that P*t*Bu$_3$ modified **7** can achieve significantly higher levels of regioselectivity when compared to the parent complex in the hydrosilylation of alkyl and aryl acetylenes as shown by the hydrosilylation of **13**. This is in agreement with the work of Procter *et al* who likewise observed a similar selectivity increase when studying the hydrosilylation of propargylic alcohols such as **15**.[20, 21]



Scheme 4 The increased selectivities achieved by application of phosphine ligands as reported by Denmark (top) and Procter (bottom)

While these results certainly represent an advance on the previously discussed catalyst system, they still do not permit exclusive access to a single regioisomer of the hydrosilylated product, while additionally relying on air-sensitive ligands such as P*t*Bu$_3$. To this end, the 2008 report by Alami *et al* represents a significant advancement on the aforementioned approaches. In this work the authors reported the extremely high activity and selectivity afforded by complexes of PtO_2/$PtCl_2$ and XPhos. The efficacy of this system is best illustrated by the comparison of results shown (**Scheme 5**). The authors report that even under systems bearing high levels of electronic bias towards the α-isomer, such as ester **18**, the β-vinyl silane can be accessed as a single regioisomer. The only substrate which resulted in a relatively poor regioselectivity was *ortho*-substituted

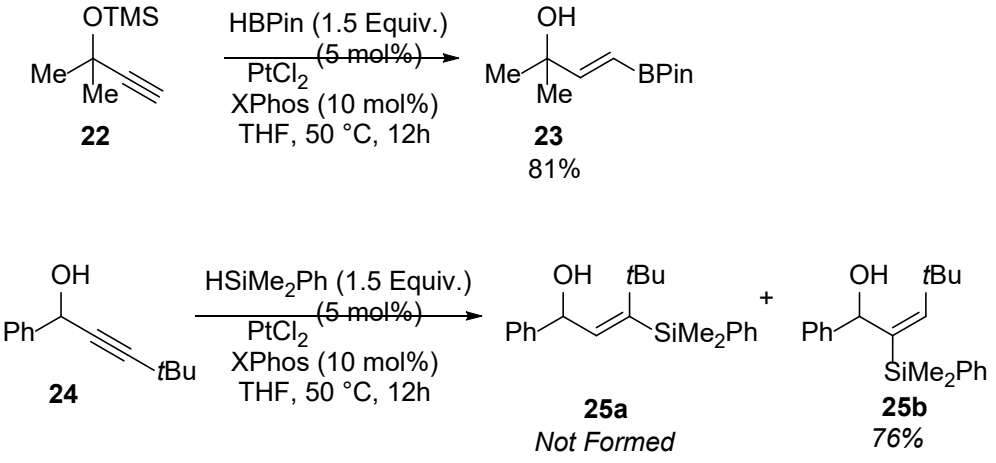
ester **20** which likely suffers from an *ortho* directing effect by virtue of the ester moiety.[22, 23]



Scheme 5 Highly selective $PtCl_2$/XPhos catalysed hydrosilylation

The use of these complexes was further expanded upon by Cook & McLaughlin who detailed the high selectivity achieved by these complexes in the hydrosilylation of propargylic alcohols (**Scheme 6**).[24, 25] The authors noted the systems large functional group tolerance with a range of oxyheterocycles tolerated in addition to demonstrating chemoselective alkyne reduction in the presence of other olefins. While broadly compatible with a range of substrates, the a decrease in yield was noted when propargyl alcohol itself was employed as a substrate, as well as demonstrating that the selectivity can be scrambled when non-terminal alkynes are employed as substrates, as shown by the hydrosilylation of internal alkyne **24**. Another key finding of this work is the efficiency of $PtCl_2(XPhos)_2$ at catalysing the hydroboration of TMS-protected alcohol **22** with pinacol borane affording vinyl borane **23** (**Scheme 6**). This is notable as it represents one of the few applications of platinum in the context of hydrometallation chemistry beyond hydrosilylations. A discussion of the limited examples of platinum catalysed hydrostannylation is provided in **Chapter 4.1**,

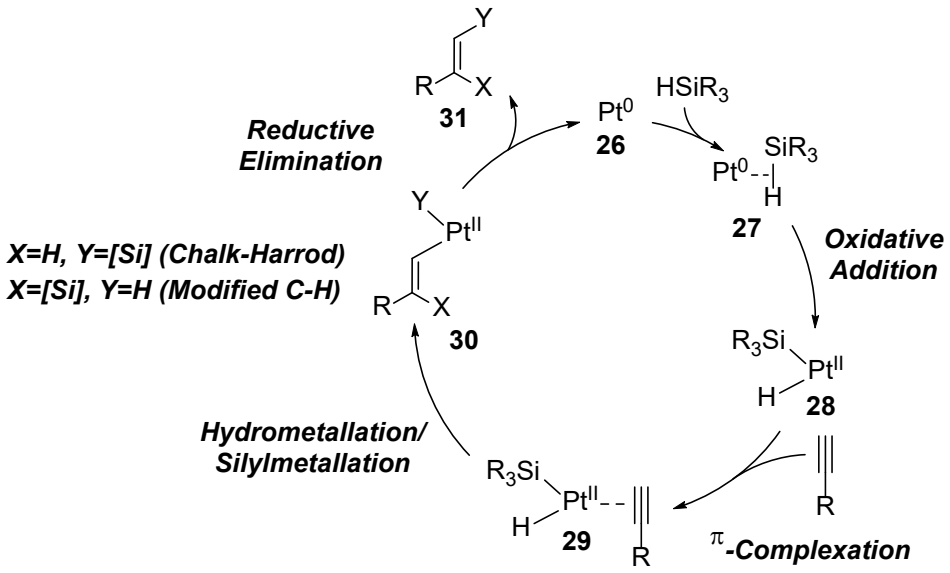
and a single example of a study on platinum catalysed hydroboration of unsaturated carbon-carbon bonds has previously been reported.[26] Aside from phosphine ligands, NHC-Pt complexes have also been employed for the purpose of realising highly selective hydrosilylations based on the initial report by Markó *et al* in 2002.[27] While a more in depth discussion of the application of NHC ligands in the context of hydrosilylation chemistry is provided in **Chapter 5.1**, it is of note that the activity of these complexes is dramatically higher than of the analogous phosphine-ligated complexes.



Scheme 6 $PtCl_2$/XPhos catalysed hydrometallation of propargylic alcohols

1.3 Mechanism of Platinum Catalysed Hydrosilylation

As discussed, platinum catalysis is ubiquitous in the field of hydrosilylation chemistry due to the high levels of control afforded by complexes bearing bulky phosphine ligands. In order to understand the origin of this selectivity in aid of designing more selective and facile processes, a range of studies have been carried out in order to elucidate the mechanism through which platinum catalysed hydrosilylations proceed. The generally accepted mechanism for most *syn*-hydrosilylations, typically achieved under platinum catalysis, is either *via* the Chalk-Harrod or modified Chalk-Harrod mechanisms, as shown in **Scheme 7**.[28, 29] The mechanism can be described as follows; oxidative addition of a Pt(0) species into the Si-H bond of the silyl hydride affords Pt(II) complex of general structure **28**, which can subsequently undergo π-complexation with the substrate of interest, with a discussion of this bonding discussed later in this chapter. Subsequent insertion of the substrate into either the Pt-H or Pt-SiR_3 designates the mechanism the Chalk-Harrod or modified Chalk-Harrod mechanism respectively affording hydroplatinated or silylplatined intermediate **30**. Reductive elimination releases vinyl silane **31** while regenerating Pt(0) species **26**. While the mechanism assumes the application of a Pt(0) complex for the reaction, work by Pregosin *et al* showed that upon treatment with silyl hydrides, complexes of the general structure $PtCl_2(PR_3)_3$ are readily reduced to $Pt(PR_3)_2$ with concomitant formation of $ClSiR_3$ and liberation of hydrogen gas, explaining how Pt(II) complexes such as those detailed by Alami are able to act as suitable precatalysts for these processes.[30] It should be noted at this point that while this mechanism adequately describes the observed reactivity for *syn*-hydrometallations, the mechanism through which specific catalyst systems operate is often distinct. For example, cationic ruthenium complexes have been shown operate by a distinct silyl migration pathway whereas Rh complexes have previously displayed a hydrometallation/carbene mediated isomerisation route to access structurally distinct vinyl silanes.[31-34]



Scheme 7 Chalk-Harrod and modified Chalk-Harrod hydrosilylation mechanisms for platinum catalysed hydrosilylation

As noted, a key step of the mechanism is the interaction between the π-electrons of the olefin/alkyne and the metal centre resulting in the formation of a π-complex. The general bonding description of complexes of this type is shown in **Figure 2** as described by the Dewar-Duncanson-Chatt model.[35] The bonding consists of donation of electron density from the π-orbital of the substrate into a vacant d-orbital of the metal centre (**32a**). This ligand-metal donation is accompanied by metal-ligand backdonation from a filled d-orbital into the π* orbital of the substrate (**32b**), resulting in a lowered bond order of the π-bond and as such an increased ease of reactivity such as nucleophilic attack or, as in the case of hydrosilylation, migratory insertion. The resultant π-complex can be envisaged as one of two extremes depending on the nature of the metal centre. Complexes with higher degrees of electron density at the metal centre, such as those featuring early transition metals or metals in low oxidation states, permit higher degrees of backdonation, lowering the bond order of the substrate to such an extent that it is best described as the metallacyclopropane **33b**. Conversely, late transition metals or metals in higher oxidation states display decreased backbonding and as such the bond order of the substrate remains closer to its initial value, and the complex is better described by the Dewar-Duncanson-Chatt model (**33a**). Due to the decreased backbonding by these complexes, the vinylic carbons possess a

greater cationic nature and as such are more electrophilic than an analogous complex displaying higher degrees of backbonding.

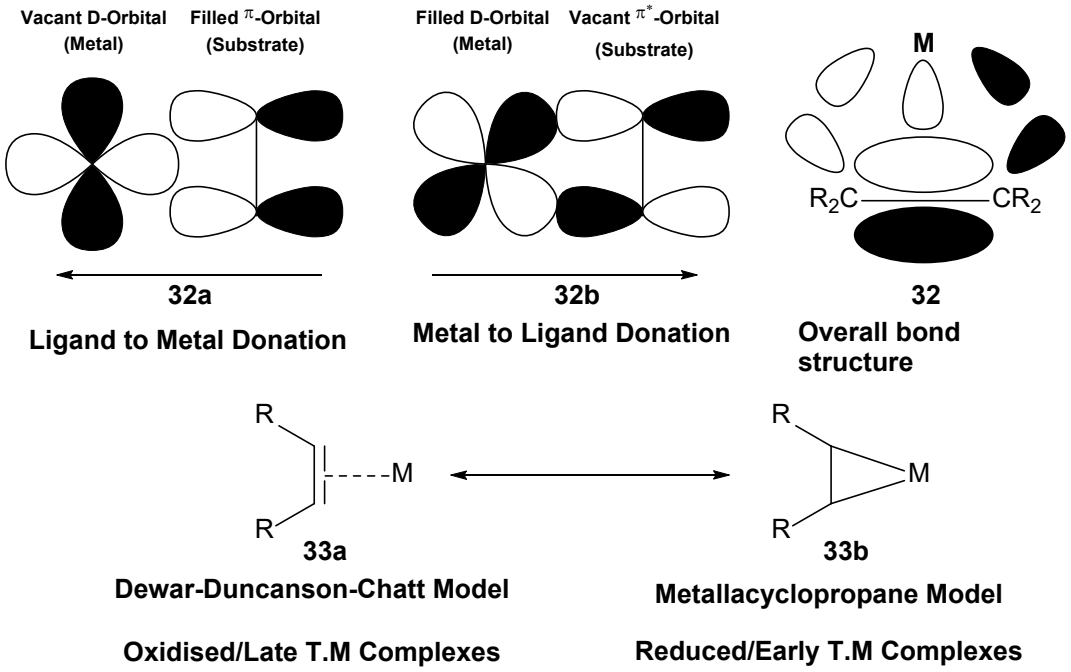
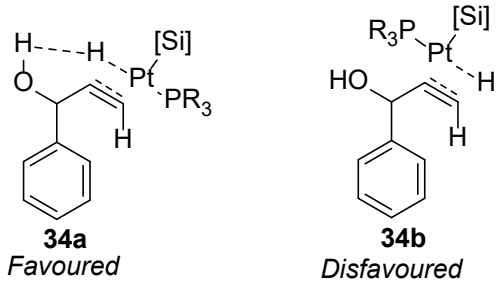


Figure 2 Bonding models for transition metal π-complexes

The high levels of regioselectivity afforded by $PtCl_2(XPhos)_2$ can be rationalised based on the Chalk-Harrod mechanism as demonstrated by Cook *et al*. The authors suggest that the high levels of regioselectivity achieved by this catalyst is due to the propensity of the alkyne to orient itself in a manner which minimises steric bulk (**Scheme 8**) whilst additionally proposing a hydrogen bonding interaction between the hydroxyl group which facilitates increased regioselectivity.

Further mechanistic studies suggest hydrosilylations mediated by this complex do in fact proceed *via* the Chalk-Harrod mechanism with deuteration studies suggesting with the rate determining step to be alkyne hydroplatination. This is in keeping with other mechanistic studies on platinum catalysed hydrosilylation employing Karstedt's catalyst.[36]



Scheme 8 Proposed regioselectivity model for $PtCl_2$/XPhos catalysed alkyne hydrosilylation

Chapter 2: Synthesis and Reactivity of Vinyl Silanes Bearing Tethered Nitrogenous Functional Groups

The work detailed in this section has been published in part as: D. D. Roberts and M. G. McLaughlin, *Org. Lett.*, 2021, **23**, 4463-4467.[37]

2.1 Introduction

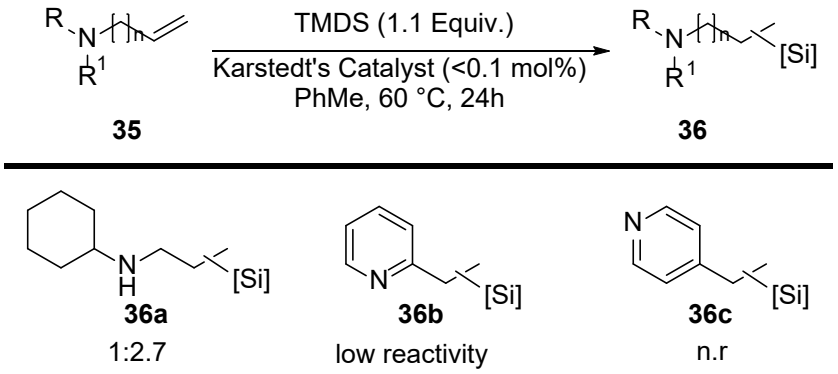
2.1.1 Hydrometallation of Nitrogen Containing Compounds

Whilst hydrosilylation is well established as a robust method to access olefins bearing an organosilicon handle amenable to subsequent functionalisation, the lack of methods available to achieve the hydrosilylation of propargylic amines is notable in comparison to other types of alkyne-containing scaffold. As this would in principle represent a straightforward way to access allylic amines, the synthetic utility of which is discussed in **Chapter 2.1.2**, this represents a significant gap in the field.

The hydrosilylation of propargylic amines and other nitrogen containing compounds has been shown to be non-trivial due to the highly coordinating nature of the nitrogen atom. Early work by Speier and Saam on the hydrosilylation of *N*-trimethylsilyl allylamine outlines the difficulty in achieving this transformation. [38] The authors attempted to employ hexachloroplatinic acid for the hydrosilylation the protected allyl amine, noting the formation of 'hydrogen and unidentified products, presumably aminosilanes'. Protection of the amine with a TMS group does minimise this, though no data on the isomeric identity of the silane afforded by the reaction was reported.

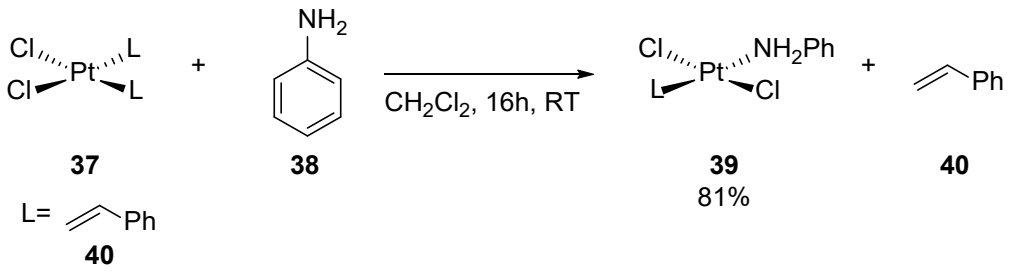
Work by Chechelska-Noworyta demonstrated the limitations of platinum complexes in catalysing the hydrosilylation of olefins bearing tethered amines.[39] Allyl amines bearing a variety of aromatic and alkyl substituents were shown to result in mixtures of regioisomers under hydrosilylation using Karstedt's catalyst with incomplete reactions observed in all cases, though allyl aniline derivatives were shown to be the most active substrates likely due to the decreased nucleophilicity of the *N*-donor. The authors also note increased activity can be achieved by steric crowding of the nitrogen donor, presumably to minimise unwanted substrate/catalyst interactions. Vinyl pyridines **35b** and **35c** perform even more poorly, with little to no turnover observed for in these cases (**Scheme 9**). This catalyst poisoning effect is corroborated by the work of Endo *et al* who investigated the retarding effects of aminated polymers on the hydrosilylation of olefins with hexachloroplatinic acid and found that at amine/platinum ratios as low as 2:1, conversion dropped by a factor of 3 even when the reaction was

carried out at 140 °C in comparison to at room temperature without the polymer. Aminated polymers with a higher density of aminated monomers showed high inhibition of hydrosilylation, further providing evidence of catalyst inhibition by nitrogen poisoning.[40]



Scheme 9 Poor Selectivity in hydrosilylations catalysed by Karstedt's catalyst

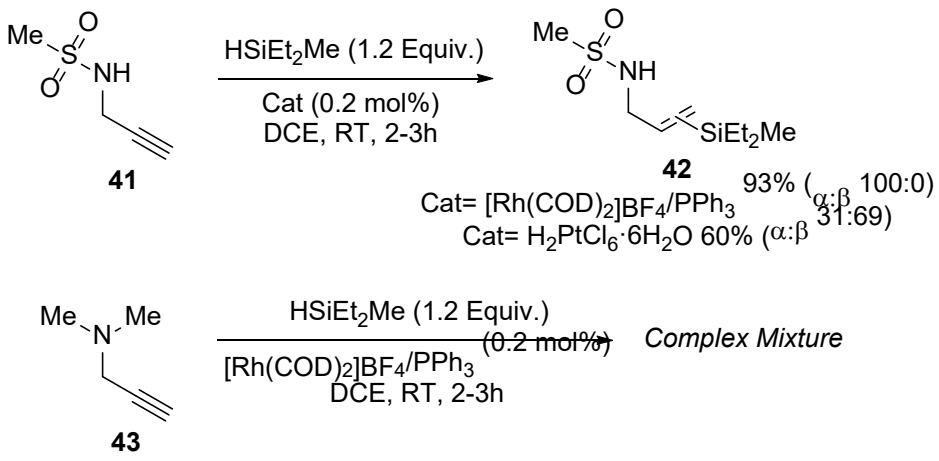
Potential modes for deactivation of platinum catalysts by nitrogen containing compounds can be found in reports on the reactivity of Pt(II)-olefin complexes with nucleophiles such as phosphines and amines. This work, reported by Storlie and co-workers showed that with a 10-30 fold excess of pyridine, olefins can be irreversibly displaced from platinum centres to afford the corresponding platinum-amino complex.[41] The same amine displacement of olefinic ligands at complex **37** was later also reported by Pregosin who demonstrated that the same displacement occurs with much lower loadings of amine relative to platinum as well as additionally occurring with amines of much lower nucleophilicity such as aniline (**Scheme 10**).[30]



Scheme 10 Displacement of π-ligands by *N*-donor ligands

These well documented inhibiting effects of nitrogen donors on traditional hydrosilylation catalysts likely explain why the hydrosilylation of propargylic

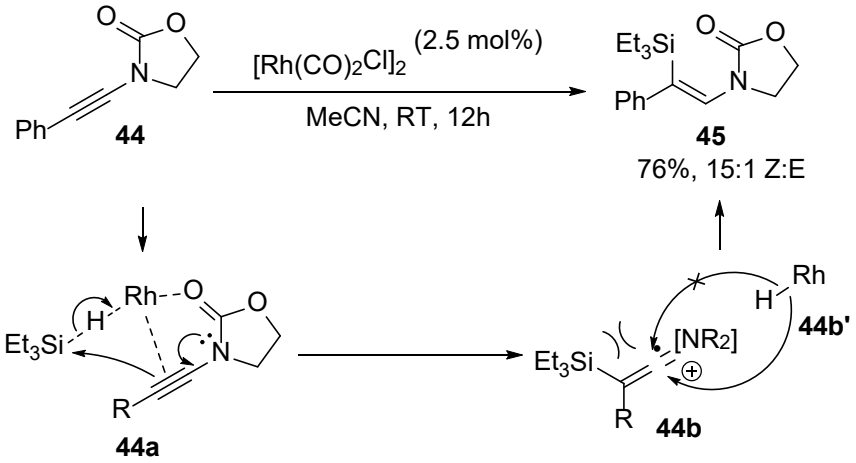
amines has remained largely undeveloped as an area. One of the few examples of this reaction was reported by Ebata and Takeuchi who studied the hydrosilylation of *N*-Sulfonylpropargyl amine derivatives.[42] The authors report that when treated with hexachloroplatinic acid, sulfonamide **41** undergoes hydrosilylation to afford **42** as a 31:69 mixture of regioisomers, though this selectivity is increased when cationic rhodium complexes such as $[Rh(COD)_2]BF_4$ are employed. It should be noted that this system is heavily deactivated by the presence of the sulfonyl group, and yet even so, the selectivity of the system is relatively poor and is only able to achieve a moderate 60% combined yield. The necessity to deactivate the nitrogen centre is further established when the authors attempted the hydrosilylation of *N,N*-dimethylpropargylamine, which resulted in the formation of a polymeric mixture of products, though rhodium catalysed polymerisation of alkynes under hydrosilylation conditions had previously been reported.[43]



Scheme 11 Hydrosilylation of deactivated nitrogen containing substrates

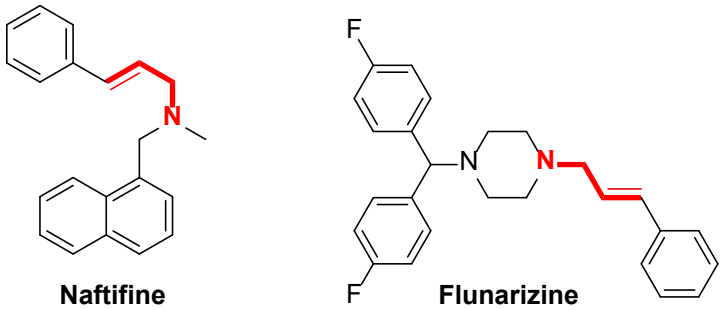
It is noticeable that while there are relatively few examples of hydrosilylation of propargyl amines, the hydrometallation of ynamides has received significantly more attention.[44,45] The increased prevalence of work on these substrates can likely be attributed to the deactivated nature of the ynamide moiety in comparison to amines not bearing strongly electron withdrawing groups. Work by Song in 2018 described the Rh-catalysed *trans*-hydrosilylation of internal ynamides **44**, affording β-silylated products **45** as single regioisomers although Z:E selectivity varied from 1:1 to >20:1. Rather than a traditional Chalk-Harrod hydrosilylation

mechanism, the authors instead propose that the reaction proceeds through the formation of silylated ketene-iminium **44b** which subsequently undergoes reduction *via* hydride delivery from rhodium-hydride species **44b'** generated *in-situ* in a similar manner to what has been proposed for the same reaction catalysed by $B(C_6F_5)_3$.[46,47]



Scheme 12 Rh catalysed ynamide hydrosilylation

2.1.2 Synthesis and Applications of Allylic Amines

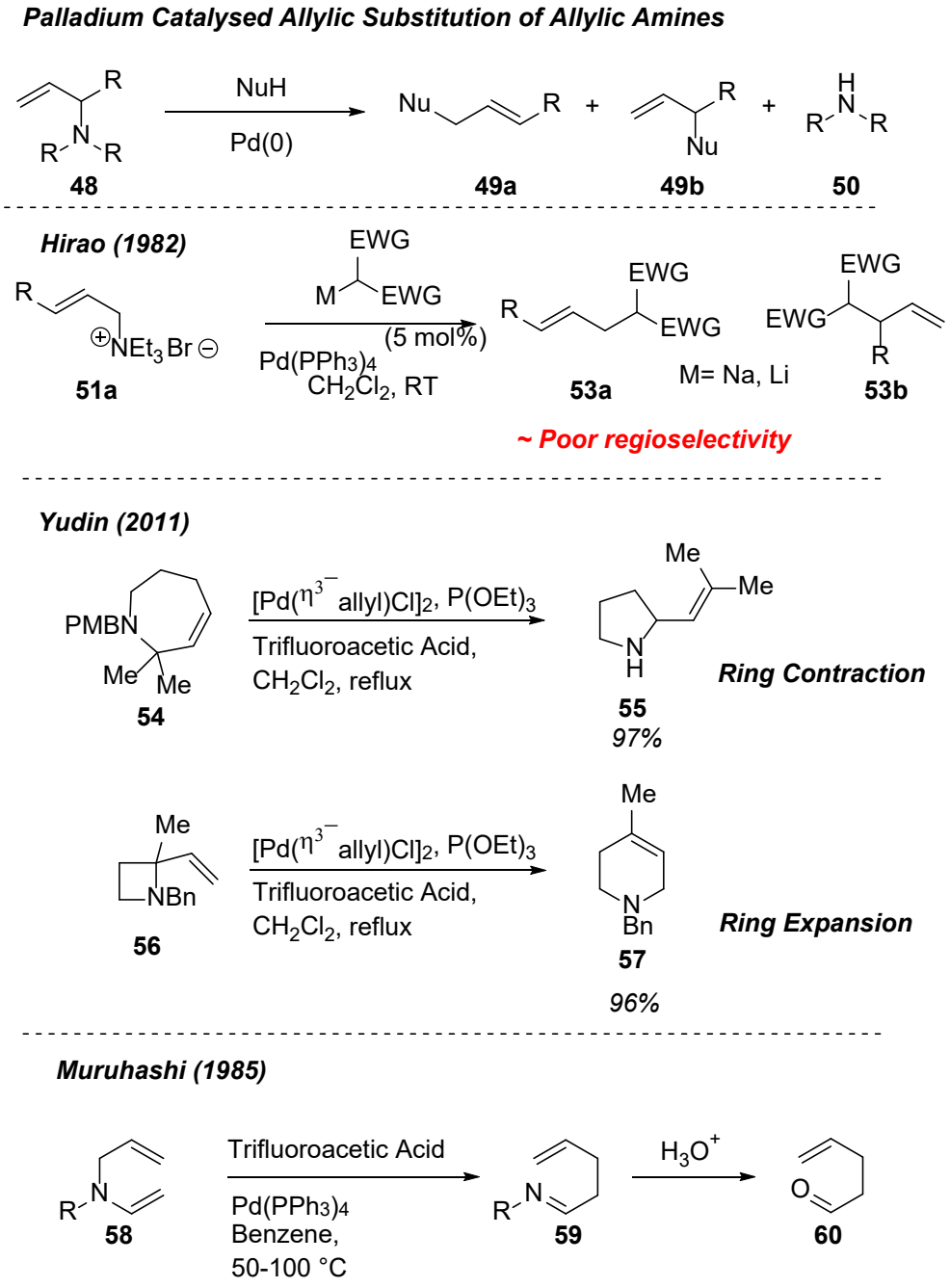


Naftifine
46

Flunarizine
47

Figure 3 Allyl amine (left) and occurance of the moeity in pharmaceutically active compounds

As has previously been discussed, the application of hydrosilylation chemistry to access allylic amines is largely unrealised, meaning access to these scaffolds bearing organosilicon handles is also challenging. This is perhaps surprising due to the prevalence of the scaffold in modern organic chemistry with the motif present in a range of both biologically active compounds and natural products. For example, the antifungal drug Naftifine **46** features an cinnamylamine core as one of its core structural features, and is structurally distinct from other related antifungal compounds to the extent that it has resulted in a branch of antifungal compounds derived from its core structure such as Flunarizine **47**.[48,49]

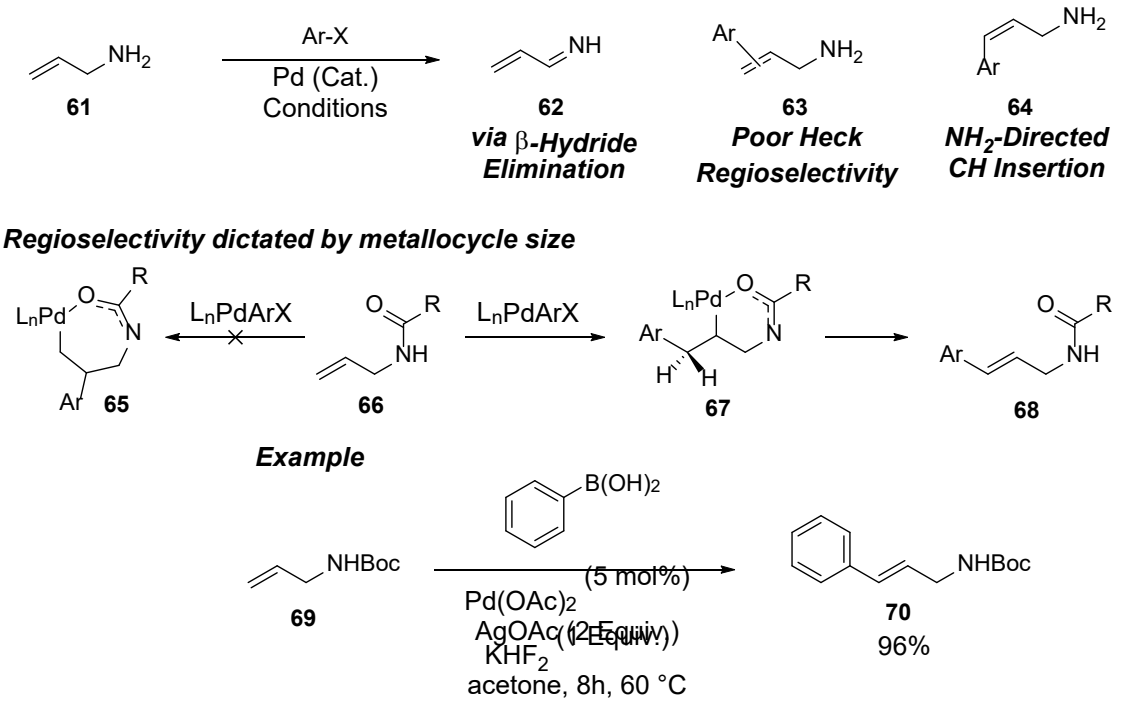


Scheme 13 Synthetic utiliity of allylic amines

Aside from the allylamine core being present in bioactive compounds, these moieties have also proven to be versatile synthetic intermediates in a range of synthetically useful transformations. For example, whilst the well-studied Tsuji-Trost reaction typically employs substrates such as allylic esters and halides, it has been well documented that allylic amines are also able to act as electrophiles in these reactions. Due to the poor leaving group ability of the amino group (pK_a ~ 35), these type of allylations are generally shown to require modifications in

reaction conditions to in comparison to substrates with more traditional leaving groups. As such, Hirao reported that ammonium bromide salts **51** readily undergo Pd catalysed substitution with sodium enolates **52** to afford allylated products **53a** and **53b**.[50] Aside from preactivation of the electrophile, utilisation of cyclic allylamine derivatives **54** and **56** in the Tsuji-Trost reaction affords either ring-expanded or ring-contracted products **55** and **57** with the driving force being the formation of more favourable ring sizes.[51] Formation of η^3 π-allyl Pd species from allyl amines has also been shown to have synthetic applications beyond electrophilic trapping, with Muruhashi describing a Pd catalysed formal aza-Cope rearrangement of *N*-Allylenamines **58** into imines **59**, which can be readily hydrolysed into the corresponding aldehyde or ketone.[52]

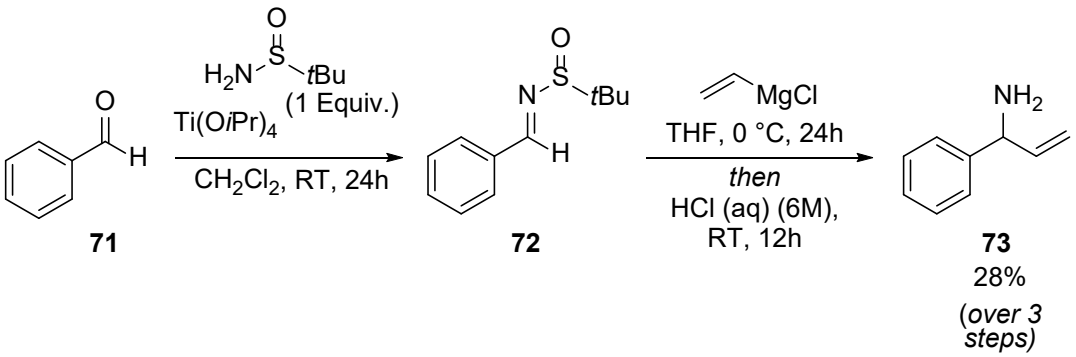
Allylic amines have also been shown to be suitable substrates for functionalisation by the Mizoroki-Heck reaction, although the free amines have proven to be challenging substrates due to competing side reactions as shown from compounds. For example, amines have been shown to be highly prone to oxidation in the presence of transition metals due to facile β-hydride elimation, resulting in the formation of unstable imine or iminium ion intermediates **62**.[53] Additionally, it is often necessary to modulate catalyst/amine coordination to minimise side reactions arising from C-H insertion or control regioselectivity (**63** & **64**). Typically, this is achieved *via* incorporation of an electron withdrawing group on the nitrogen atom. This results in regioselective carbopalladation of the olefin during the course of the reaction, whilst also serving to reduce oxidation of the amine by minimising N-Pd interactions, with an example of such a reaction as reported by Xiao and co-workers (**Scheme 14**). Suitable amine protecting groups include carbamates, imides and amides.[54,55]



Scheme 14 Challenges assocatied with Heck couplings employing allylic amines and influence of the *N*-donor on regioselectivity

As this motif is of high importance within synthetic chemistry, it follows suit that a wide variety of elegant methods have been developed to access compounds of this type. While the parent molecule is made industrially *via* treatment of allyl bromide or allyl chloride with ammonia, access to derivatives bearing substituents at the allylic position is less trivial.

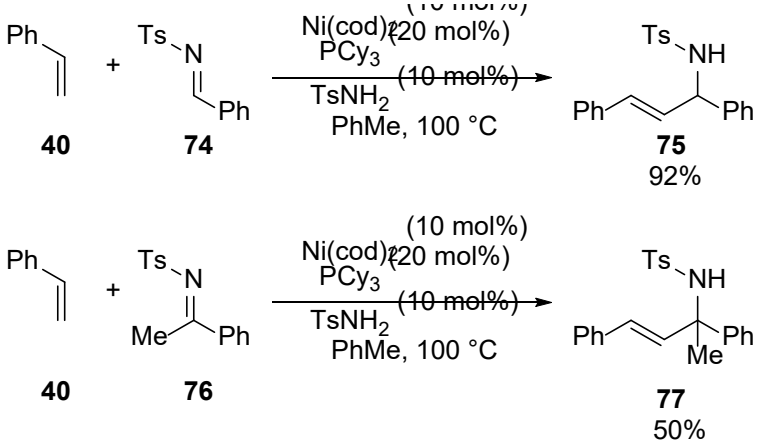
While addition of an organometallic reagent to an imine has been well documented and is perhaps the most intuitive approach to these compounds, the inherent strongly basic nature of these reagents makes this route unappealing for structures with base sensitive functionalities. This is well documented by Hull and co-workers, who accessed a range of allyl amines *via* addition of vinyl magnesium chloride to Ellman imines **72**, with the sulfinamide moiety presumably installed to render the imine sufficiently electrophilic as to undergo reaction. Whilst this does afford the desired allylic amines **73**, the yields of the reactions are observed to be low (<30%) with acid mediated cleavage of the sulfinamide group required, in addition to multiple chromatographic and distillation purifications required.[56]



Scheme 15 Synthesis of allylic amines by Lewis acid mediated addition of vinyl magnesium bromide into Ellman imines

In 2018, Zhou *et. al.* described the nickel catalysed hydroalkenylation of *N*-Tosyl aldimine **74** with styrene **40** to afford *N*-sulfonyl allyl amine **75** (**Scheme 16**).[57] While the method allows access to allyl sulfonamides derived from aryl and aliphatic aldimines, aliphatic olefins were noted to perform poorly in these reactions, affording mixtures of allylic and homoallylic products. In addition, utilisation of ketimine **76** derived from acetophenone resulted in a dramatic reduction in yield, with sulfonamide **77** afforded in a modest 50% yield, though the authors note it is not atypical for ketimines to perform poorly in these types of reactions.

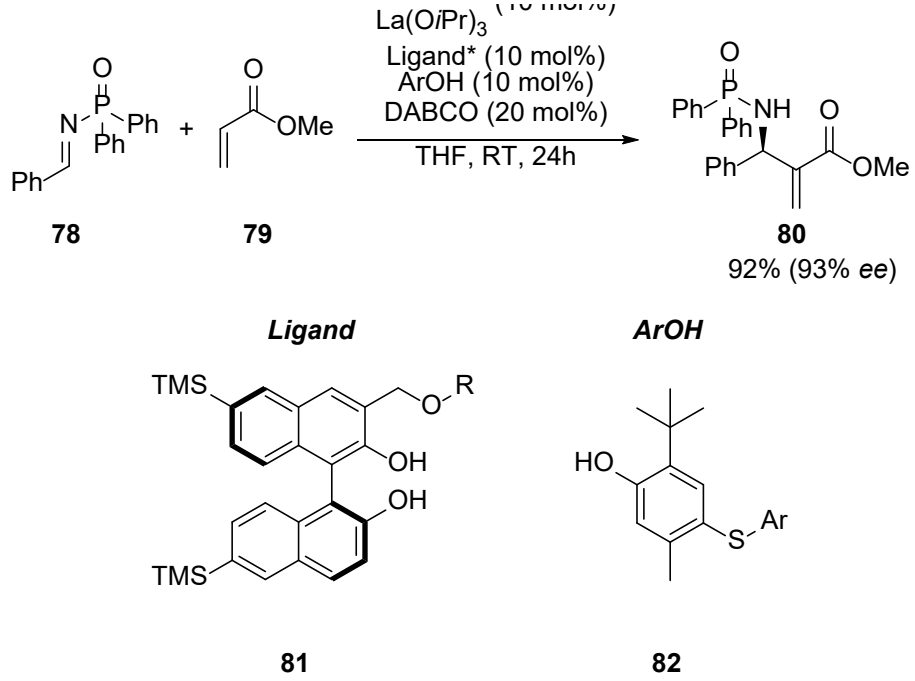
Another key limitation was the absence of any substrates bearing non-deactivating groups on the nitrogen, presumably due to the increased coordinative ability of these substrates. Subsequent studies by the group demonstrated similar chemistry utilising a tethered alkenes to afford cyclic allyl sulfonamides.[58]



Scheme 16 Synthesis of *N*-Sulfonyl allylic amines *via* nickel catalysed imine hydroalkenylation

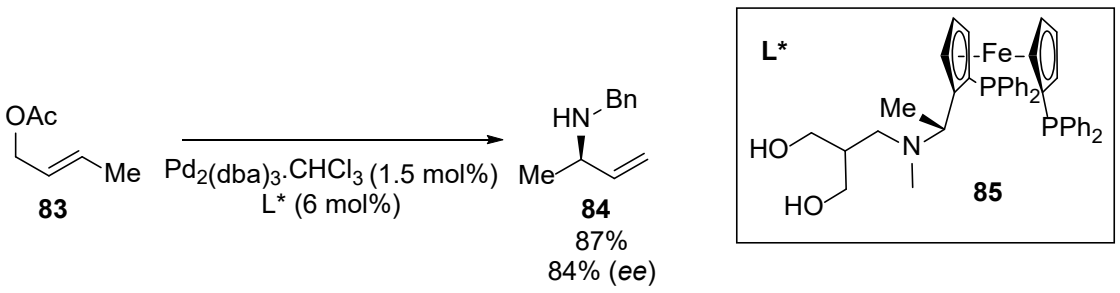
Aside from transition metal mediated processes, functionalisation of imines has also been *via* Lewis acid mediated processes. This is well demonstrated by the 2010 study by Shibasaki and co-workers who employed an asymmetric Morita-Bayliss-Hillman reaction to achieve allylation of *N*-Phenylphosphinoyl imine **78** with methyl acrylate **79**. In this study the authors utilised La/linked-BINOL complex to activate the imine as an electrophile.

The authors report that the rate determining step is the 1,4-addition of DABCO to **79**, with the catalyst showing a zero-order dependency in this process, ruling out the possibility of the catalyst activating methacrylate. Instead the authors suggest **78** is activated by the catalyst towards nucleophilic attack by the intermediary enolate whilst additionally serving to increase the nucleophilicity of said enolate.[59]



Scheme 17 Application of the Morita-Bayliss-Hillman reaction towards the synthesis of enantioenriched allylic amines

While allylic amines themselves have found application as electrophiles within the Tsuji-Trost reaction, the reaction can be used to access the amines *via* allylic amination of suitable electrophiles such as allylic acetates.[60,61] Key considerations when employing this methodology general concern control over the regioselectivity of the nucleophilic attack, as well as epimerisation of double bonds, which results in a loss of geometric purity of the resultant olefin. Early work by Ito and co-workers demonstrated these factors can be controlled *via* careful choice of ligand, with Pd ligated to optically active DPPF derivative **85** shown to catalyse amination of allylic esters such as **83** with high levels of regiocontrol and enantioselectivity to afford amines such as **84**.[62]

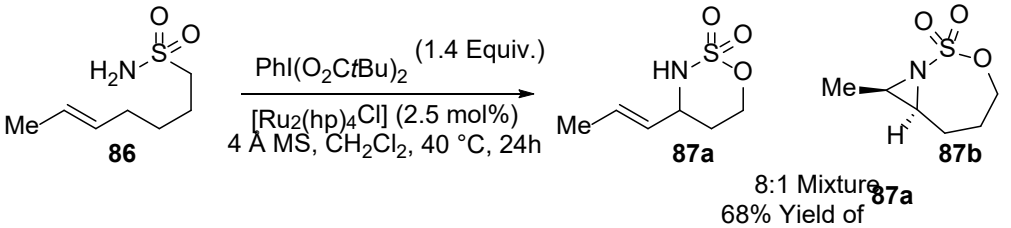


Scheme 18 Synthesis of allylic amines by allylic amination

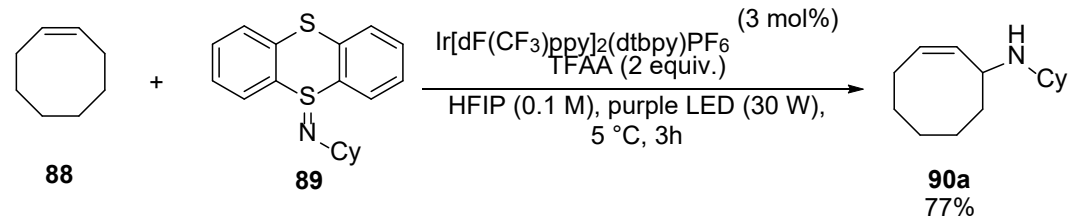
Allylic amination has also been achieved through methods aside from traditional Tsuji-Trost chemistry *via* the functionalisation of activated allylic C-H bonds. This approach is well demonstrated by Ritter and co-workers in their photocatalytic approach to this transformation. The use of photocatalysis to enable C-H amination of an allylic system is beneficial in that it enables avoidance of nitrene chemistry which, whilst effective, suffers from competing aziridination of the nearby olefin as has been noted by Du Bois and co-workers in the C-H amination of **86** which affords both **87a** and **87b**.[63,64] Additionally the authors note the benefit of this methodology in that it permits the use of more strongly basic alkyl amines which shut down catalysts in traditional photoredox chemistry or nitrene chemistry.

The approach by Ritter *et al* relies on the formation of iminothianthrenes **89** which under the reaction conditions allows formations of radical ion pair **92**. The amino radical cation then undergoes addition to the π-bond of the allyl system affording intermediate radical cation **93**, which subsequently recombines with thianthrenium radical cation **93** to afford dicationic species **94**. Subsequent regeneration of the thianthrene *via* E_2 elimination affords the desired product.[65]

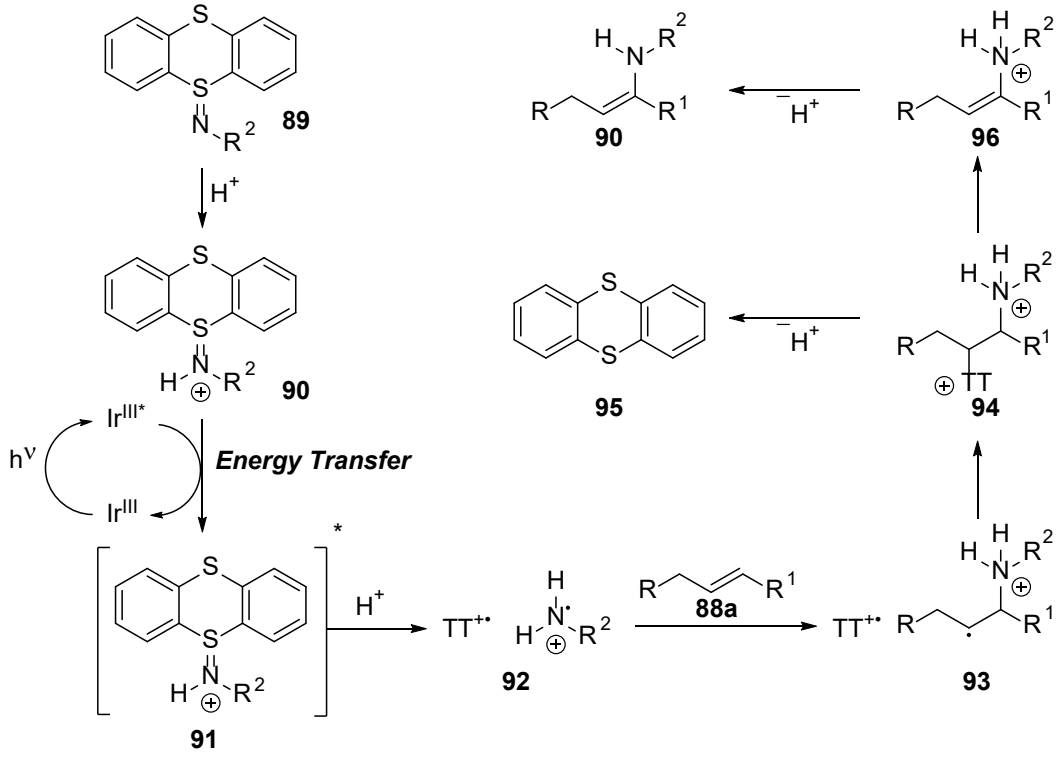
Du Bois (2011)



Ritter (2020)



Proposed Mechanism

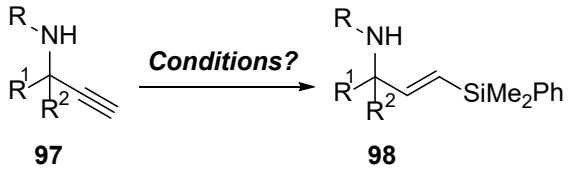


Scheme 19 Photocatalytic allylic C-H amination

As discussed, a variety of methods have been reported over the course of several decades to access diverse allylic amine scaffolds, though this does not extend typically to the synthesis of substrates possessing an organosilane handle within the allyl group. These methodologies generally rely on the functionalisation of an activated imine or the amination of a pre-existing allyl system. While these methods do allow access to the desired scaffolds, the difficulty in control over

reaction selectivities, difficulty in using highly coordinating nitrogen motifs with transition metal catalysts and requirements for specialist reagents/conditions means scope exists for the development of other complimentary methods.

2.2 Aims



97 **98**

Project Aims
- *Access Necessary Starting Materials*
- *Identify Optimal Hydrosilylation Conditions*
- *Explore Substrate Scope*
- *Investigate Synthetic Utility of Products*

Scheme 20 Project Aims

As discussed, allylic amines are highly versatile synthetic intermediates, though access to substituted derivatives is not trivial. Additionally, access to derivatives which provide a handle for functionalisation *via* cross-coupling chemistry is even more scarce. The work in this chapter aims to address this limitation in the current literature, by developing a method for the synthesis of allylic amines and their derivatives *via* catalytic hydrosilylation of propargyl alkynes. This simultaneously addresses the limitation of previously reported hydrosilylation catalyst systems in their poor reactivity and selectivity towards the hydrosilylation of nitrogen containing substrates.

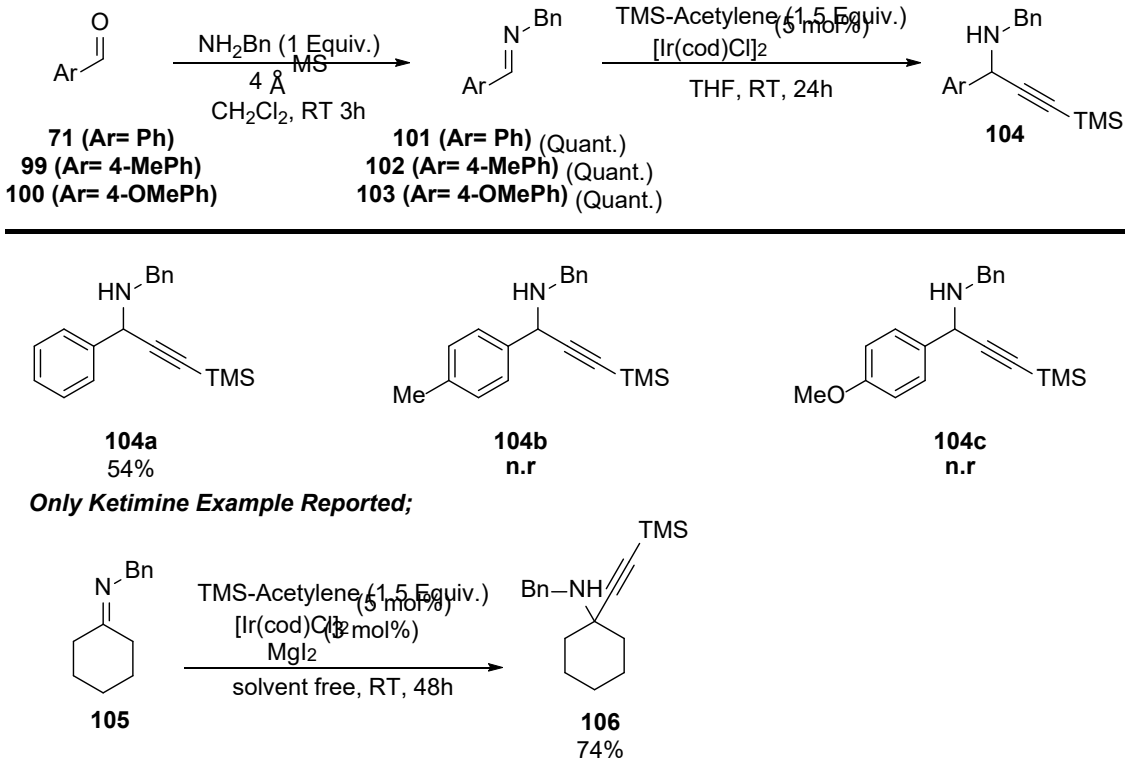
The work aims to achieve this transformation with high levels of stereocontrol and regiocontrol over the delivery of the metal hydride to the π-system of the alkyne to afford a single product. To achieve this high selectivity, a range of structurally diverse phosphine ligands will be screened, based on the high selectivity of previously reported $PtCl_2$/Phosphine complexes in hydrosilylation catalysis. The tolerance of the reaction to a range of sterically and electronically varied substrates will be explored, with any notable limitations of the methodology reported. An exploration on the scalability of the methodology will also be explored. As the resultant organosilanes have not been previously reported, synthetic potential of the products will be studied, with a particular interest in their reactivity towards electrophiles owing to the well-established β-silicon effect.

2.3 Preparation of Propargyl Amines

As the work in this chapter required access to a diverse range of propargyl amines, the initial focus was to establish viable synthetic procedures to allow access to these scaffolds. A survey of the literature revealed one of the more prominent routes to access propargylic amines is the copper catalysed coupling of an aldehyde, an amine and an alkyne in an A^3 coupling. While useful in principle, these reactions typically employ chiral catalysts to impart enantioselectivity on the reaction, with PyBOX derivatives being particularly commonplace. Due to the costly nature of these ligands, in addition to the lack of need to access optically active propargyl amines, A^3 coupling was not pursued as a method to access propargyl amines.[66]

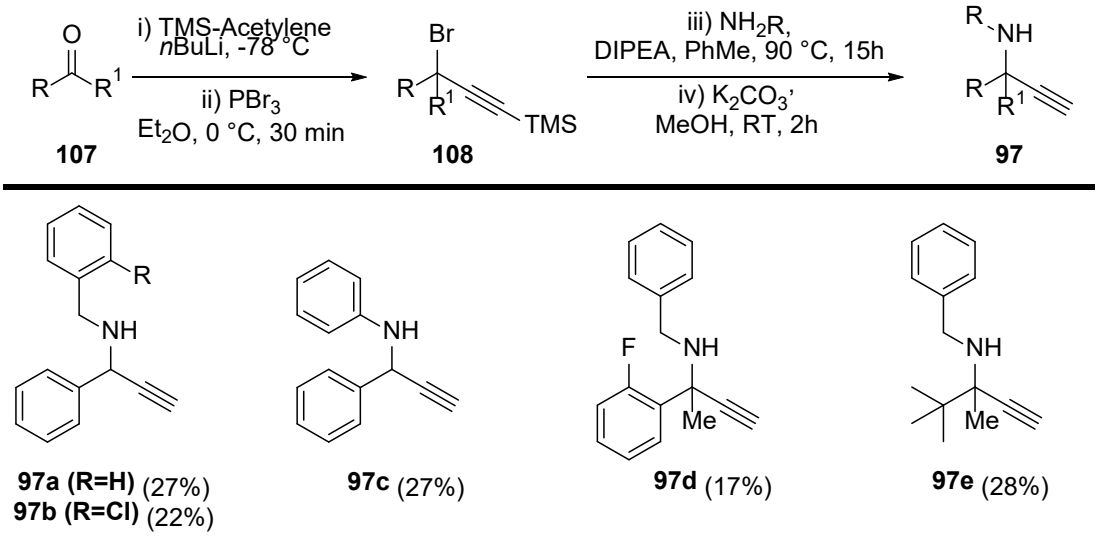
The route reported by Carreira *et al* wherein $[Ir(COD)Cl]_2$ (COD=1,5-cyclooctadiene) is shown to catalyse the addition of trimethylsilylacetylene into aldimines **101**-**103** to afford propargylic amines **104a**-**104c** (**Scheme 21b)** was first examined.[67] To this end, *N*-Benzyl aldimines **101**-**103** were prepared from benzaldehyde, *p*-tolualdehyde and *p*-anisaldehyde respectively using the conditions reported by Melen *et al*.[68] With aldimines in hand, the addition of TMS-acetylene was next explored. Employing aldimine **101** under the conditions reported by Carreira, amine **104a** was isolated in a modest 54% yield. Conversely, when aldimines **102** and **103** were employed in the reaction, no reaction was observed presumably due to the decreased electrophilicity of these substrates. It should be noted that in the initial publication, the scope of aldimines is very limited (6 examples) and contains no examples of electron rich aromatic systems. A subsequent study by the same group does suggest that reactivity can be enhanced by employing Lewis acids to activate the aldimine towards addition of the proposed intermediary iridium acetylide. Additionally, whilst the follow-up study does report the synthesis of propargyl amine **106** bearing a cyclohexyl group from the parent ketimine, this is the only example of a tertiary centre being accessed using this chemistry.[69] Given that cyclohexylketimines are inherently more electrophilic than other ketimine derivatives this example is likely unrepresentative of ketimines in general and it was therefore concluded this

method would be unsuitable for the synthesis of the amines required for this study.[70] To this end, this route was not pursued further.



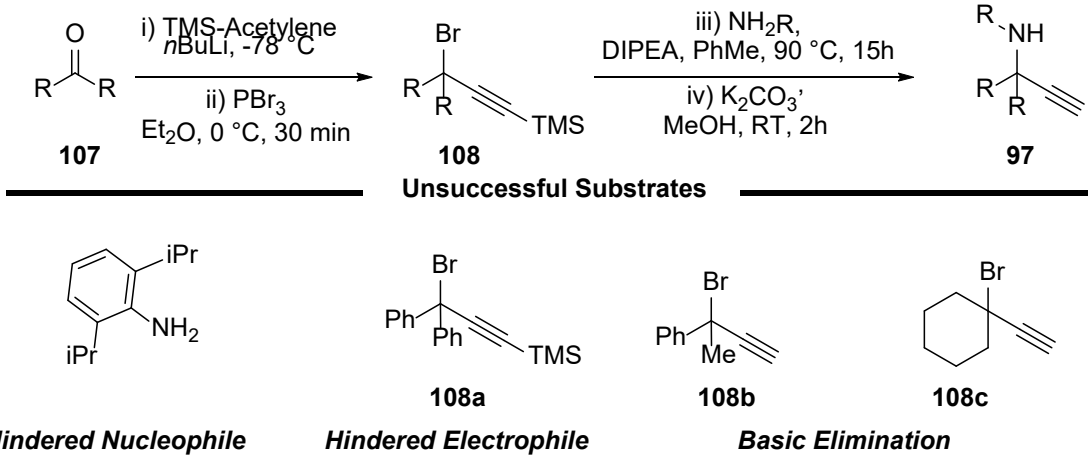
Scheme 21 Application and limitations of Ir catalysed alkynylation of aldimines

Attention therefore turned to the route reported by Ogiwara and co-workers.[71] In this route, addition of lithium trimethylsilylacetylide to an aldehyde or ketone affords a TMS-protected propargylic alcohol, which can subsequently undergo conversion into propargyl bromide **108** by treatment with an excess of phosphorus tribromide. This bromide can then be treated with a desired amine nucleophile, undergoing nucleophilic substitution to afford a TMS-protected propargylic amine which is subsequently deprotected *via* basic methanolysis to afford propargyl amine **97**. Using this route, amines **97a**, **97b**, and **97c** could be accessed from benzaldehyde by treatment of a common propargyl bromide intermediate with benzylamine, 2-chlorobenzylamine and aniline respectively. Treatment of the propargyl bromides derived from 2-fluoroacetophenone and pinacolone with benzylamine afforded amines **97d** and **97e**.



Scheme 22 Synthesis of propargylic amines by nucleophilic substitution of propargylic bromides

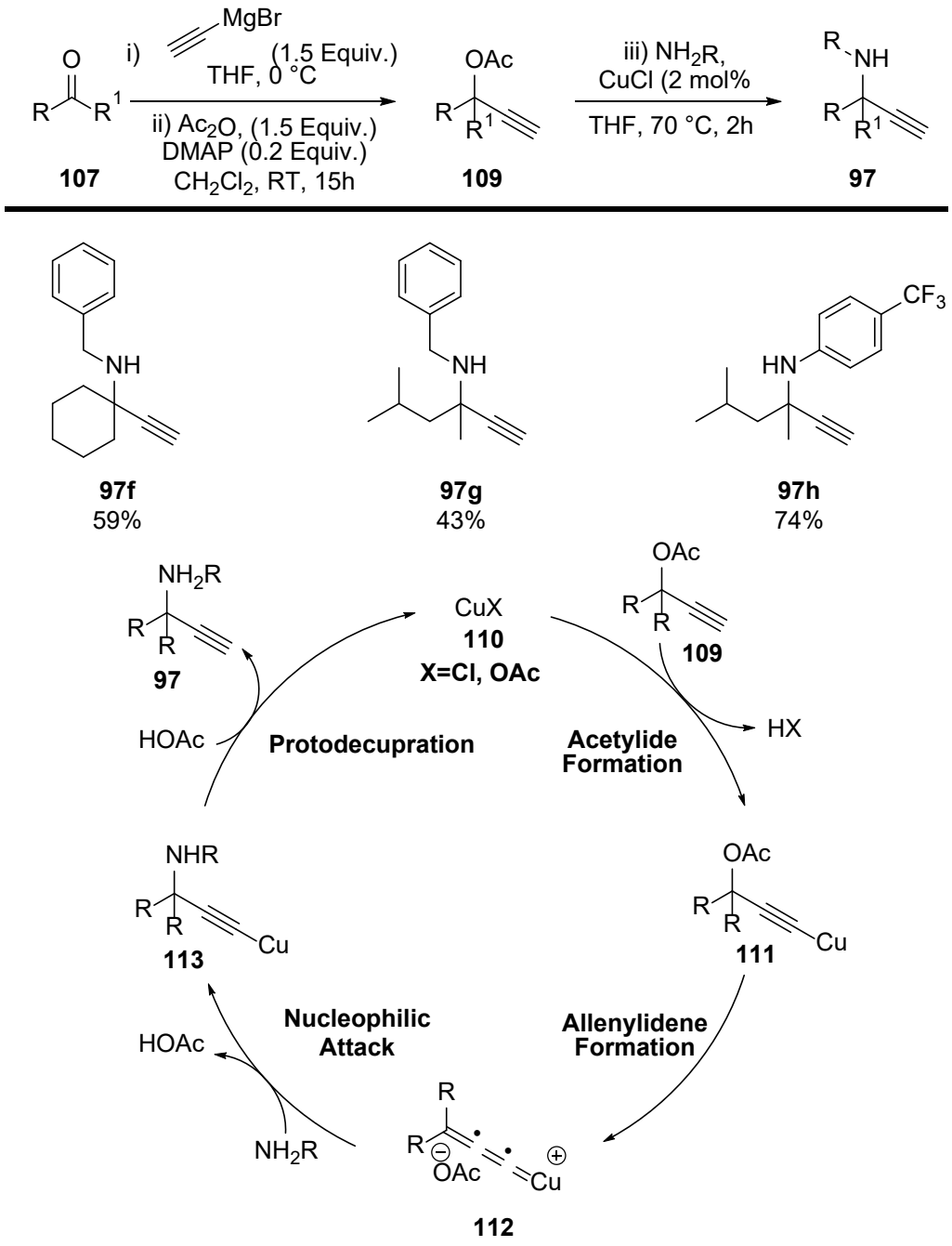
Whilst this route did allow us to access amines **97a**-**97e** (**Scheme 22**), there were several cases where the method showed limitations (**Scheme 23**). When the propargyl bromide used to access amines **97a**-**97c** was treated with 2,6-diisopropylaniline, no reaction was observed presumably due to the sterically encumbered nature of the nucleophile. Likewise, when sterically encumbered propargyl bromide **108a** was employed, no reaction occurred. Treatment of bromides **108b** and **108c** with benzylamine resulted only in elimination of the halide. To address these limitations, additional routes were therefore examined.



Scheme 23 Limitations of the route shown in Scheme 22

To this end, the route reported by Muruhashi and co-workers was next utilised. This route permits access to tertiary propargylic amines *via* copper catalysed

coupling of amines with propargyl acetates and has been shown to be suitable for accessing cycloalkyl substrates which had previously proven challenging.[72] Mechanistically, treatment of propargyl acetates **109** with copper(I) chloride forms copper-allenylidine complex **112** which acts as the active electrophile which can subsequently undergo nucleophilic trapping to afford the corresponding propargyl amine **97**. Access to propargylic esters was straightforward with propargylic alcohols, (**Scheme 22**), readily undergoing quantitative conversion into the corresponding ester by acetylation with acetic anhydride in the presence of catalytic amounts of DMAP. As before, the reaction can be telescoped mitigating the amount of purification steps. Using this method, alkynes bearing tertiary aliphatic centres could readily be isolated with **97f**, **97g**, and **97h** isolated in 59%, 43% and 74% yields respectively, (**Scheme 24**).



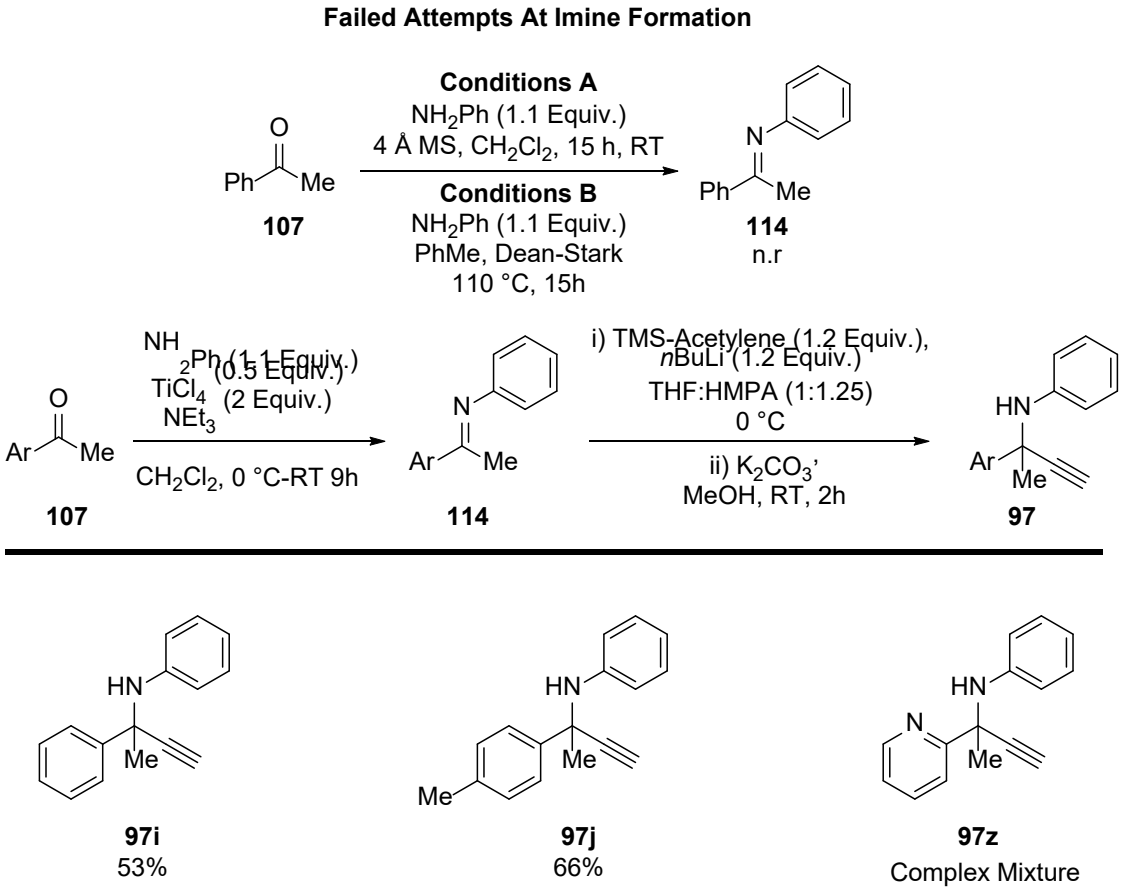
Scheme 24 Scope and mechanism of Cu catalysed amination of propargylic esters

Finally the method reported by Oshima and Dorey wherein lithium trimethylsilyl acetylide undergoes nucleophilic addition to a ketimine to afford a TMS-protected propargyl amine was explored (**Scheme 25**).[73,74] As ketimines are not sufficiently electrophilic to react with lithium acetylides, HMPA is used as an additive in the reaction. HMPA along with compounds like TMEDA and crown ethers are used to solvate cations thereby breaking up organometallic oligomers in solution, affording a more reactive organometallic species, in this case mitigating the

decreased electrophilicity of the starting material.[75] To illustrate the strength of the HMPA-Li interaction, the coordination has been shown to be approximately 300 times stronger than the THF-Li interaction.

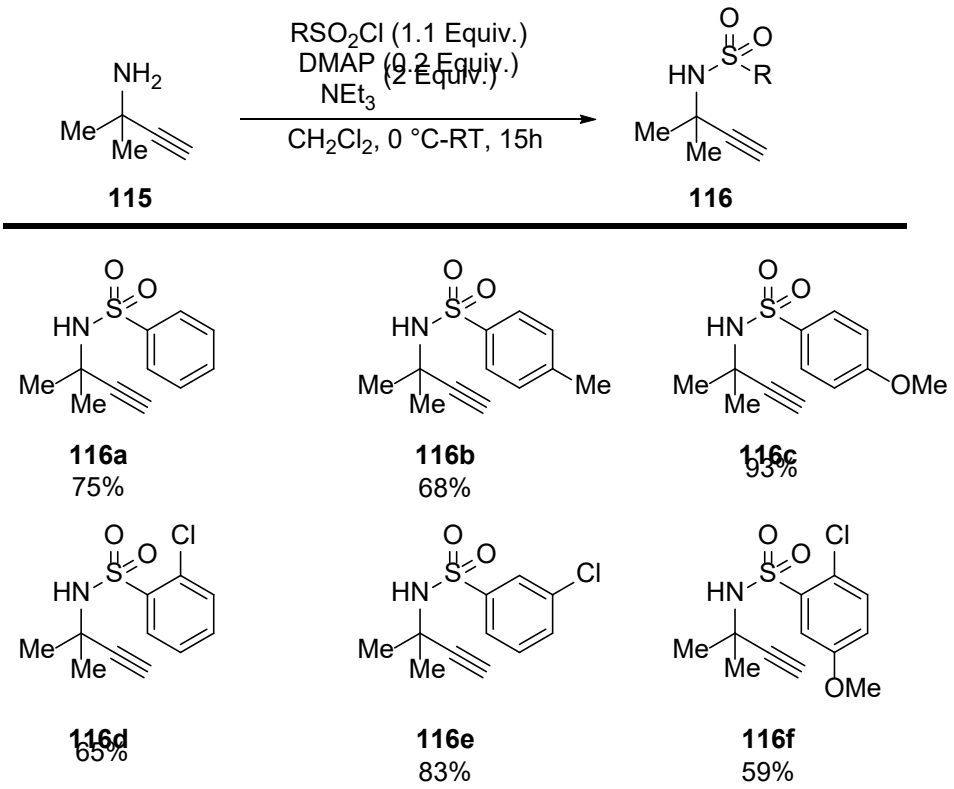
As the aldimines discussed previously (**Scheme 21**) had been accessed *via* the simple condensation reported by Melen, initial attempts to access the requisite ketimines also utilised this approach, though no reaction occurred (**Scheme 25**, **Conditions A**).[68] Other reports had also employed Dean-Stark apparatus to remove water from the reaction vessel, although it was observed that this again led no observable formation of the desired ketimine (**Scheme 25**, **Conditions B**). A survey of the literature found titanium tetrachloride has frequently been employed to mediate this reaction, likely serving a dual purpose as both a Lewis acid to activate the ketone towards nucleophilic attack by the amine in addition to acting as a desiccant to remove the water produced in the reaction by hydrolysis of $TiCl_4$ into TiO_2 and HCl, and using these conditions ketimines derived from acetophenone, 4-methyl acetophenone and 2-acetylpyridine could be readily accessed.[76]

The ketimines were readily converted into a mixture of both TMS-protected propargyl amines and the deprotected derivative when treated with lithium TMS-acetylide in the presence of HMPA. Following treatment of this mixture with potassium carbonate in methanol, alkynes **97i** and **97j** were accessed in moderate yields. Unfortunately, when attempting to access pyridyl alkyne **97z** *via* this methodology, the acetylide addition resulted in the formation of an inseparable mixture of products, likely due to competing directed-metalation pathways resulting from the presence of the pyridyl ring.



Scheme 25 Synthesis of propargylic amines by addition of lithium trimethylsilylacetylide to *N*-Phenyl ketimines

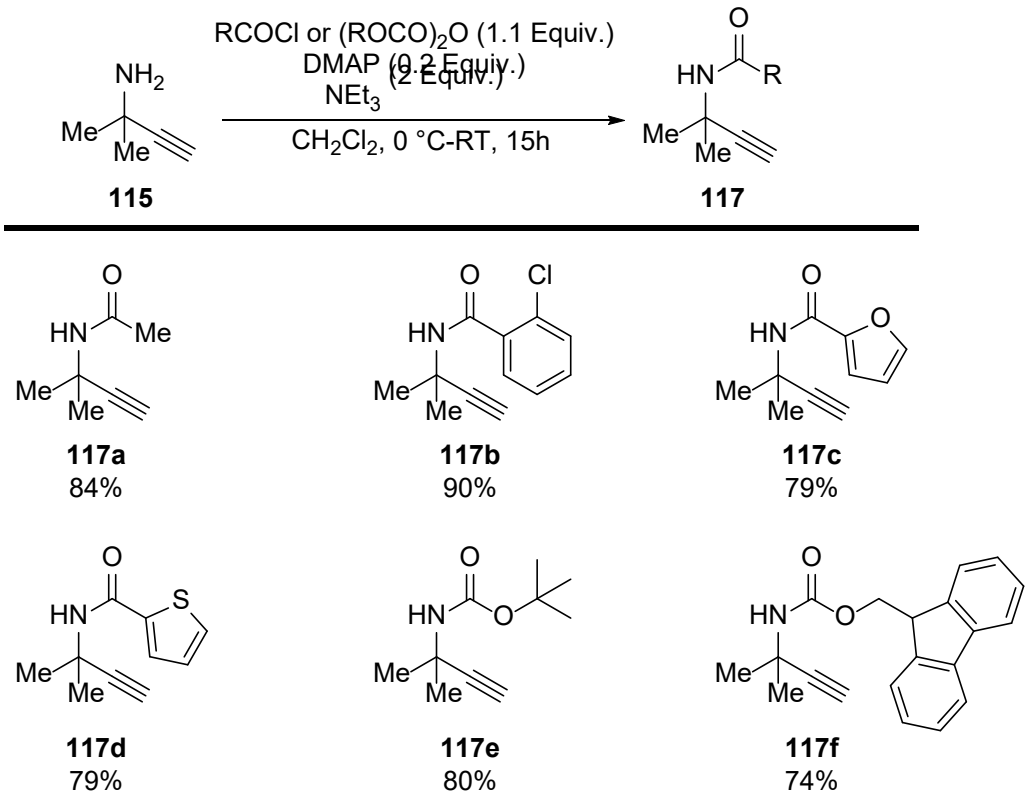
In order to probe the tolerance of the hydrosilylation reaction to a range of nitrogen containing functionalities other than amines, a range of propargylic sulfonamides were synthesised from the commercially available amine **115**. Treatment of **115** with a range of sulfonyl chlorides in the presence of triethylamine and catalytic amounts of DMAP allowed for facile synthesis of a range of sulfonamide derivatives **116a-f** in good yields (**Scheme 26**).



Scheme 26 Synthesis of propargylic sulfonamides

Under the same conditions, a range of propargylic amides and carbonates could be accessed by treatment of 2-methyl-3-butyn-2-amine **115** with the requisite acyl chloride or acid anhydride, affording access to structurally diverse propargylic amides **117a-117d** in yields ranging from 79-90%. Notably this also afforded access to scaffolds bearing heterocyclic motifs.

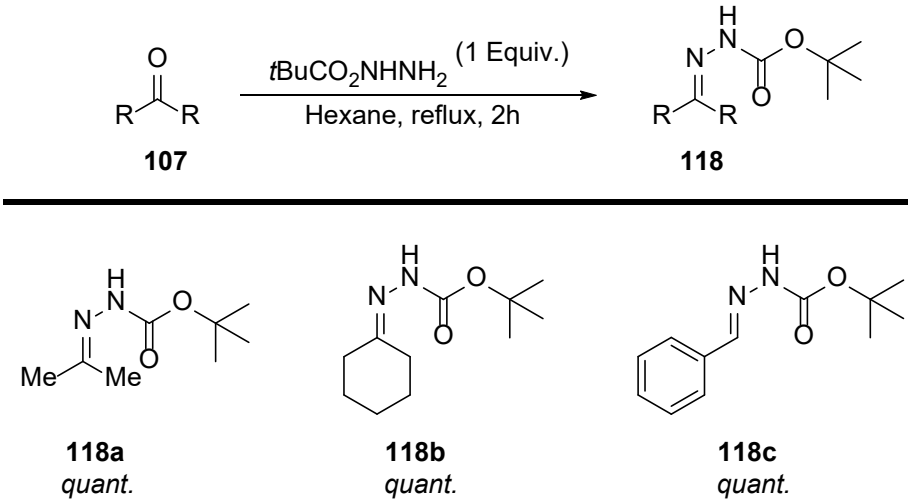
By treatment of **115** with di-*tert*-butyl dicarbonate and fluorenylmethyloxycarbonyl chloride, both Boc and Fmoc protected propargylic amines **117e** and **117f** could be accessed in good yields, providing access to scaffolds with orthogonal modes of deprotection.



Scheme 27 Synthesis of propargylic amides and carbamates

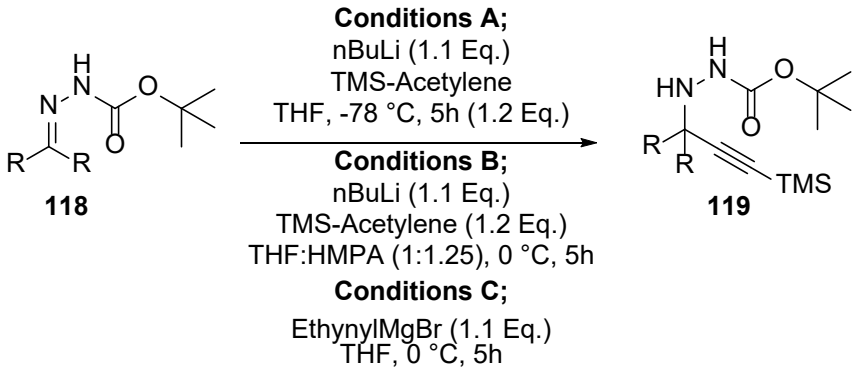
As an extension to substrates containing a single nitrogen atom at the propargylic position, the synthesis of propargylic hydrazines was attempted. It was envisaged that a similar approach to substrates **97i** and **97j** could be used, although in this case rather than an imine electrophile, a hydrazone electrophile of general formula **118** would be employed.

To this end, a range of hydrazones were prepared to probe the feasibility of this method. Hydrazones **118a**-**118c** were prepared *via* condensation between the requisite aldehyde or ketone and *tert*-butyl carbazate in quantitative yields (**Scheme 28**).



Scheme 28 Synthesis of hydrazones

When attempting to convert *N*-Boc protected hydrazones **118a-118c** into the corresponding propargylic hydrazines, complete lack of reactivity towards nucleophilic attack by lithium acetylides was observed. The addition of HMPA could seemingly not overcome this apparent lack of reactivity, with starting material recovered even in the case of the more electrophilic hydrazone **118c**. This lack of reactivity is likely due to a deprotonation of the relatively acidic carbazate proton, resulting in the formation of a hydrazonate anion, effectively shutting down the little reactivity the substrate possesses to start with. It is not immediately clear why this lack of reactivity was observed when other related organometallic additions to hydrazones has been previously reported by Huang *et al*.[77] Nonetheless, a range of structurally diverse alkynes bearing nitrogen containing functionalities at the propargylic position had been synthesised therefore optimisation of the hydrosilylation conditions was next studied.

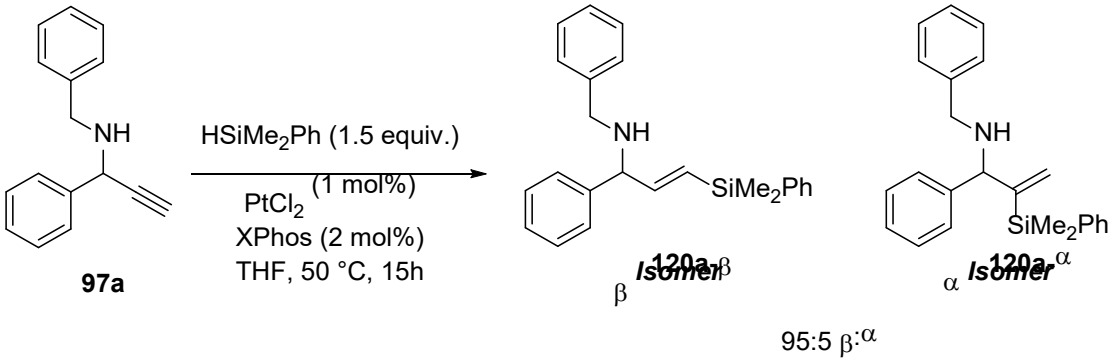


Scheme 29 Attempted synthesis of propargylic hydrazines

2.4 Optimisation of Hydrosilylation Conditions

With the requisite starting materials now in hand, the next focus was on screening conditions to establish an optimised set of reaction conditions to allow facile and selective hydrosilylation of the alkynes. As previously discussed, a plethora of platinum-based catalyst systems have been reported for alkyne hydrosilylation, though this study began by employing complexes of $PtCl_2$ alongside a range of monodentate diarylbialkylphosphines. This is based on the work reported by both Alami and Cook wherein the authors disclose the high levels of selectivity afforded by this complex when utilised as hydrosilylation catalysts, with much higher levels of selectivity and activity than under ligand free conditions. In particular, the work by Cook & McLaughlin demonstrates the efficacy of a $PtCl_2$/XPhos catalyst system for the hydrosilylation of propargylic alcohols and given the substrates in this body of work also bear Lewis basic heteroatoms at this site, it was reasoned that this complex represented an ideal starting point for the study.[24,22]

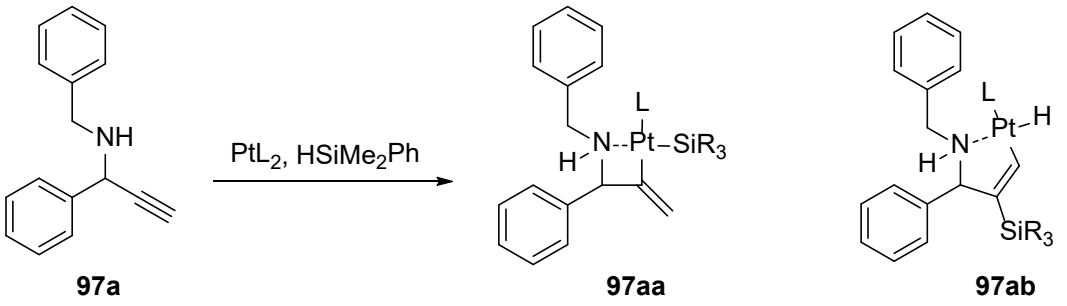
When amine **97a** was treated with dimethylphenyl silane in the presence of $PtCl_2$ (10 mol%) and XPhos (20 mol%), complete consumption of the starting alkyne was observed over a period of 15 hours. Lowering the loading of $PtCl_2$ to 5, 2 and 1 mol% had negligible impact on conversion, with full consumption of the alkyne observed in each case. This alleviated early concerns that the strongly coordinating nature of the nitrogen atom would inhibit catalytic activity. It was noted that while the catalyst was highly effective at mediating the delivery of the metal hydride to the π-system, the ^{1}H NMR spectrum of the isolated silane possessed a minor olefinic side product. This olefinic side product, which also resulted in a twinning of each of the peaks in the NMR spectrum was assigned to the formation of small amounts of α-regioisomer **120a-α** in addition to **120a-β**.



