Pergamon

Tetrahedron, Vol. 52, No. 22, pp. 7599-7662, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00038-5

TETRAHEDRON REPORT NUMBER 401

The Oxidation of the Carbon-Silicon Bond

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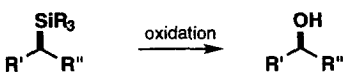
I. INTRODUCTION

The pioneering work of Tamao and Kumada[1] and Fleming[2] has introduced synthetic organic chemists to the concept of using a silicon group as a masked hydroxy group. This methodology is now recognized as a powerful synthetic tool and opens up areas of chemistry that would not otherwise be accessible. Although boron may be regarded as a competitor,[3] its Lewis acidic nature requires that it is oxidised immediately after its introduction into a carbon framework, whereas the neutral silicon group is stable to a wide range of reaction conditions and can therefore be carried along a multistep synthesis. Similarly, the protection-deprotection sequence required for hydroxy functions during total synthesis may sometimes be troublesome, whereas a silicon group, once it has been introduced, can be simply converted to a hydroxy group in a single oxidation step. This oxidation also allows silicon containing reagents to be classified as a wide variety of synthetic equivalents for the hydroxy group which would not otherwise be as readily available.



Scheme 1

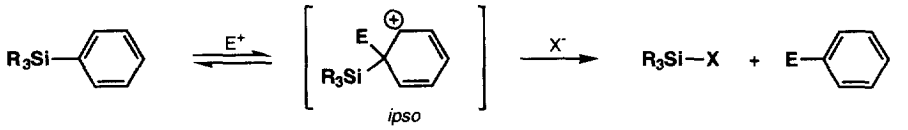
Perhaps more interesting from the view of stereocontrol,[4] is that a silicon group has certain properties that are complementary to a hydroxy group. First, the electropositive silicon centre and electronegative hydroxy group introduce opposite electronic effects and second, because of its large size, the silicon group always exerts a strong steric effect within a molecule. Similarly, in contrast to hydroxy groups, a silicon centre does not possess a lone pair of electrons and thus does not co-ordinate with incoming organometallic reagents, electrophiles or Lewis acids.

This review concentrates on the oxidation of the carbon silicon bond and in particular on the oxidation of silicon groups that can be carried through long synthetic sequences. More importantly, emphasis has been placed upon the compatibility of the oxidation conditions with various functionalities, an aspect that has not previously been covered.[5] To add a further dimension, compatibility tables have been added at the end, which the reader can use as a quick reference guide.

II. MECHANISM

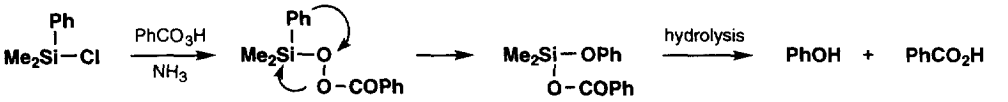
1. The Fleming oxidation

The Fleming oxidation[2] of phenyl(dimethyl)silyl groups can be considered in two distinct steps : protodesilylation and oxidation. Precedent for the first step came from mechanistic studies reported by Eaborn in the late fifties on protodesilylation and cleavage of aryl-silicon bonds by electrophiles.[6] Eaborn reported that :*"the Ph-Si bond was found to be much more readily cleaved than alkyl-Si bonds"* using electrophilic reagents. This cleavage, which can be treated as a classical electrophilic aromatic substitution, leads, via an *ipso* substitution,[6c] to the expected electrophile-substituted arene, and in addition, the corresponding R_3Si-X compound (Scheme 2).



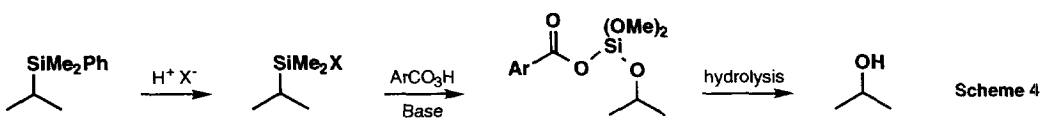
Scheme 2

The second peracid oxidation step of a halosilane was first reported by Buncel,[7] who found that, during attempts to prepare peroxysilanes, substituents underwent a 1,2-migration from silicon to oxygen (Scheme 3).



Scheme 3

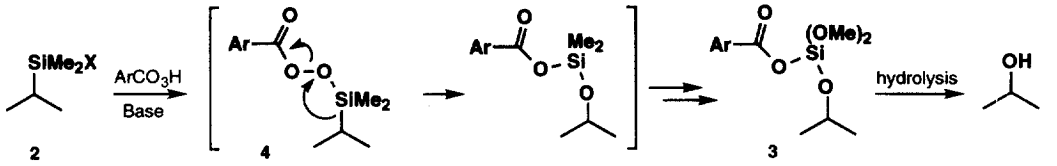
Therefore, using $PhMe_2Si$ (**1**) as the silicon moiety and H^+ as the electrophile (E^+), Fleming found that it was possible to displace the phenyl group on silicon to give benzene and the silicon intermediate **2** having the counter-ion X as a new substituent (Scheme 4). This heteroatom-substituted silane then underwent oxidation with peroxide (AcOOH or H_2O_2), giving the siloxane **3** which on hydrolysis produced the desired alcohol. In the original report by Fleming, this appeared as a two-step sequence,[2a] protodesilylation using $H^+BF_4^-$ (X = F), followed by oxidation with peracetic acid. However, it was later found that by using Hg^{2+} or Br^+ as the electrophile, the two steps could be carried out in one-pot.[2b]



Scheme 4

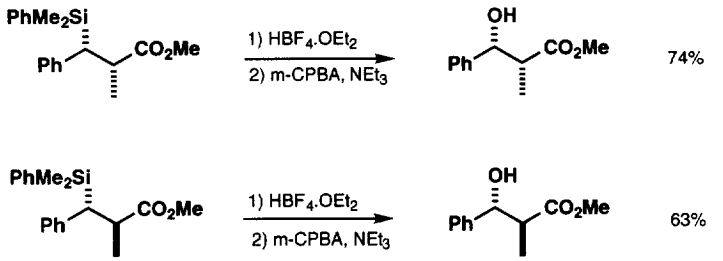
1 2 3

Fleming's proposed mechanism is centred around the observation that the oxidation reaction requires the presence of a base. The base is thought to promote the nucleophilic attack of m-CPBA at the silicon centre of **2** with the simultaneous loss of the nucleofugal group (either halide or acetate) to produce a tetraco-ordinated silyl peroxide such as **4**. This then undergoes a migration that is analogous to the mechanism of the Baeyer-Villiger reaction and the oxidation of organoboranes[3] (Scheme 5).



Scheme 5

Perhaps the most important feature of the transformation of a C-Si bond into a C-OH bond is that it occurs *stereospecifically with retention of configuration* at the carbon centre.[2,8] This was proved by converting β-silylesters of known relative configurations into the known corresponding β-hydroxyesters (Scheme 6).

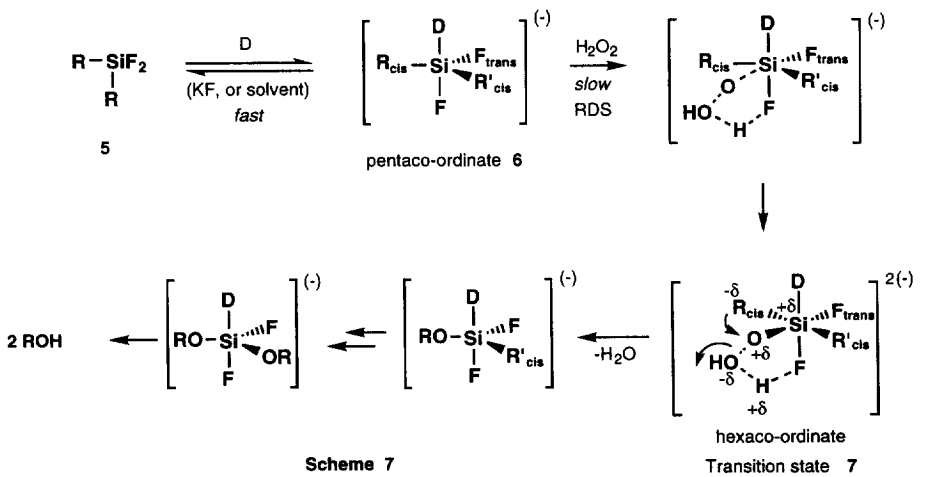


Scheme 6

2. The Tamao-Kumada oxidation

Tamao and Kumada have published extensively on the oxidation of carbon-silicon bonds with silicon groups of type SiR_2X (with X = Cl, F, H, OR, NR_2).[1,9,10] The oxidants (H_2O_2 or m-CPBA) are the same as those employed by Fleming and similarly the conversion of the C-Si bond has been proven to be stereospecific.

It is not possible to state exactly what the mechanism is under the standard basic conditions of H_2O_2, $KHCO_3$, KF in DMF because no kinetic measurements have been made under these conditions. However, Tamao has proposed a mechanism based on a series of observations made using H_2O_2 as oxidant together with a variety of different fluoride sources and solvents and a number of different substrates.[10a]

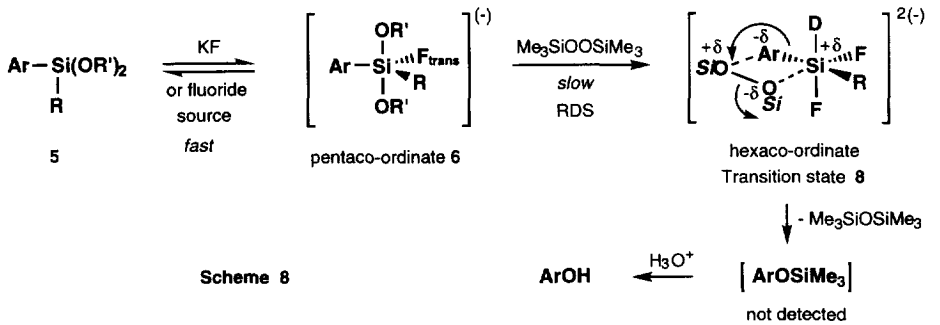


Scheme 7

The starting fluorosilane is immediately attacked by fluoride (or a donor solvent : DMF or HMPA) in a fast and reversible step to produce a pentaco-ordinated species **6**. The resulting pentaco-ordinate silicon of **6** is more electrophilic, thus promoting attack by the nucleophilic oxidant to produce the hexaco-ordinate species **7**. Tamao[10] had previously proposed, based on kinetic studies, that this step was rate determining (RDS) and that the large negative entropy, resulted from such a well-organised transition state[11] (i.e. **7**, Scheme 7).

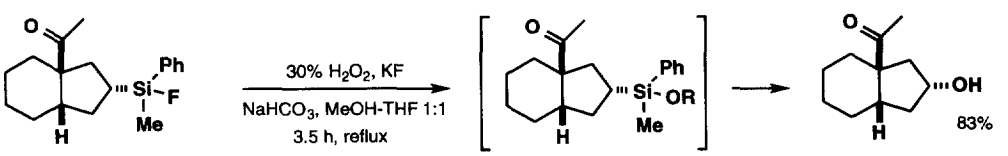
Further studies by Tamao on the steric and electronic effects of different groups attached to the silicon led him to suggest that attack by the oxidant *trans* to the electronegative fluoride group is energetically favoured. The group *cis* to the peroxide oxygen in **7** then migrates preferentially, thus explaining the retention of configuration at the carbon centre as being a result of "front side attack" of the oxidant. Acceleration of the oxidative cleavage by electron-withdrawing substituents (in R_{cis}) is also consistent with the partial negative charge on the migrating group and the overall charge distribution illustrated in transition state **7**. Finally the new silicon-oxygen bond of the pentaco-ordinate species is hydrolysed by water in the reaction medium to produce the expected alcohol.

In a recent work, Dunoguès[12a] proposed an alternative hexaco-ordinate transition state (i.e. **8**) based on some observations made during the C-Si bond oxidative cleavage using anhydrous conditions and $Me_3SiOOSiMe_3$[12b] as oxidant. According to the authors, the reaction might proceed through a four centered concerted mechanism (i.e. **8**) with the silylated phenol (or the alcohol when H_2O_2 was the oxidant) being produced directly (Scheme 8). Unfortunately, this silylether (i.e. $ArOSiMe_3$) has not been isolated or even detected. However, it must be emphasised that the free phenol is not present in the reaction mixture before work-up, supporting a possible concerted migration as illustrated in scheme 8.



Scheme 8

Finally, it is worth mentioning a recent work by Knölker[13] who showed that the intermediate methoxysilane **10** and silanol **11** could be isolated during the oxidation of the fluorosilane **9** in Tamao's basic conditions (H_2O_2, MeOH/THF, $KHCO_3$, KF) (Scheme 9). These alkoxy and hydroxysilanes could be synthesised independently using appropriate nucleophilic substitution conditions and were readily oxidised in the same conditions as the fluorosilane to give the alcohol **12**. This demonstrates that at least in these conditions, the Tamao-Kumada oxidation proceeds through the intermediacy of the methoxysilane and the silanol. However, it is not clear if these are common intermediates in the oxidation of all fluorosilanes.

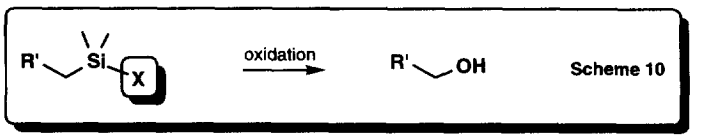


Scheme 9

The debate about the mechanism of the oxidation is sure to continue and more work will be required to clarify the area. However, when considering the wide variety of reaction conditions used, with respect to oxidant, solvent, fluoride source or other additives, it seems unlikely that all reactions will occur via only one mechanism and common intermediate.

III. DIFFERENT MASKED HYDROXY GROUPS

As already discussed, the oxidation conditions very much depend on the nature of the substituents attached to the silicon atom. Therefore, the following sections have been organised according to the nature of the specific substituent X attached to the silicon, with the compatibility of the oxidation conditions being reviewed for each individually (Scheme 10). Particular emphasis has been placed on the widely used alkoxysilanes (X = OR) and arylsilanes (X = Ph).



Scheme 10

1. Alkoxysilanes as masked hydroxy groups (X = OR)

1.1. The oxidation of acyclic alkoxysilanes

This section has been divided into three parts, the first reviews the methods of oxidation of alkoxysilanes, the second is concerned with the use of alkoxysilanes containing methoxy and ethoxy groups and the third with the chemistry of alkoxysilanes containing *iso*-propoxy and butoxy groups.

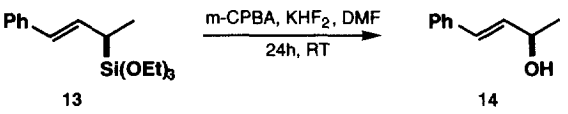
1.1.1. Oxidation conditions

As can be seen in Table 1 below, a wide variety of oxidation conditions can be used to oxidise alkoxysilanes.

Table 1. Oxidation conditions.

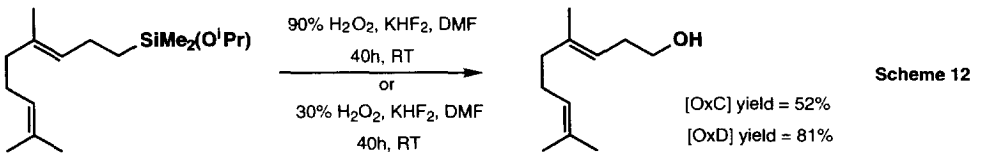
Condition	Oxidant	Fluoride	Additive	Solvent	References
[OxA]	m-CPBA	KF or KHF_2	-	DMF	9
[OxB]	m-CPBA	-	Na_2HPO_4	MeOH	16
[OxC]	30% H_2O_2	KF or KHF_2	-	DMF	1b
[OxD]	90% H_2O_2	KF or KHF_2	-	DMF	1a
[OxE]	30% H_2O_2	KF or KHF_2	Ac_2O	DMF	1b
[OxF]	45% AcOOH	KF or KHF_2	-	DMF	1a
[OxG]	30% H_2O_2	-	$NaHCO_3$ or $KHCO_3$	MeOH, THF	1a
[OxH]	30% H_2O_2	KF or KHF_2	$NaHCO_3$ or $KHCO_3$	MeOH, THF	1a
[OxI]	30% H_2O_2	KF	$KHCO_3$	DMF	57b
[OxJ]	30% H_2O_2	-	KOH	MeOH, THF	61b

The first methods employed m-CPBA as the oxidising agent in either neutral [OxA][9,14,15] or basic conditions [OxB].[16] Under the neutral conditions, the allylsilane **13** could be cleanly oxidised into the allylalcohol **14** without epoxidation of the double bond (Scheme 11).[15]



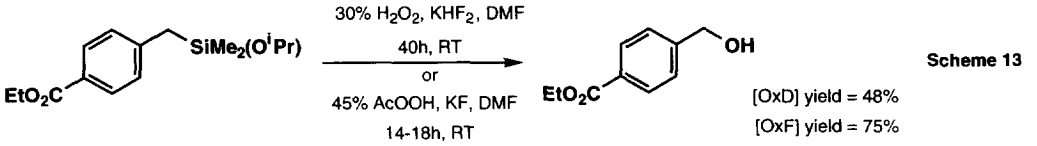
13 14 **Scheme 11**

These conditions have now been largely replaced by the development of a range of acidic, alkaline and neutral conditions in which inexpensive hydrogen peroxide is the oxidising agent.[1b] The neutral [OxC], [OxD] and acidic [OxE], [OxF] conditions rely upon a fluoride salt, either KF or KHF_2, being added as a promoter in the reaction, with DMF being used as a polar/donor solvent. The range of functional groups that have been shown to be stable under neutral conditions includes cyclopropanes,[17a] alkylbromides,[1b] esters,[1] epoxides,[17b,18] pyridines,[1a] thiophenes[1a] and both isolated[1a,18,19] and allylsilane[1a,17] double bonds. For substrates containing double bonds the conditions using 90% H_2O_2 [OxD] give much enhanced yields over the normal 30% H_2O_2 (Scheme 12).[1a]



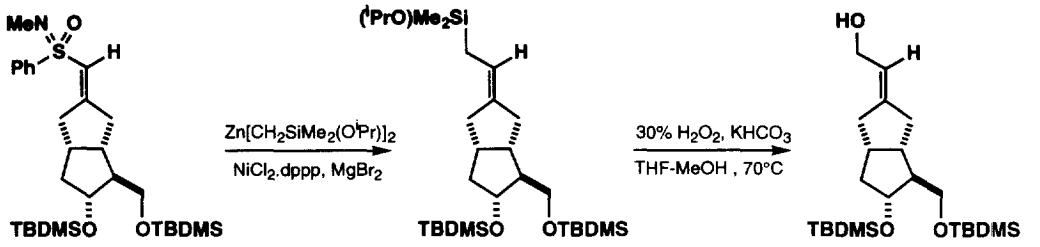
Scheme 12

To achieve acidic conditions, using hydrogen peroxide as the oxidant, acetic anhydride is added to the reaction mixture, which forms acetic acid *in situ* [OxE].[1b] There has been speculation that under these conditions the actual oxidising agent is peracetic acid, though this has not been proved. The conditions using peracetic acid as the oxidant [OxF] have been recommended for use with benzylic substrates substituted with electron withdrawing groups (Scheme 13).[1a] Both of these conditions have found little use, probably because of the incompatibility of protecting groups with such strongly acidic conditions.[1a]



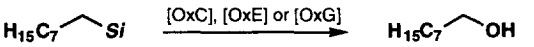
Scheme 13

Under basic conditions [OxG], it is not necessary to add a fluoride source, though lower reaction temperatures can be used if it is added [OxH]. Ketones,[1b] alkenes,[20,21,22] dienes,[23] α-hydroxy,[20,21,24,25] enones[26] and acetals[21,26] have all been shown to be unaffected by these conditions and *tert*-$BuMe_2Si$ ethers (TBDMS) are even stable under the unactivated conditions [OxG] (Scheme 14).[22]



Scheme 14

The ease of oxidation is a balance between the number of silicon oxygen bonds and the size of the ether groups.[1b] Methoxy and ethoxy substituted silyl groups are oxidised with ease under all conditions (Scheme 15, Table 2). Under neutral conditions, trialkoxysilanes have a tendency to form polysiloxanes, and, in both cases, the reaction with the di-*tert*-butoxysilanes is very slow. Under neutral and acidic conditions, the *iso*-propoxy and *tert*-butoxy groups can also be cleaved. However, under basic conditions the di-*iso*-propoxy, di-*tert*-butoxy and *tert*-butoxy[20] groups are resistant to cleavage.

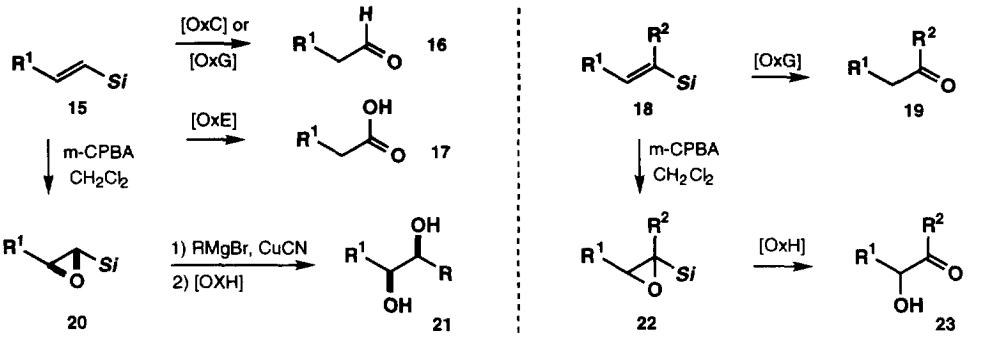


Scheme 15

Table 2. Alkoxy and polyalkoxysilanes.

