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Enhancing the Synthetic Utility of Silicon: An Investigation into Organosilicon Chemistry



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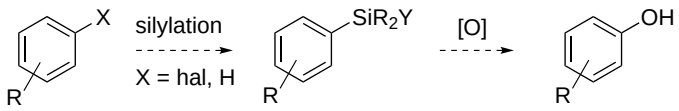
Abstract

The aims of this work were two-fold - to enhance the 'latent functionality' of a silicon centre by expanding the range of functionalisation reactions available to such compounds, and to develop novel silicon-tethered transformations in order to increase the utility of this attractive synthetic strategy.

1. Aryl Silane Oxidation

Building upon the earlier work of Tamao and co-workers, we have developed a mild, functional group-tolerant oxidation of arylsilanes (Scheme 0.1), allowing a wide range of phenols to be readily accessed. One key insight uncovered during this work was the observation that this oxidation could be acheived with **sub-stoichiometric** quantities of a fluoride promoter, thus allowing several TBS-protected substrates to be oxidised without any concomitant loss of the protecting group.

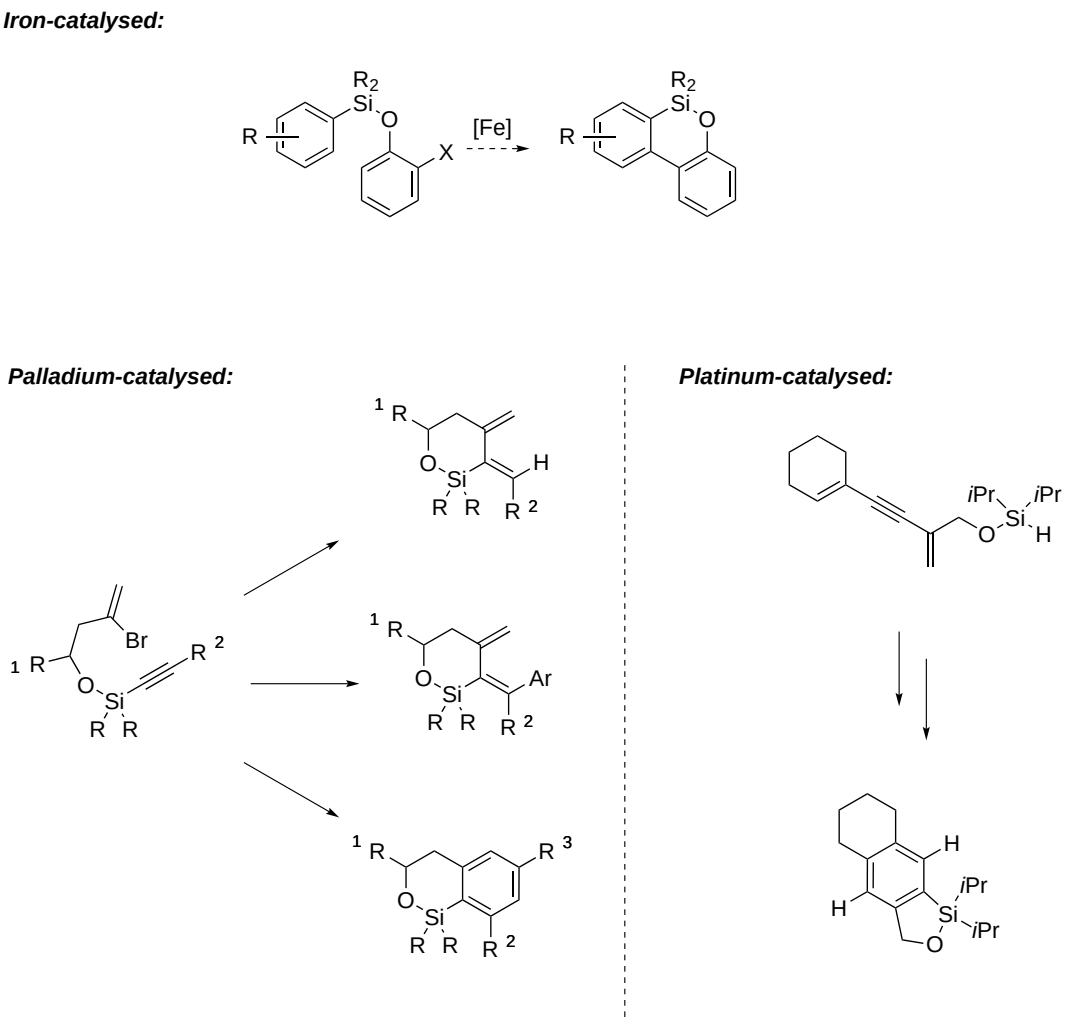


Scheme 0.1 Aryl Silane Oxidation Methodology

2. Silicon-Tethering Methodology

In order to utilise our recently acquired expertise in the field of alkoxy arylsilane synthesis, we sought to develop a novel silicon-tethered iron-catalysed biaryl coupling (Scheme 0.2). Unfortunately, despite our considerable efforts, this methodology was found to suffer from reproducibility issues, and thus our attentions subsequently turned to silicon-tethered palladium- and platinum-catalysed processes.

These investigations proved to be more fruitful, with the palladium-catalysed methodology affording



Scheme 0.2 Silicon-Tethering Methodology

a small range of silicon-tethered products. Finally, a novel platinum-catalysed hydro-silylation / electrocyclisation cascade was also developed, allowing a substituted arene to be accessed from a dienyne precursor.

Acknowledgements

To Ed Anderson, for all his help and support over the last three years, and for providing me with the opportunity to explore this exciting area of chemistry.

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And last but not least, to my best friend and labmate Jem, for always making me laugh through thick and thin, success and failure and numerous late nights and weekends spent in the lab. We made it!!

Abbreviations

Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitrile
app	apparent
Ar	aryl
Bu	butyl
^{13}C	carbon 13
cat.	catalytic
cm^{-1}	wavenumber
COD	cyclooctadiene
conc.	concentration
Cp^*	pentamethylcyclopentadienyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethylene
DCM	dichloromethane
DIBAL	di*iso*-butylaluminium hydride
DMA	dimethylacetamide
DMAP	*4*-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethyl ethylene glycol
DMEDA	*N,N'*-dimethylethylenediamine
DMF	*N,N*-dimethylformamide
dmpe	1,2-bis(dimethylphosphino)ethane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DVDS	1,1,3,3,-tetramethyl-1,3,-divinyldisiloxane
eq.	equivalent(s)
Et	ethyl
FT-IR	Fourier transform infra red spectroscopy
Grubbs I	benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
^1H	proton
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	Hertz
i-	iso
imid.	imidazole
Ind	η_5-C_9H_7
IR	infra red
J	coupling constant
LDA	lithium diisopropylamide
L(i)HMDS	lithium hexamethyldisilazide
IPr·HCl	1,3-bis-(2,6-diisopropylphenyl)-imidazolium chloride
LiTMP	lithium tetramethylpiperidide

L_n	unspecified number of ligands
m-	meta
M	molar, g per dm^3
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitre
mm Hg	millimetre of mercury
mmol	millimole
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Np	naphthalene
o-	ortho
p-	para
P.E.	petroleum ether
Ph	phenyl
PhMe	toluene
Pin	pinacol
Piv	pivaloyl
Pr	propyl
i-PrOH	*iso*-propanol
ppb	parts per billion
ppm	parts per million
pydic	pyridine-2,6-dicarboxylate
pyr	pyridine
quant.	quantitative
R	unspecified substituent
RCM	ring-closing metathesis
R_f	thin layer chromatography retention factor
r.t.	room temperature
s-	sec
Schrock catalyst	2,6-di*iso*-propylphenylimidoneophylidene molybdenum(VI) bis(hexafluoro-t-butoxide)
t-	tertiary
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
Ts	tosyl, *p*-toluenesulfonyl
TST(s)	temporary silicon tether(s)
UHP	anhydrous hydrogen peroxide-urea adduct
X_n	unspecified number of halogens

Contents

Abstract I
1. Aryl Silane Oxidation . . . I
2. Silicon-Tethering Methodology . . . I

Acknowledgements III

Abbreviations IV

1. Introduction 1
1.1. Overview . . . 1
1.2. Silicon-Tethering Methodology . . . 1
1.2.1. Tether Synthesis . . . 3
1.2.2. Metathesis . . . 5
1.2.3. Palladium-Catalysed Cross-Coupling . . . 10
1.2.4. Carbocyclisations . . . 13
1.2.5. Hydrosilylation and Carbosilylation . . . 18
1.2.6. Miscellaneous Reactions . . . 25
1.3. Latent Functionality . . . 28

2. Aryl Silane Oxidation - New Routes to Hydroxylated Aromatics 30
2.1. Overview . . . 30
2.2. Introduction . . . 30
2.3. Methodology Development . . . 33
2.3.1. Aryl Silane Synthesis . . . 33
2.3.2. Oxidation Optimisation . . . 41
2.3.3. Substrate Scope . . . 45
2.3.4. Mechanistic Considerations . . . 48
2.4. Further Investigations . . . 52
2.5. Conclusions . . . 53

3. Silicon-Tethering in Iron-Mediated Chemistry 54
3.1. Overview . . . 54
3.2. Introduction . . . 54
3.2.1. Iron-Catalysed Cross-Coupling . . . 57
3.3. Substrate Synthesis . . . 62
3.4. Iron-Catalysed Cyclisation . . . 63
3.4.1. Attempted Cyclisations - Employing the Iodo Derivative . . . 63
3.4.2. Attempted Cyclisations - Employing the Bromo Derivative . . . 69
3.4.3. Test Coupling Reactions . . . 77
3.4.4. The Search for an Additive . . . 81
3.5. Conclusions . . . 83

4. Silicon-Tethering in Palladium-Mediated Chemistry 84
4.1. Overview . . . 84
4.2. Introduction . . . 84

4.3. Substrate Synthesis . . . 88
4.4. Initial Studies . . . 97
4.5. Reductive Cyclisation . . . 100
4.5.1. Initial Optimisation . . . 100
4.5.2. Further Studies . . . 103
4.5.3. Mechanistic Investigations . . . 106
4.5.4. Expanding the Substrate Scope . . . 111
4.6. Tandem Heck / Suzuki Coupling . . . 112
4.6.1. Initial Optimisation . . . 112
4.6.2. Further Studies . . . 113
4.7. Heck / Suzuki / Electrocyclisation Cascade - Inital Studies . . . 117
4.8. Investigating Alternative Substrates . . . 119
4.9. Oligocyclisation . . . 120
4.9.1. Substrate Synthesis . . . 120
4.9.2. Cyclisation Reactions . . . 122
4.10. Further Functionalisation and Substrate Variations . . . 125
4.11. Conclusion . . . 130

5. Silicon-Tethering in Platinum-Mediated Chemistry 131
5.1. Overview . . . 131
5.2. Introduction . . . 132
5.3. Substrate Synthesis . . . 134
5.3.1. Initial Attempts . . . 134
5.3.2. Modified Route . . . 139
5.4. Hydrosilylation and Electrocyclisation . . . 143
5.4.1. First Attempts . . . 143
5.4.2. Reproducibility Issues and Expansion of Methodology . . . 145
5.4.3. Test Reaction Attempts . . . 146
5.4.4. Alternative Catalyst Synthesis and Final Attempts . . . 147
5.5. Conclusions and Future Work . . . 149

6. Conclusions and Future Work 151
6.1. Aryl Silane Oxidation . . . 151
6.2. Silicon-Tethering Methodology . . . 151

7. Experimental 154
7.1. General Comments . . . 154
7.2. Aryl Silane Oxidation - New Routes to Hydroxylated Aromatics . . . 155
7.2.1. Preparation of Reagents . . . 155
7.2.2. Preparation of Starting Materials . . . 156
7.2.3. Aryl Isopropoxysilane Preparation . . . 162
7.2.4. Aryl Silane Oxidations . . . 179
7.2.5. Fluorosilane Synthesis . . . 193
7.3. Silicon-Tethering in Iron-Mediated Chemistry . . . 194
7.3.1. Preparation of Substrates . . . 194
7.3.2. Cyclisation . . . 196
7.3.3. By-Product Characterisation . . . 197
7.3.4. Test Coupling Reactions . . . 198
7.4. Silicon-Tethering in Palladium-Mediated Chemistry . . . 200
7.4.1. Preparation of Initial Substrates . . . 200
7.4.2. Preparation of Additional Substrates . . . 206
7.4.3. Initial Studies . . . 219

7.4.4. Reductive Cyclisation - Initial Studies . . . 221
7.4.5. Reductive Cyclisation - Further Studies . . . 221
7.4.6. Tandem Suzuki Coupling - Initial Studies . . . 225
7.4.7. Tandem Suzuki Coupling - Further Studies . . . 226
7.4.8. Oligocyclisation . . . 232
7.4.9. Alternative Tether Synthesis . . . 239
7.5. Silicon-Tethering in Platinum-Mediated Chemistry . . . 247
7.5.1. Initial Substrate Route . . . 247
7.5.2. Protected Alcohol Route . . . 252
7.5.3. Modified Route . . . 261
7.5.4. Test Substrates . . . 269
7.5.5. Hydrosilylation / Electrocyclisation / Oxidation . . . 273

A. Appendix **275**
A.1. Selected NMR Spectra . . . 275

References **310**

1. Introduction

1.1. Overview

Organosilicon species possess a number of properties that are highly attractive to the organic chemist, and thus the development of methodology based around such compounds is an exciting and synthetically useful area of research. Organosilicon reagents are considerably less toxic than other semi-metal compounds, such as organostannanes, yet these silicon-containing molecules retain many of the key reactivity modes exhibited by their more toxic analogues. Furthermore, the reagents utilised in the synthesis of organosilicon compounds are inexpensive and readily available, this factor representing another significant advantage offered by this area of chemistry. As a result, the introduction of new organosilicon methodologies to the reaction toolbox is likely to be of considerable benefit to the synthetic community.

1.2. Silicon-Tethering Methodology

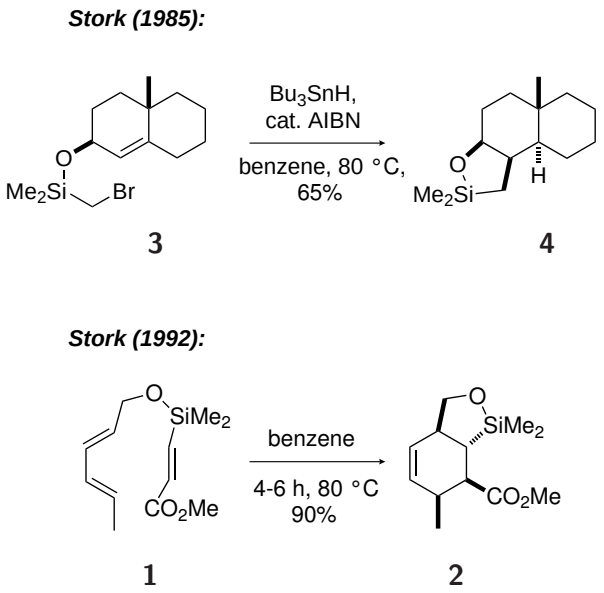
By tethering two or more components of a chemical reaction together, a previously intermolecular process can be rendered intramolecular. This is a well established synthetic strategy,[1] as tethered substrates exhibit several significant advantages over their intermolecular counterparts, and as a result such linkers are often employed to overcome many of the problems associated with multi-molecular reactions. Proximity effects, which provide a higher effective concentration of the reacting partners, act to dramatically increase the rate of an intramolecular process relative to that of the corresponding intermolecular process. Reduced entropic contributions towards the reaction activation energy also arise as a result of intramolecularisation, and this factor again acts in concert to increase the rate of reaction. Furthermore, the regio- and stereoselectivity of a chemical process is often enhanced or altered when it is rendered intramolecular, thanks to the increase in conformational restriction that arises when the reaction components are tethered together. Thus,

adopting a tethering strategy in a synthetic route can have positive implications for both the **reactivity** and **selectivity** of future reactions.

A tether must possess a number of important properties if it is to be appropriate for use as an intramolecularising agent. As two additional synthetic steps are necessarily added to the synthetic sequence when a tether is employed, one of the most important considerations is that the linker be readily introduced in an efficient and high-yielding manner. Once in place, the tether should be stable to a wide range of reaction conditions, but equally must be easily removed or transformed into other functional groups under specific conditions. This final attribute introduces the concept of 'latent functionality' - the most synthetically valuable tethers are those which can undergo conversion into a wide range of functionalities following cyclisation.

Thus, when taking into account these necessary attributes, the properties of organosilicon compounds suggest that these species would make ideal tethering agents. The seminal work of Itoh[2] and Stork[3] (Scheme 1.1) on the application of silicon-tethering methodology to radical addition reactions illustrated that this was indeed the case, thus introducing this synthetic strategy to the organic chemist's reaction toolbox. Other early examples of this methodology included the application of silicon tethering to Diels-Alder chemistry,[4–8] allowing this classic [4+2] proccess to be achieved in a completely regio- and stereoselective manner (**1** → **2**). Indeed, it is the much increased selectivity imparted by the tethering of the reaction components in these two examples that truly highlights and emphasises the synthetic utility of this methodology.

Following these initial examples of the use of 'temporary silicon tethers' ('TSTs') in organic chemistry, this intramolecularisation approach has been subsequently applied to a wide variety of reactions in the intervening twenty-five years.[1,9–12] As this methodology has matured, so the field of metal-mediated reactions has dramatically expanded, and thus the application of silicon tethering in this particular area of chemistry is currently of considerable interest. To date, the benefits of silicon tethers have been realised across a range of metal-mediated processes, including metathesis, palladium-catalysed chemistry and hydrosilylation. However, there remains considerable scope for further development in this field, with the application of TSTs to numerous reactions still remaining unexplored.



Scheme 1.1 Seminal Examples of Silicon-Tethering Methodology

1.2.1. Tether Synthesis

The most common silicon-based functionalities employed as TSTs are the siloxane linker **5** and the disiloxane linker **6** (Fig. 1.1), thanks to both their ease of formation and their considerable potential for further functionalisation. Silane linkers (**7**) are also used, but to a lesser extent as such an oxygen-free tethering system is both more difficult to synthesise, and more difficult to subsequently functionalise following the tethered reaction.

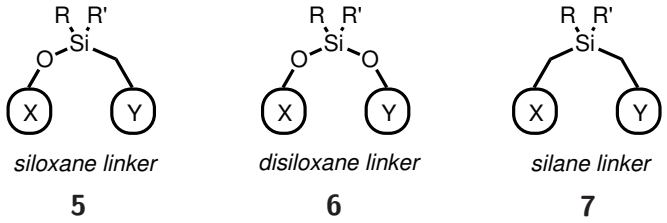
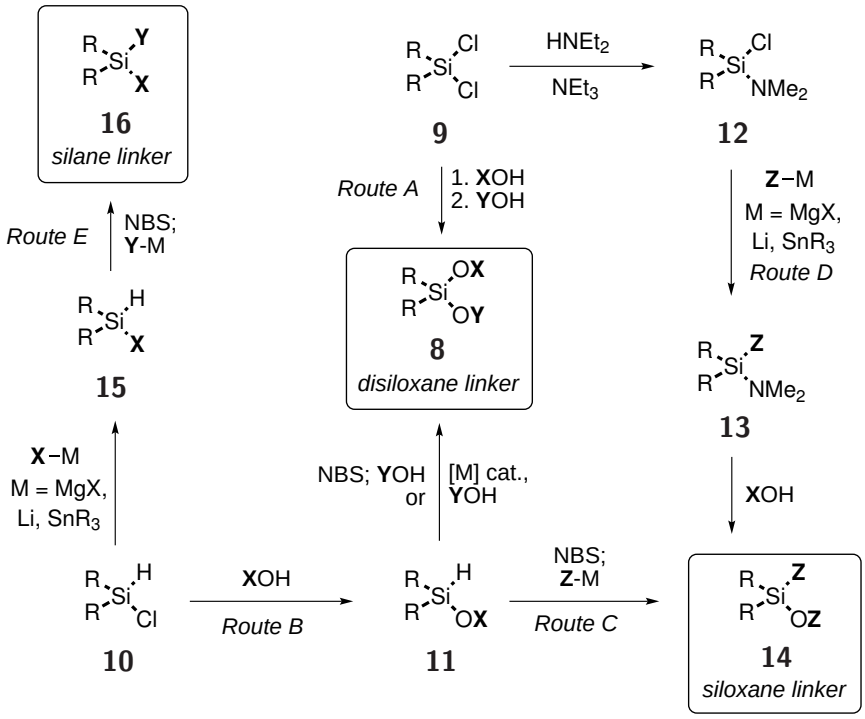


Fig. 1.1. Common Silicon Tethers

The disiloxane functionality **8** can be readily approached from the appropriate dichlorosilane reagent **9** (*Route A*), the stepwise addition of two alcohol building blocks affording the desired disiloxane linker **8** in a synthetically friendly one-pot procedure (Scheme 1.2). However, although this process can be high-yielding, the presence of two displaceable chloride species on the silicon centre imparts some limitations upon this approach. In order to achieve only a single addition of the first alcohol species to the silicon centre, the dichlorosilane **9** must be used in considerable excess, and subsequently removed under reduced pressure before introduction of the second alcohol.

Thus, the volatility of the dichlorosilane reagent **9** is an important consideration when assessing the suitability of this route. As an alternative, a route from the analogous chlorosilane reagent **10** can also be envisaged (*Route B*),[13] whereby an initial addition of an alcohol affords the alkoxysilane intermediate **11**. The Si-H bond present in this species provides a reactive handle, and this functionality can now be activated *in situ* to the more reactive bromosilane, or directly coupled with a second alcohol in the presence of an appropriate metal catalyst. In contrast to the dichlorosilane pathway, this second route provides considerably more control over the synthetic sequence and allows the disiloxanes **8** to be approached in a highly efficient manner, although it should be noted that in this instance such enhanced selectivity comes at the cost of introducing a second reaction step.



Scheme 1.2 Synthetic Routes for TST Incorporation

Chlorosilane reagents **10** also provide a starting point for synthesis of the siloxane linkers **14** (*Route C*). Initial alcohol addition again affords alkoxysilane intermediate **11**, and once again this species can then be activated towards attack by an appropriate carbon nucleophile upon treatment with *N*-bromosuccinimide. This sequence of events can also be reversed if necessary due to sensitive functionalities in the tether building blocks. The dichlorosilanes **9** can also be employed as starting material for the synthesis of siloxane motifs **14** (*Route D*), as reaction with diethylamine allows the reactive chloroaminosilane intermediate **12** to be readily synthesised.[14,15] It

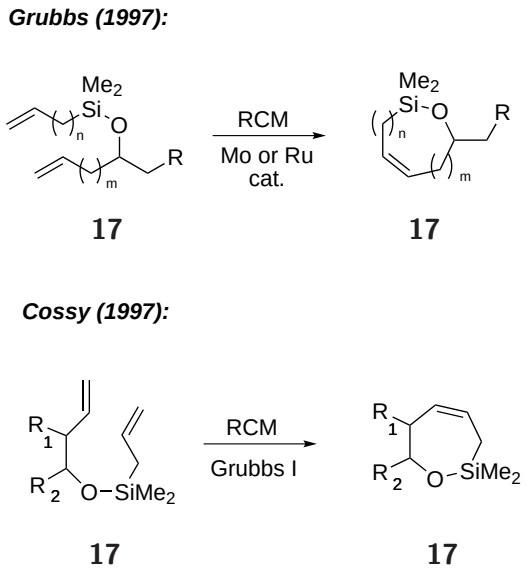
is well precedented that such an aminated intermediate will undergo a single, controlled addition of a metal nucleophile at low temperatures, affording intermediate **13**, and this species can then undergo reaction with an alcohol *in situ* to yield the siloxane functionality **14**. This second pathway has the advantage of being achieved in a single pot once the required aminosilane **12** has been synthesised, although difficulties in preparation and storage of these sensitive species does somewhat decrease the synthetic utility of this approach.

Finally, the chlorosilane reagents **10** can also be utilised as starting materials in the synthesis of silane linkers **16** (*Route E*). Once again, a reaction/activation/reaction sequence can be employed to provide access to this functionality in an efficient and high-yielding manner, with the stepwise nature of this process allowing considerable levels of synthetic control to be achieved.

These routes towards the disiloxane, siloxane and silane functionalities are both highly flexible and highly efficient for the most part, and can be readily employed to provide access to a considerable library of silicon-tethered compounds. In silicon-tethering methodology, the challenge often comes in balancing the steric bulk of the substituents at the silicon centre, and thus the stability of the tether under certain reaction conditions, with the ease of reaction and subsequent functionalisation. Thus, the ability to efficiently and rapidly synthesise a range of tethered substrates is of considerable benefit, as it allows the effect of steric bulk on the reaction pathway to be readily explored. In the following sections, previous examples of TST use in metal-mediated reactions are discussed, this area being the main focus of this dissertation.

1.2.2. Metathesis

To date, silicon-tethering methodology has been widely applied to metal-catalysed metathesis processes,[16–18] with early work in this area[19–22] highlighting the observation that introduction of a TST will transform a cross-metathesis reaction into a ring-closing metathesis (Scheme 1.3). Given the low selectivities and efficiencies of cross-metathesis procedures, by tethering the reaction components together these disadvantages can be readily overcome. However, perhaps the most powerful effect of employing this methodology in metathesis chemistry is the *Z*-selectivity that results from introducing a cyclic constraint, providing a valuable synthetic alternative to the *E*-selective cross-metathesis process.

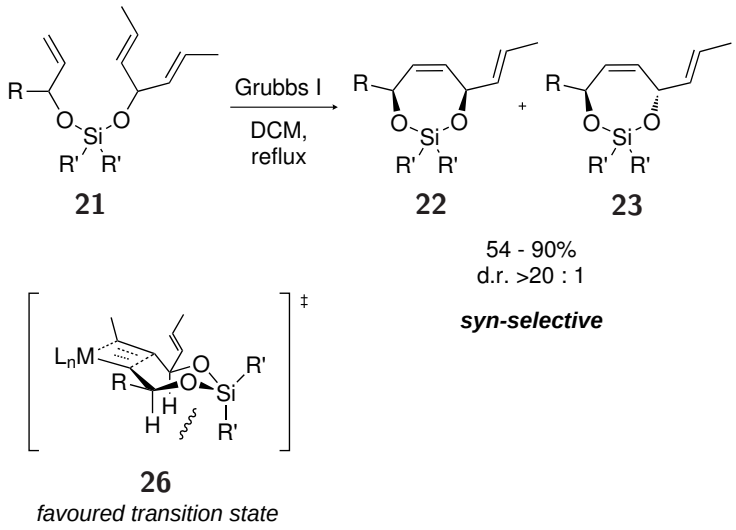


Scheme 1.3 Seminal Examples of TSTs in Metathesis Chemistry

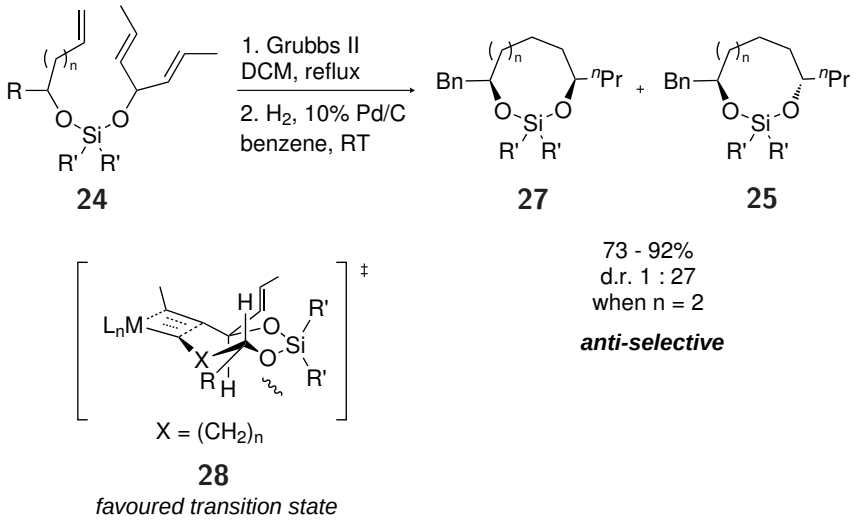
More recently, the work of Evans and co-workers on long-range diastereomeric induction in silicon-tethered metathesis reactions has further extended the synthetic utility and importance of this strategy (Scheme 1.4).[23] In this study, one of the tethered components is a prochiral alcohol, and following ring-closing metathesis in the presence of Grubbs I catalyst, considerable diastereoselectivity is observed in the 1,4-, 1,5- and 1,6 silaketal products. Most interesting, however, is the dramatic shift in selectivity that occurs upon moving to a larger tether size. In the 1,4 systems, the prochiral starting material **21** is transformed into the *syn* silaketal **22** with a selectivity of greater than 20 : 1 observed over the *anti* silaketal **23**. In stark contrast, when the 1,5 and 1,6 precursors **24** are subjected to similar conditions, the levels of selectivity remain as high, but the *anti* product **25** is now favoured over the *syn*. It should be noted that the role of the subsequent reduction step employed in this instance is to avoid analytical complications due to the formation of *E* and *Z* double bond isomers.

By examining the proposed transition states **26** and **28** for the two systems, the origin of this selectivity becomes apparent. It is notable that bulky substituents on the silicon centre were necessary for such high diastereoselectivities to be achieved, and it is the interactions between these alkyl groups and the other substituents present that governs the results observed. Di*iso*-propyl tethers were found to give the greatest diastereoselectivities, and in the 1,4 system the favoured transition state **26** is arranged such that the propenyl group is placed in a pseudoequatorial

1,4-silaketals:



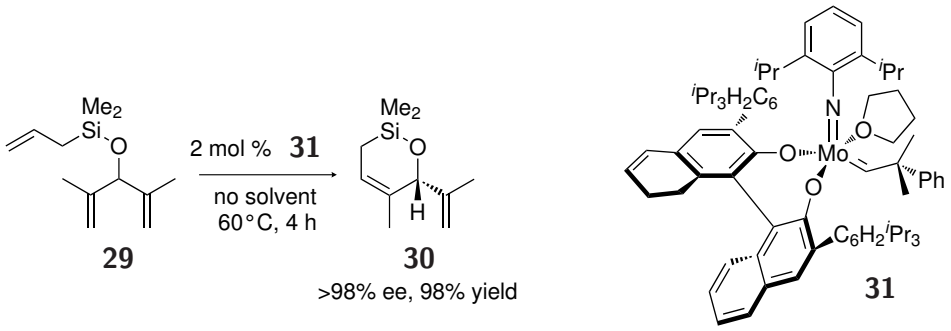
1,5- and 1.6-silaketals:



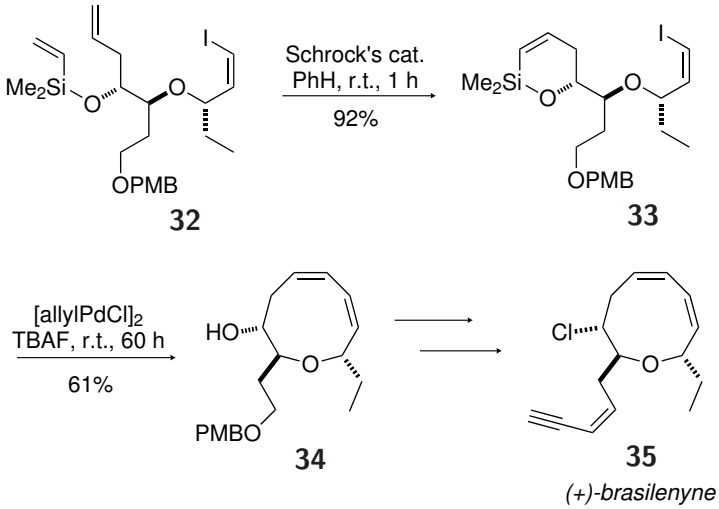
Scheme 1.4 Long-Range Diastereoselectivity in Silicon-Tethered Metathesis Reactions

position so as to minimise steric interactions with the silicon substituents. The propenyl group is also placed pseudoequatorially in the favoured transition state **28**, but the conformation of the seven- or eight-membered ring arrangement that arises is such that the substituent on the other alcohol can also be placed pseudoequatorially, giving rise to the *anti* selectivity observed.

TSTs have also seen application in asymmetric induction processes, with the chiral molybdenum catalyst **31** providing access to desymmetrised cyclic siloxane **30** in an impressive 98% yield and 98% ee.[24,25] Indeed, the stereoinduction achieved in both these processes is reflective of how powerful silicon-tethering methodology can be.



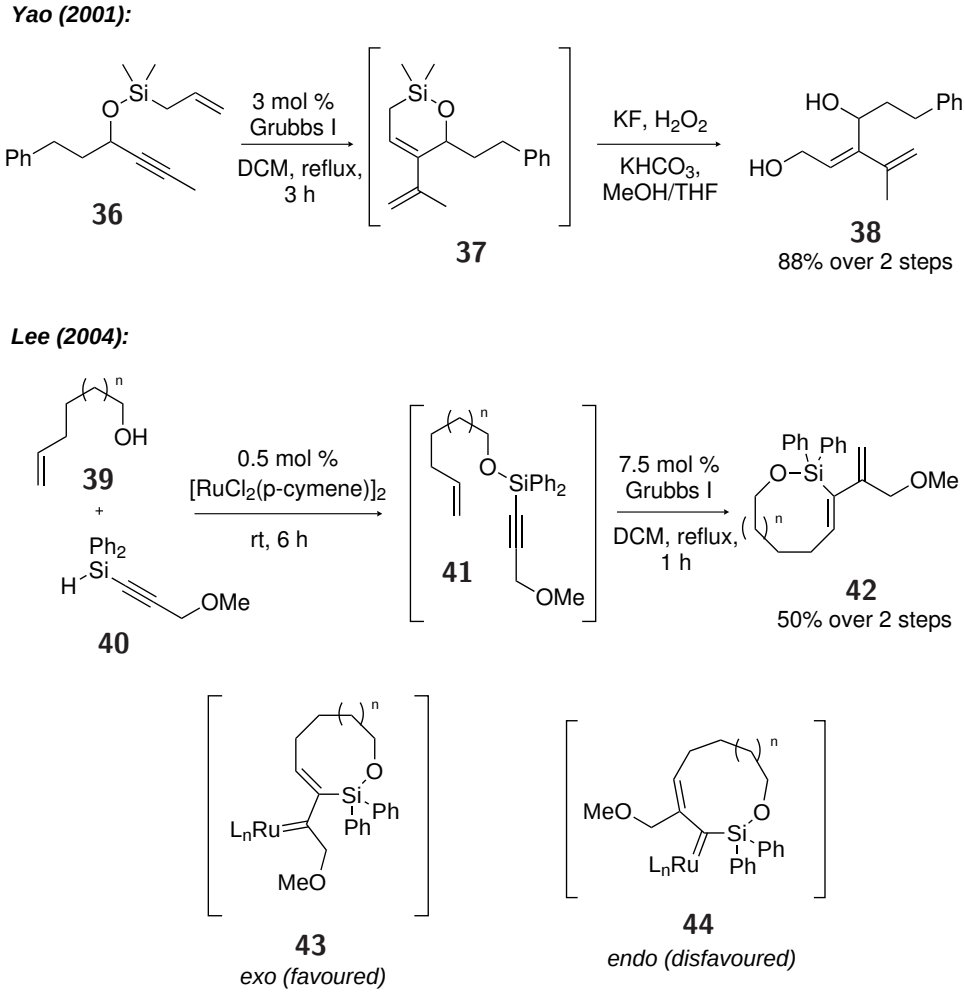
Scheme 1.5 Enantioselective Silicon-Tethered Ring-Closing Metathesis



Scheme 1.6 Sequential TST RCM / Hiyama Coupling in the Total Synthesis of (+)-brasilenyne

As might be expected, the use of TSTs in a metathesis context has also been explored in a number of natural product total syntheses to date. In 2002, the Denmark group reported the total synthesis of (+)-brasilenyne,[26,27] employing a route that capitalised on their development of a tandem silicon-tethered RCM / Hiyama coupling process (Scheme 1.6).[28,29] Medium-sized rings can be highly challenging to synthesise, but by employing such a sequential strategy the group was able to access the nine-membered ring ether of (+)-brasilenyne with complete stereoselectivity for the *Z,Z*-diene motif present (**32** → **33** → **34**, 56 % yield). Of particular interest in this example is the use of Schrock's molybdenum-based catalyst in achieving the desired ring-closing metathesis. The proximity of the silicon centre to the reacting double bond of the vinyl silane motif imparts considerable steric bulk upon the system, and as a result ruthenium-based metathesis catalysts will not induce cyclisation in this instance.

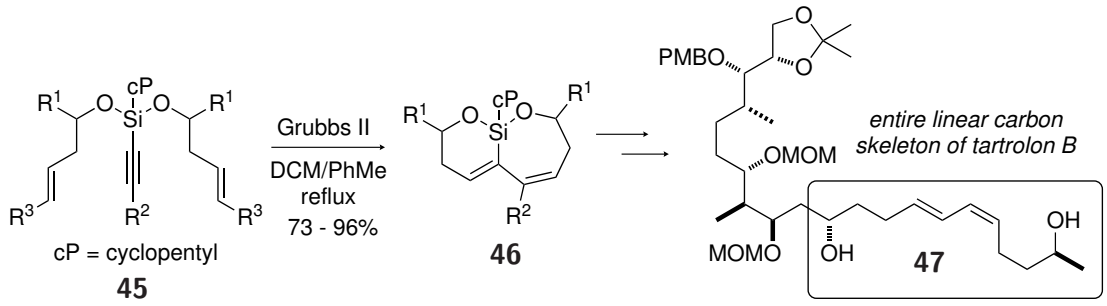
Silicon-tethering methodology has also been applied to both enyne and dienyne ring-closing metathesis.



Scheme 1.7 Silicon-Tethering in Enyne RCM

This area was first explored by Yao and co-workers, who reported that a range of tri-substituted dienes **38** could be synthesised in a highly regio- and stereoselective manner *via* a tethered enyne RCM approach (Scheme 1.7).[30] The Lee group further extended this methodology in employing alkynyl siloxanes **41** as tethering species, thus providing access to a range of medium- and large-ring cyclic siloxanes **42**.[31,32] This last example is notable thanks to the *exo* mode of cyclisation **43** that is observed in this instance - RCM of larger ring systems is usually found to be selective for the *endo* mode. It is proposed that in this case the *exo* selectivity arises as a result of steric clashing between the two phenyl silicon substituents and the ruthenium alkylidene (**44**), this result once again emphasising the significant effect that silicon tethering can have on the selectivity of a given reaction.

Finally, Lee and co-workers have devised a further TST RCM strategy, whereby incorporation of an additional alkene functionality allows a tethered dienyne metathesis process to take place



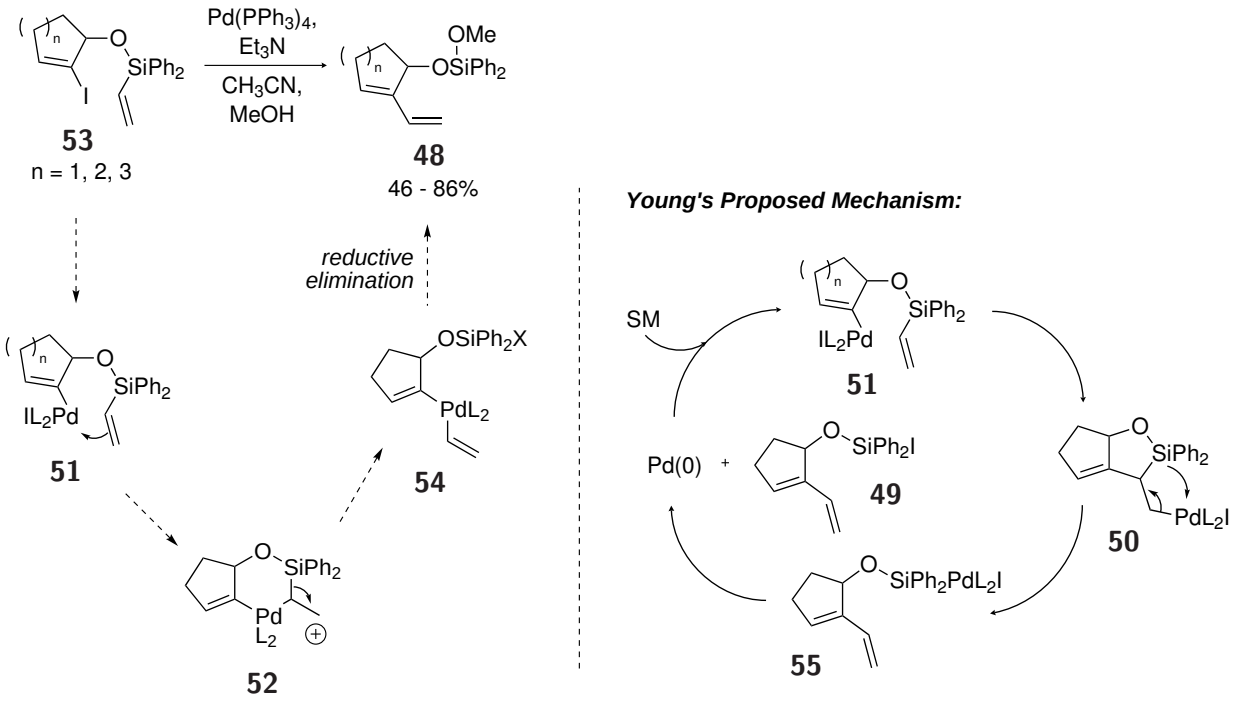
Scheme 1.8 Silicon-Tethered Dienyne RCM

(Scheme 1.8).[33] Following the initial cyclisation step, the resulting ruthenium alkylidene species can then undergo a second cyclisation with the remaining free alkene, thus providing access to a range of bicyclic disiloxanes **46**, and 1,4-disubstituted *E,Z*-dienes **47** upon removal of the silicon tether. This structural motif is common to a number of natural products, and as such the Lee group have applied this TST methodology to both a partial synthesis of tartrolon B,[34] and a formal synthesis of (-)-cochleamycin A.[35]

1.2.3. Palladium-Catalysed Cross-Coupling

Interestingly, silicon tethering methodology has thus far found only limited application in palladium-catalysed chemistry. In 2001 the Young group reported a tethered Heck reaction, in which a vinyl group was transferred onto a small range of cyclic systems (Scheme 1.9).[36] The group proposed a catalytic cycle to explain the unexpected observation that the silicon tether was cleaved under the reaction conditions, thus affording the product disiloxanes **48** in moderate yields. Interestingly, it was suggested that silyl iodide **49** arises as an intermediate species during this transformation, following γ-silyl transfer to the palladium centre and subsequent reductive cyclisation (**50** $\rightarrow$ **49**). We have proposed an alternative mechanism, whereby vinyl addition to the palladium centre present in intermediate **51** would afford stabilised β-silyl cation **52**. Finally, a subsequent reductive elimination step would give rise to the observed product **48**.

More recently, a further application of TSTs has been found in the intramolecularisation of palladium-catalysed C-H activation processes. The Hiyama group found that a range of tethered aryl triflates **56** underwent cyclisation to the corresponding siloles **57** upon treatment with $Pd(OAc)_2$ and PCy_3 in the presence of Et_2NH.[37] The steric bulk of the silicon substituents was found to be crucial in obtaining good yields for this process, this effect most likely arising as a result of both the Thorpe-Ingold effect and the reduced vulnerability of the silicon centre towards nucleophilic attack when

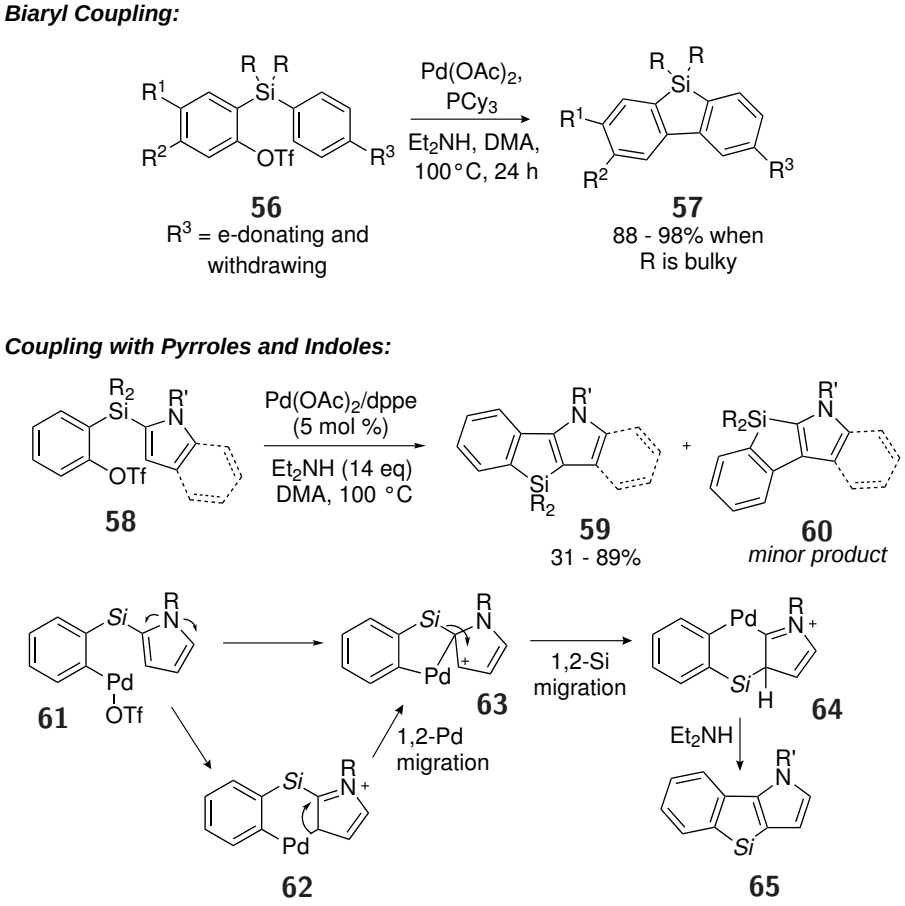


Scheme 1.9 Silicon-Tethered Heck Reaction

bulky substituents are present. Thus, we can observe once again that the nature of the silicon tether itself often plays a crucial role in governing the reactivity of the system.

In expanding their methodology towards tethered pyrrole and indole systems **58**, Hiyama and co-workers found an intriguing switch in regioselectivity (Scheme 1.10).[38] Upon exposure to similar conditions, these substrates preferentially formed the inverted isomer **59**, with the expected product **60** being synthesised in much reduced amounts. The group proposed a mechanism invoking the electron-donating properties of indolic and pyrrolic systems to explain this unexpected result, with the nitrogen-containing ring system directly attacking the palladium centre to afford intermediate **63** or **62**. It is likely that the indole substrates will undergo attack at the 3-position to give this latter intermediate **62**, which can then undergo a subsequent 1,2-palladium migration to converge upon intermediate **63**. 1,2- silyl migration then provides the inverted regioisomer **65**.

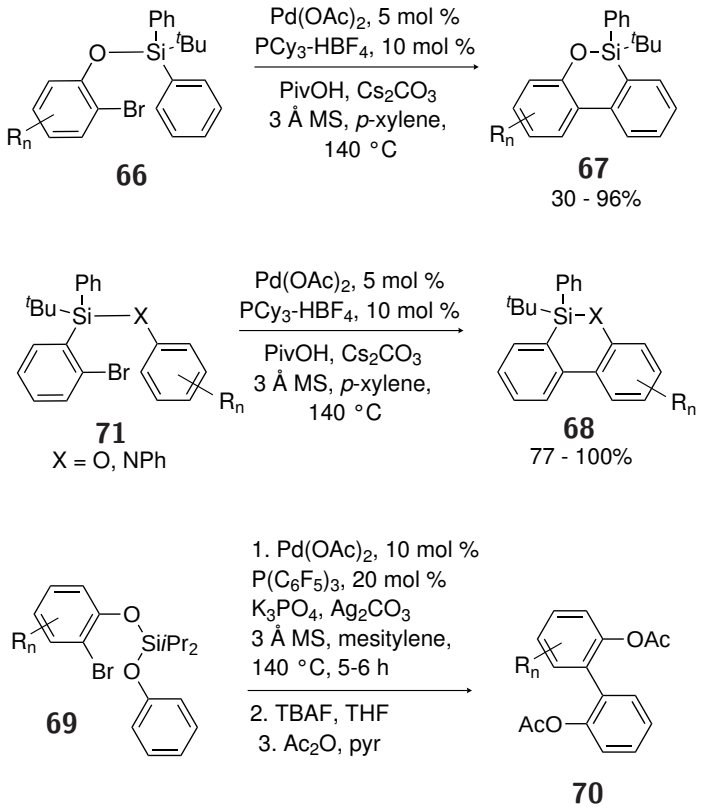
In their work on silicon-tethered C-H activation processes, the Gevorgyan group have instead employed a siloxane linker, their initial substrates **66** arising from the simple protection of a range of 2-bromophenols with the commercially available *tert*-butyldiphenylsilyl group (TBDPS, Scheme 1.11).[39] Upon treatment with $Pd(OAc)_2$ and PCy_3-HBF_4,[40] these protected phenols cyclised to give siloxanes **67** in moderate to high yields. A novel bromo-TBDPS group was also developed



Scheme 1.10 Synthesis of Silicon-Bridged Biaryls Using C-H Activation

so as to allow access to a wider variety of siloxanes **68**, thus eliminating the necessity for the phenol building blocks to be brominated in the *ortho*-position. Finally, a disiloxane variant **69** was also explored, allowing a further range of biaryls **70** to be synthesised following tether cleavage and acetylation.[41] For all three processes, a range of electron-withdrawing and donating substituents were found to be readily tolerated under the reaction conditions.

It should be noted that one crucial advantage afforded by the incorporation of a silicon tether in a C-H activation process is the possibility of subsequent tether cleavage. While intramolecularisation provides much enhanced reactivity and selectivity in these processes, previous examples employing this tactic showed limited synthetic utility thanks to the permanent nature of the tethering structure employed. In contrast, the 'latent functionality' of a TST allows the linker to be readily removed following reaction, thus retaining all the advantages of intramolecularisation while minimising the disadvantages.

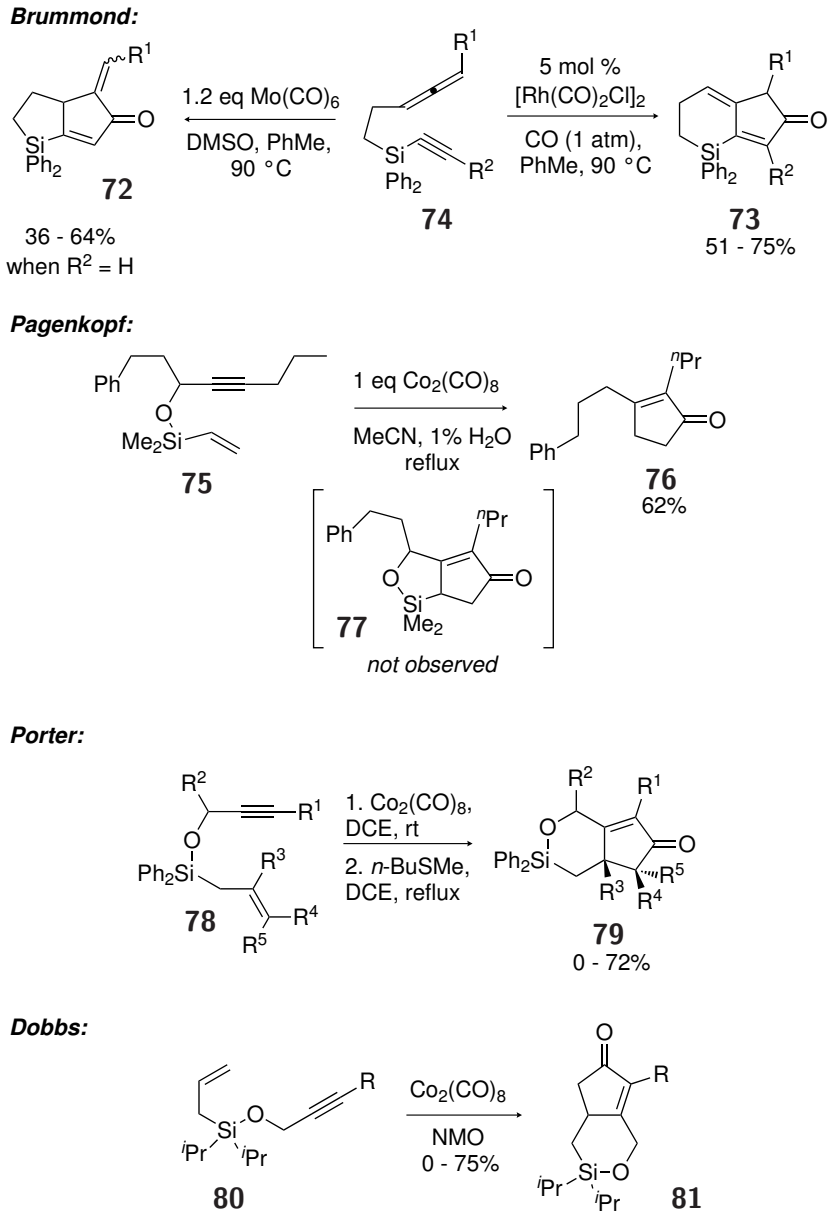


Scheme 1.11 Siloxane Tethers in C-H Activation

1.2.4. Carbocyclisations

Interestingly, Pauson-Khand cyclocarbonylation chemistry is one of the few fields in which the application of silicon-tethering methodology has been predominantly unsuccessful. Despite the extensive efforts of a number of research groups, there remain only a few examples where a silicon-tethered Pauson-Khand reaction has been efficiently achieved, and then usually only for the simplest, most unsubstituted member of the structural family being investigated. In 2002, Brummond and co-workers reported an allenic silicon-tethered Pauson-Khand process, in which two cyclic isomers **72** and **73** could be synthesised depending on the metal catalyst employed (Scheme 1.12).[42] The group found siloxane tethers to be too labile under the reaction conditions utilised, and thus a recourse to the more stable silane-tethered systems **74** was necessary.

In contrast, the all-carbon silane tethers were found to be unsuitable for the normal mode Pauson-Khand cyclisation,[43] and thus the Pagenkopf,[44] Porter[45] and Dobbs[43] groups all employed siloxane tethers in their investigations (Scheme 1.12). In each instance, although a successful cyclisation was achieved to afford products **76**, **79** and **81**, the substrate scope was found to be highly limited. Intriguingly, in the example reported by Pagenkopf and co-workers,[44] a reductive cleavage of the

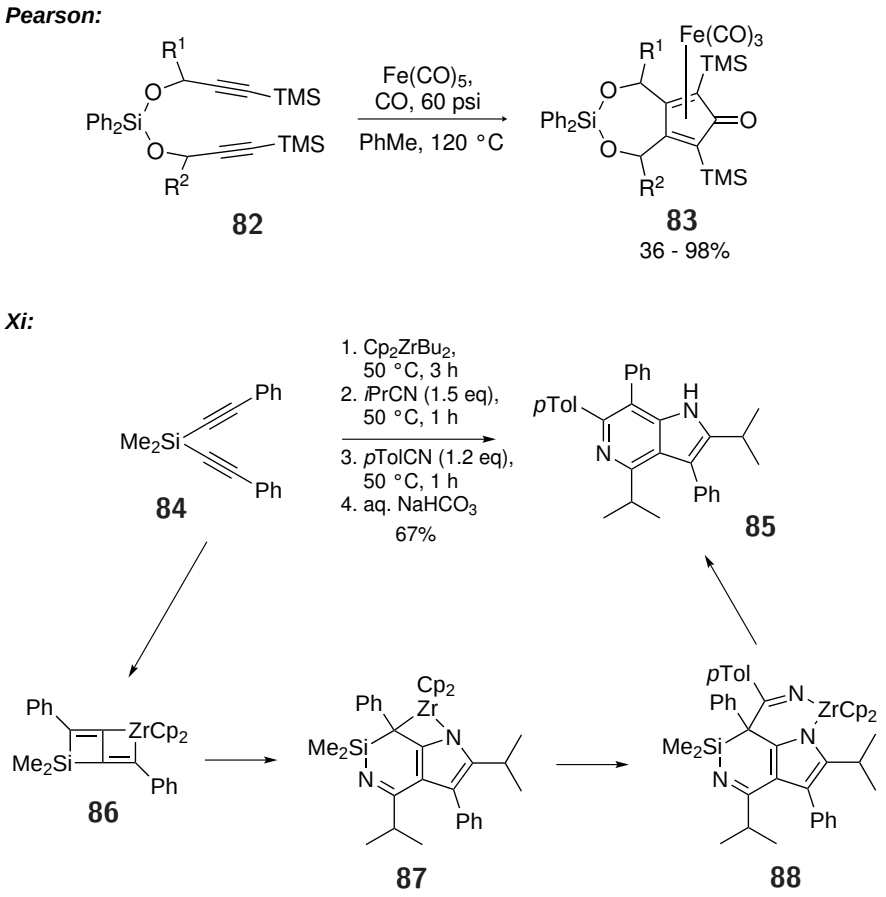


Scheme 1.12 Silicon-Tethering in Pauson-Khand Chemistry

silicon tether was observed *in situ*, with the expected product **77** not arising under the reaction conditions. Thus, the successful application of silicon-tethering methodology to Pauson-Khand processes has not been achieved beyond a very narrow range of examples, suggesting perhaps that in this instance the introduction of a silicon tether is somehow detrimental to the reaction pathway. This may be due to both steric effects associated with the bulky silicon centre, and the potentially unfavourable conformational restrictions that a tether imposes upon the reaction components.

In a related process, the Pearson group has successfully applied a disiloxane tethering motif **82** to the synthesis of cyclopentadienones **83** *via* a dienyne carbocyclisation mediated by stoichiometric

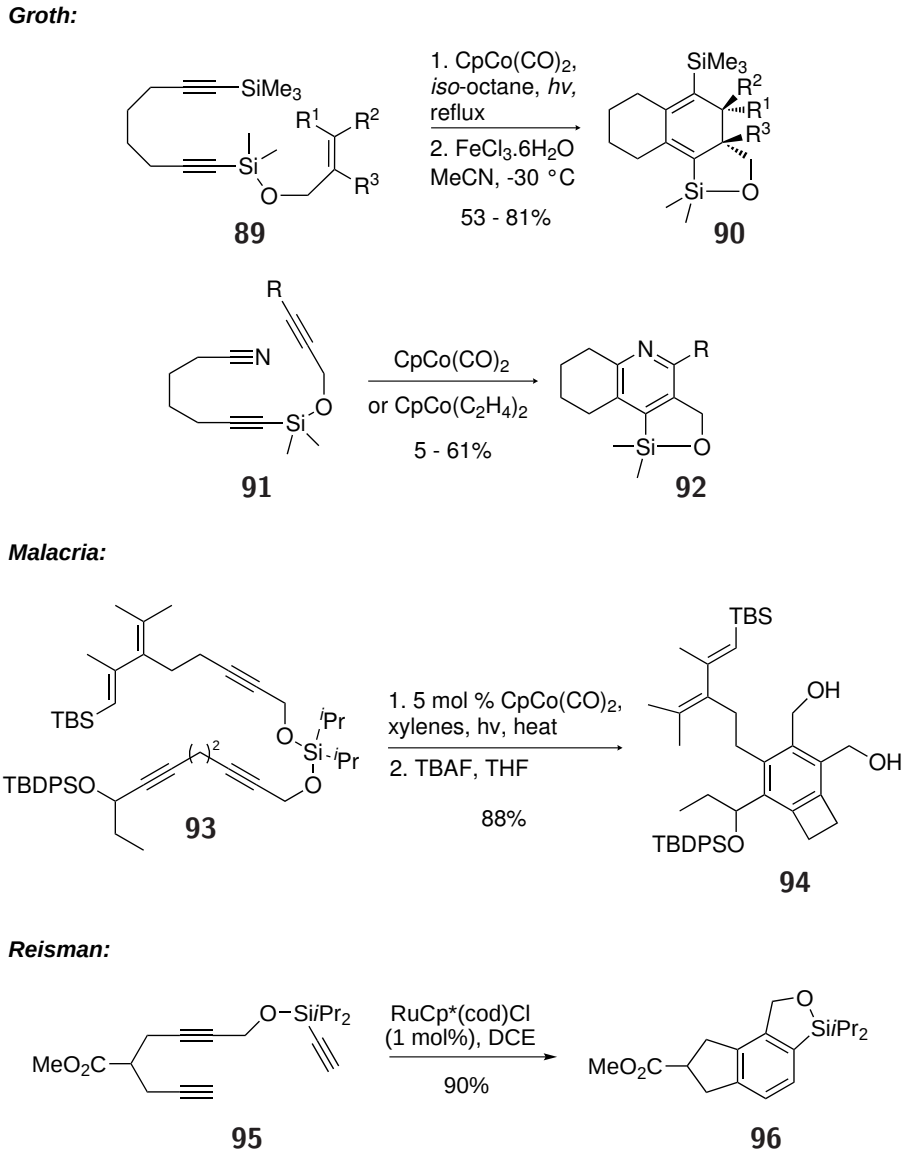
quantities of $Fe(CO)_5$.[46] The use of a silicon tether in this reaction allows alkyne heterocoupling to be achieved, rather than the homocoupling that is observed in the intermolecular case.[47] Once again, however, the substrate scope was found to be limited, thus reducing the synthetic utility of this coupling process.



Scheme 1.13 Further Silicon-Tethered Carbocyclisations

In a more exotic application of silicon tethering to carbocyclisation processes, Xi and co-workers have utilised a TST diyne substrate **84** in their zirconocene-mediated synthesis of azaindoles **85** (Scheme 1.13). An initial addition step afforded the previously reported zirconocyclobutene-silacyclo-butene complex **86**,[48,49] which was then proposed to undergo reaction with two organonitrile molecules to yield intermediate **87**. Finally, insertion of a second organonitrile functionality afforded intermediate **88**, with subsequent hydrolysis giving rise to the product species **85**. This proposed mechanism, although unusual, is strongly supported by the isolation and characterisation of **88** as a crystalline solid.[50–52] In subsequent work it was also found that the zirconocene intermediate **86** was able to undergo reaction with a wide variety of other electrophiles, thus expanding the synthetic utility of this process. The presence of a silicon linker is crucial to the reaction in this

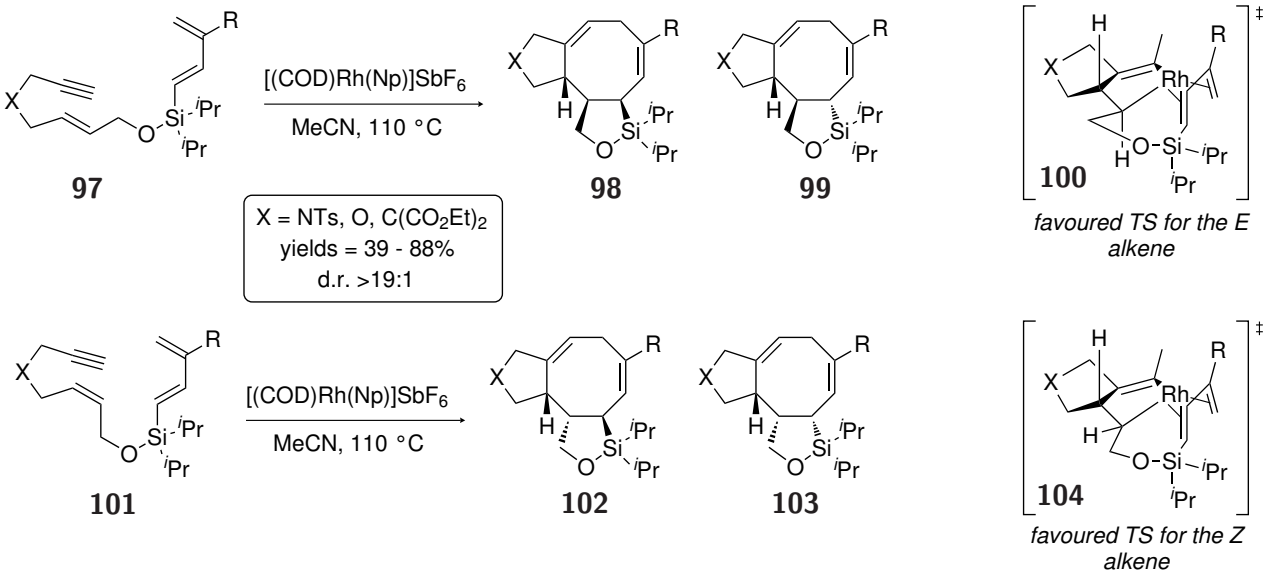
instance, as the strain provided by the tether in species **86** gives rise to the considerable reactivity of this intermediate. Furthermore, the dimethyl tether is also sufficiently labile so as to be cleaved in the final hydrolysis step, allowing cyclisation to the product **85** to readily take place.



Scheme 1.14 Application of TSTs to [2+2+2] Cyclotrimerisations

TSTs have also seen considerable application in [2+2+2] cyclotrimerisation processes. In 2003, the Groth group reported a cobalt-catalysed cyclisation of tethered endiynes **89**, giving rise to a range of dienes **90** in good to excellent yields (Scheme 1.14).[53] The group further extended this methodology to enable the *de novo* synthesis of pyridyl systems **92** from acyclic, tethered substrates **91**.[54] Malacria and co-workers have subsequently expanded this methodology, and have utilised a range of siloxane and disiloxane tethers in their exploration of cyclotrimerisation chemistry.[55,56,57] Perhaps

the most impressive example of the synthetic potential of this methodology is the cyclotrimerisation of linear disiloxane precursor **93** to afford hexasubstituted arene **94** in an outstanding 88% yield. The group note that employing a silicon tether in this instance allows the cyclisation to be achieved in a completely chemo- and regioselective fashion. Finally, the more recent work of Reisman and co-workers has shown that this field is not limited to the use of cobalt catalysts - in this instance, cyclisation to arene **96** in the presence of a ruthenium catalyst can readily be achieved under considerably milder conditions.



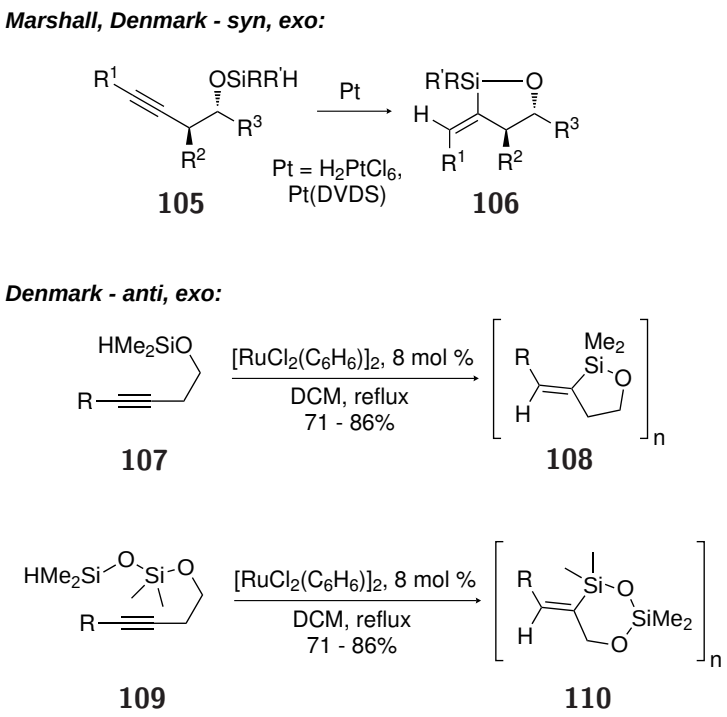
Scheme 1.15 Silicon-Tethered [4+2+2] Cyclotrimerisation

In 2004, the Evans group reported a stunning application of silicon tethers,[58] this methodology building upon earlier work encompassing the development of an intermolecular rhodium-catalysed [4+2+2] carbocyclisation (Scheme 1.15).[59,60] Yet again, this is a further example of how the regioselectivity and reactivity of a process may be heightened upon introduction of a TST, as employing this strategy allowed the substrate scope of this reaction to be expanded to include substituted dienes **97** and **101**. Previously, this process was limited to simple unsubstituted substrates, and in the presence of catalytic [(COD)Rh(Np)]SbF_6, a range of tethered substrates could be cyclised in an efficient fashion. Interestingly, the stereochemistry of the enyne component was found to influence the geometry of the final siloxane product, with diastereoselectivities of greater than 19 : 1 being reported for siloxanes **98** and **102**. The group rationalised that the transition states **100** and **104** would be favoured for the *E* and *Z* starting materials respectively, as such arrangements allow steric interactions between the bulky di*iso*-propyl substituents of the silicon centre and the

tethered diene to be minimised.

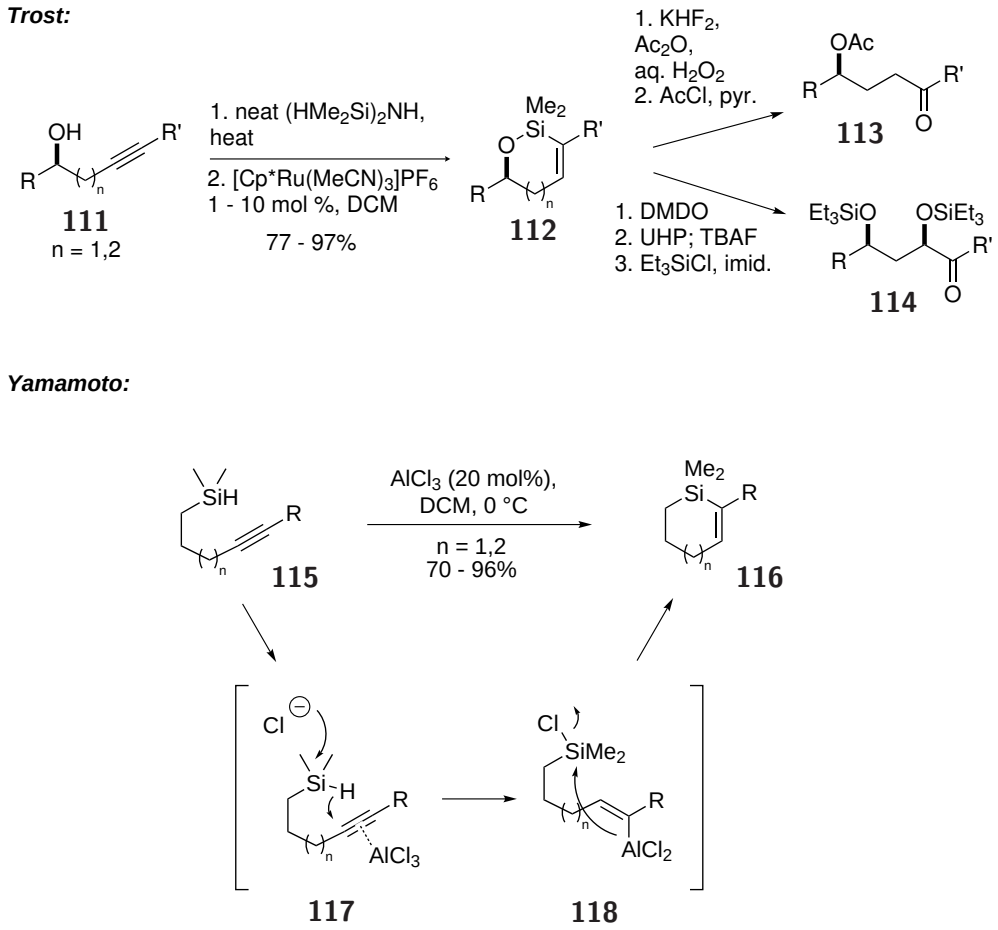
1.2.5. Hydrosilylation and Carbosilylation

The application of silicon tethering methodology to the silylation of unsaturated systems is one of the most well developed areas in this field. Rather than simply being a spectator to the reaction pathway, the tether may now be considered a crucial component of the reaction itself and it is this intimate involvement in the reaction mechanism that makes such TST silylation processes unique. The first example of an intramolecular alkyne hydrosilylation was reported by Tamao and co-workers in 1988,[61] and since this early report a number of hydrosilylation catalysts have been developed, providing access to a complete range of regio- and stereoisomeric vinyl silane products. Tamao's seminal work employed Speier's catalyst (hexachloro*cis*platinic acid, H_2PtCl_6) to give rise to the *syn*, *exo* hydrosilylation product, and the Marshall[62] and Denmark[63,64] groups have subsequently extended the substrate scope and utility of this process (Scheme 1.16). Using either Speier's catalyst or Pt(1,1,3,3-tetramethyl-1,3-divinyldisiloxane) (Pt[DVDS]), a range of substituted silanes **105** underwent hydrosilylation in a highly selective fashion to afford the *exo*-siloxanes **106** in high yields. These products could then undergo further functionalisation, either through application of a Tamao oxidation protocol, or *via* Hiyama coupling to give a substituted alkene product.



Scheme 1.16 *Exo*-Hydrosilylation Reactions

The Denmark group noted that by employing a ruthenium catalyst, a switch from the *syn* to the *anti* mode of *exo*-hydrosilylation will take place (Scheme 1.16), thus giving access to a complimentary range of vinyl siloxane products **108**. By utilising the unusual disilyl disiloxane tether in substrate **109**, Denmark and co-workers were also able to achieve the hydrosilylation of propargyl alkynes (**110**), a transformation that would otherwise be highly challenging. Although these processes do allow access to both the *E* and *Z* products in an efficient and selective fashion, the propensity of the *anti* products **108** and **110** to undergo polymerisation is a notable drawback of this approach. However, it was found that these polymeric species were still able to act as substrates for a subsequent Hiyama coupling step, and thus this outcome does not present a significant disadvantage for this methodology.

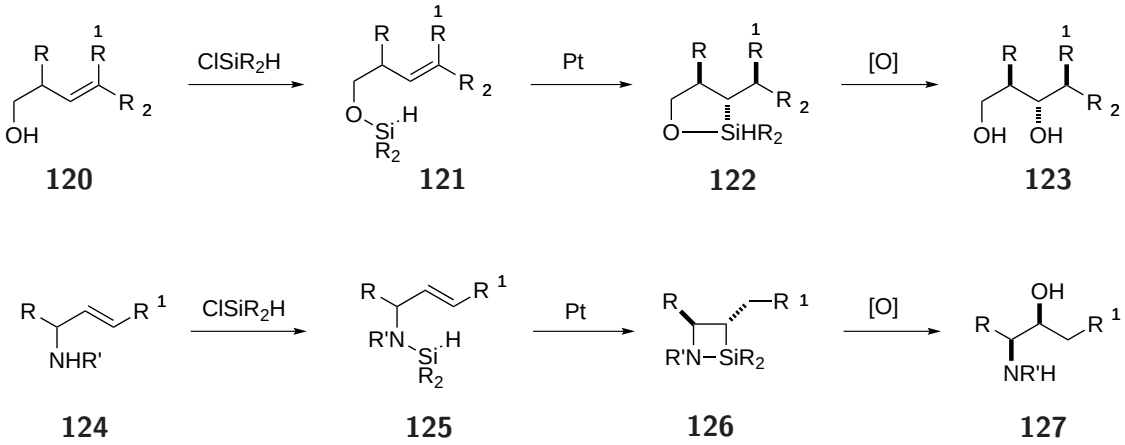


Scheme 1.17 *Endo*-selective Hydrosilylation

In contrast, Trost and co-workers found by employing the cationic ruthenium catalyst [Cp*Ru(MeCN)$_3$]PF$_6$, the *endo*, *anti* mode of cyclisation was observed to take place, yielding the six-membered ring vinyl siloxane products **112** (Scheme 1.17).[65] This intriguing selectivity was observed even for 1,4-alkynol

substrates (**111**, n = 2), with hydrosilylation affording the seven-membered ring *endo* product rather than the more stable 6-*exo* product. Further work by the group emphasised the synthetic utility of this methodology, with intermediate cyclic siloxane **112** undergoing oxidation to afford homoaldol products **113**, or α,γ- and α,δ-dihydroxyketones **114**.[66]

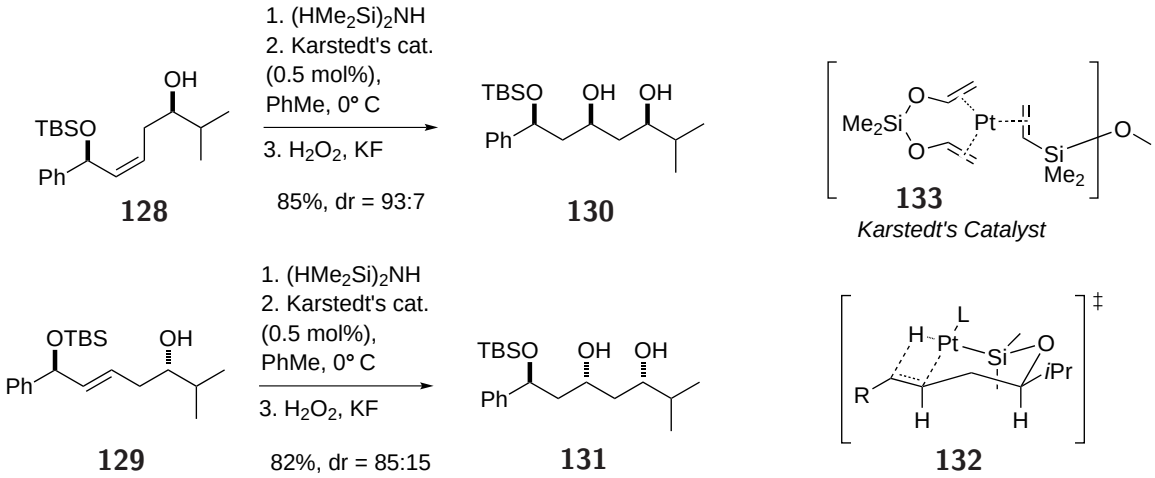
A related *endo*, *anti* mode of hydrosilylation was observed by the Yamamoto group in their work on the Lewis-acid mediated cyclisation of silane-tethered substrates **115**.[67] In the presence of sub-stoichiometric amounts of $AlCl_3$, transfer of a hydride to the activated alkyne (**117**) occurred with high regio- and stereoselectivity when R groups with limited cation-stabilising ability were present (R = H, alkyl, TMS). Subsequent C-Si bond formation (**118**) afforded the cyclic product **116** in high yield. However, when R groups with enhanced cation-stabilising ability were employed (R = aryl), a preference for the *exo* mode of cyclisation was instead observed, giving rise to five-membered ring products **119**.



Scheme 1.18 Seminal Work on the Hydrosilylation of Alkenes

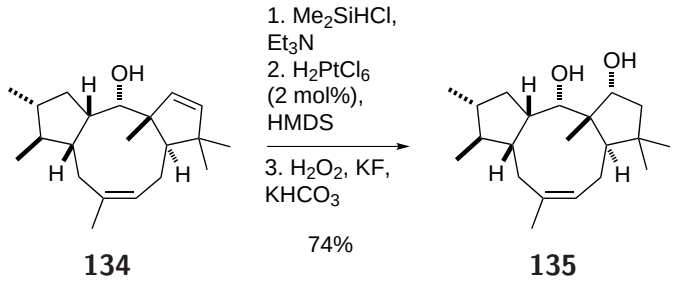
The application of silicon-tethering strategies to alkene hydrosilylation is a well-established synthetic strategy, with the Tamao group having conducted much of the seminal work on this topic in the 1980s (Scheme 1.18).[68] This methodology allows one or two new stereocentres to be formed, and early work focused upon utilising the effects of 1,2- and 1,3-allylic strain in controlling the stereochemistry of the products **123** formed.[69–72] More recently, Roush and co-workers found that they could access a range of polyacetate motifs by employing Karstedt's catalyst in the hydrosilylation step,[73] instead of the more substituted polypropionate units whose synthesis dominated earlier work in this field (Scheme 1.19). The group found that both *E* and *Z* alkenes **128** and **129**

could be utilised to give access to both the *syn*, *syn* (**130**) and *syn*, *anti* (**131**) 1,3,5-triols, with high levels of steroinduction being observed. It was proposed that chair-like transition state **132** provided the best explanation for the diastereomeric ratios obtained.



Scheme 1.19 Silicon-Tethered Alkene Hydrosilylation in the Synthesis of Polyacetates

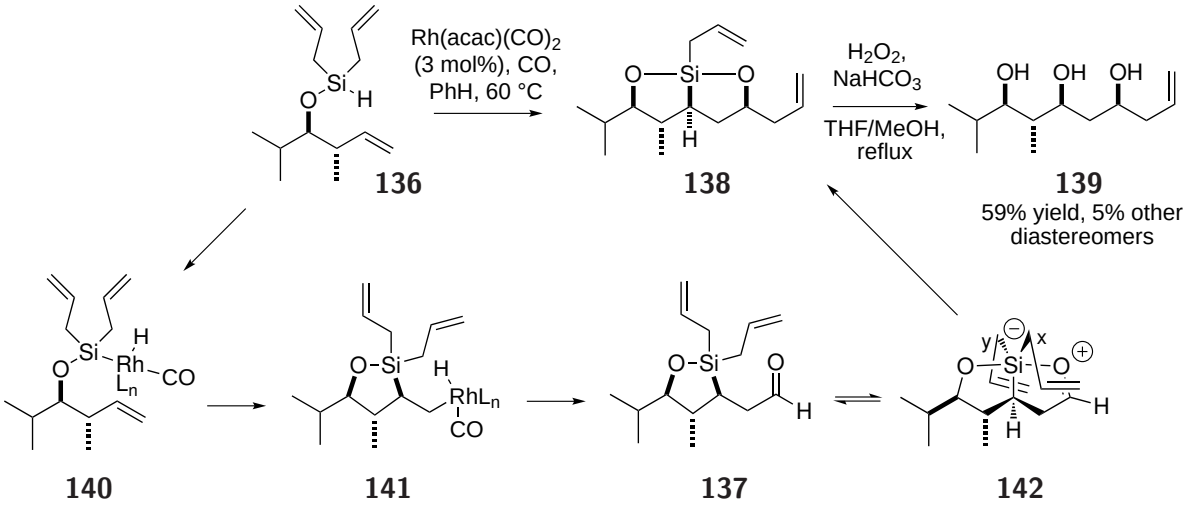
As expected, tethered alkene hydrosilylation has seen considerable application in natural product synthesis, with not only polyketide systems[74–76] but also more exotic structures[77,78] being approached *via* such methodology. One particularly impressive example was reported by Paquette and co-workers in their total synthesis of the diterpenoids jatrophatrione and citlalitrione,[79] in which hydrosilylation and oxidation of the complex precursor **134** provided access to the diol **135** in a synthetically useful 74% yield (Scheme 1.20). It should be noted that in this instance the stereoselectivity was not important, as both alcohols eventually underwent oxidation to the corresponding ketones. However, the utility and generality of alkene hydrosilylation methodology is still apparent in this synthetic route.



Scheme 1.20 Hydrosilylation in the Total Synthesis of Jatrophatrione and Citlalitrione

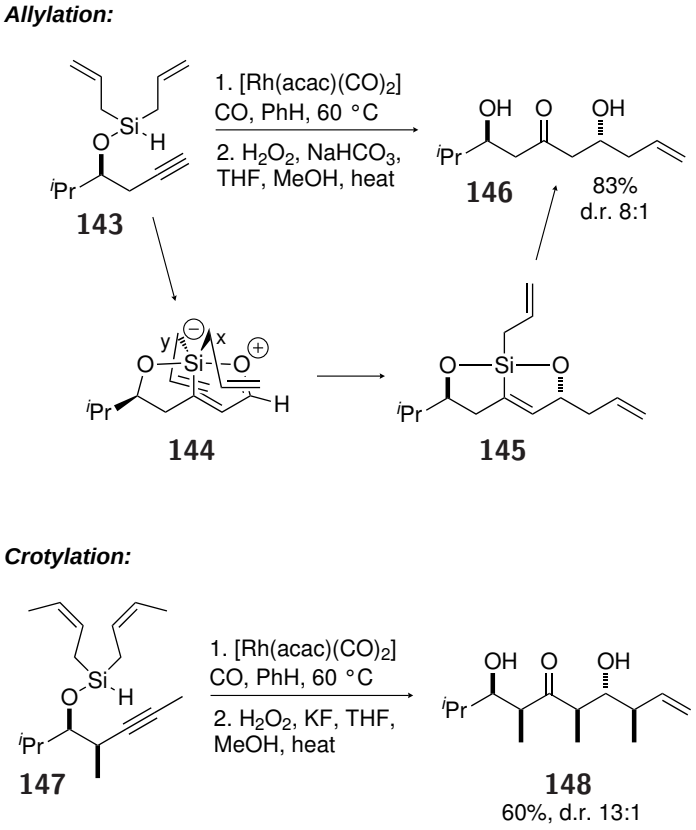
In a natural extension of hydrosilylation chemistry, there has also been considerable development

of **carbo**silylation methodology. The Leighton group has conducted much of the pioneering work in this field, exploring the synthetic possibilities of TSTs in a tandem silylformylation / allylation approach to polyketide frameworks. Investigation into alkene-containing substrates **136** formed the basis of their initial investigations (Scheme 1.21),[80] with rhodium-catalysed silylformylation affording intermediate **137**. *In situ* allylation of the nascent aldehyde functionality subsequently yielded cyclic siloxane **138**, which could then undergo a Tamao oxidation to produce 1,3,5-triols **139** in a high yielding and highly diastereoselective fashion.



Scheme 1.21 Tandem Silylformylation / Allylation of Alkenes

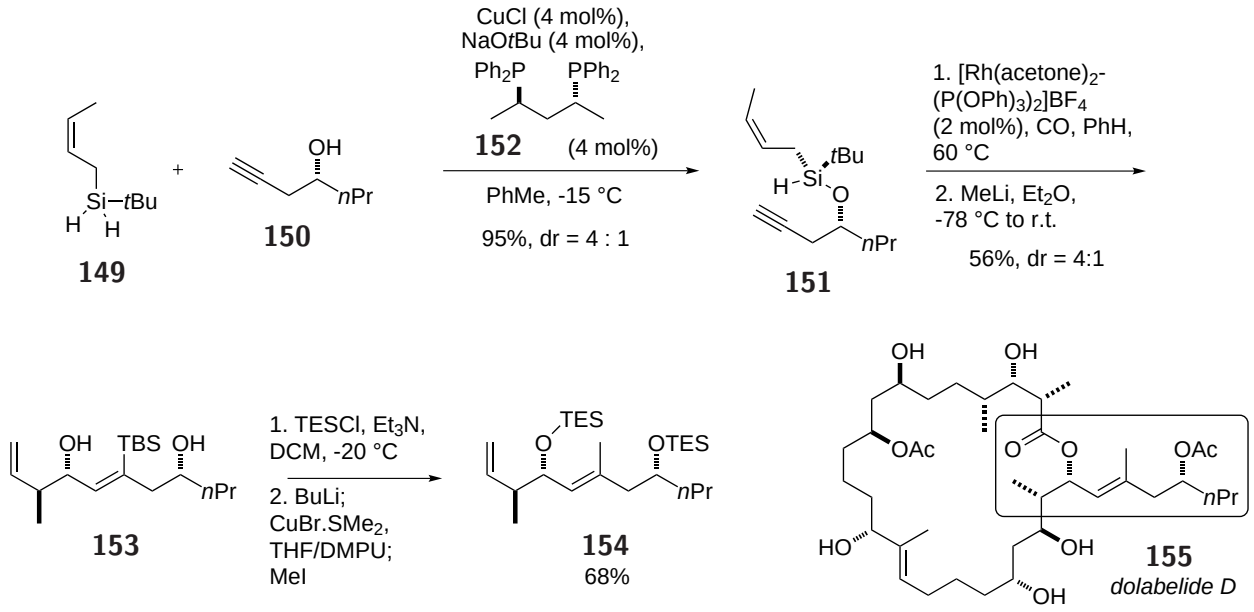
Of particular note is the selectivity and reactivity observed in the final allylation step, and the group proposed that this was likely to occur *via* formation of an 'ate' intermediate **142**. The prior cyclic intermediate **137** is thought to be under considerable strain given the unfavourable 95° C-Si-O bond angle which must necessarily be adopted, and thus formation of the 'ate' complex **142** is favourable on the grounds that the resulting trigonal bipyramidal geometry offers some strain release. As a result, the aldehyde is now activated towards nucleophilic attack, while the negative charge arising at the silicon centre enables transfer of an allyl group to readily take place. The diastereoselectivity observed arises as a result of the preferential transfer of allyl group 'x', which lies in closer proximity to the aldehyde functionality. The release of ring strain as a driving factor for reaction in silicon-containing cyclic systems has been used to rationalise the reactivity of a number of other processes, including the unactivated aldol reactions of enoxysilacyclobutanes,[81–83] and the ability of silacyclobutanes to act as allylating agents or cross-coupling partners.[84]



Scheme 1.22 Silylformylation / Allylation of Alkynes

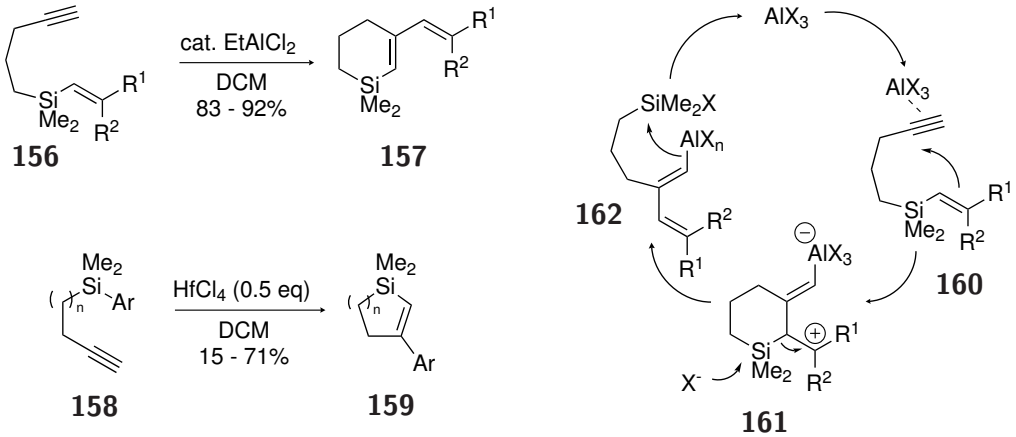
Leighton and co-workers have subsequently expanded the scope of this work to include both terminal[85] and internal[86] alkynyl substrates (**143** and **147**, Scheme 1.22), as well as utilising both allyl- and crotyl-containing[87] species. Of particular note is the selectivity observed for the formation of the *anti* diastereomer **146** in this instance, giving rise to 1,5-stereoinduction in the products **146** and **148**. Once again, an 'ate' complex transition state **144** can be invoked to explain the selectivity that arises, with the allyl group 'y' instead being transferred from the less hindered face of the aldehyde. The added complexity provided by the internal alkyne crotyl silane substrates **147** allowed access to a range of highly substituted polyketide motifs **148** with impressive diastereoselectivities, emphasising the considerable synthetic utility of this methodology. Indeed, the Leighton group have subsequently applied this TST strategy to the partial synthesis of the natural products spongistatin 1,[86] zincophorin,[86] and dolabelides A and B.[88]

In an intriguing extension of this chemistry, Leighton and co-workers found that the diastereoselectivity of the silylformylation / crotylation process could be influenced by employing a stereogenic silicon centre.[89] In a subsequent total synthesis of the polyketide dolabelide D **155**[90] (Scheme 1.23), a copper-catalysed asymmetric silane alcoholysis in the presence of chiral diphosphine ligand **152**



Scheme 1.23 Asymmetric Silylformylation / Crotylation in the Total Synthesis of dolabelide D

was employed to synthesise the desired chiral silane **151** as a 4 : 1 mixture of diastereomers. Stereochemical transfer was then achieved with high fidelity in the subsequent silylformylation / crotylation process to afford intermediate **153**, again as a 4 : 1 diastereomeric mixture thanks solely to the ratio of products obtained in the previous step. Thus, the 1,5-*syn* relationship between the two hydroxy substituents in the key precursor **154** could be realised in a selective manner, with extensive molecular complexity being generated in just three steps. To date, this remains one of the very few examples where a chiral TST has been employed in silicon-tethering methodology, and the potential of these systems in asymmetric induction processes is likely to be explored to a much greater extent in the future.

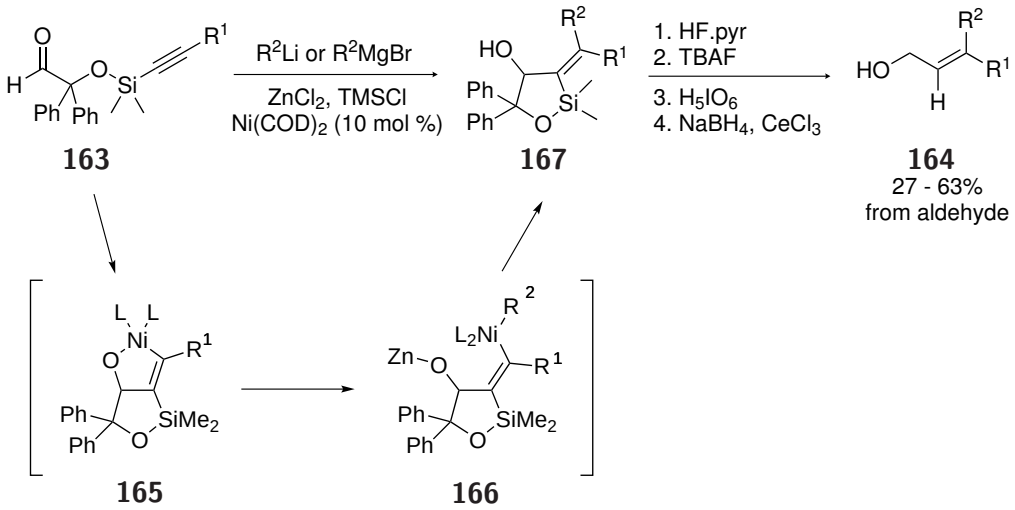


Scheme 1.24 Silicon-Tethered Carbosilylation

Finally, a Lewis acid-catalysed intramolecular *trans*-carbosilyation process has been reported by Yamamoto and co-workers (Scheme 1.24),[91,92] in a similar vein to their silicon-tethered hydrosilylation work discussed earlier (Scheme 1.17). In the presence of sub-stoichiometric amounts of $EtAlCl_2$ or $HfCl_4$, cyclisation of vinyl or aryl substrates (**156** and **158** respectively) afforded the cyclic products **157** and **159**. A mechanism was proposed by the group to explain the product formation observed, their postulations again capitalising upon the well-known ability of silicon to stabilise β-carbocation intermediates such as silacycle **161**.

1.2.6. Miscellaneous Reactions

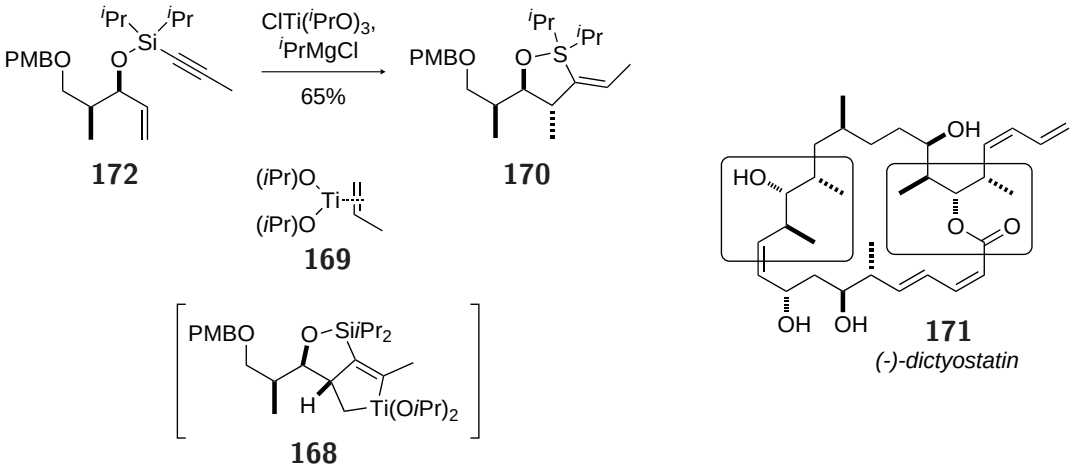
Silicon tethers have also found application in a wide variety of other metal-mediated processes. The Montgomery group reported a nickel-catalysed cyclisation in 2001, in which the unusual alkynyl siloxane substrates **163** underwent a number of transformations to eventually afford the trisubstituted allylic alcohols **164** (Scheme 1.25).[93] It is thought that the reaction proceeds *via* the nickelocyclic intermediate **165**,[94] which can then undergo transmetallation with a range of organozinc or organomagnesium species. This process afforded intermediate **166**, with a subsequent reductive elimination step yielding the cyclic siloxane **167**.



Scheme 1.25 Synthesis of Trisubstituted Allyl Alcohols *via* Nickel Catalysis

A related titanocyclic intermediate **168** can also be observed in the work of Phillips and co-workers on the development of a titanium-mediated reductive cyclisation (Scheme 1.26).[95–98] The active species in this process is likely to be the $Ti(OiPr)_2(\eta^2$-propene) complex **169**, formed *in situ* from

the reduction of stoichiometric ClTi(O*i*Pr)$_3$ by *i*PrMgCl. Following the formation of intermediate **168** *via* oxidative addition, subsequent loss of the titanium centre afforded siloxane **170** in a moderate yield. Using this strategy, the Philips group were able to readily establish the contiguous *syn*, *syn*, *anti* stereotriad that is found twice in the complex polyketide (−)-dictyostatin **171**, and a total synthesis of this natural product was subsequently completed.

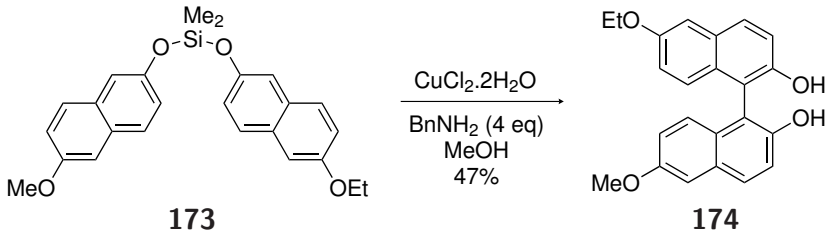


Scheme 1.26 Titanium-Mediated Reductive Cyclisation

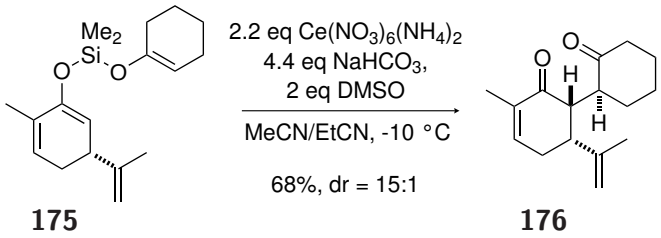
TSTs have also been applied to a number of oxidative coupling strategies. Schmittel and co-workers reported the copper-mediated oxidative cyclisation of disiloxane-linked naphthyl units **173** to the binaphthol derivatives **174**, a process which proceeds *via* a single electron transfer mechanism (Scheme 1.27).[99] This methodology is notable for the complete *ortho* selectivity that arises during the coupling reaction, a result that could not be readily achieved in the absence of a tethering system. The Thomson group have also investigated the oxidative coupling of bis-enol ether substrates **175**,[100] in this instance using cerium ammonium nitrate as a stoichiometric single electron oxidant to promote cyclisation and *in situ* desilylation to the bis-ketone product **176**. In this example, a pleasing diastereomeric ratio of 15 : 1 was observed, and the group has more recently extended this work to encompass an intramolecular oxidative allylation protocol.[101]

In the only reported application of TSTs to a gold-catalysed process, Lee and co-workers have investigated the transformation of enynes **177** to skipped dienes **178** *via* a silyl β-carbocation intermediate **179** (Scheme 1.28).[102] Interestingly, a 6-*endo*-dig cyclisation was favoured over a 5-*exo*-dig process, and we propose that it is the stabilising effect of the neighbouring double bond in hexacyclic intermediate **179** that drives this selectivity. It was found that the subsequent alcoholysis

Schmittel:



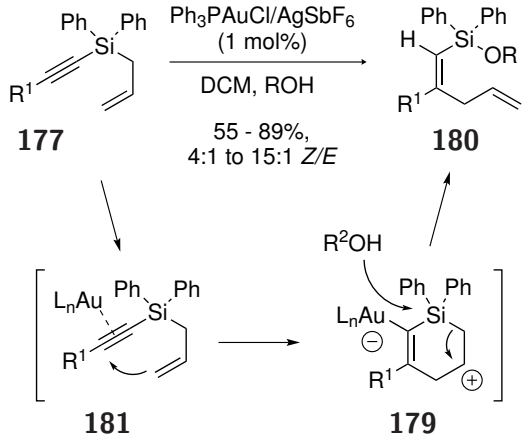
Thomson:



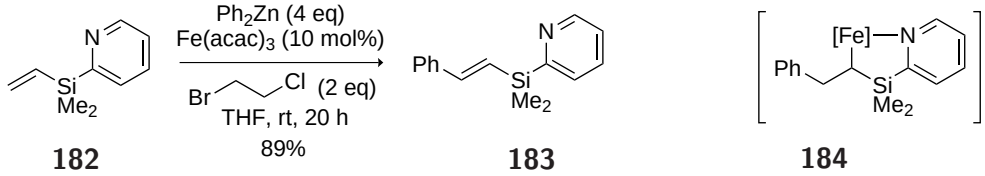
Scheme 1.27 Silicon-Tethered Oxidative Couplings

step could proceed with a wide variety of functionalised alcohols, thus providing considerable opportunity for further transformations of the diene products **180**.