Scheme 30 $PtCl_2$/XPhos catalysed hydrosilylation of 97a

This loss of selectivity in the $PtCl_2$/XPhos catalyst system was unforeseen, with the work reported by both Cook and Alami reporting complete regioselectivity except in cases wherein the alkyne is strongly polarised *via* electron deficient aromatic systems. As this system is not polarised in any significant manner and there is no steric argument to be made for this loss of regioselectivity in comparison to the substrates reported by Cook, it was reasoned that the presence of the nitrogen was the cause of the decrease in selectivity. Whilst formation of the metallacycles (**Scheme 31**) adequately explain the observed α-isomer, the strained nature of **97aa** and the requirement for an unusual *anti*-silylplatination to afford **97ab** means the formation of these intermediates is rather unlikely. More likely is the displacement of a phosphine ligand on-cycle by the large excess of N-donor ligands, resulting in the formation of a complex which, while able to catalyse the hydrosilylation of **97a** with high levels of conversion, displays decreased selectivity relative to the diphosphine complex.

Potential Modes of Directed Metallation

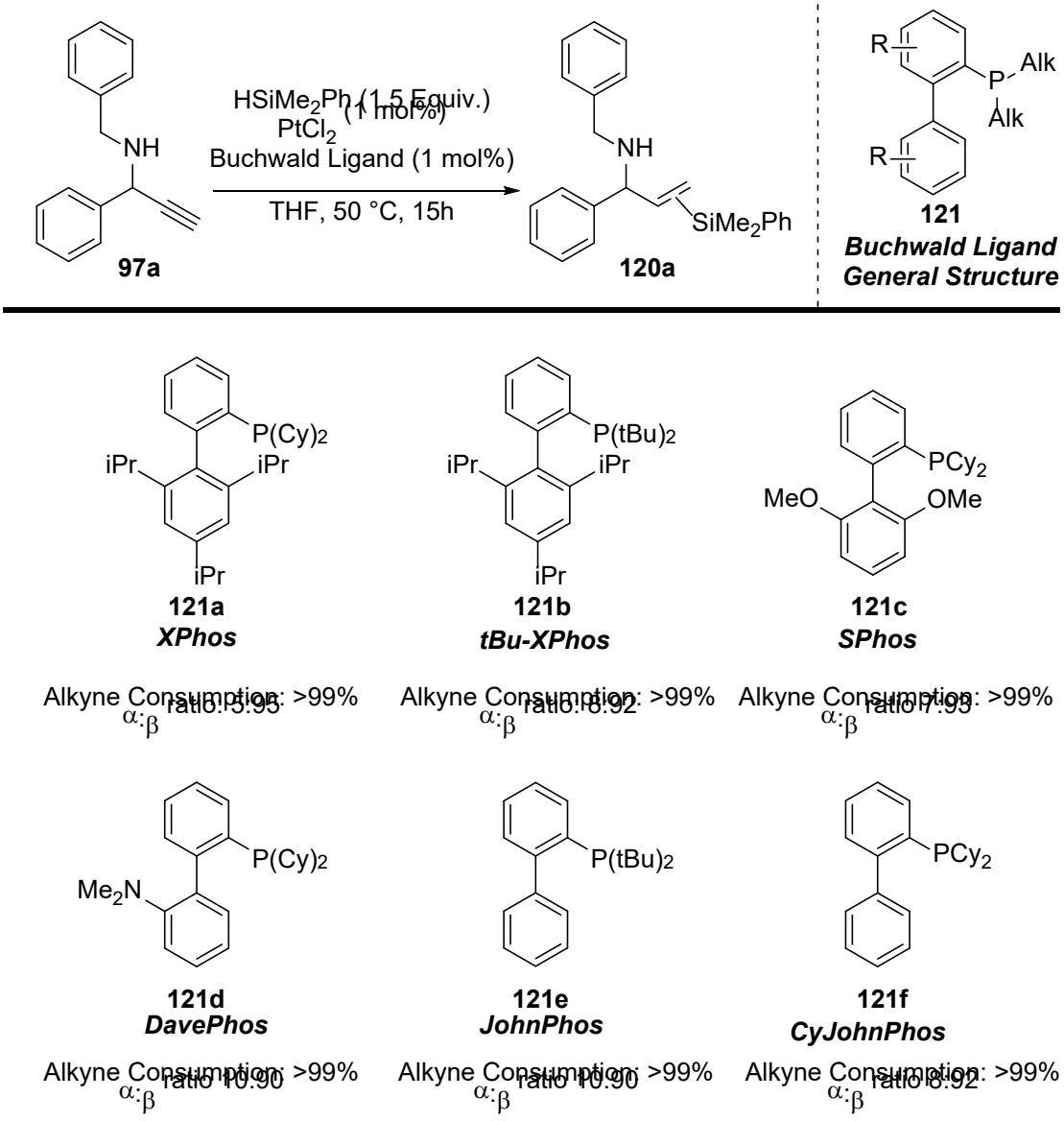


Scheme 31 Metallacycle intermediates leading to formation of 120a-α

Regarding why this has not been observed in propargylic alcohols, this is attributed to two factors: the azaphilicity of platinum versus its relative lack of oxophilicity and the inherent increased basicity of amines vs alcohols. The second point is relatively self-explanatory, the pK_a differential between alcohol (~15) and the general pK_a for secondary amines (~35) shows the significant difference in basicity and therefore coordinative ability between the two individual substrates. This, in combination with the inherent lack of oxophilicity of platinum, would further dissuade any substrate/catalyst interactions through the heteroatom. In the case of the amines, a new mode of complexation is available, and thus a method for catalyst inhibition exists.

Given that the isomers could not be separated by chromatographic means, a systematic screening of ligands was carried out in the hope of obtaining higher levels of selectivity. A range of biaryldialkyl phosphine ligands (Buchwald Ligands) were screened to assess their efficacy at modulating the regioselectivity of the reaction. The selectivity for the reaction was assessed by ^{1}H NMR analysis, with the results alongside the structure of the ligand employed tabulated in **Scheme 32**.

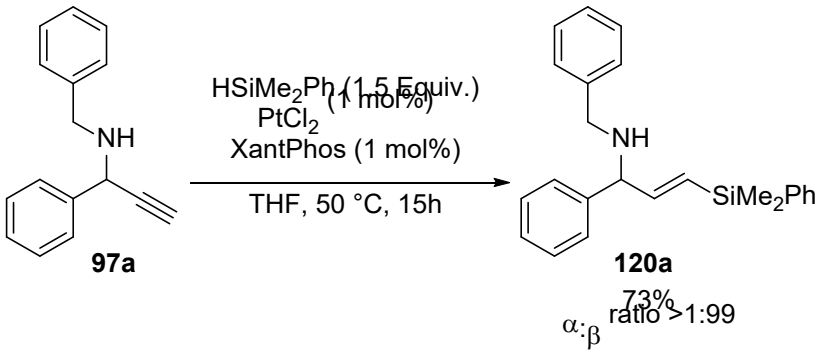
As shown, the steric and electronic nature of the Buchwald ligand seemingly bears little effect on the selectivity achieved, with comparable regioselectivities achieved in all cases. This aligns with the previous proposal of the ligand displacement resulting in a loss of regioselectivity. This is most well illustrated by comparison of the results afforded by **121a** and **121b** respectively. Given the larger steric bulk of **121b**, it would reasonably be expected that higher levels of selectivity would be achieved. Given that it falls short of the selectivity afforded by **121a**, this suggests loss of one or multiple of the phosphines to a common platinum intermediate accessed irrespective of the ligand employed.



Scheme 32 Ligand Screen Results. Alkyne consumption & isomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture

It was then hypothesised that utilisation of a bidentate ligand could inhibit phosphine displacement by taking advantage of the chelate effect. The chelate effect results in an increased affinity for polydentate ligands by a metal centre when compared to related monodentate ligands. The effect is entropic in nature, with the driving force being the liberation of a greater number of free molecules in solution when a polydentate ligand of donor number *n* is bound in comparison to *n* monodentate ligands. The decreased modes of free rotation available in the chelated complex is also a factor, although much less so than the aforementioned molecule liberation. To examine whether bidentate ligand systems could increase the selectivity of the reaction, XantPhos was next employed as a ligand,

in a decreased ratio of 1:1 metal: ligand reflective of the bidentate nature of the ligand. Under these conditions, the selectivity dramatically increased, with no α-isomer present in the ^{1}H NMR of the crude reaction mixture (**Scheme 33**). Finally, two control experiments were conducted, carrying out the reaction both without ligand or metal and in both cases no reaction was observed.



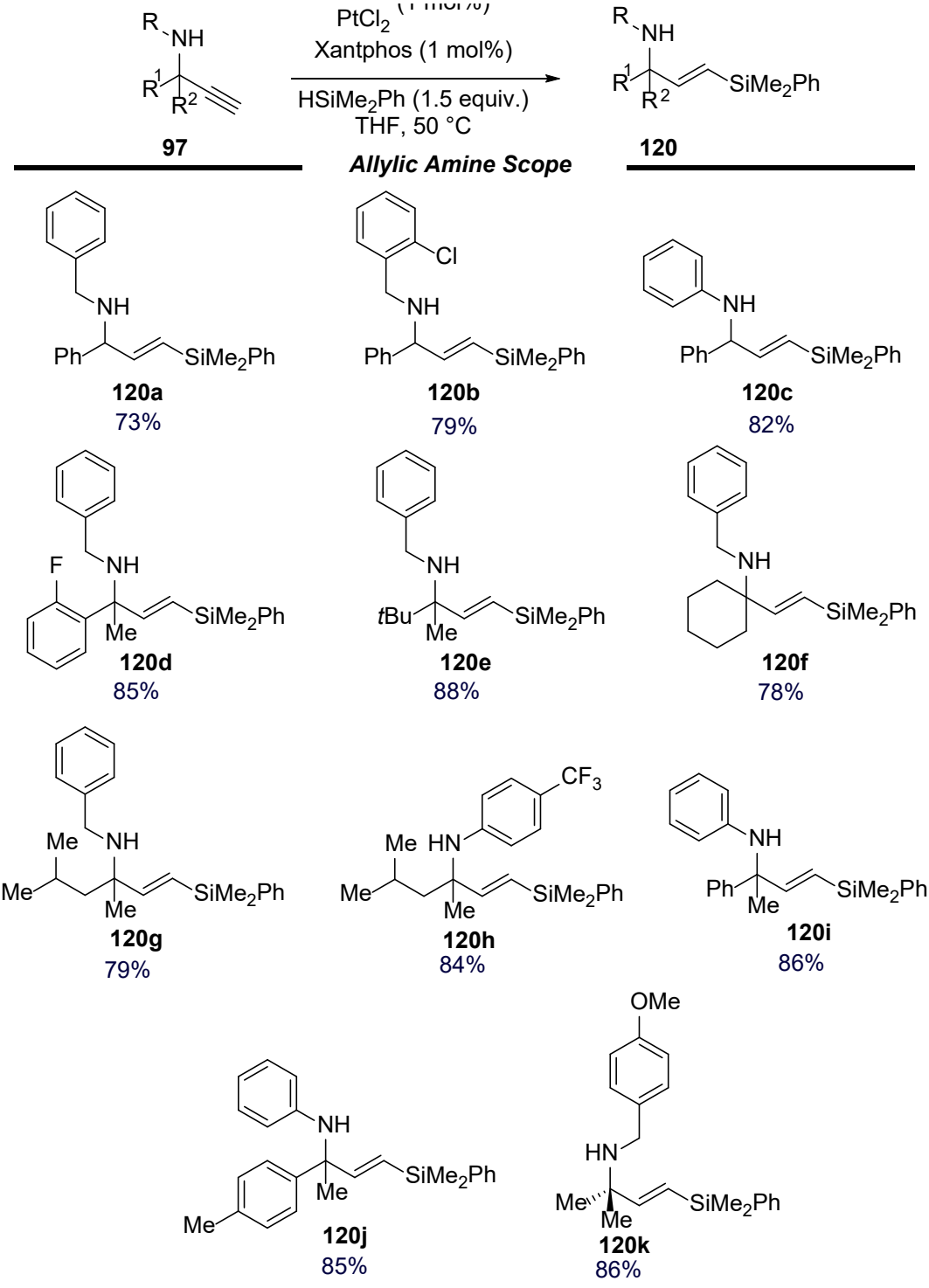
Scheme 33 $PtCl_2$/XantPhos catalysed hydrosilylation of 97a

2.5 Substrate Scope

Having identified the unique ability of $PtCl_2$/XantPhos to carry out the hydrosilylation of **97a** with complete control over stereoselectivity and regioselectivity, a screening of the amines synthesised in **Chapter 2.3** was carried out to identify any limitations which exist within the methodology. The isolated yields of the compounds afforded by examining the substrate scope can be seen in **Scheme 34**.

Initial focus was paid to substrates bearing a tertiary centre at the propargylic position to minimise steric bulk. Under the optimised conditions, aniline derivative **120c** was readily afforded in 82% yield, with no decrease in regioselectivity observed. Introduction of halogen functionalities onto the *N*-Benzyl substituent was equally tolerated, with **120b** isolated in 79% yield with no observed formation of side products arising from halide reduction. Next, more sterically encumbered substrates were studied, with all amines now bearing quaternary carbon centres at the propargylic position, with the increase in steric bulk having no adverse effects on reaction efficacy.

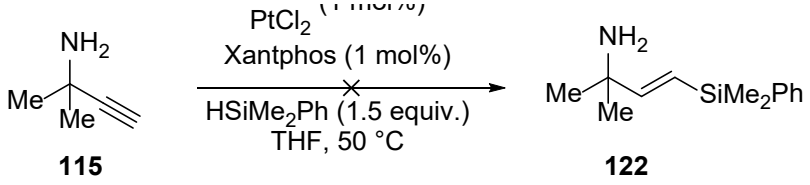
Aliphatic substrates **120e**-**120g** were all afforded in high yields, as were quaternary centres bearing aromatic substituents as shown by **120d**, **120i** and **120j**. Substrates bearing quaternary centres at the propargylic position in addition to functionalised benzyl or aryl nitrogen substituents were also suitable substrates for the reaction as shown by the synthesis of silanes **120h** and **120k**.



Scheme 34 Scope of allylic amines. Substrates afforded as single regio and stereoisomers.

Having explored a range of amines bearing substitution on the nitrogen, the commercially available **115** was next examined. Under the optimised conditions, **115** proved unsuitable as a substrate, with no formation of **122** observed in the ^{1}H NMR of the crude reaction mixture. Even carrying out the reaction at higher temperature did not result in formation of the desired organosilane. This observed

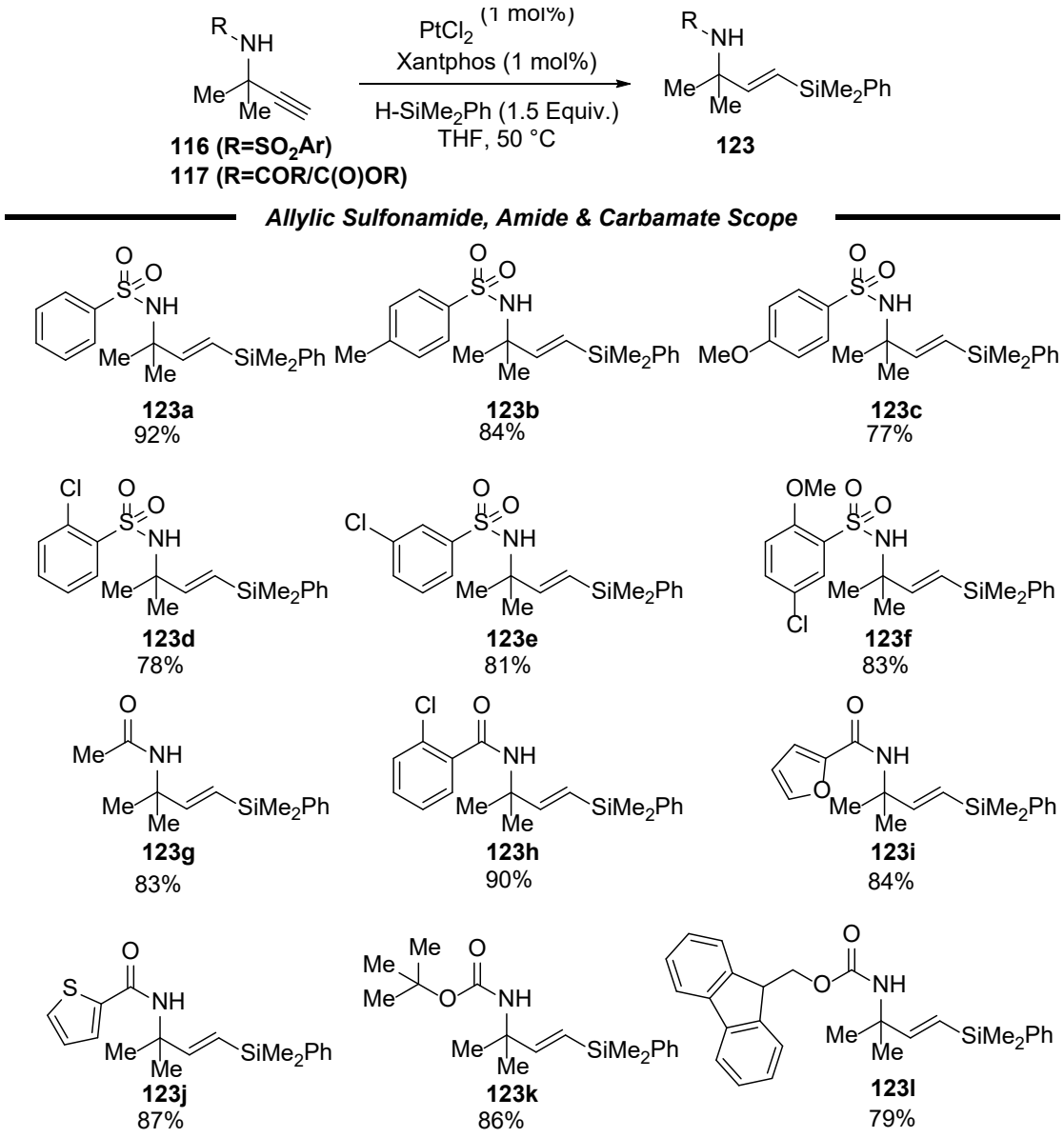
lack of reactivity likely arises from the presence of the free NH_2 inhibiting catalytic turnover.



115 **122**

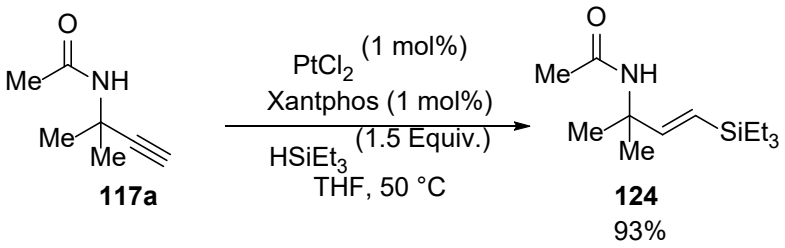
Scheme 35 Failed hydrosilylation of free amine 115

The next substrates to be examined were the propargylic sulfonamides, amides and carbamates synthesised in **Chapter 2.3**. Initial concern that the additional points of contact between the substrate and catalyst could reintroduce the aforementioned regioselectivity issues turned out to thankfully be unfounded, with sulfonamide **116a** readily undergoing hydrometallation affording silane **123a** in 92% yield under the optimised conditions, with no decrease in selectivity. The reaction proved tolerant to electron donating functionalities in the *para* position of the aryl sulfonamide as demonstrated by silanes **123b** and **123c** which were isolated in 84% and 77% yields respectively, while halogenated substrates **123d** and **123e** were also isolated in good yields. Propargyl acetamide **117a** proved an excellent substrate for the reaction affording **123g** in 83% yield. Other amides were also viable, with heterocyclic amides well tolerated to afford silanes **123i** and **123j** in 84% and 87% yield respectively. Both Boc and Fmoc protected derivatives also underwent selective metalation, affording silanes **123k** and **123l** in 86% and 79% yields, providing access to scaffolds with orthogonal modes of deprotection.



Scheme 36 Scope of allylic sulfonamides, amides and carbamates. Substrates afforded as single regio and stereoisomers.

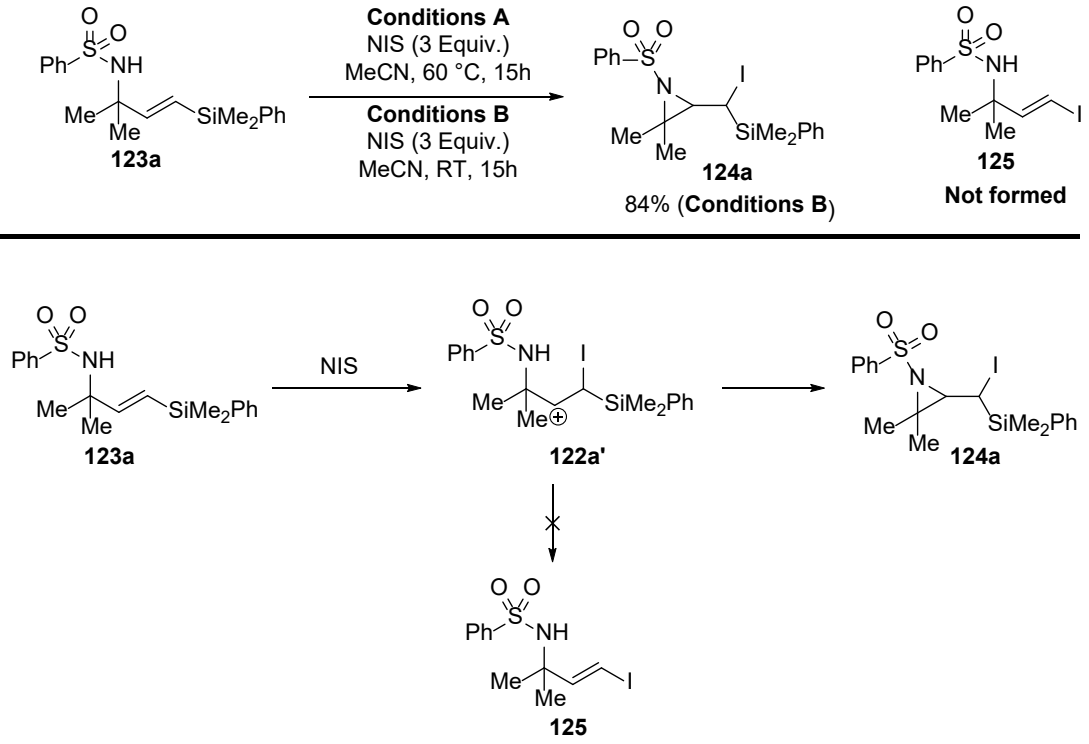
All substrates to this point had been synthesised by hydrosilylation using dimethylphenylsilane. To demonstrate the viability of carrying out the reaction using a different silicon hydride, triethylsilane was employed for the hydrosilylation of acetamide **117a** which afforded triethylsilane derivative **124** in an excellent 93% yield.



Scheme 37 Application of other silanes

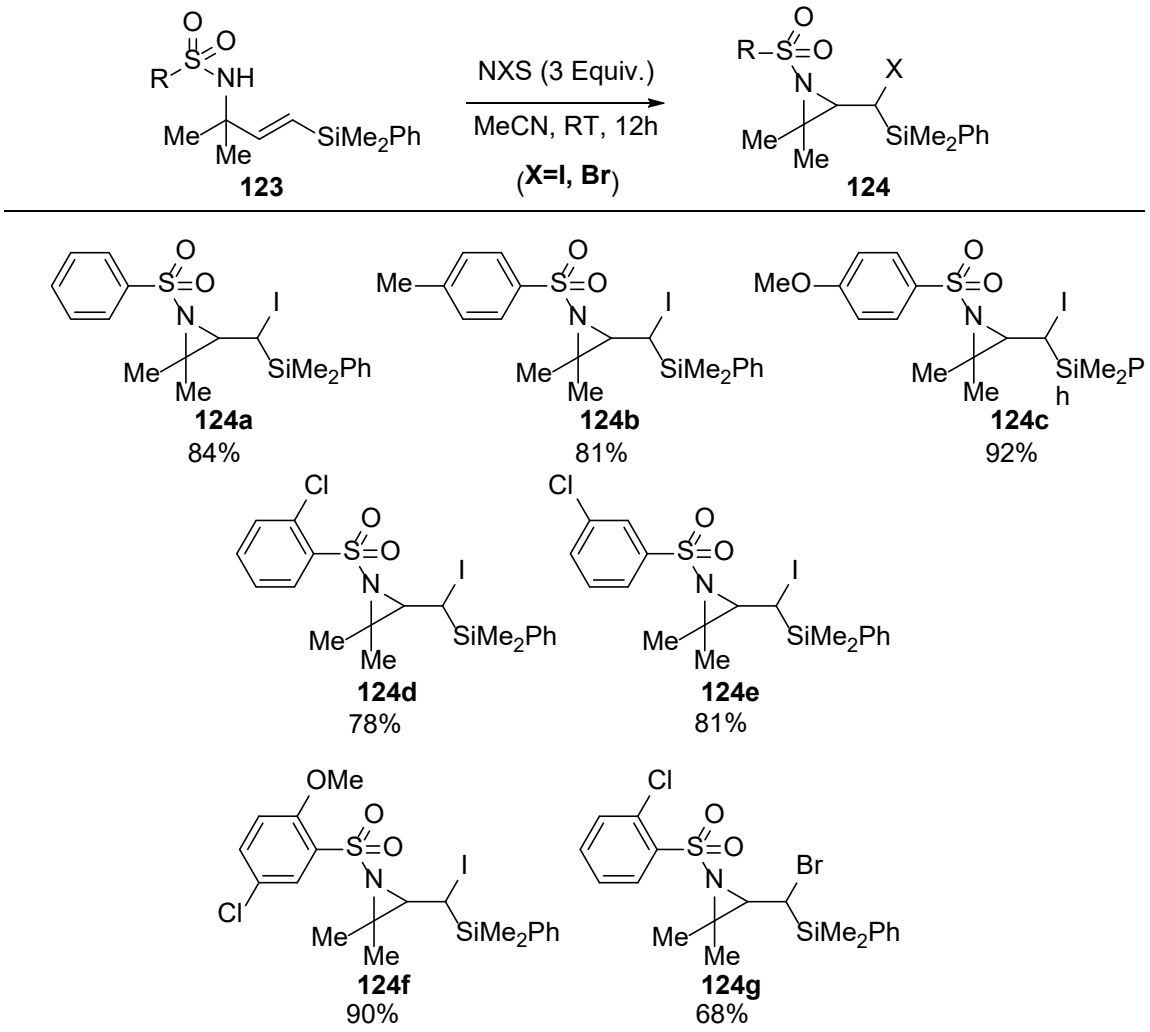
2.6 Product Diversification

As a range of vinyl silanes had been synthesised, the synthetic utility of the products was next explored. One of the principle reactions of vinyl silanes aside from cross-couplings is their ability to undergo electrophilic substitution, with the reaction proceeding *via* an intermediate cation stabilised by the β-silicon effect.[78] To this end, the reactivity of the silanes towards these reagents was first explored. Initially this substitution was attempted by employing the conditions reported by Nicolaou and co-workers and as such, silane **123a** was treated with a 3-fold excess of *N*-Iodosuccinimide (NIS) in acetonitrile at 60 ˚C.[79] Under these conditions, rather than clean conversion into the expected iodide **125** a complex mixture of products arose, though it was noted that no vinyl silane remained in the reaction mixture. It was reasoned that the iodide was potentially sensitive to elevated temperatures and thus the reaction was repeated at room temperature, this time undergoing clean conversion into aziridine **124a**. The formation of **124a** likely arises *via* electrophilic activation of **123a** in the expected manner, though rather than quenching of the intermediary cation **122a'** *via* loss of the silyl group, the cation is instead quenched *via* an intramolecular trapping event to instead afford **124a** in a formal 3-exo-trig cyclisation.



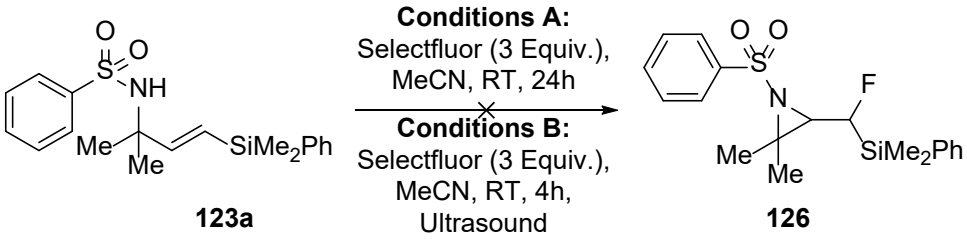
Scheme 38 Electrophile triggered aziridination of 123a

As access to aziridines typically relies on highly forcing basic conditions, or nitrene chemistry employing bespoke reagents and catalysts, the scope of this remarkably mild cyclisation procedure was next explored.[80] When exploring the scope of this reaction, it was observed that under the same conditions as before, a range of *N*-Sulfonyl aziridines could be afforded in excellent yields. Aziridines bearing electron rich *N*-Arylsulfonamide substituents such as **124b** and **124c** were afforded in 81% and 92% yield, while halogenated derivatives **124d** and **124e** were likewise isolated in high yield. Gratifyingly the cyclisation could also be triggered by treatment with *N*-Bromosuccinimide (NBS) to afford brominated derivative **124g** albeit in a slightly decreased 68% yield.



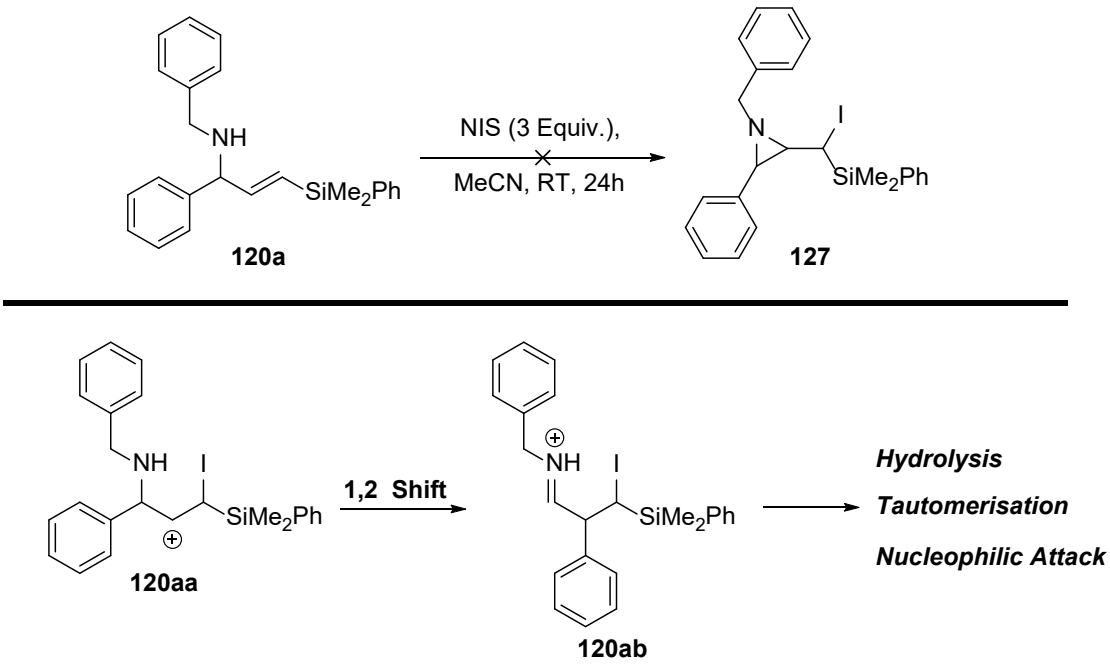
Scheme 39 Scope of *N*-Sulfonylaziridines

When attempting to trigger the cyclisation of **123a** using Selectfluor, no reaction was observed. This is in keeping with previous reports of poor reactivity of vinyl silanes towards Selectfluor, with work by the Gouverneur describing the reaction with trimethylstyrylsilane which shows less than 30% conversion even after 24 hours.[81] Previous work has suggested that the application of ultrasound can accelerate the rate of reaction between trimethylsilylalkenes and Selectfluor.[82] To this end, the reaction was repeated under sonication and again no reaction was observed. Presumably this poor reactivity is a consequence of the poor matching of reactive species, with the reaction employing a soft nucleophile in the silane with a relatively hard electrophile.



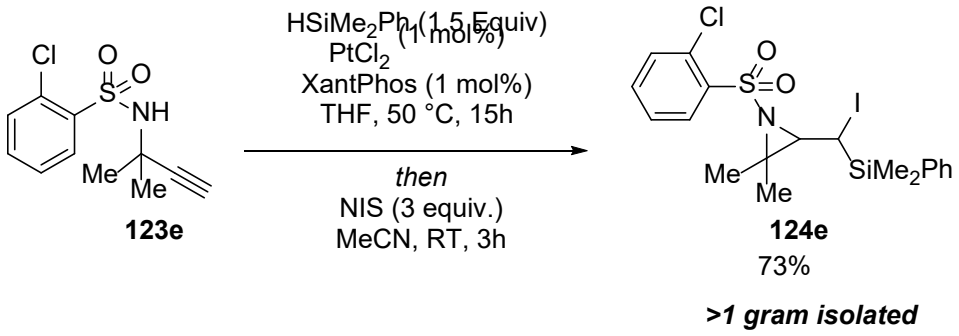
Scheme 40 Attempted synthesis of fluorinated aziridines

When amine **120a** was employed as a substrate other limitations became apparent. In this instance, the reaction quickly forms a complex mixture of products, with the formation of various highly downfield peaks visible in both the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture, assigned to the formation of various imine and carbonyl containing compounds. This likely occurs *via* formation of the expected β-silyl cation **120aa** with the cyclisation then outcompeted by a silicon-directed Aza-Semi Pinacol rearrangement *via* 1,2-shift of the phenyl group to afford **120ab** which can then undergo degradation by multiple pathways, resulting in the formation of a complex mixture of products. This proposal is discussed in more depth and validated in **Chapter 3.7**. When attempting the reaction allyl acetamide **123g**, the formation of several inseparable products was again observed, likely due to competing cyclisation modes which have previously been reported for similar systems. [83]



Scheme 41 Attempted synthesis of *N*-Benzylaziridine 127

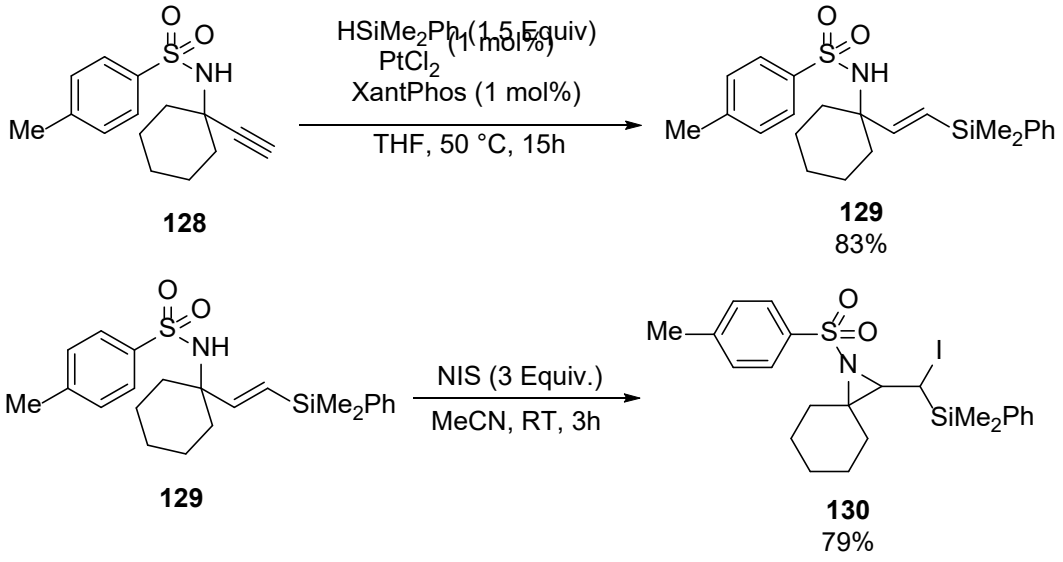
Telescoping the hydrosilylation and subsequent cyclisation is an appealing approach, as this minimises the amount of chromatography steps required in the synthesis, saving both time and material. To this end, the telescoped sequence outlined in **Scheme 42** was attempted, affording **124e** in 73% yield over two steps. Notably, this telescoped sequence was performed on gram scale, allowing for gram-scale synthesis of **124e**.



Scheme 42 Telescoped gram scale hydrosilylation/cyclisation sequence

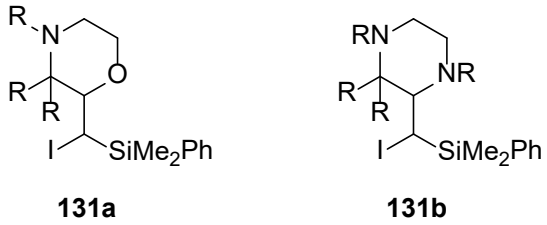
The hydrosilylation/cyclisation sequence could also be applied to the synthesis of spirocyclic aziridine **130** from sulfonamide **128**. Following hydrosilylation under the previously optimised conditions **129** was isolated as a single isomer in 83%

yield. Subjecting **129** to the same conditions as previously employed resulted in the formation of spirocycle **130** after 3 hours in 79% yield.



Scheme 43 Synthesis of spirocyclic aziridines by hydrosilylation/cyclisation of propargylic sulfonamides

As it had been demonstrated that aziridines could readily be accessed by this hydrosilylation/cyclisation approach, it was postulated that other heterocycles could be afforded by a similar approach. In particular, the synthesis of piperazine and morpholine derivatives **131a** and **131b** was proposed.

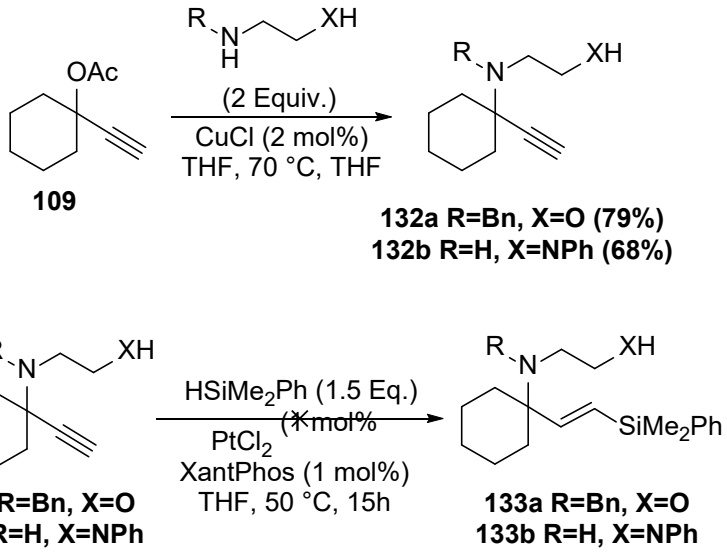


131a **131b**

Scheme 44 Proposed heterocycles to be accessed by iodination/cyclisation methodology

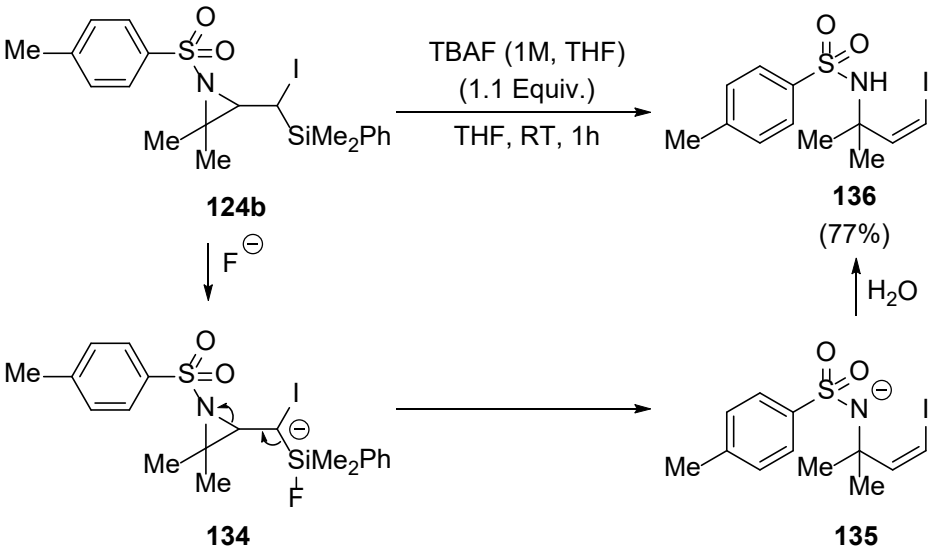
To this end, **132a** and **132b** were prepared *via* the Cu-catalysed amination of **109**, using ethanolamine and 1,2-ethylenediamine derived nucleophiles. Unfortunately, when attempting to carry out the hydrosilylation of **132a** and **132b**, they were found to be unsuitable for the reaction with no formation of the desired vinyl silane observed, even when the reaction was attempted at elevated

temperature. This lack of reactivity for these types of substrates is likely due to the chelating nature of the ethanolamine or diamine pendant arm.



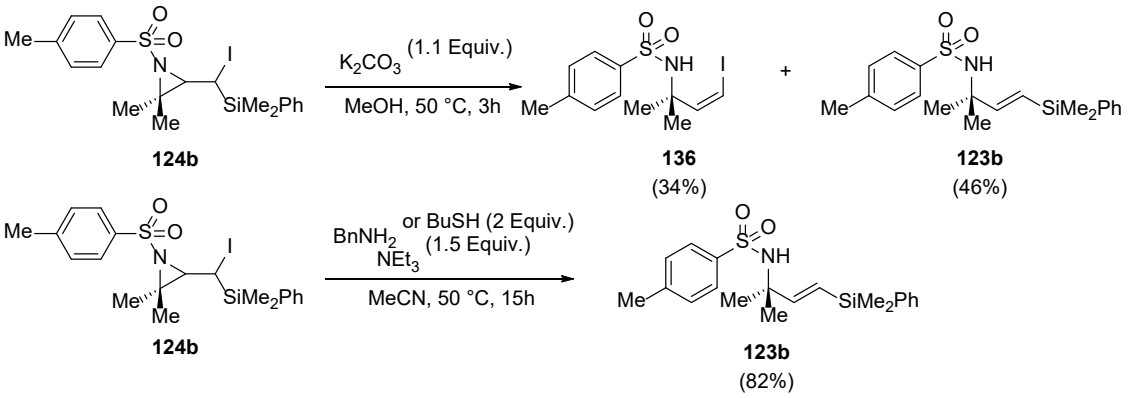
Scheme 45 Attempted hydrosilylation of 132a and 132b

With a range of aziridines in hand, the synthetic utility of the products was next investigated, with particular focus paid to the reactivity of the unique α-iodosilane motif installed by virtue of the cyclisation. Whilst relatively uncommon, this motif has shown to have synthetic utility, with work by Oestreich and co-workers displaying the application of these type of scaffolds as electrophiles in enantioselective Negishi cross-couplings.[84] The study began with attempted desilylation of **124b** by treatment with TBAF. Instead of the expected desilylation product, **136** was instead isolated. Interestingly, when compared to the stereochemistry of silane **123b**, from which **124b** is derived, the geometry of iodide **126** has inverted resulting in a formal stereoinvertive substitution of the silane. Presumably this arises from the mechanism proposed in **Scheme 46** wherein upon fluoride activation to silicon-ate complex **134**, rather than hydrolysis upon workup, the aziridine undergoes ring opening to afford vinyl iodide **136**.



Scheme 46 Synthesis of vinyl iodide 136 by TBAF mediated desilylation of 124b.

Attempt to desilylate **124b** by treatment with potassium carbonate in methanol led to a mixture of iodide **136** and surprisingly, silane **123b**. The formation of vinyl iodide can be rationalised *via* a similar mechanism to that proposed for the TBAF mediated ring opening shown in **Scheme 46**. The formation of **123b** can be rationalised by nucleophilic attack of a methoxide anion at iodine with concomitant ring opening resulting in the formation of **123b**. This proposal was validated *via* treatment of **124b** with benzylamine, which resulted in clean formation of **123b** in an 82% yield. The lack of formation of **136** in this case can be attributed for the affinity of silicon for oxygen and fluoride nucleophiles. As a nitrogen nucleophile is employed in this case, attack occurs exclusively at iodine, resulting in clean conversion to **123b**. That the reaction is likely dictated by hard-soft interactions is corroborated by the application of butylthiol which also results in the formation of **123b**.



Scheme 47 Reactivity of α-iodosilyl groups towards various nucleophiles

2.7 Conclusions

A method for the selective and facile hydrosilylation of amines bearing tethered nitrogen containing functionalities has been developed, addressing a previous limitation of common hydrosilylation catalysts. The starting alkynes were synthesised using a combination of 3 synthetic routes starting from commercially available aldehydes and ketones. The first synthetic route initially converts the starting carbonyl compound into the corresponding propargylic alcohol *via* addition of lithium TMS-acetylide. Subsequent bromination with phosphorus tribromide and nucleophilic substitution with an amine nucleophile afforded the TMS-protected alkynes which could readily be deprotected *via* basic methanolysis. The second route employed a copper(I) chloride catalysed amination of propargylic esters, while the final route employed a HMPA-assisted organometallic addition into ketimines.

While a range of $PtCl_2$-monodentate phosphine complexes were able to carry out hydrosilylation of the amines with low catalyst loadings, $PtCl_2$(XantPhos) was unique in its ability to carry out this transformation with complete control of regiochemistry. This high level of regiocontrol is likely afforded by the denticity of the ligand rather than any steric or electronic factors, given the diverse range of monodentate ligands screened all afforded commensurate selectivities. Under a set of optimised conditions, $PtCl_2$(XantPhos) was shown to be amenable to a wide variety of amines bearing a range of electronic and steric properties. The catalyst system was also applicable to the hydrosilylation of propargyl amides, sulfonamides and carbamates, showing a diverse functional group tolerance. The applicability of the catalyst to selectively carrying out hydrosilylations with other hydrosilanes has also been demonstrated through the synthesis of **124**.

The synthetic utility of the resultant silanes was explored, with the unexpected conversion of **123a** into aziridine **124a** in the presence of NIS *via* formal 3-exo-trig cyclisation being a particularly noteworthy result. This methodology was applied to the synthesis of a range of halogenated aziridines with limitations of non-*N*-sulfonyl substrates in competing rearrangements and cyclisation processes noted. Other *N*-Halosuccinimides are shown to be viable electrophiles for this process as demonstrated by the synthesis of bromo-aziridine **124g**. The

approach can also be used to access spirocyclic aziridines with a unique [5,2] spiro-centre, providing access to these compounds without relying on nitrene or nitrenoid chemistry. The reaction can be telescoped from the alkyne to the aziridine and additionally has been shown to be scalable up to the gram-scale.

The reactivity of the aziridines was investigated with the propensity of the ring system to ring-open limiting most conventional synthetic utility of the unique exocyclic α-halosilane. Under nucleophilic conditions, the aziridines undergo facile ring-opening *via* presumed nucleophilic attack at the halide to afford the silane from which the aziridine was formed. Upon treatment with TBAF, rather than desilylation to afford an alkyl halide the aziridine again undergoes a ring-opening reaction, this time *via* loss of the silyl group to afford *Z*-vinyl iodide **136**, in a 2-step formal stereoinvertive electrophilic substitution.

2.8 Experimental Procedures and Characterisation Data

Solvents & reagents

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, TCI, Fisher Scientific or Sigma Aldrich. All solvents were purchased from commercial sources and used without purification (reagent grade). Metal salts and ligands were stored in a desiccator when not in use. Anhydrous solvent was prepared by storing solvent over activated 4Å MS for 72 hours. Standard vacuum line techniques were used, and glassware was oven dried prior to use. Organic solvents were dried during workup using anhydrous Na_2SO_4. All reactions were performed using DrySyn heating mantles and pressure regulated vials or round bottom flasks.

Purification and chromatography

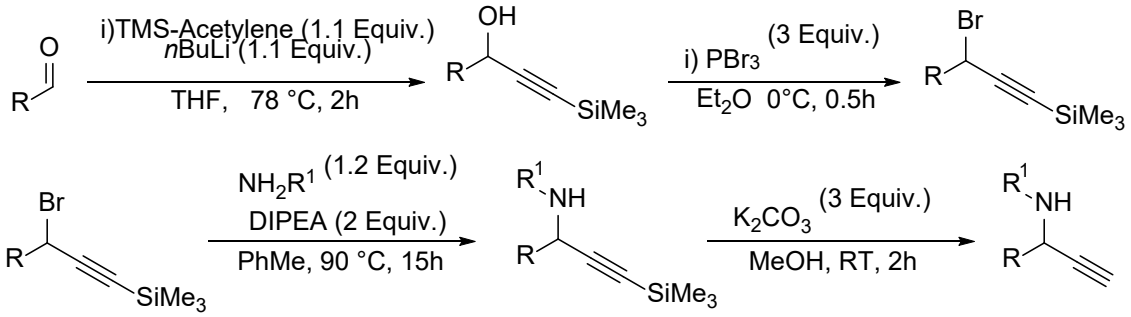
Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F254 silica gel. Plates were visualised using UV light (254 or 365 nm) and developed with iodine and basic permanganate solution. Flash chromatography was performed on VWR Silica gel 60, 40–63 microns RE as the stationary phase and the solvents employed were of reagent grade.

Characterisation

^{1}H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ^{13}C NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemicalshifts are reported in parts per million (δ) relative to residual $CHCl_3$ (δH = 7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm, central line). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer.

2.8.1 General Procedures

General Procedure 2A



To an oven dried flask equipped with a magnetic stirrer under an argon atmosphere was added TMS acetylene (1.1 Equiv.) followed by anhydrous THF (0.5 M.) The solution was then cooled to –78 °C before *n*BuLi (1.1 equiv, 1.6M in hexanes) was added dropwise. The solution was stirred for 30 minutes at –78 °C before the requisite aldehyde or ketone (1 Equiv.) was added dropwise and the solution allowed to warm to room temperature before being stirred for a further 2 hours. After this time, the reaction was quenched *via* addition of a saturated aqueous solution of NH_4Cl (20 mL) and extracted into CH_2Cl_2 (3 × 10 mL) before being dried over $MgSO_4$ to afford the corresponding propargylic alcohol.

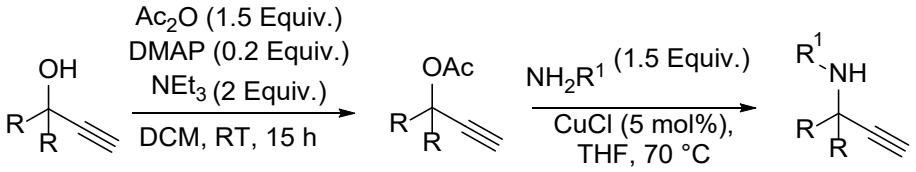
To an oven dried flask equipped with a magnetic stirrer under an argon atmosphere was added the propargylic alcohol in anhydrous Et_2O (1M.) To this solution was added PBr_3 (3 Equiv.) dropwise (Warning-Exotherm) at 0 °C and the reaction was stirred at the same temperature for 30 minutes. The reaction mixture was poured into an ice bath and neutralized with aqueous saturated $NaHCO_3$ solution. The two layers were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL) before the combined organic layers were washed with aqueous sodium chloride, dried over MgSO4 before volatiles were removed under vacuum to afford the corresponding propargylic bromide.

To an oven dried flask equipped with a magnetic stirrer was added a solution of amine (1.2 Equiv.) in toluene (0.5 M) under a nitrogen atmosphere was added the propargyl bromide and diisopropylethylamine (1.2 Equiv.) sequentially, before the resulting mixture was stirred for 24 h at 90 °C. The reaction mixture was then diluted with EtOAc (10 mL) and a saturated aqueous solution $NaHCO_3$

(10 mL) was added. The two layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL) before the combined organics were washed with aqueous sodium chloride, dried over Na_2SO_4 and volatiles removed under vacuum to afford crude TMS protected propargylic amine.

The crude amine was then dissolved in methanol (0.5 M) and K_2CO_3 (3 equiv.) added in one portion before the resulting suspension was stirred at room temperature for two hours. After this time, the reaction was quenched with H_2O (10 mL) and EtOAc (10 mL), before being extracted into EtOAc (3× 10 mL.) The combined organics were then washed with aqueous sodium chloride, dried over Na_2SO_4 before volatiles were removed under reduced pressure and the resultant residue purified by flash column chromatography to afford the corresponding amine. Yields are reported over 4 steps.

General Procedure 2B



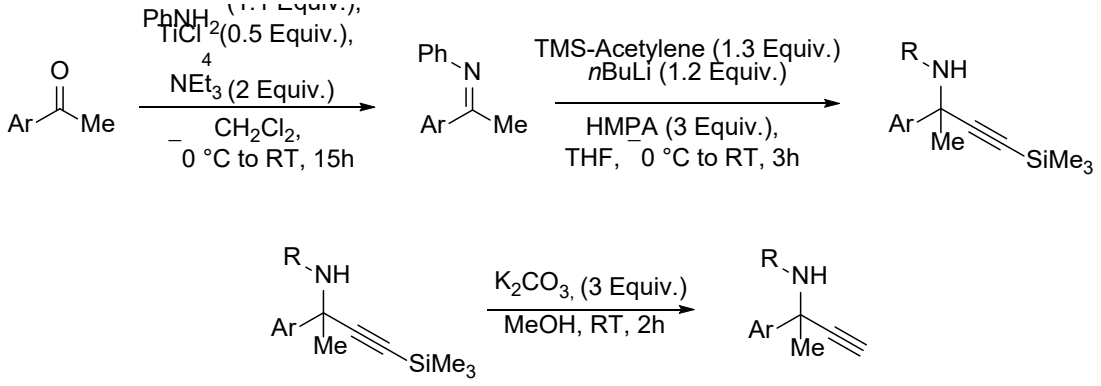
To an oven dried round bottom flask equipped with a magnetic stirrer was added the requisite ketone followed by anhydrous THF (0.5 M) under a nitrogen atmosphere. This solution was then cooled to 0 ˚C, before ethynyl magnesium bromide (1.5 equiv.) was added dropwise. The solution was then allowed to warm to room temperature and the reaction was then stirred until TLC analysis showed complete consumption of the starting material. After this time, the reaction was quenched *via* addition of aqueous ammonium chloride (20 mL) and extracted into ethyl acetate (3 × 15 mL.) The extracts were washed with aqueous sodium chloride, dried over $MgSO_4$ before volatiles were removed under reduced pressure, and the resultant residue purified by flash chromatography.

To an oven dried flask equipped with a magnetic stirrer was added the propargylic alcohol in CH_2Cl_2 (0.5 M), acetic anhydride (1.5 Equiv.) and DMAP (20 mol%) This solution was stirred until TLC analysis showed complete

consumption of the starting material, typically overnight. After this time, the reaction was quenched with water (10 mL) and extracted into CH_2Cl_2 (3 × 10 mL) The extract was dried over Na_2SO_4 before removal of solvent in vacuo to afford the requisite ester.

To a solution of copper(I) chloride (5 mol%) in THF (0.5 M) was added propargyl acetate and the requisite amine (1.5 equiv.). This solution was heated to reflux under argon for 2 hours, after which time the solution was concentrated. The resultant residue was purified by flash column chromatography to afford the corresponding amine. Yields are reported over 2 steps.

General Procedure 2C



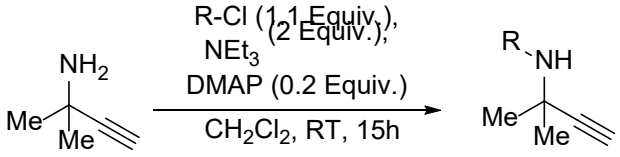
To an oven dried flask equipped with a magnetic stirrer was added aryl ketone (1 Equiv.) in CH_2Cl_2 (0.5 M), amine (1.1 Equiv.) and triethylamine (2 Equiv.) under an argon atmosphere. The solution was cooled to 0 ˚C before $TiCl_4$ (0.5 Equiv.) was added dropwise over the course of an hour resulting in the formation of a bright orange precipitate. The suspension was stirred overnight before the reaction was quenched *via* addition of aqueous potassium carbonate (20 mL) The mixture was filtered through a pad of celite before the organic layer was separated and dried over Na_2SO_4. Volatiles were removed under vacuum and the resultant ketimine purified by recrystallisation from hot ethanol.

To a solution of trimethylsilylacetylene (1.3 Equiv.) in THF (1 M) was added *n*BuLi (1.2 Equiv.) at 0 °C. This solution was then stirred at the same temperature for 30 minutes before hexamethylphosphoramide (3 Equiv.) and ketimine were added to the reaction mixture. The resultant black solution was slowly warmed to

room temperature before being stirred for a further 2 h. After this time, the reaction was quenched *via* addition of aqueous NH_4Cl (10 mL) before being extracted into a 4:1 mixture of Hexane:EtOAc (3 × 10 mL.) The extract was dried over Na_2SO_4 before volatiles were removed under vacuum to afford the crude TMS-protected propargylic amine

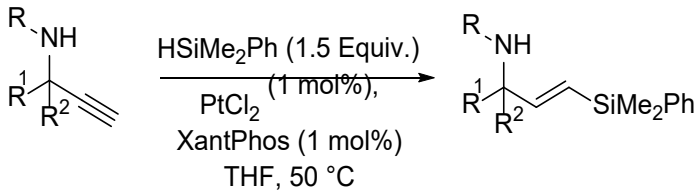
The crude amine was then dissolved in methanol (0.5 M) and K_2CO_3 (3 equiv.) added in one portion before the resulting suspension was stirred at room temperature for two hours. After this time, the reaction was quenched with H_2O (10 mL) and EtOAc (10 mL), before being extracted into EtOAc (3× 10 mL.) The combined organics were then washed with aqueous sodium chloride, dried over Na_2SO_4 before volatiles were removed under reduced pressure and the resultant residue purified by flash column chromatography to afford the corresponding amine. Yields are reported over 3 steps.

General Procedure 2D



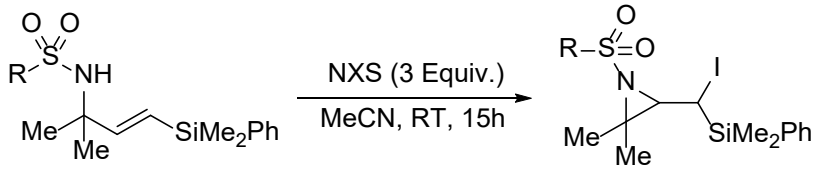
To an oven dried flask equipped with a magnetic stirrer was added 2-methyl-3-butyn-2-amine (1 Equiv.) in CH_2Cl_2 (0.5 M), DMAP (20 mol%) and triethylamine (2 Equiv.) before the resultant solution was cooled to 0 °C. The requisite sulfonyl chloride, acyl chloride/acid anhydride or carbonate (1.1 Equiv.) was then added, before the solution was allowed to warm to room temperature and stir overnight. After this time, the reaction was quenched with H_2O (10 mL) and CH_2Cl_2 (10 mL), before being extracted into CH_2Cl_2 (3 × 10 mL.) The combined organics were then washed with aqueous sodium chloride, dried over Na_2SO_4 before volatiles were removed under reduced pressure and the resultant residue purified by flash column chromatography to afford the corresponding alkyne.

General Procedure 2E



To an oven dried 22 mL vial and magnetic stirrer was added $PtCl_2$ (1 mol%) and 4,5- Bis(diphenylphosphino)-9,9-dimethylxanthene (1 mol%) (XantPhos). The flask was then flushed quickly with argon and anhydrous THF was added (0.3M). The mixture was then stirred at 50 °C for 30 minutes until a yellow homogenous mixture was obtained. The corresponding propargyl amine (1 equiv.) was added followed by the silane (1.5 equiv.) *via* syringe and the solution was stirred at 50 °C overnight. Volatiles were removed under vacuum before the resultant residue was purified by flash column chromatography to afford the pure silane.

General Procedure 2F

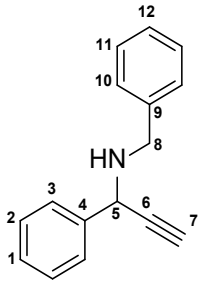


To an oven dried vial was added vinyl silane and N-Iodosuccinimide (3 equiv.) The vial was then flushed with argon and dry acetonitrile (0.2 M) was added. The mixture was then stirred overnight at room temperature. The reaction was then quenched with saturated $Na_2S_2O_3$. The mixture was then extracted into DCM (3 × 5mL) and the solvent removed under reduced pressure. The residue was then purified by column chromatography to afford the corresponding N-Sulfonyl aziridine.

2.8.2 Synthesis of Propargyl Amines

N-benzyl-1-phenylprop-2-yn-1-amine 97a

The title compound was prepared according to **General Procedure 2A**, from benzaldehyde (1g, 9.4 mmol) and benzylamine. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97a** as a yellow oil. (453 mg, 22%). Spectral data in accordance with literature reports.[71]

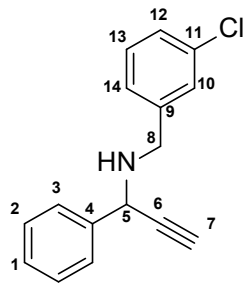


Rf (9:1 Hexane/EtOAc): 0.27

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 3H, (**H**$_{\text{Aromatic}}$)), 7.44 – 7.33 (m, 4H, (**H**$_{\text{Aromatic}}$)), 7.33 – 7.26 (m, 1H, (**H**$_{\text{Aromatic}}$)), 4.57 (d, *J* = 2.2 Hz, 1H, (**H5**)), 3.96 (d, *J* = 13.4 Hz, 1H, (**H8**)), 3.92 (d, *J* = 13.0 Hz, 1H, (**H8**)), 2.59 (d, *J* = 2.2 Hz, 1H, (**H7**)), 1.73 (br s, 1H, (**NH**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (**C9**), 139.4 (**C4**), 128.5 (**C**$_{\text{Aromatic}}$), 128.4 (**C**$_{\text{Aromatic}}$), 127.8 (**C**$_{\text{Aromatic}}$), 127.5 (**C**$_{\text{Aromatic}}$), 127.1 (**C**$_{\text{Aromatic}}$**)**, 126.5 (**C**$_{\text{Aromatic}}$), 83.6 (**C6**), 73.6 (**C7**), 52.8 (**C5**), 50.9 (**C8**)

***N*-[(3-chlorophenyl)methyl]-1-phenylprop-2-yn-1-amine 97b**



The title compound was prepared according to **General Procedure 2A** from benzaldehyde (1g, 9.4 mmol) and 3-chlorobenzylamine. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97b** as a yellow oil. (468 mg, 22%).

Rf (9:1 Hexane/EtOAc): 0.22

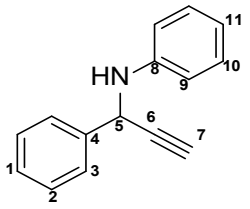
IR υmax (cm^{-1}) 3516, 3042, 3021, 3009, 2986

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{18}NO$ 255.0815; Found 255.0804

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H, (**H**$_{Aromatic}$)), 7.41 – 7.34 (m, 3H, (**H**$_{Aromatic}$)), 7.33 – 7.30 (m, 1H, (**H**$_{Aromatic}$)), 7.28 – 7.22 (m, 3H, (**H**$_{Aromatic}$)), 4.58 (d, *J* = 2.2 Hz, 1H, (**H5**)), 3.96 – 3.86 (m, 2H, (**H8**)), 2.56 (d, *J* = 2.3 Hz, 1H,(**H7**), 1.69 (br s, 1H, (**NH**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (**C9**), 139.6 (**C4**), 134.4 (**C11**), 129.8 (**C**$_{Aromatic}$), 128.7 (**C**$_{Aromatic}$), 128.6 (**C**$_{Aromatic}$), 128.1 (**C**$_{Aromatic}$), 127.6, (**C**$_{Aromatic}$), 127.4 (**C**$_{Aromatic}$), 126.6 (**C**$_{Aromatic}$), 83.5 (**C6**), 73.9 (**C7**), 53.0 (**C5**), 50.5 (**C8**).

***N*-[2-phenylbut-3-yn-2-yl]aniline 97c**



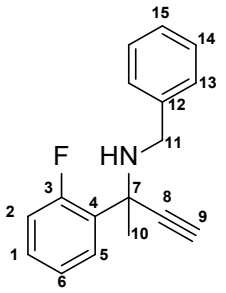
The title compound was prepared according to **General Procedure 2A**, from benzaldehyde (1 g, 9.4 mmol) and aniline. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97c** as a colourless oil. (534 mg, 27%). Spectral data in accordance with literature reports.[71]

Rf (9:1 Hexane/EtOAc): 0.29

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.2 Hz, 2H, (**H2**)), 7.36 (m, 3H, (**H1** & **H3**)), 7.21 (dd, *J* = 8.3, 7.5 Hz, 2H, (**H10**)), 6.79 (t, *J* = 7.4 Hz, 1H, (**H11**)), 6.73 (d, *J* = 7.7 Hz, 2H, (**H9**)), 5.29 (d, *J* = 2.2 Hz, 1H, **H5**), 4.05 (br s, 1H, (**NH**)), 2.47 (d, *J* = 2.3 Hz, 1H, (**H7**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 (**C8**), 139.2 (**C4**), 129.4 (**C2**), 128.9 (**C3**), 128.4 (**C1**), 127.4 (**C10**), 118.9 (**C11**), 114.2 (**C9**), 83.2 (**C6**), 73.3 (**C7**), 49.9 (**C5**).

***N*-benzyl-2-(2-fluorophenyl)but-3-yn-2-amine 97d**



The title compound was prepared according to **General Procedure 2A**, from 2-fluoroacetophenone (500 mg, 3.62 mmol), and benzylamine. Following

conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97d** as a colourless oil. (153 mg, 17%)

Rf (9:1 Hexane/EtOAc) 0.25

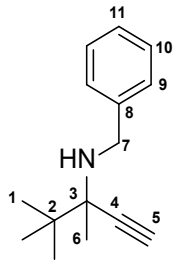
IR υmax (cm^{-1}) 3543, 3097, 3065, 3001, 2974

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{17}H_{16}NF$ 254.1345; Found 254.1341

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 16.2, 8.4, 1.6 Hz, 1H, (**H2**)), 7.36 – 7.21 (m, 6H, ($\mathbf{H_{Aromatic}}$)), 7.15 – 7.07 (m, 2H, ($\mathbf{H_{Aromatic}}$)), 3.91 (d, *J* = 12.2 Hz, 1H, (**H11**)), 3.47 (d, *J* = 12.3 Hz, 1H (**H11**)), 2.67 (br s, 1H, (**NH**)), 1.94 (s, 1H, (**H9**)), 1.85 (s, 3H, (**H10**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (d, *J*= 249 Hz, (**C3**)), 140.4 (**C12**), 134.7 (d, *J* = 19.7 Hz, (**C4**)), 130.1 (d, *J* = 9.2 Hz, (**C1** or **C5**)) 129.7 ($\mathbf{C_{Aromatic}}$), 129.6. (d, *J* = 8.7 Hz, (**C1** or **C5**)), 128.5, ($\mathbf{C_{Aromatic}}$) 127.1 ($\mathbf{C_{Aromatic}}$), 124.1, (d, *J* = 3.4 Hz, (**C5**)), 116.6 (d, *J* = 23.0 Hz, (**C2**)), 86.1 (**C8**), 73.4 (**C9**), 56.7 (**C7**), 49.4 (**C11**), 30.1 (**C10**)

***N*-benzyl-3,4,4-trimethylpent-1-yn-3-amine 97e**



The title compound was prepared according to **General Procedure 2A**, from pinacolone (500 mg, 5 mmol) and benzylamine. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97e** as a yellow oil. (303 mg, 28 %)

Rf (9:1 Hex:EtOAc) 0.26

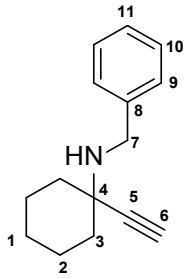
IR υmax (cm^{-1}) 3541, 3054, 3025, 2999, 2992

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{15}H_{21}N$ 216.1758; Found 216.1755

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 2H, (**H10**)), 7.32 (t, *J* = 7.5 Hz, 2H, (**H9**)), 7.23 (d, *J* = 7.2 Hz, 1H, **H11**), 3.96 (d, *J* = 12.4 Hz, 1H, (**H7**)), 3.80 (d, *J* = 12.4 Hz, 1H, (**H7**)), 2.35 (s, 1H, (**H5**)), 1.31 (s, 3H, (**H6**)), 1.06 (s, 9H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (**C8**), 128.5 (**C10** or **C9**), 128.4 (**C10** or **C9**), 126.9 (**C11**), 87.9 (**C4**), 71.7 (**C5**), 60.2 (**C3**), 48.9 (**C7**), 37.6 (**C2**), 25.5 (**C6**), 21.3 (**C1)**.

***N*-benzyl-1-ethynylcyclohexan-1-amine 97f**



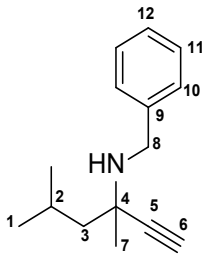
The title compound was prepared according to **General Procedure 2B**, from 1-ethynyl-1-cyclohexanol (250 mg, 2 mmol) and benzylamine. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97f** as a colourless oil. (254 mg, 59%). Spectral data in accordance with literature reports.[72]

Rf (9:1 Hexane/EtOAc): 0.29

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.2 Hz, 2H, **H10**), 7.35 (d, *J* = 7.4 Hz, 2H, **H9**), 7.30 – 7.25 (m, 1H, **C11**), 3.91 (s, 2H, (**H7**)), 2.43 (s, 1H, (**H6**)), 1.19-1.82 (m, 11H, **H1, H2, H3** & **NH**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (**C8**), 128.6 (**C10**), 128.5 (**C9**), 127.0 (**C11**), 88.1 (**C5**), 72.1 (**C6**), 54.8 (**C4**), 48.0 (**C7**), 38.0 (**C2** or **C3**), 25.9 (**C1**), 22.8 (**C2** or **C3**).

***N*-benzyl-3,5-dimethylhex-1-yn-3-amine 97g**



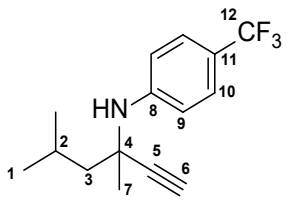
The title compound was prepared according to **General Procedure 2B** from 3,5-dimethylhex-1- yn-3-ol (250 mg, 2 mmol) and benzylamine. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97g** as a colourless oil. (180 mg, 43%). Data in accordance with literature reports.[85]

Rf (9:1 Hexane/EtOAc): 0.31

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H, (**$H_{Aromatic}$**)), 3.93 (d, *J* = 11.9 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 2.37 (s, 1H, (**H6**)), 1.90 (td, *J* = 12.8, 6.4 Hz, 1H, (**H2**)), 1.63 – 1.50 (m, 2H, (**H3**)), 1.39 (s, 3H, (**H7**)), 1.00 (d, *J* = 6.7 Hz, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7 (**C9**), 128.5 (**C11**), 128.5 (**C10**), 127.1 (**C12**), 83.6 (**C5**), 68.1 (**C6**), 54.1 (**C4**), 50.4 (**C2**), 48.6 (**C8**), 27.3 (**C3**), 25.7 (**C7**), 24.6 (**C1**).

***N*-(3,5-dimethylhex-1-yn-3-yl)-4-(trifluoromethyl)aniline 97h**



The title compound was prepared according to **General Procedure 2B** from 3,5-dimethyl-hex-1- yn-3-ol and 4-trifluoromethylaniline (250 mg, 2 mmol). Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97h** as an orange oil. (398 mg, 74%)

Rf (9:1 Hexane/EtOAc): 0.29

IR υmax (cm^{-1}) 3512, 3004, 2994, 2983, 2970

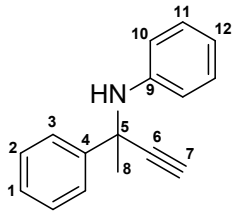
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{15}H_{18}F_3N$ 270.1470; Found 270.1475

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H, (**H10**)), 6.91 (d, *J* = 8.5 Hz, 2H, (**H9**)), 4.00 (br s, 1H, (**NH**)), 2.44 (s, 1H), 1.98 (dt, *J* = 12.7, 6.3 Hz, 1H, (**H2**)), 1.82 (dd, *J* = 14.0, 5.9 Hz, 1H, (**H3**)), 1.71 (dd, *J* = 14.0, 5.8 Hz, 1H (**H3**)), 1.60 (s, 3H, (**H7**)), 1.06 (d, *J* = 6.6 Hz, 3H, (**H1**)), 0.99 (d, *J* = 6.7 Hz, 3H) (**H1**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (**C8**), 126.3 (dd, *J* = 7, 3.4 Hz, (**C10**)), 125.0 (q, *J* = 270 Hz, (**C12**), 119.4 (q, *J* = 32.6 Hz, (**C11**)), 114.6 (**C9**), 86.2 (**C5**), 72.5 (**C6**), 51.2 (**C4**), 50.4 (**C3**), 28.6 (**C7**), 25.0 (**C2**), 24.5 (**C1**), 24.5 (**C1**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -61.04.

***N*-(1-phenylprop-2-yn-1-yl)aniline 97i**



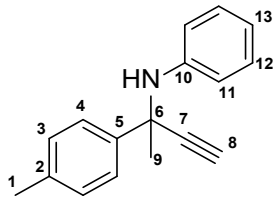
The title compound was prepared according to **General Procedure 2C** from acetophenone (500 mg, 4.2 mmol) and aniline. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97i** as a white solid. (481 mg, 53%). Spectral data in accordance with literature reports.[86]

Rf (9:1 Hexane/EtOAc): 0.26

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.2, 1.1 Hz, 2H (**H2**)), 7.33 (dd, *J* = 8.2, 6.7 Hz, 2H (**H3**)), 7.27 (d, *J* = 7.3 Hz, 1H (**H1**), 7.05 (dd, *J* = 8.4, 7.4 Hz, 2H (**H10**)), 6.69 (t, *J* = 7.3 Hz, 1H (**H12**)), 6.55 – 6.49 (m, 2H, (**H10**)), 4.24 (s, 1H, (**NH**)), 2.47 (s, 1H, (**H7**)), 1.80 (s, 3H, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (**C9**), 139.1 (**C4**), 129.3 (**C11**), 128.9 (**C2**), 128.3 (**C1**), 127.3 (**C3**), 118.9 (**C12**), 114.1 (**C10**), 83.1 (**C6**), 73.2 (**C7**), 49.9. (**C5**), 35.0 (**C8**).

***N*-[2-(4-methylphenyl)but-3-yn-2-yl]aniline 97j**



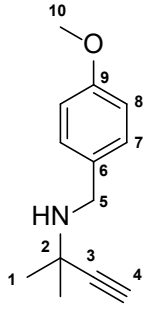
The title compound was prepared according to **General Procedure 2C** from 4-methylacetophenone (500 mg, 3.7 mmol) and aniline. Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **97j** as a white solid. (579 mg, 66%). Spectral data in accordance with literature reports.[86]

Rf (9:1 Hexane/EtOAc): 0.26

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H,(**H3**)), 7.13 (d, *J* = 8.3 Hz, 2H, (**H4**)), 7.05 (dd, *J* = 8.5, 7.4 Hz, 2H, (**H12**)), 6.68 (s, 1H, (**H13**)), 6.53 (d, *J* = 7.8 Hz, 2H,(**H11**)), 4.22 (br s, 1H, **NH**), 2.46 (s, 1H, (**H8**)), 2.33 (s, 3H, (**H1**)), 1.78 (s, 3H,(**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (**C10**), 141.1 (**C5**), 137.1 (**C2**), 129.4 (**C3**), 128.7 (**C12**), 125.5 (**C4**), 118.5 (**C13**), 115.9 (**C11**), 86.3 (**C7**), 72.3 (**C8**), 55.2 (**C6**), 36.0 (**C9**), 21.2 (**C1**)).

***N*-[(4-methoxyphenyl)methyl]-2-methylbut-3-yn-2-amine 97k**



To a solution of 4-methoxybenzaldehyde (80 mg, 0.6 mmol) in methanol (2 mL) was added 1,1 dimethyl propargyl amine (50 mg, 0.6 mmol). The solution was

stirred overnight at room temperature. To this solution was added $NaBH_4$ and the reaction was stirred for 1 hour at room temperature. After this time, the reaction mixture was quenched with water (5 mL) and extracted into CH_2Cl_2 (3×5 mL), before volatiles were removed under vacuum. The resultant mixture was then purified by flash column chromatography (EtOAc:Hex 9:1) to afford **97k** as a white solid (91 mg, 75%).

Rf (9:1 Hexane/EtOAc): 0.19

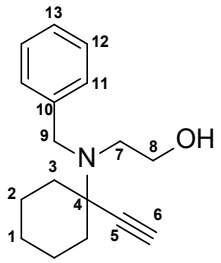
IR υmax (cm^{-1}) 3519, 3089, 3045, 3000, 2979

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{18}NO$ 204.1388; Found 204.1395

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H, (**H7**)), 6.85 (d, *J* = 8.5 Hz, 2H, (**H8**)), 3.80 (s, 2H, (**H5**)), 3.78 (s, 3H, (**H10**)), 2.35 (s, 1H, (**H4**)), 1.41 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (**C6**), 132.8 (**C9**), 129.7 (**C7**), 113.9 (**C8**), 89.2 (**C3**), 69.9 (**C4**), 55.4 (**C5**), 50.1 (**C2**), 48.5 (**C10**), 29.6 (**C1**).

2-[benzyl-(1-ethynylcyclohexyl)amino]ethanol 132a



The title compound was prepared according to **General Procedure 2B**, from 1-ethynylcyclohexanol (250 mg, 2 mmol) and *N*-Benzylethanolamine (605 mg, 4 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **132a** as a brown oil. (407 mg, 79%).

Rf (9:1 Hexane/EtOAc): 0.22

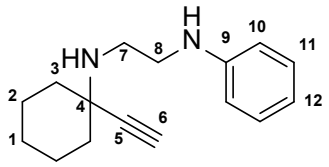
IR υmax (cm^{-1}) 3493, 3310, 3102, 3045, 2950

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{17}H_{24}NO$ 258.1858; Found 258.1850

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 2H, (**H12**)), 7.33 – 7.29 (m, 2H, (**H11**)), 7.25 – 7.21 (m, 1H, (**H13**)), 3.84 (s, 2H, (**H9**)), 3.38 (t, *J* = 5.7 Hz, 2H, (**H8**)), 2.88 (t, *J* = 5.7 Hz, 2H, (**H7**)), 2.40 (s, 1H, (**H6**)), 2.24 – 2.16 (br s, 1H, **OH**), 2.10 – 1.93 (m, 2H, (**H$_{Cyclohexyl}$**)), 1.76 – 1.52 (m, 5H, (**H$_{Cyclohexyl}$**)), 1.42 (td, *J* = 12.3, 3.8 Hz, 2H, (**H$_{Cyclohexyl}$**)), 1.25 – 1.09 (m, 1H, (**H$_{Cyclohexyl}$**)).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (**C10**), 128.5 (**C12**), 128.0 (**C11**), 126.8 (**C13**), 85.6 (**C5**), 73.0 (**C6**) , 60.6 (**C9**), 60.3(**C4**), 55.4 (**C8**), 52.8 (**C7**), 37.4 (**C$_{cylohexyl}$**), 25.5 (**C$_{cylohexyl}$**), 23.2 (**C$_{cylohexyl}$**).

***N'*-(1-ethynylcyclohexyl)-*N*-phenyl-ethane-1,2-diamine 132b**



The title compound was prepared according to **General Procedure 2B**, from 1-ethynylcyclohexanol (250 mg, 2 mmol) and *N*-phenylethylenediamine (545 mg, 4 mmol.) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **132b** as a brown oil. (298 mg, 68%).

Rf (9:1 Hexane/EtOAc): 0.23

IR υmax (cm^{-1}) 3533, 3345, 3058, 3001, 2969

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{16}H_{23}N_2$ 243.1861; Found 243.1843

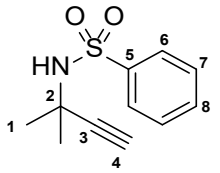
^{1}H NMR (500 MHz, DMSO-d6) δ 7.08 – 6.83 (m, 2H, (**H11**)), 6.54 – 6.50 (m, 2H, 9**H10**)), 6.47 (tt, *J* = 7.3, 1.1 Hz, 1H, (**H12**)), 5.41 (t, *J* = 5.6 Hz, 1H, (**NH$_{Aniline}$**)), 3.08 (s, 1H, (**H6**)), 3.04 (dd, *J* = 12.3, 6.5 Hz, 2H, (**H8**)), 2.75 (t, *J* = 6.6 Hz, 2H, (**H7**)), 1.91 (br s, 1H, **NH**), 1.71 (d, *J* = 12.5 Hz, 2H, (**H$_{Cyclohexyl}$**)), 1.56 (ddd, *J* =

12.7, 8.6, 4.0 Hz, 2H, (**H$_{Cyclohexyl}$**)), 1.51 – 1.36 (m, 3H, (**H$_{Cyclohexyl}$**)), 1.29 (td, *J* = 12.4, 3.5 Hz, 2H, (**H$_{Cyclohexyl}$**)), 1.15 (dtd, *J* = 14.2, 10.6, 3.7 Hz, 1H, (**H$_{Cyclohexyl}$**)).

^{13}C NMR (126 MHz, DMSO-d6) δ 149.0 (**C9**), 128.8 (**C11**), 115.5 (**C12**), 112.0 (**C10**), 88.1 (**C5**), 73.9 (**C6**), 53.3 (**C4**), 43.7 (**C7**), 41.8 (**C8**), 37.4 (**C$_{Cyclohexyl}$**), 25.4 (**C$_{Cyclohexyl}$**), 22.2 (**C$_{Cyclohexyl}$**).

2.8.3 Synthesis of Propargylic Amides, Carbamates and Sulfonamides

***N*-(2-methylbut-3-yn-2-yl)benzenesulfonamide 116a**



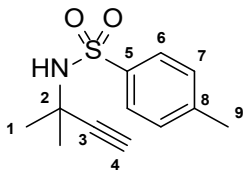
The title compound was prepared according to **General Procedure 2D**, from benzenesulfonyl chloride (210 mg, 1.2 mmol). Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **116a** as a white solid (200 mg, 75%) Spectral data in accordance with literature reports.[87]

Rf (4:1 Hexane/EtOAc): 0.24

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.87 (m, 3H, (**H6** & **H8**), 7.24 – 7.10 (m, 2H, (**H7**)), 4.75 (s, 1H, **NH**), 2.08 (s, 1H, (**H4**)), 1.55 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (**C5**), 132.7 (**C8**), 128.8 (**C7**), 127.8 (**C6**), 85.4 (**C3**), 71.4 (**C4**), 50.2 (**C2**), 30.9 (**C1**).

4-methyl-*N*-(2-methylbut-3-yn-2-yl)benzene-1-sulfonamide 116b



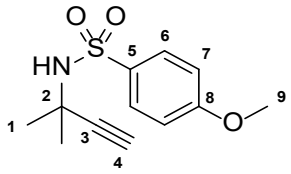
The title compound was prepared according to **General Procedure 2D**, from 4-methylphenylsulfonyl chloride (228 mg, 1.2 mmol). Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **116b** as a white solid (193 mg, 68%). Spectral data in accordance with literature reports.[88]

Rf (4:1 Hexane/EtOAc): 0.28

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H, (**H6**)), 7.27 (d, *J* = 8.3 Hz, 2H, (**H7**)), 4.82 – 4.59 (m, 1H, **NH**), 2.41 (s, 3H, (**H9**)), 2.09 (d, *J* = 1.1 Hz, 1H, (**H4**)), 1.54 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (**C5**), 139.3 (**C8**), 129.5 (**C6**), 127.8 (**C7**), 85.2 (**C3**), 70.9 (**C4**), 50.2 (**C2**), 30.5 (**C1**), 21.8 (**C9**)

4-methoxy-*N*-(2-methylbut-3-yn-2-yl)benzene-1-sulfonamide 116c



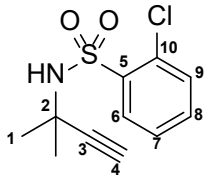
The title compound was prepared according to **General Procedure 2D**, from 4-methoxybenzene sulfonyl chloride (247 mg, 1.2 mmol). Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **116c** as a white solid (282 mg, 93%). Spectral data in accordance with literature reports.[87]

Rf (4:1 Hexane/EtOAc): 0.21

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.72 (m, 4H, (**H6** & **H7**)), 4.85 (s, 1H, **NH**), 3.85 (s, 3H, (**H9**)), 2.09 (s, 1H, (**H4**)), 1.53 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (**C8**), 133.4 (**C5**), 129.9 (**C6**), 113.9 (**C7**), 85.6 (**C3**), 71.3 (**C4**), 55.7 (**C9**), 50.0 (**C2**), 30.8 (**C1**).