Si Group	neutral [OxC]	acidic [OxE]	basic [OxG]
$Si(OMe)_3$	polysiloxanes	+	+
$Si(OEt)_3$	polysiloxanes	+	+
$SiMe(OMe)_2$	+	+	+
$SiMe(OEt)_2$	+	+	+
$SiMe(O^iPr)_2$	+	+	no reaction
$SiMe(O^tBu)_2$	slow reaction	slow reaction	no reaction
$SiMe_2(OMe)$	+	+	+
$SiMe_2(OEt)$	+	+	+
$SiMe_2(O^iPr)$	+	+	+
$SiMe_2(O^tBu)$	prolonged heating	+	no reaction

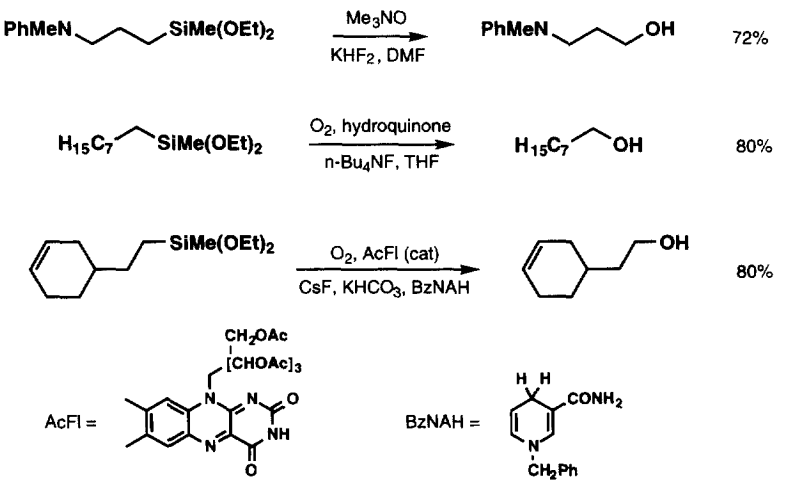
Depending upon the oxidation conditions and the substitution pattern, vinylsilanes such as **15** and **18** are oxidised into the corresponding carbonyl compounds. If the substituent on the carbon bearing the silicon is a hydrogen, then under neutral [OxC] or basic [OxG] conditions the aldehyde **16** is the oxidation product, whereas acidic conditions [OxE] lead to the formation of the carboxylic acid **17** (Scheme 16).[27]



Scheme 16

Vinylsilanes substituted at the carbon bearing the alkoxysilane group **18** can either be oxidised to the corresponding ketone **19**,[27] or epoxidised using m-CPBA to the epoxysilane **22** which can then be oxidised to the α-hydroxyketone **23**.[28] Alternatively, when *Si* = $SiMe_2(O^iPr)$, the vinylsilane can be epoxidised using m-CPBA to the epoxysilane **20** and then opened selectively using a copper(I) cyanide catalysed Grignard addition. Sometimes, the epoxide opening leads to Peterson elimination products, however in the majority of cases the β-hydroxysilane is the major product which is then oxidised into the 1,2-diol **21** (Scheme 16).

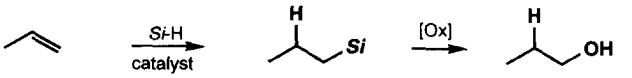
Other less common oxidising systems which have been shown to be effective are trimethylamine N-oxide,[29] oxygen from the air in the presence of hydroquinone[30] and oxygen and a flavin catalyst[31] (Scheme 17). These conditions have been tested on a range of primary and secondary silanes and all have been shown to proceed via the same *stereospecific* mechanism as the peroxide reactions. Esters, ethers, alkylhalides, amines, thiols and isolated double bonds are all stable under the trimethylamine N-oxide oxidation conditions.[29]



Scheme 17

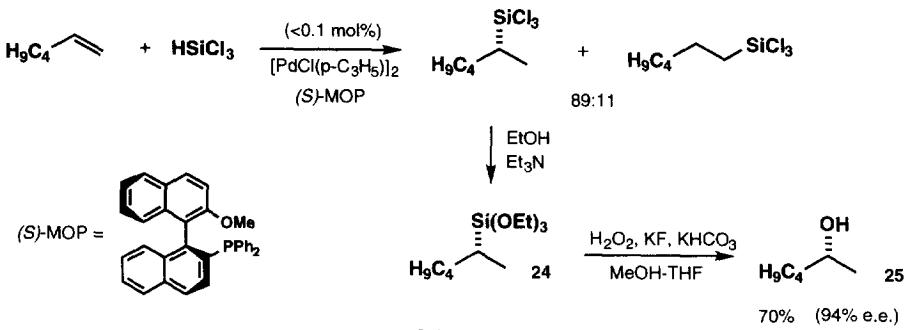
1.1.2. Methoxy and ethoxy substituted alkoxysilanes

By far the most widely used method of introducing methoxy and ethoxy alkoxysilane groups is the transition metal catalysed hydrosilylation of alkenes and alkynes[32] to give alkoxysilanes and vinyl alkoxysilanes respectively (Scheme 18). Although both triethoxysilane[16] and (diethoxy)methylsilane[27] have been used as the hydrosilylating reagent, it is more common to use a chlorosilane and then to react the product with an alcohol to give the alkoxysilane which is then oxidised.[14,33-35]



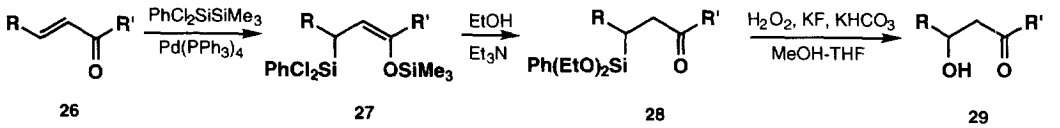
Scheme 18

Whereas hydrosilylation of alkenes using platinum or rhodium complexes produces *anti*-Markovnikoff addition products,[1b] palladium catalysts have been reported to give regioselectively Markovnikoff products when using trichlorosilane as the hydrosilylating reagent.[14,33] Hayashi[33] demonstrated that by using a chiral ligand, this reaction can produce alkoxysilanes and hence alcohols such as **25** in high enantiomeric excess (Scheme 19). Like hydroboration, oxidation of the C-Si bond is usually carried out routinely during the work up of the reaction.



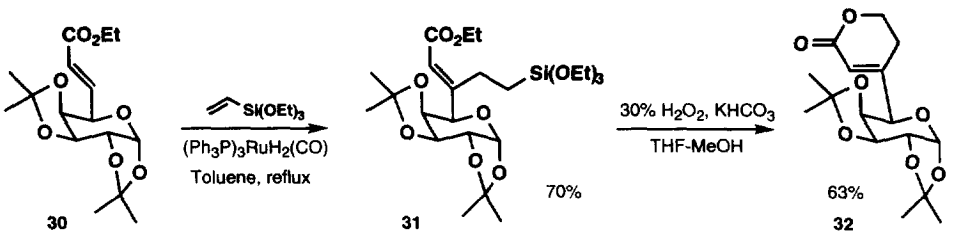
Scheme 19

Hayashi[36] also found that 1,1-dichloro-1-phenyl-2,2,2-trimethyldisilane would undergo 1,4-addition to an enone **26** in the presence of a palladium catalyst, to give initially the silylenolether **27**. Transformation of the chlorosilane group in **27** into the ethoxysilane **28** led to hydrolysis of the silylenolether, which following oxidation gave the corresponding β-hydroxyketone **29** (Scheme 20).



Scheme 20

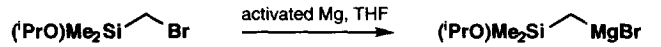
An interesting new method of introducing a triethoxysilane group has recently been developed by Trost.[26] Ruthenium catalysed insertion of triethoxyvinylsilane into the vinylic C-H bond of an enone **30** gives trisubstituted enones such as **31**, the triethoxysilane group of which can be oxidised to the alcohol, which in this case undergoes cyclisation to give the lactone **32** (Scheme 21). This example again shows the compatibility of the oxidation conditions with substrates containing sensitive groups.



Scheme 21

1.1.3. *Iso*-propoxy and butoxy substituted alkoxysilanes

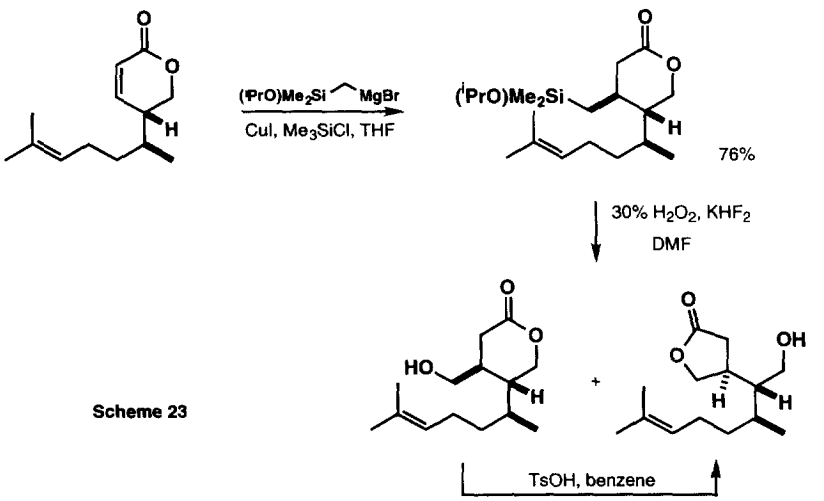
There are a few examples of further chemistry being carried out on molecules containing an alkoxysilane group, however these are limited to those in which the alkoxy group is large and resistant to nucleophilic cleavage (RO = ^{i}PrO and BuO). Surprisingly, the $SiMe_2(O^{i}Pr)$ group is sufficiently stable to be introduced as part of the Grignard reagent **33** (Scheme 22),[1a] in contrast to the corresponding ethoxy derivative which undergoes polymerisation.



33

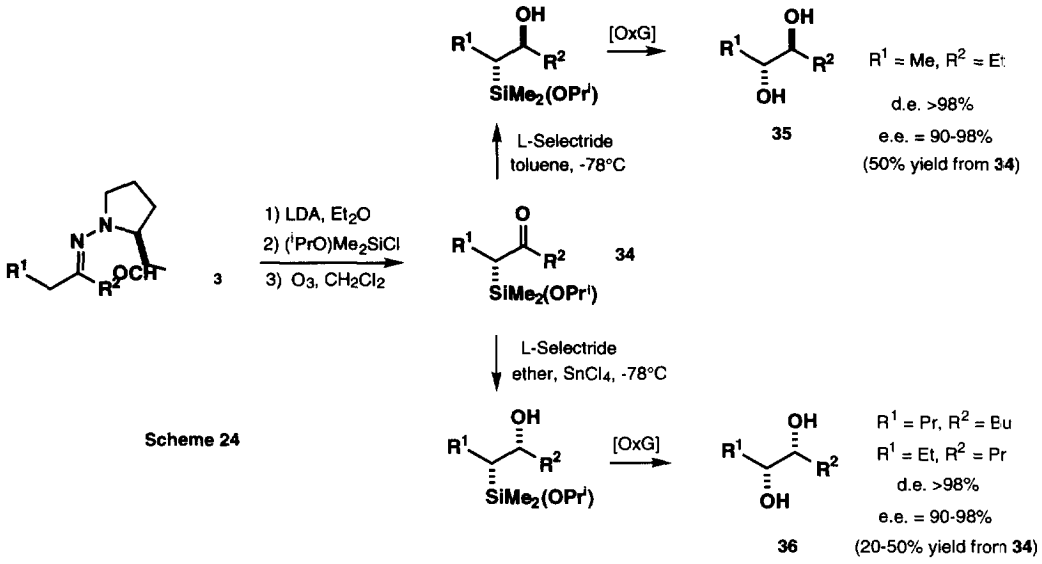
Scheme 22

This reagent can undergo nucleophilic addition to aldehydes and ketones to produce 1,2-diols,[23,24,37] Ni or Pd complex catalysed cross-coupling reactions with alkyl, vinyl or aryl halides[1a,18], or Cu(I) catalysed 1,4-addition to enones (Scheme 23).[19] It can also be converted into a zinc reagent which undergoes cross-coupling with sulphoximine in the presence of $NiCl_2$.dppp as the pre-catalyst and $MgBr_2$ as the co-catalyst (Scheme 14).[22] All of this chemistry makes the Grignard reagent **33** a highly versatile hydroxymethyl anion equivalent.



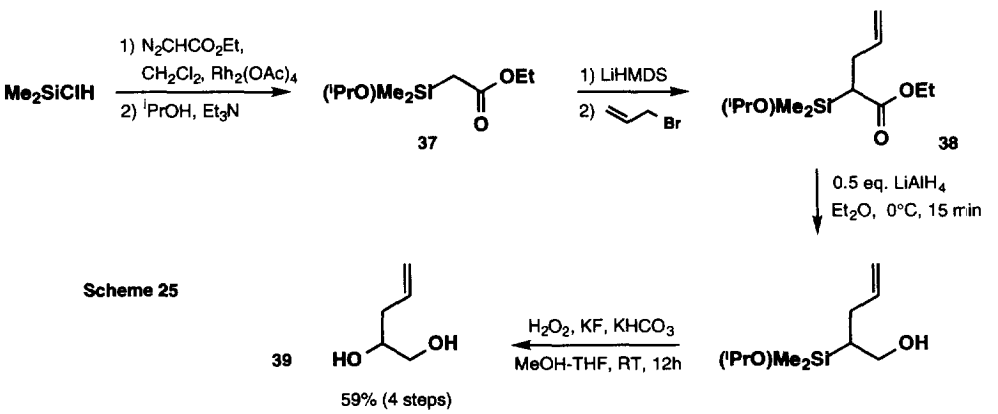
Scheme 23

Enders[25] showed that the $SiMe_2(O^iPr)$ group was stable to a number of hydride reducing reagents when preparing the *anti* and *syn* 1,2-diols **35** and **36** (Scheme 24). The homochiral α-silylketone precursors **34** were synthesised by the silylation of metallated SAMP and RAMP hydrazones with dimethyl(*iso*-propoxy)silyl chloride.[25]



Scheme 24

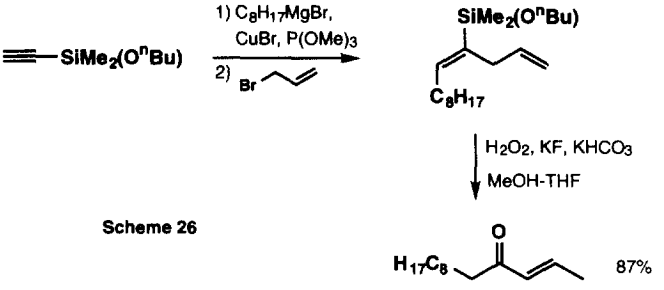
α-Silylacetic esters such as **37** can be prepared by carbene insertion into the Si-H bond of HMe_2SiCl, followed by work-up with isopropanol and triethylamine.[20,38] Subsequent deprotonation using LiHMDS and alkylation with a range of alkyl halides gave access to α-silylesters of type **38**. Reduction to the β-hydroxysilane proceeded cleanly at 0°C using 0.5 equivalents of $LiAlH_4$ which after oxidation gave the 1,2-diol **39**. However, the use of 3 equivalents of $LiAlH_4$ led to hydride substitution of the *iso*-propoxy group on the silicon (Scheme 25).



Scheme 25

Finally, in an alternative method of preparation of vinylsilanes, the regioselective addition of organocuprates to ethynylsilanes[39] shows the stability of *n*-butoxy substituents to organometallic reagents. Oxidation leads to the

carbonyl and, in this particular case, isomerisation of the double bond to give the α,β-unsaturated ketone (Scheme 26).



Scheme 26

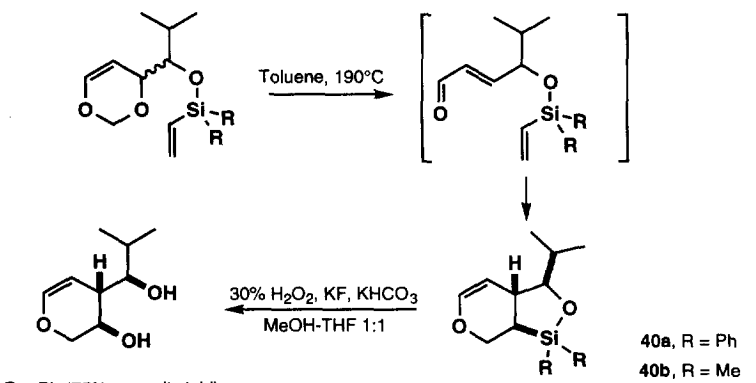
1.2. The oxidation of cyclic alkoxysilanes

In the first part of this section the oxidation of cyclic alkoxysilanes is discussed, comparing the ease of oxidation with exchange of non-participatory groups attached to silicon and highlighting a useful opening/protection, oxidation method. This is then followed by examples of the oxidation of cyclic alkoxysilanes that are the products of either intramolecular radical cyclisation (1.2.2), hydrosilylation (1.2.3) or cycloaddition (1.2.4).

1.2.1. Oxidation conditions

In a large majority of cyclic alkoxysilanes the two by-stander groups attached to the silicon are methyl groups, and for these substrates, the basic [OxG], activated basic [OxH], and neutral oxidation conditions [OxC] have been used with great success. As is demonstrated later, the mildness of these oxidation conditions make them compatible with a wide range of other functional groups.

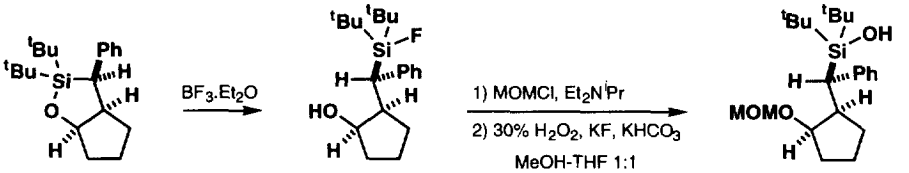
Changing the two by-stander groups attached to the silicon from methyl to phenyl dramatically changes the ease of oxidation. Fortunately, a direct comparison can be made between diphenyl and dimethyl alkoxysilanes since both have been used as tethers in intramolecular cycloaddition reactions.[40] The diphenyl derivative **40a** was reported to require more forcing conditions to undergo oxidation than the dimethyl derivative **40b** (reflux compared to room temperature) (Scheme 27).



R = Ph (75%, overall yield)
R = Me (40%, overall yield)

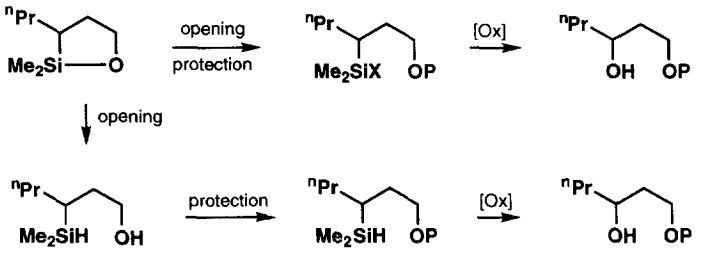
Scheme 27

Moreover, in the case of the di-*tert*-butyl derivative **41** it has been shown that although the cyclic alkoxysilane can be opened, the resulting monofluorosilane is completely resistant to oxidation (Scheme 28).[41] This is presumably because the steric bulk of the two *tert*-butyl groups and the benzyl substituent significantly retards the oxidation.



Scheme 28

As an alternative to the routine oxidation of cyclic alkoxysilanes to a diol, Tamao developed procedures whereby the ring is first opened with simultaneous protection of the oxygen and then the silicon group is oxidised, thus differentiating between the two alcohols.[42a] Thus, for MOM and benzoate (Bz) protections, this can be carried out directly in a simple two step protection / ring opening and oxidation protocol, whereas for TBDMS, THP and trityl the ring has to first be opened by reduction thus producing a free hydroxy group which is protected and a silane that can undergo oxidation (Scheme 29, Table 3).

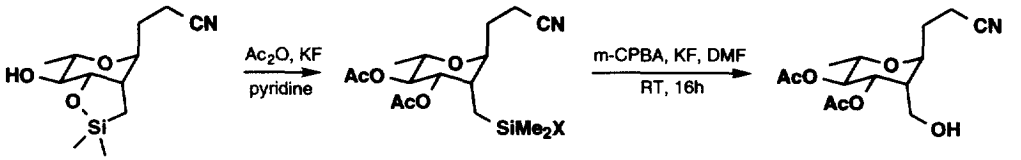


Scheme 29

Table 3. Opening of cyclic siloxanes.

Protecting Group	opening	protection	X	[Ox]
MOM		MOMCl, CsF	F	[OxH]
Ac		AcCl, $ZnCl_2$	Cl	[OxH]
Bz		BzCl, $ZnCl_2$	Cl	[OxH]
Piv		PivCl, $ZnCl_2$	Cl	[OxH]
TBDMS	DIBAL	TBDMSCl, Et_3N	H	[OxG]
THP	DIBAL	dihydropyran, p-TsOH	H	[OxH]
Trityl	DIBAL	TrCl, Et_3N	H	[OxH]

Fraser-Reid[42b] successfully applied this methodology though slightly modified to oxidise the cyclic alkoxysilane **42** to give a 9:1 mixture of the acetate protected silanol **43a** and the silylfluoride **43b** which together were cleanly oxidised using m-CPBA conditions [OxA] to the desired alcohol **44** (Scheme 30).