Lee:



Nakamura:



Scheme 1.28 Gold- and Iron-Catalysed Silicon-Tethered Reactions

Finally, the Nakamura group have recently developed an iron-catalysed cross-coupling process that is thought to proceed *via* a silicon-tethered intermediate **184** (Scheme 1.28).[103] In this instance, the use of a tether enables the addition of an organozinc species to the vinyl silane substrate **182** in a chemo- and regioselective fashion, affording the substituted vinyl silanes **183** in high yields.

1.3. Latent Functionality

While an organosilicon compound is often inert to a wide range of reaction conditions (thus explaining the widespread use of alkyl silanes as protecting groups and even tethers in organic synthesis), when it is exposed to certain reagents the silicon centre and surrounding carbon framework can be transformed into a variety of other functional groups. This reactivity reintroduces the concept of 'latent functionality', whereby a silicon atom can be viewed as a precursor to a range of silicon-free functionalities. For silicon-tethered products **185** (Fig. 1.2), the key reactivity modes include the Fleming-Tamao oxidation, in which an oxygen atom is introduced (**186**), the Hiyama cross-coupling (**187**), halogenation (**188**), and finally protodesilylation (**189**).

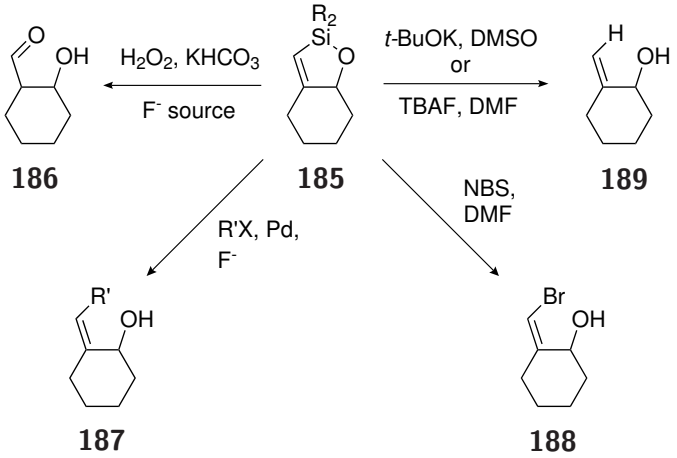


Fig. 1.2. Transformations Occurring at the Silicon Centre

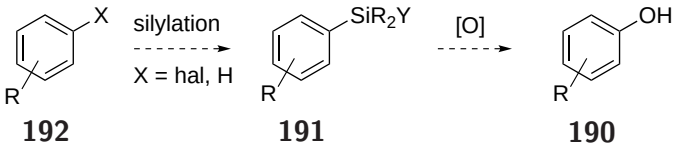
It is the ability of silicon to undergo such a range of transformations that once again emphasises the potential synthetic utility of silicon-tethering methodology. Use of a TST strategy not only allows the reactivity and selectivity of a reaction to be enhanced, but also provides the opportunity for a wide variety of products to be approached following cyclisation. Thus, enhancing the scope of such 'latent functionality' is likely to provide considerable benefits, both with regards to silicon tethering methodology, and with regards to the utility of organosilicon chemistry as a whole.

The scope of this thesis encompasses work conducted on the introduction of functional silicon centres to aryl systems, and the subsequent exploration of the 'latent reactivity' of such compounds (Chapter 2). Furthermore, as a result of our considerable interest in this rapidly developing field, a number of novel silicon-tethered metal-mediated processes have also been investigated. In building upon our earlier work on the synthesis and reactivity of aryl silanes, we were initially attracted by the prospect of a iron-catalysed silicon-tethered aryl coupling (Chapter 3). Later work focused upon the relatively unexplored area of TST use in palladium-mediated reactions (Chapter 4), with a brief investigation into a silicon-tethered platinum-catalysed hydrosilylation cascade concluding this dissertation (Chapter 5).

2. Aryl Silane Oxidation - New Routes to Hydroxylated Aromatics

2.1. Overview

With the concept of 'latent functionality' in mind, we sought to further expand the range of transformations that an organosilicon centre could undergo. Our aim was to develop a mild and synthetically attractive route towards phenolic compounds **190** by subjecting the correpsonding aryl silane species **191** to a modified Tamao oxidation protocol (Scheme 2.1).



Scheme 2.1 Aryl Silane Oxidation Methodology

2.2. Introduction

Phenols are ubiquitous in both medicinal and natural product chemistry,[104,105] this motif being found in bioactive molecules as diverse as reversatrol **193**, piericidin A **194**, the khellinones **195** and platensimycin **196** (Fig. 2.1). However, despite the importance of this functional group, the introduction of a phenol into an aromatic compound can be challenging. More traditional methods of phenolation often require harsh reaction conditions and display limited functional group tolerance,[106] and as a result the required aromatic hydroxyl functionality is usually introduced during the early steps of a synthetic pathway. However, an aromatic hydroxyl strongly modulates the reactivity and selectivity of subsequent reactions involving the aryl system, potentially limiting the scope of further synthetic steps due to regiocontrol issues. Furthermore, phenols may also

require protection to enable compatibility with subsequent reaction conditions, thus reducing the step economy of an envisaged synthetic pathway and making the late-stage introduction of a phenol a highly desirable goal.

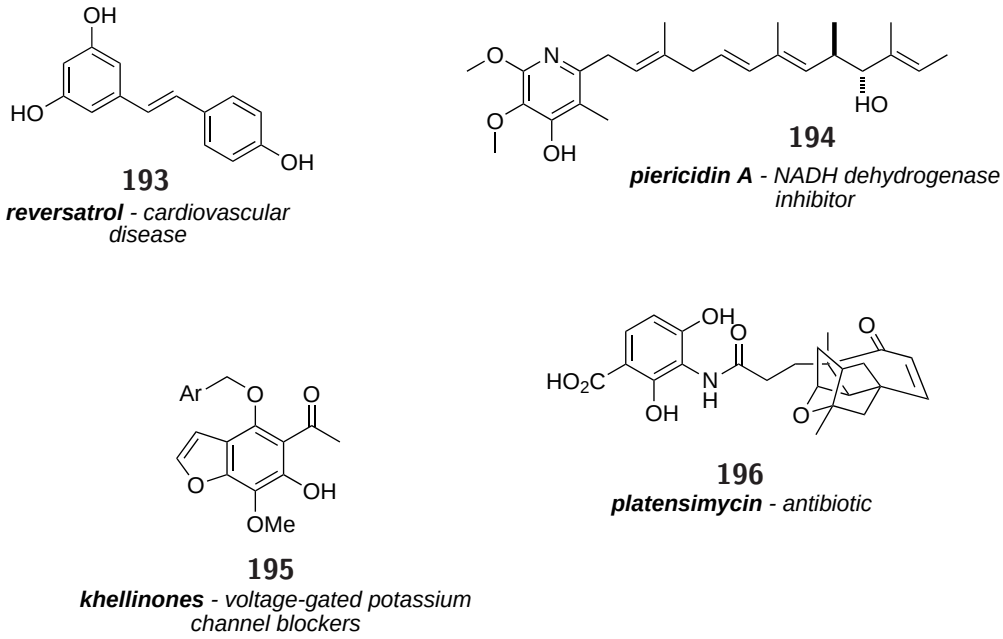
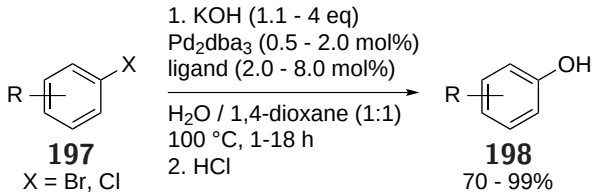


Fig. 2.1. Some Examples of Phenol Natural Products

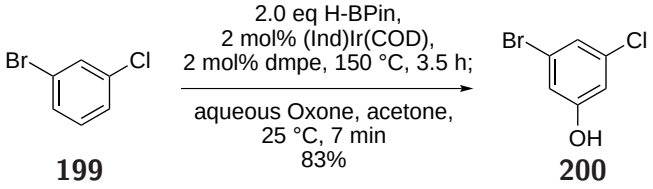
With such a goal in mind, several groups have recently reported elegant strategies based on transition-metal catalysed aryl halide hydroxylation[107–113] or C-H activation / oxidation (Scheme 2.2).[114,115] However, despite the ease with which the desired phenols can be accessed under such transition-metal catalysed conditions, it is important to note that all these methodologies require exposure of the substrates to considerable temperatures. We propose that the introduction of a temporary, yet stable oxidisable group could be considered as an alternative strategy, whereby oxidation to the desired aromatic hydroxyl could occur at a subsequent point in the synthesis, under mild and functional group-tolerant conditions.[116]

The seminal work of Tamao[117–121] on the oxidation of activated organosilanes provided the base upon which to build this phenolation methodology. While such oxidation is well precedented for aliphatic systems, the application of this chemistry to aromatic silanes remains surprisingly limited, and it was thus envisaged that a phenol motif may be accessed *via* the introduction and subsequent oxidation of an appropriate organosilane substituent. The non-toxic and inexpensive nature of silicon-based reagents increased the appeal of this strategy.[122–127]

Palladium Catalysed (Buchwald, 2006):

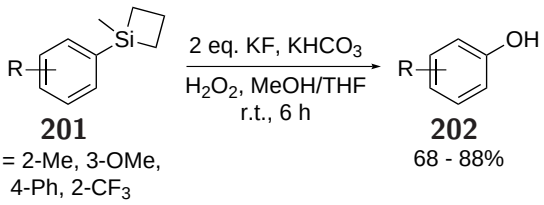


Iridium-catalysed (Smith, 2003):



Scheme 2.2 Recent Metal-Catalysed Routes Towards Phenols

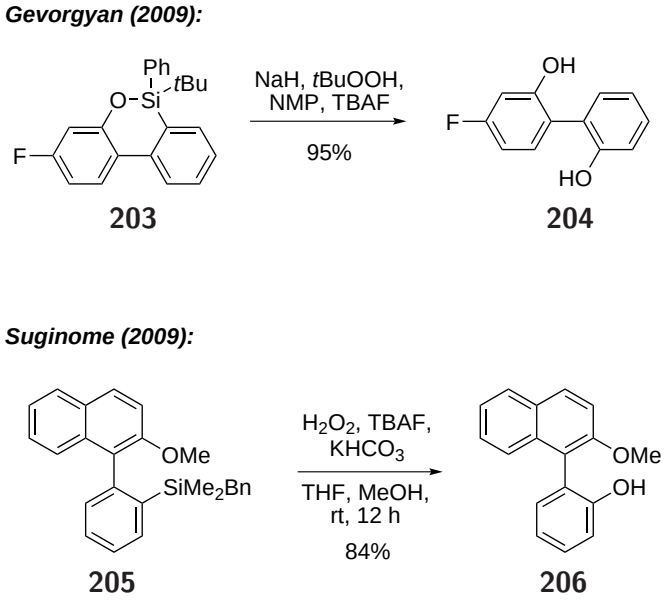
To date, the main example of such an aryl silane oxidation is found in Dudley's work (Scheme 2.3),[128–130] where functionalised arylsiletanes **201** were subjected to oxidation under Tamao conditions with KF (2 eq), $KHCO_3$ and H_2O_2 (30.5 eq) in MeOH/THF (1:1) at room temperature for 6 hours. While the yields for this transformation are mostly high, and the aryl siletanes are stable functionalities, this methodology does require the use of expensive and sensitive siletanyl chlorides, which suffer from difficulties in preparation. Several isolated examples of other aromatic Tamao oxidations have also been reported,[131,132,117] but the full scope of this reaction was not explored in these publications.



Scheme 2.3 Dudley's Aryl Siletane Oxidation

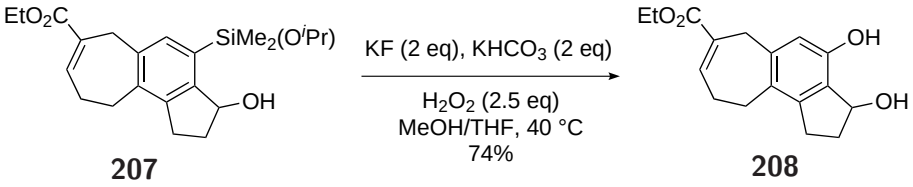
Two further isolated examples of aryl silane oxidation have recently been published,[133,39] reiterating the need for a detailed study and optimisation of this phenolation methodology (Scheme 2.4). Currently, the major drawback in all previously reported examples of aryl silane oxidation is the use of stoichiometric amounts of a fluoride source as an organosilane activator, thus limiting the

functional-group tolerance of this desirable transformation.



Scheme 2.4 Recent Non-General Examples of Aryl Silane Oxidation

Work carried out in our group towards the total synthesis of rubriflordilactone A made use of this aryl silane oxidation methodology,[134] employing the dimethyl *iso*-propoxysilyl group as a masked phenol (Scheme 2.5). The desired oxidation took place in a 74% yield (**207** → **208**), prompting us to further explore the synthetic utility of this transformation *via* the synthesis of a range of oxidisable aryl silanes.



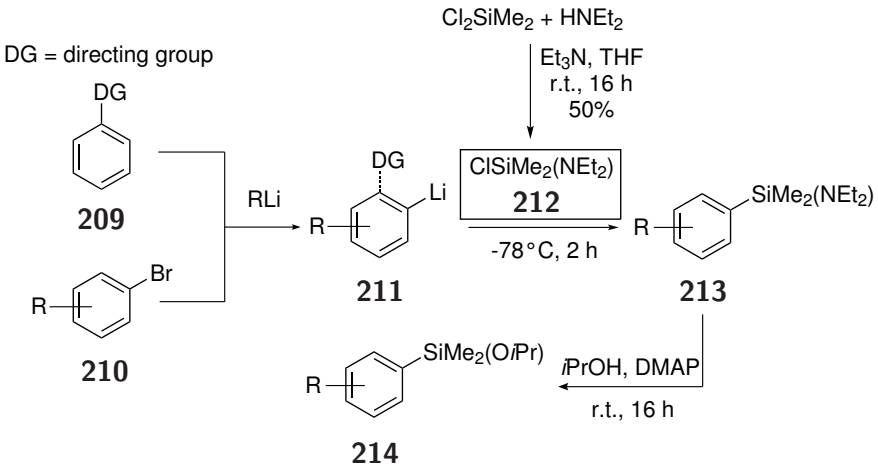
Scheme 2.5 Preliminary Aromatic Tamao Oxidation Towards the Total Synthesis of Rubriflordilactone A

2.3. Methodology Development

2.3.1. Aryl Silane Synthesis

Two routes were envisaged to access the desired aryl silanes in a regiocontrolled fashion, initiating from either the directing group-substituted arenes **209** or the bromo-derivatives **210**. Bromine-

lithium exchange or directed *ortho*-lithiation would provide access to an intermediate aryllithium species **211**, which would then be subjected to trapping with an appropriate silylating reagent (Scheme 2.6). From the variety of organosilane species available for such a process, $ClSiMe_2(NEt_2)$ **212** was selected to be the most appropriate, as this compound is known to undergo only a single addition of a carbon nucleophile to the silicon centre at low temperatures.[15,135] Previous studies have shown that organometallic reagents will undergo multiple addition to other silylating agents such as dimethyl dichlorosilane.[136]



Scheme 2.6 Aryl silane synthesis

While the aminosilane reagent **212** is commercially available at a moderate cost, it may also be readily and inexpensively synthesised on a multigram scale *via* the slow addition of Et_2NH to a solution of Et_3N and Cl_2SiMe_2 in THF.[135] $ClSiMe_2(NEt_2)$ **212** could be subsequently isolated from the reaction mixture *via* distillation, with care being taken to avoid exposure of the sensitive aminosilane to moisture.

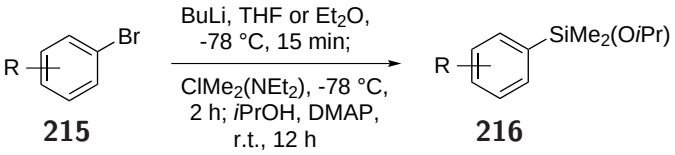
Following addition of $ClSiMe_2(NEt_2)$ **212** to a lithiated aryl species **211**, the resulting aryl amino silane **213** could be subsequently reacted with an alcohol of choice in the presence of DMAP (Scheme 2.6). A brief survey of simple alkoxysilane derivatives* resulted in the selection of *iso*-propanol for this purpose, the *iso*-propoxy arylsilane **214** being sufficiently stable to allow purification by flash column chromotography. Furthermore, it was anticipated that such a derivative would display the optimum balance between oxidative reactivity and silane stability.

*Methoxy, ethoxy and *iso*-propoxy derivatives were investigated.

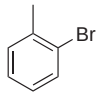
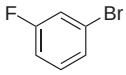
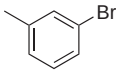
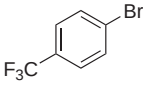
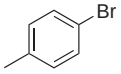
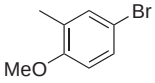
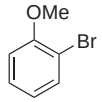
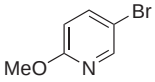
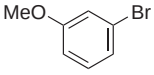
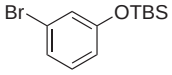
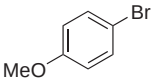
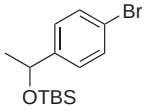
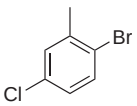
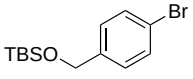
Bromine-Lithium Exchange Substrates

The use of bromine-lithium exchange / silylation chemistry allowed a variety of substituted aryl *iso*-propoxysilanes to be readily synthesised. Either *n*-BuLi (1.2 eq) or *t*-BuLi (2.0 eq) were employed as lithiating species in THF or Et_2O at −78 °C, allowing the desired products to be synthesised cleanly and in high yields (Table 2.1).

Table 2.1. Aryl Silane Synthesis *via* Bromine-Lithium Exchange



215 **216**

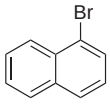
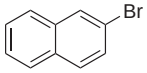
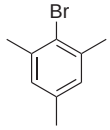
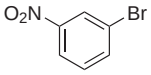
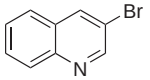
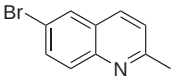
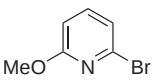
		Conditions	Yield[a]			Conditions	Yield[a]
1		*n*-BuLi, THF	99%	8		*n*-BuLi, THF	83%
2		*n*-BuLi, THF	99%	9		*n*-BuLi, THF	95%
3		*n*-BuLi, THF	99%	10		*t*-BuLi, THF	85%
4		*n*-BuLi, THF	94%	11		*n*-BuLi, Et_2O	99%
5		*t*-BuLi, THF	99%	12		*t*-BuLi, THF	76%
6		*t*-BuLi, THF	97%	13		*t*-BuLi, THF	89%
7		*n*-BuLi, THF	90%	14		*n*-BuLi, THF	99%

[a] *Iso*-propoxysilane **216** yield.

Of these substrates, it is particularly notable that both 3-bromo-anisole **217** and 4-bromoanisole

218 (entries 5 and 6) required the use of *t*-BuLi in order for the bromine-lithium exchange reaction to proceed to completion. This result is likely to reflect the effect of the electron-donating methoxy substituent, whereby the reactivity of the C-Br bond towards this metal-halide exchange process is reduced thanks to the relatively electron-rich nature of the arene. This effect is overridden in the case of 2-bromoanisole **219** (entry 4), where the adjacent methoxy group may coordinate to the lithiating species and can direct the exchange process, thus allowing the milder *n*-BuLi reagent to be used. The nature of the ethereal solvent used was also found to be important, with the pyridyl substrate alone requiring Et_2O to be employed if successful bromine-lithium was to be achieved (entry 11).

Table 2.2. Problematic Substrates for Bromine-Lithium Exchange

		Conditions[a]	**Yield**[b]
1		*t*-BuLi, Et_2O	89%[c]
2		*t*-BuLi, Et_2O	88%[c]
3		*t*-BuLi, THF	0%
4		PhLi, THF	0%
5		*t*-BuLi, Et_2O	72%
6		*n*-BuLi, Et_2O	n.c.[d]
7		*n*-BuLi, THF	56%

[a]Conditions: RLi, THF or Et_2O, −78 °C; $ClSiMe_2(NEt_2)$, −78 °C, 2 h; [i]PrOH, DMAP, r.t., 12 h. [b]Yield of the *iso*-propoxysilane **216**. [c]Contaminated with naphthalene. [d]Not Calculated.

While bromine-lithium exchange proved to be a robust method for the synthesis of aryl silanes in many cases, there were a number of substrates that were found to be problematic (Table 2.2). The naphthyl derivatives **220** and **221** (entries 1 and 2) were found to be particularly susceptible towards protonation upon formation of the lithiated aryl, despite rigorous drying of solvents and glassware, and the non-volatile naphthlene by-product proved difficult to remove from the desired *iso*-propoxy silane. It was postulated that this protonation may be arising because the naphthyl anion formed is able to eliminate HBr from the *t*-butylbromide byproduct competitively with the second equivalent of *t*-BuLi. In contrast, bromomesitylene (entry 3) did not undergo lithiation at all, even in the presence of highly reactive *t*-BuLi. It is the sterically-demanding nature of the methyl substitutents adjacent to the carbon-bromine bond that is thought to be the major contributing factor towards this lack of reactivity. The nitrobenzene-derived silane also could not be synthesised in any detectable amount (entry 4), with 3-bromonitrobenzene **222** yielding a complex mixture following treatment with a range of lithiating species. With these difficult substrates, and others with alkyllithium-sensitive functionalities, formation of the analogous Grignard species may allow the corresponding aryl silane to be synthesised.

Of greater interest is the difficulty found in lithiating a number of pyridyl-based species (entries 5 - 7). While the initial yield for the lithiation and silylation of 3-bromoquinoline **223** was acceptable, difficulties arose when attempting to reproduce this result, with further attempts giving a complex mixture of byproducts. A complex mixture was also observed during the attempted lithiation of 6-bromo-2-methylquinoline **224**, and subsequent consultation of the literature found this result to be consistent with Davis' observation that treatment of a 2-methylquinoline derivative with *n*-BuLi results in both bromine-lithium exchange, and addition of an *n*-butyl chain to the 2-methyl substituent.[137] Further attempts with *t*-BuLi also yielded a complex mixture. Given the difficulties experienced in lithiating these quinoline derivatives, it is notable that such chemsitry also finds little application in the current literature.

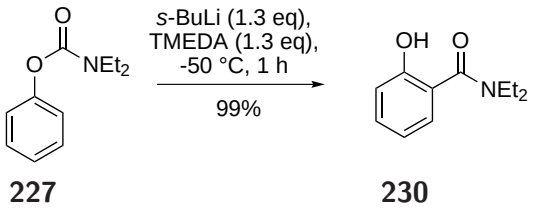
While considerable success was achieved with 5-bromo-2-methoxy-pyridine **225** (Table 2.1, entry 11), this could not be replicated when attempts were made to lithiate and silylate 6-bromo-2-methoxypyridine **226** (Table 2.2, entry 7). Although the desired product could be isolated in 56% yield, the silylated species displayed a reduced stability towards flash column chromatography, and subsequent attempts to repeat this lithiation gave a number of byproducts. Although there is a

considerable amount of research focusing on the synthesis and applications of lithiated heterocycles,[138] subsequent difficulties in the oxidation of these heteroaromatic arylsilanes prompted us to focus on more amenable carbocyclic substrates.

Directed ortho-Lithiation Substrates

The use of *ortho*-lithiation methodology enabled a complementary selection of substrates to be approached, and removed the dependence upon a bromine substituent in determining the regiocontrol of the silylation process. Based on extensive literature precedents in the field of directed *ortho*-lithiation,[139] a variety of bases were employed for this process, which allowed access to the desired aryl silanes in good to excellent yields (Table 2.3).

It was gratifying to note that the use of literature conditions with *N,N*-diethyl phenyl carbamate **227**,[140] anisole **228**[141] and *N,N*-di*iso*-propylbenzamide **229**[123] (entries 1 - 3) yielded the desired aryl silanes in excellent yields. However, the importance of the cryogenic conditions was underlined in early attempts at carbamate **227** lithiation, with a 1,3-carbamoyl migration occurring to give the resulting 2-hydroxy benzamide **230** in high yields.[140] The desired silylation product **231** was absent from the reaction mixture (Scheme 2.7), and further studies found that this rearrangement proceeds rapidly at −50 °C.



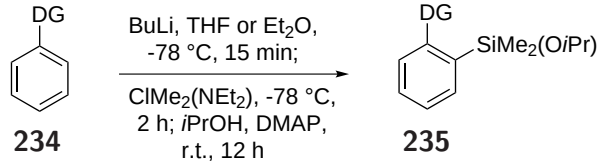
227 **230**

Scheme 2.7 Unexpected Rearrangement of Carbamate **227**

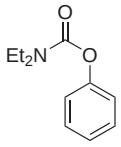
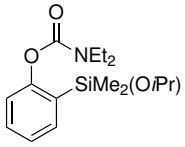
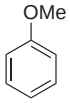
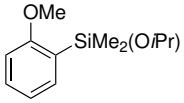
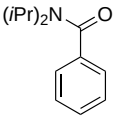
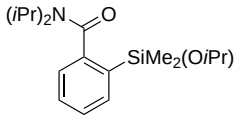
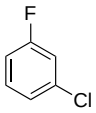
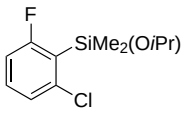
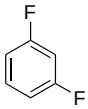
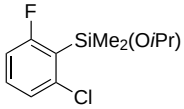
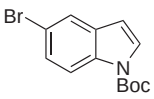
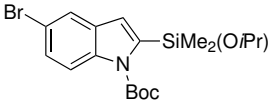
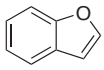
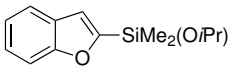
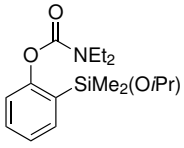
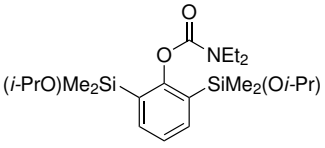
Deprotonation and silylation could also be achieved for several 1,3-dihalide species (entries 4 and 5) upon treatment with *n*-BuLi and TMEDA.[142] The electron-withdrawing nature of the neighbouring halogen substituents renders the central C-H bond relatively labile, thus enabling functionalisation to take place with high efficiency. It should be noted that at the low temperatures employed, no elimination to form the corresponding benzyne species takes place. Pleasing results were also obtained from the five-membered ring heterocycles **232** and **233** (entries 6 and 7), thus further

enhancing the variety of aryl silanes that could be subjected to subsequent oxidation.

Table 2.3. Aryl Silane Synthesis *via* Directed *ortho*-Lithiation



234 **235**

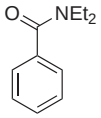
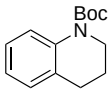
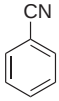
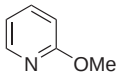
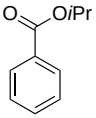
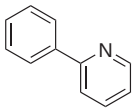
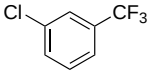
	RLi[a]		**Yield**
1		*s*-BuLi		88%
2		*n*-BuLi		92%
3		*s*-BuLi		98%
4		*n*-BuLi		99%
5		*n*-BuLi		81%
6		LDA		96%
7		*s*-BuLi		99%
8		*s*-BuLi		74%

[a]Lithiation and trapping with $ClSiMe_2(NEt_2)$ as per literature protocol.

However, despite the success of the carbamate, methoxy and di*iso*propyl amide directing groups

(Table 2.3, entries 1 - 3) under our *ortho*-lithiation / silylation strategy, *N,N*-diethyl benzamide **236** (Table 2.4, entry 1) was found to be more problematic. Initial attempts yielded a number of undesired products, most likely as a result of the side reactions that may be envisaged under lithiation conditions: addition of the alkyllithium species to the amide carbonyl, self-condensation, and deprotonation adjacent to the nitrogen atom have all been observed in such a context.[123,143] Further attempts did allow the desired product to be isolated, but only in an unsatisfactory 46% yield.

Table 2.4. Problematic Substrates for Directed *ortho*-Lithiation

		Yield[a]			**Yield**
1		46%	5		0%
2		n.c.[b]	6		47%
3		0%	7		n.c.
4		0%			

[a]Conditions: lithiation as per literature protocol; $ClSiMe_2(NEt_2)$, −78 °C, 2 h; ^{i}PrOH, DMAP, r.t., 12 h.
[b]Not Calculated - a mixture of mono- and bis-silylated products was obtained.

So that the effect of π electron-withdrawing groups on the aryl silane oxidation might be further examined, our attention was turned to the lithiation of aryls with other carbonyl-like substituents. Unfortunately, lithiation and silylation of benzonitrile **237** (entry 2) gave a mixture of the mono- and di-substituted silanes, this result being consistent with the observations reported by Martin and co-workers.[144] Additionally, *iso*propyl benzoate **238** (entry 3) was found to yield a complex mixture of products upon attempted lithiation with LiTMP, despite some literature precedent suggesting trapping with a silicon-based electrophile under these conditions would be successful.[145] A similar result was observed with Boc-protected tetrahydroquinoline **239** (entry 5), again despite some

positive literature precedent.[146] Building upon the successful reactions observed when lithiating and silylating 1-chloro-3-fluorobenzene and difluorobenzene (Table 2.3, entries 4 and 5), an attempt was made to employ 1-chloro-3-trifluoromethylbenzene (entry 4) as a substrate. However, this compound also afforded a complex mixture of products when subjected to identical literature conditions (*n*-BuLi, TMEDA).[142]

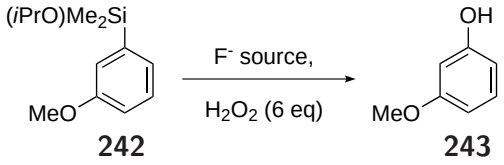
Finally, several attempts to utilise this directed *ortho*-lithiation / silylation strategy with several pyridyl-based species (entries 6 and 7) were unsuccessful. Although alkyllithiums may be readily used in the lithiation of five-membered ring heterocycles, as demonstrated in our synthesis of the indole **240** and benzofuran **241** derivatives (Table 2.3, entries 6 and 7), these same lithiating agents seem to undergo addition to the electron-deficient pyridyl ring instead of effecting deprotonation. Subsequent reactions may also take place between the lithiated heterocycle and the starting material, resulting in the formation of homocoupled products.[138] Although there has been much work done in the area of pyridyl lithiation,[147,148] these methodologies often require a high loading of the lithiating species and therefore the incoming electrophile, rendering such conditions inappropriate for this work. Furthermore, as previously mentioned, subsequent difficulties in the oxidation of pyridyl-derived aryl silanes prompted us to neglect further exploration of the lithiation of these substrates.

2.3.2. Oxidation Optimisation

Using the 3-bromoanisole-derived aryl silane **242**, a number of reactions were carried out to find optimised conditions for this oxidation, with the aim of enhancing the functional group-tolerance of this transformation firmly in mind. Under Tamao's well-documented oxidation conditions (2 eq. of KF or TBAF, $KHCO_3$, aq. H_2O_2, 40 - 60 °C in THF / MeOH), we were pleased to note that silane **242** was readily oxidised to the corresponding phenol **243** (Table 2.5).

While initial attempts with stoichiometric KF gave rise to promising results (entry 1), it is known that a variety of fluoride sources may be used in the Tamao oxidation,[121] and so further attempts were conducted with TBAF (entries 2 - 6). To our considerable surprise, the yield of this transformation was not compromised upon reducing the loading of this fluoride source, and we were pleased to note that oxidation of **242** to **243** could be achieved in 81% yield in the presence of **sub-stoichiometric**

Table 2.5. *Iso*propoxy Silane Oxidation



242 **243**

	F^- Source	**Eq.**	**Temp (°C)**	**Yield**[a]
1	KF	2.0	60	70%
2	TBAF	2.0	60	62%
3	TBAF	1.0	40	65%
4	TBAF	0.1	40	74%
5	TBAF	0.1	r.t.	81%
6	TBAF	0.05	r.t.	70%
7	KF	0.1	60	29%
8	KF	0.1	r.t.	26%
9	no F^-	-	r.t.	**243** : **242** = 1 : 0.4[b]
10	no F^-	-	r.t.	1%[c]
11	no F^-	-	60	7%[c]

[a]Conditions: $KHCO_3$ (2.0 eq), H_2O_2 (6 eq), MeOH/THF (1:1), 16 h. [b]Ratio obtained from crude NMR only. [c]12 eq of H_2O_2.

TBAF at room temperature (entries 5 and 6). It should be noted that these conditions are considerably milder than those previously reported for the oxidation of arylsilanes, suggesting that the functional group tolerance of this reaction is likely to be considerable. Interestingly, although ^{1}H NMR spectroscopic analysis of the crude reaction mixture suggested that complete conversion had been achieved, considerably lower yields were obtained when attempting this same oxidation in the presence of sub-stoichiometric KF (entries 7 and 8). It is thus perhaps likely that the Bu_4N cation present may play an important role in allowing the product phenol to be readily extracted from the reaction mixture.

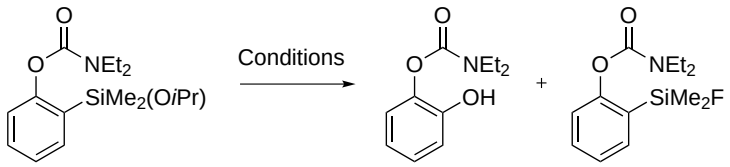
There have been a number of examples to date of Tamao oxidations conducted in the absence of a fluoride source, the most relevant of these being the study done by Tamao on the oxidation of β-alkoxy *iso*-propoxydimethyl silanes,[149] and this work prompted us to attempt the oxidation of arylsilane **242** in the absence of a fluoride source (entries 9 - 11). At room temperature the reaction did not proceed to completion overnight when treated with 6 equivalents of H_2O_2, but the addition of more oxidant and heat did result in the loss of starting material from the reaction mixture. Once again, however, despite crude NMR spectroscopic analysis suggesting a quantitative yield from this process, a poor isolated yield of 7% resulted from this reaction, reinforcing the suggestion that the TBAF somehow facilitates a clean isolation of the phenol.

In reference to the compromised oxidation yields, it should be emphasised that protodesilylation has never been observed for this reaction. NMR spectroscopy and TLC analysis did not show any evidence of the protodesilylated anisole byproduct, and furthermore in studies conducted with less-volatile substrates this process was never seen to compromise the oxidation yield. This observation is consistent with that noted by Dudley in his aryl siletane oxidation work.[128] Unless indicated otherwise, crude NMR spectroscopic analysis showed only the desired phenol, so it is likely that the lower isolated yields are due to problems during work-up and / or purification. To this end, a number of work-up protocols were attempted for the reaction, and treatment with 1N HCl gave the best results as reported in Table 2.5.

It should be noted that the data given in Table 2.5 represents the best yields obtained for each set of conditions, with considerable variation being observed between repeat attempts. Given these inconsistencies, a further round of optimisation screening was subsequently carried out using the carbamate-derived silane **231** as a test substrate (Table 2.6). In this instance, a considerably more uniform distribution of results was obtained, suggesting that the high variability in yield observed for the methoxy-substituted substrate **242** may be arising due to complexities associated with isolating and purifying the product phenol, rather than the reaction conditions alone.

This second attempt at optimisation provided an intriguing set of results, with the fluorosilane derivative **245** now being observed under certain conditions. A significant amount of this species was first noted upon attempting an oxidation with 2 equivalents of TBAF at room temperature,

Table 2.6. Further *Iso*propoxy Silane Oxidation Optimisation



231 **244** **245**

	F^- Source	Eq.	Temp (°C)	Yield[a]	Ratio (244:245)[b]
1	TBAF	2.0	60	99%	-
2	TBAF	2.0	r.t.	99%[d]	3.4 : 1
3	KF	2.0	60	99%	-
4	KF	2.0	r.t	99%	-
5	TBAF	1.0	r.t.	99%[d]	1.7 : 1
6	KF	1.0	r.t.	97%[d]	1.9 : 1
7	TBAF	0.1	r.t.	99%	-
8	KF	0.1	r.t.	99%	-
9	no F^-	-	r.t.	99%[d]	1.5 : 1[c]

[a]Conditions: $KHCO_3$ (2.0 eq), H_2O_2 (6 eq), MeOH/THF (1:1), 16 h. [b]Ratio obtained from ^{1}H NMR. [c] Ratio of **231**:**244**. [d] Combined yield.

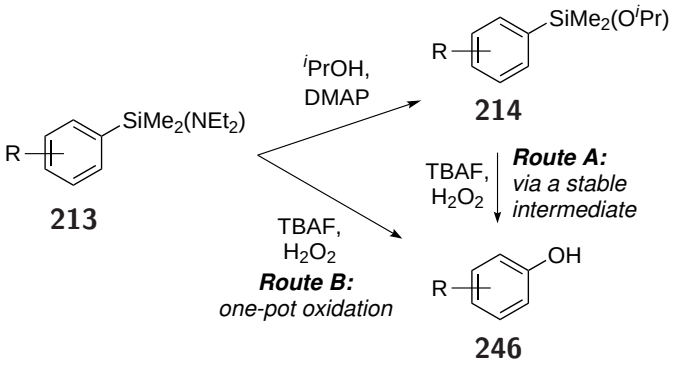
with a 2:1 ratio of product phenol **244** to fluorosilane **245** being obtained (entry 2). Reasoning that the formation of this byproduct was likely to be a competitive side reaction, we expected to observe a reduced amount of fluorosilane **245** upon reducing the loading of the fluoride activator. However, in the presence of 1 equivalent of both TBAF and KF, an **increased** amount of fluorosilane **245** was instead obtained (entries 5 and 6), leading to concerns that the sub-stoichiometric conditions utilised earlier in the oxidation of methoxy aryl silane **242** would not prove to be generally applicable.

In the event, these fears were unfounded, and sub-stoichiometric amounts of **both** TBAF and KF were found to effect oxidation of the carbamate-derived silane **231** to the corresponding phenol **244** in quantitative yield, with no fluorosilane **245** contamination observed (entries 7 and 8). That this

desirable transformation readily takes place at room temperature serves to further emphasise the mild nature of this oxidiation, although once again a fluoride promoter was found to be necessary to effect complete conversion. A 1.5 : 1 ratio of starting material **231** to phenol **244** was obtained in the absence of any fluoride source (entry 9), suggesting that these ions act to accelerate the oxidation process while also being recycled during the reaction pathway.

2.3.3. Substrate Scope

In addition to the isolation and oxidation of the stable *iso*-propoxyl aryl silanes **214**, we also envisaged a direct oxidation of the intermediate aminosilanes **213**,[120] thus giving rise to a **one-pot protocol**. Gratifyingly, it was found that such a one-pot oxidation could be readily achieved in an efficient fashion for carbamate **227**, giving rise to the desired phenol **244** in 85% yield following lithiation, trapping and oxidation in the presence of sub-stoichiometric quantities of TBAF. The combination of these two routes to the desired phenol provides our methodology with greater flexibilty as a result (Scheme 2.8).



Scheme 2.8 Routes to the Desired Phenol

Application of the optimised conditions showed that aryl silane oxidation can be achieved for a wide variety of *iso*-propoxy and aminosilane substrates under mild and functional group-tolerant conditions (Table 2.7). The yields for these transformations are good to excellent, although there are several disappointing exceptions (entries 4, 8 and 10). Of particular note is the observation that a TBS ether is stable under the one-pot oxidation conditions investigated (entries 11 - 13), with none of the deprotected product observed following ^{1}H NMR spectroscopic analysis of the crude reaction mixture. This result suggests that reaction occurs solely at the aryl silicon centre, allowing oxidation to be favoured over desilylation in this instance. From this result a parallel

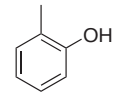
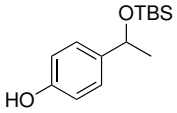
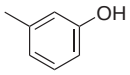
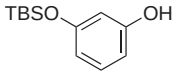
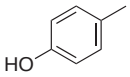
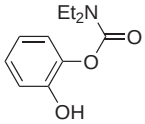
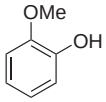
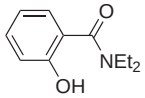
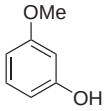
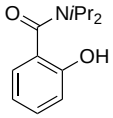
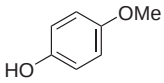
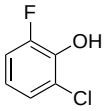
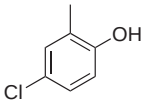
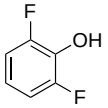
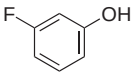
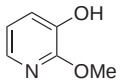
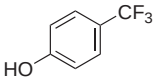
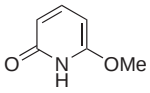
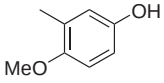
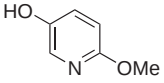
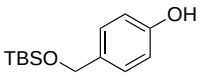
may be drawn with Dudley's work, as his aliphatic siletanes could also be oxidised in the presence of a TBS ether.[128] He comments that such selectivity would be impossible with the more labile heteroatom-substituted silanes required for the "traditional Tamao oxidation", but it appears that under our catalytic conditions this desired orthogonality may be achieved despite the presence of a heteroaromatic substituent at the aryl silicon centre.

However, a functional group-tolerant oxidation of the *iso*-propoxy derivative cannot be achieved for the aryl TBS ether **247** (entry 13), with only the deprotected and oxidised resorcinol product being obtained. This result suggests that a catalytic TBAF deprotection of an aryl TBS ether is being achieved, and serves to further emphasise the intricate balance between the reactivity that different silicon centres display in the presence of fluoride. Furthermore, in light of this observation, it can be proposed that the aminosilane functionality is more susceptible than the *iso*-propoxylsilane functionality towards nucleophilic attack. In contrast, the oxidised products could be obtained from the *iso*-propoxysilanes featuring primary and secondary benzylic TBS ether functionalities (entries 11 and 12), with ^{1}H NMR spectroscopic analysis suggesting that no deprotection takes place. This latter result is somewhat surprising, particularly for the primary benzylic TBS ether substrate (entry 11), but does suggest that this methodology may be of considerable utility in multistep synthesis.

Of particular note is the observation that a one-pot oxidation could not be achieved in the presence of sub-stoichiometric amounts of fluoride for the 3- and 4-methoxy-substituted arenes (entries 5 and 6). In this instance, stoichiometric amounts of a fluoride promoter were required to maintain reactivity, suggesting that electronic considerations may play a crucial, yet subtle role in governing the reaction pathway. It should also be noted that application of the catalytic TBAF conditions to a number of heteroaromatic substrates (entries 19, 20 and 21) proved difficult, and the reaction did not proceed to completion with fewer than 2 equivalents of the fluoride source. Further studies on the oxidation of such substrates is required in order to fully expand this methodology to heteroaromatic systems.

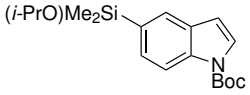
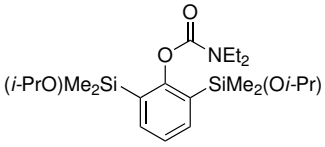
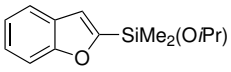
Despite the considerable substrate scope that these two reaction pathways were found to exhibit, there were several *iso*-propoxysilane derivatives that proved challenging to oxidise under the optimised conditions (Table 2.8). The indole and benzofuran derivatives (entries 1 and 2) did not undergo

Table 2.7. Investigation of Substrate Scope

		Yield[a]			**Yield**[a]
1		A: 90%, B: 87%	12		A: 76%, B: 99%
2		A: 72%, B: 88%	13		A: 0%,[e] B: 76%
3		A: 81%, B: 99%	14		A: 99%, B: 85%
4		A: 35%, B: 90%,[b] B: 99%[c]	15		A: 68%, B: 44%
5		A: 81%, B: 99%[d]	16		A: 99%, B: 77%
6		A: 90%, B: 82%[d]	17		A: 94%, B: 99%
7		A: 74%, B: 78%	18		A: 61%,[f] B: 89%[f]
8		A: 52%, B: 43%	19		A: 50%[g], B: 44%[g]
9		A: 87%, B: 59%	10		A: -%, B: 46%[h]
10		A: 55%, B: 52%	21		A: 68%[g], B: 75%[g]
11		A: 99%, B: 99%			

[a]Conditions: TBAF (0.1 eq), $KHCO_3$ (2.0 eq), H_2O_2 (6 eq), MeOH/THF (1:1), 16 h. A = from *iso*-propoxysilane. B = one-pot protocol. [b]From 2-bromoanisole. [c]From anisole. [d]1 eq of TBAF. [e]The aryl TBS ether was also cleaved. [f]NMR yield based on an internal standard (mesitylene), due to product volatility. [g]2 eq of KF, 60 °C. [h]2 eq of TBAF, 60 °C.

Table 2.8. Problematic Oxidation Substrates

1		3	
2			

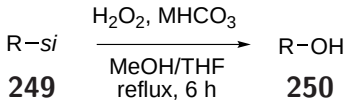
clean oxidation to the desired products, with attempts at this transformation affording complex product mixtures. This result is perhaps unsurprising given the relatively reactive nature of such heteroaromatic functionalities, and it is plausible that oxidation of the double bond in the nitrogen- or oxygen-containing ring system could occur even under such mild conditions, giving rise to a number of unwanted by-products. The inability to oxidise doubly-substituted aryl disilane **248** was perhaps more surprising, particularly given the ease with which oxidation of the singly-substituted system takes place. As a result, the carbamate-derived pyrogallol product could not be isolated from the reaction mixture, although it is possible that this outcome is perhaps due to difficulties in isolating the polar diol product from the aqueous phase during workup.

2.3.4. Mechanistic Considerations

There have been a number of mechanistic studies conducted on this oxidation reaction, with the role of the fluoride ion being a particular area of debate.[150,151] While we have noted that our aromatic oxidation does proceed in the absence of a fluoride ion source, the reaction does not go to completion in a 16-hour timeframe. The need for a fluoride promoter was confirmed by the work of Yoshida on the oxidation of a 2-pyridyl-substituted silicon centre,[152] in which he suggests that fluoride plays an important role. It has subsequently been postulated that the bond between silicon and fluorine is critical in stabilising hypervalent transition states or intermediates.[153] However, there are also a number of similar oxidation processes that have been achieved without fluoride promotion, dating back to work reported by the Tamao group in 1984 (Table 2.9).[120] This observed discrepancy over the need for fluoride in such oxidations suggests that this oxidation is mechanistically complex, with different reaction pathways arising depending on the precise nature of the species being oxidised.

It is thought that a pentavalent silicon species is likely to be of considerable mechanistic importance

Table 2.9. Tamao's Work on Fluoride-Free Organosilicon Oxidation



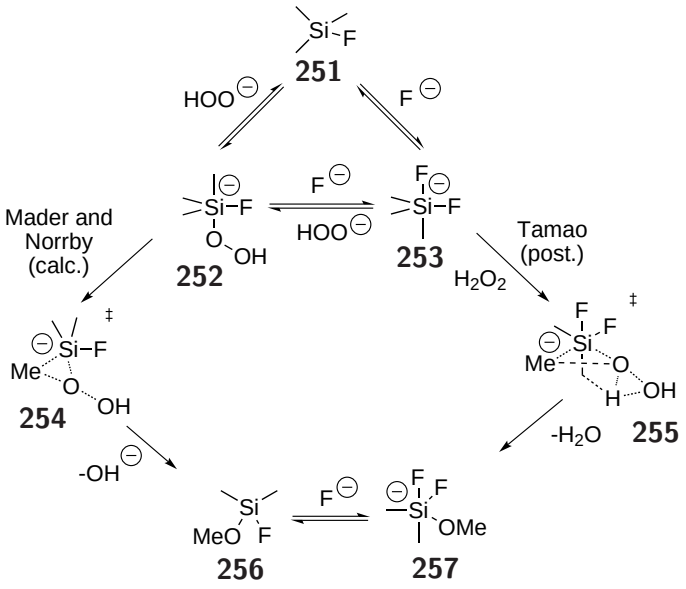
si=	Yield	*si*=	Yield
-$SiMe_2H$	100%	-$SiMe_2(NEt_2)$	83%
-$SiMe_2OSiMe_2R$[a]	72%	$SiMe_2F$	92%
-$SiMe_2OEt$	94%	-$SiMe_2$(allyl)[a]	100%
-$SiMe_2Cl$	93%	-$SiMe(OEt)_2$	96%
-$SiMe_2Ph$[a]	70%	-$SiMeCl_2$	77%
-$Si(OEt)_3$	91%	-$SiCl_3$	68%

[a]Must be cleaved to the fluorosilane first.

in this transformation, in an analogous fashion to the tetravalent boron intermediate formed during hydroboration / oxidation reactions. The work of Corriu suggests that a pentavalent silicon species will undergo nucleophilic displacement more readily than the corresponding tetravalent species,[154] and it is thus likely that the exchange of nucleophiles about such a centre is crucial to the mechanistic pathway of this reaction.

Computational studies carried out by Mader and Norrby[153] on the oxidation of organofluorosilanes (Scheme 2.9) have suggested that the pathway proposed by Tamao[150] (*via* hexaco-ordinate intermediate **255**) is likely to be strongly disfavoured over their own postulated mechanism. Mader and Norrby suggest that oxidation occurs *via* pentaco-ordinate intermediate **254** following peroxide attack upon fluorosilane **251**, although they concede that Tamao's mechanism may be operative under certain conditions. As noted earlier, our arylsilane oxidation readily proceeds in the presence of sub-stoichiometric quanitities of fluoride, and this observation is thought to support the proposed lability of nucleophiles about a pentavalent silicon centre. As a result, this 'catalytic' reactivity of fluoride is likely to be consistent with both mechanisms given above.

However, a number of further observations made throughout our study may shed further light on the

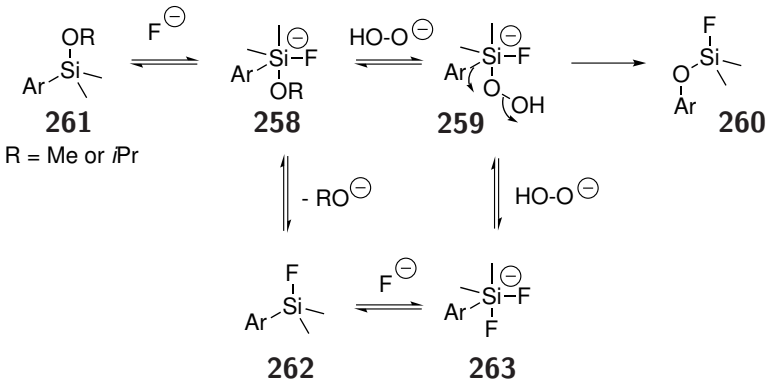


Scheme 2.9 Proposed Mechanistic Pathways for the Tamao Oxidation

mechanistic pathway through which alkoxysilane oxidation proceeds (Scheme 2.10). It is important to note that in the presence of a methanolic solvent system, the one-pot aminosilane intermediate is thought to be very short-lived, with NMR spectroscopic analysis supporting the proposal that oxidation occurs from the corresponding methoxysilane when this pathway is employed.

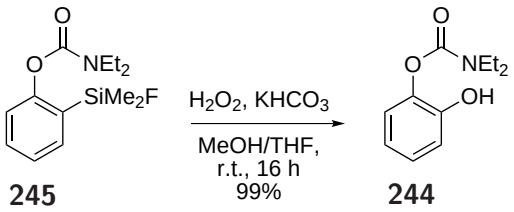
In the presence of sub-stoichiometric amounts of fluoride, it is likely that initial attack of this nucleophilic ion on the silicon centre will give rise to pentaco-ordinate intermediate **258**. This intermediate will undergo a subsequent nucleophile exchange to form the peroxide species **259**. It is from this intermediate, similar to that proposed by Mader and Norrby (**252**, Scheme 2.9), that migration is proposed to take place, giving rise to the final oxidised species **260**. This compound likely undergoes further exchange of nucleophiles about the silicon centre to release both the product phenol, and the fluoride ion so that subsequent oxidative cycles can take place.

The observation of a fluorosilane intermediate **245** in the oxidation optimisation work carried out with carbamate-derived silane **231** (Table 2.6) suggests that this species may be a competing intermediate in the reaction pathway. We propose that loss of the alkoxy group from pentaco-ordinate intermediate **258** would afford stable fluorosilane **262**, and earlier results suggest that the formation of this species is favoured over oxidation when 1 equivalent of either TBAF or KF is present in the reaction mixture. It was assumed that additional fluoride would be required for such a fluorosilane intermediate to undergo oxidation, but to our considerable surprise, complete



Scheme 2.10 Proposed Mechanism for Aryl Silane Oxidation

conversion of isolated fluorosilane intermediate **245** to phenol **244** could be achieved in the absence of any addition flouride source (Scheme 2.11). This result indicates that perhaps availability of the hydrogen peroxide oxidant may be crucial to the success of this oxidation process - when fluorosilane **262** is formed during the reaction pathway, additional H_2O_2 must be present to enable the desired oxidation to take place.

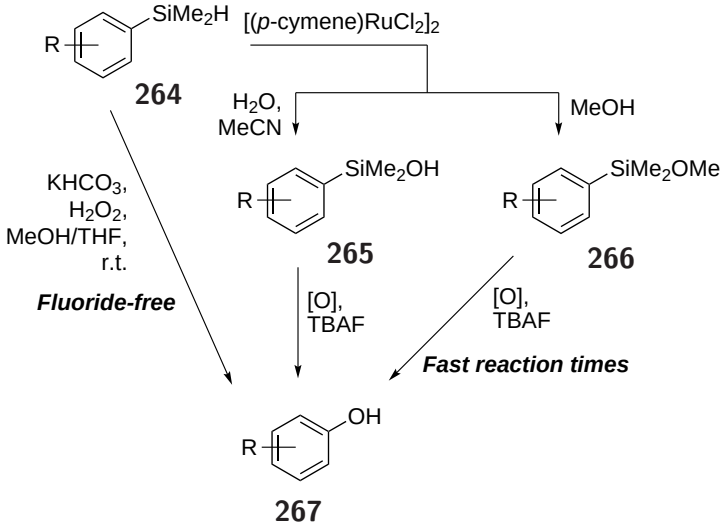


Scheme 2.11 Oxidation of Fluorosilane Intermediate **245**

Furthermore, there are a number of conflicting results obtained throughout this study that suggest this oxidation may be more mechanistically complex than previously supposed. In particular, the observation that stoichiometric quantities of a fluoride source are required for oxidation of the 3- and 4-methoxy *iso*-propoxyarylsilanes appears to suggest that electronic factors may be crucial in governing the reactivities observed. In contrast, the one-pot oxidation from the corresponding methoxy-substituted aminosilane intermediates can be achieved with sub-stoichiometric TBAF, once again emphasising the surprising complexity of this reaction pathway. These conflicting results perhaps suggest that the exact route by which this oxidation takes place is dependent upon the precise nature of the substrates undergoing oxidation.

2.4. Further Investigations

Further work within the group has provided additional insights into the mechanism by which this transformation proceeds, and has also enabled the substrate scope to be further expanded. Notably, by employing the cheap, commercially-available silane $ClSiMe_2H$ as a silylating agent, the dependence of this methodology upon the unstable and highly reactive aminosilane **212** could be avoided. Pleasingly, it was found that the silane intermediate **264** could be oxidised to the corresponding phenol, as could the silanol and methoxysilane derivatives **265** and **266** (Scheme 2.12). These oxygen-containing aryl silanes could be readily synthesised *via* a ruthenium-catalysed dehydrogenative coupling,[155] this rapid process affording the desired derivatives in less than a minute without the need for subsequent chromatographic purification.



Scheme 2.12 Further Work on Aryl Silane Oxidation

NMR spectroscopic studies showed that silanol derivative **265** was an intermediate species in the oxidation of both silanes **264** and methoxysilanes **266**, even when TBAF was used as a promoting agent. It was also found that methoxysilanes **266** undergo oxidation most rapidly, followed by silanols **265** and finally silanes **264**. Further mechanistic work is ongoing, but a clearer picture of this aryl oxidation is beginning to emerge. In particular, the discovery that silanols **265** play a crucial role in the reaction pathway for this transformation is a key insight, and has enabled a wider variety of aryl silane species to be proposed as substrates for our phenolation strategy.

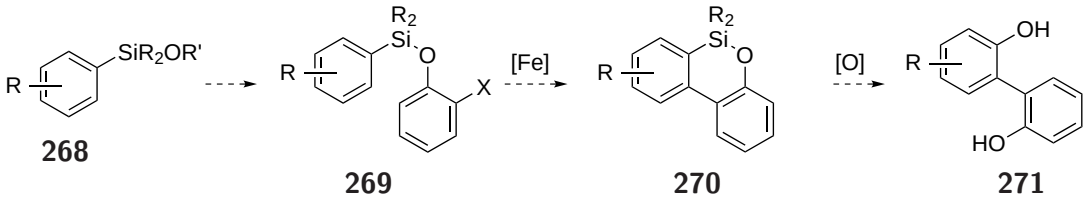
2.5. Conclusions

We have developed a novel phenolation strategy which capitalises upon the 'latent functionality' that a silicon centre possesses, allowing access to a wide range of hydroxylated aromatics in good to excellent yields. This methodology begins with a lithiation step, enabling both bromine-substituted compounds and aryl derivatives with a directing group to be employed as substrates. Oxidation to the corresponding phenol can occur *via* a stable, isolable *iso*-propoxy silane intermediate, or directly following lithiation in a one-pot protocol. Thanks to the mild reaction conditions, the width of the substrate scope suggests that this is a highly functional-group tolerant process. As a result, this aryl silane oxidation is a potentially powerful strategy when considering a late-stage phenolation as part of a synthetic pathway. The limitations of this methodology stem mostly from the harsh reagents that must necessarily be used in the lithiation step, thus reducing the functional-group tolerance of this process. Further limitations may also be seen in the oxidation of heteroaromatic substrates, although additional optimisation may increase the oxidation scope in this regard. However, despite these reservations, once the oxidisable silicon centre is in place this remains a mild and functional-group tolerant transformation, and one which is a beneficial addition to the organic chemist's reaction toolkit.

3. Silicon-Tethering in Iron-Mediated Chemistry

3.1. Overview

Following our successful development of a novel aryl silane oxidation that utilises the 'latent functionality' of a silicon centre, we decided to build upon this methodology by exploring the chemistry of substrates obtained from the substitution of the *iso*-propoxy substituent with a more highly functionalised alcohol. Our considerable interest in silicon-tethered processes prompted a desire to examine this area further, and we wished to employ aromatic substrates in our investigations so as to be able to utilise our newly-developed expertise in synthesising such species. Furthermore, such investigations would also provide an opportunity to showcase our aryl silane oxidation methodology in a synthetic context. It was proposed that the nascent and highly topical field of iron-mediated biaryl coupling would be an excellent area in which to begin this research (Scheme 3.1).



Scheme 3.1 Moving Towards Silicon-Tethered Iron-Mediated Chemistry

3.2. Introduction

One of the most attractive facets of employing iron compounds as catalysts in organic reactions is the very low price of such species.[156] Iron is the second most abundant metal in the Earth's crust (4.7 wt %),[156] and it is thus considerably more plentiful than other transition metals which see frequent application in metal-catalysed processes (Fig. 3.1). The increased demand for these precious metals in the fine chemical and pharmaceutical industries has seen the prices of many

of these species rise dramatically, with considerable pressure being exerted upon existing natural deposits of the metal ores. In contrast, the much greater availablitiy of iron is reflected in the significantly lower prices at which commercially available iron complexes are sold, making this element an economically-friendly alternative if suitable catalytic pathways can be developed.

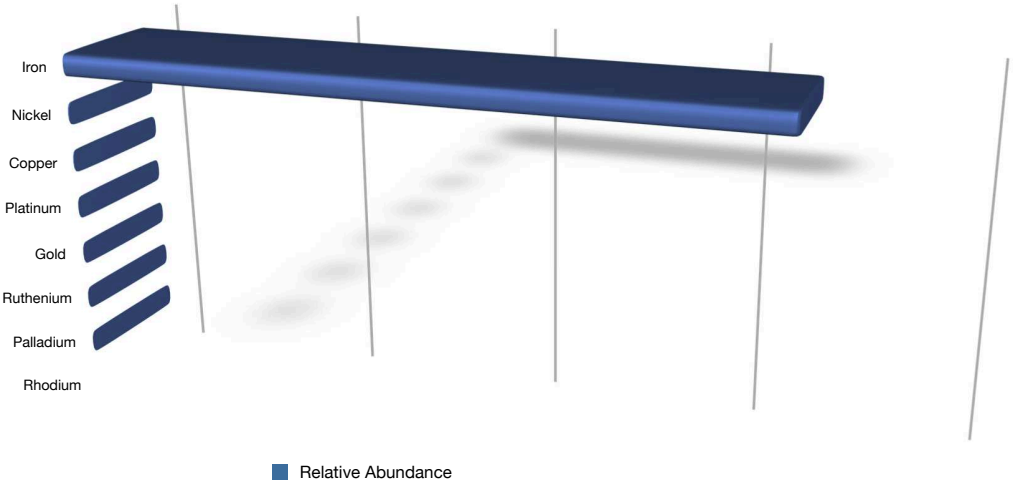


Fig. 3.1. Relative Abundance of Transition Metal Elements Commonly Employed in Catalysis

The other considerable advantage of iron-catalysed methodology is the benign and environmentally friendly nature of most iron compounds. Unlike most other transition metal catalysts, iron plays a significant role in a number of biological processes - perhaps the most readily recognisable example is the presence of an iron centre in the haem family of metalloproteins (Fig. 3.2). These complexes are responsible for the transport of molecular oxygen around the body, and also play a crucial role in the mitochondrial electron transfer system, amongst numerous other roles. Thus, iron complexes are often non-toxic in nature, while other precious metals used in catalysis possess considerable toxicity profiles. The cheap and environmentally benign nature of silicon compounds has previously been emphasised, and by partnering silicon-based methodology with the rapidly expanding area of iron-catalysed synthesis, a highly attractive yet relatively unexplored field can be envisaged.

Iron exhibits several characteristics which in principle make this element an ideal candidate for employment in the catalysis of organic reactions. One such characteristic is the ease with which the oxidation state of iron is altered during the course of a reaction, and thus it can be imagined that iron could readily play a catalytic role in a reaction pathway where oxidation and reduction steps are

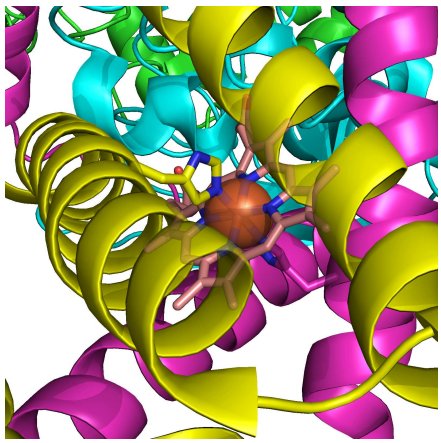
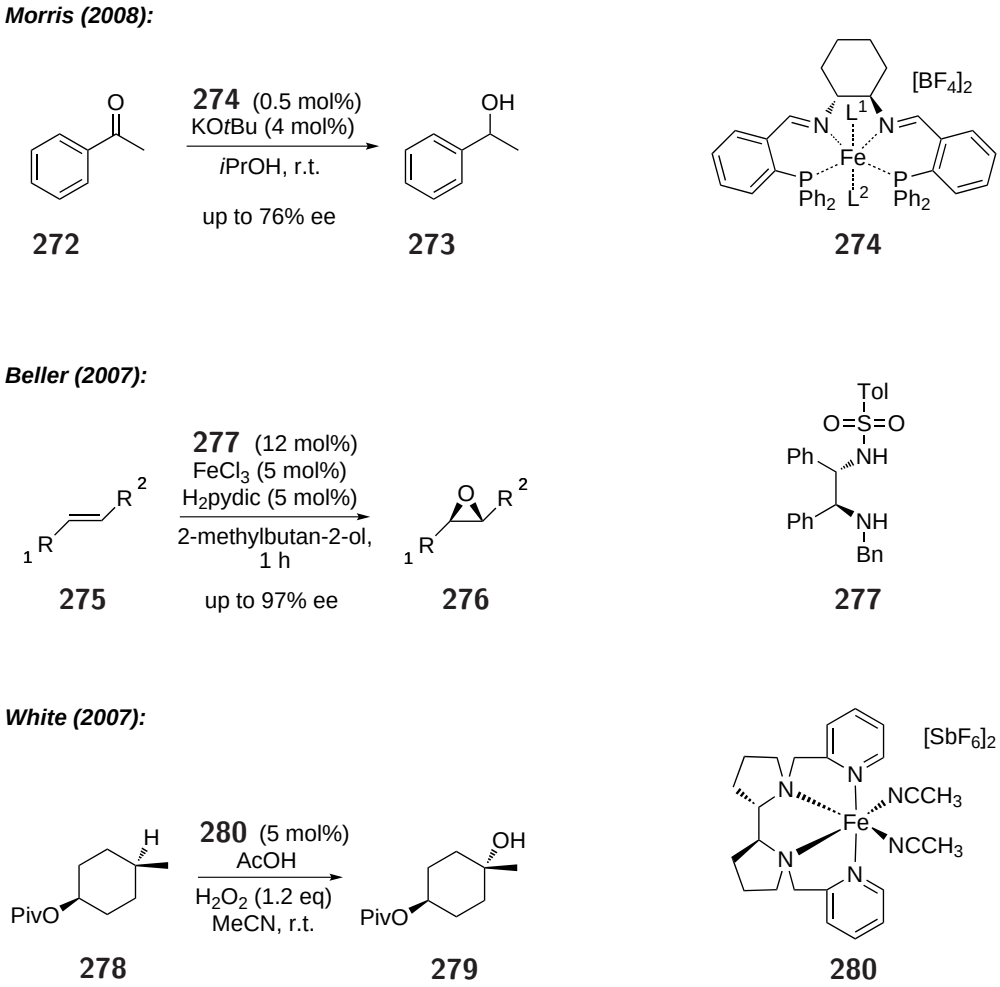


Fig. 3.2. The Haem Group Present in Succinate Dehydrogenase

critical. Furthermore, iron also possesses a strongly Lewis acidic nature when in higher oxidation states, making this metal a suitable additive in processes where activation of an electron-donating substrate is required. However, despite these favourable traits, iron catalysis has traditionally shown relatively limited synthetic applicability, and as such these catalysts have, until recently, been under-utilised in organic chemistry.[156] Considerable opportunities exist for significant advances to be made in this field, and perhaps unsurprisingly research into iron-catalysed organic reactions has shown appreciable activity in recent years.[157]

Our focus is primarily on the role and utility of iron catalysis in cross-coupling processes, but there have been several impressive recent developments in the field as a whole that should be briefly highlighted (Scheme 3.2). The first of these is the promising iron-catalysed asymmetric reduction of ketones (**272** → **273**) pioneered by Morris and co-workers.[158] Although the levels of asymmetric induction were not high (up to 76% ee), an excellent turnover frequency of the catalyst **274** was achieved, suggesting that this process may be a viable alternative to ruthenium-based reduction chemistry in the future. It should be noted that *iso*-propanol is employed as a hydrogen source in this transformation. The work of the Beller group has shown that $FeCl_3$, in the presence of a suitable ligand **277** and oxidant (H_2O_2 in this instance), can oxidise a range of alkenes **275** to the corresponding epoxides **276**.[159] Enantiometric excesses of up to 97% were reported for this oxidation. Finally, the elegant work of Chen and White has uncovered a novel branch of iron chemistry, allowing non-activated sp^3 C-H bonds to be oxidised in the presence of H_2O_2 and iron catalyst **280**, thus affording an alcohol product (**278** → **279**).[160] This oxidation proceeded under mild conditions and in the absence of a directing group, highlighting the considerable synthetic power of iron catalysis. These examples illustrate the rapidly changing and topical nature of this



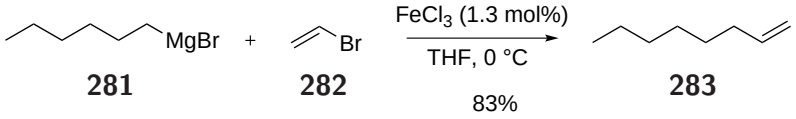
Scheme 3.2 Novel Iron-Catalysed Reactions

field, and suggest that many exciting developments are still to come.[161]

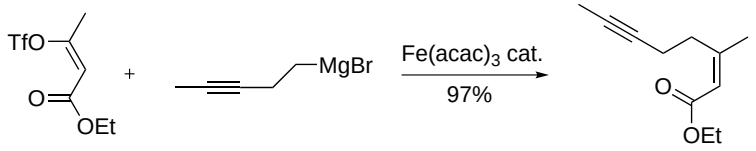
3.2.1. Iron-Catalysed Cross-Coupling

Tamura and Kochi reported as early as 1971 that iron could be employed as a catalyst in the cross-coupling of alkyl Grignard species **281** with vinyl bromides **282** (Scheme 3.3).[162–167] Since these early investigations, considerable developments have been made in this field,[157,168,169] and a wide range of iron-catalysed cross-coupling reactions can now be achieved. Of particular note is the application of iron catalysis in the total synthesis of the macrolide latrunculin B reported by Fürstner and co-workers.[170] In this example, catalytic $Fe(acac)_3$ effects the cross-coupling of alkyl Grignard species **285** with enol triflate **284**, affording the trisubstituted enoate **286** in an impressive 97% yield, despite the presence of potentially sensitive functionalities. The Nakamura group has also contributed widely to this field, and has recently reported a novel iron-catalysed

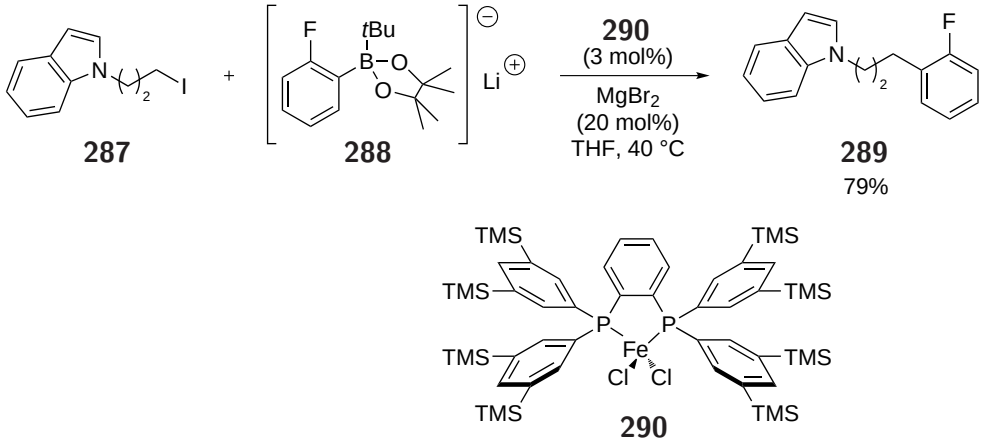
Kochi (1971):



Furstner (2003):



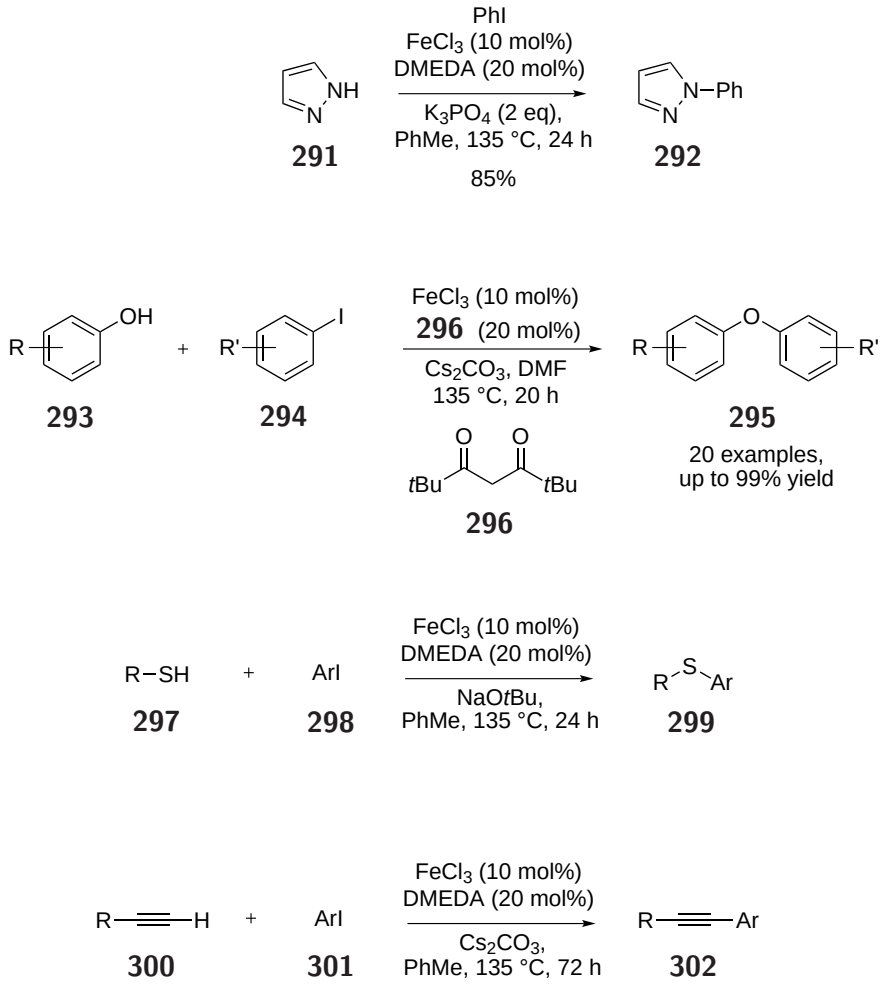
Nakamura (2010):



Scheme 3.3 Iron-Catalysed Cross-Coupling Methodology

Suzuki-Miyaura coupling between aryl borates **288** and a variety of alkyl halides **287**.[171] In the presence of the well-defined iron diphosphine catalyst **290** and sub-stoichiometric quantites of $MgBr_2$, a range of challenging cross-coupling reactions could be achieved with excellent yields. It is thought that in this instance the $MgBr_2$ additive is acting to accelerate the rate of transmetallation between the borate **288** and the iron catalyst.

Bolm and co-workers have recently reported a range of iron-catalysed direct cross-couplings, in which an organometallic species is not required as a substrate (Scheme 3.4). In the presence of catalytic quantities of $FeCl_3$, a range of nitrogen arylations (**291** $\rightarrow$ **292**),[172–175] oxygen arylations

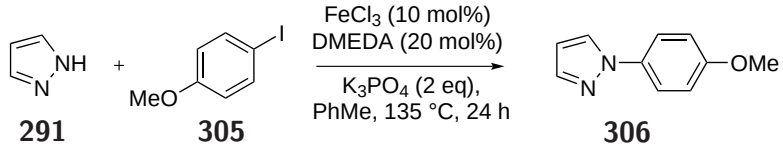


Scheme 3.4 Bolm's Work on Iron-Catalysed Direct Cross Coupling

(**293** → **295**)[176,177] and sulfur arylations (**303** → **304**)[178] could be readily achieved. It was found that the presence of a base was necessary for these transformations to take place, along with sub-stoichiometric amounts of either *N,N'*-dimethylethylenediamine (DMEDA) or the dicarbonyl species **296** to act as a ligand for the iron. Perhaps more excitingly, an iron-catalysed Sonogashira reaction was also reported by the group,[179,180] allowing access to a range of aryl acetylenes **302**. These results therefore suggest that iron compounds have the potential to match the synthetic utility displayed by more traditional transition metal catalysts, such as palladium and copper.

However, observations made by Buchwald and co-workers suggested that perhaps these results were not as definitive as they might have appeared. In repeating several of the *N*- and *O*-arylation processes with $FeCl_3$ samples of varying purity, it was found that considerably higher yields were obtained with lower purity salts (Table 3.1).[181] Furthermore, it was found that the reported efficiencies could be regained upon addition of a very small amount of Cu_2O, suggesting

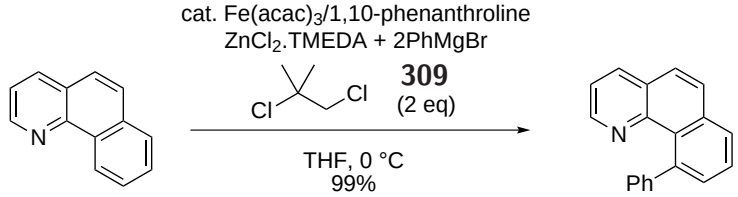
Table 3.1. The Role of Iron in *N*-Arylation Catalysis



291 **305** **306**

$FeCl_3$	GC Yield
>98% (Merck)	87%
>98% (Aldrich)	26%
>99.99% (Aldrich)	9%
>99.99% + 5 ppm Cu_2O	78%
>99.99% + 10 ppm Cu_2O	79%
no Fe + ligand + 5 ppm Cu_2O	77%
no Fe + no ligand + 5 ppm Cu_2O	23%

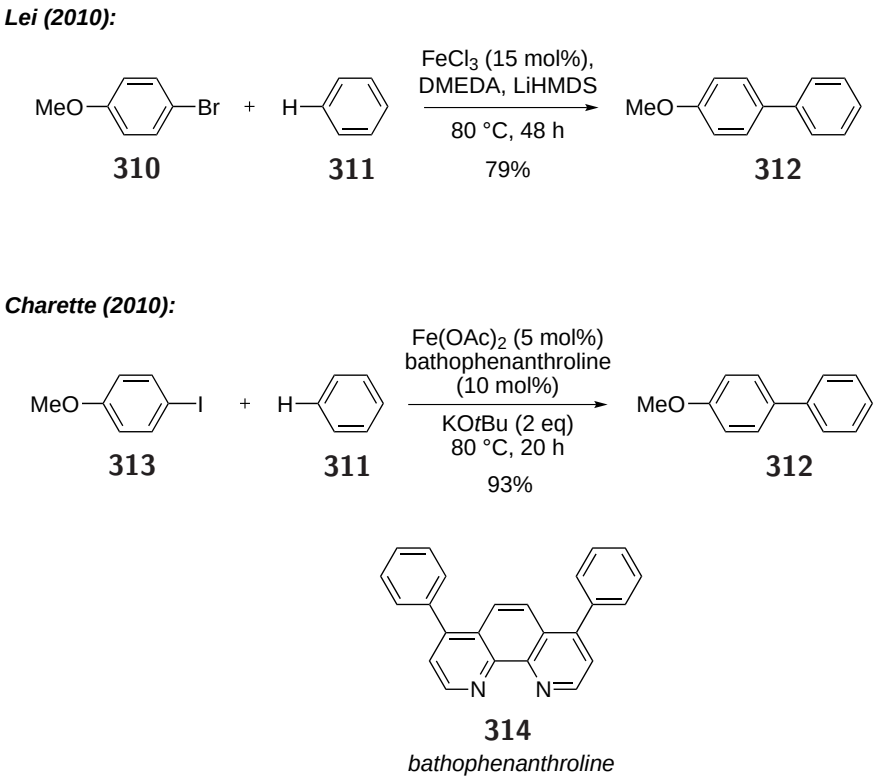
that trace amounts of copper were responsible for catalysing this transformation. This proposal was supported by the observation that similar yields could be obtained when parts per million amounts of Cu_2O were employed as the sole catalytic species.[182] Further research published by the group on this matter suggests that copper may also be the true catalytic species responsible for the Sonogashira-type coupling previously reported, with sub-mol% amounts of a copper salt capable of effecting this Castro-Stephens transformation.[183] As a result, the discovery that iron is not actually responsible for these cross-coupling processes has somewhat muddied the water of this developing field.



307 **308**

Scheme 3.5 Nakamura's Work on an Iron-Catalysed Direct Arylation

In 2008, the Nakamura group reported one of the first synthetically viable examples of iron-catalysed C-H activation (Scheme 3.5),[184–186] in which coupling between an arylzinc reagent and a heterocycle-containing system **307** could be achieved in high yield. The presence of 1,2-dichloro-2-methylpropane **309** was found to be essential, with only very limited reactivity being observed in the absence of this species. The group have subsequently expanded this methodology to encompass a range of other systems, including aryl imines[187] and aliphatic amines (*via* a 1,5-hydrogen transfer process).[188]



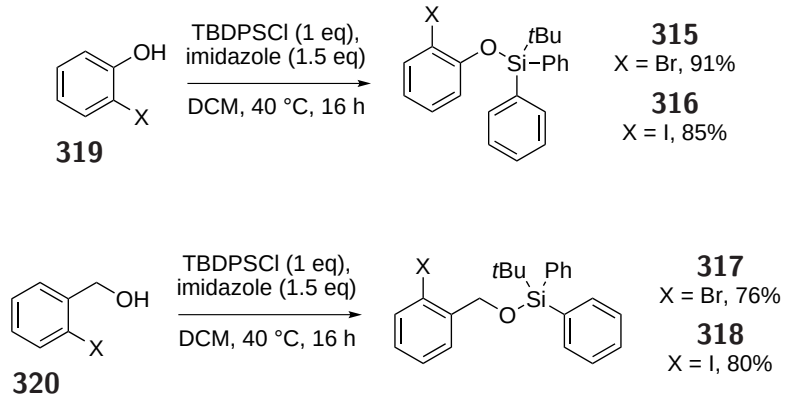
Scheme 3.6 Recent Advances in Iron-Catalysed Direct Arylation

Recently, a number of C-H activation / cross-coupling reactions have been reported in which no organometallic component is needed,[189] including a range of oxidative processes.[190–193] In 2010, the groups of Lei[194] and Charette[195] concurrently reported the synthesis of a range of biaryl compounds **312** through the direct coupling of aryl halides **310** and **313** with benzene in a highly efficient fashion (Scheme 3.6). It was these publications that inspired our work on silicon methodology to move in new directions, and we proposed that a silicon tether could readily be applied to this arylation process. Such a TST would potentially convey three key benefits upon this reaction, perhaps the most dramatic of which would be the increase in the selectivity of the C-H activation step. Furthermore, silicon tethering may also enable this transformation to be achieved under

milder conditions, while the 'latent functionality' of the silicon centre enhances the synthetic utility of the cyclic products formed. Thus, with these reasons in mind, we set out to investigate this novel area of silicon chemistry.

3.3. Substrate Synthesis

Preliminary work on this transformation suggested that a dimethyl-based silicon tether would be too labile under the basic conditions necessary, and thus inspiration was drawn from Gevorgyan's work on silicon-tethered palladium-catalysed C-H activation (Scheme 1.11).[39] In this transformation, the group employed the *tert*-butyldiphenylsilyl (TBDPS) group as an 'aryl donor', thus allowing a wide range of appropriate substrates to be readily synthesised thanks to the commercial availability of TBDPSCl. Therefore, both 2-bromo- and 2-iodophenol were subjected to reaction with TBDPSCl in the presence of imidazole, affording the protected derivatives **315** and **316** in 91% and 85% yields respectively. Several benzyl alcohol-based substrates **317** and **318** were also synthesised, although reduced yields were noted when identical conditions were employed. This result may arise due to the increased lability of silyl-protected primary benzylic alcohols.



Scheme 3.7 Synthesis of Substrates

The ease with which these substrates could be synthesised is particularly notable, and the potential for expanding the substrate range is therefore considerable. Thus, with these TBDPS-protected phenols in hand, the stage was now set to attempt a C-H activation / cyclisation process under iron-catalysed conditions.

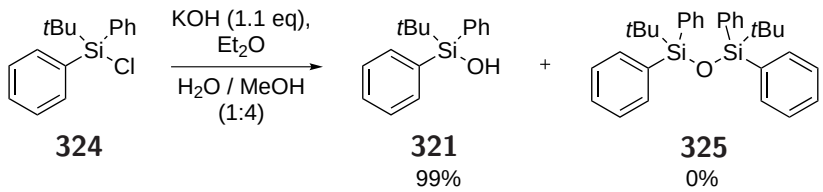
3.4. Iron-Catalysed Cyclisation

3.4.1. Attempted Cyclisations - Employing the Iodo Derivative

Initial Investigations

Our initial investigations into this novel silicon-tethered cyclisation began with the iodo derivative **316**, as it was hoped that the greater ease with which such aryl halides undergo oxidative addition might be beneficial to promoting reactivity. Thus, TBDPS-protected iodophenol **316** was subjected to conditions derived from the methodology of both Lei[194] and Charette,[195] with a 15 mol% loading of the iron catalyst being deemed an appropriate quantity at which to begin our experiments (Table 3.2). In the presence of $FeCl_3$ and DMEDA (entry 1), silanol **321** was the only product formed when KO*t*-Bu was employed as a base. In contrast, use of LiHMDS (entry 2) resulted in no discernable reaction taking place, despite the considerable reaction time.

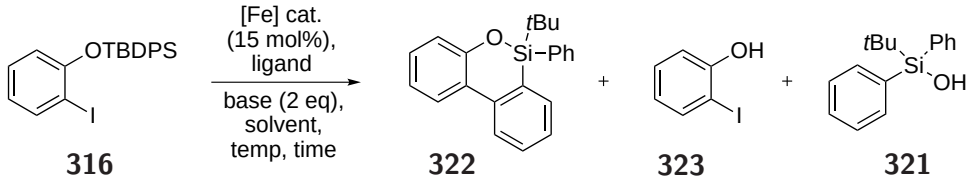
Although both Lei and Charette observed that the nature of the iron catalyst had little effect on the success of their respective arylation processes, it was decided that the tris(acetylacetonato) iron(III) catalyst ($Fe(acac)_3$) should instead be investigated, this derivative being less hygroscopic than $FeCl_3$ and thus easier to handle. Gratifyingly, initial results with this catalytic species proved promising (entries 3 and 4). Although use of KO*t*-Bu once again resulted in hydrolysis to the silanol **321**, treatment with LiHMDS effected transformation to the desired cyclisation product **322**, with a 3.2 : 1 product to starting material ratio being obtained after 48 hours of reaction time at 80 °C. It should be noted that that $FeBr_2$ was also selected as an appropriate catalytic species (entry 5), following the discovery that iron(II) salts are known to form a distinct complex upon reaction with LiHMDS.[196,197] This complex, $Fe[N(SiMe_3)_2]_2$, has recently been utilised by Yang and Tilley as an effective catalyst for the hydrosilylation of carbonyl compounds,[198] and thus it was hoped this species might promote the formation of cyclised product **322**. However, in the event the starting material was once again returned unchanged.



324 → **321** 99% + **325** 0%

Scheme 3.8 Independent Characterisation of Silanol **321**

Table 3.2. Initial Studies on the Iron-Catalysed C-H Activation / Cyclisation of Iodo Derivative **316**



	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$FeCl_3$	DMEDA (0.3)	KO*t*-Bu	PhH	80	48	**321** only
2	$FeCl_3$	DMEDA (0.3)	LiHMDS	PhH	80	48	**316** only
3	$Fe(acac)_3$	DMEDA (0.3)	KO*t*-Bu	PhH	80	48	**321** only
4	$Fe(acac)_3$	DMEDA (0.3)	LiHMDS	PhH	80	48	3.2 **322** : 1 **316**
5	$FeBr_2$	DMEDA (0.3)	LiHMDS	PhH	80	16	**316** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis.

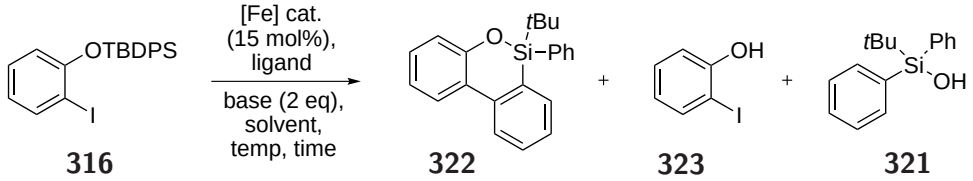
To confirm the formation of silanol by-product **321**, it was proposed that this compound be independently synthesised. The procedure described by Sommer and Tyler was employed,[199,200] affording *tert*-butyldiphenylsilanol **321** in 99% yield (Scheme 3.8). Previous observations have suggested that *tert*-butyl-substituted silanols show considerable resistance towards condensation and thus disiloxane **325** formation,[199] and therefore we were confident that silanol **321** was the sole product formed in this transformation. In the event, analysis of this compound by ^{1}H NMR spectroscopy confirmed that silanol **321** was indeed a by-product formed under some of the iron-catalysed conditions employed while investigating this cyclisation methodology (entries 1 and 3).

Changing the Ligand

With these promising initial results in hand, we set out to explore the effect that the iron ligand has on this transformation. Moving from DMEDA to 1,10-phenanthroline was thought to be an appropriate first step, given the considerable structural similarity to the bathophenanthroline ligand employed by Charette and co-workers in their studies (Scheme 3.6).[195] However, on application of these modified conditions to the TBDPS substrate **316** it was disappointing to note that only

starting material was returned (Table 3.3, entries 1 and 2). Addition of imidazole was then attempted, as this compound has previously been successfully used as an appropriate ligand for iron.[201] Pleasingly, addition of this species did result in a small amount of product formation (entry 3), albeit at a much reduced level of conversion than was previously observed.

Table 3.3. Ligand Effects on the Iron-Catalysed C-H Activation / Cyclisation of Iodo Derivative **316**



	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$Fe(acac)_3$	1,10-phenanthroline (0.3)	LiHMDS	PhH	80	48	**316** only
2	$Fe(acac)_3$	1,10-phenanthroline (0.3)	LiHMDS	PhMe	110	48	**316** only
3	$Fe(acac)_3$	DMEDA (0.3)[d]	LiHMDS	PhH	80	48	10 **321** : 1 **322**
4	$Fe(acac)_3$	TMEDA (0.3)	LiHMDS	PhH	80	48	**316** only
5	$Fe(acac)_3$	DMEDA (2.0)	LiHMDS	PhH	80	48	**316** only
6	$Fe(acac)_3$	DMEDA (0.3)	LiHMDS	PhH	80	48	**321** only
7	$Fe(acac)_3$	DMEDA (0.3)[e]	LiHMDS	PhH	80	48	**316** only
8	$Fe(acac)_3$	DMEDA (30)	LiHMDS	PhH	80	48	**321** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]2 equivalents of imidazole added. [e]DMEDA was freshly distilled.

Use of TMEDA as a ligand also resulted in return of starting material, as did the addition of stoichiometric quanities of DMEDA (entries 4 and 5). Puzzled by these results, a return to the

initially successful conditions was attempted, but silanol **321** was the only product to be isolated from this reaction (entry 6). At this juncture it was proposed that perhaps the quality of the DMEDA was crucial to the success of the reaction, and so this ligand was freshly distilled from calcium hydride and used directly in an iron-catalysed transformation. Confusingly, this attempt, under otherwise identical conditions to the previous example, resulted only in return of starting material (entry 7). Finally, employing 30 equivalents of DMEDA yielded silanol **321** alone (entry 8).

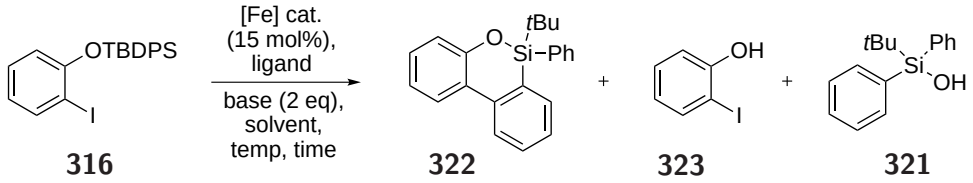
Changing the Base

Given the conflicting results obtained when investigating ligand effects and the inconsistent formation of **322**, our attention turned to the nature of the base employed in this transformation. While earlier attempts with KO*t*-Bu resulted in silanol **321** formation, use of K_3PO_4, a base commonly used in other iron-catalysed processes, resulted in return of starting material (Table 3.4, entries 1 and 2). In contrast, use of the organometallic base *n*-BuLi gave a promising mix of product **322**, starting material **316** and silanol **321** (entry 4), but a further attempt employing TMEDA as a ligand resulted in no conversion (entry 5).

At this juncture, it was proposed that perhaps our sample of KO*t*-Bu might not be sufficiently dry, thus driving the formation of silanol **321** when this compound is used as a base. However, despite vacuum drying a small sample, which was subsequently stored in a glovebox under nitrogen, cleavage of the starting material was still observed to take place (entry 6). Despite such efforts, it is likely that a simple vacuum drying step would not be sufficient to remove potentially deleterious contaminants such as KOH, and to ensure complete purity of this basic species a sublimation step would be necessary. That KO*t*-Bu was the culprit behind this cleavage process was confirmed by reactions conducted in the absence of a base, and in the absence of an iron catalyst (entries 7 and 8) - the starting material was returned unchanged in the first example, while silanol **321** was the only product observed in the second. These reactions were conducted over a 16 hour timescale, rather than 48 hours, as it was presumed that tether cleavage is a relatively rapid process.

At this point, there was some concern that cleavage may be arising *via* a more complex mechanistic process than simple hydrolysis of the silyl ether linker. This fear was compounded by the realisation that 2-iodophenol **323** had not been observed following ^{1}H NMR spectroscopic analysis of the crude

Table 3.4. Effects of the Base on the Iron-Catalysed C-H Activation / Cyclisation of Iodo Derivative **316**

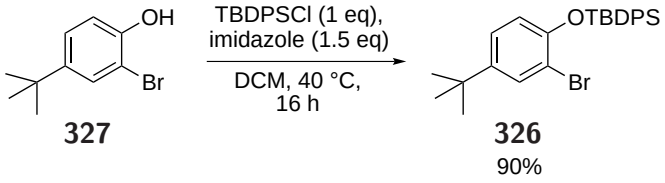


	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$Fe(acac)_3$	DMEDA (0.3)	K_3PO_4	PhH	80	48	**316** only
2	$Fe(acac)_3$	DMEDA (0.3)	K_3PO_4	PhMe	110	48	**316** only
3	$Fe(acac)_3$	DMEDA (0.3)	KO*t*-Bu	PhMe	80	48	**321** only
4	$Fe(acac)_3$	DMEDA (0.3)	*n*-BuLi	PhH	80	48	0.65 **322** : 1 **316** : 1 **321**
5	$Fe(acac)_3$	TMEDA (0.3)	*n*-BuLi	PhH	80	48	**316** only
6	$Fe(acac)_3$	DMEDA (0.3)	KO*t*-Bu[d]	PhH	80	48	**321** only
7	$Fe(acac)_3$	DMEDA (0.3)	-	PhH	80	48	**316** only
8	-	DMEDA (0.2)	KO*t*-Bu	PhH	80	16	**321** only
9	$Fe(acac)_3$	DMEDA (0.3)	KO*t*-Bu	PhH	80	16	**321** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]KO*t*-Bu was vacuum-dried and stored under nitrogen.

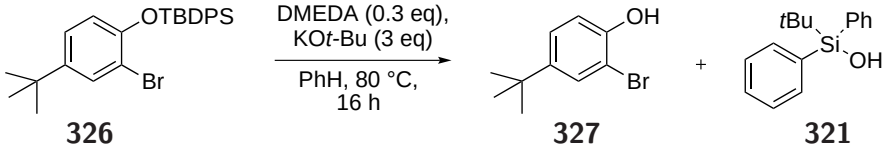
reaction mixtures, despite being an expected by-product upon hydrolysis to silanol **321**. Thus, the 4-*tert*-butyl derivative **326** was synthesised (Scheme 3.9), in the hope that if non-phenolic by-products were formed in this reaction, then the heavier *tert*-butyl group might allow for isolation of such compounds. Only the required bromo-substituted phenol **327** was commercially available, and so our investigations necessarily proceeded with this derivative.

In the event, subjecting TBDPS ether **326** to the KO*t*-Bu-mediated conditions in both the presence and absence of an iron catalyst (Scheme 3.10) resulted in cleavage of the tether to a 1:1 mixture of phenol **327** and silanol **321**. From this result we concluded that tether cleavage in the presence



Scheme 3.9 Synthesis of *tert*-Butyl Derivative

of KO*t*-Bu was indeed occurring *via* a hydrolytic mechanism, presumably due to the presence of adventitious water in the reaction mixture, and the considerable basicity of this alkoxide. It is presumed that the expected phenol by-product **323** was simply not being isolated following reaction, perhaps due to the workup protocol employed.

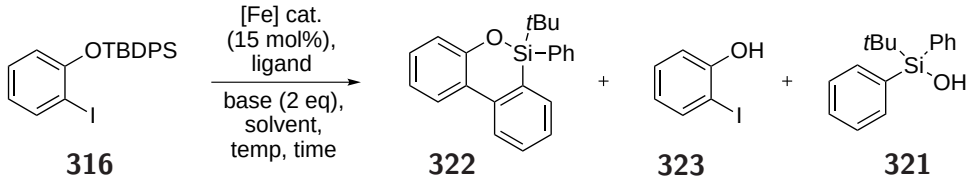


Scheme 3.10 Investigating the Products from the Cleavage of TBDPS Ether **326**

Changing the Solvent

With this knowledge in hand, a small solvent screen was attempted in the hope that more promising results might be obtained (Table 3.5). When conducted in toluene, THF and 1,4-dioxane (entries 1, 3 and 4) this process returned the starting material unchanged after 48 hours. In contrast, reaction in acetonitrile (entry 2) afforded silanol **321** and phenol **323** in a 1:1 mixture by crude ^{1}H NMR spectroscopic analysis. Although the optimisation attempts had thus far yielded few tangible results, the examples where cyclisation had been observed proved too tantilising to ignore, and thus our attentions were transferred to the bromo-substituted derivative **315** in the hope that further reactivity would be observed.

Table 3.5. Solvent Effects on the Iron-Catalysed C-H Activation / Cyclisation of Iodo Derivative **316**



	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$Fe(acac)_3$	DMEDA (0.3)	LiHMDS	PhMe	110	48	**316** only
2	$Fe(acac)_3$	DMEDA (0.3)	LiHMDS	MeCN	80	48	1 **321** : 1 **323**
3	$Fe(acac)_3$	DMEDA (0.3)	LiHMDS	THF	60	48	**316** only
4	$Fe(acac)_3$	DMEDA (0.3)	LiHMDS	1,4-dioxane	80	48	**316** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis.

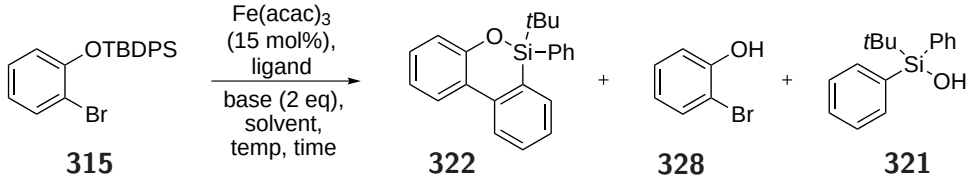
3.4.2. Attempted Cyclisations - Employing the Bromo Derivative

Initial Investigations

We decided to begin our investigations into the iron-catalysed cyclisation of this compound by employing identical conditions to those that had proved promising in our previous studies. In the presence of sub-stoichiometric quantities of DMEDA, only the starting material **315** was returned (Table 3.6, entries 1 and 2). However, when super-stoichiometric amounts of this ligand were instead employed, conversion to the cyclisation product was observed in a 3.5:1 ratio with the starting material (entry 3). It was proposed that the basic characteristics of DMEDA might be promoting this transformation, and thus we returned to sub-stoichiometric quantities of this ligand with 30 equivalents of Et_2NH added to instead act as a base (entry 4) . No reaction was observed, but contradictorily when Et_2NH alone was employed, some conversion to the desired product did indeed take place (entry 5).

In contrast to benzene, toluene was shown to be an inappropriate solvent for this reaction (entries 7 - 9), with all attempts affording either starting material alone, or the hydrolysis product **321**.

Table 3.6. Iron-Catalysed C-H Activation / Cyclisation of Bromo Derivative **315** - Initial Studies



	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	DMEDA (0.3)	LiHMDS	PhH	80	48	**315** only
2	DMEDA (0.3)[d]	LiHMDS	PhH	80	48	**315** only
3	DMEDA (30)	LiHMDS	PhH	80	48	3.5 **322** : 1 **321**
4	DMEDA (0.3)[e]	LiHMDS	PhH	80	48	**315** only
5	-[e]	LiHMDS	PhH	80	48	1.9 **322** : 1 **315**
6	DMEDA (0.3)[e]	LiHMDS	PhH	80	48	**315** only
7	DMEDA (30)	LiHMDS	PhMe	110	48	1 **315** : 2 **321**
8	DMEDA (0.3)[e]	LiHMDS	PhMe	110	24	**315** only
9	-[e]	LiHMDS	PhMe	110	24	**315** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]Freshly distilled DMEDA. [e]Addition of 30 equivalents of Et_2NH.

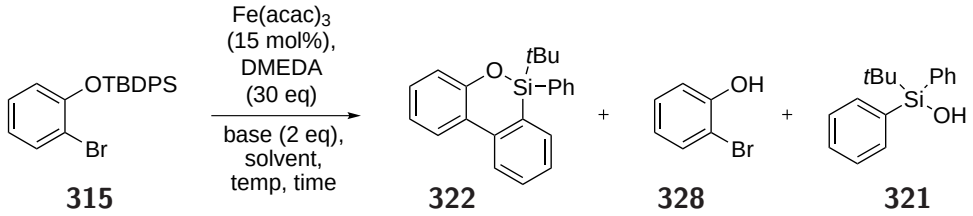
Given the promising levels of conversion observed in the presence of super-stoichiometric quantities of DMEDA, it was proposed that such a generous loading of this ligand was necessary for the desired cyclisation to take place, and thus further optimisation efforts focused on employing such conditions.