2-chloro-*N*-(2-methylbut-3-yn-2-yl)benzene-1-sulfonamide 116d



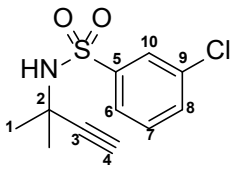
The title compound was prepared according to **General Procedure 2D**, from 2-chlorobenzene sulfonyl chloride (253 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **116d** as a white solid (200 mg, 65%). Spectral data in accordance with literature reports.[89]

Rf (4:1 Hexane/EtOAc): 0.26

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.4, 3.4 Hz, 1H, (**H6**)), 7.57 – 7.45 (m, 2H, (**H9** & **H8**)), 7.25 (m, 1H, (**H7**)), 4.83 (s, 1H, **NH**), 2.05 (s, 1H, (**H4**)), 1.55 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (**C5**), 137.6 (**$C_{Aromatic}$**), 135.3 (**C10**) 132.6 (**$C_{Aromatic}$**), 128.8 (**$C_{Aromatic}$**), 127.7 (**$C_{Aromatic}$**), 85.3 (**C3**), 71.4 (**C4**), 50.1 (**C2**), 30.8 (**C1**).

3-chloro-*N*-(2-methylbut-3-yn-2-yl)benzene-1-sulfonamide 116e



The title compound was prepared according to **General Procedure 2D**, from 3-chlorobenzene sulfonyl chloride (253 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **116e** as a white solid (255 mg, 83%).

Rf (4:1 Hexane/EtOAc): 0.24

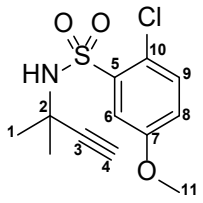
IR υmax (cm^{-1}) 3503, 3285, 3095, 3022, 2957

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{11}H_{13}ClNO_2S$ 258.0356; Found 258.0362

^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, *J* = 1.9 Hz, 1H, (**H10**)), 7.83 – 7.75 (m, 1H, (**H6**)), 7.55 – 7.48 (m, 1H, (**H8**)), 7.42 (t, *J* = 7.9 Hz, 1H, (**H7**)), 4.85 (s, 1H, **NH**), 2.11 (s, 1H, (**H4**)), 1.56 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (**C5**), 134.8 (**C9**), 132.7 (**C8**), 130.1 (**C7**), 127.9 (**C10**), 125.8 (**C6**), 85.0 (**C3**), 71.8 (**C4**), 50.3 (**C2**), 30.9 (**C1**).

5-chloro-2-methoxy-*N*-(2-methylbut-3-yn-2-yl)benzene-1-sulfonamide 116f



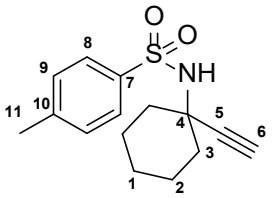
The title compound was prepared according to **General Procedure 2D**, from 2-methoxy-5-chlorobenzene sulfonyl chloride (286 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **116f** as a yellow solid (203 mg, 59%). Spectral data in accordance with literature reports.[89]

Rf (4:1 Hexane/EtOAc): 0.23

^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.6 Hz, 1H, (**H6**)), 7.46 (dd, *J* = 8.8, 2.7 Hz, 1H (**H8**)), 6.93 (d, *J* = 8.8 Hz, 1H, (**H9**)), 5.12 (s, 1H, **NH**), 3.97 (s, 3H, (**H11**)), 1.91 (s, 1H, (**H4**)), 1.55 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (**C5**), 133.9 (**C6**), 130.4 (**C7**), 130.1 (**C8**), 125.8 (**C10**), 113.33 (**C9**), 84.5 (**C3**), 71.2 (**C4**), 56.8 (**C11**), 49.9 (**C2**), 31.0 (**C1**).

***N*-(1-ethynylcyclohexyl)-4-methyl-benzenesulfonamide 128**



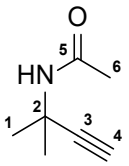
The title compound was prepared according to **General Procedure 2D**, from 4-methylphenylsulfonyl chloride (229 mg, 1.2 mmol) and 1-ethynyl cyclohexylamine (123 mg, 1.00 mmol). Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **128** as a white solid (219 mg, 79%). Data in accordance with literature reports.[90]

Rf (4:1 Hexane/EtOAc): 0.25

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H, (**H8**)), 7.26 (d, *J* = 7.9 Hz, 2H, (**H9**)), 4.95 (br s, 1H, (**NH**)), 2.41 (s, 3H, (**H11**)), 2.12 (s, 1H, (**H6**)), 2.01 (dd, *J* = 15.2, 12.7 Hz, 2H, (**H$_{Cyclohexyl}$**)), 1.72 – 1.48 (m, 8H, (**H$_{Cyclohexyl}$**)).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2 (**C10**), 139.3 (**C7**), 129.3 (**C8**), 127.7 (**C9**), 83.9 (**C5**), 73.9 (**C6**), 53.6 (**C4**), 38.8 (**C11**), 25.0 (**C$_{Cyclohexyl}$**), 22.4 (**C$_{Cyclohexyl}$**) , 21.7 (**C$_{Cyclohexyl}$**)

***N*-(2-methylbut-3-yn-2-yl)acetamide 117a**



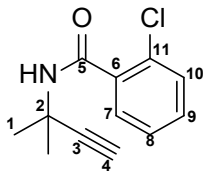
The title compound was prepared according to **General Procedure 2D**, from acetic anhydride (122 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **117a** as a white solid (126 mg, 84%). Spectral data in accordance with previous reports.[91]

Rf (4:1 Hexane/EtOAc): 0.31

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H, **NH**), 2.31 (s, 1H, (**H4**)), 1.93 (d, *J* = 1.8 Hz, 3H, (**H6**)), 1.61 (d, *J* = 2.8 Hz, 6H,(**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (**C5**), 87.3 (**C3**), 69.1 (**C4**), 47.6 (**C6**), 29.1 (**C1**), 24.2 (**C2**).

2-chloro-*N*-(2-methylbut-3-yn-2-yl)benzamide 117b



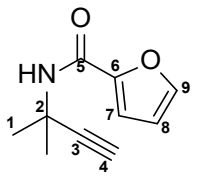
The title compound was prepared according to **General Procedure 2D**, from 2-chlorobenzoyl chloride (210 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **117b** as a white solid (209 mg, 79%). Spectral data in accordance with literature reports.[92]

Rf (4:1 Hexane/EtOAc): 0.29

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.3, 1.9 Hz, 1H, (**H7**)), 7.42 – 7.37 (m, 1H, (**H8**)), 7.37 – 7.29 (m, 2H, (**H9** and **H10**), 5.11 (s, 1H, **NH**), 2.27 (s, 1H, (**H4**)), 1.62 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (**C5**), 135.3 (**C6**), 133.4 (**C11**), 131.4 (**C7**), 130.6 (**C9**), 130.2 (**C10**), 127.2 (**C8**), 86.8 (**C3**), 69.7 (**C4**), 48.5 (**C2**), 29.0 (**C1**).

***N*-(2-methylbut-3-yn-2-yl)furan-2-carboxamide 117c**



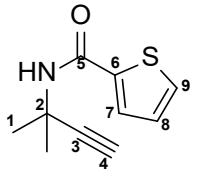
The title compound was prepared according to **General Procedure 2D**, from 2-furoyl chloride (156 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **117c** as a white solid (191 mg, 90%). Spectral data in accordance with previous reports.[87]

Rf (4:1 Hexane/EtOAc): 0.25

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H, (**H7**), 7.39 (d, *J* = 8.4 Hz, 1H, (**H9**), 6.62 (s, 1H, (**NH**)), 6.59 – 6.50 (m, 1H, (**H8**)), 2.53 (s, 1H, (**H4**)), 1.89 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (**C5**), 148.3 (**C6**), 143.9 (**C9**), 114.6 (**C8**), 112.5 (**C7**), 87.0 (**C3**), 69.7 (**C4**), 47.9 (**C2**), 29.4 (**C1**).

***N*-(2-methylbut-3-yn-2-yl)thiophene-2-carboxamide 177d**



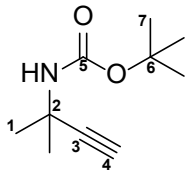
The title compound was prepared according to **General Procedure 2D**, from 2-thiophenecarbonyl chloride (174 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **117d** as a white solid (175 mg, 76%).

Spectral data in accordance with literature reports.[92]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 4.0 Hz, 1H, (**H7**), 7.41 (d, *J* = 4.1 Hz, 1H, (**H9**)), 7.09 (m, 1H, (**H8**)), 6.06 (br s, 1H, (**NH**)), 2.42 (s, 1H, (**H4**)), 1.70 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (**C5**), 139.6 (**C6**), 130.0 (**C9**), 128.7 (**C8**), 127.5 (**C7**), 87.0 (**C3**), 69.4 (**C4**), 48.6 (**C2**), 29.3 (**C1**).

tert-butyl (2-methylbut-3-yn-2-yl)carbamate 117e



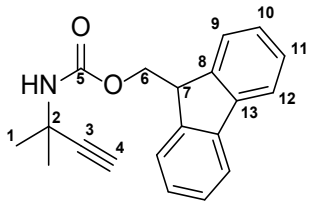
The title compound was prepared according to **General Procedure 2D**, from di-tert butyl carbonate (261 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **117e** as a white solid (175 mg, 80%). Spectral data in accordance with literature reports.[93]

Rf (4:1 Hexane/EtOAc): 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 1H, **NH**), 2.28 (s, 1H, (**H4**)), 1.56 (s, 6H,(**H1**)), 1.43 (s, 9H (**H7**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (**C5**), 87.5 (**C3**), 79.8 (**C4**), 68.8 (**C7**), 47.0 (**C2**), 29.5 (**C1**), 28.5 (**C7**).

(4b,8a,9,9a-tetrahydro-4aH-fluoren-9-yl)methyl (2-methylbut-3-yn-2-yl)carbamate 117f



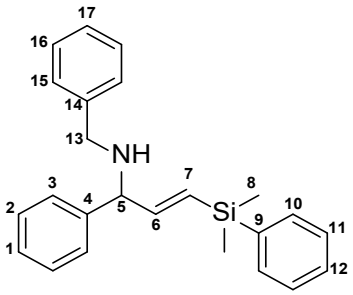
The title compound was prepared according to **General Procedure 2D**, from fluorenylmethyloxycarbonyl chloride (309 mg, 1.2 mmol) Following conversion to the product and column chromatography (9:1 Hexane/EtOAc) afforded **117f** as a white solid (270 mg, 74%). Spectral data in accordance with literature reports.[94]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H, (**H9** or **H12**), 7.62 (d, *J* = 7.4 Hz, 2H,(**H9** or **H12**), 7.44 – 7.37 (m, 2H, (**H10** or **H11**), 7.32 (td, *J* = 7.4, 1.1 Hz, 2H, (**H10** or **H11**), 5.00 (s, 1H, **NH**), 4.43 (d, *J* = 4.1Hz, 2H, (**C6**)), 4.23 (t, *J* = 6.7 Hz, 1H, (**C7**)), 2.34 (s, 1H, (**H4**)), 1.57 (S, 6H, (**H1**))

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (**C5**), 144.1 (**C8** or **C13**), 141.4 (**C8** or **C13**), 127.8 (**C9**, **C10**, **C11** or **C12**), 127.1 (**C9**, **C10**, **C11** or **C12**), 125.1 (**C9**, **C10**, **C11** or **C12**), 120.1 (**C9**, **C10**, **C11** or **C12**), 87.1 (**C3**), 69.3 (**C4**), 66.4 (**C7**), 47.3 (**C2**), 29.4 (**C1**), 27.0 (**C6**).

2.8.4 Synthesis of Allylic Amines

(2E)-*N*-benzyl-3-[dimethyl(phenyl)silyl]-1-phenylprop-2-en-1-amine 120a



The title compound was prepared according to **General Procedure 2E**, from *N*-benzyl-1- phenylprop-2-yn-1-amine (50 mg, 0.23 mmol) and dimethylphenylsilane (46.2 mg, 0.33 mmol) using $PtCl_2$ (0.6 mg, 2.3 µmol) and XantPhos (1.3 mg, 2.3 µmol) which following conversion to the vinyl silane and column chromatography (7:3 Hexane/CH_2Cl_2) afforded **120a** (61 mg, 70 %) as a yellow oil.

Rf (9:1 Hexane/EtOAc): 0.44

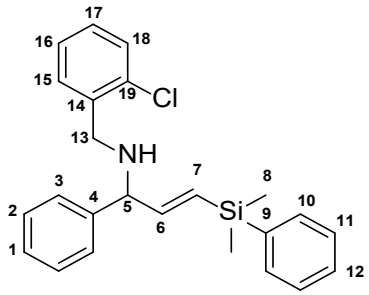
IR υmax ($cm^{-1)}$ 3083, 3064, 3024, 2954, 2900

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{24}H_{27}NSi$ 358.1991; Found 358.1987

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H, (**H**$_{\text{Aromatic}}$)), 7.39 (d, *J* = 5.2 Hz, 2H, **H**$_{\text{Aromatic}}$), 7.37 (t, *J* = 2.3 Hz, 4H, **H**$_{\text{Aromatic}}$), 7.35 (dd, *J* = 3.6, 2.1 Hz, 2H, **H**$_{\text{Aromatic}}$), 7.33 (d, *J* = 2.9 Hz, 3H, **H**$_{\text{Aromatic}}$), 7.32 – 7.30 (m, 1H, **H**$_{\text{Aromatic}}$), 7.29 – 7.27 (m, 1H, **H**$_{\text{Aromatic}}$), 6.24 (dd, *J* = 18.5, 6.3 Hz, 1H (**H6**)), 6.03 (dd, *J* = 18.6, 1.0 Hz, 1H, (**H7**)), 4.30 (dd, *J* = 6.3, 1.0 Hz, 1H (**H5**)), 3.96 (d, *J* = 13.0 Hz, 1H, (**H13**)), 3.92 (d, *J* = 13.0 Hz, 1H, (**H13**)), 1.69 (s, 1H (**NH**)), 0.35 (s, (**H8**)), 0.34 (s, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (**C6**), 142.6 (**C4** or **C14**), 140.5 (**C4** or **C14**), 138.8 (**C9**), 133.9 (**C11**), 129.1 (**C12**), 128.6 (**C**$_{\text{Aromatic}}$), 128.5 (**C**$_{\text{Aromatic}}$), 128.3 (**C**$_{\text{Aromatic}}$), 128.1 (**C**$_{\text{Aromatic}}$), 127.8 (**C10**), 127.6 (**C**$_{\text{Aromatic}}$), 127.3 (**C**$_{\text{Aromatic}}$), 127.0 (**C7**), 67.3 (**C5**), 51.5 (**C13**), -2.5 (**C8**).

(2E)-*N*-[(3-chlorophenyl)methyl]-3-[dimethyl(phenyl)silyl]-1-phenylprop-2-en-1- amine 120b



The title compound was prepared according to **General Procedure 2E**, from 2-chloro-4-methyl-*N*-[(3-chlorophenyl)methyl]-1-phenylprop-2-yn-1-amine (50 mg, 0.19 mmol) and dimethylphenylsilane (40 mg, 0.29 mmol) using $PtCl_2$ (1.1 mg, 1.9 µmol) and XantPhos (2.3 mg, 1.9 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **120b** (58 mg, 79 %) as a yellow oil.

Rf (19:1 Hexane/EtOAc): 0.39

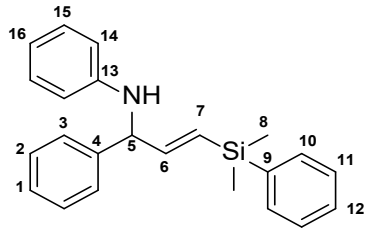
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{24}H_{26}ClNSi$ 392.1601; Found 392.1593

IR υmax (cm^{-1}) 3065, 3024, 2965, 2825

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 11.9, 7.1 Hz, 1H, (**$H_{Aromatic}$**)), 7.59 – 7.41 (m, 3H, (**$H_{Aromatic}$**)), 7.41 – 7.29 (m, 8H, (**$H_{Aromatic}$**)), 7.28 – 7.18 (m, 4H, (**$H_{Aromatic}$**)) , 7.16 (d, *J* = 6.5 Hz, 1H, (**$H_{Aromatic}$**)), 6.17 (dd, *J* = 18.6, 6.3 Hz, 1H, (**H6**)), 5.99 (d, *J* = 18.6 Hz, 1H, (**H7**)), 4.23 (d, *J* = 6.2 Hz, 1H, (**H5**)), 3.69 (d, *J* = 13.7 Hz, 1H, (**H13**)), 3.65 (d, *J* = 13.6 Hz, 1H, (**H13**)), 1.63 (s, 1H, (**NH**)), 0.31 (s, 3H, (**H8**)), 0.30 (s, 3H, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7 (**C6**), 142.7 (**C14**), 142.5 (**C4**), 138.8 (**C9**), 134.3 (**$C_{Aromatic}$**), 133.9 (**C11**), 129.8 (**$C_{Aromatic}$**), 129.1 (**C12**), 128.7 (**$C_{Aromatic}$**), 128.5 (**$C_{Aromatic}$**), 128.4 (**$C_{Aromatic}$**), 127.9 (**C10**), 127.6 (**$C_{Aromatic}$**), 127.4 (**$C_{Aromatic}$**), 127.2, 126.4 (**C7**), 67.4 (**C7**), 51.0 (**C13**) , -2.4 (**C8**).

***N*-[(E)-3-[dimethyl(phenyl)silyl]-1-phenyl-allyl]aniline 120c**



The title compound was prepared according to **General Procedure 2E** from *N*-[2-phenylbut-3-yn-2-yl]aniline (50 mg, 0.21 mmol) and dimethylphenylsilane (43.4 mg, 0.32 mmol) using $PtCl_2$ (0.6 mg, 2.1 µmol) and XantPhos (1.2 mg, 2.1 µmol) which following conversion to the vinyl silane and column chromatography (7:3 Hexane/CH_2Cl_2) afforded **120c** (59 mg, 82%) as a colourless oil.

Rf (9:1 Hexane/CH_2Cl_2): 0.44

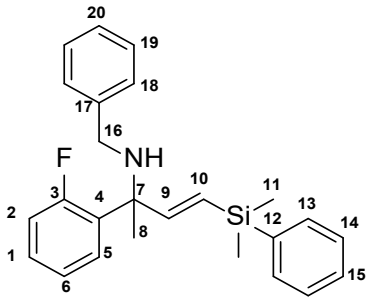
IR υmax (cm^{-1}) 3413, 3051, 2957, 2845, 1600, 1501

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{25}NSi$ 344.1835; Found 344.1828

^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 2H, (**H10**)), 7.38 – 7.27 (m, 8H, (**$H_{Aromatic}$**)), 7.13 (t, *J* = 7.7 Hz, 2H, (**H15**)), 6.69 (t, *J* = 7.4 Hz, 1H, (**H16**)), 6.59 (d, *J* = 8.0 Hz, 2H, (**H14**)), 6.27 (dd, *J* = 18.6, 5.1 Hz, 1H, (**H6**)), 6.08 (d, *J* = 18.6 Hz, 1H, (**H7**)), 4.96 (t, *J* = 5.0 Hz, 1H, (**H5**)), 4.06 (d, *J* = 4.8 Hz, 1H, (**NH**)), 0.33 (s, 6H, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (**C6**), 147.3 (**C13**), 141.9 (**C4**), 138.6 (**C9**), 134.0 (**C11**), 129.2 (**C12**), 129.1 (**$C_{Aromatic}$**), 128.9 (**$C_{Aromatic}$**), 128.7 (**$C_{Aromatic}$**), 127.9 (**C10**), 127.5 (**$C_{Aromatic}$**), 127.4 (**$C_{Aromatic}$**), 117.7 (**C16**), 113.7 (**C14**), 62.8 (**C5**), -2.4 (**C8**), -2.5 (**C8**).

(3E)-*N*-benzyl-4-[dimethyl(phenyl)silyl]-2-(2-fluorophenyl)but-3-en-2-amine 120d



The title compound was prepared according to **General Procedure 2E**, from *N*-[2-(2-fluorophenyl)but-3-yn-2-yl]aniline (50 mg, 0.2 mmol) and dimethylphenylsilane (41 mg, 0.3 mmol) using $PtCl_2$ (0.5 mg, 2 µmol) and XantPhos (1.2 mg, 2 µmol) which following conversion to the vinyl silane and column chromatography (7:3 Hexane/ CH_2Cl_2) afforded **120d** (63 mg, 85%) as a colourless oil.

Rf (7:3 Hexane/ CH_2Cl_2): 0.26 IR υmax ($cm^{-1)}$ 3066, 3026, 2956, 2900, 2844

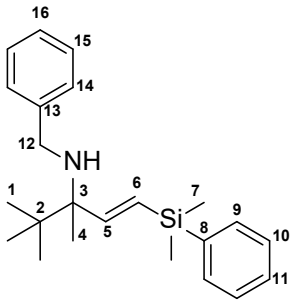
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{25}H_{28}NFSi$ 390.2053; Found 390.2058

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H, (**H13**)), 7.46 (td, *J* = 8.1, 1.7 Hz, 1H, (**H1**)), 7.34 (m, 3H, (**H**$_{\text{Aromatic}}$)), 7.32 – 7.20 (m, 8H, (**H**$_{\text{Aromatic}}$), 7.13 (t, *J* = 7.2 Hz, 1H, **H6**)), 7.05 (ddd, *J* = 12.3, 8.2, 0.7 Hz, 1H, (**H2**)), 6.39 (d, *J* = 19.0 Hz, 1H), 5.89 (d, *J* = 19.0 Hz, 1H) 3.52 (dd, *J* = 39.2, 12.2 Hz, 2H, (**H16**)), 2.00 (s, 1H, (**NH**)), 1.65 (s, 3H, (**H8**)), 0.34 (s, 6H, (**H11**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (d, *J* = 247.7 Hz, (**C3**)), 153.0 (**C9**), 140.9 (**C17**), 139.0 (**C12**), 134.0 (**C14**), 132.7 (d, *J* = 9.7 Hz, (**C1**)), 129.0 (**C15**), 128.8 (d, *J* = 8.9 Hz, (**C5**)), 128.5 (**C19**), 128.4 (**C18**), 127.8 (**C13**), 127.0 (**C20**), 124.7 (**C10**), 124.0 (d, *J* = 2.4 Hz, (**C6**)), 116.4 (d, *J* = 23.3 Hz, (**C2**)), 61.6 (**C7**), 48.0 (**C16**), 25.4 (**C8**), -2.3 (**C11**).

C4 not observed

(1E)-*N*-benzyl-1-[dimethyl(phenyl)silyl]-3,4,4-trimethylpent-1-en-3-amine 120e



The title compound was prepared according to **General Procedure 2E**, from *N*-benzyl-3,4,4- trimethylpent-1-yn-3-amine (50 mg, 0.23 mmol) and dimethylphenylsilane (47.5 mg, 0.32 mmol) using $PtCl_2$ (0.6 mg, 2.3 µmol) and XantPhos (1.3 mg, 2.3 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **120e** (69 mg, 86%) as a colourless oil.

Rf (9:1 Hexane/EtOAc): 0.63

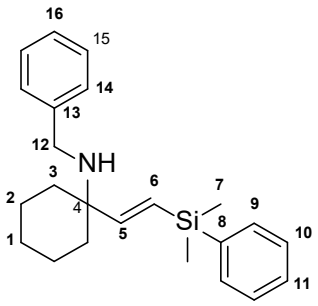
IR υmax (cm^{-1}) 3085, 3067, 2955, 1247

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{33}NSi$ 352.2461; Found 352.2455

^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (dd, *J* = 6.5, 3.0 Hz, 2H, **H9**), 7.36 – 7.28 (m, 7H, $\mathbf{H_{Aromatic}}$), 7.24 – 7.20 (m, 1H, ($\mathbf{H_{Aromatic}}$)), 6.10 (d, *J* = 19.3 Hz, 1H (**H5**)), 5.78 (d, *J* = 19.4 Hz, 1H (**H6**)), 3.61 (d, *J* = 12.7 Hz, 1H, **H12**), 3.52 (d, *J* = 12.8 Hz, 1H, **H12**), 1.16 (s, 3H, **H4**), 0.91 (s, 9H, **H1**), 0.34 (s, 6H, (**H7**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (**C5**), 142.5 (**C13**), 139.4 (**C8**), 134.0 (**C10**), 129.0 (**C11**), 128.4 ($\mathbf{C_{Aromatic}}$), 128.2 ($\mathbf{C_{Aromatic}}$), 127.9 (**C9**), 126.7 ($\mathbf{C_{Aromatic}}$), 126.7 ($\mathbf{C_{Aromatic}}$), 63.3 (**C3**), 47.7 (**C12**), 37.5 (**C2**), 25.6 (**C1**), 17.5 (**C4**), -2.0 (**C7**), -2.1 (**C7**).

***N*-benzyl-1-[(E)-2-[di methyl(phenyl)silyl]ethenyl]cyclohexan-1-amine 120f**



The title compound was prepared according to **General Procedure 2E**, from *N*-benzyl-1- ethynylcyclohexan-1-amine (50 mg, 0.23 mmol) and dimethylphenylsilane (47.9 mg, 0.35 mmol) using $PtCl_2$ (0.6 mg, 2.3 µmol) and XantPhos (1.4 mg, 2.3 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **120f** (82 mg, 77%) as a colourless oil.

Rf (9:1 Hexane/EtOAc): 0.61

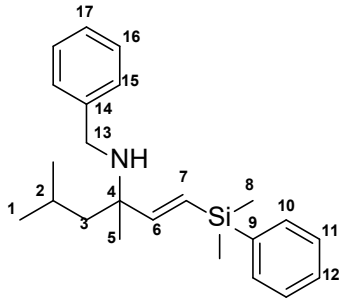
IR υmax (cm^{-1}) 3069, 3026, 2956, 2940, 2898

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{31}NSi$ 350.2304; Found 350.2301

^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.5, 3.0 Hz, 2H, (**H9**)), 7.39 – 7.33 (m, 3H, (**H**$_{\textbf{Aromatic}}$)), 7.30 (d, *J* = 4.4 Hz, 4H, **H**$_{\textbf{Aromatic}}$)), 7.25 – 7.21 (m, 1H, **H**$_{\textbf{Aromatic}}$)), 5.97 (d, *J* = 19.3 Hz, 2H), 5.87 (d, *J* = 19.3 Hz, 2H), 3.53 (s, 2H), 1.77 – 1.51 (br s, 6H (**H**$_{\textbf{Cyclohexyl}}$)), 1.44 (br s, 4H, (**H**$_{\textbf{Cyclohexyl}}$)), 0.37 (s, 6H, (**H7**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (**C5**), 141.7 (**C13**), 139.4 (**C8**), 134.0 (**C10**), 129.0 (**C11**), 128.5 (**C14**), 127.9 (**C9**), 126.8 (**C16**), 125.4 (**C6**), 57.5 (**C4**), 46.5 (**C12**), 35.4 (**C3**), 26.3 (**C1**), 22.2 (**C2**), -2.1 (**C7**).

(1E)-*N*-benzyl-1-[dimethyl(phenyl)silyl]-3,5-dimethylhex-1-en-3-amine 120g



The title compound was prepared according to **General Procedure 2E**, from *N*-benzyl-3,5- dimethylhex-1-yn-3-amine (75 mg, 0.35 mmol) and dimethylphenylsilane (71.2 mg, 0.53 mmol) using $PtCl_2$ (0.9 mg, 3.5 µmol) and XantPhos (2 mg, 3.5 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **120g** (122 mg, 79 %) as a colourless oil.

Rf (9:1 Hexane/EtOAc): 0.48

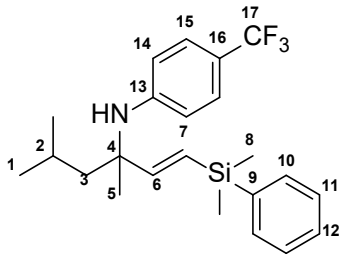
IR υmax (cm^{-1}) 3067, 3026, 2954, 2868, 1606

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{33}NSi$ 352.2461; Found 352.2455

^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.4, 3.1 Hz, 2H, (**H10**)), 7.35 (dd, *J* = 4.6, 1.9 Hz, 3H ($\mathbf{H_{Aromatic}}$)), 7.30 (d, *J* = 4.4 Hz, 4H $\mathbf{H_{Aromatic}}$), 7.25 – 7.19 (m, 1H, (**H17**)), 6.03 (d, *J* = 19.1 Hz, 1H, (**H6**)), 5.83 (d, *J* = 19.2 Hz, 1H, (**H7**)), 3.61 (d, *J* = 12.1 Hz 1H, (**H13**)), 3.57 (d, *J* = 12.1 Hz, 1H (**H13**)), 1.71 (dt, *J* = 12.3, 5.9 Hz, 1H, (**H2**)), 1.48 – 1.38 (t, *J* = 4.4 Hz, 2H, (**H3**)), 1.23 (s, 3H, (**H5**)), 0.91 (dd, *J* = 9.0, 6.7 Hz, 6H, (**H1**)), 0.35 (s, 6H, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (**C6**), 141.6 (**C14**), 139.2 (**C9**), 134.0 (**C11**), 129.0 (**C12**), 128.5 (**C16**), 128.4 (**C15**), 127.9 (**C10**), 126.9 (**C17**), 124.8 (**C7**), 59.0 (**C4**), 50.2 (**C3**), 47.2 (**C13**), 25.3 (**C1**), 25.1 (**C1**), 24.2 (**C5**), 22.8 (**C2**), -2.2 (**C8**).

***N*-[(1E)-1-[dimethyl(phenyl)silyl]-3,5-dimethylhex-1-en-3-yl]-4-(trifluoromethyl)aniline 120h**



The title compound was prepared according to **General Procedure 2E**, from *N*-(3,5-dimethylhex1-yn-3-yl)-4-(trifluoromethyl)aniline (50 mg, 0.21 mmol) and dimethylphenylsilane (43.4 mg, 0.32 mmol) using $PtCl_2$ (0.6 mg, 2.1 µmol) and XantPhos (1.2 mg, 2.1 µmol) which following conversion to the vinyl silane and column chromatography (7:3 Hexane/ CH_2Cl_2) afforded **120h** (70 mg, 89%) as a colourless oil.

Rf (7:3 Hexane: CH_2Cl_2): 0.48

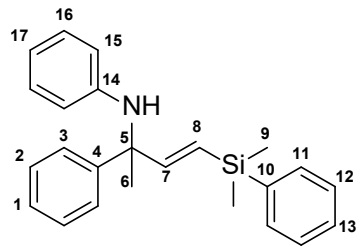
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{30}F_3NSi$ 406.2178; Found 406.2177 IR υmax (cm^{-1}) 3067, 3022, 2955, 2869, 1614

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H, (**H10**), 7.39 – 7.32 (m, 3H, (**H11** & **H12**)), 7.28 (d, *J* = 8.6 Hz, 2H, (**H15**)), 6.61 (d, *J* = 8.5 Hz, 2H, (**H14**)), 6.14 (d, *J* = 19.0 Hz, 1H, (**H6**)), 5.93 (d, *J* = 19.2 Hz, 1H (**H7**)), 4.09 (s, 1H (**NH**),), 1.83 – 1.71 (m, 1H, (**H2**),), 1.66 (dd, *J* = 14.0, 5.6 Hz, 1H, (**H3**)), 1.54 (dd, *J* = 13.4, 6.2 Hz, 1H, (**H3**)), 1.40 (s, 3H, (**H5**)), 0.95 (d, *J* = 6.7 Hz, 3H, (**H1**)), 0.89 (d, *J* = 6.6 Hz, 3H, (**H1**)), 0.34 (s, 6H, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (**C6**), 149.2 (**C13**), 138.7 (**C9**), 133.9 (**C11**), 129.0 (**C12**), 127.9 (**C10**), 127.8 (q, *J* = 257 Hz (**C17**)) 126.6 (**C7**), 126.0 (q, *J* = 3.5 Hz, (**C15**)), 118.3 (q, *J* = 32.8 Hz, (**C16**)), 114.3 (**C14**), 59.2 (**C4**), 50.3 (**C2**), 25.2 (**C5**), 24.9 (**C1**), 24.8 (**C1**), 24.1 (**C2**), -2.4 (**C5**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -60.84.

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-phenylbut-3-en-2-yl]aniline 120i**



The title compound was prepared according to **General Procedure 2E**, from *N*-[2-phenylbut-3- yn-2-yl]aniline (50 mg, 0.23 mmol) and dimethylphenylsilane (46.2 mg, 0.34 mmol) using $PtCl_2$ (0.6 mg, 2.3 µmol) and XantPhos (1.3 mg, 2.3 µmol) which following conversion to the vinyl silane and column chromatography (7:3 Hexane/ CH_2Cl_2) afforded **120i** (69 mg, 85%) as a colourless oil.

Rf(7:3 Hexane/ CH_2Cl_2): 0.60

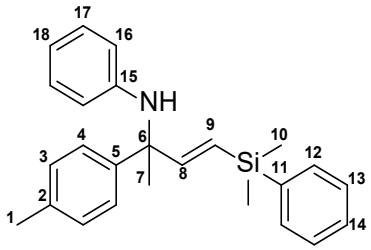
IR υmax (cm^{-1}) 3411, 3053, 3016, 2960, 1599

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{24}H_{28}NSi$ 358.1991; Found 358.1985

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H, (**H11**)), 7.46 – 7.41 (m, 2H, (**H**$_{\text{Aromatic}}$)), 7.36 – 7.28 (m, 5H, **H**$_{\text{Aromatic}}$), 7.23 (d, *J* = 7.6 Hz, 1H, (**H**$_{\text{Aromatic}}$) (**Overlaps with $CDCl_3$ signal**)), 7.01 (t, *J* = 7.9 Hz, 2H, (**H**$_{\text{aromatic}}$)), 6.63 (td, *J* = 7.3, 0.7 Hz, 1H, (**H17**), 6.54 (d, *J* = 18.9 Hz, 1H, (**H7**)), 6.41 (dd, *J* = 7.9, 0.7 Hz, 2H, (**H15**)), 6.02 (d, *J* = 18.8 Hz, 1H (**H8**)), 4.18 (s, 1H, (**NH**)), 1.70 (s, 3H, (**H6**)), 0.32 (s, 6H, (**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (**C7**), 145.8 (**C14**), 145.4 (**C4**), 138.8 (**C10**), 134.0 (**C12**), 129.1 (**C**$_{\text{Aromatic}}$), 128.7 (**C**$_{\text{Aromatic}}$), 128.6 (**C**$_{\text{Aromatic}}$), 127.9 (**C11**), 126.8 (**C**$_{\text{Aromatic}}$), 126.6 (**C**$_{\text{Aromatic}}$), 126.0 (**C8**), 117.4 (**C17**), 116.0 (**C15**), 61.7 (**C5**), 29.4 (**C6**), -2.4 (**C9**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-(4-methylphenyl)but-3-en-2-yl]aniline 120j**



The title compound was prepared according to **General Procedure 2E**, from *N*-[2-(4- methylphenyl)but-3-yn-2-yl]aniline (50 mg, 0.21 mmol) and dimethylphenylsilane (43.4 mg, 0.32 mmol) using $PtCl_2$ (0.6 mg, 2.1 µmol) and XantPhos (1.2 mg, 2.1 µmol) which following conversion to the vinyl silane and column chromatography (7:3 Hexane/ CH_2Cl_2) afforded **120j** (70 mg, 89%) as a colourless oil.

Rf (7:3 Hexane/ CH_2Cl_2): 0.54

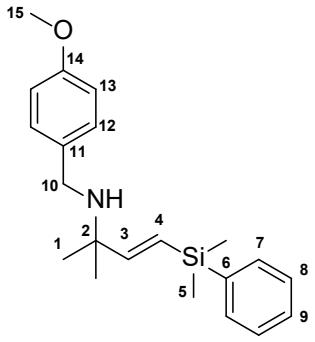
IR υmax (cm^{-1}) 3409, 3018, 2973, 1602, 1501

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{25}H_{29}NSi$ 372.2148; Found 372.2140

^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H, (**H12**)), 7.39 – 7.31 (m, 5H, (**H$_{Aromatic}$**)), 7.15 (d, *J* = 8.0 Hz, 2H, (**H$_{Aromatic}$**)), 7.02 (t, *J* = 7.7 Hz, 2H, (**H17**)), 6.64 (t, *J* = 7.6 Hz, 1H, (**H18**)), 6.54 (d, *J* = 18.8 Hz, 1H, (**H8**)), 6.44 (d, *J* = 8.5 Hz, 2H, (**H16**)), 6.02 (d, *J* = 18.8 Hz, 1H, (**H9**)), 4.17 (s, 1H, (**NH**)), 2.35 (s, 3H, (**H1**)), 1.69 (s, 3H, (**H7**)), 0.33 (s, 6H, (**H10**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3 (**C8**), 146.0 (**C15**), 142.4 (**C5**), 138.8 (**C11**), 136.3 (**C2**), 134.0 (**C13**), 129.3 (**C14**), 129.1 (**C$_{Aromatic}$**), 128.7 (**C$_{Aromatic}$**), 127.9 (**C12**), 126.5 (**C$_{Aromatic}$**), 125.8 (**C9**), 117.4 (**C18**), 116.0 (**C16**), 61.5 (**C6**), 29.4 (**C1**), 21.1 (**C7**), -2.3 (**C10**), -2.4 (**C10**).

(3E)-4-[dimethyl(phenyl)silyl]-*N*-[(4-methoxyphenyl)methyl]-2-methylbut-3-en-2- amine 120k



The title compound was prepared according to **General Procedure 2E**, from *N*-[(4- methoxyphenyl)methyl]-2-methylbut-3-yn-2-amine (30 mg, 0.148 mmol) and dimethylphenylsilane (30 mg, 0.22 mmol) using $PtCl_2$ (0.4 mg, 1.5 µmol) and XantPhos (0.9 mg, 1.5 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **120k** (43 mg, 86%) as a colourless oil.

Rf (9:1 Hexane:EtOAc): 0.19

IR υmax (cm^{-1}) 3098, 3044, 2995, 2970 2825

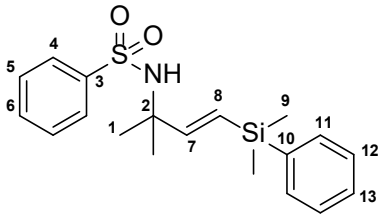
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{21}H_{30}NOSi$ 340.2097; Found 340.2091

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 2H, (**H7**)), 7.36 (m, 3H, (**H8** & **H9**)), 7.24 – 7.18 (m, 2H, (**H12**)), 6.92 – 6.72 (m, 2H, (**H13**)), 6.08 (d, *J* = 19.1 Hz, 1H, (**H3**)), 5.84 (d, *J* = 19.0 Hz, 1H, (**H4**)), 3.79 (s, 3H, (**H15**)), 3.54 (s, 2H, (**H10**)), 1.23 (s, 6H, (**H1**)), 0.37 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (**C14**), 155.8 (**C11**), 139.2 (**C6**), 133.9 (**C8**), 129.5 (**C9**), 129.0 (**C12**), 127.9 (**C7**), 124.3 (**C4**), 113.9 (**C13**), 56.0 (**C2**), 55.4 (**C15**), 47.2 (**C10**), 27.1 (**C1**), -2.2 (**C5**).

2.8.5 Synthesis of Allylic Amides, Carbamates and Sulfonamides

N-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]-benzene-1-sulfonamide 123a



The title compound was prepared according to **General Procedure 2E**, from *N*-(2-methylbut-3- yn-2-yl)benzenesulfonamide (75 mg, 0.31 mmol) and dimethylphenylsilane (69 mg, 0.51 mmol) using $PtCl_2$ (0.9 mg, 3.2 µmol) and XantPhos (1.8 mg, 3.2 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123a** (94 mg, 92 %) as a white solid.

Rf (4:1 Hexane/EtOAc): 0.28

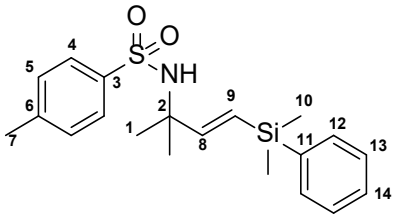
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{25}NO_2SSi$ 360.1454; Found 360.1460

IR υmax (cm^{-1}) 3275, 3069, 2976, 2943, 1613

^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H, (**H**$_{Aromatic}$)), 7.49 (m, 1H, (**H**$_{Aromatic}$)), 7.42 – 7.40 (m, 4H, (**H**$_{Aromatic}$)), 7.37 – 7.32 (m, 3H, (**H**$_{Aromatic}$), 5.94 (d, *J* = 18.9 Hz, 1H, (**H7**)), 5.83 (d, *J* = 18.9 Hz, 1H, (**H8**), 4.57 (s, 1H, (**NH**)), 1.31 (s, 6H, (**H1**)), 0.22 (s, 6H, (**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (**C7**), 143.1 (**C3**), 138.4 (**C10**), 133.9 (**C12**), 132.4 (**C6**), 129.2 (**C13**), 129.0 (**C11**), 128.0 (**C5**), 127.3 (**C4**), 125.4 (**C8**), 58.7 (**C2**), 28.1 (**C1**), -2.7 (**C9**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]-4-methylbenzene-1- sulfonamide 123b**



The title compound was prepared according to **General Procedure 2E**, from 4-methyl-*N*-(2- methylbut-3-yn-2-yl)benzene-1-sulfonamide (75 mg, 0.31 mmol) and dimethylphenylsilane (69 mg, 0.51 mmol) using $PtCl_2$ (0.9 mg, 3.1 µmol) and XantPhos (1.8 mg, 3.1 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123b** (118 mg, 84 %) as a pale-yellow solid.

Rf (4:1 Hexane/EtOAc): 0.28

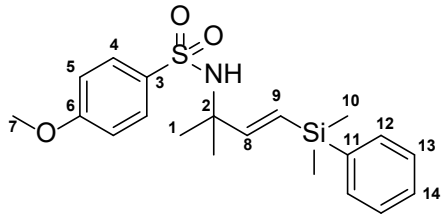
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{27}NO_2SSi$ 374.1610; Found 374.1605

IR υmax (cm^{-1}) 3294, 2978, 1723, 1699

^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H, (**H4**)), 7.47 – 7.40 (m, 2H, (**H13**)), 7.35 (dd, *J* = 5.6, 1.1 Hz, 3H, (**H12** & **H14**)), 7.21 (d, *J* = 8.1 Hz, 2H, (**H5**)), 5.95 (d, *J* = 18.8 Hz, 1H, (**H8**)), 5.82 (d, *J* = 18.9 Hz, 1H, (**H9**)), 4.81 (s, 1H, (**NH**)), 2.39 (s, 3H, (**H7**)), 1.31 (s, 6H, (**H1**)), 0.22 (s, 6H, (**H10**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (**C8**), 143.0 (**C3**), 140.2 (**C6**), 138.5 (**C11**), 133.9 (**C13**), 129.6 (**C5**), 129.2 (**C14**), 127.9 (**C12**), 127.3 (**C4**), 125.2 (**C9**), 58.5 (**C2**), 21.6, (**C1**), -2.7 (**C10**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]-methoxybenzene-1- sulfonamide 123c**



The title compound was prepared according to **General Procedure 2E**, from 4-methoxy-*N*-(2- methylbut-3-yn-2-yl)benzene-1-sulfonamide (75 mg, 0.3 mmol) and dimethylphenylsilane (65 mg, 0.47 mmol) using $PtCl_2$ (0.8 mg, 3 µmol) and XantPhos (1.7 mg, 3 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123c** (115 mg, 77 %) as a yellow oil.

Rf (4:1 Hexane/EtOAc): 0.22

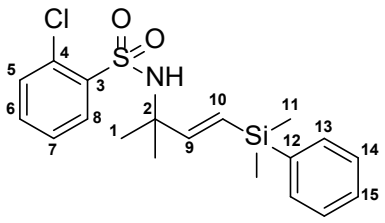
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{27}NO_3SSi$ 390.1559; Found 390.1554

IR υmax (cm^{-1}) 3292, 3029, 2995, 2951, 1723, 1694

^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H, (**H4**)), 7.48 – 7.40 (m, 2H, (**H13**)), 7.37 – 7.32 (m, 3H, (**H12** & **H14**)), 6.86 (d, *J* = 8.8 Hz, 2H, (**H5**)), 5.95 (d, *J* = 18.8 Hz, 1H, (**H8**)), 5.81 (d, *J* = 18.9 Hz, 1H, (**H9**)), 4.84 (s, 1H, (**NH**)), 3.82 (s, 3H, (**H7**)), 1.30 (s, 6H, (**H1**)), 0.23 (s, 6H (**H10**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (**C6**), 152.1 (**C8**), 138.5 (**C11**), 134.7 (**C3**), 133.9 (**C13**), 129.4 (**C14**), 129.2 (**C4**), 127.9 (**C12**), 125.1 (**C9**), 114.1 (**C5**), 58.4 (**C2**), 55.7 (**C7**), 28.0 (**C1**), -2.7 (**C10**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]-2-chlorobenzene-1- sulfonamide 123d**



The title compound was prepared according to **General Procedure 2E**, from 2-chloro-*N*-(2- methylbut-3-yn-2-yl)benzene-1-sulfonamide (75 mg, 0.3 mmol) and dimethylphenylsilane (60 mg, 0.45 mmol) using $PtCl_2$ (0.8 mg, 3 µmol) and XantPhos (1.7 mg, 3 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123d** (90 mg, 78 %) as a white solid.

Rf (4:1 Hexane/EtOAc): 0.29

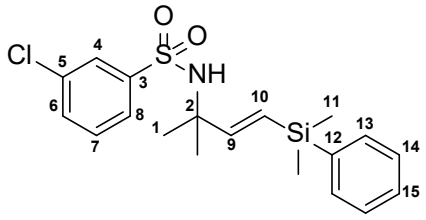
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{24}ClNO_2SSi$ 394.1064; Found 394.1074

IR υmax (cm^{-1}) 3292, 3093, 3066, 2976, 2931

^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.5 Hz, 1H (**H8**)), 7.45 (dd, *J* = 6.3, 4.8 Hz, 1H, (**H6**)), 7.43 – 7.37 (m, 1H, (**H5** or **H7**), 7.36 – 7.31 (m, 2H, (**H14**)), 7.28 (m, 4H, (**H13**, **H15** & **H5** or **H7**)), 5.91 (d, *J* = 18.8 Hz, 1H, (**H9**)), 5.83 (d, *J* = 18.8 Hz, 1H, (**H10**)), 5.07 (s, 1H, (**NH**)), 1.32 (s, 6H (**H1**)), 0.18 (s, 6H (**H11**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 (**C9**), 140.3 (**C4**), 138.3 (**C12**), 133.8 (**C13**), 133.3 (**C3**), 131.5 (**C7**), 131.3 (**C4**), 130.8 (**C5**), 129.2 (**C15**), 127.8 (**C13**), 127.3 (**C6**), 125.7 (**C10**), 58.7 (**C2**), 27.9 (**C1**), -2.8 (**C11**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]-3-chlorobenzene-1- sulfonamide 123e**



The title compound was prepared according to **General Procedure 2E**, from 3-chloro-*N*-(2- methylbut-3-yn-2-yl)benzene-1-sulfonamide (50 mg, 0.19 mmol) and dimethylphenylsilane (40 mg, 0.30 mmol) using $PtCl_2$ (0.5 mg, 1.9 µmol) and XantPhos (1.1 mg, 1.9 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **123e** (62 mg, 81 %) as a pale-yellow solid.

Rf (4:1 Hexane/EtOAc): 0.31

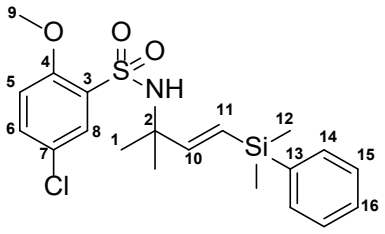
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{24}ClNO_2SSi$ 394.1064; Found 394.1073

IR υmax (cm^{-1}) 3250, 3069, 3048, 2987, 2866, 1612

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, *J* = 2.0 Hz, 1H, (**H$_{Aromatic}$**)), 7.70 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H, (**H$_{Aromatic}$**)), 7.47 (ddd, *J* = 8.2, 2.0, 1.2 Hz, 1H, (**H$_{Aromatic}$**)), 7.45 – 7.40 (m, 2H, (**H$_{Aromatic}$**)), 7.37 – 7.31 (m, 4H, (**H$_{Aromatic}$**)), 5.94 (d, *J* = 18.9 Hz, 1H, (**H9**)), 5.84 (d, *J* = 18.8 Hz, 1H, (**H10**)), 4.59 (s, 1H, (**NH**)), 1.33 (s, 6H, (**H1**)), 0.24 (s, 6H, (**H11**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (**C9**), 144.8 (**C3**), 138.2 (**C12**), 135.1 (**C5**), 133.8 (**C14**), 132.5 (**C$_{Aromatic}$**), 130.3 (**C$_{Aromatic}$**), 129.2 (**C14**), 127.9 (**C13**), 127.3 (**C$_{Aromatic}$**), 125.9 (**C$_{Aromatic}$**), 125.3 (**C10**), 58.9 (**C2**), 28.1 (**C1**), -2.8 (**C11**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]-2-methoxy-5-chlorobenzene-1-sulfonamide 123f**



The title compound was prepared according to **General Procedure 2E**, from 2-methoxy-5-chloro-*N*-(2-methylbut-3-yn-2-yl)benzene-1-sulfonamide (50 mg, 0.17 mmol) and dimethylphenylsilane (35 mg, 0.26 mmol) using $PtCl_2$ (0.5 mg, 1.7 µmol) and XantPhos (1.1 mg, 1.7 µmol) which following conversion to the vinyl silane and column chromatography (9:1 Hexane/EtOAc) afforded **123f** (61 mg, 83%) as a white solid.

Rf (4:1 Hexane/EtOAc): 0.21

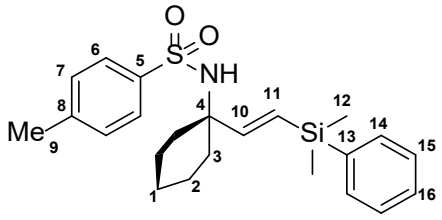
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{26}ClNO_3SSi$ 424.1169; Found 424.1157

IR υmax (cm^{-1}) 3250, 3070, 3049, 2972, 1611

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.7 Hz, 1H, (**H8**)), 7.44 – 7.37 (m, 3H, (**H15** & **H6**)), 7.36 – 7.31 (m, 3H, (**H14** & **H16**)), 6.87 (d, *J* = 8.9 Hz, 1H, (**H5**)), 5.89 (d, *J* = 18.8 Hz, 1H, (**H10**)), 5.80 (d, *J* = 18.9 Hz, 1H, (**H11**)), 5.00 (s, 1H, (**NH**)), 3.88 (s, 3H, (**H9**)), 1.31 (s, 6H, (**H1**)), 0.20 (s, 6H, (**H12**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (**C4**), 151.3 (**C10**), 138.2 (**C13**), 133.9 (**C15**), 133.7 (**C7**), 133.1 (**C6**), 132.3 (**C5**), 129.2 (**C16**), 127.9 (**C14**), 126.1 (**C3**), 125.5 (**C11**), 113.5, 58.5 (**C2**), 56.6 (**C9**), 27.9 (**C1**), -2.8 (**C12**).

***N*-[1-[(E)-2-[dimethyl(phenyl)silyl]vinyl]cyclohexyl]-4-methyl-benzenesulfonamide 129**



The title compound was prepared according to **General Procedure 2E**, from **128** (50 mg, 0.18 mmol) and dimethylphenylsilane (37 mg, 0.27 mmol) using $PtCl_2$ (2.4 mg, 9 µmol) and XantPhos (4.5 mg, 9 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **129** as a white solid. (87 mg, 83 %)

Rf (4:1 Hexane/EtOAc): 0.36

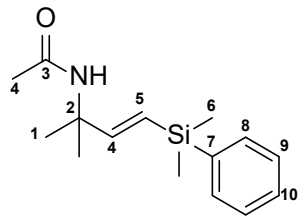
IR υmax (cm^{-1}) 3098, 300, 2934, 1756

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{32}NO_2SSi$ 414.1923; Found 414.1932

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H, (**H6**)), 7.48 – 7.38 (m, 2H, (**H15**)), 7.38 – 7.30 (m, 3H, (**H14** & **H16**)), 7.16 (d, *J* = 7.9 Hz, 2H, (**H7**)), 5.85 (s, 2H, (**H10** & **H11**)), 4.54 (br s, 1H, (**NH**)), 2.37 (s, 3H, (**H9**)), 1.85 (m, 2H, (**H$_{Cyclohexyl}$**)), 1.68 – 1.56 (m, 2H, (**H$_{Cyclohexyl}$**)), 1.56 – 1.43 (m, 4H, (**H$_{Cyclohexyl}$**)), 0.16 (s, 6H, (**H12**)).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0 (**C10**), 142.9 (**C8**) , 140.4 (**C5**), 138.6 (**C13**), 133.9 (**C15**), 129.5 (**C7**), 129.1 (**C16**), 127.9 (**C14**), 127.3 (**C6**), 127.1 (**C11**), 60.3 (**C4**), 36.2 (**C$_{Cyclohexyl}$**), 25.5 (**C$_{Cyclohexyl}$**), 22.0 (**C$_{Cyclohexyl}$**), 21.6 (**C$_{Cyclohexyl}$**), -2.8 (**C12**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]acetamide 123g**



The title compound was prepared according to **General Procedure 2E**, from *N*-(2-methylbut-3- yn-2-yl)acetamide (50 mg, 0.4 mmol) and dimethylphenylsilane (82 mg, 0.6 mmol) using $PtCl_2$ (1.1 mg, 4 µmol) and XantPhos (2.3 mg, 4 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123g** (87 mg, 83 %) as a white solid.

Rf (4:1 Hexane/EtOAc): 0.33

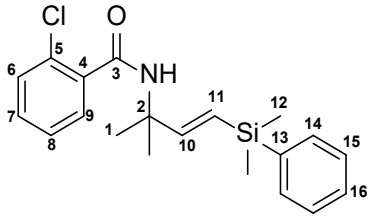
IR υmax (cm^{-1}) 3278, 3069, 3012, 2963, 1643

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{15}H_{24}NOSi$ 262.1627; Found 262.1622

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H, (**H9**)), 7.39 – 7.32 (m, 3H, (**H8** & **H10**)), 6.23 (d, *J* = 19.0 Hz, 1H, (**H4**)), 5.80 (d, *J* = 19.0 Hz, 1H, (**H5**)), 5.41 – 5.30 (s, 1H, (**NH**)), 1.94 (s, 3H, (**H4**)), 1.43 (s, 6H, (**H1**)), 0.34 (s, 6H, (**H6**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (**C3**), 153.2 (**C4**), 138.9 (**C7**), 134.0 (**C9**), 129.1 (**C10**), 127.9 (**C8**), 123.4 (**C5**), 55.8 (**C2**), 27.2 (**C1**), 24.7 (**C4**), -2.4 (**C6**).

2-Chloro-*N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]benzamide 123h



The title compound was prepared according to **General Procedure 2E**, from 2-chloro-*N*-(2- methylbut-3-yn-2-yl)benzamide (75 mg, 0.33 mmol) and dimethylphenylsilane (73 mg, 0.54 mmol) using $PtCl_2$ (1.8 mg, 6.7 µmol) and XantPhos (3.9 mg, 6.7 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123h** (109 mg, 90 %) as an orange oil.

Rf (4:1 Hexane/EtOAc): 0.43

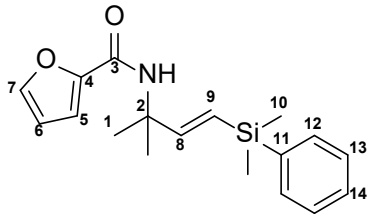
IR υmax (cm^{-1}) 3429, 3281, 3068, 2961, 1649

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{24}ClNOSi$ 358.1394; Found 358.1388

^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.0, 1.5 Hz, 1H, (**H9**)), 7.54 (m, 2H (**H**$_{\text{Aromatic}}$), 7.39 – 7.35 (m, 4H, (**H**$_{\text{Aromatic}}$), 7.35 – 7.29 (m, 2H, (**H**$_{\text{Aromatic}}$)), 6.34 (d, *J* = 19.0 Hz, 1H, (**H10**)), 6.07 (s, 1H, (**NH**)), 5.95 (d, *J* = 18.9 Hz, 1H, (**H11**)), 1.57 (s, 6H, **H1**)), 0.37 (s, 6H, (**H12**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (**C3**), 152.7 (**C10**), 138.8 (**C13**), 136.3 (**C4**), 134.0 (**C15**), 133.2 (**C**$_{\text{Aromatic}}$), 131.0 (**C5**), 130.2 (**C**$_{\text{Aromatic}}$), 129.9 (**C16**), 129.1 (**C**$_{\text{Aromatic}}$), 127.9 (**C14**), 127.2 (**C**$_{\text{Aromatic}}$), 124.0 (**C11**), 56.7, (**C2**), 27.2 (**C1**), -2.4 (**C12**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]furan-2-carboxamide 123i**



The title compound was prepared according to **General Procedure 2E**, from *N*-(2-methylbut-3- yn-2-yl)furan-2-carboxamide (50 mg, 0.28 mmol) and dimethylphenylsilane (61 mg, 0.42 mmol) using $PtCl_2$ (1.5 mg, 5.7 µmol) and XantPhos (3.3 mg, 5.7 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123i** (89 mg, 84 %) as a white solid.

Rf (4:1 Hexane/EtOAc): 0.38

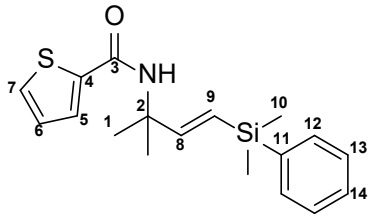
IR υmax (cm^{-1}) 3243, 3120, 3063, 2972, 1640, 1572

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{18}H_{23}NO_2Si$ 314.1576; Found 314.1571

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.2, 3.3 Hz, 2H, (**H13**), 7.41 (m, 1H, (**H7**)), 7.38 – 7.32 (m, 3H, (**H12** & **H14**), 7.07 (d, *J* = 3.0 Hz, 1H, (**H5**)), 6.48 (dd, *J* = 3.5, 1.8 Hz, 1H, **H6**)), 6.31 (m, 2H, (**H8** and **NH**), 5.88 (d, *J* = 19.0 Hz, 1H, (**H9**)), 1.54 (s, 6H, (**H1**)), 0.35 (s, 6H, (**H10**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (**C3**), 152.8 (**C8**), 148.8 (**C4**), 143.5 (**C7**), 138.8 (**C11**), 134.0 (**C13**), 133.1, 129.1 (**C14**), 127.9 (**C12**), 123.7 (**C9**), 113.8 (**C5**), 112.2 (**C6**), 55.9 (**C2**), 27.3 (**C1**), -2.4 (**C10**).

***N*-[(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]thiophene-2-carboxamide 123j**



The title compound was prepared according to **General Procedure 2E**, from *N*-(2-methylbut-3- yn-2-yl)thiophene-2-carboxamide (50 mg, 0.28 mmol) and dimethylphenylsilane (61 mg, 0.42 mmol) using $PtCl_2$ (0.7 mg, 2.8 µmol) and XantPhos (1.7 mg, 2.8 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123j** (76 mg, 87 %) as a white solid.

Rf (4:1 Hexane/EtOAc): 0.42

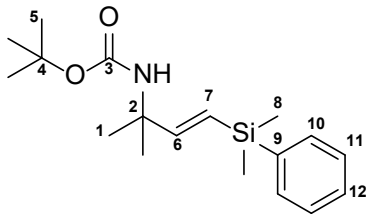
IR υmax (cm^{-1}) 3255, 3103, 3089, 2966, 1622

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{18}H_{23}NOSSi$ 330.1348; Found 330.1356

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.3, 3.1 Hz, 2H, (**H7** & **H5**)), 7.48 – 7.40 (m, 2H, (**H13**)), 7.39 – 7.32 (m, 3H, (**H12** & **H14**)), 7.09 – 7.02 (m, 1H, (**H6**)), 6.33 (d, *J* = 18.9 Hz, 1H, (**H8**)), 5.90 (s, 1H, (**NH**)) 5.89 (d, *J* = 18.9 Hz, 1H, (**H9**)), 1.55 (s, 6H, (**H1**)), 0.36 (s, 6H, (**H10**)).

^{13}C NMR (101 MHz. $CDCl_3$) δ 161.0 (**C3**), 152.9 (**C8**), 140.4 (**C4**), 138.8 (**C11**), 134.0 (**C13**), 129.6 (**C14**), 129.1 (**C6**), 127.9 (**C12**), 127.7 (**C5**), 127.6 (**C7**) 123.8 (**C9**), 56.4 (**C2**), 27.3 (**C1**), -2.4 (**C10**).

***tert*-butyl [(3E)-4-[dimethyl(phenyl)silyl]-2-methylbut-3-en-2-yl]carbamate 123k**



The title compound was prepared according to **General Procedure 2E**, from tert-butyl (2- methylbut-3-yn-2-yl)carbamate (50 mg, 0.27 mmol) and dimethylphenylsilane (69 mg, 0.51 mmol) using $PtCl_2$ (0.7 mg, 2.7 µmol) and XantPhos (1.7 mg, 2.7 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123k** (74 mg, 86 %) as a pale-yellow solid.

Rf (4:1 Hexane/EtOAc): 0.41

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{18}H_{29}NO_2Si$ 320.2046; Found 320.2040

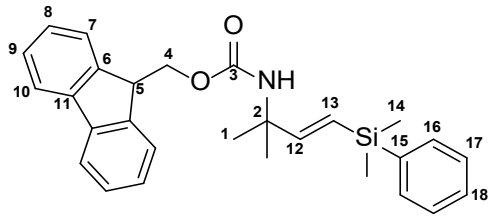
IR υmax (cm^{-1}) 3358, 3069, 2973, 2930, 1723, 1695

^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, *J* = 6.4, 3.0 Hz, 2H, (**H11**)), 7.35 – 7.31 (m, 3H, (**H10** & **H12**), 6.15 (d, *J* = 18.9 Hz, 1H, (**H8**)), 5.80 (d, *J* = 18.9 Hz, 1H, (**H7**)), 4.58 (s, 1H, (**NH**)), 1.41 (s, 9H, (**H5**)), 1.36 (s, 6H, (**H1**)), 0.33 (s, 6H, (**H8**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (**C6**), 139.0 (**C9**), 134.0 (**C11**), 129.1 (**C12**), 127.9 (**C10**), 123.1 (**C7**), 54.8 (**C2**), 28.5 (**C5**), 27.6 (**C1**), -2.3 (**C8**).

****C3 Not Observed****

(4b,8a,9,9a-Tetrahydro-4aH-fluoren-9-yl)methyl [(3E)-4-[dimethyl(phenyl)silyl]-2- methylbut-3-en-2-yl]carbamate 123k



The title compound was prepared according to **General Procedure 2E**, from (4b,8a,9,9a-tetrahydro-4aH-fluoren-9-yl)methyl (2-methylbut-3-yn-2-yl)carbamate (75 mg, 0.31 mmol) and dimethylphenylsilane (69 mg, 0.51 mmol) using $PtCl_2$ (0.9 mg, 3.1 µmol) and XantPhos (1.8 mg, 3.2 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **123k** (92 mg, 78 %) as a colourless oil.

Rf (4:1 Hexane/EtOAc): 0.47

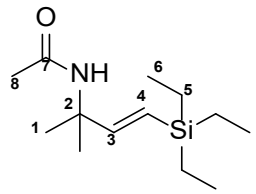
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{28}H_{31}NO_2Si$ 442.2202; Found 442.2197

IR υmax (cm^{-1}) 3412, 3340, 3067, 2961, 1708

^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H, (**H**$_{Aromatic}$)), 7.59 (d, *J* = 7.4 Hz, 2H, (**H**$_{Aromatic}$), 7.50 (s, 2H) (**H**$_{Aromatic}$), 7.39 (t, *J* = 7.4 Hz, 2H (**H17**)), 7.36 – 7.25 (m, *J* = 14.7, 7.3 Hz, 5H (**H**$_{Aromatic}$)), 6.19 (m, (**H**$_{Aromatic}$)), 5.82 (d, *J* = 18.9 Hz, 1H, (**H13**)), 4.81 (s, 1H, (**NH**)), 4.37 (d, *J* = 5.0 Hz, 2H, (**H6**)), 4.19 (t, *J* = 6.2 Hz, 1H, (**H5**)), 1.41 (s, 6H, (**H1**)), 0.33 (s, 6H, (**H14**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (**C12**), 144.2 (**C**$_{Aromatic}$), 141.4 (**C**$_{Aromatic}$), 138.9 (**C15**), 134.0 (**C17**), 129.1 (**C18**), 127.9 (**C**$_{Aromatic}$), 127.8 (**C16**), 127.2 (**C**$_{Aromatic}$), 125.2 (**C**$_{Aromatic}$), 123.7 (**C13**), 120.1 (**C**$_{Aromatic}$), 66.1 (**C6**), 55.1 (**C2**), 47.5 (**C5**), 27.4 (**C5**), -2.4 (**C14**).

***N*-[(3E)-4-[triethylsilyl]-2-methylbut-3-en-2-yl]acetamide 124**



The title compound was prepared according to **General Procedure 2E**, from *N*-(2-methylbut-3-yn-2-yl)acetamide (50 mg, 0.40 mmol) and triethylsilane (69 mg, 0.60 mmol) using $PtCl_2$ (1.2 mg, 4 µmol) and XantPhos (2.4 mg, 4 µmol) which following conversion to the vinyl silane and column chromatography (4:1 Hexane/EtOAc) afforded **124** (92 mg, 78 %) as a colourless oil.

Rf (9:1 Hexane/EtOAc): 0.31

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{28}NOSi$ 242.1940; Found 242.1932

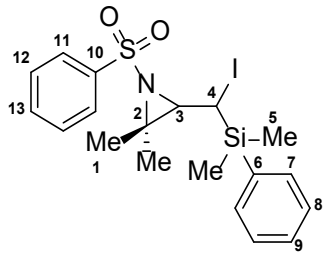
IR υmax (cm^{-1}) 3390, 3092, 3003, 2988

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.59 (d, *J* = 19.2 Hz, 1H, (**H4**)), 5.36 (br s, 1H, (**NH**)), 1.94 (s, 3H, (**H8**)), 1.42 (s, 6H, (**H1**)), 0.92 (t, *J* = 7.9 Hz, 9H, (**H6**)), 0.57 (q, *J* = 7.8 Hz, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (**C7**), 152.9 (**C3**), 121.5 (**C4**), 55.9 (**C2**), 27.2 (**C1**), 24.7 (**C4**), 7.5 (**C6**), 3.5 (**C5**).

2.8.6 Synthesis of Aziridines & Other Derivatives

1-(benzenesulfonyl)-3-[[dimethyl(phenyl)silyl](iodo)methyl]-2,2-dimethylaziridine 124a



The title compound was prepared according to **General Procedure 2F**, from **123a** (30 mg, 0.084 mmol) and *N*-Iodosuccinimide (56 mg, 0.25 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124a** as a colourless oil (34 mg, 84%).

Rf (4:1 Hexane/EtOAc): 0.43

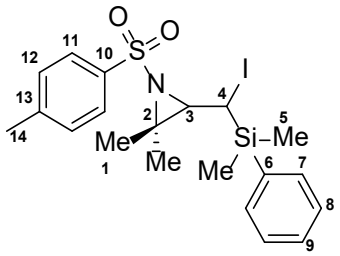
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{25}INO_2SSi$ 486.0420; Found 486.0412

IR υmax (cm^{-1}) 3070, 2981, 2940, 2922, 1593

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 2H, (**H11**)), 7.61 – 7.54 (m, 3H, (**H$_{Aromatic}$**)), 7.48 (t, *J* = 7.6 Hz, 2H, (**H$_{Aromatic}$**), 7.41 – 7.33 (m, 3H), 3.21 (d, *J* = 11.7 Hz, 1H, (**H3**)), 2.94 (d, *J* = 11.7 Hz, 1H, (**H4**)), 1.57 (s, 3H, (**H1**)), 1.30 (s, 3H, (**H1**)), 0.35 (s, 3H, (**H5**)), 0.25 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7 (**C10**), 135.5 (**C6**), 134.6 (**C8**), 133.2 (**C11**), 129.9 (**C9**), 128.9 (**C13**), 127.8 (**C7**), 127.7 (**C12**), 53.1 (**C3**), 29.8 (**C2**), 21.0 (**C1**), 19.7 (**C1'**), 15.3, -2.3 (**H5**), -4.3 (**H5**).

3-[[Dimethyl(phenyl)silyl](iodo)methyl]-2,2-dimethyl-1-(4-methylbenzene-1-sulfonyl)aziridine 124b



The title compound was prepared according to **General Procedure 2F**, from **123b** (50 mg, 0.134 mmol) and *N*-Iodosuccinimide (90 mg, 0.4 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124b** as a white solid (56 mg, 84%).

Rf (4:1 Hexane/EtOAc): 0.41

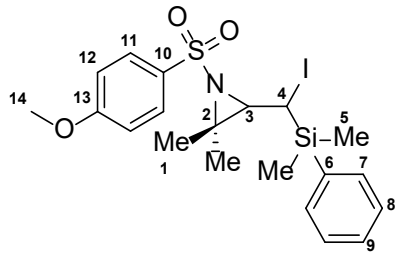
IR υmax (cm^{-1}) 3069, 2991, 2968, 2922, 1598

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{27}INO_2SSi$ 500.0576; Found 500.0575

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H, (**H11**)), 7.57 (m, 2H, (**H8**)), 7.38 (m, 3H, (**H7** & **H9**)), 7.27 (d, *J* = 8.3 Hz, 2H (**H12**)), Overlaps with $CDCl_3$), 3.19 (d, *J* = 11.8 Hz, 1H, (**H3**)), 2.94 (d, *J* = 11.7 Hz, 1H, (**H4**)), 2.41 (s, 3H, (**H14**)), 1.54 (s, 3H, (**H1**)), 1.28 (s, 3H, (**H1**)), 0.37 (s, 3H, (**H5**)), 0.28 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (**C13**), 137.8 (**C10**), 135.5 (**C6**), 134.7 (**C8**), 129.9 (**C9**), 129.5 (**C11**), 127.8 (**C7**), 127.7 (**C12**), 52.9 (**C3**), 52.7 (**C2**), 21.7 (**C14**), 20.9 (**C1**), 19.7 (**C1'**), 15.4 (**C4**), -2.3 (**C5**), -4.2 (**C5**).

3-[[Dimethyl(phenyl)silyl](iodo)methyl]-1-(4-methoxybenzene-1-sulfonyl)-2,2- dimethylaziridine 124c



The title compound was prepared according to **General Procedure 2F**, from **123c** (40 mg, 0.103 mmol) and *N*-Iodosuccinimide (69 mg, 0.31 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124c** as a colourless oil (45 mg, 85%).

Rf (4:1 Hexane/EtOAc): 0.32

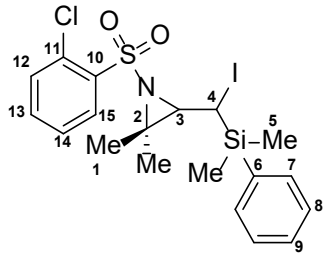
IR υmax (cm^{-1}) 3071, 3002, 2967, 2933, 2851

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{20}H_{27}INO_3SSi$ 516.0526; Found 516.0526

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 2H, (**H8**)), 7.57 (dd, *J* = 7.6, 1.6 Hz, 2H, (**H11**)), 7.41 – 7.32 (m, 3H, (**H7** & **H9**)), 6.96 – 6.88 (m, 2H, (**H12**)), 3.86 (s, 3H, (**H14**)), 3.18 (d, *J* = 11.7 Hz, 1H, (**H3**)), 2.94 (d, *J* = 11.7 Hz, 1H, (**H4**)), 1.54 (s, 3H, (**H1**)), 1.27 (s, 3H, (**H1**)), 0.38 (s, 3H, (**H5**)), 0.29 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (**C13**), 134.6 (**C10**) , 134.1 (**C8**), 132.4 (**C6**), 129.9 (**C9**), 129.9 (**C11**), 127.8 (**C7**), 114.0 (**C12**) , 55.7 (**C14**), 52.9 (**C3**), 52.5 (**C2**), 20.8 (**C1**), 19.8 (**C1'**), 15.4 (**C4**), -2.3 (**C5**), -4.1 (**C5**).

3-[[dimethyl(phenyl)silyl](iodo)methyl]-1-(2-chlorobenzene-1-sulfonyl)-2,2-dimethylaziridine 124d



The title compound was prepared according to **General Procedure 2F**, from **123d** (30 mg, 0.075 mmol) and *N*-Iodosuccinimide (52 mg, 0.225 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124d** as a white solid (49 mg, 74%).

Rf (4:1 Hexane/EtOAc): 0.47

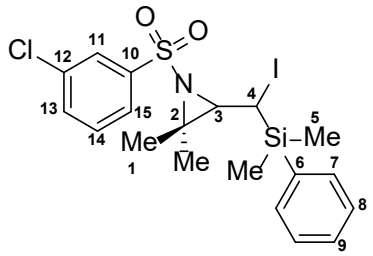
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{24}ClINO_2SSi$ 520.0030; Found 520.0011

IR υmax (cm^{-1}) 3068, 2971, 2967, 1563

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.3 Hz, 1H, (**H15**)), 7.58 – 7.43 (m, 4H (**H8, H13** & **H12**)), 7.43 – 7.28 (m, 4H, (**H7**, **H9** & **H14**)), 3.31 (d, *J* = 11.7 Hz, 1H, (**H3**)), 2.92 (d, *J* = 11.7 Hz, 1H, (**H4**)), 1.70 (s, 3H, (**H1**)), 1.42 (s, 3H, (**H1**)), 0.29 (s, 3H (**H5**)), 0.22 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (**C10**), 135.4 (**C6**), 134.5 (**C8**), 134.0 (**C15**), 133.3 (**C11**), 132.1 (**C13**), 130.1 (**C14**), 129.9 (**C9**), 127.8 (**C7**), 126.7, 54.7 (**C2**), 53.4 (**C3**), 22.6 (**C1**), 19.4 (**C1'**), 15.2 (**C4**), -2.8 (**C5**), -4.2 (**C5**).

3-[[dimethyl(phenyl)silyl](iodo)methyl]-1-(3-chlorobenzene-1-sulfonyl)-2,2-dimethylaziridine 124e



The title compound was prepared according to **General Procedure 2F**, from **123e** (30 mg, 0.075 mmol) and *N*-Iodosuccinimide (52 mg, 0.225 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124e** as a white solid (31 mg, 78%).

Rf (4:1 Hexane/EtOAc): 0.48

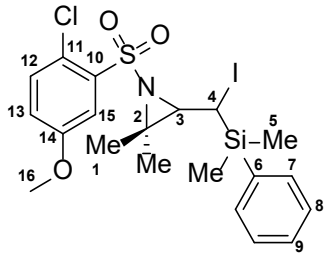
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{24}ClINO_2SSi$ 520.0030; Found 520.0016

IR υmax (cm^{-1}) 3043, 2964, 2911, 2879, 1589

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, *J* = 1.8 Hz, 1H (**H11**)), 7.74 (dt, *J* = 7.9, 1.5 Hz, 1H (**H15**)), 7.56 – 7.49 (m, 3H, (**H8** & **H13**)), 7.43 – 7.33 (m, 4H (**H7**, **H9** and **H14**)), 3.24 (d, *J* = 11.7 Hz, 1H, (**H3**)), 2.95 (d, *J* = 11.8 Hz, 1H, (**H4**)), 1.60 (s, 3H, (**H1**)), 1.33 (s, 3H, (**H1**)), 0.33 (s, 3H, (**H5**)), 0.29 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (**C10**), 135.3 (**C12**), 135.1 (**C6**), 134.6 (**C8**), 133.3 (**C11**), 130.3 (**C15**), 130.0 (**C9**), 127.9 (**C13**), 127.8 (**C7**), 125.7 (**C14**), 53.8 (**C2**), 53.7 (**C3**), 21.5 (**C1**), 19.8 (**C1'**), 14.9 (**C4**), -2.5 (**C5**), -3.8 (**C5**).

3-[[dimethyl(phenyl)silyl](iodo)methyl]-1-(2-methoxy-5-chlorobenzene-1-sulfonyl)-2,2-dimethylaziridine 124f



The title compound was prepared according to **General Procedure 2F**, from **123f** (30 mg, 0.070 mmol) and *N*-Iodosuccinimide (48 mg, 0.210 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124f** as a yellow oil (35 mg, 90%).

Rf (4:1 Hexane/EtOAc): 0.33

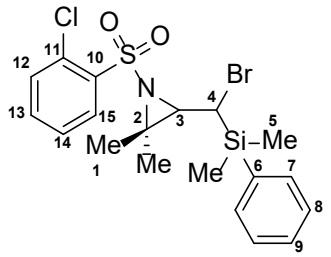
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{26}ClINO_3SSi$ 550.0136; Found 550.0126

IR υmax (cm^{-1}) 3082, 2950, 2909, 2892 1578

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 2.7 Hz, 1H, (**H15**)), 7.64 – 7.53 (m, 2H, (**H8**)), 7.46 (dd, *J* = 8.8, 2.7 Hz, 1H, (**H13**)), 7.42 – 7.29 (m, 3H, (**H7** & **H9**)), 6.93 (d, *J* = 8.9 Hz, 1H, (**H12**)), 3.96 (s, 3H, (**H16**)), 3.27 (d, *J* = 11.7 Hz, 1H, (**H3**)), 2.94 (d, *J* = 11.6 Hz, 1H, (**H4**)), 1.66 (s, 3H, (**H1**)), 1.36 (s, 3H, (**H1**)), 0.39 (s, 3H, (**H5**)), 0.36 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (**C14**), 135.5 (**C10**), 134.5 (**C6**), 134.3 (**C8**), 130.3 (**C11**), 129.8 (**C9**), 129.3 (**C13**), 127.8 (**C7**), 125.2 (**C12**), 113.9 (**C15**), 56.7 (**C16**), 54.8 (**C2**), 52.8 (**C3**), 22.3 (**C1**), 19.7 (**C1'**), 15.7 (**C4**), -2.9 (**C5**), -3.8 (**C5**).

3-[[dimethyl(phenyl)silyl](bromo)methyl]-1-(2-chlorobenzene-1-sulfonyl)-2,2- dimethylaziridine 124g



The title compound was prepared according to **General Procedure 2F**, from **123d** (30 mg, 0.075 mmol) and *N*-Bromosuccinimide (41 mg, 0.225 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **124g** as a colourless oil (25 mg, 68%).

Rf (4:1 Hexane/EtOAc): 0.35

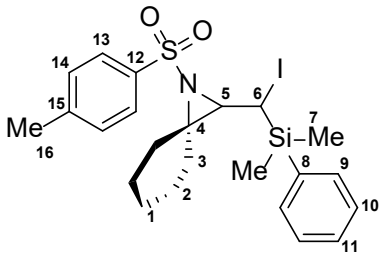
IR υmax (cm^{-1}) 3056, 3033, 2978, 2898 1584

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{19}H_{24}ClBrNO_2SSi$ 472.0169; Found 472.0173

^{1}H NMR (400 MHz $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.4 Hz, 1H, (**H15**)), 7.56 – 7.49 (m, 4H, (**H8**, **H12** & **H13**)), 7.37 (m, 4H, (**H7**, **H9** and **H14**)), 3.24 (d, *J* = 11.4 Hz, 1H, (**H3**)), 3.01 (d, *J* = 11.4 Hz, 1H, (**H4**)), 1.72 (s, 3H, (**H1**)), 1.45 (s, 3H, (**H1**)), 0.26 (s, 3H, (**H5**)), 0.22 (s, 3H (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (**C10**), 134.6 (**C6**), 134.0 (**C8**), 133.3 (**C15**), 133.1 (**C11**), 132.1(**C12**), 130.1 (**C14**), 129.9 (**C9**), 127.9 (**C7**), 126.7, 54.1, (**C2**), 51.9 (**C3**), 37.8, (**C4**), 22.9, (**C1**), 20.0, (**C1'**), -3.7 (**C5**), -4.8 (**C5**).

[iodo-[1-(p-tolylsulfonyl)-1-azaspiro[2.5]octan-2-yl]methyl]-dimethyl-phenyl-silane 130



The title compound was prepared according to **General Procedure 2F**, from **129** (30 mg, 0.07 mmol) and *N*-Iodosuccinimide (49 mg, 0.22 mmol) which following conversion to the aziridine and column chromatography (4:1 Hexane/EtOAc) afforded **130** as a white solid. (31 mg, 79%).

Rf (4:1 Hexane/EtOAc): 0.33

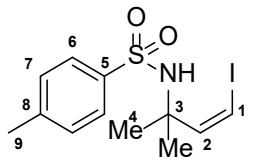
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{31}INO_2SSi$ 540.0889; Found 540.0894

IR υmax (cm^{-1}) 2999, 2965, 2902, 2839

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H, (**H13**)), 7.59 – 7.56 (m, 2H, (**H10**), 7.42 – 7.33 (m, 3H, (**H9** & **H11**)), 7.23 (d, *J* = 7.9 Hz, 2H, (**H14**)), 3.30 (d, *J* = 11.4 Hz, 1H, (**H5**)), 3.07 (d, *J* = 11.4 Hz, 1H, (**H6**)), 2.41 (s, 3H, (**H16**)), 2.05 – 1.92 (m, 2H, (**H$_{Cyclohexyl}$**)), 1.91 – 1.71 (m, 2H, (**H$_{Cyclohexyl}$**)), 1.67 – 1.58 (m, 3H, (**H$_{Cyclohexyl}$**)), 1.56 – 1.49 (m, 2H (**Overlaps with H$_2$O**), (**H$_{Cyclohexyl}$**)), 1.41 – 1.30 (m, 1H, (**H$_{Cyclohexyl}$**)), 0.44 (s, 3H, (**H7**)), 0.30 (s, 3H, (**H7**)).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9 (**C15**) ,137.9 (**C12**), 136.4 (**C8**), 134.6 (**C10**), 129.7 (**C11**), 129.5 (**C13**), 127.9 (**C9**), 127.8 (**C14**), 57.7 (**C4**) , 54.1 (**C5**), 31.4 (**C$_{Cyclohexyl}$**), 30.7 (**C$_{Cyclohexyl}$**), 25.6 (**C$_{Cyclohexyl}$**), 25.5 (**C$_{Cyclohexyl}$**), 25.2 (**C$_{Cyclohexyl}$**), 21.7 (**C16**), 14.2 (**C6**), -2.3 (**C7**), -4.1 (**C7**).

***N*-[(Z)-3-iodo-1,1-dimethyl-allyl]-4-methyl-benzenesulfonamide 136**



To a solution of **124b** (80 mg, 0.16 mmol) in THF (0.16 mL) was added TBAF (1M, THF) (0.05 mL, 0.18 mmol) at RT. The reaction was allowed to stir at room temperature for one hour. After this time, the reaction was diluted with 5 mL of CH_2Cl and washed with H_2O (5 mL). The organic extracts were then dried over Na_2SO_2 before being concentrated under reduced pressure. The resultant residue was then purified by flash chromatography to afford **136** as a colourless oil (45 mg, 77%)

Rf (4:1 Hexane/EtOAc): 0.41

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{12}H_{17}INO_2S$ 366.0025; Found 366.0017

IR υmax (cm^{-1}) 3043, 3010, 2985, 2900

^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H, (**H6**)), 7.27 (d, *J* = 8.3 Hz, 2H, (**H7**)), 6.57 (d, *J* = 8.6 Hz, 1H, (**H2**)), 6.20 (d, *J* = 8.6 Hz, 1H, (**H1**), 5.17 (s, 1H, (**NH**)), 2.42 (s, 3H, (**H9**)), 1.47 (s, 6H, (**H4**)).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0 (**C2**), 143.3 (**C5**), 139.9 (**C8**), 129.6 (**C7**), 127.5 (**C6**), 78.3 (**C1**), 57.4 (**C3**), 28.4 (**C4**), 21.7 (**C9**).