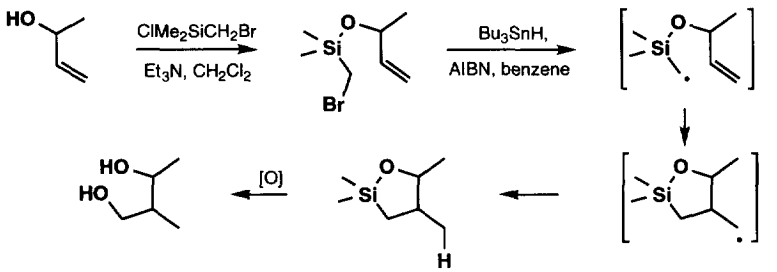


42 43a, X = OH 43b, X = F 44

Scheme 30

1.2.2. Radical cyclisations

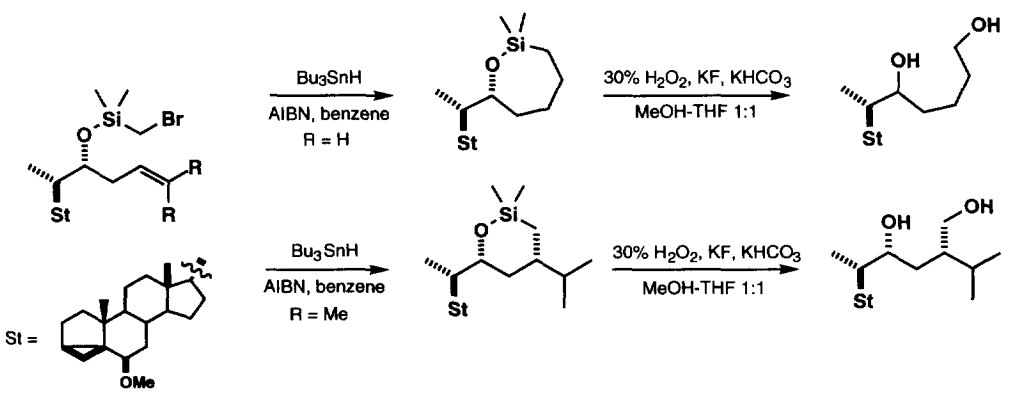
The intramolecular radical cyclisation of allylic (bromomethyl)silyl ethers was independently introduced by Stork[43] and Nishiyama[44] and it now occupies an important place in organic synthesis (Scheme 31). The original 5-*exo*-trig cyclisation has been developed and now examples of 5-*exo*-dig,[45] 6-*exo*-trig,[45f,46] 6-*endo*-trig[44,47] and 7-*endo*-trig[46] cyclisation have all been reported. A number of comprehensive reviews on these cyclisations have been published.[48]



Scheme 31

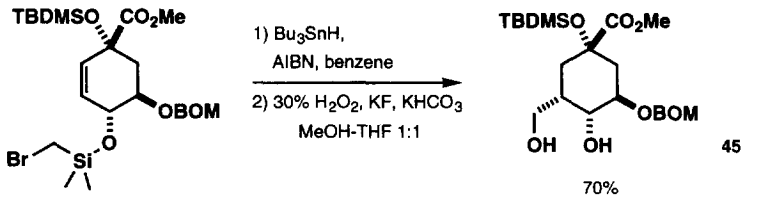
This sequence of formation of the silylether, radical cyclisation and oxidation to the diol is usually carried out without purifying the intermediates. Overall, this is a convenient method of introducing a hydroxymethyl group stereoselectively into a substrate containing a radical acceptor group with a free hydroxyl in the near vicinity.

The first area in which this methodology found utility was in the synthesis of steroid side chains,[43,49] an area which has been further developed by Koreeda, who demonstrated that the regioselectivity of the cyclisation is controlled by substitution of the double bond (Scheme 32).[46]



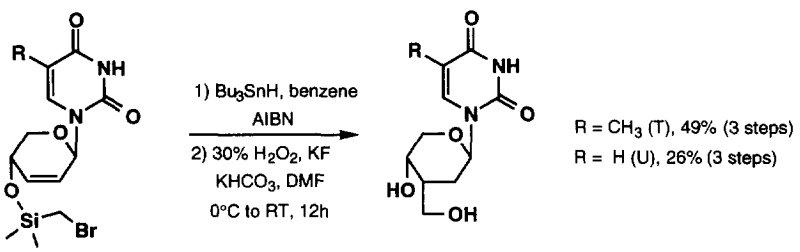
Scheme 32

More recently this methodology has been applied to the total synthesis of (±)-14-deoxyisoamijiol,[50] (-)-talaromycin A,[51] and to modify sugars,[52,53] pseudo-sugars[54,55] and nucleic acids.[56,57] These are particularly challenging substrates because of their sensitivity and the wide range of hydroxy protecting groups which have to withstand the oxidation conditions. Amongst protecting groups found to be stable under the basic non-fluoride activated conditions [OxG] are acetals, BOM (benzyloxymethyl ether), acetate and TBDMS, which is exemplified in the synthesis of pseudo-sugar **45** (Scheme 33).[55] However, under the fluoride-activated basic conditions [OxH], it has been reported that the TBDMS group is cleaved.[53a,c]



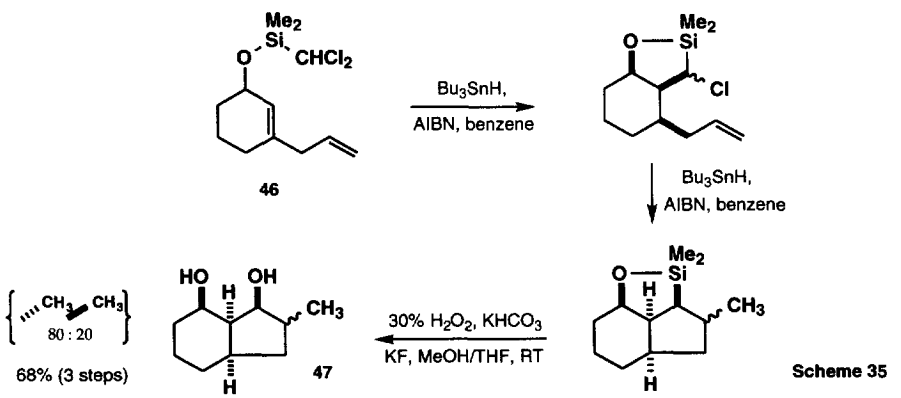
Scheme 33

The modified oxidation conditions [OxI], in which the usual MeOH/THF solvent has been exchanged for DMF, was used to oxidise a number of "pyranosyl" nucleosides containing thymine and uracil bases (Scheme 34).[57b]



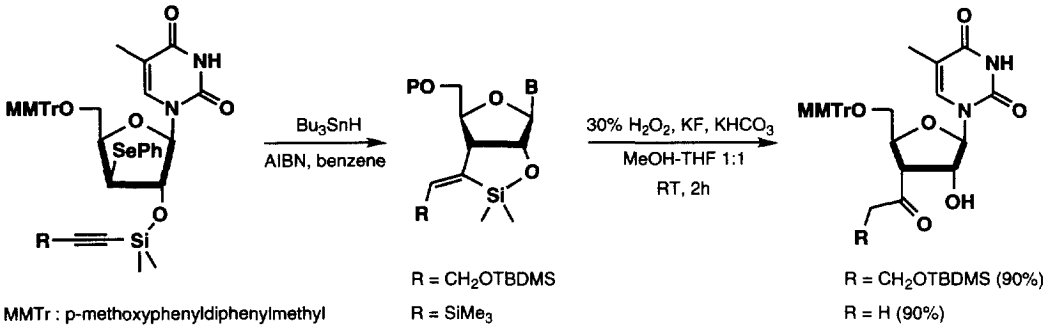
Scheme 34

(1-Bromovinyl)dimethylsilyl ethers can be used to introduce ketone functionality in a similar radical cyclisation.[58a] (Dichloromethyl)dimethylsilyl ethers[58b] **46** can either be oxidised after the initial cyclisation to give an aldehyde or, more interestingly, the second chlorine can be used to generate another radical centre which can then undergo further cyclisation. This was elegantly demonstrated by Tamao in his synthesis of the *cis*-hydrindan system **47** (Scheme 35).[58b]



Scheme 35

An alternative strategy introduced by Stork[59] is the cyclisation of radicals onto silylalkynes, to produce a vinylsilane that can be oxidised to a ketone. This strategy was applied by Chattopadhyaya[60] to synthesize 2' and 3'-C-branched nucleosides. Interestingly, in this case a TBDMS protected primary hydroxy group was not cleaved, reflecting the increased reactivity of the vinylsilane system to oxidation conditions (Scheme 36).



MMTr : p-methoxyphenyldiphenylmethyl

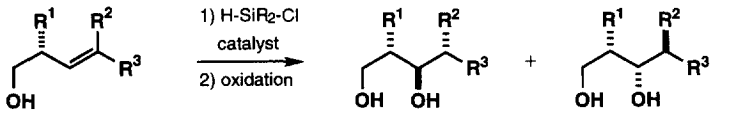
R = $CH_2OTBDMS$
R = $SiMe_3$

R = $CH_2OTBDMS$ (90%)
R = H (90%)

Scheme 36

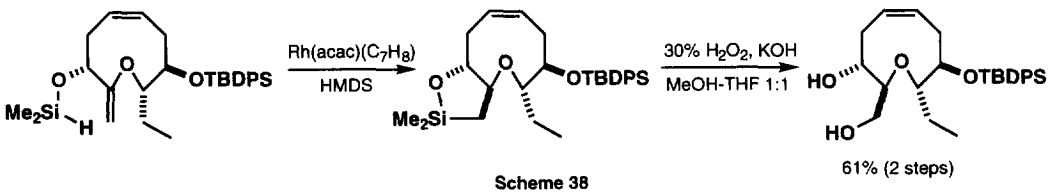
1.2.3. Intramolecular hydrosilylations

Intramolecular hydrosilylations have found less use in synthesis,[61-65] however they can be a useful alternative to radical cyclisations. The silane group is similarly tethered to an allylic alcohol and then treated with a catalyst to promote the hydrosilylation and the product oxidised to the diol. It should be noted that intramolecular hydrosilylation gives complementary regioselectivity to the intermolecular hydroboration of the same allylic or homoallylic alcohol substrates (Scheme 37).[61b,62]



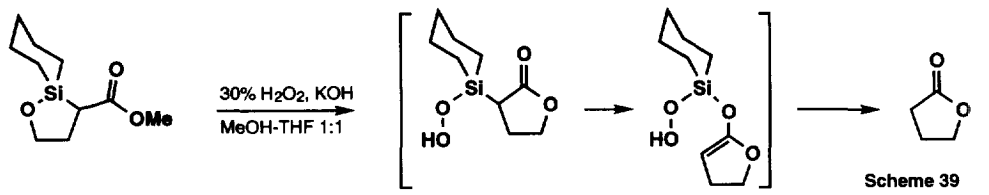
Scheme 37

An example of the use of this methodology by Holmes[63] was his studies towards the synthesis of the *Laurencia* natural product obtusenyne. The hydrosilylation was selective for the *trans* product and a $^tBuPh_2Si$ ether withstood the basic oxidation conditions [OxJ] which used potassium hydroxide as the base instead of a hydrogen carbonate salt (Scheme 38).



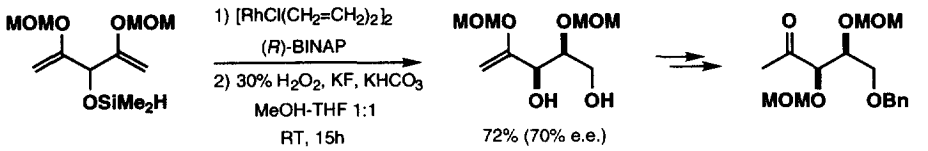
Scheme 38

During an extensive study[64] into the effects of the catalyst and silyl group upon the enantioselectivity of intramolecular hydrosilylation reactions of allylic alcohol derivatives, Bosnich showed that oxidation of a silyl group α to a carbonyl led to desilylation and not to the desired α-hydroxyester[20a,b] (Scheme 39).



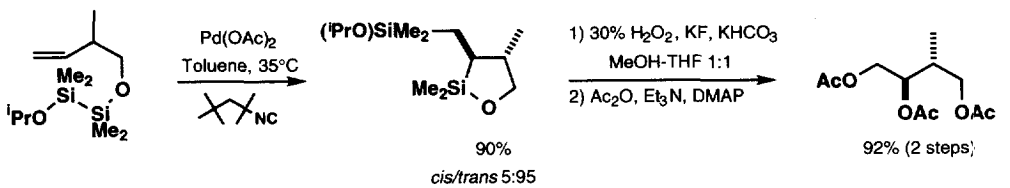
Scheme 39

These asymmetric intramolecular hydrosilylations have been elegantly utilised in the desymmetrisation of *meso* substrates giving ready access to enantiomerically enriched polyhydroxylated fragments (Scheme 40).[65]



Scheme 40

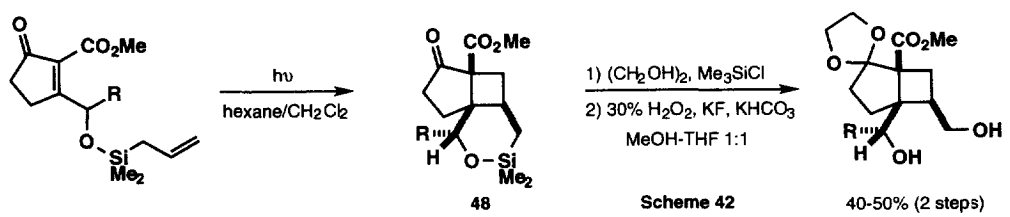
An interesting extension of intramolecular hydrosilylation is intramolecular bis-silylation in which two silicon groups are added across a double bond.[66] Upon oxidation, this results in a triol which allows easy access to polypropionate fragments in racemic series (Scheme 41).[66a]



Scheme 41

1.2.4. Intramolecular cycloadditions

The use of silyl groups to tether two partners of a cycloaddition reaction together is not limited to bis-silylether linkages, with a number of examples of [4+2],[40,67] [5+2],[68] [2+2][69] and [3+2][70] cycloaddition reactions being reported on tethered allyl and vinylsilanes. In the case of the cycloaddition of vinylsilanes, a five membered ring alkoxysilane is produced whereas with allylsilanes the result is a six membered ring. In the example below of a [2+2] cycloaddition, direct oxidation of the ketone **48** led to Baeyer-Villiger oxidation, so a strategy invoking prior ketal protection was employed (Scheme 42).[69]



48

Scheme 42

40-50% (2 steps)

2. Halosilanes as masked hydroxy groups (X = F, Cl)

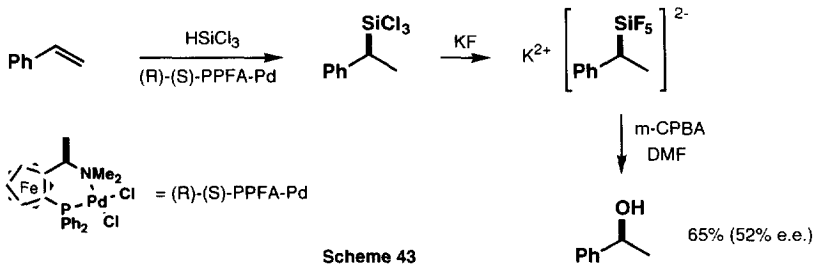
The trichlorosilyl group is most commonly introduced into a molecule by the hydrosilylation of an alkene or an alkyne with trichlorosilane.[71] In addition there are a number of examples of the Diels Alder reaction with vinyltrichlorosilane and ethynyltrichlorosilane which have been reported.[72] Once the trichlorosilyl group has been introduced into a molecule, it can either be :

- converted to the pentafluorosilicate and then oxidised,
- converted to the trifluorosilane and then oxidised,
- oxidised directly, or
- treated with an alcohol to form an alkoxysilane and then oxidised.[32-35]

The last of these options has already been discussed (see section 1.1.2), and therefore this section will limit itself to a brief discussion of the oxidation of pentafluorosilicates, the oxidation of trifluoro, difluoro and fluorosilanes and finally, the direct oxidation of trichlorosilanes.

2.1. The oxidation of pentafluorosilicates

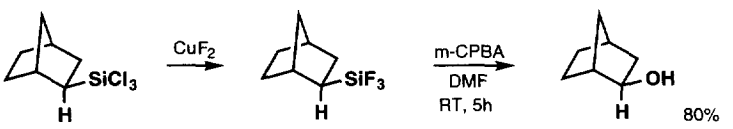
The oxidation of pentafluorosilicates has been reviewed extensively[73] and is principally of mechanistic interest. The pentafluorosilicate is most commonly generated by the fluorination of trichlorosilane with five equivalents of potassium fluoride and oxidation is carried out using m-CPBA in DMF.[9,71,74] The reaction is extremely sensitive to changes in the solvent, and addition of fluoride salts significantly retards the reaction and can even stop it. As with all other C-Si to C-O bond oxidations, it has been proven to occur with retention of configuration at the carbon centre (Scheme 43). This sequence of hydrosilylation, fluorination and oxidation has been carried out in the presence of esters and isolated double bonds.



Scheme 43

2.2. The oxidation of trifluorosilanes, difluorosilanes and fluorosilanes

Reaction of an excess of copper fluoride with a trichlorosilane cleanly exchanges the chlorines to give the trifluorosilane which then readily undergoes oxidation by m-CPBA in DMF. Again, the oxidation occurs with retention of configuration at the carbon centre (Scheme 44).[9,72]

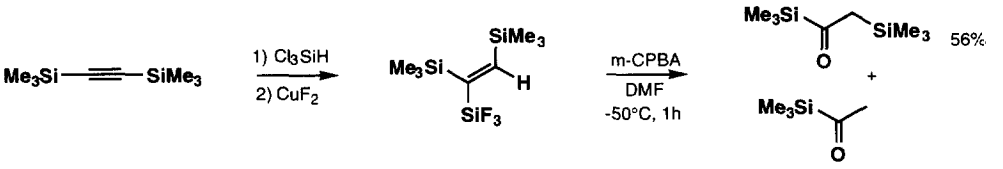


Scheme 44

These trifluorosilanes are more reactive than the corresponding pentafluorosilicates, the reaction being strongly exothermic upon addition of the oxidant. This is further demonstrated by the oxidation of the sterically hindered (2-methyl-2-phenylpropyl)trifluorosilane into the corresponding alcohol in good yield,[9] a reaction that does not proceed with the corresponding pentafluorosilicate (Scheme 45).[74]

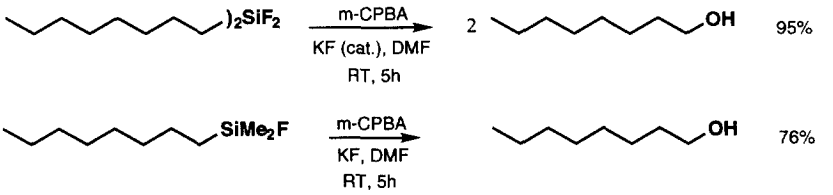
Scheme 45

Hydrosilylation of alkynes with trichlorosilane, followed by halide exchange and then oxidation leads to the corresponding carbonyl compounds. These vinyltrifluorosilanes are even more reactive than the saturated substrates with reactions occurring at -50°C.[72] This procedure can be carried out on alkynes bearing trimethylsilyl groups. However, significant amounts of desilylated methyl ketones were also isolated as unwanted secondary products (Scheme 46).



Scheme 46

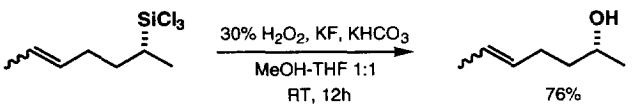
An alternative oxidising agent is trimethylamine-N-oxide which reacts easily at room temperature to give the alcohol with retention of configuration at the carbon centre.[29] m-CPBA oxidation of difluorosilanes requires the presence of a catalytic amount of potassium fluoride, and oxidation of fluorosilanes requires the presence of an excess of potassium fluoride (Scheme 47).[9]



Scheme 47

2.3. The oxidation of trichlorosilanes

Trichlorosilanes are oxidised in low yields using m-CPBA in the presence of an excess of potassium fluoride.[9] A much improved method uses hydrogen peroxide as the oxidising agent with potassium fluoride and potassium bicarbonate in large excess (6 equivalents)[OxH] (Scheme 48).[1c,75]



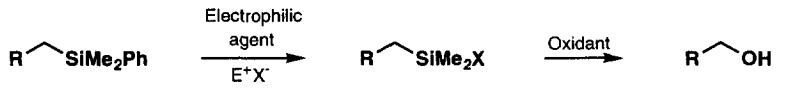
Scheme 48

3. Arylsilanes as masked hydroxy groups (X = Ar)

3.1. Oxidation of the $PhMe_2Si$ group

In a seminal paper published in 1984, Fleming[2a] described a two-step procedure (procedure K) which converted the C-Si bond of a $PhMe_2Si$ group into the corresponding C-OH bond (Scheme 49). As explained above (Section II.1), protodesilylation using dry HCl, CF_3CO_2H,[66] HBF_4-OEt_2 or the superior BF_3-2AcOH affords the corresponding fluorosilane which is isolated and then directly oxidised to the alcohol using either AcOOH in AcOH, m-CPBA and Et_3N, or H_2O_2 and KF. The protodesilylation is generally carried out in CH_2Cl_2 and the oxidation is performed either in ether (m-CPBA), DMF (m-CPBA) or neat (AcOOH in AcOH). It is also noteworthy that an excess of peracid is always used in order to ensure that all the groups on silicon will migrate, and that peracetic acid is recommended for oxidations on a large scale.