Increasing the DMEDA Loading

Disappointingly, these initially promising results proved difficult to repeat (Table 3.7), despite replicating the previously successful conditions a number of times (entries 1, 3, 5 and 9). However, to our surprise a successful cyclisation was once again achieved during further experiments (entries 10 and 11) conducted under the same conditions, with a 4.4 to 1 ratio of product **322** to hydrolysed

silanol **321** being obtained in the first instance.

Table 3.7. Iron-Catalysed C-H Activation / Cyclisation of Bromo Derivative **315** - Increasing the DMEDA Loading



	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	LiHMDS	PhH	80	48	**321** only
2	-	PhH	80	48	0.61 **321** : 1 **315**
3	LiHMDS[d]	PhH	80	48	0.46 **321** : 1 **315**
4	Cs_2CO_3	PhH	80	48	**321** only
5	LiHMDS	PhH	80	48	**321** only[e]
6	KO*t*-Bu[f]	PhH	80	48	**321** only
7	LiHMDS	PhMe	80	48	**321** only
8	LiHMDS	PhH	80	24	**321** only
9	LiHMDS	PhH	80	48	**321** only
10	LiHMDS	PhH	80	48	4.4 **322** : 1 **321**
11	LiHMDS	PhH	80	48	1.3 **322** : 1 **321**
12	LiHMDS	PhH[g]	80	48	**321** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis.[d]0.5 equivalent added. [e]1 equivalent of TEMPO added. [f]KO*t*-Bu was vacuum dried and stored under nitrogen. [g]Reaction conducted under air.

Given the considerable inconsistency of these results, the reaction was conducted under air in the hope that further clues might be obtained regarding the precise nature of the conditions that this cyclisation requires to proceed. However, in the event we were disappointed to note that hydrolysis

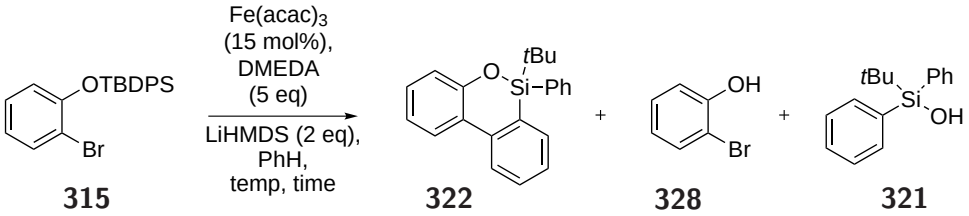
to the silanol **321** was alone observed (entry 12). In light of these contradictory results and the considerable expense of the DMEDA ligand, it was proposed that further optimisation work be conducted in the presence of 5, rather than 30 equivalents of this bidentate species.

Reducing the DMEDA Loading

Although our first cyclisation attempt under these reduced loading conditions was not successful (Table 3.8, entry 1), to our great delight complete conversion to the cyclisation product **322** was obtained on our second attempt (entry 2). A quantitative yield of the desired siloxane **322** was obtained following isolation, and further analysis fully confirmed that the expected tricyclic species was indeed being formed. This excellent result proved to be repeatable (entry 3), and we were pleased to note that complete conversion could also be achieved when conducting this reaction at 50 °C (entry 4). To our surprise, further optimisation found that partial conversion could readily be achieved in the absence of any external heat source (entry 5), while complete conversion was possible at 50 °C after only a 16 hour period (entry 6).

Subsequent attempts to further reduce the loading of DMEDA returned only starting material (entries 7 and 8), and thus our attention turned to understanding the mechanism by which this transformation proceeds. We were interested to note that no conversion to the desired product **322** was observed when the radical scavenger TEMPO was added to the reaction mixture (entry 9), suggesting that this cyclisation process may be radical-based.

Table 3.8. Iron-Catalysed C-H Activation / Cyclisation of Bromo Derivative **315** - Reducing the DMEDA Loading



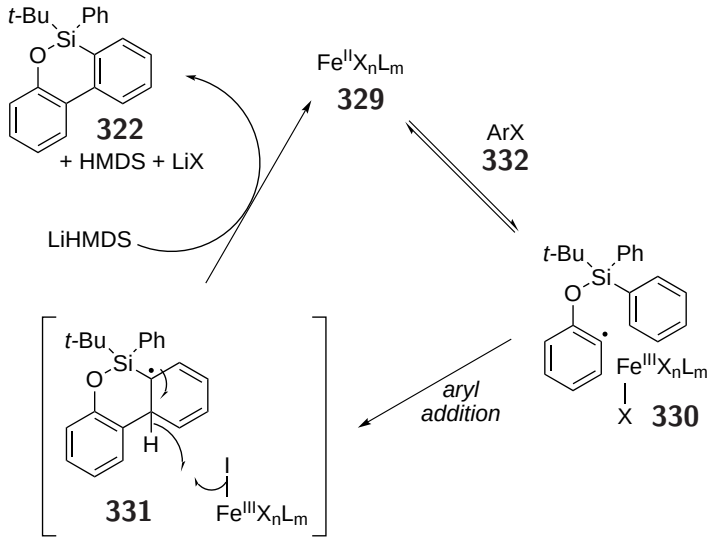
	Temp (°C)	Time (h)	Result[c]
1	80	48	**321** only
2	80	48	99% **322**[d]
3	80	48	99% **322**[d,e]
4	50	48	98% **322**[d]
5	r.t.	48	1.9 **322** : 1 **315**
6	50	16	99% **322**[d]
7	r.t.	24	**315** only[g]
8	r.t.	24	**315** only[h]
9	50	16	**315** only[f]

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]Isolated yield. [e]Reaction conducted with 10 equivalents of DMEDA. [f]1 equivalent of TEMPO added. [g]0.3 equivalents of DMEDA. [h]1.0 equivalents of DMEDA.

Mechanistic Considerations

Following a number of mechanistic investigations, the Charette group proposed that their iron-catalysed direct arylation process was taking place *via* a radical pathway,[195] this postulation being supported by the observation that the reaction was completely inhibited in the presence of radical scavengers. The group reported that no reaction was obtained in the absence of an iron catalyst, but some conversion could be effected when the process was conducted in the presence of AIBN and KO*t*-Bu alone. Based on the pathway suggested by Charette and co-workers and our own mechanistic studies, we have proposed a route *via* which our cyclisation transformation is thought to proceed. An initial reversible cleavage of the aryl-iodide bond in the presence of iron catalyst

329 and DMEDA affords the radical intermediate **330**, which can then undergo intramolecular addition to yield the intermediate **331** (Scheme 3.11). Subsequent loss of HI would give rise to the bisaryl product **322**.



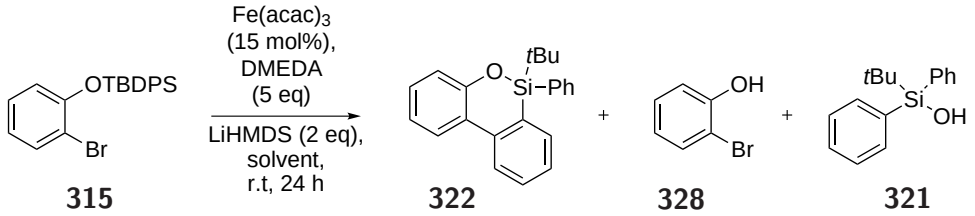
Scheme 3.11 Mechanistic Proposal for the Direct Arylation Reaction

The Charette group suggested that this pathway can be described as a metal-catalysed living radical polymerisation, and hypothesised that the success of this transformation relies upon the presence of a low concentration of active radical species and a high concentration of dormant species (the pendant phenyl substituent in this instance). Thus, as observed in our own work, direct coupling can be achieved efficiently with limited contamination from potential side reaction by-products. With the exception of hydrolysis product **321**, no further byproducts were observed in the reaction mixture during our optimisation studies, confirming the high fidelity nature of this intriguing radical cyclisation.

Room Temperature Optimisation and Solvent Screening

As noted earlier, we were astonished to discover that our silicon-tethered cyclisation does undergo partial conversion to the siloxane product **322** at room temperature. This observation is in keeping with Charette's report that intermolecular coupling will also occur at considerably reduced temperatures,[195] and thus we proposed to further optimise our cyclisation transformation in the absence of any heat source (Table 3.9).

Table 3.9. Iron-Catalysed C-H Activation / Cyclisation of Bromo Derivative **315** - Solvent Screening



	Solvent	Result[c]		Solvent	Result[c]
1	PhH	**315** only	11	PhH	**315** only
2	PhMe	1 **322** : 2 **315**	12	Et_2O	1 **322** : 2 **315**[e]
3	pentane	**315** only	13	*t*BuOMe	**315** only
4	Et_2O	1 **322** : 1 **315**	14	Et_2O	**315** only[f]
5	EtOAc	**321** only	15	*t*BuOMe	**315** only[g]
6	THF	99% **321**[d]	16	DCM	**315** only
7	MeCN	1 **328** : 1 **321**	17	DCM	**315** only[h]
8	acetone	99% **321**[d]	18	DCE	**315** only
9	MeOH	99% **321**[d]	19	Et_2O	1 **322** : 2 **315**[i]
10	EtOH	99% **321**[d]	20	Et_2O	1.6 **322** : 1 **315** : 1.7 **321**[j]

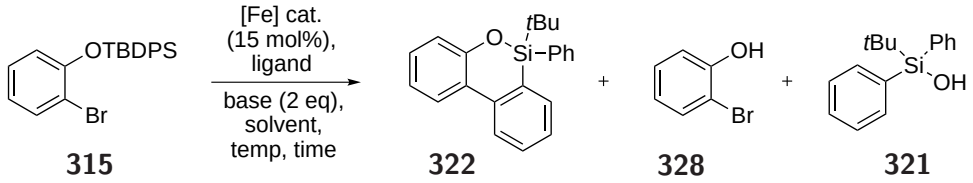
[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]Isolated yield. [e]Reaction left for 48 h. [f]Reaction conducted at 35 °C. [g]Reaction conducted at 50 °C. [h]Reaction conducted at 40 °C. [i]Reaction conducted with 10 equivalents of DMEDA. [j]Reaction conducted with KHMDS and 10 equivalents of DMEDA.

A solvent screen was therefore attempted, and we were pleased to note that some conversion could be achieved when the reaction was conducted in toluene (entry 2) and Et_2O (entries 4, 12, 19 and 20). However, to our surprise, conversion was no longer observed when benzene was employed as a solvent (entries 1 and 11), prompting fears that the reproducibility of this cyclisation was once again proving to be a considerable issue. Thus, as a result the room temperature solvent screen was halted, and the decision was made to return to the conditions under which considerable success was previously achieved.

Final Attempts

To our dismay, attempts at repeating the previously successful conditions resulted only in return of the starting material **315** (Table 3.10, entries 1 and 2), thus further confirming our fears. In the hope that some further clues could be obtained, a brief screen of conditions was conducted, but we were once again disappointed to note that no conversion was taking place. Despite the clear inconsistencies exihibited by this cyclisation, the previous excellent results were too promising to discount, and therefore it was proposed that the literature reactions which inspired this work should be more closely investigated.

Table 3.10. Iron-Catalysed C-H Activation / Cyclisation of Bromo Derivative **315** - Final Attempts



	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$Fe(acac)_3$	DMEDA (5.0)	LiHMDS	PhH	50	24	**315** only
2	$Fe(acac)_3$	DMEDA (5.0)	LiHMDS[d]	PhH	50	24	**315** only
3	$Fe(acac)_3$	DMEDA (10)	$KOSiMe_3$	Et_2O	r.t.	24	**321** only
4	$Fe(acac)_3$	1,10-phenanthroline (5.0)	LiHMDS	PhH	50	24	**321** only
5	$Fe(acac)_3$	TMEDA (0.3)	LiHMDS	PhH	50	24	**315** only
6	$Fe(acac)_3$	TMEDA (5.0)	LiHMDS	PhH	50	24	**315** only
7	$Fe(acac)_3$	bipy (0.3)	LiHMDS	PhH	50	24	**315** only
8	$Fe(acac)_3$	dppe (0.3)	LiHMDS	PhH	50	24	**315** only
9	$FeCl_3$	DMEDA (5.0)	LiHMDS	PhH	50	24	**315** only
10	$FeCl_3$	-	LiHMDS	PhH	50	24	**315** only

[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]3 equivalents of LiHMDS used. [e]DMEDA used directly from the bottle.

3.4.3. Test Coupling Reactions

In order to investigate this beguiling process further, a number of intermolecular test coupling reactions were carried out. 4-Bromoanisole **218** was heated at reflux in benzene for 48 hours in the presence of $FeCl_3$, DMEDA and LiHMDS. Gratifyingly, some direct arylation was observed, although ^{1}H NMR spectroscopic analysis showed that conversion to the biaryl product **333** was only 39% (Scheme 3.12). While this yield was perhaps disappointing in light of the 79% yield

reported by Lei and co-workers under identical conditions,[194] it did indicate that this coupling could be achieved in our hands.



Scheme 3.12 Test Coupling of 4-Bromoanisole with Benzene

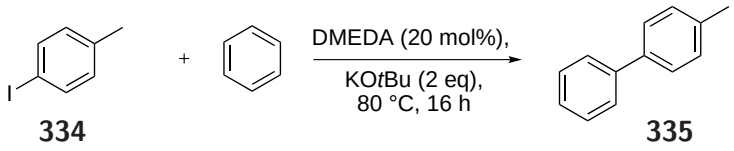
Perhaps even more intriguing was the report published in mid-2010 by the Lei group,[202] while the bulk of this work was being conducted. In this publication, an 'organocatalytic' cross-coupling process was reported, in which DMEDA catalysed the direct C-H arylation of benzene. Coupling of 4-iodotoluene **334** with benzene in the presence of KO*t*-Bu was reported to afford biaryl **335** in an 84% yield, with a radical-based mechanism being proposed to explain this transformation.[203,204] The addition of the radical scavengers TEMPO and diyldibenzene resulted in a complete loss of conversion, thus supporting the proposal that formation of an aryl radical anion was taking place. It should be noted that concurrent reports from the Shi[205] and Hayashi[206] groups suggested that a similar transformation could be achieved when phenanthroline derivatives were employed in the absence of a metal catalyst.

It has been known for some time that primary and secondary amines undergo base-catalysed one-electron reduction in the presence of Fe(III) porphyrins, with subsequent dissociation of the nascent amine radical then taking place.[207,208] Conversely, these more recent 'metal-free' cross-coupling reports suggest that KO*t*-Bu may be more intimately involved in the radical-forming step, with previous publications suggesting that metal alkoxides and amides are able to act as single electron donors.[209,210] Regardless of the precise nature of the single electron oxidant, it is at least well-precedented that an aryl halide will undergo halogen abstraction and thus aryl radical formation in the presence of such an oxidant.[211] Homolytic aromatic substitution - the addition of a radical species to an aryl system, followed by loss of a hydrogen radical - is also an established process.[212]

Although we had shown that our cyclisation process appears to require the presence of an iron catalyst (Table 3.4, entry 8), Liu's proposed 'organocatalytic' coupling was met with some surprise

by both our group and the wider synthetic community, and so the decision was made to investigate this transformation further. Our first attempt at repeating the literature procedure with distilled DMEDA resulted in no conversion after heating to 80 °C for 16 hours, suggesting that perhaps something was amiss (Table 3.11, entry 1). Notably, addition of catalytic $Fe(acac)_3$ was found to afford complete conversion to the biaryl product **335** (entry 2). Upon examining the supporting information for Liu's paper, it was noted that no comments were made relating to the purification and preparation of DMEDA before use in this reaction. Therefore, the reaction was attempted in the absence of iron, and with DMEDA taken directly from the bottle. In this instance, complete conversion to biaryl **335** was once again observed, suggesting that there is perhaps some active contaminant of DMEDA that is removed during the distillation process (entry 3).

Table 3.11. Test Coupling of 4-Iodotoluene with Benzene



334 **335**

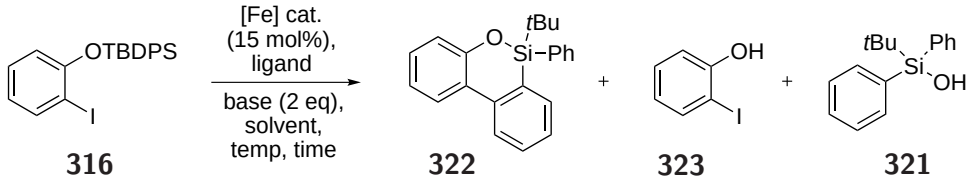
	Conditions	Yield[a]
1	Distilled DMEDA	0%
2	Distilled DMEDA + $Fe(acac)_3$ (15 mol%)	99%
3	Undistilled DMEDA	99%
4	no DMEDA or [Fe], 0.5 eq of H_2O	0%
5	Distilled DMEDA + 0.5 eq of H_2O	1 **335** : 3 **334**

[a]By ^1H NMR spectroscopic analysis.

It was presumed that distillation over calcium hydride would readily remove water from a sample of DMEDA, and thus the reaction was attempted in the absence of both DMEDA and iron, but in the presence of sub-stoichiometric quantities of water (entry 4). Unsurprisingly, no conversion was observed, but to our considerable astonishment some reactivity could be restored upon addition of 0.5 equivalents of water to the distilled DMEDA additive (entry 5). With these baffling results in hand, a small range of silicon-tethered iron-catalysed cyclisations were attempted in the presence

of DMEDA taken directly from the bottle - up to this point, only distilled DMEDA had been employed as a ligand.

Table 3.12. Cyclisations with DMEDA Direct from the Bottle

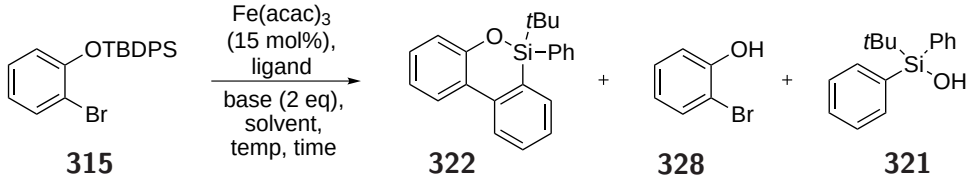


	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$Fe(acac)_3$	DMEDA (0.3)[d]	KO*t*-Bu	Et_2O	r.t.	16	**316** only
2	$Fe(acac)_3$	DMEDA (0.3)[d]	LiHMDS	PhH	80	16	0.14 **322** : 1 **316**
3	$Fe(acac)_3$	DMEDA (0.3)[d]	LiHMDS	Et_2O	r.t.	16	**316** only
4	$Fe(acac)_3$	DMEDA (0.3)[d]	LiHMDS	PhH	80	16	0.21 **322** : 1 **316**
5	$FeBr_2$	DMEDA (0.3)[d]	LiHMDS	PhH	80	16	**316** only

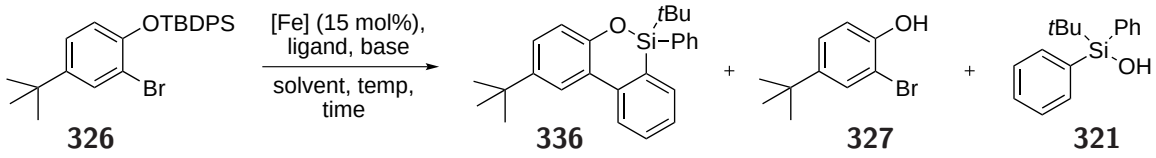
[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]DMEDA used directly from the bottle.

Unfortunately, these attempts proved unsuccessful in the majority, with only two examples displaying any evidence of conversion (Table 3.12, entries 2 and 4). This result proved to be unrepeatable, thus suggesting that the reaction was probably not being catalysed by a DMEDA-derived impurity. Whether or not both Liu and Shi's 'organocatalytic' processes are truly metal-free remains a contentious issue,[213] particularly given other 'metal-free' reactions have been unmasked as being truly catalysed by trace (ppb) amounts of metal contaminants.[214,215]

Table 3.13. Cyclisations with DMEDA Direct from the Bottle



	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
1	$Fe(acac)_3$	DMEDA (0.3)[d]	LiHMDS	PhH	80	16	**315** only
2	$Fe(acac)_3$	DMEDA (30)[d]	LiHMDS	PhH	80	16	**315** only



	[Fe] cat.[a]	Ligand (eq)	Base[b]	Solvent	Temp (°C)	Time (h)	Result[c]
3	$Fe(acac)_3$	DMEDA (30)[d]	LiHMDS	PhH	80	16	**326** only
4	$Fe(acac)_3$	DMEDA (30)[d]	LiHMDS	Et_2O	r.t.	16	**326** only

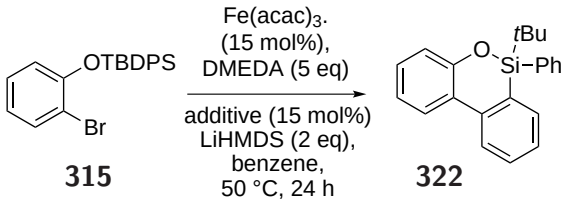
[a]15 mol% catalyst loading. [b]2 equiv. [c]By ^{1}H NMR spectroscopic analysis. [d]DMEDA used directly from the bottle.

3.4.4. The Search for an Additive

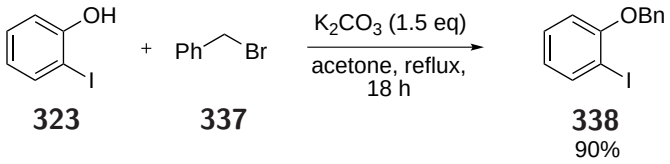
With no real insights into which compound was promoting cyclisation to **322**, our investigations were expanded to include other sources of impurities. Given the discovery by Bolm and Buchwald that copper, not iron, was responsibile for catalysing a range of cross-coupling processes (Scheme 3.4 and Table 3.1),[181] this metal was thought to be the most likely culprit. Thus, the reaction was doped with 15 mol% loadings of CuI (Table 3.14, entry 1), $CuSO_4$ (entry 3) and $CuBr_3{\cdot}6H_2O$ (entry 5). Once again, no successful conversion was observed, thus ruling out copper as the catalytic species in this instance. It should be noted that Charette and co-workers, being aware of the potential contamination of iron salts by ppm quanitites of copper species, tested their cross-

coupling methodology fully and concluded that iron, not copper, was indeed the catalytic metal.[195]

Table 3.14. Searching For an Additive



	Additive		Additive
1	CuI	8	Pd_2dba_3
2	$PdCl_2(PPh_3)_2$	9	$Pd(PPh_3)_4$
3	$CuSO_4$	10	$Ti(O\textit{i}Pr)_4$
4	$Ni(PPh_3)_2Cl_2$	11	$CrCl_2$
5	$CuBr_3{\cdot}6H_2O$	12	$Mn(OAc)_2{\cdot}7H_2O$
6	$CoBr_2$	13	butylamine
7	*t*BuOOH	14	water



Scheme 3.13 Synthesis of Benzyl Derivative

In light of these negative results, a thorough survey was taken of the reactions conducted in our laboratory during the periods when successful cyclisations were achieved. It was proposed that perhaps trace metal contaminants present on stirrer bars or distillation apparatus may instead be responsible for catalysing this cyclisation, and thus an extensive campaign was mounted to unearth a potential catalytic species. A range of additives, including nickel and palladium species, were investigated, but sadly to no avail. With the growing realisation that this was a potentially futile campaign, the decision was made to cease work on this project after almost 200 attempts at cyclisation, with the mystery remaining unsolved.

Perhaps interesting to note is that another tethered substrate **338** was synthesised (Scheme 3.13) and subjected to a wide range of iron-catalysed cyclisation conditions. Once again, no successful reaction was observed in any of the experiments conducted, further emphasing our limited understanding of which species is truly responsible for mediating this cyclisation.

3.5. Conclusions

Unfortunately, despite our best attempts we were not able to shed any further light upon the limited reproducibility of our C-H activation / cyclisation process. DMEDA is well known to be a particularly good 'metal sponge', and thus it is quite likely that a particular sample of the ligand contained a contaminant that was in fact responsible for driving this transformation. It would be a considerable undertaking to test for all possible contaminants exhaustively, and there remains the possibility that the contaminant may in fact be non-metallic in nature. During the preparation of this dissertation, a comment by Nakamura and co-workers[184] particularly resonated, thus enabling this chapter to be concluded with perhaps a more solid hypothesis as to why our cyclisation proved to be so erratic.

The group reported that they spent 2 years optimising their iron-catalysed C-H activation reaction (Scheme 3.5), and found that adventitious molecular oxygen was necessary to make the process catalytic. However, excess oxygen resulted in the entire catalytic system being shut down, suggesting that control needed to be exercised over the precise levels of oxidant present in the system. The bulk of the investigations described earlier were conducted in a fume cupboard containing an ozonolysis machine and an oxygen line, so it is very likely that the molecular oxygen (and ozone) levels in this space would have varied considerably on a day-to-day basis. Furthermore, the reaction never worked again after a rearrangement in the laboratory resulted in a shift to a non-ozonolysis fumehood. Thus, our current hypothesis is that molecular oxygen may be responsible for the success of transformation, be it promoting the reaction or shutting down conversion when high oxygen levels are present.

4. Silicon-Tethering in Palladium-Mediated Chemistry

4.1. Overview

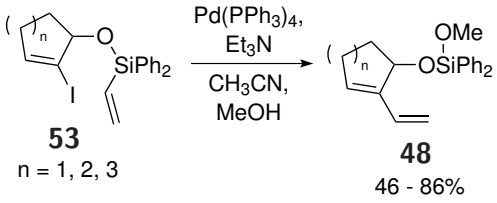
Despite the frustrating conclusions reached by our investigations into the development of a silicon-tethered iron-catalysed cyclisation, we were keen to explore TST methodology further, with palladium-catalysed processes being a region of particular interest. Our research group has considerable expertise in non-silicon tethered palladium-catalysed reactions, and as noted in the introductory chapter, silicon tethers have thus far seen little application in this area. Therefore, it was proposed that this relatively unexplored field would be an exciting and potentially fruitful area of research to move into.

4.2. Introduction

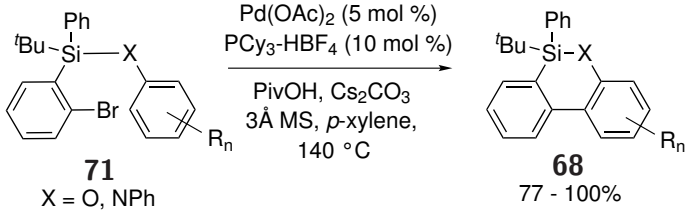
It is perhaps somewhat surprising that silicon tethers have seen so little application thus far in palladium-mediated processes. To date, this emerging field has been mostly focused on C-H activation methodology, with examples being reported by the groups of Hiyama[37,38] and Gevorgyan[39,41] (Scheme 4.1). The only example of TSTs being employed in a more 'traditional' palladium-catalysed transformation is an isolated report by Mayasundari and Young,[36] in which it was found that a vinyl group could be transferred to a ring-bound vinyl iodide *via* a silicon tether (Scheme 4.1). The substrate scope for this process was found to be limited, and it should be noted that the silicon tether undergoes cleavage under the reaction conditions, as discussed in Chapter 1.

Both our group[216] and the Suffert group[217–219] have developed a range of tethered palladium-mediated electrocyclisation cascade processes (Scheme 4.2). In this methodology, the acyclic bromo-

Young (2001):

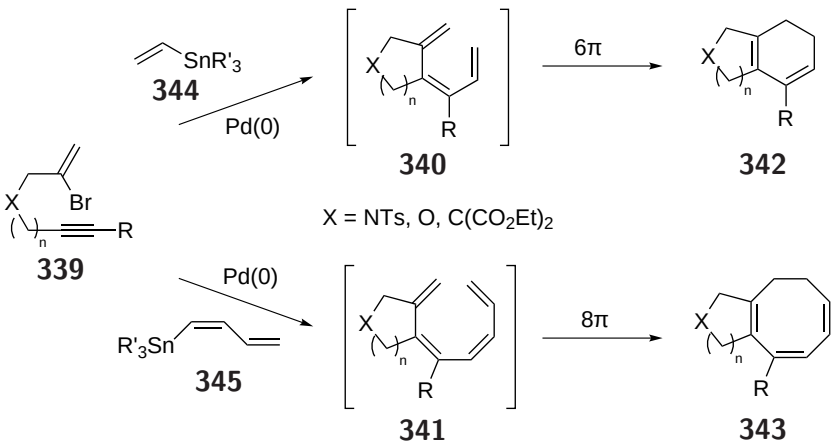


Gevorgyan (2010):



Scheme 4.1 Selected Examples of Silicon-Tethered Palladium-Catalysed Methodology

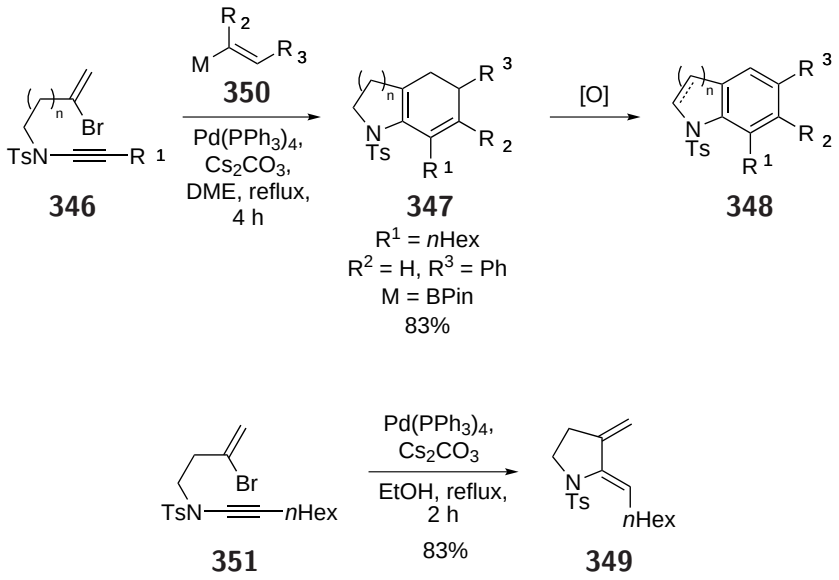
ene-yne precusors **339** are subjected to an initial tandem Heck / Stille coupling, giving rise to the conjugated polyene intermediates **340** and **341**. Under the reaction conditions, these intermediates subsequently undergo electrocyclisation to the diene or triene products **342** and **343**. Thus, a range of bicyclic systems could be readily synthesised in good to excellent yields, with tether lengths of n = 1 to n = 3 displaying reactivity under these conditions. Furthermore, some variation in the nature of the tethering system was also tolerated, with nitrogen-, oxygen- and carbon-based tethers all allowing access to the corresponding bicycles **342** and **343**.



Scheme 4.2 Development of a Tethered Palladium-Catalysed Heck / Suzuki / Electrocyclisation Cascade

Recent work in our group has further extended this methodology to bromoeneynamide precursors

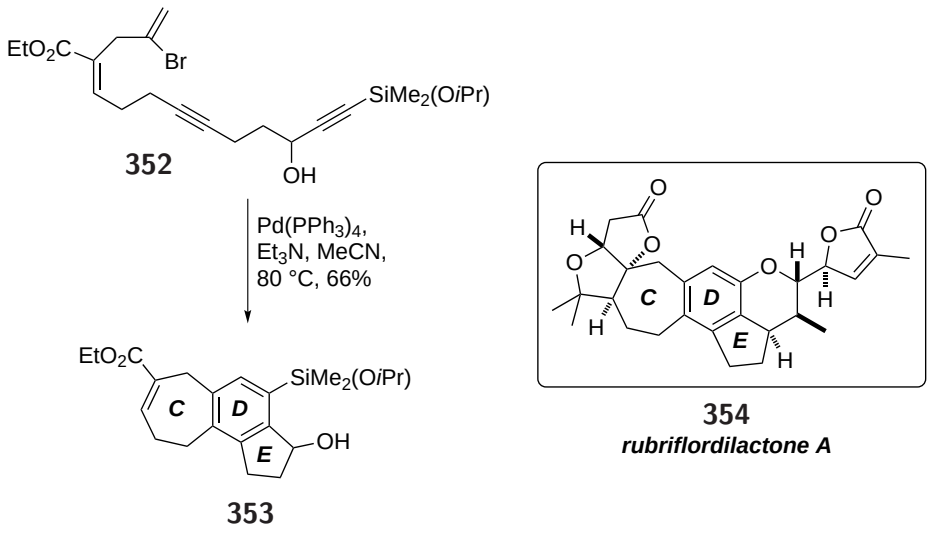
346, thus allowing a wide range of azabicycles to be readily synthesised (Scheme 4.3). Once again, an initial tandem Heck / Stille or Heck / Suzuki process is presumed to afford an intermediate triene, which undergoes 6π electrocyclisation to the azadiene product **347** under the reaction conditions. A subsequent oxidation step leads to the highly substituted aromatic derivatives **348**. Furthermore, during these investigations it was discovered that a reductive cyclisation process could also be achieved under similar conditions, affording aminodiene **349**. This alternative pathway was first noted when attempting a tandem Heck / Suzuki transformation with ethanol as the solvent, and subsequent investigations in the absence of a boron-based coupling partner demonstrated that diene **349** could be synthesised in a synthetically useful 83% yield.



Scheme 4.3 Extension of Palladium-Catalysed Cascade Methodology to Azabicycle Synthesis

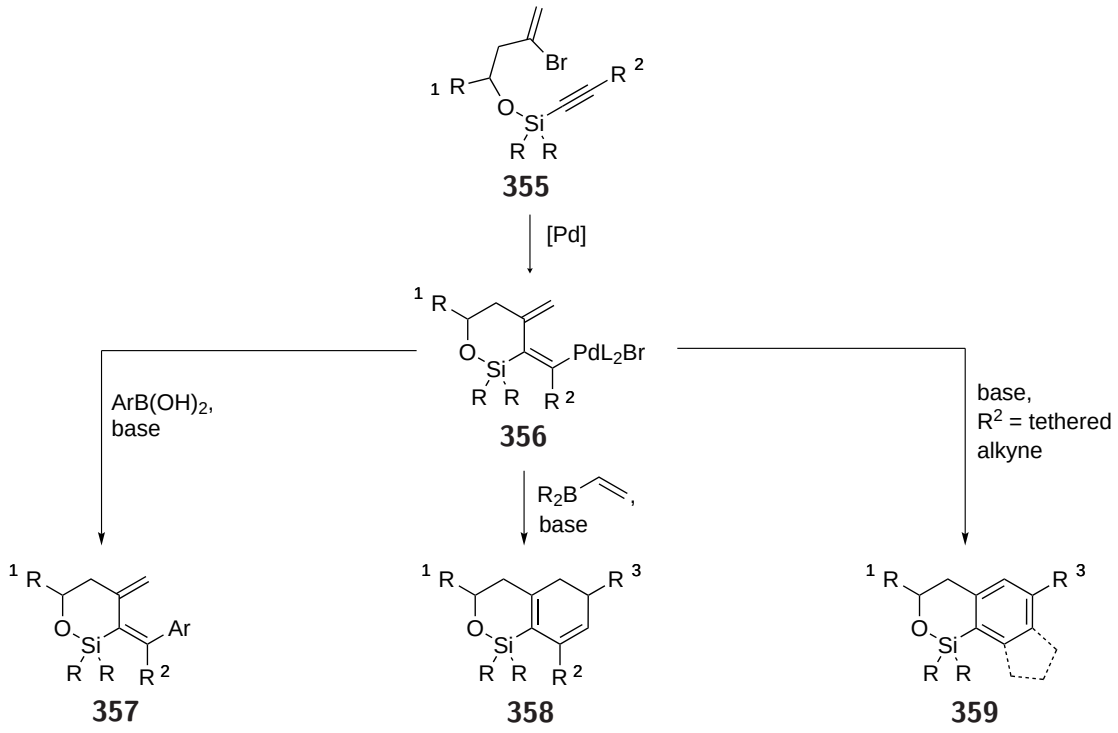
Building upon the elegant work of Negishi[220] and de Meijere,[221–223] our group has also employed a fully intramolecular palladium-mediated oligocyclisation cascade in work conducted towards a total synthesis of the natural product rubriflordilactone A (Scheme 4.4).[134,224–226] From the acyclic bromene-diyne precursor **352**, treatment with catalytic $Pd(PPh_3)_4$ and Et_3N in MeCN afforded the tricyclic derivative **353**, thus allowing the CDE core of the desired natural product **354** to be constructed in a single step.

Therefore, given our extensive expertise in permanently-tethered palladium-mediated cascade cyclisation methodology, and the surprisingly limited applications that TSTs have seen in this field, we proposed to explore this area more fully. The siloxane-tethered bromoenyne substrate **355** was



Scheme 4.4 Palladium-Mediated Cascade Reactions in the Total Synthesis of rubriflordilactone A

thought to be the most logical starting point, from which palladium-catalysed carbopalladation would afford the cyclised intermediate **356** (Scheme 4.5). This cyclic siloxane **356** would then be able to undergo further transformations depending upon the conditions employed, and three potential products were thought to be synthetically accessible from this juncture. Cross-coupling with a boron- or tin-based coupling partner would provide access to highly conjugated dienes **357** or bicyclic electrocyclisation products **358**. Alternatively, if a second alkyne was incorporated in the starting material **355**, a range of arenes **359** could also be readily approached. This final pathway would provide a further outlet for our aryl silane oxidation chemistry, as it was expected that oxidation of the aromatic products **359** would afford the corresponding highly substituted phenols.



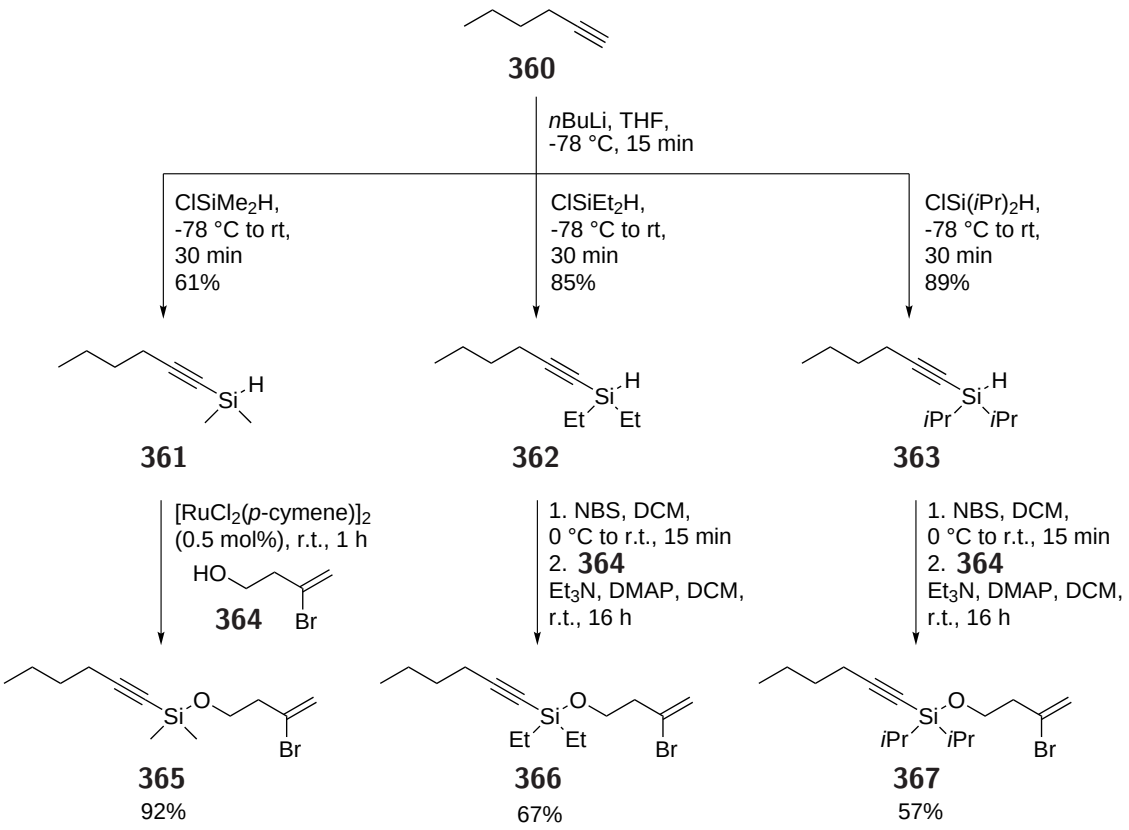
Scheme 4.5 Proposed Application of Silicon-Tethering Methodology to Palladium-Mediated Cascade Processes

4.3. Substrate Synthesis

In our initial investigations we set out to broadly examine the feasibility of our proposed silicon-tethered palladium-catalysed methodology. The substrates were explicitly designed with ease of synthesis in mind, and by utilising a series of sequential additions at the silicon centre we were able to access the desired siloxy alkyne motifs in an efficient fashion. It was proposed that the inherent flexibility in this pathway would allow a wide variety of alkyne and alcohol building blocks to be coupled together, thus enabling the scope of these reactions to be investigated over a wide range of substituents and functional groups. Furthermore, this synthetic route also allowed the alkyl substituents at the silicon centre to be readily varied, enabling the stability and reactivity of the dimethyl, diethyl and di*iso*-propylsilyl linkers to be compared.

In these early studies, 1-hexyne **360** was employed as the alkyne building block (Scheme 4.6). Deprotonation at the alkyne terminus with *n*-BuLi under cryogenic conditions was followed by addition of the appropriate dialkylchlorosilane species. The use of such a silylating agent is based upon the work of Malacria and co-workers,[55] and the presence of a single displaceable group at the silicon centre ensured that only one addition of the organometallic nucleophile would take

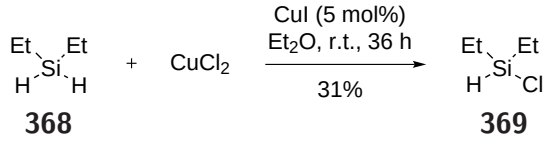
place. A parallel should be drawn here with our earlier work on the oxidation of aryl silanes, where a chloroaminosilane reagent was employed. Again, for such reagents the single addition of an organometallic species to the silicon centre is well documented[15,135] However, use of a commercially available chlorosilane reagent avoids the need to prepare and store the sensitive chloroaminosilane derivative, while achieving the same goal of nucleophile mono-addition. Furthermore, the silane intermediates are stable and can be isolated, yet under certain conditions the Si-H bond can be activated, allowing a subsequent nucleophilic addition step to take place.



Scheme 4.6 Synthesis of Silicon-Tethered Substrates

It should be noted that while both chlorodimethylsilane and chlorodi*iso*-propylsilane are commercially available, chlorodiethylsilane cannot be readily purchased. Thus, it was necessary to synthesise this reagent, and the method described by Kunai and Ohshita[227] was judged to be the most synthetically appealing. In the event, addition of two equivalents of copper(II) chloride to diethylsilane **368** in the presence of catalytic copper(I) iodide afforded chlorodiethylsilane **369** in a disappointing 31% yield, following some difficulties in purification. Despite repeated attempts at distilling the chlorosilane product, a number of minor impuritites remained present in our final synthetic sample, and perhaps access to this compound may be better acheived by following another of the published

protocols.[228,229]



Scheme 4.7 Synthesis of Chlorodiethylsilane

With the appropriate dialkylchlorosilane reagents in hand, the silyl alkynes **361**, **362** and **363** could now be readily synthesised (Scheme 4.6). While they display limited stability towards flash column chromatography, these silanes are bench stable and can be easily isolated from the reaction mixture. It is thought that the lower yield reported for the synthesis of dimethylalkynylsilane **361** is reflective of this compound's volatile nature. The stage was now set for coupling with the desired alcohol building block, in this instance commercially-available bromoalkene **364**, and this step was acheived *via* two different means. The limited steric constraints offered by both this primary alcohol and the intermediate silane **361** allowed Lee's ruthenium-catalysed Si-H bond activation / alcohol coupling methodology to be employed in the synthesis of the dimethyl-substituted tethering motif.[155,230] Treatment of neat silane **361** and alcohol **364** with 0.5 mol% $[RuCl_2(p\text{-cymene})]_2$ afforded alkoxysilane **365** in a pleasing 92% yield after a reaction time of only one hour at room temperature. While this product is unstable towards chromatographic separation, the absence of any byproduct formation during the preparation of substrate **365** meant that a simple filtration over Celite proved sufficient in yielding a clean sample of the desired compound.

In contrast, both the diethyl and di*iso*-propyl intermediate silanes **362** and **363** were found to possess silicon centres that were too sterically hindered to enable use of the aforementioned ruthenium-catalysed silane-alcohol coupling. Although access to the desired alkoxysilanes **366** and **367** *via* this synthetic pathway was possible, both extended reaction times and heating of the neat mixture was found to be necessary. Furthermore, it became apparent that heating in particular was encouraging the formation of a number of unidentifiable byproducts,* and thus an alternative route to these substrates was sought. Following the lead of the Malacria group,[55] it was found that the Si-H bond could instead be activated upon treatment with *N*-bromosuccinimide, affording a highly reactive bromosilane intermediate. Addition of the alcohol **364** could then take place under

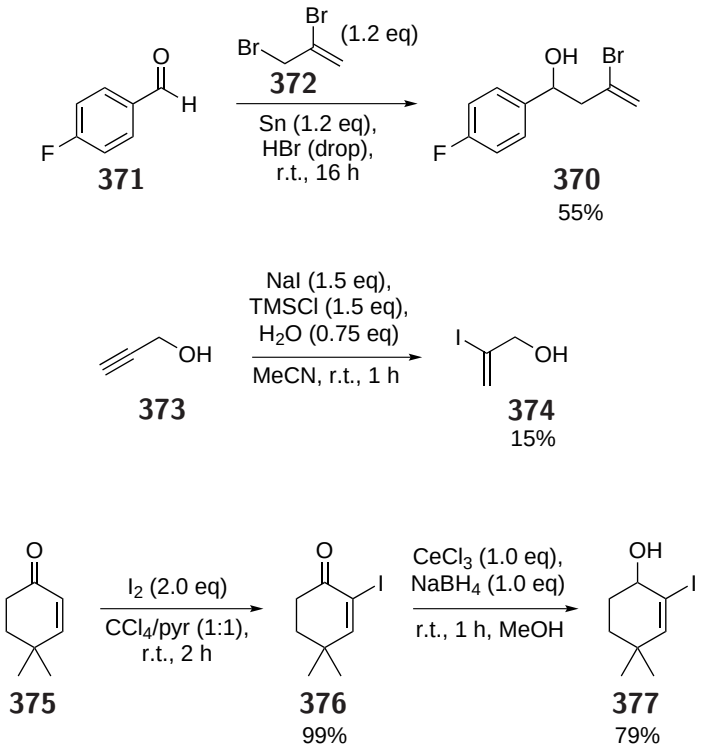
*Alkene hydrogenation and alkyne hydrosilylation are two potential side reactions that could be envisaged under these reaction conditions.

standard silylation conditions (Et_3N, DCM), giving rise to the desired alkoxysilanes **366** and **367** in a 67% and 57% yield, respectively. Although the efficiency of these couplings was disappointing, upon workup the di*iso*propyl derivative **367** could be isolated cleanly without any need for further purification. Unfortunately, this was not the case for the diethyl derivative **366**, most likely due to the presence of inseparable impurities that arose during the synthesis of the chlorodiethylsilane reagent **369**.

The non-polar nature of these alkoxysilane compounds, coupled with their sensitivity towards traditional chromatography, made purification a challenge. For the most part, the routes employed in the synthesis of substrates **365**, **366** and **367** were highly reliable and byproduct free, allowing the siloxane linkers to be assembled without the need for recourse to flash column chromatography for purification. However, in order to enhance the stability and perhaps reactivity of these substrates, a variety of alternative scaffolds were proposed, utilising a range of alcohol and alkyne building blocks. It was hoped that these alternative starting materials would confer more desirable properties upon the alkoxysilane substrates than could currently be obtained by utilising the bromoalkene building block **364** alone.

Employing secondary, rather than primary alcohol components seemed a logical first step in enhancing substrate stability, and thus investigations were made into the synthesis of vinyl bromide **370** *via* a tin-mediated Barbier allylation (Scheme 4.8).[231] Surprisingly, initial attempts at this transformation resulted in return of unreacted 4-fluorobenzaldehyde **371**, despite considerable literature precedent suggesting this allylation process should take place readily. After numerous failed experiments, it was found that the nature of the HBr solution used was key to the success of this reaction - previous attempts had employed an aqueous HBr / acetic acid reagent, while the desired transformation was eventually realised in the presence of a commercially available 48% wt. solution of HBr in water. Despite the presence of only a few drops of HBr solution in the reaction mixture, this additive is thought to be crucial in cleaning the surface of the tin metal, therefore allowing insertion into the allyl bromide moiety to take place. Thus, the secondary alcohol building block **370** could be readily generated in 55% yield, with this reaction being amenable towards multigram scale synthesis.

Vinyl iodide **374** was proposed to be an attractive building block thanks to both the potential



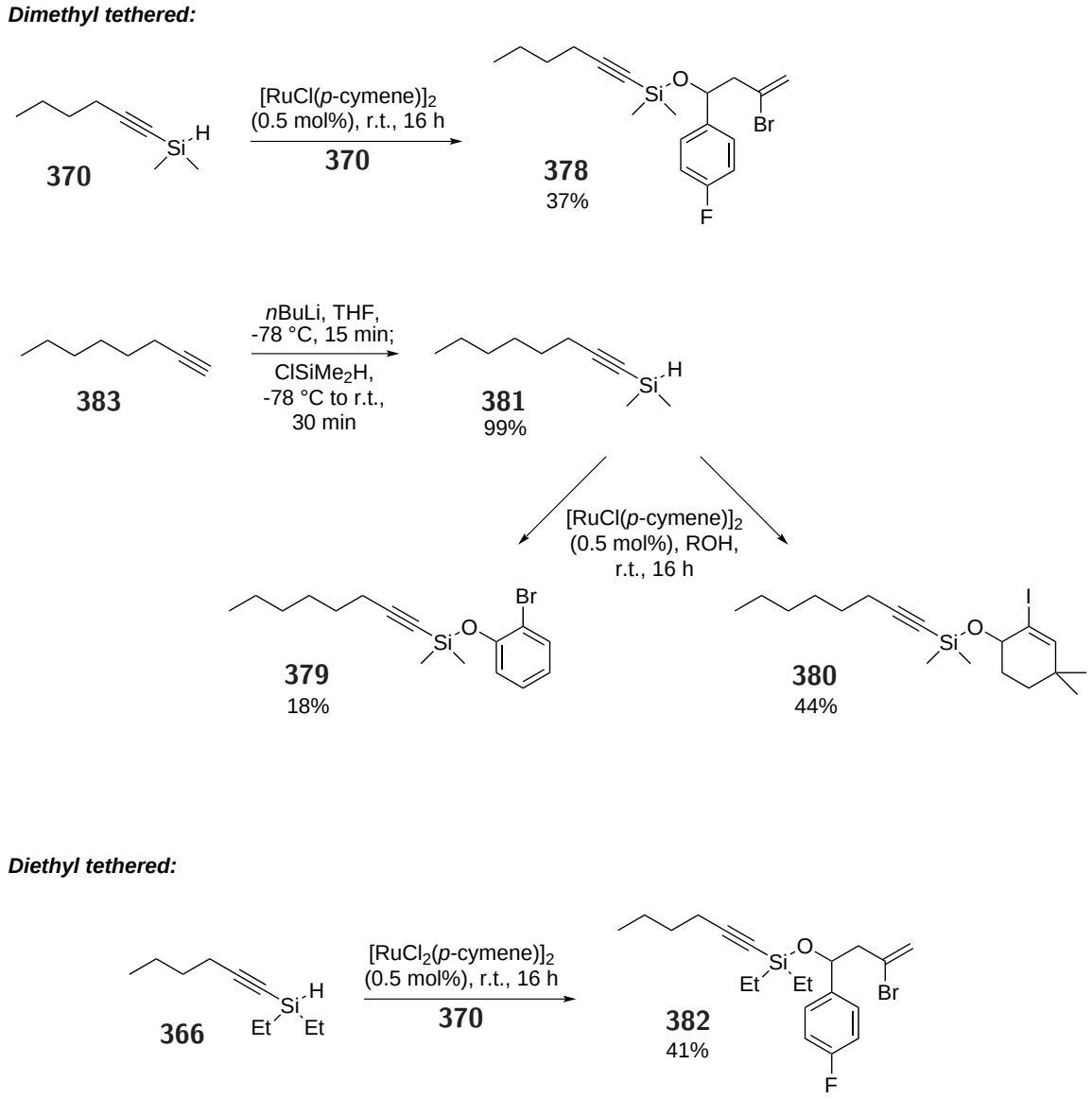
Scheme 4.8 Synthesis of Alcohol Building Blocks

increase in reactivity offered by the iodide functionality, and the opportunity to explore the effects that a five-membered ring tether would have on the reactivity of these palladium-mediated processes. Based upon work conducted by Kamiya and co-workers,[232] this desired compound was approached *via* the addition of HI to propargyl alcohol **373** (Scheme 4.8). This reactive reagent was generated *in situ* from the reaction of chlorotrimethylsilane, sodium iodide and water, thus affording alcohol **374** in a disappointing 15% yield. It is thought that the low efficiency of this process is likely to arise as a result of difficulties in isolation and purification of the desired compound **374**, and therefore further attempts at this literature procedure would likely improve the yield obtained.

Finally, a second vinyl iodide **377** was proposed to be an appropriate building block for this silicon-tethered methodology. Such a compound would incorporate both the positive enhancement in reactivity that the vinyl iodide group would provide, along with the additional stability conveyed by the secondary nature of the alcohol functionality. Furthermore, the presence of a cyclohexene ring system would allow a variety of highly substituted bicyclic systems to be readily approached. In the event, compound **377** was efficiently synthesised in a 78% overall yield from commercially available dimethyl cyclohexenone **375**, this transformation proceeding *via* iodinated intermediate **376** (Scheme 5.16).[233,234] Thus, with these three alcohol building blocks in hand, a wide range of

alkynyl siloxanes could now be synthesised, utilising both the ruthenium-catalysed alcohol / silane coupling and the bromosilane pathways employed previously.

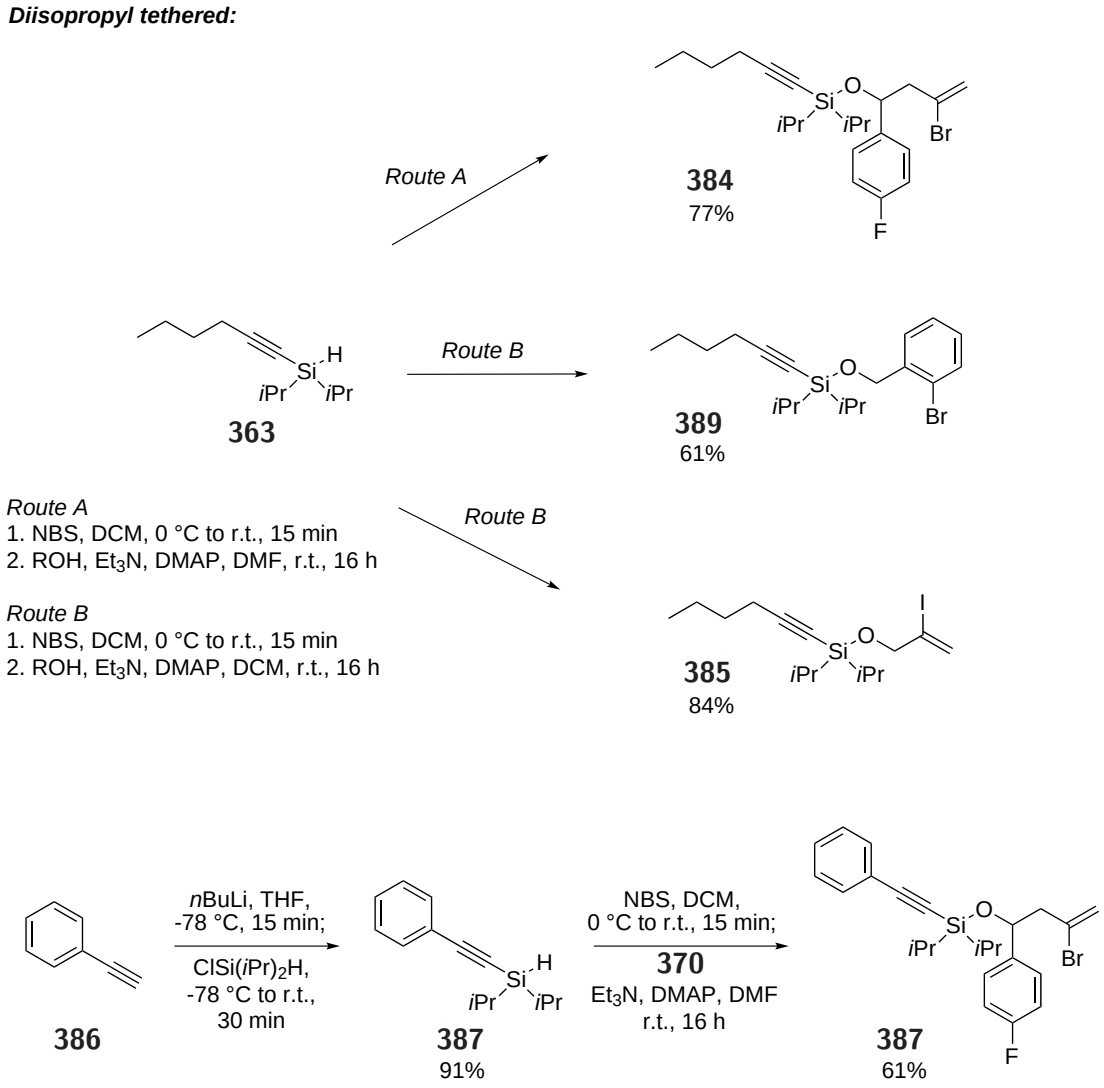
A variety of dimethylsilyl- and diethylsilyl-tethered substrates were initially approached, and thus alkynyl siloxane **378** was synthesised in 37% yield from hexyne-derived dimethylsilane **361** (Scheme 4.9). The siloxanes **379** and **380** were approached from the octyne-derived silane **381**, emphasising the flexibility of this route in enabling a wide range of alkyne substituents to be incorporated. It is thought that the disappointing 18% yield obtained for the synthesis of compound **379** is likely to be reflective of the considerable instability of this phenol-derived linker. Finally, siloxane **382** was also synthesised from hexyne-derived diethylsilane **366** in 41% yield. However, as previously, it was found that compound **382** was contaminated with a number of inseparable apolar byproducts, and thus no further diethylsilyl-tethered substrates were synthesised *via* this route.



Scheme 4.9 Synthesis of Dimethylsilyl- and Diethylsilyl-Tethered Substrates

In contrast, both the hexyne-derived di*iso*-propylsilyl substrates **384** and **385** were synthesised cleanly and in good yields, these results perhaps being indicative of the enhanced stability conferred by the bulky di*iso*-propyl substituents (Scheme 4.10). The range of substrates was further expanded *via* the deprotonation and silylation of phenylacetylene **386**, affording the silane intermediate **387** in excellent yield. Subsequent bromosilane formation and alcohol **370** addition allowed the desired compound **388** to be readily approached in a 61% yield. Once again, this series of reactions readily provided access to the di*iso*propyl-tethered siloxanes in a high fidelity fashion, with little contamination or evidence of byproduct formation.

It should also be noted that initial attempts at the synthesis of secondary alcohol-derived di*iso*-

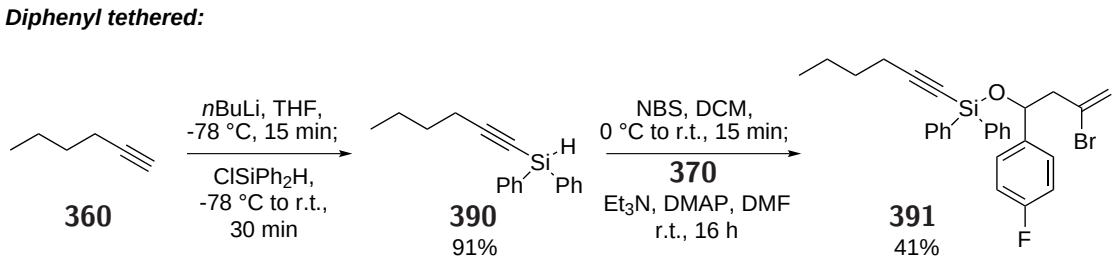


Scheme 4.10 Synthesis of Di*iso*propyl-Tethered Substrates

propyl siloxanes **384** and **387** resulted in failure, with only alkynyl silanol and alcohol **370** being isolated from the reaction mixture following workup. Subsequent experiments found that addition of alcohol **370** as a solution in DMF (*Route A*), rather than DCM (*Route B*), was necessary for coupling with the intermediate bromosilane to take place. Given the considerable steric hindrance introduced by the presence of the *para*-fluorophenyl substituent, it is perhaps unsurprising that a more polar solvent is needed in this instance.

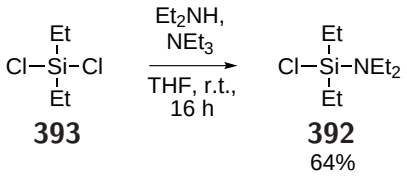
Efforts were also made to vary the silicon substituents further, and the diphenyl derivative was identified as an appropriate target. Thus, deprotonation of hexyne **360** and silylation with chlorodiphenylsilane afforded alkynyl silane **390** in a pleasing 91% yield (Scheme 4.11). Once again, subsequent bromination of the Si-H bond and addition of the secondary alcohol **370** yielded

the desired diphenyl siloxane **391**, although significant contamination of the final product by an unidentifiable byproduct was noted. Further purification of this compound proved difficult, and thus no further diphenyl substrates were synthesised - it was proposed that the Si-Ph bond present in intermediate **390** may be undergoing reaction in the presence of *N*-bromosuccinimide, affording bromobenzene as an inseparable byproduct.



Scheme 4.11 Synthesis of Diphenylsilyl-Tethered Substrates

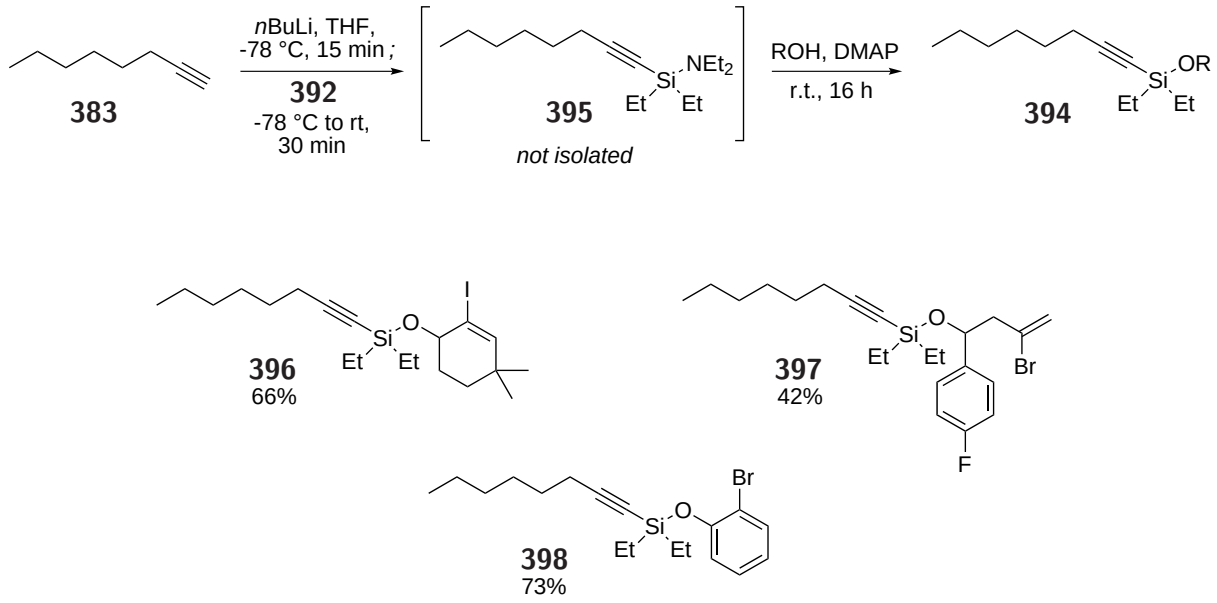
Finally, a new route to the desired diethylsilyl-tethered substrates was devised, utilising chlorodiethylaminosilane **392** as a silylating agent. This reactive species was synthesised in a similar manner to the dimethyl analogue **212**, *via* the mono-addition of diethylamine to dichlorodiethylsilane **393** in the presence of triethylamine (Scheme 4.12). During the preparation of this reagent the additional stability conferred upon the silicon centre by the diethyl substituents was noted, and this aminosilane **392** could be handled much more easily than the corresponding dimethyl reagent **212**, which was used extensively in the previously reported arene oxidation chemistry.



Scheme 4.12 Chlorodiethylaminosilane Synthesis

With the desired aminosilane **392** in hand, our attentions could now be focused upon the synthesis of a range of diethyl-tethered alkynyl siloxanes **394** (Scheme 4.13). Deprotonation of octyne **383** and addition of **393** afforded the reactive intermediate **395**, which could then be directly treated with a range of alcohols in a one-pot procedure. This sequence allowed the desired siloxanes **396**, **397** and **398** to be synthesised cleanly in moderate yields. It is particularly notable that unlike the products obtained from the silane intermediate **366**, these samples do not suffer from the presence

of byproduct contaminants.



Scheme 4.13 Revised Synthesis of Diethyl-Tethered Substrates

The ease by which a wide range of siloxane-tethered substrates could be synthesised serves to highlight the flexibility and efficiency of the routes described. Although the yields were sometimes moderate, the majority of substrates could be approached with limited byproduct contamination, a considerable benefit given the non-polar nature of these tethered species. Thus, with this synthetic pathway now established, we could move our focus to examining the viability of our proposed palladium-mediated cascade cyclisations.

4.4. Initial Studies

Our initial investigations were conducted with the primary alcohol-derived substrate **367**, and the conditions utilised by both our group and the Oh group[235] when effecting the palladium-catalysed carbopalladation / cross-coupling of bromoalkene substrates provided a logical starting point for our investigations. Thus, the di*iso*-propylsilyl-tethered substrate **367** was heated in ethanol to 80 °C for 16 h in the presence of phenylboronic acid, cesium carbonate and catalytic $Pd(PPh_3)_4$ (10 mol% loading), and the resulting crude reaction mixture was subjected to ^{1}H NMR spectroscopic analysis (Table 4.1, entry 1). In this instance, the direct coupling product **399** was found to dominate, with the cleavage / direct coupling product **400** arising in reduced quantities. Promisingly, a small

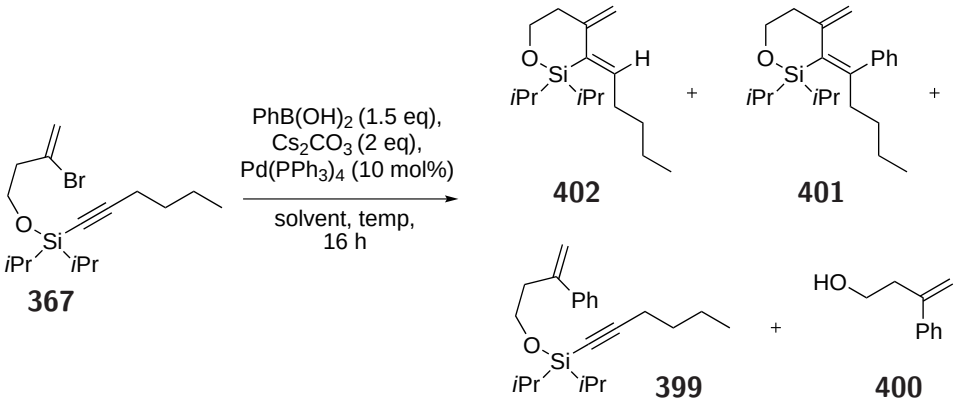
quanitity of the Suzuki product **401** was also detected in the crude reaction mixture, suggesting that the desired cascade cyclisation process could indeed be achieved for these silicon-tethered substrates.

Interestingly, decreasing the concentration of the reaction mixture was found to favour formation of the cleavage / direct coupling product **400** (entries 2 to 5). Given that tether cleavage most likely occurs *via* an alcoholysis-type mechanism, this observation is perhaps not surprising, suggesting that the lability of this siloxy linker may prove to be an issue under the basic reaction conditions. At very low concentrations, we were surprised to note that the unexpected reductive cyclisation product **402** began to appear in the reaction mixture (entry 4), and when a concentration of 0.0058 mmol/mL was employed (entry 5, corresponding to 20 mg of **367** in 10 mL of EtOH), compound **402** was the only species present. Two further cyclisations were conducted in the absence of $PhB(OH)_2$, and to our delight it was noted that the reductive cyclisation product **402** could be synthesised under more concentrated conditions (entry 6). Intriguingly, carrying out the same reaction at a concentration of 0.0058 mmol / mL this time resulted in decomposition of the starting material, suggesting that perhaps the boronic acid species is acting to promote rapid formation of the necessary palladium hydride intermediate and thereby limiting the amount of time that sensitive reaction intermediates must be present in the reaction media. It is proposed that this effect may be arising due to the formation of an 'ate' complex between ethanol and the boronic acid.

In an effort to avoid formation of the reductive cyclisation product **402**, a small solvent screen was attempted. Gratifyingly, when toluene was employed as the solvent (entry 8), only formation of the tandem Heck / Suzuki product **401** was observed in a 26% isolated yield. However, when considerably more dilute conditions were investigated, the starting material **367** was returned unchanged (entry 9). The use of THF provided a more disappointing collection of results (entries 11 to 14), with a mixture of the desired product **402** and the undesired direct coupling product **399** being obtained in each instance.

In order to confirm the proposed geometries of the products obtained, a crude sample of reductive cyclisation product **402** and tandem Heck / Suzuki product **401** were submitted for nOe analysis. As expected, correlations were observed between the protons indicated in Fig. 4.1, thus suggesting that no double bond isomerisation was occurring upon formation of the carbopalladation intermediate

Table 4.1. Examining Palladium-Catalysed Reaction Conditions



	Solvent	Conc. (mmol/mL)	Temp. (°C)	Result[a]
1	EtOH	0.12	80	1 **400** : 5 **399** : 0.7 **401**
2	EtOH	0.058	80	1 **400** : 2 **399** : 0.5 **401**
3	EtOH	0.029	80	1 **400** : 1.6 **399** : 0.3 **401**
4	EtOH	0.015	80	1 **399** : 0.6 **401** : 0.1 **402**
5	EtOH	0.0058	80	**402** only
6	EtOH	0.029	80	38% **402**[b,c]
7	EtOH	0.0058	80	decomp.[b]
8	PhMe	0.015	80	26% **401**[c]
9	PhMe	0.0058	80	**367** only
10	PhMe	0.029	80	1 **401** : 0.4 **399**
11	THF	0.12	65	1 **401** : 2.6 **399**
12	THF	0.058	65	1 **401** : 1.6 **399**
13	THF	0.029	65	1 **401** : 0.4 **399**
14	THF	0.015	65	1 **401** : 0.4 **399**

[a]By ^{1}H NMR spectroscopic analysis. [b]No $PhB(OH)_2$ present. [c]Isolated yield.

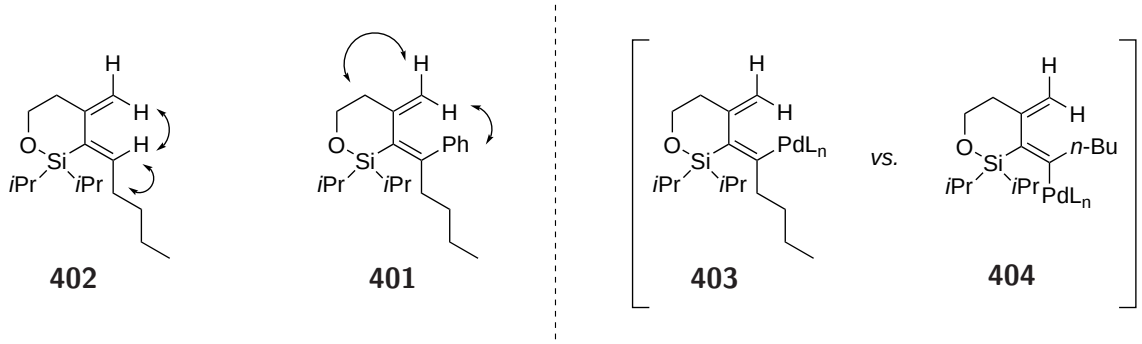


Fig. 4.1. Confirmation of Product Geometry by nOe Analysis

356 (Scheme 4.5). The presence of any minor double bond isomers could not be detected by ^{1}H NMR spectroscopic analysis, suggesting that the selectivity for the geometries indicated is greater than 20 : 1. The considerable selectivity of this reaction is in contrast to results obtained previously by our group,[216] whereby a mixture of double bond isomers was observed to arise under similar conditions. It is thought that the steric hindrance arising between the di*iso*-propyl substituents and the palladium centre of isomerisation intermediate **404** is likely to prevent the formation of this species from taking place, thus conveying considerable isomeric selectivity upon both these carbopalladation-derived processes.

Thus, with our understanding of the formation of these highly-substituted, silicon-tethered diene systems **402** and **401** now considerably more established, we decided to explore each process in more detail. Our initial investigations on this palladium-mediated methodology had yielded some promising early results (Table 4.1, entries 6 and 8), and our aim was now to arrive at an optimised set of conditions for each process.

4.5. Reductive Cyclisation

4.5.1. Initial Optimisation

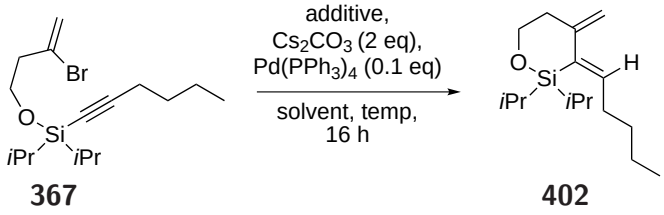
Our first efforts focused upon optimising the reductive cyclisation process. When this transformation was conducted in EtOH, disappointing isolation yields were obtained (Table 4.2, entries 1 and 2). It was proposed that the siloxane tether may be undergoing cleavage in the basic, alcoholic reaction media, resulting in a low recovery of the desired cyclisation product **402**. Thus, subsequent efforts at optimisation were directed at utilising stoichiometric amounts of an alcoholic additive to promote

this reductive process. Octanol was first employed as an additive (entries 3 and 4), as it was thought that the high molecular weight of this compound might allow potential byproducts to be more readily observed, thus giving some insight into the mechanistic pathway through which this transformation proceeds. In the presence of 5 equivalents of octanol, the desired siloxane **402** was synthesised in 47% yield, with octanal being detected in the crude ^{1}H NMR spectrum. The octanal aldehyde peak was found to integrate to 0.73 relative to the product signals, with a noticeable amount of an unidentifiable byproduct also present following reaction. In contrast, the reaction did not proceed to completion in the presence of one equivalent of octanol, and in this instance no aldehyde peak was observed despite some conversion to **402** taking place.

Intriguingly, use of *tert*-butanol as an additive also resulted in the formation of siloxane **402**, although the yield obtained was a disappointing 35% (entry 5). Water was also found to be a suitable additive (entry 6), while DME also promoted this reductive cyclisation when employed as a solvent (entry 7), albeit in very low yields. Finally, when the reaction took place in 1,4-dioxane, a 1 : 0.2 ratio of product **402** to starting material **367** was observed. The use of DME and dioxane as more unusual 'reducing agents' was based upon earlier reports by the Keay[236] and Lautens[237] groups (Scheme 4.14). In 2001, Keay and co-workers reported that they observed a 'hydride transfer' from dioxane while investigating palladium-catalysed polyene cyclisations (**405** $\rightarrow$ **406**). More recently, Lautens and co-workers observed that DME was also able to act as a hydride transfer agent, and the group was able to effect an 80% incoporation of deuterium when using d_{10}-DME as a solvent (**407**). Thus, our results are consistent with these earlier observations that both DME and dioxane can act as 'hydride donors' in palladium-catalysed processes.

Further investigations also found that more functionalised alcohols could act as hydride donors (entry 9), with benzaldehyde being apparent in the crude ^{1}H NMR spectrum when benzyl alcohol was employed as an additive. Interestingly, when toluene was used as a solvent (entries 10 - 12), incomplete conversion was observed to take place when a number of different alcoholic species were utilised as hydride transfer agents. These results are in contrast to the complete conversion to **402** observed when similar alcohols were reacted in THF, suggesting that perhaps solubility of these additives is a crucial consideration. Alternatively, it was proposed that THF itself may be capable of effecting this transformation, but the complete absence of conversion observed when no alcoholic additive was employed (entry 13) confirmed that this was not the case.

Table 4.2. Reductive Cyclisation Optimisation

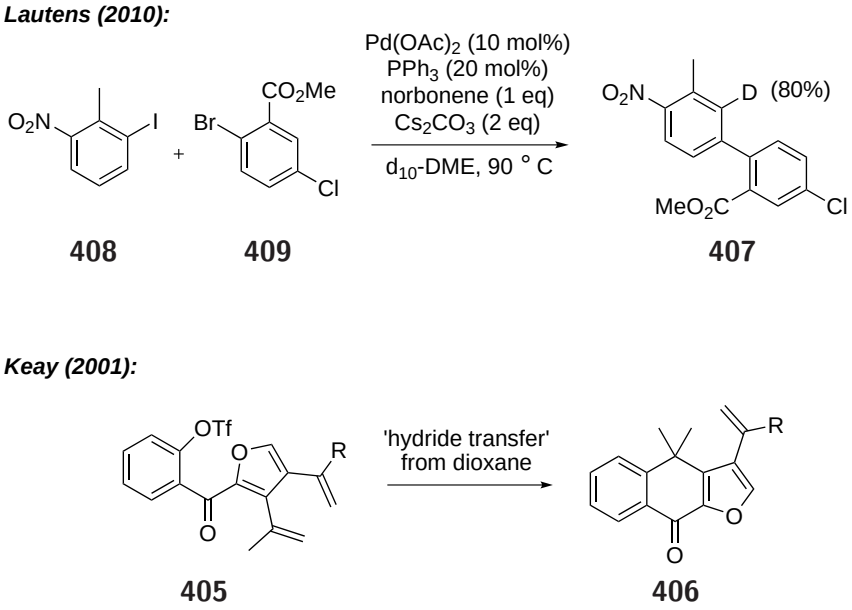


367 **402**

	Solvent	Additive (eq)	Temp. (°C)	Result[a]
1	EtOH	-	70	39% **402**[b,c]
2	EtOH	-	67	22% **402**[b]
3	THF	octanol (5)	67	47% **402**[d]
4	THF	octanol (1)	67	1 **402** : 1 **367**
5	THF	*t*-BuOH (5)	67	35% **402**[b]
6	THF	H_2O (5)	67	19% **402**[b]
7	DME	-	67	9% **402**[b]
8	dioxane	-	67	1 **402** : 0.2 **367**
9	THF	benzyl alcohol (5)	67	2 **402** : 1 **367**[d]
10	PhMe	*t*-BuOH (5)	67	2 **402** : 1 **367**
11	PhMe	MeOH (5)	67	4 **402** : 1 **367**
12	PhMe	EtOH (5)	67	**367** only
13	THF	-	67	**367** only

[a]By ^{1}H NMR spectroscopic analysis. [b]Isolated Yield. [c]1.5 eq $PhB(OH)_2$ present. [d]Aldehyde peak present in the crude NMR.

Thus, although a range of different conditions were employed in the optimisation of this process, yields above 50% could not be realised. A number of experiments were also attempted with milder bases, including K_2CO_3 and Na_2CO_3, but in such cases conversion to the siloxane product **402**



Scheme 4.14 Similar Reports of 'Hydride Transfer' from DME and Dioxane

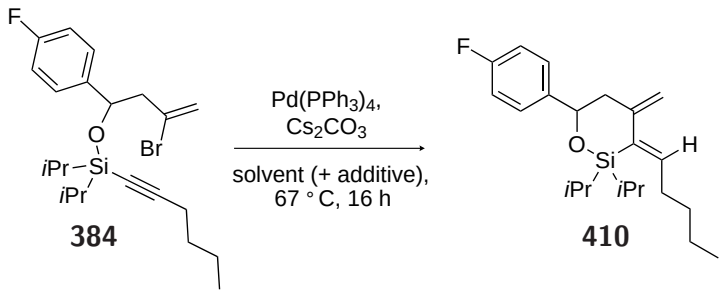
was found to be limited. Furthermore, purification of the product was found to be challenging, as it appeared that decomposition was taking place during flash column chromatography, despite the use of basified silica. It was thus concluded that the starting material **367** was most likely too sensitive under the highly basic, alcoholic conditions necessary for the desired transformation to take place. The surprisingly delicate nature of the diene product **402** limited the ammenability of this compound towards standard purification techniques, and thus it was proposed that further efforts should focus on the reductive cyclisation of more stable tethered substrates. It should also be noted that the diethylsilyl- and dimethylsilyl-tethered substrates **365** and **366** were found to be highly labile under these basic conditions.

4.5.2. Further Studies

The alkynyl siloxane **384** was selected as the most appropriate substrate on which to conduct further optimisation studies, thanks to the enhanced stability offered by both the secondary alcohol building block and the bulky *iso*-propyl silicon substituents (Table 4.3). When octanol was employed as an additive with toluene as a solvent, a 49% yield of the desired product **410** was obtained (entry 1). A more promising yield of 67% was obtained with a *tert*-butanol / THF reaction mixture (entry 2), while conducting the reaction in ethanol alone afforded cyclic siloxane **410** in only a 28% yield (entry 3). Pleasingly, on returning to a toluene solvent system, a 92% yield was realised when

employing *iso*propyl alcohol as a hydride transfer agent (entry 4). In contrast, for this substrate **384** the reaction did not go to completion in the presence of DME and 1,4-dioxane alone (entries 5 and 6). It should be noted that once again only a single isomer of the product **410** was observed following ^{1}H NMR spectroscopic analysis.

Table 4.3. Reductive Cyclisation Optimisation

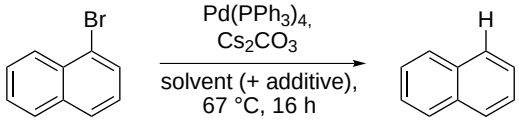


	Solvent	**Additive (eq)**	**Yield**[a]
1	PhMe	octanol (5.0)	49%
2	THF	*t*-BuOH	67%
3	EtOH	-	28%
4	PhMe	*iso*propyl alcohol (5.0)	92%
5	DME	-	74% (2.1 **384** : 1 **410**)[b]
6	1,4-dioxane	-	72% (0.79 **384** : 1 **410**)[b]

[a]Isolated yield. [b]Combined yield.

As an aside, we were intrigued as to the generality of this reductive process, and proposed to explore the possibility of applying such conditions to an aryl halide substrate (Table 4.4). Thus, bromonaphthelene **411** was subjected to a small range of palladium-catalysed conditions, in the hope that the non-volatile dehalogenated derivative naphthalene **412** could be synthesised. To our surprise, in the presence of ethanol, complete conversion to the product **412** was observed (entry 1). Use of octanol as an additive resulted in partial conversion (entry 2), while employing *tert*-butanol / THF and DME reaction conditions gave only recovered starting material **411** (entries 3 and 4).

Table 4.4. Investigation the Generality of Palladium-Catalysed Dehalogenation

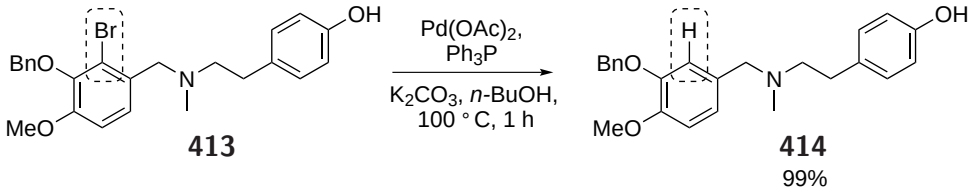


411 **412**

	Solvent	Additive (eq)	Result[a]
1	EtOH	-	99% **412**
2	PhMe	octanol (5.0)	3 **412** : 1 **411**
3	THF	*t*-BuOH (5.0)	**411** only
4	DME	-	**411** only

[a]Isolated yields and by ^{1}H NMR spectroscopic analysis.

A more thorough investigation of the literature found that this dehalogenation process had been previously reported by Chen and co-workers in a 2007 publication (Scheme 4.15).[238] The group found their relatively mild, palladium-catalysed conditions could be applied to a wide range of substrates, including the complex polyarene **413**. Thus, we were confident that the alcohol additive employed in these transformations was responsible for the formation of a palladium hydride intermediate species, and so our attentions turned to fully understanding the mechanism of our silicon-tethered reductive cyclisation transformation.



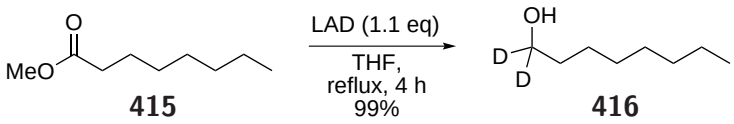
413 **414** 99%

Scheme 4.15 Chen's Palladium-Catalysed Dehalogenation

4.5.3. Mechanistic Investigations

Initial Studies

During our optimisation efforts, a number of studies were concurrently conducted into elucidating the mechanism by which this reductive cyclisation transformation takes place. In particular, the presence of an aldehyde peak in the crude reaction mixture was noted earlier when heavier alcohols were employed as hydride donors (Table 4.2, entries 3 and 9). These results suggested that the alcohol additive was undergoing oxidation to the corresponding aldehyde, resulting in the formation of a palladium hydride intermediate. Thus, it was expected that deuterium transfer to the reductive cyclisation product would be observed when an appropriate deuterated additive was present in the reaction mixture. Interestingly, our first attempt at investigating this hypothesis with primary alcohol-derived substrate **367** resulted in no deuterium incorporation when D_2O was employed as an additive (Table 4.5, entry 1). However, it was proposed that the reaction may be proceeding under a different mechanism when water is present, and so we sought to examine the effect that deuterated alcohol species would have on the reaction.

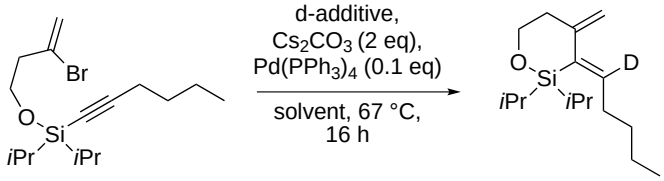


Scheme 4.16 Synthesis of Deuterated Octanol

Deuterated octanol **416** was readily synthesised in quantitative yield following the reduction of commercially-available methyl octanoate with lithium aluminium deuteride. Utitilising this species as a hydride donor in THF resulted in 50% deuterium incorporation into the product **417** (entry 2), suggesting that perhaps another hydride source was also present. Intriguingly, by instead employing toluene as a reaction solvent, the level of deuterium incorporation was found to increase to 75% (entry 3). Conducting the reaction in benzene instead of toluene disproved the hypothesis that transfer of a benzylic hydride from this aromatic solvent was taking place, with a 75% level of deuteration still apparent (entry 5).

It was further proposed that the octanol -O<u>H</u> proton might be somehow involved in the formation of a palladium hydride intermediate, thus resulting in an incomplete transfer of deuterium from d_2-octanol **416**. Thus, we attempted to generate d_2-octanol-O<u>D</u> by repeatedly washing d_2-octanol-OH

Table 4.5. Initial Mechanistic Investigations



367 **417**

	Solvent	d-Additive (eq)	Result[a]
1	THF	D_2O (5)	No D incorporation
2	THF	**416** (5)	50% D incorporation
3	PhMe	**416** (5)	75% D incorporation
4	PhH	**416** (5)	75% D incorporation
5	PhMe	**416** (5)[b]	85% D incorporation
6	PhMe	octanol-OD (5)	25% D incorporation
7	d_8-THF	*tert*BuOH (5)	No D incorporation

[a]By ^{1}H NMR spectroscopic analysis. [b]d_2-octanol-O<u>D</u> was employed.

416 with D_2O and extracting the product into diethyl ether. Using this additive further increased the level of deuterium incorporation to 85% (entry 5), implying that the -OH proton may also be involved in the generation of a palladium hydride intermediate. This implication was further solidified upon noting that deuterium could be incorporated at a level of 25% when using octanol-OD as an additive (entry 6), although it is difficult to envisage an appropriate mechanism by which such incorporation could take place. It is possible that the levels of deuterium incorporation observed in the presence of octanol-OD may be within experimental error, given the difficulties in accurately integrating the appropriate peaks on the scale investigated.

In examining the ^{2}H NMR spectrum of the crude reaction mixture, it was noted that four deuterium-containing products could be observed. The product, d_2-octanol and d-octanal peaks could be readily identified, but identification of the fourth proved more challenging. By closely examining the corresponding ^{1}H NMR spectra obtained following cyclisation with both deuterated and non-deuterated octanol additives, it was established that the additional byproduct was octyl octanoate.

It was proposed that further oxidation from an octanal / octanol hemiacetal species would allow formation of this compound to occur under the reaction conditions, thus providing another means by which a palladium hydride species could arise. However, the generation of this intermediate does not explain the 15% level of hydride incorporation still unaccounted for, and it was proposed that perhaps continuing these investigations with a more stable substrate might allow a clearer picture of the reaction mechanism to be elucidated.

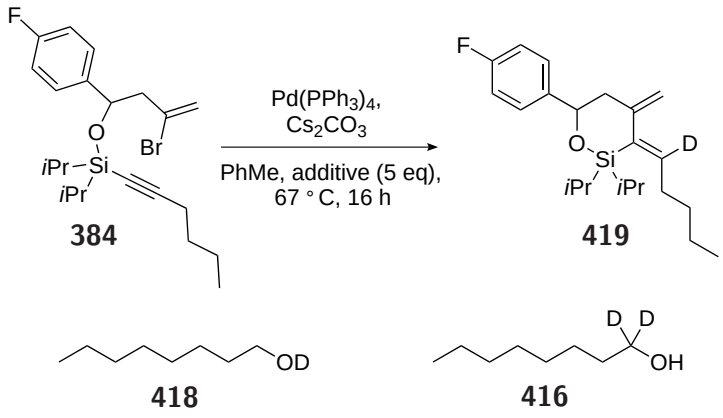
The mechanism by which hydride transfer takes place under the *tert*-butanol / THF conditions remains unclear, as this tertiary alcohol additive cannot undergo oxidation. Thus, it was thought that perhaps the *tert*-butanol was able to promote transfer of a hydride species from the solvent, and so the reaction was conducted in the presence of d_8-THF. Bafflingly, under these conditions no deuterium incorporation was observed, leaving many questions unanswered regarding the mechanism of this reductive cyclisation transformation.

Further Studies

In order to better understand the mechanistic pathway through which this reaction proceeds, several deuterated additives were employed during the reductive cyclisation of secondary alcohol-derived substrate **384** (Table 4.6). In the presence of octanol-OD **418**, no deuterium incorporation was observed (entry 1). However, to our delight, utilising deuterated octanol **416** as an additive resulted in a 100% level of deuterium incorporation (entry 3). This result confirmed our hypothesis that the formation of a palladium hydride species was occurring *via* oxidation of an alcoholic additive, thus allowing a reasonable mechanistic pathway to be proposed for this transformation.

Just prior to the completion of this work, a manuscript was published by Beller and co-workers on the palladium-catalysed coupling of aryl halides with primary alcohols.[239] In this publication, the group reported that reduction of the aryl halide substrates was found to be an undesired side-reaction, thanks to the ease with which palladium hydride intermediates can be generated in the presence of alcohols. A mechanistic pathway was proposed by the Beller group to explain this observation, and was found to be in complete agreement with the pathway proposed for our silicon-tethered reductive cyclisation methodology (Scheme 4.17). From the appropriate palladium(0) species **420**, oxidative insertion of aryl halide **421** affords the palladium(II) intermediate **422**.

Table 4.6. Reductive Cyclisation Mechanistic Investigations



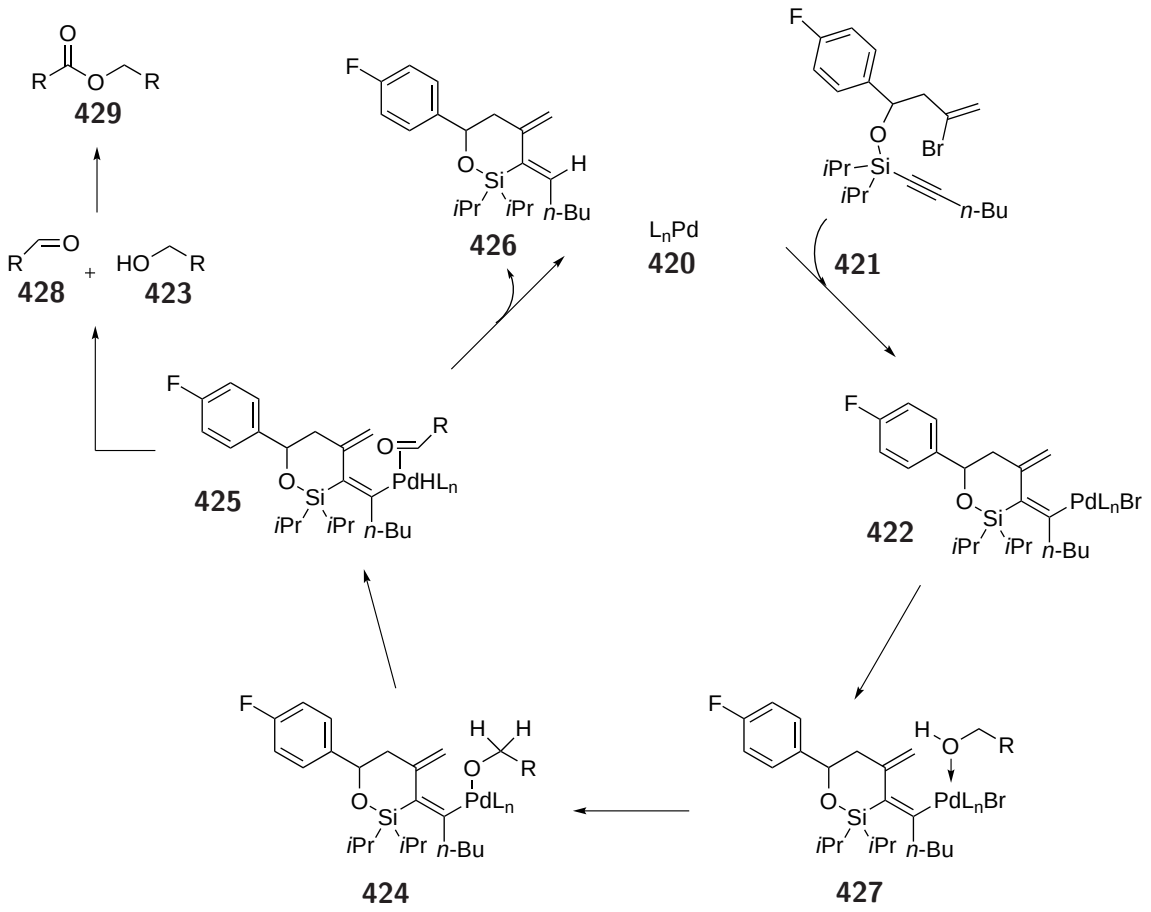
	Additive	Result[a]
1	**418**	No D incorporation
2	**416**	100% D incorporation

[a]By ^{1}H NMR spectroscopic analysis.

Coordination of the alcohol **423** and subsequent displacement of the halide anion yields intermediate **424**, which can undergo β-hydride elimination to give palladium hydride species **425**. Finally, reductive elimination would afford the dehalogenated product **426**.

The Beller group also noted that formation of an ester species **429** could be observed in the reaction mixture, and it was proposed than this byproduct was arising as a result of over-oxidation of the nascent aldehyde **428**. This observation is consistent with the concomitant generation of octyl octanoate that was noted when employing octanol as an additive during earlier attempts at determining the mechanism of our reductive cyclisation process.

It is notable that when the reaction was conducted in the presence of THF with *tert*-butanol as an additive, an inseparable byproduct was obtained (Table 4.3, entry 2). ^{13}C NMR spectroscopic analysis of the isolated product suggested that this contaminant contained a carbonyl group, and through further analysis the byproduct was determined to be the oxidation product of the alcohol building block (**370** → **430**, Fig. 4.2). It was proposed that under the basic reaction conditions, the di*iso*-propyl tether is undergoing some cleavage to the alcohol building block **370**. This alcohol can then be oxidised to the corresponding ketone, thus generating a palladium hydride species in



Scheme 4.17 Reductive Cyclisation Mechanistic Proposal

a similar manner to the other alcohol additives employed. The reductive cyclisation would then be able to take place as expected, giving rise to the product **410**, albeit in a much reduced yield.

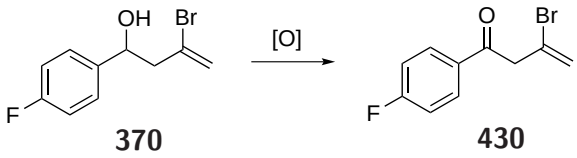


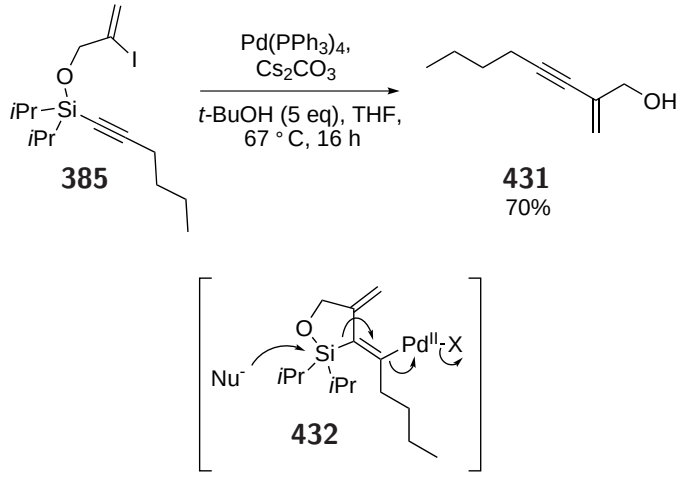
Fig. 4.2. Reductive Cyclisation byproduct

This observation provides an explanation for the 'hydride transfer' behaviour of *tert*-butanol in THF, despite this species being a non-oxidisable tertiary alcohol. Furthermore, it is likely that a certain amount of tether cleavage occurred when the more labile primary alcohol-derived substrate **367** was reacted in the presence of toluene and deuterated octanol, thus providing the 'background' levels of hydride incorporation that were consistently observed (Table 4.5, entry 6). Therefore, we can conclude that this reductive cyclisation transformation occurs due to concomitant palladium hydride formation in the presence of an alcohol species, yielding the diene product **410** as desired.

It should be noted that a very small amount of contamination from byproduct **430** was observed even when the reaction was conducted in *iso*-propyl alcohol / toluene, but the minimal levels of this contamination suggest that the starting material **384** is mostly stable under these reaction conditions.

4.5.4. Expanding the Substrate Scope

Following these successful mechanistic studies, attempts were made to broaden the substrate scope of this transformation. Disappointingly, the dimethylsilyl-, diethylsilyl- and diphenylsilyl-tethered substrates showed very limited stability under these basic conditions, even in the presence of milder inorganic bases. No reaction was observed with the phenylacetylene-derived substrate **388**, suggesting that the additional steric demands introduced by the aryl substituent prohibit the carbopalladation process from taking place. In contrast, some reaction was observed when the reductive cyclisation of vinyl iodide substrate **385** was attempted in the presence of *tert*-butanol and THF, although the product obtained was not the desired five-membered cyclic siloxane.



Scheme 4.18 Unexpected Reductive Cyclisation Product

^{1}H NMR spectroscopic analysis suggested that the product formed was enyne **431** (Scheme 4.18). It was proposed that the steric constraints introduced by the shorter tether length were likely to activate the reaction intermediate **432** towards tether cleavage, potentially *via* nucleophilic attack upon the silicon centre. Concomitant loss of the palladium species would result in the reformation of the triple bond, thus affording the primary alcohol product **431**. Alternatively, a Sonogashira-type mechanism could be envisaged, whereby initial cleavage under the basic reaction conditions

would afford alcohol **374** and the appropriate desilylated alkyne. Cross-coupling between the vinyl iodide moiety and the terminal alkyne could then take place, generating the same enyne product **431**.

Thus, although the substrate scope of this transformation was found to be surprisingly limited, the reductive cyclisation of siloxane **384** could be achieved in a pleasing 92% yield. Furthermore, by utilising a small series of deuterated additives, the mechanism of this pathway was determined, and the confusing results obtained in previous mechanistic studies were explained.

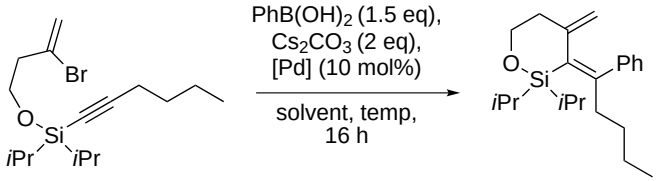
4.6. Tandem Heck / Suzuki Coupling

4.6.1. Initial Optimisation

Having successfully obtained the tandem Heck / Suzuki coupling product **401** in 26% yield during our initial investigations into the application of silicon-tethering methodology to palladium-mediated processes, the stage was now set to conduct an optimisation study for this transformation. Disappointingly, our initial results proved difficult to repeat, with incomplete conversion observed in toluene, despite attempts to increase the reaction concentration (Table 4.7, entries 1 and 2). In contrast, complete decomposition of the starting material **367** was found to arise when THF was employed as the solvent for this process (entry 3). Further optimisation found DME to be a more appropriate solvent, with a reaction solution concentration of 0.015 mmol/mL (corresponding to 20 mg of **367** in 4 mL) yielding the desired product **401** in 28% yield (entries 4 and 5). Varying the catalyst to $Pd(dppf)Cl_2$ resulted in incomplete conversion to **401** over the same 16-hour timescale (entries 6 and 7), and thus it was concluded that $Pd(PPh_3)_4$ was an appropriate catalytic species for this transformation in the absence of a further catalyst screen.