Chapter 3: Synthesis and Silicon-Directed Cyclisation of Homoallylic Alcohols

The work detailed in this section has been published in part as: D. D. Roberts and M. G. McLaughlin, *Chem. Commun.*, 2022, **58**, 8376-8379.[95] Additionally, sections of the introduction also feature in the following review article: D. D. Roberts and M. G. McLaughlin, *Adv. Synth. Cat.*, 2022, **364**, 2307-2332. [78]

3.1 Synthesis and Applications of Oxetanes

3.1.1 Applications of Oxetanes in Medicinal and Organic Chemistry

In recent years focus has shifted away from highly planar molecules to more 3-dimensional scaffolds in the context of drug discovery.[96] The focus on the design and synthesis of these scaffolds has resulted in the development of elegant methodologies for the synthesis of small saturated ring systems, with particular attention paid to the development of routes to afford saturated cage structures such as bicycloalkanes and cubanes due to their potential for bioisosteric replacement of phenyl rings for tuning of ADMET properties (**Figure 4**).[97, 98]

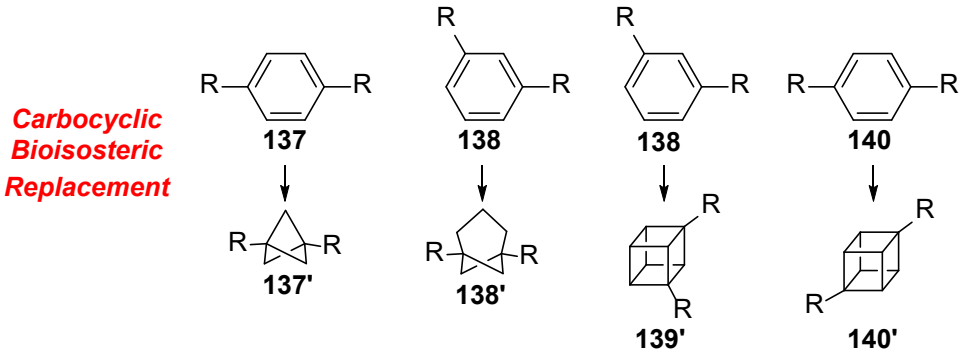
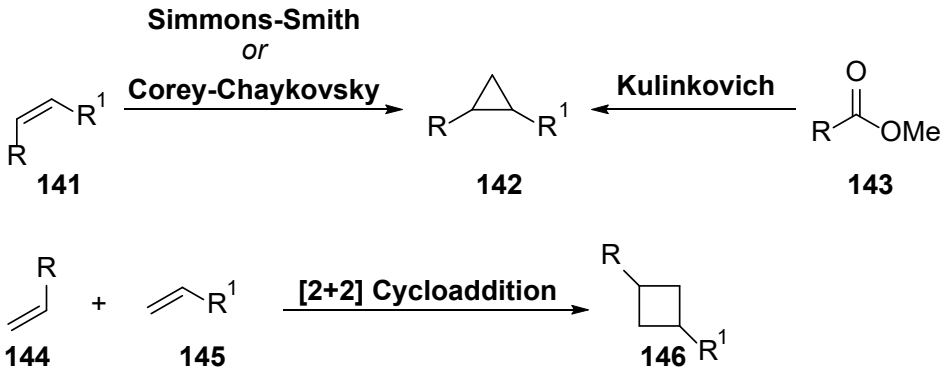


Figure 4 Carbocyclic biososteric replacement of phenyl rings

More classically, cyclopropyl and cyclobutyl rings feature in a wide range of biologically active compounds.[99,100] This is likely due to the ease of installing these moieties into compounds with the Simmons-Smith,[101] Corey-Chaykovsky[102] and Kulinkovich[103] reactions all serving as classical methods for the installation of cyclopropyl rings from a variety of functional groups. Likewise, the [2+2] cycloaddition between two olefins is a well-established and robust method for the installation of cyclobutane rings (**Scheme 47**).[104]



Scheme 48 Traditional approaches to the synthesis of strained carbocycles

While the synthesis of epoxides is readily achieved *via* mCPBA olefin oxidation, the synthesis of oxetanes is much less developed. Despite this, the utility of oxetanes in the design of biologically active compounds has been well studied. Oxetanes, in comparison to cyclobutanes and azetidines, are highly planar.[105] This arises from the decreased gauche interactions in the ring as a consequence of the presence of the oxygen atom.[106] Due to the highly strained COC bond system, the lone pairs of the oxygen atom are highly available, resulting in a more strongly Lewis basic system than, for example, tetrahydrofuran. In fact, oxetanes are stronger hydrogen bond acceptors than ketones, esters and aliphatic aldehydes, with the respective hydrogen bond acceptor avidities shown in **Figure 5**.[107]

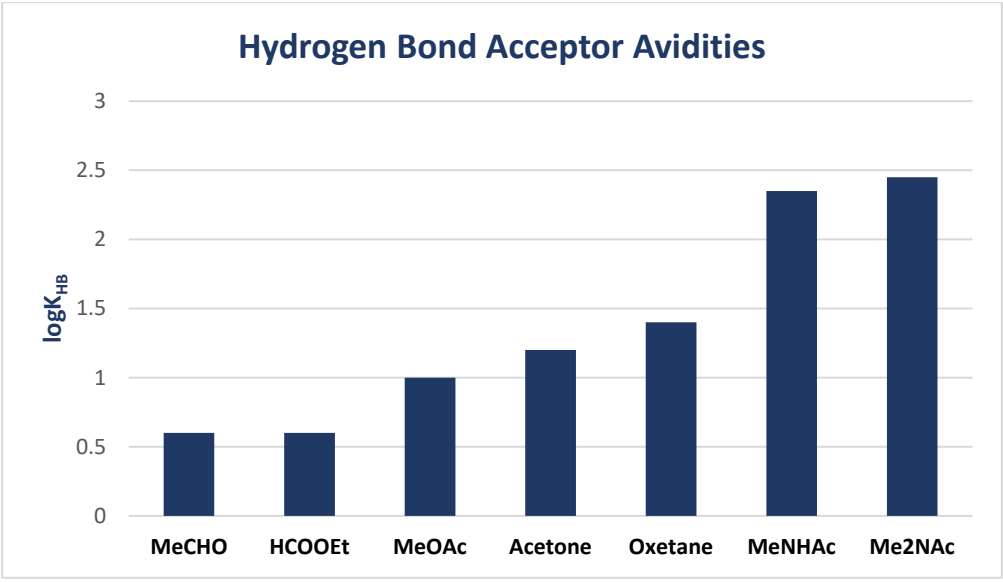


Figure 5 Hydrogen bond avidities of various H-bond acceptor

In addition to being excellent hydrogen bond acceptors, oxetanes have also demonstrated to be effective pKa modulators of nearby groups due to their excellent σ-electron withdrawing capability. Carreira *et al* demonstrated this by studying the effect of installing an oxetane substituent on the pKa of a neighbouring alkyl amine relative to alkyl amine **147**. As the site bearing the oxetane becomes more remote, the pKa of the amine becomes closer to that of the parent molecule. Conversely when the oxetane is located α to the amine, the pKa is lowered by almost 3 orders of magnitude.[107]

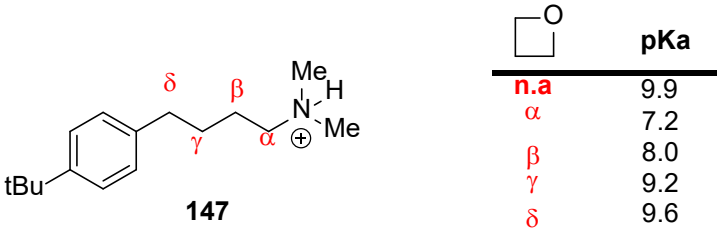


Figure 6 pKa modulation effect of oxetanes by σ-electron withdrawing effect

Oxetanes are also bioisosteric of a variety of functional groups commonplace within modern medicinal chemistry. These groups, summarised in **Figure 7** include carboxylic acids,[108] esters,[109] thioesters,[110] amides,[107] *gem*-diMe, ketones[107] and *tert*-butyl groups. In turn, these bioisosteric replacements can be combined to further include groups such as lactam and morpholine isosteres, in addition to being incorporated into several peptidomimetics.[107,111]

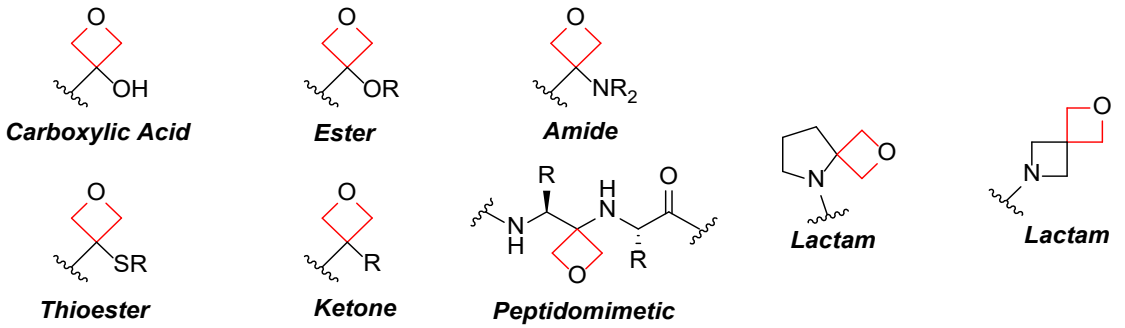
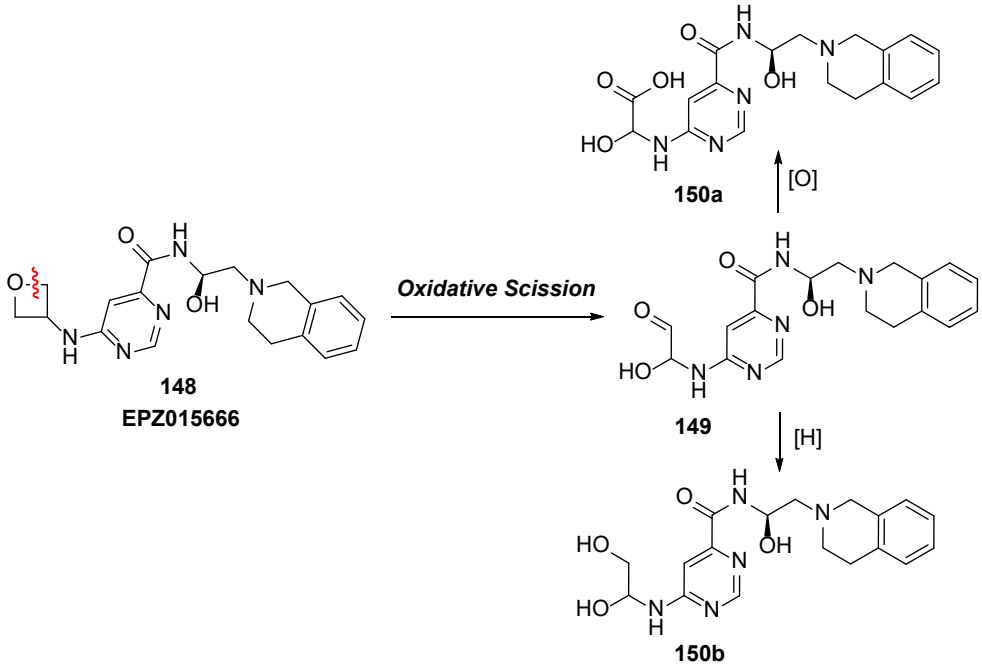


Figure 7 Oxetanes as bioisosteric replacement of common functional groups

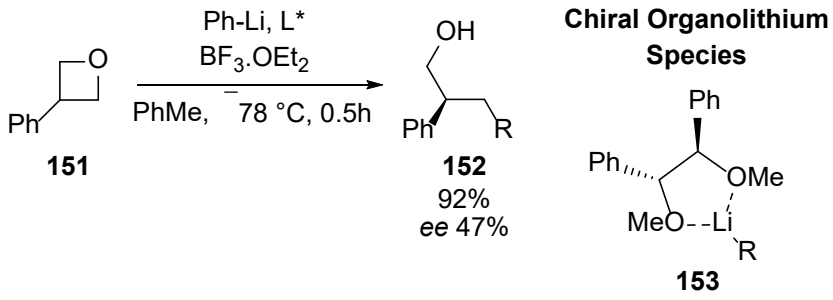
While these bioisosteres may initially appear attractive due to the aformentioned lipophilicity/acidity tuning, incorporation of an oxetane group into a molecule isn't without its liabilities, namely the metabolic factors which come into play alongside this incorporation. Due to the inherent ring strain of oxetanes they are more prone

to oxidative scission by CYP450 than their carbocyclic counterparts. This was demonstrated by Rioux and co-workers on the protein arginine methyltransferase-5 (PRMT5) inhibitor EPZ015666 **148**, where the 2 major metabolites identified were diol **150b** and hydroxypropionic acid **150a** derived from initial oxidative cleavage of the oxetane to afford β-hydroxyaldehyde **149** and then subsequent oxidation or reduction to afford **150a** or **150b** respectively.[112]



Scheme 49 Metabolic pathways *via* oxidative scission of EPZ015666

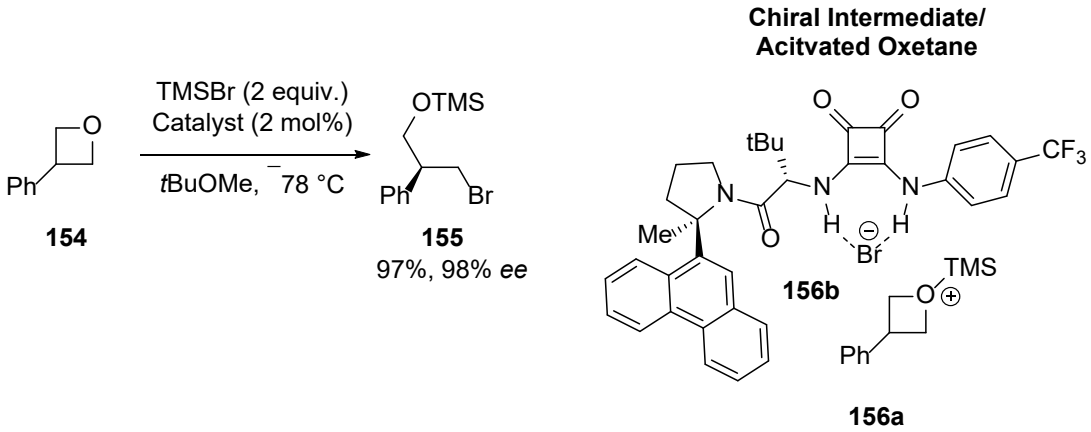
Aside from the application of oxetanes as valuable motifs within medicinal chemistry, they are also versatile synthetic intermediates which can be manipulated further to yield other privileged scaffolds. As is the case with epoxides, a driving force of oxetane reactivity is the relief of ring strain upon nucleophilic ring opening or ring expansion. When chiral nucleophiles are employed, this results in the possibility for enantioselective ring opening. Early work by Tomioka *et al* demonstrated this *via* utilisation of a chiral ethylene glycol derived ligand in conjunction with phenyl lithium, to form chiral organolithium complex **153** *in-situ* which subsequently undergoes stereoselective ring opening of **151** to afford **152** in 90% yield with moderate enantioselectivity.[113]



Scheme 50 Enantioselective ring opening of oxetanes employing chiral organolithium nucleophiles

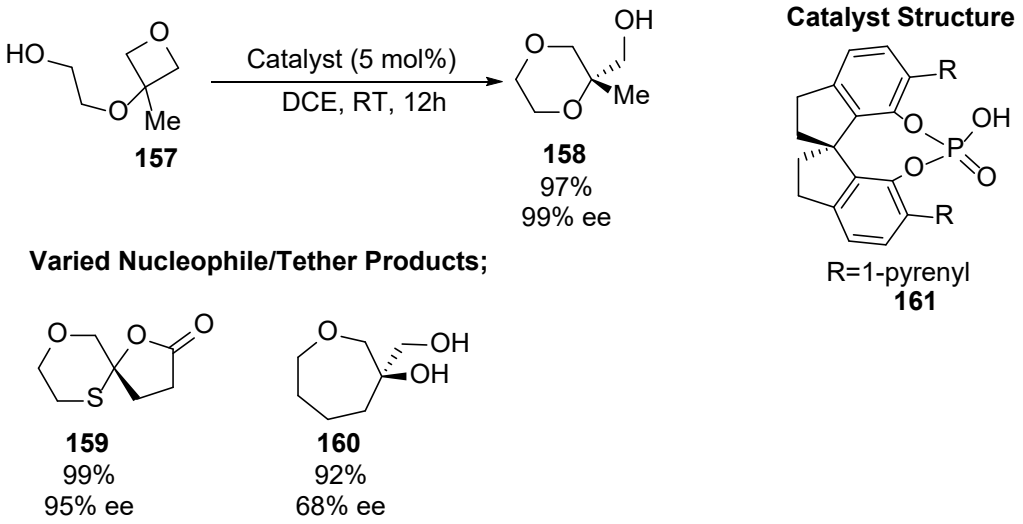
Since this early study, a plethora of developments have been made in the field. One such method is the application of squaramide H-bonding organocatalysis to the ring opening of oxetanes with trimethylsilylbromide as reported by Jacobsen *et al.* [114] In this work the use of harsh organometallic reagents is avoided, and the degree of enantioselectivity is much higher, reaching as high as 99% *ee*, while maintaining excellent yields.

The reaction proceeds *via* liberation of a bromide anion *via* interaction between **154**, and Lewis acidic silane, with the liberated bromide ion abstracted by the catalyst to form activated oxetane **156a** ion paired with catalyst bound anion **156b** (**Scheme 51**). This study serves as a demonstrating that while oxetanes can be ring-opened employing strong basic organometallic reagents (**Scheme 50**), upon activation with a suitable acid, much less forcing conditions can be employing to achieve the same transformation.



Scheme 51 Organocatalytic enantioselective ring opening of 2,2-disubstituted oxetanes

This concept of activating oxetanes with an acidic reagent prior to reaction with a nucleophile was also explored by Sun *et al* in 2016, though in this case the nucleophile is tethered to the 3-position of the oxetane resulting in the formation of ring expansion products such as **158** (**Scheme 52**). A range of chiral phosphoric acid derivatives were screened with spiroindane derived **161** providing the best activity in conjunction with excellent enantioselectivities. Though the example provided in **Scheme 52** shows the application of a tethered hydroxyl group acting as a nucleophile, both the tether length and nucleophile can be altered to afford varying ring sizes and allow for the incorporation of various heteroatoms into the products as shown by the synthesis of **159** and **160**.[115]

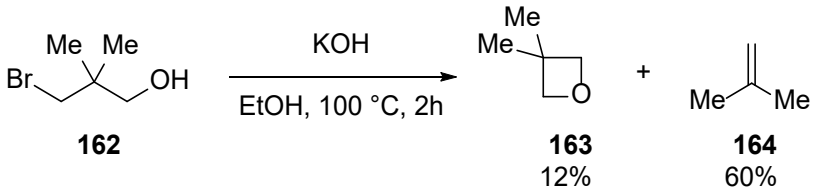


Scheme 52 Intramolecular ring opening of oxetanes by tethered heteroatomic nucleophiles

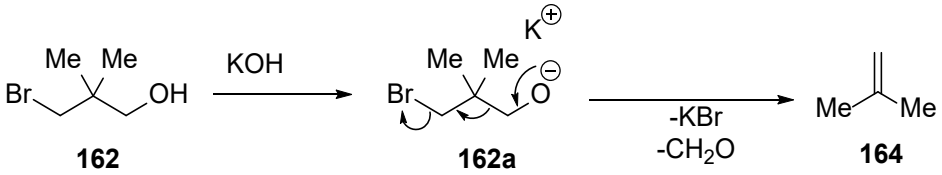
3.1.2 Access to Oxetanes *via* Existing Methods

One of the classical methods for the assembly of oxetane scaffolds is *via* the formation of the C-O bond *via* intramolecular Williamson ether synthesis though in practice this transformation possesses significant limitations. The difficulty in this method arises from the kinetic unfavorability of forming 4 membered rings in comparison to 3, 5 and 6 membered rings.[116]

The issues associated with the application of Intramolecular ether syntheses were documented in early work by Witsiepe *et al* wherein competing Grob fragmentation of brominated alcohol **162** results in formation of **164** when attempting the synthesis of **163**.[117] While more sterically encumbered starting materials and higher loadings of base affords a higher selectivity for the oxetane, the competing fragmentation was never be completely suppressed and complete conversion could not be achieved. [118]



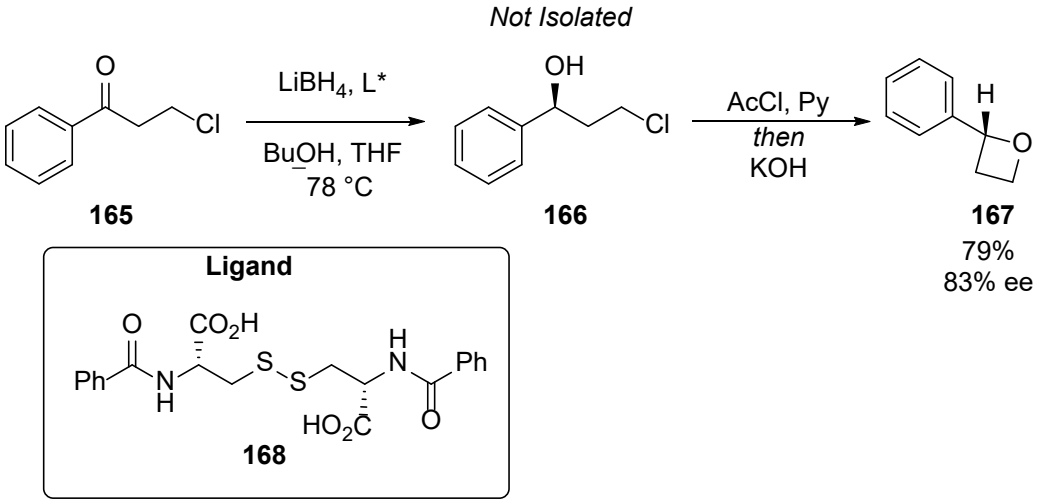
Competing Grob Fragmentation



Scheme 53 Intramolecular ether synthesis with competing Grob fragmentation

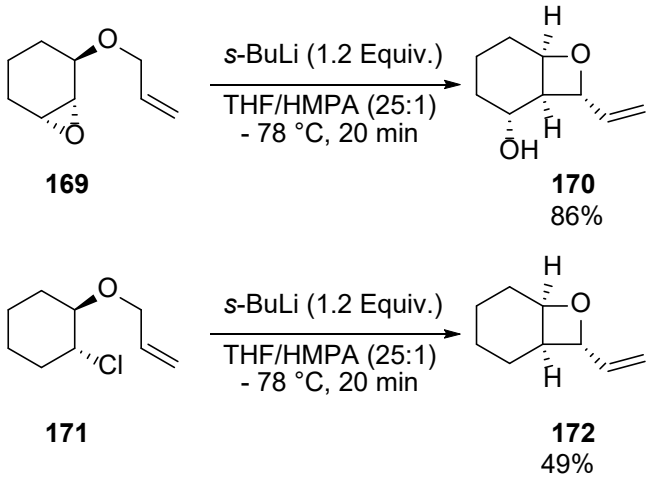
Though oxetane synthesis through intramolecular etherification possesses inherent limitations, it does provide the opportunity for the synthesis of enantioenriched oxetanes by cyclisation of optically active alcohols. This is demonstrated by Ishizaki who demonstrated the ligand controlled enantioselective reduction and subsequent cyclisation of β-haloketone **165** to afford oxetane **167** in 79% yield and 83% *ee via* intramolecular cyclisation of **166**.

Subsequently this approach has been employed by other groups in the synthesis of optically active oxetanes. [119, 120]



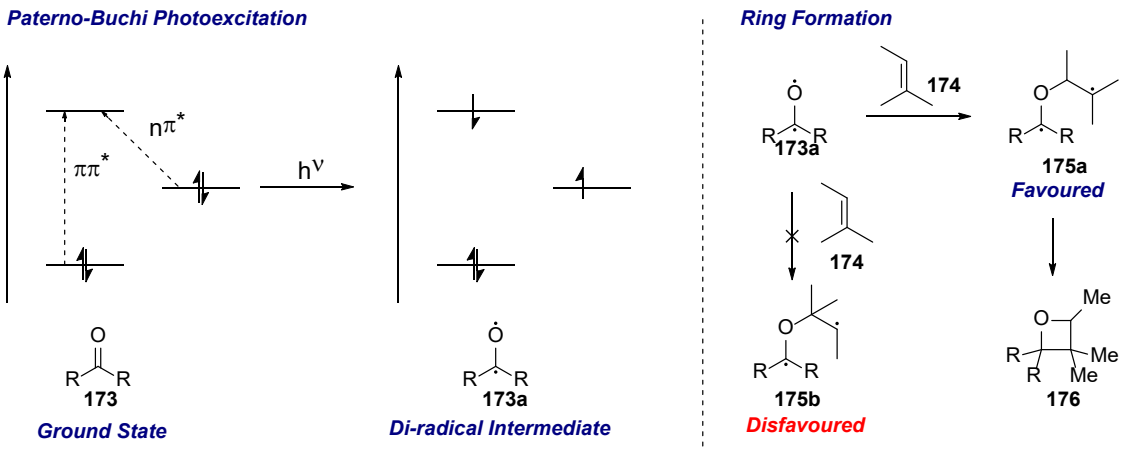
Scheme 54 Synthesis of optically active oxetanes by enantioselective ketone reduction

While formation of a C-O bond *via* polar chemistry is the more typical approach taken, C-C bond formation has also been employed in the synthesis of oxetanes. Typically, this involves the deprotonation of an acyclic ether which undergoes intramolecular nucleophilic substitution to afford an oxetane. Still *et al* reported this type of approach, employing a *s*-BuLi mediated cyclisation of **169** and **171** bearing epoxide and halide electrophiles respectively to afford 6,4-fused rings **170** and **172** in 86% and 49% yield with high levels of chemoselectivity. [121] This approach has subsequently been employed for the cyclisation of a variety of allyl, benzyl and sulfonyl ethers.[122, 123]



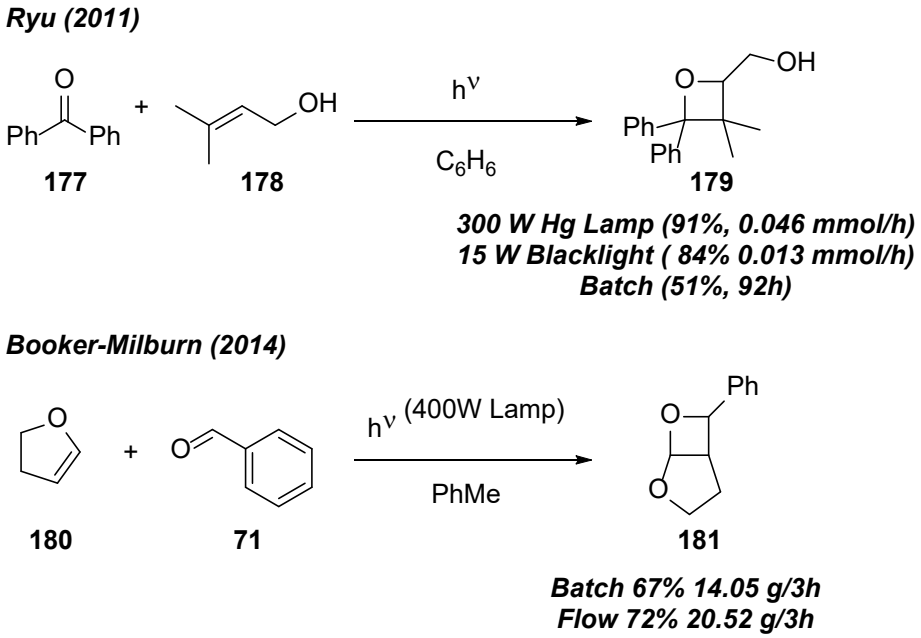
Scheme 55 Synthesis of oxetanes *via* C-C bond formation

More typical than using traditional polar chemistry is the synthesis of oxetanes *via* the Paternò–Büchi reaction.[124] The Paternò–Büchi reaction is the formal [2+2] cycloaddition between an alkene and a carbonyl under photochemical conditions to afford substituted oxetanes.[125] Mechanistically the reaction proceeds by photochemical excitation of an aldehyde or ketone forming diradical intermediate **173a** which undergoes reaction either from the singlet or triplet state with an olefin, in the case of **Scheme 56** represented by **174**. Recombination of diradical **175a** affords cyclised product **176**. Competing olefin dimerization is a frequently reported side reaction, though recent work by Coote *et al* has demonstrated the utility of triplet quenching additives in supressing this in the cases of substrates known to react through the singlet state such as aliphatic ketones.[126]



Scheme 56 Generalised Paternò–Büchi reaction mechanism

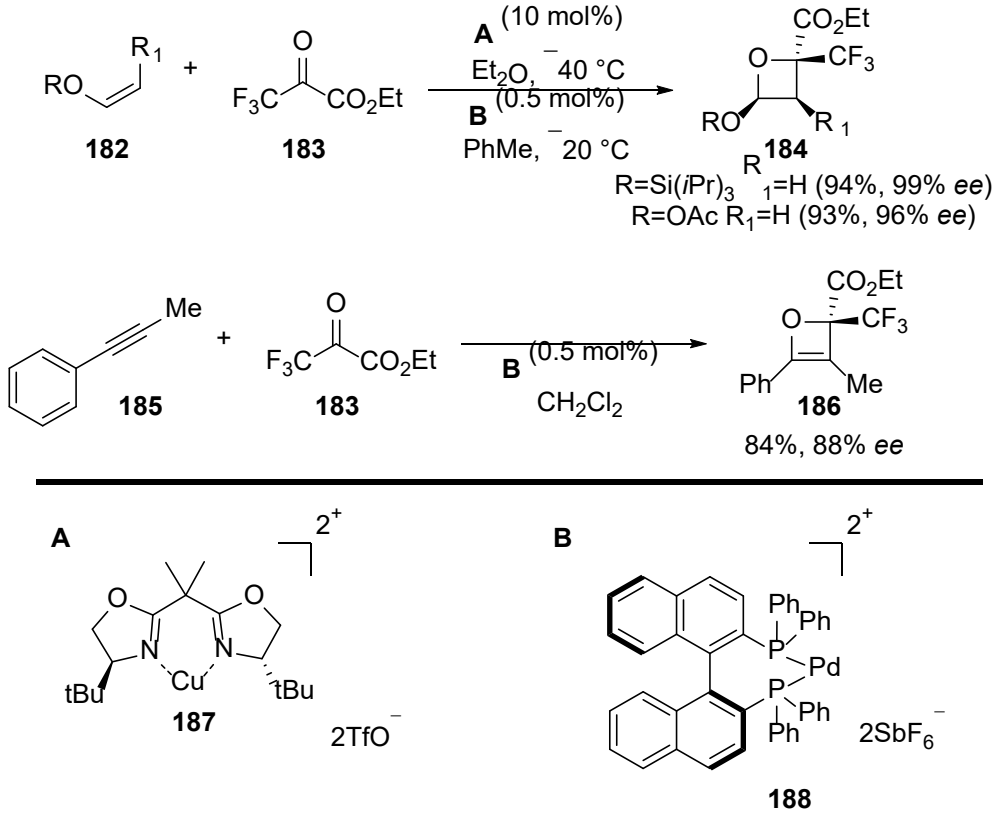
One of the principal limitations associated with the Paternò–Büchi, and photochemistry in general, is the limitation on scale imposed by the necessity for high levels of light penetration required to achieve high conversions.[127] A general approach to mitigating this limitation is the use of flow chemistry, and resultantly the Paternò–Büchi reaction has also been carried out under flow conditions. Ryu and co-workers demonstrated that **177** and **178** can undergo cyclisation under irradiation from either a 15 W blacklight or 300 W tungsten bulb under flow conditions, with the throughput significantly increased in comparison to the same process carried out in batch.[128] Booker-Millburn *et al* demonstrated a similar increase in efficacy when studying the Paternò–Büchi reaction between 2,3-dihydrofuran **180** and **71**. Though the increase in yield in this case was not as dramatic as in the previous example, the throughput was significantly increased in the flow process in comparison to the analogous reaction carried out in batch.[127]



Scheme 57 Benefits of flow versus batch chemistry in the context of Paternò–Büchi reactions

By activation of the carbonyl compound with a chiral Lewis acid, the Paternò–Büchi reaction can proceed in an enantioselective manner to afford optically active oxetanes. This was demonstrated by Mikami and co-workers who report the cyclisation of activated alkenes **182** with trifluoropyruvate **183** under Lewis acid catalysis to afford trifluoromethyloxetanes **184**. The choice of Lewis acid is

substrate dependent; silyl enol ethers **182** utilised Cu-BOX complex **187** whereas vinyl esters employed Pd-BINAP complex **188**.[129] The same group also used a similar method to access a variety of oxetenes **186**, which could subsequently be reduced to oxetanes by palladium mediated hydrogenation. In this case, trifluoropyruvate was activated with the aforementioned Pd-BINAP complex **188**, before undergoing [2+2] cycloaddition with a variety of substituted alkynes (**Scheme 56**).[130]

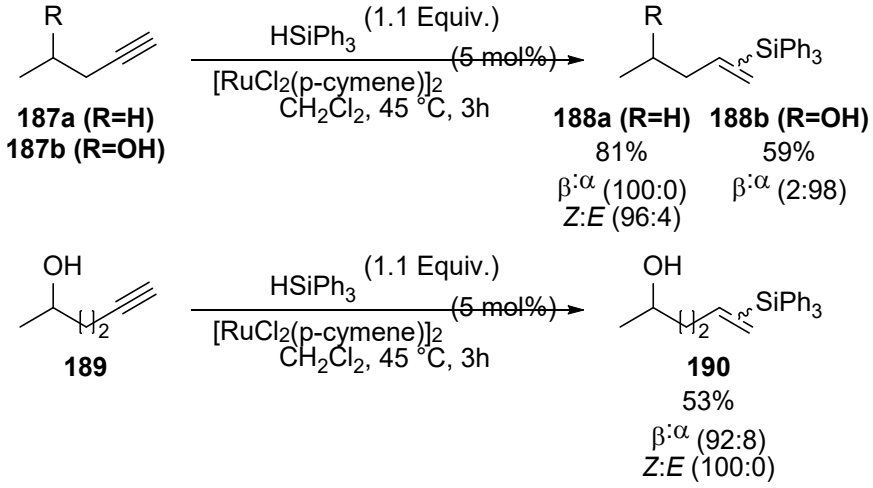


Scheme 58 Asymmetric Paternò–Büchi reactions employing chiral Lewis acid catalysts

3.2 Synthesis of Homoallylic alcohols bearing tethered organosilanes

One of the most intuitive ways to access homoallylic alcohols bearing an organosilicon functionality at the olefin is *via* hydrosilylation of homopropargylic alcohols. The positioning of a coordinating functional group at the homopropargylic position of an alkyne introduces issues in regiocontrol due to the propensity of these substrates to act as intramolecular directing groups. As a result of this they have largely remained underexplored as hydrosilylation substrates.

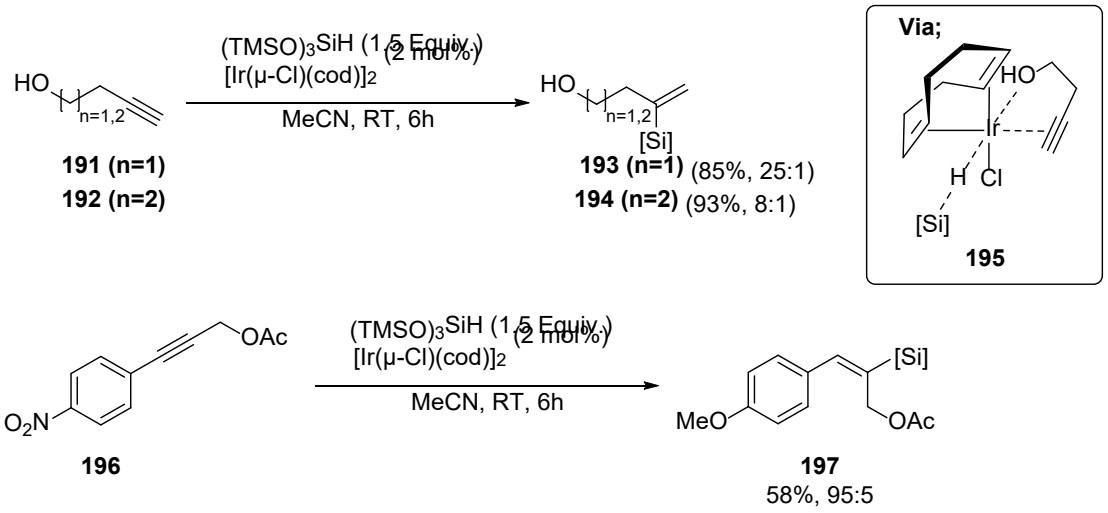
This intramolecular direction is exemplified by work reported by Chang *et al*, wherein the $[RuCl_2(p\text{-cymene})]_2$ catalysed hydrosilylation of terminal alkynes was shown to be highly prone to intramolecular direction by coordinating functionalities at the homopropargylic position. This is demonstrated by comparison of the results for the hydrosilylation of **187a** and **187a**. Hydroxyl directed hydrometallation results in the formation of branched **188b**, however in the absence of this directing group, **188a** is afforded exclusively as the linear isomer. The site-dependence of the functional group on its directing group ability was also noted, as can be seen in the difference in regiochemical outcome between substrates **187b** and **189**. [131]



Scheme 59 Effect of hydroxyl groups at the homopropargylic position on the regioselectivity of Ru catalysed hydrosilylation

The interaction between Lewis basic moieties at this site and transition metal catalysts has been reported for other metals aside from the aforementioned

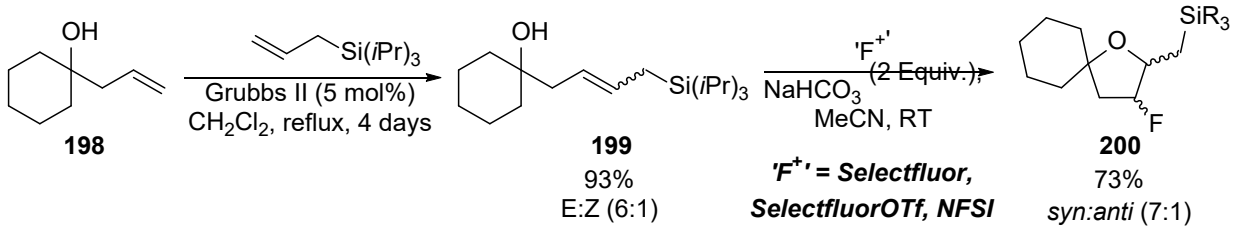
ruthenium complex. Ding and co-workers have extensively studied the hydrosilylation of both internal and terminal alkynes employing directing groups at this position under iridium catalysis, with particular focus on oxygen-containing functionalities.[132] The 2021 study by the same group in particular presents a systematic screening of the efficacy of different substituents as directing groups when installed at this site, with alcohols, ethers and esters significantly out performing amines, carbamates and thioesters. The efficacy of these directing group is such that it can overcome the inherent regioselectivity which would be expected to arise from the hydrosilylation of a polarised alkyne such as **196**. [133] The authors propose that the selectivity of the reaction is imparted by the intramolecular directing model as shown in **195** (**Scheme 60**).



Scheme 60 Directing group ability of homopropargyl esters and alcohols in Ir catalysed hydrosilylations

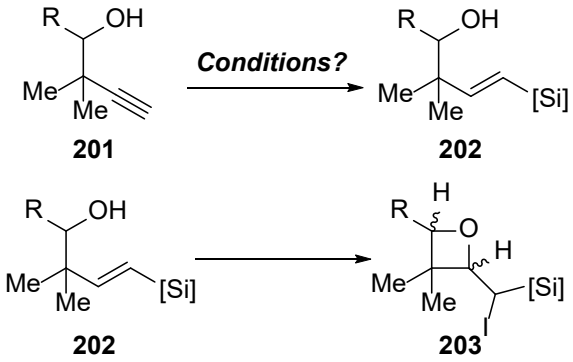
Work by Gouverneur *et al* reported the fluorocyclisation of allyl silanes *via* trapping of a β-silyl cation with a tethered oxygen nucleophile. In order to access the requisite allyl silanes, Grubbs cross metathesis between a homoallylic alcohol and an allyl silane in the presence of Grubbs 2nd generation catalyst.[134] While this does provide access to the necessary starting material, it only allows minimal control over the geometry of the resultant olefin, often providing relatively poor *E:Z* ratios. As the cyclisation procedure reported in the same paper proceeds in a stereospecific manner, this means that the diastereomeric ratio of the heterocycles afforded is limited by the selectivity of the Grubbs chemistry as

demonstrated by the 2-step synthesis of spirocyclic furan **200** from homoallylic alcohol **198** (**Scheme 61**).[135]



Scheme 61 Synthesis of silylated homoallylic alcohols by Grubbs chemistry affords limited stereocontrol

3.3 Aims



Project Aims

- *Establish a synthetic route to access homopropargyl alcohols*
- *Synthesis of a range of homoallylic alcohols via alkyne hydrosilylation*
- *Explore cyclisation of alcohols into oxetanes*

Scheme 62 Project aims

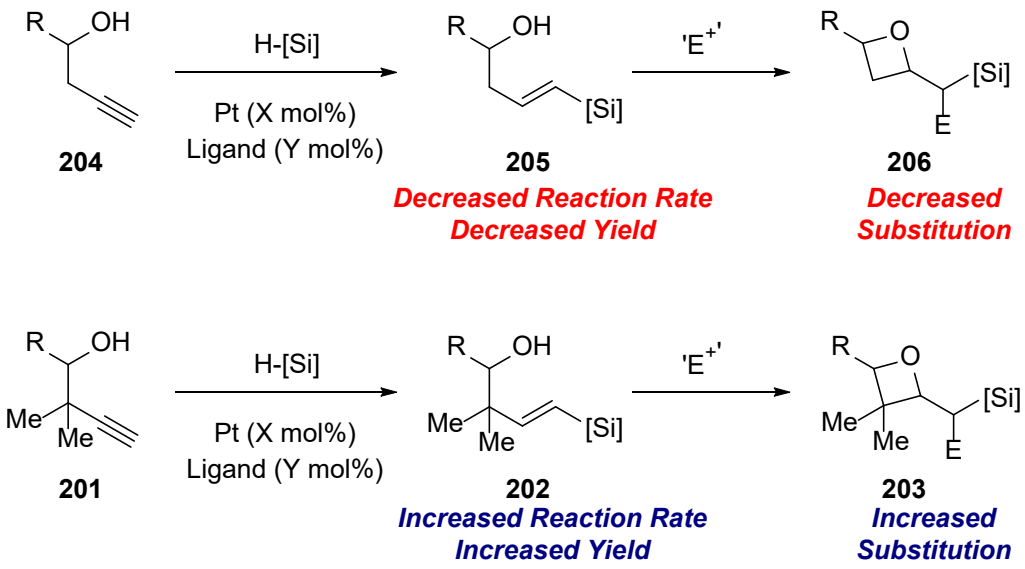
This chapter aims to explore the viability of applying a hydrosilylation/cyclisation sequence to the synthesis of a range of diverse oxygen-containing heterocycles, with particular focus paid to the synthesis of oxetanes. This route will allow for the synthesis of valuable heterocyclic scaffolds whilst avoiding the necessity for strong bases to facilitate an intramolecular ether synthesis as well as removing the need for bespoke photochemical rection setups, the limitations of each approach having been previously discussed.

The silanes which will be utilised as cyclisation precursors will be accessed *via* hydrosilylation of homopropargylic alcohols. As access to homopropargylic alcohols is rarely reported within the literature, especially with higher degrees of substitution at the propargylic/homopropargylic positions, a route to access these substrates will be established. As noted by Gouverneur *et al*, cyclisation of unsaturated organosilanes proceeds with stereoretention, and as such carrying out the reaction with a geometrically pure olefin should afford high levels of diastereoselectivity in the oxetanes. To this end, a robust hydrosilylation procedure will be developed which will allow for access to vinyl silanes in high levels of stereoselectivity and regioselectivity. This work will be based on the work carried out in **Chapter 2.4** as well as previously published studies on Pt/PR_3 complexes in hydrosilylation catalysis.[23,24] Once a set of conditions have been identified, a range of diverse vinyl silanes will be synthesised, with focus paid to the range of functionalities tolerated by the reaction as well as the range of silicon

hydrides which can successfully be utilised in the reaction. Once synthesised, the viability of cyclisation of the organosilanes into the corresponding oxetanes *via* electrophilic activation will be explored. Particular focus will be paid to the levels of diastereoselectivity afforded by this transformation. Should the reaction proceed in a diastereoselective manner, the relative stereochemistry of the ring systems will be assigned *via* NOESY studies. The same type of chemistry will also be applied to the synthesis of other oxygen-containing heterocycles to ascertain the generality of the method.

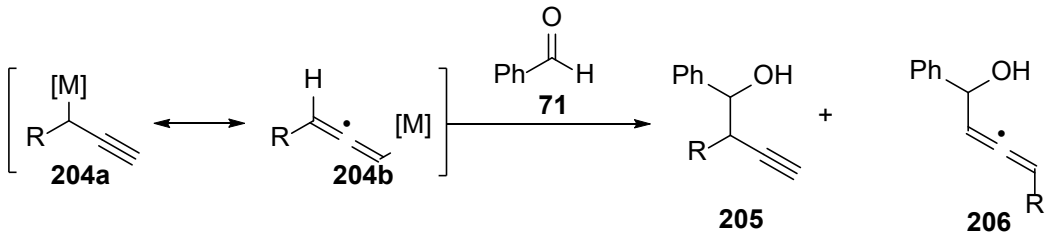
3.4 Synthesis of Homopropargylic Alcohols

An initial survey of the literature quickly revealed there was no general method for the synthesis of homopropargyl alcohols with substituents at both the propargylic and homopropargylic position, introducing several issues for the proposed work. As noted by Cook and co-workers, substitution at the propargylic position results in increased activity towards hydrosilylation.[24] Additionally, as the project aimed to explore the cyclisation of the hydrosilylation products into the corresponding oxetanes, increasing the levels of substitution within the starting materials translates to greater 3-dimensionality in the afforded oxetanes. As has been discussed in **Chapter 3.1.1**, 3-dimensionality in medicinally relevant compounds is beneficial due to the greater propensity for protein-ligand interactions.[96] Greater degrees of substitution would additionally facilitate a more facile cyclisation as a result of the Thorpe-Ingold effect.[136]



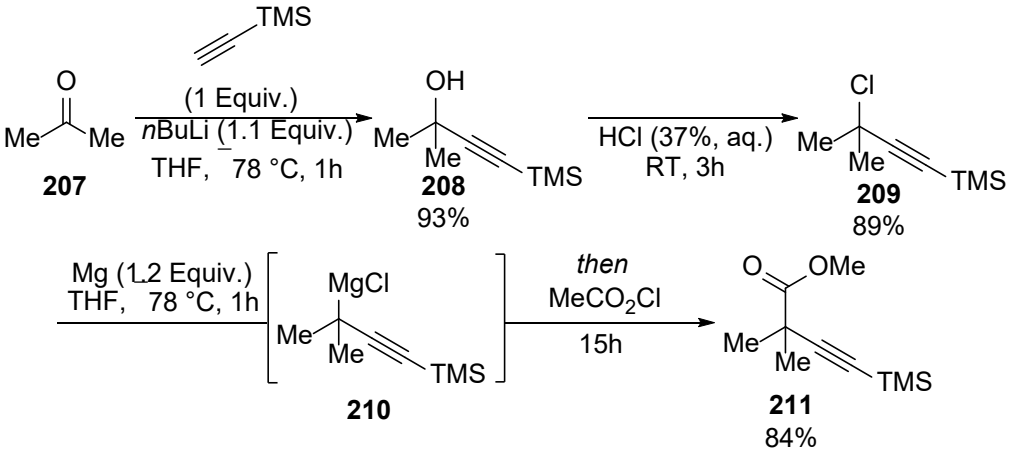
Scheme 63 Benefits of increased substitution patterns

The lack of literature methods to prepare substrates of this nature can be attributed to the known isomerisation of propargylic organometallic species such as Grignard reagents and organozinc reagents to the corresponding allenylic organometallics as shown in **Scheme 64**.[137] Although addition of mercuric chloride to the reaction media has shown to minimise this isomerisation, due to toxicity concerns associated with mercury salts, this route was not considered viable.[138]



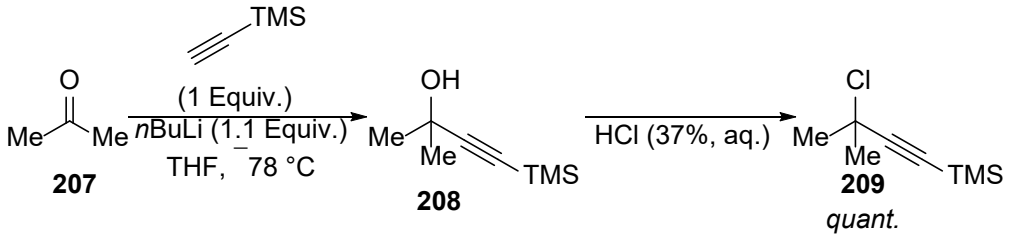
Scheme 64 Isomerisation of propargyl-allenyl organometallic species

In spite of the aforementioned isomerisation of these types of organometallic reagents, Wang and co-workers reported the formation of Grignard reagent **210** from propargyl chloride **209** in the synthesis of homopropargylic esters **211**, with no reported competing allenylation.[139] It was envisaged that the same Grignard reagent could be employed to access homopropargylic alcohols by trapping of **210** with a range of ketones and aldehydes.



Scheme 65 Synthesis of homopropargyl esters *via* Grignard reagent 210

To this end, **209** was prepared by addition of lithium trimethylsilylacetylide to acetone to afford alcohol **208** which subsequently underwent chlorination upon treatment with aqueous hydrochloric acid to afford **209** in quantitative yield.

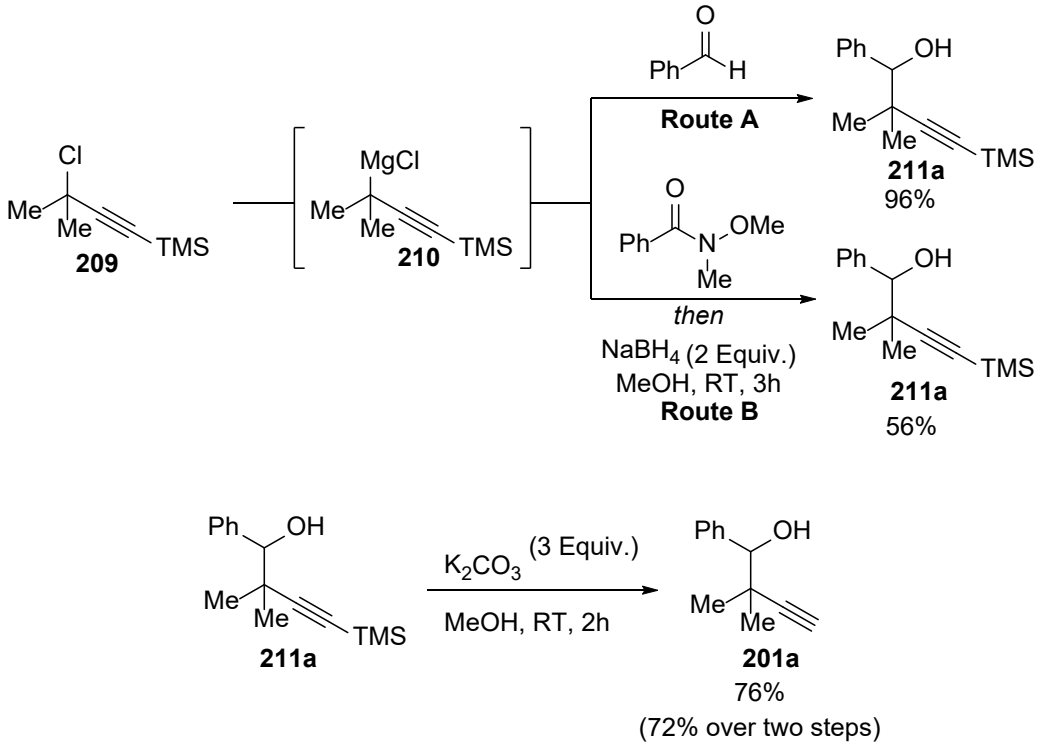


Scheme 66 Synthesis of propargyl chloride 209

209 in hand, the formation of the corresponding Grignard reagent was next explored alongside its subsequent trapping with various electrophiles. Two reactions were run in parallel employing benzaldehyde and phenyl Weinreb amide as electrophilic partners. Formation of **210** readily occurred within one hour with 10 mol% $C_2H_4Br_2$ as an activator, with **210** trapped by both electrophiles employed. In each case, the allenylated alcohol was not observed in the ^1H NMR of the crude reaction mixture. While trapping with benzaldehyde afforded access to **211a** in one step, employing the Weinreb amide as an electrophile afforded the expected intermediate ketone which could readily undergo reduction with sodium borohydride in methanol to afford **201a** (**Route 2**, **Scheme 67**).

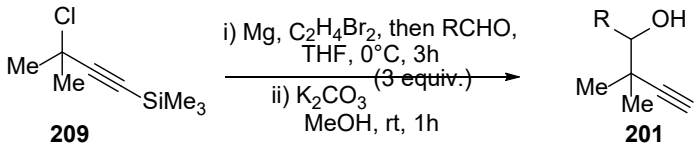
While both routes provide access to **211a**, **Route 1** was chosen as it removes the necessity for reduction of the intermediate ketone while additionally allowing for ketones to be used as electrophiles to increase the degree of substitution

within the product. **211a** was readily deprotected *via* basic methanolysis to afford **201a** in 73% yield over two steps.



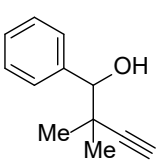
Scheme 67 Synthesis of homopropargyl alcohols by electrophilic trapping of 210

A variety of secondary homopropargylic alcohols were next synthesised *via* this route. By employing halogenated benzaldehyde derivatives, alcohols **201b** and **201c** were afforded in 70% and 51% yield respectively over two steps. Employing substrates bearing electron donating functionalities in the *para* position, **201d** and **201e** were isolated in 64% and 29% yields. Application of aliphatic aldehydes afforded cyclohexyl alcohol **201f** and *tert*-butyl alcohol **201h** in synthetically useful yields**.** Alcohols bearing aromatic heterocycles could also be accessed using this methodology, with thiophene-2-carboxaldehyde and pyridine-4-carboxaldehyde affording the corresponding alcohols albeit in a relatively poor 27% yield in the case of **201i**. 4-Nitrobenzaldehyde and 4-cyanobenzaldehyde proved to be unsuitable substrates for this reaction, likely due to the incompatibility of the electrophilic functionalities in conjunction with the strongly nucleophilic Grignard reagent.

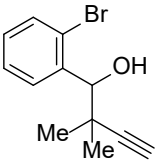


209 **201**

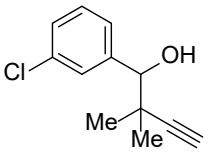
Secondary Alcohol Scope



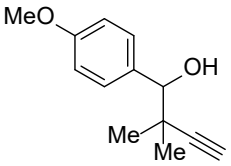
201a
72%



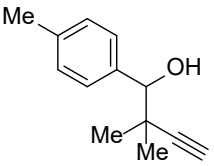
201b
70%



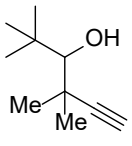
201c
51%



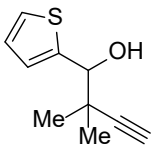
201d
64%



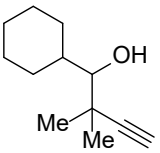
201e
29%



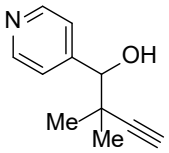
201f
73%



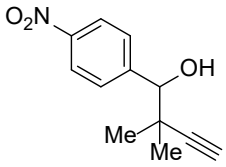
201g
73%



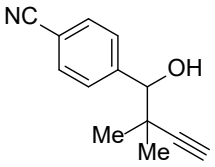
201h
46%



201i
27%



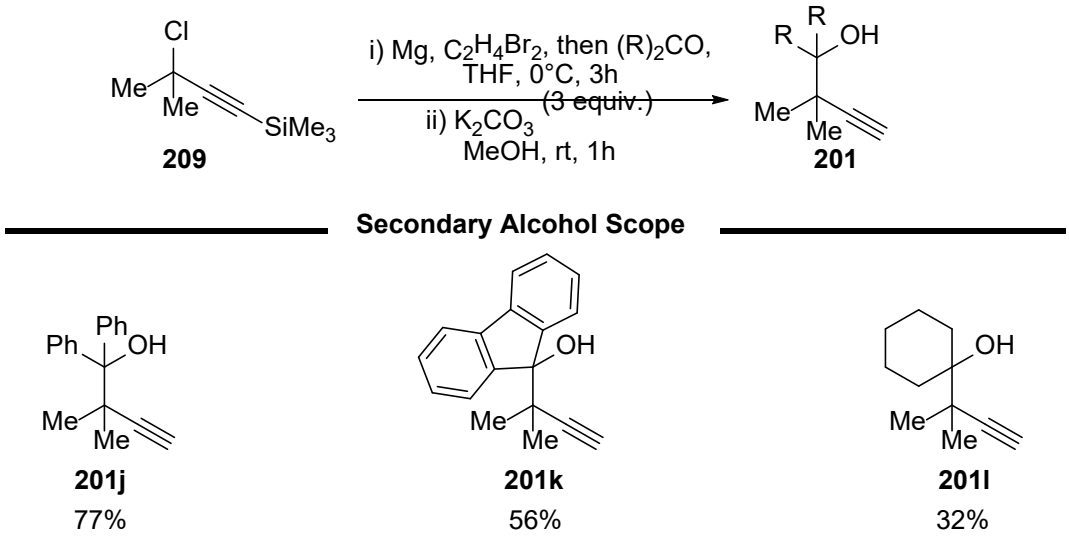
201aa
2a, *Complex Mixture*



201ab
2a, *Complex Mixture*

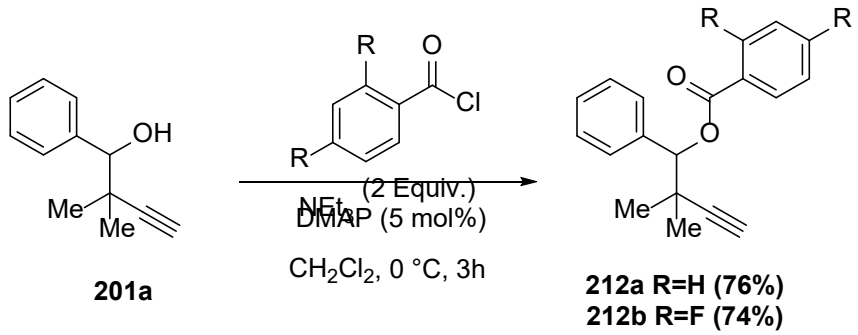
Scheme 68 Scope of secondary homopropargylic alcohols

A range of ketone electrophiles were next used to afford the corresponding tertiary homopropargylic alcohols. Employing benzophenone, 9-fluorenone and cyclohexanone, the alcohols **201j**, **201k** & **201l** could be accessed in 64%, 28% and 32% yields accordingly (**Scheme 68**).



Scheme 69 Scope of tertiary homopropargylic alcohols

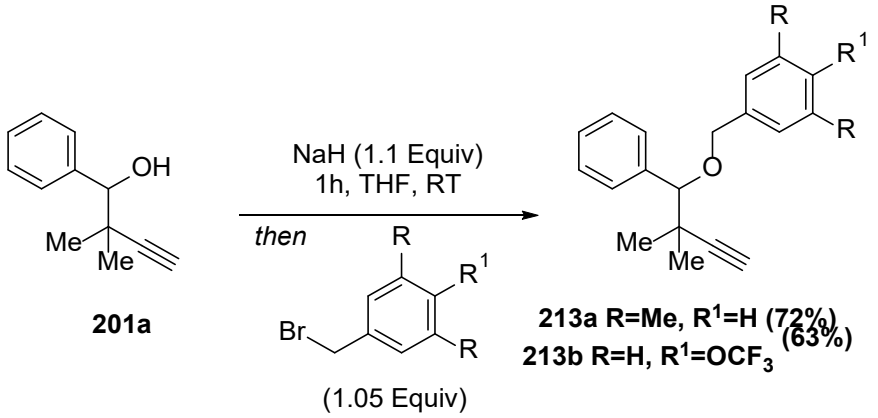
A range of alcohol derivatives were next synthesised to further probe the functional group tolerance of the reaction. Homopropargylic esters **212a** and **212b** were prepared from alcohol **201a** *via* acylation with benzoyl chloride and 2,4-difluorobenzoyl chloride respectively in the presence of triethylamine and DMAP.



Scheme 70 Synthesis of homopropargylic esters

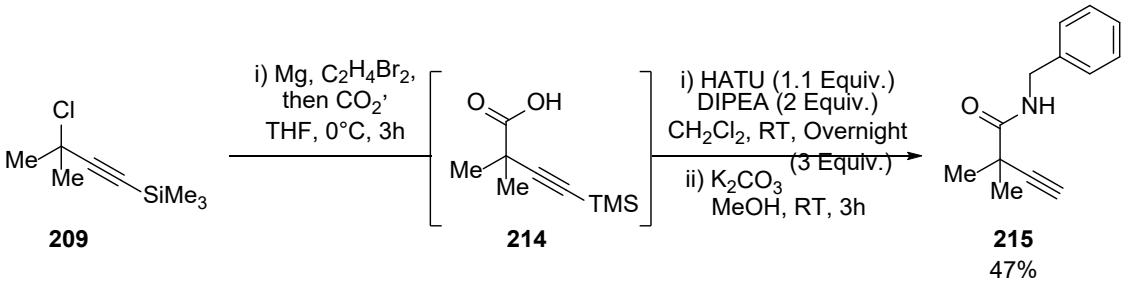
The synthesis of substrates bearing ethers at the homopropargylic position was next considered. The synthesis of these substrates was relatively straightforward with alcohol **201a** readily undergoing alkylation with a benzyl bromide derivative

in the presence of sodium hydride to afford the desired ether. Under the conditions outlined in **Scheme 71** and employing both 3,5-dimethylbenzylbromide and 4-trifluoromethoxybenzyl bromide as electrophiles, ethers **213a** and **213b** could be isolated in 72% and 63% yield.



Scheme 71 Synthesis of homopropargylic ethers

Finally, in order to explore the hydrosilylation of homopropargylic amides, access to acid **214** was required. It was envisaged that this could be accessed *via* trapping of Grignard reagent **210** with carbon dioxide, with subsequent coupling of the acid with an amine set to afford the desired amide. To this end, solid CO_2 was treated with Grignard reagent derived from **209** affording acid **214**. Crude **214** readily underwent HATU mediated coupling with benzylamine to afford *N*-Benzyl amide **215** in 47% yield.

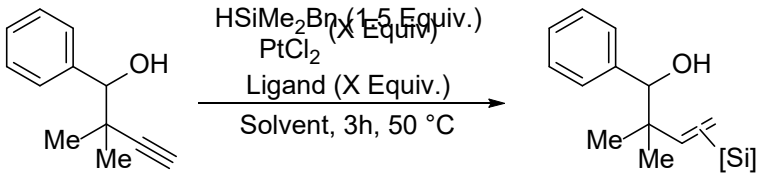


Scheme 72 Synthesis of homopropargylic amides

3.5 Optimisation of Hydrosilylation Conditions and Substrate Scope

With a range of diverse alkynes now in hand, attention turned to development of the hydrosilylation protocol. As the cyclisation selectivity is dependent on the geometric purity of the vinyl silane, the ability to access the silanes as a single isomer was of key importance. A hydrosilylation procedure which results in poor stereoselectivity is likely to result in a mixture of diastereomers in the oxetane which is clearly of detriment to the overall process.[135] A hydrosilylation which achieves poor levels of regioselectivity introduces separate problems in the cyclisation. Given that the cyclisation is directed by the silicon atom as a consequence of the β-silicon effect, a mixture of regioisomers would lead to a mixture of cyclised oxetane and furan products.

As noted, the work reported by Cook *et al* detailed the efficacy of a $PtCl_2$/XPhos catalyst for the hydrosilylation of propargylic alcohols. Due to the structural similarities between the substrates in that report and the substrates employed herein, it was this catalyst with which the study began.[24] Treating **201a** with 10 mol% $PtCl_2$, 20 mol% XPhos and 1.5 equivalents of dimethylbenzylsilane under the conditions shown in **Scheme 73**, complete consumption of the alkyne was observed in 3 hours, with the hydrosilylation proceeding with complete stereocontrol and regiocontrol, affording silane **202a** as a single isomer. Attempts to lower the catalyst loading were next carried out. Lowering the loading of platinum and ligand was successful, with no observable decrease in activity noted even at 1 and 2 mol% loadings of metal and ligand respectively. While XantPhos could be employed in the reaction as shown in **Chapter 2**, this led to a dramatic increase in required reaction time, in addition to a slight loss of selectivity. Switching solvent to CH_2Cl_2 or toluene led to decreased selectivities and reactivity, likely due to the poorly soluble nature of the complex in these solvents.



201a **202a**

Entry	Ligand	Loading (X)	Solvent	Selectivity β:α	Alkyne Consumption (%)
1	XPhos	10	THF	99:1	>99
2	XantPhos	10	THF	94:6	94[a]
3	XPhos	5	THF	99:1	>99
4	XPhos	2	THF	99:1	>99
5	XPhos	1	THF	99:1	>99
6	XPhos	1	PhMe	99:1	Complex Mixture
7	XPhos	1	CH_2Cl_2	99:1	Complex Mixture

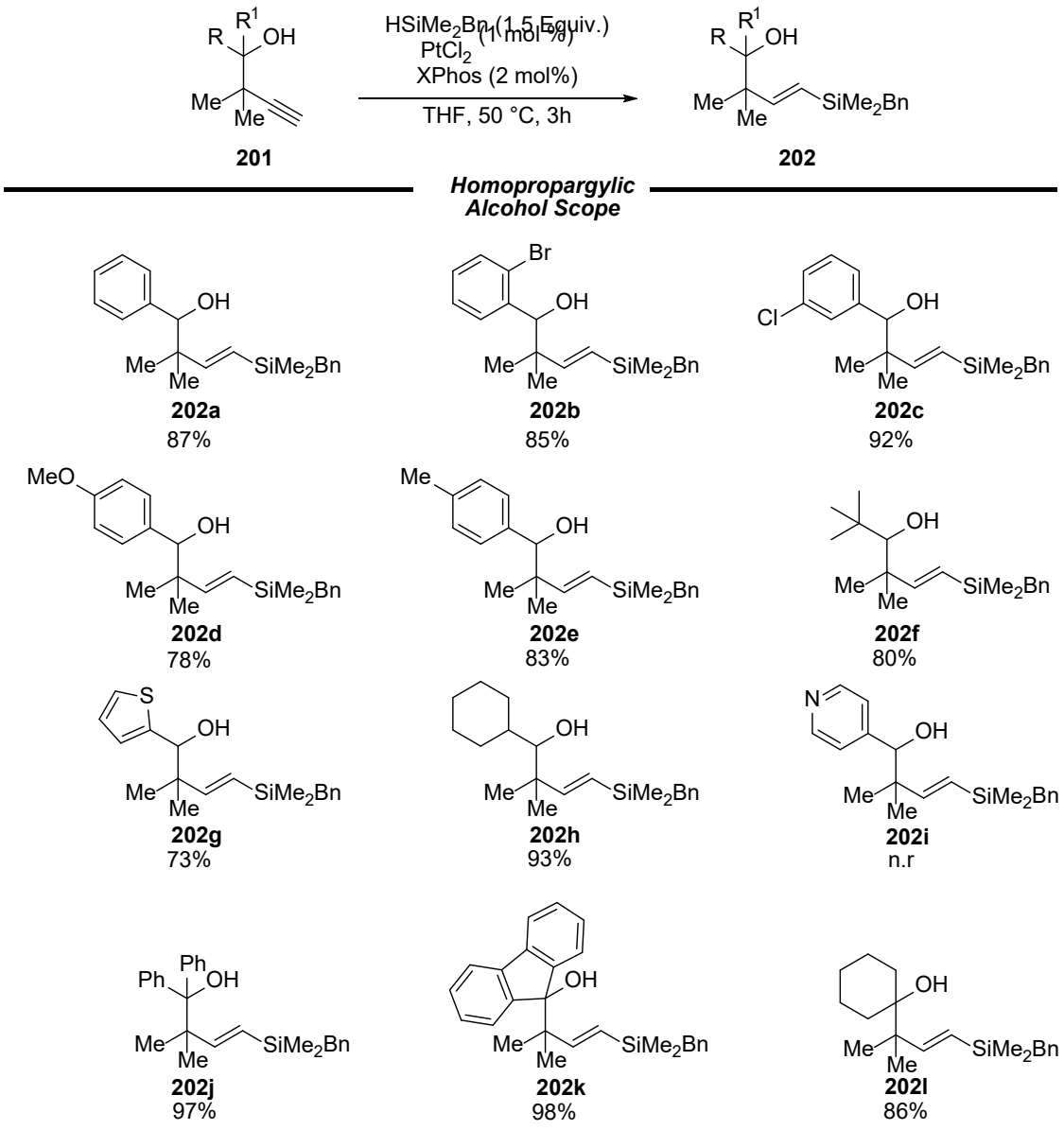
[a] Reaction was carried out for 15 hours

Scheme 73 Optimisation data for homopropargylic alcohol hydrosilylation. Alkyne consumption & isomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture

As a set of optimised reaction conditions had been identified, the focus shifted to exploring the suitability of the various alkynes prepared in **Chapter 3.4** for application in this chemistry. When aryl halides **201b** and **201c** were employed as substrates, no competing halide reduction was noted, and vinyl silanes **202b** and **202c** were isolated as single isomers in 85% and 92% yields. When substrates bearing more electron rich aromatic systems were employed the hydrosilylation again proceeded smoothly, with **202d** and **202e** isolated in 78% and 83% yield.

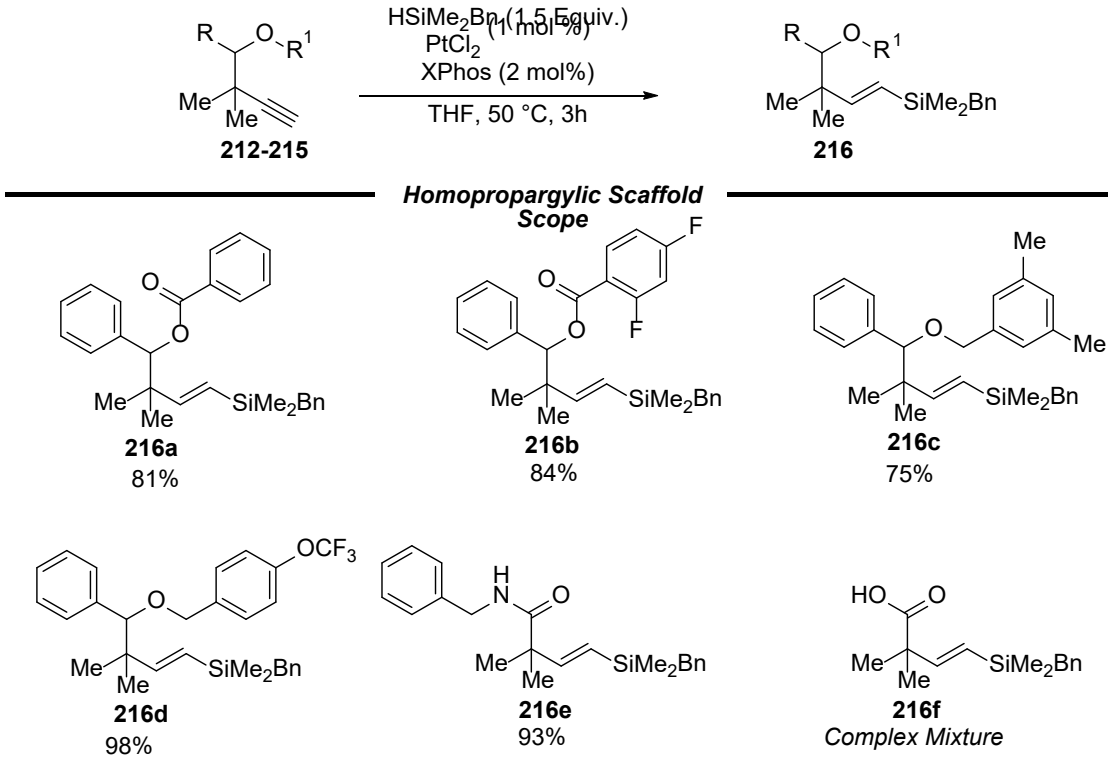
Alkyl substituents were likewise tolerated, despite initial concerns that the steric bulk of **201f** could hamper catalyst-substrate coordination. These concerns were unfounded, with both **201f** and **201h** undergoing facile hydrometallation into the desired silanes. Examining tertiary alcohol substrates, the increased steric bulk of the substrates appeared to be beneficial to reaction efficacy, with **202j** and **202k** isolated in near quantitative yield. Presumably the increase in steric bulk in these substrates facilitates a more facile reductive elimination as has been previously proposed.[25]

When pyridyl alcohol **202l** was employed a substrate, only unreacted starting material was recovered. As discussed in **Chapter 2.1.2**, nitrogenous substrates typically perform poorly due to the highly coordinating nature of the substrate. In this case, the pyridyl ring likely inhibits catalyst turnover by displacement of the phosphine ligands due to the large excess of substrate relative to ligand.



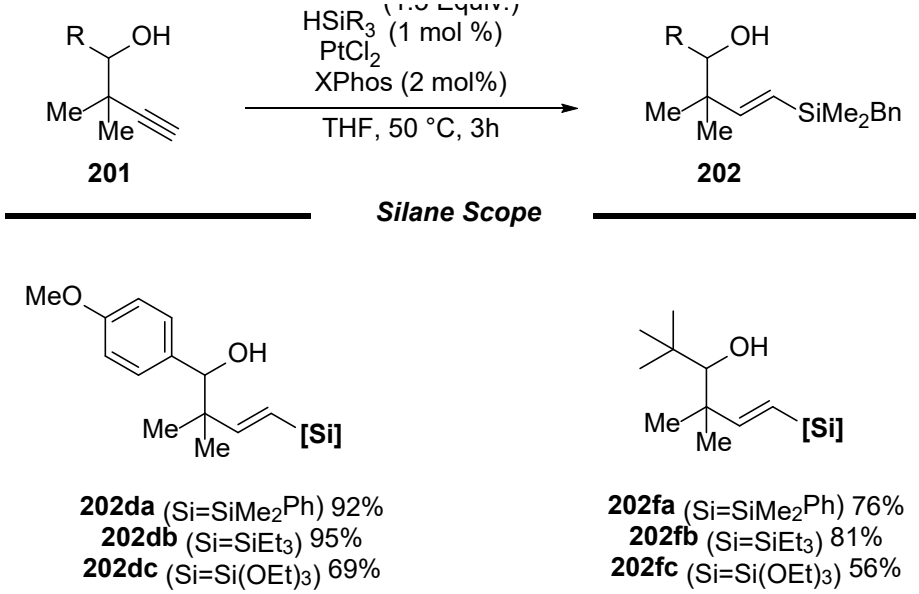
Scheme 74 Scope of allylic alcohols. Substrates afforded as single regio and stereoisomers.

When esters **212a** and **212b** were examined as substrates, the reaction again proceeded smoothly, affording silanes **216a** and **216b** in 81% and 84% yields. Employing homopropargyl ethers **213a** and **213b** as substrates, complete conversion into the corresponding vinyl silane was observed under the optimized conditions allowing for isolation of **216c** and **216d** in 75% and 98% yield. Despite the previously noted issues in hydrosilylation of nitrogen containing substrates,[39, 42] amide **215** readily underwent facile and selective hydrosilylation to afford **216e** in 93% yield, presumably due to the deactivated nature of the nitrogen atom. Employing acid **214** as substrate resulted in the formation of a complex mixture of products, with no discernable formation of **216f** observed in the ^{1}H NMR of the reaction mixture.



Scheme 75 Scope of allylic ethers, esters and amides. Substrates afforded as single regio and stereoisomers.

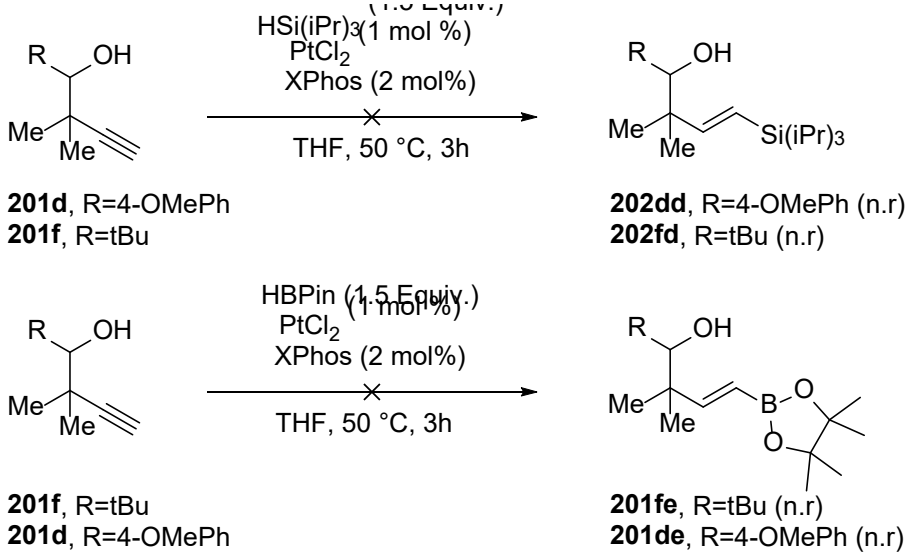
As all hydrosilylations in this chapter thus far had employed dimethylbenzylsilane as a silicon hydride, the range of silyl hydrides which can be delivered to the alkyne was next explored. As with the work in **Chapter 2**, dimethyl phenyl silane could readily be utilised in the hydrosilylation of alcohols **201d** and **201f**, affording **202da** (92%) and **202fa** (76%). The same was true of triethylsilane, which afforded silanes **202db** and **202fb** in high yields. Employing triethoxysilane likewise permitted access to heteroatom substituted silanes **202dc** and **202fc** albeit with a noticeable decrease in yield.



Scheme 76 Scope of other silanes. Substrates afforded as single regio and stereoisomers.

When triisopropylsilane was employed as the silane source, no reaction occurred. This is in keeping with literature reports and has previously been attributed to the large bulk of the isopropyl groups rendering oxidative addition to the silicon-hydrogen bond sluggish, shutting down reactivity. This is supported by the lack of hydrogen evolution observed in the case of these reactions, suggesting that Pt(II)-Pt(0) reduction is occurring.

Likewise, attempting to carry out the hydroboration of **201d** and **201f** under the optimised conditions likewise proved ineffective, likely due to unwanted interactions between the hydroxyl group of the starting materials and the highly oxophilic boron species. Previous work employing the same catalyst supports this, with protection of the hydroxyl group as the corresponding silyl ether allowing the reaction to proceed, presumably by disrupting unwanted O-B interactions.[24] The application of $PtCl_2(XPhos)_2$ as a catalyst for hydrometallations beyond hydrosilylation is discussed further in **Chapter 4**.



201d, R=4-OMePh
201f, R=tBu

202dd, R=4-OMePh (n.r)
202fd, R=tBu (n.r)

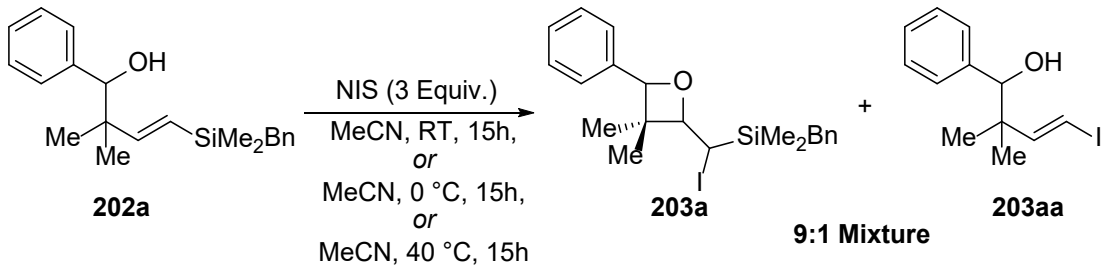
201f, R=tBu
201d, R=4-OMePh

201fe, R=tBu (n.r)
201de, R=4-OMePh (n.r)

Scheme 77 Limitations of bulky silyl groups and boranes

3.6 Iodination/Cyclisation of Homoallylic Alcohols

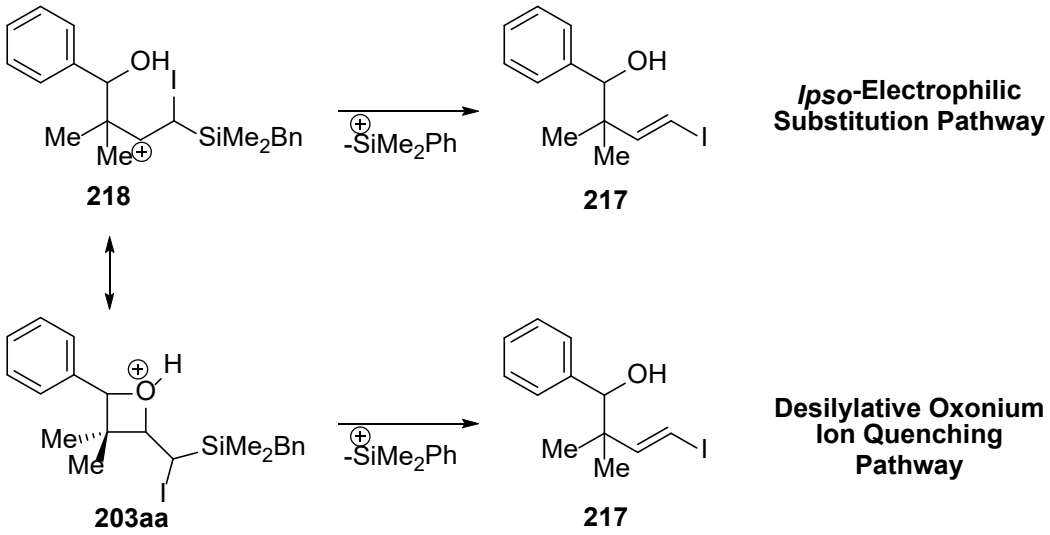
With a range of homoallylic alcohols in hand, attention turned to exploring the cyclisation of these substrates into the corresponding oxetanes. While this transformation has not been reported previously, the study began by attempted utilisation of the conditions reported in **Chapter 2.6** for the related synthesis of aziridines. With this in mind, silane **202a** was treated with NIS in acetonitrile at room temperature and under these conditions, full consumption of the starting alcohol was observed. Unfortunately, this did not equate to clean conversion into the desired oxetane, and it was noted that the expected oxetane was formed in approximately a 9:1 ratio alongside vinyl iodide **203aa** as calculated by ^{1}H NMR analysis of the crude reaction mixture. The ratio of oxetane:vinyl iodide was unchanged regardless of reaction temperature.