Then, in the later report in 1987,[2b] the oxidation was simplified with three different one-step procedures being reported (procedures L, M and N). The first two involved the direct mixing of the silicon substrate with an electrophile, either $Hg(OAc)_2$ (L) or Br_2 (M), in AcOOH and AcOH as solvent with a catalytic amount of H_2SO_4 (present in commercial peracid). The third method (N) is a slight modification of the second in so much as the electrophilic bromine is generated *in situ* from the reaction of KBr and peracetic acid. These different conditions are now widely used and some refinements have been made which will be discussed later.



procedure K (2 steps) : Electrophilic agent : HBF_4 or BF_3-2AcOH, or CF_3CO_2H or ICl
Oxidant : (AcOOH in AcOH, H_2SO_4 (cat.) or m-CPBA or H_2O_2)
Base : NEt_3 or KF

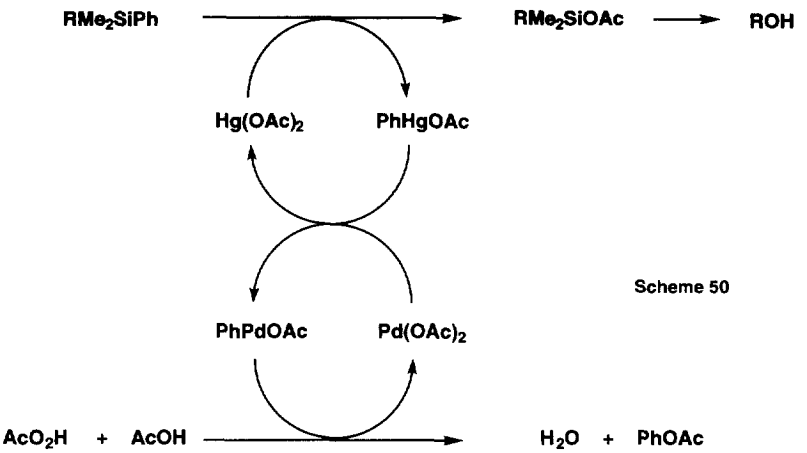
procedure L (one pot) : Electrophilic agent : $Hg(OAc)_2$
Oxidant : AcOOH in AcOH, H_2SO_4 (cat.)

procedure M (one pot) : Electrophilic agent : Br_2
Oxidant : AcOOH in AcOH, H_2SO_4 (cat.)

Scheme 49

procedure N (one pot) : Electrophilic agent : KBr + AcOOH
Oxidant : AcOOH in AcOH, H_2SO_4 (cat.), NaOAc (buffer)

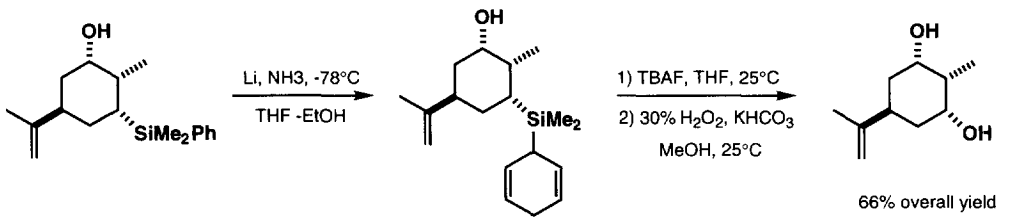
A catalytic procedure using only $Hg(OAc)_2$ and $Pd(OAc)_2$ has also been reported,[2b,8] the former initiates the electrophilic reaction on the phenyl ring of $PhMe_2Si$ and the latter transforms the arylmercury intermediate into an arylpalladium which is then oxidised by the peracid (Scheme 50). A catalytic cycle involving only the mercury salt is not possible because arylmercury compounds are not oxidised by peracids. This reduces the amount of metal required with only 0.2 eq. of $Hg(OAc)_2$ and 0.1 eq. of $Pd(OAc)_2$ being used. However, the method is limited to those silanes which are readily oxidised because of the competition with the palladium catalysed decomposition of peracetic acid.



Scheme 50

The optimized oxidation conditions for the $PhMe_2Si$ group described above have also been extended to *p*-TolylMe_2Si, Ph_3Si and Ph_2MeSi groups (see also 3.5) and there is no obvious reason why they could not be used with other types of arylsilanes.

Another approach to the oxidation of the $PhMe_2Si$ group has recently been proposed by Taber,[76] which involves the Birch reduction of the phenyl ring into the corresponding 1,4-cyclohexadiene which is then easily displaced by a fluorine source. The resulting fluorosilane is then easily oxidised to the desired alcohol using one of the procedures described before (Scheme 51). This method is convenient and can be applied to substrates possessing a remote double bond. This transformation has not been carried out in the presence of the more reactive double bond of an allylsilane.

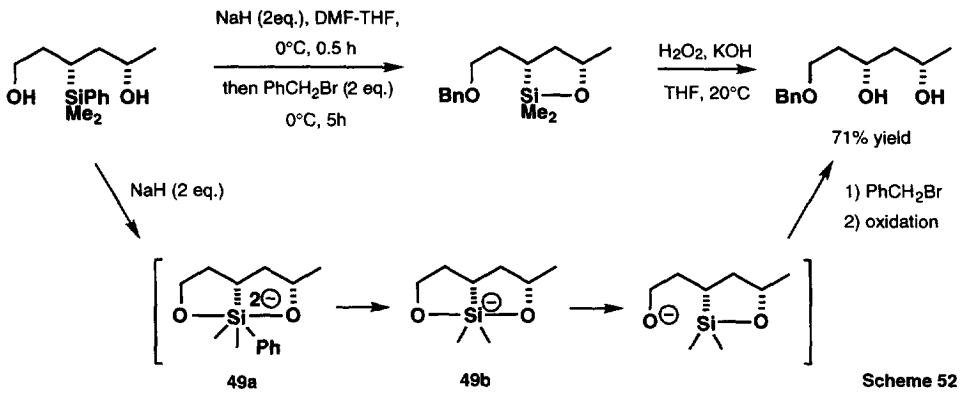


Scheme 51

A modification of the initial Fleming's one pot procedure has been proposed by Ley[77] and applied to a complex substrate in a synthesis of azadirachtin (see also chapter 3.4). It was found that mercury acetate was particularly sluggish for the mercuri-desilylation of a sterically hindered phenyltrialkylsilane. Thus, replacement of $Hg(OAc)_2$ with $Hg(TFA)_2$[78] caused a more rapid displacement of the phenyl ring (10 min), after which peracetic acid was added at 10°C, oxidising the carbon-silicon bond in good yield. Other electrophilic reagents that have been used for the cleavage of the Si-Ph bond include ICl or ICl / Ag^+ which Ito recently introduced in order to prevent Friedel-Crafts-type reactions which sometimes occur during protodesilylation with CF_3CO_2H.[66c,79]

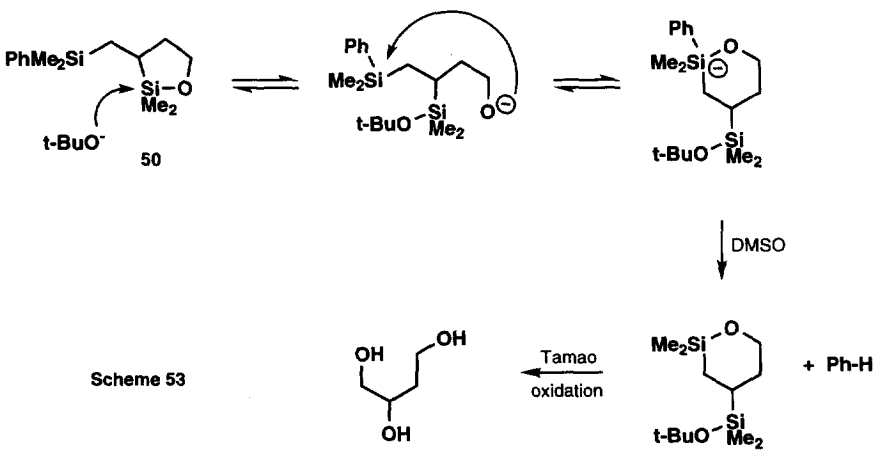
With specific substrates such as γ-hydroxysilanes, the phenyl group on silicon can also be removed using nucleophilic conditions. This method has been applied successfully by Harada[80] and Fleming[4b,81] to the stereocontrolled synthesis of polyhydroxylated fragments. Deprotonation of the hydroxy groups and addition of benzyl bromide produced the corresponding benzyl protected alkoxysilane which was then easily oxidised using Tamao conditions (Scheme 52). It was suggested that the mechanism involves the initial formation of the

intermediate hexaco-ordinate species **49a**, followed by loss of the phenyl group to give a pentaco-ordinate species **49b** which is then benzylated at the less hindered end.[80]



Scheme 52

It is noteworthy that such a strategy has only been observed as an intramolecular process and that the direct intermolecular nucleophilic displacement of the phenyl ring from silicon is known to be slow. Ito reported that the intermolecular cleavage of the Si-Ph bond in $PhMe_2Si(n\text{-}Bu)$ using *t*-BuOK in DMSO was much slower than the intramolecular displacement of the phenyl group of the cyclic alkoxysilane **50**, assisted by a neighbouring alcoholate function (Scheme 53).[66]



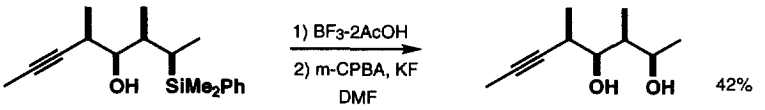
Scheme 53

3.2. Compatibility of the oxidation with various functionalities

- *Multiple bonds*

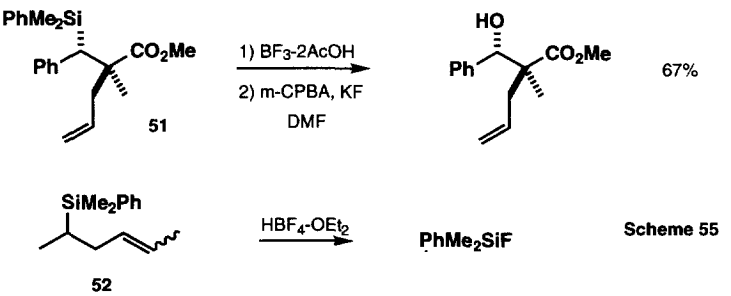
Fleming's oxidation is compatible with multiple bonds such as C=O bonds but is usually incompatible with C=C double bonds. Except in a few cases, alkenes and alkynes do react with electrophiles such as proton, mercury ions or bromine during the preliminary protodesilylation. The exceptions are difficult to predict because the

structure of the substrate has a large influence on the success of the oxidation. An example of a C-Si oxidation in the presence of a triple bond has been reported by Fleming,[4b] although in somewhat moderate yield (Scheme 54).



Scheme 54

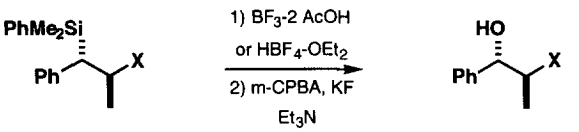
When considering the compatibility of alkenes, it is necessary to pay attention to the amount of substitution on the double bond since more highly substituted double bonds are more reactive towards electrophiles. Therefore, whereas the terminal double bond in **51** survives the protodesilylation conditions, the disubstituted double bond in **52** does not (Scheme 55).[8] It is noteworthy that the oxidation step itself, involving the electrophile m-CPBA, is not problematic since the peroxide rearrangement (Scheme 5) appears to be much faster than epoxidation.



Scheme 55

Many examples in the literature have shown that isolated phenyl rings, even those with donor groups (OMe), do not react under the protodesilylation, mercuri-desilylation or bromo-desilylation conditions.

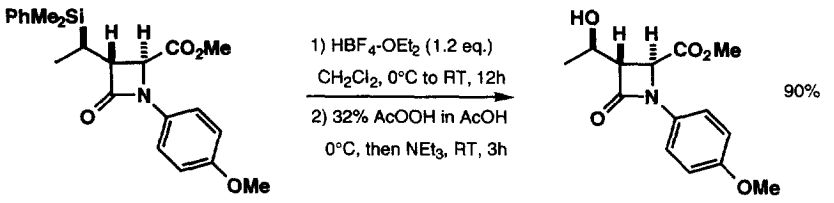
Hetero multiple bonds are usually not affected by the protodesilylation or the oxidation of the $PhMe_2Si$ group, with esters,[82] carboxylic acids,[83] primary and tertiary amide,[8] nitrile,[8] lactones,[84] lactams,[85] acetates and benzoates[86] all being compatible. In the examples shown below (Scheme 56), the oxidation was carried out using the two-step [OxK], but there is nothing to suggest that the one-step procedures would not work.[8]



X = CO_2H	X = CO_2H (89%)
X = CO_2Me	X = CO_2Me (75-85%)
X = $CONH_2$	X = $CONH_2$ (81%)
X = CONEt2	X = CONEt2 (88%)
X = CH_2CN	X = CH_2CN (64%)
X = CN	X = CN (80%)
X = COPh	X = COPh (49%)

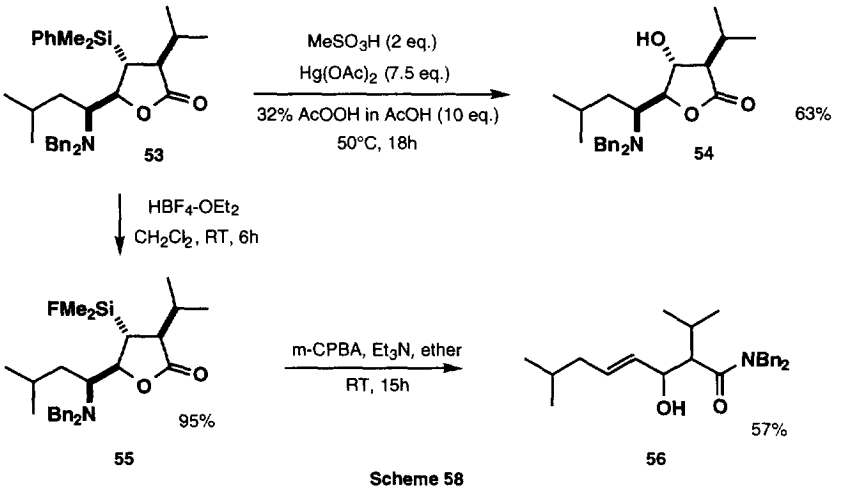
Scheme 56

Palomo[85a] and Hart[85b] showed that protected lactams are compatible with the oxidation conditions (Scheme 57), however, oxidation of the unprotected lactam was not as clean.



Scheme 57

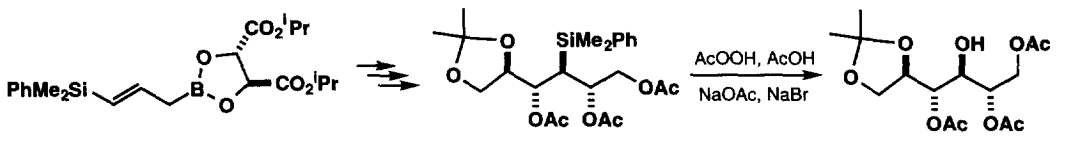
Similarly, Hoppe[87] found during the unmasking of a $PhMe_2Si$ group on the lactone **53** that although protodesilylation gave the expected fluorosilane **55**, the subsequent oxidation with m-CPBA gave the ring opened amide **56**. Fortunately, quaternization of the amine using $MeSO_3H$ followed by mercuri-desilylation and acidic oxidation gave the desired lactone **54** in respectable yield (Scheme 58). Furthermore, the authors found that debenzylation and quaternization prior to the oxidation step afforded the product in even better yield.



Scheme 58

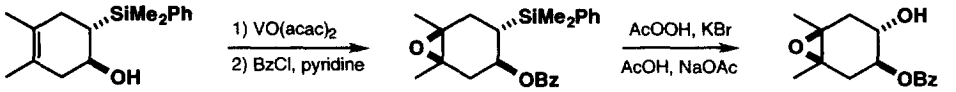
- *Ethers, Cyclic Ethers, Epoxides and Acetals*

Aromatic ethers are not affected by the oxidation conditions as illustrated by the use of PMP (*p*-methoxyphenyl) as protective group of the nitrogen lactam (Scheme 57).[85a] Acetals are stable under these conditions[8] and thus allow selective protection of polyols before the oxidation of the C-Si bond, as illustrated by Roush's methodology (Scheme 59).[88] [OxN] seems to be the most appropriate in this case.



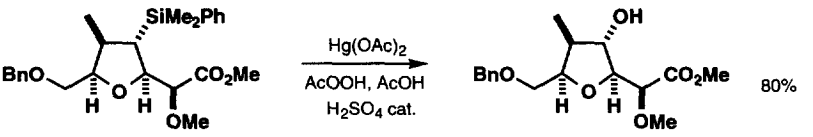
Scheme 59

Singleton[89] recently used the $PhMe_2Si$ group as a latent hydroxy group in order to selectively differentiate between two hydroxy groups, during the course of which he demonstrated that epoxides are stable to the buffered oxidative conditions of procedure N (Scheme 60).



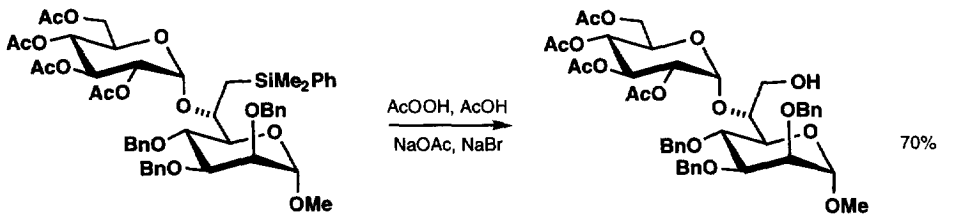
Scheme 60

Hydroxy tetrahydrofurans have been successfully prepared using the $PhMe_2Si$ as a masked hydroxy group, again showing the versatility and the compatibility of the method with a range of functionality (Scheme 61).[84b,90]



Scheme 61

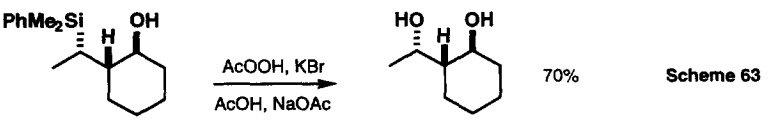
The oxidation of the $PhMe_2Si$ group on a disaccharide skeleton[91] is particularly relevant because of the multitude of acetate and benzyl hydroxy protecting groups, as well as an acetal and the glycosidic bond, all of which are not affected by the oxidation conditions N (Scheme 62). No Peterson elimination[92] was observed with these substrates using this procedure.



Scheme 62

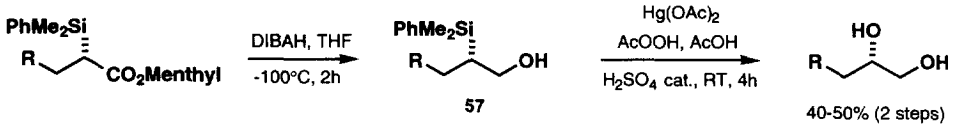
- *Alcohols and Polyols*

It is often desirable to be able to differentiate between the hydroxy functions in polyols and there are many examples where the $PhMe_2Si$ group has been oxidised in the presence of various hydroxy protecting groups to realise this objective[88,89] (see Scheme 59-62). However, it would be tedious if a hydroxy group always had to be protected and in many cases, hydroxy groups are found to be stable to the oxidation conditions[93] (Scheme 63).



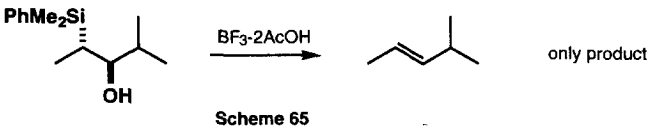
Scheme 63

Unfortunately, with β-hydroxysilanes, the acid-catalysed Peterson elimination can become a competing reaction, depending upon the substitution at the alcohol centre.[8] Hence, oxidation of the primary β-hydroxysilanes **57** using mercury acetate in AcOOH and AcOH ([OxL]) gave the expected 1,2-diols and no elimination products (Scheme 64).[94]



Scheme 64

However, upon exposure to protodesilylation ([OxK]), the secondary β-hydroxysilanes underwent elimination exclusively to afford the corresponding olefins (Scheme 65).[8] The oxidation conditions L used above are also unsuitable for the oxidation of *syn* or *anti* β-hydroxysilanes.[95]

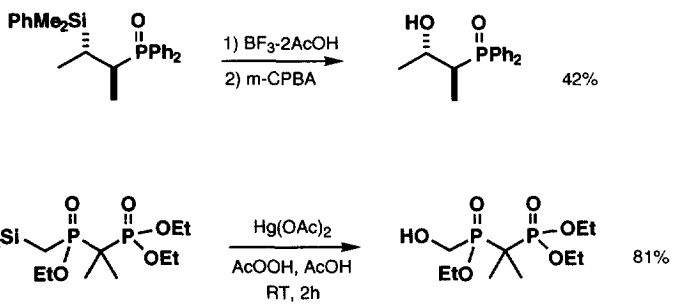


Scheme 65

However, Koreeda[96] and Fleming[8] have reported that secondary β-hydroxysilanes are oxidised to diols in good yields, using the buffered conditions N (see also section 3.4).