Once again, considerable difficulties were found in achieving a satisfactory yield for this transformation, and it was proposed that the delicate siloxy alkyne functionality present in the starting material **433** is most likely undergoing some decomposition under the basic reaction conditions. In a similar fashion to the reductive cyclisation cascade, the reaction was found to be sluggish in the presence of milder bases, while the diethylsilyl- and dimethylsilyl-tethered substrates **365** and **366** displayed very limited stability in such basic media. Furthermore, separation of the product diene **401** from

Table 4.7. Tandem Heck / Suzuki Optimisation



367 **401**

	[Pd]	Solvent	Conc. (mmol/mL)	Temp. (°C)	Result[a]
1	$Pd(PPh_3)_4$	PhMe	0.0073	80	1 **367** : 1 **401**
2	$Pd(PPh_3)_4$	PhMe	0.015	80	1 **367** : 1 **401**
3	$Pd(PPh_3)_4$	THF	0.0073	65	decomp.
4	$Pd(PPh_3)_4$	DME	0.029	75	1 **401** : 0.3 **399**[c]
5	$Pd(PPh_3)_4$	DME	0.015	80	28% **401**
6	$Pd(dppf)Cl_2$	DME	0.029	85	2 **401** : 1 **399**[c]
7	$Pd(dppf)Cl_2$	DME	0.015	85	3 **401** : 1 **399**[c] : 1 **402**[d]

[a]By ^{1}H NMR spectroscopic analysis. [b]No $PhB(OH)_2$ present. [c]Direct coupling product. [d]Reductive cyclisation product.

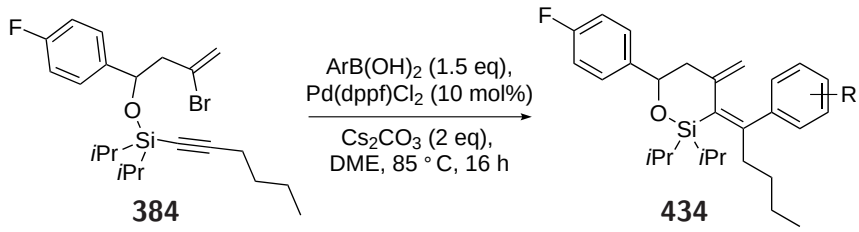
the 1,1'-biphenyl byproduct formed concomitantly during the reaction proved challenging given the non-polar nature of both these species. Thus, further work in this area was proposed to employ both a more stable substrate, and a substituted aryl boronic acid coupling partner whose dimer might be more readily separated from the products obtained.

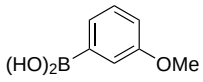
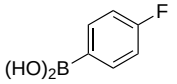
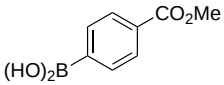
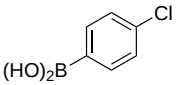
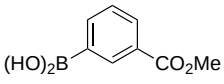
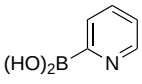
4.6.2. Further Studies

Once again, our further studies on the silicon-tethered tandem Suzuki coupling process were initiated with the secondary alcohol-derived di*iso*propyl substrate **384**. Initial results suggested that unwanted dimerisation of the aryl boronic acid coupling partner could be minimised when $Pd(dppf)Cl_2$ was used as a catalytic species instead of $Pd(PPh_3)_4$, and thus this catalyst was employed in all further tandem Suzuki coupling transformations. In order to explore the substrate

scope of this process, a range of boronic acids were selected whose corresponding dimers would be polar enough to be readily separable from the apolar diene products **434** (Table 4.8). Gratifyingly, by employing 3-methoxyphenylboronic acid as a coupling partner in a DME solvent system, the desired cyclisation product was obtained in a 73% yield (entry 1). Further experiments demonstrated that electron-deficient aryl boronic acids were also appropriate reagents for this transformation (entries 2 and 3), although some reduction in yield was observed. In contrast, pleasing yields of 67% and 55% were obtained when employing *para*-chloro- and *para*-fluoro-substituted phenyl boronic acids respectively (entries 4 and 5). Finally, an attempt was made to conduct the tandem Suzuki process in the presence of 3-pyridyl boronic acid (entry 6), but no reaction was observed. This last result presumably arises due to the relatively unreactive nature of this heteroaromatic species.

Table 4.8. Investigation of Tandem Suzuki Coupling Substrate Scope

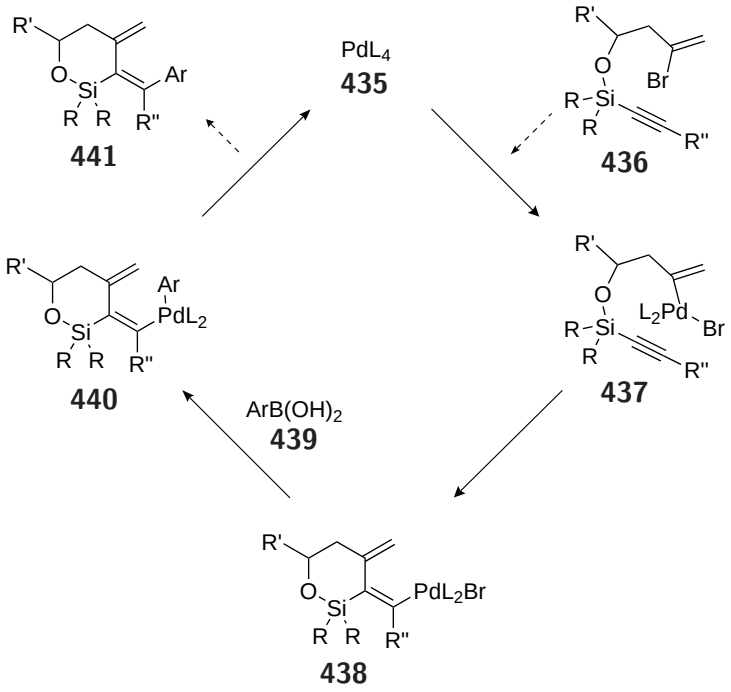


		Yield[a]			Yield[a]
1		73%	4		55%
2		38%	5		67%
3		46%	6		-[b]

[a]Isolated yield. [b]No reaction, **384** returned.

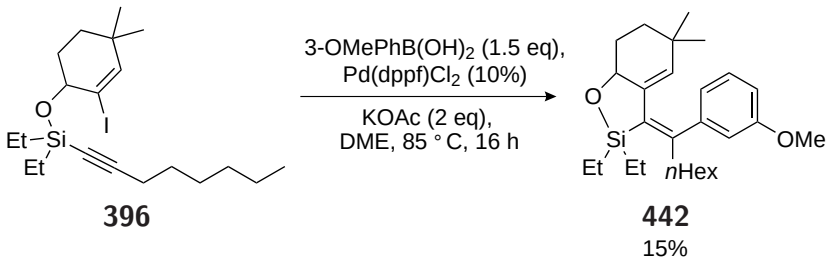
A mechanism for this reaction was proposed, whereby oxidative insertion of a palladium (0) species **435** in the substrate **436** constitutes the first step of the pathway (Scheme 4.19). Palladium (II) intermediate **437** can then undergo carbopalladation across the pendent alkyne to afford diene

intermediate **438**. Subsequent transmetallation of the boronic acid coupling partner **439** would afford intermediate **440**, from which reductive elimination could take place to generate the final product **441**. The results obtained for this transformation suggest that secondary alcohol-derived substrates, such as compound **384**, are considerably more stable under the basic reaction conditions, although it is likely that some tether cleavage is still taking place. It should be noted that no conversion to the desired products was noted with either of the other di*iso*-propylsilyl-tethered substrates **388** and **385**.



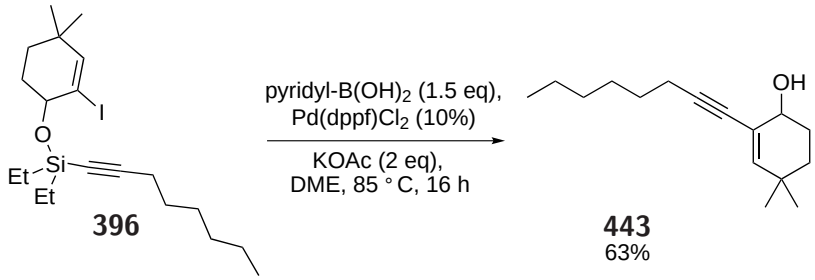
Scheme 4.19 Proposed Tandem Suzuki Coupling Mechanism

While the dimethylsilyl- and diphenylsilyl-tethered substrates were found to be wholly unstable under such conditions, even in the presence of a milder inorganic base, the diethylsilyl-tethered species **396** did show some conversion to the desired product **442** when coupling with 3-methoxyphenyl boronic acid (Scheme 4.20). In this instance, it was necessary to employ potassium acetate as a base, given the considerable degradation of the starting material **396** observed when Cs_2CO_3 was present. However, despite numerous attempts to improve this result, the highest yield realised was 15%. It was proposed that the highly strained nature of the resulting conjugated bicyclic compound **442** was likely to promote tether cleavage and *in situ* degradation. Furthermore, the product **442** obtained showed limited stability towards flash column chromatography, therefore further compromising the isolated yield of this transformation.



Scheme 4.20 Reaction of Diethyl-Tethered Substrate **396**

Intriguingly, when a similar reaction was attempted with 3-pyridyl boronic acid as a coupling partner, the enyne **443** was unexpectedly obtained (Scheme 4.21). This result is similar to that reported earlier for the di*iso*propyl vinyl iodide substrate **385** (Scheme 4.18), suggesting that a similar 'silyl-transfer' process is taking place. Again, the five-membered ring carbopalladated intermediate through which this transformation proceeds is likely to experience considerable allylic strain, thus encouraging opening of the cyclic siloxane system *via* nucleophilic attack upon the silicon centre. As with the previous example of 'silyl-transfer', a two-step cleavage / Sonogashira mechanism could also be envisaged.

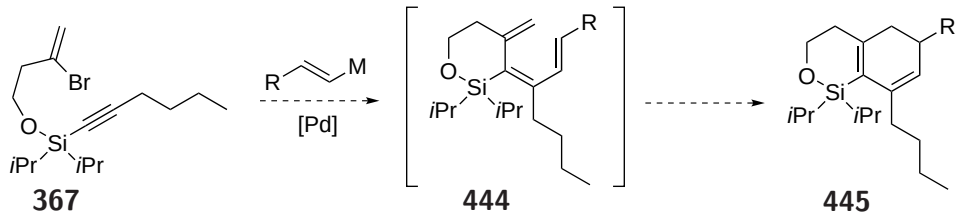


Scheme 4.21 Unexpected Formation of Enyne **443**

Thus, when utilising the more stable secondary alcohol-derived substrate **384**, a small selection of substituted dienes could be synthesised in moderate to good yields (Table 4.8). However, once again the basic conditions necessary for promoting this transformation prohibit the use of dimethylsilyl- and diphenylsilyl-tethered substrates, while only one of the diethyl-tethered compounds displayed any conversion to the desired product. The sensitive nature of the silyl alkyne linker moiety therefore limits the substrate scope of this transformation, with the presence of bulky alkyl substituents on the silicon centre being a necessity if conversion to the diene products is to take place.

4.7. Heck / Suzuki / Electrocyclisation Cascade - Inital Studies

A number of initial investigations were also conducted into the feasibility of a silicon-tethered, palladium-mediated Heck / Suzuki / electrocyclisation cascade, in which the use of a vinylic coupling partner would enable the intermediate triene **444** to be approached in a single step (Scheme 4.22). A 6π electrocyclisation process was then envisaged to take place under the reaction conditions, affording the cyclic diene **445** *via* a one-pot protocol.



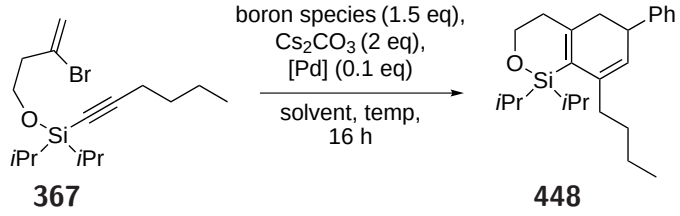
Scheme 4.22 Silicon-Tethered Heck / Suzuki / Electrocyclisation Cascade

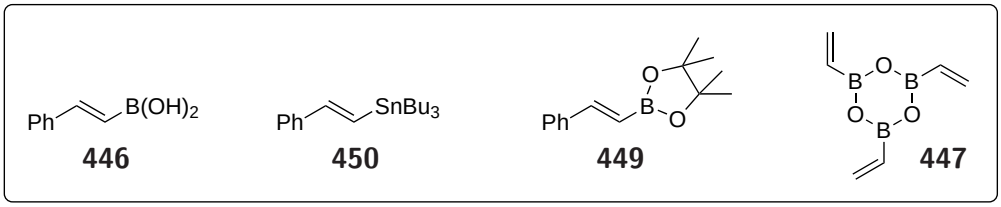
Our first attempts at effecting this desirable transformation focused upon the use of styrenyl boronic acid **446** as a coupling partner (Table 4.7). In contrast to the results reported above for our optimisation of the Heck / Suzuki coupling process (Table 4.7), conducting the reaction in toluene resulted in decomposition of the starting material **367** (entry 1), while employing THF as a solvent offered no discernable reaction (entries 2 and 3). Unsurprisingly, an ethanol solvent system gave complete conversion to the reductive cyclisation product **402** (entry 4), while only the starting material **367** was present in the reaction mixture following an attempted cross-coupling / electrocyclisation in DME (entry 5).

Boronic acids are known to readily undergo dehydration to the corresponding anhydride species **447**,[240] and thus it was proposed that the addition of water to the reaction mixture might rehydrate the trimer and promote the desired cross-coupling reaction. Disappointingly, no conversion to the desired product **448** was observed to take place in THF, toluene or dioxane (entries 6 - 8), and so the reaction was instead conducted with the commercially available pyridine complex of the boroxine **447** (entry 9). Once again, the starting material **367** was returned unchanged under these reaction conditions, and thus recourse to a different coupling partner was thought to be necessary.

Given the successful use of this coupling partner in palladium-mediated cascade reactions by other members of the group, it was proposed that the pinacol ester **449** might be a more appropriate

Table 4.9. Initial Studies on the Heck / Suzuki / Electrocyclisation Cascade





	Reagent	Solvent	Conc. (mmol/mL)	Temp. (°C)	Result[a]
1	**446**	PhMe	0.029	80	decomp.
2	**446**	THF	0.015	65	**367** only
3	**446**	THF	0.0097	65	**367** only
4	**446**	EtOH	0.015	70	**402** only
5	**446**	DME	0.015	75	**367** only
6	**446**	THF	0.015	65	**367** only[b]
7	**446**	PhMe	0.015	80	decomp.[b]
8	**446**	dioxane	0.015	120	decomp.[b]
9	**447**	THF	0.015	65	**367** only[b]
10	**449**	THF	0.015	65	decomp.
11	**449**	PhMe	0.015	80	decomp.
12	**449**	dioxane	0.015	100	decomp.
13	**449**	DME	0.015	85	decomp.
14	**449**	DME	0.015	67	decomp.
15	**450**	PhMe	0.015	100	**367** only[c]

[a]By ^{1}H NMR spectroscopic analysis. [b]1.5 equivalents of H_2O added. [c]$Pd(PPh_3)_2Cl_2$ employed.

vinylic boron reagent for this transformation. However, despite attempting this reaction in a variety of solvents (entries 10 - 14), decomposition of the starting material **367** was always observed to take place. Finally, a Heck / Stille / electrocyclisation cascade was also attempted with vinyl stannane **450** (entry 15), but in contrast to the results reported previously siloxane substrate **367** remained unchanged by the reaction conditions.

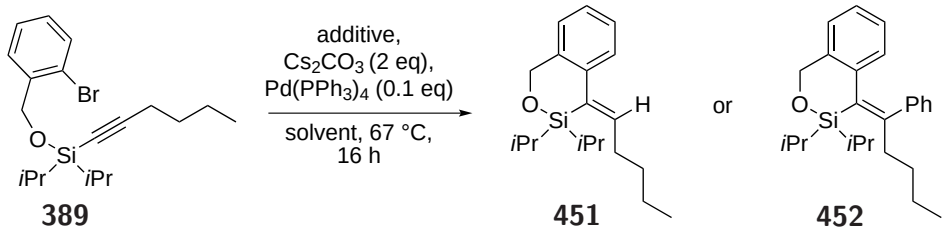
Following this disappointing series of results, the decision was made to abandon further investigations into our proposed Heck / Suzuki / electrocyclisation cascade process. Unlike the reductive cyclisation and Heck / Suzuki transformations reported above, not even trace amounts of the desired product **448** were detected during these experiments, and thus it was thought that further efforts would be better focused on the development of alternative methodologies.

4.8. Investigating Alternative Substrates

A number of experiments were also carried out to investigate the feasibility of initiating the desired palladium-mediated cascade from insertion into an aryl bromide functionality, rather than a vinyl bromide. The desired substrate **389** was subjected to a wide range of palladium-catalysed conditions, in the hope that the substrate scope of our silicon-tethered methodology could be expanded beyond vinyl bromide siloxanes. However, the results of these initial studies were not promising, with either decomposition or no reaction taking place under all the conditions investigated. These outcomes suggest that the benzyl siloxane tether present in substrate **389** exhibits greater sensitivity to the basic reaction media than the corresponding vinyl bromide substrate **367**, thus leading to decomposition at high temperatures (entries 5 and 6), and in an alcoholic solvent system (entry 1). Conversely, the unreactive nature of this compound **389** at lower temperatures (entries 2, 3, 4 and 7) may indicate that the aryl bromide moiety imparts some steric constraints upon the initial oxidative insertion or carbopalladation steps.

The somewhat disappointing results obtained in this final investigation suggests that the substrate scope of this palladium-mediated tandem methodology might be more limited than expected. Once again, the instability of this benzylic alcohol-derived substrate **389** proved to be a limiting factor in this instance, with steric concerns also apparent. The failure of this substrate to undergo

Table 4.10. Reactions of Alternative Substrates



389 **451** **452**

	Solvent	Additive (eq)	Temp. (°C)	Result[a]
1	EtOH	-	67	decomp.
2	THF	H_2O (5)	67	**389** only
3	THF	EtOH (5)	67	**389** only
4	THF	$PhB(OH)_2$ (1.5)	67	**389** only
5	DMF	Et_3SiH (2)	80	decomp.
6	DME	$PhB(OH)_2$ (1.5)	80	decomp.
7	DME	$PhB(OH)_2$ (1.5)	65	**389** only[b]

[a]By ^{1}H NMR spectroscopic analysis. [b]$Pd(dppf)Cl_2$ employed.

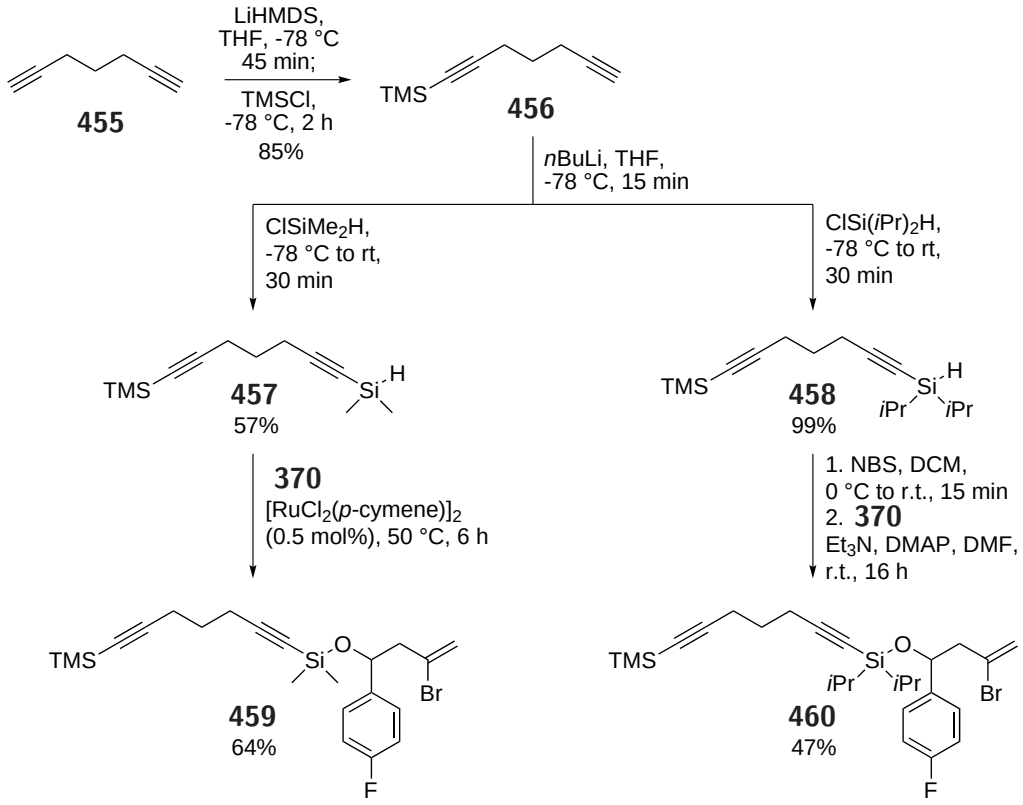
any productive reaction suggests that aryl bromide species are not appropriate carbopalladation precursors in this instance, and thus as a result our attention turned to the investigation of the proposed oligocyclisation cascade process.

4.9. Oligocyclisation

4.9.1. Substrate Synthesis

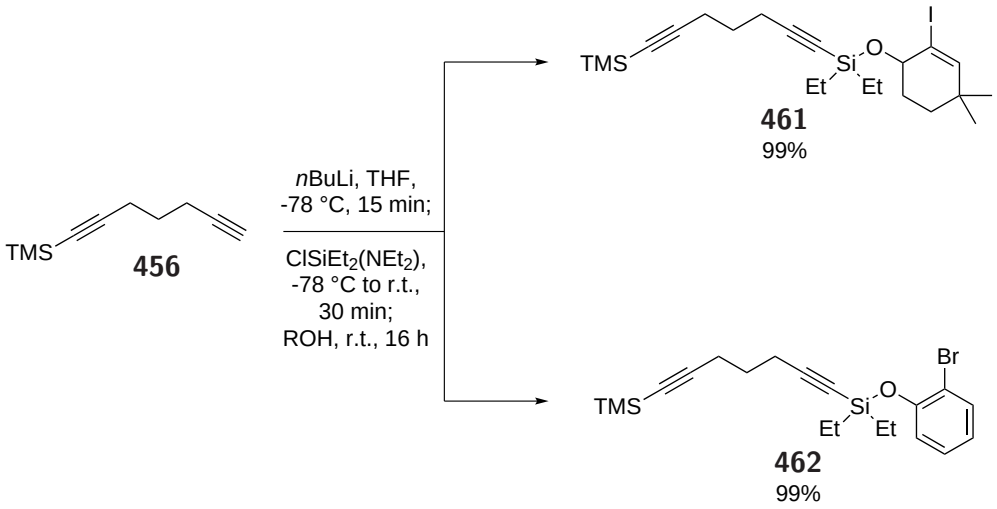
In order to investigate the role that silicon-tethering might play in a palladium-mediated oligocyclisation process, it was necessary to synthesise a small range of diyne-containing substrates (Scheme 4.23). Thus, 1,6-heptadiyne **455** was mono-silylated with chlorotrimethylsilane, following deprotonation in the presence of LiHMDS. This protocol was found to afford very little contamination from the undesired bis-silylation byproduct, providing the TMS-diyne **456** in 85% yield. A second

deprotonation and silylation step afforded the bis-silyl intermediates **457** and **458**, and subsequent activation of the nascent Si-H bond and substitution with alcohol **370** gave rise to **459** and **460** in 64% and 47% yields respectively.



Scheme 4.23 Synthesis of Oligocyclisation Substrates

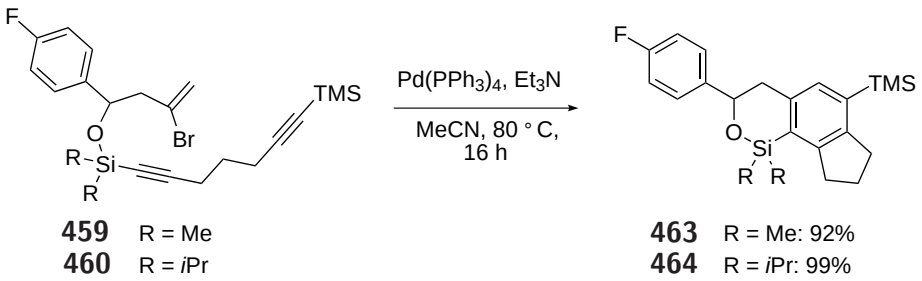
Several diethylsilyl-tethered substrates were also approached, utilising the appropriate aminosilane **392** as a silylating agent (Scheme 4.24). As a result, siloxane diynes **461** and **462** could be synthesised in excellent yields *via* this synthetically attractive one-pot protocol.



Scheme 4.24 Synthesis of Diethylsilyl-Tethered Oligocyclisation Substrates

4.9.2. Cyclisation Reactions

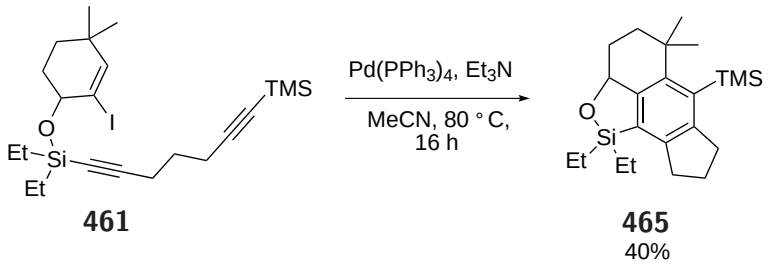
Gratifyingly, when cyclisation of dimethylsilyl-tethered diyne **459** was attempted under de Meijere's conditions ($Pd(PPh_3)_4$ and Et_3N in acetonitrile),[224] the desired arene product **463** was isolated in 92% yield (Scheme 4.25). The di*iso*-propylsilyl-tethered substrate **460** was also found to be amenable towards cyclisation, this process affording the highly-substituted product **464** in 99% yield. The excellent yields obtained for these transformations are reflective of the much milder conditions under which this palladium-catalysed cyclisation will take place. Specifically, triethylamine is sufficiently basic to promote β-hydride elimination to the cyclic products **463** and **464**, and thus recourse to stronger inorganic bases such as Cs_2CO_3 is not necessary. As a result, no *in situ* degradation of the delicate siloxy alkyne starting materials was observed, allowing high levels of conversion to be realised.



Scheme 4.25 Oligocyclisation of Dimethylsilyl- and Di*iso*-propylsilyl-Tethered Bromoenediynes

Interestingly, a considerably lower yield of 40% was obtained when palladium-mediated oligocyclisation of the diethylsilyl-tethered substrate **461** was attempted (Scheme 4.26). It was proposed that this

result was most likely due to the inherent strain present in the arene product **465**, with the formation of a 5, 5, 6, 6-tetracyclic system taking place under the reaction conditions. Steric considerations, particularly with regards to the final palladated intermediate before β-hydride elimination takes place, may also be a driving factor for the lower conversions observed in this example.

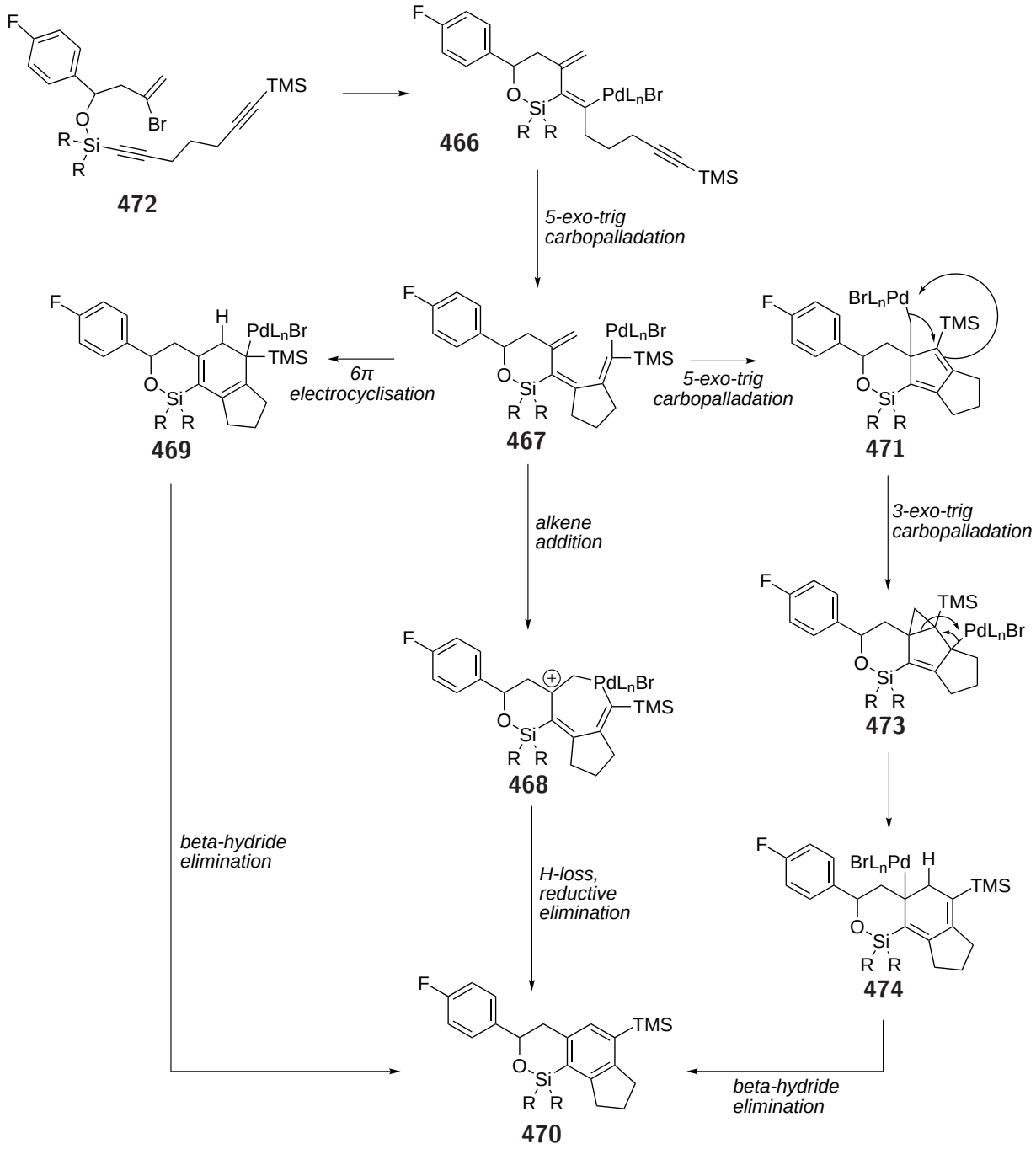


461 **465** 40%

Scheme 4.26 Oligocyclisation of Diethyl-Tethered Diynes

Influenced by the work of de Meijere and co-workers,[224] we propose that there are three possible mechanistic pathways through which these highly-substituted arene products could arise (Scheme 4.27). As with the previously-discussed reductive cyclisation and tandem Suzuki processes, this oligocyclisation reaction initiates with a 6-*exo*-dig carbopalladation step, affording intermediate **466**. A subsequent 5-*exo*-dig carbopalladation affords compound **467**, from which point the three pathways diverge. The rigid triene system of intermediate **467** seems perfectly poised to undergo a 6π-electrocyclisation, and thus this is one of the proposed routes to the final arene product **468**. Such a pericyclic process would give rise to intermediate **469**, from which β-hydride elimination would provide access to **468**. Alternatively, alkene addition would provide access to cationic intermediate **468**, with proton loss and reductive elimination yielding arene **470**. Finally, triene **467** could undergo a further 5-*endo*-trig carbopalladation to afford intermediate **471**, from which **470** could be approached following subsequent ring expansion rearrangement and β-hydride elimination.

Thus, by utilising silicon-tethered diyne substrates, a small range of highly-substituted arene products could be readily approached. The pleasing yields obtained for these transformations, and for the sensitive dimethylsilyl-tethered substrate **459** in particular, are reflective of the considerably milder conditions under which these reactions take place. Although similar reaction temperatures were required, this transformation occurs in the presence of a relatively weak organic base, rather than the strong inorganic bases that were necessarily employed in the reductive cyclisation and

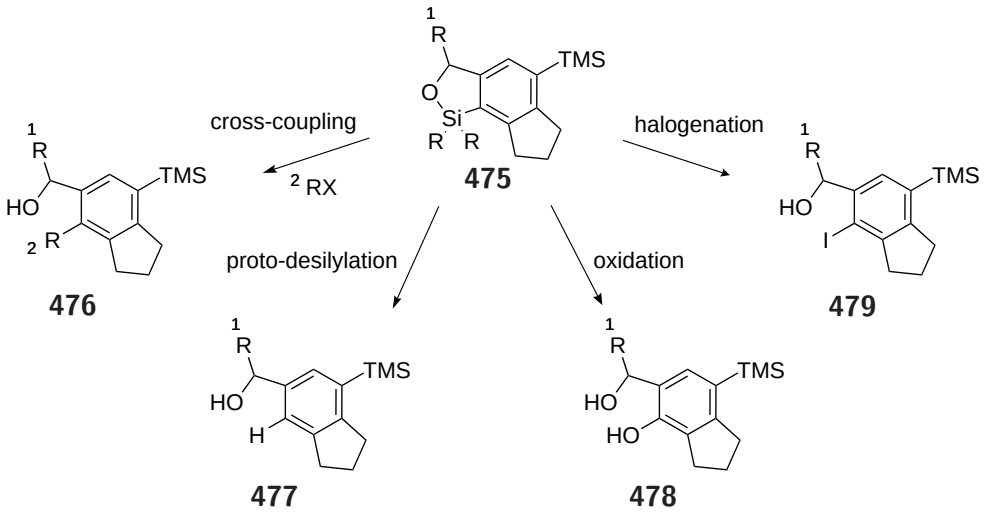


Scheme 4.27 Proposed Oligocyclisation Mechanism

tandem Suzuki processes. The silyl alkyne substrates display considerable stability under these conditions, and as a result this oligocyclisation reaction affords the desired silicon-tethered arenes in excellent yields.

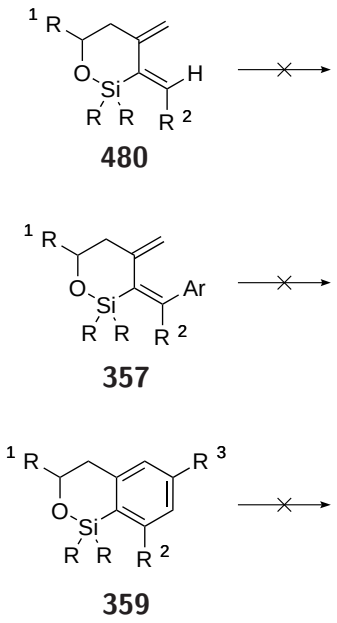
4.10. Further Functionalisation and Substrate Variations

With a range of silicon-tethered products now in hand, our attentions turned to the further functionalisation of these molecules, thus utilising the 'latent functionality' that a silicon tether possesses. Taking the oligocyclisation product **475** as an example, it was proposed that four functionalisation reactions could be attempted (Scheme 4.28). Palladium-catalysed cross-coupling would afford penta-substituted arene **476**, while proto-desilylation would yield tetra-substituted arene **477**. Alternatively, oxidation under our previously described conditions would give rise to phenol **478**, or halogenation would afford aryl halide **479**. This range of possible reactions serves to emphasise the inherent flexibility that a silicon tether provides with regards to further functionalisation, thus allowing a variety of products to be obtained from a single silicon-tethered species **475**.



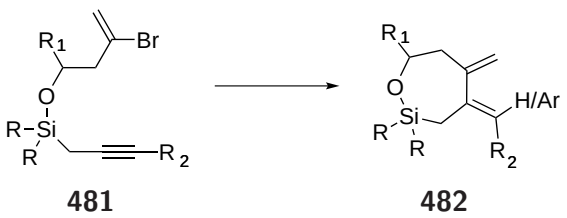
Scheme 4.28 Proposed Further Functionalisation of Silicon-Tethered Products

However, in the event no successful functionalisation reactions could be achieved with any of the products obtained (Scheme 4.29). A wide range of both mild and more forcing reaction conditions were attempted, with the silicon-tethered compounds **480**, **357** and **359** being returned unchanged in most cases. Contrastingly, when strongly acidic conditions were employed, all three species were found to decompose. Given the extensive effort put into optimising and expanding the scope of the reductive cyclisation, tandem Suzuki and oligocyclisation processes, this was a most disappointing and initially surprising result. Perhaps notable is that even the single dimethylsilyl-tethered product, compound **463**, did not show any of the desired reactivity.



Scheme 4.29 Failure of Further Functionalisation Reactions

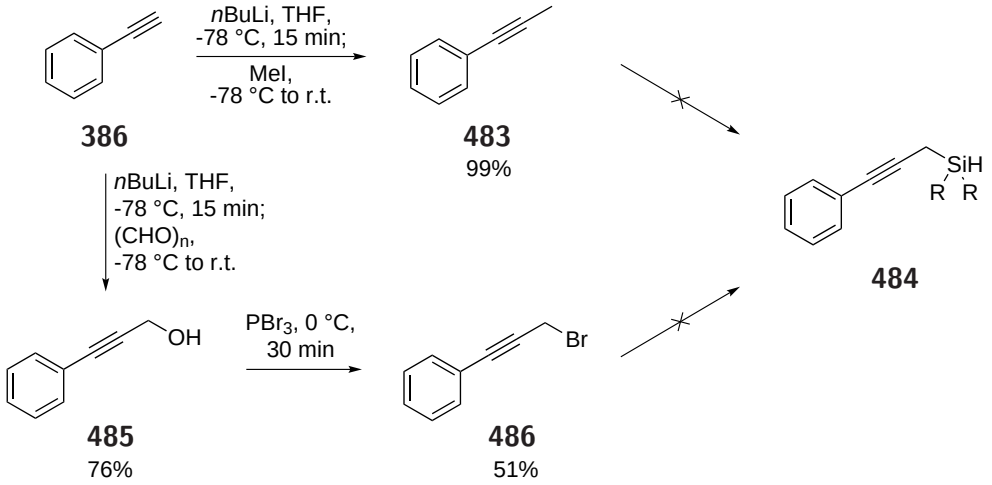
On further examination of the literature, it is perhaps unsurprising that further functionalisation of these silicon-tethered compounds proved so challenging. In particular, Denmark has noted that cross-coupling of di*iso*propyl silicon-tethered alkenes is highly challenging when the silicon centre is *syn* to the alkene substituent.[241] All of our substrates **480**, **357** and **359** bear a substituent adjacent to the silicon atom, and thus this reactive centre is likely to experience considerable steric hindrance with regards to nucleophilic attack. The need to employ bulky di*iso*-propylsilyl-tethered substrates in order to enhance the stability of the starting materials is likely to further hinder the reactivity of the final product, although as noted above, the dimethylsilyl-tethered compound **463** was also found to be unreactive.



Scheme 4.30 Proposed Cyclisation of Propargyl Silane Tethered Substrates

In light of these results, several other tethering motifs were proposed in the hope that their cyclisation products might be more amenable towards functionalisation. The first of these motifs was the propargyl silane-tethered substrate **481** (Scheme 4.30), with the resulting allyl silane functionality present in cyclisation product **482** likely to be more responsive towards further

transformations. Thus, we set out to synthesise a small range of compounds containing this more desirable motif.

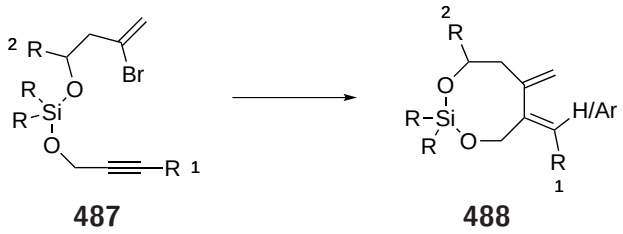


Scheme 4.31 Attempted Synthesis of Propargyl Silane Tethers

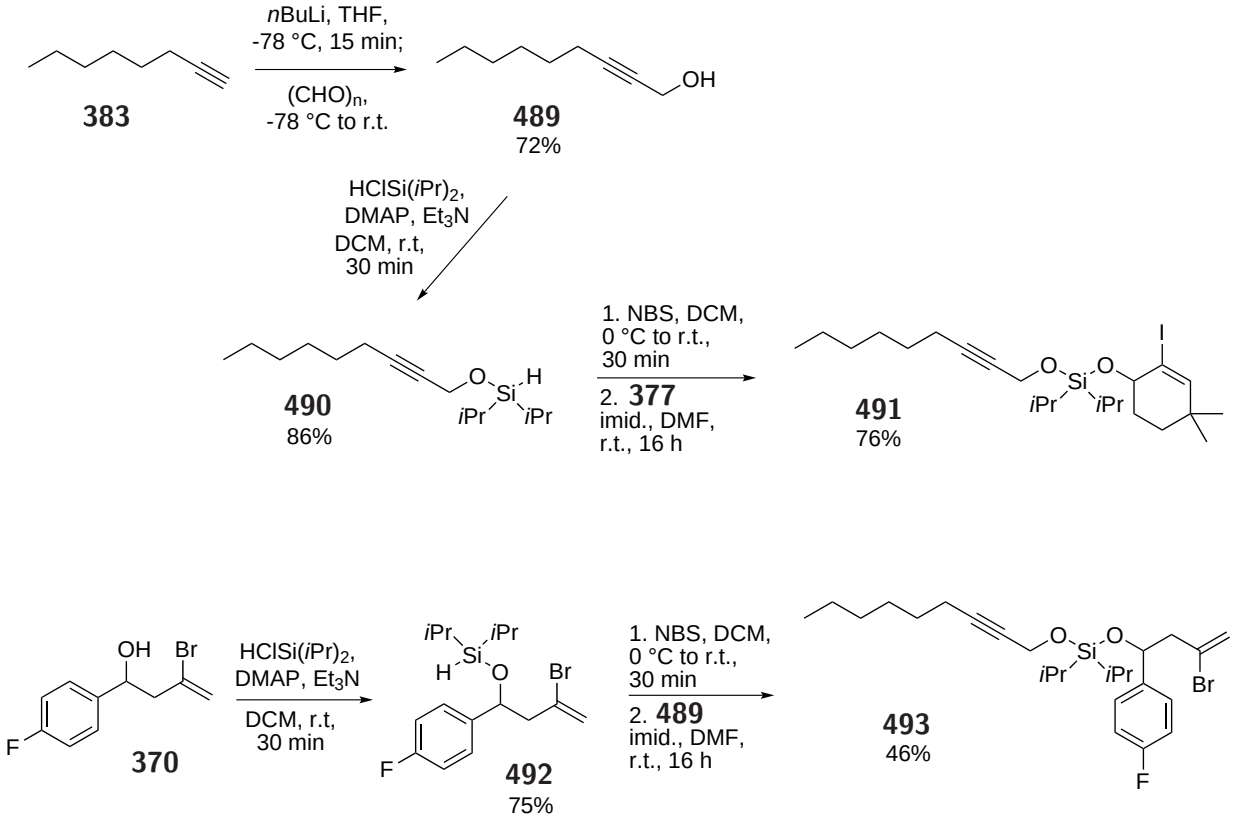
From phenylacetylene **386**, the desired internal alkyne starting material **483** could be readily synthesised in 99% yield *via* lithiation and methylation (Scheme 4.31). Based on extensive literature precedent,[242–247] compound **483** was subjected to a wide range of lithiation / silylation conditions, but all attempts at synthesising the desired propargyl silane **484** were found to be unsuccessful.

Undeterred, we proposed that compound **484** could be approached *via* bromo-lithium exchange methodology, and thus a suitable route to propargyl bromide **486** was devised. Phenylacetylene **386** was again lithiated, and then treated with paraformaldehyde to afford the propargyl alcohol **485** in a 76% yield. Bromination of this primary alcohol afforded the desired precursor **486**, but once again the propargyl silane **484** could not be approached under a wide variety of conditions. Given the disappointing outcome of these silylation reactions, further attempts at synthesising the tethered substrates **481** were ultimately abandoned, and efforts were instead focused upon exploring alternative tethering motifs.

The disiloxane-tethered species **487** were thought to be viable substrates for these cyclisations, potentially affording the eight-membered ring diene products **488** under palladium-mediated conditions (Scheme 4.32). There is extensive literature precedent describing the removal of a disiloxane tether, and thus it was hoped that although the further functionalisation options for this species **488** are limited, the tether itself could at least be cleaved.



Scheme 4.32 Proposed Cyclisation of Disiloxane Tethered Substrates

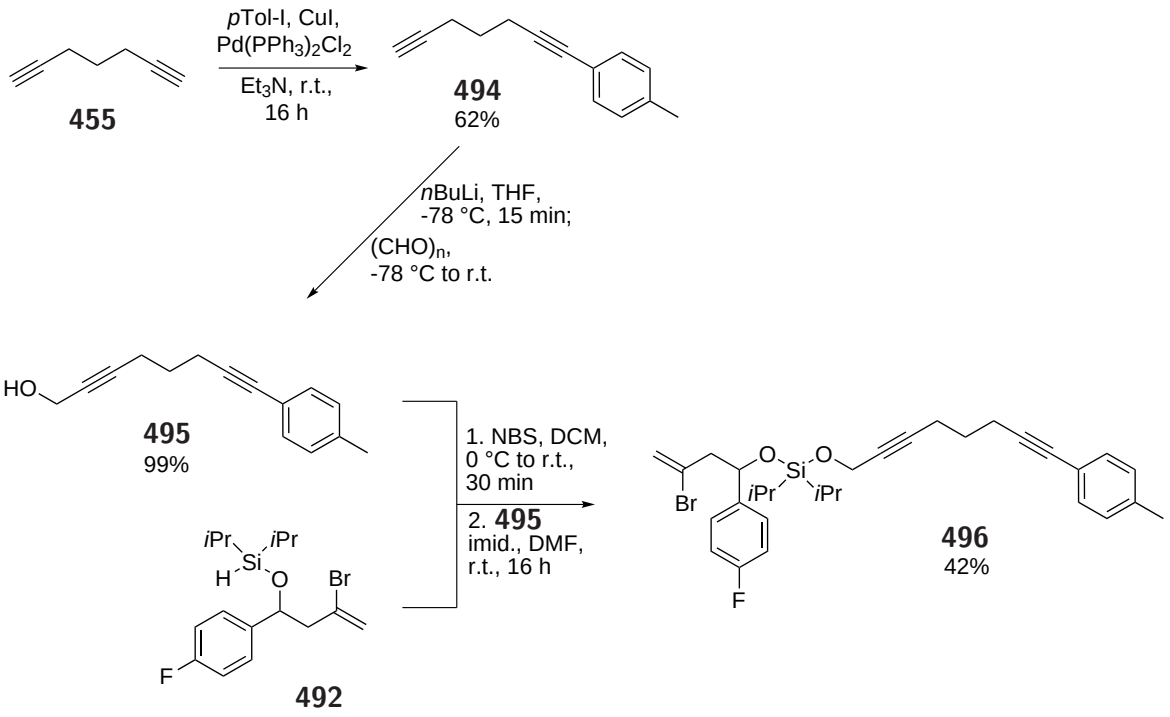


Scheme 4.33 Synthesis of Disiloxane Tethers

Our synthesis of the desired disiloxane substrates **487** initiated with the synthesis of propargyl alcohol **489** in a 72% yield. Silylation of this species afforded siloxane **490** in a 86% yield, from which coupling with alcohol **377** could take place to synthesise disiloxane substrate **491** in a pleasing 76% yield. Additionally, propargyl alcohol **489** could also be coupled with alcohol **370** *via* *N*-bromosuccinimide activation of siloxane **492**, affording a further disiloxane substrate **493** in a 46% yield.

However, initial attempts at cyclising these substrates under palladium-mediated cascade conditions resulted solely in tether cleavage. It is thought that this disappointing result is due to the

enhanced sensitivity of the disiloxane motif towards basic conditions, with even the bulky *iso*-propyl groups on the silicon centre unable to prevent decomposition of the tether. Once again, the failure of these substrates to cyclise under the reaction conditions emphasises the delicate balance between substrate stability and further functionalisation ability - a balance that has thus far been unachievable for these silicon-tethered reactions.



Scheme 4.34 Synthesis of Disiloxane-Tethered Diyne Substrates

Our final efforts in this area focused on the synthesis of the corresponding disiloxane-tethered diyne substrates. It was proposed that these delicate di*iso*-propylsilyl linkers might exhibit greater stability under the milder oligocyclisation conditions, and thus a route towards diyne **496** was devised. From 1,6-heptadiyne **455**, mono-Sonogashira coupling afforded diyne **494** in 62% (although some contamination from the bis-coupled byproduct was apparent). Subsequent lithiation and trapping with paraformaldehyde yielded propargyl alcohol **495**, which was then coupled with silane **492** *via* *N*-bromosuccinimide activation, affording disiloxane **496** in 42% yield.

Despite the considerably milder nature of the oligocyclisation reaction conditions, we were disappointed to note that tether cleavage was once again observed. With this result in hand, time constraints dictated that these investigations be abandoned, and our attentions were turned towards more fruitful areas of silicon-tethered research.

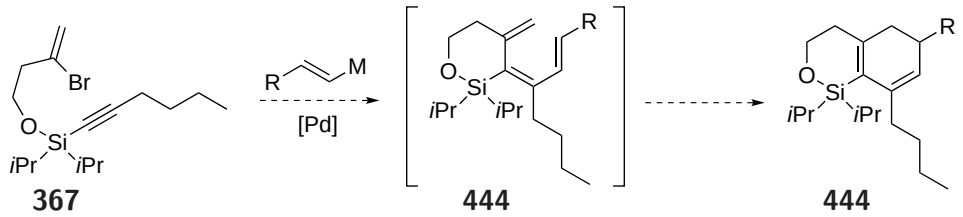
4.11. Conclusion

Following extensive work on the optimisation of both reaction conditions and substrates, three silicon-tethered palladium-mediated cyclisation processes have been achieved. Although only one product was obtained during our investigations into a reductive cyclisation transformation, valuable mechanistic understanding was gained through a range of deuterium-transfer experiments. A small range of highly substituted tandem Suzuki and oligocyclisation products were also obtained, although further work showed that functionalisation of the synthesised compounds was highly challenging. Despite this disappointing finale to our methodology, we have demonstrated that silicon-tethering strategies can be applied to a range of palladium-catalysed cascade processes, allowing considerable molecular complexity to be gained in a single step.

5. Silicon-Tethering in Platinum-Mediated Chemistry

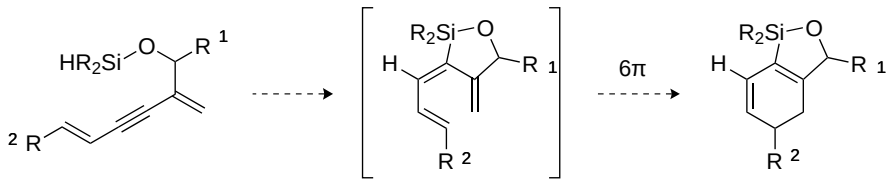
5.1. Overview

During our previous investigations into the application of silicon-tethering methodology to palladium-mediated processes, we were disappointed to note that a tandem Suzuki coupling could not be achieved with a vinylic metal reagent (Scheme 5.1).



Scheme 5.1 Proposed Tandem Heck / Suzuki / Electrocyclisation Methodology

Instead, we proposed that a similar triene intermediate **497** could be approached *via* the *syn*-hydrosilylation of dienyne **498**, allowing a silicon-tethered electrocyclisation to take place (Scheme 5.2). This route has several benefits over the palladium-catalysed cascade - in particular, a terminal alkyne cannot be employed in this methodology, and thus a substituent will always be positioned adjacent to the silicon centre in the product diene **445**. As previously mentioned in Chapter 4, such a substituent is likely to hinder further functionalisation of the silicon centre, and represents a significant limitation of this palladium-catalysed process.



498 **497** **499**

Scheme 5.2 Proposed Hydrosilylation / Electrocyclisation Cascade

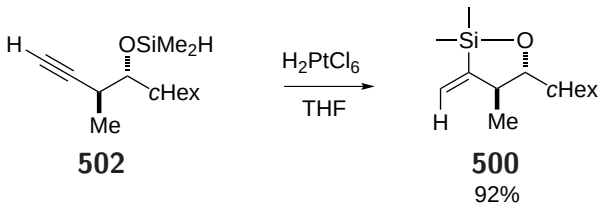
In contrast, our proposed hydrosilylation / electrocyclisation cascade would afford a product that does not possess a substituent adjacent to the silicon centre (**499**). Therefore, it is likely that such a species would be considerably more amenable towards further functionalisation, thus greatly enhancing the synthetic utility of such a compound. Furthermore, it is likely that the stability of diene **499** would be increased over that of diene **445** due to the reduced allylic strain that this product experiences.

5.2. Introduction

As described in the introductory chapter of this dissertation, considerable efforts have been made to enhance the synthetic utility of intramolecular hydrosilylation methodology. The Marshall and Denmark groups have been particularly active in the area of *syn*-hydrosilylation (Scheme 5.3),[62–64,75] and we proposed to utilise this methodology in accessing the desired electrocyclisation precursors **497**. It is interesting to note that two different catalysts were employed by the two groups in their synthesis of the exocyclic vinyl siloxanes **500** and **501**. The acidic Speier's catalyst, H_2PtCl_6, was used by Marshall and co-workers to effect *syn*-hydrosilylation of silane **502**. In contrast, Denmark and Pan employed Karstedt's catalyst, Pt(DVDS) (**133**), to achieve their desired hydrosilylation of unstable intermediate **503**.[248] In this instance, the final siloxane product **501** was not isolated, and instead subjected directly to palladium-catalysed Hiyama cross-coupling conditions.

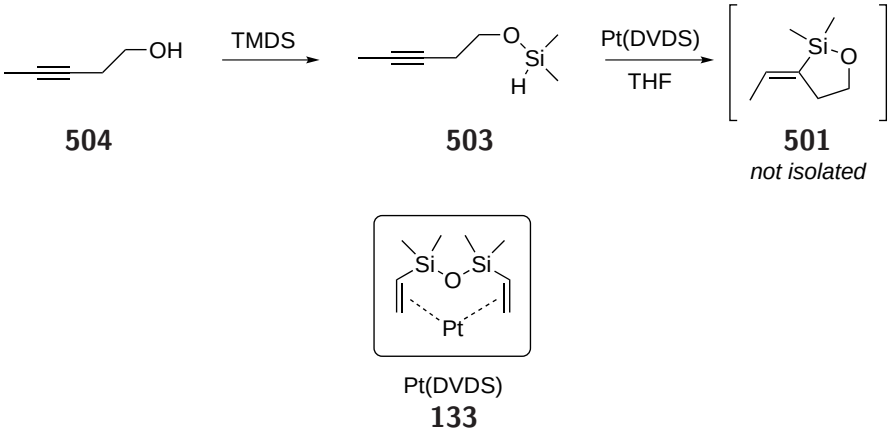
Despite the considerable amount of work conducted in the field of hydrosilylation methodology,[249] enyne substrates have seen very little application thus far. The Trost group reported a single example of enyne hydrosilylation in 2005, where diene **505** was synthesised in a 63% yield *via* the intermolecular *anti*-hydrosilylation of conjugated precursor **506** (Scheme 5.4).[250] The cationic ruthenium catalyst **507** was employed to achieve this transformation.

Marshall (2001):



502 **500** 92%

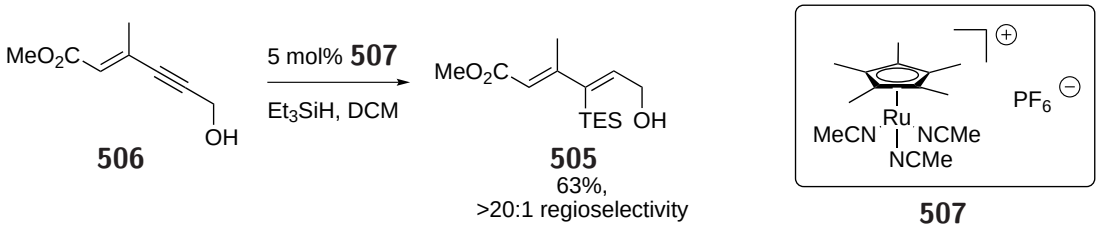
Denmark (2001):



504 **503** **501** *not isolated*

133

Scheme 5.3 Intramolecular *Syn*-Hydrosilylation Methodology

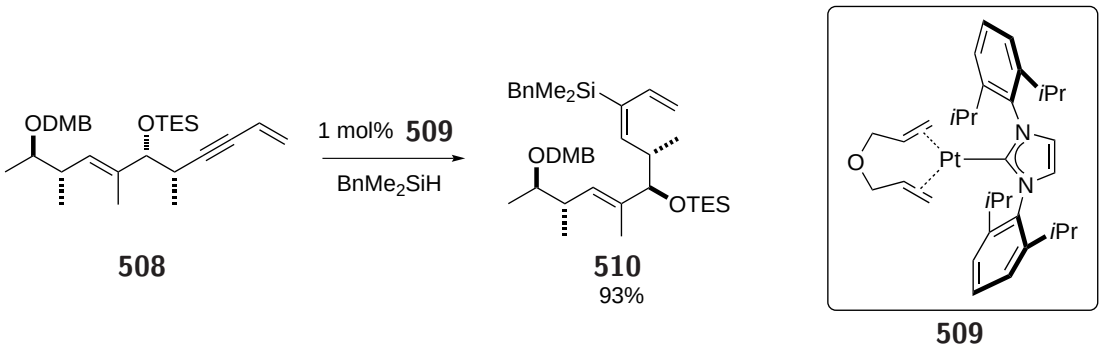


506 **505** 63%, >20:1 regioselectivity **507**

Scheme 5.4 Trost's *Anti*-Hydrosilylation of an Enyne Substrate

More recently, Fürstner and Gallenkamp reported a total synthesis of lactimidomycin, in which an intermolecular *syn*-hydrosilylation step was utilised in the stereoselective construction of a diene motif (Scheme 5.5).[251] Enyne **508** was treated with neat benzyldimethylsilane in the presence of modified Karstedt's catalyst **509**, affording the desired diene **510** in an impressive 93% yield. Fürstner and Gallenkamp specifically comment that only very limited application of hydrosilylation methodology to conjugated enyne substrates has been seen so far, and proposed that a more thorough study should be conducted following their promising initial results in this field.

Perhaps surprisingly, both examples of enyne hydrosilylation reported above were intermolecular in nature, with no examples of intramolecular enyne hydrosilylation having been reported in the



508 **510** 93% **509**

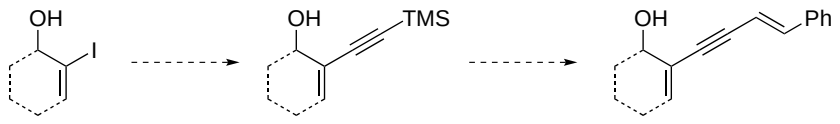
Scheme 5.5 Fürstner's Use of Enyne *Syn*-Hydrosilylation During the Total Synthesis of Lactimidomycin

literature to the best of our knowledge. Despite the very limited number of previous investigations into such methodology, we remained hopeful that our desired hydrosilylation of dienyne substrate **498** could be readily achieved, thus enabling the proposed 6π-electrocyclisation cascade to take place (Scheme 5.2).

5.3. Substrate Synthesis

5.3.1. Initial Attempts

Initially, a stepwise route to the desired dienyne substrates was envisaged, in which the highly conjugated ene-yne-ene system would be sequentially constructed *via* a series of Sonogashira reactions (Scheme 5.6). From the vinyl iodide precursors **511**, initial Sonogashira coupling with trimethylsilyl-acetylene would afford the enyne intermediate **512**. Finally, deprotection of the alkyne and subsequent Sonogashira coupling with an appropriate vinyl iodide or vinyl bromide would afford the dienyne **513** in three steps.

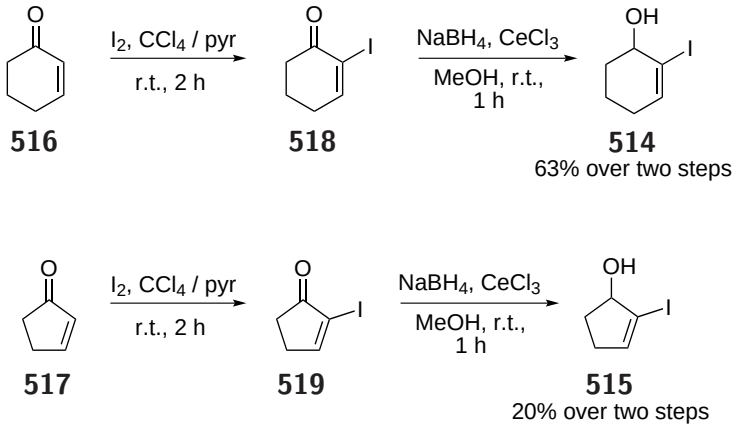


511 **512** **513**

Scheme 5.6 Proposed Route to Dienyne Precursors

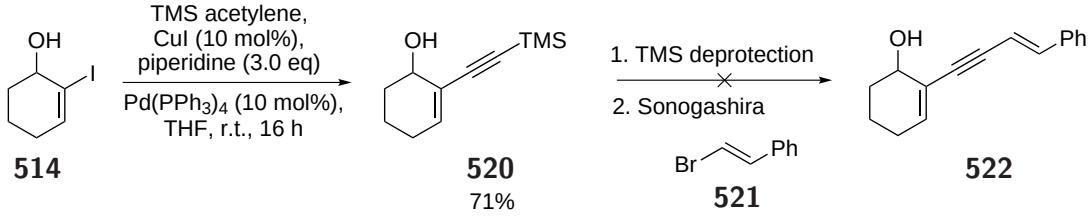
Two cyclic vinyl iodides, **514** and **515**, were proposed as appropriate building blocks on which the conjugated dienyne system could be constructed. From the commercially-available starting materials **516** and **517**, iodination afforded the intermediate vinyl iodides **518** and **519** (Scheme 5.7).

These compounds were then taken crude to the subsequent Luche reduction step,[234] affording the cyclohexene derivative **514** in a 63% yield, and the cyclopentene derivative **515** in a disappointing 20% yield.



Scheme 5.7 Synthesis of Vinyl Iodide Alcohols

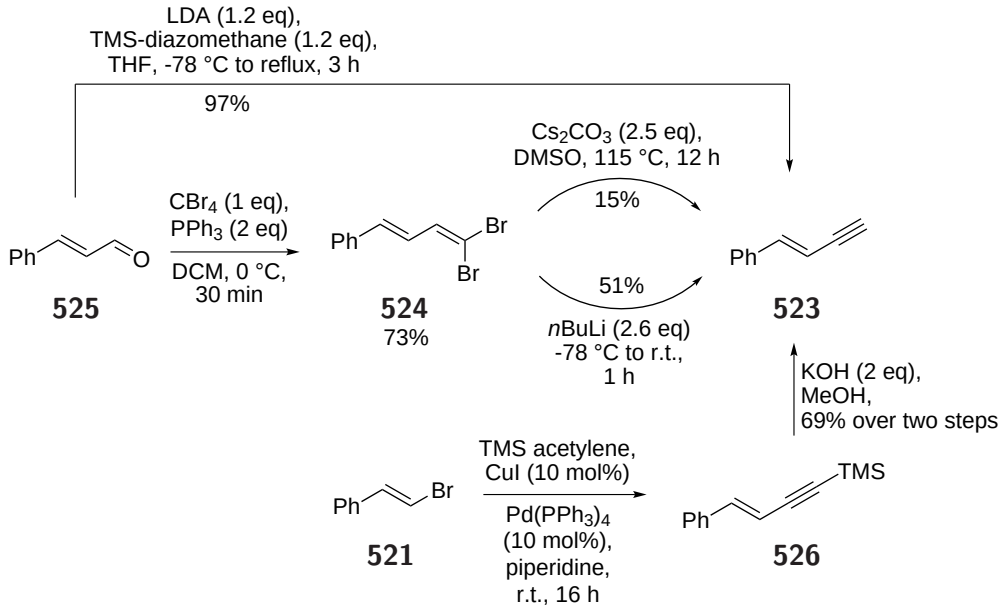
With these vinyl iodide substrates now in hand, our attentions were transferred to the construction of the conjugated dienyne system. After investigating a considerable range of conditions, it was found that the initial Sonogashira reaction could be successfully achieved at room temperature in the presence of stoichiometric quantities of piperidine in THF (Scheme 5.8, **514** → **520**). However, to our disappointment the subsequent deprotection and Sonogashira processes were found to be highly challenging. Although the intermediate terminal alkyne could be synthesised relatively cleanly, the subsequent coupling with vinyl bromide **521** could not be achieved, and thus the desired dienyne **522** remained elusive. Intriguingly, it should be noted that there is only limited literature precedent for the synthesis of such highly conjugated systems in the presence of an alcohol substituent.



Scheme 5.8 Failed Sequential Coupling Route

A change in synthetic strategy was thus proposed, whereby the vinyl iodide substrate **511** would now couple directly with an appropriate terminal enyne species in a more convergent fashion.

Enyne **523** was deemed to be a suitable coupling partner, and thus we set out to synthesise this species in an efficient fashion. Our initial attempt proceeded *via* vinyl dibromide **524**, which could be synthesised from *trans*-cinnamaldehyde **525** in a 73% yield (Scheme 5.9). According to the recently published work of Yang and co-workers,[252] formation of the desired terminal alkyne **523** could be achieved following prolonged heating of bromodiene **524** in the presence of DMSO and Cs_2CO_3. It should be noted that this process is somewhat reminiscent of our earlier work on palladium-catalysed silicon-tethered reductive cyclisation methodology.

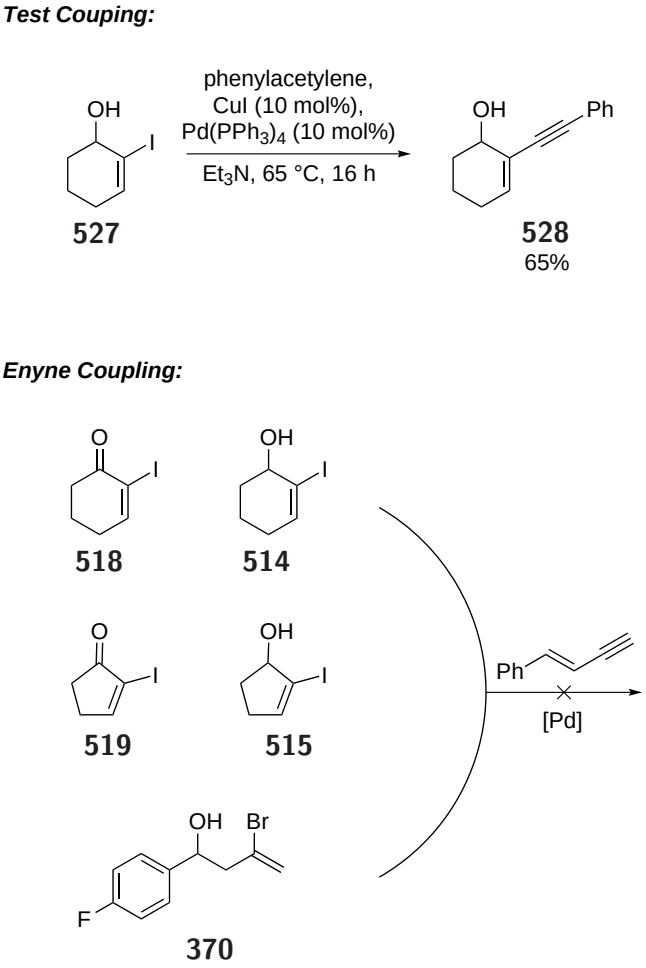


Scheme 5.9 Synthesis of Enyne Coupling Partner

In the event, enyne **523** was synthesised cleanly *via* this route, but in an unappealing 15% yield. Recourse to more traditional Corey-Fuchs methodology allowed enyne **523** to be approached in a more synthetically useful 51% yield.[253,254] However, this route resulted in considerable contamination of the desired product, and purification to appropriate levels of cleanliness proved to be challenging. A further pathway to enyne **523** was therefore sought, and so β-bromostyrene **521** was coupled with trimethylsilyl acetylene to afford the protected intermediate **527**. This species was then directly submitted to silyl alkyne deprotection conditions, affording enyne **523** cleanly in a 69% yield over the two steps described.

Finally, a fourth route to the enyne precursor **523** was proposed, in which synthesis of this species could be achieved in a single step from *trans*-cinnamaldehyde **525**. Under Colvin rearrangement

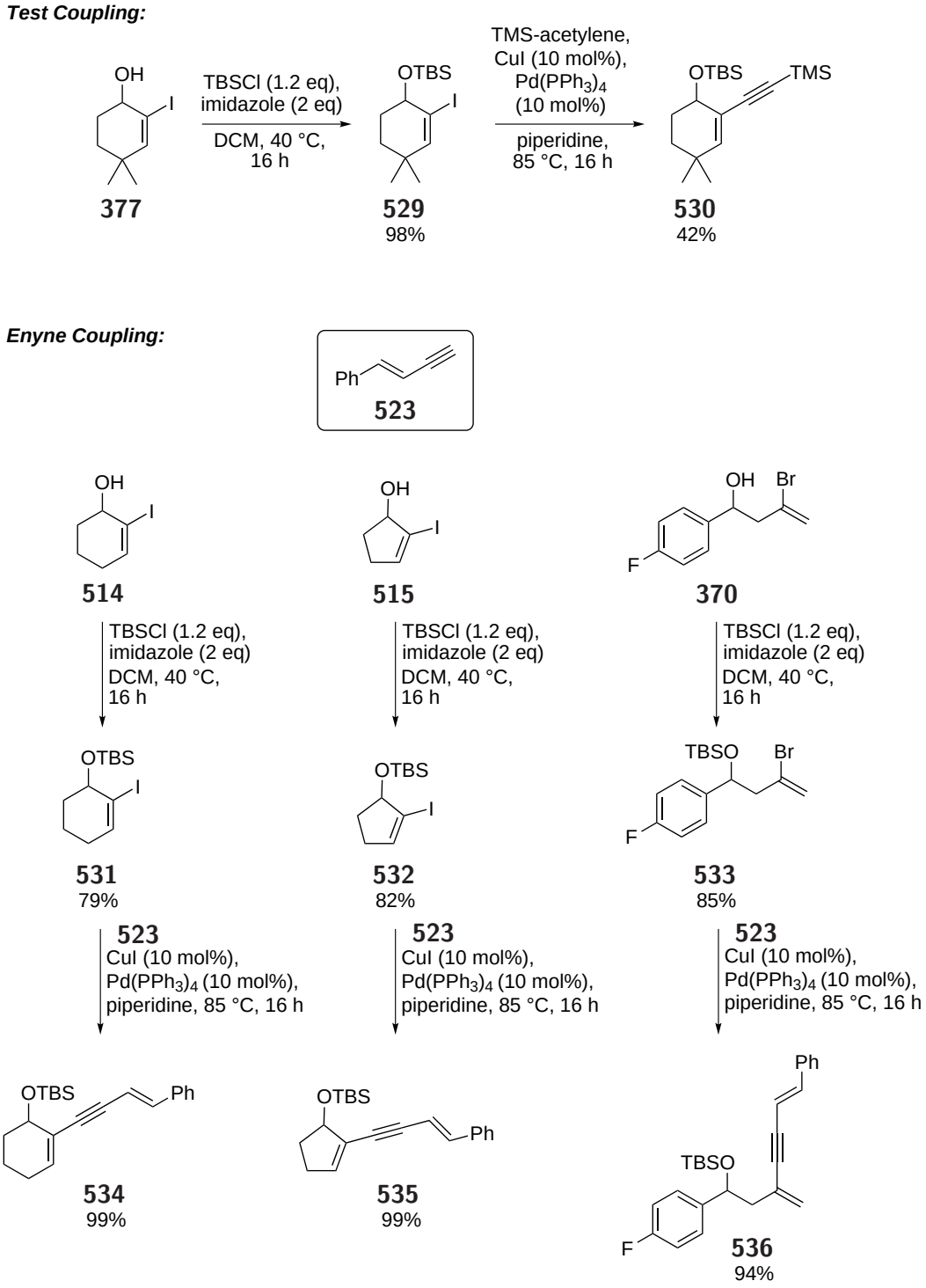
conditions,[255–257] the addition of lithiated trimethylsilyl diazomethane to aldehyde **525** proceeded smoothly, providing access to the enyne **523** relatively cleanly in an excellent 97% yield.



Scheme 5.10 Enyne Coupling Reactions

The stage was now set to attempt the coupling between enyne **523** and the vinyl iodide building blocks. A test reaction was successfully carried out between alcohol **514** and phenylacetylene, affording the conjugated product **528** in a 65% yield (Scheme 5.10). It should be noted that heating and prolonged reaction times were found to be necessary for this reaction to succeed, this factor perhaps being reflective of the potential coordination that could arise between the rigidly-positioned neighbouring alcohol group and the palladium centre following oxidative addition. However, despite the success of this test reaction, coupling with enyne **523** could not be achieved with vinyl iodides **518**, **514**, **519**, **515** or vinyl bromide **370**, and the starting materials were returned on every occasion. Once again, this result may arise due to the coordinating ability of the neighbouring free alcohol functionality, coupled with the comparatively unreactive nature of the conjugated coupling

partner **523**. It should also be noted that competing enyne dimerisation was observed in some cases.



Scheme 5.11 Further Enyne Coupling Reactions

Given these disappointing results, we resolved that the free alcohol substituent should be protected before proceeding with the Sonogashira coupling process. A test reaction was again performed, in which TBS-protected vinyl iodide **529** was coupled with trimethylsilyl acetylene in a 42% yield

(Scheme 5.11). A considerable range of Sonogashira conditions were attempted before the desired level of reactivity was obtained for this process, with higher temperatures found to be necessary for this coupling reaction to take place. In this instance, it was proposed that the steric bulk of the TBS protecting group is likely to be the major contributing factor towards such harsh conditions being required. Pleasingly, enyne **523** readily underwent coupling with TBS-protected building blocks **531**, **532** and **533** to afford dienynes **534**, **535** and **536** in excellent yields.

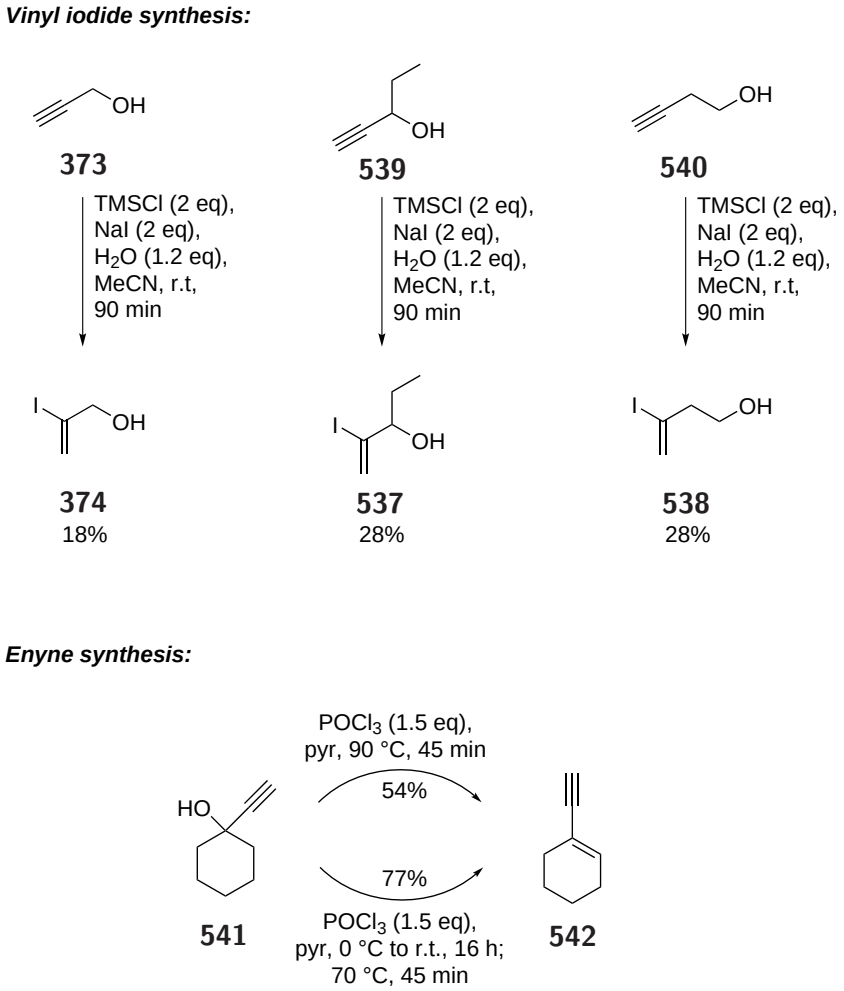
However, once again, problems with this route subsequently became apparent. It appeared that coupling could only be achieved with samples of enyne **523** synthesised *via* the low-yielding Cs_2CO_3 / DMSO route, perhaps due to the presence of trace contaminants in the other samples acting to inhibit this sensitive coupling procedure. Furthermore, despite the initial success in achieving the synthesis of dienyne **536** in 94% yield, this reaction showed very limited reproducibility. Finally, and most disappointingly, the TBS group could not be removed from the product dienynes **534** and **535** without concurrent substrate decomposition, despite numerous attempts.*

5.3.2. Modified Route

Given the considerable challenges experienced thus far in the synthesis of the required dienyne substrates, a new route to these conjugated species was sought. Inspired by a recent report from Rominger and co-workers,[258] the cyclic vinyl iodide substrates were abandoned thanks to the difficulties experienced while attempting to couple the free alcohol building blocks with enyne **523**. Instead, a small range of acyclic vinyl iodides **374**, **537** and **538** were synthesised from the corresponding alkynol species **373**, **539** and **540** respectively (Scheme 5.12). Although very poor yields were obtained for these transformations, perhaps due to difficulties in product isolation, all could be readily purified to the desired level of cleanliness *via* flash column chromatography.

It was proposed that the highly conjugated, electron-deficient nature of the phenyl-substituted enyne **523** was potentially detrimental towards the success of the Sonogashira coupling procedure, and thus a different enyne coupling partner was sought. Cyclohexene-based enyne **542** was thought to be an appropriate candidate, and could be approached *via* $POCl_3$ treatment of commercially-available ethynyl cyclohexanol **541**. Simple addition of the dehydrating agent, followed by heating

*A number of fluoride- and acid-mediated deprotection conditions were attempted.

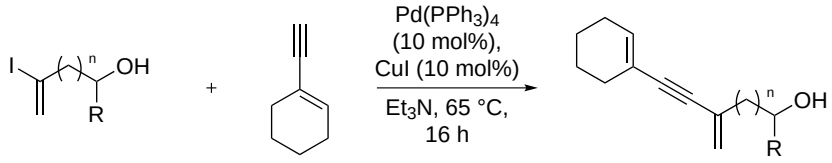


Scheme 5.12 Synthesis of Dienyne Building Blocks

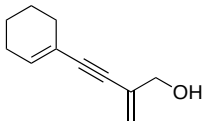
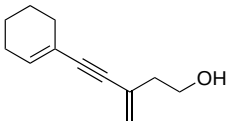
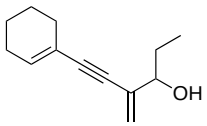
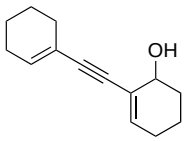
to 90 °C for 45 minutes afforded the desired product **542** in 54% yield. However, this protocol suffered from considerable reproducibility issues, and thus recourse to the methodology described by Alexakis and co-workers was found to be neccessary.[259] In this instance, $POCl_3$ was added slowly at 0 °C, before the reaction mixture was stirred overnight. Subsequent heating at 70 °C for 45 minutes afforded the desired enyne **542** in a pleasing 77% yield, with no further purification necessary.

The stage was now set for attempting the desired Sonogashira couplings between our small range of vinyl iodide substrates **543** and the enyne **542**. Pleasingly, in the presence of catalytic $Pd(PPh_3)_4$ and CuI, a variety of free alcohol dienyne species **544** could be readily synthesised (Table 5.1). Interestingly, the lowest yields for this coupling process were observed when the free alcohol substituent was placed directly adjacent to the vinyl iodide moiety (entries 1, 2 and 4), suggesting that the proximity of this coordinating functionality is indeed responsible for making this coupling

Table 5.1. Synthesis of Dienyne Substrates



543 **542** **544**

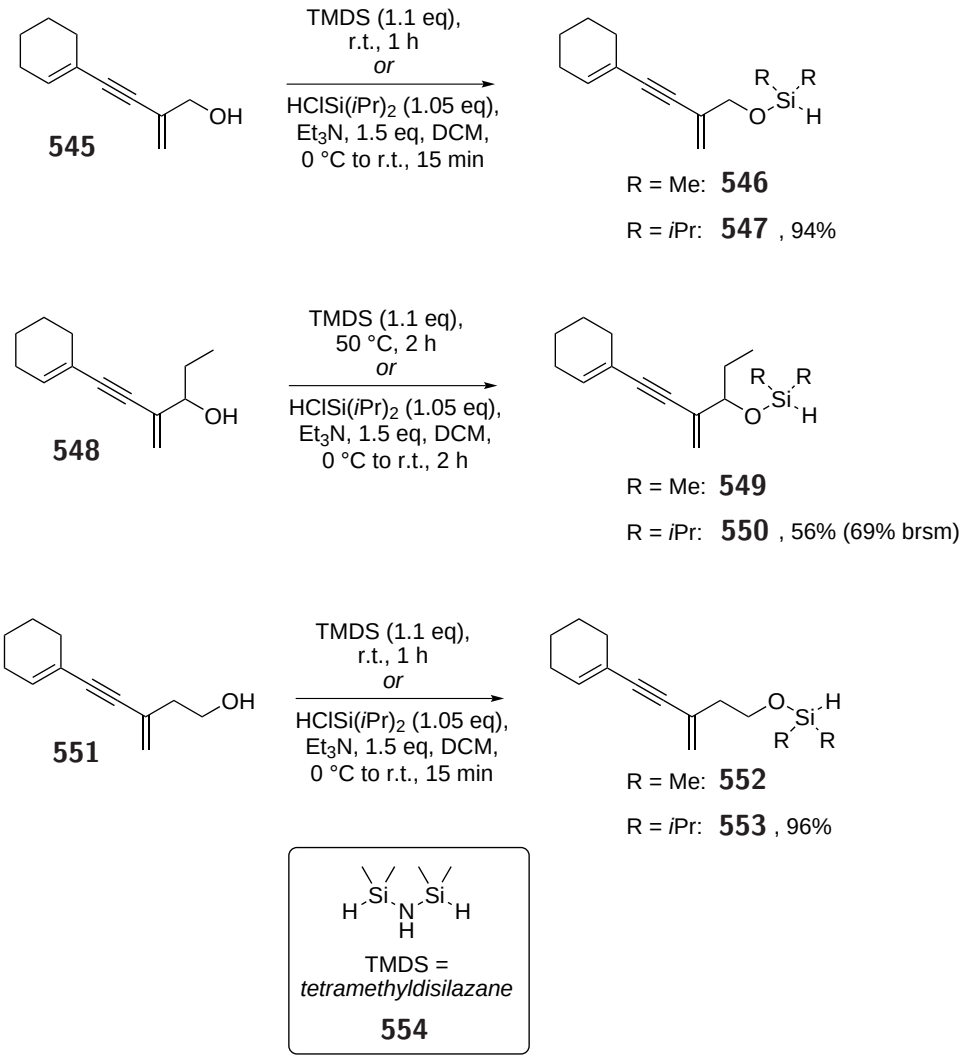
		Yield[a]			**Yield**[a]
1		49%	3		72%
2		44%	4		38%

[a]Isolated yield.

process more challenging. In contrast, when the alcohol substituent was located further away from the reactive centre (entry 3), a much more pleasing yield of 72% was obtained. It is interesting to note that this Sonogashira process could now be successfully achieved with a cyclic vinyl iodide substrate (entry 4), this observation supporting our previous hypothesis that phenyl-substituted enyne **523** was a poor coupling partner for this difficult transformation.

With the desired dienyne compounds now in hand, our attentions were turned towards the synthesis of the requisite silane hydrosilylation precursors. The dimethylsilane derivatives could be readily approached *via* the use of neat TMDS (tetramethyldisilazane, **554**), as described by Trost and Ball.[65] This methodology provided access to dimethyl silanes **546**, **549** and **552**, although these sensitive compounds were not directly isolated (Scheme 5.13). Of particular note is the synthetically attractive workup procedure for this reaction - the excess TMDS is simply removed under vacuum, and the nascent dimethyl silane may then be subjected directly to hydrosilylation conditions.

The more stable di*iso*-propyl silanes were also synthesised, in the hope that by employing such substrates the reaction pathway could be better understood through the isolation of stable intermediates. Some difficulties were initially experienced in the synthesis of silanes **547**, **550** and **553**, with



Scheme 5.13 Synthesis of Silane Substrates

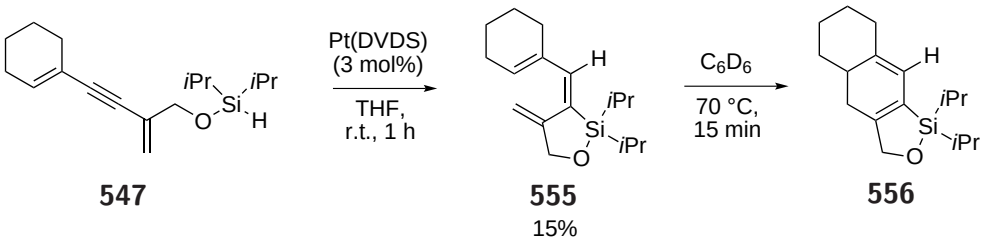
product degradation being observed during workup. A 2008 publication from Nelson and co-workers reported similar difficulties in silane synthesis,[260] and described a milder workup procedure developed in order to overcome these issues. This protocol was adopted for our substrates, and thus upon completion of the silylation reaction, the mixture was cooled to 0 °C before methanol was added to quench the excess chlorodi*iso*-propyl silane present. The resulting solution was then concentrated *in vacuo*, and filtered through Celite to afford the desired di*iso*-propyl silane compound in high yields. It is notable that the silylation reaction did not proceed to completion for the secondary alcohol substrate **548**, with the desired silane **550** being isolated in a 56% yield. Given the more hindered nature of the alcohol group in this substrate, this result is perhaps unsurprising, but unfortunately time constraints did not allow for further optimisation of this silylation to take place.

Thus, despite some initial difficulties, a small range of dienyne silanes could be readily synthesised *via* a synthetically attractive two-step pathway. Of key importance is the absence of any contaminating byproducts in our samples of these dienyne substrates, a factor that was thought to be crucial if the desired hydrosilylation / electrocyclisation cascades were to be successfully achieved. While the overall yields obtained for the vinyl iodide synthesis and subsequent Sonogashira coupling reactions were disappointingly low, it is hoped that further optimisation of these processes might allow the desired compounds to be synthesised in a more efficient manner.

5.4. Hydrosilylation and Electrocyclisation

5.4.1. First Attempts

To our immense gratification, when hydrosilylation of dienyne **547** was attempted on a small scale in the presence of Pt(DVDS), the desired triene **555** was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Scheme 5.14). Surprisingly, we were able to isolate this electrocyclisation intermediate in 15% yield, although some degradation during flash column chromatography was observed. The major byproduct arising during this reaction was noted to be the de-silylated free alcohol **545**.



Scheme 5.14 Initial Hydrosilylation Studies

With the delicate triene intermediate **555** now in hand, the stage was set to attempt the desired 6π-electrocyclisation reaction. The sample obtained was dissolved in d_6-benzene, and variable temperature NMR techniques were employed to monitor the progress of this transformation over a small range of temperatures. Fig. 5.1 illustrates the spectral changes observed during this NMR experiment, with the bottom spectra representing the triene **555** at room temperature. The ambient probe temperature was increased until a noticeable change in the spectra was observed, with this desired event taking place at 70 °C. The probe temperature was then maintained at this level until

the cyclisation reaction was deemed to be complete. The timescale for this process was noted to be approximately 15 minutes from when the first signs of reaction were observed at 70 °C.

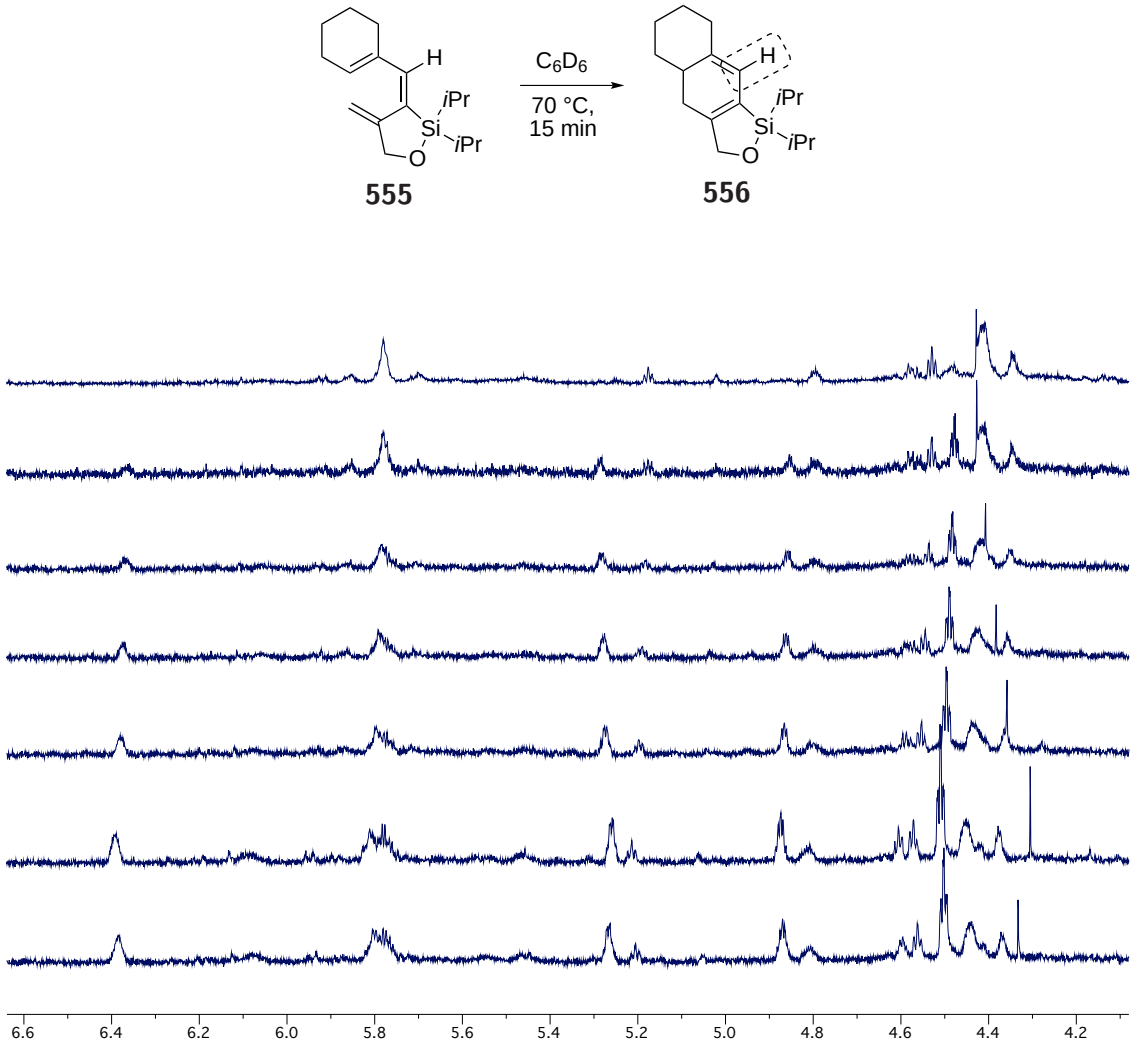
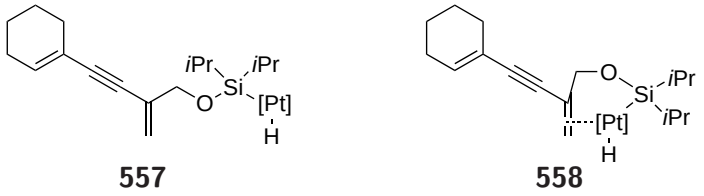


Fig. 5.1. Cyclisation of Triene Intermediate **555** to Diene **556**

Thus, the top spectra of Fig. 5.1 represents the desired cyclised diene **556**, with the single peak at 5.8 ppm corresponding to the sole alkenyl proton indicated. Although the initial triene sample shows considerable contamination from an unknown source, the proposed electrocyclisation process monitored by this experiment is undoubtedly taking place. This result was most pleasing, particularly in light of the considerable difficulties experienced during the synthesis of the dienyne substrates, and thus we sought to expand this methodology as rapidly as possible in the face of considerable time constraints.

5.4.2. Reproducibility Issues and Expansion of Methodology

To our disappointment, subsequent attempts at repeating the hydrosilylation of substrate **547** were met with failure, affording a mixture of starting material, hydrosilylation product **555** and de-silylated alcohol **545** regardless of the catalyst loading, reaction timescale or temperature. It should be noted that the initial catalyst loading of 3 mol% employed in Scheme 5.14 is approximately ten times higher than the loadings reported in previous work on the intramolecular hydrosilylation of alkynes[63] - despite this discrepancy, it was found that reducing the amount of catalyst present had little effect on the success of this process. Disappointingly, similar results were observed for the dimethylsilane derivative **546**, although no hydrosilylation was found to be taking place in this instance.

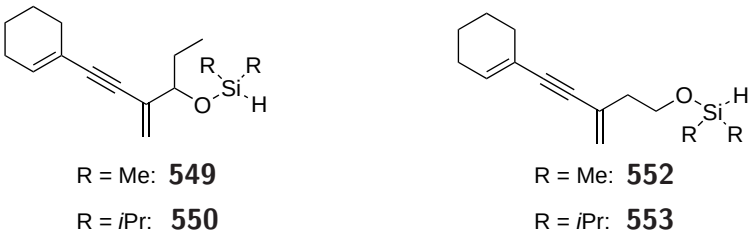


557 **558**

Fig. 5.2. Potential Hydrosilylation Intermediates

It was proposed that the potential hydrosilylation intermediates **557**, **558** and **559** were likely to be highly susceptible towards nucleophilic attack at the silicon centre, and thus desilylation (Fig. 5.2). Thus, considerable efforts were made to ensure that no water was present in the reaction mixture. Attempts were also made to limit the amount of dissolved oxygen present in the solvent, but unfortunately this increased stringency had little effect upon the outcome of the hydrosilylation process. In 2003, while investigating the hydrosilylation of sensitive dimethyldisiloxane substrates, Denmark and Pan reported a mild diethylamine-buffered protocol.[64] It was hoped that these buffered conditions would inhibit the levels of desilylation observed, but once again this change in reaction conditions had little positive effect.

Application of these hydrosilylation conditions to the substrates **549**, **550**, **552** and **553** also gave little joy. Interestingly, the levels of desilylation observed were greater for the di*iso*-propyl secondary-alcohol derived substrate **550**. In contrast, however, the longer chain substrates **552** and **553** showed very limited reactivity, with the starting materials being returned unchanged in the majority of cases. Speier's catalyst, H_2PtCl_6, was also employed as a hydrosilylation promoter, but



R = Me: **549**
R = *i*Pr: **550**

R = Me: **552**
R = *i*Pr: **553**

Fig. 5.3. Alternative Hydrosilylation Substrates

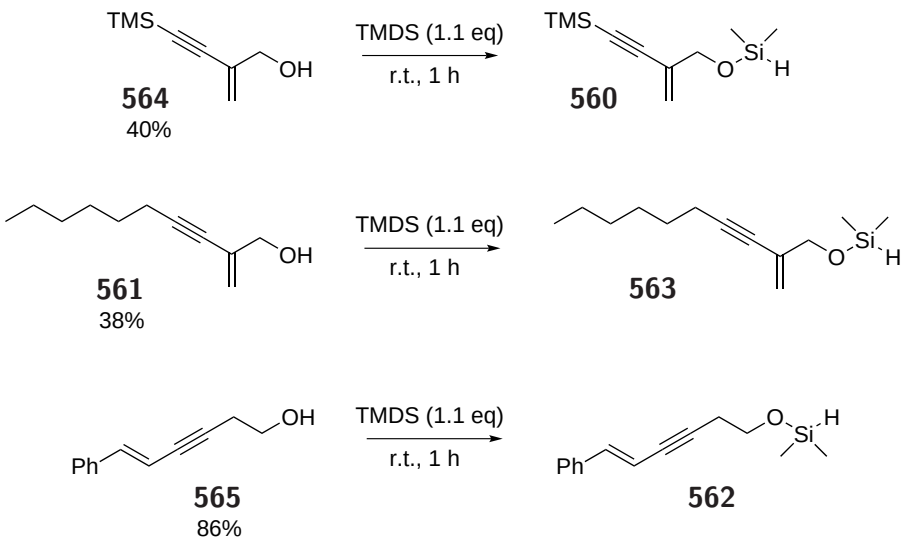
considerable degradation of the substrates was observed to take place. This result is likely to have arisen due to the sensitivity of the highly conjugated dienyne system toward such an acidic reagent.

5.4.3. Test Reaction Attempts

In light of the difficulties found in repeating the desired transformation, it was proposed that one of the alkene moieties may be responsible for severely limiting the reactivity of the alkyne functionality. This effect may arise as a result of alkene complexation to the platinum centre at some stage during the reaction pathway, thus rendering the catalyst inactive. If such deactivation occurs following metal insertion into the Si-H bond, it is quite likely that desilylation will result, given the extended periods of time for which this potentially sensitive intermediate (i.e. **558** or **559**) is now present in the reaction mixture.

In order to test this hypothesis, a small range of enyne substrates were synthesised *via* standard Sonogashira protocols (Scheme 5.15). These primary alcohols were then silylated, and the dimethylsilane products **560**, **561** and **562** subjected directly to hydrosilylation conditions. It was proposed that by removing each double bond systematically, more information could be obtained regarding which alkene moiety is likely to have the greater effect upon reactivity. It should be noted that two non-linear enynes **560** and **563** were synthesised, as it was proposed that the bulky nature of the trimethylsilyl substitutent in **560** might adversely affect the reactivity of this species.

Unfortunately, once again no productive hydrosilylation was observed for any of these substrates and the starting material was returned intact following each attempt. With such limited information available regarding the reactivity of these conjugated systems in the presence of a hydrosilylation catalyst, these test reactions were therefore abandoned, and an alternative strategy was sought.

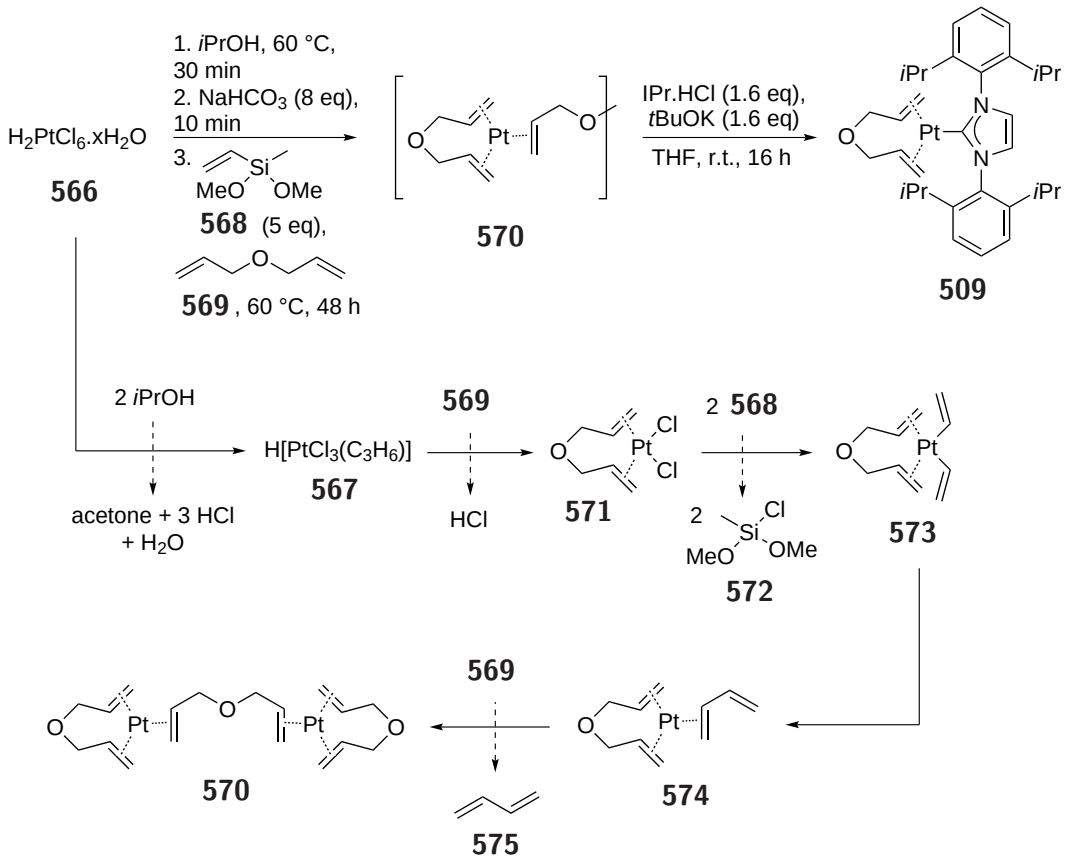


Scheme 5.15 Synthesis of Enyne Test Substrates

5.4.4. Alternative Catalyst Synthesis and Final Attempts

Given the difficulties experienced thus far, it was proposed that the *N*-heterocyclic carbene catalyst **509** previously utilised by Fürstner and Gallenkamp[251] should be considered as a potential catalytic species. The synthesis of platinum compound **509** was first described by Marko and co-workers,[261] who later reported that this catalyst displayed considerable reactivity and selectivity in alkyne hydrosilylation processes.[262] The Marko group described that Speier's catalyst **566** was initially heated in the presence of *iso*-propanol, resulting in the reduction of this platinum(IV) complex to the platinum(II) species **567** (an analogue of Zeise's salt, Scheme 5.16). Acetone, water and hydrogen chloride were concommitantly generated, and therefore $NaHCO_3$ was subsequently added to neutralise the acidic reaction media.