Scheme 78 Iodination/Cylisation of 202a in the presence of NIS under various conditions

The formation of this vinyl iodide can likely be explained through the reaction mechanism shown in **Scheme 79**. Upon activation of silane **202a** to afford transient cation **218**, rather than quenching *via* nucleophilic attack by the hydroxyl group, instead, **218** is instead quenched *via* elimination of the silyl group to afford vinyl iodide **217** in a traditional electrophilic substitution. It was also postulated that even if **218** did undergo the desired intramolecular trapping, oxonium ion **203aa** can readily be quenched by loss of the silyl group again affording **217**. Acid mediated ring opening of **203a** would also result in the formation of **217** *via* **203aa**, though due to the relatively low acidity of the succinimide byproduct (pKa ~ 9.5) this was not considered a viable reaction pathway. To circumvent this elimination, the reaction was carried out in the presence of $NaHCO_3$ to both facilitate an increased nucleophilicity of the hydroxyl group while also allowing

deprotonation of **203aa**, theoretically shutting down both proposed pathways for the formation of **217**. When carried out under basic conditions, the formation of **217** is sequestered, with **203a** the only product isolated post-chromatography. Under these conditions, the loading of NIS could successfully be lowered to 1.5 equivalents, with the optimised conditions shown in **Scheme 80**. Carrying out the reaction in CH_2Cl_2 resulted in a decrease in conversion was noted, likely as a result of the decreased solubility of NIS in this solvent in comparison to MeCN. When the reaction was attempted in toluene, no reaction was observed.

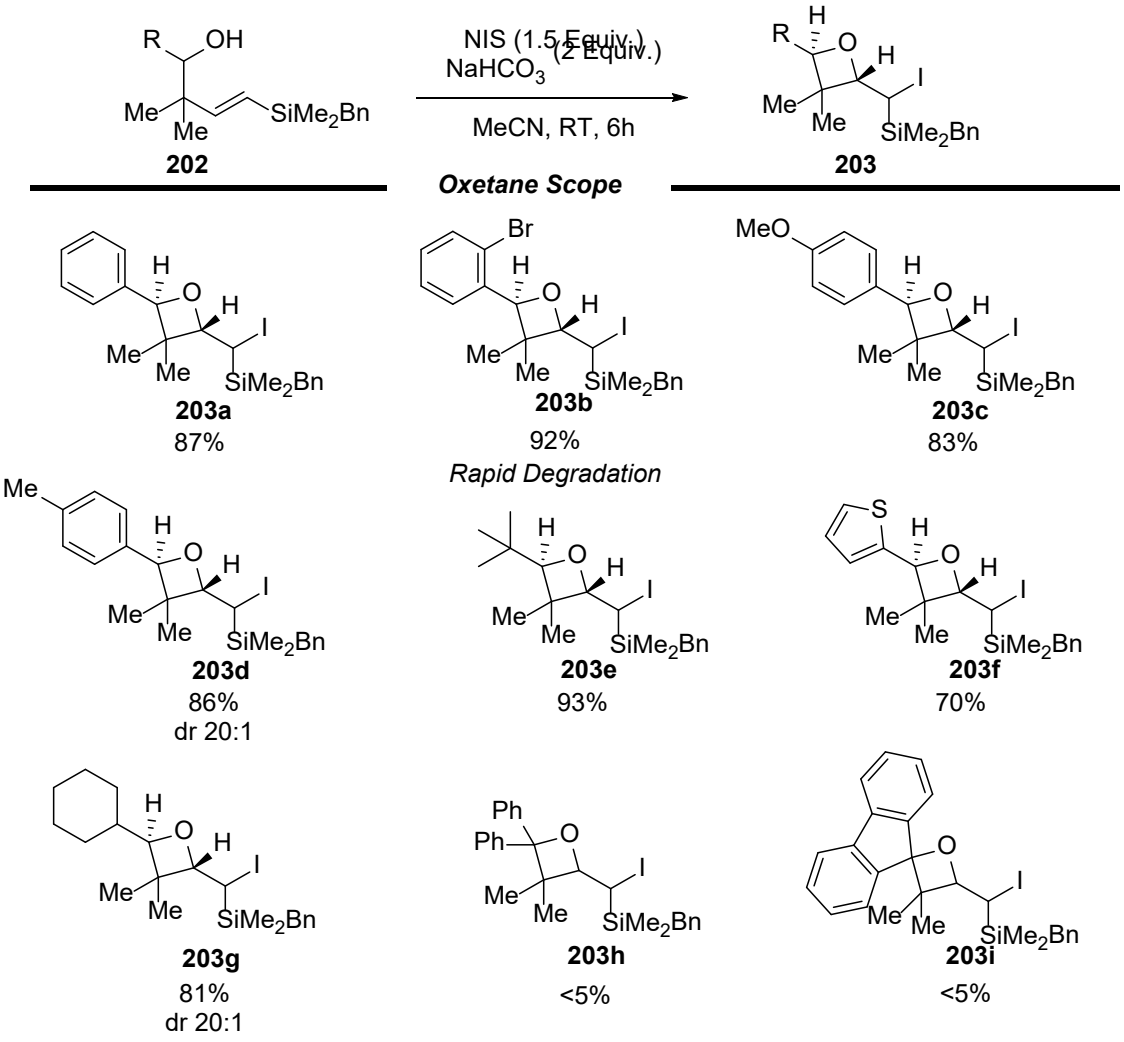


Scheme 79 Mechanism of formation for vinyl iodide 217

With a set of optimised reaction conditions established, focus shifted to exploring the cyclisation of the homoallylic alcohols synthesised in **Chapter 3.5**. When alcohols bearing electron-rich aromatic systems were employed, oxetanes **203c** and **203d** were afforded in excellent yield, though **203d** was isolated as a 20:1 mixture of diastereomers. Assignment of the major diastereomer is expanded upon later in this section.

Employing **202b** as a substrate, oxetane **203b** was isolated in 92% yield. Post isolation, it was noted that this compound is extremely prone to degradation, undergoing complete decomposition in a matter of days even when stored at <0 ˚C and in the dark. Alkyl substituted oxetanes **203g** and **203e** were isolated in 81% and 93% yields respectively. Thiophenyl oxetane **203f** could also be accessed *via* this method and was isolated in 70% yield. Tertiary alcohols proved

less viable as substrates, with less than 5% conversion into **203h** and **203i** observed in the ^{1}H NMR of the crude reaction mixture when these transformations were attempted. Carrying out the reaction at elevated temperatures proved unsuccessful, only resulting in the formation of a complex mixture of products. The poor reactivity of this substrate is likely due to the high levels of transannular strain in the product rendering the cyclisation highly unfavourable.



Scheme 80 Scope of oxetanes afforded by iodination/cyclisation of vinyl silanes 202. Diastereoselectivity determined by ^{1}H NMR analysis of the crude reaction mixture

As previously noted, the cyclisation proceeds with high levels of diastereoselectivity, in several cases affording the resultant oxetane as a single diastereomer. While assigning the relative stereochemistry of all three

stereocentres is relatively challenging due to the acyclic nature of the α-iodosilyl centre, assignment of the relative relationship of the groups at the 1 and 3 positions of the oxetane system is much more straightforward. If these groups are mutually *syn* then the protons on the same carbons would be expected to show a nuclear Overhauser effect (NOE) interaction, whereas the *anti*-product would show no NOE interactions. To this end, oxetane **203g** was studied by NOE Spectroscopy (NOESY). The relevant section of the spectrum is shown in **Figure 8** alongside the peak assignments. As can be seen, no NOE interaction is observed between the 2 protons and as such, they are mutually *trans*.

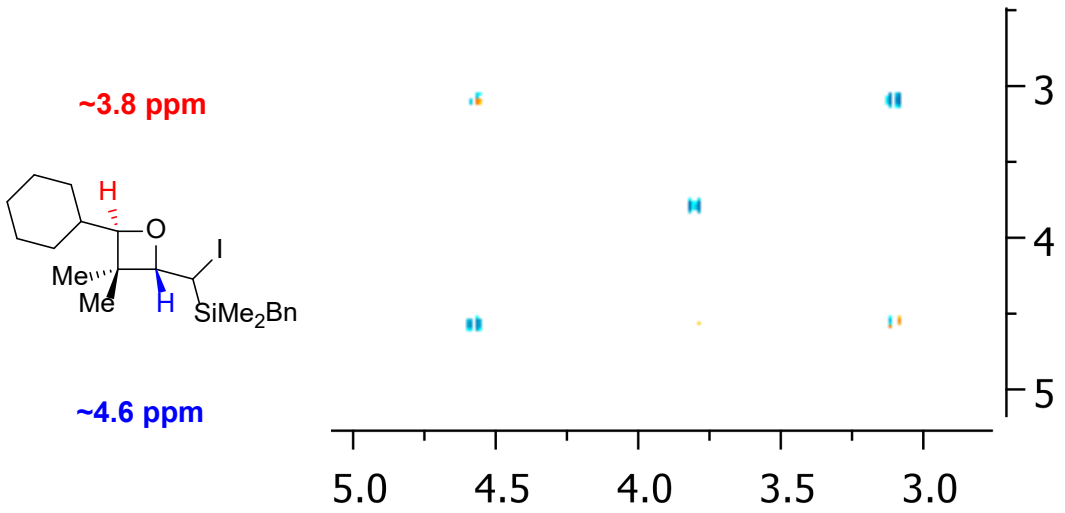
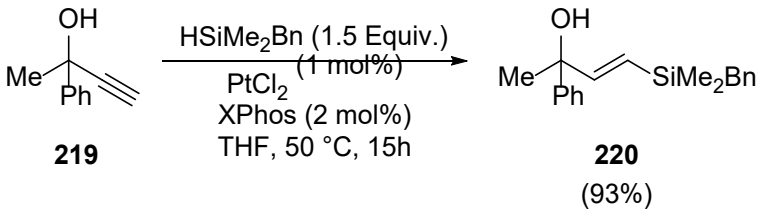


Figure 8 Selected region (3-5ppm) of NOESY spectrum of 203g showing the *trans*-relationship of the oxetane substituents

3.7 Attempted Synthesis of Epoxides and 2,5-dihydrofurans and Further Diversifications

As the synthesis of oxetanes through a hydrosilylation/cyclisation sequence had been demonstrated, a similar approach was next employed to access other oxygen-containing heterocycles was next attempted, specifically epoxides and furans. Given that the synthesis of the 3-membered rings by a similar approach had been achieved (see **Chapter 2.6**), epoxides were chosen as the first synthetic target. Silane **220** was readily accessed in high yield and as a single isomer by hydrosilylation of propargylic alcohol **219** to afford the requisite cyclisation precursor under the conditions reported by Cook *et al*.[24]

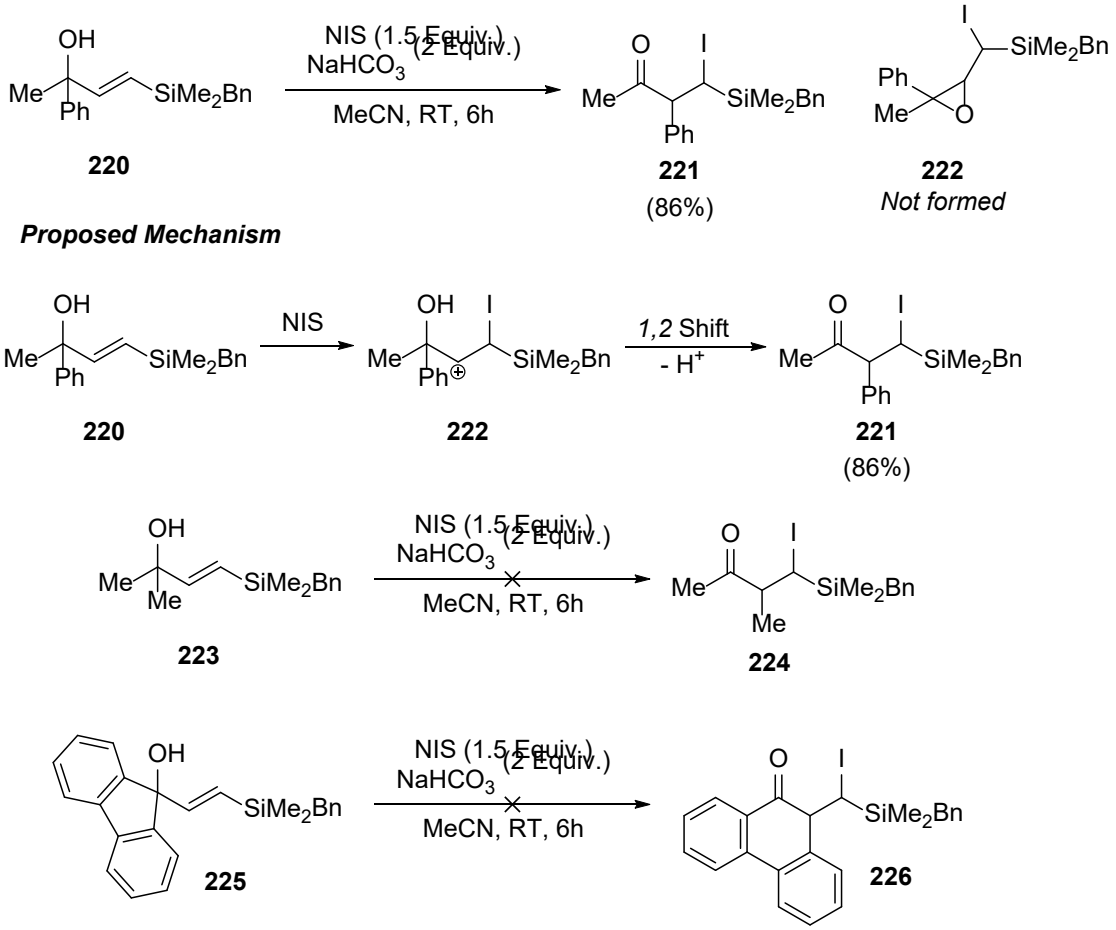


219 **220** (93%)

Scheme 81 Synthesis of silane 220 as a precursor to epoxides

220 was then subjected to the optimised conditions reported in **Chapter 3.6**. Under these conditions, rather than observing **222**, **221** was instead isolated in 86% yield. The formation of **221** can be explained by the mechanism shown in **Scheme 82**, where expected electrophilic activation of **220** forms cation **222** after which 1,2-shift of the aryl group *via* a silicon-direct semi-Pinacol rearrangement affords ketone **221** as a single diastereomer. No product was detected which would arise by competing shift of the methyl group, and when dimethyl alcohol **223** was subjected to the same reaction conditions, no reaction occurred. Attempting to use the same chemistry to trigger a diastereoselective ring expansion of **225** led to an unidentifiable mixture of products. Attempting to trigger the rearrangement of **220** with Eschemoser's salt likewise led to no reaction. It is notable that the discovery of this silicon-directed rearrangement

supports the noted poor suitability of more allylic amines for the aziridination work discussed in **Chapter 2.7**.

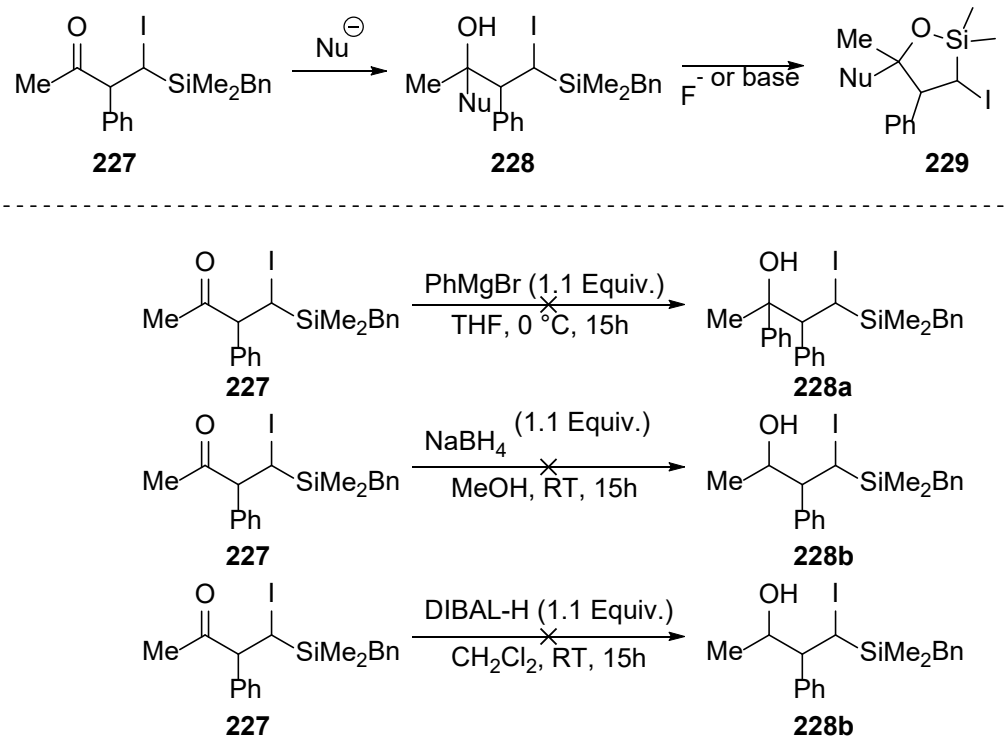


Scheme 82 Semi-pinacol rearrangement of silanes under electrophilic activation

In order to establish the relative stereochemistry of **227**, the synthesis of **229** *via* debenzylative O-Si bond formation in a similar to manner to that reported by Anderson *et al* was proposed.[140, 141] It was envisaged that **228** could be accessed by reduction of **227** followed by subsequent TBAF mediated Si-O bond formation with concomitant silyl-debenzylation. Unfortunately, when attempting the addition phenyl magnesium bromide to **227**, complete degradation of the starting material was observed, presumably due to the highly basic nature of the nucleophile in conjunction with the acidic nature of **227** and the competing elimination of the bromide. Attempted reduction of the ketone with DIBAL and

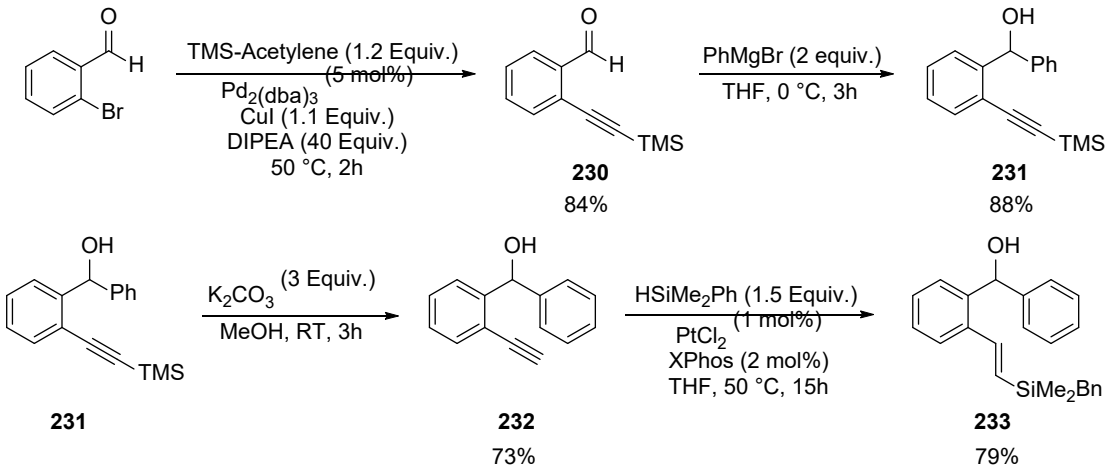
$NaBH_4$ again led to decomposition of the starting material. As such, the relative stereochemistry of **221** was left unassigned.

Proposed Method for Stereochemical Assigment



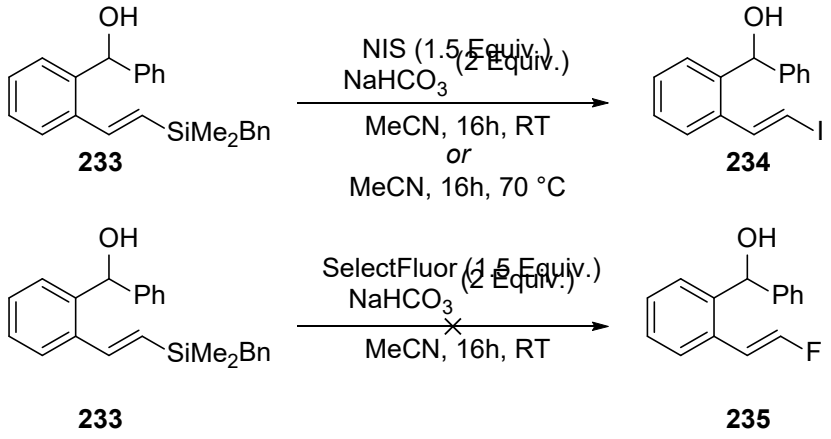
Scheme 83 Attempted synthesis of oxysilacycle 229

The synthesis of 5-membered ring systems was next studied. Due to the ease of preparation of the necessary starting materials, 2,5-dihydrobenzofurans were chosen as the target molecules, with the synthetic procedure to the starting materials shown in **Scheme 84**. 2-Bromobenzaldehyde underwent Sonagashira coupling with TMS-acetylene to afford phenylacetylene derivative **230** in 84% yield. Treatment of **230** with an excess of phenyl magnesium bromide afforded **231** in 88% yield, which could subsequently undergo TMS-cleavage *via* basic methanolysis to afford **232** in 73% yield. **232** underwent facile $PtCl_2$/XPhos catalysed hydrosilylation to afford vinyl silane **233** as a single isomer in 79% yield.



Scheme 84 Synthesis of silane 234

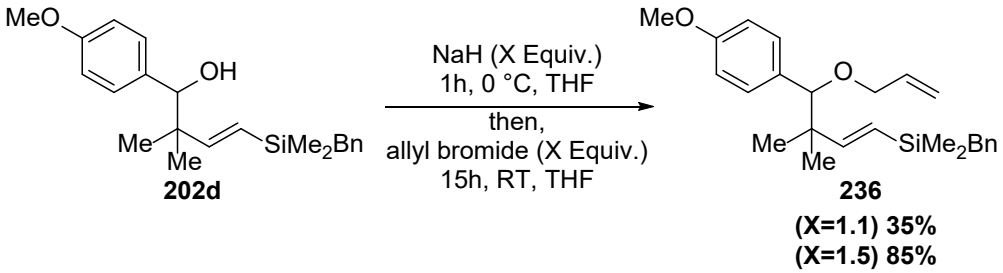
When alcohol **233** was subjected to the optimised reaction conditions, no formation of the desired heterocycle was observed. Instead, complete conversion to iodide **234** occurred, which itself proved highly prone to degradation on silica gel, rendering purification difficult. Repeating the reaction at elevated temperature still resulted only in the formation of **234**. As was the case with the silanes studied in **Chapter 2.7**, **233** proved entirely unreactive towards SelectFluor™.



Scheme 85 Attempted halogenation/cyclisation of 223

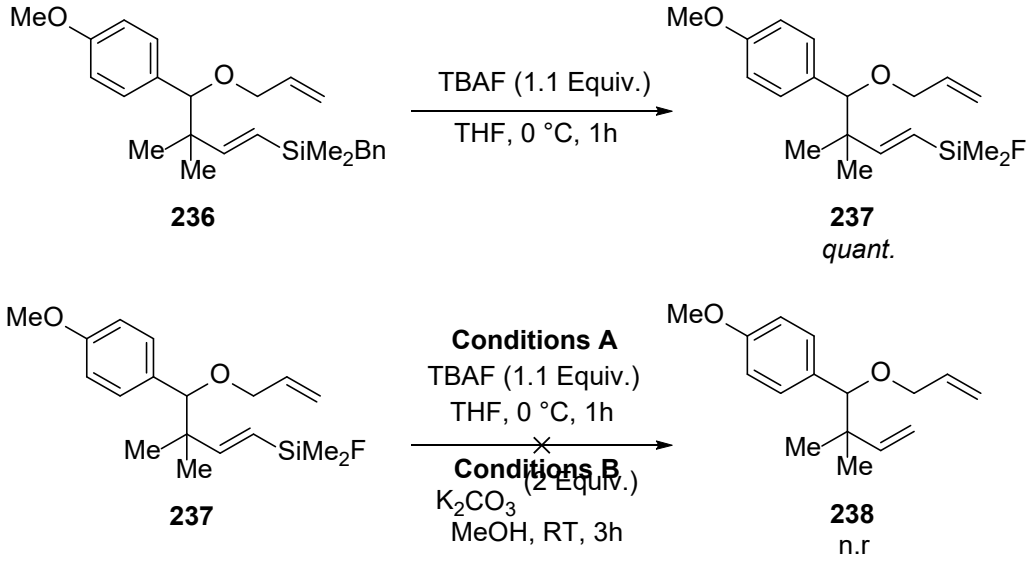
With the scope and limitations of the halogenation/cyclisation reactions suitably explored, focus shifted to other avenues for potential diversification of the

homoallylic alcohols. It was envisaged that by allylation of the hydroxyl group and fluoride mediated desilylation of the olefin, bis-olefinic ether **238** could be accessed, providing a platform to access pyran derivatives by Grubbs metathesis. Resultantly, **202d** was treated with allyl bromide in the presence of sodium hydride. When the reaction was carried out using 1.1 equivalents of both allyl bromide and sodium hydride relative to **236**, the corresponding allyl ether could be isolated in a 35% yield. Allowing time for the preformation of the intermediate alkoxide before addition of the allyl bromide, in addition to raising the equivalents of both allyl bromide and sodium hydride permitted isolation of **236** in 85% yield (**Scheme 86**).



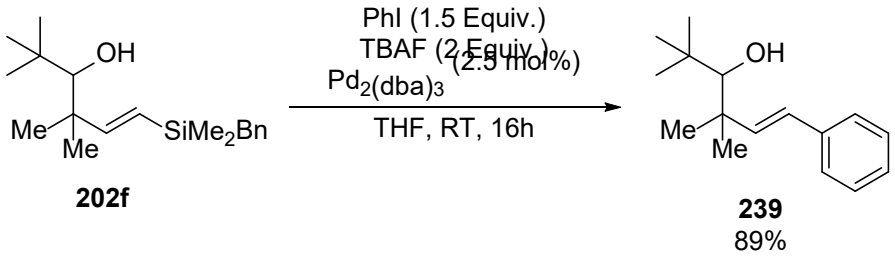
Scheme 86 Allylation of 202d

With **236** in hand, attention turned to desilylation of the olefin to provide the platform for cross-metathesis. Though it was expected that reaction between **236** and TBAF would allow access to **238**, silyl fluoride **236** was instead afforded as a result of fluoride mediated silyl-debenzylation. Treatment of **236** with further equivalents of TBAF proved ineffective in cleaving the silyl group, as did treatment with potassium carbonate, even at elevated temperatures. As desilylation had proven difficult to realise, the synthesis of pyrans by this method was not pursued further.



Scheme 87 Attempted desilylation of 236 and 237

To further demonstrate utility of the products, **202f** was subjected to palladium catalysed Hiyama cross-coupling with iodobenzene. Under the conditions shown in **Scheme 88**, as reported by McLaughlin and Cook, **202** underwent facile coupling to afford homoallylic alcohol **239** in 89% yield.[142] Pleasingly no loss in the geometric purity of the olefin was observed during the course of the cross-coupling.



Scheme 88 Synthesis of homoallylic alcohol 239 by Hiyama cross-coupling

3.8 Conclusions

In summary, an investigation into the synthesis of oxetanes *via* the hydrosilylation/cyclisation of homopropargyl alcohols has been carried out. A synthetic procedure to afford a range of 2,2-dimethyl homopropargylic alcohols **202** has been developed and used to access both tertiary and secondary alcohols, which be further diversified into ether, esters and amides **212**-**215** allowing for access to 18 alkynes with varying functionality at the homopropargylic position. A set of optimal conditions for the hydrosilylation was identified, with XPhos and $PtCl_2$ shown to catalyse the reaction with complete stereo and regiocontrol over the delivery of the silyl hydride to the alkyne. Using these optimised conditions, a diverse range of vinyl silanes were synthesised in generally excellent yields and selectivities. The same catalyst was shown to be active towards a range of silicon hydrides, though bulky silanes and boranes proved unsuitable as hydrometallating agents.

The silicon directed cylisation of homoallylic alcohols has been achieved, affording tetrasubstituted oxetanes **203** in high levels of diastereoselectivity and avoiding the necessity of carrying out the reaction using stoichiometric amounts of strong bases or complex photochemical reaction setups. The reaction was tolerant to a range of secondary alcohols, though utilisation of tertiary alcohols resulted in a dramatic decrease in reactivity. Through NOESY studies, the relative stereochemistry of the groups in the 1 & 3 positions of the ring were shown to be mutually *trans*.

Attempting to apply the same method to the synthesis of epoxides and furans was unsuccessful. In the case of the attempted synthesis of epoxides, a competing semi-Pinacol rearrangement occurs to afford β-keto-α-iodosilane. The vinyl silanes proved to be amenable to functionalisation *via* cross-coupling, with alcohol **239** afforded by palladium catalysed Hiyama cross-coupling of **202f** with iodobenzene.

3.9 Experimental Procedures and Characterisation Data

Solvents & reagents

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, TCI, Fisher Scientific or Sigma Aldrich. All solvents were purchased from commercial sources and used without purification (reagent grade). Metal salts and ligands were stored in a desiccator when not in use. Anhydrous solvent was prepared by storing solvent over activated 4Å MS for 72 hours. Standard vacuum line techniques were used, and glassware was oven dried prior to use. Organic solvents were dried during workup using anhydrous Na_2SO_4. All reactions were performed using DrySyn heating mantles and pressure regulated vials or round bottom flasks.

Purification and chromatography

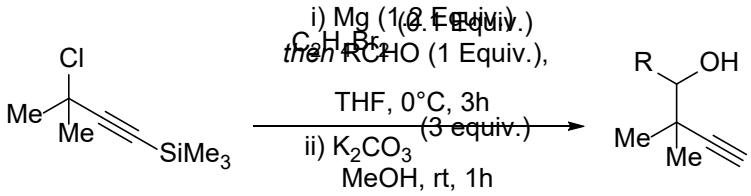
Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F254 silica gel. Plates were visualised using UV light (254 or 365 nm) and developed with iodine and basic permanganate solution. Flash chromatography was performed on VWR Silica gel 60, 40–63 microns RE as the stationary phase and the solvents employed were of reagent grade.

Characterisation

^{1}H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ^{13}C NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemicalshifts are reported in parts per million (δ) relative to residual $CHCl_3$ (δH = 7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm, central line). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer.

3.9.1 General Procedures

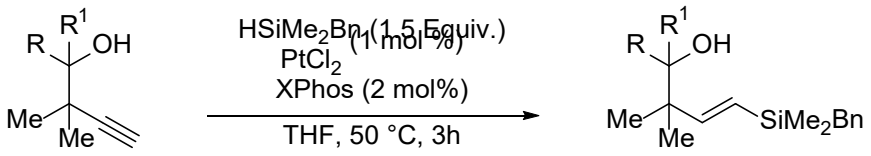
General Procedure 3A



(3-Chloro-3-methyl-but-1-ynyl)-trimethyl-silane was synthesised according to previously published procedures.[139] To an oven dried flask under a nitrogen atmosphere was added magnesium turnings (1.2 equiv.) followed by THF (0.5 M) and 1,2-dibromoethane (0.1 equiv.) with the resulting suspension then stirred for 20 minutes at room temperature. After this time, propargyl chloride (2 equiv.) was added to the suspension, and the mixture left for 1 hour to form the active Grignard reagent. During this time, a separate oven dried flask was charged with the desired aldehyde/ketone and placed under a nitrogen atmosphere at 0 ˚C. Once formed, the Grignard reagent was added dropwise to the aldehyde or ketone (1 equiv.), warmed to room temperature and stirred until indicated complete by TLC analysis. After this time, the reaction was quenched *via* addition of aqueous HCl (10 mL, 1M) and extracted into CH_2Cl_2 (3 × 10 mL) before being dried over $MgSO_4$. Volatiles were then removed under vacuum, and the resultant residue purified by flash column chromatography to afford the corresponding TMS-protected homopropargyl alcohol.

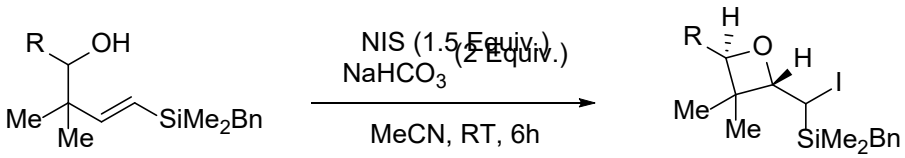
To an oven dried flask containing TMS-protected homopropargyl alcohol dissolved in methanol (0.5 M) was added potassium carbonate (3 equiv.) and the resulting suspension stirred for 2 hours. After this time, the reaction was quenched with water (10 mL) and extracted into CH_2Cl_2 (3 × 10 mL) before being dried over $MgSO_4$. Volatiles were then removed under vacuum, and the resultant residue purified by flash column chromatography to afford the corresponding pure homopropargyl alcohol.

General Procedure 3B



To an oven dried 22 mL vial equipped with a magnetic stirrer was added $PtCl_2$ (1 mol%) and 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (2 mol%) (XPhos). The flask was then flushed quickly with nitrogen and anhydrous THF was added. The mixture was then stirred at 50 ˚C for 20 minutes until a yellow homogenous mixture was obtained. The corresponding alkyne (1 eq.) was added followed by the silane (1.5 eq.) *via* syringe (CAUTION: Rapid evolution of hydrogen gas) and the solution was stirred at 50 ˚C for 3 hours. Volatiles were removed under vacuum before the resultant residue was purified by flash column chromatography to afford the pure silane.

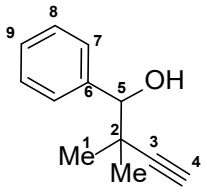
General Procedure 3C



An oven dried flask containing NIS (1.5 Equiv.) and $NaHCO_3$ (2 Equiv.) was placed under a nitrogen atmosphere. To this flask was added a 0.1 M solution of homoallylic alcohol in anhydrous MeCN. The resultant suspension was stirred at room temperature for 6 hours. After this time, an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) was added to the reaction. The mixture was then extracted into CH_2Cl_2 (3 × 10mL) and washed with brine before being dried over Na_2SO_4. Volatiles were removed under vacuum before the resultant residue was purified by flash column chromatography to afford the pure oxetane

3.9.2 Synthesis of Homopropargylic Alcohols

2,2-dimethyl-1-phenyl-but-3-yn-1-ol 201a

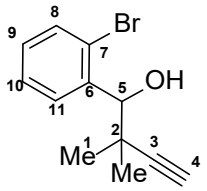


The title compound was prepared according to **General Procedure 3A** from Benzaldehyde (424 mg, 4 mmol). Following conversion to product and flash chromatography **201a** was isolated as a pale-yellow oil (501 mg, 72%). Spectral data in accordance with literature reports.[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H, (**H8**)), 7.36 – 7.29 (m, 3H, (**H7** & **H9**)), 4.52 (d, *J* = 4.0 Hz, 1H, (**H5**)), 2.41 (d, *J* = 4.0 Hz, 1H, (**OH**)), 2.26 (s, 1H, (**H4**)), 1.28 (s, 3H, (**H1**)), 1.11 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (**C6**), 128.4 (**C8**), 127.5 (**C9**), 127.3 (**C7**), 90.8, (**C4**), 81.2 (**C5**), 79.4 (**C4**), 39.5 (**C2**), 26.5 (**C1**), 24.4 (**C1**).

2,2-dimethyl-1-(2-bromophenyl)-but-3-yn-1-ol 201b



The title compound was prepared according to **General Procedure 3A** from 2-Bromobenzaldehyde (250 mg, 1.35 mmol). Following conversion to product and flash chromatography **201b** was isolated as a pale-yellow oil (240 mg, 70%).

Rf (19:1 Petroleum Ether:EtOAc): 0.26

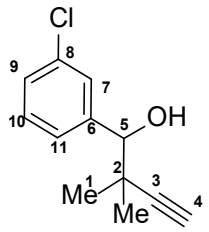
IR υmax (cm^{-1}) 3449, 3296, 3063, 2976, 2935

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{12}H_{14}BrO$ 253.0228; Found 253.0235

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.9, 1.7 Hz, 1H, (**H8**)), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H, (**H10**)), 7.38 – 7.30 (m, 1H, (**H11**)), 7.16 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H, (**H9**), 5.09 (d, *J* = 5.2 Hz, 1H, (**H5**)), 2.42 (d, *J* = 5.2 Hz, 1H, (**OH**)), 2.31 (s, 1H, (**H4**)), 1.44 (s, 3H, (**H1**)), 1.16 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (**C6**), 132.6 (**C8**), 129.4 (**C9** or **C11**), 129.3 (**C9** or **C11**), 127.2 (**C10**), 124.3 (**C7**), 88.6 (**C4**), 77.1 (**C5**), 71.5 (**C3**), 38.9 (**C2**), 27.5 (**C1**), 24.5 (**C1**).

2,2-dimethyl-1-(3-chlorophenyl)-but-3-yn-1-ol 201c



The title compound was prepared according to **General Procedure 3A** from 3-chlorobenzaldehyde (281 mg, 2 mmol). Following conversion to product and flash chromatography **201c** was isolated as a pale-yellow oil (214 mg, 51%).

Rf (19:1 Petroleum Ether:EtOAc): 0.25

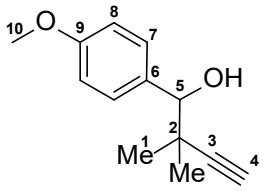
IR υmax (cm^{-1}): 3436, 3299, 3004, 2966, 2918

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{12}H_{14}ClO$ 209.0733; Found 209.0724

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, (**H7**)), 7.30 – 7.23 (m, 3H, (**$H_{Aromatic}$**)), 4.49 (d, *J* = 4.0 Hz, 1H, (**H5**)), 2.45 (s, 1H, (**H4**)), 2.28 (d, *J* = 0.8 Hz, 1H, (**OH**)), 1.27 (s, 3H, (**H1**)), 1.12 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, (**C6**), 133.9 (**C8**), 129.1 (**$C_{Aromatic}$**), 128.2 (**$C_{Aromatic}$**), 128.0 (**$C_{Aromatic}$**), 126.1 (**$C_{Aromatic}$**), 88.9 (**C3**), 79.7 (**C5**), 71.4 (**C4**), 37.9 (**C2**), 26.3 (**C1**), 24.5 (**C1**).

2,2-dimethyl-1-(4-methoxyphenyl)-but-3-yn-1-ol 201d

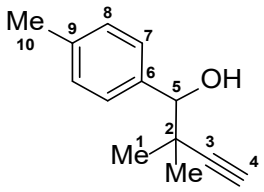


The title compound was prepared according to **General Procedure 3A** from 4-anisaldehyde (272 mg, 2 mmol). Following conversion to product and flash chromatography **201d** was isolated as a pale-yellow oil (261 mg, 64%). Spectral data in accordance with literature reports.[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H (**H7**)), 6.87 (d, *J* = 8.8 Hz, 2H (**H8**)), 4.47 (d, *J* = 3.8 Hz, 1H (**H5**)), 3.81 (s, 3H, (**H10**)), 2.34 (d, *J* = 3.8 Hz, 1H, (**OH**)), 2.25 (s, 1H, (**H4**)), 1.27 (s, 3H, (**H1**)), 1.10 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (**C9**), 132.2 (**C6**), 129.0 (**C7**), 113.3 (**C8**), 89.6 (**C3**), 80.0 (**C5**), 70.8 (**C4**), 55.4 (**C10**), 38.0 (**C2**), 26.6 (**C1**), 24.4, (**C1**).

2,2-dimethyl-1-(4-methylphenyl)-but-3-yn-1-ol 201e

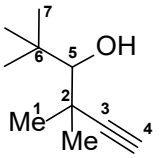


The title compound was prepared according to **General Procedure 3A** from 4-tolualdehyde (240 mg, 2 mmol). Following conversion to product and flash chromatography **201e** was isolated as a pale-yellow oil (112 mg, 29%). Spectral data in accordance with literature reports.[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H, (**C7**)), 7.14 (d, *J* = 7.8 Hz, 2H, (**H8**)), 4.48 (d, *J* = 3.9 Hz, 1H, (**H5**)), 2.35 (d, *J* = 3.9 Hz, 1H, (**OH**)), 2.35 (s, 3H, (**H10**)), 2.25 (s, 1H, (**H4**)), 1.28 (s, 3H, (**H1**)), 1.11 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (**C9**), 137.0 (**C6**), 128.6 (**C7**), 127.8 (**C8**), 89.6 (**C3**), 80.3 (**C5**), 70.8 (**C4**), 37.9 (**C2**), 26.6 (**C10**), 24.5 (**C1**), 21.3 (**C1**).

2,2,4,4-tetramethylhex-5-yn-3-ol 201f



The title compound was prepared according to **General Procedure 3A** from Pivaldehyde (172 mg, 2 mmol). Following conversion to product and flash chromatography **201f** was isolated as a colourless oil (224 mg, 73%).

Rf (19:1 Petroleum Ether:EtOAc): 0.29

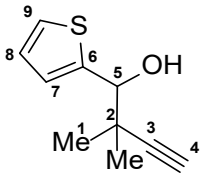
IR υmax (cm^{-1}): 3501, 3308, 2957, 2871, 1729

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{10}H_{19}O$ 155.1436; Found 155.1422

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (d, *J* = 8.0 Hz, 1H, (**H5**)), 2.22 (s, 1H, (**H4**)), 1.92 (d, *J* = 8.0 Hz, 1H, (**OH**)), 1.37 (s, 3H, (**H6**)), 1.35 (s, 3H, (**H6**)), 1.08 (s, 9H, (**H7**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 90.5 (**C3**), 83.8 (**C5**), 71.4 (**C4**), 37.8 (**C6**), 37.4 (**C2**), 29.3 (**C1**), 28.4 (**C7**), 28.3 (**C1**).

2,2-dimethyl-1-(2-thiophenyl)-but-3-yn-1-ol 201g

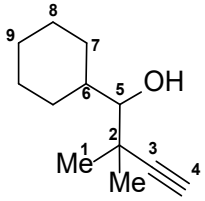


The title compound was prepared according to **General Procedure 3A** from thiophene-2-carboxaldehye (224 mg, 2 mmol). Following conversion to product and flash chromatography **201g** was isolated as a colourless oil (262 mg, 73%). Spectral data in accordance with literature reports.[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H (**Overlaps with $CDCl_3$**), (**H9**)), 7.07 (d, *J* = 3.4 Hz, 1H, (**H7**)), 6.98 (m, 1H, (**H8**)), 4.75 (d, *J* = 4.8 Hz, 1H, (**H6**)), 2.46 (d, *J* = 4.8 Hz, 1H, (**OH**)), 1.34 (s, 3H, (**H1**)), 1.18 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (**C6**), 126.3 (**C9**), 126.1 (**C8**), 125.1 (**C7**), 89.0 (**C3**), 77.2 (**C5**), 71.5 (**C4**), 38.1 (**C2**), 26.5 (**C1**), 24.8 (**C1**).

2,2-dimethyl-1-(2-cyclohexyl)-but-3-yn-1-ol 201h

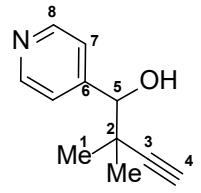


The title compound was prepared according to **General Procedure 3A** from cyclohexanecarboxaldehyde (224 mg, 2 mmol). Following conversion to product and flash chromatography **201h** was isolated as a pale-yellow oil (165 mg, 46%). Spectral data in accordance with literature reports.[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (dd, *J* = 8.9, 2.6 Hz, 1H, (**H5**)), 2.19 (s, 1H, (**H4**)), 2.00 (d, *J* = 12.6 Hz, 1H, (**OH**)), 1.74 (dd, *J* = 15.0, 10.7 Hz, 3H, (**H$_{Cyclohexyl}$**)), 1.69 – 1.51 (m, 4H, (**H$_{Cyclohexyl}$**)), 1.41 (ddd, *J* = 24.7, 12.3, 3.4 Hz, 1H, (**H$_{Cyclohexyl}$**)), 1.31 (s, 3H, (**H1**)), 1.23 (s, 3H, (**H1**)), 1.22 – 1.09 (m, 3H, (**H$_{Cyclohexyl}$**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 89.8 (**C3**), 81.8 (**C5**), 71.3 (**C4**), 40.3 (**C$_{Cyclohexyl}$**), 36.9, (**C2**) 32.7 (**C$_{Cyclohexyl}$**), 28.2 (**C$_{Cyclohexyl}$**), 26.9 (**C$_{Cyclohexyl}$**), 26.5 (**C$_{Cyclohexyl}$**), 26.4 (**C1**), 25.9 (**C1**).

2,2-dimethyl-1-(4-pyridyl)but-3-yn-1-ol 201i



The title compound was prepared according to **General Procedure 3A** from Pyridine-4-carboxaldehyde (321 mg, 3 mmol). Following conversion to product and flash chromatography **201i** was isolated as a white solid (143 mg, 27%).

Rf (9:1 Petroleum Ether:EtOAc): 0.21

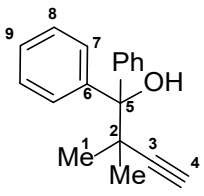
IR υmax (cm^{-1}): 3511, 3299, 3101, 3054, 2902

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{11}H_{14}NO$ 176.1075; Found 176.1080

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.51 (m, 2H, (**H8**)), 7.33 (dd, *J* = 4.7, 1.4 Hz, 2H (**H7**)), 4.50 (s, 1H, (**H5**)), 2.28 (s, 1H, (**H4**)), 1.28 (s, 3H, (**H1**)), 1.14 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (**C6**), 148.5 (**C8**), 123.2 (**C7**), 88.8 (**C3**), 78.4 (**C4**), 71.3 (**C5**), 37.3 (**C2**), 25.5 (**C1**), 25.3 (**C1**).

2,2-dimethyl-1,1-diphenyl-but-3-yn-1-ol 201j



The title compound was prepared according to **General Procedure 3A** from Benzophenone (245 mg, 1.35 mmol). Following conversion to product and flash chromatography **201j** was isolated as a colourless oil (260 mg, 77%).

Rf (19:1 Petroleum Ether:EtOAc): 0.29

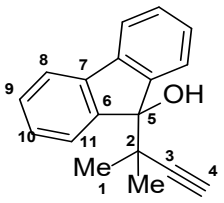
IR υmax (cm^{-1}): 3608, 3300, 3058, 3032, 2985

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{18}H_{19}O$ 251.1436; Found 251.1424

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.1, 1.4 Hz, 4H, (**H8**)), 7.32 – 7.27 (m, 2H, (**H9**)), 7.27 – 7.20 (m, 4H, (**H7**)), 2.55 (br s, 1H, (**OH**)), 2.39 (s, 1H, (**H4**)), 1.38 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (**C6**), 128.7 (**C8**), 127.4 (**C9**), 127.1 (**C7**), 91.1 (**C3**), 81.6 (**C5**), 73.2 (**C4**), 39.6 (**C3**), 26.8 (**C1**).

9-(1,1-dimethylprop-2-ynyl)fluoren-9-ol 201k



The title compound was prepared according to **General Procedure 3A** from 9-Fluorenone (270 mg, 1.5 mmol). Following conversion to product and flash chromatography **201k** was isolated as a colourless oil (210 mg, 56%).

Rf (19:1 Petroleum Ether:EtOAc): 0.33

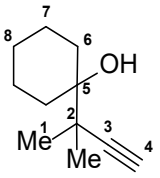
IR υmax (cm^{-1}): 3431, 3293, 2976, 2935, 2870

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{18}H_{17}O$ 249.1279; Found 249.1289

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H, (**H8**)), 7.61 (ddd, *J* = 7.5, 1.2, 0.7 Hz, 2H, (**H10**)), 7.37 (td, *J* = 7.5, 1.1 Hz, 2H, (**H9**)), 7.27 (td, *J* = 7.5, 1.2 Hz, 2H, (**H11**)), 2.72 (s, 1H, (**OH**)), 2.43 (s, 1H, (**H4**)), 1.18 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8 (**C6**), 140.8 (**C7**), 129.3 (**C10**), 127.3 (**C9**), 125.5 (**C11**), 119.8 (**C8**), 89.8 (**C4**), 85.2 (**C5**), 71.5 (**C3**), 40.6 (**C2**) , 25.3 (**C1**).

1-(1,1-dimethylprop-2-ynyl)cyclohexanol 201l



The title compound was prepared according to **General Procedure 3A** from Cyclohexanone (294 mg, 3 mmol). Following conversion to product and flash chromatography **201l** was isolated as a pale-yellow oil (158 mg, 32%)

Rf (9:1 Petroleum Ether:EtOAc): 0.56

IR υmax (cm^{-1}): 3037, 2999, 2948, 2921

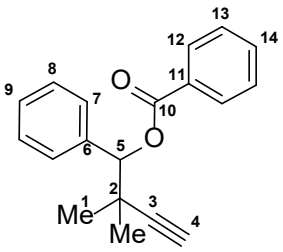
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{11}H_{19}O$ 167.1436; Found 167.1439

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 1H, (**H4**)), 1.77 – 1.72 (m, 2H, (**$H_{Cyclohexyl}$**)), 1.71 – 1.55 (m, 6H, (**$H_{Cyclohexyl}$**)), 1.50 (dd, *J* = 11.4, 6.0 Hz, 2H, (**$H_{Cyclohexyl}$**)), 1.45 (s, 1H, (**OH**)), 1.24 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 90.7 (**C3**), 74.2 (**C5**), 70.1 (**C4**), 41.0 (**$C_{Cyclohexyl}$**), 31.4 (**C2**), 25.9 (**$C_{Cyclohexyl}$**), 24.1 (**$C_{Cyclohexyl}$**), 22.0 (**C1**).

3.9.3 Synthesis of Homopropargylic Esters, Ethers and Amides

(2,2-dimethyl-1-phenyl-but-3-ynyl) benzoate 212a



To a solution of 1a (50 mg, 0.29 mmol) in CH_2Cl_2 (0.2M) was added triethylamine (0.08mL, 0.58 mmol) and DMAP (1.75mg, 0.01 mmol). Benzoyl chloride (0.05 mL, 0.43 mmol) was then added dropwise at 0 ˚C. The resulting mixture was allowed to warm to room temperature, before being stirred for 3 hours. After this time, the reaction was quenched *via* addition of aqueous ammonium chloride, before being extracted into CH_2Cl_2 (3 × 5mL). The combined extracts were then dried over $MgSO_4$ before volatiles were removed under reduced pressure. The resultant residue was then purified by flash chromatography to afford **212a** as a colourless oil (61mg, 76%).

Rf (19:1 Petroleum Ether:EtOAc): 0.43

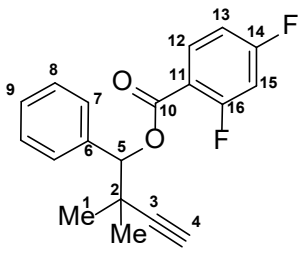
IR υmax (cm^{-1}): 3102, 3092, 3044, 2995, 1733

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{19}O_2$ 279.1385; Found 279.1394

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.10 (m, 2H, (**H12**)), 7.59 (ddd, *J* = 7.4, 4.1, 1.4 Hz, 1H, (**H14**)), 7.53 – 7.45 (m, 4H, (**H$_{Aromatic}$**)), 7.37 – 7.28 (m, 3H, (**H$_{Aromatic}$**)), 5.82 (s, 1H, (**H5**)), 2.23 (s, 1H, (**H4**)), 1.38 (s, 3H, (**H1**)), 1.27 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (**C10**), 137.4 (**C11**), 133.3 (**C12**), 130.4 (**C6**), 129.9 (**C$_{Ar}$**), 128.6 (**C$_{Ar}$**), 128.4 (**C9**), 128.2 (**C$_{Ar}$**), 127.9 (**C$_{Ar}$**), 88.3 (**C3**), 81.2 (**C5**), 70.8 (**C4**), 36.6, (**C3**), 26.6 (**C1**), 26.2 (**C1**).

(2,2-dimethyl-1-phenyl-but-3-ynyl) 2,4-difluorobenzoate 212b



To a solution of 1a (100 mg, 0.58 mmol) in CH_2Cl_2 (0.2M) was added triethylamine (0.16 mL, 1.16 mmol) and DMAP (3.5 mg, 0.03 mmol). 2,4-Difluorobenzoyl chloride (0.1mL, 0.86 mmol) was then added dropwise at 0 ˚C. The resulting mixture was allowed to warm to room temperature, before being stirred for 3 hours. After this time, the reaction was quenched *via* addition of aqueous ammonium chloride, before being extracted into CH_2Cl_2 (3 × 5mL). The combined extracts were then dried over $MgSO_4$ before volatiles were removed under reduced pressure. The resultant residue was then purified by flash chromatography to afford **212b** as a colourless oil (133 mg, 74%).

Rf (19:1 Petroleum Ether:EtOAc): 0.46

IR υmax (cm^{-1}): 3045, 3037, 3012, 2956, 1722

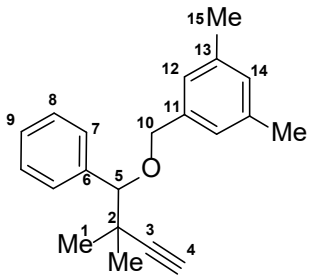
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{17}F_2O_2$ 315.1197 ; Found 315.1194

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (m 1H, (**H12**)), 7.50 (m, 2H, (**H$_{Aromatic}$**)), 7.36 – 7.30 (m, 3H, (**H$_{Aromatic}$**)), 6.98 – 6.87 (m, 2H, (**H$_{Aromatic}$**)), 5.87 (s, 1H, (**H5**)), 2.21 (s, 1H, (**H4**)), 1.35 (s, 3H, (**H1**)), 1.28 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (d, *J* = 11.9 Hz, (**C10**)), 164.5 (dd, *J* = 22.2, 12.3 Hz, (**C16** or **C14**)), 162.1 (dd, *J* = 74.4, 8.5 Hz, (**C16** or **C14**)), 136.8 (**C6**), 134.2 (dd, *J* = 10.6, 2.4 Hz), 128.3 (**C9**)), 128.1 (**C7** or **C8**), 127.8 (**C7** or **C8**), 115.1 (dd, *J* = 9.9, 3.7 Hz, (**C12**)), 111.7 (dd, *J* = 21.5, 3.9 Hz, (**C13**)), 105.4 (dd, *J* = 26.2, 25.3 Hz, (**C15**)), 88.2 (**C3**), 81.7 (**C5**), 70.7 (**C4**), 36.4 (**C3**), 26.0 (**C1**), 25.9 (**C1**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -101.62 (d, *J* = 12.7 Hz), -102.96 (d, *J* = 12.7 Hz).

1-[(2,2-dimethyl-1-phenyl-but-3-ynoxy)methyl]-3,5-dimethyl-benzene 213a



To a solution of **201a** (100 mg, 0.58 mmol) in THF (0.3 M) was added sodium hydride (26 mg, 0.63 mmol) under an N_2 atmosphere. The resultant suspension was stirred for 1 hour at room temperature, before 3,5-dimethylbenzyl bromide (120 mg, 0.6 mmol) was added dropwise. The reaction was then stirred at room temperature for 16 hours, before being quenched *via* addition of aqueous ammonium chloride, before being extracted into CH_2Cl_2 (3 × 5mL). The combined extracts were then dried over $MgSO_4$ before volatiles were removed under reduced pressure. The resultant residue was then purified by flash chromatography to afford **213a** as a colourless oil (121 mg, 72%).

Rf (9:1 Petroleum Ether:EtOAc): 0.67

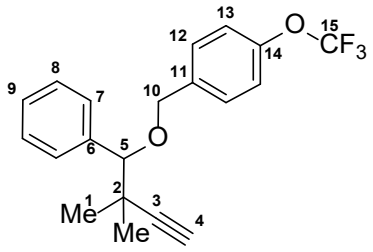
IR υmax (cm^{-1}): 3100, 3078, 3045, 2990, 2943

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{25}O$ 293.1905; Found 293.1912

^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (dt, *J* = 4.3, 2.3 Hz, 2H, (**H8**)), 7.39 – 7.31 (m, 3H, (**H7** & **H9**)), 6.93 (m, 3H, (**H12** & **H14**)), 4.49 (d, *J* = 12.1 Hz, 1H, (**H10**)), 4.15 (d, *J* = 12.0 Hz, 1H, (**H10**)), 4.12 (s, 1H, (**H5**)), 2.31 (d, *J* = 0.5 Hz, 6H, (**H15**)), 2.15 (s, 1H, (**H4**)), 1.26 (s, 3H, (**H1**)), 1.19 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4 (**C6**), 137.9 (**C11**), 129.2 (**C9**), 129.0 (**C8**), 128.0 (**C14**), 127.7 (**C7**) , 127.0 (**C13**), 125.8 (**C12**), 90.0 (**C3**), 86.5 (**C5**), 71.0 (**C4**), 70.1 (**C10**), 34.1 (**C2**), 26.5 (**C15**), 25.9 (**C1**), 21.4 (**C1**).

1-[(2,2-dimethyl-1-phenyl-but-3-ynoxy)methyl]-4-trifluoromethoxybenzene 213b



To a solution of **201a** (100 mg, 0.58 mmol) in THF (0.3 M) was added sodium hydride (26 mg, 0.63 mmol) under an N_2 atmosphere The resultant suspension was stirred for 1 hour at room temperature, before 4-trifluoromethoxybenzyl bromide (0.1 mL, 0.6 mmol) was added dropwise. The reaction was then stirred at room temperature for 16 hours, before being quenched *via* addition of aqueous ammonium chloride, before being extracted into CH_2Cl_2 (3 × 5 mL). The combined extracts were then dried over $MgSO_4$ before volatiles were removed under reduced pressure. The resultant residue was then purified by flash chromatography to afford **213b** as a colourless oil (123 mg, 63%).

Rf (9:1 Petroleum Ether:EtOAc): 0.56

IR υmax (cm^{-1}): 3037, 2999, 2948, 2921

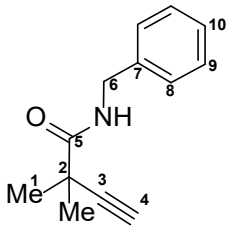
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{20}H_{20}F_3O_2$ 349.1415; Found 349.1408

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 7H, (**H$_{Aromatic}$**)), 7.17 (d, *J* = 8.2 Hz, 2H, (**H13**)), 4.52 (d, *J* = 12.3 Hz, 1H, (**H10**)), 4.25 (d, *J* = 12.2 Hz, 1H, (**H10**)), 4.12 (s, 1H, (**H5**)), 2.16 (s, 1H, (**H4**)), 1.27 (s, 3H, (**H1**)), 1.18 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (q, *J* = 2.0 Hz, (**C14**), 138.0 (**C6**), 137.3 (**C11**), 129.1 (**C$_{Aromatic}$**), 128.8 (**C$_{Aromatic}$**), 128.2 (**C9**), 127.9 (**C$_{Aromatic}$**), 120.9 (q, *J* = 0.8 Hz, (**C13**)), 119.4 (q, *J* = 257.0 Hz, (**C15**), 89.7 (**C3**), 87.0 (**C5**), 70.1 (**C4** or **C10**), 70.1 (**C4** or **C10**), 37.0, (**C2**), 26.3 (**C1**), 26.2 (**C1**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -57.85.

***N*-benzyl-2,2-dimethyl-but-3-ynamide 215**



(3-Chloro-3-methyl-but-1-ynyl)-trimethyl-silane was synthesised according to previously published procedures.[139] To an oven dried flask under a nitrogen atmosphere was added magnesium turnings (2.5 equiv.) followed by THF (0.5 M) and 1,2-dibromoethane (0.1 equiv.) with the resulting suspension then stirred for 20 minutes at room temperature. After this time, propargyl chloride (348 mg, 2.00 mmol) was added to the suspension, and the mixture left for 1 hour to form the active Grignard reagent. During this time, a separate oven dried flask was charged with an excess of solid CO_2 and placed under a nitrogen atmosphere at −78 ˚C. Once formed, the Grignard reagent was added dropwise to CO_2 and slowly allowed to warm to room remperature (**Note**: **Rapid CO_2 evolution.**) Once the reaction had been judged to be complete by TLC analysis, 10 mL HCl (aq, 1M) was added, and the mixture washed with CH_2Cl_2 (3 × 10 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure to afford crude 2,2-dimethyl-but-3-ynoic acid. The crude acid was dissolved in CH_2Cl_2 (1M) and placed under a nitrogen atmosphere, before NEt_3 (2 equiv.) and HATU (1.1 Equiv.) were added. The reaction was stirred at room temperature for one hour before benzylamine was added and the reaction was stirred at room temperature overnight. After this time, 10 mL HCl (aq, 1M) was added, and the mixture washed with CH_2Cl_2 (3 × 10 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was then purified by flash chromatography (9:1 Petroleum Ether:EtOAc) to afford **215** as a colourless oil (186 mg, 47%).

Rf (9:1 Petroleum Ether:EtOAc): 0.33

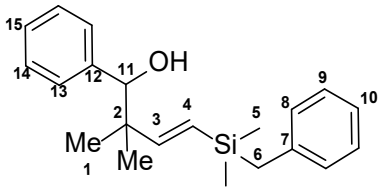
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{13}H_{16}NO$ 202.1232 Found 202.1236

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H, (**H9**)), 7.32 – 7.26 (m, 3H, (**H10** & **H8**)), 7.01 (br s, 1H, (**NH**)), 4.46 (d, *J* = 5.7 Hz, 2H, (**H6**)), 2.43 (s, 1H, (**H4**), 1.50 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$): 173.3 (**C10**), 138.0 (**C7**), 128.8 (**C9**), 127.4 (**C110**), 126.7 (**C8**), 87.4 (**C3**), 73.1 (**C5**), 43.8 (**C8**), 38.5 (**C2**), 27.2 (**C1**)

3.9.4 Synthesis of Homoallylic Alcohols

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-phenyl-but-3-en-1-ol 202a



The title compound was prepared according to **General Procedure 3B** from **201a** (200 mg, 1.15 mmol) and dimethylbenzylsilane (0.27 mL, 1.72 mmol) using $PtCl_2$ (3 mg, 12 µmol) and XPhos (11 mg, 24 µmol) which following conversion to the vinyl silane and column chromatography afforded **202a** as a colourless oil (325 mg, 87%).

Rf (EtOAc:Heptane, 19:1): 0.42

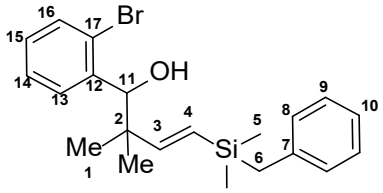
IR υmax (cm^{-1}): 3540, 3033, 3019, 2999

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{29}OSi$ 325.1988; Found 325.1985

^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 4H, (**$H_{Aromatic}$**)), 7.23 – 7.16 (m, 4H, (**$H_{Aromatic}$**)), 7.06 (m, 1H, (**$H_{Aromatic}$**)), 6.99 – 6.95 (m, 2H, (**$H_{Aromatic}$**)), 5.97 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.64 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.37 (d, *J* = 3.6 Hz, 1H, (**H11**)), 2.14 (s, 2H, (**H6**)), 1.83 (d, *J* = 3.6 Hz, 1H, (**OH**)), 0.98 (s, 3H, (**H1**)), 0.93 (s, 3H, (**H1**)), 0.07 (s, 3H, (**H5**)), 0.07 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1 (**C3**), 140.9 (**C7**), 140.2 (**C12**), 128.3 (**C8**), 128.3 (**C9**), 127.9 (**C14**), 127.6 (**C13**), 127.5 (**C15**), 126.7 (**C4**), 124.2 (**C10**), 80.7 (**C11**), 43.8 (**C2**), 26.4 (**C6**), 24.2 (**C1**), 21.6 (**C1**), -3.1 (**C5**), -3.2 (**C5**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-(2-bromophenyl)-but-3-en-1-ol 202b



The title compound was prepared according to **General Procedure 3B** from **202b** (200 mg, 0.79 mmol) and dimethylbenzylsilane (0.19 mL, 1.19 mmol) using $PtCl_2$ (2 mg, 8 µmol) and XPhos (8 mg, 16 µmol) which following conversion to the vinyl silane and column chromatography afforded **202b** as a colourless oil (270 mg, 85%).

Rf (EtOAc:Heptane, 19:1): 0.51

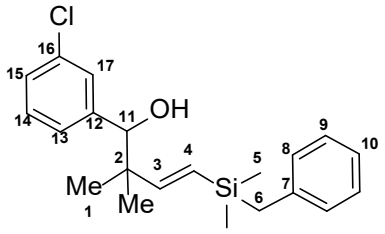
IR υmax (cm^{-1}): 3548, 3042, 3024, 2967, 1599

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{28}BrOSi$ 403.1093; Found 403.1097

^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H, (**$H_{Aromatic}$**)), 7.30 – 7.23 (m, 2H, (**$H_{Aromatic}$**)), 7.23 – 7.17 (m, 2H, (**$H_{Aromatic}$**)), 7.13 – 7.02 (m, 2H, (**$H_{Aromatic}$**)), 6.99 – 6.93 (m, 2H, (**$H_{Aromatic}$**)), 6.08 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.60 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.99 (d, *J* = 4.1 Hz, 1H, (**H11**)), 2.14 (s, 2H, (**H6**)), 1.84 (d, *J* = 4.1 Hz, 1H, (**OH**)), 1.09 (s, 3H, (**H1**)), 1.02 (s, 3H, (**H1**)), 0.07 (s, 3H, (**H5**)), 0.07 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (**C3**), 140.5 (**C7**), 140.3 (**C12**), 132.6 (**$C_{Aromatic}$**), 129.8 (**$C_{Aromatic}$**), 129.0 (**$C_{Aromatic}$**), 128.3 (**C8**), 128.3 (**C9**), 126.9 (**C17**), 126.8 (**C4**), 124.3 (**$C_{Aromatic}$**), 124.2 (**C10**), 77.7 (**C11**), 45.0 (**C2**), 26.4 (**C6**), 24.0 (**C1**), 22.1 (**C1**), -3.1, (**C5**), -3.3 (**C5**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-(3-chlorophenyl)-but-3-en-1-ol 202c



The title compound was prepared according to **General Procedure 3B** from **201c** (100 mg, 0.48 mmol) and dimethylbenzylsilane (0.12 mL, 0.77 mmol) using $PtCl_2$ (1 mg, 5 µmol) and XPhos (5 mg, 10 µmol) which following conversion to the vinyl silane and column chromatography afforded **202c** as a pale-yellow oil (158 mg, 92%).

Rf (EtOAc:Heptane, 19:1): 0.48

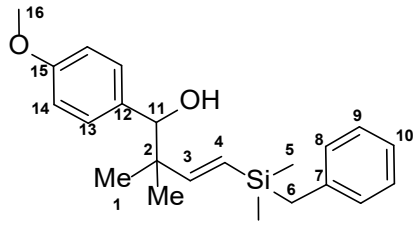
IR υmax (cm^{-1}): 3440, 3022, 2959, 2871

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{28}ClOSi$ 359.1598 ; Found 359.1603

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 5H, (**H$_{Aromatic}$**)), 7.11 – 7.01 (m, 2H, (**H$_{Aromatic}$**)), 7.00 – 6.90 (m, 2H, (**H$_{Aromatic}$**)), 5.92 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.63 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.34 (d, *J* = 3.5 Hz, 1H, (**H11**)), 2.14 (s, 2H, (**H6**)), 1.84 (d, *J* = 3.3 Hz, 1H, (**OH**)), 0.98 (s, 3H, (**H1**)), 0.93 (s, 3H, (**H1**)), 0.08 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (**C3**), 143.0 (**C12**), 140.2 (**C7**), 133.6 (**C16**), 128.8 (**C$_{Aromatic}$**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 128.0 (**C$_{Aromatic}$**), 127.7 (**C$_{Aromatic}$**), 127.3 (**C$_{Aromatic}$**), 126.1 (**C4**), 124.2 (**C10**), 80.1 (**C11**), 43.8 (**C2**), 26.4 (**C6**), 24.0 (**C1**), 21.7 (**C1**), -3.1 (**C5**), -3.2 (**C5**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-(4-methoxyphenyl)-but-3-en-1-ol 202d



The title compound was prepared according to **General Procedure 3B** from **201d** (0.64 mL, 4.1 mmol) using $PtCl_2$ (7 mg, 27 µmol) and XPhos (26 mg, 54 µmol) which following conversion to the vinyl silane and column chromatography afforded **202d** as a pale-yellow oil (746 mg, 78%).

Rf (EtOAc:Heptane, 19:1): 0.28

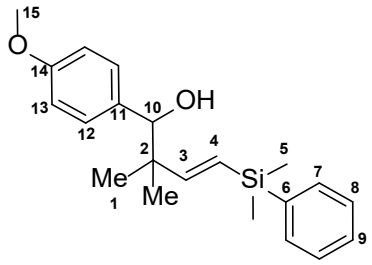
IR υmax (cm^{-1}): 3568, 3027, 2955, 2836

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{22}H_{31}O_2Si$ 355.2093; Found 355.2087

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 14.7, 7.3 Hz, 2H, (**H9**)), 7.13 (dd, *J* = 15.9, 7.9 Hz, 3H, (**H8** & **H10**)), 7.03 (d, *J* = 7.9 Hz, 2H, (**H13**)), 6.86 (d, *J* = 8.2 Hz, 2H, (**H14**)), 6.03 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.68 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.38 (s, 1H, (**H11**)), 3.84 (s, 3H, (**H16**)), 2.19 (s, 2H, (**H6**)), 1.88 (br s, 1H, (**OH**)), 1.02 (s, 3H, (**H1**)), 0.97 (s, 3H, (**H1**)), 0.12 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (**C15**), 154.3 (**C3**), 140.2 (**C7**), 133.1 (**C12**), 128.9 (**C13**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 126.5 (**C4**), 124.2 (**C10**), 113.0 (**C14**), 80.3 (**C11**), 55.3 (**C11**), 43.9 (**C2**), 26.4 (**C6**), 24.2 (**C1**), 21.6 (**C1**), -3.1 (**C5**), -3.2 (**C5**).

(E)-4-[phenyl(dimethyl)silyl]-2,2-dimethyl-1-(4-methoxyphenyl)-but-3-en-1-ol 202da



The title compound was prepared according to **General Procedure 3B** from **201d** (100 mg, 0.48 mmol) and dimethylphenylsilane (0.11 mL, 0.72 mmol) using $PtCl_2$ (1 mg, 5 µmol) and XPhos (5 mg, 10 µmol) which following conversion to the vinyl silane and column chromatography afforded **202da** as a pale-yellow oil (153 mg, 92%).

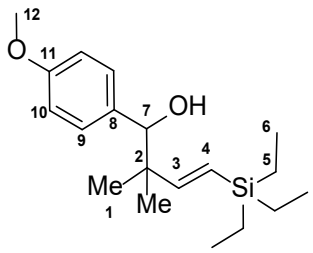
Rf (EtOAc:Heptane, 19:1): 0.28

IR υmax (cm^{-1}): 3533, 3068, 3029, 2985

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 6.5, 3.0 Hz, 2H, (**H8**)), 7.41 – 7.31 (m, 3H, (**H7** & **H9**)), 7.16 (dd, *J* = 8.9, 0.5 Hz, 2H, (**H12**)), 6.81 (d, *J* = 8.8 Hz, 2H, (**H13**)), 6.18 (d, *J* = 19.1 Hz, 1H, (**H3**)), 5.79 (d, *J* = 19.1 Hz, 1H, (**H4**)), 4.41 (s, 1H, (**H10**)), 3.80 (s, 3H (**H15**)), 1.02 (s, 3H, (**H1**),), 0.97 (s, 3H, (**H1**)), 0.35 (s, 3H, (**H5**)), 0.34 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (**C14**), 154.9 (**C3**), 139.2 (**C6**), 134.0 (**C8**), 133.2 (**C11**), 129.1 (**C9**), 128.9 (**C12**), 127.9 (**C7**), 126.4 (**C4**), 113.0 (**C13**), 80.5 (**C10**), 55.4 (**C15**), 44.1 (**C2**), 24.2 (**C1**), 21.8 (**C1**), -2.3 (**C5**), -2.3, (**C5**).

((E)-4-[triethylsilyl]-2,2-dimethyl-1-(4-methoxyphenyl)-but-3-en-1-ol 202db



The title compound was prepared according to **General Procedure 3B** from **201d** (100 mg, 0.48 mmol) and triethylsilane (0.21 mL, 0.72 mmol) using $PtCl_2$ (1 mg, 5 µmol) and XPhos (5 mg, 10 µmol) which following conversion to the vinyl silane and column chromatography afforded **202db** as a pale-yellow oil (149 mg, 95%).

Rf (EtOAc:Heptane, 19:1): 0.29

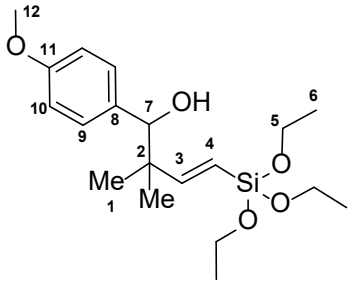
IR υmax (cm^{-1}): 3528, 3100, 3022, 2942, 2901

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{33}O_2Si$ 321.2250; Found 321.2257

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.3 Hz, 2H, (**H9**)), 6.83 (d, *J* = 8.6 Hz, 2H, (**H10**)), 6.09 (d, *J* = 19.3 Hz, 1H, (**H3**)), 5.62 (d, *J* = 19.3 Hz, 1H, (**H4**)), 4.40 (s, 1H, (**H7**)), 3.80 (s, 3H, (**H12**)), 1.91 (br s, 1H, (**OH**)), 0.99 (s, 3H, (**H1**)), 0.96 – 0.93 (m, 9H, (bH6**)**), 0.91 (s, 3H, (**H1**)), 0.58 (q, *J* = 7.9 Hz, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (**C11**), 154.4 (**C3**), 133.1 (**C8**), 129.0 (**C9**), 124.9, (**C4**) 113.0 (**C10**), 80.3 (**C7**), 55.4 (**C12**), 44.2 (**C2**), 24.6 (**C1**), 21.4 (**C1**) , 7.6 (**C6**), 3.7 (**C5**).

(E)-4-[triethoxysilyl]-2,2-dimethyl-1-(4-methoxyphenyl)-but-3-en-1-ol 202dc



The title compound was prepared according to **General Procedure 3B** from **201d** (100 mg, 0.48 mmol) and triethoxysilane (0.14 mL, 0.72 mmol) using $PtCl_2$ (1 mg, 5 µmol) and XPhos (5 mg, 10 µmol) which following conversion to the vinyl silane and column chromatography afforded **202dc** as a pale-yellow oil (124 mg, 69%).

Rf (EtOAc:Heptane, 19:1): 0.13

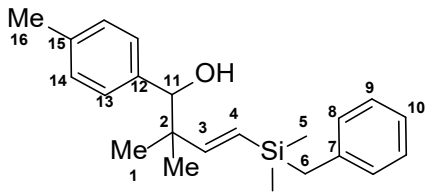
IR υmax (cm^{-1}): 3587, 3103, 3069, 3014, 2937

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{33}O_5Si$ 369.2097; Found 369.2090

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H, (**H9**)), 6.88 – 6.80 (m, 2H, (**H10**)), 6.52 (d, *J* = 19.3 Hz, 1H, (**H3**)), 5.44 (d, *J* = 19.3 Hz, 1H, (**H4**)), 4.44 (s, 1H, (**H7**)), 3.82 (q, *J* = 7.0 Hz, 6H (**H5**)), 3.80 (s, 3H, (**H12**),), 1.23 (t, *J* = 7.0 Hz, 9H, (**H6**)), 1.01 (s, 3H, (**H1**)), 0.97 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (**C3**)), 159.1 (**C11**), 133.2 (**C8**), 128.9 (**C9**), 117.8 (**C4**), 113.1 (**C10**), 80.4 (**C7**), 58.7 (**C5**), 55.4 (**C12**), 44.2 (**C2**), 24.1 (**C1**), 21.4 (**C1**), 18.4 (**C6**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-(4-methylphenyl)-but-3-en-1-ol 202e



The title compound was prepared according to **General Procedure 3B** from **201e** (100 mg, 0.53 mmol) and dimethylbenzylsilane (0.13 mL, 0.79 mmol) using $PtCl_2$ (1 mg, 5 µmol) and XPhos (5 mg, 10 µmol) which following conversion to the vinyl silane and column chromatography afforded **202e** as a colourless oil (149mg, 83%).

Rf (EtOAc:Heptane, 19:1): 0.44

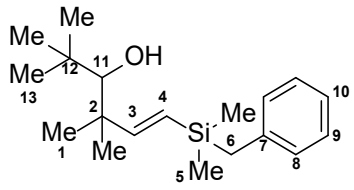
IR υmax (cm^{-1}): 3510, 3132, 3043, 3002, 2973, 2968

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{22}H_{31}OSi$ 339.2144; Found 339.2147

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H, (**H9**)), 7.10 – 7.03 (m, 5H, (**H13**, **H8** & **H10**)), 6.99 – 6.95 (m, 2H, (**H14**)), 5.97 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.63 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.34 (d, *J* = 3.6 Hz, 1H, (**H11**)), 2.33 (s, 3H (**H16**)), 2.13 (s, 2H, (**H6**),), 1.78 (d, *J* = 3.6 Hz, 1H, (**OH**)), 0.97 (s, 3H, (**H1**)), 0.92 (s, 3H, (**H1**)), 0.03 (s, 3H, (**H5**)), 0.03 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (**C3**), 140.2 (**C7**), 138.0 (**C15**)), 137.0 (**C12**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 128.2 (**C13**), 127.7 (**C14**), 126.4 (**C4**), 124.2 (**C10**), 80.6 (**C11**), 43.8 (**C2**), 26.4 (**C6**), 24.2 (**C1**), 21.7 (**C1**), 21.2 (**C16**), -3.1 (**C5**), -3.2 (**C5**).

(E)-6-[benzyl(dimethyl)silyl]-2,4,4-trimethyl-hex-5-en-3-ol 202f



The title compound was prepared according to **General Procedure 3B** from **201f** (0.12 mL, 0.78 mmol) using $PtCl_2$ (1 mg, 5 μmol) and XPhos (5 mg, 10 μmol) which following conversion to the vinylsilane and column chromatography afforded **202f** as a colourless oil which solidified upon standing (126 mg, 80%).

Rf (EtOAc:Heptane, 19:1): 0.49

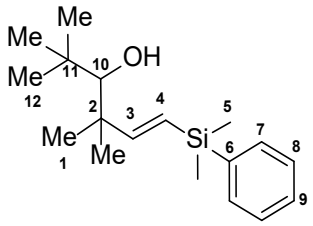
IR υmax (cm^{-1}): 3512, 3041, 3009, 2931, 2895

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{33}OSi$ 305.2301; Found 305.2307

^1H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.14 (m, 2H, (**H9**)), 7.06 (t, *J* = 7.4 Hz, 1H, (**H10**)), 7.01 – 6.94 (m, 2H, (**H8**)), 6.11 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.56 (d, *J* = 19.2 Hz, 1H, (**H4**)), 3.06 (d, *J* = 6.0 Hz, 1H, (**H11**)), 2.12 (s, 2H, (**H6**)), 1.51 (d, *J* = 6.0 Hz, 1H, (**OH**)), 1.10 (s, 3H, (**H1**)), 1.09 (s, 3H, (**H1**)), 0.93 (s, 9H, (**H13**)), 0.04 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (**C3**), 140.2 (**C7**), 128.3 (**C8** or **C9**), 128.2 (**C9** or **C9**), 124.1 (**C10**), 123.0 (**C4**), 84.8 (**C11**), 45.1 (**C2**), 37.5 (**C12**), 28.8 (**C13**), 26.9 (**C1**), 26.3 (**C6**), 24.5 (**C1**), -3.1 (**C5**), -3.3 (**C5**).

(E)-6-[phenyl(dimethyl)silyl]-2,4,4-trimethyl-hex-5-en-3-ol 202fa



The title compound was prepared according to **General Procedure 3B** from **201f** (100 mg, 0.64 mmol) and dimethylphenylsilane (0.18 mL, 0.97 mmol) using $PtCl_2$ (2 mg, 6.5 µmol) and XPhos (5 mg, 13 µmol) which following conversion to the vinyl silane and column chromatography afforded **202fa** as a colourless oil (143 mg, 76%).

Rf (EtOAc:Heptane, 19:1): 0.49

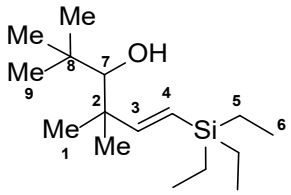
IR υmax (cm^{-1}): 3543, 3051, 3033, 3010, 2995

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{18}H_{31}OSi$ 291.2144; Found 291.2151

^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H, (**H8**)), 7.35 (m, 3H, (**H7** & **H9**)), 6.26 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.75 (d, *J* = 19.2 Hz, 1H, (**H4**)), 3.12 (d, *J* = 5.8 Hz, 1H, (**H10**)), 1.58 (d, *J* = 5.8 Hz, 1H, (**OH**)), 1.13 (s, 3H (**H1**)), 1.12 (s, 3H, (**H1**),), 0.97 (s, 9H, (**H12**)), 0.33 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (**C3**), 139.2 (**C6**), 133.9 (**C8**), 129.0 (**C9**), 127.9 (**C7**), 122.6 (**C4**), 84.9 (**C10**), 45.2 (**C2**), 37.5 (**C11**), 28.8 (**C12**), 27.1 (**C1**), 24.3 (**C1**), -2.4, (**C5**).

(E)-6-[triethylsilyl]-2,4,4-trimethyl-hex-5-en-3-ol 2-2fb



The title compound was prepared according to **General Procedure 3B** from **201f** (100 mg, 0.64 mmol) and triethylsilane (0.15 mL, 0.97 mmol) using $PtCl_2$ (2 mg, 6.5 µmol) and XPhos (5 mg, 13 µmol) which following conversion to the vinyl silane and column chromatography afforded **202fb** as a colourless oil (142 mg, 81%).

Rf (EtOAc:Heptane, 19:1): 0.54

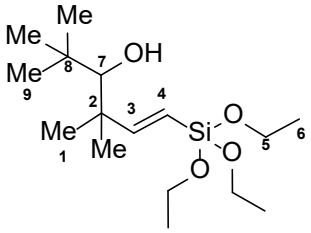
IR υmax (cm^{-1}): 3567, 3020, 3001, 2940, 2919

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{16}H_{35}OSi$ 271.2457; Found 271.2463

^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, *J* = 19.3 Hz, 1H (**H3**)), 5.56 (d, *J* = 19.3 Hz, 1H, (**H4**)), 3.11 (s, 1H, (**H7**),), 1.58 (br s, 1H, (**OH**)), 1.12 (s, 3H, (**H1**)), 1.11 (s, 3H, (**H1**)), 0.98 (s, 9H (**H9**)), 0.92 (t, *J* = 7.9 Hz, 9H, (**H6,**)), 0.56 (q, *J* = 7.9 Hz, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (**C3**), 121.5 (**C4**), 84.7 (**C7**), 45.3 (**C2**), 37.4 (**C8**), 28.9 (**C9**), 26.8 (**C1**), 24.7 (**C1**), 7.6 (**C6**), 3.6 (**C5**).

(E)-6-[triethoxysilyl]-2,4,4-trimethyl-hex-5-en-3-ol 202fc



The title compound was prepared according to **General Procedure 3B** from **201f** (75 mg, 0.48 mmol) and triethoxysilane (0.14 mL, 0.73 mmol) using $PtCl_2$ (1 mg,

4.9 µmol) and XPhos (5 mg, 9.7 µmol) which following conversion to the vinyl silane and column chromatography afforded **202fc** as a colourless oil (86 mg, 56%).