- *Phosphorus derivatives*

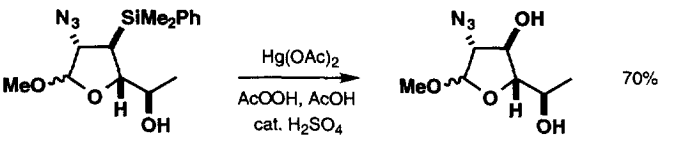
It has been established recently that the diphenylphosphine oxide group is compatible with the two-step $PhMe_2Si$ unmasking (Scheme 66).[97a] Interestingly, phosphonate and phosphonic acid monoesters also survive the one-pot conditions L, as demonstrated by Prashad et al.[97b]



Scheme 66

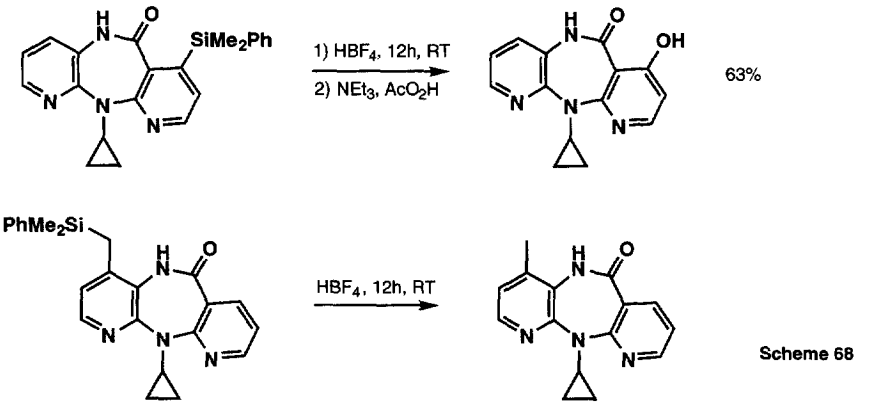
- *Miscellaneous functionalities*

Azido substituents were found to survive the oxidative conversion of the $PhMe_2Si$ group using [OxL],[98] nor did the presence of a catalytic amount of H_2SO_4 interfere with other functionalities present in the substrate (Scheme 67).



Scheme 67

Heterocycles such as pyridine are not affected by the oxidation conditions as illustrated by the studies of Proudfoot (Scheme 68).[99] Significantly, the cyclopropyl substituent was not opened under the oxidation conditions K (see section 3.3). However, it was shown that under protodesilylation conditions, the pyridine nitrogen was protonated which led to desilylation of a benzylic silyl group.



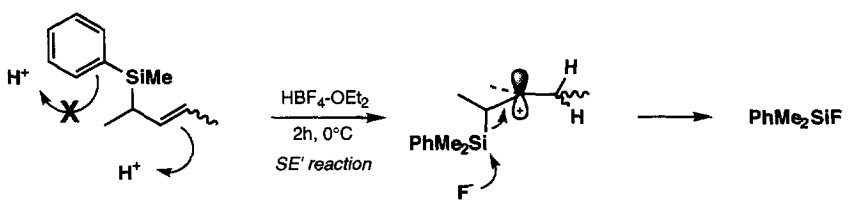
Scheme 68

3.3. Incompatibility of the oxidation with various functionalities

The incompatibility of various functions with the conditions of unmasking of the $PhMe_2Si$ group is most commonly a consequence of the strong electrophilic conditions needed to remove the aryl group and not the oxidation itself.

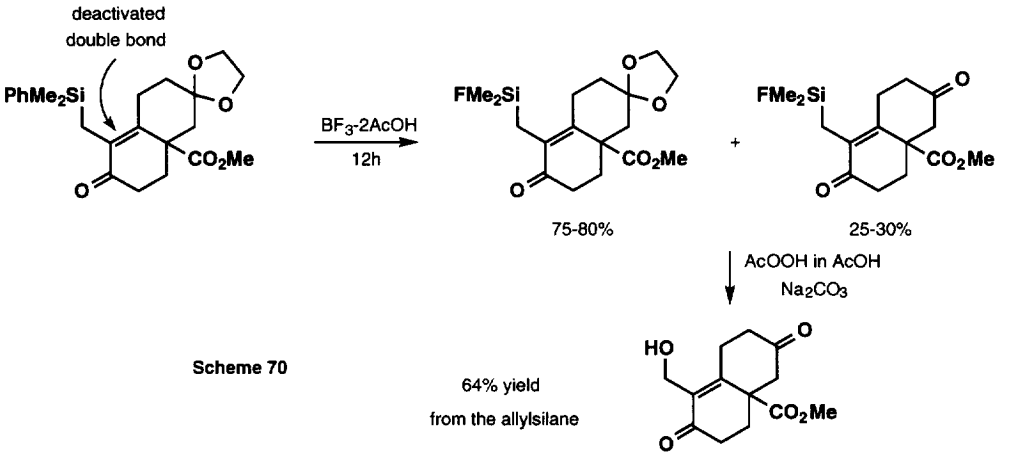
- *Allylsilanes*

Allylsilane double bonds are more reactive towards electrophiles than a phenyl group or an isolated double bond, due to the stabilization of the carbocation intermediate through hyperconjugation (β-silicon effect,[100] Scheme 69). Therefore, *the oxidative conversion of the C-Si bond of an allylsilane is usually not possible if $PhMe_2Si$ is used as a masked hydroxy group.* [8]



Scheme 69

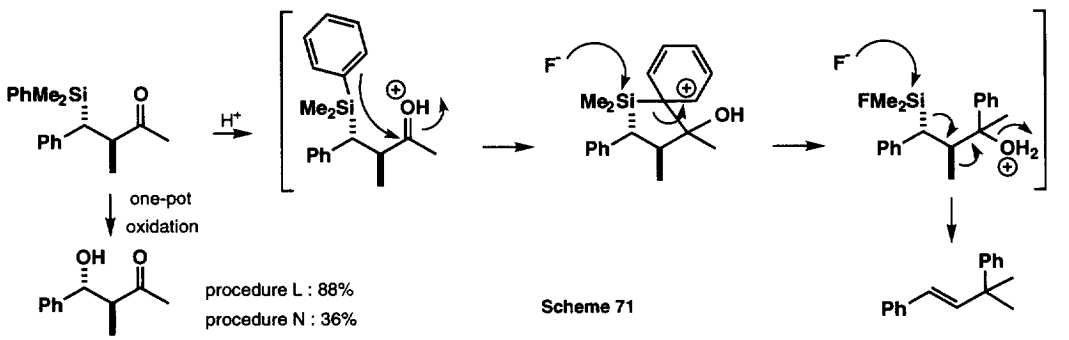
However, an exception to this "rule" has been reported by Fuchs[101] who showed that the oxidation of the $PhMe_2Si$ group of an allylsilane can be successful so long as the double bond is deactivated by conjugation with an electron-withdrawing carbonyl group (Scheme 70).



Scheme 70

- *Ketones*

Fleming's conditions usually enable the oxidation of the C-Si bond without the concurrent Baeyer-Villiger rearrangement.[8,36,102] However, in certain cases, more electrophilic ketones can undergo rearrangements such as the migration of the phenyl group onto the carbon centre of the carbonyl followed by migration of the methyl group and loss of the silicon.[8,66,93c] A similar rearrangement was observed by Fuchs[103] during the attempted oxidation of an advanced intermediate in the synthesis of phorbol. Fortunately, the one-pot procedures L-N do afford the desired alcohol in variable yield, the bromine-based method [OxN] being less efficient probably because of the α-bromination of the ketone (Scheme 71).[8]

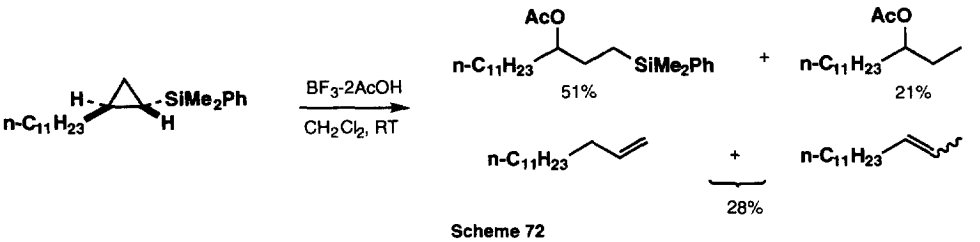


Scheme 71

- *Cyclopropanes*

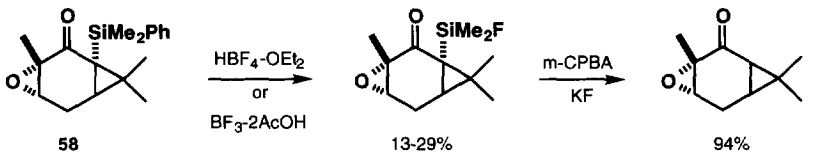
It is well known that cyclopropanes show a very similar reactivity to that of double bonds and consequently they are not compatible with the electrophilic conditions.[20c,104] The silicon group probably accelerates the electrophilic attack on the cyclopropane ring by stabilising the carbocation intermediate through hyperconjugation (Scheme

72).[105] Consequently, a $PhMe_2Si$ group on a cyclopropane cannot be converted into a OH group using the procedures described above (Scheme 49). Similarly, the homologous cyclopropylmethylsilanes cannot be converted into the corresponding cyclopropylmethanols.[20c,104a]



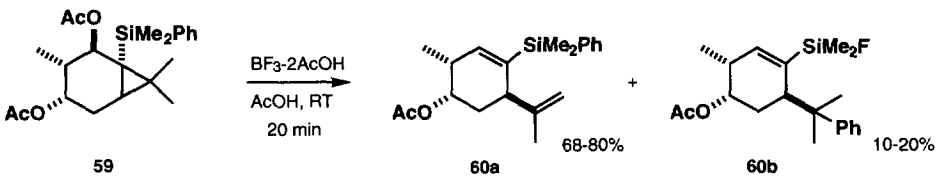
Scheme 72

Recent attempts by Fuchs[103] to protodesilylate the phenyldimethylcyclopropane **58** afforded a very low yield of the fluorosilane and oxidation led solely to the desilylated product and not to the desired alcohol (Scheme 73).



Scheme 73

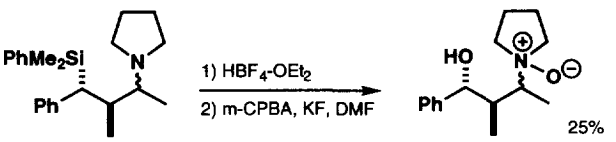
In order to avoid the very favourable desilylation of the α-silylketone, they repeated the oxidation starting from the acetate **59**. Rearrangement of the cyclopropyl group, followed partially by an *"ipso"* attack on the phenyl ring of $PhMe_2Si$, produced the vinylsilanes **60a** and **60b** (Scheme 74).[103]



Scheme 74

- *Amines and Sulfides*

Oxidation of the $PhMe_2Si$ group into a hydroxy group has been used several times in total synthesis of alkaloids and in all cases the amine function was recovered unchanged (see section 3.4).[106] However, as the example shows[8] (Scheme 75), there is a possibility of oxidising the amine to the amine-oxide function when using m-CPBA as oxidant. This should be taken into account in the planning of a synthesis, though it is possible that the amine function can be regenerated by reduction of the amine-oxide. A more satisfactory solution is to use H_2O_2 as the oxidant which is less likely to oxidise the amine.



Scheme 75

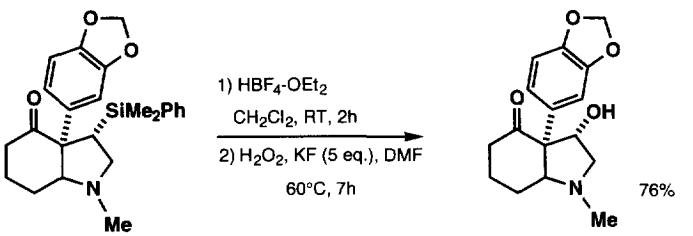
Similarly, sulfides should be converted into the corresponding sulfoxides in the above conditions and therefore are not compatible with the $PhMe_2Si$ group oxidation.[8] The resistance of the sulfoxide towards the oxidation conditions has not been tested so far but is unlikely. Although Takaki recently prepared some β-silylsulfoxides, the oxidation of the C-Si bond was always performed after the removal of the sulfoxide moiety.[107]

3.4. Utilisation of $PhMe_2Si$ group as a hydroxy equivalent in total synthesis

Recent applications of the C-Si oxidation to the total synthesis of complex natural products indicate that this method has now been recognized as a powerful tool for organic synthesis. The fact that the $PhMe_2Si$ group is the most generally employed for this purpose lies in its excellent stability towards a large variety of reagents. It is also easily introduced by silyl-cupration, hydrosilylation, and some other less utilised methods.[4,5]

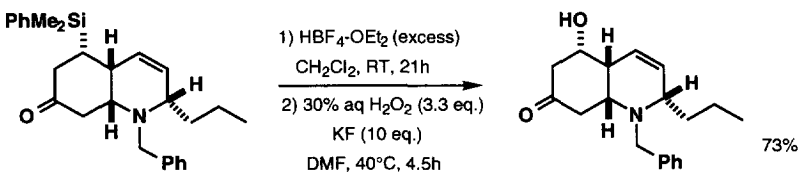
- *Alkaloids*

Overman's[108] formal total synthesis of (+)-6a-epipretazettine is a good illustration of the compatibility of the H_2O_2 oxidation of the $PhMe_2Si$ in a molecule containing a tertiary amine and a ketone (Scheme 76).



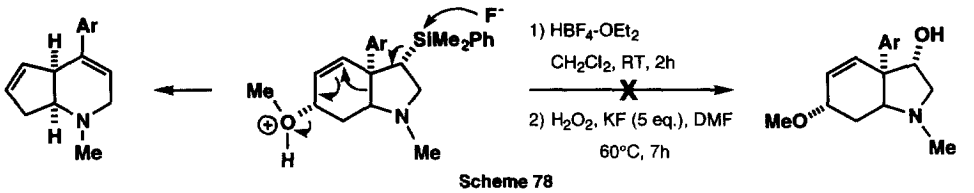
Scheme 76

Similarly, Polniaszek[109] in his total synthesis of the decahydroquinoline alkaloids (±)-195A and (±)-2-*epi*-195A found that the oxidation conditions were compatible with a benzyl protected amine and an isolated double bond (Scheme 77). This clearly shows that using H_2O_2 as the oxidant, one can avoid the overoxidation of the nitrogen function.



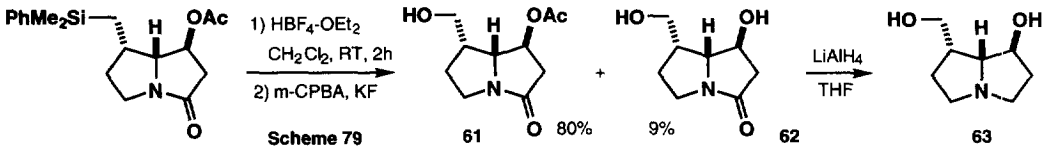
Scheme 77

However, the studies of Pearson[110] on a very similar skeleton to that of Overman shows that there is always the possiblity of unforseen rearrangements (Scheme 78). In this case, the acidic conditions required for the protodesilylation initiated a Wagner-Merwein rearrangement and even after transformation of the allylic ether functionality into the corresponding unsaturated ketone, the C-Si oxidation failed.



Scheme 78

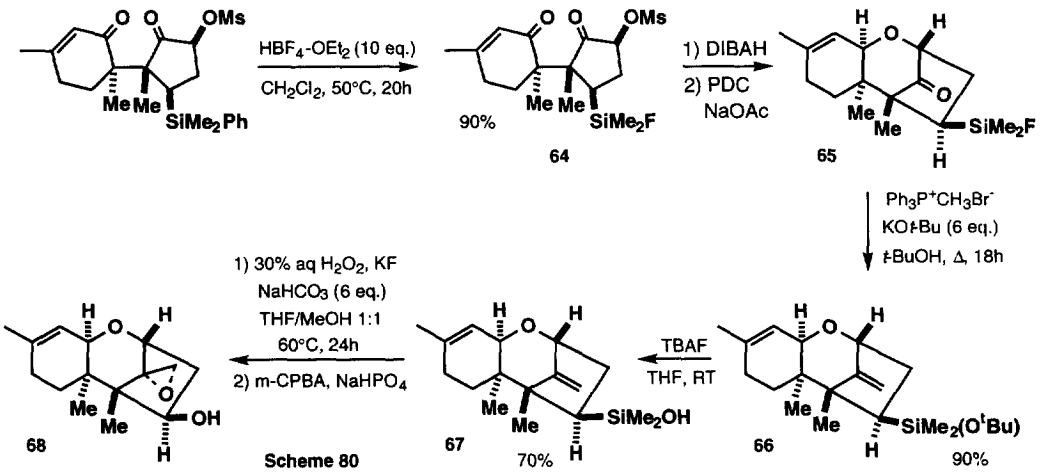
Oxidation of the C-Si bond attached to a bicyclic lactam demonstrated its compatibility with Fleming's conditions, though partial deacetylation was observed giving a mixture of the acetate **61** and the diol **62**. Although these were contaminated with *m*-chlorobenzoic acid, direct reduction of the lactam using $LiAlH_4$ gave (-)-dihydroheliotridine **63** (Scheme 79).[111]



Scheme 79

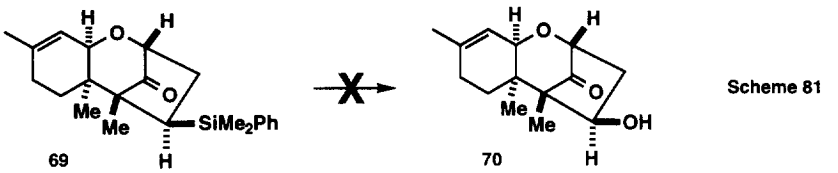
- *Sesquiterpenes*

The total synthesis of sesquiterpenes has probably been the most challenging area in which the use and oxidation of the $PhMe_2Si$ group has been applied, because of the high complexity of the molecules and the sensitivity of the functional groups. During the synthesis of (±)-trichodermol, Pearson[112] found that an isolated double bond, two different ketones and more significantly a mesylate withstood the protodesilylation and the formation of the fluorosilane. The displacement of the fluorine by *t*-BuOK during the Wittig reaction gave the alkoxysilane which would not undergo oxidation because of steric hindrance of the *t*-BuO group. However, when **66** was treated with TBAF in water, the alkoxysilane was converted to the fluorosilane which was hydrolysed in the reaction medium to the silanol **67**, isolated along with a small amount of the expected fluorosilane. Finally, oxidation of the silanol was carried out using [OxH] to give (+/-)-trichodermol **68** (Scheme 80).



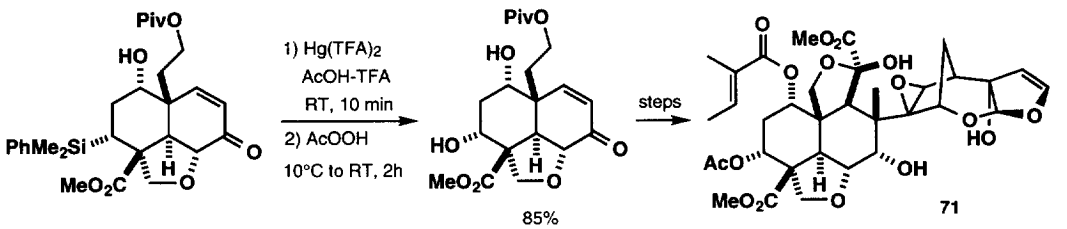
Scheme 80

Several attempts at oxidation of the $PhMe_2Si$ group had been made at different stages of the synthesis, but with little success. For example, direct oxidation of the $PhMe_2Si$ group in **69** did not afford the desired alcohol **70** even when the double bond had been brominated prior to the oxidation (Scheme 81). It was suggested that the sensitivity of the trichotocene ring system towards acidic conditions was at the origin of this failure. Oxidation of **65** (H_2O_2, KF, $NaHCO_3$, THF-MeOH 1:1) did afford the required alcohol but only on a small scale, and attempts to scale up this reaction resulted in the Baeyer-Villiger reaction of the cyclopentanone ring. Finally, although oxidation of **64** using the same conditions gave the alcohol in 80% yield, this strategy was found to be inconvenient, requiring protection and deprotection of the new alcohol function (Scheme 80).



Scheme 81

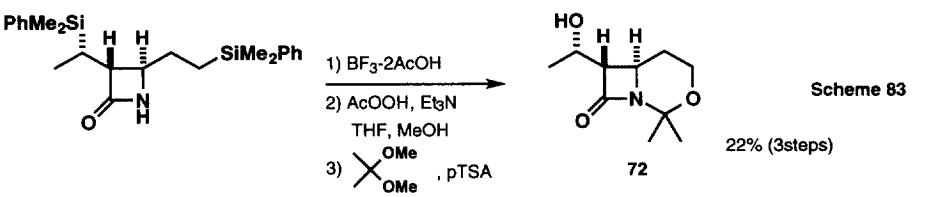
Similarly, the total synthesis of azadirachtin **71** reported by Ley[77] illustrates well the versatility of the $PhMe_2Si$ group and the compatibility of the oxidation conditions with many different functional groups such as ethers, alcohols, esters and an α,β-unsaturated ketone. The large steric hindrance around the $PhMe_2Si$ group led the authors to introduce a modification to Fleming's original conditions. Oxidation using $Hg(OAc)_2$ was found to be rather sluggish, but it could be successfully replaced by the more reactive $Hg(TFA)_2$. The premixing of the substrate with AcOH/TFA/$Hg(TFA)_2$ ensured a rapid displacement of the phenyl ring before the oxidation with the peracid which occurred in excellent yield (Scheme 82).