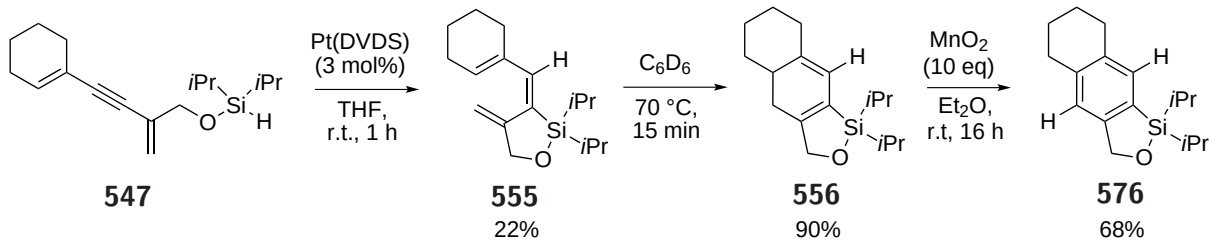
Dimethoxymethylvinyl silane **568** and diallyl ether **569** were then added, resulting in ligand exchange to form complex **571**. From this species, a double transmetallation with vinyl silane **568** was thought to take place, affording platinum(II) complex **573** and chlorosilane byproduct **572**. Finally, a reductive elimination step would afford platinum(0) intermediate **574**, from which an additional ligand exchange process was proposed to generate the bimetallic complex **570**. To conclude the synthesis of platinum(0) catalyst **509**, simple addition of NHC salt IPr·HCl and potassium *tert*-butoxide was found to afford this monometallic species, with a 70% yield being reported by Marko and co-workers.



Scheme 5.16 Synthesis of Hydrosilylation Catalyst **509**

Interestingly, the group commented that the rate-determining step of the catalyst activation process is known to be decoordination of the alkene-based ligands.[263–268] Given the considerable π-acceptor strength of the DVDS ligand, it was proposed that exchanging this vinylic species for a weaker π-acceptor, such as diallyl ether **569**, would thus enhance the reactivity of the resulting catalyst. This result was indeed observed, and therefore it was hoped that the synthesis of this reactive platinum(0) complex **509** might alleviate our current synthetic difficulties.

However, in the event the intermediate platinum species **570** could not be synthesised, despite numerous attempts and the literature precedents described above. With deadlines now looming, the decision was made to abandon the synthesis of this promising catalyst **509**, and the desired hydrosilylation was attempted one final time on a 170 mg scale (Scheme 5.17). Utilising Pt(DVDS) as the catalyst, we were surprised to observe that the desired reaction proceded cleanly, allowing the triene **555** to be isolated in a slightly improved 22% yield. Once again, it is thought that the instability of this conjugated species towards flash column chromatograpy is likely to be the primary cause behind the disappointing yield reported.



547 **555** 22% **556** 90% **576** 68%

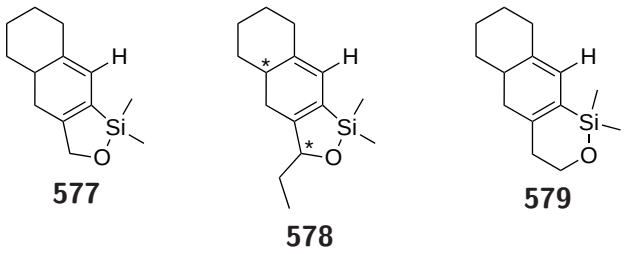
Scheme 5.17 Final Hydrosilylation / Electrocyclisation Attempt

Cyclisation of triene **555** in deuterated benzene afforded diene **556** in a 90% yield. Interestingly, this derivative was also found to degrade in the presence of silica gel, even when base-washing techniques were employed, and thus no further purification was attempted. It was proposed that the instability of this species may arise as a result of the potentially nucleophilic nature of the unsaturated system, and thus diene **556** was subsequently oxidised in the presence of manganese dioxide to afford the stable, highly-substituted arene **576** in a 68% yield. This aromatic species could be readily purified by flash column chromatography, and full characterisation confirmed that the compound obtained was indeed oxidised product **576**.

5.5. Conclusions and Future Work

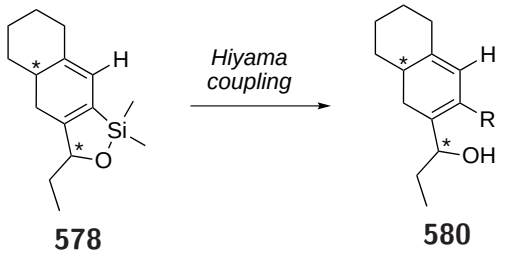
Thus, despite numerous synthetic challenges, the proposed hydrosilylation / electrocyclisation cascade was achieved, suggesting that future work might allow the utility of this methodology to be greatly enhanced. While time constraints prevented this process from being explored further, it was proposed that the dimethyl derivatives **577**, **578** and **579** would be the most attractive targets for this cascade reaction (Scheme 5.18). The presence of methyl, rather than *iso*-propyl substituents on the silicon atom would allow further functionalisation of these product dienes to occur more readily, thus reducing the likelihood that the silicon tether would remain a permanent fixture.

Most excitingly, by employing a secondary alcohol-derived substrate the possibility of diastereoselective induction is introduced. With such substrates, the diastereomeric ratio observed in the product diene **578** could be measured, thus providing interesting information about the level of conformational restriction offered by the silicon tether in the electrocyclisation transition state. A further Hiyama



Scheme 5.18 Proposed Future Targets

cross-coupling would provide access to the substituted decalin **580** (Scheme 5.19), allowing a range of bicyclic scaffolds to be readily synthesised *via* this route. Thus, this novel hydrosilylation cascade shows considerable potential for further development, and may provide access to a wide variety of synthetically useful products in a diastereoselective fashion.

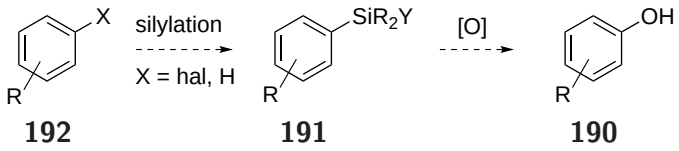


Scheme 5.19 Synthesis of Substituted Decalin Systems

6. Conclusions and Future Work

6.1. Aryl Silane Oxidation

In aiming to further enhance the synthetic utility of organosilicon chemistry, we have successfully developed an aryl silane oxidation, which allows phenolic compounds **190** to be readily accessed from the corresponding silicon-containing arenes **191** (Scheme 6.1). This methodology capitalises upon the 'latent functionality' that a silicon centre possesses, and thus our mild and functional group-tolerant process further expands the range of transformations available to a silicon-containing compound. The 'latent functionality' of silicon centres is particularly valuable when considering silicon-tethering methodology, as it allows the tethered reaction products to be further transformed into a wide variety of functionalised compounds.



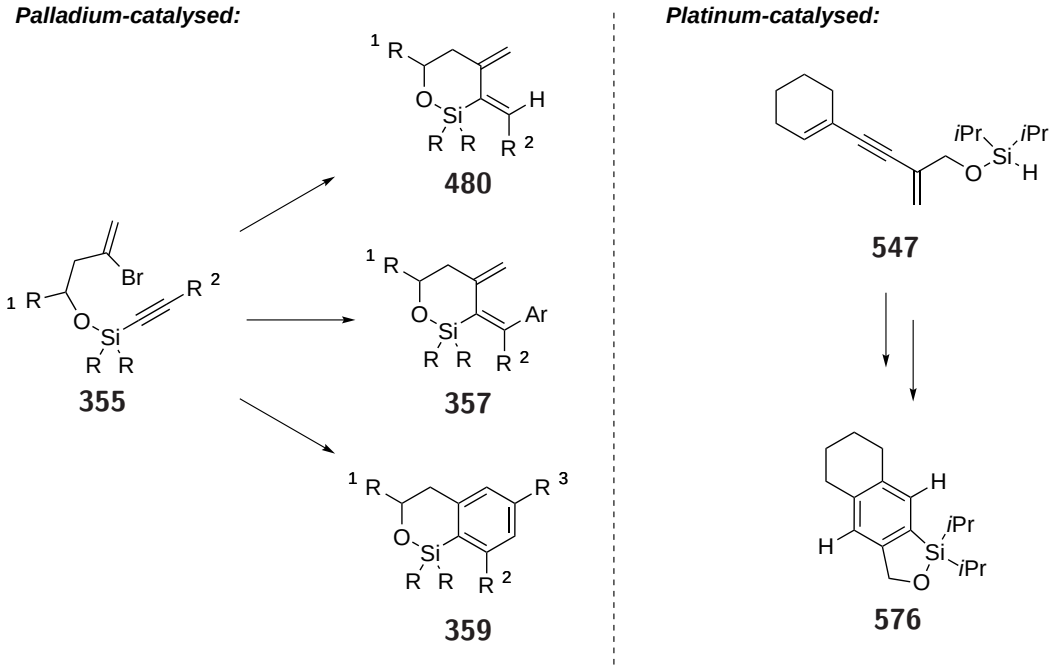
Scheme 6.1 Aryl Silane Oxidation Methodology

6.2. Silicon-Tethering Methodology

Following our work on the oxidation of aryl silanes, we hoped to build upon this methodology by developing a range of novel silicon-tethered reactions. While our attempts at applying this strategy to an iron-catalysed biaryl coupling were mostly unsuccessful, pleasing results were obtained with silicon-tethered palladium- and platinum-catalysed processes (Scheme 6.2).

During the development of these tethered metal-mediated reactions, a number of limitations have become clear with regards to the reactivity of such silicon-containing substrates. The first of these

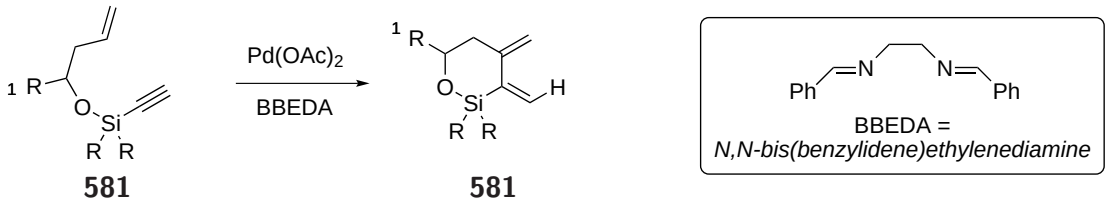
limitations is the somewhat surprising sensitivity of silyl alkyne substrates towards basic reaction media. This is best illustrated by the considerable difficulties experienced when attempting to conduct our palladium-catalysed reductive cyclisation (**355** → **480**) and tandem Suzuki coupling processes (**355** → **357**) with dimethylsilyl-, diethylsilyl- and diphenylsilyl-substituted silicon tethered substrates. In contrast, the oligocyclisation cascade (**355** → **359**) could be readily achieved with both dimethyl- and di*iso*-propyl-substituted substrates, thanks to the considerably milder reaction conditions under which this cyclisation takes place.



Scheme 6.2 Successful Silicon-Tethered Palladium- and Platinum-Catalysed Reactions

Given the instability of these substrates under basic conditions, Trost's palladium-catalysed cycloisomerisation methodology could be alternatively considered as a route to the desired silicon-tethered dienes (**581**, Scheme 6.3).[269] The reaction conditions employed in this instance are considerably milder than those utilised during our reductive cyclisation process (Chapter 4), and thus it is possible that this diene-forming transformation could be achieved with less bulky silicon substitutents. Furthermore, the presence of a bromoalkene moiety and a non-terminal alkyne functionality in the reaction substrate **581** are not necessary for this cycloisomerisation to be successfully achieved.

During our exploration of silicon-tethered palladium-catalysed transformations, it was noted that the presence of a substituent adjacent to the silicon centre in the cyclised products is likely to



Scheme 6.3 Potential Application of Trost's Cycloisomerisation Methodology

severely hinder the further functionalisation of the resulting siloxane compounds. The considerable allylic strain present in such species also proved to be a hindrance when attempting to cyclise shorter tethers, and thus we propose that further work in this field should focus on compounds that do not possess such a motif. This limitation was addressed by our more recent work on the development of a platinum-catalysed hydrosilylation / electrocyclisation cascade, and it is hoped that as a result this area of research will ultimately display greater synthetic utility than our palladium-mediated methodology.

7. Experimental

7.1. General Comments

^{1}H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ_H 7.26 ppm) or C_6D_6 (δ_H 7.15 ppm) at ambient probe temperatures on the following instruments: Bruker AVII 500 (500 MHz), Bruker DPX400 (400 MHz), Bruker DPX250 (250 MHz) and Bruker DPX200 (200 MHz) spectrometers. Data are presented as follows: chemical shift (in ppm on a δ scale relative to $\delta_{TMS} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sex = sextet, sep = septet, m = multiplet, br = broad, obs = obscured, *app* = apparent), coupling constant (J / Hz) and assignment. Assignments were determined either on the basis of unambiguous chemical shift or coupling pattern, COSY experiments, or by analogy to fully interpreted spectra for related compounds. ^{13}C spectra were recorded by broadband proton spin decoupling, at ambient probe temperatures on the following instruments: Bruker AVII 500 (125 MHz), Bruker AV400 (100 MHz) and Bruker DPX250 (62.9 MHz) using an internal deuterium lock for $CDCl_3$ (δ_C 77.0). Chemical shifts are given in ppm on a δ scale relative to $\delta_{TMS} = 0$.

Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. The sample was prepared as a thin film between NaCl plates or as a KBr disc. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}.

Low resolution mass spectra were recorded on a Waters LCT Premier EX mass spectrometer, using electron spray (ES^+, ES^-) techniques. High resolution mass spectra were recorded by the Departmental Mass Spectrometry Service, University of Oxford, using electron spray ionisation (ESI^+) and field ionisation (FI) techniques. The parent ion $[M]^+$, $[M+H]^+$ or $[M+Na]^+$ is quoted.

Melting points were obtained using a Reichert-Koffler block and are uncorrected.

Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualisation by ultraviolet light (254 nm) and potassium permanganate dip. Flash column chromatography was carried out on Merck Kieselgel 60 (230 - 400 mesh) under positive pressure using distilled solvents; the procedure includes the subsequent evaporation of solvents *in vacuo*.

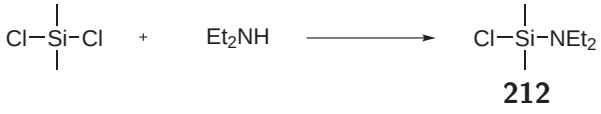
Reagents and solvents were purified by standard means.[270] Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were passed through an activated alumina column under an argon atmosphere; diethyl ether (Et_2O), methanol (MeOH), ethanol (EtOH), toluene (PhMe) and benzene (PhH) were distilled from calcium hydride and stored under an argon atmosphere. Triethylamine (Et_3N), pyridine (pyr) and *N,N'*-dimethylethylenediamine (DMEDA) were distilled from and stored over calcium hydride. All other chemicals were used as received, except where otherwise noted in the experimental text. All solutions of sodium bicarbonate ($NaHCO_3$), ammonium chloride (NH_4Cl), and sodium thiosulfate ($Na_2S_2O_3$) were aqueous and saturated. The term 'brine' is used to describe a saturated aqueous solution of sodium chloride (NaCl).

All experiments were performed under anhydrous conditions under an atmosphere of argon, except where stated, using oven-dried apparatus and employing standard techniques for handling air-sensitive materials. Unless stated otherwise, reactions were performed at room temperature (r.t.).

7.2. Aryl Silane Oxidation - New Routes to Hydroxylated Aromatics

7.2.1. Preparation of Reagents

1-Chloro-N,N-diethyl-1,1-dimethylsilanamine (212)[135]



212

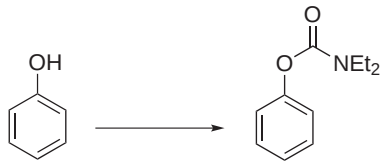
To a stirred solution of dichlorodimethylsilane (30 mL, 249 mmol, 1.0 eq) and Et_3N (38.1 mL, 274 mmol, 1.1 eq) in THF (30 mL) at 0 °C was added distilled Et_2NH (25.7 mL, 249 mmol, 1.0

eq) in THF (30 mL) over a period of 2 h. Following addition of a further 40 mL of THF, the resulting reaction mixture was left to stir at r.t. overnight. Subsequent dilution with pentane (50 mL), filtration over celite, and concentration *in vacuo* yielded the crude product, which was purified by vacuum distillation to afford aminosilane **212** (20.6 g, 124 mmol, 50%) as a colourless liquid; **bp** 84 °C, 110 mbar (lit.[135] bp 84 - 87 °C, 90 mmHg); ^{1}**H NMR** (400 MHz, C_6D_6) δ_H 2.69 (4H, q, J = 7.0 Hz, N(C$\underline{H}_2$CH_3)$_2$), 0.89 (6H, t, J = 7.0 Hz, N(CH_2C$\underline{H}_3$)$_2$), 0.32 (6H, s, $SiMe_2$).

This data is in agreement with that reported by Beignet *et al.*[271]

7.2.2. Preparation of Starting Materials

Phenyl diethylcarbamate (227)[272]



227

To a stirred solution of NaH (1.28 g, 31.9 mmol, 3.0 eq of a 60% dispersion in mineral oil) in THF (4 mL) was added a solution of phenol (1.00 g, 10.6 mmol, 1.0 eq) in THF (4 mL). The resulting reaction mixture was stirred for 2 h, then *N,N*-diethylcarbamoylchloride (2.7 mL, 21.3 mmol, 2.0 eq) in THF (4 mL) was added, and stirring continued for 8 h. The reaction was quenched with NH_4Cl solution (12 mL), the layers separated and the aqueous phase extracted with Et_2O (2 x 15 mL). The combined organic phases were concentrated *in vacuo* and the resulting crude mixture was purified by vacuum distillation to afford phenyl diethylcarbamate **227** (3.07 g, 15.9 mmol, 75%) as a colourless oil; **bp** 116 °C, 1 mmHg (lit. bp 107 - 108 °C, 1 mmHg); $\mathbf{R_f}$ 0.48 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 - 7.38 (5H, m, ArH), 3.39 (4H, q, J = 7.2 Hz, N(C$\underline{H}_2$CH_3)$_2$), 1.20 (6H, t, J = 7.2 Hz, N(CH_2C$\underline{H}_3$)$_2$).

This data is in agreement with that reported by Sibi *et al.*[273]

N,N-Diethylbenzamide (236)[274]

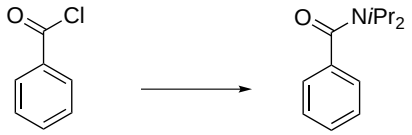


236

To a stirred solution of diethylamine (2.43 mL, 23.5 mmol, 1.1 eq) and Et_3N (3.72 mL, 26.7 mmol, 1.25 eq) in DCM (40 mL) at r.t. was slowly added benzoyl chloride (2.48 mL, 21.3 mmol, 1.0 eq) over a period of 10 min. The reaction mixture was stirred for 20 min, then diluted with DCM (20 mL) and washed with 1N HCl solution (60 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford benzamide **236** (3.74 g, 21.1 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.30 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.39-7.35 (5H, m, ArH), 3.55 (2H, br s, $NC\underline{H}_2CH_3$), 3.25 (2H, br s, $NC\underline{H}_2CH_3$), 1.25 (3H, br s, $NCH_2C\underline{H}_3$), 1.10 (3H, br s, $NCH_2C\underline{H}_3$).

This data is in agreement with that reported by Hans *et al.*[275]

N,N-Diisopropylbenzamide (229)[276]



229

To a stirred solution of di*iso*-propylamine (1.10 mL, 7.83 mmol, 1.1 eq) and Et_3N (1.24 mL, 8.89 mmol, 1.25 eq) in DCM (14 mL) at r.t. was slowly added benzoyl chloride (0.83 mL, 7.11 mmol, 1.0 eq) over a period of 10 min. The reaction mixture was stirred for 20 min, then diluted with DCM (7 mL) and washed with 1N HCl solution (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50 % Et_2O / P.E. 40 - 60) to afford benzamide **229** (1.39 g, 6.75 mmol, 95 %) as a white solid; mp 63.8 − 65.5 °C; $\mathbf{R_f}$ 0.29 (50 % Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.36 (3H, m, ArH), 7.32-7.30 (2H, m, ArH), 3.84 (1H, br s, $NC\underline{H}(CH_3)_2$), 3.54

(1H, br s, NC<u>H</u>$(CH_3)_2$), 1.53 (6H, br s, NCH$(C\underline{H}_3)_2$), 1.16 (6H, br s, NCH$(C\underline{H}_3)_2$).

This data is in accordance with that reported by Huckin et al.[277]

(3-Bromophenoxy)(tert-butyl)dimethylsilane (582)

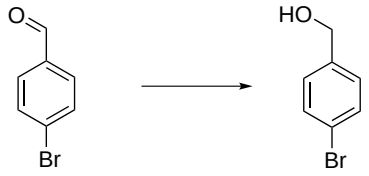


583 **582**

To a stirred solution of 3-bromophenol **583** (500 mg, 2.89 mmol, 1.0 eq) and imidazole (492 mg, 7.23 mmol, 2.5 eq) in DCM (7 mL) at 0 °C was added TBSCl (523 mg, 3.47 mmol, 1.2 eq) following the dissolution of imidazole. The reaction mixture was subsequently stirred at r.t. for 30 min, then quenched with NH_4Cl solution (7 mL), the phases were separated, and the aqueous phase was extracted with DCM (2 x 7 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded aryl TBS ether **582** (744 mg, 2.59 mmol, 90%) as a colourless oil; $\mathbf{R}_f$ 0.65 (20% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.10-7.08 (2H, m, ArH), 7.03-7.01 (1H, m, ArH), 6.78-6.75 (1H, m, ArH), 0.98 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.20 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$).

This data is in agreement with that reported by Barrett *et al.*[278]

(4-Bromophenyl)methanol (584)



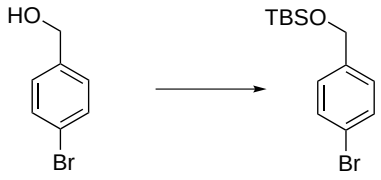
584

To a stirred solution of 4-bromobenzaldehyde (519 mg, 2.80 mmol, 1.0 eq) in EtOH (25 mL) was added $NaBH_4$ (159 mg, 4.20 mmol, 1.5 eq) at r.t. After stirring for 3 h, the reaction mixture was concentrated *in vacuo*, diluted with DCM (10 mL) and washed with water (10 mL). The organic

phase was dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude alcohol **584** as a white solid of sufficient purity to submit to the following step; $\mathbf{R_f}$ 0.43 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.50 (2H, d, J = 8.6 Hz, ArH), 7.26 (2H, d, J = 8.6 Hz), 4.67 (2H, d, J = 6.0 Hz, $ArCH_2OH$), 1.66 (1H, t, J = 6.0 Hz, OH).

This data is in agreement with that reported by Chen *et al.*[279]

(4-Bromobenzyloxy)(tert-butyl)dimethylsilane (585)

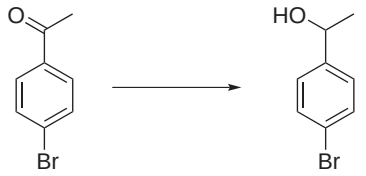


584 **585**

To a stirred solution of crude alcohol **584** and imidazole (477 mg, 7.00 mmol, 2.5 eq) in DCM (6 mL) at 0 °C was added TBSCl (506 mg, 3.36 mmol, 1.2 eq) following the dissolution of imidazole. The reaction was stirred at r.t. for 30 min, then quenched with NH_4Cl solution (6 mL). The phases were separated, the aqueous phase extracted with DCM (2 x 6 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded silylation product **585** (513 mg, 2.74 mmol, 98% over two steps) as a colourless oil; $\mathbf{R_f}$ 0.67 (20% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.46 (2H, d, J = 8.5 Hz, ArH), 7.20 (2H, d, J = 8.5 Hz), 4.69 (1H, s, $ArCH_2OTBS$), 0.94 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.10 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$).

This data is in agreement with that reported by Bennett *et al.*[280]

1-(4-Bromophenyl)ethanol (586)

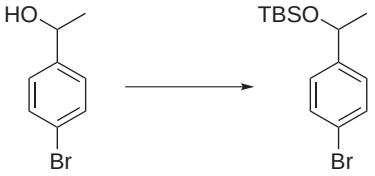


587 **586**

To a stirred solution of 4-bromoacetophenone **586** (0.50 g, 2.51 mmol, 1.0 eq) in EtOH (25 mL) was added $NaBH_4$ (105 mg, 2.76 mmol, 1.1 eq) at r.t. After stirring for 3 h, the reaction mixture was concentrated *in vacuo*, diluted with DCM (10 mL) and washed with water (10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude alcohol **586** as a yellow solid of sufficient purity to submit to the following step; $\mathbf{R_f}$ 0.45 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 (2H, td, J = 1.9, 8.4 Hz, ArH), 7.25 (2H, td, J = 1.9, 8.4 Hz), 4.90 - 4.84 (1H, m, ArC<u>H</u>(OH)CH_3), 1.80 (1H, d, J = 3.7 Hz, OH), 1.47 (3H, d, J = 6.5 Hz, ArCH(OH)C<u>H</u>$_3$).

This data is in agreement with that reported by Chen *et al.*[281]

(1-(4-Bromophenyl)ethoxy)(tert-butyl)dimethylsilane (588)

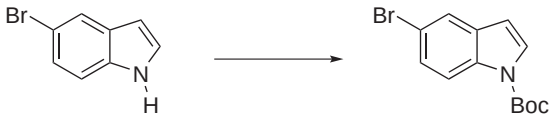


586 **588**

To a stirred solution of crude alcohol **586** and imidazole (0.43 g, 6.28 mmol, 2.5 eq) in DCM (6 mL) at 0 °C was added TBSCl (0.46 g, 3.01 mmol, 1.2 eq) following the dissolution of imidazole. The reaction was stirred at r.t. for 30 min, then quenched with NH_4Cl solution (6 mL). The phases were separated, the aqueous phase extracted with DCM (2 x 6 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded silylation product **588** (670 mg, 2.12 mmol, 85% over two steps) as a colourless oil; $\mathbf{R_f}$ 0.70 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2956, 2929, 2858,

1593, 1489, 1472, 1404, 1369, 1257, 1204, 1095, 1032, 1010, 958, 835, 777, 668; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 (2H, d, J = 8.5 Hz, ArH), 7.20 (2H, d, J = 8.5 Hz), 4.82 (1H, q, J = 6.4 Hz, ArC<u>H</u>(OTBS)CH_3), 1.37 (3H, d, J = 6.4 Hz, ArCH(OTBS)C<u>H</u>$_3$), 0.89 (9H, s, Si$(CH_3)_2$C(C<u>H</u>$_3)_3$), 0.05 (3H, s, Si(C<u>H</u>$_3)_2$C$(CH_3)_3$), 0.03 (3H, s, Si(C<u>H</u>$_3)_2$C$(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.0, 131.2, 127.0, 120.3, 70.3, 27.2, 25.8, 18.2, -4.83; **HRMS** (FI) calculated for $C_{14}H_{23}^{79}$BrOSi $[M]^+$ 314.0702, found 314.0705.

tert-Butyl 5-bromo-1H-indole-1-carboxylate (232)[282]

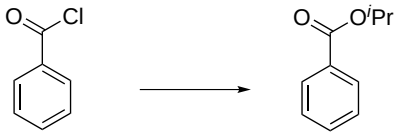


589 **232**

To a stirred solution of 5-bromoindole **589** (2.00 g, 10.2 mmol, 1.0 eq) and DMAP (24.9 mg, 0.20 mmol, 0.02 eq) in DCM (10 mL) was added di-*tert*-butyl dicarbonate (2.45 g, 11.2 mmol, 1.1 eq). The reaction mixture was left to stir at r.t. for 1 h, before quenching with 1N HCl solution (10 mL). The phases were separated, the aqueous phase extracted with DCM (2 x 10 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* to afford Boc-indole **232** (2.78 mg, 9.38 mmol, 92%) as a yellow solid; $\mathbf{R_f}$ 0.60 (50% Et_2O / P.E. 40 - 60); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.02 (1H, d, J = 8.9 Hz, ArH), 7.69 (1H, d, J = 1.7 Hz, ArH), 7.58 (1H, d, J = 3.7 Hz, ArH), 7.40 (1H, dd, J = 1.7, 8.9 Hz, ArH), 6.50 (1H, d, J = 3.7 Hz, ArH), 1.67 (9H, NC(O)OC$(CH_3)_3$).

This data is in agreement with that reported by Prieto *et al.*[283]

Isopropyl benzoate (238)



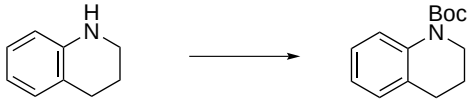
238

To a stirred solution of *i*-PrOH (0.985 mL, 10.7 mmol, 1.5 eq) in THF (12 mL) at 0 °C was added *n*BuLi (4.27 mL of a 2.5 M solution in hexanes, 10.7 mmol, 1.5 eq) dropwise. After stirring for

30 min, benzoyl chloride (0.83 mL, 1.00 g, 7.11 mmol, 1.0 eq) was added dropwise. The reaction mixture was then warmed to r.t. and stirred for 2 h before addition of aqueous NH_4Cl solution (10 mL), extraction with Et_2O (3 x 10 mL), drying of the combined organic phases ($MgSO_4$) and concentration *in vacuo* afforded ester **238** (1.11 g, 6.75 mmol, 95%) as a colourless oil; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 8.07-8.04 (2H, m, ArH), 7.57-7.53 (1H, m, ArH), 7.46-7.42 (2H, m, ArH), 5.27 (1H, sep, J = 6.3 Hz, OC$\underline{H}$(CH_3)$_2$), 1.38 (6H, d, J = 6.3 Hz, OCH(C$\underline{H}_3$)$_3$).

This data is in agreement with that reported by Hu *et al.*[284]

tert-Butyl 3,4-dihydroquinoline-1(2H)-carboxylate (239)



239

To a stirred solution of tetrahydroquinoline (0.94 mL, 1.00 g, 7.51 mmol, 1.0 eq) and DMAP (18.3 mg, 0.15 mmol, 0.02 eq) in DCM (5 mL) at r.t. was added di-*tert*-butyl dicarbonate (2.13 g, 9.76 mmol, 1.3 eq) before stirring for 45 min. The reaction mixture was quenched with 1N HCl solution (10 mL), extracted with DCM (3 x 10 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* before purification by flash column chromatography (50% Et_2O / P.E.) afforded protected quinoline **239** (1.47 g, 6.30 mmol, 84%) as a white solid; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.65 (1H, d, J = 8.3 Hz, ArH), 7.16-7.11 (1H, m, ArH), 7.09-7.07 (1H, m, ArH), 6.98 (1H, tt, J = 7.4, 1.3 Hz, ArH), 3.72 (2H, td, J = 6.1, 1.5 Hz, N(Boc)CH_2), 2.77 (2H, t, J = 6.6 Hz, N(Boc)CH_2C$\underline{H}_2$), 1.96-1.90 (2H, m, N(Boc)CH_2CH_2C$\underline{H}_2$), 1.53 (9H, s, *t*Bu).

This data is in agreement with that reported by Minatti *et al.*[285]

7.2.3. Aryl Isopropoxysilane Preparation

General Protocol for the Preparation of Bromo-Lithium Exchange Substrates

To a stirred solution of the aryl bromide (250 mg, 1.0 eq) in THF or Et_2O (5 mL) at −78 °C was added *n*- or *t*-BuLi (1.2 - 2.0 eq). $ClSiMe_2(NEt_2)$ **212** (1.4 eq) was subsequently added, and stirring continued for a further 2 h at − 78°C. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP

(1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (Et_2O / P.E. 40 - 60) to afford the silylation product (56 - 99%) as a colourless or pale yellow oil.

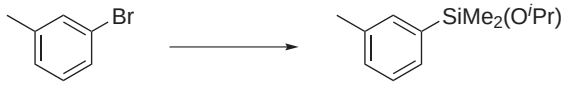
Isopropoxydimethyl(o-tolyl)silane (590)



591 **590**

Following the general bromo-lithium exchange protocol with 2-bromotoluene **591** (250 mg, 1.46 mmol, 1.0 eq) and *n*-BuLi (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **590** (302 mg, 1.45 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.68 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2971, 1450, 1381, 1368, 1252, 1130, 1025, 881, 832, 782, 747; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.53 (1H, dd, J = 1.7, 7.7 Hz, ArH), 7.29 (1H, dt, J = 1.4, 7.7 Hz, ArH), 7.19 - 7.16 (2H, m, ArH), 3.99 (1H, sep, J = 5.9 Hz, OC$\underline{H}$$(CH_3)_2$), 2.53 (3H, s, ArMe), 1.51 (6H, d, J = 5.9 Hz, OCH($C\underline{H}_3$)$_2$), 0.43 (6H, s, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 143.8, 136.7, 134.6, 129.8, 129.7, 124.7, 65.3, 25.6, 22.6, -0.1; **HRMS** (FI) calculated for $C_{12}H_{20}OSi$ $[M]^+$ 208.1283, found 208.1281.

Isopropoxydimethyl(m-tolyl)silane (592)

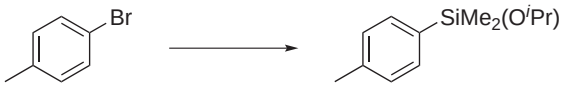


593 **592**

Following the general bromo-lithium exchange protocol with 3-bromotoluene **593** (250 mg, 1.46 mmol, 1.0 eq) and *n*-BuLi (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **592** (301 mg, 1.45 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.61 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2971, 1381, 1368, 1252, 1120, 1029, 883, 867, 810, 772; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.41 - 7.40 (2H, m, ArH), 7.28 (1H, t, J = 7.7 Hz, ArH), 7.22 (1H, d, J = 7.7 Hz, ArH), 4.00 (1H, sep, J = 5.9 Hz, OC$\underline{H}$$(CH_3)_2$), 2.38 (3H, s, ArMe), 1.15

(6H, d, J = 5.9 Hz, OCH(C$\underline{H}_3$)$_2$), 0.38 (6H, s, $SiMe_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 138.3, 136.9, 134.1, 130.5, 130.4, 127.7, 65.2, 25.7, 21.5, -1.1; **HRMS** (FI) calculated for $C_{12}H_{20}OSi$ $[M]^+$ 208.1283, found 208.1285.

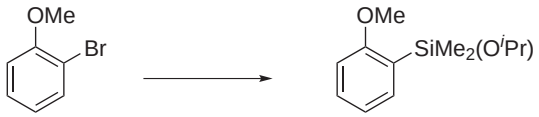
Isopropoxydimethyl(p-tolyl)silane (594)



595 **594**

Following the general bromo-lithium exchange protocol with 4-bromotoluene **595** (250 mg, 1.46 mmol, 1.0 eq) and n-BuLi (0.70 mL of a 2.5 M solution in hexanes, 1.75 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **594** (302 mg, 1.45 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.62 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2971, 1381, 1368, 1251, 1111, 1030, 882, 832, 782; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.50 (2H, d, J = 7.6 Hz, ArH), 7.21 (2H, d, J = 7.6 Hz, ArH), 4.00 (1H, sep, J = 6.0 Hz, OC$\underline{H}$(CH_3)$_2$), 2.37 (3H, s, ArMe), 1.14 (6H, d, J = 5.9 Hz, OCH(C$\underline{H}_3$)$_2$), 0.38 (6H, s, $SiMe_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 139.3, 136.3, 133.7, 128.5, 65.2, 25.5, 21.6, -1.1; **HRMS** (FI) calculated for $C_{12}H_{20}OSi$ $[M]^+$ 208.1283, found 208.1289.

Isopropoxy(2-methoxyphenyl)dimethylsilane (596)

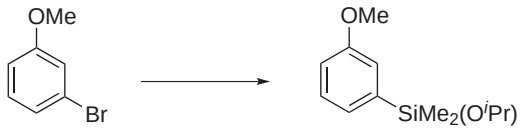


219 **596**

Following the general bromo-lithium exchange protocol with 2-bromoanisole **219** (250 mg, 1.34 mmol, 1.0 eq) and n-BuLi (0.64 mL of a 2.5 M solution in hexanes, 1.61 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **596** (283 mg, 1.26 mmol, 94%) as a colourless oil; $\mathbf{R_f}$ 0.66 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2970, 1590, 1572, 1463, 1429, 1381, 1367, 1238, 1174, 1130, 1085, 1027, 881, 833, 784, 758; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53 (1H, dd, J = 1.8, 7.4 Hz, ArH), 7.38 (1H, dd, J = 1.8, 8.0 Hz, ArH), 6.98 (1H, d, J = 7.4 Hz, ArH), 6.85 (1H, d, J = 8.0 Hz), 4.06 (1H, sep, J = 6.1 Hz, OC$\underline{H}$(CH_3)$_2$), 3.82 (3H, s, ArOMe), 1.17 (6H, d, J =

6.1 Hz, OCH(C$\underline{H}_3$)$_2$), 0.39 (6H, s, $SiMe_2$); ^{13}**C NMR** (62.9 MHz, $CDCl_3$) δ_C 164.1, 135.5, 131.2, 126.2, 120.3, 109.4, 65.1, 54.8, 25.7, -0.5; **HRMS** (ESI^+) calculated for $C_{12}H_{20}O_2SiNa$ $[M+Na]^+$ 247.1125, found 247.1125.

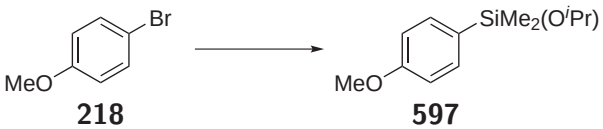
Isopropoxy(3-methoxyphenyl)dimethylsilane (242)



217 **242**

Following the general bromo-lithium exchange protocol with 3-bromoanisole **217** (250 mg, 1.34 mmol, 1.0 eq) and *t*-BuLi (2 mL of a 1.6 M solution in pentane, 2.68 mmol, 2.0 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **242** (297 mg, 1.32 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.60 (30% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2970, 1571, 1482, 1464, 1408, 1283, 1249, 1230, 1173, 1122, 1027, 860, 809, 778, 697; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (1H, t, J = 7.7 Hz, ArH), 7.19 - 7.14 (2H, m, ArH), 6.94 (1H, dd, J = 2.8, 8.2 Hz, ArH), 4.00 (1H, sep, J = 6.0 Hz, OC$\underline{H}$(CH_3)$_2$), 3.84 (3H, s, ArOMe), 1.15 (6H, d, J = 6.0 Hz, OCH(C$\underline{H}_3$)$_2$), 0.38 (6H, s, $SiMe_2$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 158.9, 140.2, 129.0, 125.8, 118.9, 114.7, 65.3, 55.1, 25.7, -1.1; **HRMS** (FI) calculated for $C_{12}H_{20}O_2Si$ $[M]^+$ 224.1233, found 224.1234.

Isopropoxy(4-methoxyphenyl)dimethylsilane (597)

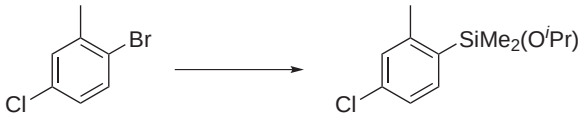


218 **597**

Following the general bromo-lithium exchange protocol with 4-bromoanisole **218** (250 mg, 1.34 mmol, 1.0 eq) and *t*-BuLi (2 mL of a 1.6 M solution in pentane, 2.68 mmol, 2.0 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **597** (292 mg, 1.30 mmol, 97%) as a colourless oil; $\mathbf{R_f}$ 0.56 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2971, 1596, 1504, 1464, 1381, 1368, 1311, 1279, 1249 ,1182, 1116, 1029, 881, 832, 783; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.53 (2H, d, J = 8.6 Hz, ArH), 6.93 (2H, d, J = 8.6 Hz, ArH), 3.97 (1H, sep, J = 6.1 Hz, OC$\underline{H}$(CH_3)$_2$), 3.83 (3H, s, ArOMe), 1.13

(6H, d, J = 6.1 Hz, OCH(C$\underline{H}_3$)$_2$), 0.37 (6H, s, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 160.7, 135.1, 129.5, 113.5, 65.1, 55.0, 25.7, -1.1; **HRMS** (FI) calculated for $C_{12}H_{20}O_2Si$ $[M]^+$ 224.1233, found 224.1230.

(4-Chloro-2-methylphenyl)(isopropoxy)dimethylsilane (598)



599 **598**

Following the general bromo-lithium exchange protocol with 1-bromo-4-chloro-2-methylbenzene **599** (250 mg, 1.22 mmol, 1.0 eq) and n-BuLi (0.58 mL of a 2.5 M solution in hexanes, 1.46 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **598** (267 mg, 1.10 mmol, 90%) as a colourless oil; $\mathbf{R}_f$ 0.63 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2972, 1581, 1551, 1470, 1381, 1255, 1172, 1124, 1026, 873, 811, 781; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.45 (1H, d, J = 7.9 Hz, ArH), 7.17 - 7.15 (2H, m, ArH), 3.99 (1H, sep, J = 6.0 Hz, OC$\underline{H}$(CH_3)$_2$), 2.50 (3H, s, ArMe), 1.15 (6H, d, J = 6.0 Hz, OCH(C$\underline{H}_3$)$_2$), 0.42 (6H, s, $SiMe_2$); ^{13}**C NMR** (500 MHz, $CDCl_3$) δ_C 145.7, 135.9, 135.7, 135.3, 129.8, 125.1, 65.4, 25.5, 22.5, -0.2; **HRMS** (FI) calculated for $C_{12}H_{19}OSi^{35}Cl$ $[M]^+$ 242.0894, found 242.0888.

(3-Fluorophenyl)(isopropoxy)dimethylsilane (600)

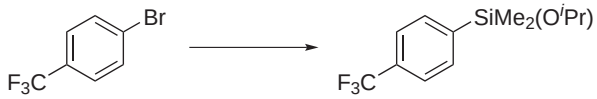


601 **600**

Following the general bromo-lithium exchange protocol with 1-bromo-3-fluorobenzene **601** (250 mg, 1.43 mmol, 1.0 eq) and n-BuLi (0.68 mL of a 2.5 M solution in hexanes, 1.72 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **600** (253 mg, 1.19 mmol, 83%) as a pale yellow oil; $\mathbf{R}_f$ 0.63 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2973, 1575, 1478, 1406, 1259, 1218, 1173, 1124, 1106, 1030, 886, 812, 781, 690; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.37 - 7.35 (2H, m, ArH), 7.27 (1H, dd, J = 2.7, 8.9 Hz, ArH), 7.09 - 7.05 (1H, m, ArH), 4.00 (1H, sep, J = 6.2 Hz, OC$\underline{H}$(CH_3)$_2$),

1.16 (6H, d, J = 6.2 Hz, OCH(C$\underline{H}_3$)$_2$), 0.39 (6H, s, $SiMe_2$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 162.6 (d, J^1_{C-F} = 248 Hz), 141.7 (d, J^3_{C-F} = 3.8 Hz), 129.5 (d, J^3_{C-F} = 7.1 Hz), 128.9 (d, J^4_{C-F} = 2.9 Hz), 119.7 (d, J^2_{C-F} = 18.9 Hz), 116.2 (d, J^2_{C-F} = 20.9 Hz), 65.5, 25.5, -1.2; **HRMS** (FI) calculated for $C_{11}H_{17}OFSi$ $[M]^+$ 212.1033, found 212.1023.

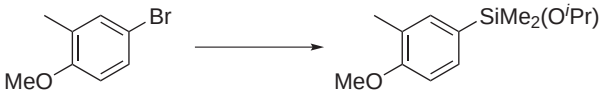
Isopropoxydimethyl(4-(trifluoromethyl)phenyl)silane (602)



603 **602**

Following the general bromo-lithium exchange protocol with 1-bromo-4-(trifluoromethyl)benzene **603** (250 mg, 1.11 mmol, 1.0 eq) and *n*-BuLi (0.53 mL of a 2.5 M solution in hexanes, 1.33 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **602** (276 mg, 1.03 mmol, 95%) as a colourless oil; $\mathbf{R}_f$ 0.66 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2974, 1391, 1327, 1256, 1167, 1129, 1061, 1033, 884, 830, 786, 699; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, J = 7.8 Hz, ArH), 7.61 (2H, d, J = 7.8 Hz, ArH), 4.00 (1H, sep, J = 6.1 Hz, OC$\underline{H}$(CH_3)$_2$), 1.15 (6H, d, J = 6.1 Hz, OCH(C$\underline{H}_3$)$_2$), 0.40 (6H, s, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 143.5, 133.7, 131.3 (q, J^2_{C-F} = 32.6 Hz), 124.3 (q, J^3_{C-F} = 3.6 Hz), 124.2 (q, J^1_{C-F} = 271.7 Hz), 65.6, 25.6, -1.3; **HRMS** (FI) calculated for $C_{12}H_{17}OF_3Si$ $[M]^+$ 262.1001, found 262.0991.

Isopropoxy(4-methoxy-3-methylphenyl)dimethylsilane (604)

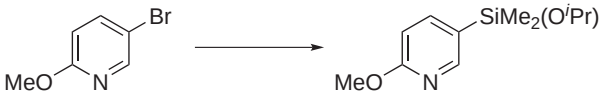


605 **604**

Following the general bromo-lithium exchange protocol with 4-bromo-1-methoxy-2-methylbenzene **605** (250 mg, 1.24 mmol, 1.0 eq) and *t*-BuLi (1.56 mL of a 1.6 M solution in pentane, 2.49 mmol, 2.0 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **604** (250 mg, 1.05 mmol, 85%) as a colourless oil; $\mathbf{R}_f$ 0.58 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2970, 1594, 1498, 1465, 1381, 1368, 1284, 1250, 1112, 1029, 897, 808, 783; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.41 (1H, d, J = 8.0 Hz,

ArH), 7.34 (1H, s, ArH), 6.85 (1H, d, J = 8.0 Hz, ArH), 3.97 (1H, sep, J = 6.1 Hz, OC<u>H</u>$(CH_3)_2$), 3.84 (3H, s, ArOMe), 2.24 (3H, s, ArMe), 1.13 (6H, d, J = 6.1 Hz, OCH(C<u>H</u>$_3)_2$), 0.35 (6H, s, $SiMe_2$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 159.0, 135.9, 132.7, 129.0, 125.9, 109.9, 65.1, 55.1, 25.5, 16.2, -1.0; **HRMS** (FI) calculated for $C_{13}H_{22}O_2Si$ $[M]^+$ 238.1389, found 238.1391.

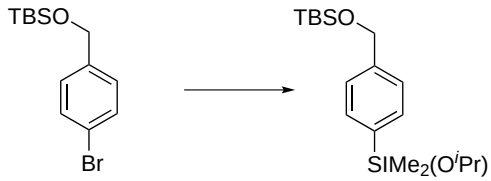
5-(Isopropoxydimethylsilyl)-2-methoxypyridine (606)



225 **606**

Following the general bromo-lithium exchange protocol with 5-bromo-2-methoxypyridine **225** (250 mg, 1.33 mmol, 1.0 eq) and *n*-BuLi (0.64 mL of a 2.5 M solution in hexanes, 1.60 mmol, 1.2 eq) in Et_2O, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **604** (297 mg, 1.32 mmol, 99%) as a pale yellow oil; $\mathbf{R_f}$ 0.48 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2972, 1587, 1557, 1488, 1355, 1286, 1253, 1174, 1118, 1027, 883, 839, 786; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 8.29 (1H, s, ArH), 7.69 (1H, td, J = 2.1, 8.2 Hz, ArH), 6.72 - 6.70 (1H, m, ArH), 3.95 (1H, sep, J = 6.0 Hz, OC<u>H</u>$(CH_3)_2$), 3.91 (3H, s, ArOMe), 1.09 (6H, d, J = 6.0 Hz, OCH(C<u>H</u>$_3)_2$), 0.33 (6H, s, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 165.1, 152.1, 143.5, 124.8, 110.7, 65.4, 53.2, 25.7, -1.0; **HRMS** (ESI^+) calculated for $C_{11}H_{20}NO_2Si$ $[M+H]^+$ 226.1258, found 226.1255.

tert-Butyl(4-(iso-propoxydimethylsilyl)benzyloxy)dimethylsilane (607)

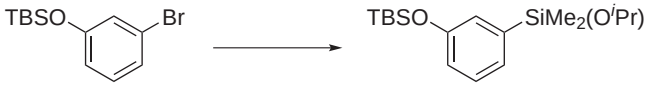


585 **607**

Following the general bromo-lithium exchange protocol with (4-bromobenzyloxy)(tert-butyl)dimethylsilane **585** (250 mg, 0.83 mmol, 1.0 eq) and *n*BuLi (0.40 mL of a 2.5 M solution in hexanes, 1.00 mmol, 1.2 eq) in THF, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **607** (278 mg, 0.82 mmol, 99%) as a colourless oil;

$\mathbf{R_f}$ 0.64 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2958, 2858, 1463, 1369, 1254, 1173, 1088, 1030, 882, 836, 778, 666; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.57 (2H, d, J = 8.0 Hz, ArH), 7.34 (2H, d, J = 8.0 Hz, ArH), 4.76 (2H, s, $ArCH_2OTBS$), 3.98 (1H, sep, J = 6.0 Hz, $OC\underline{H}(CH_3)_2$), 1.14 (6H, d, J = 6.0 Hz, $OCH(C\underline{H}_3)_2$), 0.96 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.38 (6H, s, $SiMe_2$), 0.16 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 142.8, 136.8, 135.5, 125.4, 65.2, 64.9, 26.0, 25.7, 18.5, -1.0, -5.2; **HRMS** (ESI^+) calculated for $C_{18}H_{34}NaO_2Si_2$ $[M+Na]^+$ 361.1990, found 361.1983.

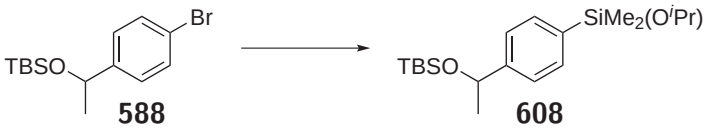
tert-Butyl(3-(isopropoxydimethylsilyl)phenoxy)dimethylsilane (247)



582 **247**

Following the general bromo-lithium exchange protocol with (3-bromophenoxy)(*tert*-butyl)dimethylsilane **582** (170 mg, 0.59 mmol, 1.0 eq) and *t*-BuLi (0.74 mL of a 1.6 M solution in pentane, 1.18 mmol, 2.0 eq) in THF, the resulting crude mixture was purified by flash column chromatography (20% Et_2O / P.E. 40 - 60) to afford silylation product **608** (145 mg, 0.45 mmol, 76%) as a colourless oil; $\mathbf{R_f}$ 0.70 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2960, 2931, 2860, 1587, 1570, 1479, 1398, 1264, 1114, 1029, 951, 881, 835, 782; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 (1H, d, J = 7.8 Hz, ArH), 7.16 (1H, d, J = 7.4 Hz, ArH), 7.06 (1H, d, J = 2.5 Hz, ArH), 6.87 - 6.83 (1H, m, ArH), 3.98 (1H, sep, J = 6.2 Hz, $OC\underline{H}(CH_3)_2$), 1.13 (6H, d, J = 6.2 Hz, $OCH(C\underline{H}_3)_2$), 0.99 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.36 (6H, s, $SiMe_2$), 0.20 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.1, 140.1, 129.0, 126.3, 124.9, 121.3, 65.3, 25.72, 25.67, 18.4, -1.2, -4.4; **HRMS** (ESI^+) calculated for $C_19H_{36}NaO_2Si_2$ $[M+Na]^+$ 375.2146, found 375.2145.

tert-Butyl(1-(4-(isopropoxydimethylsilyl)phenyl)ethoxy)dimethylsilane (608)



588 **608**

Following the general bromo-lithium exchange protocol with (1-(4-bromophenyl)ethoxy)(*tert*-butyl)-dimethyl-silane **588** (250 mg, 0.80 mmol, 1.0 eq) and *t*-BuLi (1.00 mL of a 1.6 M solution in

pentane, 1.60 mmol, 2.0 eq) in THF, the resulting crude mixture was purified by flash column chromatography (20% Et_2O / P.E. 40 - 60) to afford silylation product **608** (250.4 mg, 0.71 mmol, 89%) as a colourless oil; $\mathbf{R_f}$ 0.66 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2958, 2930, 2859, 1472, 1383, 1368, 1253, 1095, 1031, 959, 882, 835, 778, 665; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.54 (2H, d, J = 8.0 Hz, ArH), 7.34 (2H, d, J = 8.0 Hz, ArH), 4.87 (1H, q, J = 6.3 Hz, ArC<u>H</u>(OTBS)CH_3), 3.99 (1H, sep, J = 6.1 Hz, OC<u>H</u>$(CH_3)_2$), 1.14 (3H, d, J = 6.3 Hz, ArCH(OTBS)C<u>H</u>$_3$), 1.13 (6H, d, J = 6.1 Hz, OCH(C<u>H</u>$_3)_2$), 0.91 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.38 (6H, s, $SiMe_2$), 0.06 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$), -0.02 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 148.2, 136.5, 133.4, 124.6, 70.8, 65.2, 27.2, 25.9, 25.7, 18.3, -1.1, -4.8; **HRMS** (ESI^+) calculated for $C_{19}H_{36}NaO_2Si_2$ $[M+Na]^+$ 375.2146, found 375.2145.

Isopropoxydimethyl(naphthalen-1-yl)silane (609)



220 **609**

Following the general bromo-lithium exchange protocol with 1-bromonaphthalene **220** (250 mg, 1.21 mmol, 1.0 eq) and *t*-BuLi (1.51 mL of a 1.6 M solution in pentane, 2.49 mmol, 2.0 eq) in Et_2O, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **609** (262 mg, 1.07 mmol, 88%) as a colourless oil contaminated with naphthalene; $\mathbf{R_f}$ 0.66 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 8.36 (1H, dd, J = 1.3, 7.8 Hz, ArH), 7.90 - 7.84 (2H, m, ArH), 7.74 (1H, dd, J = 1.3, 6.8 Hz, ArH), 7.54 - 7.44 (3H, m, ArH), 4.00 (1H, sep, J = 6.1 Hz, OC<u>H</u>$(CH_3)_2$), 1.13 (6H, d, J = 6.1 Hz, OCH(C<u>H</u>$_3)_2$), 0.55 (6H, s, $SiMe_2$). Further characterisation was not completed due to difficulties in isolating pure isopropoxydimethyl(naphthalen-1-yl)silane **609**.

Isopropoxydimethyl(naphthalen-2-yl)silane (610)



221 **610**

Following the general bromo-lithium exchange protocol with 1-bromonaphthalene **220** (250 mg, 1.21 mmol, 1.0 eq) and *t*-BuLi (1.51 mL of a 1.6 M solution in pentane, 2.49 mmol, 2.0 eq) in Et_2O, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **610** (262 mg, 1.07 mmol, 88%) as a colourless oil contaminated with naphthalene; $\mathbf{R_f}$ 0.65 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 8.08 (1H, s, ArH), 7.88 - 7.82 (3H, m, ArH), 7.67 (1H, dd, J = 1.1, 8.1 Hz, ArH), 7.52 - 7.47 (2H, m, ArH), 4.03 (1H, sep, J = 6.1 Hz, OC<u>H</u>$(CH_3)_2$), 1.16 (6H, d, J = 6.1 Hz, OCH(C<u>H</u>$_3)_2$), 0.47 (6H, s, $SiMe_2$). Further characterisation was not completed due to difficulties in isolating pure isopropoxydimethyl(naphthalen-2-yl)silane **610**.

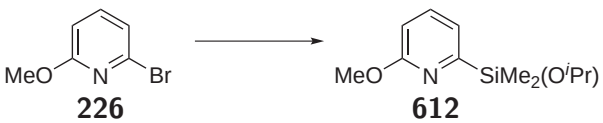
3-(Isopropoxydimethylsilyl)quinoline (611)



223 **611**

Following the general bromo-lithium exchange protocol with 1-bromonaphthalene **220** (250 mg, 1.20 mmol, 1.0 eq) and *t*-BuLi (1.51 mL of a 1.6 M solution in pentane, 2.49 mmol, 2.0 eq) in Et_2O, the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **611** (211 mg, 0.86 mmol, 72%) as a yellow oil; $\mathbf{R_f}$ 0.40 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 9.05 (1H, d, J = 1.6 Hz, ArH), 8.35 (1H, s, ArH), 8.10 (1H, d, J = 8.4 Hz, ArH), 7.83 (1H, d, J = 8.4 Hz, ArH), 7.76 - 7.71 (1H, m, ArH), 7.58 - 7.54 (1H, m, ArH), 4.06 (1H, sep, J = 6.0 Hz, OC<u>H</u>$(CH_3)_2$), 1.18 (6H, d, J = 6.0 Hz, OCH(C<u>H</u>$_3)_2$), 0.46 (6H, s, $SiMe_2$). Further characterisation was not completed due to difficulties reproducing the protocol above.

2-(Isopropoxydimethylsilyl)-6-methoxypyridine (612)



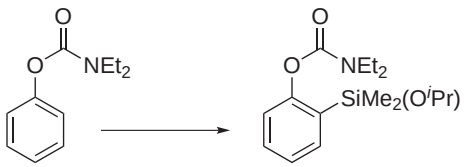
226 **612**

Following the general bromo-lithium exchange protocol with 2-bromo-6-methoxypyridine **226** (250 mg, 1.33 mmol, 1.0 eq) and *n*-BuLi (0.64 mL of a 2.5 M solution in hexanes, 1.60 mmol, 1.2 eq)

in THF, the resulting crude mixture was purified by flash column chromatography (30% Et_2O / P.E. 40 - 60) to afford silylation product **612** (169 mg, 0.75 mmol, 56%) as a colourless oil; $\mathbf{R_f}$ 0.52 (20% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.50 (1H, dd, J = 6.9, 8.5 Hz, ArH), 7.18 (1H, dd, J = 6.9, 0.7 Hz, ArH), 6.67 (1H, dd, J = 0.7, 8.5 Hz, ArH), 4.14 (1H, sep, J = 6.1 Hz, OC$\underline{H}(CH_3)_2$), 3.95 (3H, s, ArOMe), 1.16 (6H, d, J = 6.1 Hz, OCH($C\underline{H}_3)_2$), 0.39 (6H, s, $SiMe_2$). Further characterisation was not completed due to difficulties reproducing the protocol above.

Protocol for the Preparation of Directed ortho-Lithiation Substrates

2-(Isopropoxydimethylsilyl)phenyl diethylcarbamate (231)[140]

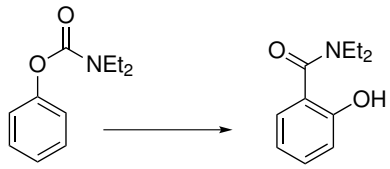


227 **231**

To a stirred solution of phenyl diethylcarbamate **227** (250 mg, 1.29 mmol, 1.0 eq) and TMEDA (0.25 mL, 1.68 mmol, 1.3 eq) in THF (5 mL) at −78 °C was added *s*-BuLi (1.21 mL of a 1.3 M solution in cyclohexane/hexane, 1.68 mmol, 1.3 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.39 mL, 1.94 mmol, 1.5 eq), then stirring was continued at −78 °C for another 2 h. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (30% Et_2O / P.E. 40 - 60) to afford silylation product **231** (349 mg, 1.13 mmol, 88%) as a pale yellow oil; $\mathbf{R_f}$ 0.36 (40% Et_2O / P.E. 40 - 40); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2972, 1721, 1595, 1469, 1416, 1381, 1317, 1259, 1226, 1194, 1156, 1080, 1026, 962, 882, 834, 786, 755, 719, 638; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.56 (1H, dd, J = 1.7, 7.3 Hz, ArH), 7.40 (1H, dt, J = 1.7, 7.9 Hz, ArH), 7.19 (1H, t, J = 7.3 Hz, ArH), 7.09 (1H, d, J = 7.9 Hz, ArH), 3.99 (1H, sep, J = 6.2 Hz, OC$\underline{H}(CH_3)_2$), 3.50 (2H, q, J = 7.1 Hz, NC$\underline{H}_2CH_3$), 3.40 (2H, q, J = 7.1 Hz, NC$\underline{H}_2CH_3$), 1.26 (3H, t, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.19 (3H, t, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.14 (6H, d, J = 6.2 Hz, OCH($C\underline{H}_3)_2$), 0.37 (6H, s, $SiMe_2$); ^{13}**C NMR** (62.9 MHz, $CDCl_3$) δ_C 156.2, 154.3, 135.2, 130.8, 129.9, 124.7, 122.3, 65.5, 42.0, 41.6, 25.6, 14.2, 13.3, -0.4;

HRMS (ESI$^+$) calculated for $C_{16}H_{27}NNaO_3Si$ $[M+Na]^+$ 332.1652, found 332.1648.

N,N-Diethyl-2-hydroxybenzamide (230)



227 **230**

To a stirred solution of phenyl diethylcarbamate **227** (250 mg, 1.29 mmol, 1.0 eq) and TMEDA (0.25 mL, 1.68 mmol, 1.3 eq) in THF (5 mL) at −78 °C was added *s*-BuLi (1.21 mL of a 1.3M solution in cyclohexane/hexane, 1.68 mmol, 1.3 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.39 mL, 1.94 mmol, 1.5 eq), then stirring was continued at −50 °C for another 2 h. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP (crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford rearrangement product **230** (248 mg, 1.28 mmol, 99%) as a pale yellow oil; **mp** 89.7 °C (lit.[286] mp 103 - 104 °C*); $\mathbf{R_f}$ 0.11 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 9.79 (1H, s, OH), 7.34 - 7.26 (2H, m, ArH), 7.00 (1H, dd, J = 1.1, 8.3 Hz, ArH), 6.84 (1H, dt, J = 1.1, 7.8 Hz, ArH), 3.53 (4H, q, J = 7.1 Hz, $N(C\underline{H}_2CH_3)_2$), 1.28 (6H, t, J = 7.1 Hz, $N(CH_2C\underline{H}_3)_2$).

This spectroscopic data is in agreement with that reported by Beak *et al.*[123]

Isopropoxy(2-methoxyphenyl)dimethylsilane (596)[141]



219 **596**

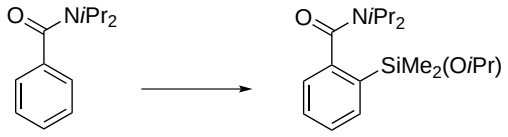
To a solution of anisole **228** (250 mg, 2.31 mmol, 1.0 eq) and TMEDA (0.45 mL, 3.00 mmol, 1.3 eq) in Et_2O (5 mL) at −78 °C was added *n*-BuLi (1.20 mL of a 2.5 M solution in hexanes, 3.00 mmol,

*A more accurate melting point may be obtained by attempting to crystallise the phenol obtained.

1.3 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.69 mL, 3.47 mmol, 1.5 eq), then stirring was continued at −78 °C for a further 2 h. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP (crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **596** (478 mg, 2.13 mmol, 92%) as a colourless oil; $\mathbf{R_f}$ 0.66 (20% Et_2O / P.E. 40 - 60); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53 (1H, dd, J = 1.8, 7.6 Hz, ArH), 7.38 (1H, dd, J = 1.8, 8.0 Hz, ArH), 6.98 (1H, d, J = 7.2 Hz, ArH), 6.85 (1H, d, J = 8.0 Hz), 4.06 (1H, sep, J = 6.1 Hz, $OC\underline{H}(CH_3)_2$), 3.82 (3H, s, ArOMe), 1.17 (6H, d, J = 6.1 Hz, $OCH(C\underline{H}_3)_2$), 0.39 (6H, s, $SiMe_2$).

This data is in agreement with that recorded above for isopropoxy(2-methoxyphenyl)dimethylsilane **596**.

2-(Isopropoxydimethylsilyl)-N,N-diisopropylbenzamide (613)[123]

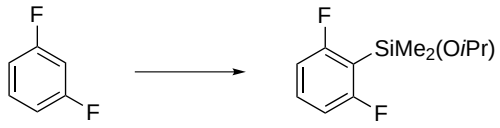


229 **613**

To a solution of *N,N*-di*iso*-propylbenzamide **229** (250 mg, 1.19 mmol, 1.0 eq) and TMEDA (0.23 mL, 1.55 mmol, 1.3 eq) in THF (5 mL) at −78 °C was added *s*-BuLi (1.19 mL of a 1.3 M solution in hexanes, 1.55 mmol, 1.3 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.35 mL, 1.79 mmol, 1.5 eq), then stirring was continued at −78 °C for a further 2 h. Upon warming to r.t., *i*PrOH (1 mL) and DMAP (crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50 % Et_2O / P.E. 40 60) to afford silylation product **613** (373 mg, 1.16 mmol, 98%) as a white solid; mp 67.6 72.7 °C; $\mathbf{R_f}$ 0.29 (50% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (KBr disc) / cm^{-1} 2972, 1624, 1439, 1368, 1338, 1130, 1019, 876, 795, 756; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 7.84 (1H, m, ArH), 7.39 7.32 (2H, m, ArH), 7.19 7.15 (1H, m, ArH), 4.11 (1H, sep, J = 6.1 Hz, $OC\underline{H}(CH_3)_2$), 3.84 (1H, br s, $NC\underline{H}(CH_3)_2$), 3.50 (1H, br s, $NC\underline{H}(CH_3)_2$), 1.56 (6H, br s, $NCH(C\underline{H}_3)_2$), 1.20 (6H, d, J = 6.1 Hz, $OCH(C\underline{H}_3)_2$), 1.16 (6H, br

s, NCH(C$\underline{H}_3$)$_2$), 0.42 (6H, s, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.3, 143.7, 136.9, 135.8, 128.6, 127.8, 124.9, 65.2, 50.9, 45.8, 25.8, 20.6, 0.4; **HRMS** (FI) calculated for $C_{18}H_{31}NO_2Si$ $[M]^+$ 321.2124, found 321.2117.

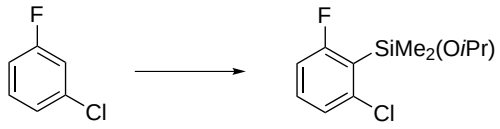
(2,6-Difluorophenyl)(isopropoxy)dimethylsilane (614)[142]



614

To a solution of 1,3-difluorobenzene (250 mg, 2.19 mmol, 1.0 eq) and TMEDA (0.39 mL, 2.63 mmol, 1.2 eq) in THF (5 mL) at −78 °C was added *n*-BuLi (1.05 mL of a 2.5 M solution in hexanes, 2.63 mmol, 1.2 eq). The resulting mixture was stirred for 3 h before addition of $ClSiMe_2(NEt_2)$ (0.61 mL, 3.07 mmol, 1.4 eq), then stirring was continued at −78 °C for a further 2 h. Upon warming to r.t., *i*PrOH (2 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **614** (408 mg, 1.77 mmol, 81%) as a colourless oil; $\mathbf{R}_f$ 0.71 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2974, 1611, 1556, 1446, 1383, 1369, 1252, 1220, 1174, 1123, 1107, 1034, 977, 886, 824, 795; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.30 (2H, m, ArH), 6.83 (1H, t, J = 7.9 Hz, ArH), 4.06 (1H, sep, J = 6.1 Hz, OC$\underline{H}$(CH_3)$_2$), 1.15 (6H, d, J = 6.1 Hz, OCH(C$\underline{H}_3$)$_2$), 0.49 (6H, t, J^5_{H-F} = 1.9 Hz, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.0 (dd, J^1_{C-F} = 245.4 Hz, J^3_{C-F} = 15.3 Hz), 132.5 (t, J^3_{C-F} = 10.5 Hz), 112.2 (t, J^2_{C-F} = 33.5 Hz), 111.1 (d, J^2_{C-F} = 30.4 Hz), 65.8, 25.4, 1.0 (t, J^4_{C-F} = 3.1 Hz); **HRMS** (FI) calculated for $C_{11}H_{16}F_2OSi$ $[M]^+$ 230.0939, found 230.0949.

(2-Chloro-6-fluorophenyl)(isopropoxy)dimethylsilane (615)[142]

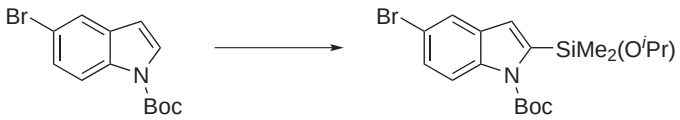


615

To a solution of 1-chloro-3-difluorobenzene (250 mg, 1.91 mmol, 1.0 eq) and TMEDA (0.34 mL, 2.30 mmol, 1.2 eq) in THF (5 mL) at −78 °C was added *n*-BuLi (0.92 mL of a 2.5 M solution in hexanes,

2.30 mmol, 1.2 eq). The resulting mixture was stirred for 3 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.53 mL, 2.67 mmol, 1.4 eq), then stirring was continued at −78 °C for a further 2 h. Upon warming to r.t., *i*PrOH (2 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **615** (467 mg, 1.89 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.69 (20% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2973, 1590, 1562, 1432, 1261, 1229, 1124, 1107, 1032, 876, 823, 791; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (1H, *app* q, J = 6.7 Hz, ArH), 7.16 (1H, d, J = 8.1 Hz, ArH), 6.91 (1H, *app* t, J = 8.1 Hz, ArH), 4.06 (1H, sep, J = 6.1 Hz, OC$\underline{H}(CH_3)_2$), 1.17 (6H, d, J = 6.1 Hz, OCH(C$\underline{H}_3)_2$), 0.54 (6H, d, J = 3.1 Hz, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 167.2 (d, J^1_{C-F} = 246.2 Hz), 141.2 (d, J^3_{C-F} 13.7 Hz), 132.0 (d, J^3_{C-F} = 10.5 Hz), 125.9 (d, J^4_{C-F} = 3.2 Hz), 124.7 (d, J^2_{C-F} 27.3 Hz), 113.7 (d, J^2_{C-F} 27.8 Hz), 66.2, 25.7, 2.0 (d, J^4_{C-F} = 4.8 Hz); **HRMS** (FI) calculated for $C_{11}H_{16}F^{35}ClOSi$ $[M]^+$ 246.0643, found 246.0642.

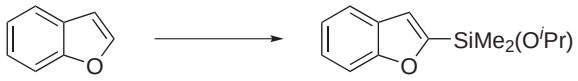
tert-Butyl 5-bromo-2-(isopropoxydimethylsilyl)-1H-indole-1-carboxylate (240)[282]



232 **240**

To a stirred solution of *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate **232** (250 mg, 0.84 mmol, 1.0 eq) and $ClSiMe_2(NEt_2)$ **212** (0.25 mL, 1.27 mmol, 1.5 eq) in THF (1.3 mL) at 0 °C was added LDA (1.09 mL of a 1 M solution in THF, 1.3 eq) over 1 h. The resulting mixture was stirred for 30 min, then warmed to r.t. and *i*-PrOH (1 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **240** (331, 0.80 mmol, 96%) as a brown oil; $\mathbf{R_f}$ 0.30 (100% P.E. 40 - 40); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2973, 1727, 1439, 1373, 1326, 1251, 1164, 1141, 1059, 1029, 876, 788; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.86 (1H, d, J = 8.7 Hz, ArH), 7.69 (1H, d, J = 1.9 Hz, ArH), 7.37 (1H, dd, J = 1.9, 8.7 Hz, ArH), 6.96 (1H, s, ArH), 4.13 (1H, sep, J = 6.0 Hz, OC$\underline{H}(CH_3)_2$), 1.71 (9H, s, C(O)OC(C$\underline{H}_3)_3$), 1.22 (6H, d, J = 6.0 Hz, OCH(C$\underline{H}_3)_2$), 0.46 (6H, s, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 150.9, 142.1, 136.3, 132.8, 127.3, 123.5, 119.4, 116.9, 115.7, 84.6, 65.4, 28.2, 25.9, -0.1; **HRMS** (FI) calculated for $C_{18}H_{26}^{79}BrNO_3Si$ $[M]^+$ 411.0865, found 411.0855.

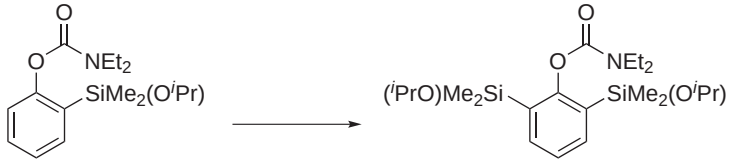
Benzofuran-2-yl(isopropoxy)dimethylsilane (241)[287]



233 **241**

To a stirred solution of benzofuran **233** (250 mg, 2.12 mmol, 1.0 eq) in THF (5 mL) at −78 °C was added *s*-BuLi (1.95 mL of a 1.3 M solution in cyclohexane/hexane) dropwise. After stirring for 15 min, $ClSiMe_2(NEt_2)$ **212** (0.59 mL, 2.96 mmol, 1.4 eq) was added and the reaction mixture was warmed to r.t. *i*-PrOH (1 mL) and DMAP (1 crystal) were subsequently added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **241** (492 mg, 2.10 mmol, 99%) as a yellow oil; $\mathbf{R_f}$ 0.34 (100% P.E. 40 - 40); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2972, 1527, 1471, 1442, 1382, 1369, 1255, 1223, 1114, 1069, 1031, 921, 886, 819, 792, 743, 656; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.61 (1H, d, J = 7.7 Hz, ArH), 7.57 (1H, d, J = 8.2 Hz, ArH), 7.36 - 7.32 (1H, m, ArH), 7.27 - 7.23 (1H, m, ArH), 7.11 (1H, s, ArH), 4.16 (1H, sep, J = 5.9 Hz, $OC\underline{H}(CH_3)_2$), 1.21 (6H, d, J = 5.9 Hz, $OCH(C\underline{H}_3)_2$), 0.52 (6H, s, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 161.3, 158.0, 127.7, 124.8, 122.4, 121.3, 117.2, 111.5, 66.0, 25.5, -1.5; **HRMS** (FI) calculated for $C_{13}H_{18}O_2Si$ $[M]^+$ 234.1076, found 234.1077.

2,6-bis(Isopropoxydimethylsilyl)phenyl diethylcarbamate (248)[140]

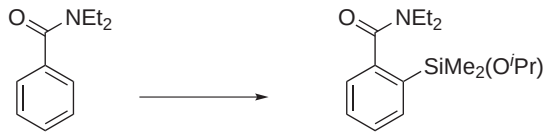


231 **248**

To a stirred solution of 2-(*iso*propoxydimethylsilyl)phenyl diethylcarbamate **231** (250 mg, 0.65 mmol, 1.0 eq) and TMEDA (0.13 mL, 0.84 mmol, 1.3 eq) in THF (5 mL) at −78 °C was added *s*-BuLi (0.65 mL of a 1.3 M solution in cyclohexane/hexane, 0.84 mmol, 1.3 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.19 mL, 0.98 mmol, 1.5 eq), then stirring was continued at −78 °C for another 2 h. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O

/ P.E. 40 - 60) to afford silylation product **248** (183 mg, 0.43 mmol, 66%) as a colourless oil; $\mathbf{R_f}$ 0.36 (20% Et_2O / P.E. 40 - 40); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2972, 1581, 1470, 1381, 1172, 1124, 1071, 1026, 873, 811, 781; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, J = 7.2 Hz, ArH), 7.24 (1H, t, J = 7.2 Hz, ArH), 3.99 (2H, sep, J = 6.0 Hz, OC$\underline{H}(CH_3)_2$), 3.57 (2H, q, J = 7.1 Hz, NC$\underline{H}_2CH_3$), 3.36 (2H, q, J = 7.1 Hz, NC$\underline{H}_2CH_3$), 1.29 (3H, t, $\underline{J}$ = 7.1 Hz, $NCH_2C\underline{H}_2$), 1.18 (3H, t, J = 7.1 Hz, $NCH_2C\underline{H}_2$), 1.13 (12H, d, J = 6.0 Hz, $OCH(C\underline{H}_3)_2$), 0.35 (6H, s, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 160.2, 154.6, 137.5, 131.1, 124.7, 65.2, 41.3, 41.1, 25.5, 13.7, 13.0, -0.3; **HRMS** (FI) calculated for $C_{21}H_{39}NO_4Si_2$ $[M]^+$ 425.2418, found 425.2423.

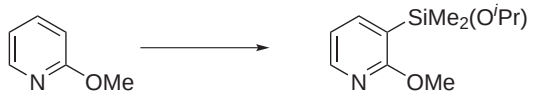
N,N-Diethyl-2-(isopropoxydimethylsilyl)benzamide (616)[123]



236 **616**

To a stirred solution of *N,N*-diethyl benzamide **236** (250 mg, 1.41 mmol, 1.0 eq) and TMEDA (0.25 mL, 1.69 mmol, 1.2 eq) in THF (5 mL) at −78 °C was added *s*-BuLi (1.3 mL of a 1.3 M solution in cyclohexane/hexane, 1.69 mmol, 1.2 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.39 mL, 1.97 mmol, 1.4 eq), then stirring was continued at −78 °C for another 2 h. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **616** (190 mg, 0.65 mmol, 46%) as a colourless oil contaminated with starting material; $\mathbf{R_f}$ 0.30 (50% Et_2O / P.E. 40 - 40); ^{1}**H NMR** (250 MHz, $CDCl_3$) δ_H 7.81 - 7.77 (1H, m, ArH), 7.63 - 7.60 (1H, m, ArH), 7.41 - 7.35 (1H, m, ArH), 7.21 - 7.17 (1H, m, ArH), 4.09 (1H, sep, J = 6.1 Hz, OC$\underline{H}(CH_3)_2$), 3.62 - 3.44 (2H, m, NC$\underline{H}_2CH_3$), 3.32 - 3.17 (2H, m, NC$\underline{H}_2CH_3$), 1.32 - 1.06 (12H, m, $NCH_2C\underline{H}_2$ and $OCH(C\underline{H}_3)_2$), 0.37 (6H, s, $SiMe_2$). Further characterisation was not completed due to difficulties in isolating a pure sample of **616**.

3-(Isopropoxydimethylsilyl)-2-methoxypyridine (617)



618 **617**

To a stirred solution of 2-methoxypyridine **618** (250 mg, 2.29 mmol, 1.0 eq) in THF (5 mL) at −78 °C was added *t*-BuLi (1.86 mL of a 1.6 M solution in pentane, 2.98 mmol, 1.3 eq). The resulting mixture was stirred for 1 h before addition of $ClSiMe_2(NEt_2)$ **212** (0.69 mL, 3.44 mmol, 1.5 eq), then stirring was continued at −78 °C for another 2 h. Upon warming to r.t., *i*-PrOH (1 mL) and DMAP (1 crystal) were added before stirring overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude mixture was purified by flash column chromatography (50% Et_2O / P.E. 40 - 60) to afford silylation product **617** (243 mg, 1.08 mmol, 47%) as a colourless oil; $\mathbf{R_f}$ 0.50 (20% Et_2O / P.E. 40 - 40); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 8.17 (1H, dd, J = 2.1, 5.1 Hz, ArH), 7.79 (1H, dd, J = 2.1, 7.0 Hz, ArH), 6.87 (1H, dd, J = 5.1, 7.0 Hz, ArH), 4.06 (1H, sep, J = 6.0 Hz, $OC\underline{H}(CH_3)_2$), 3.93 (3H, s, ArOMe), 1.17 (6H, d, J = 6.0 Hz, $OCH(C\underline{H}_3)_2$), 0.37 (6H, s, $SiMe_2$). Further characterisation was not completed due to extensive by-product formation and poor yields.

7.2.4. Aryl Silane Oxidations

General Protocol for the Oxidation of the Aryl iso-Propoxy Silane Substrates

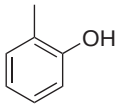
To a stirred solution of the aryl silane (50 - 243 mg, 1.0 eq) in MeOH/THF (1:1, 1 mL) was added $KHCO_3$ (2.0 eq), TBAF (0.1, 1.0 or 2.0 eq of a 1.0 M solution in THF) or KF (2.0 eq) and H_2O_2 (6.0 eq of a 35% w/w aqueous solution). The reaction mixture was stirred at r.t. or 60 °C for 16 h, before quenching with NH_4Cl or 1N HCl solution. The phases were separated, the aqueous phase extracted with Et_2O (2 x 2 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography afforded the phenol (31 - 99%).

General Protocol for the One-Pot Oxidation of the Aryl Amino Silane Intermediates

The appropriate lithiation protocol was followed to afford the aryl amino silane intermediate, omitting the introduction of *i*-PrOH and DMAP to the reaction vessel. The reaction mixture

was concentrated *in vacuo*, and MeOH/THF was added (1:1, 3 mL) followed by $KHCO_3$ (2.0 eq), TBAF (0.1, 1.0 or 2.0 eq of a 1.0 M solution in THF) or KF (2.0 eq) and H_2O_2 (6.0 eq of a 35% w/w aqueous solution). The reaction mixture was stirred at r.t. or 60 °C for 16 h, before quenching with NH_4Cl or 1N HCl solution. The phases were separated, the aqueous phase extracted with Et_2O (2 x 2 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography afforded the phenol (43 - 99%).

o-Cresol (619)



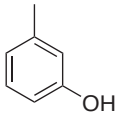
619

Following the *iso*-propoxy silane oxidation protocol (63 mg, 0.30 mmol, 1.0 eq of **590**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **619** (29.7 mg, 0.27 mmol, 90%) as an orange oil; $\mathbf{R_f}$ 0.42 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.13 (1H, d, J = 7.4 Hz, ArH), 7.09 (1H, t, J = 7.8 Hz, ArH), 6.85 (1H, t, J = 7.4 Hz, ArH), 6.77 (1H, d, J = 7.8 Hz, ArH), 4.85 (1H, br s, OH), 2.26 (3H, s, ArMe).

Following the one-pot oxidation protocol (250 mg, 1.46 mmol, 1.0 eq of 2-bromotoluene **591**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **619** (137 mg, 1.27 mmol, 87%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for *o*-cresol **619**.

This data is in agreement with that reported by Sunderhaus *et al.*[128]

m-Cresol (620)



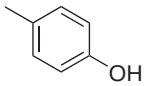
620

Following the *iso*-propoxy silane oxidation protocol (100 mg, 0.48 mmol, 1.0 eq of **592**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **620** (37.4 mg, 0.35 mmol, 72%) as a pale pink oil; $\mathbf{R_f}$ 0.42 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.12 (1H, t, J = 7.8 Hz, ArH), 6.75 (1H, d, J = 7.8 Hz, ArH), 6.67 - 6.62 (2H, m, ArH), 5.45 (1H, br s, OH), 2.31 (3H, s, ArMe).

Following the one-pot oxidation protocol (250 mg, 1.46 mmol, 1.0 eq of 3-bromotoluene **593**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **620** (139 mg, 1.29 mmol, 88%) as a pale pink oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for *m*-cresol **620**.

This data is in agreement with that reported by Mirza-Aghayan *et al.*[288]

p-Cresol (621)



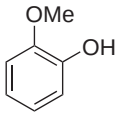
621

Following the *iso*-propoxy silane oxidation protocol (62 mg, 0.48 mmol, 1.0 eq of **594**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **621** (26.2 mg, 0.24 mmol, 81%) as an orange oil; $\mathbf{R_f}$ 0.41 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.04 (2H, d, J = 8.3 Hz, ArH), 6.73 (2H, d, J = 8.3, ArH), 4.82 (1H, br s, OH), 2.28 (3H, s, ArMe).

Following the one-pot oxidation protocol (250 mg, 1.46 mmol, 1.0 eq of 4-bromotoluene **595**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **621** (156.5 mg, 1.45 mmol, 99%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for *p*-cresol **621**.

This data is in agreement with that reported by Mirza-Aghayan *et al.*[288]

2-Methoxyphenol (622)



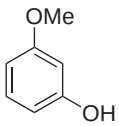
622

Following the *iso*-propoxy silane oxidation protocol (58.4 mg, 0.26 mmol, 1.0 eq of **596**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **622** (9.9 mg, 0.08 mmol, 31%) as an orange oil; $\mathbf{R_f}$ 0.38 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.95 - 6.85 (4H, m, ArH), 5.63 (1H, s, OH), 3.89 (3H, s, ArOMe).

Following the one-pot oxidation protocol (250 mg, 1.34 mmol, 1.0 eq of 2-bromoanisole **219**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **622** (149 mg, 1.20 mmol, 90%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 2-methoxyphenol **622**.

This data is in agreement with that reported by Anderson *et al.*[107]

3-Methoxyphenol (243)



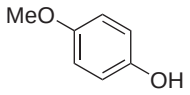
623

Following the *iso*-propoxy silane oxidation protocol (150 mg, 0.69 mmol, 1.0 eq of **242**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **243** (66.8 mg, 0.54 mmol, 81%) as an orange oil; $\mathbf{R_f}$ 0.37 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.13 (1H, td, J = 1.4, 8.3 Hz, ArH), 6.51 - 6.48 (1H, m, ArH), 6.44 - 6.41 (2H, m, ArH), 5.02 (1H, br s, OH), 3.79 (3H, s, ArOMe).

Following the one-pot oxidation protocol (250 mg, 1.34 mmol, 1.0 eq of 3-bromoanisole **217**) with 1.0 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **243** (165 mg, 1.33 mmol, 99%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 3-methoxyphenol **243**.

This data is in agreement with that reported by Sunderhaus *et al.*[128]

4-Methoxyphenol (624)



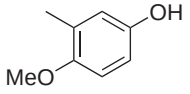
624

Following the *iso*-propoxy silane oxidation protocol (66 mg, 0.29 mmol, 1.0 eq of **597**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **624** (32.7 mg, 0.26 mmol, 90%) as an light orange solid; **mp** 52.5 °C (lit.[289] mp 52 - 53 °C); $\mathbf{R_f}$ 0.32 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.77 (4H, *app* s, ArH), 4.61 (1H, br s, OH), 3.76 (3H, s, ArOMe).

Following the one-pot oxidation protocol (250 mg, 1.34 mmol, 1.0 eq of 4-bromoanisole **218**) with 1.0 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **624** (137 mg, 1.10 mmol, 82%) as a light orange solid; **mp**, $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 4-methoxyphenol **624**.

This data is in agreement with that reported by Anderson *et al.*[107]

4-Methoxy-3-methylphenol (625)



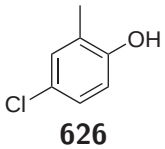
625

Following the *iso*-propoxy silane oxidation protocol (69 mg, 0.29 mmol, 1.0 eq of **604**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **625** (22.0 mg, 0.16 mmol, 55%) as an orange oil; $\mathbf{R_f}$ 0.38 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.70 - 6.60 (3H, m, ArH), 4.31 (1H, br s, OH), 3.78 (3H, s, ArOMe), 2.18 (3H, s, ArMe).

Following the one-pot oxidation protocol (250 mg, 1.24 mmol, 1.0 eq of 4-bromo-1-methoxy-2-methylbenzene **605**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **625** (88.4 mg, 0.64 mmol, 52%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 4-methoxy-3-methylphenol **625**.

This data is in agreement with that reported by Vyvyan *et al.*[290]

4-Chloro-2-methylphenol (626)



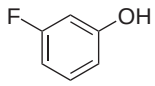
626

Following the *iso*-propoxy silane oxidation protocol (69 mg, 0.29 mmol, 1.0 eq of **598**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **626** (22.0 mg, 0.16 mmol, 55%) as an orange oil; $\mathbf{R_f}$ 0.42 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.10 (1H, d, J = 2.5 Hz, ArH), 7.03 (1H, dd, J = 2.5, 8.5 Hz, ArH), 6.69 (1H, d, J = 8.5 Hz, ArH), 4.73 (1H, br s, OH), 2.22 (3H, s, ArMe).

Following the one-pot oxidation protocol (250 mg, 1.22 mmol, 1.0 eq of 1-bromo-4-chloro-2-methylbenzene **599**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **626** (136 mg, 0.95 mmol, 78%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 4-chloro-2-methylphenol **626**.

This data is in agreement with that reported by Wang *et al.*[291]

3-Fluorophenol (627)



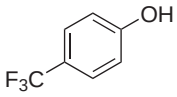
627

Following the *iso*-propoxy silane oxidation protocol (69 mg, 0.33 mmol, 1.0 eq of **600**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **627** (18.9 mg, 0.17 mmol, 52%) as a light orange oil; $\mathbf{R_f}$ 0.38 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.21 - 7.15 (1H, m, ArH), 6.67 - 6.55 (3H, m, ArH), 5.08 (1H, br s, OH).

Following the one-pot oxidation protocol (250 mg, 1.43 mmol, 1.0 eq of 1-bromo-3-fluorobenzene **601**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **627** (69.7 mg, 0.62 mmol, 43%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 3-fluorophenol **627**.

This data is in agreement with that of commercially available 3-fluorophenol **627** (Aldrich).

4-(Trifluoromethyl)phenol (628)



628

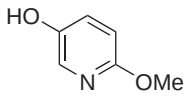
Following the *iso*-propoxy silane oxidation protocol (100 mg, 0.38 mmol, 1.0 eq of **602**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **628** (53.7 mg, 0.33 mmol, 87%) as a yellow oil; $\mathbf{R_f}$ 0.49 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.51 (2H, d, J = 8.6 Hz, ArH), 6.90

(2H, d, J = 8.6 Hz, ArH), 5.37 (1H, br s, OH).

Following the one-pot oxidation protocol (250 mg, 1.11 mmol, 1.0 eq of 1-bromo-4-(trifluoromethyl)benzene **603**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **628** (108 mg, 0.66 mmol, 59%) as a yellow oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 4-(trifluoromethyl)phenol **628**.

This data is in agreement with that reported by Tordeux *et al.*[292]

6-Methoxypyridin-3-ol (629)



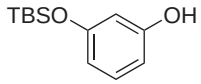
629

Following the *iso*-propoxy silane oxidation protocol (50 mg, 0.22 mmol, 1.0 eq of **606**) with 2.0 eq of KF at 60 °C and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **629** (18.8 mg, 0.15 mmol, 68%) as an brown solid; **mp** 81.1 °C (lit. mp 80 - 82°C); $\mathbf{R_f}$ 0.16 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.76 (1H, d, J = 2.8 Hz, ArH), 7.39 (1H, br s, OH), 7.24 (1H, dd, J = 2.8, 8.9 Hz, ArH), 6.68 (1H, d, J = 8.9 Hz, ArH), 3.87 (3H, s, ArOMe).

Following the one-pot oxidation protocol (250 mg, 1.33 mmol, 1.0 eq of 5-bromo-2-methoxypyridine **225**) with 2.0 eq of KF at 60 °C and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **629** (124.8 mg, 1.00 mmol, 75%) as a brown solid; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 6-methoxypyridin-3-ol **629**.

This data is in agreement with that reported by Bierer *et al.*[293]

3-(tert-Butyldimethylsilyloxy)phenol (630)

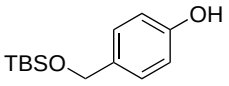


630

Following the one-pot oxidation protocol (250 mg, 0.87 mmol, 1.0 eq of aryl bromide **582**) with 0.1 eq of TBAF at r.t. and quenching with NH_4Cl solution, purification by flash column chromatography (20% Et_2O / P.E. 40 - 60) afforded phenol **630** (147 mg, 0.66 mmol, 76%) as a light orange oil; $\mathbf{R_f}$ 0.50 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.07 (1H, t, J = 8.1 Hz, ArH), 6.44 - 6.41 (2H, m, ArH), 6.35 (1H, t, J = 2.2 Hz, ArH), 4.75 (1H, br s, OH), 0.97 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.19 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$).

This data is in agreement with that reported by Holladay *et al.*[294]

4-((tert-Butyldimethylsilyloxy)methyl)phenol (631)



631

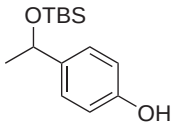
Following the *iso*-propoxy silane oxidation protocol (103 mg, 0.30 mmol, 1.0 eq of **607**) with 0.1 eq of TBAF at r.t. and quenching with NH_4Cl solution, purification by flash column chromatography (20 % Et_2O / P.E. 40 60) afforded phenol **631** (71.7 mg, 0.30 mmol, 99 %) as a pale yellow oil; $\mathbf{R_f}$ 0.38 (50 % Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.20 (2H, d, J = 8.6 Hz, ArH), 6.80 (2H, d, J = 8.6 Hz, ArH), 4.72 (1H, br s, OH), 4.67 (2H, s, $ArCH_2OTBS$), 0.93 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.09 (6H, s, $Si(C\underline{H}_3)_2C(H_3)_3$).

Following the one-pot oxidation protocol (250 mg, 0.83 mmol, 1.0 eq of aryl bromide **585**) with 0.1 eq of TBAF at r.t. and quenching with NH_4Cl solution, purification by flash column chromatography (20 % Et_2O / P.E. 40 60) afforded phenol **631** (196 mg, 0.82 mmol, 99 %) as a pale yellow oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that reported above for 4-((tert-butyldimethylsilyloxy)methyl)phenol

631.

This data is in agreement with that reported by Oyama et al.[295]

4-(1-(tert-Butyldimethylsilyloxy)ethyl)phenol (632)

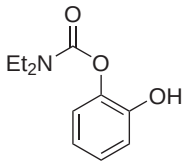


632

Following the *iso*-propoxy silane oxidation protocol (48.1 mg, 0.14 mmol, 1.0 eq of **608**) with 0.1 eq of KF at r.t. and quenching with NH_4Cl solution, purification by flash column chromatography (20% Et_2O / P.E. 40 - 60) afforded phenol **632** (24.8 mg, 0.09 mmol, 70%) as an orange oil; $\mathbf{R_f}$ 0.45 (50% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3347 (br), 2957, 2858, 1615, 1514, 1472, 1369, 1254, 1170, 1092, 1031, 960, 834, 777; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.19 (2H, d, J = 8.4 Hz, ArH), 6.77 (2H, J = 8.4 Hz, ArH), 4.81 (1H, q, J = 6.5 Hz, ArC<u>H</u>(OTBS)CH_3), 4.69 (1H, br m, OH), 1.37 (3H, J = 6.5 Hz, ArCH(OTBS)C<u>H</u>$_3$), 0.88 (9H, s, Si$(CH_3)_2$C(C<u>H</u>$_3)_3$), 0.03 (3H, s, Si(C<u>H</u>$_3)_2$C$(CH_3)_3$), -0.05 (3H, s, Si(C<u>H</u>$_3)_2$C$(CH_3)_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 154.7, 138.8, 126.6, 115.1, 70.7, 27.3, 26.0, 18.3, -4.7, -4.8; **HRMS** (FI) calculated for $C_{14}H_{24}O_2Si$ $[M]^+$ 252.1546, found 252.1546.

Following the one-pot oxidation protocol (250 mg, 0.79 mmol, 1.0 eq of aryl bromide **588**) with 0.1 eq of TBAF at r.t. and quenching with NH_4Cl solution, purification by flash column chromatography (20% Et_2O / P.E. 40 - 60) afforded phenol **632** (197 mg, 0.78 mmol, 99%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that reported above for 4-(1-(*tert*-butyldimethylsilyloxy)ethyl)phenol **632**.

2-Hydroxyphenyl diethylcarbamate (244)



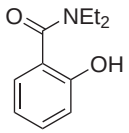
244

Following the *iso*-propoxy silane oxidation protocol (100 mg, 0.32 mmol, 1.0 eq of **231**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (70% Et_2O / P.E. 40 - 60) afforded phenol **244** (66.3 mg, 0.32 mmol, 99%) as an orange solid; **mp** 56.1 °C (lit.[296] mp 75 °C†); $\mathbf{R_f}$ 0.14 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (1H, br s, OH), 7.11 (1H, dt, J = 1.7, 8.1 Hz, ArH), 7.04 (1H, dd, J = 1.6, 8.3 Hz, ArH), 7.02 (1H, dd, J = 8.1, 1.6 Hz, ArH), 6.89 (1H, dt, J = 8.3, 1.7 Hz, ArH), 3.48 (2H, q, J = 7.1 Hz, $NC\underline{H}_2CH_3$), 3.42 (2H, q, J = 7.1 Hz, $NC\underline{H}_2CH_3$), 1.29 (3H, t, J = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.22 (3H, t, J = 7.1 Hz, $NCH_2C\underline{H}_3$).

Following the one-pot oxidation protocol (250 mg, 1.29 mmol, 1.0 eq of phenyl diethylcarbamate **227**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (70% Et_2O / P.E. 40 - 60) afforded phenol **244** (228 mg, 1.09 mmol, 85%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 2-hydroxyphenyl diethylcarbamate **244**.

This spectroscopic data is in agreement with that reported by Julia *et al.*[126]

N,N-Diethyl-2-hydroxybenzamide (230)



230

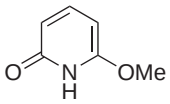
Following the *iso*-propoxy silane oxidation protocol (64 mg, 0.12 mmol, 1.0 eq of **616**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (80% Et_2O / P.E. 40 - 60) afforded phenol **230** (29.1 mg, 0.15 mmol, 68%) as a pale yellow solid; **mp** 89.7 °C (lit.[286] mp 103 - 104 °C‡); $\mathbf{R_f}$ 0.11 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 9.79 (1H, s, OH), 7.34-7.26 (2H, m, ArH), 7.00 (1H, dd, J = 8.3, 1.1 Hz, ArH), 6.84 (1H, dt, J = 7.8, 1.1 Hz, ArH), 3.53 (4H, q, J = 7.1 Hz, $N(C\underline{H}_2CH_3)_2$), 1.28 (6H, t, J = 7.1 Hz, $N(CH_2C\underline{H}_3)_2$).

†A more accurate melting point may be obtained by attempting to crystallise the product phenol.
‡A more accurate melting point may be obtained by attempting to crystallise the phenol obtained.

Following the one-pot oxidation protocol (250 mg, 1.41 mmol, 1.0 eq of *N,N*-diethylbenzamide **236**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (80% Et_2O / P.E. 40 - 60) afforded phenol **633** (120 mg, 0.62 mmol, 44%) as a pale yellow solid; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for *N,N*-diethyl-2-hydroxybenzamide **230**.

This spectroscopic data is in agreement with that reported by Beak *et al.*[123]

6-Methoxypyridin-2(1H)-one (634)

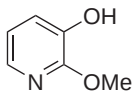


634

Following the one-pot oxidation protocol (250 mg, 1.33 mmol, 1.0 eq of 2-bromo-6-methoxypyridine **226**) with 2.0 eq of TBAF at 60 °C and quenching with 1N HCl solution, purification by flash column chromatography (80% Et_2O / P.E. 40 - 60) afforded pyridone **634** (76.6 mg, 0.61 mmol, 46%) as a brown solid; $\mathbf{R_f}$ 0.10 (80% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 11.26 (1H, br s, NH), 7.43 (1H, dd, J = 8.9, 7.8 Hz, ArH), 6.22 (1H, d, J = 8.9 Hz, ArH), 5.69 (1H, d, J = 7.9 Hz, ArH), 3.86 (3H, s, ArOMe). A melting point was not recorded due to the tendency of this solid to sublime.

This data is in agreement with that reported by Kaneko *et al.*[297]

2-Methoxypyridin-3-ol (635)



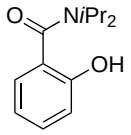
635

Following the *iso*-propoxy silane oxidation protocol (243 mg, 1.24 mmol, 1.0 eq of **617**) with 2.0 eq of KF at 60 °C and quenching with 1N HCl solution, purification by flash column chromatography

(35% EtOAc / P.E. 40 - 60) afforded phenol **635** (77.7 mg, 0.62 mmol, 50%) as a light yellow solid; **mp** 64.5 °C; $\mathbf{R_f}$ 0.34 (70% Et_2O / P.E. 40 - 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3203 (br), 2959, 1609, 1577, 1453, 1383, 1257, 1108, 1021, 778; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.67 (1H, d, J = 5.0 Hz, ArH), 7.10 (1H, d, J = 7.8 Hz, ArH), 6.81 - 6.77 (1H, m, ArH), 5.95 (1H, br s, OH), 3.99 (3H, s, ArOMe); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 153.0, 140.8, 137.0, 121.0, 117.7, 53.6; **HRMS** (FI) calculated for $C_6H_7NO_2$ $[M]^+$ 125.0477, found 124.0510.