Rf (EtOAc:Heptane, 19:1): 0.27

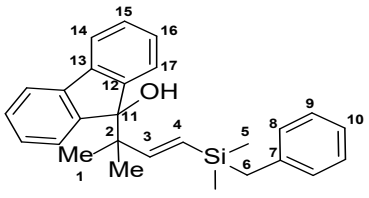
IR υmax (cm^{-1}): 3523, 3045, 3014, 2984, 2911

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{16}H_{35}O_4Si$ 319.2305; Found 319.2311

^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, *J* = 19.3 Hz, 1H, (**H3**)), 5.40 (d, *J* = 19.3 Hz, 1H, (**H4**)), 3.81 (q, *J* = 7.0 Hz, 6H, (**H5**)), 3.16 (s, 1H, (**H7**)), 1.58 (br s, 1H, (**OH**)), 1.23 (t, *J* = 7.0 Hz, 9H, (**H6**)), 1.13 (s, 3H, (**H1**)), 1.12 (s, 3H, (**H1**)), 0.98 (s, 9H, (**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (**C3**), 114.3 (**C4**), 84.8 (**C7**), 58.6 (**C5**), 45.3 (**C2**), 37.5 (**C8**), 28.7 (**C9**), 27.2 (**C1**), 23.8 (**C1**), 18.4 (**C6**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-thienyl-but-3-en-1-ol 202g



The title compound was prepared according to **General Procedure 3B** from **201g** (100 mg, 0.55 mmol) and dimethylbenzylsilane (0.13 mL, 0.83 mmol) using $PtCl_2$ (2 mg, 6 µmol) and XPhos (5 mg, 11 µmol) which following conversion to the vinyl silane and column chromatography afforded **202g** as a yellow oil (146 mg, 76%).

Rf (EtOAc:Heptane, 19:1): 0.41

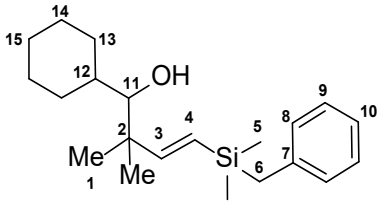
IR υmax (cm^{-1}): 3544, 3045, 3031, 3003, 2980

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{27}OSSi$ 331.1552; Found 331.1546

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 3H, (**$H_{Aromatic}$**)), 7.13 – 7.02 (m, 1H, (**$H_{Aromatic}$**)), 7.00 – 6.91 (m, 3H, (**$H_{Aromatic}$**)), 6.87 (d, *J* = 2.9 Hz, 1H, (**H14**)), 6.08 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.70 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.66 (d, *J* = 3.7 Hz, 1H, (**H11**)), 2.15 (s, 2H, (**H6**)), 1.95 (d, *J* = 3.8 Hz, 1H, (**OH**)), 1.05 (s, 3H, (**H1**)), 1.01 (s, 3H, (**H1**)), 0.08 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (**C3**), 144.7 (**C12**), 140.2 (**C7**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 127.3 (**$C_{Thiophene}$**), 126.1 (**C4**), 125.5 (**$C_{Thiophene}$**), 124.5 (**$C_{Thiophene}$**), 124.1 (**C10**), 77.5 (**C11**), 43.8 (**C2**), 26.3 (**C6**), 24.1 (**C1**), 22.1 (**C1**), -3.2 (**C5**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-cyclohexyl-but-3-en-1-ol 202h



The title compound was prepared according to **General Procedure 3B** from **201h** (100 mg, 0.55 mmol) and dimethylbenzylsilane (0.13 mL, 0.83 mmol) using $PtCl_2$ (2 mg, 6 µmol) and XPhos (5 mg, 12 µmol) which following conversion to the vinyl silane and column chromatography afforded **202h** as a colourless oil (170 mg, 93%).

Rf (EtOAc:Heptane, 19:1): 0.50 IR υmax (cm^{-1}): 3500, 3032, 3007, 2975, 2899

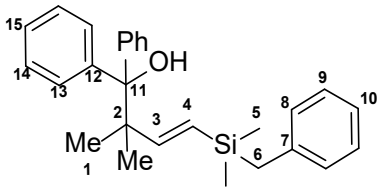
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{35}OSi$ 331.2457 ; Found 331.2460

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H, (**H8**)), 7.10 – 7.02 (m, 1H, (**H10**)), 7.01 – 6.95 (m, 2H, (**H8**)), 6.03 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.59 (d, *J* = 19.2 Hz, 1H, (**H4**)), 3.05 (dd, *J* = 6.6, 2.5 Hz, 1H, (**H11**)), 2.12 (s, 2H, (**H6**)), 1.76 – 1.44 (m, 5H, (**$H_{Cyclohexyl}$**)), 1.29 – 1.09 (m, 5H, (**$H_{Cyclohexyl}$**)), 1.02 (s, 3H, (**H1**)), 1.01 (s, 3H, (**H1**)), 0.94 – 0.83 (m, 1H, (**$H_{Cyclohexyl}$**)), 0.04 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (**C3**), 140.3 (**C7**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 125.0 (**C4**), 124.1 (**C10**), 82.6 (**C11**), 43.9 (**C2**), 39.6 (**$C_{Aliphatic}$**), 33.5

(**C**$_{\text{Aliphatic}}$), 27.5 (**C**$_{\text{Aliphatic}}$), 27.0 (**C**$_{\text{Aliphatic}}$), 26.5 (**C**$_{\text{Aliphatic}}$), 26.4 (**C**$_{\text{Aliphatic}}$), 26.4 (**C**$_{\text{Aliphatic}}$), 24.4 (**C**$_{\text{Aliphatic}}$), 24.0 (**C**$_{\text{Aliphatic}}$), -3.0 (**C5**), -3.2 (**C5**).

(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1,1-diphenyl-but-3-en-1-ol 202j



The title compound was prepared according to **General Procedure 3B** from **201j** (110 mg, 0.44 mmol) and dimethylbenzylsilane (0.10 mL, 0.66 mmol) using $PtCl_2$ (1 mg, 4 µmol) and XPhos (4 mg, 9 µmol) which following conversion to the vinyl silane and column chromatography afforded **202j** as a colourless oil (170 mg, 97%).

Rf (EtOAc:Heptane, 19:1): 0.48

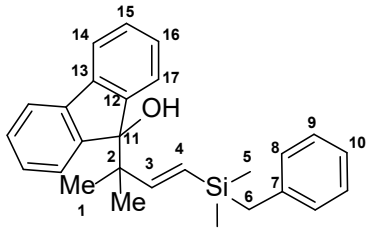
IR υmax (cm^{-1}): 3512, 3041, 3009, 2931, 2895

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{27}H_{33}OSi$ 401.2301 ; Found 401.2297

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 4H, (**H**$_{\text{Aromatic}}$)), 7.25 – 7.16 (m, 7H, (**H**$_{\text{Aromatic}}$)), 7.07 (td, *J* = 7.1, 1.2 Hz, 1H, (**H**$_{\text{Aromatic}}$)), 6.98 (d, *J* = 7.7 Hz, 2H, (**H**$_{\text{Aromatic}}$)), 6.30 (d, *J* = 19.3 Hz, 1H, (**H3**)), 5.79 (d, *J* = 19.3 Hz, 1H, (**H4**)), 2.37 (s, 1H, (**OH**)), 2.14 (s, 2H, (**H6**)), 1.15 (s, 6H, (**H1**)), 0.04 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (**C3**), 145.7 (**C12**), 140.2 (**C7**), 128.6 (**C**$_{\text{Aromatic}}$), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 127.3 (**C**$_{\text{Aromatic}}$), 126.8 (**C4**), 124.8 (**C**$_{\text{Aromatic}}$), 124.1 (**C10**), 81.91 (**C11**), 46.8 (**C2**), 26.3 (**C6**), 24.3 (**C1**), -3.2 (**C5**).

9-[(E)-3-[benzyl(dimethyl)silyl]-1,1-dimethyl-allyl]fluoren-9-ol 202k



The title compound was prepared according to **General Procedure 3B** from **201k** (110 mg, 0.44 mmol) and dimethylbenzylsilane (0.10 mL, 0.66 mmol) using $PtCl_2$ (1 mg, 4 µmol) and XPhos (4 mg, 9 µmol) which following conversion to the vinyl silane and column chromatography afforded **202k** as a colourless oil (173 mg, 98%).

Rf (EtOAc:Heptane, 19:1): 0.49

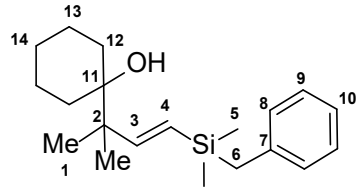
IR υmax (cm^{-1}): 3545, 3103, 3098, 3043, 3006

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{27}H_{31}OSi$ 399.2144; Found 399.2150

^1H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (dt, *J* = 8.8, 7.6 Hz, 2H, (**$H_{Aromatic}$**)), 7.38 – 7.28 (m, 4H, (**$H_{Aromatic}$**)), 7.24 – 7.12 (m, 4H, (**$H_{Aromatic}$**)), 7.08 – 6.96 (m, 3H, (**$H_{Aromatic}$**)), 6.38 (d, *J* = 19.3 Hz, 1H, (**H3**)), 5.59 (d, *J* = 19.3 Hz, 1H, (**H4**)), 2.16 (s, 2H, (**H6**), 0.97 (s, 6H, (**H1**)), 0.10 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (**C3**), 148.2 (**C12** or **C13**), 140.7 (**C12** or **C13**), 140.3 (**C7**), 128.8 (**$C_{Aromatic}$**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 126.8 (**$C_{Aromatic}$**), 126.4 (**C4**), 125.4 (**$C_{Aromatic}$**), 124.2 (**C10**), 119.6 (**$C_{Aromatic}$**), 86.8 (**C11**), 45.4 (**C2**), 26.4 (**C6**), 22.5 (**C1**), -3.2 (**C5**).

1-[(E)-3-[benzyl(dimethyl)silyl]-1,1-dimethyl-allyl]cyclohexanol 202l



The title compound was prepared according to **General Procedure 3B** from **201l** (0.07 mL, 0.35 mmol) using $PtCl_2$ (1 mg, 3 µmol) and XPhos (3 mg, 6 µmol) which following conversion to the vinyl silane and column chromatography afforded **202l** as a colourless oil (82 mg, 86%).

Rf (EtOAc:Heptane, 19:1): 0.46

IR υmax (cm^{-1}): 3510, 3036, 3017, 2997, 2933

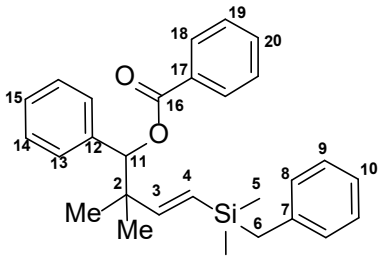
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{20}H_{33}OSi$ 317.2301; Found 317.2295

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H, (**H9**)), 7.09 – 7.02 (m, 1H, (**H10**)), 7.00 – 6.95 (m, 2H, (**H8**)), 6.08 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.59 (d, *J* = 19.2 Hz, 1H, (**H4**)), 2.13 (s, 2H, (**H6**)), 1.67 – 1.60 (m, 1H, ($\mathbf{H_{Cyclohexyl}}$)), 1.56 – 1.44 (m, 6H, ($\mathbf{H_{Cyclohexyl}}$)), 1.40 – 1.22 (m, 3H, ($\mathbf{H_{Cyclohexyl}}$)), 0.99 (s, 6H, (**H1**)), 0.07 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (**C3**), 140.3 (**C7**), 128.3 (**C8** or **C9**), 128.3 (**C8** or **C9**), 126.0 (**C4**), 124.1 (**C10**), 74.6 (**C11**), 45.7 (**C2**), 31.5 ($\mathbf{C_{Aliphatic}}$), 26.5 ($\mathbf{C_{Aliphatic}}$), 26.0 ($\mathbf{C_{Aliphatic}}$), 22.1 (**C1**), 21.9 ($\mathbf{C_{Aliphatic}}$), -3.0 (**C5**).

3.9.5 Synthesis of Homoallylic Esters, Ethers and Amides

[(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-phenyl-but-3-enyl] benzoate 216a



The title compound was prepared according to **General Procedure 3B** from **212a** (50 mg, 0.18 mmol) and dimethylbenzylsilane (0.042 mL, 0.27 mmol) using $PtCl_2$ (1 mg, 1.8 µmol) and XPhos (2 mg, 3.6 µmol) which following conversion to the vinyl silane and column chromatography afforded **216a** as a colourless oil (63 mg, 81%).

Rf (EtOAc:Heptane, 19:1): 0.55

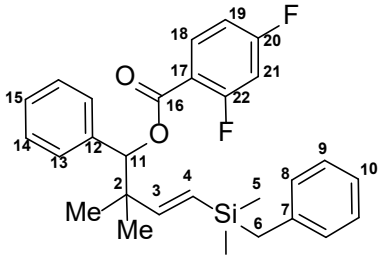
IR υmax (cm^{-1}): 3102, 3045, 2996, 2954, 1744

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{28}H_{33}O_2Si$ 429.2250; Found 429.2261

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.4, 1.4 Hz, 2H, (**H18**)), 7.60 – 7.55 (m, 1H, (**H20**)), 7.49 – 7.44 (m, 2H, (**H**$_{\text{Aromatic}}$), 7.31 – 7.24 (m, 5H, (**H**$_{\text{Aromatic}}$)), 7.20 – 7.14 (m, 2H, (**H**$_{\text{Aromatic}}$)), 7.07 – 7.02 (m, 1H, (**H**$_{\text{Aromatic}}$)), 6.93 (ddd, *J* = 3.2, 2.2, 1.7 Hz, 2H, (**H7**)), 6.09 (d, *J* = 19.1 Hz, 1H, (**H3**)), 5.80 (s, 1H, (**H11**)), 5.61 (d, *J* = 19.1 Hz, 1H, (**H4**)), 2.08 (s, 2H, (**H6**)), 1.11 (s, 3H, (**H1**)), 1.10 (s, 3H, (**H1**)), 0.02 (s, 3H, (**H5**)), -0.00 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (**C16**), 152.9 (**C3**), 140.1 (**C7**), 138.0 (**C12**), 133.1 (**C17**), 129.7 (**C**$_{\text{Aromatic}}$), 128.6 (**C18**), 128.4 (**C**$_{\text{Aromatic}}$), 128.2 (**C**$_{\text{Aromatic}}$), 128.0 (**C**$_{\text{Aromatic}}$), 127.9 (**C**$_{\text{Aromatic}}$), 127.7 (**C**$_{\text{Aromatic}}$), 126.1 (**C4**), 124.1 (**C10**), 82.4 (**C11**), 43.0 (**C2**) , 26.2 (**C6**), 23.8 (**C1**), 23.0, (**C1**), -3.2, (**C5**), -3.3, (**C5**).

[(E)-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-1-phenyl-but-3-enyl] 2,4-dlifluorobenzoate 216b



The title compound was prepared according to **General Procedure 3B** from **212a** (50 mg, 0.15 mmol) and dimethylbenzylsilane (0.038 mL, 0.24 mmol) using $PtCl_2$ (1 mg, 1.5 µmol) and XPhos (2 mg, 3.0 µmol) which following conversion to the vinyl silane and column chromatography afforded **216b** as a colourless oil (63 mg, 81%).

Rf (EtOAc:Heptane, 19:1): 0.58

IR υmax (cm-1): 3095, 3059, 3010, 2995, 1723

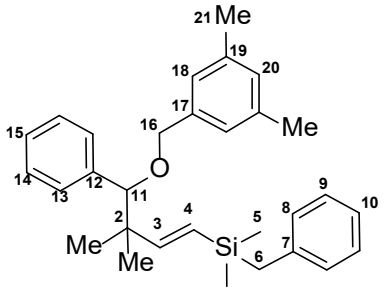
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{28}H_{31}F_2O_2Si$ 465.2061; Found 465.2057

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 1H, (**H21**)), 7.27 (m, 5H, (**H$_{Aromatic}$**)), 7.20 – 7.13 (m, 2H, (**H$_{Aromatic}$**)), 7.08 – 7.00 (m, 1H, (**H$_{Aromatic}$**)), 6.97 – 6.86 (m, 4H, (**H$_{Aromatic}$**)), 6.10 (d, *J* = 19.1 Hz, 1H, (**H3**)), 5.80 (s, 1H, (**H11**)), 5.56 (d, *J* = 19.1 Hz, 1H, (**H4**)), 2.08 (s, 2H, (**H6**)), 1.08 (s, 3H, (**H1**)), 1.07 (s, 3H, (**H1**)), 0.01 (s, 3H, (**H5**)), -0.01 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (dd, *J* = 256.4, 11.9 Hz) (**C22**), 162.9 (dd, *J* = 263.2, 12.5 Hz, (**C20**)), 162.8 (d, *J* = 4.3 Hz, (**C16**)), 152.6 (**C3**), 140.2 (**C7**), 137.6 (**C$_{Aromatic}$**), 134.2 (dd, *J* = 10.6, 2.4 Hz, (**C17**)), 128.4 (**C$_{Aromatic}$**), 128.2 (**C$_{Aromatic}$**), 128.1 (**C$_{Aromatic}$**), 128.0 (**C$_{Aromatic}$**), 127.7 (**C$_{Aromatic}$**), 126.2 (**C4**), 124.1 (**C10**), 115.4 (dd, *J* = 10.3, 3.7 Hz, (**C18**)), 111.8 (dd, *J* = 21.5, 3.8 Hz, (**C19**)), 105.4 (dd, *J* = 26.5, 25.4 Hz, (**C21**)), 83.3 (**C11**), 42.9 (**C2**), 26.2 (**C6**), 23.9 (**C1**), 22.8 (**C1**), -3.3 (**C5**), -3.3 (**C5**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -101.87 (d, *J* = 12.5 Hz), -102.91 (d, *J* = 12.6 Hz).

benzyl-[(E)-4-[(3,5-dimethylphenyl)methoxy]-3,3-dimethyl-4-phenyl-but-1-enyl]-dimethyl-silane 216c



The title compound was prepared according to **General Procedure 3B** from **213b** (50 mg, 0.17 mmol) and dimethylbenzylsilane (0.04 mL, 0.26 mmol) using $PtCl_2$ (1 mg, 1.7 µmol) and XPhos (2 mg, 3.4 µmol) which following conversion to the vinyl silane and column chromatography afforded **216c** as a colourless oil (57 mg, 75%).

Rf (EtOAc:Heptane, 19:1): 0.66

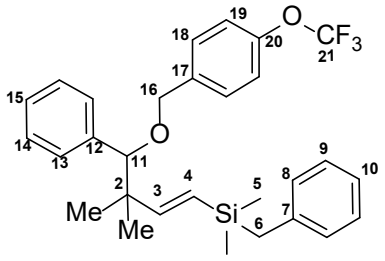
IR υmax (cm^{-1}): 3090, 3027, 2963, 2930

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{30}H_{39}OSi$ 443.2770 Found 443.2774

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H, (**H**$_{\text{Aromatic}}$)), 7.24 – 7.20 (m, 2H, (**H**$_{\text{Aromatic}}$)), 7.19 – 7.14 (m, 2H (**H**$_{\text{Aromatic}}$)), 7.11 – 7.02 (m, 2H, (**H**$_{\text{Aromatic}}$),), 6.96 – 6.89 (m, 5H, (**H**$_{\text{Aromatic}}$)), 6.12 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.44 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.37 (d, *J* = 11.8 Hz, 1H, (**H16**)), 4.11 (d, *J* = 11.8 Hz, 1H, (**H16**)), 4.05 (s, 1H, (**H11**)), 2.31 (d, *J* = 0.5 Hz, 6H (**H21**)), 2.09 (s, 2H, (**H6**)), 1.00 (s, 3H, (**H1**)), 0.99 (s, 3H, (**H1**)), 0.02 (s, 3H, (**H5**)), 0.02 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (**C3**), 140.4 (**C7**), 139.6 (**C12**), 139.3 (**C19**), 138.9 (**C19**), 137.8 (**C17**), 129.1 (**C**$_{\text{Aromatic}}$), 128.8 (**C8** or **C9**), 128.5 (**C8** or **C9**), 128.4 (**C**$_{\text{Aromatic}}$), 128.3 (**C**$_{\text{Aromatic}}$), 128.1 (**C**$_{\text{Aromatic}}$), 127.5 (**C**$_{\text{Aromatic}}$), 127.4 (**C4**), 125.6 (**C**$_{\text{Aromatic}}$), 124.2 (**C10**), 124.1 (**C**$_{\text{Aromatic}}$), 124.0 (**C**$_{\text{Aromatic}}$), 88.5 (**C11**), 71.0 (**C16**), 43.4 (**C2**), 28.7 (**C21**), 26.5 (**C6**), 23.7 (**C1**), 23.3 (**C1**), 21.5 (**C21**), - 3.2, (**C5**), -3.2, (**C5**).

benzyl-[(E)-3,3-dimethyl-4-phenyl-4-[[4-(trifluoromethoxy)phenyl]methoxy]but-1-enyl]-dimethylsilane 216d



The title compound was prepared according to **General Procedure 3B** from **213b** (50 mg, 0.14 mmol) and dimethylbenzylsilane (0.034 mL, 0.22 mmol) using $PtCl_2$ (1 mg, 1.4 µmol) and XPhos (2 mg, 2.9 µmol) which following conversion to the vinyl silane and column chromatography afforded **216d** as a colourless oil (70 mg, 98%).

Rf (EtOAc:Heptane, 19:1): 0.64

IR υmax (cm-1): 3056, 3023, 2956, 2932

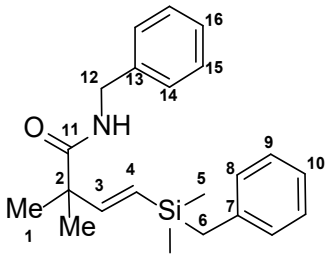
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{29}H_{34}F_3O_2Si$ 499.2280; Found 499.2285

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 5H, (**H$_{Aromatic}$**)), 7.23 – 7.16 (m, 6H, (**H$_{Aromatic}$**)), 7.09 – 7.04 (m, 1H, (**H$_{Aromatic}$**)), 6.99 – 6.92 (m, 2H, (**H19**)), 6.10 (d, *J* = 19.2 Hz, 1H, (**H3**)), 5.48 (d, *J* = 19.2 Hz, 1H, (**H4**)), 4.45 (d, *J* = 12.2 Hz, 1H, (**H16**)), 4.20 (d, *J* = 12.2 Hz, 1H, (**H16**)), 4.07 (s, 1H, (**H11**)), 2.12 (s, 2H, (**H6**)), 1.03 (s, 3H, (**H1**)), 1.01 (s, 3H, (**H1**)), 0.04 (s, 3H, (**H5**)), 0.04 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (**C3**), 148.5 (**C20**), 140.3 (**C7**), 138.9 (**C12**), 137.8 (**C17**), 128.8 (**C8** or **C9**), 128.7 (**C8** or **C9**), 128.4 (**C$_{Aromatic}$**), 128.2 (**C$_{Aromatic}$**), 127.6 (**C$_{Aromatic}$**), 127.6 (**C$_{Aromatic}$**), 124.5 (**C4**), 124.0 (**C10**), 120.9 (**C$_{Aromatic}$**), 120.5 (q, *J* = 256.7 Hz, (**C21**)), 88.8 (**C11**), 70.0 (**C16**), 43.4, (**C2**), 26.4, (**C6**), 23.8, (**C1**), 23.1 (**C1**), -3.2, (**C5**), -3.2 (**C5**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -57.85

(E)-N-benzyl-4-[benzyl(dimethyl)silyl]-2,2-dimethyl-but-3-enamide 216e



The title compound was prepared according to **General Procedure 3B** from **215** (50 mg, 0.25 mmol) and dimethylbenzylsilane (0.059 mL, 0.37 mmol) using $PtCl_2$ (1 mg, 2.5 µmol) and XPhos (2 mg, 5.0 µmol) which following conversion to the vinyl silane and column chromatography afforded **216e** as a colourless oil (81 mg, 93%).

Rf (EtOAc:Heptane, 19:1): 0.34

IR υmax (cm^{-1}): 3090, 3041, 3003, 2969, 2920

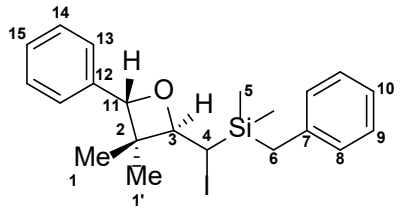
HRMS (ESI) m/z: [M+H]+ Calcd for $C_{22}H_{30}NOSi$ 352.2097; Found 352.2090

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H, (**H15**)), 7.29 – 7.24 (m, 1H, (**H16**)), 7.21 – 7.17 (m, 2H, (**H9**)), 7.15 – 7.10 (m, 2H, (**H15**)), 7.04 – 6.98 (m, 1H, (**H10**)), 6.95 – 6.91 (m, 2H, (**H8**)), 6.09 (d, *J* = 19.1 Hz, 1H (**H3**)), 5.79 (d, *J* = 19.1 Hz, 1H, (**H4**),), 5.74 (br s, 1H, (**NH**), 4.37 (d, *J* = 5.8 Hz, 2H, (**H12**)), 2.12 (s, 2H, (**H6**)), 1.28 (s, 6H, (**H1**)), 0.07 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (**C11**), 152.0 (**C3**), 139.9 (**C7**), 138.7 (**C13**), 128.8 (**C8**), 128.2 (**C9**), 127.5 (**C14**), 127.4 (**C4** or **C16**), 127.4 (**C4** or **C16**), 124.2 (**C10**), 47.1 (**C22**), 43.6 (**C12**), 26.1 (**C6**), 24.8 (**C1**), -3.2 (**C5**).

3.9.6 Synthesis of Oxetanes *via* Iodocyclisation of Vinyl Silanes and Further Diversifications

Benzyl-[(3,3-dimethyl-4-phenyl-oxetan-2-yl)-iodo-methyl]-dimethyl-silane 203a



The title compound was prepared according to **General Procedure 3C** from **202a** (50 mg, 0.15 mmol), NIS (52 mg, 0.25 mmol) and $NaHCO_3$ (26 mg, 0.3 mmol) which following conversion to product and column chromatography afforded **203a** as a colourless oil (60 mg, 87%).

Rf (Petrol:EtOAc 19:1): 0.52

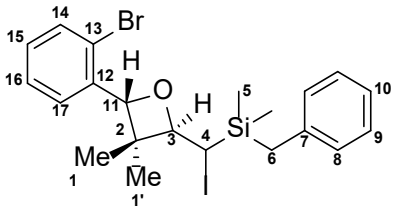
IR υmax (cm^{-1}) 3080, 3024, 2957, 2871, 1718, 1492

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{28}IOSi$ 451.0954; Found 451.0960

^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H, (**$H_{Aromatic}$**)), 7.26 – 7.20 (m, 4H, (**$H_{Aromatic}$**)), 7.16 – 7.09 (m, 3H, (**$H_{Aromatic}$**)), 6.99 (m, 1H, (**H10**)), 5.33 (s, 1H, (**H11**)), 4.86 (d, *J* = 12.1 Hz, 1H, (**H3**)), 3.23 (d, *J* = 12.1 Hz, 1H, (**H4**)), 2.52 (d, *J* = 13.7 Hz, 1H, (**H6**)), 2.43 (d, *J* = 13.7 Hz, 1H, (**H6**)), 1.48 (s, 3H, (**H1**)), 0.84 (s, 3H, (**H1'**)), 0.25 (s, 3H, (**H5**)), 0.24 (s, 3H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6 (**C7**), 139.4 (**C12**), 128.6 (**C8** or **C9**), 128.4 (**C8** or **C9**), 128.2 (**$C_{Aromatic}$**), 127.4 (**$C_{Aromatic}$**), 125.2 (**$C_{Aromatic}$**), 124.4 (**C10**), 87.8 (**C11** or **C3**), 87.8 (**C11** or **C3**), 46.1 (**C2**), 27.3 (**C6**), 25.5 (**C3**), 15.7 (**C1'**), 14.3 (**C1**), -2.8 (**C5**), -3.6 (**C5**)

benzyl-[[3,3-dimethyl-4-(2-bromophenyl)oxetan-2-yl]-iodo-methyl]-dimethyl-silane 203b



The title compound was prepared according to **General Procedure 3C** from **202b** (100 mg, 0.25 mmol), NIS (83 mg, 0.38 mmol) and $NaHCO_3$ (41 mg, 0.5 mmol) which following conversion to product and column chromatography afforded **203b** as a colourless oil (122 mg, 92%).

Note; Product highly prone to degradation

Rf (Petroleum Ether:EtOAc 19:1): 0.54

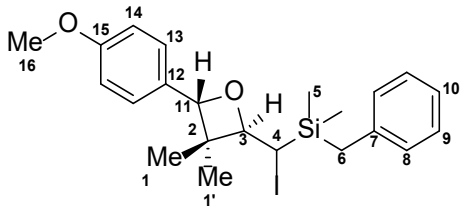
IR υmax (cm^{-1}) 3065, 3007, 2978, 2863, 1725

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{27}IBrOSi$ 529.0059; Found 529.0032

^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (ddd, *J* = 7.4, 3.1, 1.3 Hz, 2H, (**H14** & **H16**), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H, (**H15**)), 7.26 (m, 2H, ($\mathbf{H_{Aromatic}}$)), 7.18 – 7.11 (m, 4H, ($\mathbf{H_{Aromatic}}$)), 5.60 (s, 1H, (**H11**)), 4.87 (d, *J* = 12.1 Hz, 1H, (**H3**)), 3.22 (d, *J* = 12.1 Hz, 1H, (**H4**)), 2.51 (d, *J* = 13.7 Hz, 1H, (**H6**)), 2.40 (d, *J* = 13.7 Hz, 1H, (**H6**)), 1.70 (s, 3H, (**H1**)), 0.91 (s, 3H, (**H1'**)), 0.26 (d, *J* = 3.6 Hz, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5 (**C7** or **C12**), 139.5 (**C7** or **C13**), 132.3 (**C14**), 128.8 (**C8** or **C9**), 128.6 (**C8** or **C9**), 128.5 ($\mathbf{C_{Aromatic}}$), 128.2 ($\mathbf{C_{Aromatic}}$), 127.3 ($\mathbf{C_{Aromatic}}$), 124.5 (**C10**), 121.0 (**C13**), 87.6 (**C3** or **C11**), 87.1 (**C3** or **C11**), 46.2 (**C2**), 28.2 (**C6**), 25.4 (**C4**), 15.6 (**C1**), 14.2 (**C1'**), -2.8 (**C5**), -3.3 (**C5**).

benzyl-[[3,3-dimethyl-4-(4-methoxyphenyl)oxetan-2-yl]-iodo-methyl]-dimethyl-silane 203c



The title compound was prepared according to **General Procedure 3C** from **202d** (40 mg, 0.11 mmol), NIS (38 mg, 0.17 mmol) and $NaHCO_3$ (19 mg, 0.22 mmol) which following conversion to product and column chromatography afforded **203c** as a pale-yellow oil (45 mg, 83%).

Rf (Petrol:EtOAc 19:1): 0.42

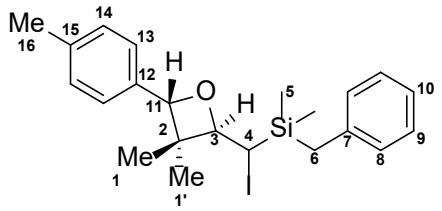
IR υmax (cm^{-1}) 2955, 2871, 2834, 1669, 1601

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{22}H_{30}IO_2Si$ 481.1060; Found 481.1055

^1H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.16 (m, 2H, (**$H_{Aromatic}$**)), 7.16 – 7.07 (m, 5H, (**$H_{Aromatic}$**)), 6.87 (d, *J* = 8.7 Hz, 2H, (**H14**)), 5.25 (s, 1H, (**H11**)), 4.81 (d, *J* = 12.1 Hz, 1H, (**H3**)), 3.80 (s, 3H, (**H16**)), 3.21 (d, *J* = 12.1 Hz, 1H, (**H4**)), 2.49 (d, *J* = 13.9 Hz, 1H, (**H6**)), 2.41 (d, *J* = 13.9 Hz, 1H, (**H6**)), 1.43 (s, 3H, (**H1**)), 0.82 (s, 3H, (**H1'**)), 0.22 (s, 6H, (**H5**)).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (**C15**), 139.6 (**C7**), 131.5, 128.6 (**C8** or **C9**), 128.4 (**C8** or **C9**), 126.6, 124.4 (**C10**), 113.6, 87.8 (**C3** or **C11**), 87.7 (**C3** or **C11**), 55.4 (**C16**), 46.1 (**C2**), 27.3 (**C6**), 25.5 (**C4**), 15.7 (**C1'**), 14.5 (**C1**), -2.8 (**C5**), -3.5 (**C5**).

benzyl-[[3,3-dimethyl-4-(4-methylphenyl)oxetan-2-yl]-iodo-methyl]-dimethyl-silane 203d



The title compound was prepared according to **General Procedure 3C** from **202e** (50 mg, 0.15 mmol), NIS (50 mg, 0.23 mmol) and $NaHCO_3$ (25 mg, 0.3 mmol) which following conversion to product and column chromatography afforded **203d** as a colourless oil (59 mg, 86%).

Rf (Petrol:EtOAc 19:1): 0.56

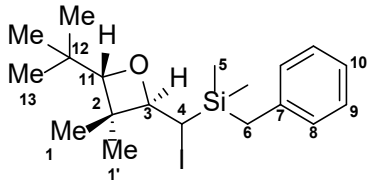
IR υmax (cm^{-1}) 3022, 2957, 2870, 1675, 1599

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{22}H_{30}IOSi$ 465.1111; Found 465.1116

^1H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H, (**$H_{Aromatic}$**)), 7.15 – 7.07 (m, 7H, (**$H_{Aromatic}$**), 5.28 (s, 1H, (**H11b)**), 4.82 (d, *J* = 12.1 Hz, 1H, (**H3**)), 3.21 (d, *J* = 12.1 Hz, 1H, (**H4**)), 2.52 (d, *J* = 13.7 Hz, 1H, (**H6**)), 2.42 (d, *J* = 13.7 Hz, 1H, (**H6**)), 2.34 (s, 3H, (**H16**)), 1.44 (s, 3H, (**H1**)), 0.82 (s, 3H, (**H1'**)), 0.22 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (**C7**), 137.1 (**C15**), 136.3 (**C12**), 128.9 (**C14**), 128.6 (**C8** or **C9**), 128.4 (**C8** or **C9**), 125.2 (**C13**), 124.4 (**C10**), 87.9 (**C3** or **C11**), 87.7 (**C3** or **C11**), 46.0 (**C2**), 27.3 (**C6**), 25.5 (**C4**), 21.3 (**C16**), 15.7 (**C1'**), 14.5 (**C1**), -2.8 (**C5**), -3.6 (**C5**).

benzyl-[(4-tert-butyl-3,3-dimethyl-oxetan-2-yl)-iodo-methyl]-dimethyl-silane 203e



The title compound was prepared according to **General Procedure 3C** from **202f** (50 mg, 0.16 mmol), NIS (55 mg, 0.24 mmol) and $NaHCO_3$ (28 mg, 0.32 mmol) which following conversion to product and column chromatography afforded **203e** as a colourless oil (62 mg, 88%).

Rf (Petrol:EtOAc 19:1): 0.63

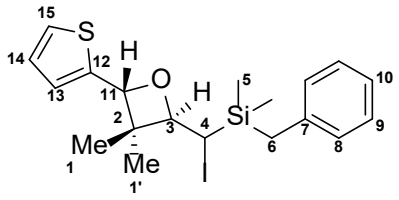
IR υmax (cm^{-1}) 3040, 3018, 2849, 1601,1489

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{32}IOSi$ 431.1267; Found 431.1264

^1H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H, (**H9**)), 7.13 – 7.04 (m, 3H, (**H8** & **H10**)), 4.57 (d, *J* = 12.0 Hz, 1H, (**H3**)), 3.87 (s, 1H, (**H11**)), 3.17 (d, *J* = 12.0 Hz, 1H, (**H4**)), 2.41 (d, *J* = 13.7 Hz, 1H, (**H6**)), 2.34 (d, *J* = 13.7 Hz, 1H, (**H6**)), 1.33 (s, 3H, (**H1**)), 1.31 (s, 3H, (**H1'**)), 0.93 (s, 9H, (**H13**)), 0.15 (s, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9 (**C7**), 128.6 (**C8** or **C9**), 128.3 (**C8** or **C9**), 124.3 (**C10**), 94.2 (**C11**), 87.1 (**C3**), 46.1 (**C2**), 34.7 (**C12**), 29.6 (**C6**), 26.2 (**C13**), 25.5 (**C4**), 15.6 (**C1**), 14.7 (**C1'**), -2.7 (**C5**), -3.7 (**C5**).

benzyl-[[3,3-dimethyl-4-(2-thienyl)oxetan-2-yl]-iodo-methyl]-dimethyl-silane 203f



The title compound was prepared according to **General Procedure 3C** from **203g** (50 mg, 0.15 mmol), NIS (51 mg, 0.23 mmol) and $NaHCO_3$ (25 mg, 0.3 mmol) which following conversion to product and column chromatography afforded **203f** as a yellow oil (48 mg, 70%).

Rf (Petrol:EtOAc 19:1): 0.57

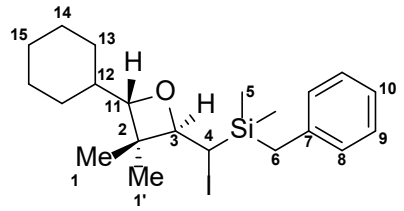
IR υmax (cm^{-1}) 3078, 3022, 2957, 2870, 1653, 1599

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{26}IOSSi$ 457.0518; Found 457.0512

^1H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 4H, (**$H_{Aromatic}$**)), 7.11 (m, 3H, (**$H_{Aromatic}$**)), 7.04 – 6.97 (m, 1H, (**H13**)), 6.88 (d, *J* = 3.2 Hz, 1H, (**H14**)), 5.47 (s, 1 H, (**H11**)), 4.78 (d, *J* = 12.1 Hz, 1H, (**H3**)), 3.27 (d, *J* = 12.1 Hz, 1H, (**H4**)), 2.46 (d, *J* = 13.6 Hz, 1H, (**H6**)), 2.40 (d, *J* = 13.6 Hz, 1H, (**H6**)), 1.42 (s, 3H, (**H1**)), 1.01 (s, 3H, (**H1'**)), 0.20 (s, 6H, (**H5**)).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 (**C12**), 139.6 (**C7**), 128.6 (**C8** or **C9**), 128.4 (**C8** or **C9**), 127.0 (**C15**), 124.9 (**C14**), 124.4 (**C10**), 123.9 (**C13**), 88.1 (**C11**), 85.2 (**C3**), 46.6 (**C2**), 27.3 (**C6**), 25.5 (**C4**), 15.7 (**C1**), 14.5 (**C1'**), -2.7 (**C5**), -3.6 (**C5**).

benzyl-[(4-cyclohexyl-3,3-dimethyl-oxetan-2-yl)-iodo-methyl]-dimethyl-silane 203g



The title compound was prepared according to **General Procedure 3C** from **202h** (50 mg, 0.15 mmol), NIS (51 mg, 0.23 mmol) and $NaHCO_3$ (25 mg, 0.3 mmol) which following conversion to product and column chromatography afforded **203g** as a colourless oil (56 mg, 81%).

Rf (Petrol:EtOAc 19:1): 0.65

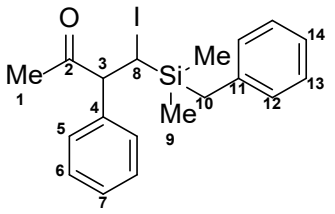
IR υmax (cm^{-1}) 3058, 3022, 2934, 1599, 1492

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{21}H_{34}IOSi$ 457.1424; Found 457.1421

^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 2H, (**H9**)), 7.13 – 7.05 (m, 3H, (**H8** & **H10**)), 4.55 (d, *J* = 12.0 Hz, 1H, (**H3**)), 3.78 (d, *J* = 10.3 Hz, 1H, (**H11**)), 3.08 (d, *J* = 12.0 Hz, 1H, (**H4**)), 2.38 (d, *J* = 13.5 Hz, 1H, (**H6**)), 2.31 (d, *J* = 13.5 Hz, 1H, (**H6**)), 1.90 – 1.58 (m, 5H, (**H$_{Cyclohexyl}$**)), 1.46 (d, *J* = 14.0 Hz, 1H), 1.27 (s, 3H, (**H1**)), 1.22 (s, 3H, (**H1'**)), 1.21 – 1.10 (m, 2H, (**H$_{Cyclohexyl}$**)), 0.92 – 0.77 (m, 3H, (**H$_{Cyclohexyl}$**)), 0.14 (d, *J* = 4.7 Hz, 6H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8 (**C7**), 128.5 (**C8** or **C9**), 128.2 (**C8** or **C9**), 124.1 (**C10**), 90.8 (**C11**), 86.8 (**C3**), 43.5 (**C2**), 39.8 (**C$_{Cyclohexyl}$**), 28.6 (**C$_{Cyclohexyl}$**), 28.0 (**C$_{Cyclohexyl}$**), 27.6 (**C6**), 26.6, 25.5 (**C3** or **C$_{Cyclohexyl}$**), 25.5 (**C3** or **C$_{Cyclohexyl}$**), 25.3 (**C$_{Cyclohexyl}$**), 14.4 (**C1**), 13.9 (**C1'**), -2.6 (**C5**), -4.3 (**C5**).

4-[benzyl(dimethyl)silyl]-4-iodo-3-phenyl-butan-2-one 221



Allylic alcohol **220** was prepared according to literature procedure.[25] The title compound was prepared according to **General Procedure 3C** from **220** (50 mg, 0.17 mmol), NIS (56 mg, 0.25 mmol) and $NaHCO_3$ (28 mg, 0.34 mmol) which following conversion to product and column chromatography afforded **221** as a colourless oil (62 mg, 86%).

Rf (Petroleum Ether:EtOAc 19:1): 0.57

IR υmax (cm^{-1}) 3034, 2953, 2910, 1744

HRMS (ESI) m/z: [M+H]+ Calcd for $C_{19}H_{24}IOSi$ 423.0461; Found 423.0460

^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 3H, (**H13** & **H14**)), 7.22 – 7.17 (m, 2H, (**H8**)), 7.15 – 7.11 (m, 2H, (**H12**)), 7.11 – 7.05 (m, 1H, (**H7**)), 6.95 – 6.91 (m, 2H, (**H5**)), 4.27 (d, *J* = 12.3 Hz, 1H, (**H3**)), 4.03 (d, *J* = 12.3 Hz, 1H, (**H4**)), 2.13 (s, 3H, (**H1**)), 2.08 (d, *J* = 13.7 Hz, 1H, (**H10**)), 1.83 (d, *J* = 13.7 Hz, 1H, (**H10**)), -0.24 (s, 3H, (**H9**)), -0.26 (s, 3H, (**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4 (**C2**), 139.4 (**C11**), 137.2 (**C4**), 129.3 (**C6**), 129.0 (**C5**), 128.8 (**C7**), 128.5 (**C12** or **C13**), 128.4 (**C12** or **C13**), 124.5 (**C14**), 64.3 (**C3**), 29.7 (**C1**), 25.1 (**C10**), 18.9 (**C8**), -2.8 (**C9**), -3.0 (**C9**).

Chapter 4: Studies on the viability of Platinum Catalysed Hydrostannylation of Alkynes

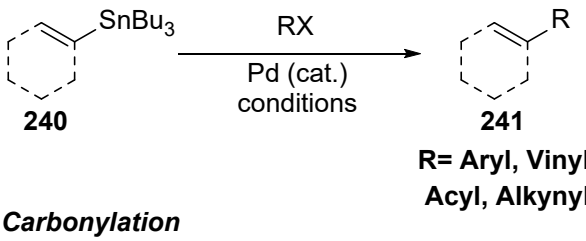
The work detailed in this section has been published in part as: D. D. Roberts and M. G. McLaughlin, *Adv. Synth. Cat.*, 2023, **365**, 1602-1606.[144] Additionally, sections of the introduction also feature in the following review article: D. D. Roberts and M. G. McLaughlin, *Eur. J. Org. Chem.*, 2023, **26**, e202300755.[145]

4.1 Introduction

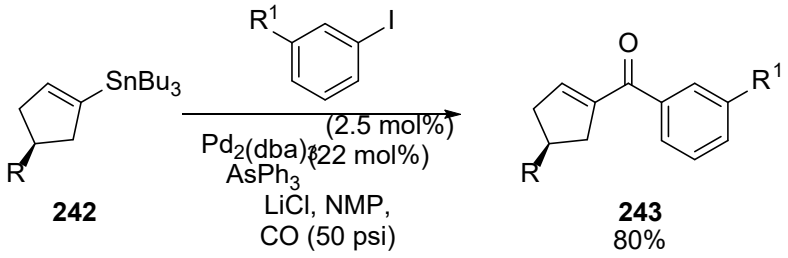
4.1.1 Organostannanes in Organic Synthesis

Organostannanes are a fundamental class of reagents in organic chemistry. In particular, vinyl stannanes are particularly commonplace due to their prevalence in the Stille cross-coupling, one of the most frequently employed methods to form carbon-carbon bonds.[3,146,147] Typically, the reaction is employed to form C(sp^2)-C(sp^2) bonds, although examples of the reaction to assemble other types of carbon-carbon bond have been reported, including C(sp^2)-C(sp^3) and C(sp^2)-C(sp).[148-150] Of particular note with the Stille reaction is its efficacy when acyl halides are employed as electrophiles, allowing for facile construction of ketones.[151] This same construction of ketones can also be realised by carrying out the coupling of two non-acyl components under an atmosphere of carbon monoxide, a transformation utilised to excellent effect in the synthesis of **243**, a key intermediate in the Overman synthesis of strychnine (**Scheme 89**).[152]

Classical Stille Coupling



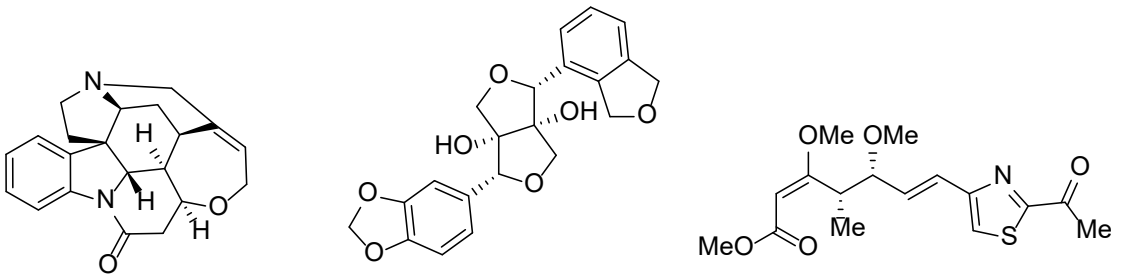
Stille Carbonylation



Scheme 89 General Stille cross-coupling reaction & Stille-Carbonylation

In comparison to other cross-couplings the Stille coupling possesses several key benefits and limitations. Organostannanes are relatively air and moisture stable in comparison to other nucleophilic coupling partners such as organozinc compounds and Grignard reagents. Additionally in comparison to cross-couplings such as the Suzuki[1] and Hiyama[2] cross-couplings which employ

organoboranes and organosilanes as nucleophilic components respectively, the Stille coupling is comparatively tolerant of more complex molecules due to the midler conditions at which these reactions typically occur and the lack of metalloid preactivation required, versus the aforementioned reagents which require basic conditions or treatment with a fluoride source. This has resulted in the application of the Stille reaction in the synthesis of a variety of complex natural products such as the aforementioned Overman strychnine (**244**) synthesis as well as the synthesis of Wodeshiol (**245**) and Melithiazole C (**246**) by the Corey and Cossey groups respectively (**Figure 9**).[153,154] The toxicity concerns associated with organotin compounds is perhaps the most notable drawback of the reaction. Although the toxicity of the tetraorganotin compounds frequently employed in Stille couplings is often exaggerated (LD_{50}~200 mg kg^{-1}), the potential for tin contamination of products cannot be ignored.[155] Additional limitations, as with the majority of cross-coupling reactions, is the frequent use of palladium based catalysts- palladium being a highly expensive and non-abundant metal. To circumvent this significant progress has been made in the area of non-palladium catalysed Stille couplings, with manganese,[156] copper[157] and nickel[158] having all been successfully used for this purpose.

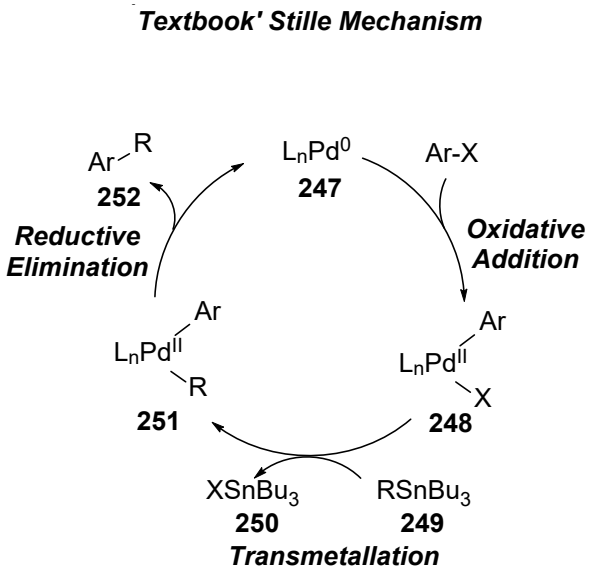


244 ***Strychnine*** **245** ***Wodeshiol*** **246** ***Melithiazole C***

Figure 9 Natural products synthesised by application of the Stille reaction

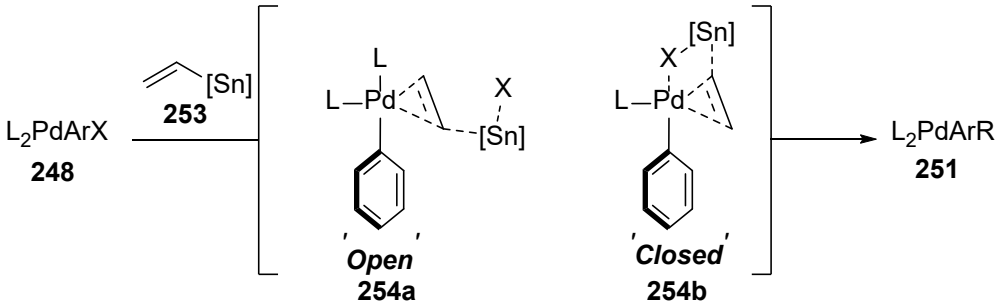
Mechanistically, the Stille coupling follows the classical Pd cross-coupling catalytic cycle, with a simplified version shown in **Scheme 90** being the mechanism initially proposed by Stille in 1986.[159] In this 'textbook' mechanism, a Pd^0 species undergoes oxidative addition an aryl halide/pseudohalide. Subsequent tin-palladium transmetallation affords palladium complex **251**, which

can subsequently undergo reductive elimination to afford cross coupled product **252** and regenerate the active catalytic species **247**. In reality, the mechanism is much more complex, with particular debate about the manner in which the transmetallation occurs.



Scheme 90 The 'textbook' Stille coupling mechanism

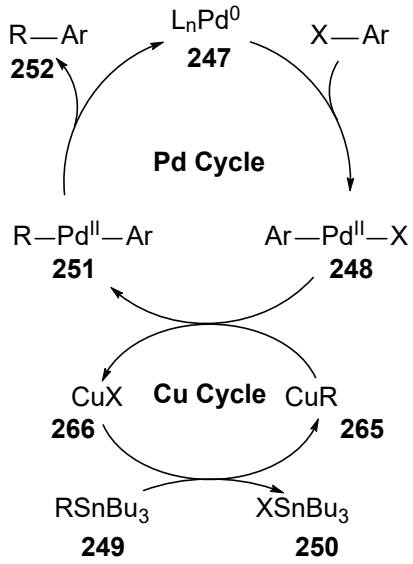
As the transmetallation can occur with either retention or inversion of stereochemistry at the carbon centre, multiple mechanisms exist to rationalise this observation. For cases where stereochemistry is retained, the transmetallation is proposed to proceed *via* a 'closed' transition state **254b**, as shown in **Scheme 91**.[160] For cases of stereochemical inversion, the 'open' transition state **254a** is proposed and it is believed that this is the mechanism through which most reactions proceed, particularly in the case of highly electrophilic Pd centres such as those bearing weakly coordinating ligands such as the triflate ligand which is readily displaced by solvent molecules with coordinative ability such as THF, DMF and acetonitrile.[161]



Scheme 91 'Open' and 'Closed' transmetallation transition states

While organostannanes do not require preactivation to facilitate their transmetallation as is the case with organoboranes and organosilanes, copper additives are frequently employed to increase the rate of the cross-coupling. The rate increasing effect of copper additives in Stille couplings is well known with the mechanism through which the rate enhancement operates dependent on the nature of the reaction solvent. This solvent dependent rate enhancement was studied by Liebeskind and co-workers in their 1984 study on the 'copper-effect' [162]

This study showed that in polar solvents such as NMP and DMF, the addition of copper salts facilities a transmetallation from tin to copper, forming organocuprate **265** which possesses a much faster rate of transmetallation to palladium than the parent organostannanes (**Scheme 92**). In less polar solvents such as THF, the rate enhancement still exists but is driven predominantly by the copper acting as a scavenger for free ligands in solution which are known to inhibit the rate-determining transmetallation *via* occupation of coordination sites on the catalyst.[163]

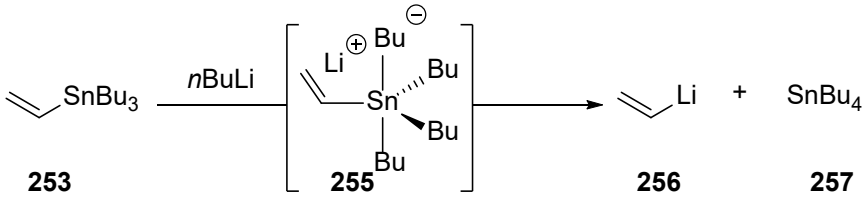


Scheme 92 Mechanism of the 'copper effect'

The synthetic utility of organostannanes is not limited to reagents for cross-coupling however, as they find frequent application in lithium/tin exchange reactions to access carbanion equivalents. The metalation, which proceeds through 'ate' complexes such as **255** (**Scheme 93**), is facile enough to be carried out at relatively mild conditions and possesses several advantages over the more frequently employed lithium halogen exchange.

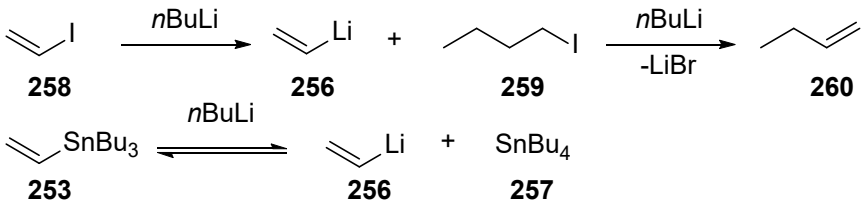
Firstly, the equivalents of organolithium required to metalate the stannane is lowered, as sequestering of the organometallic by elimination of the alkyl iodide **259** formed *in-situ* is not an issue when stannanes are employed, although this does mean the metalation cannot be rendered irreversible. As halides are very good leaving groups, this limits the ability for the utilisation of these substrates in compounds containing nucleophilic components (**261** and **263**) due to instability of the requisite starting material, an issue mitigated in the case of the corresponding organostannane. This is well exemplified by the synthesis of α-aminoalkyllithium **262** and α-alkoxylithium **264** by Peterson and Seebach respectively.[164,165]

Tin-Lithium Exchange Mechanism



253 **255** **256** **257**

Non Degradable Side Products



258 **256** **259** **260**

253 **256** **257**

Access to Anion Equivalents with Neighbouring Nucleophiles

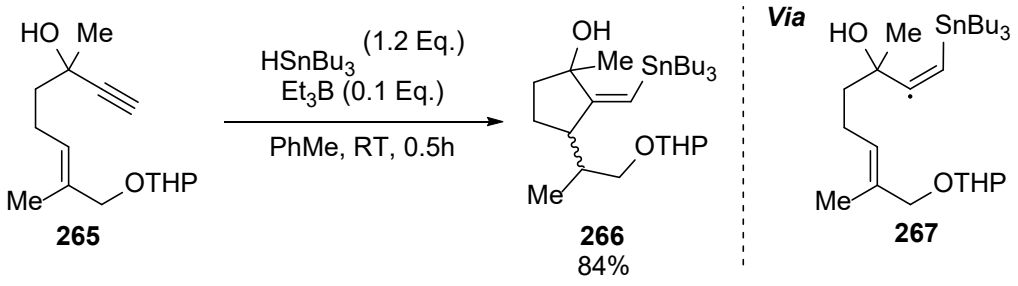
261 (M=$SnBu_3$)
262 (M=Li)

263 (M=$SnBu_3$, R=H)
264 (M=Li, R=Li)

Scheme 93 Lithium-tin exchange mechanism and benefits versus lithium-halogen exchange

4.1.2 Catalytic Alkyne Hydrostannylation

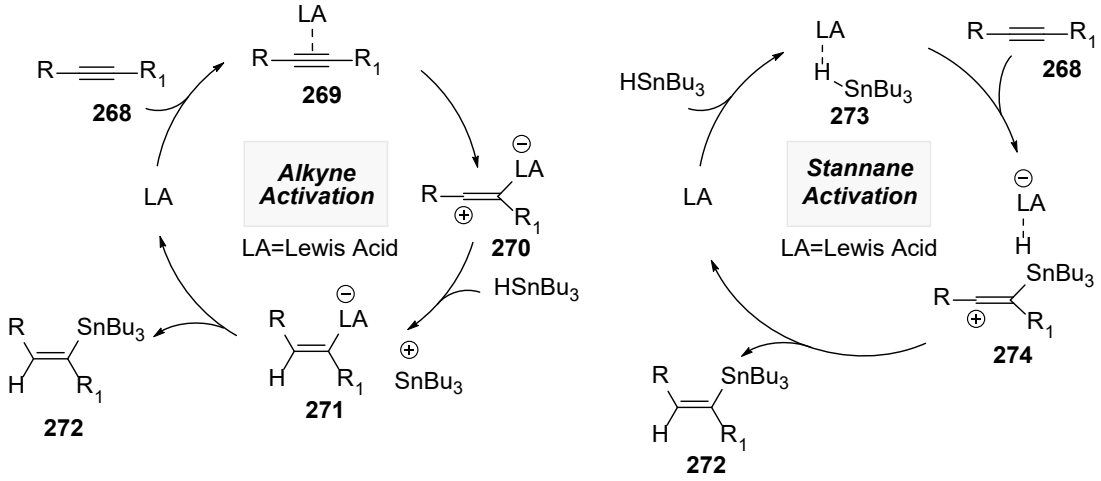
Given the rich synthetic chemistry displayed by organotin compounds discussed in **Chapter 4.1.1**, it is of no surprise that a plethora of methods have been developed to access the scaffold. One of the principal approaches to the synthesis of alkenyl stannanes is the hydrostannylation of an alkyne. While this can be achieved under radical conditions, typically the reaction is carried out in the presence of a catalyst to allow greater levels of selectivity in the reaction while also mitigating the issue of unwanted side reactions occurring due to the presence of the transient reactive radical intermediates. The issue of competing reactions arising from radical intermediates is illustrated by Uchimoto and co-workers wherein the hydrostannylation of alkyne **265** using Et_3B as a radical initiator resulted in the formation of stannane **266** *via* 5-exo-trig cyclisation due to the presence of intermediary radical species **267**.[166]



Scheme 94 Potential side reactions arising from radical hydrostannylation of alkynes

Two distinct approaches have been utilised in the catalytic hydrostannylation of alkynes; processes catalysed by Lewis acids and processes catalysed by transition metals. Lewis acids that have been shown to be suitable for this transformation have included magnesium complexes, as reported by Rueping and co-workers, zirconium chloride as reported by Yamamoto *et al* as well as metal-free methods employing the trityl cation as reported by Oestreich.[16, 167, 168] These processes typically operate *via* formation of a vinyl cation **270**/**274** either by direct catalyst-alkyne interaction (**269**) or by hydride abstraction from the stannane (**273**). In either case, the stereoelectronic requirements of the reduction of the intermediate cation results in an unusual *trans*-hydrometallation with the *Z*-vinyl stannane formed preferentially, though isomerisation of the stannanes to

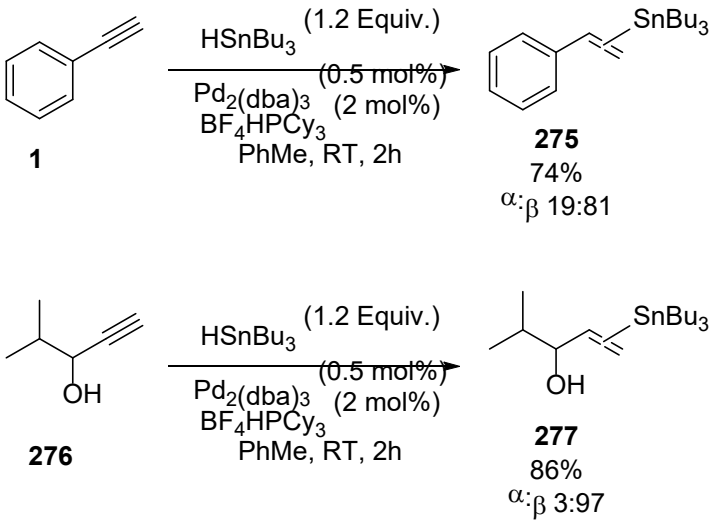
the more thermodynamically stable *E*-isomer *via* Lewis acid catalysis was reported by Rueping.[169]



Scheme 95 Lewis acid catalysed hydrostannylation mechanism

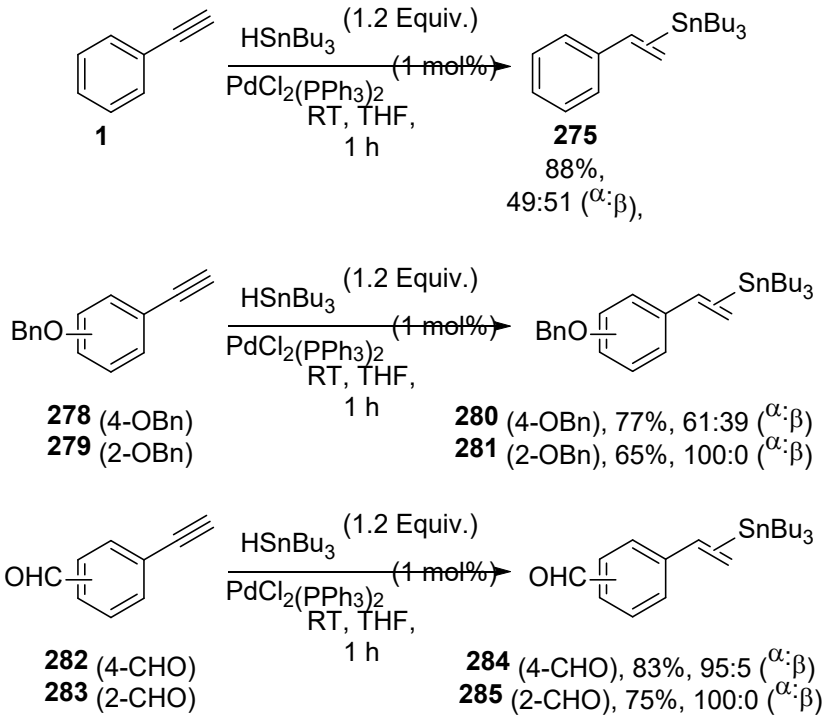
Transition metal catalysis remains the most well utilised approach in the hydrostannylation of alkynes, with palladium being the most frequently employed metal for this purpose. This is due to the largely predictable *syn* delivery of the metal hydride to the alkyne resulting in predictable stereochemical outcomes for the reaction.[170]

Control over the regioselectivity of the reaction has proven more challenging, particularly when substrates which do not provide a steric or electronic bias. This is well demonstrated by the work reported by Chong and co-workers wherein selective application of phosphine ligands in combination with palladium precatalysts allows particularly high levels of selectivity for the *E*-vinyl stannane to be achieved. The reaction selectivity is highly dependent on ligand choice, with more sterically encumbered phosphines providing much higher levels of regioselectivity. Notably however, the selectivity for the reaction is significantly diminished when **1** is employed as a substrate, with a 19:81 mixture of regioisomers formed. In comparison, when the more sterically encumbered alcohol **276** was employed, the selectivity increased to 3:97 (**Scheme 96**).[171]



Scheme 96 Ligand effects in stereo and regiocontrolled hydrostannylation

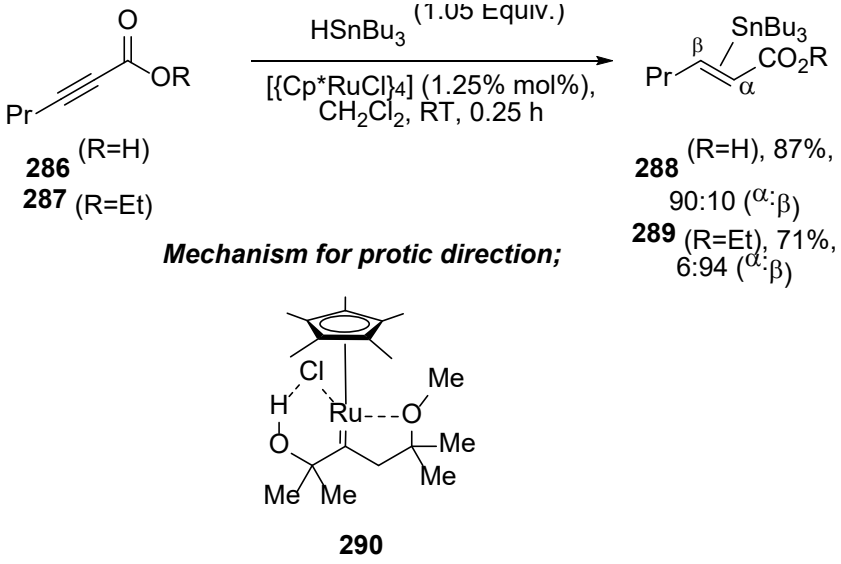
Unsurprisingly the nature of the substrate is also central to the selectivity which can be achieved *via* transition metal catalysed hydrostannylation. For example, Alami and co-workers described unusual Markovnikov hydrostannylation of *ortho*-substituted phenyl acetylene derivatives facilitated by an unusual ortho directing effect of groups not traditionally thought of as directing groups, including methyl groups, cyano groups and halides. This was proven to arise from an *ortho*-directing effect (ODE) rather than an electronic bias within the substrate, as the same groups placed in the *para* position of the substrate do not induce the formation of the same isomer as can by seen by the difference in hydrostannylation selectivity between **278** and **279**. Additionally, when the alkyne is heavily polarised by introduction of a strong electron withdrawing group at the *para* (**282**) or *ortho* (**283**) position of the ring, the α-isomer is again preferentially formed.[172, 173]



Scheme 97 Influence of substrate nature on palladium catalysed hydrostannylation selectivity

The influence of heteroatom containing functionalities on the selectivity of ruthenium catalysed hydrostannylation was reported by Fürstner and co-workers wherein the differing influence between protic and non-protic functionalities were explored. This influence was noted in the study on the hydrostannylation of alkynes under ruthenium catalysis, and it should be noted that as in the case of the analogous hydrosilylation process, ruthenium mediated hydrostannylation proceeds through a unique *trans*-delivery of the metal hydride, unlike the more typical *syn* delivery.[31,174] The work by Fürstner and co-workers describes the switch in regioselectivity between the hydrostannylation of **286** and **287** which only differ by the presence of a protic functionality. This is holds true for other hydrometallations and hydrogenations as was disclosed in a subsequent report by the same group which also disclosed the origin of the regiodivergency. By isolation of carbene complex **290** and SCXRD analysis, intramolecular hydrogen bonding is shown to exist between the protic hydroxyl group and the halide ligand of the catalyst, allowing the hydroxyl group to direct the selectivity of the ruthenium delivery. The presence of the methoxy group within the complex also serves to demonstrate that this simply with the metal centre in a traditional Lewis acid/base interaction.[175,176] This protic interaction is not present when

hydrostannylation of hydroxyl containing substrates is carried out under palladium catalysis, with numerous studies ruling out the possibility of interactions between hydroxyl groups and the catalyst. In these cases, steric factors are the determining factor in reaction selectivity.[171, 177]

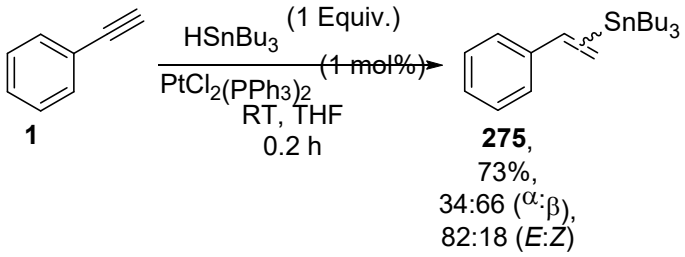


Scheme 98 Protic versus non-protic substrates in ruthenium controlled hydrostannylation

Palladium represents by far the most well studied metal centre for the catalytic hydrostannylation of alkynes, with molybdenum and ruthenium also having been the subject of numerous reports.[178] The application of catalysts based on first row transition metals has blossomed in recent years, with catalysts bearing iron, copper and manganese all being recently disclosed.[15,179] While still relatively underdeveloped in comparison to later catalysts based on late transition metals, these next generation catalysts represent significant progress in the effort to making this transformation more environmentally benign and fundamentally 'greener.'

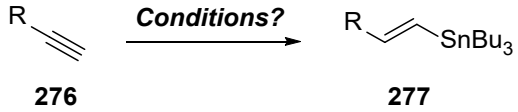
It is perhaps surprising, given the prevalence of platinum in hydrosilylation reactions, that a study on the activity of platinum catalysts for the purpose of hydrostannylation has not yet been reported. A single entry from a systematic screening of metal salts in 1988 by Kiyoshi and co-workers appears to be the only report of such a reaction.[180]

In this case, the authors reported the hydrostannylation of phenylacetylene **1** using $PtCl_2(PPh_3)$ at a loading of 1 mol% which afforded **275** as a 34:66 mixture of regioisomers after 30 minutes. The stereoselectivity of the reaction was also somewhat poor, with **275β** formed as a 82:12 mixture of *E:Z* isomers (**Scheme 99**). As the selectivity increasing effect of Buchwald type ligands is known for the analogous hydrosilylation process, it was believed that this represented an excellent opportunity to study the efficacy of platinum complexes of this type in the context of hydrostannylation.



Scheme 99 Poor selectivity in the single report of platinum catalysed hydrostannylation

4.2 Aims



276 277

Project Aims
- *Access Necessary Starting Materials*
- *Validate Pt as a hydrostannylation catalyst*
- *Explore Ligand Influence*
- *Investigate Substrate Scope*
- *Derivatise Products*

Scheme 100 Generalised chapter 4 aims

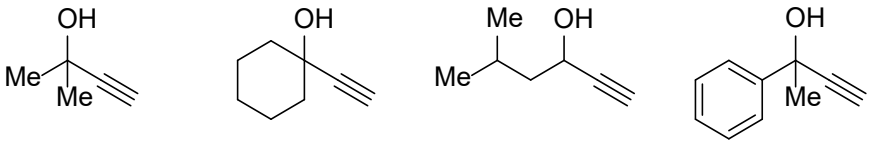
As discussed in **Chapter 4.1**, as a result of the rich synthetic utility of vinyl stannanes, a plethora of methods to access these compounds have been developed. These methods in general employ transition metal catalysts to allow high levels of control over the delivery of the tin hydride to the alkyne. Despite the popularity of platinum based hydrosilylation catalysts, there has been almost no reports of platinum being utilised as a catalyst for the hydrostannylation of alkynes.

The work in this chapter aims to explore the viability of platinum catalysed hydrostannylation of terminal alkynes. A range of alkynes bearing diverse substituents will first be synthesised, providing access to the requisite starting materials. Following this, the competence of platinum complexes as hydrostannylation catalysts will next be validated, with particular focus paid to exploring the effect of modifying the catalysts coordination sphere on both catalyst activity and reaction selectivity.

Subsequently, a robust set of optimised conditions will be established which will then be used to explore the scope of this hydrometallation, establishing both its benefits and limitations in comparison to other more frequently employed palladium catalyst systems. Finally, the application of the stannylated products will be explored, with the utility of the products in a telescoped hydrometallation/cross-coupling sequence being central to the envisaged applications. This will provide a method to access functionalised stereodefined olefins whilst minimising handling of potentially toxic or unstable stannylated intermediates

4.3 Starting Material Synthesis

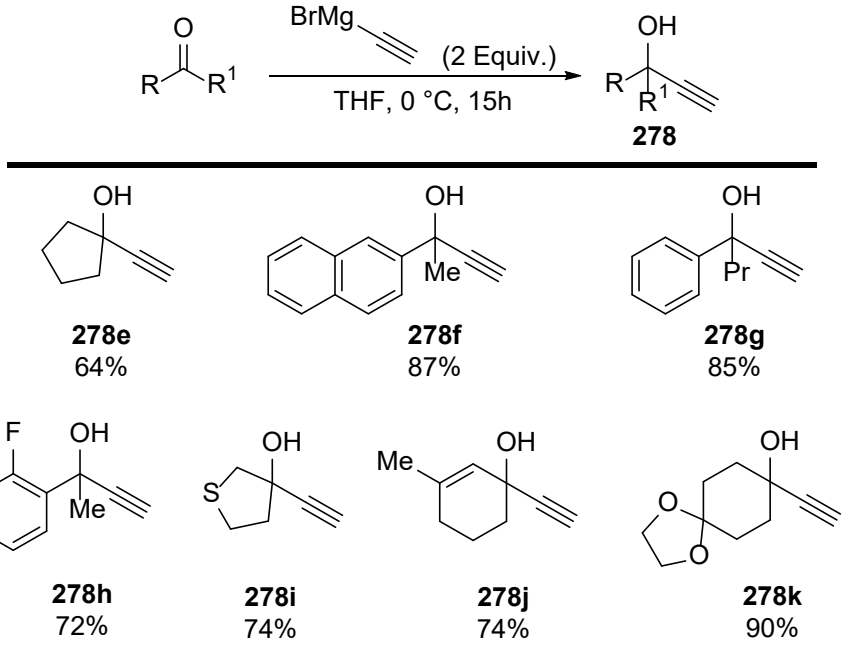
Propargylic alcohols were selected as the first class of substrates to be examined as it was envisaged that the presence of a polar handle in the molecule would facilitate easier purification of the otherwise extremely non-polar stannanes *via* silica gel chromatography. Alcohols **278a**-**278d** were commercially available, and therefore purchased and used as received.



278a **278b** **278c** **278d**

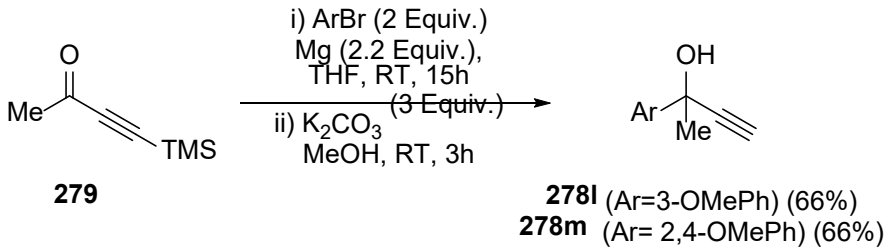
Figure 10 Alcohols purchased from commercial sources

Propargyl alcohols were readily accessed *via* addition of ethynyl magnesium bromide to ketones as shown in **Scheme 101.** This approach was chosen over the previously utilised lithium trimethylsilylacetylide as it removes the need for a secondary deprotection step. Using this approach, a range of propargylic alcohols were afforded, including heterocyclic substrates **278i** and **278k**. While there had been concern that utilisation of 3-methylcyclohexeneone to access allyl alcohol **278j** could result in a mixture of 1,2- and 1,4- addition products, **278j** was afforded in 74% yield. While the approach proved extremely general, it was noted that utilisation 2,4,6-trimethylacetophenone as an electrophile was not viable, with no formation of the desired product observed. This is presumably due to the sterically encumbered nature of the mesityl group blocking any approach from the incoming nucleophile.



Scheme 101 Scope of alcohols synthesised by alkyne addition to ketones

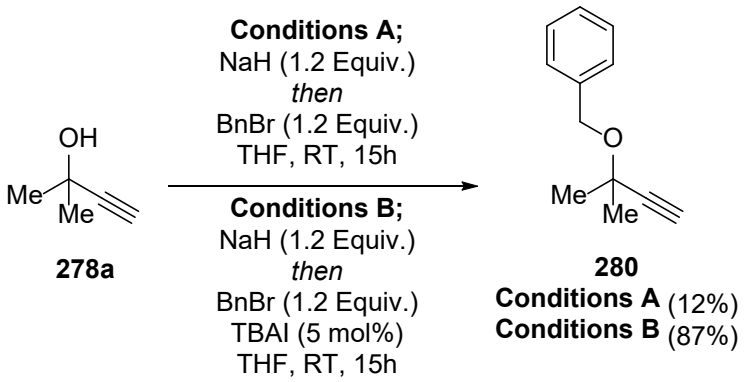
To access alcohols **278l** and **278m** bearing aryl ethers, a different route was chosen due to the more readily available nature of aryl halides in comparison to functionalised acetophenone derivatives. The corresponding Grignard reagents derived from 3-methoxybromobenzene and 2,4-dimethoxybromobenzene were readily trapped with 4-(trimethylsilyl)-3-butyn-2-one to afford the corresponding TMS protected alkynol which underwent facile methanolysis under basic conditions to afford both alkynols in 66% yield.



Scheme 102 Alcohols synthesised by aryl Grignard addition to ynone 279

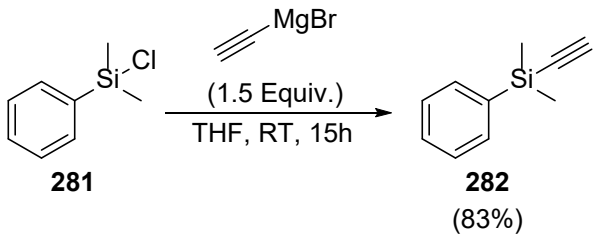
The synthesis of benzyl ether **280** from alcohol **278a** was next targeted. This substrate was prepared as a probe to investigate whether the presence of a hydrogen bond donor is required in the propargylic position, as previous reports into platinum catalysed hydrosilylations of propargylic alcohols have invoked the potential of a H-Bonding interaction between the proton of the hydroxyl group and

the hydride of the intermediary Pt π-Complex, as well as the aforementioned effect of protic functionalities on the selectivity of ruthenium catalysed hydrostannylations.[25,175] The benzylation of **278a** was initially attempted *via* initial deprotonation with sodium hydride in THF, with subsequent trapping of the alkoxide with benzyl bromide. This attempt however led to very poor isolated yield of **280**. This yield was dramatically improved upon the addition of tetrabutylammonium iodide (TBAI) to the reaction, with **280** isolated in an 87% yield.



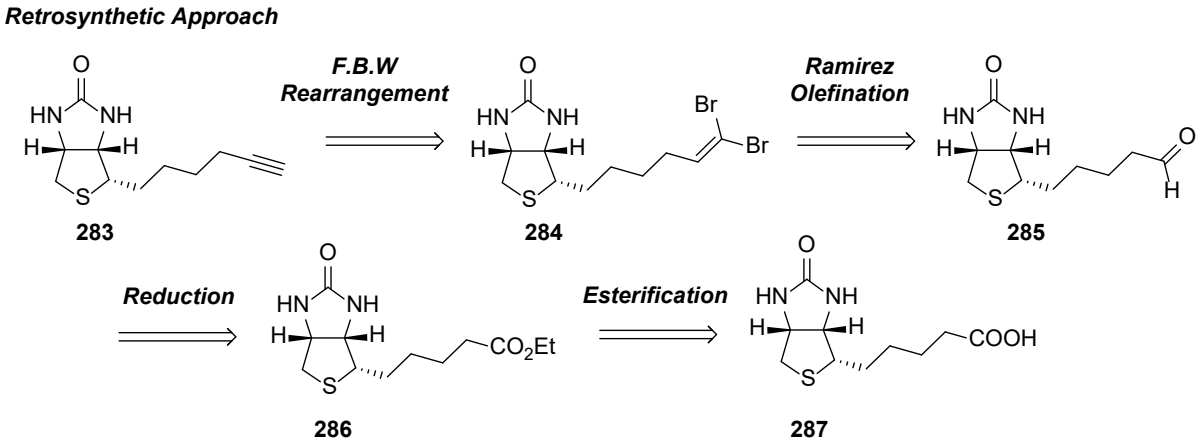
Scheme 103 Synthesis of benzyl ether 280

As a method to access 1,2-dimetallated olefins, the hydrostannylation of silyl alkynes was also a goal of the project. Accordingly, two silyl alkynes were selected as substrates; TMS acetylene and phenyldimethylsilyl (DMPS) acetylene. While TMS actylene is commercially available, DMPS acetylene is not, and as such was prepared in-house according to literature procedure.[181] This was achieved *via* addition of ethynyl magnesium bromide to phenyldimethylsilylchloride, which following purification afforded the desired silyl alkyne **282** in 83% yield.



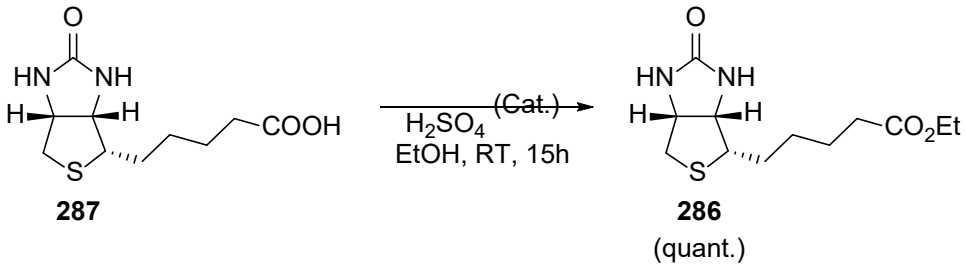
Scheme 104 Synthesis of silyl alkyne 282

It was initially envisaged that the developed hydrometallation approach could be employed to realise the stannylation of complex natural products. Consequently, alkyne **283** derived from vitamin B7 was selected as a substrate to demonstrate this. The retrosynthetic approach to provide access **283** is outlined in **Scheme 105**. A Fritsch–Buttenberg–Wiechell rearrangement would allow access to alkyne **283** from dibromoolefin **284**, which can itself be accessed *via* Ramirez olefination of aldehyde **285**. Aldehyde **285** could in principle be accessed *via* DIBAL-H reduction of **286** in turn readily accessed from commercially biotin **287**.