Scheme 82

- *Penicillin*

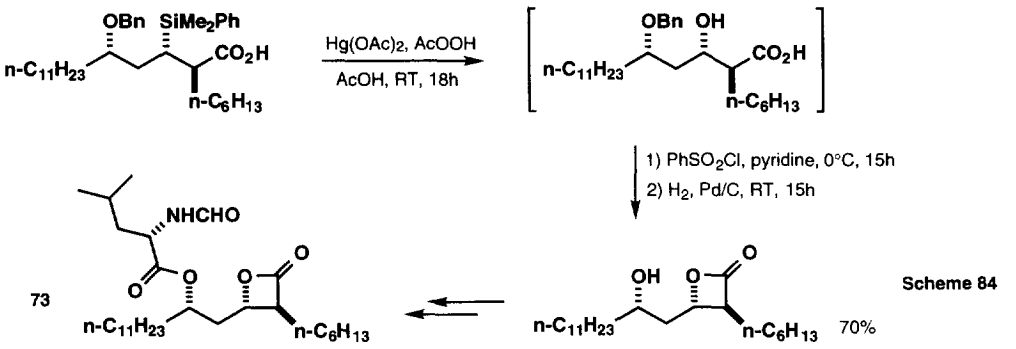
During Fleming's synthesis[113] of thienamycin **72** it was demonstrated that the double oxidation of the $PhMe_2Si$ group occurred cleanly by the two step procedure to give the corresponding diol in the presence of a β-lactam (Scheme 83). Subsequently, the same oxidation conditions were used by Palomo[85a] to unmask a $PhMe_2Si$ group in a penicillin derivative (Scheme 57).



Scheme 83

• *Esterase Inhibitor*

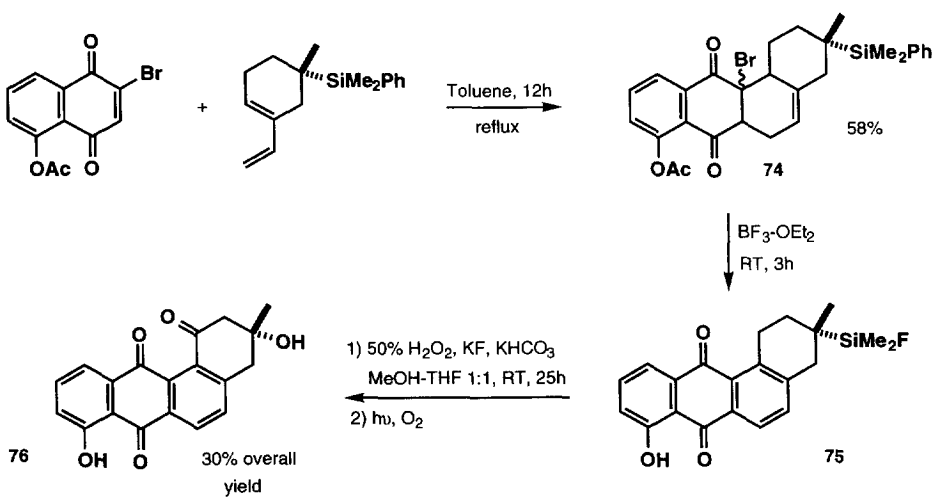
During the total synthesis of tetrahydrolipstatin **73**, the β-lactone ring of this esterase inhibitor is generated in the latter stages of the synthesis from the corresponding α-hydroxyacid obtained via the oxidation of a C-Si bond.[114] It is noteworthy that the hydroxy equivalent is not isolated but directly converted into the β-lactone and that benzyloxy and carboxylic groups were not affected by the mercury acetate mediated oxidation of the silicon group (Scheme 84).



Scheme 84

• *Anthracyclines*

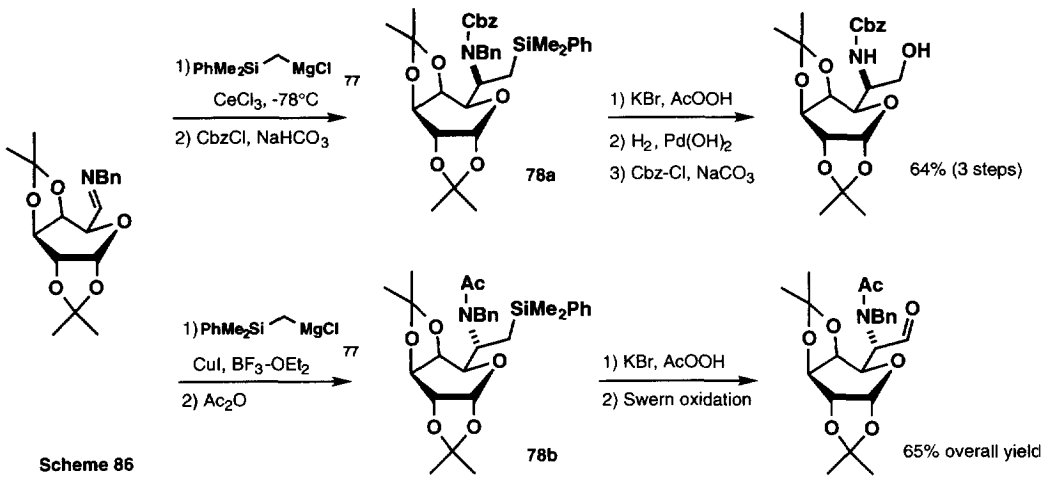
Recent progress in the field of anthracyclines has also been possible using the $PhMe_2Si$ group as a masked hydroxy group. Conversion of the tertiary silicon moiety in **74** gave a good yield of the desired alcohol. It is noteworthy because the synthesis of tertiary alcohols by oxidation of a C-Si bond are rare.[8] BF_3-OEt_2 was used instead of the usual BF_3-2AcOH. This allowed a four-step sequence to be carried out in one pot : deacetylation, dehydrobromination, aromatisation and finally protodesilylation to furnish the fluorosilane **75**. This latter was then oxidised into the desired alcohol which on photochemical oxygenation produced (+/-)-tetrangomycin **76** (Scheme 85).[115]



Scheme 85

- *Sugar and Sugar derivatives*

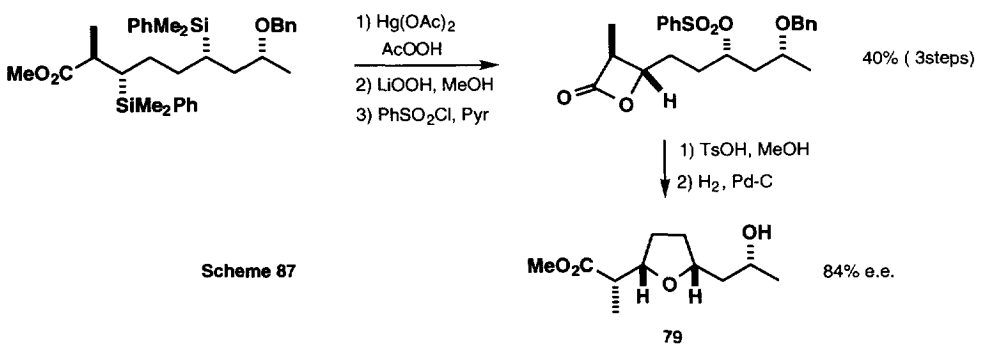
The oxidative unmasking of the $PhMe_2Si$ group has also been found to be very convenient in carbohydrate chemistry where sensitive functional groups require that mild conditions are used. In the synthesis of the precursors of the aminosugars destomic acid and lincosamine, van Boom[116] used the $CeCl_3$ or CuI/BF_3-Et_2O catalysed addition of the silyl Grignard reagent **77** to give diastereoselectively the aminosilyl intermediates **78a** and **78b**. The mild procedure N was then employed to oxidise the $PhMe_2Si$ group in the presence of acetonides, acetal and carbamate functions (Scheme 86). These authors also successfully applied this methodology to the synthesis of the antibiotic 1-deoxy-nojirimycin, a naturally occuring α-glycosidase inhibitor.[117]



Scheme 86

- *Nonactic acid*

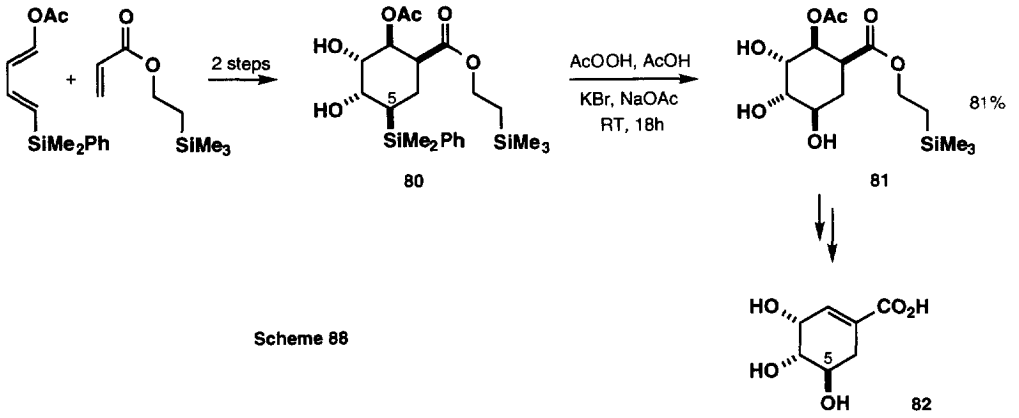
In his synthesis of methyl-(+)-nonactate **79**, Fleming[118] again showed that the simultaneous oxidation of two $PhMe_2Si$ groups was possible and in this case they could be differentiated by the intramolecular formation of a β-lactone (Scheme 87). However this synthesis has now been superseded by a shorter more efficient synthesis by the same author that utilises the *p*-tolyldimethylsilane (see section 3.5).



Scheme 87

- *Shikimic acid*

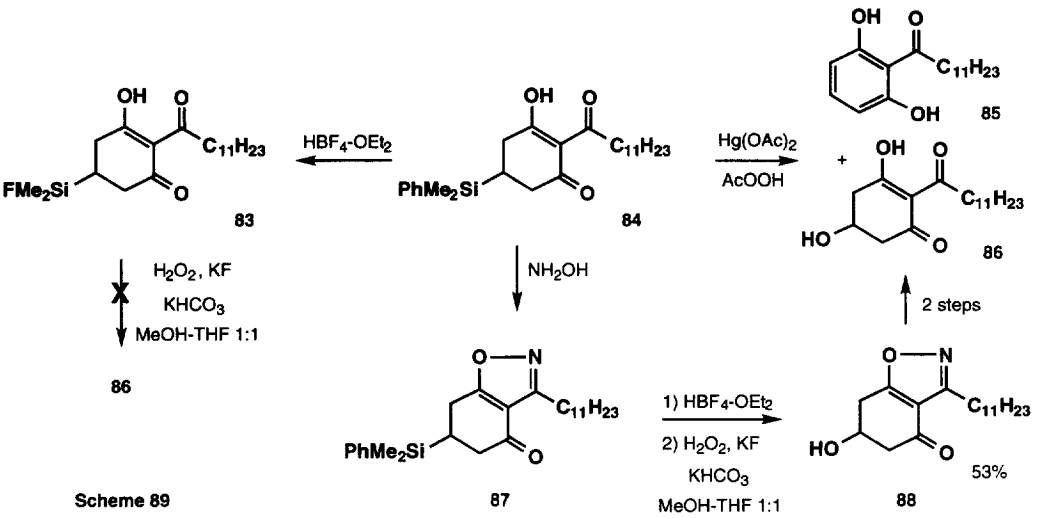
Shikimic acid **82** is an important intermediate in the biosynthesis of a large number of natural products. Koreeda[96] made use of an elegant Diels-Alder strategy to form the requisite 6-membered ring. The hydroxy group on C-5 was thus introduced as a $PhMe_2Si$ group attached to the starting diene (Scheme 88). The silicon intermediate **80** was then converted with an excellent yield into the desired polyol **81**, which was in turn transformed into (+/-)-shikimic acid. Again, the compatibility of the oxidation with the pre-existing functionalities is excellent using [OxN]. It is also important to note that the utilization of the two-step oxidation procedure K on a precursor structurally close to **80** (HBF_4, then m-CPBA) gave the Peterson elimination product after the protodesilylation step.



Scheme 88

- *Acetogenins*

The oxidation of a function into an unsaturated 6-membered ring may sometimes be tedious due to the propensity of these systems to aromatize. Oliver[119a] faced this problem during studies directed towards the total synthesis of a constituent of andromeda lace bugs, *Stephanitis takeyai*. The one-step oxidation carried out on **84** [OxL] gave the desired product **86**, but accompanied with a large amount of the fully aromatized system **85**. Concurrent protodesilylation of **84** using HBF_4-OEt_2 produced the fluorosilane **83**, which upon treatment with H_2O_2 afforded decomposition products (dodecanoic acid being one of the major by-products). Finally it was discovered[119b] that conversion of the 1,3-dicarbonyl moiety into an isoxazole (**87**) prior to the unmasking of $PhMe_2Si$ was the best alternative to produce the desired hydroxylated precursor **88**. This latter was then converted using a two-step sequence into the natural product **86** (Scheme 89).

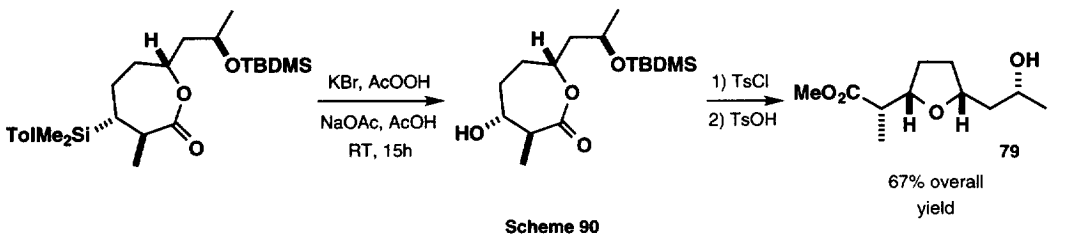


Scheme 89

3.5. Oxidation of other arylsilanes

- *The p-tolyldimethylsilyl group*[120,121]

The *p*-tolMe$_2$Si group has been used as a valuable surrogate of the PhMe$_2$Si group by Fleming as illustrated in the alternative synthesis of methyl-(+)-nonactate **79** (Scheme 90).[120] It possesses a higher crystallinity than its parent phenyl and is more easily oxidised.[121] The oxidative conditions are similar to those described for the PhMe$_2$Si group ([OxN], Scheme 49), however it is important to notice that in contrast with the PhMe$_2$Si group, the *p*-tolyl analogue cannot be introduced using the silyl-cuprate methodology, since the *p*-TolMe$_2$SiLi cannot be generated from the corresponding chlorosilane.[122]

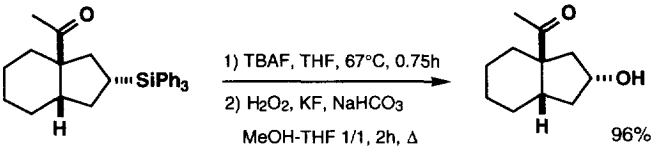


Scheme 90

- *The triphenylsilyl group*[13,85a,123]

The bulky Ph$_3$Si group is particularly convenient when a large silyl group is needed to increase the steric hindrance around a reactive centre to favour a given pathway. Reactions of allylsilanes with α,β-unsaturated ketones in the presence of a Lewis acid give good yields of the [3+2] cyclisation products, when Ph$_3$Si is used.[13] Smaller silicon groups (Me$_3$Si or PhMe$_2$Si) give mainly 1,4-addition product through the Sakurai reaction. Knölker[13] recently showed that the Ph$_3$Si group can be converted into a OH group using very mild, basic conditions (Scheme 91). This oxidation was suggested to occur via the intermediacy of the corresponding silanol,

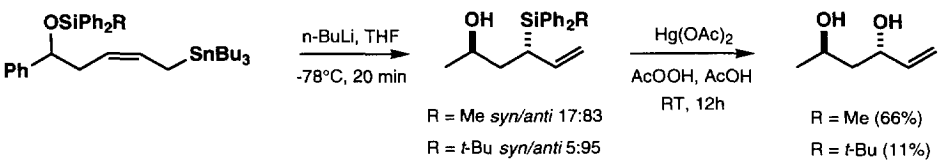
silandiol and then silantriol intermediates by iterative substitution of the Ph groups. The Ph_3Si group can also be simply oxidised using the one-pot conditions L.[123]

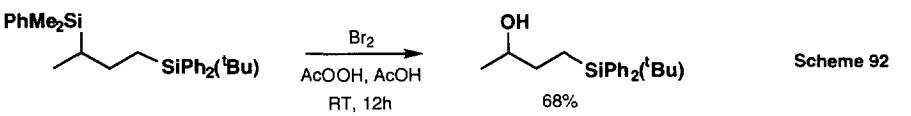


Scheme 91

- *The diphenylmethylsilyl*[13,123,124a,b] and *diphenyl(tert-butyl)silyl groups*[85a,124]

Ph_2RSi groups (R = Me, *t*-Bu) have been employed by Brückner[124a,b] in the stereocontrolled retro-[1,4]-Brook rearrangement (Scheme 92). It was found that Ph_2(*t*-Bu)Si induced much higher stereocontrol than its parent Ph_2MeSi. On the other hand the bulky *t*-Bu group on silicon can only be oxidised in low yield.[124] This poor reactivity of the phenyl groups towards an electrophile (Hg^{2+}) in the Ph_2(*t*-Bu)Si group has been used by Fleming and Pulido[124c] who demonstrated that a $PhMe_2Si$ group can be oxidised in reasonable yield in the presence of a Ph_2(*t*-Bu)Si group without affecting the latter.

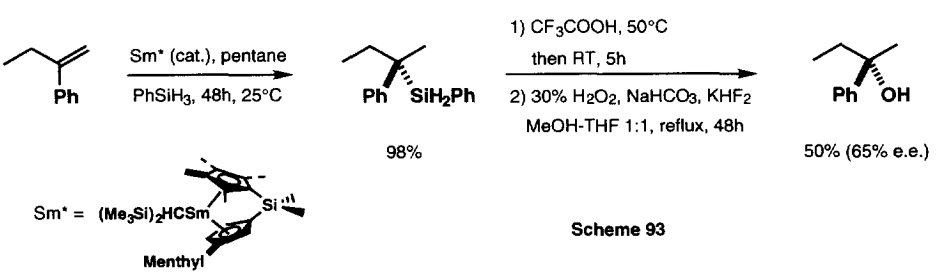




Scheme 92

- *The phenylsilyl group*[125]

The $PhSiH_2$ group is a new latent hydroxy group used very recently by Marks.[125] It was conveniently introduced through a regio- and enantioselective organolanthanide hydrosilylation using the readily available $PhSiH_3$. Its oxidation was carried out using the two-step procedure K (Scheme 93).

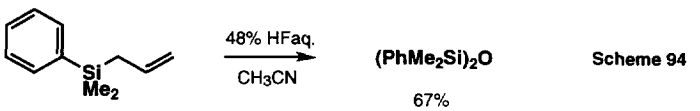


Scheme 93

4. Miscellaneous silicon groups used as masked hydroxy groups

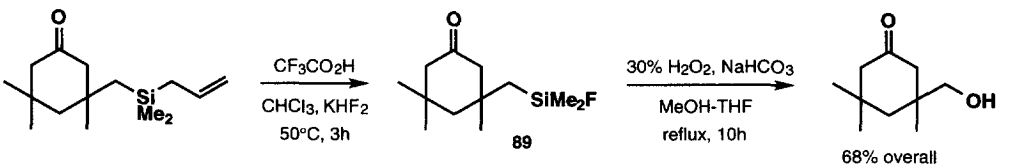
4.1. Allylsilyl groups

As already demonstrated, the oxidation of a $PhMe_2Si$ group which is part of a simple allylsilane is not possible because the allylic group is a better nucleofugal group than the phenyl (Scheme 94).[126]



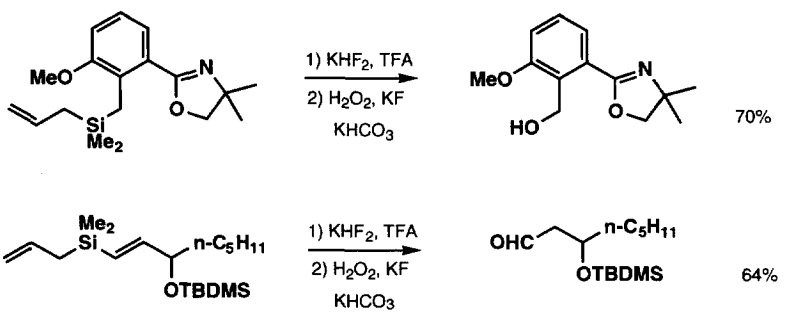
Scheme 94

This ability of the allylic moiety has been used by Tamao[127] to devise a new masked hydroxy group. He showed that the allylic residue on the silicon center was readily displaced using KHF_2/CF_3COOH to give the fluorosilane **89** which was then oxidised to the alcohol using [OxG] (Scheme 95).