Following the one-pot oxidation protocol (250 mg, 2.29 mmol, 1.0 eq of 2-methoxypyridine **618**) with 2.0 eq of KF at 60 °C and quenching with 1N HCl solution, purification by flash column chromatography (80% Et_2O / P.E. 40 - 60) afforded phenol **635** (125 mg, 1.00 mmol, 44%) as an orange oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 2-methoxypyridin-3-ol **635**.

2-Hydroxy-N,N-diiso-propylbenzamide (636)



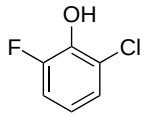
636

Following the *iso*-propoxy silane oxidation protocol (47.3 mg, 0.15 mmol, 1.0 eq of **613**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 60) afforded phenol **636** (32.8 mg, 0.15 mmol, 99%) as a white solid; mp 151.0 158.4 °C; $\mathbf{R_f}$ 0.16 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.34-7.26 (1H, m, ArH), 7.21-7.16 (1H, m, ArH), 7.03-6.98 (1H, m, ArH), 6.89-6.81 (1H, m, ArH), 3.96 (2H, br s, NC$\underline{H}(CH_3)_2$), 1.42 (6H, br s, NCH(C$\underline{H}_3)_2$), 1.39 (6H, br s, NCH(C$\underline{H}_3)_2$).

Following the one-pot oxidation protocol (250 mg, 1.19 mmol, 1.0 eq of *N,N*-diiso-propylbenzamide **229**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 - 60) afforded phenol **636** (203 mg, 0.92 mmol, 77%) as an white solid; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 2-hydroxy-*N,N*-di*iso*-propylbenzamide **636**.

This data is in agreement with that reported by Naka et al.[298]

2-Chloro-6-fluorophenol (637)



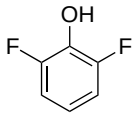
637

Following the iso-propoxy silane oxidation protocol (98 mg, 0.40 mmol, 1.0 eq of **615**) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 60) afforded phenol **637** (54.5 mg, 0.37 mmol, 94%) as a thick yellow oil; $\mathbf{R_f}$ 0.51 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.16-6.97 (2H, m, ArH), 6.87-6.76 (1H, m, ArH), 5.89 (1H, br s, OH).

Following the one-pot oxidation protocol (250 mg, 1.91 mmol, 1.0 eq of 1-chloro-3-fluorobenzene) with 0.1 eq of TBAF at r.t. and quenching with 1N HCl solution, purification by flash column chromatography (50% Et_2O / P.E. 40 60) afforded phenol **637** (277 mg, 1.89 mmol, 94%) as a thick yellow oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 2-chloro-6-fluorophenol **637**.

This data is in agreement with that of a commercially available sample (Aldrich).

2,6-Difluorophenol (638)



638

Following the iso-propoxy silane oxidation protocol (98 mg, 0.43 mmol, 1.0 eq of **614**) with 0.1 eq of TBAF and mesitylene (29.6 L, 0.21 mmol, 0.5 eq) at r.t. and quenching with 1N HCl solution,

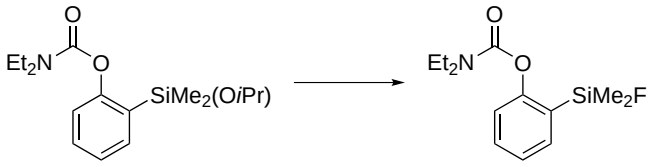
phenol **638** (0.26 mmol, 61% by NMR measured against an internal standard) was obtained; $\mathbf{R_f}$ 0.52 (50% Et_2O / P.E. 40 - 60); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.90-6.70 (3H, m, ArH).

Following the one-pot oxidation protocol (250 mg, 2.19 mmol, 1.0 eq of 1e) with 0.1 eq of TBAF and mesitylene (152 L, 1.10 mmol, 0.5 eq) at r.t. and quenching with 1N HCl solution, phenol **638** (1.95 mmol, 89% by NMR measured against an internal standard) was obtained; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that recorded above for 2,6-difluorophenol **638**.

This data is in agreement with that of a commercially available sample (Aldrich).

7.2.5. Fluorosilane Synthesis

2-(Fluorodimethylsilyl)phenyl diethylcarbamate (245)



231 **245**

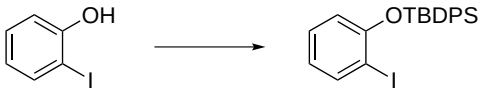
To a stirred solution of 2-(Iso-propoxydimethylsilyl)phenyl diethylcarbamate **231** (103mg, 0.33 mmol, 1.0 eq) in MeOH / THF (1 : 1, 2 mL) was added TBAF (0.66 mL of a 1 M solution in THF, 0.66 mmol, 2.0 eq) and $KHCO_3$ (0.67 mg, 0.66 mmol, 2.0 eq). The reaction mixture was stirred at r.t. for 16 h before quenching with 1N HCl solution. The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*, then purification by flash column chromatography (50% Et_2O / P.E. 40 60) afforded fluorosilane **245** (87.8 mg, 0.33 mmol, 99%) as a pale yellow oil; $\mathbf{R_f}$ 0.41 (50 % Et_2O / P.E. 40 60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2975, 1724, 1596, 1470, 1417, 1381, 1274, 1196, 1154, 1082, 961, 875, 841, 798, 755; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.56 (d, J = 7.5 Hz, ArH), 7.46 (t, J = 8.1 Hz, ArH), 7.24 (t, J = 7.5 Hz, ArH), 7.13 (d, J = 8.1 Hz, ArH), 3.48 (q, J = 7.0 Hz, $NC\underline{H}_2CH_3$), 3.40 (q, J = 7.0 Hz, $NC\underline{H}_2CH_3$), 1.26 (t, J = 7.0 Hz, $NCH_2C\underline{H}_3$), 1.21 (t, J = 7.0 Hz, $NCH_2C\underline{H}_3$), 0.49 (d, J^3_{H-F} = 7.6 Hz, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 155.9, 154.1, 134.4, 131.6, 129.2, 125.0, 122.3, 42.1, 41.7, 14.2, 13.3, -0.5 (d, J^2_{C-F} = 15.3 Hz); ^{19}**F NMR** (377

MHz, $CDCl_3$) δ_F -162.7 (sep, J^3_{H-F} = 7.6 Hz); **HRMS** (FI) calculated for $C_{13}H_{20}FNO_2Si$ [M]+ 269.1247, found 269.1243.

7.3. Silicon-Tethering in Iron-Mediated Chemistry

7.3.1. Preparation of Substrates

tert-Butyl(2-iodophenoxy)diphenylsilane (316)[37]

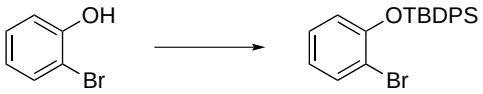


316

To a solution of 2-iodophenol (500 mg, 2.27 mmol, 1.0 eq) and imidazole (235 mg, 3.41 mmol, 1.5 eq) in DCM (5 mL) was added *tert*-butyl(chloro)diphenylsilane (600 μL, 625 mg, 2.27 mmol, 1.0 eq). After stirring for 16 h at 40 °C, the reaction mixture was quenched with NH_4Cl solution and the phases separated. The aqueous phase was washed with DCM (2 x 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O / P.E.) afforded TBDPS ether **316** (896 mg, 1.95 mmol, 85%) as a pale yellow solid; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.81-7.72 (5H, m, ArH), 7.50-7.34 (5H, m, ArH), 6.87 (1H, ddd, J = 8.1, 7.5, 1.5 Hz, ArH), 6.60 (1H, dt, J = 7.5, 1.5 Hz, ArH), 6.40 (1H, dd, J = 8.1, 1.5 Hz, ArH), 1.17 (9H, s, Si*t*-Bu).

This data is in agreement with that reported by Huang *et al.*[299]

tert-Butyl(2-bromophenoxy)diphenylsilane (315)[37]



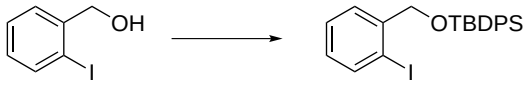
315

To a solution of 2-bromophenol (335 μL, 500 mg, 2.89 mmol, 1.0 eq) and imidazole (295 mg, 4.34 mmol, 1.5 eq) in DCM (5 mL) was added *tert*-butyl(chloro)diphenylsilane (752 μL, 794 mg, 2.89 mmol, 1.0 eq). After stirring for 16 h at 40 °C, the reaction mixture was quenched with NH_4Cl

solution and the phases separated. The aqueous phase was washed with DCM (2 x 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O / P.E.) afforded TBDPS ether **315** (1.08 g, 2.64 mmol, 91%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.80-7.72 (4H, m, ArH), 7.54 (1H, dd, J = 7.6, 1.8 Hz, ArH), 7.47-7.34 (6H, m, ArH), 6.85 (1H, ddd, J = 8.0, 7.6, 1.8 Hz, ArH), 6.73 (1H, dt, J = 7.6, 1.6 Hz, ArH), 6.47 (1H, dd, J = 8.0, 1.6 Hz, ArH), 1.15 (9H, s, Si*t*-Bu).

This data is in agreement with that reported by Huang *et al.*[299]

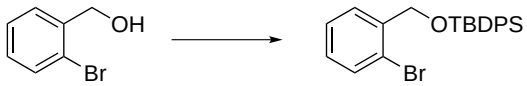
tert-Butyl((2-iodobenzyl)oxy)diphenylsilane (318)[37]



318

To a solution of 2-iodobenzylalcohol (200 mg, 0.86 mmol, 1.0 eq) and imidazole (87.3 mg, 1.28 mmol, 1.5 eq) in DCM (2 mL) was added *tert*-butyl(chloro)diphenylsilane (222 μL, 235 mg, 0.86 mmol, 1.0 eq). After stirring for 16 h at 40 °C, the reaction mixture was quenched with NH_4Cl solution and the phases separated. The aqueous phase was washed with DCM (2 x 2 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O / P.E.) afforded TBDPS ether **318** (325 mg, 0.688 mmol, 80%) as a colourless oil; $\mathbf{R_f}$ 0.53 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3070, 2931, 2857, 1588, 1566, 1471, 1428, 1375, 1205, 1114, 1090, 1043, 1013, 825, 744, 702, 616; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.87-7.79 (6H, m, ArH), 7.55-7.46 (7H, m, ArH), 7.07-7.03 (1H, m, ArH), 4.81 (2H, s, $ArCH_2OTBDPS$), 1.25 (9H, s, Si*t*-Bu); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 142.7, 138.8, 135.6, 133.3, 129.9 (2 x C), 128.7, 128.3, 127.9, 96.1, 70.1, 27.3, 19.5; **HRMS** (ESI^+) calculated for $C_{23}H_{25}INaOSi$ 495.0612, found 495.0604.

tert-Butyl((2-bromobenzyl)oxy)diphenylsilane (317)[37]



317

To a solution of 2-bromobenzylalcohol (500 mg, 2.67 mmol, 1.0 eq) and imidazole (273 mg, 4.01 mmol, 1.5 eq) in DCM (2 mL) was added *tert*-butyl(chloro)diphenylsilane (694 μL, 734 mg, 2.67 mmol, 1.0 eq). After stirring for 16 h at 40 °C, the reaction mixture was quenched with NH_4Cl solution and the phases separated. The aqueous phase was washed with DCM (2 x 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O / P.E.) afforded TBDPS ether **317** (861 mg, 2.02 mmol, 76%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.80-7.70 (5H, m, ArH), 7.54-7.33 (9H, m, ArH), 7.21-7.11 (1H, m, ArH), 4.82 (2H, s, $ArCH_2OSi$), 1.16 (9H, s, Si*t*-Bu).

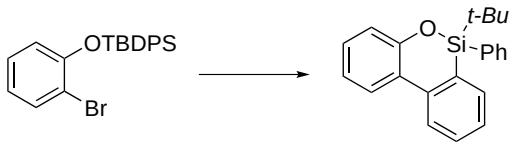
This data is in agreement with that reported by Takacs *et al.*[300]

7.3.2. Cyclisation

General Cyclisation Protocol

To a solution of the starting material (50 mg, 1.0 eq) and DMEDA (5.0 eq) in solvent (1.25 mL) was added $Fe(acac)_3$ (6.5 mg, 0.15 eq) and LiHMDS (3.0 eq of a 1.06 M solution in THF), before stirring for 24 h or 48 h at 50 °C or 80 °C. The reaction mixture was concentrated *in vacuo* and the residue redissolved in Et_2O. Filtration through a silica plug and subsequent concentration *in vacuo* afforded the cyclisation product for crude ^{1}H NMR analysis.

6-(tert-Butyl)-6-phenyl-6H-dibenzo[c,e][1,2]oxasiline (322)[194]



315 **322**

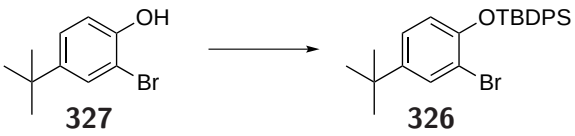
Following the general cyclisation protocol with *tert*-butyl(2-bromophenoxy)diphenylsilane **315** (50 mg, 0.109 mmol, 1.0 eq) in benzene over 24 h at 50 °C afforded cyclisation product **322** (35.7 mg, 0.108 mmol, 99%) as a pale yellow oil; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.99 (1H, d, J = 8.2 Hz, ArH), 7.88 (1H, dd, J = 1.6, 8.0 Hz, ArH), 7.82-7.72 (3H, m, ArH), 7.56 (1H, ddd, J = 1.6, 7.4, 8.1 Hz, ArH), 7.45-7.14 (6H, m, ArH), 7.04 (1H, ddd, J = 1.7, 6.9, 8.0 Hz, ArH), 1.13 (9H,

s, Si*t*-Bu); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 153.5, 141.1, 134.5, 133.6, 133.4, 130.7, 129.9, 129.4, 128.5, 127.8, 126.6, 125.9, 124.9, 124.0, 121.4, 121.0, 26.1, 20.0.

This data is in agreement with that reported by Huang *et al.*[299]

7.3.3. By-Product Characterisation

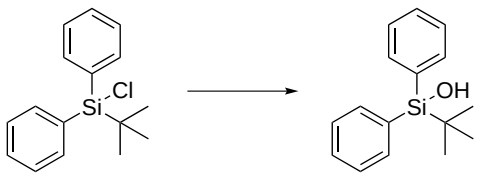
(2-Bromo-4-(tert-butyl)phenoxy)(tert-butyl)diphenylsilane (326)[37]



327 **326**

To a solution of 4-*tert*-butyl-2-bromophenol **327** (200 mg, 0.873 mmol, 1.0 eq) and imidazole (89 mg, 1.31 mmol, 1.5 eq) in DCM (2 mL) was added *tert*-butyl(chloro)diphenylsilane (227 μL, 240 mg, 0.873 mmol, 1.0 eq). After stirring for 16 h at 40 °C, the reaction mixture was quenched with NH_4Cl solution and the phases separated. The aqueous phase was washed with DCM (2 x 2 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E.) afforded TBDPS ether **326** (366 mg, 0.782 mmol, 90%) as a white crystalline solid; **mp** 69.5 - 73.2 °C; $\mathbf{R_f}$ 0.64 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (KBr disc) / cm^{-1} 3071, 2962, 2931, 2857, 1599, 1500, 1429, 1390, 1292, 1271, 1113, 1048, 931, 853, 815, 746, 703, 614, 534, 501; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.81-7.73 (4H, m, ArH), 7.53 (1H, d, J = 2.4 Hz, ArH), 7.50-7.34 (6H, m, ArH), 6.85 (1H, dd, J = 2.5, 8.6 Hz, ArH), 6.39 (1H, d, J = 8.6 Hz, ArH), 1.22 (9H, s, Ar*t*-Bu), 1.14 (9H, s, Si*t*-Bu); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 149.8, 145.1, 135.5, 132.6, 130.2, 130.0, 127.8, 124.9, 119.0, 114.0, 34.1, 31.3, 26.5, 19.7; **HRMS** (FI) calculated for $C_{26}H_{31}O^{79}BrSi$ $[M]^+$ 466.1328, found 4661326.

tert-Butyldiphenylsilanol (321)[301]



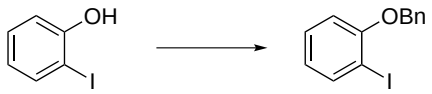
321

To a solution of *tert*-butylchlorodiphenylsilane (95 μL, 100 mg, 0.364 mmol, 1.0 eq) in Et_2O (0.3 mL) was added KOH (22.4 mg, 0.400 mmol, 1.1 eq) in H_2O-MeOH (0.2 mL, 1:4) before stirring for 24 h at r.t. The phases were separated, the aqueous phase was extracted with Et_2O (2 x 0.5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford silanol **321** (92.4 mg, 0.360 mmol, 99%) as a white solid; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.77-7.68 (4H, m, ArH), 7.44-7.36 (6H, m, ArH), 2.14 (1H, br s, SiOH), 1.08 (9H, s, Si*t*-Bu).

This data is in agreement with that reported by Sieburth *et al.*[200]

7.3.4. Test Coupling Reactions

1-((Benzyloxy)methyl)-2-iodobenzene (338)[302]

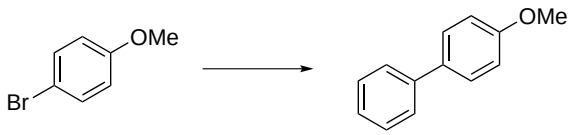


338

To a suspension of 2-iodophenol (500 mg, 2.27 mmol, 1.0 eq) and K_2CO_3 (471 mg, 3.41 mmol, 1.5 eq) in acetone (12 mL) was added benzyl bromide (300 μL, 428 mg, 2.50 mmol, 1.1 eq), and the resulting mixture was refluxed for 18 h. Upon cooling to r.t., the solvent was removed *in vacuo* before the addition of water (6 mL) and extraction with Et_2O (2 x 6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E $\rightarrow$ 50% Et_2O / P.E.) afforded benzyl ether **338** (635 mg, 2.05 mmol, 90%) as a colourless oil, ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.82 (1H, dd, J = 1.6, 7.8 Hz, ArH), 7.56-7.25 (6H, m, ArH), 6.88 (1H, dd, J = 8.2, 1.4 Hz, ArH), 6.74 (1H, dt, J = 7.6, 1.4 Hz, ArH), 5.17 (2H, s, OCH_2Ph).

This data is in agreement with that reported by Sanz *et al.*[303]

4-Methoxy-1,1'-biphenyl (333)[194]

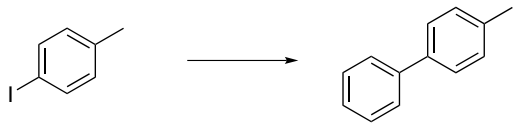


333

To a solution of 4-bromoanisole (20 mg, 0.107 mmol, 1.0 eq) and DMEDA (3.5 μL, 2.82 mg, 0.0321 mmol, 0.3 eq) in benzene (1 mL) was added iron(III) chloride (2.6 mg, 0.0161 mmol, 0.15 eq) and LiHMDS (303 μL, 0.321 mmol, 3.0 eq of a 1.06 M solution in THF), before stirring for 48 h at 80 °C. The reaction mixture was concentrated *in vacuo* and the residue redissolved in Et_2O. Filtration through a silica plug and subsequent concentration *in vacuo* afforded a pale yellow oil which was subjected to crude NMR analysis, giving a starting material to product **333** ratio of 1.5 : 1; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.31-7.60 (7H, m, ArH), 6.99 (2H, d, J = 8.9 Hz, ArH), 3.86 (3H, s, ArOMe).

This data is in agreement with that reported by Liu *et al.*[194]

4-Methyl-1,1'-biphenyl (335)[202]



335

To a solution of 4-iodotoluene (50 mg, 0.229 mmol, 1.0 eq) and undistilled DMEDA (5 μL, 4.05 mg, 0.0459 mmol, 0.2 eq, 95% purity) in benzene (2 mL) was added potassium *tert*-butoxide (77 mg, 0.688 mmol, 3.0 eq), before stirring for 16 h at 80 °C. The reaction mixture was concentrating *in vacuo* and the residue dissolved in Et_2O. Filtration through a silica plug and subsequent concentration *in vacuo* afforded coupled product **335** (34.7 mg, 0.206 mmol, 90%) as a white solid; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.64-7.26 (9H, m, ArH), 2.43 (3H, s, ArMe).

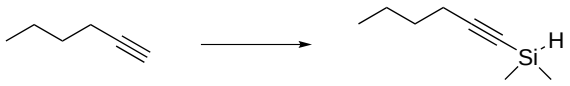
This data is in agreement with that of commercially available 4-methyl-1,1'-biphenyl **335** (Aldrich).

7.4. Silicon-Tethering in Palladium-Mediated Chemistry

7.4.1. Preparation of Initial Substrates

Test Couplings

Hex-1-yn-1-yldimethylsilane (361)[13]

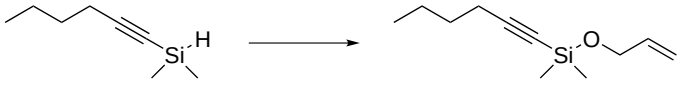


361

To a solution of 1-hexyne (699 μL, 500 mg, 6.09 mmol, 1.0 eq) in THF at −78 °C was added *n*-BuLi (2.68 mL, 6.70 mmol, 1.1 eq of a 2.5 M solution in hexanes) dropwise. After stirring for 15 min at −78 °C, chlorodimethylsilane (811 μL, 691 mg, 7.30 mmol, 1.2 eq) was added and the reaction mixture warmed to r.t. before dilution with Et_2O (6 mL). The resulting suspension was washed with water (12 mL), the phases separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to afford silane **361** (522 mg, 3.72 mmol, 61%) as a colourless oil which was taken on crude to the next step; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 4.12 (1H, sep of t, J = 7.5, 1.2 Hz, SiH), 2.24 (2H, td, J = 7.0, 1.1 Hz, SiC≡CC$\underline{H}_2C_3H_7$), 1.60-1.30 (4H, m, SiC≡CC$H_2C_2\underline{H}_4CH_3$), 0.92 (3H, t, J = 7.1 Hz, SiC≡CC$H_2C_2H_4C\underline{H}_3$), 0.22 (6H, d, J = 3.7 Hz, $SiMe_2$). The moderate yield of this reaction is likely to be due to the volatility of the product.

This data is in agreement with that reported by Petit *et al.*[13]

(Allyloxy)(hex-1-yn-1-yl)dimethylsilane (639)[31]

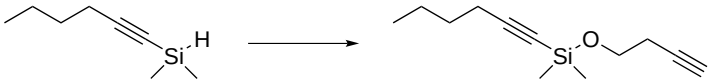


361 **639**

To a neat mixture of silane **361** (522 mg, 3.72 mmol, 1.0 eq) and allyl alcohol (253 μL, 216 mg, 3.72 mmol, 1.0 eq) was added $[RuCl_2(p\text{-cymene})]_2$ (11.4 mg, 0.0186 mmol, 0.005 eq), before stirring for 16 h at r.t. The reaction mixture was then flushed through silica following addition of Et_2O / P.E (1:3), and concentration *in vacuo* afforded siloxane **639** (522 mg, 2.66 mmol, 71%) as a colourless oil; $\mathbf{R_f}$ 0.74 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2961, 2935, 2874, 2176, 1255, 1136, 1081,

919, 861, 830, 792, 672; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.97 (1H, tdd, J = 5.1, 10.3, 17.1 Hz, C$\underline{H}$=CH_2), 5.28 (1H, qd, J = 1.8, 17.1 Hz, CH=C$\underline{H}_2$), 5.12 (1H, qd, J = 1.7, 10.3 Hz, CH=C$\underline{H}_2$), 4.24 (2H, td, J = 1.6, 5.0 Hz, SiOC$\underline{H}_2$CH=CH_2), 2.25 (2H, t, J = 6.9 Hz, SiC≡CC$\underline{H}_2C_3H_7$), 1.60-1.32 (4H, m, C≡$CCH_2C_2\underline{H}_4CH_3$), 0.923 (3H, t, J = 7.2 Hz, C≡$CC_3H_6C\underline{H}_3$), 0.256 (6H, s, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.8, 114.6, 108.1, 82.0, 64.2, 30.5, 21.8, 19.3, 13.5, 0.2; **HRMS** (FI) calculated for $C_{11}H_{21}OSi$ $[M]^+$ 197.1362, found 197.1362.

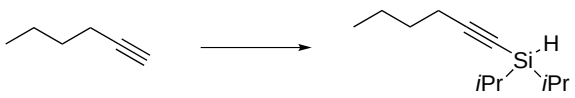
(But-3-yn-1-yloxy)(hex-1-yn-1-yl)dimethylsilane (640)



361 **640**

To a stirred solution of silane **361** (262 mg, 1.87 mmol, 1.0 eq) in DCM (3 mL) at 0 °C was added *N*-bromosuccinimide (333 mg, 1.87 mmol, 1.0 eq) before warming to r.t. and stirring for 15 min. A solution of 3-butyn-1-ol (127 μL, 1.68 mmol, 0.90 eq), Et_3N (261 μL, 1.87 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (2 mL) was added *via* cannula, and the reaction mixture was stirred at r.t. for 12 h before concentration *in vacuo* and purification by flash column chromatography (100 % P.E.) afforded siloxane **640** (219 mg, 1.05 mmol, 63 %) as a colourless oil; $\mathbf{R_f}$ 0.55 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3311, 2960, 2876, 2175, 1467, 1255, 1100, 953, 924, 829, 793, 636; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 3.78 (2H, t, J = 7.3 Hz, $SiOCH_2$), 2.43 (2H, td, J = 7.3, 2.7 Hz, $SiOCH_2CH_2C\underline{H}_2$), 2.22 (2H, t, J = 7.0 Hz, $SiC{\equiv}CCH_2$), 1.95 (1H, t, J = 2.7 Hz, CCH), 1.53-1.35 (4H, m, $SiC{\equiv}CCH_2C_2\underline{H}_4CH_3$), 0.90 (3H, t, J = 7.3 Hz, $SiC{\equiv}CC_3H_6C\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 108.4, 81.8, 81.2, 69.3, 61.7, 30.5, 22.4, 21.9, 19.4, 13.5, 0.1; **HRMS** (FI) calculated for $C_{12}H_{21}OSi$ $[M]^+$ 209.1362, found 209.1353.

Hex-1-yn-1-yldiisopropylsilane (363)[13]



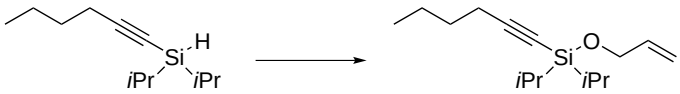
363

To a solution of 1-hexyne (699 μL, 500 mg, 6.09 mmol, 1.0 eq) in THF at −78 °C was added *n*-BuLi (2.68 mL, 6.70 mmol, 1.1 eq of a 2.5 M solution in hexanes) dropwise. After stirring for 15 min at

−78 °C, chlorodi*iso*propyllsilane (1.25 mL, 1.10 g, 7.30 mmol, 1.2 eq) was added and the reaction mixture warmed to r.t. before dilution with Et_2O (6 mL). The resulting suspension was washed with water (12 mL), the phases separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to afford silane **363** (1.07 g, 5.45 mmol, 89%) as a colourless oil which was taken on crude to the next step; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 3.67 (1H, br s, SiH), 2.27 (2H, dt, J = 1.19, 6.83 Hz, SiC≡CC$\underline{H}_2$C$_3$H$_7$), 1.61-1.32 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$CH$_3$), 1.13-1.01 (14H, m, Si(i-Pr)$_2$), 0.924 (3H, t, J = 7.2 Hz, C≡CC$_3$H$_6$C$\underline{H}_3$).

This data is in agreement with that reported by Petit *et al.*[13]

(Allyloxy)(hex-1-yn-1-yl)diisopropylsilane (641)



363 **641**

Via Bromo-Silane Formation[13]

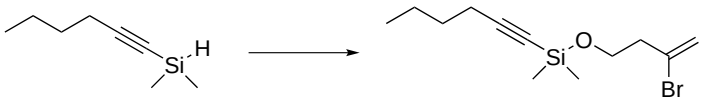
To a solution of silane **363** (1.32 g, 6.71 mmol, 1.0 eq) in DCM (5 mL) at 0 °C was added *N*-bromosuccinimide (1.19 g, 6.71 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of allyl alcohol (0.411 mL, 351 mg, 6.04 mmol, 0.9 eq), NEt_3 (0.935 mL, 679 mg, 6.71 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (5 mL) before stirring for 12 h at r.t. Concentration of the crude reaction mixture *in vacuo* and purification by flash column chromatography (100% P.E.) afforded siloxane **641** (1.03 g, 5.24 mmol, 87%) as a colourless oil; $\mathbf{R}_f$ 0.74 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2943, 2867, 2173, 1464, 1141, 1089, 1034, 919, 883, 805; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.05-5.86 (1H, m, C$\underline{H}$=CH$_2$), 5.29 (1H, dq, J = 17.1, 1.9 Hz, CH=C$\underline{H}_2$), 5.09 (1H, dq, J = 10.4, 1.8 Hz, CH=C$\underline{H}_2$), 4.30 (2H, td, J = 4.8, 1.7 Hz, SiOC$\underline{H}_2$CH=CH$_2$), 2.28 (2H, t, J = 6.8 Hz, SiC≡CC$\underline{H}_2$C$_3$H$_7$), 1.61-1.34 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$CH$_3$), 1.08-1.01 (14H, m, Si(i-Pr)$_2$), 0.93 (3H, t, J = 7.2 Hz, C≡CC$_3$H$_6$C$\underline{H}_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 137.2 (C=C), 114.0 (C=C), 109.6 ($\underline{C}$≡CSi), 78.6 (C≡$\underline{C}$Si), 65.1 (C-O), 30.7 (n-Bu), 21.8 (n-Bu), 19.3 (n-Bu), 17.1 (SiiPr$_2$), 17.0 (SiiPr$_2$), 13.4 (n-Bu), 13.1 (SiiPr$_2$); **HRMS** (FI) calculated for $C_{15}H_{28}OSi$ 252.1909 [M]$^+$, found 252.1912.

Via Ruthenium-Catalysed Silane-Alcohol Coupling[31]

To a neat mixture of silane **363** (1.07 g, 5.45 mmol, 1.0 eq) and allyl alcohol (371 μL, 317 mg, 5.45 mmol, 1.0 eq) was added $[RuCl_2(p\text{-cymene})]_2$ (16.7 mg, 0.0273 mmol, 0.005 eq), before stirring at 50 °C for 16 h. The reaction mixture was then flushed through silica following addition of Et_2O / P.E (1:3), and concentration *in vacuo* afforded siloxane **641** (1.15 g, 4.56 mmol, 84%) as a colourless oil; $\mathbf{R_f}$ and ^{1}**H NMR** data in agreement with that reported above for (allyloxy)(hex-1-yn-1-yl)diisopropylsilane **641**.

Dimethyl Substrates

((3-Bromobut-3-en-1-yl)oxy)(hex-1-yn-1-yl)dimethylsilane (365)[31]

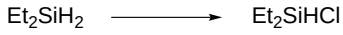


361 **365**

To a neat mixture of silane **361** (339 mg, 2.42 mmol, 1.0 eq) and 3-bromobut-3-en-1-ol (240 μL, 365 mg, 2.42 mmol, 1.0 eq) was added $[RuCl_2(p\text{-cymene})]_2$ (7.35 mg, 0.0121 mmol, 0.005 eq), before stirring for 16 h at r.t. The reaction mixture was then flushed through silica following addition of Et_2O / P.E (1:3), and concentration *in vacuo* afforded siloxane **365** (644 mg, 2.22 mmol, 92%) as a colourless oil; $\mathbf{R_f}$ 0.73 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2961, 2935, 2874, 2177, 1466, 1255, 1054, 953, 862, 833, 795, 674; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 5.67-5.46 (2H, m, CBr=C$\underline{H}_2$), 3.88 (2H, t, J = 6.5 Hz, SiOC$\underline{H}_2$CH$_2$CBr=CH$_2$), 2.69 (2H, dt, J = 0.93, 6.50 Hz, SiOCH$_2$C$\underline{H}_2$CBr=CH$_2$), 2.29-2.20 (2H, m, SiC≡CC$\underline{H}_2$C$_3$H$_7$), 1.59-1.33 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$CH$_3$), 0.96-0.89 (3H, m, C≡CC$_3$H$_6$C$\underline{H}_3$), 0.25 (6H, d, J = 1.1 Hz, SiMe$_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 130.5 (Br$\underline{C}$=C), 118.7 (BrC=$\underline{C}$), 106.4 ($\underline{C}$≡CSi), 83.9 (C≡$\underline{C}$Si), 59.8 (C-O), 44.3 ($\underline{C}$-CBr), 30.4 (*n*-Bu), 21.8 (*n*-Bu), 19.2 (*n*-Bu), 13.4 (*n*-Bu), 2.12 (SiMe$_2$); **HRMS** (FI) calculated for $C_{12}H_{21}^{79}BrOSi$ $[M]^+$ 213.1050, mass not found.

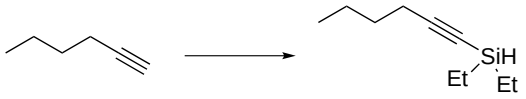
Diethyl Substrates

Chlorodiethylsilane[227]



To a suspension of $CuCl_2$ (6.16 g, 45.8 mmol, 2.02 eq) and CuI (256 mg, 1.13 mmol, 0.05 eq) in Et_2O (60 mL) was added diethylsilane (2.94 mL, 2.00 g, 22.7 mmol, 1.0 eq). The resulting reaction mixture was stirred at r.t. for 36 h, before filtration over celite and concentration of the filtrate *in vacuo*. The crude residue was distilled to afford chlorodiethylsilane (863 mg, 7.04 mmol, 31%) as a colourless oil; **bp** 100 °C, 1013 mbar (lit. bp[304] 99.7 °C, 760 Torr); ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 4.49 (1H, quin, J = 2.3 Hz), 1.03-0.94 (6H, m, $CH_2C\underline{H}_3$), 0.69-0.56 (4H, m, $C\underline{H}_2CH_3$). Further characterisation was not completed due to difficulties in purification.

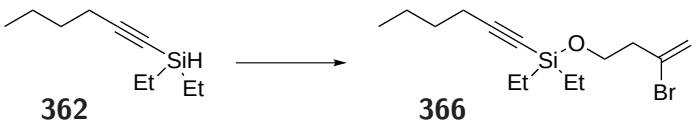
Diethyl(hex-1-yn-1-yl)silane (362)[13]



362

To a stirred solution of 1-hexyne (350 μL, 250 mg, 3.05 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added n-BuLi (1.34 mL, 3.36 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorodiethylsilane (505 μL, 449 mg, 3.66 mmol, 1.2 eq) was added and the reaction mixture warmed to r.t. before dilution with Et_2O (2.5 mL). The resulting suspension was washed with water (5 mL), the phases separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to afford silane **362** (508 mg, 3.02 mmol, 85%) as a colourless oil which was inseperable from a number of impurities; $\mathbf{R}_f$ 0.68 (10% Et_2 / P.E. 40-60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2958, 2877, 2176, 1460, 1414, 1241, 1068, 1009, 855, 735; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 3.77-3.73 (1H, m, SiH), 2.28-2.20 (2H, m, C≡CC$\underline{H}_2$C$_3$H$_7$), 1.57-1.27 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$CH$_3$), 1.57-1.27 (9H, m, Si(CH$_2$C$\underline{H}_3$)$_2$, C≡CC$_3$H$_6$C$\underline{H}_3$), 0.70-0.48 (4H, m, Si(C$\underline{H}_2$CH$_3$)$_2$); ^{13}**C NMR** 125.1, 82.3, 30.6, 21.9, 19.4, 8.2, 6.8, 6.6, 6.5, 6.4; **HRMS** (FI) calculated for $C_{10}H_{20}Si$ $[M]^+$ 168.1334, not found.

((3-Bromobut-3-en-1-yl)oxy)diethyl(hex-1-yn-1-yl)silane (366)[13]



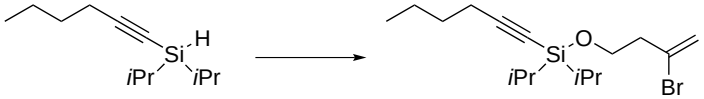
362 **366**

To a solution of silane **362** (500 mg, 2.97 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added N-bromosuccinimide (529 mg, 2.97 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15

min at r.t. The resulting suspsension was then added *via* cannula to a solution of 3-bromobut-3-en-1-ol (403 mg, 2.67 mmol, 0.9 eq), NEt_3 (0.414 mL, 301 mg, 2.97 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (3 mL) before stirring for 12 h at r.t. Concentration of the crude reaction mixture *in vacuo* and purification by flash column chromatography (100% P.E.) afforded siloxane **366** (546 mg, 1.72 mmol, 64%) as a colourless oil; $\mathbf{R_f}$ 0.58 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2958, 2877, 2175, 1631, 1460, 1413, 1240, 1052, 1006, 889, 736; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.66-5.66 (1H, m, $=CH_2$), 5.48 (1H, d, J = 1.6 Hz, $=CH_2$), 3.76 (2H, t, J = 6.1 Hz, $SiOCH_2$), 2.62 (2H, td, J = 6.1, 1.0 Hz, $SiOCH_2C\underline{H}_2$), 2.18 (2H, dtd, J = 6.8, 4.5, 2.3 Hz, $SiC{\equiv}CCH_2$), 1.50-1.27 (4H, m, $SiC{\equiv}CCH_2C_2\underline{H}_4CH_3$), 0.99-0.84 (9H, m, $Si(CH_2C\underline{H}_3)_2$), $SiC{\equiv}CC_3H_6C\underline{H}_3$), 0.61-0.45 (4H, m, $Si(C\underline{H}_2CH_3)_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 130.5 (Br$\underline{C}$=C), 118.9 (BrC=$\underline{C}$), 106.9 ($\underline{C}{\equiv}CSi$), 82.2 (C$\equiv\underline{C}$Si), 59.9 (C-O), 44.3 ($\underline{C}$-CBr), 30.6 (*n*-Bu), 21.8 (*n*-Bu), 19.3 (*n*-Bu), 13.4 (*n*-Bu), 8.2 ($SiEt_2$), 7.3 ($SiEt_2$), 6.5 (2 x C, $SiEt_2$); **HRMS** (FI) calculated for $C_{14}H_{25}OSi^{79}Br$ 316.0858, not found.

Diiso-propyl Substrates

((3-Bromobut-3-en-1-yl)oxy)(hex-1-yn-1-yl)diisopropylsilane (367)[13]



363 **367**

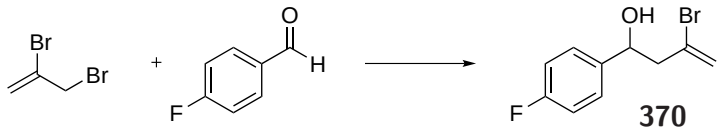
To a solution of silane **363** (1.24 g, 6.31 mmol, 1.0 eq) in DCM (5 mL) at 0 °C was added *N*-bromosuccinimide (1.12 g, 6.31 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of 3-bromobut-3-en-1-ol (0.564 mL, 858 mg, 5.68 mmol, 0.9 eq), NEt_3 (0.879 mL, 639 mg, 6.71 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (5 mL) before stirring for 12 h at r.t. Concentration of the crude reaction mixture *in vacuo* and purification by flash column chromatography (100% P.E.) afforded siloxane **367** (1.11 g, 3.21 mmol, 57%) as a colourless oil; $\mathbf{R_f}$ 0.73 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2943, 2866, 2172, 1631, 1464, 1103, 994, 884, 750, 646; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 5.67-5.46 (2H, m, CBr=C$\underline{H}_2$), 3.93 (2H, t, J = 6.5 Hz, $SiOC\underline{H}_2CH_2CBr{=}CH_2$), 2.68 (2H, td, J = 6.5, 1.1 Hz, $SiOCH_2C\underline{H}_2CBr{=}CH_2$), 2.29 (2H, t, J = 6.8 Hz, $SiC{\equiv}CC\underline{H}_2C_3H_7$), 1.62-1.42 (4H, m, $C{\equiv}CCH_2C_2\underline{H}_4CH_3$), 1.10-0.88 (17H, m, Si(*i*-Pr)$_2$, $C{\equiv}CC_3H_6C\underline{H}_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 130.7 (Br$\underline{C}$=C), 118.0 (BrC=$\underline{C}$), 109.7 ($\underline{C}{\equiv}CSi$), 78.5 (C$\equiv\underline{C}$Si), 62.0 (C-O), 44.5 ($\underline{C}$-CBr), 30.7

(*n*-Bu), 21.8 (*n*-Bu), 19.4 (*n*-Bu), 17.2 (Si*i*Pr$_2$), 17.0 (Si*i*Pr$_2$), 13.5 (*n*-Bu), 13.1 (Si*i*Pr$_2$); **HRMS** (FI) calculated for $C_{16}H_{30}O^{79}BrSi$ 345.1249, found 345.1257.

7.4.2. Preparation of Additional Substrates

Alcohol Synthesis

3-Bromo-1-(4-fluorophenyl)but-3-en-1-ol (370)[231]

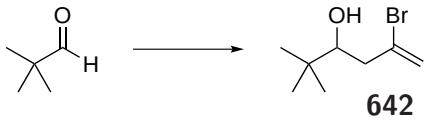


370

To a suspension of tin (1.15 g, 9.69 mmol, 1.2 eq) and 2,3-dibromopropene (0.945 mL, 9.69 mmol, 1.2 eq) in Et_2O/H_2O (1:1, 20 mL) was added 4-fluorobenzaldehyde (0.864 mL, 1.00g, 8.07 mmol, 1.0 eq) and HBr (several drops). The reaction mixture was stirred at r.t. for 16 h, extracted with Et_2O (10 mL) and H_2O (10 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded alcohol **370** (1.07 g, 4.43 mmol, 55%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.41-7.34 (2H, m, ArH), 7.11-7.01 (2H, m, ArH), 5.68 (1H, dt, J = 1.7, 0.9 Hz, =CH_2), 5.55 (1H, d, J = 1.7 Hz, =CH_2), 5.04 (1H, dd, J = 8.3, 4.7 Hz, ArC<u>H</u>OHCH$_2$CBrCH$_2$), 2.83-2.74 (2H, m, ArCHOHC<u>H$_2$</u>C^{79}BrCH$_2$).

This data is in agreement with that reported by Beruben *et al.*[305]

5-Bromo-2,2-dimethylhex-5-en-3-ol (642)[231]



642

To a suspension of tin (827 mg, 6.97 mmol, 1.0 eq) and 2,3-dibromopropene (0.681 mL, 6.97 mmol, 1.0 eq) in Et_2O/H_2O (1:1, 14 mL) was added trimethylacetaldehyde (0.910 mL, 720 mg, 8.36 mmol, 1.2 eq) and HBr (several drops). The reaction mixture was stirred at r.t. for 16 h, extracted with Et_2O (7 mL) and H_2O (7 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10% → 100% Et_2O / P.E. 40-60) afforded

alcohol **642** (712 mg, 3.43 mmol, 49%) as a colourless oil; $\mathbf{R_f}$ 0.14 (10% Et_2 / P.E. 40-60); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3445, 2959, 2872, 1632, 1480, 1365, 1291, 1210, 1129, 1069, 1007, 888; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 5.72 (1H, td, J = 1.5, 0.47 Hz, $=CH_2$), 5.55 (1H, dd, J = 1.6, 0.66 Hz, $=CH_2$), 3.58 (1H, dd, J = 10.2, 1.8 Hz, C$\underline{H}$OH), 2.62 (1H, ddt, J = 14.3, 2.3, 1.0 Hz, CBrC$\underline{H}_x$H$_y$), 2.44-2.39 (1H, m, CBrCH$_x\underline{H}_y$), 1.69 (1H, br s, OH), 0.95 (9H, s, t-Bu); ^{13}**C NMR** 132.3, 119.5, 76.2, 44.3, 34.4, 25.8; **HRMS** (FI) calculated for $C_8H_{15}^{79}BrO$ $[M]^+$ 206.0306, found 206.0302.

2-Iodoprop-2-en-1-ol (374)[232]

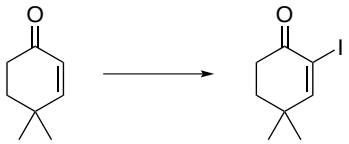


374

A suspension of sodium iodide (2.01 g, 13.4 mmol, 1.5 eq), chlorotrimethylsilane (1.70 mL, 1.46 g, 13.4 mmol, 1.5 eq) and H_2O (0.12 mL, 6.69 mmol, 0.75 eq) in CH_3CN (10 mL) was stirred for 10 min at r.t., before the addition of propargyl alcohol (0.52 mL, 500 mg, 8.92 mmol, 1.0 eq). The reaction mixture was stirred for 1 h, then quenched with H_2O (15 mL) and extracted with Et_2O (5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O / P.E. 40-60) afforded alcohol **374** (251.4 mg, 1.37 mmol, 15%) as a yellow oil which darkened upon standing; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.41 (1H, *app* q, J = 1.7 Hz, $=CH_2$), 5.88 (1H, *app* qt, J = 1.9, 1.2 Hz, $=CH_2$), 4.22-4.17 (2H, m, C$\underline{H}_2$OH).

This data is in agreement with that reported by Lai *et al.*[306]

2-Iodo-4,4-dimethylcyclohex-2-enone (376)[307]



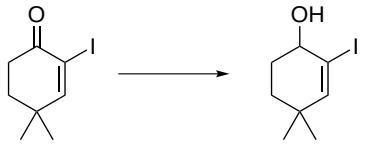
376

To a stirred solution of 4,4'-dimethyl-2-cyclohexen-1-one (530 μL, 500 mg, 4.03 mmol, 1.0 eq) in CCl_4 / pyridine (20 mL, 1:1) at 0 °C was added iodine (2.04 g, 8.05 mmol, 2.0 eq) in CCl_4 / pyridine

(20 mL, 1:1) dropwise. The resulting mixture was stirred for 2h at rt, before dilution with Et_2O (20 mL), phase separation and washing of the organic phase with water (30 mL), 1N HCl solution (30 mL) and aqueous $Na_2S_2O_3$ solution (30 mL). Concentration *in vacuo* afforded cyclohexenone **376** (998 mg, 3.99 mmol, 99%) as a yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.47 (1H, t, J = 0.7 Hz, C=CH), 2.72-2.66 (2H, m, $C(=O)CH_2$), 1.97-1.90 (2H, m, $C(=O)CH_2C\underline{H}_2$), 1.21 (6H, s, Me_2).

This data is in agreement with that reported by Pandey *et al.*[308]

2-Iodo-4,4-dimethylcyclohex-2-enol (377)[309]



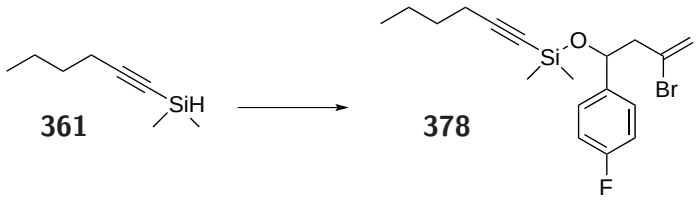
376 **377**

To a stirred solution of cyclohexenone **376** (998 mg, 3.99 mmol, 1.0 eq) in MeOH (12 mL) at 0 °C was added $CeCl_3$ (983 mg, 3.99 mmol, 1.0 eq) before stirring for 10 min at 0 °C. $NaBH_4$ (226 mg, 5.99 mmol, 1.0 eq) was added at 0 °C and the resulting suspension was warmed to rt and stirred for 1 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). Concentration *in vacuo* afforded alcohol **377** (793 mg, 3.15 mmol, 79%) as a pale yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.24 (1H, d, J = 0.4 Hz, C=CH), 4.14 (1H, q, J = 4.9 Hz, $C\underline{H}OH$), 2.18-1.43 (4H, m, C_2H_4), 1.04 (3H, s, Me), 1.01 (3H, s, Me).

This data is in agreement with that reported by Kim *et al.*[310]

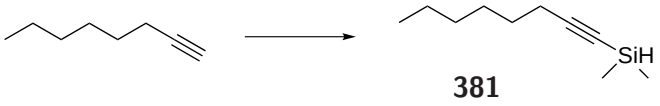
Dimethyl Substrates

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)(hex-1-yn-1-yl)dimethylsilane (378)



To a neat mixture of silane **361** (256 mg, 1.82 mmol, 1.0 eq) and alcohol **370** (447 mg, 1.82 mmol, 1.0 eq) was added $[RuCl_2(p\text{-cymene})]_2$ (5.57 mg, 9.10 μmol, 0.005 eq), before stirring for 16 h at rt. The reaction mixture was then flushed through silica following addition of P.E, and concentration *in vacuo* afforded siloxane **378** (217 mg, 0.654 mmol, 31%) as a colourless oil; $\mathbf{R_f}$ decomp. (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2960, 2176, 1885, 1605, 1510, 1407, 1254, 1225, 1042, 832, 792, 674; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.37-7.30 (2H, m, ArH), 7.06-6.97 (2H, m, ArH), 5.64-5.62 (1H, m, $=CH_2$), 5.53-5.51 (1H, m, $=CH_2$), 5.00 (1H, dt, J = 8.6, 4.3 Hz, ArCHOSi), 2.84-2.66 (2H, m, $CBrCH_2$), 2.24-2.20 (2H, m, $SiC{\equiv}CC\underline{H}_2C_3H_7$), 1.55-1.38 (4H, m, $C{\equiv}CCH_2C_2\underline{H}_4CH_3$), 0.94-0.90 (3H, m, $C{\equiv}CC_3H_6C\underline{H}_3$), 0.25 (6H, d, J = 1.0 Hz, $SiMe_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.3 (d, J^1_{C-F} = 246 Hz, ArF), 138.6 (ArF), 129.8 (Br$\underline{C}$=C), 127.5 (d, J^3_{C-F} = 8.4 Hz, ArF), 120.1 (BrC=$\underline{C}$), 115.3 (d, J^2_{C-F} = 21.6 Hz, ArF), 106.8 ($\underline{C}{\equiv}CSi$), 84.1 ($C{\equiv}\underline{C}Si$), 71.0 (C-O), 51.4 (C-CBr), 30.5 (*n*-Bu), 21.9 (*n*-Bu), 19.4 (*n*-Bu), 13.5 (*n*-Bu), 2.3 ($SiMe_2$); **HRMS** (FI) calculated for $C_{18}H^{79}_{24}BrFOSi$ $[M]^+$ 384.0745, not found.

Dimethyl(oct-1-yn-1-yl)silane (381)

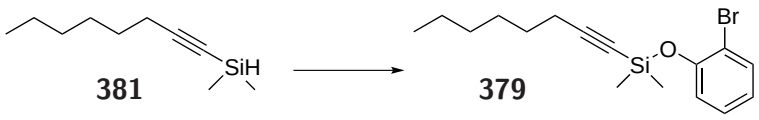


To a stirred solution of 1-octyne (335 μL, 250 mg, 2.27 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*-BuLi (1.00 mL, 2.50 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorodimethylsilane (302 μL, 257 mg, 2.72 mmol, 1.2 eq) was added and the reaction mixture warmed to r.t. before dilution with Et_2O (2.5 mL). The resulting suspension was washed with water (5 mL), the phases separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to afford silane **381** (378 mg, 2.25 mmol, 99%) as a colourless oil taken on

crude to the next step; ^{1}**H NMR** 4.15-4.08 (1H, m, SiH), 2.27-2.15 (2H, m, C≡CC$\underline{H}_2$C$_5$H$_{11}$), 1.60-1.20 (8H, m, C≡CCH$_2$C$_4\underline{H}_8$CH$_3$), 0.96-0.83 (3H, m, C≡CC$_5$H$_{10}$C$\underline{H}_3$), 0.27-0.17 (6H, m, SiMe$_2$).

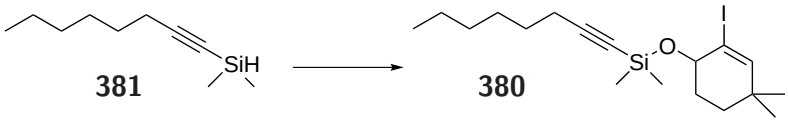
This data is in agreement with that reported by Tamao *et al.*[14]

((2-Bromophenoxy)dimethyl(oct-1-yn-1-yl)silane (379)



To a neat mixture of silane **381** (382 mg, 2.27 mmol, 1.0 eq) and 2-bromophenol (263 μL, 392 mg, 2.27 mmol, 1.0 eq) was added [RuCl$_2$(*p*-cymene)]$_2$ (6.95 mg, 1.14 μmol, 0.005 eq), before stirring for 16 h at rt. Purification by flash column chromatography (10 % Et$_2$O / P.E.) afforded siloxane **379** (141.5 mg, 0.417 mmol, 18%) as a colourless oil; $\mathbf{R}_f$ 0.72 (10% Et$_2$O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2927, 2176, 1886, 1587, 1477, 1254, 1045, 922, 832, 794, 752; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ_H 7.55-7.51 (1H, m, ArH), 7.21-7.13 (1H, m, ArH), 6.92-6.81 (2H, m, ArH), 2.26-2.20 (2H, m, C≡CC$\underline{H}_2$), 1.44-1.22 (8H, m, C≡CCH$_2$C$_4\underline{H}_8$CH$_3$), 0.90 (3H, *app* dt, J; = 7.4, 3.9 Hz, C≡CC$_5$H$_{10}$C$\underline{H}_3$), 0.26 (6H, s, SiMe$_2$); **HRMS** (FI) calculated for C$_{18}$H$_{24}^{79}$BrFOSi [M]$^+$ 384.0745, not found. Further characterisation was not completed due to difficulties in obtaining a clean sample of this compound.

((2-Iodo-4,4-dimethylcyclohex-2-en-1-yl)oxy)dimethyl(oct-1-yn-1-yl)silane (380)

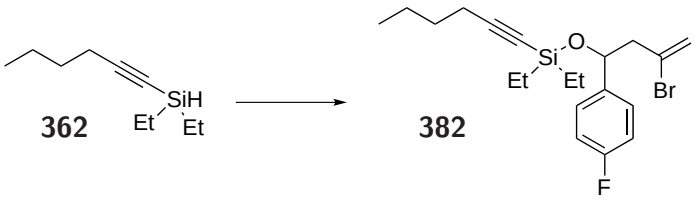


To a neat mixture of silane **381** (200 mg, 1.19 mmol, 1.0 eq) and alcohol **376** (134 mg, 1.19 mmol, 1.0 eq) was added [RuCl$_2$(*p*-cymene)]$_2$ (3.64 mg, 5.94 μmol, 0.005 eq), before stirring for 16 h at rt. The reaction mixture was then flushed through silica following addition of P.E, and concentration *in vacuo* afforded siloxane **380** (220 mg, 0.526 mmol, 44%) as a colourless oil; $\mathbf{R}_f$ 0.67 (10% Et$_2$O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2927, 2857, 2175, 1456, 1456, 1359, 1252, 1059, 929, 885, 834, 789, 673; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ_H 6.23 (1H, s, =CH), 4.33 (1H, t, J = 5.3

Hz, CHOSi), 2.27-2.20 (2H, m, SiC≡CC$\underline{H}_2$C$_5$H$_{11}$), 2.18-1.87 (4H, m, OCHC$_2\underline{H}_2$C(CH$_3$)$_2$), 1.70-1.22 (8H, m, C≡CCH$_2$C$_4\underline{H}_8$CH$_3$), 1.03 (3H, s, C(C$\underline{H}_3$)(CH$_3$), 0.99 (3H, s, C(C$\underline{H}_3$)(CH$_3$), 0.92-0.87 (3H, m, C≡CC$_5$H$_{10}$C$\underline{H}_3$), 0.36 (3H, s, SiMe$_2$), 0.28 (3H, s, SiMe$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 150.1 (I$\underline{C}$=C), 108.8 (IC=$\underline{C}$), 102.3 ($\underline{C}$≡CSi), 82.4 (C≡$\underline{C}$Si), 72.3 (C-O), 37.2 (*c*-Hex), 32.4 (*c*-Hex), 31.3 (*n*-Hex), 30.0 (*n*-Hex), 28.7 (Me), 28.5 (Me), 28.4 (*n*-Hex), 28.2 (*n*-Hex), 22.6 (*n*-Hex), 19.8 (*c*-Hex), 14.0 (*n*-Hex), 1.4 (SiMe$_2$); **HRMS** (ESI$^+$) calculated for C$_{18}$H$_{31}$INaOSi [M+Na]$^+$ 441.1081, found 441.1072.

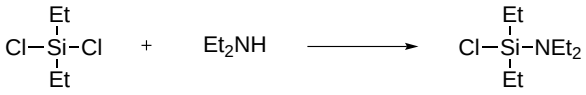
Diethyl Substrates

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diethyl(hex-1-yn-1-yl)silane (382)[13]



To a solution of silane **362** (259 mg, 1.54 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added *N*-bromosuccinimide (274 mg, 1.54 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of alcohol **370** (340 mg, 1.39 mmol, 0.9 eq), NEt$_3$ (0.215 mL, 159 mg, 1.54 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (3 mL) before stirring for 12 h at r.t. Concentration of the crude reaction mixture *in vacuo* and purification by flash column chromatography (10% Et$_2$O / P.E. 40-60) afforded siloxane **382** (277 mg, 0.63 mmol, 41%) as a colourless oil; $\mathbf{R_f}$ 0.60 (10% Et$_2$O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2959, 2877, 2175, 1633, 1606, 1460, 1226, 1084, 1009, 890, 815, 736; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.36-7.31 (2H, m, ArH), 7.03-6.97 (2H, m, ArH), 5.50 (1H, dd, J = 1.7, 0.7 Hz, =C$\underline{H}_x$H$_y$), 5.40 (1H, t, J = 1.7 Hz, =CH$_x\underline{H}_y$), 5.17 (1H, dd, J = 7.5, 5.5 Hz, SiOCH), 2.89 (1H, ddd, J = 14.2, 7.5, 0.8 Hz, SiOCHC$\underline{H}_x$H$_y$), 2.63 (1H, ddd, J = 14.2, 5.4, 0.9 Hz, SiOCHCH$_x\underline{H}_y$), 2.28-2.20 (2H, m, C≡CCH$_2$), 1.55-1.38 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$), 1.06-0.90 (6H, m, Si(CH$_2$C$\underline{H}_3$)$_2$), 0.844 (3H, t, J = 7.9 Hz, CH$_3$), 0.70-0.45 (4H, m, Si(C$\underline{H}_2$CH$_3$)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 161.7 (d, J^1_{C-F} = 245 Hz, ArF), 139.4 (ArF), 130.0 (Br$\underline{C}$=C), 127.7 (d, J^3_{C-F} = 8.1 Hz, ArF), 119.4 (BrC=$\underline{C}$), 114.8 (d, J^2_{C-F} = 20.9 Hz, ArF), 109.6 ($\underline{C}$≡CSi), 80.0 (C≡$\underline{C}$Si), 72.6 (C-O), 52.4 ($\underline{C}$-CBr), 30.5 (*n*-Bu), 21.8 (*n*-Bu), 19.4 (*n*-Bu), 13.5 (*n*-Bu), 7.4 (SiEt$_2$), 7.0 (SiEt$_2$), 6.6 (SiEt$_2$), 6.4 (SiEt$_2$); **HRMS** (FI) calculated for C$_{20}$H$_{28}^{79}$BrOSiF [M]$^+$ 412.1059, found 412.0952.

1-Chloro-N,N-diethyl-1,1-diethylsilanamine (392)[135]

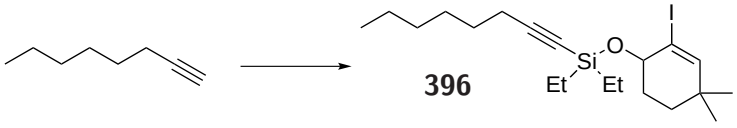


392

To a stirred solution of dichlorodiethylsilane (20.0 mL, 21.0 g, 134 mmol, 1.0 eq) and Et_3N (20.6 mL, 14.9 g, 147 mmol, 1.1 eq) in THF (20 mL) at 0 °C was added distilled Et_2NH (13.8 mL, 9.76 g, 134 mmol, 1.0 eq) in THF (6 mL) over a period of 2 h. The resulting reaction mixture was stirred for 12 h at r.t. Subsequent dilution with pentane (20 mL), filtration over celite, and concentration *in vacuo* under a N_2 atmosphere yielded the crude product, which was purified by vacuum distillation to afford aminosilane **212** (16.6 g, 85.7 mmol, 64%) as a pale yellow liquid; **bp** 94 °C, 34 mbar (lit.[271] 104-108 °C, 56 Torr); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 2.88 (4H, q, J = 7.0 Hz, $N(C\underline{H}_2CH_3)_2$), 1.07-0.99 (12H, m, $N(CH_2C\underline{H}_3)_2$, $Si(CH_2C\underline{H}_3)_2$), 0.90 (4H, q, J = 6.5 Hz, $Si(CH_2C\underline{H}_3)_2$).

This data is in agreement with that reported by Beignet *et al.*[271]

Diethyl((2-iodo-4,4-dimethylcyclohex-2-en-1-yl)oxy)(oct-1-yn-1-yl)silane (396)

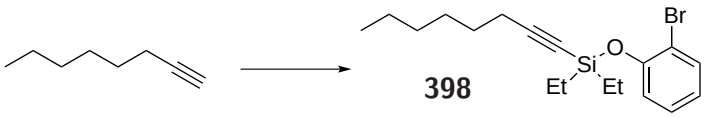


396

To a stirred solution of 1-octyne (97.5 μL, 72.8 mg, 0.661 mmol, 1.0 eq) in THF (1 mL) at −78 °C was added *n*-BuLi (0.291 mL, 0.727 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorosilane **392** (158 μL, 141 mg, 0.727 mmol, 1.1 eq) was added and the reaction mixture warmed to rt. Alcohol **376** (200 mg, 0.793 mmol, 1.2 eq) and DMAP (1 crystal) were added before stirring for 16 h at rt. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (100 % P.E.) afforded siloxane **396** (194 mg, 0.435 mmol, 66%) as a colourless oil; $\mathbf{R}_f$ 0.66 (10% Et_2O / P.E.); $\boldsymbol{\nu}_{max}$ (thin film) / cm^{-1} 2932, 2172, 1883, 1459, 1359, 1235, 1084, 1060, 1009, 928, 873, 820, 733, 638; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.22 (1H, s, =CH), 4.33 (1H, t, J = 5.2 Hz, CHOSi), 2.28-2.24 (2H, m, $SiC{\equiv}CC\underline{H}_2C_5H_{11}$), 2.06-1.98

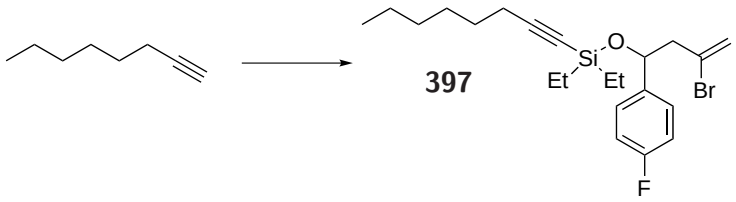
(1H, m, SiOCHC$\underline{H}_x$H$_y$), 1.93-1.85 (1H, m, SiOCHCH$_x\underline{H}_y$), 1.66 (1H, ddd, J = 13.2, 9.8, 3.2 Hz, SiOCHCH$_2$C$\underline{H}_x$H$_y$), 1.58-1.26 (9H, m, C≡CCH$_2$C$_4\underline{H}_8$CH$_3$, SiOCHCH$_2$CH$_x\underline{H}_y$), 1.09-0.96 (12H, m, Si(CH$_2$C$\underline{H}_3$)$_2$, C(C$\underline{H}_3$)$_2$), 0.91-0.88 (3H, m, C≡CC$_5$H$_1$0C$\underline{H}_3$), 0.83-0.58 (4H, m, Si(C$\underline{H}_2$CH$_3$)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 149.9 (I$\underline{C}$-C), 109.7 (IC=$\underline{C}$), 102.3 ($\underline{C}$≡CSi), 80.4 (C≡$\underline{C}$Si), 73.3 (C-O), 37.2 (*c*-Hex), 32.3 (*c*-Hex), 31.3 (*n*-Hex), 30.1 (*n*-Hex), 28.7 (Me), 28.5 (Me), 28.4 (*n*-Hex), 28.2 (*n*-Hex), 22.6 (*n*-Hex), 19.8 (*c*-Hex), 14.0 (*n*-Hex), 7.4 (SiEt$_2$), 7.1 (SiEt$_2$), 6.7 (2 x C, SiEt$_2$); **HRMS** (ESI$^+$) calculated for C$_{20}$H$_{35}$IOSiNa [M+Na]$^+$ 469.1393, found 469.1396.

(2-Bromophenoxy)diethyl(oct-1-yn-1-yl)silane (398)



To a stirred solution of 1-octyne (335 μL, 250 mg, 2.27 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*-BuLi (1.00 mL, 2.50 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorosilane **392** (543 μL, 484 mg, 2.50 mmol, 1.1 eq) was added and the reaction mixture warmed to rt. 2-bromophenol (315 μL, 471 mg, 2.72 mmol, 1.2 eq) and DMAP (1 crystal) were added before stirring for 16 h at rt. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (100 % P.E.) afforded siloxane **398** (610 mg, 1.66 mmol, 73%) as a colourless oil; $\mathbf{R}_f$ 0.57 (10% Et$_2$O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2932, 2173, 1889, 1585, 1476, 1440, 1283, 1246, 1047, 1029, 918, 739, 709, 637; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.53 (1H, dd, J = 7.9, 1.4 Hz, ArH), 7.24-7.17 (2H, m, ArH), 6.87-6.83 (1H, m, ArH), 2.28 (2H, t, J = 7.0 Hz, SiC≡CC$\underline{H}_2$C$_5$H$_{11}$), 1.58-1.51 (2H, m, C≡CCH$_2$C$\underline{H}_2$C$_3$H$_7$), 1.45-1.26 (6H, m, C≡CC$_2$H$_4$C$_3\underline{H}_6$CH$_3$), 1.12-1.08 (6H, m, Si(CH$_2$C$\underline{H}_3$)$_2$), 0.94-0.83 (7H, m, C≡CC$_5$H$_1$0C$\underline{H}_3$, Si(C$\underline{H}_2$CH$_3$)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 152.3 (Ar), 133.1 (Ar), 128.1 (Ar), 122.6 (Ar), 120.5 (Ar), 115.2 (Ar), 110.7 ($\underline{C}$≡CSi), 79.9 (C≡$\underline{C}$Si), 31.3 (*n*-Hex), 29.8 (*n*-Hex), 28.4 (*n*-Hex), 28.3 (*n*-Hex), 22.6 (*n*-Hex), 14.0 (*n*-Hex), 6.8 (SiEt$_2$), 6.5 (SiEt$_2$); **HRMS** (FI) calculated for C$_{18}$H$_{27}^{79}$BrOSi [M]$^+$ 366.1015, found 366.1012.

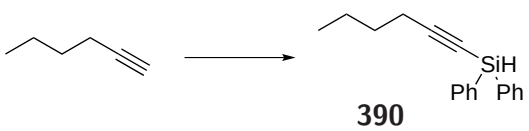
((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diethyl(oct-1-yn-1-yl)silane (397)



To a stirred solution of 1-octyne (97.5 μL, 72.7 mg, 0.660 mmol, 1.0 eq) in THF (1 mL) at −78 °C was added *n*-BuLi (0.291 mL, 0.727 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorosilane **392** (158 μL, 141 mg, 0.727 mmol, 1.1 eq) was added and the reaction mixture warmed to rt. Alcohol **370** (194 mg, 0.793 mmol, 1.2 eq) and DMAP (1 crystal) were added before stirring for 16 h at r.t. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (100% P.E.) afforded siloxane **397** (121 mg, 0.275 mmol, 42%) as a colourless oil; $\mathbf{R_f}$ 0.68 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2933, 2173, 1632, 1606, 1509, 1459, 1224, 1081, 1007, 948, 888, 856, 833, 733, 638; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.35-7.31 (2H, m, ArH), 7.02-6.98 (2H, m, ArH), 5.50 (1H, s, CBr=C$\underline{H}_x$H$_y$), 5.40 (1H, dd, J = 1.5, 0.82 Hz, CBr=CH$_x\underline{H}_y$), 5.16 (1H, dd, J = 7.4, 5.5 Hz, ArCHOSi), 2.89 (1H, dd, J = 14.2, 7.5 Hz, ArCHOSiC$\underline{H}_x$H$_y$), 2.63 (1H, dd, J = 14.2, 5.4 Hz, ArCHOSiCH$_x\underline{H}_y$), 2.22 (2H, t, J = 7.0 Hz, SiC≡CC$\underline{H}_2$C$_5$H$_{11}$), 1.03-0.96 (3H, m, Si(CH$_2$C$\underline{H}_3$)), 0.93-0.89 (3H, m, Si(CH$_2$C$\underline{H}_3$)), 0.87-0.82 (3H, m, C≡CC$_5$H$_{10}$C$\underline{H}_3$), 0.72-0.58 (2H, m, Si(C$\underline{H}_2$CH$_3$)), 0.51-0.45 (2H, m, Si(C$\underline{H}_2$CH$_3$)); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.2 (d, J^1_{C-F} = 244 Hz, ArF), 139.4 (d, J^4_{C-F} = 3.2 Hz, ArF), 130.0 (Br$\underline{C}$=C), 127.7 (d, J^3_{C-F} = 8.0 Hz, ArF), 119.4 (BrC=$\underline{C}$), 114.8 (d, J^2_{C-F} = 22.3 Hz, ArF), 109.7 ($\underline{C}$≡CSi), 80.0 (C≡$\underline{C}$Si), 72.6 (C-O), 52.4 ($\underline{C}$-CBr), 31.3 (*n*-Hex), 28.5 (*n*-Hex), 28.4 (*n*-Hex), 22.6 (*n*-Hex), 19.7 (*n*-Hex), 14.0 (*n*-Hex), 6.8 ($SiEt_2$), 6.6 (2 x C, $SiEt_2$), 6.5 ($SiEt_2$); **HRMS** (FI) calculated for $C_{22}H_{32}^{79}BrFOSi$ $[M]^+$ 440.1372, found 440.1785.

Diphenyl Substrates

Hex-1-yn-1-yldiphenylsilane (390)[13]

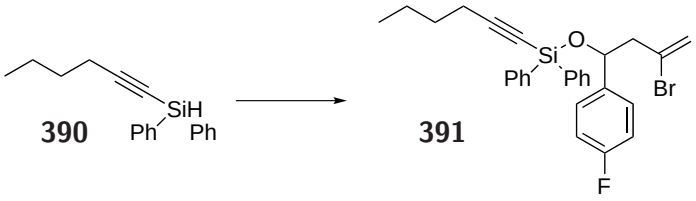


390

To a stirred solution of 1-hexyne (350 μL, 250 mg, 3.05 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*-BuLi (1.34 mL, 3.36 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorodiphenylsilane (714 μL, 798 mg, 3.66 mmol, 1.2 eq) was added and the reaction mixture warmed to r.t. before dilution with Et_2O (2.5 mL). The resulting suspension was washed with water (5 mL), the phases separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to afford silane **390** (734 mg, 2.77 mmol, 91%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H7.71-7.63 (4H, m, ArH), 7.47-7.33 (6H, m, ArH), 5.15 (1H, t, J = 1.2 Hz, SiH), 2.37 (2H, td, J = 7.0, 1.2 Hz, C≡CC$\underline{H}_2$C$_3$H$_7$), 1.67-1.37 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$CH$_3$), 0.94 (3H, t, J = 7.2 Hz, C≡CC$_3$H$_6$C$\underline{H}_3$).

This data is in agreement with that reported by Miller *et al.*[230]

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)(hex-1-yn-1-yl)diphenylsilane (391)[13]

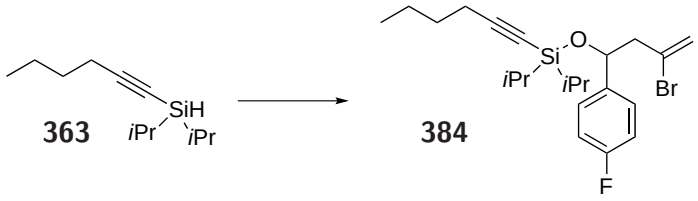


To a solution of silane **390** (259 mg, 1.54 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added *N*-bromosuccinimide (274 mg, 1.54 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of alcohol **370** (340 mg, 1.39 mmol, 0.9 eq), NEt_3 (0.215 mL, 159 mg, 1.54 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (3 mL) before stirring for 12 h at r.t. Concentration of the crude reaction mixture *in vacuo* and purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded siloxane **391** (277 mg, 0.63 mmol, 41%) as a colourless oil; $\mathbf{R_f}$ 0.49 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3070, 2958, 2175, 1632, 1605, 1509, 1429, 1224, 1120, 1075, 699; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.91-7.87 (2H, m, $SiPh_2$), 7.79-7.75 (2H, m, $SiPh_2$), 7.57-7.40 (9H, m, $SiPh_2$, ArH), 7.11-7.07 (2H, m, ArH), 5.62-5.62 (1H, m, =C$\underline{H}_x$H$_y$), 5.52 (1H, d, J = 1.6 Hz, =CH$_x\underline{H}_y$), 5.41 (1H, dd, J = 7.1, 6.0 Hz, SiOCH), 3.20 (1H, ddd, J = 14.2, 7.3, 0.8 Hz, SiOCHC$\underline{H}_x$H$_y$), 2.86 (1H, ddd, J = 14.18, 5.81, 0.78 Hz, SiOCHCH$_x\underline{H}_y$), 2.44 (1H, t, J = 7.0 Hz, C≡CCH$_2$), 1.71-1.54 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$), 1.09 (3H, t, J = 7.3 Hz, CH$_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.2 (d,

J^1_{C-F} = 246 Hz, ArF), 138.6 (ArF), 135.0 (SiPh), 134.8 (SiPh), 130.2 (SiPh), 130.0 (SiPh), 127.9 (d, J^3_{C-F} = 12.8 Hz, ArF), 119.9 (ArF), 114.9 (d, J^2_{C-F} = 20.8 Hz, ArF), 112.3 (C≡CSi), 79.4 (C≡CSi), 73.5 (C-O), 52.3 (C-CBr), 30.5 (*n*-Bu), 22.1 (*n*-Bu), 19.8 (*n*-Bu), 13.8 (*n*-Bu); **HRMS** (FI) calculated for $C_{28}H^{79}_{29}BrFOSi$ $[M]^+$ 509.1139, not found.

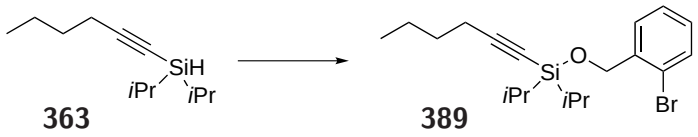
Diiso-propyl Substrates

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)(hex-1-yn-1-yl)diisopropylsilane (384)[13]



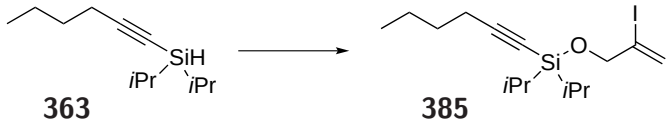
To a solution of silane **363** (355 mg, 1.81 mmol, 1.0 eq) in DCM (3 mL) at 0 °C was added *N*-bromosuccinimide (322 mg, 1.81 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of alcohol **370** (400 mg, 1.63 mmol, 0.9 eq) and imidazole (246 mg, 3.62 mmol, 2.0 eq) in DMF (5 mL) before stirring for 12 h at r.t. The reaction mixture was diluted with P.E. 40-60 (5 mL), washed with H_2O (4 x 5 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E. 40-60) afforded siloxane **384** (555 mg, 1.26 mmol, 77%) as a colourless oil; $\mathbf{R_f}$ 0.60 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2943, 2866, 2173, 1506, 1464, 1225, 1084, 885, 851; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.35-7.30 (2H, m, ArH), 7.03-6.97 (2H, m, ArH), 5.42-5.42 (1H, m, =CH_2), 5.36 (1H, d, J = 1.6 Hz, =CH_2), 5.20 (1H, *app* t, J = 6.6 Hz, ArCHOSi), 2.96 (1H, ddd, J = 14.0, 6.6, 0.9 Hz, CBrC$\underline{H}_x$H$_y$), 2.64 (1H, ddd, J = 14.0, 6.6, 0.7 Hz, CBrCH$_x\underline{H}_y$), 2.25 (2H, t, J = 6.9 Hz, C≡CC$\underline{H}_2$C$_3$H$_7$), 1.55-1.40 (4H, m, C≡CCH$_2$C$_2\underline{H}_4$CH$_3$), 1.09-0.83 (17H, m, Si(*i*-Pr)$_2$, C≡CC$_3$H$_6$C$\underline{H}_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.2 (d, J^1_{C-F} = 244 Hz, ArF), 139.4 (d, J^4_{C-F} = 3.2 Hz, ArF), 130.0 (BrC=C), 127.7 (d, J^3_{C-F} = 8.0 Hz, ArF), 119.5 (BrC=C), 114.7 (d, J^2_{C-F} = 22.3 Hz, ArF), 110.2 (C≡CSi), 78.7 (C≡CSi), 73.1 (C-O), 52.6 (C-CBr), 30.6 (*n*-Bu), 21.9 (*n*-Bu), 19.3 (*n*-Bu), 17.2 (Si(*i*-Pr)$_2$), 17.1 (Si(*i*-Pr)$_2$), 13.6 (*n*-Bu), 13.3 (Si(*i*-Pr)$_2$); **HRMS** (FI) calculated for $C_{22}H_{32}FOSi^{79}Br$ 438.1390, not found.

((2-Bromobenzyl)oxy)(hex-1-yn-1-yl)diisopropylsilane (389)[13]



To a solution of silane **363** (1.09 g, 5.37 mmol, 1.0 eq) in DCM (5 mL) at 0 °C was added *N*-bromosuccinimide (991 mg, 5.37 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of 2-bromobenzyl alcohol (937 mg, 5.01 mmol, 0.9 eq), NEt_3 (0.776 mL, 564 mg, 5.57 mmol, 1.0 eq) and DMAP (1 crystal) in DCM(5 mL) before stirring for 12 h at r.t. Concentration *in vacuo* of the crude reaction mixture and purification by flash column chromatography (100% P.E. 40-60) afforded siloxane **389** (1.28 g, 3.36 mmol, 67%) as a colourless oil; $\mathbf{R_f}$ 0.60 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2957, 2866, 2172, 1703, 1465, 1379, 1204, 1121, 1043, 1026, 994, 883, 859, 820, 748, 650; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.63-7.60 (1H, m, ArH), 7.51 (1H, dd, J = 7.9, 1.1 Hz, ArH), 7.37-7.33 (1H, m, ArH), 7.15-7.10 (1H, m, ArH), 4.91 (2H, s, $ArCH_2$), 2.29 (2H, t, J = 6.9 Hz, C≡CC$\underline{H}_2C_3H_7$), 1.57-1.42 (4H, m, C≡CC$H_2C_2\underline{H}_4CH_3$), 1.15-1.03 (14H, m, Si(i-Pr)$_2$), 0.95-0.91 (3H, m, C≡C$C_3H_6C\underline{H}_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 140.2 (Ar), 131.9 (Ar), 128.1 (Ar), 127.7 (Ar), 127.2 (Ar), 121.1 (Ar), 110.3 ($\underline{C}$≡CSi), 78.4 (C≡CSi), 65.6 (C-O), 30.6 (n-Bu), 21.8 (n-Bu), 19.4 (n-Bu), 17.3 (Si(i-Pr)$_2$), 17.2 (Si(i-Pr)$_2$), 13.6 (n-Bu), 13.2 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{19}H_{29}^{79}BrOSi$ $[M]^+$ 380.1171, found 380.1183.

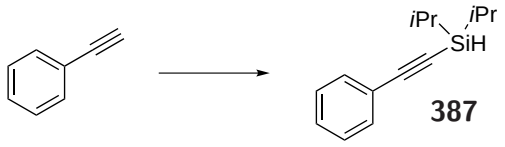
Hex-1-yn-1-yl((2-iodoallyl)oxy)diisopropylsilane (385)[13]



To a solution of silane **363** (297 mg, 1.51 mmol, 1.0 eq) in DCM (3 mL) at 0 °C was added *N*-bromosuccinimide (269 mg, 1.51 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of alcohol **374** (250 mg, 1.36 mmol, 0.9 eq) and imidazole (206 mg, 3.02 mmol, 2.0 eq) in DMF (5 mL) before stirring for 12 h at r.t. The reaction mixture was diluted with P.E. 40-60 (5 mL), washed with H_2O (4 x 5 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*.

Purification by flash column chromatography (100% P.E. 40-60) afforded siloxane **385** (430 mg, 1.14 mmol, 84%) as a colourless oil; $\mathbf{R_f}$ 0.64 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2943, 2866, 2173, 1628, 1464, 1134, 1085, 994, 883, 812, 681; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 6.45-6.43 (1H, m, $=CH_2$), 5.81 (1H, *app* q, J = 1.6 Hz, $=CH_2$), 4.31 (1H, t, J = 1.8 Hz, CH_2OSi), 2.27 (2H, t, J = 6.9 Hz, $C{\equiv}C\underline{H}_2C_3H_7$), 1.57-1.42 (4H, m, $C{\equiv}CCH_2C_2\underline{H}_4CH_3$), 1.10-0.89 (17H, m, Si(*i*-Pr)$_2$, $C{\equiv}CC_3H_6C\underline{H}_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 122.9 ($I\underline{C}{=}C$), 110.4 ($IC{=}\underline{C}$), 109.2 ($\underline{C}{\equiv}CSi$), 78.0 ($C{\equiv}\underline{C}Si$), 71.9 (C-O), 30.6 (*n*-Bu), 21.8 (*n*-Bu), 19.4 (*n*-Bu), 17.2 (Si(*i*-Pr)$_2$), 17.1 (Si(*i*-Pr)$_2$), 13.6 (*n*-Bu), 13.1 (Si(*i*-Pr)$_2$); **HRMS** (FI) calculated for $C_{15}H_{27}IOSi$ $[M]^+$ 378.0876, found 378.0888.

Diisopropyl(phenylethynyl)silane (387)[13]

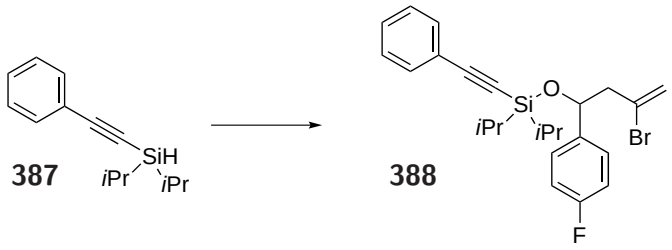


387

To a stirred solution of phenylacetylene (269 μL, 250 mg, 2.45 mmol, 1.0 eq) in THF (5 mL) at −78 °C was added *n*-BuLi (1.08 mL, 2.70 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorodi*iso*propylsilane (502 μL, 443 mg, 2.94 mmol, 1.2 eq) was added and the reaction mixture warmed to r.t. before dilution with Et_2O (2.5 mL). The resulting suspension was washed with water (5 mL), the phases separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to afford silane **387** (482 mg, 2.23 mmol, 91%) as a colourless oil which was taken on crude to the next step; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.52-7.46 (2H, m, ArH), 7.36-7.28 (3H, m, ArH), 3.84 (1H, s, SiH), 1.20-0.97 (14H, m, Si(*i*-Pr)$_2$).

This data is in agreement with that reported by Maifeld *et al.*[311]

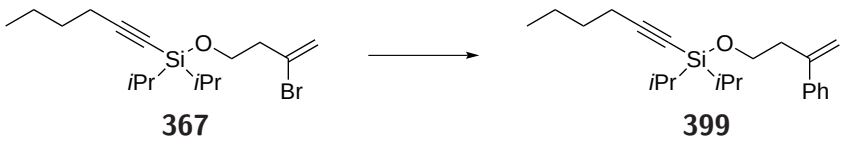
((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diisopropyl(phenylethynyl)silane (388)[13]



To a solution of silane **387** (200 mg, 0.924 mmol, 1.0 eq) in DCM (3 mL) at 0 °C was added *N*-bromosuccinimide (164 mg, 0.924 mmol, 1.0 eq) slowly over a period of 2 min, before stirring for 15 min at r.t. The resulting suspsension was then added *via* cannula to a solution of alcohol **374** (204 mg, 0.832 mmol, 0.9 eq) and imidazole (126mg, 185 mmol, 2.0 eq) in DMF (5 mL) before stirring for 12 h at r.t. The reaction mixture was diluted with P.E. 40-60 (5 mL), washed with H_2O (4 x 5 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E. 40-60) afforded siloxane **388** (261 mg, 0.567 mmol, 61%) as a colourless oil; $\mathbf{R_f}$ 0.60 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2945, 2866, 2158, 1632, 1605, 1510, 1489, 1463, 1224, 1084, 884, 853, 831, 757, 689; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.47-7.44 (2H, m, ArH), 7.37-7.29 (5H, m, ArH), 7.02-6.98 (2H, m, ArH), 5.46 (1H, dt, J = 1.6, 0.8 Hz, =CH_2), 5.38 (1H, d, J = 1.6 Hz, =CH_2), 5.27 (1H, t, J = 6.6 Hz, ArC$\underline{H}$OH), 3.00 (1H, ddd, J = 14.1, 6.9, 0.9 Hz, CBrC$\underline{H}_x$H$_y$), 2.67 (1H, ddd, J = 14.0, 6.3, 0.8 Hz, CBrCH$_x\underline{H}_y$), 1.16-0.88 (14H, m, Si(i-Pr)$_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.1 (d, J^1_{C-F} = 245 Hz, ArF), 139.2 (ArF), 132.1 (Ph), 129.8 (Br$\underline{C}$=C), 128.7 (Ph), 128.2 (Ph), 127.9 (d, J^3_{C-F} = 8.3 Hz, ArF), 122.8 (Ph), 119.7 (BrC=$\underline{C}$), 114.8 (d, J^2_{C-F} = 21.5 Hz, ArF), 107.4 ($\underline{C}$≡CSi), 88.5 (C≡$\underline{C}$Si), 73.4 (C-O), 52.6 ($\underline{C}$-CBr), 17.4 (Si(i-Pr)$_2$), 17.3 (Si(i-Pr)$_2$), 17.1 (Si(i-Pr)$_2$), 17.0 (Si(i-Pr)$_2$), 13.4 (Si(i-Pr)$_2$), 13.2 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{24}H_{28}^{79}BrOSiF$ $[M]^+$ 458.1077, found 458.1085.

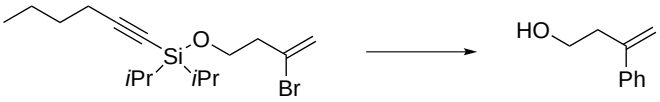
7.4.3. Initial Studies

hex-1-yn-1-yldiisopropyl((3-phenylbut-3-en-1-yl)oxy)silane (399)



To a stirred, degassed solution of alkoxysilane **367** (20 mg, 0.058 mmol, 1.0 eq) in EtOH (0.5 mL) was added phenylboronic acid (10.6 mg, 0.087 mmol, 1.5 eq), Cs_2CO_3 (37.8 mg, 0.116 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (6.7 mg, 0.0058 mmol, 0.10 eq), before heating to 70 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through a pad of Celite. ^{1}H NMR analysis showed a 5 : 1 ratio of directly coupled product **399** to alcohol **400**; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H7.49-7.28 (5H, m, ArH), 5.36 (1H, d, J = 1.5 Hz, =C$\underline{H}_x$H$_y$), 5.13 (1H, q, J = 1.3 Hz, =CH$_x\underline{H}_y$), 3.87 (2H, t, J = 7.4 Hz, C$\underline{H}_2$OH), 2.80 (2H, td, J = 7.4, 1.1 Hz, C$\underline{H}_2$H$_2$OH), 2.25 (2H, t, J = 6.8 Hz, SiC≡CCH$_2$), 1.53-1.40 (4H, m, SiC≡CCH$_2$C$_2\underline{H}_4$), 1.09-0.94 (17H, m, Si(i-Pr)$_2$, SiC≡CC$_3$H$_6$C$\underline{H}_3$). No further characterisation of this undesired by-product **399** was completed.

3-phenylbut-3-en-1-ol (400)



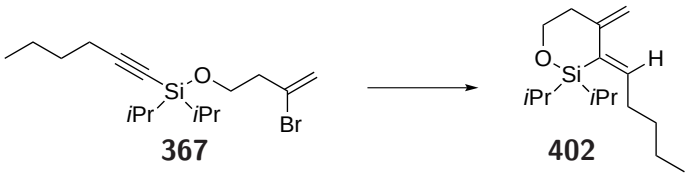
367 **400**

To a stirred, degassed solution of alkoxysilane **367** (20 mg, 0.058 mmol, 1.0 eq) in EtOH (0.5 mL) was added phenylboronic acid (10.6 mg, 0.087 mmol, 1.5 eq), Cs_2CO_3 (37.8 mg, 0.116 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (6.7 mg, 0.0058 mmol, 0.10 eq), before heating to 70 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through a pad of Celite. ^{1}H NMR analysis showed a 5 : 1 ratio of directly coupled product **399** to alcohol **400**; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.49-7.28 (5H, m, ArH), 5.43 (1H, d, J = 1.4 Hz, =C$\underline{H}_x$H$_y$), 5.18 (1H, q, J = 1.3 Hz, =CH$_x\underline{H}_y$), 3.80-3.72 (2H, m, C$\underline{H}_2$OH), 2.81-2.74 (2H, m, C$\underline{H}_2$CH$_2$OH).

This data is in agreement with that reported by Lin *et al*[312] and Reetz *et al.*[313]

7.4.4. Reductive Cyclisation - Initial Studies

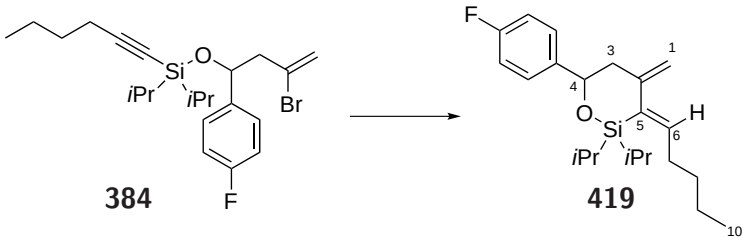
(Z)-2,2-diisopropyl-4-methylene-3-pentylidene-1,2-oxasilinane (402)



To a stirred, degassed solution of alkoxysilane **367** (20 mg, 0.058 mmol, 1.0 eq) in THF (5 mL) was added phenylboronic acid (10.6 mg, 0.087 mmol, 1.5 eq), Cs_2CO_3 (37.8 mg, 0.116 mmol, 2.0 eq), *t*-butanol (37.8 μL, 0.395 mmol, 5.0 eq) and $Pd(PPh_3)_4$ (6.7 mg, 0.0058 mmol, 0.10 eq), before heating to 70 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through a pad of Celite, before purification by flash column chromatography (5% Et_2O / P.E.) afforded cyclic siloxane **402** (15.2 mg, 0.0570 mmol, 39%) as a yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.31 (1H, t, J = 7.5 Hz, =C$\underline{H}$(*n*Bu)), 4.85 (1H, d, J = 2.4 Hz, =C$\underline{H}_x$H$_y$), 4.59 (1H, dd, J = 2.2, 1.0 Hz, =CH$_x\underline{H}_y$), 4.06-4.00 (2H, m, SiOCH_2), 2.36-2.31 (4H, m, =CHC$\underline{H}_2$), 1.51-1.32 (4H, m, =CHCH_2C$_2\underline{H}_4$CH_3), 1.15-0.97 (14H, m, Si(*i*-Pr)$_2$), 0.97-0.87 (3H, m, =CHC$_3$H$_6$C$\underline{H}_3$). Further characterisation was not completed due to difficulties in obtaining a pure sample of this compound.

7.4.5. Reductive Cyclisation - Further Studies

(Z)-6-(4-Fluorophenyl)-2,2-diisopropyl-4-methylene-3-pentylidene-1,2-oxasilinane (643)

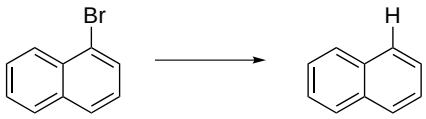


To a stirred, degassed solution of siloxane **384** (50 mg, 0.114 mmol, 1.0 eq), Cs_2CO_3 (74.5 mg, 0.228 mmol, 2.0 eq) and *iso*propyl alcohol (43.5 μL, 0.569 mmol, 5.0 eq) in toluene (5 mL) was added $Pd(PPh_3)_4$ (13.2 mg, 0.0114 mol, 0.10 eq) before heating to 67 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (5% Et_2O /

P.E., Et_3N additive) afforded diene **419** (37.7 mg, 0.105 mmol, 92%) as a yellow oil contaminated with a small amount of 3-bromo-1-(4-fluorophenyl)but-3-en-1-one; $\mathbf{R_f}$ 0.67 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2943, 2865, 1606, 1509, 1463, 1381, 1223, 1154, 1083, 993, 931, 907, 883, 831, 784, 667, 644; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.37 (2H, ddt, J = 5.9, 3.3, 2.5 Hz, ArH), 7.05-7.01 (2H, m, ArH), 6.35 (1H, t, J = 7.6 Hz, H_6), 5.01 (1H, dd, J = 10.8, 2.2 Hz, H_4), 4.93 (1H, d, J = 2.2 Hz, $\underline{H}_{1x}H_{1y}$), 4.68 (1H, t, J = 1.7 Hz, $H_{1x}\underline{H}_{1y}$), 2.50 (1H, dt, J = 13.5, 2.3 Hz, $\underline{H}_{3x}H_{3y}$), 2.27-2.22 (1H, m, $\underline{H}_{7x}H_{7y}$), 2.17 (1H, dd, J = 13.4, 8.3 Hz, $H_{3x}\underline{H}_{3y}$), 2.08 (1H, dt, J = 14.5, 7.3 Hz, $H_{7x}\underline{H}_{7y}$), 1.52-1.36 (4H, m, H_8, H_9), 1.18-1.00 (14H, m, Si(i-Pr)$_2$), 0.97-0.92 (3H, m, H_{10}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 161.8 (d, J^1_{C-F} = 244 Hz, ArF), 152.2 (C_6), 141.7 (C_1), 141.7 (d, J^4_{C-F} = 3.3 Hz, ArF), 136.2 (C_2), 126.7 (d, J^3_{C-F} = 8.2 Hz, ArF), 114.9 (d, J^2_{C-F} = 21.2 Hz, ArF), 108.3 (C_5), 77.5 (C_4), 48.0 (C_3), 33.2 (C_7), 31.9 (C_8), 22.6 (C_9), 17.8 (Si(i-Pr)$_2$), 17.8 (Si(i-Pr)$_2$), 17.1 (2 x C, Si(i-Pr)$_2$), 15.4 (C_{10}), 14.0 (Si(i-Pr)$_2$), 13.7 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{22}H_{33}OFSi$ $[M]^+$ 360.2285, found 360.2287.

Hydride Transfer Test Reactions

Naphthalene (644)[238]



644

To a stirred, degassed solution of 1-bromonaphthalene (33.6 μL, 50 mg, 0.241 mmol, 1.0 eq) and Cs_2CO_3 (157 mg, 0.483 mmol, 2.0 eq) in EtOH (5 mL) was added $Pd(PPh_3)_4$ (27.8 mg, 0.0241 mmol, 0.10 eq) before heating to 67 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and purification by filtration through a short silica plug afforded naphthalene **644** (30.6 mg, 0.238 mmol, 99%) as a white solid; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.92-7.84 (4H, m, ArH), 7.55-7.47 (4H, m, ArH).

This data is in agreement with that of commercially available naphthalene (Aldrich).

Deuterium Incorporation

1,1-Dideuterio-n-octyl alcohol (416)[314]



416

To a solution of methyl octanoate (1.14 mL, 1.00 g, 6.32 mmol, 1.0 eq) in THF (5 mL) at 0 °C was added lithium aluminium deuteride (6.95 mL, 6.95 mmol, 1.1 eq of a 1 M solution in THF) dropwise. The reaction mixture was refluxed for 4 h before cooling to 0 °C and quenching with THF/H_2O (1:1, 6 mL), then H_2O (6 mL). After the addition of 10% H_2SO_4 (10 mL) and NaKTartrate solution (10 mL), the mixture was extracted with Et_2O (30 mL), the phases were separated and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford 1,1-dideuterio-n-octyl alcohol **416** (827 mg, 6.26 mmol, 99%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 1.60-1.23 (12H, m, $C_7\underline{H}_{12}CH_2CD_2OH$), 1.19 (1H, s, OH), 0.92-0.86 (3H, m, $C_7H_{12}C\underline{H}_2CD_2OH$).

This data is in agreement with that reported by Landini *et al.*[314]

d_6-2-Phenylpropan-2-ol (645)[315]

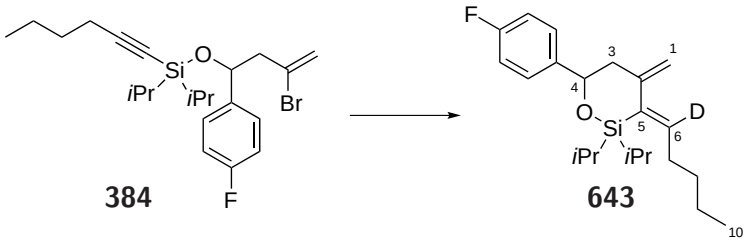


645

To a stirred solution of bromobenzene (1.11 g, 7.09 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*BuLi (2.98 mL of a 2.5 M solution in hexanes, 7.44 mmol, 1.05 eq) before stirring for 15 min. Acetone-d_6 (0.573 mL, 0.500 g, 7.80 mmol, 1.1 eq) was added dropwise, and the reaction mixture was warmed to r.t. and stirred for 2 h before quenching with water (2 mL). Extraction with Et_2O (3 x 2 mL), drying of the combined organic phases ($MgSO_4$) and concentration *in vacuo* afforded deuterated tetiary alcohol **645** (781 mg, 5.49 mmol,77 %) as a pale yellow oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.53-7.46 (2H, m, ArH), 7.40-7.21 (3H, m, ArH).

This data is in agreement with that reported by Pascal *et al.*[315]

(Z)-6-(4-Fluorophenyl)-2,2-diisopropyl-4-methylene-3-pentylidene-1,2-oxasilinane (419)



To a stirred, degassed solution of siloxane **384** (50 mg, 0.114 mmol, 1.0 eq), Cs_2CO_3 (74.5 mg, 0.228 mmol, 2.0 eq) and 1,1-dideuterio-n-octyl alcohol **416** (90 μL, 0.569 mmol, 5.0 eq) in toluene (5 mL) was added $Pd(PPh_3)_4$ (13.2 mg, 0.0114 mol, 0.10 eq) before heating to 67 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (5% Et_2O / P.E., Et_3N additive) afforded diene **643** (27.9 mg, 0.0772 mmol, 68%) as a yellow oil contaminated with deuterated octyl octanoate; $\mathbf{R_f}$ 0.67 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2928, 2864, 1735, 1606, 1509, 1464, 1362, 1223, 1154, 1084, 994, 918, 882, 918, 882, 831, 784, 666, 644; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.39-7.35 (2H, m, ArH), 7.03 (2H, ddt, J = 8.8, 6.9, 2.1 Hz, ArH), 5.01 (1H, dd, J = 10.9, 2.0 Hz, H_4), 4.92 (1H, d, J = 2.1 Hz, $\underline{H}_{1x}H_{1y}$), 4.67 (1H, t, J = 1.6 Hz, $H_{1x}\underline{H}_{1y}$), 2.50 (1H, dd, J = 13.2, 2.3 Hz, $\underline{H}_{3x}H_{3y}$), 2.31-2.28 (1H, m, $\underline{H}_{7x}H_7y$), 2.19-2.13 (1H, m, $H_{3x}\underline{H}_{3y}$), 2.10-2.03 (1H, m, J = 14.5, 7.3 Hz, $H_{7x}\underline{H}_{7y}$), 1.47-1.26 (4H, m, H_8, H_9), 1.19-1.01 (14H, m, Si(i-Pr)$_2$), 0.96-0.92 (3H, m, H_{10}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 161.9 (d, J^1_{C-F} = 244 Hz, ArF), 152.2 (br s, C_6), 141.1 (d, J^4_{C-F} = 3.0 Hz, ArF), 136.1 (C_2), 126.7 (d, J^3_{C-F} = 8.1 Hz, ArF), 114.9 (d, J^2_{C-F} = 21.6 Hz, ArF), 108.3 (C_1), 77.5 (C_4), 48.0 (C_3), 33.1 (C_7), 31.8 (C_8), 22.7 (C_9), 17.8 (Si(i-Pr)$_2$), 17.8 (Si(i-Pr)$_2$), 17.1 (2 x C, Si(i-Pr)$_2$), 15.3 (C_{10}), 14.0 (Si(i-Pr)$_2$), 13.7 (Si(i-Pr)$_2$, peak at 141.7 ppm not seen); **^{2}D NMR** (500 MHz, $CHCl_3$) δ_D 6.40 (1H, =CD), **HRMS** (FI) calculated for $C_{22}H_{33}DOFSi$ $[M]^+$ 361.2347, found 361.2343.