Scheme 105 Retrosynthetic approach to biotin-derived alkyne 283

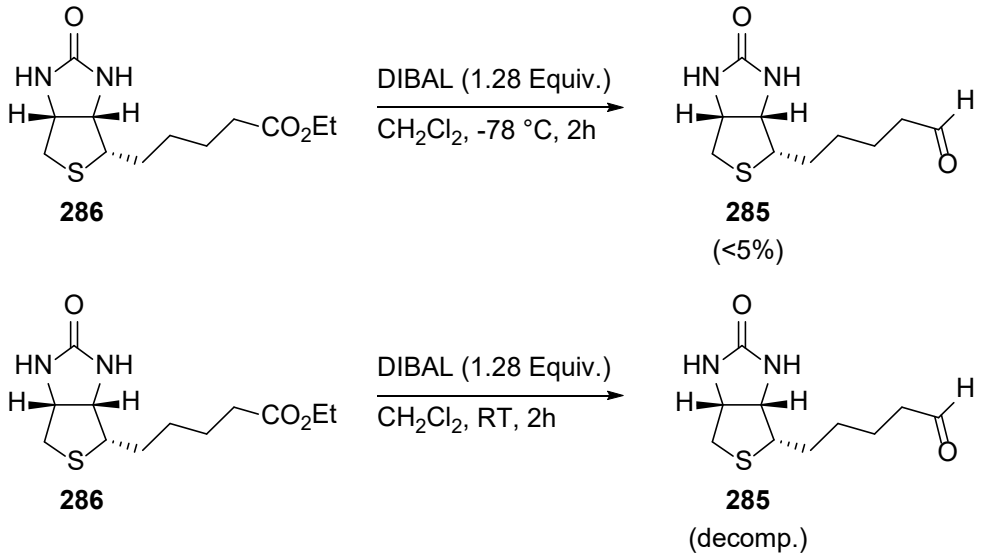
Accordingly, the synthesis of **286** from **287** was first attempted. Gratifyingly, this was achieved with relative ease, with treatment of **287** with catalytic amounts of sulfuric acid in ethanol readily afforded **286** in quantitative yield and sufficient purity as to not require further purification as reported by Fang and co-workers.[182]



Scheme 106 Synthesis of ethyl ester 286

With **286** in hand, the reduction to aldehyde to **285** was next targeted. To achieve this transformation the conditions reported by Gaunt and co-workers were employed, wherein the ester undergoes reduction with DIBAL-H to afford the corresponding aldehyde.[183] Under these conditions, it was observed that

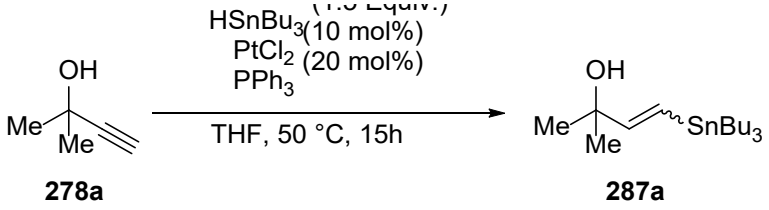
significant quantities of the ester remained in the reaction mixture. Increasing the DIBAL-H load had negligible effect on conversion, whilst carrying out the reaction at temperatures above those in the initial report led to the formation of complex mixtures of products, presumably due to a combination of over reduction as well as reduction of the other reduction sensitive functionalities within the substrate. As a result in the difficulty in realising this transformation, the attempted synthesis of alkyne **283** was not pursued further.



Scheme 107 Failed attempts at the reduction of 285

4.4 Hydrostannylation Optimisation

Unlike in **Chapter 2** and **Chapter 3**, the hydrostannylation process is effectively unreported under platinum catalysis, and as such a $PtCl_2/PPh_3$ catalyst system was chosen to begin the study as this represents a very common and basic ligand scaffold. Alcohol **278a** was chosen as a model substrate due to its relatively small steric bulk and lack of potentially interfering functionalities. Attempting the reaction employing the conditions outlined in **Scheme 108**, complete consumption of the starting material was observed by analysis of the ^1H NMR of the crude reaction mixture (**Figure 11**). The formation of the desired stannane was observed, as evidenced by the formation of the signals at ~6.6 & ~5.8 ppm with coupling constants of 19.3 Hz indicative of the *E*-vinyl stannane. Aside from the formation of the desired isomer, the formation of the *Z*-stannane was also observed as evidenced by the signals at ~6.1 ppm with much smaller coupling constants of 13.1 Hz.



278a **287a**

Scheme 108 Hydrostannylation of 278a with $PtCl_2(PPh_3)_2$

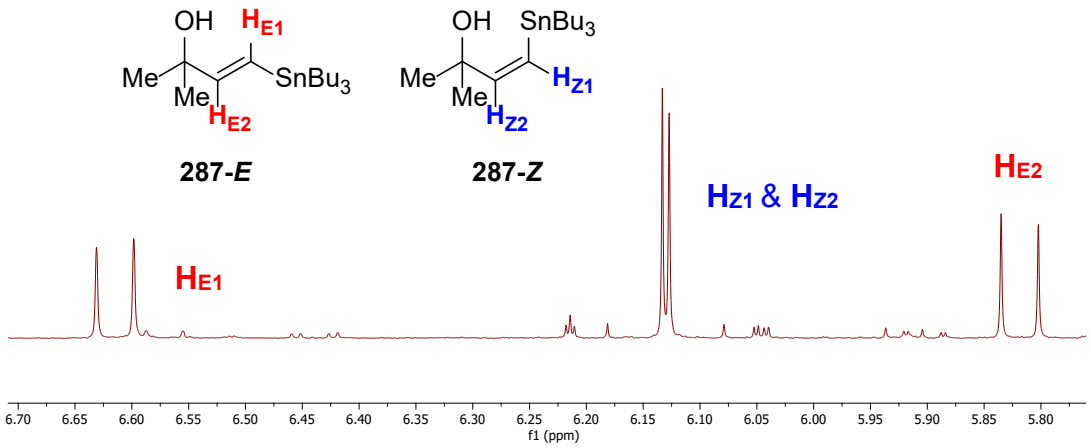
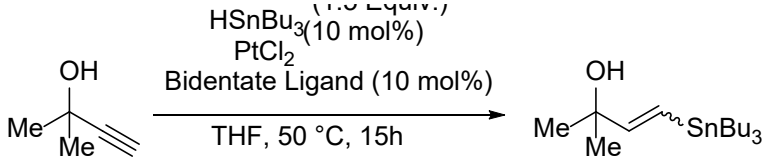


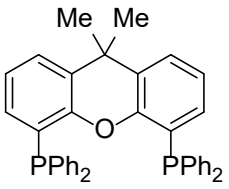
Figure 11 Crude ^1H NMR spectra of hydrostannylation of 278a with $PtCl_2(PPh_3)_3$

In keeping with the observed increase in selectivity when Buchwald ligands are employed in the analogous hydrosilylation processes, the reaction was then repeated, now employing XPhos in the place of triphenylphosphine. Under these conditions, much higher selectivity for the *E*-vinyl stannane (98:2 E/Z) was observed though it was noted that only approximately 40% **278a** had undergone conversion, a significant decrease on the triphenyl phosphine system which had seen almost complete conversion. The origin of this decreased conversion is explored later in this subsection.

In keeping with the studies carried on the efficacy of $PtCl_2$/XantPhos as a hydrosilylation catalyst in **Chapter 2**, the reaction was then repeated, this time employing 10 mol% $PtCl_2$ and 10 mol% XantPhos as a catalyst. Under these conditions, the reaction underwent a significant change in stereoselectivity from the previous results, with the reaction favouring the formation of the *Z*-vinyl stannane, with an *E:Z* ratio of 1:4. As the most obvious factor that had resulted in this dramatic selectivity change was the ligand denticity rather than any significant change in electronic properties, $PtCl_2$/dppf and $PtCl_2$/BINAP catalyst systems were then employed in the reaction to validate the effect of denticity on stereoselectivity. For both of these complexes, the same preference for the *Z*-vinyl stannane was observed, with the olefin formed in a 13:87 *E*:*Z* ratio in both cases. Again, incomplete consumption of **278a** was observed in these reactions. Interestingly, not all bidentate phosphine ligands were adequate at effecting this selectivity switch, with 3,5-dimethyl BINAP and DTBM-SEGPHOS affording almost no selectivity, with *E*:*Z* ratios of 1:1 and 55:45 respectively, despite being structurally very similar to BINAP. It is notable that the stereselectivity of the reaction does not appear to be related to the bite angle (θ) of the reaction given the difference of 6˚ between the θ values for DPPF and BINAP (99˚ and 93˚ respectively) versus the much larger θ value (108˚) for XantPhos.[184] It is of note that attempting the same reaction under ligand free conditions resulted predominantly in the formation of hexabutylditin, with only trace amounts of hydrostannylated products observed in the ^{1}H NMR of the crude reaclion mixture.

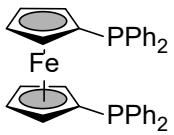


278a **287a**



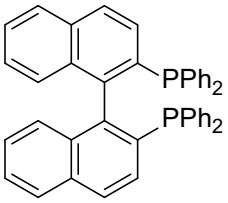
XantPhos

Conversion: 88%
E:Z ratio: 20:80



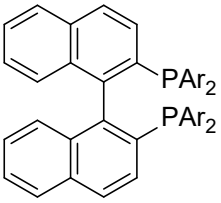
DPPF

Conversion: 76%
E:Z ratio: 13:87



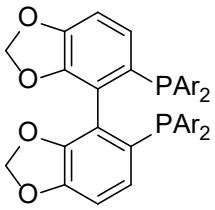
BINAP

Conversion: 52%
E:Z ratio: 13:87



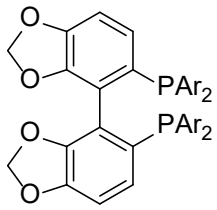
DM-BINAP

Ar= 3,5-MePh
Conversion: 57%
E:Z ratio: 50:50



DM-SEGPHOS

Ar= 3,5-MePh
Conversion: 67%
E:Z ratio: 19:81



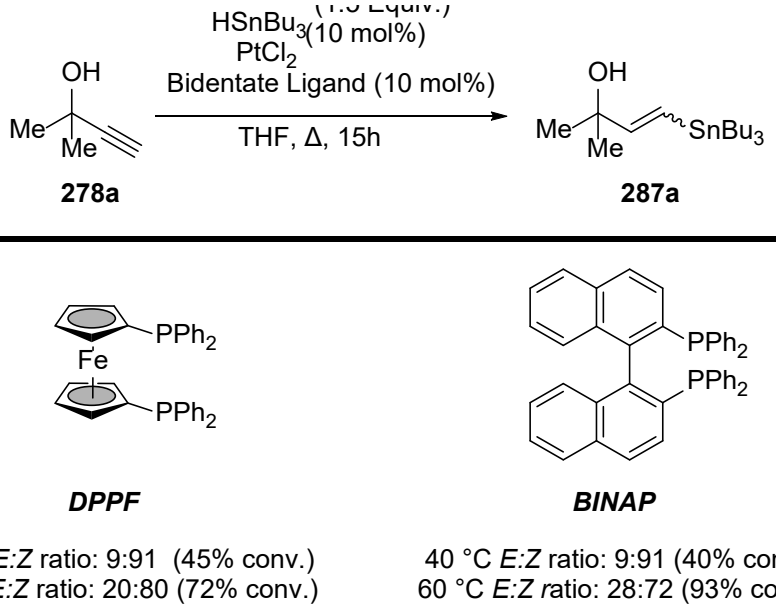
DTBM-SEGPHOS

Ar= 3,5-*t*Bu-4-OMePh
Conversion: 27%
E:Z ratio: 63:37

Scheme 109 Optimisation data for bidentate phosphine ligands in the hydrostannylation of 278a. Alkyne consumption & isomeric ratio determined ^{1}H NMR analysis of the crude reaction mixture

In an attempt to improve conversion, the reactions with DPPF and BINAP were repeated but at a slightly higher temperature of 60 ˚C. For DPPF, this did not result in a dramatic increase in conversion, but for the BINAP system, conversion increased to over 93%. Unfortunately, this elevated temperature decreased the reaction selectivity by approximately half, dropping from 13:87 to 28:72 for the BINAP system. When the temperature was lowered the selectivity for the DPPF catalyst system increased to 9:91 (*E*:*Z*), but conversion was decreased further to 45%. When the BINAP system was cooled slightly, conversion dropped to 40%, whilst the selectivity matched that of the DPPF catalyst at 91:9. In any case, the

conversion could not be raised to an adequate level whilst maintaining reaction selectivity.

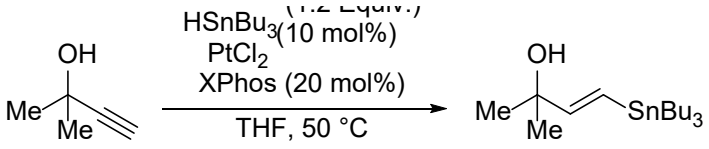


Scheme 110 Temperature effects on reaction selectivity and conversion. Alkyne consumption & isomeric ratio determined ^{1}H NMR analysis of the crude reaction mixture.

As previously noted, while the XPhos catalyst system showed high selectivity for the *E*-vinyl stannane, the conversion was relatively low. It was reasoned that two potential reasons for this low conversion could exist: catalyst deactivation or tin homocoupling. The homocoupling of tin hydrides is a well-known issue with transition metal catalysed hydrostannylation, and to confirm if this was indeed to source of the low conversion the experiment was repeated, monitoring the conversion over time, with the aim to observe if the addition of further aliquots of tin hydride after the reaction had plateaued in conversion would facilitate further turnover. If so, this would confirm the issue does not lie with catalyst inhibition or degradation. The results of this experiment are plotted in **Figure 12** where the additional aliquot of tin (0.8 equiv). was added at T=2h.

As can be seen from the graph, after the initial addition of tin hydride, the reaction plateaus after approximately 1 hour at around 35% conversion. Following the subsequent addition of a further 0.8 equivalents of tin hydride, taking the total to 2 equivalents in total, the conversion increases to approximately 55% in an hour,

before plateauing again. While this data is useful in the sense it provides evidence against catalyst deactivation, the actual conversions are likely to be underestimates of the true conversion due to the removal of catalyst each time an aliquot is taken. As this data suggests catalyst deactivation is not the cause of the observed low conversion, this observation was instead attributed to dimerization of the tributyltin hydride resulting in the formation of hexabutylditin and dihydrogen.



278a **287a**

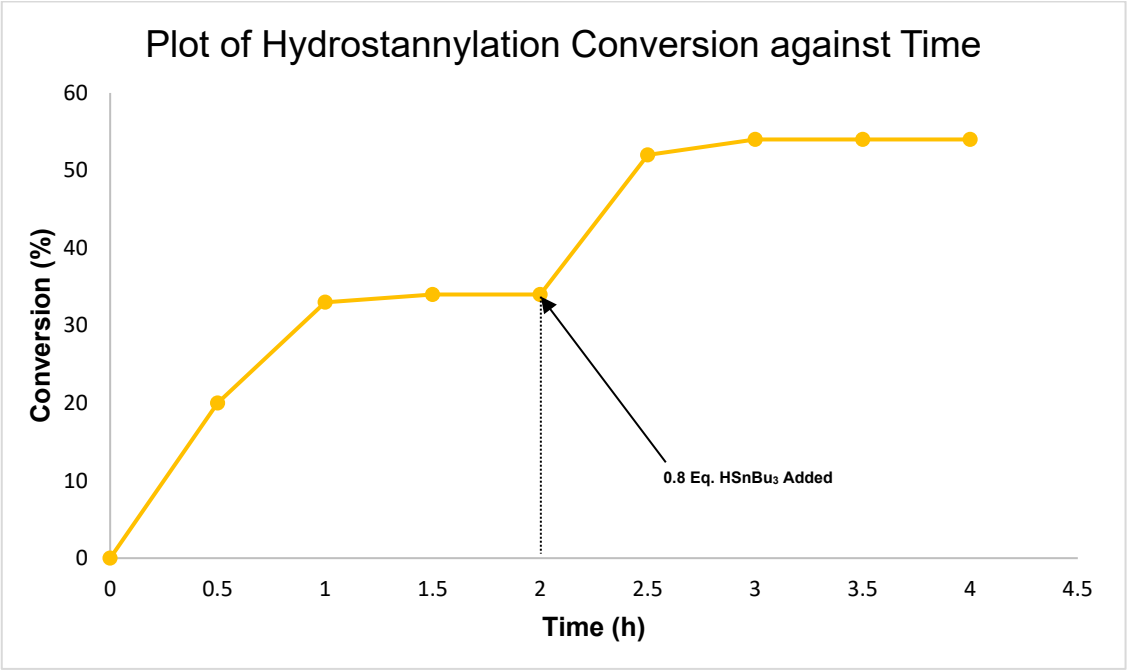
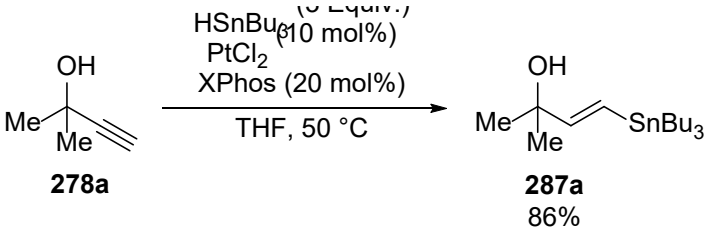


Figure 12 Plot of conversion versus time for $PtCl_2(XPhos)_2$ catalysed hydrostannylation of 278a

To minimise the concentration of tributyltin hydride in the reaction solution, the reaction was again repeated but with tributyltin hydride (3 equiv). added dropwise as a 0.1 M solution in THF over a period of 3h which resulted in complete consumption of the starting material. To facilitate a more user-friendly protocol,

the reaction was repeated a final time with 3 equivalents of neat tributyltin hydride added dropwise over a 15-minute period which again resulted in complete consumption of the starting material and allowed isolation of the hydrostannylated product in 86% yield as a single isomer (**Scheme 111**).



Scheme 111 Hydrostannylation of 287a with large excess of $HSnBu_3$ added over prolonged time period. Product isolated as a single regio and stereoisomer.

4.5 Substrate Scope

Having identified a robust set of reaction conditions which are selective for the β-*E*-vinyl stannane, attention turned to exploring the scope of alkynes which can undergo hydrostannylation, with initial attention paid to the propargylic alcohols synthesised in chapter **4.3**.

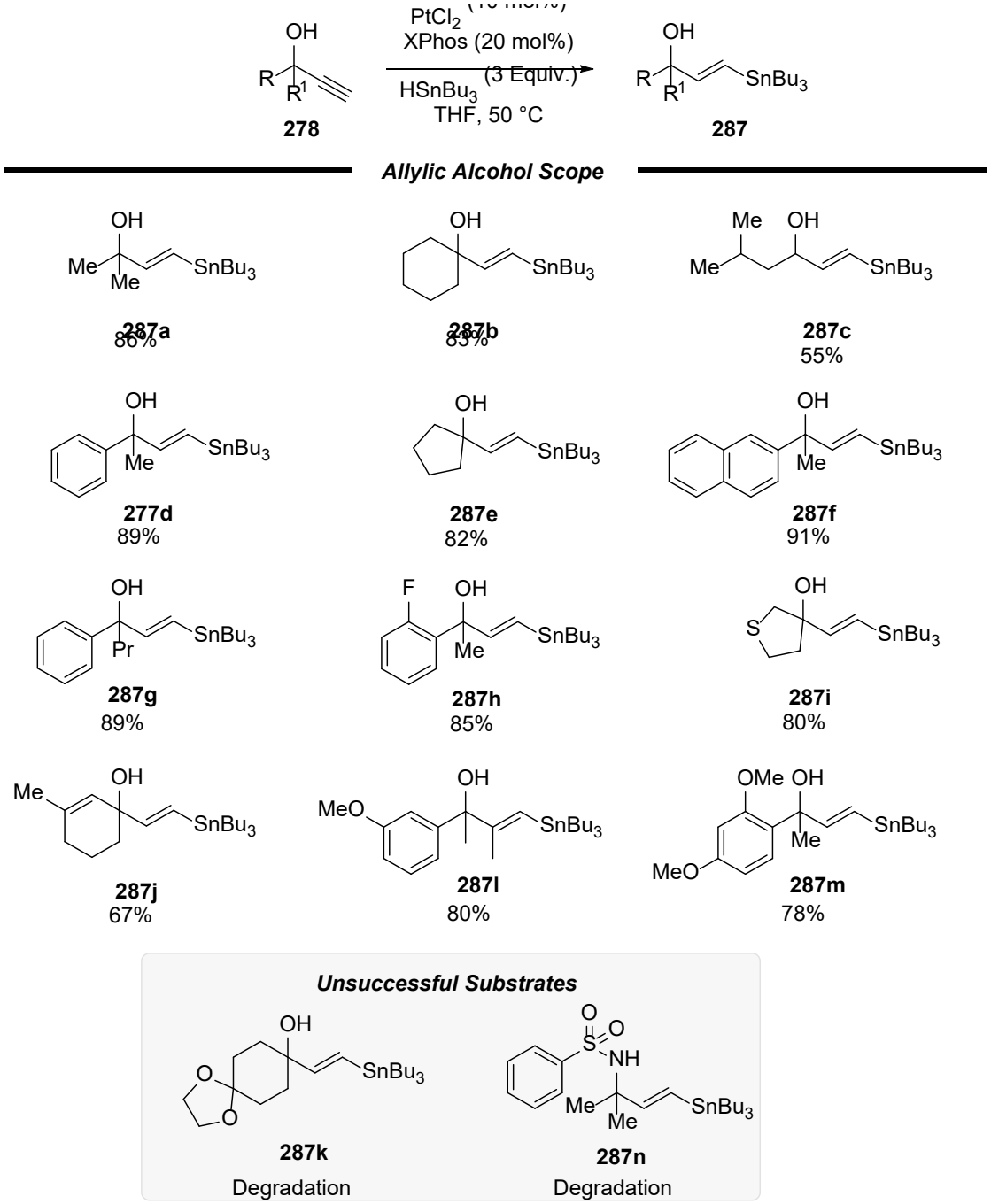
Tertiary alcohols bearing alkyl substituents **278b** and **278e** were examined, and under the optimised conditions these substrates were well tolerated with cyclic and substrates readily undergoing hydrometallation to afford **287b** and **287e** in 83% and 82% yield respectively. When examining secondary alkyl alcohol **278c**, a dramatic decrease in yield was noted, with stannane **287c** isolated in a modest 55% yield, though the decrease in steric hinderance around the reactive site had no adverse impact on reaction selectivity. This is in keeping with the observed decrease in rate of reactivity of secondary propargylic alcohols versus tertiary propargylic alcohols in the analogous hydrosilylation due to a decreased rate of reductive elimination. This decrease in reaction rate likely increases the likelihood of dimerization of the tributyltin hydride, explaining the observed incomplete conversion.

The next substrates examined were those bearing aromatic groups at the propargylic position. Under the optimised conditions complete conversion of alkyne **278d** into stannane **287d** with an isolated yield of 89% was achieved with complete selectivity. Increasing the steric bulk from a phenyl group to a naphthyl group had no adverse effect on the reaction outcome, with naphthyl stannane **287f** afforded in 91% yield.

Likewise, increasing the size of the alkyl substituent did not inhibit reactivity, with propiophenone derived alcohol readily undergoing hydrostannylation to afford **287g** in 89% yield. The reaction was also tolerant to a range of more electron rich aromatic systems, with aryl ethers **287i** and **287m** accessed in 78% and 80% yield respectively. This demonstrates tolerance to substituents at the *ortho*, *meta* and *para* sites on substrates bearing aromatic groups at this site. Likewise, electron deficient aromatic systems were suitably viable substrates, with fluorinated stannane **287h** isolated in 85% yield.

When employing tetrahydrothiophenyl alcohol **278j**, the presence of the heterocyclic moiety had no adverse effects on the selectivity of the reaction with vinyl stannane **287j** isolated in 80% yield as an isomerically pure olefin. When allylic alcohol **278j** was employed as a substrate, there was initial concern over the ability of the catalyst system to control the chemoselectivity of the reduction and indeed under the optimised conditions formation of a complex mixture of products was observed. Lowering the loading of tributyltin hydride to 2 equivalents resulted in a significantly cleaner reaction, and although the yield of **287j** is noticeably lower than other tertiary substrates, the transformation was still achieved in a synthetically useful yield.

In terms of limitations, two examples of substrates were noted where the methodology failed to provide the desired product. The first of these was ketal containing substrate **278k**, which under the reaction conditions resulted in the formation of a complex mixture of products. This is likely due to the acid sensitive nature of the ketal in conjunction with the Lewis acidity of the stannane rendering this type of functionality incompatible with such transformations. The next failed example was propargyl sulfonamide **116a**, which again resulted in the formation of a complex mixture of products. In this case the degradation is attributed to the reduction-sensitive nature of the sulfonamide, although as was discussed in **Chapter 2**, hydrometallation of propargyl amine derivatives is associated with its own distinct challenges.



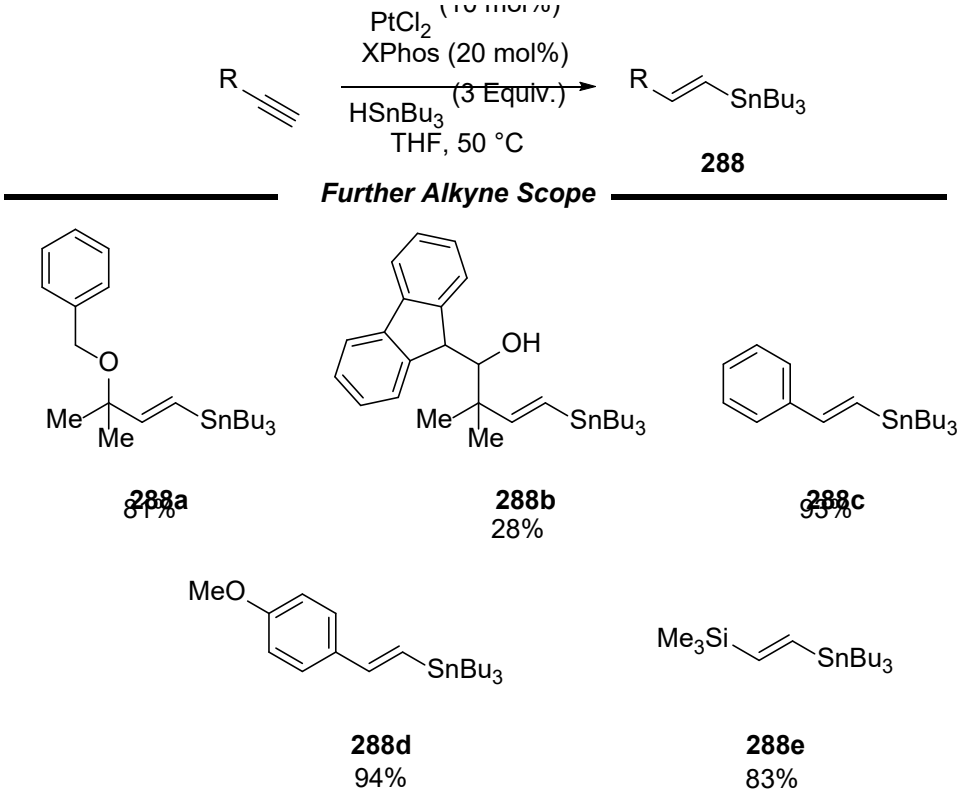
Scheme 112 Scope and limitations of $PtCl_2(XPhos)_2$ catalysed propargylic alcohol hydrostannylation. Substrates afforded as single regio and stereoisomers.

Attention next turned to examining substrates aside from propargylic alcohols. An investigation into the effects of the nearby protic functionality of the hydroxyl group was first carried out. To this end, benzyl ester **280** was employed as a substrate and despite removal of the protic functionality, no decrease in yield or activity was observed, though an instability of the product towards purification on silica gel was noted, and as such the yield was calculated by ^{1}H NMR and an internal standard (1,3,5-trimethoxybenzene). This instability was true of all

substrates in **Scheme 112** and as such all yields within are calculated in the same manner. As an interaction between the oxygen and the metal centre could not be ruled out at this stage, a homologated system was next employed in alcohol **201k**. In this case the reaction was significantly less efficient, and only a 28% yield was obtained, with the formation of several other olefinic products noted. Phenyl acetylene and 4-methoxyphenyl acetylene were next employed as substrates, removing the potential for heteroatom coordination entirely. In both cases, the desired vinyl stannane was formed in excellent yield and as a single isomer. This is particularly notable due to the comparatively poor selectivity obtained when the same reaction is carried out under palladium catalysis using $PdCl_2(PPh_3)_2$ which affords effectively a 1:1 mixture of regioisomers.[172] Finally, trimethylsilyl acetylene was examined as a substrate, with initial concern that the intrinsic polarisation of the alkyne arising from the β-silicon effect would introduce regioselectivity issues, with the hydride being delivered to the more electropositive terminus of the alkyne. Thankfully these concerns were misplaced, and under the optimised conditions, silylated stannane **288e** was obtained in an 83 % yield.

In terms of limitations, low tolerance to electron deficient alkynes such as 4-nitrophenylacetylene and 2-fluorophenylacetylene was noted. This decreased reactivity is rationalised by a reduction in the capacity of the alkyne to coordinate to the metal centre resulting in a dramatically decreased rate of metalation for these substrates. Additionally, 2-ethynyl pyridine proved completely unreactive under the optimised conditions, with no formation of the desired olefin observed in the ^1H NMR of the crude reaction mixture. This is attributed to two potential modes of deactivation available due to the basic nature of the nitrogen in the pyridyl ring. This can either shut down catalytic activity of the Pt complex, inhibiting reactivity or result in the formation of an ‘ate’ complex with the tributyltin hydride, decreasing the availability of this reagent to undergo hydrostannylation. Given the noted lack of reactivity of pyridyl containing substrates in **Chapter 3.5** it is more likely that the pyridiyl group simply coordinates to the platinum centre and shuts down turnover. It was also noted that although TMS-acetylene had proven to be a viable substrate, when DMPS alkyne **282** was employed, no formation of the desired stannane was observed. Instead, complete degradation

of the alkyne had occurred, although the mechanism of this degradation is not immediately apparent.



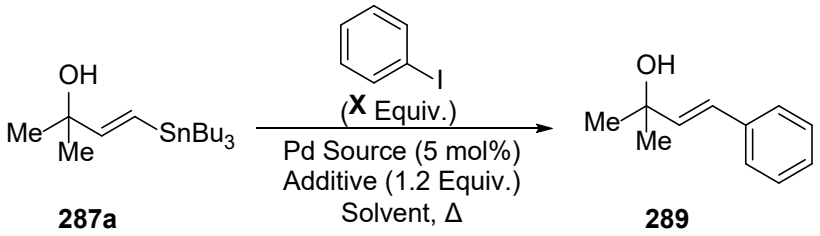
Scheme 113 Scope of other alkynes hydrostannylated by $PtCl_2(XPhos)_2$. Substrates afforded as single regio and stereoisomers.

4.6 Applications in a telescoped metalation-coupling sequence

4.6.1 Optimisation of conditions

As previously discussed, the principal application of vinyl stannanes within organic synthesis is as nucleophilic coupling partners in the Stille cross-coupling. Whilst this reaction is an extremely popular method for the assembly of carbon-carbon bonds, the toxicity associated with the manipulation of tin compounds, as well as the limited stability of organostannanes on silica gel introduces restrictions of the use of the method. As a telescoped approach from the hydrometallation to the cross-coupled product removes the need for chromatographic stannane purification, the development of such a protocol was next approached. As a set of robust conditions for selective hydrostannylation had already been identified in **Chapter 4.5**, stannane **287a** was utilised as a model substrate to identify optimal Stille coupling conditions, before attempting to combine the two into a telescoped reaction sequence.

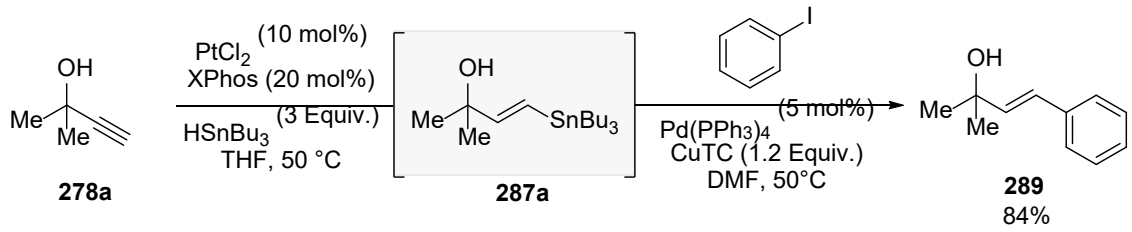
The study began by the attempted cross-coupling of **287a** with iodobenzene using 5 mol % $PdCl_2(PPh_3)_2$ as a catalyst. This afforded the cross-coupled product in a relatively low 23% yield**.** Changing the palladium source to a Pd(0) precatalyst in $Pd(PPh_3)_4$ resulted in a moderate increase in yield, with allylic alcohol **289** afforded in 34% yield. The reaction was repeated with the addition of copper(I) iodide and copper(I) thiocarboxylate (CuTC), and in both cases dramatic increase in isolated yield was achieved, with CuTC affording the coupled product in particularly high yield (**Scheme 113, Entry 4**). In the presence of CuTC, the loading of aryl halide was successfully lowered to 1.1 equivalent from 2 with negligible impact on isolated yield (**Scheme 113**, **Entry 5**). Despite the noted promoting effect of copper salts in ethereal solvents, when the reaction was carried out in THF under the same conditions a marked decrease in yield was observed (**Scheme 113**, **Entry 6**). Similarly, attempts to carry the reaction out at ambient temperatures also resulted in a dramatic decrease in efficiency (**Scheme 113**, **Entry 7**).



Entry	*Pd Source*	*Additive*	*Halide Equiv.*	*Solvent*	*Temperature*	*Yield*
1	$PdCl_2(PPh_3)_2$	None	2	DMF	50 °C	23%
2	$Pd(PPh_3)_4$	None	2	DMF	50 °C	34%
3	$Pd(PPh_3)_4$	CuI	2	DMF	50 °C	64%
4	$Pd(PPh_3)_4$	CuTc	2	DMF	50 °C	94%
5	$Pd(PPh_3)_4$	CuTc	1.1	DMF	50 °C	92%
6	$Pd(PPh_3)_4$	CuTc	1.1	THF	50 °C	34%
7	$Pd(PPh_3)_4$	CuTc	1.1	DMF	RT	45%

Scheme 114 Stille coupling optimisation data. Isolated yields.

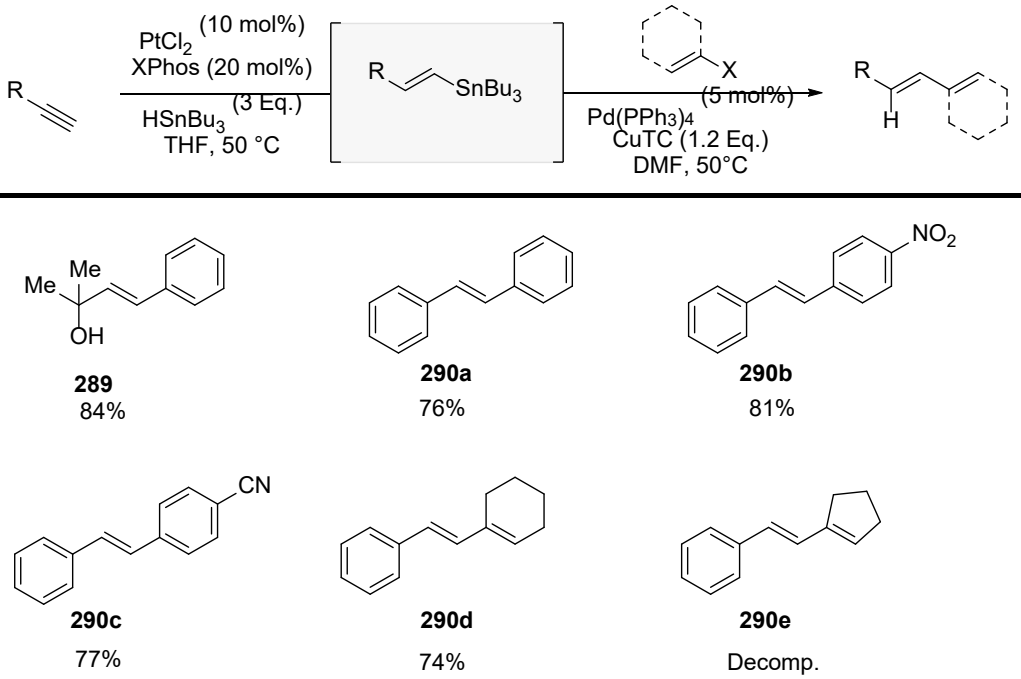
With a set of conditions for the Stille coupling established, the focus next turned to telescoping the sequence. As the cross-coupling was noted to be inefficient in THF, a solvent-swap was attempted, with removal of THF from the hydrometallation step under vacuum, before redissolution of the crude stannane in DMF to carry out the subsequent cross-coupling. In practice, this resulted in a poorly efficient reaction, with multiple side products formed in addition to incomplete consumption of the stannane. It was reasoned that the presence of excess ligand/metal from the hydrometallation step was interfering with the cross-coupling. To this end, the reaction was repeated but the hydrometallation reaction mixture was filtered through a pad of celite, aiming to remove ligand/metal salts from the reaction media before removal of THF and subsequent redissolution. With this additional step introduced, facile cross-coupling was observed, with alcohol **289** isolated in 84% yield.



Scheme 115 'Telescoped' Hydrostannylation/Stille coupling

4.6.2 Substrate Scope

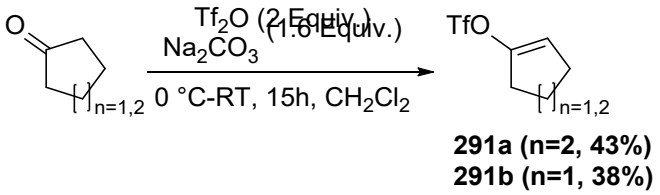
With an optimised set of conditions now in hand, the scope of the reaction sequence beyond alcohol **289** was next studied, with an initial focus on the synthesis of stilbene derivatives. Using iodobenzene as a coupling partner, stilbene **290a** was isolated in a 76% yield over 2 steps. Using 4-nitrobromobenzene and 4-cyanobromobenzene, stilbenes **290b** and **290c** could be isolated in 81% and 77% yields respectively over 2 steps.



Scheme 116 Scope of olefins synthesised by telescoped hydrometallation/cross-coupling sequence. Substrates afforded as single regio and stereoisomers.

Finally, the process was examined for its ability to furnish 1,3-dienes; motifs which find frequent application in the Diels-Alder cycloaddition. Access to the necessary electrophile to apply in these cross couplings was therefore required. Vinyl triflates **291a** and **291b** were chosen as ideal substrates to access due to the ready availability of starting materials. Despite Comins' reagent being typically utilised in the synthesis of vinyl triflates, a survey of the literature revealed that in the case of these substrates, treatment with Tf_2O under basic conditions can afford the desired triflated product. Presumably Comins' reagent in this case is not required due to the lack of acid sensitive functional groups which could be disadvantageous in the presence of the liberated triflic acid. Using the conditions reported in **Scheme 116**, vinyl triflates **291a** and **291b** were afforded in moderate yields, though an extreme instability of the smaller

homologue was noted, with **291b** highly prone to degradation overnight even if kept in the dark at temperatures < 0 ˚C. With triflates in hand, they were then employed in the telescoped sequence, with diene **290d** afforded in 74% yield over 2 steps. Unfortunately, when **291b** was used as an electrophile in the coupling, only trace amounts of the **290e** could be isolated. This was attributed to decomposition of the triflate at the elevated reaction temperatures.



291a (n=2, 43%)
291b (n=1, 38%)

Scheme 117 Synthesis of vinyl triflates 291

4.7 Conclusions

In conclusion, the first in-depth example of platinum catalysed hydrostannylation of terminal alkynes has been studied. The effect of coordination environment on the outcome of the reaction has been investigated several trends were noted. In the case of monodentate ligands, Buchwald type ligands were able to afford the requisite E-vinyl stannane in higher selectivities than other monodentate phosphine ligands such as triphenylphosphine. More notably, switching ligand denticity from monodentate to bidentate switched the stereochemical outcome of the reaction, with the Z-vinyl isomer now preferentially formed when ligands such as DPPF, BINAP and XantPhos were employed. It is proposed that this proceeds through an initial syn-hydrometallation followed by subsequent isomerisation through a Pt-Carbene intermediate, permissible by virtue of the stronger anion stabilising effect of the stannane versus the previously studied silanes.

Having identified $PtCl_2(XPhos)_2$ as the optimal catalyst to afford the desired E-vinyl stannane, the substrate scope of the reaction was explored with key successes and limitations reported. Notably, the reaction is able to chemoselectively reduce an alkyne over an alkene, and sulfur containing heterocycles were well tolerated by the reaction, as well as a range of sterically and electronically varied propargylic alcohols. Electron rich phenyl acetylene derivatives were well tolerated and were metalated in greater selectivities than previous palladium-based catalyst systems had allowed. Notable limitations were an intolerance to pyridyl functionalities and acid/reduction sensitive functionalities.

A telescoped hydrometallation/cross-coupling sequence was developed for terminal alkynes, allowing for construction of diverse olefins while lowering concerns with toxicity and decomposition associated with manipulation of vinyl stannanes. Whilst undertaking reaction optimisation, it was noted that copper additives are required in order to facilitate cross-coupling of the stannanes in synthetically useful yields. Using this telescoped sequence, a range of olefins were synthesised, including allylic alcohols, stilbenes and 1,3-dienes, synthetically useful compounds in their own regard.

The discussed work provides a platform from which other platinum based hydrometallations can be further developed, hopefully providing a complimentary method to access a range of diverse range metalloids from a single alkyne and single catalyst system, or at the minimum, complexes derived from the same metal centre. Additionally, the reported denticity controlled stereodivergency provides evidence of platinum complexes affording unusual *anti*-hydrometallation pathways.

4.8 Experimental Procedures and Characterisation Data

Solvents & reagents

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, TCI, Fisher Scientific or Sigma Aldrich. All solvents were purchased from commercial sources and used without purification (reagent grade). Metal salts and ligands were stored in a desiccator when not in use. Anhydrous solvent was prepared by storing solvent over activated 4Å MS for 72 hours. Standard vacuum line techniques were used, and glassware was oven dried prior to use. Organic solvents were dried during workup using anhydrous Na_2SO_4. All reactions were performed using DrySyn heating mantles and pressure regulated vials or round bottom flasks.

Purification and chromatography

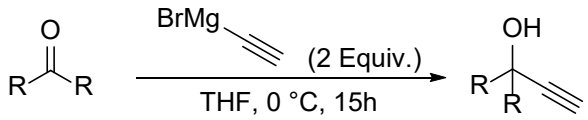
Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F254 silica gel. Plates were visualised using UV light (254 or 365 nm) and developed with iodine and basic permanganate solution. Flash chromatography was performed on VWR Silica gel 60, 40–63 microns RE as the stationary phase and the solvents employed were of reagent grade.

Characterisation

^{1}H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ^{13}C NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemicalshifts are reported in parts per million (δ) relative to residual $CHCl_3$ (δH = 7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm, central line). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer.

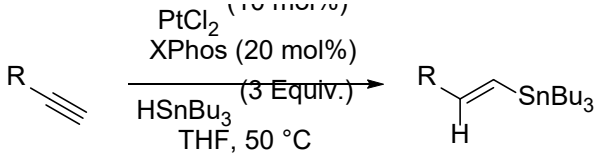
4.8.1 General Procedures

General Procedure 4A



To an oven dried round bottom flask equipped with a magnetic stirrer was added the requisite aldehyde or ketone (1 equiv.) followed by anhydrous THF (0.5M) under a nitrogen atmosphere. This solution was then cooled to 0 ˚C, before ethynyl magnesium bromide (2 equiv.) was added dropwise. The solution was then allowed to warm to room temperature and the reaction was then stirred until TLC analysis showed complete consumption of the starting material. After this time, the reaction was quenched *via* addition of aqueous ammonium chloride (20 mL) and extracted into ethyl acetate (3 × 15 mL). The extracts were dried over $MgSO_4$ before volatiles were removed under reduced pressure, and the resultant residue purified by flash chromatography.

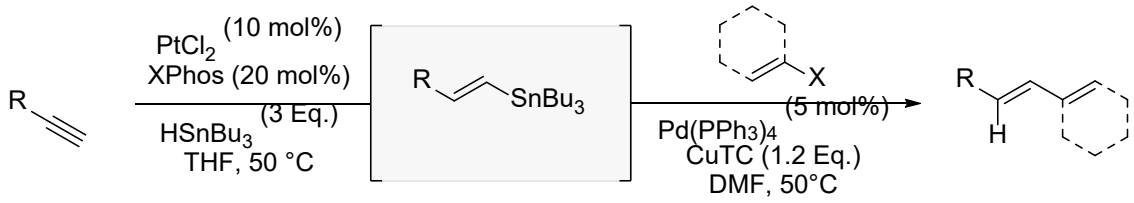
General Procedure 4B



To an oven dried 22 mL vial equipped with a magnetic stirrer was added $PtCl_2$ (10 mol%) and 2- dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) (20 mol%). The flask was then flushed quickly with nitrogen and anhydrous THF was added to form a 0.1 M solution relative to the alkyne. The mixture was then stirred at 50 ˚C for 20 minutes until a yellow homogeneous mixture was obtained indicating the formation of the active catalyst, $PtCl_2(XPhos)_2$. The corresponding alkyne (1 eq.) was added followed by the stannane (3 eq.) *via* syringe (CAUTION: Rapid evolution of hydrogen gas) and the solution was stirred at 50 ˚C for 15 hours. Volatiles were then removed under vacuum, and the resultant residue purified by flash column chromatography to afford the corresponding stannane, or a known mass of 1,3,5-trimethoxy benzene was added and the reaction yield

calculated by ^{1}H NMR analysis of the crude reaction mixture. *Note- Rapid addition of tributyltin hydride will result in formation of hexabutylditin and result in lower yield. To minimise dimerization, $HSnBu_3$ should be added dropwise over a period of 15 minutes*

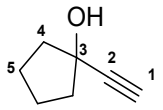
General Procedure 4C



To an oven dried 22 mL vial equipped with a magnetic stirrer was added $PtCl_2$ (10 mol%) and 2- dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (20 mol%) (XPhos). The flask was then flushed quickly with nitrogen and anhydrous THF was added to form a 0.1 M solution relative to the alkyne. The mixture was then stirred at 50 ˚C for 20 minutes until a yellow homogeneous mixture was obtained indicating the formation of the active catalyst, $PtCl_2(XPhos)_2$. The corresponding alkyne (1 equiv.) was added followed by the stannane (3 equiv.) *via* syringe (CAUTION: Rapid evolution of hydrogen gas) and the solution was stirred at 50 ˚C for 15 hours. After this time, the reaction mixture was diluted with hexane and filtered through a plug of celite. Volatiles were then removed under reduced pressure and the residue redissolved in anhydrous DMF (0.1M). The solution was placed under a nitrogen atmosphere, before the requisite coupling partner (1.1 equiv.) was added, followed by CuTC (1.2 equiv.) and $Pd(PPh_3)_4$ (5 mol%.) The reaction was then heated at 50 ˚C for 6 hours, after which time TLC analysis indicated complete consumption of the stannane. The reaction was then cooled to room temperature, diluted with Et_2O (10 mL) and washed with 5% aqueous LiCl solution. The organic extract was then dried over Na_2SO_4 before volatiles were removed under vacuum and the resultant residue purified by flash chromatography.

4.8.2 Synthesis of Propargylic Alcohols

1-ethynylcyclopentanol 278e



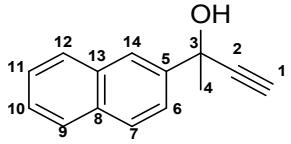
Synthesised according to **General Procedure 4A** using cyclopentanone (0.21 mL, 2.4 mmol) and ethynyl magnesium bromide (9.51 mL, 5 mmol). Following conversion to product and flash chromatography, **278e** was isolated as a colourless oil (167 mg, 64%). Spectral data is in accordance with the literature.[93]

Rf (19:1 Petroleum Ether:EtOAc): 0.22

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 1H, (**H1**)), 2.02-1.70 (m, 9H, (**H4**, **H5** & **OH**))

^{13}C NMR (101 MHz, $CDCl_3$) δ 88.3 (**C1**), 75.4 (**C2**), 70.8 (**C3**), 43.1 (**C4**), 23.5 (**C5**)

2-(2-napthyl)but-3-yn-2-ol 278f



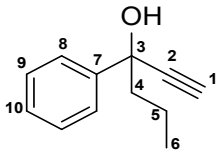
Synthesised according to **General Procedure 4A** using acetonapthone (750 mg, 4.4 mmol) and ethynyl magnesium bromide (17.6 mL, 8.8 mmol). Following conversion to product and flash chromatography, **278f** was isolated as a pale-yellow oil (756 mg, 87%). Spectral data is in accordance with the literature.[185]

Rf (19:1 Petroleum Ether:EtOAc): 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 1.8 Hz, 1H (**H14**)), 7.92 – 7.80 (m, 3H, (**H11**, **H10** and **H9**)), 7.75 (dd, *J* = 8.6, 1.9 Hz, 1H (**H12**)), 7.55 – 7.45 (m, 2H, (**H7** and **H6**), 2.74 (s, 1H (**H1**)), 2.54 (s, 1H (**OH**)), 1.88 (d, *J* = 0.5 Hz, 3H (**H4**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (**C5**), 133.1 (**C13** or **C8**), 133.1 (**C13** or **C8**), 128.5 (**C11**, **C10** or **C9**), 128.4 (**C11**, **C10** or **C9**), 127.7 (**C11**, **C10** or **C9**), 126.4 (**C7** or **C6**), 126.4 (**C7** or **C6**), 123.6 (**C12**), 123.4 (**C14**), 87.4 (**C2**), 73.5 (**C1**), 70.1 (**C3**), 33.1 (**C4**).

3-phenylhex-1-yn-3-ol 278g



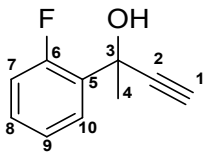
Synthesised according to **General Procedure 4A** using butyrophenone (0.49mL, 3.4 mmol) and ethynyl magnesium bromide (13.5 mL, 6.8 mmol). Following conversion to product and flash chromatography, **278g** was isolated as a colourless viscous oil (498 mg, 85%). Spectral data is in accordance with the literature.[186]

Rf (19:1 Petroleum Ether:EtOAc): 0.24

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H, (**H9**)), 7.40 – 7.34 (m, 2H (**H8**)), 7.32 – 7.27 (m, 1H (**H10**)), 2.69 (s, 1H (**H1**)), 2.36 (br s, 1H (**OH**)), 1.91 (dddd, *J* = 34.0, 13.3, 11.6, 4.9 Hz, 2H (**H4**)), 1.57 – 1.30 (m, 2H (**H5**)), 0.90 (t, *J* = 7.4 Hz, 3H (**H6**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (**C7**), 128.3 (**C9**), 127.9 (**C10**), 125.5 (**C8**), 86.5 (**C2**), 74.2 (**C1**), 73.4 (**C3**), 47.5 (**C4**), 18.1 (**C5**), 14.1 (**C6**).

2-(2-fluorophenyl)but-3-yn-2-ol 278h



Synthesised according to **General Procedure 4A** using 2-fluoroacetophenone (0.44 mL, 3.6 mmol) and ethynyl magnesium bromide (14.5 mL, 7.3 mmol). Following conversion to product and flash chromatography, **278h** was isolated

as a pale-yellow oil (428 mg, 72%). Spectral data is in accordance with the literature.[187]

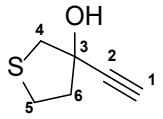
Rf (19:1 Petroleum Ether:EtOAc): 0.20

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (td, *J* = 8.0, 1.8 Hz, 1H (**H7**)), 7.37 – 7.27 (m, 1H, (**H10**)), 7.14 (td, *J* = 7.6, 1.2 Hz, 1H, (**H9**)), 7.08 (ddd, *J* = 11.9, 8.1, 1.2 Hz, 1H, (**H8**)), 2.76 (s, 1H, (**OH**)), 2.64 (d, *J* = 0.6 Hz, 1H (**H1**)), 1.90 (d, *J* = 0.8 Hz, 3H (**H4**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (d, *J* = 247.9 Hz, (**C6**)), 131.5 (d, *J* = 10.7 Hz, (**C5**)), 129.8 (d, *J* = 8.6 Hz (**C9**)), 126.7 (d, *J* = 3.3 Hz, (**C8**)), 124.0 (d, *J* = 3.6 Hz,(**C10**)), 116.3 (d, *J* = 22.4 Hz, (**C7**)), 86.2 (**C2**), 72.5 (d, *J* = 2.0 Hz, (**C1**)), 67.5 (d, *J* = 0.8 Hz, (**C3**)), 30.4 (d, *J* = 2.6 Hz, (**C4**)).

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.98 (d, *J* = 1.7 Hz).

3-ethynyltetrahydrothiophen-3-ol 278i



Synthesised according to **General Procedure 4A** using 4,5-dihydro-3(2H)-thiophenone (0.34 mL, 3.9 mmol) and ethynyl magnesium bromide (15.7 mL, 7.8 mmol). Following conversion to product and flash chromatography, **278i** was isolated as a yellow oil (370 mg, 74%).

Rf (19:1 Petroleum Ether:EtOAc): 0.22

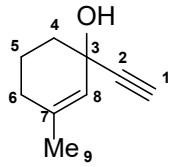
IR υmax (cm^{-1}) 3436, 3345, 3254, 2942, 2987

HRMS (ESI) m/z: [M + H]+ Calcd for C_6H_9OS 129.0374; Found 129.0371

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (d, *J* = 11.5 Hz, 1H, (**H4**)), 3.07 – 2.92 (m, 3H, (**H4** & **H5**)), 2.57 (s, 1H, (**H1**)), 2.44 (s, 1H, (**OH**)), 2.36 (dddd, *J* = 13.0, 6.4, 3.3, 1.5 Hz, 1H, (**H6**)), 2.14 (ddd, *J* = 13.0, 9.8, 8.1 Hz, 1H, (**H6**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 84.0 (**C2**), 75.2 (**C1**), 73.0 (**C3**), 44.6 (**C4**), 44.2 (**C5**), 28.6 (**C6**).

1-ethynyl-3-methyl-cyclohex-2-en-1-ol 278j



Synthesised according to **General Procedure 4A** using 3-methyl-2-cyclohexenone (0.52 mL, 4.5 mmol) and ethynyl magnesium bromide (18.2 mL, 9.1 mmol). Following conversion to product and flash chromatography, **278j** was isolated as a yellow oil (326 mg, 74%).

Rf (19:1 Petroleum Ether:EtOAc): 0.32

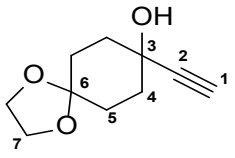
IR υmax (cm^{-1}) 3363, 3289, 2935, 2866, 2830

HRMS (ESI) m/z: [M + H]+ Calcd for $C_9H_{13}O$ 137.0966; Found 137.0968

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 – 5.49 (m, 1H, (**H8**)), 2.50 (s, 1H, (**H1**)), 2.02 – 1.73 (m, 7, (**H4**, **H5**, **H6** & **OH**)), 1.72 – 1.68 (m, 3H, (**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0 (**C7**), 124.8 (**C8**), 88.1 (**C2**), 71.2 (**C1**), 65.8 (**C3**), 37.7 (**C9**), 29.8 (**C6**), 23.6 (**C5** or **C4**), 19.4 (**C5** or **C4**)

3-phenylhex-1-yn-3-ol 278k



Synthesised according to **General Procedure 4A** using 1,4-Cyclohexanedione monoethylene acetal (0.2mL, 1.3 mmol) and ethynyl magnesium bromide (5.1 mL, 2.6 mmol). Following conversion to product and flash chromatography, **278k**

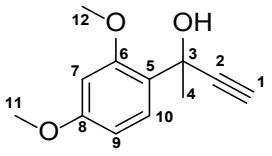
was isolated as a colourless viscous oil (209 mg, 90%). Spectral data is in accordance with the literature.[188]

Rf (19:1 Petroleum Ether:EtOAc): 0.13

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 4H, (**H7**)), 2.48 (s, 1H, (**H1**)), 2.13 – 1.87 (m, 5H, (**H$_{Cyclohexyl}$**)), 1.80 (m, 3H, (**H$_{Cyclohexyl}$**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 108.0, (**C6**), 87.1 (**C2**), 72.2 (**C1**) , 64.5 (**C7**), 64.4 (**C3**), 37.2 (**C$_{Cyclohexyl}$**), 31.4 (**C$_{Cyclohexyl}$**).

2-(2,4-dimethoxyphenyl)but-3-yn-2-ol 278l



Synthesised according to literature procedure. To a flask charged with magnesium turnings (108 mg, 4.5 mmol) was added anhydrous THF (4.6 mL) 1,2-dibromoethane (16 µL, 0.18 mmol) under a N_2 atmosphere. The suspension was stirred at room temperature for 15 minutes, after which time 1-bromo-2,4-dimethoxybenzene (510 µL, 3.6 mmol) was added dropwise. The mixture was then allowed to stir for two hours. After this time, the Grignard reagent was transferred *via* syringe into a separate flask containing a solution of 4-trimethylsilyl-3-butyn-2-one (291 µL, 1.8 mmol) in THF (1M) at 0 ˚C. The reaction was then allowed to warm to room temperature and stirred for 4 hours, after which time TLC analysis indicated complete consumption of the ketone. The reaction was then quenched *via* addition of saturated NH_4Cl (aq.) and washed with Et_2O (3 × 10 mL) before the combined organics were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The crude TMS protected alkyne was then dissolved in methanol, and potassium carbonate (3 equiv.) was added, and the resultant suspension stirred for 1 hour. After this time, 10 mL of water was added, and the mixture washed with Et_2O (3 × 10 mL) before the combined organics were dried over $MgSO_4$ and volatiles were removed under reduced

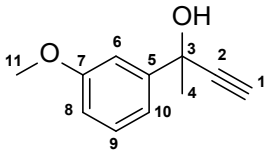
pressure. The resultant residue was then purified by flash chromatography to afford **278l** as a pale-yellow oil (243 mg, 66%). Spectral data is in accordance with the literature.[185]

Rf (9:1 Petroleum Ether:EtOAc): 0.17

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 1H, (**H10**)), 6.53 (d, *J* = 2.4 Hz, 1H (**H7**)), 6.47 (dd, *J* = 8.5, 2.4 Hz, 1H, (**H9**)), 4.39 (s, 1H, (**OH**)), 3.92 (s, 3H (**H12** or **H11**), 3.81 (s, 3H (**H12** or **H11**)), 2.54 (s, 1H, (**H1**)), 1.88 (s, 3H (**H4**)).

^{13}C NMR (101 MHz, $CDCl_3$ δ 160.7 (**C6**), 158.0 (**C8**), 127.1 (**C9**), 124.9 (**C5**), 104.3 (**C9**), 100.0 (**C7**), 87.7 (**C2**), 71.2 (**C1**), 68.6 (**C3**), 55.8 (**C12** or **C11**), 55.6 (**C12** or **C11**), 29.8 (**C4**).

2-(3-methoxyphenyl)but-3-yn-2-ol 278m



Synthesised according to literature procedure. To a flask charged with magnesium turnings (108 mg, 4.5 mmol) was added anhydrous THF (4.6 mL) 1,2-dibromoethane (16 µL, 0.18 mmol) under a N_2 atmosphere. The suspension was stirred at room temperature for 15 minutes, after which time 3-bromoanisole (451 µL, 3.6 mmol) was added dropwise. The mixture was then allowed to stir for two hours. After this time, the Grignard reagent was transferred *via* syringe into a separate flask containing a solution of 4- trimethylsilyl-3-butyn-2-one (291 µL, 1.8 mmol) in THF (1M) at 0 ˚C. The reaction was then allowed to warm to room temperature and stirred for 4 hours, after which time TLC analysis indicated complete 7 consumption of the ketone. The reaction was then quenched *via* addition of saturated NH_4Cl (aq) and washed with Et_2O (3 × 10 mL) before the combined organics were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The crude TMS protected alkyne was then dissolved in methanol, and potassium carbonate (3 equiv.) was added, and the resultant suspension stirred for 1 hour. After this time, 10 mL of water was added, and the

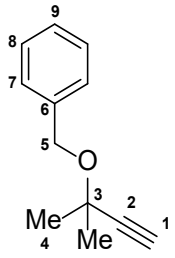
mixture washed with Et_2O (3 × 10 mL) before the combined organics were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The resultant residue was then purified by flash chromatography to afford **278m** as a pale-yellow oil (243 mg, 66%). Spectral data is in accordance with the literature.[185]

Rf (9:1 Petroleum Ether:EtOAc): 0.26

1H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.21 (m, 3H, (**H8**, **H9**, **H10**)), 6.85 (m, 1H, (**H6**)), 3.80 (s, 3H, (**H11**)), 2.63 (s, 1H, (**H1**)), 2.32 (s, 1H, (**OH**)), 1.84 (s, 3H, (**H4**))

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (**C7**), 146.9 (**C5**), 129.0 (**C9**), 117.1 (**C10**), 113.8 (**C8**), 110.3 (**C6**), 87.0 (**C2**), 73.3 (**C1**), 69.6 (**C3**), 55.5 (**C11**), 32.1 (**C4**)

1,1-dimethylprop-2-ynoxymethylbenzene 280



Synthesised according to literature procedure. Sodium hydride (34 mg, 1.4 mmol) was added in portions to a stirred solution of 2-methyl-3-butyn-2-ol (100 mg, 1.2 mmol) in THF and stirred at room temperature for one hour. After this time, TBAI (22 mg, 0.06 mmol) and benzyl bromide (0.17 mL, 1.4 mmol) was added dropwise and the resulting mixture stirred at room temperature overnight. The solution was then diluted with Et_2O (5 mL) and washed with water (3 × 5 mL) before being dried over $MgSO_4$. Volatiles were then removed under reduced pressure and the resultant residue purified by flash chromatography to afford **280** as a colourless liquid (180 mg, 87%). Spectral data is in accordance with the literature.[189]

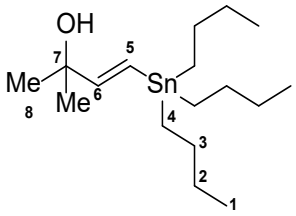
Rf (19:1 Petroleum Ether:EtOAc): 0.56

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H, (**H7**, **H8** & **H9**)), 4.64 (s, 2H, (**H5**)), 2.48 (s, 1H, (**H1**)), 1.56 (s, 6H, (**H4**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (**C6**), 128.5 (**C8**), 127.9 (**C7**), 127.5 (**C9**), 86.3 (**C2**), 72.4 (**C1**), 70.6 (**C3**), 66.7 (**C5**), 29.0 (**C4**).

4.8.3 Synthesis of Vinyl Stannanes

(E)-2-methyl-4-tributylstannyl-but-3-en-2-ol 287a



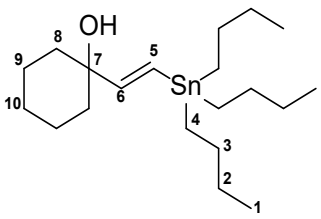
The title compound was prepared according to **General Procedure 4B** from **278a** (50 mg, 0.6 mmol) and tributyltin hydride (0.48 mL, 1.8 mmol) using $PtCl_2$ (8 mg, 30 µmol) and XPhos (28 mg, 60 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287a** as a pale-yellow oil (192 mg, 86%). Spectral data is in accordance with literature reports.[169]

Rf (49:1 Petroleum Ether:EtOAc): 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (m 1H, (**H5**), 6.11 – 5.84 (m, 1H, (**H6**), 1.54 – 1.42 (s, 6H, (**H8**)), 1.38 – 1.20 (m, 12H, (**H3** & **H4**)), 0.89 (dd, *J* = 11.7, 4.4 Hz, 15H, (**H2** & **H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (**C5**), 122.6 (**C6**), 72.6 (**C7**), 29.6 (**C8**), 29.2 (**C3**), 27.4 **(C2**), 13.9 (**C1**), 9.6 (**C4**).

1-[(E)-2-tributylstannylvinyl]cyclohexanol 287b



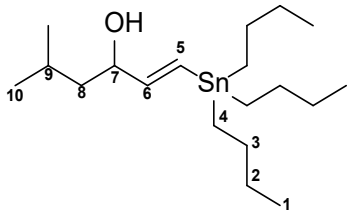
The title compound was prepared according to **General Procedure 4B** from **278b** (50 mg, 0.4 mmol) and tributyltin hydride (0.32 mL, 1.21 mmol) using $PtCl_2$ (5 mg, 20 µmol) and XPhos (19 mg, 40 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287b** as a pale-yellow oil (139 mg, 83%). Spectral data is in accordance with literature reports.[169]

Rf (49:1 Petroleum Ether:EtOAc): 0.28

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 – 6.12 (m, 1H, (**H5**)), 6.12 – 6.01 (m, 1H, (**H6**)), 1.72 – 1.42 (m, 16H, (**H4**, **H$_{Cylohexyl}$** & **OH**)), 1.35 – 1.22 (m, 8H, (**H3** and **H10**)), 0.90 (dt, *J* = 10.3, 6.8 Hz, 15H, (**H1** and **H2**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (**C5**), 123.5 (**C6**), 73.2 (**C7**), 37.8 (**C$_{Cyclohexyl}$**), 29.2 (**C$_{Cyclohexyl}$**), 27.4 (**C3**), 25.8 (**C10**), 22.4 (**C2**), 13.9 (**C1**), 9.6 (**C4**).

(E)-5-methyl-1-tributylstannyl-hex-1-en-3-ol 287c



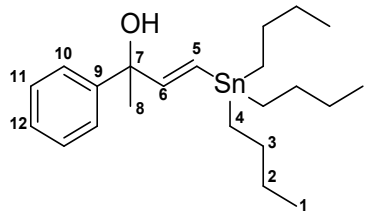
The title compound was prepared according to **General Procedure 4B** from **278c** (50 mg, 0.45 mmol) and tributyltin hydride (0.36 mL, 1.3 mmol) using $PtCl_2$ (6 mg, 22 μmol) and XPhos (21 mg, 44 μmol) which following conversion to the vinyl stannane and column chromatography afforded **287c** as a pale-yellow oil (98 mg, 55%). Spectral data is in accordance with literature reports.[171]

Rf (49:1 Petroleum Ether:EtOAc): 0.32

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 – 6.06 (m, 1H, (**H5**)), 6.06 – 5.86 (m, 1H, (**H6**)), 4.17 – 4.09 (m, 1H, (**H7**)), 1.74 (dq, *J* = 19.9, 6.6 Hz, 1H, (**H9**)), 1.55 – 1.41 (m, 8H, (**H10** & **H8**)), 1.39 – 1.24 (m, 8H, (**H$_{Sn\text{-}Bu}$** & **OH**), 0.91 (ddd, *J* = 19.2, 10.6, 5.3 Hz, 20H (**H$_{Sn\text{-}Bu}$**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (**C6**), 127.6 (**C5**), 74.1 (**C7**), 46.4 (**C8**), 29.2 (**C3**), 27.4 (**C2**), 24.8 (**C9**), 23.2 (**C10**), 22.6 (**C10**), 13.9 (**C1**), 9.6 (**C4**).

(E)-2-phenyl-4-tributylstannyl-but-3-en-2-ol 287d



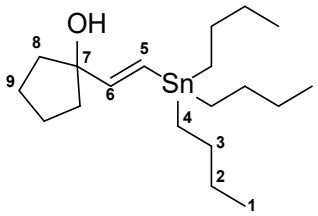
The title compound was prepared according to **General Procedure 4B** from **278d** (50 mg, 0.34 mmol) and tributyltin hydride (0.27 mL, 1.04 mmol) using $PtCl_2$ (5 mg, 17 µmol) and XPhos (16 mg, 34 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287d** as a pale-yellow oil (133 mg, 89%). Spectral data is in accordance with literature reports.[169]

Rf (49:1 Petroleum Ether:EtOAc): 0.34

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H, (**H11**)), 7.38 – 7.31 (m, 2H, (**H10**)), 7.26 – 7.21 (m, 1H, (**H12**)), 6.30 (m, 1H, (**H5**)), 6.22 (m, 1H, (**H6**)), 1.92 (s, 1H, (**OH**)), 1.64 (s, 3H, (**H8**)), 1.54 – 1.44 (m, 6H, (**H4**)), 1.35 – 1.24 (m, 6H, (**H3**)), 0.93 – 0.84 (m, 15H, (**H1** & **H2**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0 (**C6**), 146.9 (**C9**), 128.3 (**C11**), 126.9 (**C5**), 125.4 (**C10**), 124.7 (**C12**), 76.2 (**C7**), 29.5 (**C8**), 29.2 (**C3**), 27.4 (**C2**), 13.9 (**C1**), 9.7 (**C4**).

1-[(E)-2-tributylstannylvinyl]cyclopentanol 287e



The title compound was prepared according to **General Procedure 4B** from **278e** (50 mg, 0.45 mmol) and tributyltin hydride (0.36 mL, 1.4 mmol) using $PtCl_2$ (6 mg, 22 µmol) and XPhos (22 mg, 45 µmol) which following conversion to the

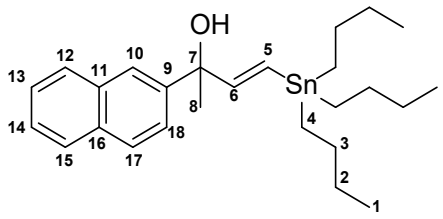
vinyl stannane and column chromatography afforded **287e** as a pale-yellow oil (149 mg, 82%). Spectral data is in accordance with literature reports.[169]

Rf (49:1 Petroleum Ether:EtOAc): 0.27

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 – 6.17 (m, 1H, (**H5**)), 6.17 – 6.07 (m, 1H, (**H6**)), 1.96 – 1.83 (m, 2H, (**H8** or **H9**), 1.78 – 1.69 (m, 4H, (**H8** or **H9**)), 1.65 (m, 2H, (**H8** or **H9**), 1.56 – 1.46 (m, 6H, (**H4**)), 1.32 (m, 6H, (**H3**)), 0.92 (m, 15H, (**H2** and **H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1 (**C5**), 122.8 (**C6**), 83.8 (**C7**), 40.6 (**C8**), 29.2 (**C9b)**, 27.4 (**C3**), 24.1 (**C2**), 13.9 (**C1**), 9.6 (**C4**).

(E)-2-napthyl-4-tributylstannyl-but-3-en-2-ol 287f



The title compound was prepared according to **General Procedure 4B** from **278f** (50 mg, 0.26mmol) and tributyltin hydride (0.21 mL, 0.76 mmol) using $PtCl_2$ (3.4 mg, 13 µmol) and XPhos (12 mg, 26 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287f** as a pale-yellow oil (113 mg, 91%).

Rf (49:1 Petroleum Ether:EtOAc): 0.35

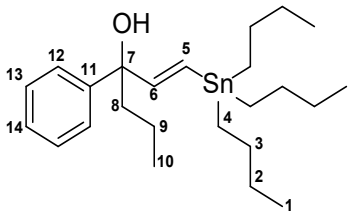
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{26}H_{41}OSn$ 489.2179; Found 489.2176

IR υmax (cm^{-1}): 3444, 3058, 2956, 2922. 2851

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.5 Hz, 1H, (**H17**)), 7.82 (m, 3H, (**H12, H15** & **H18**)), 7.55 (dd, *J* = 8.6, 1.9 Hz, 1H, (**H10**)), 7.50 – 7.42 (m, 2H, (**H13** & **H14**)), 6.37 (m, 1H, (**H5**)), 6.28 (m, 1H, (**H6**), 2.06 (d, *J* = 1.1 Hz, 1H, (**OH**)), 1.74 (s, 3H, (**H8**)), 1.50 (ddd, *J* = 12.9, 8.6, 6.4 Hz, 6H, (**H4**)), 1.30 (dd, *J* = 14.8, 7.3 Hz, 6H, (**H3**)), 0.89 (dt, *J* = 12.6, 7.7 Hz, 15H, (**H1** and **H2**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0 (**C6**), 144.3 (**C9**), 133.4 (**C11** or **C16**), 132.6 (**C11** or **C16**), 128.4 (**C$_{Aromatic}$**), 128.0 (**C$_{Aromatic}$**), 127.7 (**C$_{Aromatic}$**), 126.3 (**C$_{Aromatic}$**), 126.0 (**C$_{Aromatic}$**), 125.4 (**C$_{Aromatic}$**), 124.6 (**C$_{Aromatic}$**), 123.6 (**C$_{Aromatic}$**), 76.5 (**C7**), 29.5 (**C8**), 29.3 (**C3**), 27.5 (**C2**), 14.0 (**C1**), 9.8 (**C4**).

(E)-3-phenyl-1-tributylstannyl-hex-1-en-3-ol 287g



The title compound was prepared according to **General Procedure 4B** from **278g** (50 mg, 0.28 mmol) and tributyltin hydride (0.23 mL, 0.86 mmol) using $PtCl_2$ (4 mg, 14 μmol) and XPhos (14 mg, 28 μmol) which following conversion to the vinyl stannane and column chromatography afforded **287g** as a pale-yellow oil (119 mg, 89%).

Rf (49:1 Petroleum Ether:EtOAc): 0.39

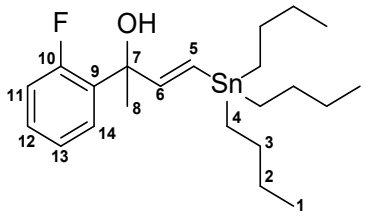
IR υmax (cm^{-1}): 3398, 3102, 3054, 2984. 2868

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{24}H_{43}OSn$ 467.2336; Found 467.2332

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H, (**H13**)), 7.37 – 7.29 (m, 2H, (**H12**)), 7.25 – 7.19 (m, 1H, (**H14**)), 6.43 – 6.28 (m, 1H, (**H5**)), 6.24 – 6.08 (m, 1H, (**H6**)), 1.99 – 1.74 (m, 3H, (**H8**)), 1.54 – 1.42 (m, 6H, (**H4**)), 1.39 – 1.14 (m, 8H, (**H3** & **H9**)), 0.99 – 0.79 (m, 18H, (**H1**, **H2** & **H10**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (**C6**), 146.3 (**C11**), 128.2 (**C13**), 126.7 (**C5**), 125.6 (**C14**), 124.6 (**C12**), 78.4 (**C7**), 44.6 (**C8**), 29.2 (**C3**), 27.4 (**C2**), 17.2 (**C9**), 14.6 (**C10**), 13.9 (**C1**), 9.7 (**C4**).

(E)-2-(2-fluorophenyl)-4-tributylstannyl-but-3-en-2-ol 287h



The title compound was prepared according to **General Procedure 4B** from **278h** (50 mg, 0.31 mmol) and tributyltin hydride (0.25 mL, 0.91 mmol) using $PtCl_2$ (4 mg, 14 µmol) and XPhos (14 mg, 28 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287h** as a colourless oil (120 mg, 85%).

Rf (49:1 Petroleum Ether:EtOAc): 0.35

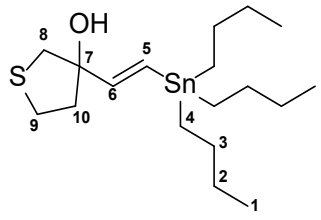
IR υmax (cm^{-1}): 3412, 3047, 2978, 2903

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{22}H_{38}FOSn$ 457.1929; Found 457.1925

^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (td, *J* = 8.0, 1.8 Hz, 1H, (**H11**)), 7.32 – 7.18 (m, 2H, (**$H_{Aromatic}$**)), 7.16 – 7.09 (m, 1H, ((**$H_{Aromatic}$**)), 7.01 (ddd, *J* = 12.0, 8.1, 1.2 Hz, 1H, (**H12**)), 6.59 – 6.30 (m, 1H, (**H5**)), 6.30 – 5.98 (m, 1H, (**H6**)), 2.35 (d, *J* = 4.0 Hz, 1H, (**OH**)), 1.69 (d, *J* = 0.6 Hz, 3H, (**H6**)), 1.53 – 1.38 (m, 5H, (**H4**)), 1.28 (tt, *J* = 14.2, 7.2 Hz, 7H, (**H3**)), 0.97 – 0.79 (m, 15H, (**H1** and **H2**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (d, *J* = 246.0 Hz, (**C10**)), 152.4 (d, *J* = 2.4 Hz, (**C6**)), 133.6 (d, *J* = 11.3 Hz, (**C9**)), 128.8 (d, *J* = 8.6 Hz, (**C12**)), 126.9 (d, *J* = 4.3 Hz, (**C5**)), 124.9 (d, *J* = 1.3 Hz, (**C13**)), 123.9 (d, *J* = 3.3 Hz, (**C14**)), 116.0 (d, *J* = 23.3 Hz, (**C11**)), 75.0 (d, *J* = 2.6 Hz, (**C7**)), 28.1 (d, *J* = 3.0 Hz, (**C8**)), 29.0 (**C3**), 27.2 (**C2**), 13.7 (**C1**), 9.5 (**C4**).

3-[(E)-2-tributylstannylvinyl]tetrahydrothiophen-3-ol 287i



The title compound was prepared according to **General Procedure 4B** from **278i** (50 mg, 0.39 mmol) and tributyltin hydride (0.32 mL, 1.17 mmol) using $PtCl_2$ (5 mg, 20 µmol) and XPhos (19 mg, 40 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287i** as a pale-yellow oil (106 mg, 80%).

Rf (19:1 Petroleum Ether:EtOAc): 0.28

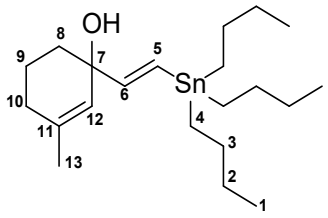
IR υmax (cm^{-1}): 3391, 3045, 2994, 2961, 2910

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{18}H_{37}OSSn$ 421.1587; Found 421.1585

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 – 6.26 (m, 1H, (**H5**)), 6.26 – 5.99 (m, 1H, (**H6**)), 3.08 (td, *J* = 10.5, 6.5 Hz, 1H, (**H8**)), 3.01 (d, *J* = 11.4 Hz, 1H, (**H8**)), 2.95 (ddd, *J* = 10.3, 7.9, 2.3 Hz, 1H, (**H9**)), 2.72 (dd, *J* = 11.4, 1.6 Hz, 1H, (**H9**)), 2.10 – 1.89 (m, 3H, (**H10** & **OH**)), 1.56 – 1.45 (m, 6H, (**H4**)), 1.31 (dq, *J* = 14.3, 7.2 Hz, 6H, (**H3**)), 1.04 – 0.78 (m, 15H, (**H1** & **H2**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (**C6**), 127.5 (**C5**), 84.3 (**C7**), 43.8 (**C8**), 42.9 (**C9**), 29.4 (**C10**), 29.2 (**C3**), 27.4 (**C2**), 13.9 (**C1**), 9.7 (**C4**).

3-methyl-1-[(E)-2-tributylstannylvinyl]cyclohex-2-en-1-ol 287j



The title compound was prepared according to **General Procedure 4B** from **278j** (50 mg, 0.37 mmol) and tributyltin hydride (0.30 mL, 1.10 mmol) using $PtCl_2$ (5 mg, 18 µmol) and XPhos (18 mg, 36 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287j** as an orange oil (106 mg, 67%).

Rf (49:1 Petroleum Ether:EtOAc): 0.33

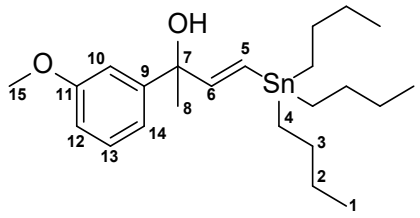
IR υmax (cm^{-1}): 3428, 3102, 2989, 2953. 2899

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{21}H_{41}OSn$ 429.2179; Found 429.2182

^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (m, 1H, (**H5**)), 6.25 (m, 1H, (**H6**)), 5.60 (s, 1H, (**H12**)), 2.24 (m, 1H, (**H10**)), 2.06 (m, 1H, (**H10**)), 1.88 – 1.59 (m, 4H, (**H9** & **H10**), 1.55 – 1.46 (m, 6H, (**H4**)), 1.41 – 1.29 (m, 9H, (**H13** & **H3**)), 0.90 (m, 15H, (**H1** & **H2**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (**C6**), 138.8 (**C11**), 134.0 (**C12**), 128.6 (**C7**), 69.0 (**C7**), 38.2 (**C13**), 29.5 (**C10**), 29.3 (**C3**), 27.5 (**C2**), 24.0 (**C8**), 19.6 (**C9**), 13.9 (**C1**), 9.6 (**C4**).

(E)-2-(3-methoxyphenyl)-4-tributylstannyl-but-3-en-2-ol 287l



The title compound was prepared according to **General Procedure 4B** from **278l** (50 mg, 0.28 mmol) and tributyltin hydride (0.23 mL, 0.85 mmol) using $PtCl_2$ (4 mg, 14 µmol) and XPhos (14 mg, 28 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287l** as a pale-yellow oil (106 mg, 80%).

Rf (19:1 Petroleum Ether:EtOAc): 0.32

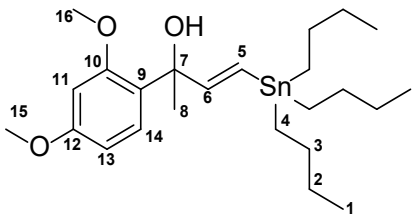
IR υmax (cm^{-1}): 3455, 2953, 2922, 2847

HRMS (ESI) m/z: [M + H]+ Calcd for $C_{23}H_{41}O_2Sn$ 469.2129; Found 469.2132

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (ddd, *J* = 8.1, 7.7, 0.4 Hz, 1H, (**H13**)), 7.03 (dddd, *J* = 9.4, 7.6, 1.7, 1.2 Hz, 2H, (**H12** & **H14**)), 6.79 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H, (**H10**)), 6.28 (m, 1H, (**H5**)), 6.22 (m, 1H, (**H6**)), 3.81 (s, 3H, (**H15**)), 1.92 (br s, 1H, (**OH**)), 1.62 (s, 3H, (**H8**)), 1.54 – 1.44 (m, 6H, (**H4**)), 1.33 – 1.26 (m, 6H, (**H3**)), 0.89 (m, 15H, (**H1** & **H2**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (**C11**), 153.8 (**C6**), 148.7 (**C9**), 129.3 (**C5**), 124.8, (**C13**), 117.9 (**C14**), 112.3 (**C10**), 111.3 (**C12**), 76.2 (**C7**), 55.3 (**C15**), 29.5 (**C8**), 29.2 (**C3**), 27.4 (**C2**), 13.8 (**C1**), 9.7 (**C4**).

(E)-2-(2,4-dimethoxyphenyl)-4-tributylstannyl-but-3-en-2-ol 287m



The title compound was prepared according to **General Procedure 4B** from **278m** (50 mg, 0.24 mmol) and tributyltin hydride (0.2 mL, 0.73 mmol) using $PtCl_2$ (3 mg, 12 µmol) and XPhos (12 mg, 24 µmol) which following conversion to the vinyl stannane and column chromatography afforded **287m** as a pale-yellow oil (94 mg, 78%).

Rf (19:1 Petroleum Ether:EtOAc): 0.23

IR υmax (cm^{-1}): 3465, 3099, 3044, 3007, 2983

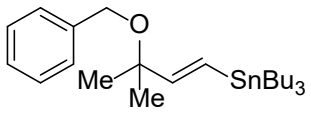
HRMS (ESI) m/z: [M + H]+ Calcd for $C_{24}H_{43}O_3Sn$ 499.2234; Found 499.2230

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 1H), (**H14**), 6.46 (m, 2H, (**H13** & **H11**)), 6.25 (m, 1H, (**H5**)), 5.98 (m, 1H, (**H6**)), 4.19 (s, 1H, (**OH**)), 3.81 (s, 6H, (**H15** & **H16**)), 1.61 (s, 3H, (**H8**)), 1.52 – 1.38 (m, 6H, (**H4**)), 1.27 (dt, *J* = 14.5, 7.3 Hz, 6H, (**H3**)), 0.84 (m, 15H, (**H1** & **H2**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (**C12** or **C10**), 158.3 (**C12** or **C10**), 154.6 (**C6**) , 127.4 (**C5**), 127.1 (**C9**), 123.0 (**C14**), 104.0 (**C13**), 99.8 (**C11**), 76.1 (**C7**), 55.5 (**C15** or **C16**), 55.4 (**C15** or **C16**), 29.2 (**C3**), 27.8 (**C8**), 27.4 (**C2**), 13.9 (**C1**), 9.6 (**C4**).