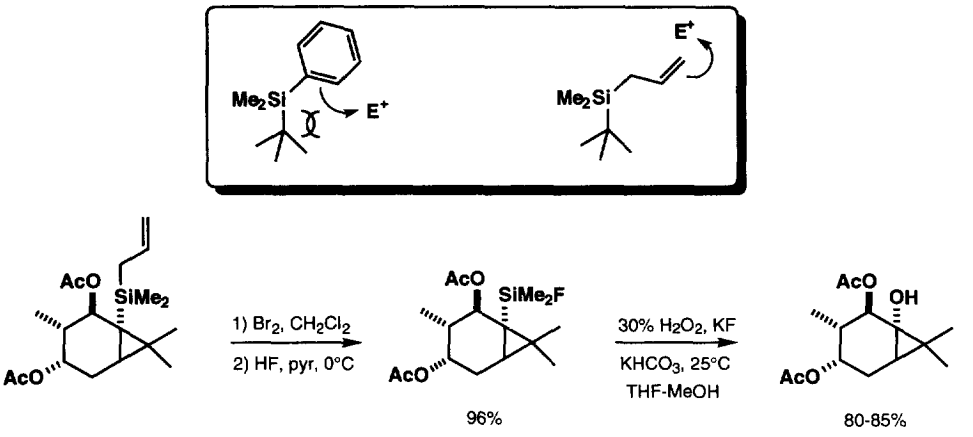
Scheme 95

This group is relatively easy to introduce as part of a Grignard reagent and its oxidation tolerates functionalities such as silyl ethers and oxazolines which are generally sensitive to an acidic medium (Scheme 96).[126]



Scheme 96

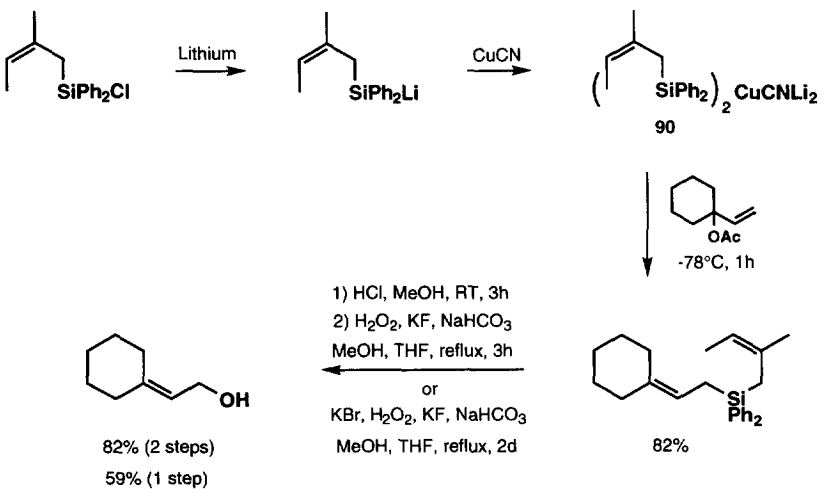
The allyldimethylsilyl group is particularly well adapted for the preparation of tertiary alcohols where steric hindrance is important. *Ipso* attack of the electrophile onto the phenyl ring of $PhMe_2Si$ is sterically hindered, whereas electrophilic attack on an allylsilane occurs well away from the silicon centre (Scheme 97). A representative example of the efficiency of the allyldimethylsilyl group was made by Fuchs[103] in his approach to the synthesis of the sesquiterpene phorbol. As already seen (Section 3.3) oxidation of the $PhMe_2Si$ group on a cyclopropane gave products of ring opening, whereas oxidation of the allyldimethylsilyl group afforded the desired tertiary alcohol in excellent yield (Scheme 97).



Scheme 97

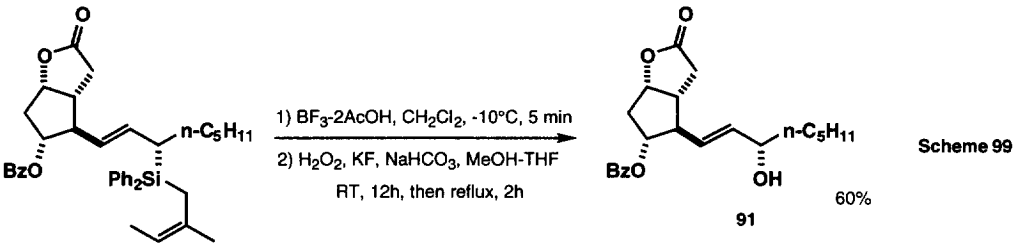
The allylic group is easily displaced using a fluoroacid medium, but it is also well established that it readily reacts with a neutral fluoride source such as TBAF ($nBu_4N^+F^-$) to give the corresponding fluorosilane,[103,128] which greatly increases the utility of the allyldimethylsilyl group.

Another allylic silyl group has recently been devised by Fleming and Winter.[129] They were searching for a silyl group which would be easily unmasked in the presence of other double bonds (especially those which are part of an allylsilane) and could be introduced by way of a silyl-cuprate reagent. This was accomplished starting from the 2-methylbut-2-enyl(diphenyl)silyl chloride which on stirring with lithium afforded the expected silyl-lithium, which in turn gave the silyl-cuprate **90**. This could be added to a variety of substrates and, satisfyingly, the selective removal of this allylic group relative to other less substituted allylic groups was possible (Scheme 98).



Scheme 98

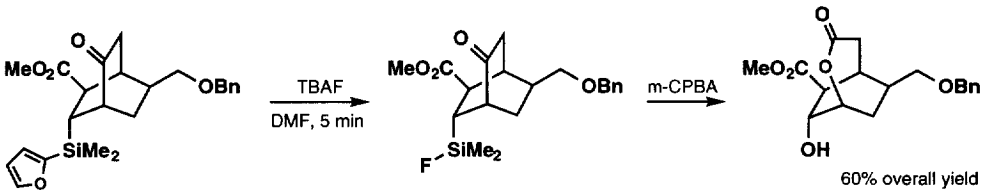
A number of oxidation conditions have been found to be effective, including a mildly basic medium ($NaHCO_3$). Fleming[130] demonstrated the utility of this group in an approach to the synthesis of the prostaglandin precursor **91** (Scheme 99).



Scheme 99

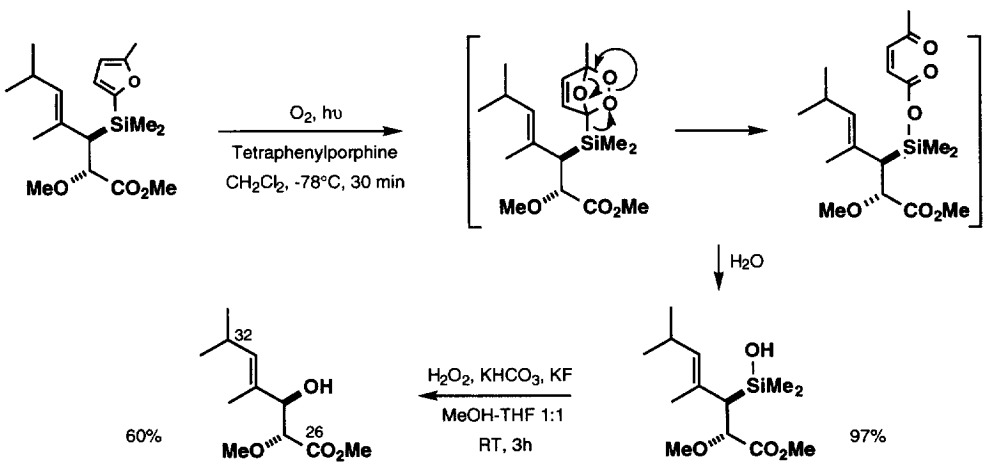
4.2. Furyl-, thienyl- and menthofurylsilyl groups

The first study of the use of a heterocycle-based silicon group as a latent hydroxy group was reported in 1989 by Stork.[131] He showed that a furan could be readily displaced using a fluoride source and that the resulting fluorosilane could then be oxidised. It is also noteworthy that a ketone group present on the substrate underwent Baeyer-Villiger rearrangement because of the intentional use of an excess of m-CPBA instead of the milder H_2O_2 oxidation conditions (Scheme 100).



Scheme 100

Kocienski[132] demonstrated that the furyl group on a silicon could also be oxidised photochemically to afford the corresponding silanol, which in turn was transformed into an alcohol using the oxidation conditions H. This mild oxidation was found to be particularly efficient for the conversion of the allylfurylsilane into the corresponding C26-C32 allylic alcohol fragment of rapamycin (Scheme 101).



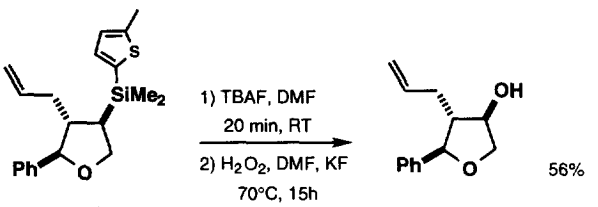
Scheme 101

It is probable that direct nucleophilic displacement using Stork's procedure would have resulted in the displacement of the allylic moiety instead of the furyl group. This is supported by the observation made in these laboratories[133] that the treatment of a thienylallysilane **92** with TBAF in THF afforded the fluorothienylsilane **93** (Scheme 102).

92 93

Scheme 102

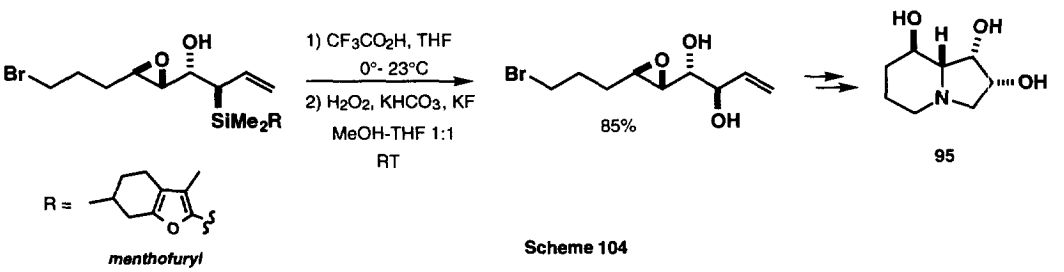
However, in other circumstances methylthienylsilanes[90b,134] such as **94** are readily converted with TBAF to the fluorosilane (not isolated) which can then be oxidised to the alcohol using H_2O_2 in DMF in the presence of KF (Scheme 103). Using these conditions, the isolated double bond was left untouched.



94

Scheme 103

Finally, Roush[135] has developed a new silicon group with a menthofuryl substituent on silicon which he used during the total synthesis of the glycosidase inhibitor swainsonine **95**. This bulky group was easily displaced using electrophilic conditions, affording the fluorosilane, which was then converted into the corresponding hydroxy group in high yield (Scheme 104). The absence of the Peterson elimination[92] and the stability of the allylic moiety and the epoxide during the protodesilylation of the menthofuryl group are remarkable and should be noted.

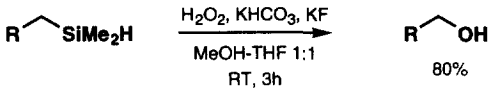


95

Scheme 104

4.3. Silanes (Si-H)

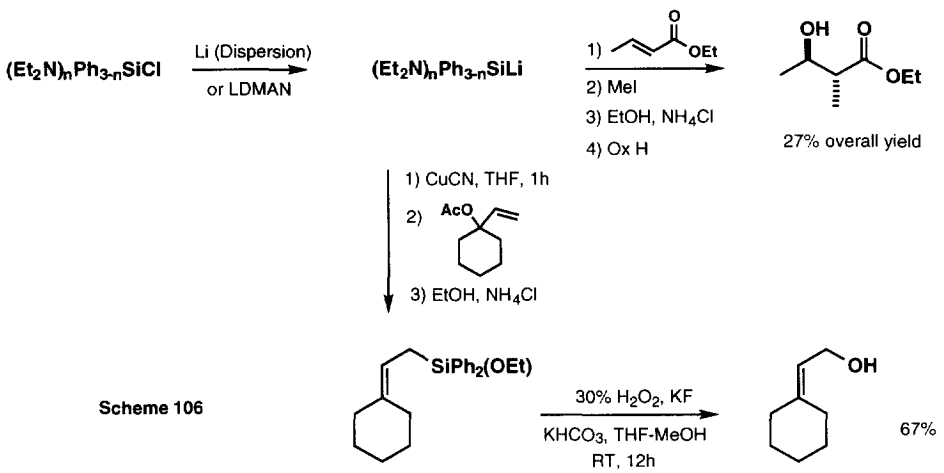
Tamao and Kumada[1c] first showed that a silane (R_3Si-H) could be oxidised in the same way as an alkoxy, a fluoro or any other silane (Scheme 105). This kind of organosilicon intermediate has been rarely used so far,[42a] though it is relatively stable and easy to handle.



Scheme 105

4.4. Aminosilyl groups (Si-N)

The Si-N bond is relatively sensitive to hydrolytic conditions and has therefore been rarely used during a multistep synthesis. A renewed interest in this kind of compound has emerged recently partly due to the efforts of Tamao and Ito. They found that like the $PhMe_2Si$ group, aminosilyl groups can be introduced into a carbon framework using the silyl-cuprate methodology.[136] The silyl-cuprate is generated *in situ* from the corresponding silyl-lithium, in turn prepared by direct reaction of aminochlorosilanes with lithium metal,[136a] or Li-1-(dimethylamino)naphthalenide (LDMAN)[136b] (Scheme 106). Some representative examples such as 1,4-addition and allylic displacement showed that, similarly to $PhMe_2Si$, aminosilyl groups can be introduced into a carbon skeleton and then oxidised using [OxH].

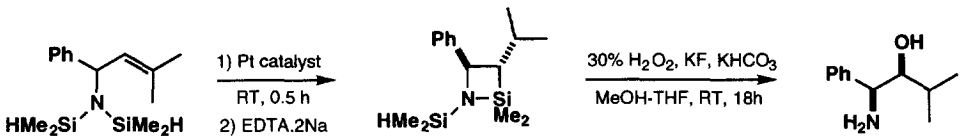


Scheme 106

Two different routes are usually employed to oxidise an aminosilyl group, either directly using H_2O_2 and a fluoride source, or the sensitive Si-N bond can be converted into a more stable Si-O bond and the resulting alkoxysilane oxidised using the Tamao conditions. These two different approaches are illustrated below (see also Scheme 106).

- *Direct oxidation of the aminosilyl group*[137]

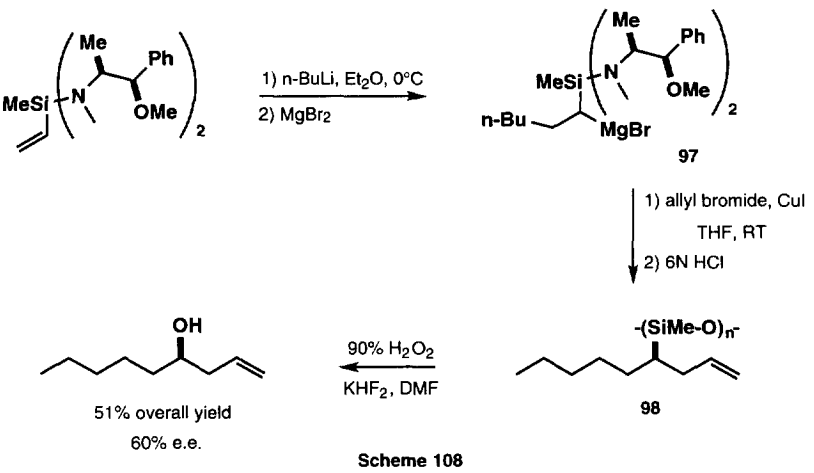
A silane tethered to an amino group has been used in intramolecular hydrosilylation leading to the unusual aza-silacyclobutane **96** (Scheme 107).[137a] This rare class of silicon compounds is thermally stable and can be isolated, and upon oxidation gives the corresponding 1,2-aminoalcohols in excellent overall yield. The high level of diastereoselectivity of the hydrosilylation process is particularly noteworthy giving a useful entry to *syn* amino-alcohols.



Scheme 107

- *Conversion of the aminosilyl into an alkoxysilyl group*[21,138]

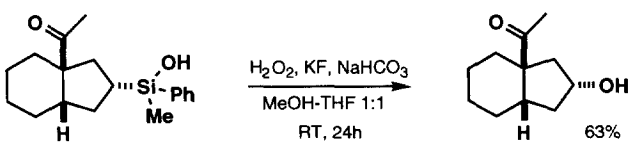
Removal of the amino group prior to the oxidation process has also been used to recover a chiral auxiliary after an asymmetric alkylation and before C-Si bond oxidation.[138a] Thus, treatment of the aminosilane **97** with allyl bromide then with aqueous HCl produced a polysiloxane **98** which was oxidised using [OxD] (Scheme 108).[1a] The oxidation could also be carried out using m-CPBA or 30% H_2O_2 but these conditions were found to be less efficient.



Scheme 108

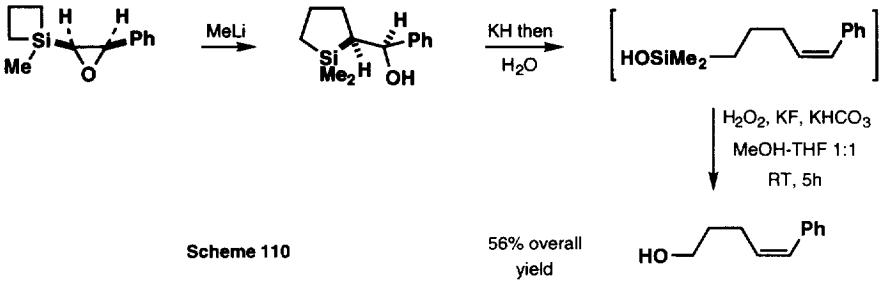
4.5. Hydroxysilyl groups (Si-OH)

Few examples of oxidative conversion of a R_3Si-OH group into the corresponding OH group have been described so far. However, as demonstrated by Knölker,[13] the Si-OH moiety is likely to be an intermediate during the oxidation of fluorosilanes using [OxH] (Scheme 109).



Scheme 109

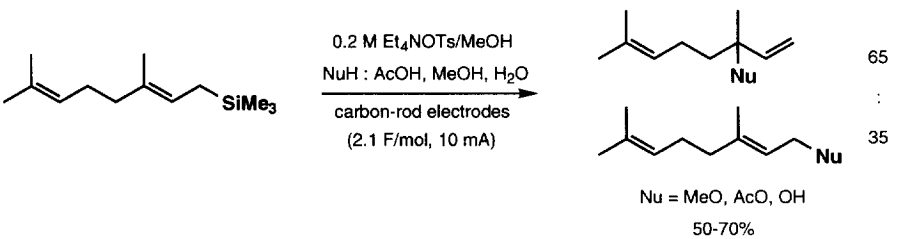
Even though in many cases silanols have been identified as intermediates, they are usually not isolated but oxidised directly, a good example being the nucleophile-induced ring enlargement methodology of Oshima and Utimoto which relies on this oxidation (Scheme 110).[139]



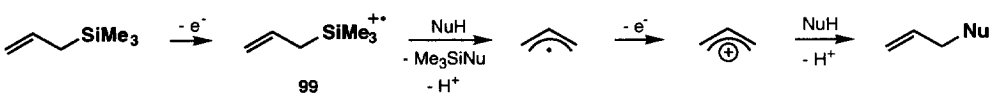
Scheme 110

4.6. Alkylsilyl groups (Si-C)

Trialkylsilanes cannot be oxidised using reagents such as H_2O_2 or m-CPBA, however, it has been shown that electrochemical[140] or photosensitised methods[141] and one-electron oxidants such as ceric ammonium nitrate[142] (CAN : $Ce(NO_3)_6(NH_4)_2$) can oxidise allyl and benzylsilanes. Yoshida[140a] has proposed a mechanism for the electrochemical oxidation that passes via the radical cation **99** from which the silicon is abstracted by a nucleophile. A second equivalent of nucleophile then attacks the allylic carbocation with the regioselectivity as shown below (Scheme 111).

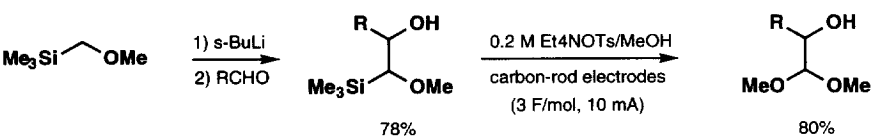


Mechanism :



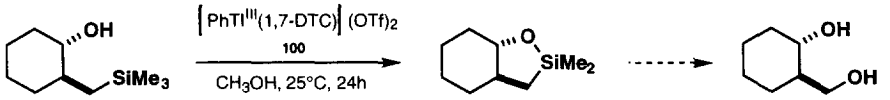
Scheme 111

Another application of the electrochemical methodology has been reported by Yoshida.[140b] Oxidation of the C-Si bond of α-silyl or α,α-bis-silyl ethers provides an interesting alternative to the classical precursors of formyl and alkoxycarbonyl anions (Scheme 112).