Unexpected Product

2-methyleneoct-3-yn-1-ol (431)



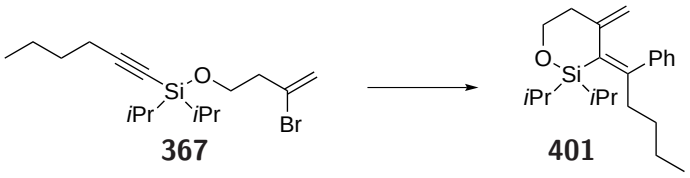
385 **431**

SB-13-18; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 5.59-5.53 (1H, m, $=C\underline{H}_xH_y$), 5.40-5.33 (1H, m, $=CH_x\underline{H}_y$), 4.27-4.21 (2H, m, $CH\underline{H}_2OH$), 2.30 (2H, t, J = 7.1 Hz, $C{\equiv}CCH_2$), 1.53-1.38 (4H, m, $C{\equiv}CCH_2C_2\underline{H}_4CH_3$), 0.94-0.91 (3H, m, $C{\equiv}CC_3H_6C\underline{H}_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 130.8, 117.6, 91.3, 78.5, 64.5, 30.7, 21.9, 19.0, 13.6.

This data is in agreement with that reported by Thongsornkleeb *et al.*[316]

7.4.6. Tandem Suzuki Coupling - Initial Studies

(E)-2,2-Diisopropyl-4-methylene-3-(1-phenylpentylidene)-1,2-oxasilinane (401)



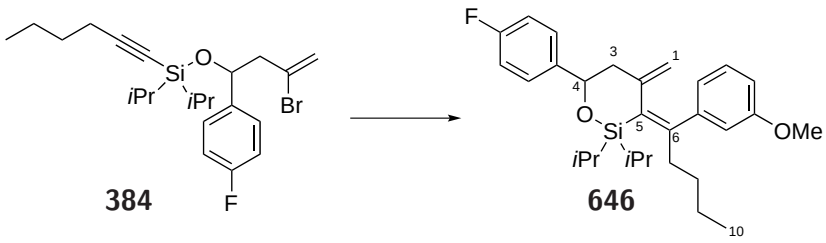
367 **401**

To a stirred, degassed solution of alkoxysilane **367** (20 mg, 0.058 mmol, 1.0 eq) in PhMe (4 mL) was added phenylboronic acid (10.6 mg, 0.087 mmol, 1.5 eq), Cs_2CO_3 (37.8 mg, 0.116 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (6.7 mg, 0.0058 mmol, 0.10 eq), before heating to 70 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through a pad of Celite, before purification by flash column chromatography (5% Et_2O / P.E.) afforded cyclic siloxane **401** (5.2 mg, 0.0151 mmol, 26%) as a yellow oil contaminated with 1,1'-diphenyl; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.64-7.58 (2H, m, ArH), 7.50-7.42 (2H, m, ArH), 4.62 (1H, dt, J = 2.0, 1.1 Hz, $=C\underline{H}_xH_y$), 4.18 (1H, d, J = 2.2 Hz, $=CH_x\underline{H}_y$), 4.10-4.03 (2H, m, $SiOCH_2$), 2.46-2.24 (2H, m, $=CHC\underline{H}_2$), 1.16-0.98 (18H, m, $=CHCH_2C_2\underline{H}_4CH_3$, Si(*i*-Pr)$_2$), 0.91-0.76 (3H, m, $=CHC_3H_6C\underline{H}_3$). Further characterisation was not completed due to difficulties in obtaining a pure sample of this compound.

7.4.7. Tandem Suzuki Coupling - Further Studies

(E)-6-(4-Fluorophenyl)-2,2-diisopropyl-3-(1-(3-methoxyphenyl)pentylidene)-4-methylene-1,2-oxasilinane

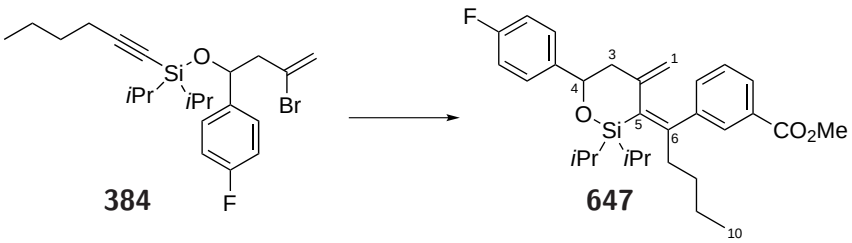
(646)



To a degassed solution of **384** (50 mg, 0.114 mmol, 1.0 eq) and 3-methoxyphenylboronic acid (34.5 mg, 0.171 mmol, 1.5 eq) in DME (5 mL) was added Cs_2CO_3 (74.3 mg, 0.228 mmol, 2.0 eq) and Pd(dppf)Cl_2 (9.3 mg, 0.0114 mmol, 0.10 eq), before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through silica. Purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded cyclisation product **646** (38.8 mg, 0.0831 mmol, 73%) as a yellow oil; $\mathbf{R_f}$ 0.52 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2956, 1575, 1509, 1464, 1222, 1086, 883, 781; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.40-7.37 (2H, m, ArH), 7.19-7.16 (1H, m, ArH), 7.06-7.01 (2H, m, ArH), 6.74 (1H, ddd, J = 8.2, 2.6, 0.78 Hz, ArH), 6.69 (1H, dt, J = 7.6, 1.1 Hz, ArH), 6.64 (1H, dd, J = 2.5, 1.5 Hz, ArH), 5.02 (1H, dd, J = 10.6, 2.7 Hz, H_4), 4.71 (1H, d, J = 1.6 Hz, H_1), 4.33 (1H, d, J = 2.1 Hz, H_1), 3.79 (3H, s, OMe), 2.52-2.46 (2H, m, H_7), 2.36 (1H, dt, J = 15.4, 7.0 Hz, $\underline{H}_{3x}H_{3y}$), 2.28-2.23 (1H, m, $H_{3x}\underline{H}_{3y}$), 1.31-1.20 (12H, m, Si(i-Pr)$_2$, H_8, H_9), 1.13 (6H, d, J = 4.1 Hz, Si(CH(C$\underline{H}_3$)$_2$)), 0.87-0.82 (3H, m, H_{10}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 161.8 (d, J^1_{C-F} = 244 Hz, ArF), 159.1 (Ar), 151.7 (C_6), 148.4 (C_2), 144.4 (Ar), 141.0 (ArF), 135.3 (C_1), 128.6 (Ar), 126.7 (d, J^3_{C-F} = 7.79 Hz, ArF), 115.0 (C_5), 114.9 (d, J^2_{C-F} = 21.2 Hz, ArF), 114.8 (Ar), 114.6 (Ar), 111.1 (Ar), 78.6 (C_4), 55.1 (C_3), 49.1 (OMe), 39.8 (C_7), 30.0 (C_8), 23.1 (C_9), 18.3 (Si(i-Pr)$_2$), 18.23 (Si(i-Pr)$_2$), 18.18 (Si(i-Pr)$_2$), 17.4 (Si(i-Pr)$_2$), 15.8 (C_{10}), 14.6 (Si(i-Pr)$_2$), 13.9 (Si(i-Pr)$_2$); **HRMS** (ESI$^+$) calculated for $C_{29}H_{39}FNaO_2Si$ $[M+Na]^+$ 489.2596, found 489.2584.

(E)-Methyl

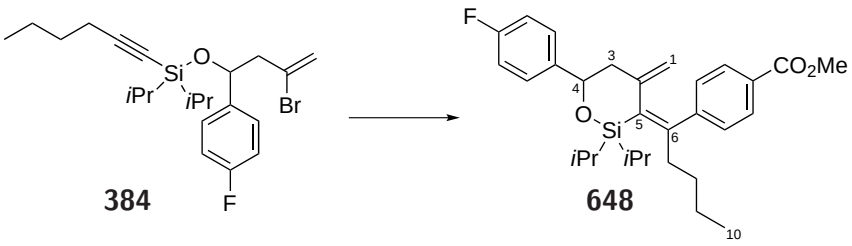
3-(1-(6-(4-fluorophenyl)-2,2-diisopropyl-4-methylene-1,2-oxasilinan-3-ylidene)pentyl)benzoate (647)



To a degassed solution of **384** (50 mg, 0.114 mmol, 1.0 eq) and (3-(methoxycarbonyl)phenyl)boronic acid (30.8 mg, 0.171 mmol, 1.5 eq) in DME (5 mL) was added Cs_2CO_3 (74.3 mg, 0.228 mmol, 2.0 eq) and Pd(dppf)Cl_2 (9.3 mg, 0.0114 mmol, 0.10 eq), before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through silica. Purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded cyclisation product **647** (26.1 mg, 0.0528 mmol, 46%) as a yellow oil; $\mathbf{R_f}$ 0.36 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2955, 2865, 1726, 1509, 1463, 1438, 1299, 1235, 1086, 995, 906, 832, 762, 649; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.88 (1H, dt, J = 7.7, 1.5 Hz, ArH), 7.78-7.78 (1H, m, ArH), 7.41-7.36 (2H, m, ArH), 7.32 (1H, td, J = 7.7, 0.36 Hz, ArH), 7.27 (1H, dt, J = 7.7, 1.5 Hz, ArH), 7.06-7.01 (2H, m, ArH), 5.02 (1H, dd, J = 10.6, 2.7 Hz, H_4), 4.69 (1H, d, J = 0.73 Hz, H_1), 4.22 (1H, d, J = 2.0 Hz, H_1), 3.91 (3H, s, OMe), 2.56 (1H, ddd, J = 14.0, 10.7, 5.5 Hz, $\underline{H}_{3x}H_{3y}$), 2.49 (1H, dd, J = 12.8, 2.7 Hz, $H_{3x}\underline{H}_{3y}$), 2.28-2.23 (1H, m, $\underline{H}_{7x}H_{7y}$), 2.30-2.24 (1H, m, $H_{7x}\underline{H}_{7y}$), 1.31-1.20 (12H, m, Si(i-Pr)$_2$, H_8, H_9), 1.14 (3H, d, J = 3.2 Hz, Si(CH(C$\underline{H}_3$)$_2$)), 1.13 (3H, d, J = 3.0 Hz, Si(CH(C$\underline{H}_3$)$_2$)), 0.831 (3H, t, J = 7.2 Hz, H_{10}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 167.2 (C=O), 161.9 (d, J^1_{C-F} = 244 Hz, ArF), 150.6 (C_6), 148.3 (C_2), 143.1 (Ar), 140.8 (ArF), 136.5 (C_1), 133.3 (Ar), 129.8 (Ar), 129.5 (Ar), 127.9 (Ar), 127.5 (Ar), 126.7 (d, J^3_{C-F} = 7.83 Hz, ArF), 115.9 (C_5), 114.9 (d, J^2_{C-F} = 21.5 Hz, ArF), 78.5 (C_4), 52.1 (C_3), 49.0 (OMe), 39.5 (C_7), 30.0 (C_8), 23.1 (C_9), 18.3 (Si(i-Pr)$_2$), 18.20 (Si(i-Pr)$_2$), 18.16 (Si(i-Pr)$_2$), 17.4 (Si(i-Pr)$_2$), 15.7 (C_{10}), 14.6 (Si(i-Pr)$_2$), 13.9 (Si(i-Pr)$_2$); **HRMS** (EI$^+$) calculated for $C_{30}H_{39}FNaO_3Si$ $[M+Na]^+$ 517.2545, found 517.2544.

(E)-Methyl

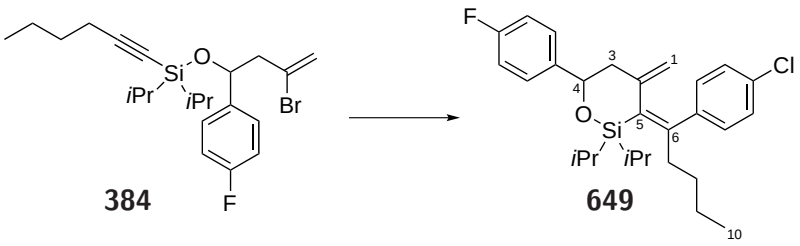
4-(1-(6-(4-fluorophenyl)-2,2-diisopropyl-4-methylene-1,2-oxasilinan-3-ylidene)pentyl)benzoate (648)



To a degassed solution of **384** (50 mg, 0.114 mmol, 1.0 eq) and (4-(methoxycarbonyl)phenyl)boronic acid (30.8 mg, 0.171 mmol, 1.5 eq) in DME (5 mL) was added Cs_2CO_3 (74.3 mg, 0.228 mmol, 2.0 eq) and Pd(dppf)Cl_2 (9.3 mg, 0.0114 mmol, 0.10 eq), before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through silica. Purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded cyclisation product **648** (21.3 mg, 0.0431 mmol, 38%) as a yellow oil; $\mathbf{R_f}$ 0.41 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2955, 2865, 1725, 1607, 1509, 1463, 1277, 1223, 1105, 1018, 884, 832, 780, 717, 648; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.95-7.92 (2H, m, ArH), 7.40-7.37 (2H, m, ArH), 7.18-7.16 (2H, m, ArH), 7.06-7.01 (2H, m, ArH), 5.02 (1H, dd, J = 10.6, 2.6 Hz, H_4), 4.69 (1H, d, J = 0.72 Hz, H_1), 4.24 (1H, d, J = 1.9 Hz, H_1), 3.91 (3H, s, OMe), 2.56-2.47 (2H, m, H_3), 2.40 (1H, ddd, J = 14.0, 11.0, 4.9 Hz, $\underline{H}_{7x}H_{7y}$), 2.28-2.24 (1H, m, $H_{7x}\underline{H}_{7y}$), 1.30-1.21 (12H, m, Si(i-Pr)$_2$, H_8, H_9), 1.14-1.12 (6H, m, Si(CH(C$\underline{H}_3$)$_2$)), 0.826 (3H, t, J = 7.2 Hz, H_{10}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 167.1 (C=O), 161.8 (d, J^1_{C-F} = 244 Hz, ArF), 150.8 (C_6), 148.2 (C_2), 148.1 (Ar), 140.8 (ArF), 136.8 (C_1), 129.2 (Ar), 128.6 (Ar), 128.0 (Ar), 126.7 (d, J^3_{C-F} = 8.21 Hz, ArF), 115.9 (C_5), 114.9 (d, J^2_{C-F} = 21.2 Hz, ArF), 78.5 (C_4), 52.0 (C_3), 49.0 (OMe), 39.4 (C_7), 30.0 (C_8), 23.0 (C_9), 18.22 (Si(i-Pr)$_2$), 18.20 (Si(i-Pr)$_2$), 18.1 (Si(i-Pr)$_2$), 17.4 (Si(i-Pr)$_2$), 15.7 (C_{10}), 14.6 (Si(i-Pr)$_2$), 13.9 (Si(i-Pr)$_2$); **HRMS** (EI$^+$) calculated for $C_{30}H_{39}FNaO_3Si$ $[M+Na]^+$ 517.2545, found 517.2544.

(E)-3-(1-(4-Chlorophenyl)pentylidene)-6-(4-fluorophenyl)-2,2-diisopropyl-4-methylene-1,2-oxasilinane

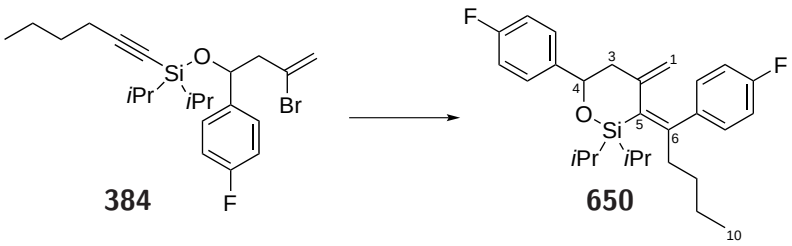
(649)



To a degassed solution of **384** (50 mg, 0.114 mmol, 1.0 eq) and 4-chlorophenylboronic acid (26.7 mg, 0.171 mmol, 1.5 eq) in DME (5 mL) was added Cs_2CO_3 (74.3 mg, 0.228 mmol, 2.0 eq) and Pd(dppf)Cl_2 (9.3 mg, 0.0114 mmol, 0.10 eq), before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through silica. Purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded cyclisation product **649** (36.1 mg, 0.0766 mmol, 67%) as a colourless oil; $\mathbf{R_f}$ 0.63 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2956, 2866, 2361, 2342, 1605, 1509, 1487, 1464, 1223, 1155, 1087, 1013, 883, 832, 773, 669, 648; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.40-7.35 (2H, m, ArH), 7.23-7.21 (2H, m, ArH), 7.07-7.00 (4H, m, ArH), 5.01 (1H, d, J = 10.2 Hz, H_4), 4.72 (1H, s, H_1), 4.25 (1H, s, H_1), 2.52-2.43 (2H, m, H_7), 2.41-2.32 (1H, m, $\underline{H}_{3x}H_{3y}$), 2.28-2.19 (1H, m, $H_{3x}\underline{H}_{3y}$), 1.31-1.15 (12H, m, Si(i-Pr)$_2$, H_8, H_9), 1.12 (6H, d, J = 7.4 Hz, Si(CH(C$\underline{H}_3$)$_2$)), 0.840 (3H, t, J = 7.0 Hz, H_{10}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 161.9 (d, J^1_{C-F} = 245 Hz, ArF), 150.5 (C_6), 148.3 (C_2), 141.3 (ArCl), 140.9 (ArF), 136.3 (C_1), 132.0 (ArCl), 129.9 (ArCl), 128.1 (ArCl), 126.7 (d, J^3_{C-F} = 7.72 Hz, ArF), 115.8 (C_5), 115.0 (d, J^2_{C-F} = 21.3 Hz, ArF), 78.6 (C_4), 49.1 (C_3), 39.7 (C_7), 30.0 (C_8), 23.1 (C_9), 18.3 (Si(i-Pr)$_2$), 18.2 (Si(i-Pr)$_2$), 17.4 (2 x C, Si(i-Pr)$_2$), 15.8 (C_{10}), 14.6 (Si(i-Pr)$_2$), 13.9 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{28}H_{36}ClFOSi$ $[M]^+$ 470.2208, found 470.2210.

(E)-3-(1-(4-Fluorophenyl)pentylidene)-6-(4-fluorophenyl)-2,2-diisopropyl-4-methylene-1,2-oxasilinane

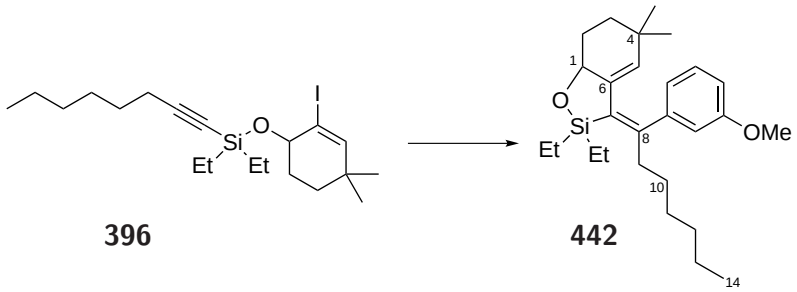
(650)



To a degassed solution of **384** (50 mg, 0.114 mmol, 1.0 eq) and 4-fluorophenylboronic acid (23.9 mg, 0.171 mmol, 1.5 eq) in DME (5 mL) was added Cs_2CO_3 (74.3 mg, 0.228 mmol, 2.0 eq) and Pd(dppf)Cl_2 (9.3 mg, 0.0114 mmol, 0.10 eq), before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in Et_2O and filtered through silica. Purification by flash column chromatography (10% Et_2O / P.E. 40-60) afforded cyclisation product **650** (28.7 mg, 0.0631 mmol, 55%) as a colourless oil; $\mathbf{R_f}$ 0.62 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2956, 2866, 2361, 1604, 1506, 1464, 1222, 1155, 1085, 1013, 883, 833, 781, 646; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.40-7.36 (2H, m, ArH), 7.07-7.00 (4H, m, ArH), 6.99-6.93 (2H, m, ArH), 5.02 (1H, d, J = 10.0 Hz, H_4), 4.72 (1H, s, H_1), 4.25 (1H, s, H_1), 2.52-2.45 (2H, m,$\underline{H}_{7x}H_{7y}$), 2.42-2.33 (1H, m, $\underline{H}_{3x}H_{3y}$), 2.28-2.21 (1H, m, $H_{3x}\underline{H}_{3y}$), 1.29-1.19 (12H, m, Si(i-Pr)$_2$, H_8, H_9), 1.13 (6H, d, J = 7.4 Hz, Si(CH(C$\underline{H}_3$)$_2$)), 0.845 (3H, t, J = 7.0 Hz, H_{10}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 162.0 (d, J^1_{C-F} = 244 Hz, ArF), 161.5 (d, J^1_{C-F} = 245 Hz, ArF), 150.8 (C_6), 148.4 (C_2), 141.0 (d, J^4_{C-F} = 2.85 Hz, ArF), 138.6 (d, J^4_{C-F} = 3.24 Hz, ArF), 136.0 (C_1), 130.0 (d, J^3_{C-F} = 7.45 Hz, ArF), 126.7 (d, J^3_{C-F} = 8.17 Hz, ArF), 115.5 (C_5), 115.0 (d, J^2_{C-F} = 21.6 Hz, ArF), 114.7 (d, J^2_{C-F} = 21.2 Hz, ArF), 78.6 (C_4), 49.1 (C_3), 39.9 (C_7), 30.0 (C_8), 23.1 (C_9), 18.3 (Si(i-Pr)$_2$), 18.2 (Si(i-Pr)$_2$), 17.4 (2 x C, Si(i-Pr)$_2$), 15.8 (C_{10}), 14.6 (Si(i-Pr)$_2$), 14.0 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{28}H_{36}F_2OSi$ $[M]^+$ 454.2504, found 454.2514.

(E)-2,2-Diethyl-3-(1-(3-methoxyphenyl)heptylidene)-5,5-dimethyl-2,3,5,6,7,7a-hexahydrobenzo[d][1,2]oxasilole

(442)

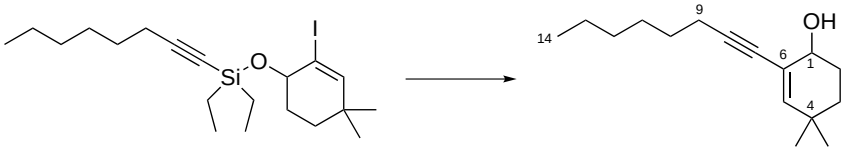


396 **442**

To a stirred, degassed solution of siloxane **396** (40 mg, 0.0896 mmol, 1.0 eq), KOAc (9.38 mg, 0.179 mmol, 2.0 eq) and 3-methoxybenzene boronic acid (21.8 mg, 0.144 mmol, 1.5 eq) in DME (4 mL) was added Pd(dppf)Cl_2 (7.8 mg, 8.96 μmol, 0.10 eq) before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (10% Et_2O / P.E.) afforded diene **442** (4.6 mg, 0.0135 mmol, 15%) as a yellow oil; $\mathbf{R_f}$ 0.60 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2955, 2928, 2361, 1596, 1462, 1286, 1044, 851, 812, 728; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.24-7.19 (1H, m, ArH), 6.80-6.70 (3H, m, ArH), 4.53 (1H, d, J = 0.5 Hz, H_5), 4.33-4.30 (1H, m, H_1), 3.80 (3H, s, OMe), 1.29-1.19 (10H, m), 1.12-1.09 (4H, m), 1.00-0.95 (7H, m), 0.87-0.82 (6H, m), 0.78 (3H, s), 0.60 (3H, s); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 159.6, 156.8, 150.2, 144.2, 138.0, 134.5, 129.2, 120.8, 114.1, 111.7, 77.2, 55.3, 41.9, 34.6, 32.9, 31.7, 31.0, 30.6, 29.9, 28.3 (2 x C), 22.6, 15.3, 7.5 ($SiEt_2$), 7.4 ($SiEt_2$), 7.2 ($SiEt_2$), 6.9 ($SiEt_2$); **HRMS** (FI) calculated for $C_{27}H_{42}O_2Si$ $[M]^+$ 426.2954, found 426.2954. Complete assignment could not be completed due to difficulties in purifying the sample further.

Unexpected Product

4,4-Dimethyl-2-(oct-1-yn-1-yl)cyclohex-2-enol (443)



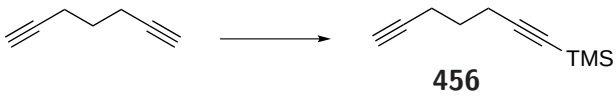
396 **443**

To a stirred, degassed solution of siloxane **396** (40 mg, 0.0896 mmol, 1.0 eq), KOAc (9.38 mg, 0.179 mmol, 2.0 eq) and pyridine-3-boronic acid (16.5 mg, 0.144 mmol, 1.5 eq) in DME (4 mL) was added $Pd(dppf)Cl_2$ (7.8 mg, 8.96 μjmol, 0.10 eq) before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vauo* and purification by flash column chromatography (50% Et_2O / P.E.) afforded enyne **443** (16.4 mg, 0.0703 mmol, 63%); $\mathbf{R_f}$ 0.13 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2956, 1729, 1460, 1243, 1075, 1008, 744, 697; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 5.82 (1H, s, H_5), 4.08 (1H, t, J = 5.9 Hz, H_1), 2.32 (2H, t, J = 7.2 Hz, H_9), 1.93 (1H, dddd, J = 13.5, 8.4, 5.2, 3.2 Hz, $\underline{H}_{2x}H_{2y}$), 1.70 (1H, tdd, J = 12.7, 6.1, 3.1 Hz, $H_{2x}\underline{H}_{2y}$), 1.61-1.50 (3H, m, H_{10}, $\underline{H}_{3x}H_{3y}$), 1.46-1.22 (6H, m, H_{11}, H_{12}, H_{13}), 1.04 (3H, s, CMe_2), 0.98 (3H, s, CMe_2), 0.90 (3H, t, J = 7.0 Hz, C_{14}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 145.1 (C_5), 122.4 (C_6), 90.8 (C_7), 78.8 (C_8), 67.4 (C_1), 33.0 (C_2), 31.3 (C_3), 28.9 (C_9), 28.85 (Me), 28.77 (Me), 28.6 (C_{10}), 27.6 (C_{11}), 22.5 (C_{12}), 19.3 (C_{13}), 14.0 (C_4), 6.5 (C_{14});**HRMS** (FI) calculated for $C_{16}H_{24}O$ 232.1827, found 234.2004.

7.4.8. Oligocyclisation

Preparation of Substrates

Hepta-1,6-diyn-1-yltrimethylsilane (456)[317]

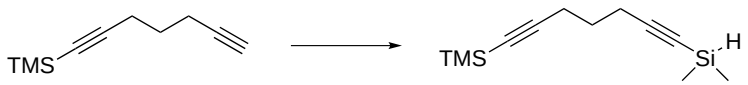


456

To a stirred solution of 1,6-heptadiyne (621 μL, 500 mg, 5.42 mmol, 1.0 eq) in THF (25 mL) at −78 °C was added LiHMDS (3.33 mL, 5.42 mmol, 1.0 eq of a 1.63 M solution in hexanes). After stirring for 45 min at −78 °C, trimethylsilylchloride (825 μL, 706 mg, 6.50 mmol, 1.2 eq) was added and the reaction mixture stirred for 2 h before the addition of aqueous NH_4Cl solution (25 mL) at −78 °C. The quenched mixture was warmed to r.t. and stirred for 30 min before extraction with Et_2O (3 x 25 mL). Concentration *in vacuo* afforded diyne **456** (756 mg, 4.60 mmol, 85%) as a colourless oil; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 2.40-2.27 (4H, m, $SiC{\equiv}CC\underline{H}_2CH_2C\underline{H}_2CCH$), 1.97 (1H, t, J = 2.7 Hz, CCH), 1.82-1.68 (2H, m, $SiC{\equiv}CCH_2C\underline{H}_2CH_2CCH$), 0.155 (9H, s, $SiMe_3$).

This data is in agreement with that reported by Wu *et al.*[317]

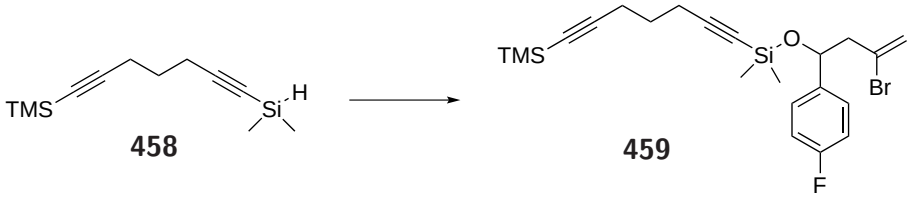
(7-(Dimethylsilyl)hepta-1,6-diyn-1-yl)trimethylsilane (457)



456 **457**

To a stirred solution of diyne **456** (200 mg, 1.22 mmol, 1.0 eq) in THF (2 mL) at −78 °C was added *n*BuLi (0.536 mL of a 2.5 M solution in hexanes, 1.34 mmol, 1.1 eq), before stirring for 15 min. Chlorodimethylsilane (162 μL, 1.46 mmol, 1.2 eq) was added, and the reaction mixture warmed to r.t. and stirred for 1 h before dilution with Et_2O (2 mL), washing with water (2 mL), drying ($MgSO_4$) and concentration *in vacuo* afforded silane **458** (156 mg, 0.701 mmol, 57%) as a colourless oil; $\mathbf{R_f}$ 0.56 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2960, 2903, 2177, 2138, 1429, 1326, 1251, 1066, 1046, 1024, 884, 842, 760, 742, 699, 667, 639; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 4.10 (1H, dtt, J = 7.5, 3.7, 1.0 Hz, SiH), 2.35-2.30 (4H, m, C≡CCH_2), 1.76-1.69 (2H, m, C≡CCH_2C$\underline{H}_2$), 0.21 (3H, s, $SiMe_2H$), 0.20 (3H, s, $SiMe_2H$), 0.137 (9H, s, $SiMe_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 107.8 (C≡C), 106.1 (C≡C), 85.1 (C≡C), 82.1 (C≡C), 27.6 (2 x C), 19.0, 0.1 ($SiMe_2$), -2.8 (TMS); **HRMS** (FI) calculated for $C_{12}H_{21}Si_2$ $[M]^+$ 221.1182, found 221.1188.

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)dimethyl(7-(trimethylsilyl)hepta-1,6-diyn-1-yl)silane (459)



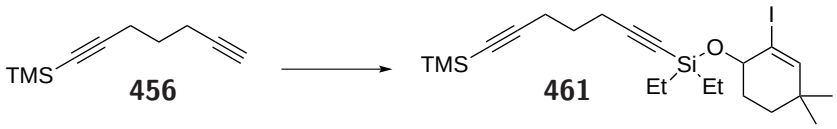
458 **459**

To stirred neat alcohol **370** (229 mg, 0.934 mmol, 1.0 eq) and silane **458** (208 mg, 0.934 mmol, 1.0 eq) was added $[RuCl_2(p\text{-cymene})]_2$ (2.86 mg, 0.00467 mmol, 0.005 eq) before heating to 50 °C. Dilution with P.E., filtration through a short silica plug and concentration *in vacuo* afforded siloxane **459** (277 mg, 0.595 mmol, 64%) as a colourless oil; $\mathbf{R_f}$ 0.55 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2959, 2175, 1509, 1250, 1224, 1045, 835, 792, 759, 698, 639; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.34-7.31 (2H, m, ArH), 7.013 (2H, ddt, J = 8.8, 6.1, 2.8 Hz, ArH), 5.52-5.51 (1H, m, CBr=C$\underline{H}_x$H$_y$), 5.42 (1H, d, J = 1.6 Hz, CBr=CH$_x\underline{H}_y$), 5.14 (1H, dd, J = 7.8, 5.2 Hz,

ArCHOSi), 2.86 (1H, ddd, J = 14.2, 7.8, 0.8 Hz, ArCH(OSi)C$\underline{H}_x$H$_y$), 2.64 (1H, ddd, J = 14.2, 5.1, 0.9 Hz, ArCH(OSi)CH$_x\underline{H}_y$), 2.36-2.27 (4H, m, SiC≡CCH$_2$), 1.72-1.66 (2H, m, SiC≡CCH$_2$C$\underline{H}_2$), 0.24 (3H, s, SiMe$_2$O), 0.17 (9H, s, SiMe$_3$), 0.10 (3H, s, SiMe$_2$O); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 162.1 (d, J^1_{C-F} = 245 Hz, ArF), 139.1 (ArF), 129.9 (Br$\underline{C}$=C), 127.6 (d, J^3_{C-F} = 7.8 Hz, ArF), 119.5 (BrC=$\underline{C}$), 114.9 (d, J^2_{C-F} = 21.3 Hz, ArF), 107.3 (C≡C), 106.1 (C≡C), 85.2 (C≡C), 82.8 (C≡C), 72.6 (C-O), 52.3 ($\underline{C}$-CBr), 27.4, 19.0, 18.8, 0.8 (SiMe$_2$), 0.6 (SiMe$_2$), 0.1 (TMS); **HRMS** (FI) calculated for C$_{22}$H$^{79}_{30}$BrFOSi$_2$ [M]$^+$ 466.0985, not found.

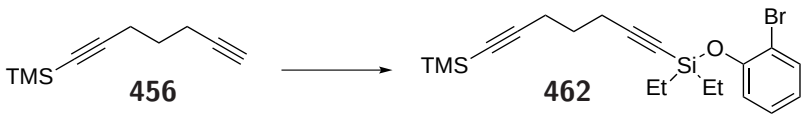
(7-(Diethyl((2-iodo-4,4-dimethylcyclohex-2-en-1-yl)oxy)silyl)hepta-1,6-diyn-1-yl)trimethylsilane

(461)



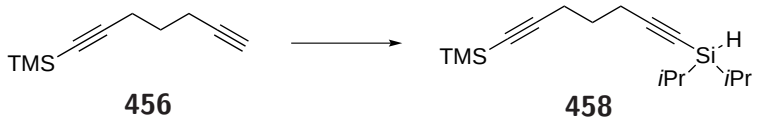
To a stirred solution of alkyne **456** (149 mg, 0.909 mmol, 1.0 eq) in THF (2 mL) at −78 °C was added *n*-BuLi (0.400 mL, 1.00 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorosilane **392** (217 μL, 194 mg, 1.00 mmol, 1.1 eq) was added and the reaction mixture warmed to r.t. Alcohol **376** (275 mg, 1.09 mmol, 1.2 eq) and DMAP (1 crystal) were added before stirring for 16 h at r.t. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (100% P.E.) afforded siloxane **461** (450 mg, 0.900 mmol, 99%) as a colourless oil; $\mathbf{R}_f$ 0.65 (10% Et$_2$O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2957, 2174, 1410, 1249, 1061, 1014, 928, 840, 734, 638; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 6.22 (1H, s, =CH), 4.32 (1H, t, J = 5.1 Hz, CHOSi), 2.40-2.31 (4H, m, SiC≡CC$\underline{H}_2$), 2.06-1.96 (1H, m, SiOCHC$\underline{H}_x$H$_y$), 1.93-1.81 (1H, m, SiOCHCH$_x\underline{H}_y$), 1.80-1.64 (4H, m, SiOCHCH$_2$C$\underline{H}_2$, SiC≡CCH$_2$C$\underline{H}_2$CH$_2$CCSi), 1.10-0.91 (12H, m, Si(CH$_2$C$\underline{H}_3$)$_2$, C(C$\underline{H}_3$)$_2$), 0.82-0.54 (4H, m, Si(C$\underline{H}_2$CH$_3$)$_2$), 0.15 (9H, s, SiMe$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 150.0 (I$\underline{C}$=C), 108.2 (IC=$\underline{C}$), 106.1 ($\underline{C}$≡CSi), 102.1 ($\underline{C}$≡CTMS), 85.2 (C≡$\underline{C}$Si), 81.3 (C≡$\underline{C}$TMS), 73.3 (C-O), 39.1 (*c*-Hex), 37.2 (*c*-Hex), 32.2, 30.1, 28.8 (Me), 28.1 (Me), 18.9 (*c*-Hex), 15.4, 7.3 (SiEt$_2$), 7.03 (SiEt$_2$), 6.99 (SiEt$_2$), 6.7 (SiEt$_2$), 0.1 (TMS); **HRMS** (FI) calculated for C$_{22}$H$_{37}$IOSi$_2$ [M]$^+$ 500.1428, not found.

(2-Bromophenoxy)diethyl(7-(trimethylsilyl)hepta-1,6-diyn-1-yl)silane (462)



To a stirred solution of alkyne **456** (250 mg, 1.52 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*-BuLi (0.668 mL, 1.67 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min at −78 °C, chlorosilane **392** (363 μL, 324 mg, 1.67 mmol, 1.1 eq) was added and the reaction mixture warmed to r.t. 2-Bromophenol (212 μL, 317 mg, 1.83 mmol, 1.2 eq) and DMAP (1 crystal) were added before stirring for 16 h at r.t. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (100% P.E.) afforded siloxane **462** (634 mg, 1.50 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.57 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2958, 2175, 1889, 1585, 1476, 1440, 1285, 1248, 1046, 916, 840, 749, 638; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.55-7.51 (1H, m, ArH), 7.21-7.15 (2H, m, ArH), 6.90-6.80 (1H, m, ArH), 2.41-2.31 (4H, m, SiC≡CC$\underline{H}_2$), 1.78-1.71 (4H, m, SiOCHCH_2C$\underline{H}_2$, SiC≡CCH_2C$\underline{H}_2$CH_2CCSi), 1.11-1.00 (6H, m, Si(CH_2C$\underline{H}_3$)$_2$), 0.92-0.79 (4H, m, Si(C$\underline{H}_2$CH_3)$_2$), 0.173 (9H, d, J = 2.2 Hz, $SiMe_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 152.2 (Ar), 133.2 (Ar), 128.1 (Ar), 122.8 (Ar), 120.4 (Ar), 115.2 (Ar), 109.2 (C≡CSi), 106.0 (C≡CTMS), 85.0 (C≡CSi), 80.7 (C≡HTMS), 27.4, 25.1, 18.9, 6.8 ($SiEt_2$), 6.5 ($SiEt_2$), -0.1 (TMS); **HRMS** (FI) calculated for $C_{20}H_{29}^{79}BrOSi_2$ $[M]^+$ 420.0940, found 420.0936.

(7-(Diisopropylsilyl)hepta-1,6-diyn-1-yl)trimethylsilane (458)

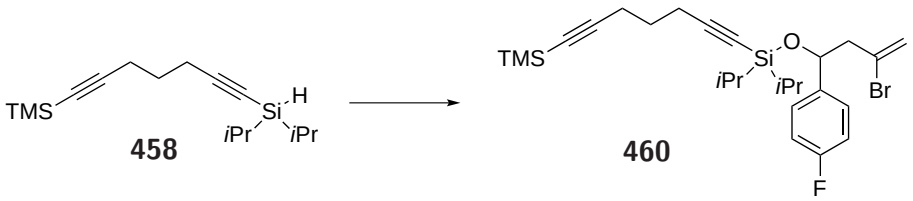


To a stirred solution of diyne **456** (200 mg, 1.22 mmol, 1.0 eq) in THF (2 mL) at −78 °C was added *n*BuLi (0.536 mL of a 2.5 M solution in hexanes, 1.34 mmol, 1.1 eq), before stirring for 15 min. Chlorodi*iso*propylsilane (249 μL, 1.46 mmol, 1.2 eq) was added, and the reaction mixture warmed to r.t. and stirred for 1 h before dilution with Et_2O (2 mL), washing with water (2 mL), drying ($MgSO_4$) and concentration *in vacuo* afforded silane **458** (335 mg, 1.21 mmol, 99%) as a colourless oil; $\mathbf{R_f}$ 0.63 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2955, 2865, 2176, 2117, 1463, 1384, 1250, 1046, 1001, 918, 882, 843, 802, 760, 698, 664, 640; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 3.67 (1H, br s,

SiH), 2.39-2.30 (4H, m, C≡CCH_2), 1.77-1.70 (2H, m, C≡CCH_2C$\underline{H}_2$), 1.07-1.00 (14H, m, Si(*i*-Pr)$_2$), 0.14 (9H, s, $SiMe_3$; ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 109.0, 106.1, 85.1, 78.5, 27.6, 19.0 (Si(*i*-Pr)$_2$), 18.4 (Si(*i*-Pr)$_2$), 13.2 (Si(*i*-Pr)$_2$), 0.1 (TMS); **HRMS** (FI) calculated for $C_{16}H_{29}Si_2$ $[M]^+$ 277.1808, found 277.1808.

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diisopropyl(7-(trimethylsilyl)hepta-1,6-diyn-1-yl)silane

(460)

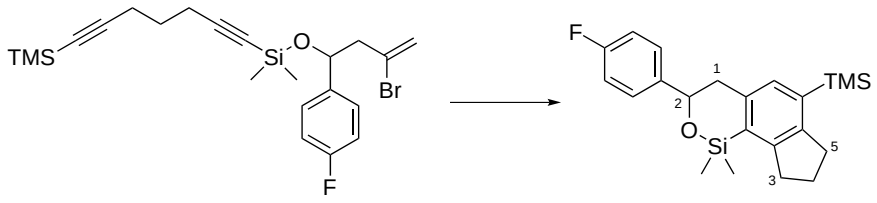


To a stirred solution of silane **458** (312 mg, 1.12 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added *N*-bromosuccinimide (199 mg, 1.12 mmol, 1.0 eq) before stirring for 30 min at r.t. A solution of alcohol **370** (248 mg, 1.01 mmol, 0.90 eq) and imidazole (153 mg, 2.24 mmol, 2.0 eq) in DMF (3 mL) was added *via* cannula, and the reaction mixture stirred at r.t. for 16 h. Following dilution with Et_2O (5 mL), the organic phase was washed with water (5 x 5 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (100% P.E.) to afford siloxane **460** (249 mg, 0.477 mmol, 47%) as a colourless oil; $\mathbf{R}_f$ 0.56 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2957, 2866, 2175, 1632, 1606, 1510, 1464, 1428, 1250, 1225, 1196, 1156, 1083, 918, 884, 844, 760, 639; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.35-7.30 (2H, m, ArH), 7.03-6.98 (2H, m, ArH), 5.42-5.41 (1H, m, CBr=C$\underline{H}_x$H$_y$), 5.36 (1H, d, J = 1.6 Hz, CBr=CH$_x\underline{H}_y$), 5.18 (1H, t, J = 6.6 Hz, ArCHOSi), 2.94 (1H, ddd, J = 14.0, 6.7, 0.8 Hz, ArCH(OSi)C$\underline{H}_x$H$_y$), 2.63 (1H, ddd, J = 14.0, 6.4, 0.7 Hz, ArCH(OSi)CH$_x\underline{H}_y$), 2.40-2.32 (4H, m, SiC≡CCH_2), 1.79-1.69 (2H, m, SiC≡CCH_2C$\underline{H}_2$), 1.08-0.83 (14H, m, Si(*i*-Pr)$_2$), 0.17 (9H, s, $SiMe_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.3 (d, J^1_{C-F} = 245 Hz, ArF), 139.3 (ArF), 129.8 (Br$\underline{C}$=C), 127.9 (d, J^3_{C-F} = 8.0 Hz. ArF), 119.6 (BrC=$\underline{C}$), 114.8 (d, J^2_{C-F} = 20.7 Hz, ArF), 108.8 ($\underline{C}$≡CSi), 106.1 ($\underline{C}$≡CTMS), 85.2 (C≡$\underline{C}$Si), 79.6 (C≡$\underline{C}$TMS), 73.2 (C-O), 52.6 ($\underline{C}$-CBr), 27.5, 19.0, 18.5, 17.3 (Si(*i*-Pr)$_2$), 17.2 (Si(*i*-Pr)$_2$), 17.03 (Si(*i*-Pr)$_2$), 16.99 (Si(*i*-Pr)$_2$), 13.3 (Si(*i*-Pr)$_2$), 13.1 (Si(*i*-Pr)$_2$), 0.14 (TMS); **HRMS** (FI) calculated for $C_{26}H^{79}_{38}BrFOSi_2$ $[M]^+$ 522.1613, not found.

Cyclisation Protocol

3-(4-Fluorophenyl)-1,1-dimethyl-6-(trimethylsilyl)-1,3,4,7,8,9-hexahydroindeno[4,5-c][1,2]oxasiline

(463)

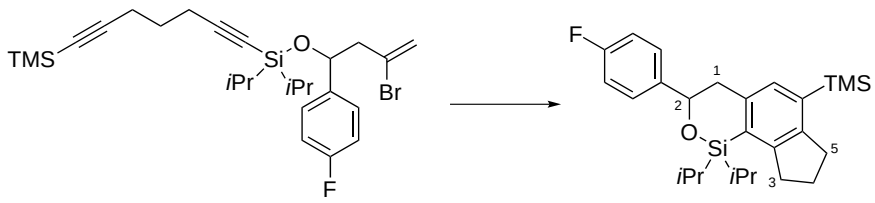


459 **463**

To a stirred, degassed solution of bromoenediyne **459** (20 mg, 0.0430 mmol, 1.0 eq) and Et_3N (35.9 μL, 0.258 mmol, 6.0 eq) or K_2CO_3 (11.9 mg, 0.0859 mmol, 2.0 eq) in MeCN (2 mL) was added $Pd(PPh_3)_4$ (5.0 mg, 4.30 μmol, 0.10 eq) before heating to 80 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (10% Et_2O / P.E.) afforded arene **463** (15.2 mg, 0.0396 mmol, 92%)as a colourless oily solid; $\mathbf{R_f}$ 0.61 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2955, 1509, 1249 1223, 1153, 1074, 942, 832, 786, 757, 672; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44 (2H, app dd, J = 8.4, 5.5 Hz, ArH), 7.07 (3H, m, ArH), 5.11 (1H, d, J = 10.1 Hz, H_1), 3.11-3.06 (1H, m, $\underline{H}_{1x}H_{1y}$), 3.00-2.84 (5H, m, $H_{1x}\underline{H}_{1y}$, H_3, H_5), 2.17-2.07 (2H, m, H_4), 0.456 (3H, s, $OSiMe_2$), 0.448 (3H, s, $OSiMe_2$), 0.311 (9H, s, $SiMe_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 162.8 (d, J^1_{C-F} = 244 Hz, ArF), 148.6 (Ar), 147.3 (Ar), 144.4 (Ar), 141.9 (ArF), 137.3 (Ar), 132.7 (2 x C, Ar), 127.7 (d, J^3_{C-F} = 8.0 Hz, ArF), 115.6 (d, J^2_{C-F} = 21.2 Hz, ArF), 75.6 (C_2), 45.4 (C_1), 35.2 (C_3), 34.1 (C_5), 26.4 (C_4), 14.7 ($SiMe_2$), 0.017 (TMS); **HRMS** (FI) calculated for $C_{22}H_{29}FOSi_2$ $[M]^+$ 384.1741, found 384.1742.

3-(4-Fluorophenyl)-1,1-diisopropyl-6-(trimethylsilyl)-1,3,4,7,8,9-hexahydroindeno[4,5-c][1,2]oxasiline

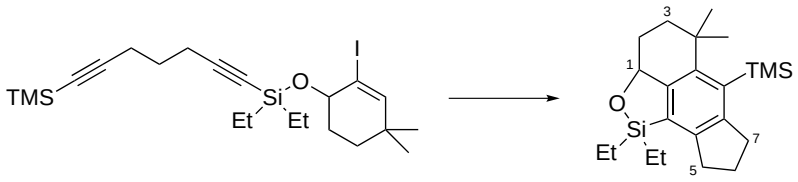
(464)



460 **464**

To a stirred, degassed solution of bromoenediyne **460** (50 mg, 0.0958 mmol, 1.0 eq) and Et_3N (40 μL, 0.575 mmol, 6.0 eq) or K_2CO_3 (39.8 mg, 0.192 mmol, 2.0 eq) in MeCN (5 mL) was added $Pd(PPh_3)_4$ (11.1 mg, 9.58 μmol, 0.10 eq) before heating to 80 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (10% Et_2O / P.E.) afforded arene **464** (41.8 mg, 0.0948 mmol, 99%) as a pale yellow oil; $\mathbf{R_f}$ 0.62 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2865, 2361, 1509, 1249, 1223, 1081, 938, 909, 832, 732, 658; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46 (2H, dd, J = 8.2, 5.6 Hz, ArH), 7.06 (3H, m, ArH), 5.06 (1H, d, J = 10.1 Hz, H_2), 3.00-2.87 (6H, m, H_1, H_3, H_5), 2.13-2.02 (2H, m, H_4), 1.39-1.33 (1H, m, SiC$\underline{H}(CH_3)_2$), 1.27-1.21 (1H, m, SiC$\underline{H}(CH_3)_2$), 1.18 (3H, d, J = 7.3 Hz, SiCH(C$\underline{H}$)$_3$), 1.12 (3H, d, J = 7.3 Hz, SiCH(C$\underline{H}_3$)), 1.04 (3H, d, J = 7.5 Hz, SiCH(C$\underline{H}_3$)), 1.00 (3H, d, J = 7.5 Hz, SiCH(C$\underline{H}_3$)), 0.308 (9H, s, $SiMe_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 162.9 (d, J^1_{C-F} = 246 Hz, ArF), 148.5 (Ar), 147.5 (Ar), 143.2 (Ar), 141.2 (ArF), 137.9 (Ar), 132.8 (Ar), 131.1 (Ar), 128.0 (d, J^3_{C-F} = 8.5 Hz, ArF), 115.8 (d, J^2_{C-F} = 20.9 Hz, ArF), 74.9 (C_2), 44.4 (C_1), 34.1 (C_3), 34.0 (C_5), 26.2 (C_4), 0.9 (Si(i-Pr)$_2$), 0.7 (Si(i-Pr)$_2$), 0.02 (Si(i-Pr)$_2$), 0.01 (2 x C, Si(i-Pr)$_2$, TMS); **HRMS** (FI) calculated for $C_{26}H_{37}FOSi_2$ $[M]^+$ 440.2367, found 440.2372.

1,1-Diethyl-5,5-dimethyl-6-(trimethylsilyl)-1,2a,3,4,5,7,8,9-octahydrocyclopenta[2,3]naphtho[1,8-cd][1,2]oxasilole (465)



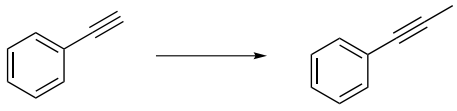
461 **465**

To a stirred, degassed solution of diyne **461** (50 mg, 0.0999 mmol, 1.0 eq) and Et_3N (83.5 μL, 0.599 mmol, 6.0 eq) or K_2CO_3 (27.6 mg, 0.200 mmol, 2.0 eq) in MeCN (5 mL) was added $Pd(PPh_3)_4$ (11.6 mg, 9.99 μmol, 0.10 eq) before heating to 80 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (10% Et_2O / P.E.) afforded arene **465** (15.0 mg, 0.0402 mmol, 40%) as a yellow oil; $\mathbf{R_f}$ 0.43 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2953, 1458, 1354, 1308, 1251, 1129, 1089, 1052, 1016, 955, 844, 814, 728, 692, 624; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 4.96 (1H, dd, J = 10.1, 5.6 Hz, H_1), 3.13-2.93 (2H, m, H_5), 2.80 (2H, app td, J = 7.2, 3.4 Hz, H_7), 2.22-2.09 (1H, m, $\underline{H}_{2x}H_{2y}$), 2.07-1.92 (2H, m, H_6), 1.89-1.61 (3H, m, $H_{2x}\underline{H}_{2y}$, H_3), 1.51 (3H, s, CMe_2), 1.37 (3H, s, CMe_2), 1.11-0.78 (10H, m, $SiEt_2$), 0.51 (9H, s, $SiMe_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 150.2 (Ar), 147.6 (Ar), 145.8 (Ar), 145.2 (Ar), 136.9 (Ar), 129.9 (Ar), 80.3 (C_1), 41.9 (C_2), 36.7 (C_5), 36.2 (C_7), 33.6 (C_4), 33.4 (Me), 33.3 (Me), 28.7 (C_3), 26.6 (C_6), 7.0 ($SiEt_2$), 6.6 ($SiEt_2$), 6.3 ($SiEt_2$), 6.2 ($SiEt_2$), 5.9 (TMS); **HRMS** (FI) calculated for $C_{19}H_{28}OSi$ $[M]^+$ 300.1909, found 300.1920.

7.4.9. Alternative Tether Synthesis

Propargyl Silane Linker

Prop-1-yn-1-ylbenzene (483)[318]

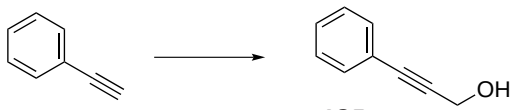


483

To a stirred solution of phenylacetylene (1.06 mL, 1.00 g, 9.79 mmol, 1.0 eq) in THF (10 mL) at −78 °C was added *n*BuLi (4.70 mL of a 2.5 M solution in hexanes, 11.8 mmol, 1.2 eq) before stirring for 15 min. Iodomethane (0.914 mL, 14.7 mmol, 1.5 eq) was then added, and the reaction mixture warmed to r.t. and stirred for 1 h before quenching with aqueous NH_4Cl solution (10 mL). Extraction with DCM (3 x 10 mL), drying of the combined organic phases ($MgSO_4$) and concentration *in vacuo* afforded methylated alkyne **483** (1.13 g, 9.69 mmol, 99%) as yellow oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.42-7.35 (2H, m, ArH), 7.32-7.26 (3H, m, ArH), 2.06 (3H, s, Me).

This data is in agreement with that reported by Stuart *et al.*[318]

3-Phenylprop-2-yn-1-ol (485)[319]

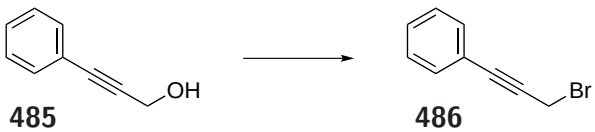


485

To a stirred solution of phenylacetylene (0.538 mL, 0.500 g, 4.90 mmol, 1.0 eq) in THF (5 mL) at −78 °C was added *n*-BuLi (2.16 mL, 5.39 mmol, 1.1 eq of a 2.5 M solution in hexanes) dropwise. After stirring for 15 min, paraformaldehyde (162 mg, 5.39 mmol, 1.1 eq) was added and the reaction mixture was warmed to r.t. and stirred for 3 h. Following quenching with NH_4Cl solution (5 mL) and extraction with EtOAc (10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **485** (492 mg, 3.72 mmol, 76%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.49-7.29 (5H, m, ArH), 4.51 (2H, d, J = 6.1 Hz, C$\underline{H_2}$OH).

This data is in agreement with that reported by Lian *et al.*[320]

(3-Bromoprop-1-yn-1-yl)benzene (486)[319]



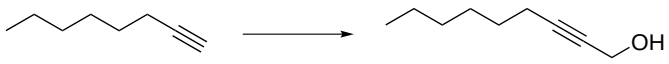
485 **486**

To alcohol **485** (492 mg, 3.72 mmol, 1.0 eq) was added PBr_3 (0.52 mL, 1.51 g, 5.58 mmol, 1.5 eq) dropwise at 0 °C. The reaction mixture was stirred at r.t. for 30 min before quenching with ice, then neutralising with $NaHCO_3$ (solid). The resulting suspension was extracted with DCM (5 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford alkyne **651** (456 mg, 2,60 mmol, 51%) as a yellow oil following purification by silica plug; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.60-7.28 (5H, m, ArH), 4.18 (2H, s, CH_2Br).

This data is in agreement with that reported by Kleinbeck *et al.*[320]

Disiloxane Linker

Non-2-yn-1-ol (489)

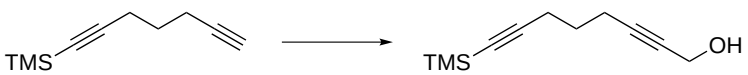


489

To a stirred solution of octyne (335 μL, 250 mg, 2.27 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*BuLi (1.00 mL, 2.50 mmol, 1.1 eq) before stirring for 15 min. Paraformaldehyde (81.7 mg, 2.72 mmol, 1.2 eq) was added, and the reaction mixture warmed to r.t. before quenching with aqueous NH_4Cl solution (3 mL). Extraction with Et_2O (3 x 3 mL), drying of the combined organic phases ($MgSO_4$) and concentration *in vacuo* afforded alcohol **489** (228 mg, 1.63 mmol, 72%) as a colourless oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 4.27 (2H, dq, J = 6.1, 2.2 Hz, C$\underline{H}_2$OH), 2.22 (2H, tt, J = 7.0, 2.2 Hz, C≡CCH_2), 1.59-1.18 (8H, m, C≡CCH_2C$_4\underline{H}_8$), 0.96-0.84 (3H, m, C≡CC$_6$H$_{10}$C$\underline{H}_3$).

This data is in agreement with that reported by Schomaker *et al.*[321]

8-(Trimethylsilyl)octa-2,7-diyn-1-ol (652)

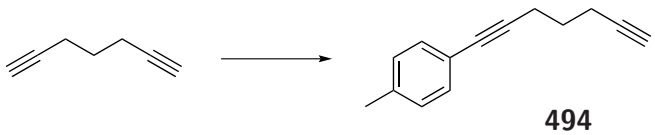


456 **652**

To a stirred solution of diyne **456** (225 mg, 1.37 mmol, 1.0 eq) in THF (2.5 mL) at −78 °C was added *n*BuLi (0.601 mL of a 2.5 M solution in hexane, 1.51 mmol, 1.1 eq) before stirring for 15 min. Paraformaldehyde (49.3 mg, 1.64 mmol, 1.2 eq) was added and the reaction warmed to r.t. and stirred for 30 min before quenching with aqueous NH_4Cl solution (3 mL). The quenched mixture was extracted with Et_2O (3 x 3 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* before purification by flash column chromatography (10 % → 100% Et_2O / P.E.) afforded alcohol **652** (250 mg, 1.29 mmol, 94%) as a pale yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 4.26 (2H, dt, J = 6.1, 2.2 Hz, C$\underline{H}_2$OH), 2.39-2.30 (4H, m, C≡CCH_2), 1.80-1.66 (2H, C≡CCH_2C$\underline{H}_2$), 1.46 (1H, t, J = 6.1 Hz, OH), 0.16 (9H, s, $SiMe_3$).

This data is in agreement with that reported by Mukai *et al.*[322]

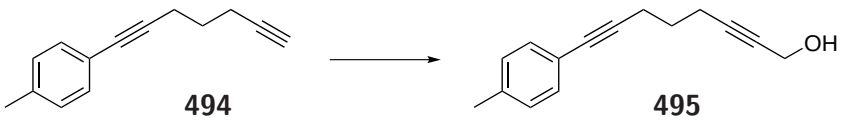
1-(Hepta-1,6-diyn-1-yl)-4-methylbenzene (494)[323]



494

To a stirred, degassed solution of 1,6-heptadiyne (621 μL, 500 mg, 5.43 mmol, 2.5 eq), 4-iodotoluene (591 mg, 2.71 mmol, 1.0 eq) and CuI (25.9 mg, 0.136 mmol, 0.05 eq) in Et_3N (7 mL) was added $Pd(PPh_3)_2Cl_2$ (95 mg, 0.136 mmol, 0.05 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (100% P.E.) afford diyne **494** (308 mg, 1.69 mmol, 62%) as a yellow oil contaminated with 1,7-di-p-tolylhepta-1,6-diyne; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62-7.56 (2H, m, ArH), 7.50-7.44 (2H, m, ArH), 2.59 (2H, t, J = 7.0 Hz, ArC≡CCH_2), 2.39 (2H, td, J = 7.0, 2.6 Hz, ArC≡CCH_2CH_2C$\underline{H}_2$), 2.00 (1H, t, J = 2.6 Hz, CCH), 1.85 (2H, *app* t, J = 7.0 Hz, ArC≡CCH_2C$\underline{H}_2$). Further characterisation was not completed as the product mix was carried through directly to the next step in an attempt to separate the di-substituted by-product.

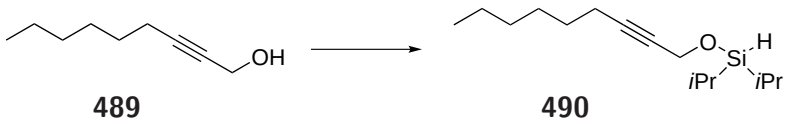
8-(p-Tolyl)octa-2,7-diyn-1-ol 495



494 **495**

To a stirred solution of diyne **494** (308 mg, 1.69 mmol, 1.0 eq) in THF (5 mL) at −78 °C was added *n*-BuLi (0.744 mL, 1.86 mmol, 1.1 eq of a 2.5 M solution in hexanes). After stirring for 15 min, paraformaldehyde (55.9 mg, 1.86 mmol, 1.1 eq) was added and the solution warmed to r.t. The reaction mixture was quenched with aqueous NH_4Cl solution (5 mL), then extracted with Et_2O (3 x 5 mL). The combined organic phases were dried ($MgSO_4$) and concentration *in vacuo*, affording alcohol **495** (357 mg, 1.68 mmol, 99%) as a pale yellow oil contaminated with 1,7-di-*p*-tolylhepta-1,6-diyne; $\mathbf{R_f}$ 0.55 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3297, 3028, 2935, 2866, 2226, 1906, 1609, 1509, 1430, 1344, 1133, 1009, 815, 636; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (2H, d, J = 7.9 Hz, ArH), 7.10 (2H, d, J = 7.9 Hz, ArH), 4.27 (2H, br s, C≡CC$\underline{H}_2$OH), 2.59 (1H, t, J = 7.0 Hz, OH), 2.53 (2H, t, J = 7.0 Hz, ArC≡CC$\underline{H}_2$), 2.42 (2H, tt, J = 7.1, 2.2 Hz, C$\underline{H}_2$C≡CCH_2OH), 2.34 (3H, s, ArMe), 1.85-1.79 (2H, ArC≡CCH_2C$\underline{H}_2$$CH_2$C≡C$CH_2$OH); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 137.6, 131.4, 130.0, 120.6, 88.2, 85.6, 81.3, 78.9, 51.4, 27.8, 21.4, 18.6, 18.0; **HRMS** (ESI^+) calculated for $C_{15}H_{16}NaO$ $[M+Na]^+$ 235.1093, found 235.1092.

Diisopropyl(non-2-yn-1-yloxy)silane (490)

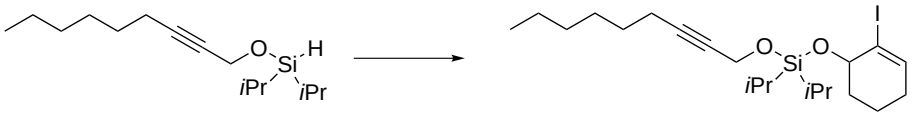


489 **490**

To a stirred solution of alcohol **489** (228 mg, 1.63 mmol, 1.0 eq), Et_3N (250 μL, 1.79 mmol, 1.1 eq) and DMAP (1 crystal) in DCM (5 mL) at r.t. was added chlorodi*iso*-propylsilane (278 μL, 1.63 mmol, 1.0 eq). The reaction mixture was stirred for 30 min, then concentrated *in vacuo*, before addition of P.E. and filtration through a short plug of silica afforded siloxane **490** (357 mg, 1.40 mmol, 86%) as a colourless oil; $\mathbf{R_f}$ 0.63 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2931, 2864, 2100, 1463, 1368, 1141, 1060, 1000, 881, 824, 667; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 4.37 (3H, t, J = 2.2 Hz, C$\underline{H}_2$OSi), 4.20 (1H, br s, SiH), 2.26-2.17 (2H, m, C≡CCH_2), 1.55-1.23 (8H, m, C≡C$CH_2C_4\underline{H}_8$), 1.10-0.96 (14H, m, Si(*i*-Pr)$_2$), 0.93-0.83 (3H, m, C≡C$C_5H_{10}C\underline{H}_3$); ^{13}**C NMR**

(100 MHz, $CDCl_3$) δ_C 86.0, 77.9, 54.1, 31.3, 28.5, 22.5, 18.7, 17.3, 17.2, 17.0, 16.9, 14.0, 12.3; **HRMS** (FI) calculated for $C_{15}H_{30}OSi$ $[M]^+$ 254.2066, found 254.2206.

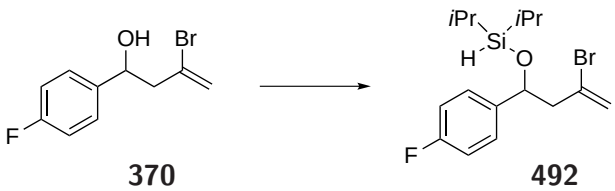
((2-Iodocyclohex-2-en-1-yl)oxy)diisopropyl(non-2-yn-1-yloxy)silane (491)



490 **491**

To a stirred solution of silane **490** (322 mg, 1.26 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added *N*-bromosuccinimide (225 mg, 1.26 mmol, 1.0 eq) before stirring for 30 min at r.t. A solution of alcohol **514** (283 mg, 1.26 mmol, 1.0 eq) and imidazole (172 mg, 2.53 mmol, 2.0 eq) in DMF (5 mL) was added *via* cannula, and the reaction mixture was stirred for 16 h. Upon dilution with Et_2O (5 mL), the mixture was washed with water (5 x 5 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by filtration through a short silica plug to afford disiloxane **491** (459 mg, 0.963 mmol, 76%) as a pale yellow oil; $\mathbf{R}_f$ 0.66 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2930, 2865, 1464, 1373, 1251, 1143, 1083, 1058, 1020, 885, 846, 801, 691; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.49-6.47 (1H, m, =CH), 4.49-4.39 (3H, m, C$\underline{\text{H}}$OSiOC$\underline{\text{H}}_2$C), 2.20 (2H, *app* tq, J = 7.1, 2.4 Hz, C≡CC$\underline{\text{H}}_2$$C_5H_{11}$), 2.16-1.78 (5H, m, *c*Hex), 1.68-1.61 (1H, m, *c*Hex), 1.55-1.46 (2H, m, C≡CCH_2C$\underline{\text{H}}_2$$C_4H_9$), 1.42-1.22 (6H, m, C≡C$C_2H_4C_3\underline{\text{H}}_6CH_3$), 1.13-1.01 (14H, m, Si(*i*-Pr)$_2$)), 0.89 (3H, t, J = 7.0 Hz, C≡CC_5H_{10}C$\underline{\text{H}}_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 140.6 (I$\underline{\text{C}}$=C), 103.0 (IC=$\underline{\text{C}}$), 85.4 (C≡$\underline{\text{C}}$C-O), 78.4 ($\underline{\text{C}}$≡CC-O), 72.8 (*c*-HexC-O), 51.9 (C-O), 33.4 (*c*-Hex), 31.4 (*n*-Hex), 29.4 (*n*-Hex), 28.6 (2 x C, *n*-Hex), 28.5 (*c*-Hex), 22.6 (*n*-Hex), 18.8 (*c*-Hex), 17.6 (Si(*i*-Pr)$_2$), 17.5 (Si(*i*-Pr)$_2$), 14.1 (*n*-Hex), 12.8 (Si(*i*-Pr)$_2$); **HRMS** (ESI^+) calculated for $C_{21}H_{37}INaO_2Si$ $[M+Na]^+$ 499.1500, found 499.1497.

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diisopropylsilane (492)

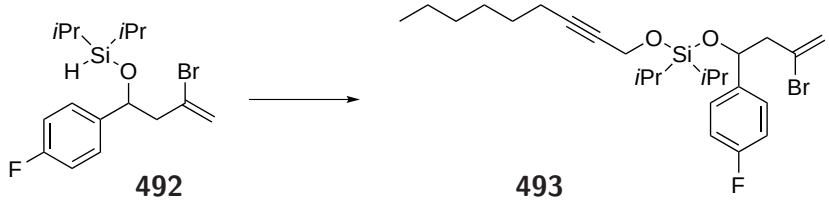


370 **492**

To a stirred solution of alcohol **370** (309 mg, 1.26 mmol, 1.0 eq) and Et_3N (263 μL, 1.89 mmol, 1.5 eq) in DCM (2.5 mL) at r.t. was added chlorodiisopropylsilane (258 μL, 1.51 mmol, 1.2 eq). After

15 min, the reaction mixture was quenched with MeOH (1 mL) and subsequently concentrated *in vacuo*. The resulting crude product was dissolved in pentane, filtered throught Celite and concentrated *in vacuo* to afforded silane **492** (339 mg, 0.943 mmol, 75%) as a colourless oil; $\mathbf{R_f}$ 0.68 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2945, 2866, 2359, 2100, 1632, 1606, 1510, 1463, 1225, 1156, 1085, 1002, 935, 883, 834, 668; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 (2H, dd, J = 8.6, 5.6 Hz, ArH), 7.02 (2H, d, J = 8.6 Hz, ArH), 5.50 (1H, s, BrC=C$\underline{H}_x$H$_y$), 5.41 (1H, d, J = 1.1 Hz, BrC=CH$_x\underline{H}_y$), 5.00 (1H, dd, J = 7.4, 5.4 Hz, ArC$\underline{H}$OH), 4.18 (1H, br s, SiH), 2.88-2.84 (1H, m, ArCH(OH)C$\underline{H}_x$H$_y$), 2.63 (1H, dd, J = 14.1, 5.3 Hz, ArCH(OH)CH$_x\underline{H}_y$), 1.07-1.00 (14H, m, Si(i-Pr)$_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.1 (d, J^1_{C-F} = 245 Hz, ArF), 139.1 (d, J^4_{C-F} = 2.9 Hz, ArF), 129.9 (Br$\underline{C}$=C), 127.6 (d, J^3_{C-F} = 7.8 Hz, ArF), 119.7 (BrC=$\underline{C}$), 115.0 (d, J^2_{C-F} = 21.7 Hz, ArF), 74.0 (C-O), 52.7 ($\underline{C}$-CBr), 17.6 (Si(i-Pr)$_2$), 17.4 (Si(i-Pr)$_2$), 17.3 (Si(i-Pr)$_2$), 17.1 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{16}H_{24}^{79}BrFOSi$ $[M]^+$ 360.0745, not found.

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diisopropyl(non-2-yn-1-yloxy)silane (493)

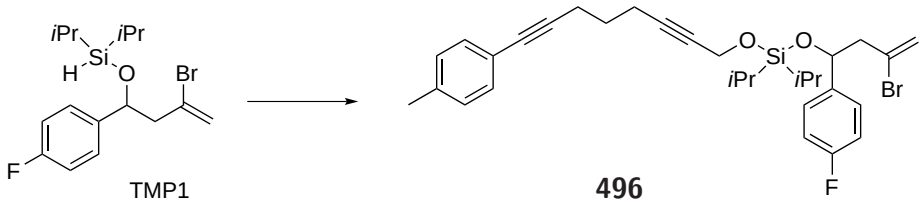


To a stirred solution of silane **492** (170 mg, 0.694 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added *N*-bromosuccinamide (124 mg, 0.694 mmol, 1.0 eq). The reaction mixture was warmed to r.t. and stirred for 15 min, then recooled to 0 °C before the addition of a solution of alcohol **489** (97 mg, 0.694 mmol, 1.0 eq), Et_3N (106 μL, 0.763 mmol, 1.1 eq) and DMAP (1 crystal) in DCM (1 mL). After stirring for 16 h at r.t., the reaction mixture was concentrated *in vacuo*, dissolved in pentane and filtered through Celite. Concentration *in vacuo* afforded disiloxane **493** (158 mg, 0.318 mmol, 46%) as a colourless oil; $\mathbf{R_f}$ 0.69 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2930, 2866, 1632, 1606, 1510, 1464, 1371, 1253, 1225, 1144, 1060, 1003, 936, 886, 834, 780, 693; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 (2H, dd, J = 8.5, 5.5 Hz, ArH), 7.01 (2H, d, J = 8.7 Hz, ArH), 5.43-5.40 (1H, m, BrC=C$\underline{H}_x$H$_y$), 5.36 (1H, d, J = 1.6 Hz, BrC=CH$_x\underline{H}_y$), 5.18 (1H, t, J = 6.5 Hz, ArC$\underline{H}$(OH)), 4.24 (1H, dt, J = 15.5, 2.2 Hz, C≡CC$\underline{H}_x$H$_y$OSi), 4.16 (1H, dt, J = 15.5, 2.2 Hz, C≡CCH$_x\underline{H}_y$OSi), 2.98-2.92 (1H, m, ArCH(OH)C$\underline{H}_x$H$_y$), 2.69-2.64 (1H, m, ArCH(OH)CH$_x\underline{H}_y$), 2.23-2.17 (2H, m, C≡CC$\underline{H}_2$C$_5$H$_{11}$), 1.54-1.46 (2H, m, C≡CCH$_2$C$\underline{H}_2$C$_4$H$_9$), 1.41-1.24 (6H, m, C≡CC$_2$H$_4$C$_3\underline{H}_6$CH$_3$),

1.10-1.01 (14H, m, Si(*i*-Pr)$_2$), 0.87 (3H, t, J = 6.4 Hz, C≡CC$_5$H$_{10}$C$\underline{\text{H}}_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.1 (d, J^1_{C-F} = 245 Hz, ArF), 139.4 (d, J^4_{C-F} = 3.5 Hz, ArF), 129.6 (Br$\underline{\text{C}}$=C), 127.7 (d, J^3_{C-F} = 7.7 Hz, ArF), 119.8 (BrC=$\underline{\text{C}}$), 114.9 (d, J^2_{C-F} = 21.0 Hz, ArF), 85.4 (C≡$\underline{\text{C}}$C-O), 78.3 ($\underline{\text{C}}$≡CC-O), 71.9 (ArC-O), 52.8 (C-O), 51.7 ($\underline{\text{C}}$-CBr), 31.4 (*n*-Hex), 28.6 (2 x C, *n*-Hex), 25.7 (*n*-Hex), 22.6 (*n*-Hex), 18.8 (*n*-Hex), 17.3 (Si(*i*-Pr)$_2$), 17.2 (Si(*i*-Pr)$_2$), 14.1 (*n*-Hex), 12.3 (Si(*i*-Pr)$_2$); **HRMS** (FI) calculated for $C_{25}H^{79}_{38}BrFO_2Si$ $[M]^+$ 498.1792, not found.

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)diisopropyl((8-(p-tolyl)octa-2,7-diyn-1-yl)oxy)silane

(496)



To a stirred solution of silane **492** (170 mg, 0.694 mmol, 1.0 eq) in DCM (2.5 mL) at 0 °C was added *N*-bromosuccinamide (124 mg, 0.694 mmol, 1.0 eq). The reaction mixture was warmed to r.t. and stirred for 15 min, then recooled to 0 °C before the addition of a solution of alcohol **495** (147 mg, 0.694 mmol, 1.0 eq), Et_3N (106 μL, 0.763 mmol, 1.1 eq) and DMAP (1 crystal) in DCM (1 mL). After stirring for 16 h at r.t., the reaction mixture was concentrated *in vacuo*, dissolved in pentane and filtered through Celite. Concentration *in vacuo* afforded disiloxane **496** (164 mg, 0.288 mmol, 42%) as a colourless oil; $\mathbf{R}_f$ 0.49 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2946, 2867, 1605, 1509, 1464, 1373, 1224, 1141, 1061, 1002, 886, 834, 816, 780, 735, 695; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (2H, dd, J = 5.9, 2.6 Hz, ArH), 7.29 (2H, m, ArH), 7.10-7.08 (2H, m, ArH), 7.01 (2H, d, J = 8.7 Hz, ArH), 5.42-5.41 (1H, m, BrC=C$\underline{\text{H}}_x$H$_y$), 5.37 (1H, d, J = 1.6 Hz, BrC=CH$_x\underline{\text{H}}_y$), 5.20-5.17 (1H, m, ArC$\underline{\text{H}}$(OH)), 4.25 (1H, dt, J = 15.5, 2.1 Hz, C≡CC$\underline{\text{H}}_x$H$_y$OSi), 4.17 (1H, dt, J = 15.6, 2.1 Hz, C≡CCH$_x\underline{\text{H}}_y$OSi), 2.97-2.92 (1H, m, ArCH(OH)C$\underline{\text{H}}_x$H$_y$), 2.69-2.65 (1H, m, ArCH(OH)CH$_x\underline{\text{H}}_y$), 2.54-2.49 (2H, m, ArC≡CC$\underline{\text{H}}_2$), 2.41-2.37 (2H, m, SiOCH$_2$C≡CC$\underline{\text{H}}_2$), 1.82-1.78 (2H, m, ArC≡CCH$_2$C$\underline{\text{H}}_2$) 1.56 (3H, s, ArMe), 1.10-1.02 (14H, m, Si(*i*-Pr)$_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 162.1 (d, J^1_{C-F} = 245 Hz, ArF), 139.4 (d, J^4_{C-F} = 2.9 Hz, ArF), 137.6 (Tol), 131.4 (Tol), 129.6 (Br$\underline{\text{C}}$=C), 128.9 (Tol), 127.7 (d, J^3_{C-F} = 8.0 Hz, ArF), 120.7 (Tol), 119.8 (BrC=$\underline{\text{C}}$), 115.0 (d, J^2_{C-F} = 21.1 Hz, ArF), 88.3 (C≡C), 84.3 (C≡C), 81.2 (C≡C), 79.0 (C≡C), 72.0

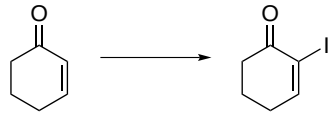
(ArC-O), 68.8 (C-O), 51.6 (C-CBr), 27.8 (Me), 25.8, 21.4, 18.7, 17.3 (Si(*i*-Pr)$_2$), 17.2 (Si(*i*-Pr)$_2$), 12.3 (Si(*i*-Pr)$_2$); **HRMS** (ESI$^+$) calculated for $C_{31}H_{38}^{79}BrFNaO_2Si$ $[M]^+$ 591.1701, found 591.1704.

7.5. Silicon-Tethering in Platinum-Mediated Chemistry

7.5.1. Initial Substrate Route

Alcohol Synthesis

2-Iodocyclohex-2-enone (518)[307]

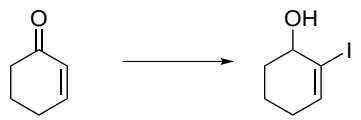


518

To a stirred solution of 2-cyclohexen-1-one (504 μL, 500 mg, 5.20 mmol, 1.0 eq) in CCl_4 / pyr (20 mL, 1:1) at 0 °C was added a solution of iodine (2.64 g, 10.4 mmol, 2.0 eq) in CCl_4 / pyr (20 mL, 1:1) dropwise. The reaction mixture was stirred for 2 h at r.t., then diluted with Et_2O and the organic phase washed with water (40 mL), 1N HCl solution (40 mL) and aqueous $Na_2S_2O_3$ solution (40 mL) to afford vinyl iodide **518** as a pale yellow oil that was taken on crude to the next step; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.78 (1H, t, J = 4.4 Hz, C=CH), 2.71-2.63 (2H, m, *c*Hex), 2.49-2.41 (2H, m, *c*-Hex), 2.16-2.03 (2H, m, *c*Hex).

This data is in agreement with that reported by Pandey *et al.*[308]

2-Iodocyclohex-2-enol (514)[309]



518 **514**

To a stirred solution of crude enone **518** in MeOH (10 mL) at 0 °C was added $CeCl_3$ (1.97 g, 5.20 mmol, 1.0 eq), before stirring for 10 min. $NaBH_4$ (197 mg, 5.20 mmol, 1.0 eq) was then added

and the reaction mixture was stirred for 1 h at r.t. Following the addition of water (10 mL), the resulting mixture was extracted with Et_2O (3 x 15 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **514** (798 mg, 3.56 mmol, 63% over two steps) as a yellow solid; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.53-6.49 (1H, m, C=CH), 4.20 (1H, t, J = 4.9 Hz, C<u>H</u>OH), 2.21-1.60 (6H, m, *c*-Hex).

This data is in agreement with that reported by Sha *et al.*[309]

2-Iodocyclopent-2-enone (519)[307]

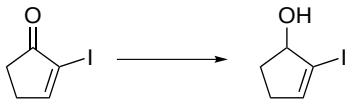


519

To a stirred solution of 2-cyclopenten-1-one (510 μL, 500 mg, 6.09 mmol, 1.0 eq) in CCl_4 / pyr (20 mL, 1:1) at 0 °C was added a solution of iodine (3.08 g, 12.2 mmol, 2.0 eq) in CCl_4 / pyr (20 mL, 1:1) dropwise. The reaction mixture was stirred for 2 h at r.t., then diluted with Et_2O and the organic phase washed with water (40 mL), 1N HCl solution (40 mL) and aqueous $Na_2S_2O_3$ solution (40 mL) to afford vinyl iodide **519** as a pale yellow oil that was taken on crude to the next step; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 8.03 (1H, t, J = 2.9 Hz, =CH), 2.82-2.76 (2H, m, C(=O)CH_2), 2.54-2.49 (2H, m, C(=O)CH_2C<u>H</u>$_2$).

This data is in agreement with that reported by Zhao *et al.*[324]

2-Iodocyclopent-2-enol (515)[309]



519 **515**

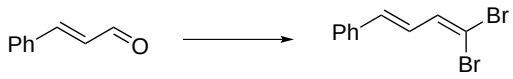
To a stirred solution of crude enone **519** in MeOH (10 mL) at 0 °C was added $CeCl_3$ (2.27 g, 6.09 mmol, 1.0 eq), before stirring for 10 min. $NaBH_4$ (230 mg, 6.09 mmol, 1.0 eq) was then added

and the reaction mixture was stirred for 1 h at r.t. Following the addition of water (10 mL), the resulting mixture was extracted with Et_2O (3 x 15 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **515** (258 mg, 1.23 mmol, 20% over two steps) as a yellow solid; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.31 (1H, tt, J = 2.4, 1.2 Hz, C=CH), 4.76-4.65 (1H, m, C<u>H</u>OH), 2.60-2.20 (3H, m, CH(O<u>H</u>)C<u>H</u>$_2$), 1.94-1.78 (2H, m, CH(OH)CH$_2$C<u>H</u>$_2$).

This data is in ageement with that reported by Kim *et al.*[310]

Coupling Partner Synthesis

(E)-(4,4-Dibromobuta-1,3-dien-1-yl)benzene (524)[325]



524

To a solution of *trans*-cinnamaldehyde (2.86 mL, 3.00 g, 22.7 mmol, 1.0 eq) and CBr_4 (7.53 g, 22.7 mol, 1.0 eq) in DCM (45 mL) at 0 °C was added a solution of PPh_3 (11.9 g, 45.3 mmol, 2.0 eq) in DCM (30 mL), before stirring at 0 °C for 30 min. The reaction mixture was warmed to r.t. and stirred for 1 h. Hexane was then added (30 mL) and the resulting suspension filtered through silica and washed with hexane, before concentration *in vacuo* afforded dibromodiene **524** (4.76 g, 16.5 mmol, 73%) as a waxy solid; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.49-7.31 (5H, m, ArH), 7.11 (1H, dd, J = 8.4, 1.2 Hz, PhCH), 6.80-6.75 (2H, m, PhCH=C<u>H</u>C<u>H</u>=CBr$_2$).

This data is in agreement with that reported by Michaelides *et al.*[326]

(E)-But-1-en-3-yn-1-ylbenzene (523)



524 **523**

Method One[252]

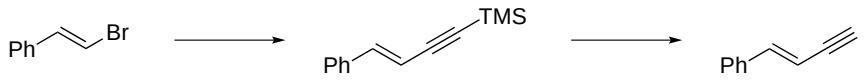
To a stirred solution of dibromodiene **524** (2.18 g, 7.57 mmol, 1.0 eq) in wet DMSO (50 mL) was added Cs_2CO_3 (6.17 g, 18.9 mmol, 2.5 eq), before heating to 115 °C for 12 h. The reaction mixture was diluted with Et_2O (100 mL) and repeatedly washed with water (5 x 100 mL), and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E.) afforded dienyne **523** (150 mg, 1.17 mmol, 15%) as an orange oil; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.29 (5H, m, ArH), 7.05 (1H, d, J = 16.4 Hz, PhCH), 6.14 (1H, dd, J = 16.4, 2.3 Hz, PhCH=C<u>H</u>), 3.06 (1H, dd, J = 2.3, 0.6 Hz, CCH).

This data is in agreement with that reported by Hoshi *et al.*[327]

Method Two[254]

To a stirred solution of dibromodiene **524** (4.76 g, 16.5 mmol, 1.0 eq) in THF (70 mL) at −78 °C was added *n*BuLi (17.2 mL of a 2.5 M solution in hexanes, 43.0 mmol, 2.6 eq) before stirring for 30 min at −78 °C and 1 h at r.t. The reaction mixture was quenched with aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 50 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E.) afforded dienyne **523** (1.08 g, 8.39 mmo, 51 %) as an orange oil; ^{1}**H NMR** data as recorded above for (E)-but-1-en-3-yn-1-ylbenzene.

Method Three

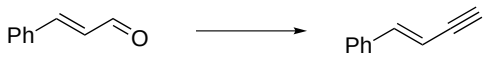


526 **653**

To a stirred, degassed solution of β-bromostyrene (700 μL, 1.00 g, 5.46 mmol, 1.0 eq), trimethylsilyl acetylene (925 μL, 6.55 mmol, 1.2 eq) and CuI (52.5 mg, 0.546 mmol, 0.10 eq) in piperidine (10 mL) was added $Pd(PPh_3)_2Cl_2$ (232 mg, 0.546 mmol, 0.10 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in P.E. and filtered through silica to afford

enyne intermediate **654** as an orange oil. To a solution of the crude material in MeOH (5 mL) was added KOH (612 mg, 10.9 mmol, 2.0 eq) before stirring at r.t. for 2 h. The reaction mixture was diluted with Et_3O (10 mL), and the organic phase washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford dienyne **523** (480 mg, 3.75 mmol, 69%) as an orange oil; ^{1}**H NMR** data as recorded above for (E)-but-1-en-3-yn-1-ylbenzene.

Method Four[257]

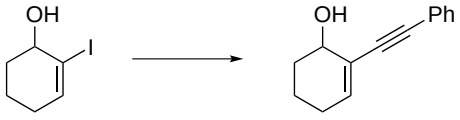


655

To a stirred solution of LDA (4.54 mmol, 1.2 eq) in THF (24 mL) at −78 °C was added trimethylsilyldiazomethane (2.27 mL of a 2M solution in diethyl ether, 4.54 mmol, 1.2 eq) dropwise, before stirring for 30 min. *Trans*-cinnamaldehyde (476 μL, 500 mg, 3.78 mmol, 1.0 eq) in THF (6 mL) was then added dropwise at −78 °C, and the resulting reaction mixture stirred for 1 h before heating to reflux for 3 h. Upon cooling to r.t., the solution was quenched with water (30 mL), extracted with Et_2O (3 x 30 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* to afford dienyne **523** (471 mg, 3.67 mmol, 97%) as an orange oil; ^{1}**H NMR** data as recorded above for (E)-but-1-en-3-yn-1-ylbenzene.

Sonogashira Couplings

2-(Phenylethynyl)cyclohex-2-enol (528)



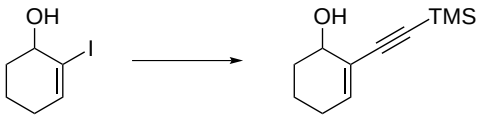
514 **528**

To a stirred, degassed solution of vinyl iodide **514** (10 mg, 0.0446 mmol, 1.0 eq), phenyl acetylene (5.88 μL, 0.0535 mmol, 1.2 eq) and CuI (0.849 mg, 0.00446 mmol, 0.10 eq) in Et_3N (0.5 mL) was added $Pd(PPh_3)_2Cl_2$ (3.13 mg, 0.00446 mmol, 0.10 eq) before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (20

% → 100% Et_2O / P.E.) afforded enyne **528** (5.75 mg, 0.0290 mmol, 65%) as a yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58-7.29 (5H, m, ArH), 6.33 (1H, td, J = 4.1, 0.8 Hz, C=CH), 4.29-4.23 (1H, m, C<u>H</u>OH), 2.28-1.49 (7H, m, *c*Hex, OH).

This data is in agreement with that reported by Praveen *et al.*[328]

2-((Trimethylsilyl)ethynyl)cyclohex-2-enol (520)



514 **520**

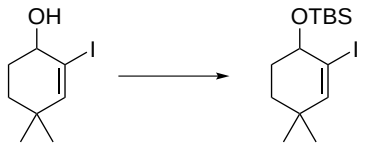
To a stirred, degassed solution of vinyl iodide **514** (10 mg, 0.0446 mmol, 1.0 eq), trimethylsilyl acetylene (5.88 μL, 0.0535 mmol, 1.2 eq), CuI (0.849 mg, 0.00446 mmol, 0.10 eq) and piperidine (13.2 μL, 0.134 mmol, 3.0 eq) in THF (0.5 mL) was added $Pd(PPh_3)_2Cl_2$ (3.13 mg, 0.00446 mmol, 0.10 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (20% → 100% Et_2O / P.E.) afforded enyne **520** (6.15 mg, 0.0317 mmol, 71%) as a yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.28 (1H, td, J = 4.1, 0.9 Hz, C=CH), 4.20-4.13 (1H, m, C<u>H</u>OH), 2.17-1.52 (7H, m, *c*Hex, OH), 0.198 (9H, m, $SiMe_3$).

This data is in agreement with that reported by Huang *et al.*[329]

7.5.2. Protected Alcohol Route

Protected Alcohol Synthesis

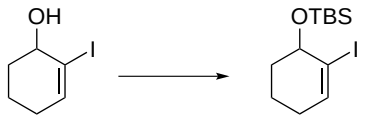
tert-Butyl((2-iodo-4,4-dimethylcyclohex-2-en-1-yl)oxy)dimethylsilane (529)



377 **529**

To a stirred solution of alcohol **377** (363 mg, 1.44 mmol, 1.0 eq) in DCM (4 mL) was added imidazole (196 mg, 2.88 mmol, 2.0 eq) and TBSCl (261 mg, 1.73 mmol, 1.2 eq) before stirring at 40 °C for 12 h. The reaction mixture was quenched with aqueous NH_4Cl solution (4 mL) and extracted with DCM (3 x 4 mL). Concentration *in vacuo* afforded protected alcohol **529** (515 mg, 1.41 mmol, 98%) as a colourless oil; $\mathbf{R_f}$ 0.65 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2929, 2856, 1462, 1360, 1251, 1084, 1062, 1014, 961, 929, 877, 831, 773, 720, 669; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.20 (1H, s, =CH), 4.13 (1H, t, J = 5.2 Hz, SiOCH), 1.99-1.92 (1H, m, SiOCHC$\underline{H}_x$H$_y$), 1.80-1.72 (1H, m, SiOCHCH$_x\underline{H}_y$), 1.66 (1H, ddd, J = 13.1, 9.8, 3.1 Hz, SiOCHCH$_2$C$\underline{H}_x$H$_y$), 1.45 (1H, ddd, J = 12.9, 9.3, 3.2 Hz, SiOCHCH$_2$CH$_x\underline{H}_y$), 1.03 (3H, s, C(CH$_3$)), 0.98 (3H, s, C(CH$_3$)), 0.94 (9H, t, J = 0.71 Hz, SiMe$_2\underline{t\text{Bu}}$), 0.21 (3H, s, Si$\underline{\text{Me}}_2t$-Bu), 0.11 (3H, s, Si$\underline{\text{Me}}_2t$-Bu); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.6, 102.9, 72.6, 37.2, 32.4, 30.6, 28.8, 28.3, 26.0, 18.2, 4.3; **HRMS** (FI) calculated for $C_{14}H_{27}IOSi$ $[M]^+$ 366.0876, found 366.0886.

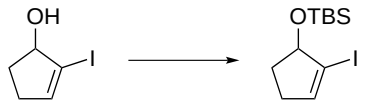
tert-Butyl((2-iodocyclohex-2-en-1-yl)oxy)dimethylsilane (531)



514 **531**

To a stirred solution of alcohol **514** (798 mg, 3.56 mmol, 1.0 eq) in DCM (5 mL) was added imidazole (485 mg, 7.12 mmol, 2.0 eq) and TBSCl (644 mg, 4.27 mmol, 1.2 eq) before stirring at 40 °C for 12 h. The reaction mixture was quenched with aqueous NH_4Cl solution (5 mL) and extracted with DCM (3 x 5 mL). Concentration *in vacuo* afforded protected alcohol **531** (948 mg, 2.80 mmol, 79%) as a yellow oil; $\mathbf{R_f}$ 0.64 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2928, 2856, 1471, 1360, 1251, 1163, 1089, 1061, 1019, 892, 827, 773, 667; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.46 (1H, t, J = 4.1 Hz, =CH), 4.20 (1H, t, J = 4.7 Hz, CHOSi), 2.16-1.58 (6H, m, $(CH_2)_3$), 0.941 (9H, s, SiMe$_2\underline{t\text{Bu}}$) 0.21 (3H, s, Si$\underline{\text{Me}}_2t$Bu), 0.12 (3H, s, Si$\underline{\text{Me}}_2t$Bu); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 140.4, 103.8, 72.8, 33.6, 39.4, 26.0, 17.6, 4.4; **HRMS** (FI) calculated for $C_{12}H_{23}IOSi$ $[M]^+$ 338.0563, found 338.0566.

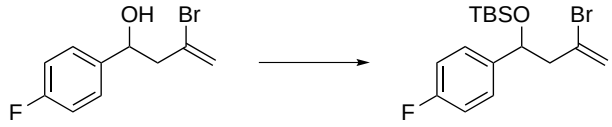
tert-Butyl((2-iodocyclopent-2-en-1-yl)oxy)dimethylsilane 532



515 **532**

To a stirred solution of alcohol **515** (258 mg, 1.23 mmol, 1.0 eq) in DCM (2 mL) was added imidazole (167 mg, 2.46 mmol, 2.0 eq) and TBSCl (222 mg, 1.47 mmol, 1.2 eq) before stirring at 40 °C for 12 h. The reaction reaction was quenched with aqueous NH_4Cl solution (2 mL) and extracted with DCM (3 x 2 mL). Concentration *in vacuo* afforded protected alcohol **532** (325 mg, 1.00 mmol, 82 %) as a yellow oil; $\mathbf{R_f}$ 0.64 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2928, 2855, 1471, 1360, 1250, 1157, 1099, 928, 835, 774, 670; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.23 (1H, td, J = 2.4, 1.2 Hz, =CH), 4.75-4.71 (1H, m, CHOSi), 2.53-2.42 (1H, m, C$\underline{H}_x H_y$), 2.30-2.18 (2H, m, CH_2), 1.85-1.77 (1H, m, $CH_x\underline{H}_y$), 0.94 (9H, s, $SiMe_2\underline{t}Bu$), 0.18 (3H, s, $Si\underline{Me}_2 t$Bu), 0.14 (3H, s, $Si\underline{Me}_2 t$Bu); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 141.5, 101.4, 82.3, 32.8, 32.6, 25.9, 18.3, 4.4; **HRMS** (FI) calculated for $C_{11}H_{21}IOSi$ $[M]^+$ 324.0406, found 324.0418.

((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)(tert-butyl)dimethylsilane (533



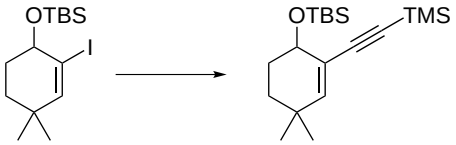
370 **533**

To a stirred solution of alcohol **370** (181 mg, 0.738 mmol, 1.0 eq) in DCM (2 mL) was added TBSCl (133 mg, 0.885 mmol, 1.2 eq) and imidazole (100 mg, 1.48 mmol, 2.0 eq) before stirring at 40 °C for 16 h. The reaction mixture was quenched with aqueous NH_4Cl solution (2 mL) and extracted with DCM (3 x 2 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afforded protected alcohol **533** (226 mg, 0.628 mmol, 85%) as a colourless oil; $\mathbf{R_f}$ 0.63 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2930, 2857, 1632, 1606, 1509, 1472, 1361, 1253, 1223, 1156, 1083, 1006, 935, 889, 860, 831, 776, 668; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.33-7.29 (2H, m, ArH), 7.04-6.98 (2H, m, ArH), 5.52 (1H, *app* d, J = 0.7 Hz, C=C$\underline{H}_x H_y$), 5.43 (1H, t, J = 1.2 Hz, C=$CH_x\underline{H}_y$), 4.96 (1H, dd, J = 8.0, 4.6 Hz, CHOTBS), 2.82-2.76 (1H, m, CH(OTBS)C$\underline{H}_x H_y$), 2.60-2.55 (1H, m, CH(OTBS)$CH_x\underline{H}_y$), 0.88 (9H, s, $SiMe_2\underline{t}Bu$), 0.09 (3H, s, $Si\underline{Me}_2 t$Bu), -0.12 (3H, s, $Si\underline{Me}_2 t$Bu); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 161.8 (d, J^1_{C-F} = 245 Hz), 154.0, 140.0 (d, J^4_{C-F}

= 3.1 Hz), 127.4 (d, J^3_{C-F} = 8.0 Hz), 130.3, 119.6, 115.0 (d, $J^2_{C_F}$ = 20.7 Hz), 72.0, 53.3, 25.8, 18.2, 5.0, 4.7; **HRMS** (FI) calculated for $C_{16}H^{79}_{24}BrFOSi$ $[M]^+$ 360.0745, found 360.0778.

Sonogashira Couplings

tert-Butyl((4,4-dimethyl-2-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)oxy)dimethylsilane (530)[330]

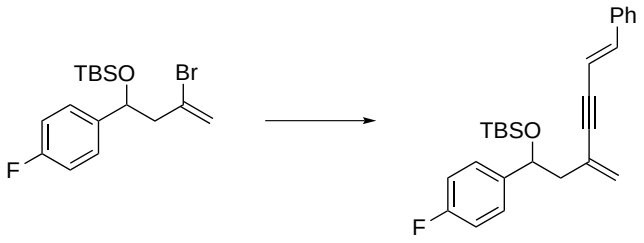


529 **530**

To a stirred, degassed solution of vinyl iodide **529** (200 mg, 0.816 mmol, 1.0 eq), trimethylsilyl acetylene (138 μL, 0.980 mmol, 1.2 eq), CuI (7.76 mg, 0.0408 mmol, 0.05 eq) and piperidine (242 μL, 2.45 mmol, 3.0 eq) in THF (2 mL) was added $Pd(PPh_3)_2Cl_2$ (57.2 mg, 0.0816 mmol, 0.10 eq) before heating to 85 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and purification by flash column chromatography (5% Et_2O / P.E.) afforded enyne **530** (116 mg, 0.345 mmol, 42%) as a yellow oil; $\mathbf{R_f}$ 0.57 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2957, 2146, 1361, 1249, 1080, 1052, 1015, 938, 834, 774, 759, 667, 647; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.96 (1H, s, C=CH), 4.13 (1H, t, J = 5.1 Hz, CHOTBS), 1.82-1.74 (1H, m, CH(OTBS)C$\underline{H}_x$H$_y$), 1.70-1.60 (2H, m, CH(OTBS)CH$_x\underline{H}_y$C$\underline{H}_x$H$_y$), 1.35 (1H, ddd, J = 12.6, 9.0, 3.1 Hz, CH(OTBS)CH$_2$CH$_x$C$\underline{H}_y$), 1.03 (3H, s, CMe_2), 0.966 (3H, s, CMe_2), 0.92-0.92 (9H, m, Si$Me_2\underline{t\text{Bu}}$), 0.18-0.18 (9H, m, $SiMe_3$), 0.15 (3H, s, Si$\underline{Me}_2t$Bu), 0.12 (3H, s, Si$\underline{Me}_2t$Bu); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 148.0, 122.7, 106.1, 92.2, 67.6, 32.8, 32.3, 29.4, 29.1, 28.4, 25.9, 0.031, -4.3, -4.7; **HRMS** (ESI+) calculated for $C_{19}H_{36}NaOSi_2$ $[M+Na]^+$ 359.2197, found 359.2185.

(E)-tert-Butyl((1-(4-fluorophenyl)-3-methylene-7-phenylhept-6-en-4-yn-1-yl)oxy)dimethylsilane

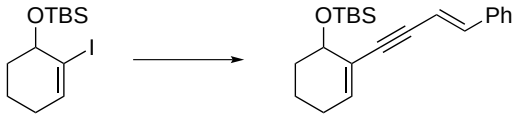
(536)[330]



533 **536**

To a stirred, degassed solution of bromoalkene **533** (10 mg, 0.0278 mmol, 1.0 eq), enyne **523** (3.56 mg, 0.0278 mmol, 1.0 eq), CuI (0.265 mg, 1.39 μmol, 0.05 eq) and piperidine (8.25 μL, 0.0835 mmol, 3.0 eq) in THF (0.5 mL) was added $Pd(PPh_3)_2Cl_2$ (1.95 mg, 2.78 μmol, 0.10 eq), before heating to 50 °C for 16 h. Concentration *in vacuo* and filtration through silica (eluting with Et_2O) afforded dienyne **536** (10.6 mg, 0.0261 mmol, 94%) as a yellow oil; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.46-7.27 (7H, ArH), 7.11 (1H, d, = 16.0 Hz, PhCH), 7.01 (2H, t, J = 8.8 Hz, ArH), 6.28 (1H, d, J = 15.9 Hz, PhCH=C$\underline{H}$), 5.52 (1H, dt, J = 1.6, 0.8 Hz, C$\underline{H}_x$H$_y$), 5.43 (1H, d, J = 1.5 Hz, CH$_x\underline{H}_y$), 4.97-4.91 (1H, m, CHOTBS), 2.78 (1H, ddd, J = 14.0, 8.0, 0.7 Hz, CH(OTBS)C$\underline{H}_x$H$_y$), 2.56 (1H, ddd, J = 14.0, 4.6, 1.0 Hz, CH(OTBS)CH$_x\underline{H}_y$), 0.87 (9H, s, SiMe$_2$$\underline{t\text{Bu}}$), 0.07 (3H, s, SiMe$_2$), -0.13 (3H, s, SiMe$_2$). Further characterisation could not be completed due to an inability to repeat this initial result.