4.8.4 Substrates Quantified by NMR Yield

[(E)-3-benzyloxy-3-methyl-but-1-enyl]-tributyl-stannane 288a



The title compound was prepared according to **General Procedure 4B** from **280** (10 mg, 57 µmol) and tributyltin hydride (0.05 mL, 0.18 mmol) using $PtCl_2$ (2 mg, 6 µmol) and XPhos. (6 mg, 12 µmol) Following conversion to the vinyl stannane, 3.5 mg of 1,3,5-trimethoxybenzene was added, and volatiles were removed under reduced pressure. Yield of **288a** was then calculated by ^1H NMR analysis of the crude reaction mixture as follows;

nA (Moles of Analyte)

nIS (Moles of Internal Standard)

rA/IS (Analyte Peak Integral/Internal Standard Peak Integral)

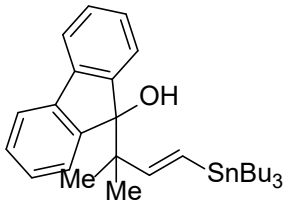
nA= nIS x rA/IS

nIS: 20.8 µmol

rA/IS: (0.74/1)/(1/3) = 2.22 nA: 46 µmol

Yield = 81%

(E)-1-(9H-fluoren-9-yl)-2,2-dimethyl-4-tributylstannyl-but-3-en-1-ol 288b



The title compound was prepared according to **General Procedure 4B** from **201k** (10 mg, 40 μmol) and tributyltin hydride (0.03 mL, 0.12 mmol) using $PtCl_2$ (1 mg, 4 μmol) and XPhos. (4 mg, 8 μmol) Following conversion to the vinyl stannane, 2 mg of 1,3,5-trimethoxybenzene was added, and volatiles were removed under reduced pressure. Yield of **288b** was then calculated by ^1H NMR analysis of the crude reaction mixture as follows;

nA (Moles of Analyte)

nIS (Moles of Internal Standard)

rA/IS (Analyte Peak Integral/Internal Standard Peak Integral)

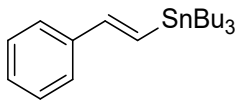
nA= nIS x rA/IS

nIS: 11.9 μmol

rA/IS: (0.31/1)/(1/3) = 0.93 nA: 11.1 μmol

Yield = 28%

tributyl-[(E)-styryl]stannane 288c



The title compound was prepared according to **General Procedure 4B** from phenyl acetylene (10 mg, 98 μmol) and tributyltin hydride (0.08 mL, 0.30 mmol) using $PtCl_2$ (3 mg, 10 μmol) and XPhos. (10 mg, 20 μmol) Following conversion to the vinyl stannane, 1.4 mg of 1,3,5-trimethoxybenzene was added, and volatiles were removed under reduced pressure. Yield of **288c** was then calculated by ^1H NMR analysis of the crude reaction mixture as follows;

nA (Moles of Analyte)

nIS (Moles of Internal Standard)

rA/IS (Analyte Peak Integral/Internal Standard Peak Integral)

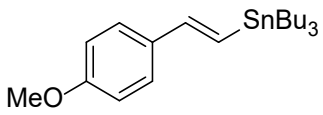
nA= nIS x rA/IS

nIS: 8.3 μmol

rA/IS: (3.71/1)/(1/3) =11.1 nA: 92 μmol

Yield = 93%

tributyl-[(E)-2-(4-methoxyphenyl)vinyl]stannane 288d



The title compound was prepared according to **General Procedure 4B** from 4-methoxyphenylacetylene (10 mg, 75 µmol) and tributyltin hydride (0.06 mL, 0.23 mmol) using $PtCl_2$ (2 mg, 7.5 µmol) and XPhos. (7.5 mg, 15 µmol) Following conversion to the vinyl stannane, 0.45 mg of 1,3,5-trimethoxybenzene was added, and volatiles were removed under reduced pressure. Yield of **288d** was then calculated by ^1H NMR analysis of the crude reaction mixture as follows;

nA (Moles of Analyte)

nIS (Moles of Internal Standard)

rA/IS (Analyte Peak Integral/Internal Standard Peak Integral)

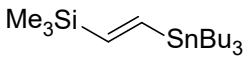
nA= nIS x rA/IS

nIS: 2.76 µmol

rA/IS: (8.42/1)/(1/3) =25.3 nA: 70 µmol

Yield = 94%

trimethyl-[(E)-2-tributylstannylvinyl]silane 288e



The title compound was prepared according to **General Procedure 4B** from trimethylsilylacetylene (10 mg, 100 µmol) and tributyltin hydride (0.08 mL, 0.3 mmol) using $PtCl_2$ (3 mg, 10 µmol) and XPhos. (10 mg, 20 µmol) Following conversion to the vinyl stannane, 10.4 mg of 1,3,5-trimethoxybenzene was added, and volatiles were removed under reduced pressure. Yield of **288e** was then calculated by ^{1}H NMR analysis of the crude reaction mixture.

nA (Moles of Analyte)

nIS (Moles of Internal Standard)

rA/IS (Analyte Peak Integral/Internal Standard Peak Integral)

nA= nIS x rA/IS

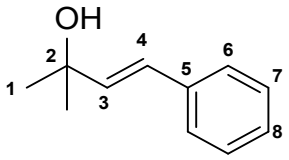
nIS: 61 µmol

rA/IS: (0.45/1)/(1/3) =1.35 nA: 83 µmol

Yield = 83%

4.8.5 Cross-Coupling Products

(E)-2-methyl-4-phenyl-but-3-en-2-ol 289



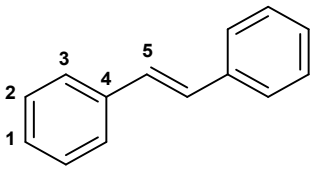
The title compound was prepared according to **General Procedure 4C** from **278a** (50 mg, 0.60 mmol) and tributyltin hydride (0.48 mL, 1.8 mmol) using $PtCl_2$ (8 mg, 30 µmol) and XPhos (29 mg, 60 µmol). Following conversion to vinyl stannane, the subsequent cross-coupling was carried out using iodobenzene (70 µL, 0.59 mmol) and copper thiocarboxylate (136 mg, 0.71 mmol) in the presence of 20 $Pd(PPh_3)_4$ (34 mg, 30 µmol). Following conversion to the coupled product, flash chromatography afforded **289** as a pale-yellow oil. (81 mg, 84%). Spectral data is in accordance with literature reports.[24]

Rf (9:1 Petroleum Ether:EtOAc): 0.19

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H, (**H7**)), 7.35 – 7.29 (m, 2H, (**H6**)), 7.27 – 7.20 (m, 1H, (**H8**)), 6.59 (d, *J* = 16.1 Hz, 1H, (**H4**)), 6.36 (d, *J* = 16.1 Hz, 1H, (**H3**), 1.43 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (**C3**), 137.1 (**C5**), 128.7 (**C7**), 127.6 (**C8**), 126.6 (**C6**), 126.5 (**C4**), 71.2 (**C2**), 30.0 (**C1**).

(E)-Stilbene 290a



The title compound was prepared according to **General Procedure 4C** from phenylacetylene (50 mg, 0.49 mmol) and tributyltin hydride (0.4 mL, 1.47 mmol) using $PtCl_2$ (13 mg, 49 µmol) and XPhos (49 mg, 98 µmol). Following conversion to vinyl stannane, the subsequent cross-coupling was carried out using

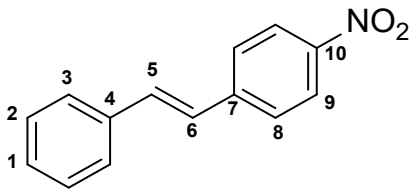
iodobenzene (60 µL, 0.54 mmol) and copper thiocarboxylate (112 mg, 0.59 mmol) in the presence of $Pd(PPh_3)_4$ (28 mg, 25 µmol). Following conversion to the coupled product, flash chromatography afforded **290a** as a white solid (66 mg, 76%). Spectral data is in accordance with literature reports.[190]

Rf (99:1 Petroleum Ether:EtOAc): 0.74

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 4H, (**H2**)), 7.40 – 7.33 (m, 4H, (**H3**)), 7.26 (ddd, *J* = 6.3, 2.7, 1.3 Hz, 2H, (**H1**)) (Signal overlaps with $CDCl_3$), 7.12 (s, 2H, (**H5**)).

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (**C4**), 128.9 (**C1**), 128.8 ©2, 127.8 (**C3**), 126.7 (**C5**). Data in agreement with previous reports.9

(E)-4-Nitrostilbene 290b



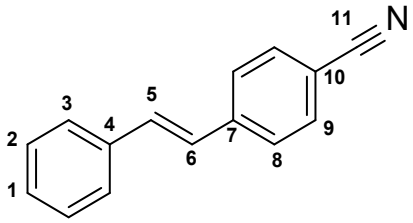
The title compound was prepared according to **General Procedure 4C** from phenylacetylene (50 mg, 0.49 mmol) and tributyltin hydride (0.4 mL, 1.47 mmol) using $PtCl_2$ (13 mg, 49 µmol) and XPhos (49 mg, 98 µmol). Following conversion to vinyl stannane, the subsequent cross-coupling was carried out using 4-nitrobromobenzene (109 mg, 0.54 mmol) and copper thiocarboxylate (112 mg, 0.59 mmol) in the presence of $Pd(PPh_3)_4$ (28 mg, 25 µmol). Following conversion to the coupled product, flash chromatography afforded **290b** as a yellow solid (87 mg, 81%). Spectral data is in accordance with literature reports.[190]

Rf (99:1 Petroleum Ether:EtOAc): 0.58

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.20 (m, 2H, (**H9**), 7.66 – 7.61 (m, 2H, (**H8**)), 7.58 – 7.53 (m, 2H, (**H2**)), 7.44 – 7.37 (m, 2H, (**H3**)), 7.37 – 7.31 (m, 1H, (**H1**)), 7.28 (d, *J* = 16.4 Hz, 1H, (**H4**) overlap with $CDCl_3$), 7.15 (d, *J* = 16.3 Hz, 1H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (**C10**), 144.0 (**C7**), 136.3 (**C4**), 133.5 (**C5**), 129.1 (**C$_{Aromatic}$**), 129.0 (**C1**), 127.2 (**C$_{Aromatic}$**), 127.0 (**C$_{Aromatic}$**), 126.4, (**C$_{Aromatic}$**), 124.3 (**C6**).

(E)-4-Cyanostilbene 290c



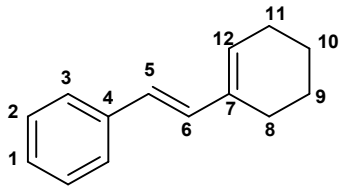
The title compound was prepared according to **General Procedure 4C** from phenylacetylene (50 mg, 0.49 mmol) and tributyltin hydride (0.4 mL, 1.47 mmol) using $PtCl_2$ (13 mg, 49 µmol) and XPhos (49 mg, 98 µmol). Following conversion to vinyl stannane, the subsequent cross-coupling was carried out using 4-cyanobromobenzene (98 mg, 0.54 mmol) and copper thiocarboxylate (112 mg, 0.59 mmol) in the presence of $Pd(PPh_3)_4$ (28 mg, 25 µmol). Following conversion to the coupled product, flash chromatography afforded **290c** as a white solid (76 mg, 77%). Spectral data is in accordance with literature reports.[190]

Rf (99:1 Petroleum Ether:EtOAc): 0.64

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 2H, (**H9**)), 7.61 – 7.56 (m, 2H, (**H8**)), 7.56 – 7.50 (m, 2H, (**H2**)), 7.43 – 7.36 (m, 2H, (**H3**)), 7.35 – 7.30 (m, 1H, (**H1**)), 7.22 (d, *J* = 16.3 Hz, 1H, (**H5**)), 7.09 (d, *J* = 16.3 Hz, 1H, (**H6**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (**C10**), 136.4 (**C7**), 132.6 (**C9**), 132.6 (**C1**), 129.0 (**C8**), 128.8 (**C5**), 127.1 (**C2** or **C3**), 127.0 (**C2** or **C3**), 126.9 (**C6**), 119.2 (**C4**), 110.7 (**C11**).

[(E)-2-(cyclohexen-1-yl)vinyl]benzene 290e



The title compound was prepared according to **General Procedure 4C** from phenylacetylene (50 mg, 0.49 mmol) and tributyltin hydride (0.4 mL, 1.47 mmol) using $PtCl_2$ (13 mg, 49 µmol) and XPhos (49 mg, 98 µmol). Following conversion to vinyl stannane, the subsequent cross-coupling was carried out using 1-Cyclohexenyl trifluoromethanesulfonate (113 mg, 0.54 mmol and copper thiocarboxylate (112 mg, 0.59 mmol) in the presence of $Pd(PPh_3)_4$ (28 mg, 25 µmol). Following conversion to the coupled product, flash chromatography afforded **290e** as a yellow oil (66 mg, 74%) **Note: Sample found to be prone to degradation in $CDCl_3$** Spectral data is in accordance with literature reports.[191]

Rf (99:1 Petroleum Ether:EtOAc): 0.84

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.2, 1.0 Hz, 2H, (**H2**)), 7.30 (t, *J* = 7.6 Hz, 2H, (**H3**)), 7.23 – 7.14 (m, 1H, (**H1**)), 6.77 (d, *J* = 16.1 Hz, 1H, (**H6**)), 6.44 (d, *J* = 16.1 Hz, 1H, (**H5**)), 5.90 (t, *J* = 4.4 Hz, 1H, (**H12**), 2.28 (t, *J* = 5.0 Hz, 2H, (**H8**)), 2.21 – 2.14 (m, 2H, (**H11**)), 1.77 – 1.69 (m, 2H, (**H10**)), 1.69 – 1.60 (m, 2H, (**H9**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (**C7**), 135.9 (**C4**), 132.6 (**C12**), 130.9 (**C1**), 128.5 (**C2**), 126.8 (**C3**), 126.2 (**C6**), 124.6 (**C5**), 26.1 (**C8**), 24.6 (**C11**), 22.6 (**C10** or **C9**), 22.5 (**C10** or **C9**).

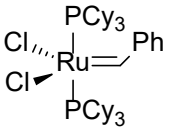
Chapter 5: Synthesis and Evaluation of Mixed:NHC Platinum Complexes as Hydrometallation Catalysts

5.1 NHC Complexes in Hydrosilylation Chemistry

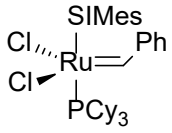
Since the initial report of the first isolable NHC by Arduengo and co-workers in 1991, transition metal NHC-complexes have become a mainstay in catalysis.[192] In comparison to phosphine ligands, NHC ligands possess several distinct differences. NHCs are stronger σ-donors but weaker π-acceptors. The result is that metal-NHC complexes possess more electron rich metal centres than the analogous phosphine complexes. This increased nucleophilicity permits, for example, application of aryl chlorides in Pd catalysed Suzuki cross-couplings.[193]

The decreased lability of the NHC ligand in comparison to phosphine ligands can also result in increased catalyst stability which in turn affords longer complex lifetime and increased turnover numbers, as demonstrated by the increase in catalytic activity between the first- and second-generation Grubbs cross-metathesis catalysts **292** & **293** (**Scheme 177**). Work by Kerr *et al* additionally represents a recent example of the increased efficacy of iridium based NHC/phosphine complex **296** in comparison to the diphosphine complex **297** when employed as catalysts for the hydrogenation of enone **294**.[194] This further reinforces the concept of the potential benefits of complexes bearing both NHC and phosphine type ligands in catalysis in comparison to complexes bearing solely phosphine ligands.

Grubbs Catalysts

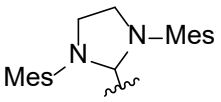


292
First Generation

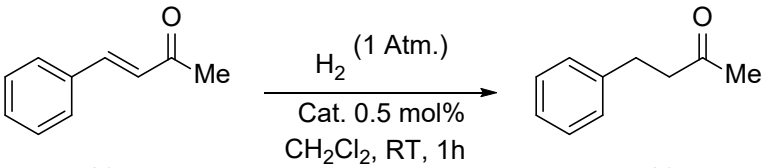


293
Second Generation

SIMes;



Kerr (2016)



294 **295**

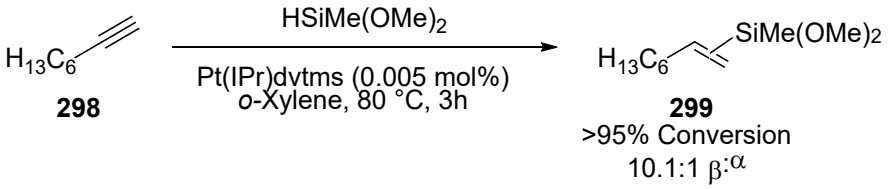
296
100% Conversion

297
33% Conversion

Scheme 118 Utility of transition metal complexes bearing both phosphine and NHC type ligands

The utility of platinum-NHC complexes in the context of hydrosilylation chemistry was first reported by Markó *et al* who demonstrated platinum-NHC complexes are highly active and selective hydrosilylation catalysts for olefin hydrosilylation. The catalytic activity is such that complete conversion can be achieved even at catalytic loadings as low as 30 ppm. The complexes, prepared from commercially available Karstedt's catalyst **7,** are air and moisture stable and display excellent chemoselectivity, being able to achieve selective olefin reduction in the presence of other reduction sensitive functionalities such as epoxides.[27] Mechanistically the complexes operate in a manner broadly similar to the Chalk-Harrod mechanism, and are able to achieve turnover numbers in excess of 10,000,000. [195] Subsequent studies by the same group showed complexes of this type are likewise able to achieve selective alkyne hydrosilylation at catalyst loadings of 0.005 mol%, again demonstrating the extremely high activity of these complexes (**Scheme 118**).[196] While these initial studies generally reported the activity of platinum complexes bearing relatively common NHC ligands such as ICy, IPr and

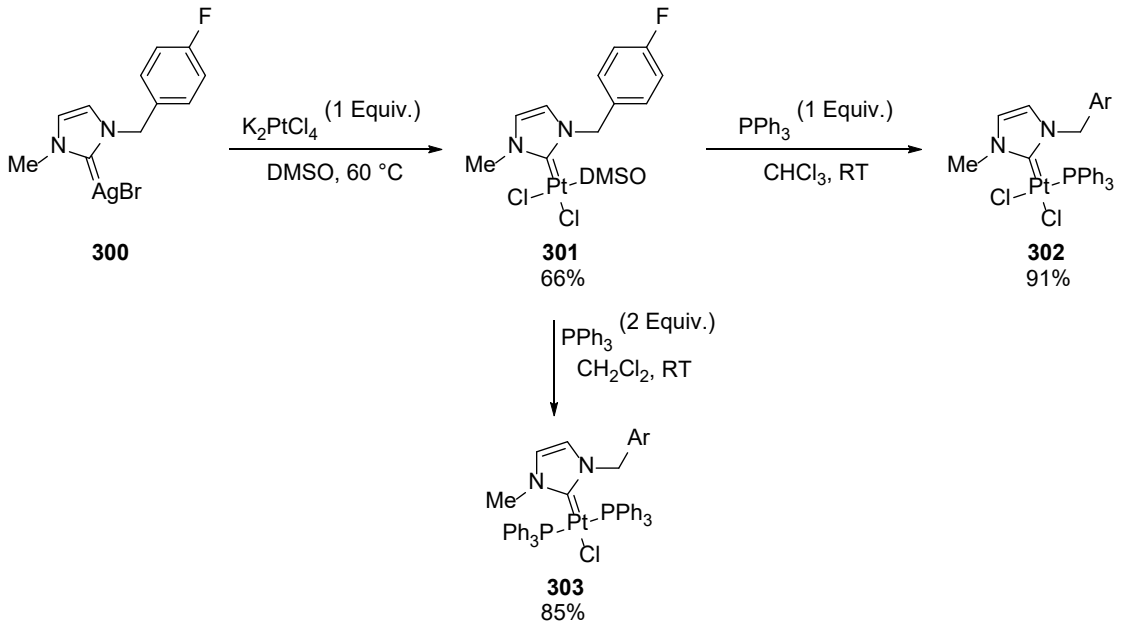
IMes, subsequent work has resulted in the screening of a wide range complexes bearing structurally diverse NHC ligands.[197-199]



Scheme 119 Application of platinum-NHC complexes as hydrosilylation catalysts

5.2 Mixed NHC-Phosphine Platinum Complexes

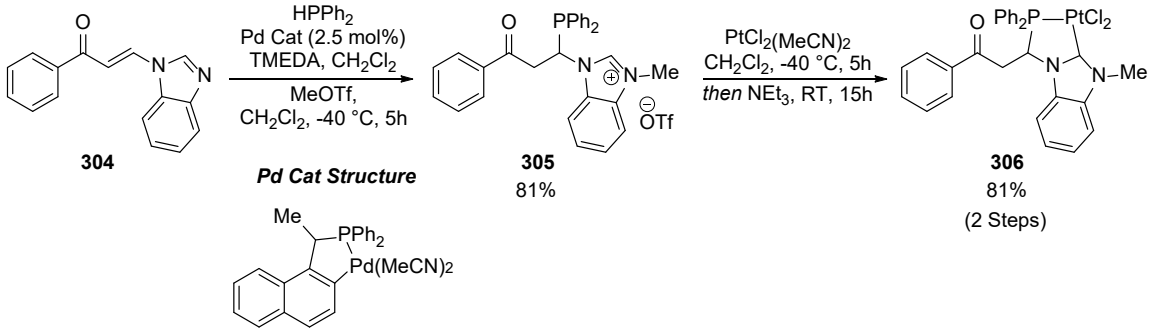
Rourke and co-workers first described the synthesis of mixed NHC-Phosphine platinum complexes in 2007 (**Scheme 119**). Here, the authors employed a silver-NHC complex as a transmetallating agent, which following treatment with potassium tetrachloroplatinate, affords platinum-DMSO complex **301**. The labile nature of the DMSO ligand within this complex means in the presence of triphenylphosphine, a ligand substitution takes place, affording complex **302** with a *cis* relationship between the NHC and phosphine ligands. This complex can subsequently undergo a second addition of triphenylphosphine to afford **303** due to the strong *trans* effect displayed by the first phosphine ligand increasing the lability of the chloride ligand.[200] While the synthesis reported by Rourke employed only 1-methyl-3-benzylimidazole systems, the same synthesis was later employed by Schobert *et al* to synthesise 1,3-dibenzylimidazol-2-ylidine platinum complexes.[201]



Scheme 120 Synthesis of mixed NHC/Phosphine platinum complexes as reported by Rourke and co-workers

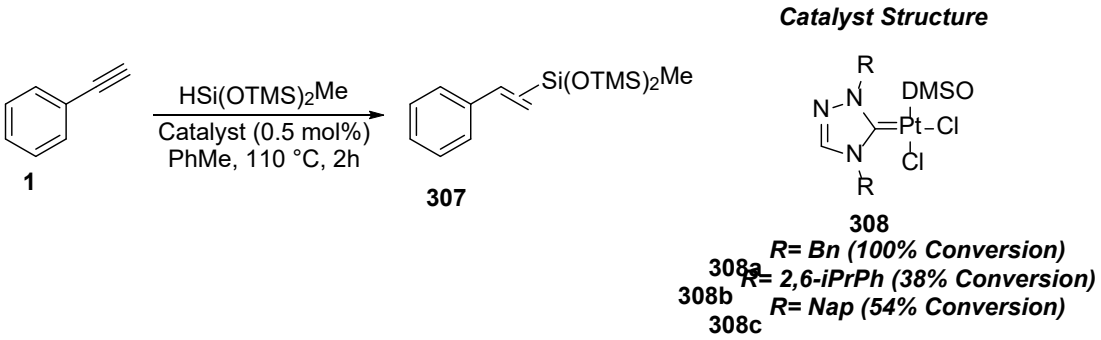
An alternative approach to the synthesis of these complexes was reported by Leung *et al* wherein the authors report the synthesis of chelating phosphino-NHC ligands *via* the route presented in **Scheme 120**. This route relies on the hydrophosphination of vinyl benzimidazoles **304** which, following subsequent

methylation, affords imidazolium salt **305**. Treatment of **305** with $PtCl_2(MeCN)_2$ affords metallocyclic complexes **306**.[202]



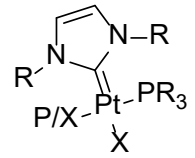
Scheme 121 Synthesis of mixed NHC/phosphine metallocyclic platinum complexes

While complexes of this type have seldom been investigated for their catalytic properties, studies of their biological properties are relatively commonplace, with particular focus on their anticancer properties due their structural similarity to cisplatin and its various analogues.[201] While the mixed NHC/phosphine platinum complexes have been seemingly overlooked in the context of catalysis, complexes structurally related to platinum-DMSO complex **301** have been evaluated. TAZY-platinum complexes **308** were studied by Huynh *et al* as catalysts for both hydration and hydrosilylation of alkynes. When screening a range of Pt-TAZY/dmso complexes, the steric bulk of the ligand, expressed as $\%V_{Bur}$, was intrinsically linked to the reaction yield as did the NHC Huynh Electronic Parameter (HEP). The HEP is a measure of a ligands σ-donicity by measuring the ^{13}C NMR shift of the carbene centre in a 1,3-diisopropylbenzimidazolin-2-ylidene ligand mutually *trans* to the ligand of interest at a metal centre, and the comparison of this value relative to the 'free' carbene. The closer the measured value is to the free NHC, the weaker the NHC-Metal bond is, and therefore the stronger the σ-donicity of the ligand of interest is. Ligands which were both electron rich and sterically bulky (**308b/308c**) performed the worst, whereas the highest performing ligands possessed either a high $\%V_{Bur}$ or high HEP value such as **308a**. This suggests catalytic activity of these complexes cannot be attributed to a single factor but rather is a fine balance of both steric and electronic factors.[203, 204]



Scheme 122 Synthetic utility of Rourkes intermediates as hydrosilylation catalysts

5.3 Aims



Catalytically Active?

Project Aims

- *Synthesise NHC precursor salts*
- *Synthesise Pt-NHC/Phosphine Complexes*
- *Validate reactivity towards hydrosilanes*
- *Investigate activity as hydrosilylation catalysts*

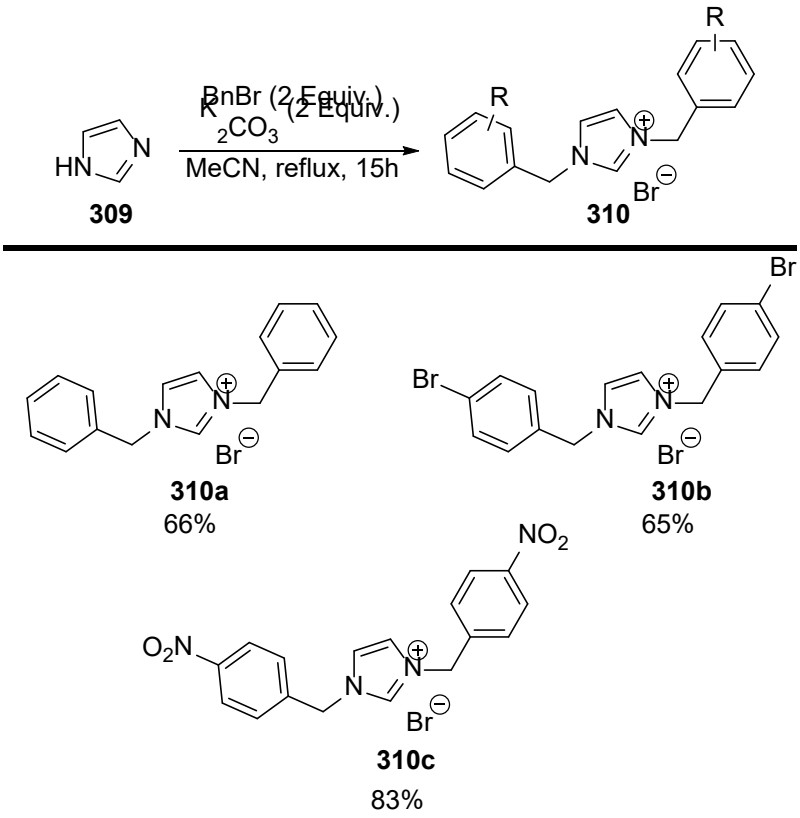
Figure 13 Generalised chapter 5 aims

Platinum-NHC/Phosphine complexes have been underexplored in catalysis despite being well studied as metal-based therapeutics. Considering the well documented application of complexes of this type employing other metal centres being employed for various catalytic processes, such as the well-known 2nd generation Grubbs catalysts, this oversight is surprising and the work in this chapter aims to explore the reactivity of these complexes further.

The work in this chapter aims to initially synthesise a diverse range of imidazolium salts to act as precursors towards NHC ligands. Platinum complexes bearing both NHC and phosphine ligands will then be synthesised *via* previously reported routes. The route proceeds first by the synthesis of a silver-carbene complex, which following transmetallation to platinum affords access to $PtCl_2$(NHC)(DMSO) as a lynchpin intermediate. Taking advantage of the lability of the DMSO ligand in a ligand substitution will permit access to complexes of general formula $PtCl_2$(NHC)PR_3 and [PtCl(NHC)$(PR_3)_2$]Cl. With complexes in hand, the activity of these complexes towards alkyne hydrosilylation will then be screened, alongside the activity of any intermediates employed through the course of the complex synthesis.

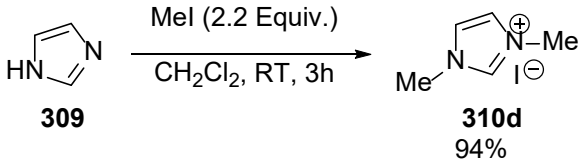
5.4 Synthesis of Mixed NHC-Phosphine Platinum Complexes

The synthesis of the mixed NHC-Pt complexes followed the route reported by Rourke and co-workers, discussed in **Chapter 5.2**. As such, a range of imidazolium salts were first prepared. Symmetrical *N*-Benzylimidazolium salts **310** were readily prepared by employing the route reported by Kerr and co-workers wherein imidazole **309** undergoes benzylation in the presence of the requisite benzyl bromide under basic conditions (**Scheme 122**).[194]



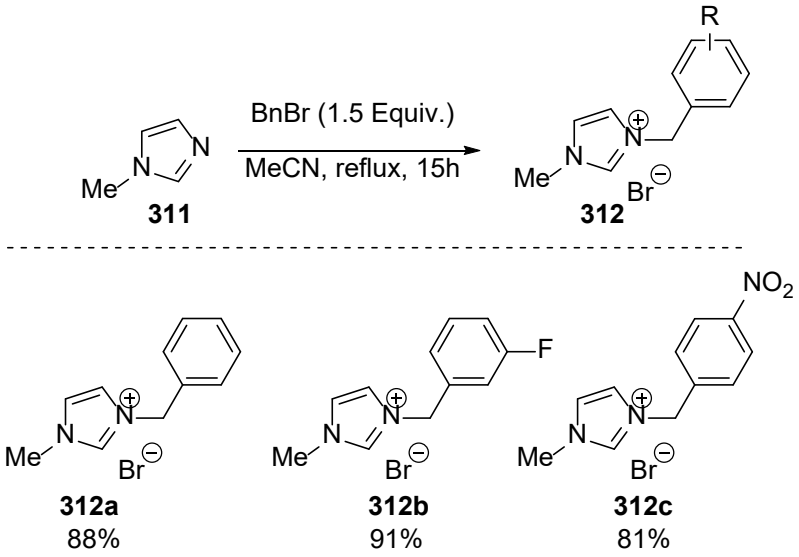
Scheme 123 Scope of symmetrical benzylimidazolium salts synthesised

1,3-dimethylimidazolium iodide **310d** was also prepared by the route outlined in **Scheme 123** as a non-benzylated symmetrical derivative in 94% yield.



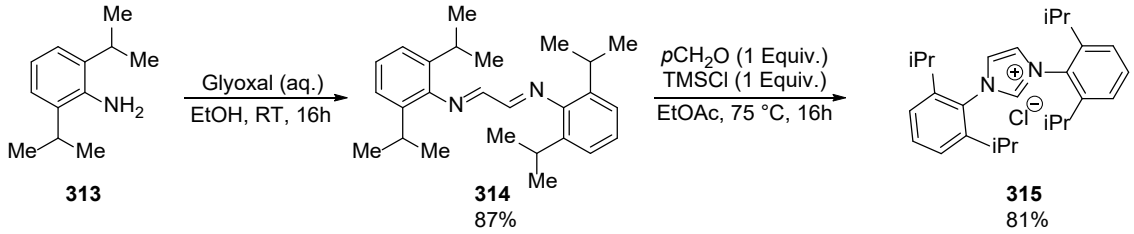
Scheme 124 Synthesis of 1,3-dimethylimidazoliium iodide

1-Me-3-Benzylimidazolium salts **312** were prepared *via* a similar route, treating 1-methylimidazole with the requisite benzyl bromide, to afford the corresponding salts in excellent yields.



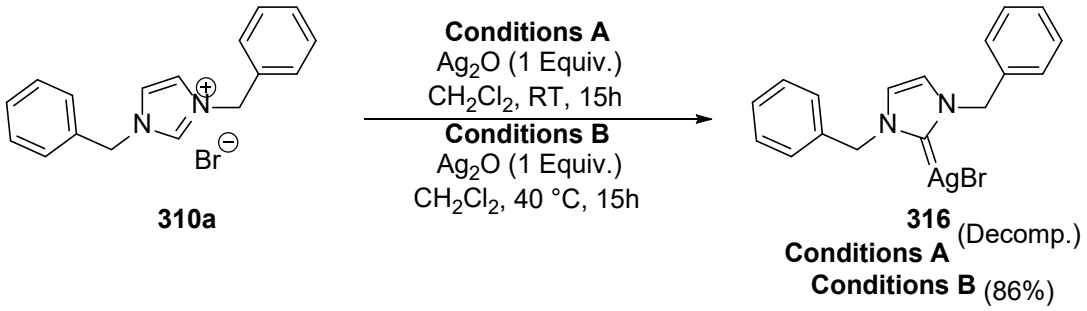
Scheme 125 Scope of unsymmetrical 1-Methyl-3-benzylimidazolium salts synthesised

Finally, as 1,3-diaryl NHC ligands such as IMes and IPr are frequently employed in catalysis, IPr.HCl was prepared analogously to the literature procedure. Initial formation of **314** by condensation between glyoxal and 2,5-diisopropylaniline **313** proceeded smoothly with **314** isolated in 87% yield. Treatment of **314** with *para*-formaldehyde in the presence of TMSCl afforded imidazolium salt **315** in 81% yield.[205]



Scheme 126

With a diverse library of imidazolium salts in hand, focus shifted to the synthesis of silver-carbene complexes. Utilising the conditions reported by Cingolani[206] wherein imidazolium salt **310a** undergoes complexation to an equimolar amount of Ag_2O, complete consumption of the ligand was observed as evidenced by the disappearance of the highly deshielded imidazolium proton in the ^1H NMR spectra of the crude reaction mixture. Unfortunately, the difficulty in removal of excess silver oxide led to rapid decomposition of the complex in the presence of light (**Scheme 127**, **Conditions A**). To this end, the reaction was repeated albeit with a decreased loading of silver, at which point the reaction became excessively sluggish. Pleasingly, upon carrying out the reaction at slightly elevated temperature, the reaction readily went to completion, affording **316** in 86% yield (**Scheme 127**, **Conditions B**).

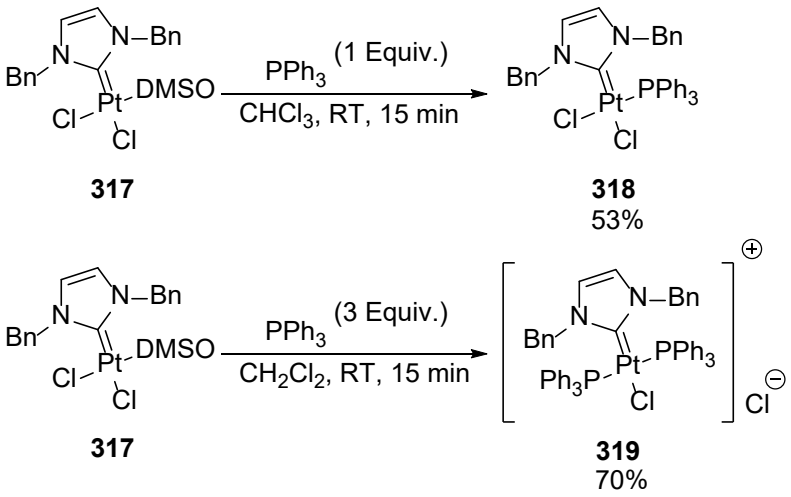


Scheme 127 Synthesis of silver carbene complex 316

As reported by Rourke *et al*, the complex afforded when **316** undergoes reaction with K_2PtCl_4 in DMSO was the mono-NHC/DMSO complex **317**, which under the conditions reported by Rourke was isolated in 73% yield. The *cis* relationship of the DMSO ligand to the NHC was confirmed by the splitting of the benzylic protons into 2 doublets, arising from hindered rotation around the Pt-NHC bond due to the presence of the DMSO methyl groups.

Scheme 128 Synthesis of platinum-DMSO complex 317

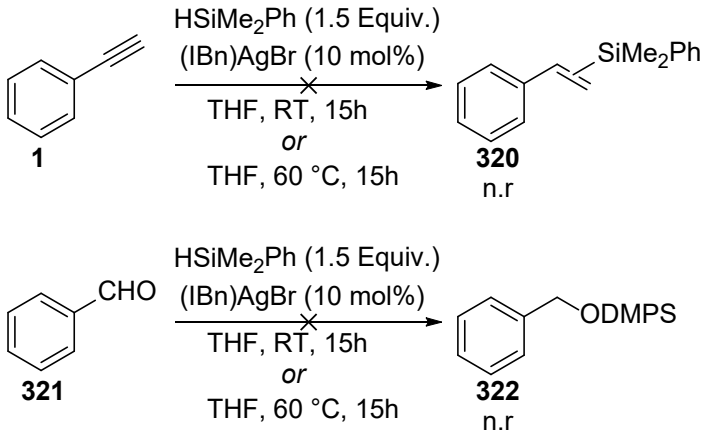
Attempting the ligand substitution of the coordinated DMSO initially proved problematic. Addition of the ligand too quickly into the reaction medium results in the formation of both **318** and **319** presumably due to the strong trans-effect of the first phosphine to coordinate to the metal centre increasing the lability of the chloride ligand to substitution by a second phosphine ligand. Nonetheless, upon careful addition of the phosphine as a solution in chloroform, **318** could be isolated in 53% yield. Diphosphine complex **319** could likewise be isolated in good yield by addition of excess triphenylphosphine to **317**. In complex **319**, the *trans* relationship of the triphenylphosphine groups can be ascertained by the nature of the signal attributed to the benzylic protons of the NHC ligand in the ^{1}H NMR alongside the single ^{31}P signal observed. With a range of complexes now in hand, attention turned to the screening of their catalytic efficacy as hydrosilylation catalysts.



Scheme 129 Synthesis of mixed NHC-Phosphine complexes 318 & 319

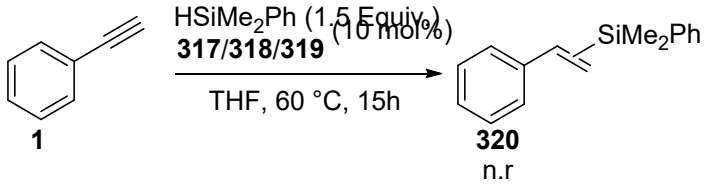
5.5 Evaluation of Complexes as Hydrosilylation Catalysts

While the primary aim of this work was the screening of the mixed ligand platinum complexes, as silver complex **316** had been synthesised as an intermediate in the course of the synthesis of the requisite platinum complexes, it was likewise screened as a catalyst. Attempting the hydrosilylation of **1** employing the conditions shown in **Scheme 129**, did not produce the desired product, with starting material recovered. This is perhaps unsurprising given that were **316** to react with $HSiMe_2Ph$ by the traditional hydrosilylation mechanism, i.e., by oxidative addition into the silicon hydride bond, it would form an extremely oxidising Ag(III) species which is likely highly energetically unfavourable. Given the lack of literature precedent in the field of silver catalysed hydrosilylation of unsaturated C-C bonds, attention instead turned to the attempted reduction of C=X bonds by silver mediated hydrosilylation. While still rare, examples of such reactions have been reported with one example being reported by Stradiotto though it should be noted that the authors propose that the particular case likely proceeds through Lewis acid activation of the electrophile rather than by Chalk-Harrod type hydrometallation.[207] Regardless, treating benzaldehyde with catalytic amounts of **316** and $HSiMe_2Ph$ under the conditions employed by Stradiotto *et al* likewise resulted in no observable aldehyde reduction. This is in keeping with the previously noted necessity for the silver complex to possess a poorly coordinating anion such as BF_4^- or TfO^- to facilitate substrate activation. As **316** had proved to be ineffective in achieving catalytic hydrosilylation of both carbon-heteroatom and carbon-carbon unsaturated bonds, this was not pursued further.



Scheme 130 Attempted hydrosilyation of phenylacetylene and benzaldehyde under silver-NHC catalysis

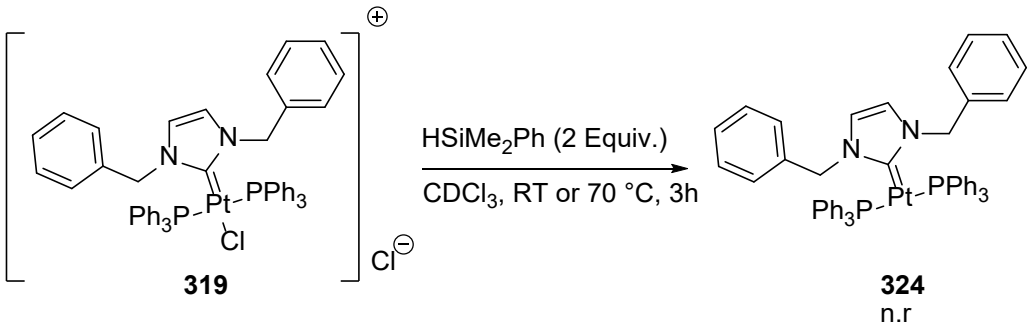
Next evaluated for its catalytic capabilities was **317**, as well as mixed ligand complexes **318** and **319**. **1** was chosen to be a model substrate on which to study hydrosilylation efficacy. As noted, the analogous TAZY complexes have been investigated for alkyne hydroelementation reactions with Hunyh *et al* noting the narrow windows of both steric and electronic properties in which these complexes are able to operate as competent hydrosilylation catalysts.[203] When **1** was treated with complex **317** in the presence of dimethylphenyl silane, no reaction was observed upon analysis of the ^{1}H NMR spectrum of the crude reaction mixture. This was again observed when mixed complexes **318** and **319** were employed, though it should be noted that **319** was entirely insoluble in the reaction medium when the reaction was carried out in THF.



Scheme 131 Attempted hydrosilylation of 1 with complexes 317, 318 and 319

To solubilise the complex as well as additionally providing a mode through which to study the observed lack of reactivity, stoichiometric studies were carried out between complex **319** and dimethylphenylsilane on NMR scale in $CDCl_3$. Monitoring of this reaction *via* ^{1}H NMR showed that the complex is unreactive towards silane mediated reduction, effectively shutting down the catalytic cycle before a single turnover has occurred by preventing access to catalytically active

Pt(0) species. This is in keeping with the observed lack of H_2 production when complexes **317**, **318** & **319** are employed. Carrying out the stoichiometric reaction at elevated temperatures was also unable to result in the desired reduction of the platinum centre. Attempted reduction of **319** with HBPin also proved unsuccessful.

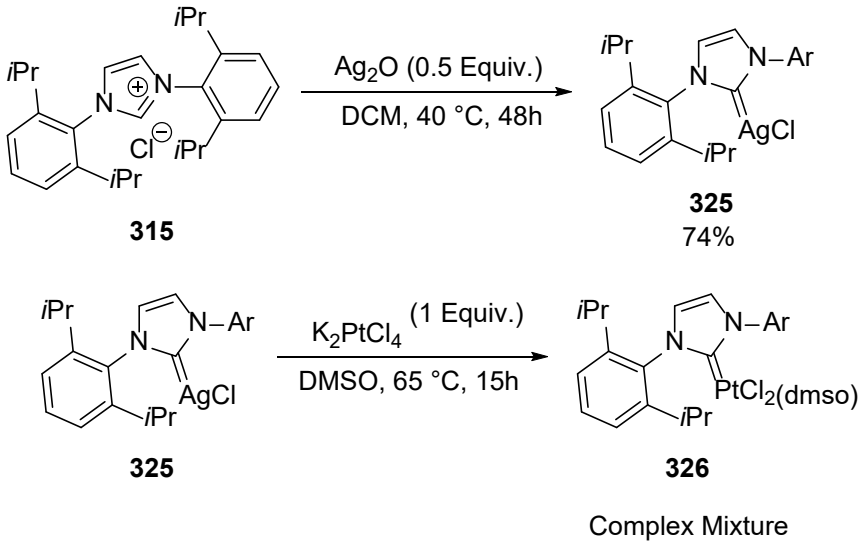


319 **324** n.r

Scheme 132

With respect to the difference in activity when compared to the aforementioned TAZY complexes, it is known that TAZY ligands possess significantly diminished σ-donor capabilities in comparison to imidazolium derived NHC ligands. This is demonstrated by the difference in HEP values of ~176.6 versus ~180.1 for TAZY-Bn versus IBn ligands.[208, 209] Given that a decrease in σ-donor ability leads to an increase in stability for low oxidation state transition metal complexes, it seems likely that the TAZY series of ligands previously examined are able to facilitate this Pt(II)-Pt(0) reduction whereas the related NHC ligands are unable to do so. This could be attenuated by application of complexes which possess *N*-arylimidazolylidene ligands which possess significantly diminished σ-donor strength (HEP~177.5). This idea further supported by other work carried out by Hunyh and co-workers who reported the efficacy of thioether-tethered benzimidazolin-2-ylidene platinum complexes at catalysing the hydrosilylation of **1**. This is relevant as the HEP donicity of benzimidazole derived NHC ligands is decreased in comparison to imidazole derived NHCs.[210] To probe the hypothesis of the complexes requiring less strong σ-donor ligands, the synthesis of platinum-IPr complexes was next attempted employing the same method as previously outlined.

Presumably due to the bulky nature of the N-Aryl groups as well as the weaker σ-donor abilities of the ligand, ligation of IPr.HCl to Ag_2O over the same time period as **316** was shown to be incomplete by analysis of the ^1H NMR of the crude reaction mixture. After 48h however, the reaction was deemed complete due to the absence of the imidazolium proton in the ^1H NMR of the crude reaction mixture and the desired silver NHC complex was isolated in 74% yield. Silver-platinum transmetallation of the NHC was next attempted. Synthesis of **326** however proved unsuccessful under the conditions previously employed. Rather than **326**, the formation of a complex mixture of products was observed, separation of which proved difficult by both crystallisation and chromatography. As this route had proved unsuccessful in the synthesis of **326** alongside time constraints, the project was not pursued beyond this point.



Scheme 133 Attempted synthesis of Pt(IPr) complex 326

5.6 Conclusions

In conclusion, preliminary studies on the application of mixed NHC/phosphine platinum complexes to alkyne hydrosilylation have been carried out. A small library of imidazolium salts was synthesised as ligand precursors by alkylation of both imidazole and 1-methylimidazole providing access to symmetrical and unsymmetrical imidazolium salts respectively. IPr.HCl was additionally synthesised by condensation between 2,5-diisopropyl aniline and glyoxal followed by subsequent condensation of the resultant Schiff base with *para*-formaldehyde. Employing imidazolium salt **310a**, silver-NHC complex **316** could readily be isolated in excellent yield following treatment with silver (I) oxide. Transmetallation to platinum to afford NHC/DMSO complex **317** was achieved with minimal difficulty, providing access to the desired platform from which to access the desired NHC/Phosphine complexes, and as such, complexes **318** and **319** were isolated in 53% and 70% yields. When screening **317**, **318** and **319** as catalysts for the hydrosilylation of **1**, no activity could be observed. The lack of activity of **317** in comparison to the closely related TAZY complexes previously studied was surprising, and suggested a fundamental difference in reactivity between the NHC and TAZY complexes. As such this was studied by undertaking stoichiometric NMR scale experiments with **319** which suggested the NHC complexes do not successfully undergo reduction upon treatment with various hydride sources, therefore shutting down catalytic activity. As such, the synthesis of the less nucleophilic platinum-IPr complex **326** was next attempted although proved ultimately unsuccessful due to unsuccessful silver-platinum transmetallation.

5.7 Experimental Procedures and Characterisation Data

Solvents & reagents

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar, Fluorochem, TCI, Fisher Scientific or Sigma Aldrich. All solvents were purchased from commercial sources and used without purification (reagent grade). Metal salts and ligands were stored in a desiccator when not in use. Anhydrous solvent was prepared by storing solvent over activated 4Å MS for 72 hours. Standard vacuum line techniques were used, and glassware was oven dried prior to use. Organic solvents were dried during workup using anhydrous Na_2SO_4. All reactions were performed using DrySyn heating mantles and pressure regulated vials or round bottom flasks.

Purification and chromatography

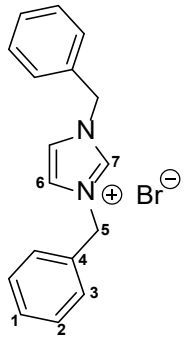
Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F254 silica gel. Plates were visualised using UV light (254 or 365 nm) and developed with iodine and basic permanganate solution. Flash chromatography was performed on VWR Silica gel 60, 40–63 microns RE as the stationary phase and the solvents employed were of reagent grade.

Characterisation

^{1}H NMR spectroscopic data were obtained on either 400 MHz instruments and ^{13}C NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemicalshifts are reported in parts per million (δ) relative to residual $CHCl_3$ (δH = 7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm, central line). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer.

5.7.1 Synthesis of Imidazolium Salts

1,3-dibenzyl-1H-imidazol-3-ium bromide 310a

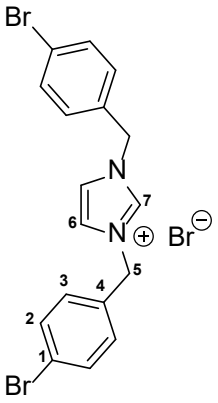


To a stirred solution of imidazole (500 mg, 7.5 mmol) in MeCN (12 mL) was added K_2CO_3 (1.5 g, 11.3 mmol) in one portion. To the resultant suspension was added benzyl bromide (1.75 mL, 15 mmol) dropwise, before the mixture was heated to reflux for 15 hours. After this time, the reaction mixture was allowed to cool to room temperature before being concentrated under reduced pressure. CH_2Cl_2 was then added to the mixture, and the suspension filtered to remove KBr. The filtrate was then taken to anhydrousness under reduced pressure, before the resultant residue was washed with Et_2O (2 × 20 mL) to afford a brown oily residue. The residue was then dried under vacuum for 6 hours affording 1,3-dibenzyl-1H-imidazol-3-ium bromide as an off white solid (1.6 g, 66%). Spectral data in agreement with literature reports.[194]

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.68 (br s, 1H, (**H7**)), 7.45 – 7.38 (m, 4H, (**H**$_{\textbf{Aromatic}}$)), 7.35 – 7.30 (6H, m, (**H**$_{\textbf{Aromatic}}$), 7.26 – 7.23 (m, 2H, (**H6**)), 5.48 (s, 4H (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2 (**C7**), 133.0 (**C4**), 129.7 (**C**$_{\textbf{Aromatic}}$), 129.6 (**C**$_{\textbf{Aromatic}}$), 129.2 (**C**$_{\textbf{Aromatic}}$), 122.1 (**C6**), 53.4 (**C5**).

1,3-di(4-bromobenzyl)-1H-imidazol-3-ium bromide 310b

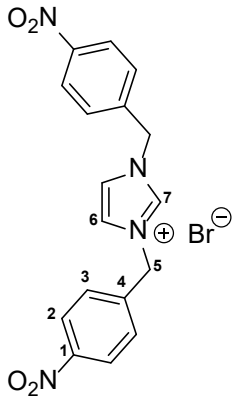


To a stirred solution of imidazole (100 mg, 1.5 mmol) in MeCN (12 mL) was added K_2CO_3 (200 mg, 1.5 mmol) in one portion. To the resultant suspension was added 4-bromobenzyl bromide (750 mg, 3 mmol) before the mixture was heated to reflux for 15 hours. After this time, the reaction mixture was allowed to cool to room temperature before being concentrated under reduced pressure. CH_2Cl_2 was then added to the mixture, and the suspension filtered. The filtered solids were then washed with water (3 × 10 mL) and Et_2O (3 × 10 mL) to afford 1,3-di(4-bromobenzyl)-1H-imidazol-3-ium bromide as a pale-yellow solid (458 mg, 65%). Spectral data in agreement with literature reports.[211]

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.46 (br s, 1H, **H7**), 7.86 (s, 2H, **H6**), 7.62 (d, *J* = 6.6 Hz, 4H, (**H2**)), 7.42 62 (d, *J* = 6.6 Hz, 4H, (**H3**)), 5.44 (s, 4H, (**H5**)).

^{13}C NMR (101 MHz, d_6-DMSO) δ 136.9 (**C7**), 134.5 (**C1**), 132.4 (**C2**), 131.2 (**C3**), 123.4 (**C4**) 122.7 (**C6**), 51.8 (**C5**).

1,3-di(4-nitrobenzyl)-1H-imidazol-3-ium bromide 310c

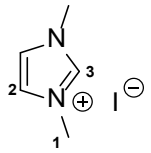


To a stirred solution of imidazole (100 mg, 1.5 mmol) in MeCN (2.25 mL) was added K_2CO_3 (300 mg, 2.25 mmol) in one portion, and the resulting suspension was allowed to stir for 15 minutes at room temperature. After this time, 4-nitrobenzylbromide (648 mg, 3 mmol) was then added in one portion, and the resulting mixture was allowed to stir for 48 hours at room temperature. After this time, the mixture was concentrated under reduced pressure, and water (10 mL) was added. The resultant precipitate was filtered off and washed with a further 10 mL of water along with Et_2O (3 × 10 mL) to afford a brown powder which was subsequently dried under vacuum to afford 1,3-di(4-nitrobenzyl)-1H-imidazol-3-ium bromide as a pale brown powder (518 mg, 83%). Spectral data in agreement with literature reports.[211]

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.51 (s, 1H, (**H7**)), 8.30 (d, J = 7.7 Hz, 2H, (**H2**)), 7.92 (s, 2H, (**H6**)), 7.70 (d, J = 7.7 Hz, 2H, (**H3**)), 5.65 (s, 2H, (**H5**)).

^{13}C NMR (101 MHz, d_6-DMSO) δ 148.1 (**C1**), 142.4 (**C7**), 130.9 (**C2**), 129.3 (**C4**), 125.3 (**C3**), 123.7 (**C6**), 51.7 (**C5**).

1,3-dimethyl-1H-imidazol-3-ium iodide 310d

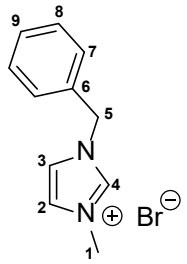


To a solution of imidazole (1.5 mL, 10 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C was added methyl iodide (1.3 mL, 22 mmol) dropwise over 15 minutes. After this time, the reaction then allowed to warm to room temperature and stirred for 16 hours. After this time, the solution was concentrated and the residue triturated with Et_2O (5 mL) which induced the precipitate of a white solid. The solid was filtered, further washed Et_2O (2 × 10 mL) and dried *in vacuo* to afford 1,3-dimethyl-1H-imidazol-3-ium iodide as a hygroscopic white solid (2.1g, 94%). Spectral data in agreement with literature reports.[194]

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.04 (s, 1H, (**H3**)), 7.69 (d, *J* = 1.0 Hz, 2H, (**H2**)), 3.85 (s, 6H, (**H1**)).

^{13}C NMR (101 MHz, d_6-DMSO) δ 137.5 (**C3**), 123.9 (**C2**), 36.2 (**C1**).

1-Benzyl-3-methyl-imidazolium bromide 312a

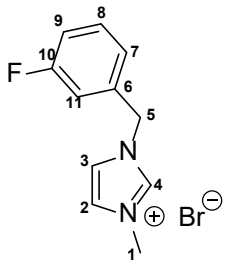


To a stirred solution of 1-methylimidazole (330 mg, 4.1 mmol) in EtOAc (7 mL) was added benzyl bromide dropwise and the turbid mixture was stirred at room temperature for 15 hours. After this time, volatiles were removed under vacuum, and the reside washed with EtOAc (2 × 10 mL) before being dried for several hours under vacuum at 60 ˚C affording 1-Benzyl-3-methyl-imidazolium bromide as a highly viscous liquid. (1.01 g, 99%). Spectral data in accordance with literature reports.[212]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H, (**H4**)), 7.51 – 7.47 (m, 2H, (**H8**)), 7.42 – 7.46 (m, 1H, (**H3**)), 7.37 – 7.41 (m, 3H, (**H7** & **H9**)), 7.34 (s, 1H, (**H2**)), 5.59 (s, 2H, (**H5**)), 4.07 (s, 3H, (**H1**))

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (**C4**), 132.9 (**C6**), 129.6 (**C7**), 129.5 (**C8**), 129.0 (**C9**), 123.5 (**C3**), 121.8 (**C2**), 53.4 (**C5**), 36.8 (**C1**).

1-(3-fluorobenzyl)-3-methyl-imidazolium bromide 312b



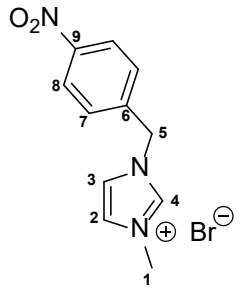
To a stirred solution of 1-methylimidazole (820 mg, 10 mmol) in EtOAc (7 mL) was added 3-fluorobenzyl bromide (2.8 g, 15 mmol) in a single portion and the turbid solution was stirred at room temperature for 15 hours. After this time, volatiles were removed under vacuum, and the reside washed with EtOAc (2 × 10 mL) before being dried for several hours under vacuum at 60 ˚C affording 1-(3-fluorobenzyl)-3-methyl-imidazolium bromide as a highly viscous liquid (2.45 g, 91%). Spectral data in agreement with literature reports.[213]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H, (**H4**)), 7.46 – 7.41 (m, 2H, (**H2** & **H3**)), 7.35 – 7.31 (m, 2H, (**H8** & **H7**)), 7.26 (m, 2H, (**H9** & **H11**)), 5.68 (s, 2H, (**H5**)), 4.08 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.5 Hz, (**C10**)), 137.8 (**C4**), 135.3 (d, *J* = 7.4 Hz, (**C6**)), 131.3 (d, *J* = 8.2 Hz, (**C8**)), 124.9 (d, *J* = 3.2 Hz (**C7**)), 123.5 (**C3**), 122.0 (**C2**), 116.6 (d *J* = 21 Hz, (**C9**)), 116.0 (d, *J* = 22.3 Hz, (**C11**)), 52.6 (d, *J* = 0.4 Hz, (**C5**)), 36.8 (**C1**).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.83

1-(4-nitrobenzyl)-3-methyl-imidazolium bromide 312c

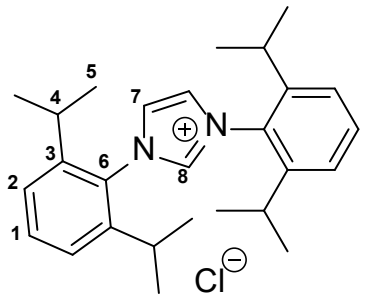


To a stirred solution of 1-methylimidazole (330 mg, 4.1 mmol) in EtOAc (7 mL) was added 4-nitrobenzyl bromide (576 mg, 7.1 mmol) in a single portion and the solution was stirred at room temperature for 15 hours over which time a white precipitate forms. After this time, the precipitate was filtered and washed with EtOAc (2 × 10 mL) before being dried for several hours under vacuum at 60 ˚C affording 1-(4-nitrobenzyl)-3-methyl-imidazolium bromide as a pale grey solid. (1.13 g, 81%). Spectral data in agreement with literature reports.[213]

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.49 (s, 1H, (**H4**)), 8.28 (d, *J* = 8.7 Hz, 2H, (**H8**)), 7.88 (s, 1H, (**H3**)), 7.80 (s, 1H, (**H2**)), 7.71 (d, *J* = 8.6 Hz, 2H, (**H7**)), 5.67 (s, 2H, (**H5**)), 3.90 (s, 3H, (**H1**)).

^{13}C NMR (101 MHz, d_6-DMSO) δ 138.7 (**C4**), 142.7 (**C9**), 138.8 (**C8**), 136.5 (**C6**), 130.1 (**C7**) 125.3 (**C3**), 123.6 (**C2**) 51.3 (**C5**), 35.8 (**C1**).

1H-Imidazolium, 1,3-bis[2,6-bis(1-methylethyl)phenyl]chloride 315



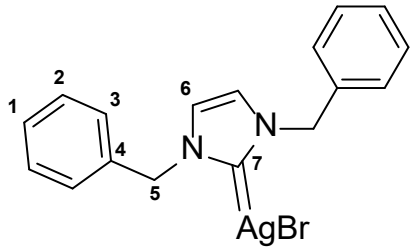
Prepared according to literature procedure.[205] To a solution of 2,6-diisopropylaniline (1 g, 5.5 mmol) in EtOH (5 mL) was added 40% aq. glyoxal (2.25 mmol) and the resulting yellow mixture was stirred at room temperature for 16 hours. After this time the reaction mixture was filtered to afford the intermediate 1,3-diimine as a bright yellow solid (1.80 g, 87%). To a solution of the diimine (1 g, 2.65 mmol) in anhydrous EtOAc (5 mL) was added *para*-formaldehyde (80 mg, 2.65 mmol) and TMSCl (0.33 mL, 2.65 mmol) under an N_2 atmosphere. The resultant solution was then stirred at 70 ˚C overnight. After this time, the mixture was allowed to cool to room temperature and the suspension filtered to afford a white solid which was further washed with EtOAc (2 × 10 mL) to afford the imidazolium salt as a white solid. (910 mg, 81%). Spectral data in accordance with literature reports. [205]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H, (**H8**)), 8.16 (s, 2H, (**H7**)) 7.58 (t, *J* = 7.8 Hz, 2H, (**H1**)), 7.36 (d, *J* = 7.8 Hz, 4H, (**H2**)), 2.46 (dt, *J* = 13.6, 6.8 Hz, 4H, (**H4**)), 1.30 (d, *J* = 6.7 Hz, 12H, (**H6**)), 1.25 (d, *J* = 6.7 Hz, 12H, (**H6**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (**C7**), 132.2 (**C1**), 129.9 (**C6**), 126.9 (**C3**), 124.8 (**C2**), 29.2 (**C4**), 24.8 (**C6**), 23.8, (**C6**).

5.7.2 Synthesis of Silver-NHC Complexes

Bromo[1,3-dihydro-1,3-bis(2,6-bis(1-methylethyl)phenyl)-2H-imidazol-2-ylidene]silver 315

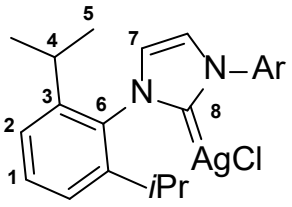


To a solution of **310a** (750 mg, 2.3 mmol) in CH_2Cl_2 (10 mL) was added silver(I) oxide (264 mg, 1.1 mmol) in a single portion. The suspension was then heated at 50 ˚C for 15 hours during which time the silver oxide is slowly solubilised. After this time, the mixture was filtered through celite and concentrated under reduced pressure to afford the desired silver complex as a pale-yellow powder (901 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 6H, (**H**$_{\text{Aromatic}}$), 7.28 – 7.21 (m, 4H, (**H**$_{\text{Aromatic}}$), 6.92 (s, 2H, (**H6**)), 5.30 (s, 4H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.1 (**C7**), 135.5 (**C**$_{\text{Aromatic}}$), 129.4 (**C4**), 128.7 (**C**$_{\text{Aromatic}}$), 128.2 (**C**$_{\text{Aromatic}}$), 120.5 (**C6**), 55.8 (**C5**).

Chloro[1,3-dihydro-1,3-bis(phenylmethyl)-2H-imidazol-2-ylidene]silver 325



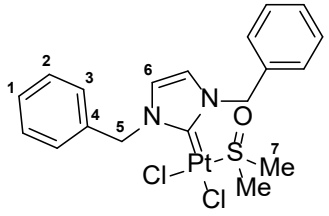
To a solution of **315** (180 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added silver(I) oxide (50 mg, 0.2 mmol) in a single portion. The suspension was then heated at 50 ˚C for 48 hours during which time the silver oxide is slowly solubilised. After this time, the mixture was filtered through celite and concentrated under reduced pressure to afford the desired silver complex as a brown solid(180 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (t, 7.50 (t, *J* = 7.8 Hz, 2H, (**H1**)), 7.30 (d, *J* = 7.8 Hz, 4H, (**H2**)), 7.22 (d, *J* = 1.8 Hz, 2H, (**H7**)), 2.54 (dt, *J* = 13.7, 6.9 Hz, 4H, (**H4**)), 1.28 (d, *J* = 6.9 Hz, 12H, (**H6**)), 1.22 (d, *J* = 6.9 Hz, 12H, (**H6**))

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (**C6**), 134.5 (**C3**), 130.8 (**C1**), 124.4 (**C2**), 123.7 (**C7**), 123.6 (**C7**), 28.7 (**C4**), 24.7 (**C6**), 24.0, (**C6**)

5.7.3 Synthesis of Platinum-NHC Complexes

cis-Dichlorido-(1,3-dibenzylimidazol-2-ylidene)(dimethyl sufoxide)platinum(II) 317

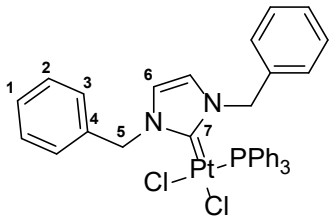


Prepared according to Rourke *et al.*[200] To a solution of **316** (50 mg, 0.12 mmol) in DMSO (5 mL) was added K_2PtCl_4 (45 mg, 0.12 mmol) in one portion. The suspension was then heated at 65 ˚C for 24 hours, over which time the K_2PtCl_4 is slowly solubilised. After this time, CH_2Cl_2 (10 mL) was added, and the mixture filtered through celite before being washed with water (2 × 25 mL) and dried over Na_2SO_4. The mixture was then concentrated under reduced pressure and precipitation induced by trituration with Et_2O afforded **317** as a pale-yellow solid. (52 mg, 73%). Spectral data in accordance with literature reports.[201]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 10H, (**H1**, **H2** & **H3**)), 6.82 (s, 2H, (**H6**)), 5.73 (d, *J* = 15.1 Hz, 2H, (**H5**)), 5.63 (d, *J* = 15.1 Hz, 2H, (**H4**)), 3.17 (s, 6H, (**H7**))

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1 (**C4**), 129.1 (**C2** or **C3**), 128.6 (**C1**), 128.3 (**C2** or **C3**), 121.3 (**C6**), 54.5 (**C5**), 45.6 (**C7**).

cis-Dichlorido-(1,3-dibenzylimidazol-2-ylidene)(triphenylphosphane) platinum(II) 318



Prepared according to Rourke *et al.*[200] Triphenylphosphine (9 mg, 0.04 mmol) in $CHCl_3$ (1 mL) was slowly added to a stirred solution of **317** (20 mg, 0.04 mmol) in $CHCl_3$ (1 mL). The reaction was then stirred at room temperature for 15 minutes before being diluted with 10 mL of $CHCl_3$ and washed with water (10 mL) and subsequently dried over $MgSO_4$. Volatiles were then removed under vacuum to afford **318** as a white solid. (18 mg, 53%). Spectral data in accordance with literature reports.[201]

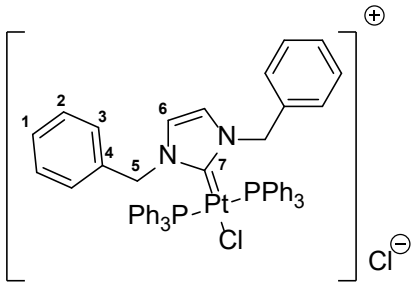
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.43 (m, 9H, (**H$_{Aromatic}$**)), 7.41 – 7.32 (m, 7H, (**H$_{Aromatic}$**)), 7.30 – 7.20 (m, 9H, (**H$_{Aromatic}$**)), 6.34 (s, 2H, (**H6**))), 5.82 (d, *J* = 14.4 Hz, 2H (**H5**)), 4.65 (d, *J* = 14.3 Hz, 2H, (**H5**)).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (**C$_{Aromatic}$**), 131.5 (**C$_{Aromatic}$**), 129.4 (**C$_{Aromatic}$**), 129.0 (**C$_{Aromatic}$**), 128.8 (**C$_{Aromatic}$**), 128.4 (**C$_{Aromatic}$**), 128.0 (**C$_{Aromatic}$**),120.0 (**C6**), 54.6 (**C5**).

(Carbene Centre Not observed)

^{31}P NMR (162 MHz, $CDCl_3$) δ 9.0 (s) *($^1J_{Pt\text{-}P}$ Not observed)*

***Trans*-Chlorido-(1,3-dibenzylimidazol-2-ylidene)bis(triphenylphosphane) platinum(II) chloride 319**



Prepared according to Rourke *et al.*[200] Triphenylphosphine (33 mg, 0.12 mmol) was added in one portion to a stirred solution of **317** (25 mg, 0.04 mmol) in CH_2Cl_2 (2 mL). The reaction was then stirred at room temperature for 15 minutes before being diluted with 10 mL of $CHCl_3$ and washed with water (10 mL) and subsequently dried over $MgSO_4$. Volatiles were then removed under vacuum to afford crude **319** as a white solid which was recrystallised from 1:1 Hexane:Et_2O (27 mg, 70%). Spectral data in accordance with literature reports.[201]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.47 (m, 30H, (**H$_{PPh3}$**)), 7.16, (t, *J* = 7.4 Hz, 2H (**H1**)), 7.07 (s, 2H (**H$_{Aromatic}$**)), 6.98 (t, *J* = 7.7 Hz, 4H, (**H$_{Aromatic}$**)), 6.85 (d, *J* = 7.1 Hz, 4H, (**H$_{Aromatic}$**)), 4.57 (s, 4H, (**H5**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (**C$_{Aromatic}$**), 131.9 (**C$_{Aromatic}$**), 129.5 (**C$_{Aromatic}$**), 129.3 (**C$_{Aromatic}$**), 129.3 (**C$_{Aromatic}$**), 129.2 (**C$_{Aromatic}$**), 129.2 (**C$_{Aromatic}$**), 129.1 (**C$_{Aromatic}$**), 129.1 (**C$_{Aromatic}$**), 128.9 (**C$_{Aromatic}$**), 54.7 (**C5**). *(Carbene Centre Not observed)*

^{31}P NMR (162 MHz, $CDCl_3$) δ 17.4 (s) *($^1J_{Pt\text{-}P}$ Not observed)*

Chapter 6: Overall Conclusions and Future Work

6.1 Overall Conclusions

At the outset, the project aimed to extend the scope of platinum catalysed hydrometallations based on precedent provided by the widespread application of platinum based hydrosilylation catalysts used both in academia and industrially. To this end, the work in this thesis has included developing protocols for the hydrosilylation of previously challenging heteroatom substrates while additionally employing platinum complexes for hydrometallation with non-silyl metal hydrides to achieve both hydrostannylation and hydroboration of alkynes. Additionally, the application of complexes previously unstudied for the hydrosilylation of alkynes has been examined.

The work in **Chapter 2** and **Chapter 3** explored the use of platinum-phosphine complexes in carrying out the hydrosilylation of substrates containing functionalities which can hamper effective hydrosilylation by catalyst inhibition or loss of selectivity *via* directing effects. In **Chapter 2**, the limitations of previous studies on the platinum catalysed hydrosilylation of nitrogen containing species was outlined, and a $PtCl_2$/XantPhos catalyst system was developed to overcome the associated issues with nitrogen containing functionalities. The scope of the reaction was explored and the catalyst shown to be tolerant to a range of nitrogen containing functionalities including benzylamines, anilines, amides, sulfonamides and carbamates. The resultant organosilanes were shown to act as latent cyclisation precursors for the synthesis of aziridines upon electrophilic activation with *N*-halosuccinimides. The scope of this cyclisation was explored as well as the reactivity of the α-iodosilyl moiety generated during the cyclisation. Attempting the desilylation of **124b** TBAF and only in the formation of vinyl iodide **136** as a result of fluoride attack at silicon with concomitant ring opening. Attempting the same desilylation *via* basic methanolysis resulted in the formation of both **136** and **123b** by nucleophilic attack at silicon or iodine respectively. Treatment of **124b** with softer nucleophiles such as benzylamine or butylthiol afforded only **123b**, presumably due to nucleophilic attack at the softer iodine centre.

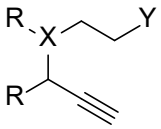
The work in **Chapter 3** explored if similar approach could be used to access tetrasubstituted oxetanes. To this end, a hydrosilylation protocol employing a $PtCl_2$/XPhos catalyst was developed and used to access a range of homoallylic alcohols bearing organosilicon handles by hydrosilylation of homopropargylic alcohols. The reaction was tolerant to a range of different silicon hydrides as well as alkynes bearing diverse substituent at the homopropargylic positions, though limitations were noted when pyridyl substituted alcohol **201i** was employed. Once synthesised, the alcohols readily underwent NIS triggered cyclisation under basic conditions to afford oxetanes of general structure **203** in high yields. Notably, the reaction proceeds with high levels of diastereoselectivity and the major diastereomer was characterised *via* NOESY and confirmed to be the *trans*-oxetane. The same hydrometallation/cyclisation sequence was also employed in attempt to synthesise epoxide **222** from allylic alcohol **220**. Rather than **222**, ketone **221** was instead isolated having formed *via* semi Pinacol type rearrangement. Attempted synthesis of benzofurans by cyclisation of **233** was similarly unsuccessful, though further synthetic utility of the silanes was demonstrated by the synthesis of allylic alcohol **239** by Hiyama coupling.

Chapter 4 detailed the efficacy of platinum-phosphine complexes in carrying out the hydrostannylation of terminal alkynes, while also revealing the profound relationship between ligand denticity and reaction stereoselectivity, with monodentate Buchwald ligands affording the desired hydrostannylated product predominantly as the *E*-isomer, whereas bidentate ligands generally afforded the stannane as the *Z*-olefin albeit in decreased selectivity than the monodentate phosphines. $PtCl_2$/XPhos was effective at carrying out the hydrostannylation of a range of propargyl alcohols and their derivatives. Additionally, when employing aryl acetylene derivatives as substrates, the selectivity achieved by this complex is significantly higher than that achieved under the more traditionally employed palladium catalysis. To mitigate the toxicity concerns associated with manipulation of organostannanes, alongside difficulties with stannane stability on silica gel, a telescoped hydrometallation/cross-coupling procedure was developed, permitting streamlined access to a range of stilbene, allyl alcohol and 1,3-diene derivatives in good yields with no loss of stereochemical identity of the hydrometallated olefin.

Chapter 5 explored the synthesis of platinum complexes bearing both NHC and phosphine ligands, with a view to employing these complexes as hydrosilylation catalysts. Complexes bearing NHC and phosphine ligands in either a ratio of 1:1 (**318**) or 1:2 (NHC:Phosphine, **319**) were synthesised with the carbene ligand derived from 1,3-bisbenzylimidazolium bromide and the chosen phosphine being triphenylphosphine. Additionally, the silver complexes used as carbene transfer agents to access the platinum complexes were screened for their efficacy as hydrosilylation catalysts. The silver complexes were entirely inactive towards both alkyne, olefin and carbonyl hydrosilylation despite prior reports of aldehyde hydrosilylation employing related silver complexes. Platinum complexes bearing NHC:Phosphine ligands in both 1:1 and 1:2 ratio were similarly unreactive towards olefin, alkyne and carbonyl hydrosilylation and hydroboration. In an attempt to elucidate the nature of this observed lack of reactivity, stoichiometric experiments revealed that the issue likely arises from the inability of the silyl hydride to reduce the Pt(II) complex to a catalytically active Pt(0) species which is required for platinum complexes to operate under the generally accepted Chalk-Harrod mechanism. This difficulty in reduction was rationalised as likely arising from the high amount of electron densitry present at the metal centre as a result of the strong donicity of the Ibn ligand, and as such the synthesis of a complex bearing the weaker σ-donor ligand IPr was attempted. While the synthesis of silver complex **325** was achieved, transmetallation of the NHC ligand to the platinum centre was ultimately not achieved.

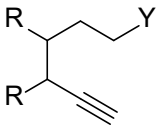
6.2 Future Work

Based on the cyclisation work reported in **Chapter 2** and **Chapter 3** the logical extension is applying the same type of procedure to the synthesis of other heterocyclic ring systems. This includes cyclisation through, for example, sulfur to afford thietanes and thiiranes. Additional efforts could be made to realise the synthesis of larger homologues of heterocycles despite the lack of reactivity of alkynes **132a** and **132b** towards hydrosilylation. If, as proposed, the lack of reactivity arises from the chelating nature of the substrate, removal of the heteroatom at the propargylic position to afford substrates of general formula **327** would circumvent this issue, allowing for the synthesis of rings of larger size. This would also mitigate the issue of the competing semi-Pinacol rearrangements noted in **Chapter 2** and **Chapter 3**.



132

Poor Hydrosilylation Substrates

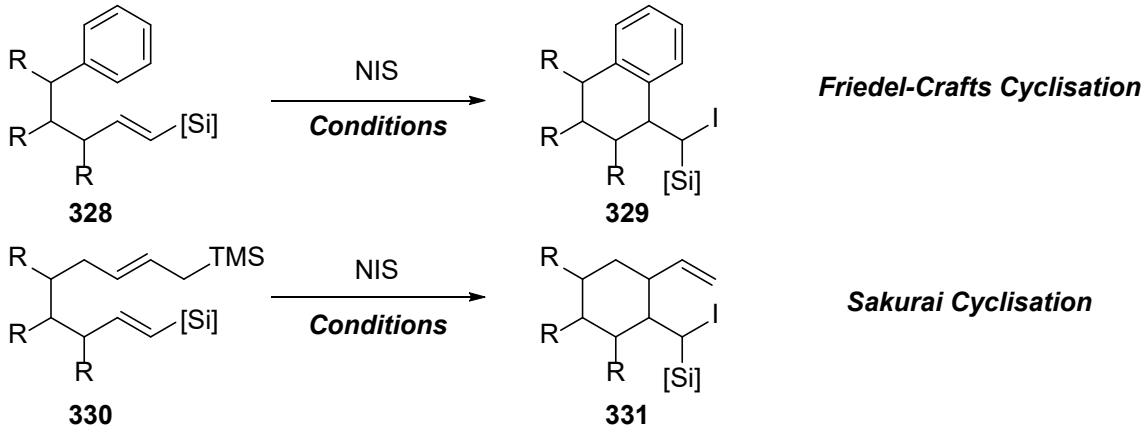


327

Potential Cyclisation Precursor

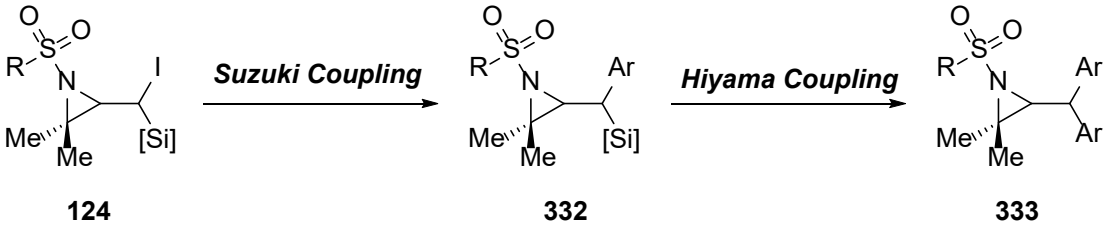
Scheme 134 Substrates to provide access to larger ring sizes using the developed hydrosilylation/cyclisation procedure

Additional avenues of study could be cyclisation *via* formation of a carbon-carbon bond by a Friedel-Crafts type reaction as shown by the proposed synthesis of **329** in **Scheme 134**. Another approach would employ the use of a tethered allyl silane and employ Sakurai-type reactivity to achieve the cyclisation, although selective activation of one olefin in **330** could prove problematic.



Scheme 135 Potential modes of cyclisations of vinyl silanes employing C-C bond formation

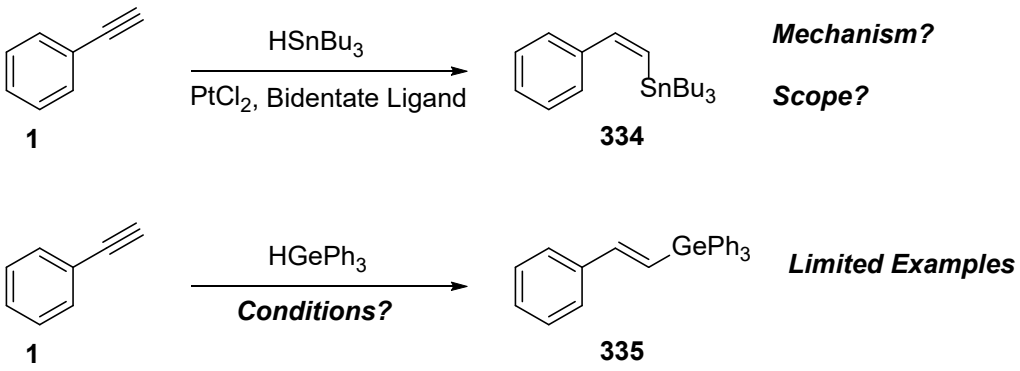
Aside from exploring the synthesis of other heterocycles, the reactivity of the heterocycles synthesised in **Chapter 2** and **Chapter 3** remains a promising avenue for further investigation. While the unique exocyclic halosilyl centre proved challenging to functionalise due to competing ring opening reactions, the nature of the ambiphilic centre presents diverse functionalisation opportunities. One particularly exciting avenue would be the difunctionalisation of this centre by sequential cross-couplings to take advantage of the orthogonal reactivity of organosilanes in comparison to organoboranes or organostannanes. For example, **124** could in principle undergo Suzuki cross-coupling to afford intermediate aziridine **332** which could be further be functionalised by Hiyama cross-coupling to afford densely functionalised aziridines of general structure **333**.



Scheme 136 Scope for further diversifications of the heterocycles synthesised in chapters 2 and 3

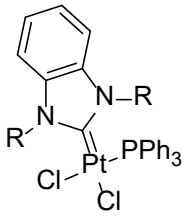
While the work in **Chapter 4** detailed the utility of platinum complexes in hydrometallations other than hydrosilylations, scope still exists for further developments in this area. Organogermanium chemistry has seen significant developments in recent years with significant contributions from the

Schoenebeck group in particular.[214] Despite this, the field of hydrogermylation remains surprisingly underdeveloped. Given the placement of germanium between silicon and tin in group 4, it seems highly likely that platinum complexes can be used to deliver a highly selective hydrogermylation process. Aside from this, the study of other hydrofunctionalisations aside from hydrometallation under platinum catalysis also represents a promising avenue for further study. Additionally, while a ligand denticity-controlled stereodivergence was noted, the mechanism through which this proceeds was not elucidated, nor was the generality of the method explored. A full study would provide an operationally simple method two access geometrically diverse vinyl stannanes from a single alkyne, providing a rapid manner for product diversification.

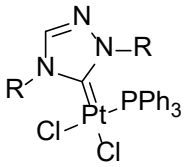


Scheme 137 Avenues for further study on the ligand controlled regiodivergent hydrostannylation and other platinum catalysed hydrometallations

While the complexes synthesised in **Chapter 5** were inactive towards alkyne hydrosilylation due to lack of observed reduction when the Pt(II) complexes are treated with silicon hydride reagents. Electrochemical studies could be carried out to corroborate the presumably lower reduction potential of $Pt(NHC)PR_3Cl_2$ complexes in comparison to the diphosphine platinum complexes. Synthesis of a range of ligands to bring the value of the NHC/Phosphine complexes into line with the reduction potential of the diphosphino complexes could then be approached which may allow the development for catalytically active analogues. Give the donicity values reported for TAZY or benzimidazole based NHC ligands, these represent the most intuitive approach to achieving this.



336



337

Potential Hydrometallation Catalysts?

Figure 14 Potential non-imidazolium based NHC-Phosphine complexes for further exploration

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