(E)-tert-Butyldimethyl((2-(4-phenylbut-3-en-1-yn-1-yl)cyclohex-2-en-1-yl)oxy)silane (534)

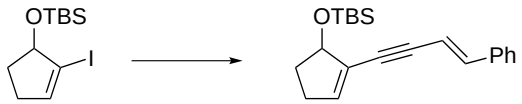


531 **534**

To a stirred, degassed solution of vinyl iodide **531** (10 mg, 0.0296 mmol, 1.0 eq), enyne **523** (3.79 mg, 0.0296 mmol, 1.0 eq), CuI (0.282 mg, 2.96 μmol, 0.10 eq) and piperidine (8.76 μL, 0.0888 mmol, 3.0 eq) in THF (0.50 mL) was added $Pd(PPh_3)_2Cl_2$ (2.08 mg, 2.96 μmol, 0.10 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (10 % Et_2O / P.E.) afforded dienyne **534** (9.9 mg, 0.0292 mmol, 99 %) as an orange

oil; $\mathbf{R_f}$ 0.40 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2928, 2856, 1471, 1360, 1251, 1163, 1089, 1061, 1019, 949, 892, 836, 774, 747, 689; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.43-7.30 (5H, m, ArH), 7.11 (1H, d, J = 16.1 Hz, ArCH), 6.47 (1H, t, J = 4.0 Hz, C≡CC=CH), 6.27 (1H, d, J = 16.0 Hz, ArCH=C$\underline{H}$), 4.22-4.18 (1H, m, CH(OTBS), 2.17-2.08 (1H, m, CH(OTBS)C$\underline{H}_x$H$_y$), 2.06-1.97 (1H, m, CH(OTBS)CH$_x\underline{H}_y$), 1.94-1.87 (1H, m, CH(OTBS)$CH_2CH_2C\underline{H}_x$H$_y$), 1.86-1.75 (2H, m, CH(OTBS)$CH_2CH_2CH_x\underline{H}_y$, CH(OTBS)$CH_2C\underline{H}_xH_y$), 1.67-1.59 (1H, m, CH(OTBS)$CH_2CH_x\underline{H}_y$), 0.95 (9H, s, SiMe$\underline{t}$Bu), 0.22 (3H, s, SiMe), 0.12 (3H, s, SiMe); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 144.4, 140.4, 135.8, 129.2 , 128.8, 126.4, 106.8, 103.8, 82.0, 76.4, 72.8, 33.6, 29.4, 25.9, 17.6, -4.2, -4.4; **HRMS** (FI) calculated for $C_{22}H_{30}OSi$ $[M]^+$ 338.2066, found 338.2078.

(E)-tert-Butyldimethyl((2-(4-phenylbut-3-en-1-yn-1-yl)cyclopent-2-en-1-yl)oxy)silane (535)

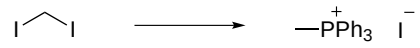


532 **535**

To a stirred, degassed solution of vinyl iodide **532** (10 mg, 0.0308 mmol, 1.0 eq), enyne **523** (2.95 mg, 0.0308 mmol, 1.0 eq), CuI (0.293 mg, 3.08 μmol, 0.10 eq) and piperidine (9.14 μL, 0.0925 mmol, 3.0 eq) in THF (0.50 mL) was added $Pd(PPh_3)_2Cl_2$ (2.16 mg, 3.08 μmol, 0.10 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purification by flash column chromatography (10% Et_2O / P.E.) afforded dienyne **534** (9.90 mg, 0.0305 mmol, 99%) as an orange oil; $\mathbf{R_f}$ 0.39 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2928, 2855, 1471, 1361, 1251, 1157, 1097, 949, 836, 776, 747, 689; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.42-7.31 (5H, m, ArH), 7.11 (1H, d, J = 16.1 Hz, ArCH), 6.27 (1H, d, J = 15.9 Hz, ArCH=C$\underline{H}$), 6.24 (1H, td, J = 2.4, 1.2 Hz, C≡CC=CH), 4.75-4.71 (1H, m, CH(OTBS), 2.51-2.44 (1H, m, CH(OTBS)C$\underline{H}_x$H$_y$), 2.29-2.20 (2H, m, CH(OTBS)CH$_x\underline{H}_y$C$\underline{H}_x$H$_y$), 1.84-1.72 (1H, m, CH(OTBS)$CH_2CH_x\underline{H}_y$), 0.94 (9H, s, SiMe$\underline{t}$Bu), 0.18 (3H, s, SiMe), 0.141 (3H, s, SiMe); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 144.4, 141.6, 135.8, 129.2, 128.8, 126.4, 106.8, 101.3, 82.3, 82.0, 76.4, 32.7, 32.6, 25.9, -4.4, -4.5; **HRMS** (FI) calculated for $C_{21}H_{28}OSi$ $[M]^+$ 324.1909, found 324.0454.

Alternative Routes

Methyltriphenylphosphonium iodide (656)[331]

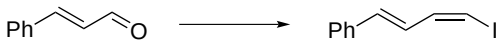


656

To a stirred solution of triphenylphosphine (5.00 g, 19.2 mmol, 1.0 eq) in toluene (5 mL) was added methylene iodide (2.00 mL, 25.0 mmol, 1.2 eq) before heating to 50 °C for 16 h. The crystals formed were isolated by filtration, washed with toluene and dried *in vacuo* for 4 h to afford iodide salt **656** (6.96 g, 17.2 mmol, 90%) as an off-white powder; ^{1}**H NMR** (400 MHz, d_6-DMSO) δ_H 7.99-7.76 (15H, m, ArH), 5.10 (3H, d, J = 8.7 Hz, CH_3).

This data is in agreement with that reported by Singh *et al.*[332]

((1E,3Z)-4-Iodobuta-1,3-dien-1-yl)benzene (657)[333]

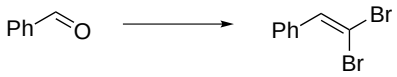


657

To a stirred suspension of iodide salt **658** (1.36 g, 1.80 mmol, 1.0 eq) in THF (5 mL) at r.t. was added NaHMDS (1.25 mL of a 2.0 M solution in THF, 1.80 mmol, 1.0 eq) dropwise, before stirring for 5 min then cooling to −78 °C. A solution of *trans*-cinnamaldehyde (238 μL, 1.89 mmol, 1.05 eq) in THF (5 mL) was then added at a rate so as to maintain the internal temperature below −70 °C. The reaction mixture was then stirred for 15 min at −78 °C before warming to r.t. and stirring for 2 h. Aqueous NH_4Cl solution (10 mL) was added, and the mixture extracted with Et_2O (10 mL) and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (100% P.E.) afforded diene **657** (463 mg, 1.81 mmol, 96%, 2.8 : 1 *E, Z* : *E, E* mixture of isomers in crude material, purification afforded an 6 : 1 ratio) as a yellow oil; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.52-7.29 (5H, m, ArH), 6.92-6.84 (3H, m, =CH), 6.37-6.34 (1H, m, =CH).

This data is in agreement with that reported by Bishop *et al.*[334]

(2,2-Dibromovinyl)benzene (659)

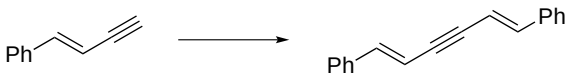


659

To a stirred solution of benzaldehyde (240 μL, 250 mg, 2.36 mmol, 1.0 eq) and CBr_4 (783 mg, 2.36 mmol, 1.0 eq) in DCM (2 mL) at 0 °C was added a solution of triphenylphosphine (1.24 g, 4.71 mmol, 2.0 eq) in DCM (3 mL) dropwise. The reaction mixture was stirred at 0 °C for 30 min, before warming to r.t. and stirring for 1 h. Upon addition of P.E. (5 mL), the resulting suspension was filtered through a short plug of silica and washed with P.E., before concentration *in vacuo* afforded dibromostyrene **659** (279 mg, 1.07 mmol, 45%) as a yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58-7.48 (3H, m, ArH), 7.50 (1H, s, ArCH), 7.44-7.29 (2H, m, ArH).

This data is in agreement with that reported by Rao *et al.*[335]

(1E,5E)-1,6-Diphenylhexa-1,5-dien-3-yne (660)

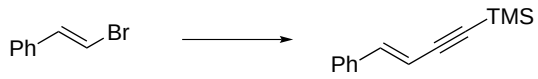


523 **660**

To a stirred, degassed solution of β-bromostyrene (100 μL, 0.780 mmol, 1.0 eq), enyne **523** (100 mg, 0.780 mmol, 1.0 eq) and CuI (7.5 mg, 0.0780 mmol, 0.10 eq) in Et_2NH (5 mL) was added $Pd(PPh_3)_2Cl_2$ (54.5 mg, 0.0780 mmol, 0.10 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purfication by filtration through a short silica plug (P.E. eluant) afforded **660** (112 mg, 0.486 mmol, 62%) as an orange oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.29 (10H, m, ArH), 7.12 (2H, d, J = 14.0 Hz, =CH), 6.78 (2H, d, J = 14.0 Hz, =CH).

This data is in agreement with that reported by Hoshi *et al.*[336]

(E)-Trimethyl(4-phenylbut-3-en-1-yn-1-yl)silane (661)

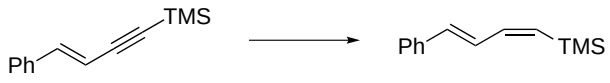


661

To a stirred, degassed solution of β-bromostyrene (237μL, 1.85 mmol, 1.0 eq), trimethylsilyl acetylene (290 μL, 200 mg, 2.04 mmol, 1.2 eq) and CuI (35.2 mg, 0.185 mmol, 0.10 eq) in Et_2NH (5 mL) was added $Pd(PPh_3)_2Cl_2$ (130 mg, 0.185 mmol, 0.10 eq) before stirring at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* and purification by filtration through a short silica plug (P.E. eluant) afforded enyne **662** (350 mg, 1.75 mmol, 94%) as an orange oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43-7.30 (5H, m, ArH), 7.02 (1H, d, J = 16.3 Hz, ArCH), 6.19 (1H, d, J = 16.3 Hz, ArCH=C<u>H</u>), 0.24 (9H, s, $SiMe_3$).

This data is in agreement with that reported by Hoshi *et al.*[327]

Trimethyl((1Z,3E)-4-phenylbuta-1,3-dien-1-yl)silane (663)[337]



663 TMP2

To a stirred solution of enyne **661** (350 mg, 1.75 mmol, 1.0 eq) in Et_2O (1.8 mL) at r.t. was added DIBAL (1.92 mL of a 1.0 M solution in cyclohexane, 1.92 mmol, 1.1 eq) before heating to 40 °C for 16 h. Upon cooling to r.t., the reaction mixture was poured into ice-cold 3N NaOH solution (10 mL), stirred for 30 min following the addition of aqueous NaKTartrate solution (5 mL) and extracted with hexane (10 mL). The organic phase was washed with 3N NaOH solution (10 mL) and aqueous NaCl solution (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford diene **663** (287 mg, 1.42 mmol, 81%) as a pale yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.22 (5H, m, ArH), 7.06-6.93 (2H, m, C<u>H</u>=C<u>H</u>TMS), 6.61-6.56 (1H, m, ArCH), 5.78-5.73 (1H, m, ArCH=C<u>H</u>),

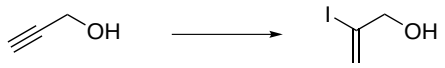
0.24 (9H, s, $SiMe_3$).

This data is in agreement with that reported by Mooiweer *et al.*[337]

7.5.3. Modified Route

Alcohol Synthesis

2-Iodoprop-2-en-1-ol (374)[258]

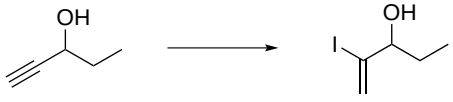


374

To a stirred solution of NaI (2.58 g, 17.2 mmol, 2.0 eq) and water (0.186 mL, 10.3 mmol, 1.2 eq) in MeCN (20 mL) was added TMSCl (2.18 mL, 17.2 mmol, 2.0 eq), and the resulting mixture stirred for 10 min. Propargyl alcohol (0.5 mL, 8.67 mmol, 1.0 eq) was then added before stirring for 90 min, upon which point the brown solution was diluted with water (50 mL) and aqueous $Na_2S_2O_3$ solution (50 mL). The quenched mixture was extracted with Et_2O (3 x 100 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O / P.E.) to afforded vinyl iodide **374** (292 mg, 1.59 mmol, 18%) as an orange oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.42 (1H, q, J = 1.7 Hz, =C$\underline{H}_x$H$_y$), 5.89-5.88 (1H, m, =CH$_x\underline{H}_y$), 4.20 (2H, dt, J = 6.8, 1.4 Hz, C$\underline{H}_2$OH), 2.03-1.98 (1H, m, OH).

This data is in agreement with that reported by Lai *et al.*[306]

2-Iodopent-1-en-3-ol (537)[258]



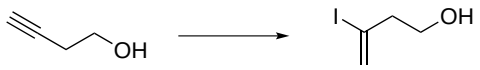
537

To a stirred solution of NaI (3.56 g, 23.8 mmol, 2.0 eq) and water (257 μL, 14.3 mmol, 1.2 eq) in MeCN (40 mL) at r.t. was added TMSCl (3.02 mL, 23.8 mmol, 2.0 eq), and the resulting mixture

stirred for 10 min. 1-Pentyn-3-ol (1.03 mL, 11.9 mmol, 1.0 eq) was then added before stirring for 90 min, upon which point the dark brown solution was diluted with water (100 mL) and aqueous $Na_2S_2O_3$ solution (100 mL). The quenched mixture was extracted with Et_2O (3 x 200 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (5% → 100% Et_2O / P.E.) afforded vinyl iodide **537** (712 mg, 3.36 mmol, 28%) as a yellow oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.37 (1H, dd, J = 1.7, 1.0 Hz, =C$\underline{H}_x$H$_y$), 5.90 (1H, d, J = 1.6 Hz, =CH$_x\underline{H}_y$), 3.57-3.47 (1H, m, C$\underline{H}$OH), 1.81 (1H, d, J = 5.7 Hz, OH), 1.68-1.54 (2H, m, CH(OH)C$\underline{H}_2$CH$_3$), 0.90 (3H, t, J = 7.0 Hz, CH(OH)CH$_2$C$\underline{H}_3$).

This data is in agreement with that reported by Taylor *et al.*[338]

3-Iodobut-3-en-1-ol (538)[258]



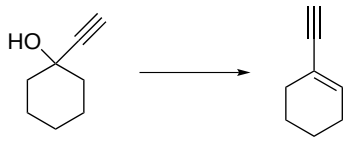
538

To a stirred solution of NaI (4.27 g, 28.5 mmol, 2.0 eq) and water (308 μL, 17.1 mmol, 1.2 eq) in MeCN (40 mL) at r.t. was added TMSCl (3.62 mL, 28.5 mmol, 2.0 eq), and the resulting mixture stirred for 10 min. 3-Butyn-1-ol (1.08 mL, 14.3 mmol, 1.0 eq) was then added before stirring for 90 min, upon which point the dark brown solution was diluted with water (100 mL) and aqueous $Na_2S_2O_3$ solution (100 mL). The quenched mixture was extracted with Et_2O (3 x 200 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (25% → 100% Et_2O / P.E.) afforded vinyl iodide **538** (778 mg, 3.93 mmol, 28%) as a yellow oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.19 (1H, q, J = 1.4 Hz, =C$\underline{H}_x$H$_y$), 5.86 (1H, dd, J = 1.5, 0.4 Hz, =CH$_x\underline{H}_y$), 3.77 (2H, q, J = 5.9 Hz, C$\underline{H}_2$OH), 2.68-2.61 (2H, m, C$\underline{H}_2$H$_2$OH).

This data is in agreement with that reported by Das *et al.*[339]

Coupling Partner Synthesis

1-Ethynylcyclohex-1-ene (542)



542

Method One

To a stirred solution of 1-ethynylcyclohexanol (1.03 mL, 8.06 mmol, 1.0 eq) in pyridine (6 mL) at r.t. was added $POCl_3$ (1.13 mL, 12.12 mmol, 1.5 eq) at a rate so as to maintain a gentle reflux. The resulting solution was heated to 90 °C for 45 min, and the reaction was quenched with water (6 mL) and extracted with Et_2O (3 x 6 mL). The combined organic phases were washed with 6N HCl (20 mL) and aqueous $NaHCO_3$ solution (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to afford enyne **542** (464 mg, 4.37 mmol, 54%) as a yellow oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.21 (1H, app tt, J = 3.8, 1.8 Hz, =CH), 2.80 (1H, d, J = 0.5 Hz, CCH), 2.20-2.05 (4H, m, *c*Hex), 1.70-1.56 (4H, m, *c*Hex).

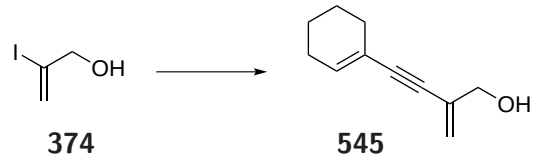
Method Two[259]

To a stirred solution of 1-ethynylcyclohexanol (1.03 mL, 8.06 mmol, 1.0 eq) in pyridine (6 mL) at 0 °C was added $POCl_3$ (1.13 mL, 12.12 mmol, 1.5 eq) over 30 min *via* syringe pump. The resulting solution was warmed to r.t. and stirred for 16 h, before heating to 70 °C for 45 min. The reaction was quenched with water (6 mL) and extracted with Et_2O (3 x 6 mL), and the combined organic phases washed with 6N HCl (20 mL) and aqueous $NaHCO_3$ solution (20 mL). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to afford enyne **542** (656 mg, 6.18 mmol, 77%) as a yellow oil; ^{1}**H NMR** data in agreement with that reported above for 1-ethynylcyclohex-1-ene **542**.

This data is in agreement with that reported by Stille *et al.*[340]

Sonogashira Couplings

4-(Cyclohex-1-en-1-yl)-2-methylenebut-3-yn-1-ol (545)[258]

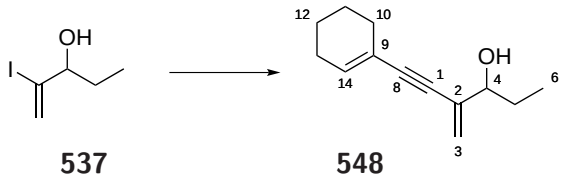


374 **545**

To a stirred, degassed solution of vinyl iodide **374** (146 mg, 0.794mmol, 1.0 eq) and enyne **542** (87.5 mg, 0.834 mmol, 1.05 eq) in Et_3N (2 mL) was added $Pd(PPh_3)_2Cl_2$ (27.8 mg, 0.079 mmol, 0.1 eq). After stirring for 10 min at r.t., CuI (7.54 mg, 0.079 mmol, 0.1 eq) was added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatograpy (5% → 30% Et_2O / P.E.) afforded dienyne **545** (63 mg, 0.388 mmol, 49%) as an orange oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.16 (1H, dt, J = 4.0, 2.0 Hz, C=CH), 5.49 (1H, q, J = 1.6 Hz, =C$\underline{H}_x$H$_y$), 5.44 (1H, q, J = 1.3 Hz, =CH$_x\underline{H}_y$), 4.16 (2H, dt, J = 6.5, 1.4 Hz, C$\underline{H}_2$OH), 2.19-2.08 (4H, m, *c*Hex), 1.72-1.54 (4H, m, *c*Hex).

This data is in agreement with that reported by Hashmi *et al.*[258]

6-(Cyclohex-1-en-1-yl)-4-methylenehex-5-yn-3-ol (548)[258]

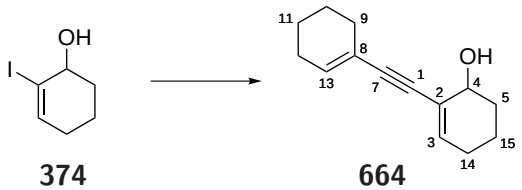


537 **548**

To a stirred, degassed solution of vinyl iodide **537** (100 mg, 0.472 mmol, 1.0 eq) and enyne **542** (60.1 mg, 0.566 mmol, 1.2 eq) in Et_3N (2 mL) was added $Pd(PPh_3)_2Cl_2$ (33.1 mg, 0.047 mmol, 0.1 eq). After stirring for 10 min at r.t., CuI (8.99 mg, 0.047 mmol, 0.1 eq) was added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatography (5% → 50% Et_2O / P.E.) afforded dienyne **548** (39.8 mg, 0.209 mmol, 44%) as a yellow oil; $\mathbf{R_f}$ 0.40 (50% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3415, 2932, 2860, 1607, 1436, 1347, 1108, 1048, 982, 904, 842, 800; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.16 (1H, tt, J

= 4.0, 1.9 Hz, H_{14}), 5.43 (1H, app q, J = 1.4 Hz, $\underline{H}_{3x}H_{3y}$), 5.42 (1H, app d, J = 1.4 Hz, $H_{3x}\underline{H}_{3y}$), 4.04-4.01 (1H, m, H_4), 2.18-2.10 (4H, m, H_{10}, H_{11}, H_{12}, H_{13}), 1.79-1.57 (6H, m, H_{10}, H_{11}, H_{12}, H_{13}, H_5), 0.94 (3H, t, J = 7.4 Hz, H_6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.6 (C_{14}), 134.7 (C_2), 120.4 (C_9), 120.0 (C_3), 93.5 (C_1), 83.9 (C_8), 76.1 (C_4), 29.2 (C_{13}), 29.0 (C_5), 25.7 (C_{10}), 22.3 (C_{12}), 21.4 (C_{11}), 9.7 (C_6); **HRMS** (ESI^+) calculated for $C_{13}H_{18}ONa$ $[M+Na]^+$ 213.1250, found 213.1249.

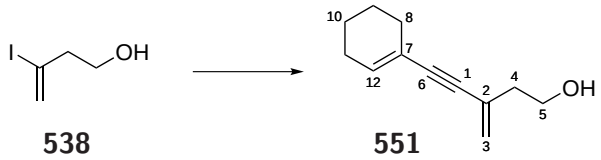
2-(Cyclohex-1-en-1-ylethynyl)cyclohex-2-enol (664)[258]



374 **664**

To a stirred, degassed solution of vinyl iodide **374** (95.7 mg, 0.427 mmol, 1.0 eq) and enyne **542** (54.4 mg, 0.513 mmol, 1.2 eq) in Et_3N (2 mL) was added $Pd(PPh_3)_2Cl_2$ (30.0 mg, 0.0427 mmol, 0.10 eq). After stirring for 10 min at r.t., CuI (8.1 mg, 0.0427 mmol, 0.10 eq) was added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatography (20% Et_2O / P.E.) afforded dienyne **664** (32.4 mg, 0.160 mmol, 38%) as an orange oil; $\mathbf{R_f}$ 0.37 (50% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3405, 2932, 2860, 1723, 1436, 1348, 1239, 1053, 985, 916, 841, 812; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.17 (1H, t, J = 3.9 Hz, H_{13}), 6.13 (1H, tq, J = 3.9, 1.9 Hz, C_3), 4.20-4.15 (1H, m, C_4), 2.19-2.07 (5H, m, H_5, H_{12}, H_{14}), 1.94-1.86 (1H, m, H_5), 1.79-1.54 (8H, m, H_9, H_{10}, H_{11}, H_{15}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.3 (C_{13}), 135.0 (C_2), 124.4 (C_8), 120.5 (C_3), 91.4 (C_1), 85.3 (C_7), 67.0 (C_4), 30.5 (C_5), 29.3 (C_{12}), 25.9 (C_{14}), 25.7 (C_9), 22.3 (C_{11}), 21.5 (C_{10}), 18.2 (C_{15}); **HRMS** (ESI^+) calculated for $C_{14}H_{18}ONa$ $[M+Na]^+$ 225.1250, found 225.1256.

5-(Cyclohex-1-en-1-yl)-3-methylenepent-4-yn-1-ol (551)[258]



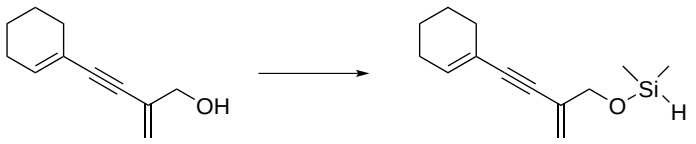
538 **551**

To a stirred, degassed solution of vinyl iodide **538** (100 mg, 0.505 mmol, 1.0 eq) and enyne **542** (64.3 mg, 0.606 mmol, 1.2 eq) in Et_3N (2 mL) was added $Pd(PPh_3)_2Cl_2$ (35.4 mg, 0.0505 mmol, 0.10 eq).

After stirring for 10 min at r.t., CuI (9.6 mg, 0.0505 mmol, 0.10 eq) was added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatography (20% → 100% Et_2O / P.E.) afforded dienyne **551** (64.4 mg, 0.365 mmol, 72%) as an orange oil; $\mathbf{R_f}$ 0.25 (50% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3359, 2932, 2189, 1723, 1606, 1436, 1348, 1049, 918, 842, 800; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.14 (1H, tt J = 3.9, 1.9 Hz, H_{12}), 5.41 (1H, d J = 1.9 Hz, $\underline{H}_{3x}H_{3y}$), 5.31 (1H, dt, J = 2.0, 1.1 Hz, $H_{3x}\underline{H}_{3y}$), 3.83-3.79 (2H, m, H_5), 2.46-2.42 (2H, m, H_4), 2.17-2.09 (4H, m, H_8, H_9, H_{10}, H_{11}), 1.68-1.58 (4H, m, H_8, H_9, H_{10}, H_{11}); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 135.5 (C_{12}), 128.2 (C_2), 122.7 (C_7), 120.4 (C_3), 92.0 (C_1), 86.2 (C_6), 61.0 (C_5), 40.7 (C_4), 29.2 (C_{11}), 25.7 (C_8), 22.3 (C_{10}), 21.4 (C_9); **HRMS** (ESI^+) calculated for $C_{12}H_{16}ONa$ $[M+Na]^+$ 199.1093, found 199.1088.

Silylation

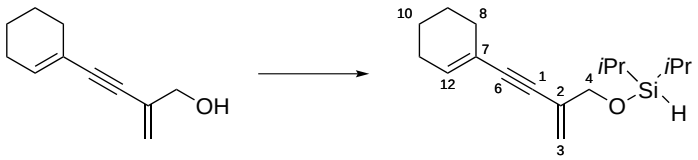
((4-(Cyclohex-1-en-1-yl)-2-methylenebut-3-yn-1-yl)oxy)dimethylsilane (546)[341]



545 **546**

To neat alcohol **545** (24.7 mg, 0.152 mmol, 1.0 eq) at 0 °C was added tetramethyldisilazane (29.7 μL, 0.167 mmol, 1.1 eq), before stirring for 5 min. The reaction mixture was then warmed to r.t., stirred for 1 h and placed under high vacuum for 1 h to afforded silane **546** as a yellow oil which was used directly in the subsequent hydrosilylation reaction; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 6.14 (1H, dt J = 4.0, 2.0 Hz, C=CH), 5.51 (1H, q, J = 1.9 Hz, C=C$\underline{H}_xH_y$), 5.42 (1H, q, J = 1.8 Hz, C=C$H_x\underline{H}_y$), 4.68 (1H, sep, J = 2.8 Hz, SiH), 4.18 (2H, t, J = 1.7 Hz, CH_2OSi), 2.21-2.06 (4H, m, *c*Hex), 1.72-1.56 (4H, m, *c*Hex), 0.264 (3H, s, SiMe), 0.250 (4H, m, *c*Hex). Further characterisation was not completed due to the unstable nature of this compound.

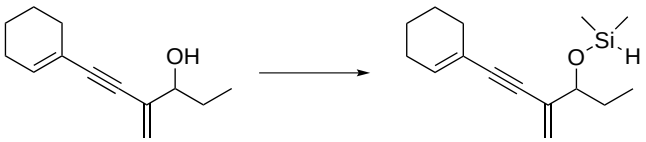
((4-(Cyclohex-1-en-1-yl)-2-methylenebut-3-yn-1-yl)oxy)diisopropylsilane (547)[260]



545 **547**

To a stirred solution of alcohol **545** (29.3 mg, 0.181 mmol, 1.0 eq) and Et_3N (37.7 μL, 0.272 mmol, 1.5 eq) in DCM (0.5 mL) at 0 °C was added chlorodiisopropylsilane (32.4 μL, 0.190 mmol, 1.05 eq). The reaction mixture was warmed to r.t. and stirred for 15 min, before recooling to 0 °C and quenching with MeOH (0.5 mL). After concentration *in vacuo*, the crude residue was dissolved in pentane and filtered through Celite to afford silane **547** (47.1 mg, 0.170 mmol, 94%) as a pale yellow oil; $\mathbf{R_f}$ 0.71 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3397, 2940, 2865, 2098, 1672, 1462, 1059, 1001, 881, 825, 733, 668; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.13 (1H, tt, J = 4.0, 1.9 Hz, H_{12}), 5.56 (1H, app q, J = 2.0 Hz, $\underline{H}_{3x}H_{3y}$), 5.42 (1H, app q, J = 1.8 Hz, $H_{3x}\underline{H}_{3y}$), 4.27-4.20 (3H, m, $C\underline{H}_2$OSi, SiH), 2.16-2.09 (4H, m, H_8, H_9, H_{10}, H_{11}), 1.67-1.56 (4H, m, H_8, H_9, H_{10}, H_{11}), 1.09-1.01 (14H, m, Si(i-Pr)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.3 (C_{12}), 130.6 (C_2), 120.5 (C_7), 118.6 (C_3), 92.2 (C_1), 84.7 (C_6), 67.4 (C_4), 29.1 (C_{11}), 25.7 (C_8), 22.3 (C_{10}), 21.5 (C_9), 17.4 (Si(i-Pr)$_2$), 17.3 (Si(i-Pr)$_2$), 12.4 (Si(i-Pr)$_2$); **HRMS** (FI) calculated for $C_{17}H_{28}OSi$ $[M]^+$ 276.1909, not found.

((6-(Cyclohex-1-en-1-yl)-4-methylenehex-5-yn-3-yl)oxy)dimethylsilane (549)[65]

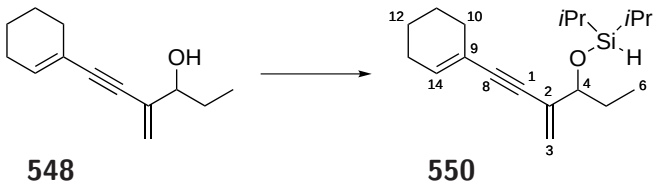


548 **549**

To neat alcohol **549** (50.6 mg, 0.266 mmol, 1.0 eq) was added tetramethyldisilazane (51.9 μL, 0.293 mmol, 1.1 eq), before heating to 50 °C for 2 h. The crude reaction mixture was then placed under high vacuum for 1 h, affording silane **549** as a yellow oil which was used directly in the subsequent hydrosilylation reaction; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.19-6.09 (1H, m, C=CH), 5.46 (1H, dd, J = 2.0, 1.4 Hz, C=C$\underline{H}_xH_y$), 5.40 (1H, dd, J = 2.0, 1.0 Hz, C=C$H_x\underline{H}_y$), 4.68-4.62 (1H, m, SiH), 4.09-4.02 (1H, m, CHOSi), 2.20-2.05 (4H, m, cHex), 1.69-1.54 (6H, m, cHex, CH(OSi)C$\underline{H}_2$CH$_3$), 0.904 (3H, t, J = 7.4 Hz, CH(OSi)CH$_2$C$\underline{H}_3$), 0.237 (3H, d, J = 1.5 Hz, SiMe), 0.223 (3H, d, J

= 1.5 Hz, SiMe). Further characterisation was not completed due to the unstable nature of this compound.

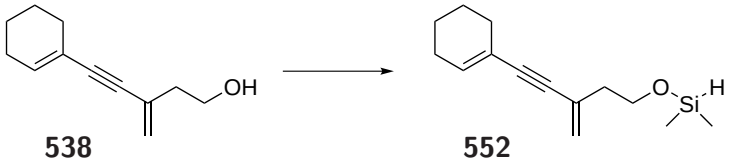
((6-(Cyclohex-1-en-1-yl)-4-methylenehex-5-yn-3-yl)oxy)diisopropylsilane (550)[260]



548 **550**

To a stirred solution of alcohol **548** (39.1 mg, 0.205 mmol, 1.0 eq) and Et_3N (43.0 μL, 0.308 mmol, 1.5 eq) in DCM (0.5 mL) at 0 °C was added chlorodi*iso*-propylsilane (36.9 μL, 0.216 mmol, 1.05 eq). After stirring for 2 h at r.t., the reaction mixture was recooled to 0 °C before quenching with MeOH (0.5 mL) and concentration *in vacuo*. Purification by flash column chromatography (10% Et_2O / P.E.) afforded silane **550** (34.9 mg, 0.115 mmol, 56%, 69% brsm) as a pale yellow oil; $\mathbf{R_f}$ 0.73 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2938, 2865, 2094, 1607, 1462, 1382, 1157, 1113, 1062, 1017, 903, 881, 842, 799, 733, 666; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 6.12 (1H, tt, J = 4.0, 1.9 Hz, H_{14}), 5.47 (1H, dd, J = 2.1, 1.3 Hz, $\underline{H}_{3x}H_{3y}$), 5.41 (1H, app d, J = 2.1, 0.7 Hz, $H_{3x}\underline{H}_{3y}$), 4.19 (1H, t, J = 1.5 Hz, SiH), 4.13 (1H, t, J = 5.6 Hz, H_2), 2.17-2.09 (4H, m,H_{10}, H_{11}, H_{12}, H_{13}), 1.77-1.56 (6H, m, H_{10}, H_{11}, H_{12}, H_{13}, H_5), 1.08-1.00 (14H, m, Si(i-Pr)$_2$), 0.89 (3H, t, J = 7.4 Hz, H_6); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 134.9 (C_{14}), 134.2 (C_2), 120.7 (C_9), 119.7 (C_3), 92.5 (C_8), 85.2 (C_1), 78.0 (C_4), 29.2 (C_{13}), 25.7 (C_{10}), 22.3 (C_{12}), 21.5 (C_{11}), 17.6 (Si(i-Pr)$_2$), 17.5 (Si(i-Pr)$_2$), 17.4 (Si(i-Pr)$_2$), 17.3 (Si(i-Pr)$_2$), 12.7 (Si(i-Pr)$_2$), 12.5 (Si(i-Pr)$_2$), 9.0 (C_6); **HRMS** (ESI$^+$) calculated for $C_{19}H_{32}NaOSi$ $[M+Na]^+$ 327.2115, found 327.2197.

((5-(Cyclohex-1-en-1-yl)-3-methylenepent-4-yn-1-yl)oxy)dimethylsilane (552)[341]

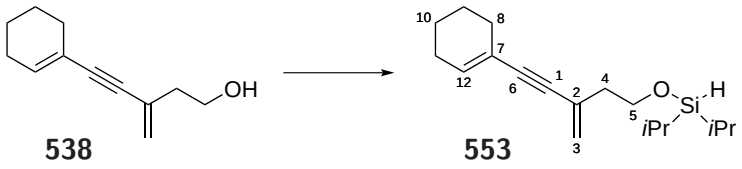


538 **552**

To neat alcohol **538** (10 mg, 0.0567 mmol, 1.0 eq) at 0 °C was added tetramethyldisilazane (11.1 μL, 0.0624 mmol, 1.1 eq), before stirring for 5 min. The reaction mixture was warmed to r.t.,

stirred for 1 h and placed under high vacuum for 1 h to afford silane **552** as a yellow oil which was used directly in the subsequent hydrosilylation step; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.17-6.09 (1H, m, C=CH), 5.36-5.34 (1H, m, C=C$\underline{H}_x$H$_y$), 5.28-5.25 (1H, m, C=CH$_x\underline{H}_y$), 4.68-4.60 (1H, m, SiH), 3.82 (2H, t, J = 6.9 Hz, CH_2OSi), 2.45-2.38 (2H, m, C$\underline{H}_2$CH$_2$OSi), 2.24-2.03 (4H, m, *c*Hex), 1.73-1.50 (4H, m, *c*Hex), 0.231 (3H, s, SiMe), 0.217 (3H, s, SiMe). Further characterisation was not completed due to the unstable nature of this compound.

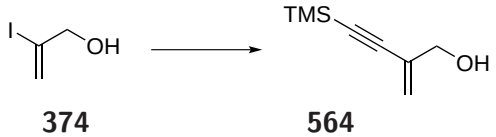
((5-(Cyclohex-1-en-1-yl)-3-methylenepent-4-yn-1-yl)oxy)diisopropylsilane (553)[260]



To a stirred solution of alcohol **538** (50.0 mg, 0.284 mmol, 1.0 eq) and Et_3N (59.4 μL, 0.426 mmol, 1.5 eq) in DCM (1 mL) at 0 °C was added chlorodiisopropylsilane (50.9 μL, 0.298 mmol, 1.05 eq). After stirring for 2 h at r.t., the reaction mixture was recooled to 0 °C before quenching with MeOH (0.5 mL) and concentration *in vacuo* afforded **553** (78.9 mg, 0.272 mmol, 96%) as a pale yellow oil; $\mathbf{R_f}$ 0.65 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2939, 2864, 2090, 1607, 1462, 1384, 1098, 1001, 919, 882, 838, 800, 667; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.12 (1H, dtt, J = 6.1, 4.1, 2.0 Hz, H_{12}), 5.34 (1H, d, J = 2.0 Hz, $\underline{H}_{3x}H_{3y}$), 5.26 (1H, t, J = 1.6 Hz, $H_{3x}\underline{H}_{3y}$), 4.16 (1H, t, J = 1.6 Hz, SiH), 3.88 (1H, t, J = 6.9 Hz, H_5), 2.42 (2H, t, J = 6.9 Hz, C_4), 2.16-2.09 (4H, m, H_8, H_9, H_{10}, H_{11}), 1.67-1.57 (4H, m, H_8, H_9, H_{10}, H_{11}), 1.06-1.01 (14H, m, Si(*i*-Pr)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.0 (C_{12}), 128.3 (C_2), 122.0 (C_7), 120.6 (C_3), 91.3 (C_1), 86.8 (C_6), 64.0 (C_5), 40.6 (C_4), 29.2 (C_{11}), 25.7 (C_8), 22.3 (C_{10}), 21.5 (C_9), 17.4 (Si(*i*-Pr)$_2$), 17.3 (Si(*i*-Pr)$_2$), 12.4 (Si(*i*-Pr)$_2$); **HRMS** (ESI$^+$) calculated for $C_{18}H_{30}NaOSi$ [M+Na]$^+$ 313.1958, found 313.1965.

7.5.4. Test Substrates

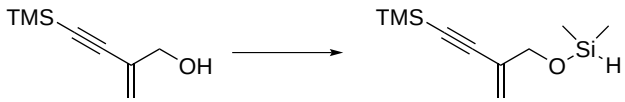
2-Methylene-4-(trimethylsilyl)but-3-yn-1-ol (564)[258]



To a degassed, stirred solution of vinyl iodide **374** (100 mg, 0.544 mmol, 1.0 eq) and trimethylsilyl acetylene (85.1 μL, 0.598 mmol, 1.1 eq) in Et_3N (2 mL) was added $Pd(PPh_3)_2Cl_2$ (38.2 mg, 0.0544 mmol, 0.10 eq), before stirring for 10 min. CuI (10.4 mg, 0.0544 mmol, 0.10 eq) was then added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatography (50 % Et_2O / P.E.) afforded enyne **564** (33.5 mg, 0.217 mmol, 40 %) as an orange oil; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 5.55 (2H, *app* dq, J = 4.2, 1.5 Hz, $=CH_2$), 4.15 (2H, dt, J = 6.5, 1.4 Hz, $C\underline{H}_2OH$), 0.209 (9H, s, $SiMe_3$).

This data is in agreement with that reported by Hashmi *et al.*[258]

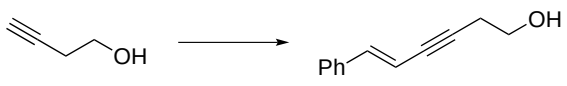
(3-(((Dimethylsilyl)oxy)methyl)but-3-en-1-yn-1-yl)trimethylsilane (560)[341]



564 **560**

To neat alcohol **564** (20 mg, 0.130 mmol, 1.0 eq) at 0 °C was added tetramethyldisilazane (25.3 μL, 0.143 mmol, 1.1 eq), before stirring for 5 min. The reaction mixture was warmed to r.t., stirred for 1 h then placed under high vacuum for 1 h to afford silane **560** as a yellow oil which was used directly in the subsequent hydrosilylation step; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 5.57 (1H, q, J = 1.9 Hz, C=C$\underline{H}_xH_y$), 5.52 (1H, q, J = 1.7 Hz, C=C$H_x\underline{H}_y$), 4.71-4.64 (1H, m, SiH), 4.17 (2H, t, J = 1.7 Hz, CH_2OSi), 0.26 (3H, s, OSiMe), 0.25 (3H, s, OSiMe), 0.20 (9H, s, $SiMe_3$). Further characterisation was not completed due to the unstable nature of this compound.

(E)-6-Phenylhex-5-en-3-yn-1-ol 565



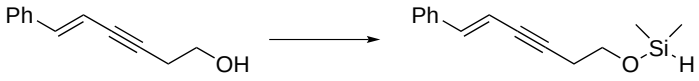
565

To a stirred, degassed solution of 3-butyn-1-ol (100 mg, 1.43 mmol, 1.0 eq) and β-bromostyrene (183 μL, 1.57 mmol, 1.1 eq) in Et_2NH was added $Pd(PPh_3)_2Cl_2$ (100 mg, 0.143 mmol, 0.10 eq)

before stirring for 10 min. CuI (27.2 mg, 0.143 mmol, 0.10 eq) was then added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatograhpy (50% → 100% Et_2O / P.E.) afforded enyne **565** (211 mg, 1.23 mmol, 86%) as an orange solid; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.41-7.28 (5H, m, ArH), 6.92 (1H, d, J = 16.3 Hz, =CH), 6.16 (1H, dt, J = 16.3, 2.2 Hz, =CH), 3.79 (2H, q, J = 6.2 Hz, C$\underline{H}_2$OH), 2.70 (2H, tdd, J = 6.2, 2.2, 0.6 Hz, C$\underline{H}_2$CH_2OH), 1.77 (1H, t, J = 6.3 Hz, OH).

This data is in agreement with that reported by Feuerstein *et al.*[342]

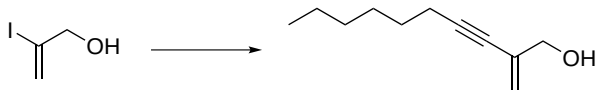
(E)-Dimethyl((6-phenylhex-5-en-3-yn-1-yl)oxy)silane (563)[341]



565 **563**

To neat alcohol **565** (50 mg, 0.290 mmol, 1.0 eq) at 0 °C was added tetramethyldisilazane (56.6 μL, 0.319 mmol, 1.1 eq) before stirring for 5 min. The reaction mixture was warmed to r.t., stirred for 1 h then placed under high vacuum for 1 h to afford silane **563** as an orange oil which was used directly in the subsequent hydrosilylation step; ^{1}**H NMR** (200 MHz, $CDCl_3$) δ_H 7.42-7.28 (5H, m, ArH), 6.90 (1H, d, J = 16.3 Hz, =CH), 6.15 (1H, dt, J = 16.3, 2.2 Hz, =CH), 4.68 (1H, *app* dt, J = 5.65, 2.83 Hz, SiH), 3.81 (1H, t, J = 7.0 Hz, CH_2OSi), 2.63 (1H, tdd, J = 7.0, 2.2, 0.5 Hz, C$\underline{H}_2$CH_2OSi), 0.27 (3H, s, SiMe), 0.25 (3H, s, SiMe). Further characterisation was not completed due to the unstable nature of this compound.

2-Methylenedec-3-yn-1-ol (561)[258]

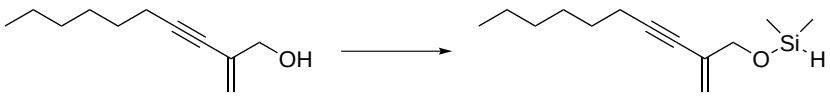


374 **561**

To a stirred, degassed solution of vinyl iodide **374** (100 mg, 0.544 mmol, 1.0 eq) and octyne (88.2 μL, 0.598 mmol, 1.1 eq) in Et_3N (2 mL) was added $Pd(PPh_3)_2Cl_2$ (38.2 mg, 0.0544 mmol, 0.10 eq)

before stirring for 10 min. CuI (10.4 mg, 0.0544 mmol, 0.10 eq) was then added before heating to 65 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatography (20% → 100% Et_2O / P.E.) afforded dienyne **561** (34.7 mg, 0.209 mmol, 38%) as a yellow oil; $\mathbf{R_f}$ 0.33 (50% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 3337, 2956, 2929, 2858, 2223, 1620, 1458, 1379, 1330, 1224, 1082, 1037, 986, 901, 723; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.43 (1H, q, J = 1.5 Hz, =C$\underline{H}_x$H$_y$), 5.39 (1H, br s, =CH$_x\underline{H}_y$), 4.12 (2H, d, J = 6.4 Hz, C$\underline{H}_2$OH), 2.32 (2H, t, J = 7.2 Hz, C≡CCH$_2$), 1.70 (1H, t, J = 6.5 Hz, OH), 1.54 (2H, m, C≡CCH$_2$C$\underline{H}_2$), 1.44-1.24 (6H, m, C≡CC$_2$H$_4$C$_3\underline{H}_6$CH$_3$), 0.90 (3H, t, J = 7.0 Hz, CH$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 131.5, 119.0, 92.5, 78.1, 65.7, 31.3, 28.6, 22.6, 19.3 (2 x C), 14.1; **HRMS** (FI) calculated for $C_{11}H_{18}Oi$ $[M+Na]^+$ 166.1358, found 166.1360.

Dimethyl((2-methylenedec-3-yn-1-yl)oxy)silane (562)[341]

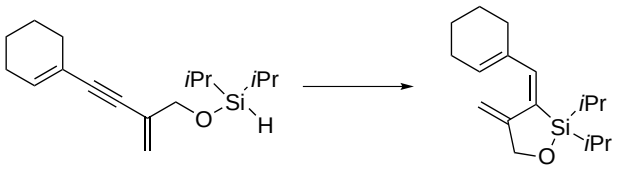


561 **562**

To neat alcohol **561** (10 mg, 0.0601 mmol, 1.0 eq) at 0 °C was added tetramethyldisilazane (11.7 μL, 0.0662 mmol, 1.1 eq) before stirring for 5 in. The reaction mixture was warmed to r.t., stirred for 1 h then placed under high vacuum for 1 h to afford silane **562** as a yellow oil which was used directly in the subsequent hydrosilylation step; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 5.46 (1H, q, J = 1.9 Hz, C=C$\underline{H}_x$H$_y$), 5.38-5.36 (1H, m, C=CH$_x\underline{H}_y$), 4.67 (1H, *app* dt, J = 5.7, 2.8 Hz, SiH), 4.14 (2H, t, J = 1.7 Hz, CH$_2$OSi), 2.31 (2H, t, J = 6.9 Hz, C≡CC$\underline{H}_2$C$_5$H$_{11}$), 1.61-1.20 (8H, m, C≡CCH$_2$C$_4\underline{H}_8$CH$_3$), 0.95-0.84 (3H, m, C≡CC$_5$H$_{10}$C$\underline{H}_3$), 0.26 (3H, s, SiMe), 0.25 (3H, s, SiMe). Further characterisation was not completed due to the unstable nature of this compound.

7.5.5. Hydrosilylation / Electrocyclisation / Oxidation

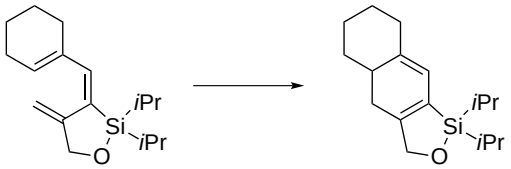
(E)-3-(Cyclohex-1-en-1-ylmethylene)-2,2-diisopropyl-4-methylene-1,2-oxasilolane (555)[63]



555 TMP2

To a stirred solution of silane **547** (170 mg, 0.615 mmol, 1.0 eq) in THF (2 mL) was added platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (0.170 mL of a 0.10 M solution in xylene, 0.017 mmol, 0.028 eq) at r.t. before stirring until TLC analysis indicated the reaction was complete. The reaction mixture was concentrated *in vacuo*, and subsequent purification by flash column chromatography (5% Et_2O / P.E., Et_3N) afforded triene **555** (38.2 mg, 0.138 mmol, 22%) as a yellow oil; $\mathbf{R_f}$ decomp. (5% Et_2O / P.E.); ^{1}**H NMR** (500 MHz, C_6D_6) δ_H 6.55 (1H, br s, *c*Hex =CH), 5.95-5.92 (1H, m, SiC=CH), 5.40 (1H, dd, J = 1.5, 0.4 Hz, C$\underline{H}_x$H$_y$), 5.00 (1H ,dt, J = 2.7, 1.4 Hz, CH$_x\underline{H}_y$), 4.68-4.66 (2H, m, CH_2OSi), 2.36-2.06 (4H, m, C$\underline{H}_2$C=CC$\underline{H}_2$), 1.66-1.53 (4H, m, *c*Hex), 1.29-1.19 (14H, m, Si(*i*-Pr)$_2$). Further characterisation was not completed due to the instability of this intermediate.

1,1-Diisopropyl-1,3,4,4a,5,6,7,8-octahydronaphtho[2,3-c][1,2]oxasilole (556)

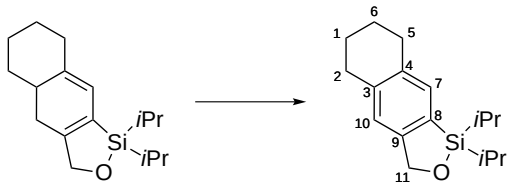


555 **556**

A solution of triene **555** (16.1 mg, 0.0582 mmol, 1.0 eq) in C_6D_6 (0.65 mL) was heated in a Bruker DPX250 NMR machine, and the reaction progress was monitored by NMR spectroscopy. Thermal electrocyclisation afforded diene **556** (34.3 mg, 0.124 mmol, 90%) as an orange oil; $\mathbf{R_f}$ decomp. (5% Et_2O / P.E.); ^{1}**H NMR** (400 MHz, C_6D_6) δ_H 5.97 (1H, t, J = 2.1 Hz, =CH), 4.60-4.59 (2H, m, CH_2OSi), 2.44-2.02 (5H, m, 2 x CH_2C=, CHC=), 1.84-1.53 (6H, m, *c*Hex), 1.34-1.18 (14H, m, Si(*i*-Pr)$_2$). Further characeterisation was not completed due to the instability of this compound,

and considerable difficulties in obtaining a clean sample.

1,1-diisopropyl-1,3,5,6,7,8-hexahydronaphtho[2,3-c][1,2]oxasilole (576)



556 **576**

To a stirred solution of diene **556** (18.5 mg, 0.0669 mmol, 1.0 eq) in wet Et_2O (2 mL) was added MnO_2 (58.2 mg, 0.669 mmol, 10 eq), before stirring at r.t. for 16 h. The reaction mixture was subsequently filtered through Celite and concentrated *in vacuo* before purification by flash column chromatograpy (5% Et_2 / P.E.) afforded arene **576** (12.6 mg, 0.0455 mmol, 68%) as a yellow oil; $\mathbf{R_f}$ 0.69 (10% Et_2O / P.E.); $\boldsymbol{\nu_{max}}$ (thin film) / cm^{-1} 2928, 2864, 1462, 1259, 1051, 919, 881, 788, 671;^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 7.26 (1H, br s, H_{10}), 6.93 (1H, br s, H_7), 5.07 (2H, br s, H_{11}), 2.80 (4H, *app* t, J = 5.3 Hz, H_2, H_5), 1.82 (4H, *app* dt, J = 6.5, 3.2 Hz, H_1, H_6), 1.24-1.16 (2H, m, $Si(C\underline{H}(CH_3)_2)_2$), 1.03 (6H, d, J = 7.4 Hz, $Si(CH(C\underline{H})_3)$), 1.01 (6H, d, J = 7.4 Hz, $Si(CH(C\underline{H}_3)_2)$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 145.0 (Ar), 138.9 (Ar), 135.6 (Ar), 132.7 (Ar), 128.5 (Ar), 121.8 (Ar), 72.1 (C_{11}), 29.8 (C_2), 29.4 (C_5), 23.4 (C_1), 23.2 (C_6), 17.0 ($Si(i\text{-}Pr)_2$), 13.1 ($Si(i\text{-}Pr)_2$); **HRMS** (ESI^+) calculated for $C_{17}H_{26}NaOSi$ 297.1645, found 297.1649.

A. Appendix

A.1. Selected NMR Spectra

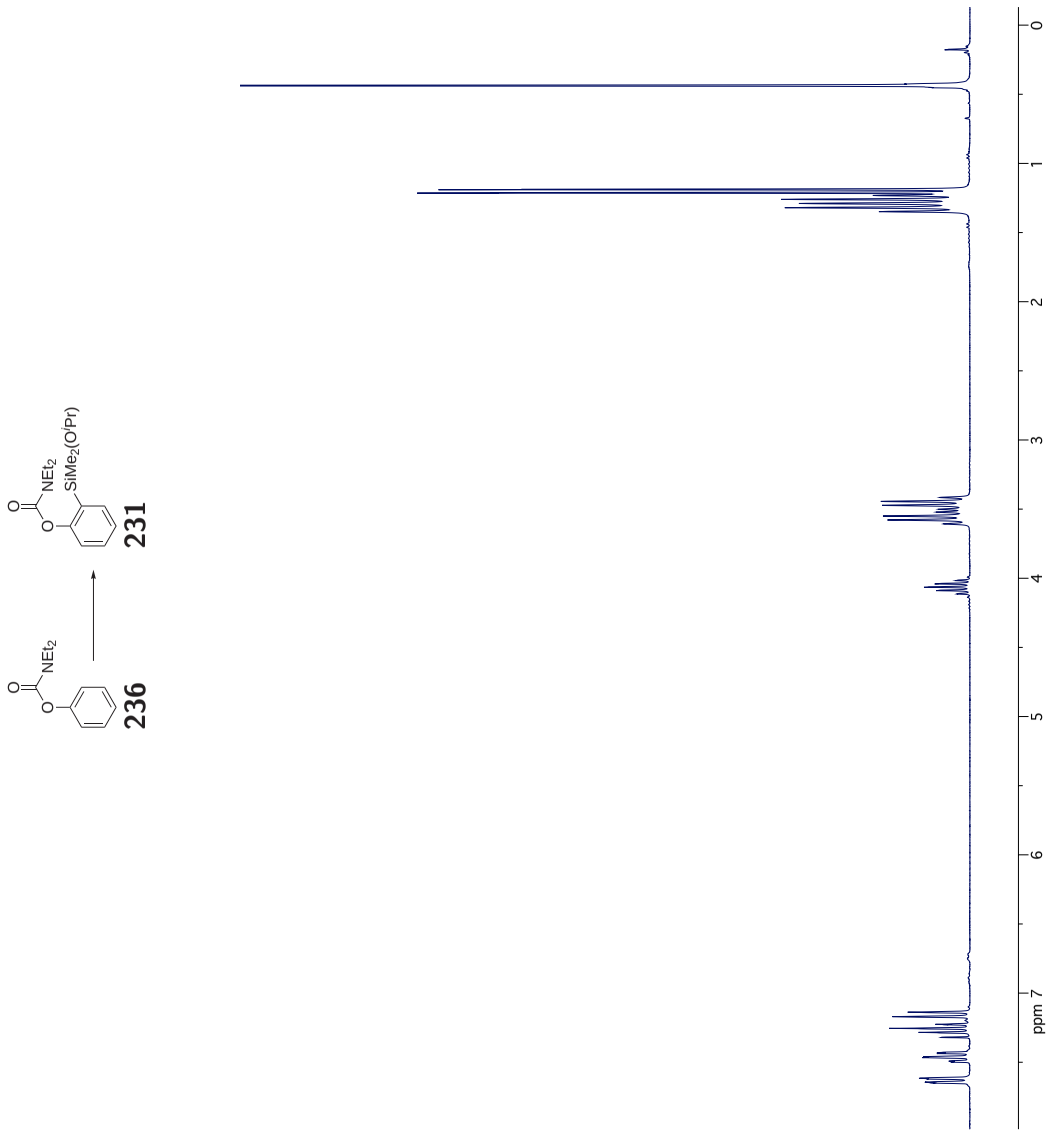


Fig. A.1. ^{1}H NMR of 2-(Isopropoxydimethylsilyl)phenyl diethylcarbamate (**231**)

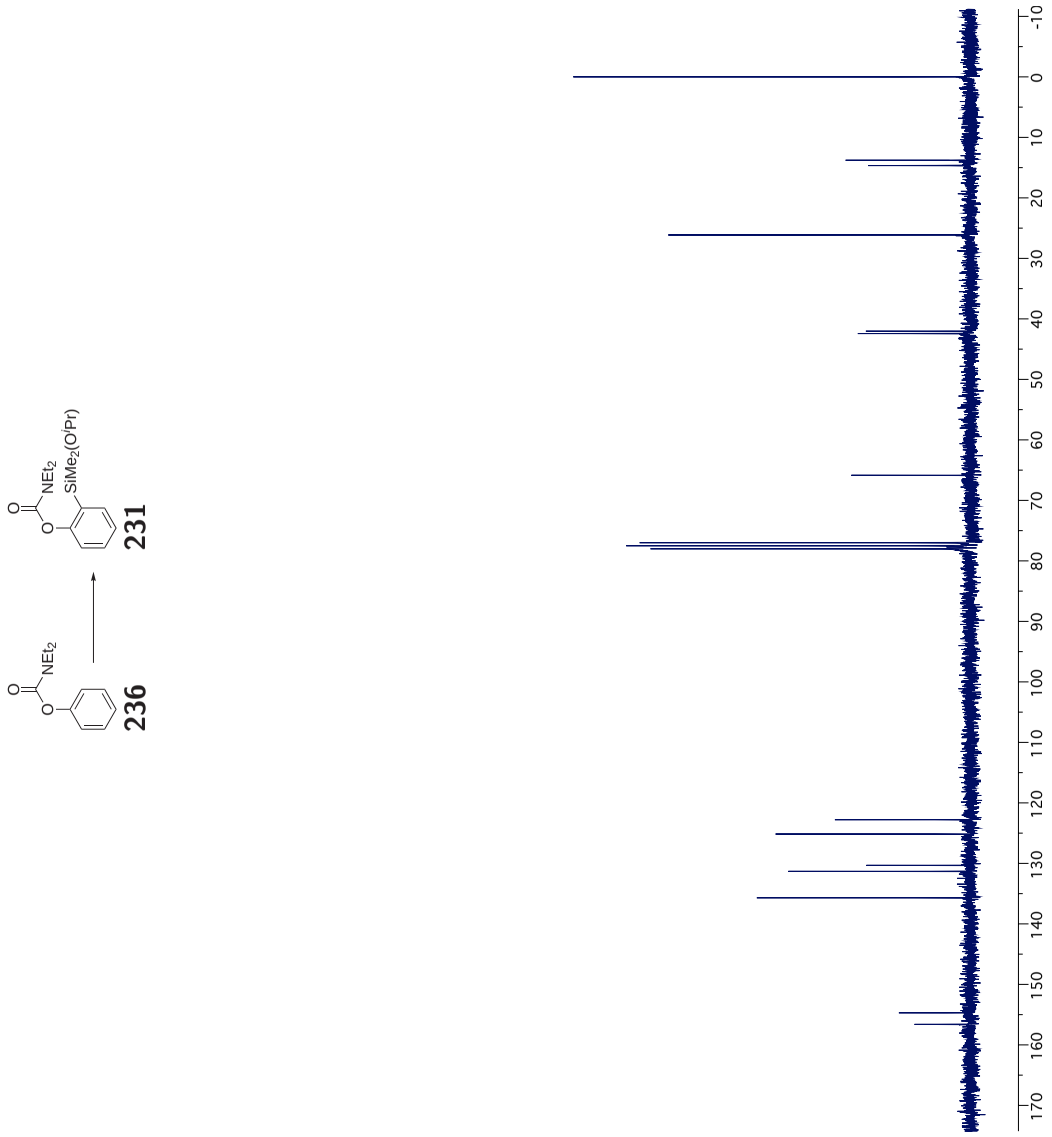


Fig. A.2. ^{13}C NMR of 2-(Isopropoxydimethylsilyl)phenyl diethylcarbamate (**231**)

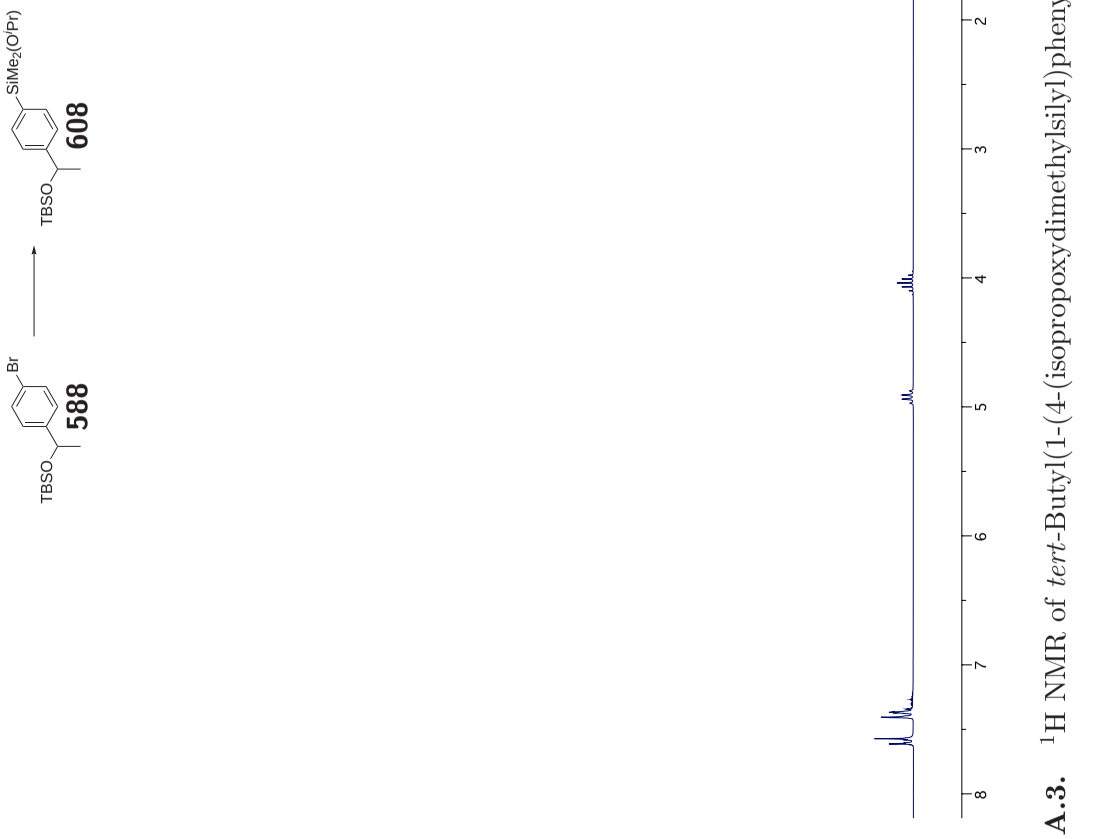


Fig. A.3. ^{1}H NMR of *tert*-Butyl(1-(4-(isopropoxydimethylsilyl)phenyl)ethoxy)dimethylsilane (**608**)

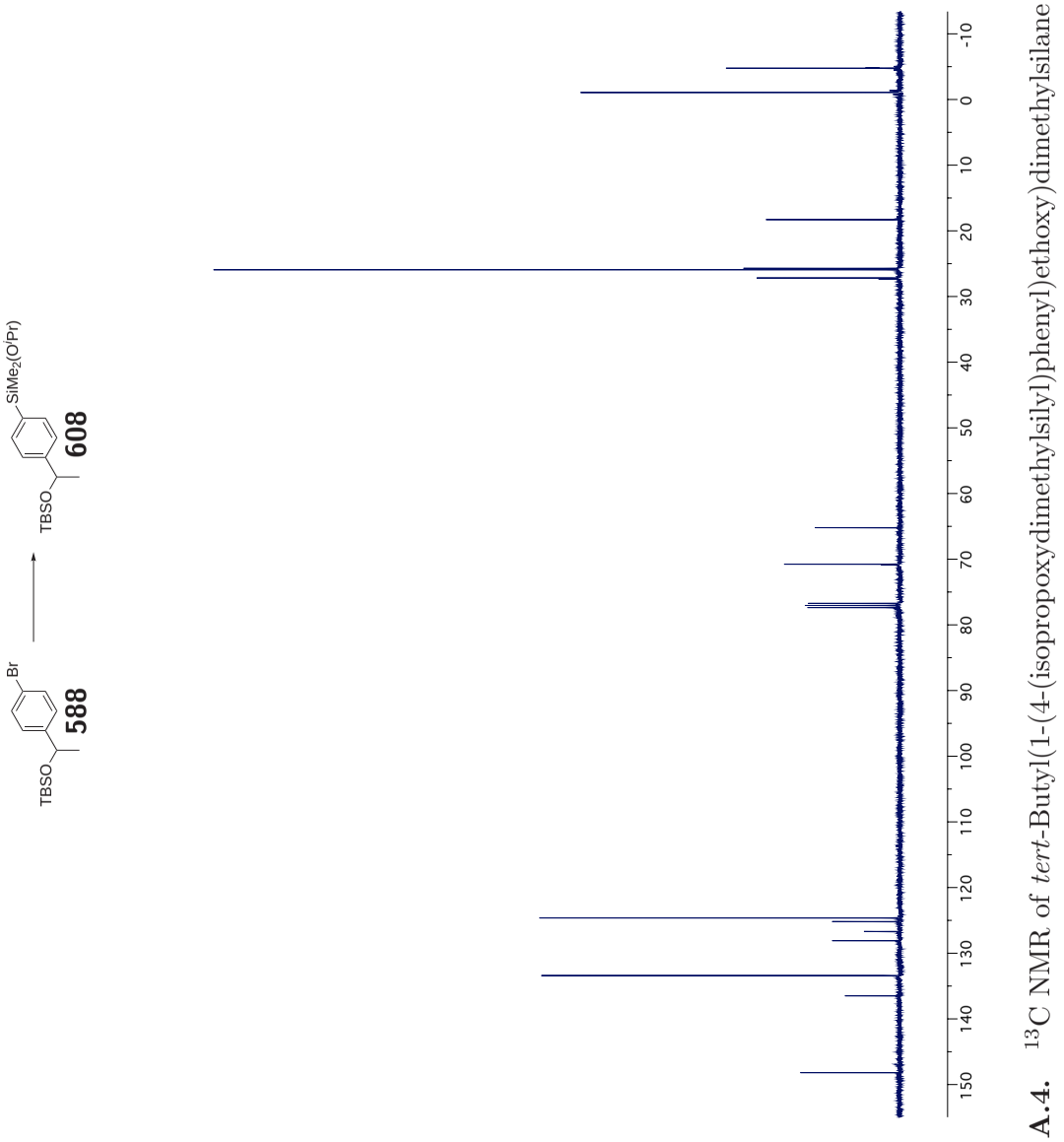


Fig. A.4. ^{13}C NMR of *tert*-Butyl(1-(4-(isopropoxydimethylsilyl)phenyl)ethoxy)dimethylsilane (**608**)

Fig. A.5. ^{1}H NMR of 6-(*tert*-Butyl)-6-phenyl-6H-dibenzo[c,e][1,2]oxasiline (**322**)

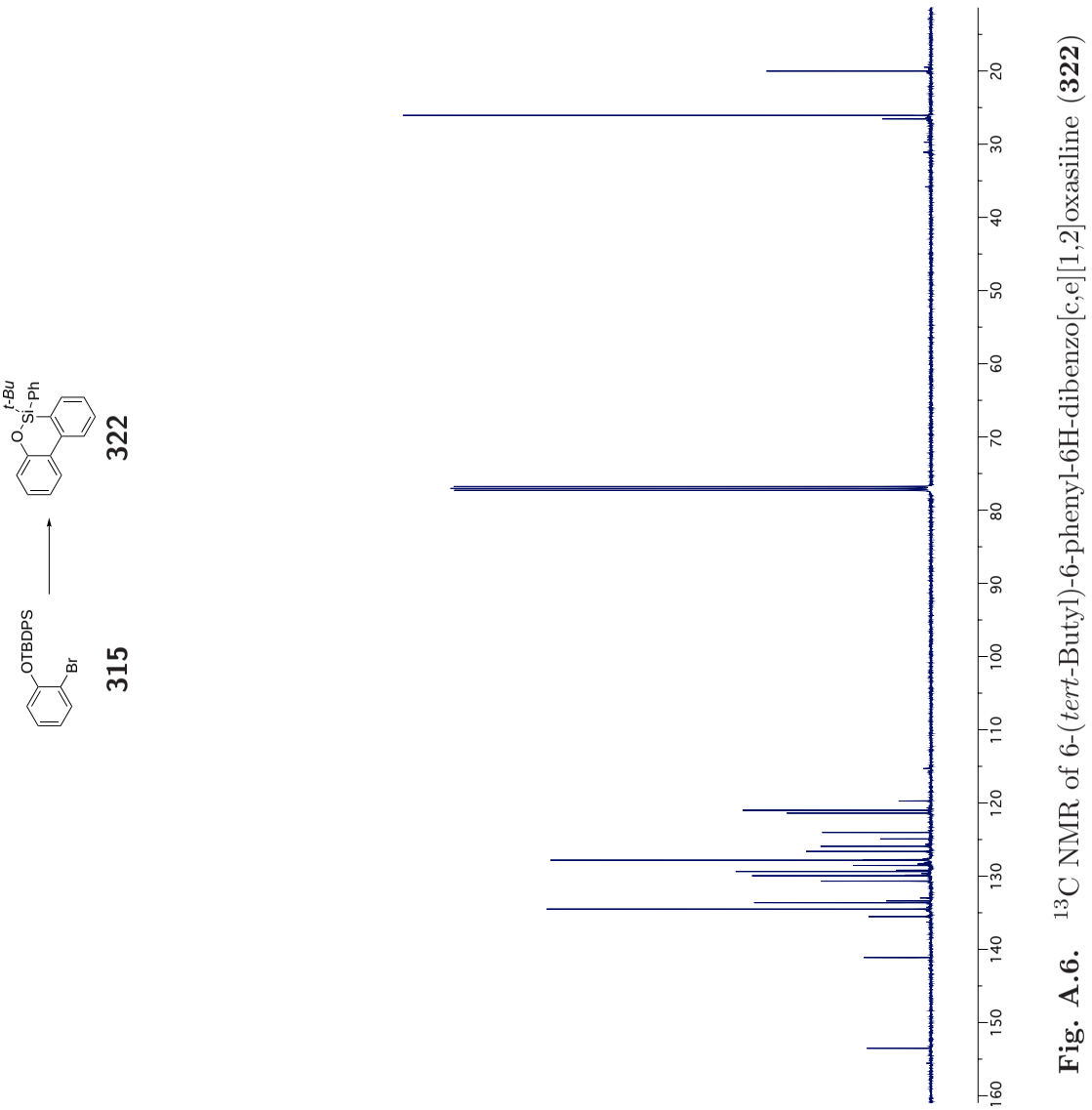


Fig. A.6. ^{13}C NMR of 6-(*tert*-Butyl)-6-phenyl-6H-dibenzo[c,e][1,2]oxasiline (**322**)

Fig. A.7. ^{1}H NMR of ((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)(hex-1-yn-1-yl)di*iso*propylsilane (**384**)

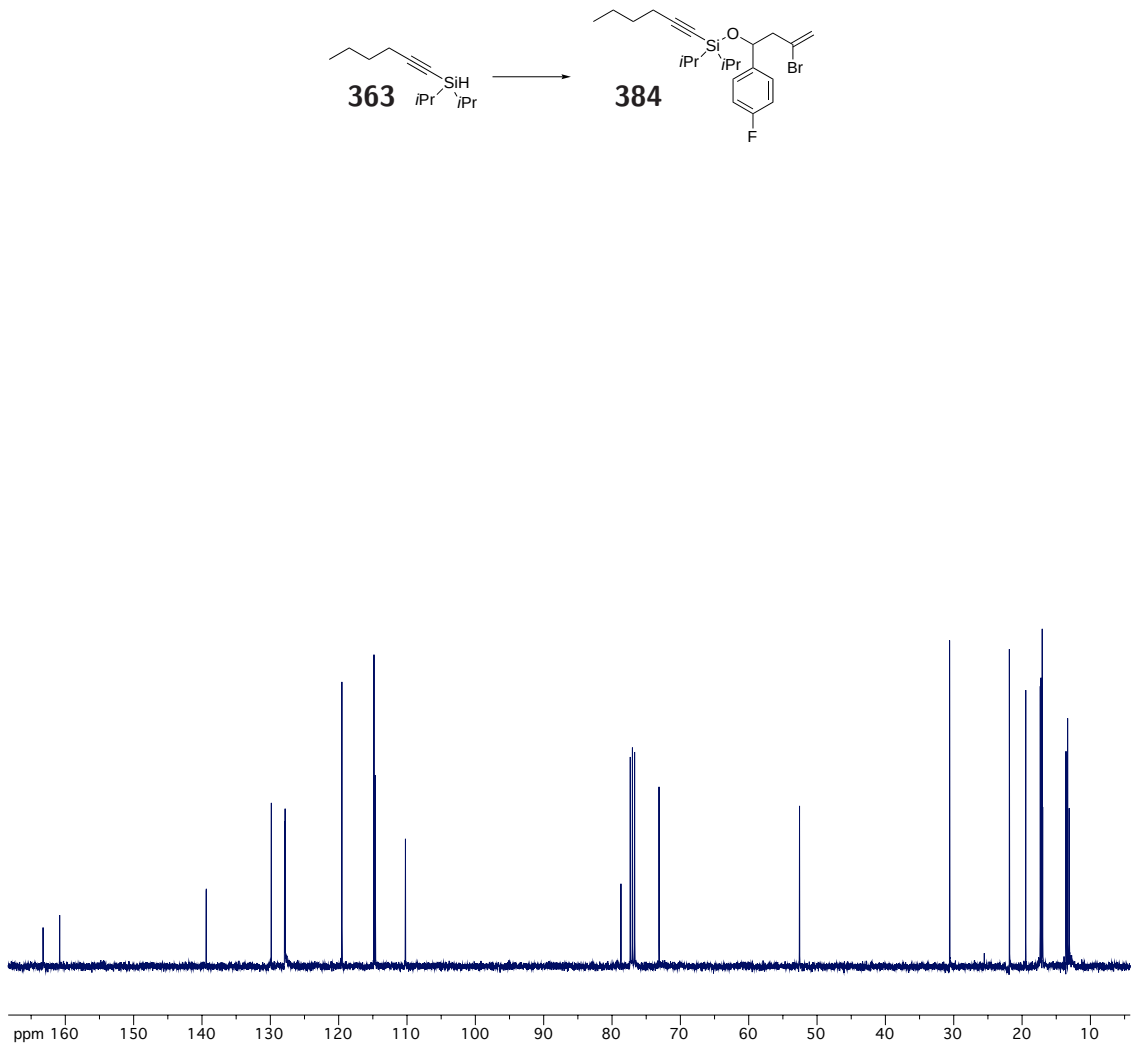


Fig. A.8. ^{13}C NMR of ((3-Bromo-1-(4-fluorophenyl)but-3-en-1-yl)oxy)(hex-1-yn-1-yl)di*iso*propylsilane (**384**)

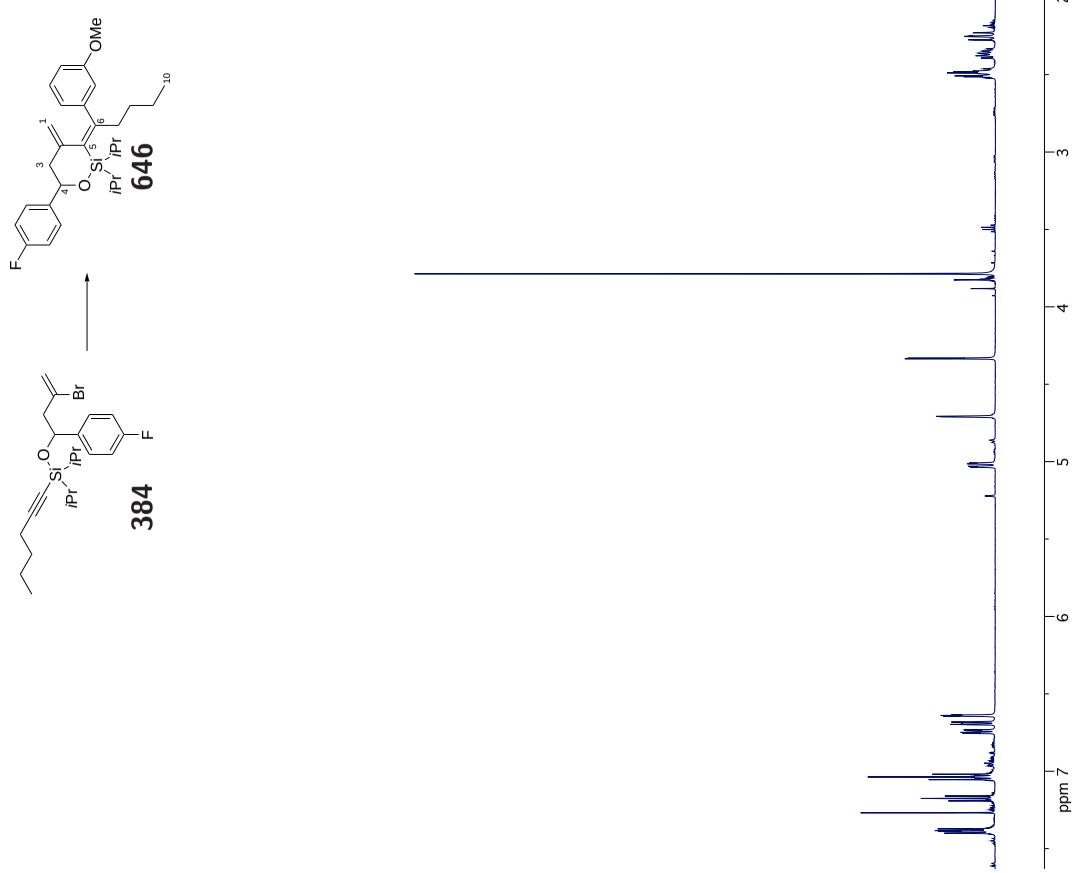


Fig. A.9. ^{1}H NMR of (E)-6-(4-Fluorophenyl)-2,2-diisopropyl-3-(1-(3-methoxyphenyl)pentylidene)-4-methylene-1,2-oxasilinane (**646**)

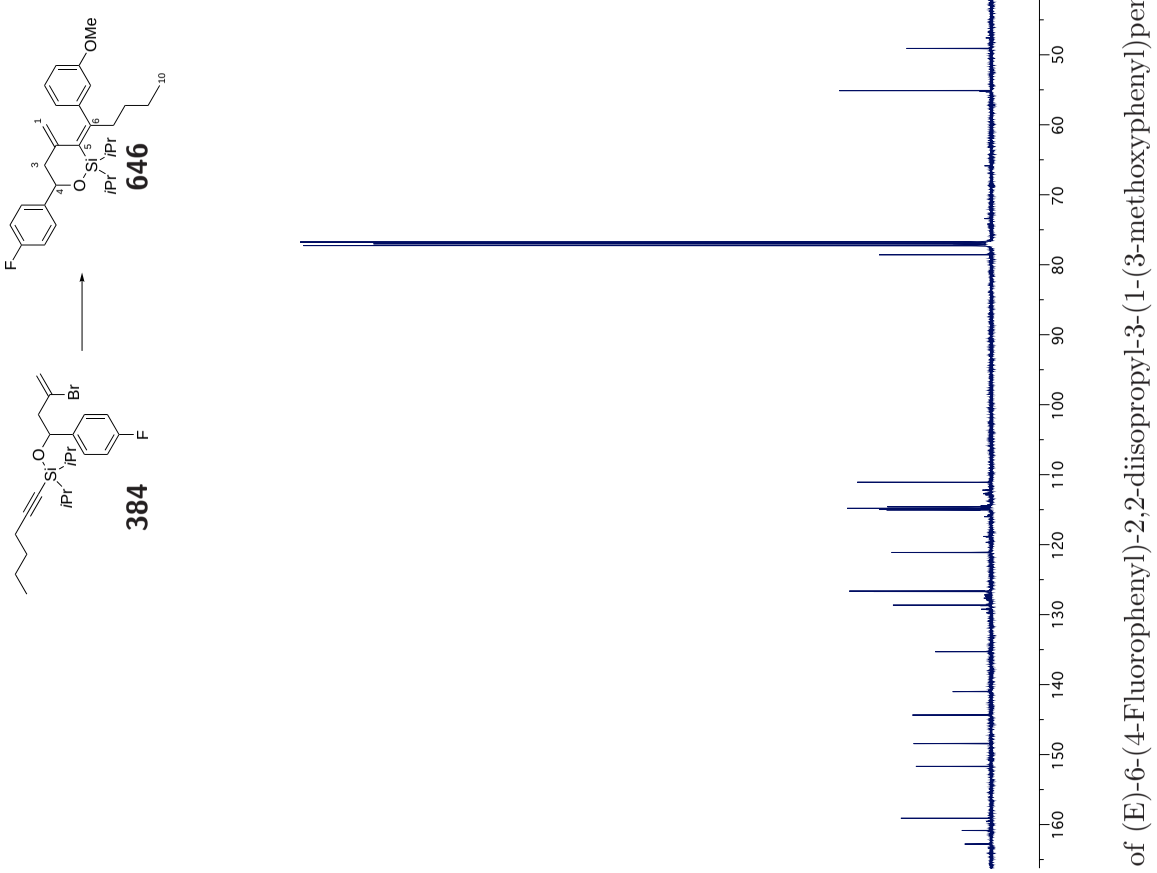


Fig. A.10. ^{13}C NMR of (E)-6-(4-Fluorophenyl)-2,2-diisopropyl-3-(1-(3-methoxyphenyl)pentylidene)-4-methylene-1,2-oxasilinane (**646**)

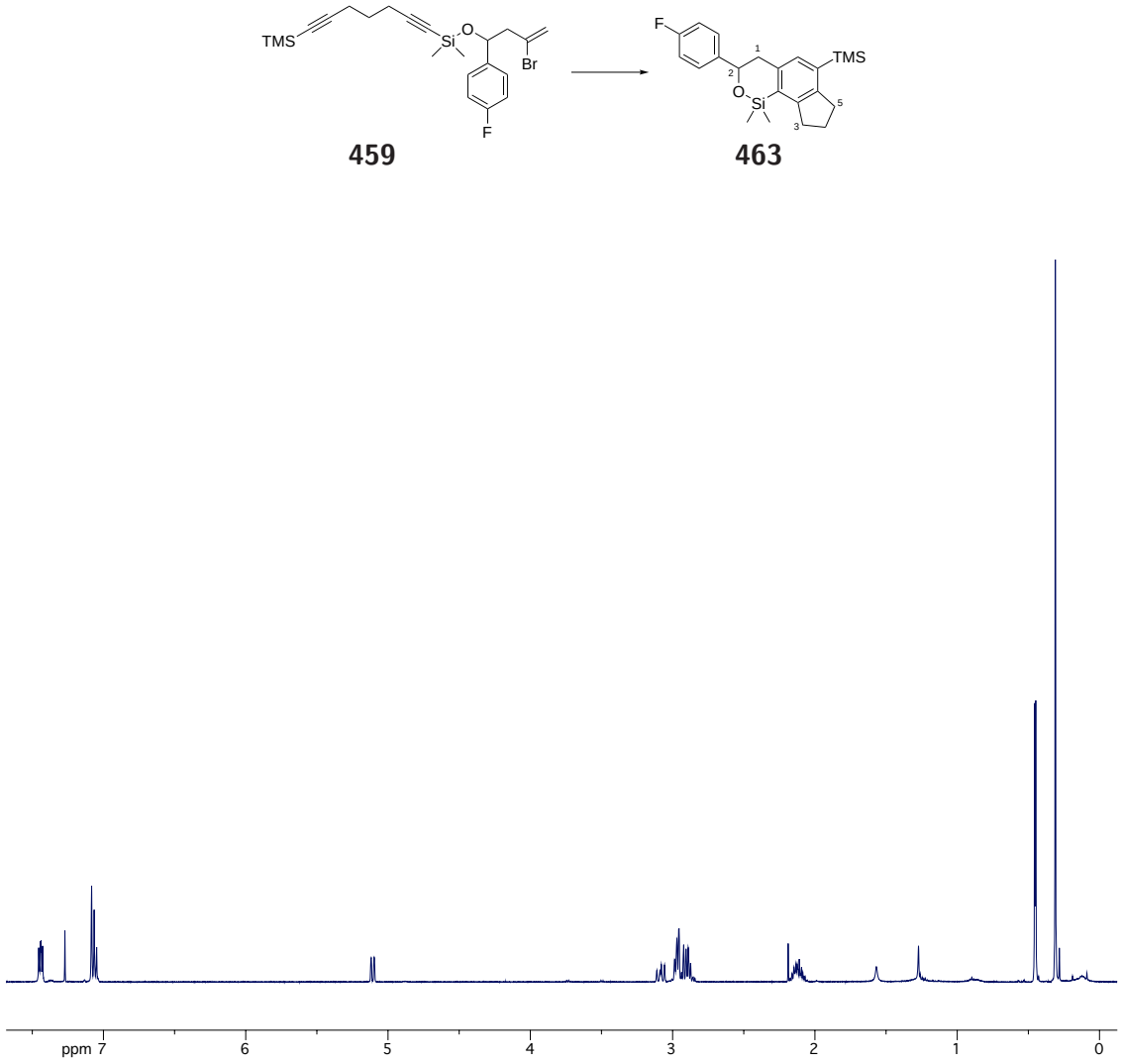


Fig. A.11. ^{1}H NMR of 3-(4-Fluorophenyl)-1,1-dimethyl-6-(trimethylsilyl)-1,3,4,7,8,9-hexahydroindeno[4,5-c][1,2]oxasiline (**463**)

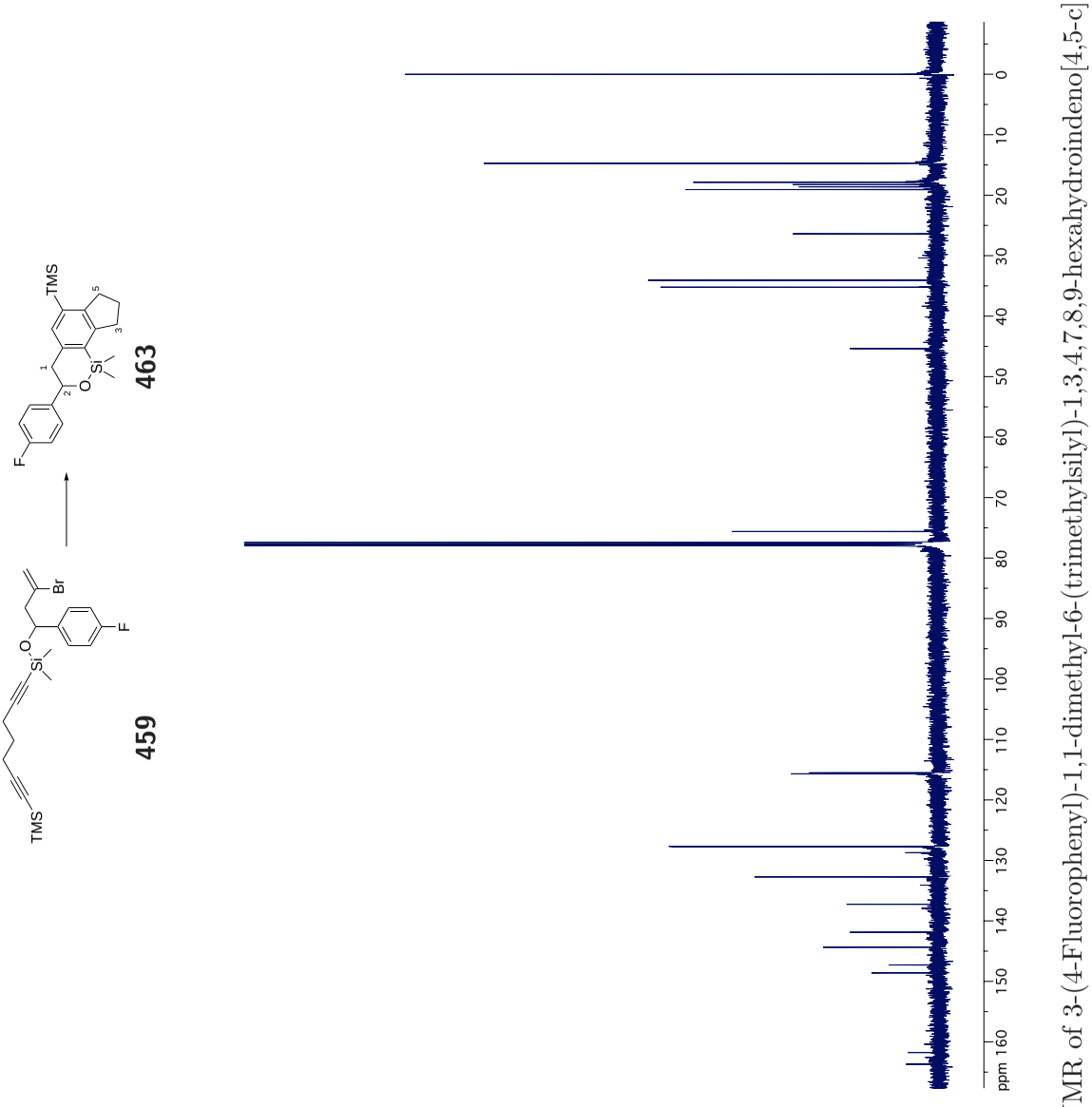


Fig. A.12. ^{13}C NMR of 3-(4-Fluorophenyl)-1,1-dimethyl-6-(trimethylsilyl)-1,3,4,7,8,9-hexahydroindeno[4,5-c][1,2]oxasiline (**463**)

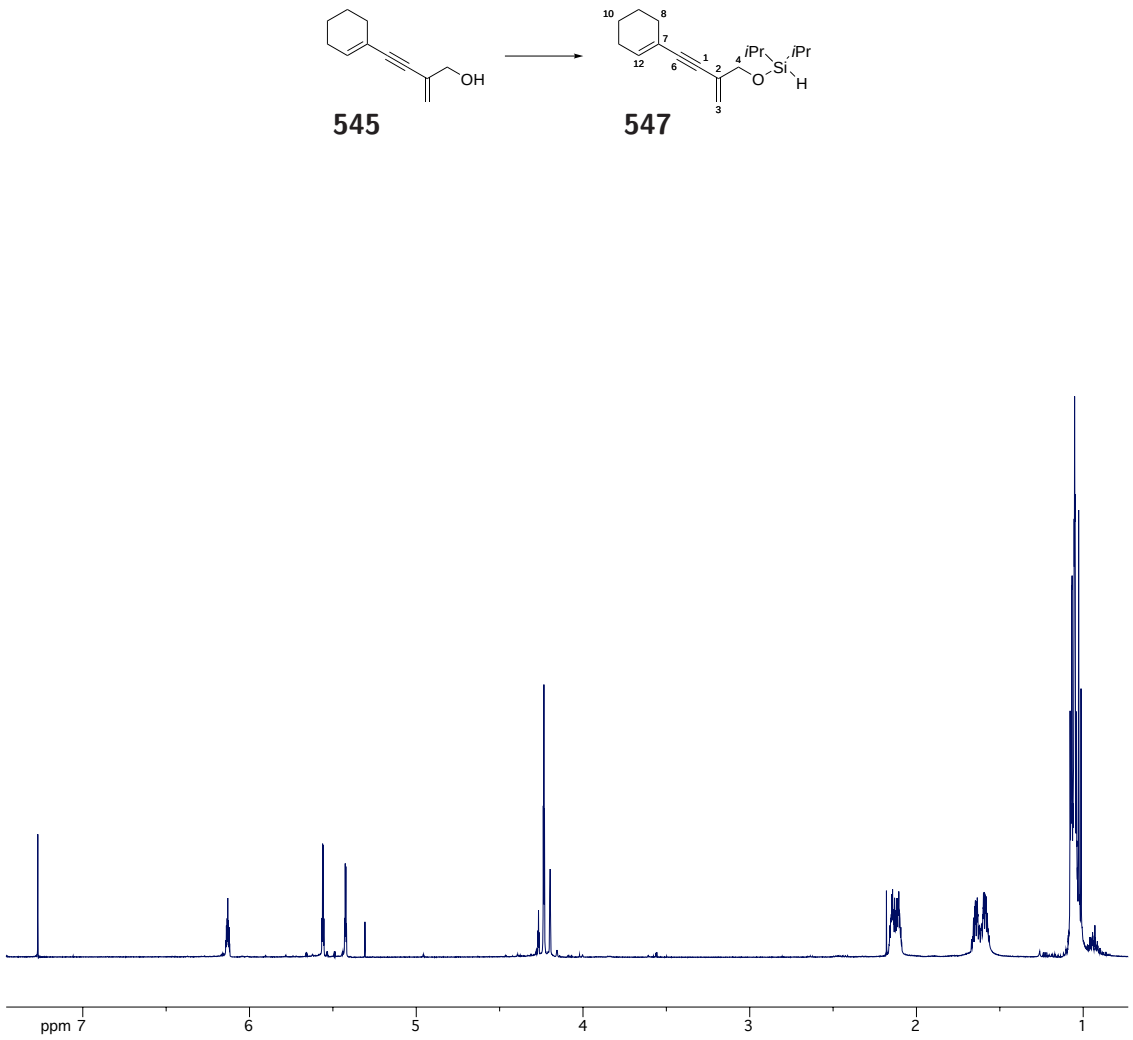


Fig. A.13. ^{1}H NMR of ((4-(Cyclohex-1-en-1-yl)-2-methylenebut-3-yn-1-yl)oxy)diisopropylsilane (**547**)

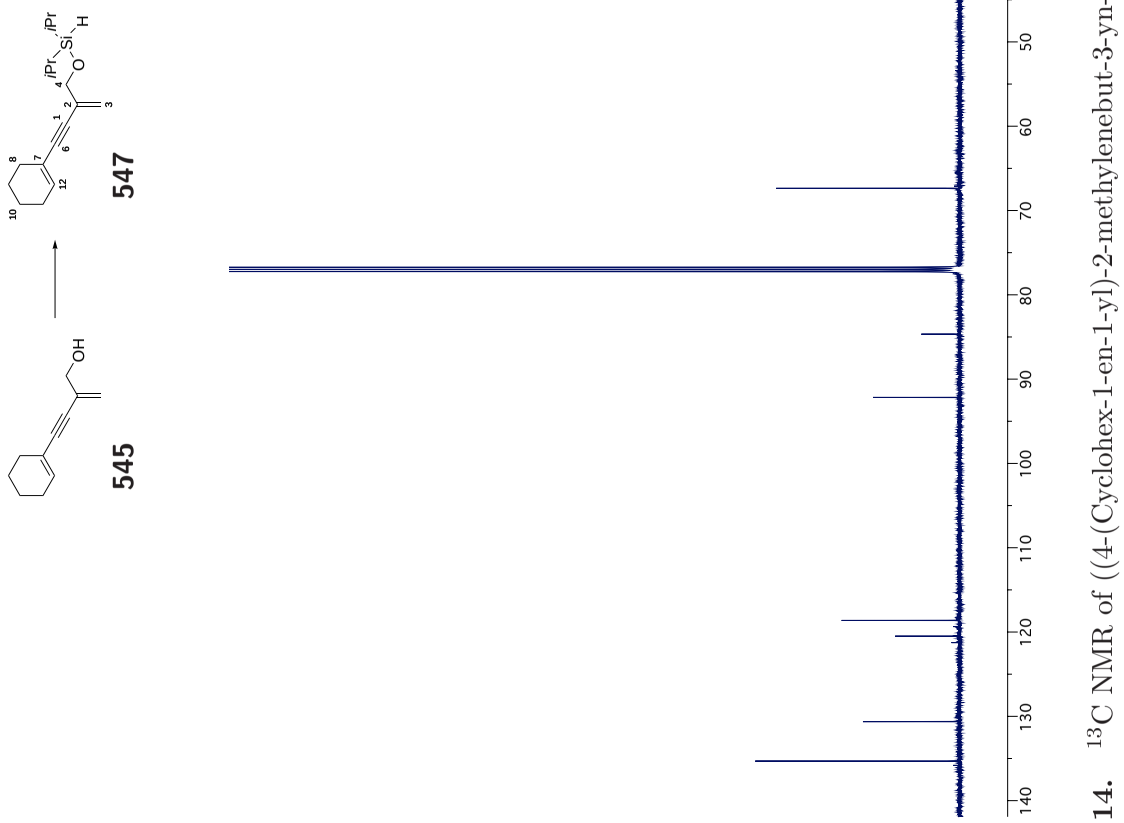


Fig. A.14. ^{13}C NMR of ((4-(Cyclohex-1-en-1-yl)-2-methylenebut-3-yn-1-yl)oxy)diisopropylsilane (**547**)

Fig. A.15. ^{1}H NMR of 1,1-diisopropyl-1,3,5,6,7,8-hexahydronaphtho[2,3-c][1,2]oxasilole (**576**)

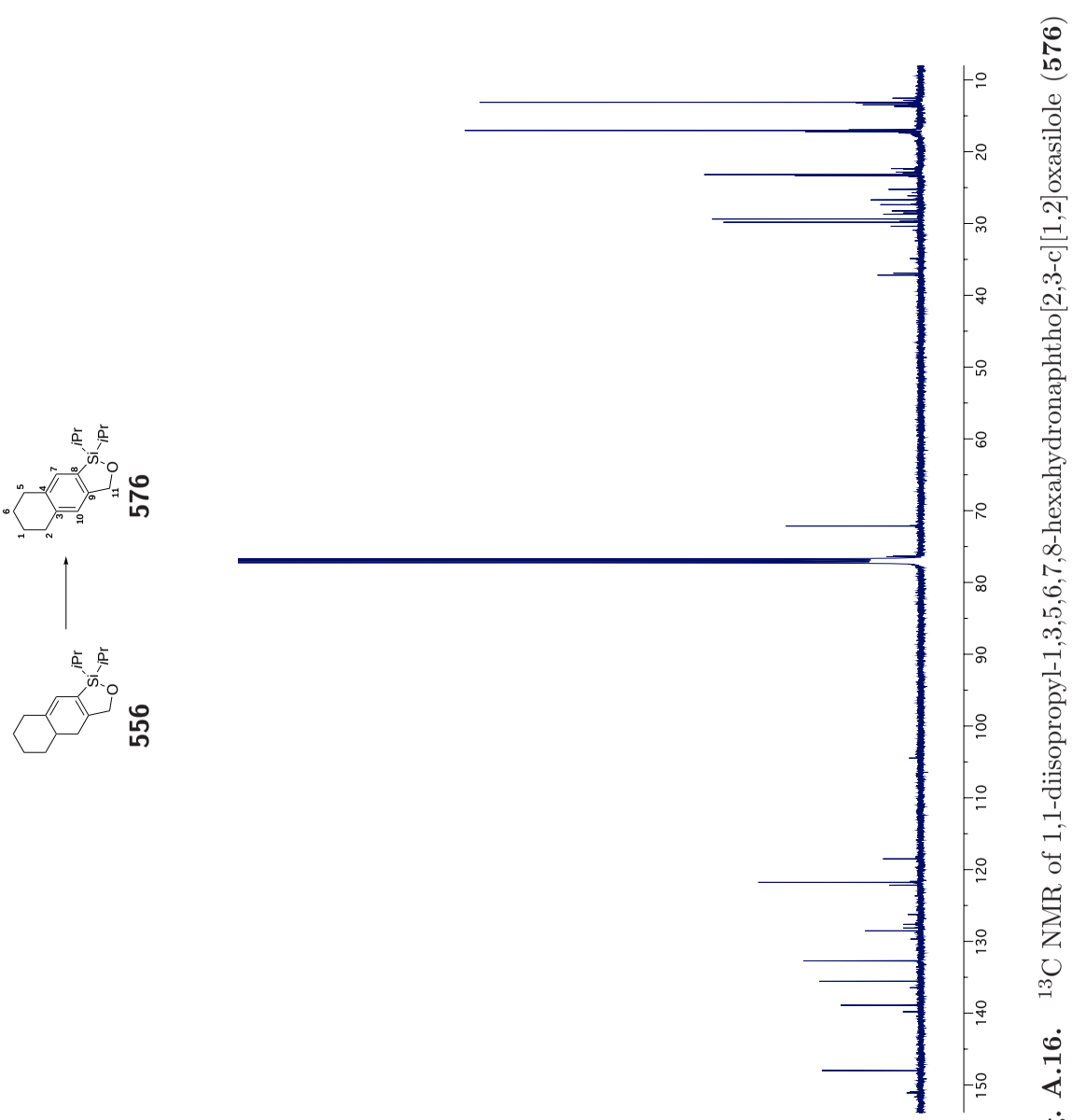


Fig. A.16. ^{13}C NMR of 1,1-diisopropyl-1,3,5,6,7,8-hexahydronaphtho[2,3-c][1,2]oxasilole (**576**)

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