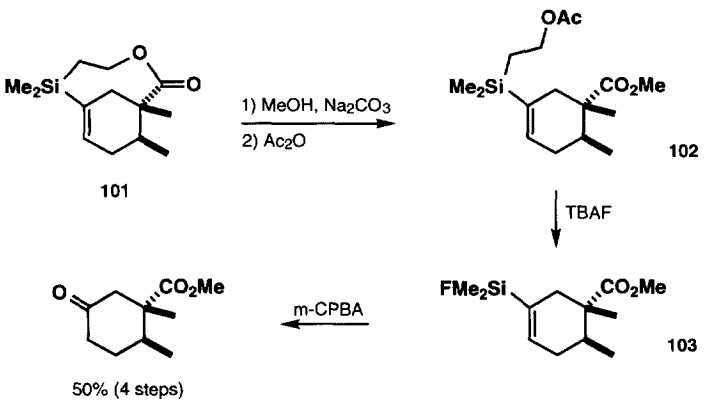
Scheme 112

The newly discovered[143] thallium-crown ether derivatives, might be a good solution to the problem of cleavage of the C-Si bond in non-activated organosilicon compounds. PhTl(III)(crown ether) **100** was shown to cleave very selectively the Si-Me bond in tetramethylsilane. More interestingly, application of this kind of reagent to trialkylsilanes having a remote nucleophilic substituent resulted in the formation of the corresponding cyclic alkoxysilane which may then be oxidised into the corresponding diol (Scheme 113). The selectivity of the cleavage of the C-Si bond is very high and therefore the silicon-methyl bond is cleaved in the presence of ethyl, vinyl, benzyl and phenyl-silicon bonds. However, the main drawback remains the stoichiometry of the reaction where one equivalent of the organometallic reagent is required for the cleavage to occur.



Scheme 113

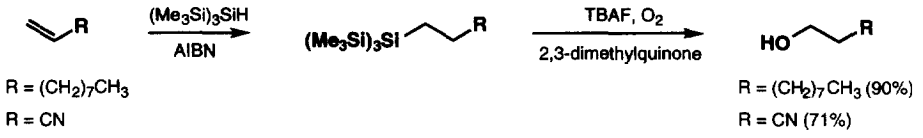
Cleavage of the alkyl-silicon bond can also be realized under very mild conditions for specific groups such as 2-acetoxyethylsilyl groups.[144] Although the direct oxidation of the C-Si bond in **101** is not possible, esterification followed by acetylation produced a β-silylacetate **102** which could be easily converted into the fluorosilane **103** using TBAF as the fluorine source. This Peterson elimination[92] thus provides a suitable silicon group for direct oxidation (Scheme 114).



Scheme 114

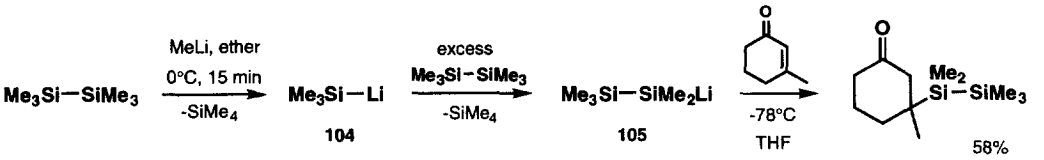
4.7. Disilyl groups (Si-Si)

The silicon-silicon bond can be oxidatively transformed into the corresponding Si-O-Si group which is then easily converted into a OH function.[29d] This interesting property of the Si-Si bond has therefore been used to allow for a facile unmasking of silicon groups containing Si-Si bonds. Chatgilialoglu's reagent $(Me_3Si)_3SiH$ can add, under free-radical conditions to various kinds of olefins.[145] The addition products have then been oxidised using TBAF and O_2-2,3-dimethylquinone as the oxidant, to give the desired alcohols (Scheme 115). The oxidation of a Si-Si bond eventually leads to the unmasking of the $(Me_3Si)_3Si$ group and therefore the $(Me_3Si)_3Si$ radical can be regarded as an OH radical equivalent (see also section IV).



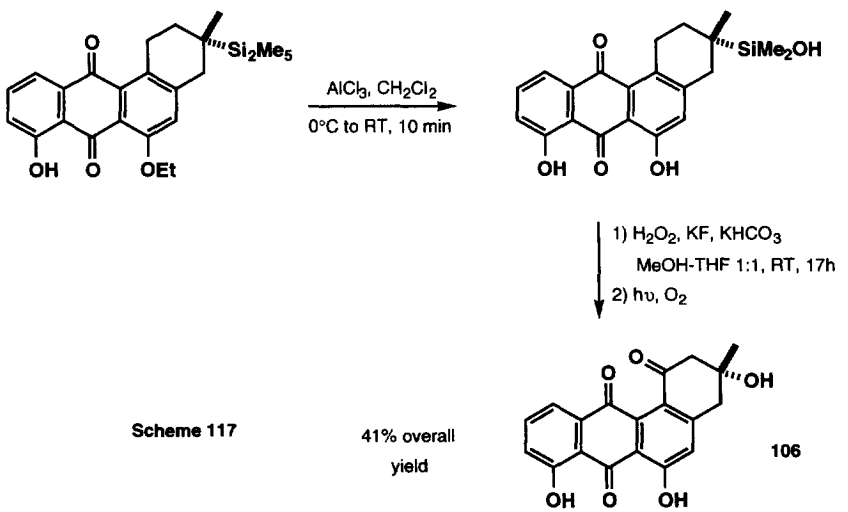
Scheme 115

One of the important aspects of the methodology described in this review is the introduction of the silicon moiety. Krohn[146] recently discovered a silicon group, possessing a Si-Si bond which can be introduced by a silyl-lithium species. While attempting to prepare Me_3SiLi using Still's procedure, it was found that on a larger scale, with a longer reaction time and higher temperature, the new silyllithium **105** was formed instead of Me_3SiLi. It was suggested that the reaction passes via the simple silyllithium **104** which then cleaves a molecule of hexamethyldisilane (Scheme 116).



Scheme 116

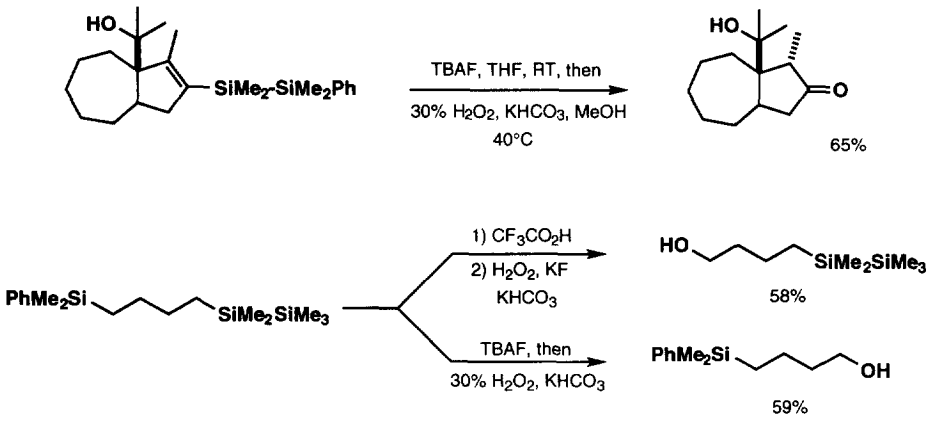
This soft silyl anion adds in a 1,4-fashion on α,β-unsaturated carbonyl compounds, without the need for a cuprate intermediate. Krohn also demonstrated that this silyl anion is relatively insensitive to steric hindrance and readily adds to polysubstituted alkenes. Tertiary alcohols are thus formed in reasonable yields after cleavage of the Si-Si bond using $AlCl_3$. The silanol obtained after workup is then oxidised into the desired alcohol in good yields. This methodology was applied successfully to the total synthesis of (+/-)-rabelomycin **106** (Scheme 117).[146]



Scheme 117

41% overall yield

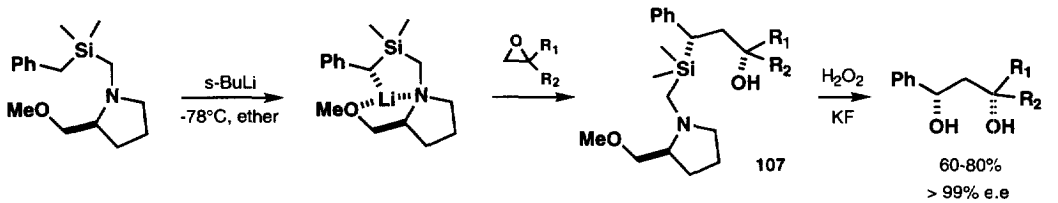
More recently, Ito[147] revisited the disilanyl group chemistry and improved Krohn's original oxidation procedure. He showed that the oxidation could be carried out using TBAF followed by oxidation with H_2O_2 (12 eq.) and $KHCO_3$ in MeOH. Nucleophilic fluorine attack on silicon atom of disilane is supposed to induce a cleavage of the Si-Si bond to form an oxidisable fluorosilane and a silicate (Scheme 118). This method is very useful as demonstrated by the examples below where an alcohol and a $PhMe_2Si$ group are left untouched after oxidation. Interestingly, it is also possible to oxidise selectively the $PhMe_2Si$ group leaving the $Me_3SiSiMe_2$ group unchanged.



Scheme 118

4.8. Aminomethylsilyl groups ($SiCH_2N$)

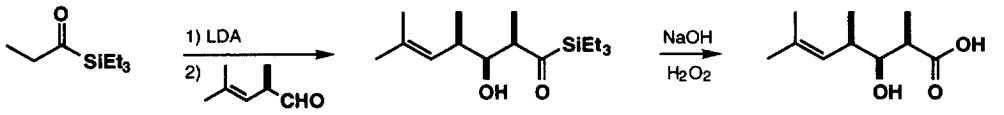
The use of a chiral auxiliary attached to the silicon center to control the stereoselectivity has recently attracted a great deal of interest. The most successful methodology in this area has been reported over a number of years by Chan[148] who used a proline-based organosilicon group to control the diastereoselectivity of the alkylation of benzylic, allylic and propargylic derivatives. This approach after oxidation of the C-Si bond gave the desired alcohols in up to 99% enantiomeric excess (Scheme 119). The unmasking of the latent hydroxy group is carried out under Tamao-Kumada conditions and is a relevant example of the oxidation of a silicon group having no nucleofugal group attached to it. The fact that the proline moiety is not recovered after the oxidation step is a serious drawback to the method and indicates that oxidation of the amino group of proline must occur prior to the oxidation of the C-Si bond. A Polonovski or sila-Pummerer type mechanism[149] involving an amine oxide intermediate attacking the silicon center is likely to be at the origin of the oxidation of the C-Si bond in **107**.



Scheme 119

4.9. Acylsilyl groups (SiC(O)R)

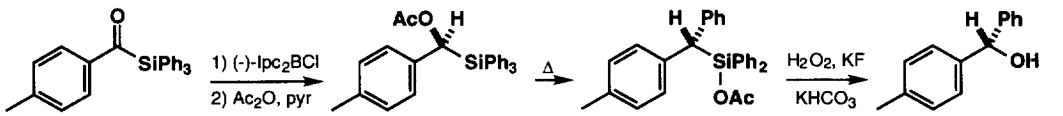
Oxidation of acysilanes using alkaline-H_2O_2 produces the corresponding carboxylic acid as a result of the oxidation of the C-Si bond through a Baeyer-Villiger type reaction.[150] Schinzer[151] made use of this transformation in a late stage of a stereocontrolled synthesis of a polypropionate fragment (Scheme 120).



Scheme 120

4.10. Acetylsilyl groups (Si-OAc)

Organosilanes having a Si-OAc bond are readily oxidised using H_2O_2 or m-CPBA and a fluoride source. Buynak[152] recently devised a stereospecific route to secondary alcohols using this last transformation. He established that stereoselective reduction of acylsilanes into the corresponding silylacetate **108**, followed by thermal rearrangement afforded the desired R_3Si-OAc derivative **109** which was oxidised into the alcohol **110** (Scheme 121). The high enantioselectivity of the process relies on the selectivity of the reduction of the acylsilane using the Itsuno reagent ((-)-Ipc_2BCl and an amino-alcohol), since the subsequent rearrangement and the C-Si bond oxidation are both stereospecific.



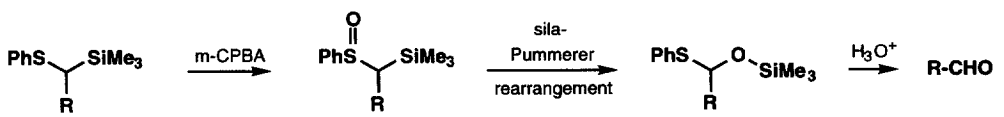
108 109 110

up to 98% e.e. (80%)

Scheme 121

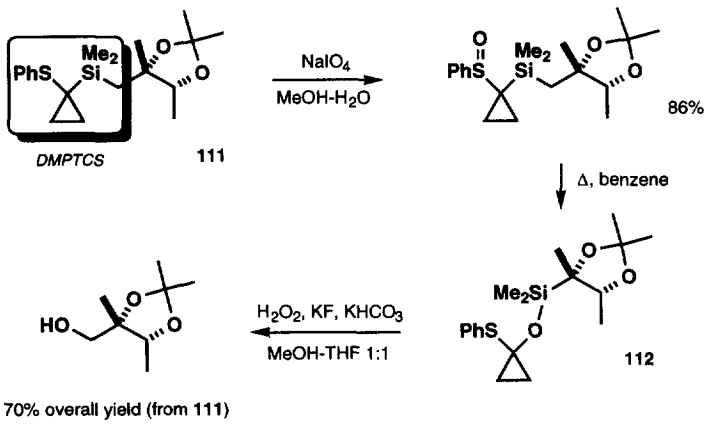
4.11. α-Silylthioether groups ($SiCH_2S$)

The oxidation of α-silylthioether into α-silylsulfoxide, followed by the sila-Pummerer rearrangement was used by Ager[153] some fifteen years ago as a straightforward route to carbonyl compounds (Scheme 122). The sila-Pummerer rearrangement which is the key-step of the sequence can be regarded as a direct conversion of a C-SiR_3 bond into the corresponding C-$OSiR_3$ bond. A similar approach by Reich[154] employed α,α-bis-silylselenoxide to prepare acylsilanes.



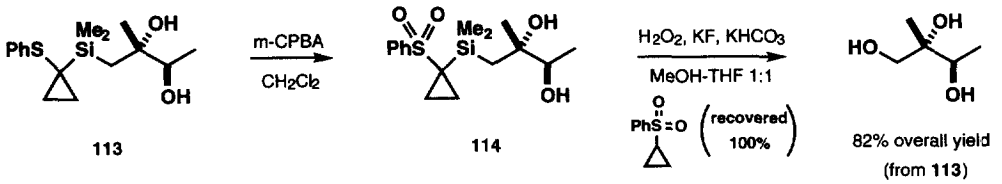
Scheme 122

During studies directed towards the development of new masked hydroxy groups, we used the above sila-Pummerer rearrangement as a mild conversion of the C-Si bond.[155] The rearrangement of an α-silylsulfoxide produces a siloxane which can undergo oxidation of the C-Si bond. The major advantage of the method lies in the late formation of the real masked hydroxy group (i.e. alkoxysilane **112**). The α-silylthioether group (as in **111**) is stable enough to be carried all along a multistep synthesis, the less stable alkoxysilane being unmasked in the last stages of the sequence, allowing the oxidation of the C-Si bond. The dimethyl-(1-phenylthio)cyclopropylsilyl group (DMPTCS) was devised as a latent hydroxy group because it is easy to prepare and it was known to undergo fast and quantitative sila-Pummerer rearrangement. As illustrated below (Scheme 123), the oxidation of the thioether function, followed by the rearrangement and oxidation of the C-Si bond using procedure H offers an efficient and high yielding entry to polyhydroxylated compounds.[155,156] DMPTCS was also found useful to prepare cyclopropyl alcohol, a transformation which is not possible using $PhMe_2Si$ group (Scheme 72).[105]



Scheme 123

Interestingly it was found that a cyclopropylphenylsulfone (**114**) is a good nucleofugal group on silicon, which can be readily displaced during C-Si oxidation.[155] The oxidation of the thioether group into the sulfone followed by silicon oxidation offers a shorter alternative to the preceding sulfoxide methodology which is compatible with the presence of free hydroxy groups in the molecule (Scheme 124).

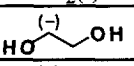
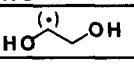
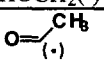
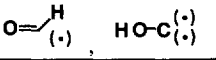
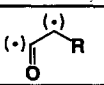
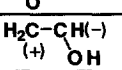
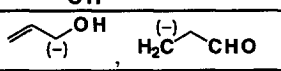
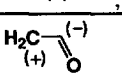
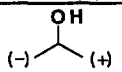


Scheme 124

IV. SYNTHETIC EQUIVALENTS

Throughout this review, the introduction of numerous silicon reagents into various substrates and the subsequent oxidation of the silicon group has been described. The table below summarises these silicon reagents along with their oxygenated synthon.

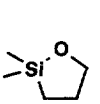
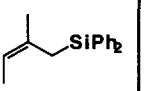
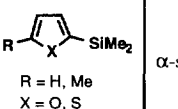
Table 4. Silicon reagents and their synthetic oxygenated equivalents.

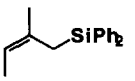
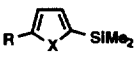
Silicon Reagent	Oxygenated Equivalent	References
$HSi(OEt)_3$ $HSiMe(OEt)_2$ $HSiCl_3$	Hydrosilylation H-OH	16 27 16, 32, 75
$(HMe_2Si)_2NH$	Intramolecular hydrosilylation H-OH	61 - 65
$PhMe_2SiSiMe_2Cl$	Intramolecular bis-silylation HO-HO	66
$(^iPrO)Me_2SiCl$	HO(+)	25
$(PhMe_2Si)_2CuCNLi_2$ $((NEt_2)Ph_2Si)_2CuCNLi_2$ $(Me_3Si)SiMe_2Li$	HO(-)	8 136 146
$Cl_2PhSiSiMe_3$	HO(-)	36
$(Me_3Si)_3SiH$	HO(·)	145
$(^iPrO)Me_2SiCH_2MgCl$	$HOCH_2$(-)	1a
$(CH_2{=}CHCH_2)Me_2SiCH_2MgCl$	$HOCH_2$(-)	127
$PhMe_2SiCH_2MgCl$	$HOCH_2$(-)	116,117
$(^iPrO)SiCH_2CO_2R$		20, 38
$(^iPrO)SiCHXCO_2R$ (X = Cl, Br, SePh)		157
$ClMe_2SiCH_2Br$	$HOCH_2$(·)	48
$ClMe_2SiC(Br){=}CH_2$		58a
$ClMe_2SiCHCl_2$		58b
$RC{\equiv}CSiMe_2Cl$		59, 60
$CH_2{=}CHSiMe_2(NR_2)$		138a,d
$CH_2{=}CHCH_2SiMe_2(NR_2)$		137b-c, 138c
$HC{\equiv}CSiMe_2(O^nBu)$		39
$CH_2{=}CHSi(OEt)_3$	Insertion into the vinylic C-H bonds of enones (±)CH_2CH_2OH	26
$CH_2{=}CHCH_2SiR_3$		13

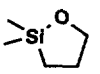
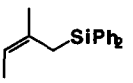
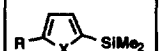
V. TABLES SUMMARIZING THE COMPATIBILITY OF VARIOUS FUNCTIONS WITH THE OXIDATION OF THE C-Si BOND

Table 5 is designed as a quick reference guide which should be useful for determining the suitability of a particular silicon masked hydroxy group, according to the nature of the other functional groups present in a substrate. The first row and first column contain the different silicon groups and the usual functional groups respectively. At the intersection, are the oxidation conditions (A to N) and the references where this silicon group has been oxidised in the presence of the designated functional group. The blank cases do not signify that the transformation is not possible, but only that it has not been reported to date. Only those silicon groups which have been oxidised in the presence of several functional groups have been included in the table.

Table 5. Compatibility of various functions with the oxidation of the C-Si bond.

Silicon groups ⇨ / **Functional groups** ⇩	$SiMe_2(O^iPr)$		$PhMe_2Si$ Ph_2MeSi Ph_3Si *p*-$TolMe_2Si$	$AllylMe_2Si$ 	 R = H, Me X = O, S Menthofuryl	α-silylthioether
isolated double bond	**C** (19); **D** (1a); **H** (20, 21, 156)	**C** (50); **G** (61a, 62); **H** (53b-d); **J** (63)	**K** (8, 82c, 109, 112)	**K** (127)	134[a]	
double bond of an allylsilane	**C, D** (1a); **G** (22); **I** (67)	**G** (45); **H** (67)	**K** (101)	**K** (129, 130)	132[a], **K** (135)	155[a]
conjugated double bond	**G** (23)	**H** (53e)	**K** (93c, 101, 105, 112); **L** (119)			
enolether		**A** (68); **H** (40, 65)				
triple bond			**K** (4b)			
cyclopropane		**C** (49b)	**K** (99)	**K** (103,126)		155[a]
ketone		**A** (68); **G** (47d)	**K** (2a, 8, 85d, 93c, 101, 102a,c,d, 108, 109, 112, 115, 119); **L** (8,93c,119); **N** (8)	(127)[a]		
ester	**F** (1a)	**H** (53a,d,e)	**K** (2a-b, 82a-e, 85a,c, 93d, 101); **L** (2b, 82g, 83, 90a, 118); **N** (96)	**K** (129); **N** (129)	131[a], 132[a]	
carboxylic acid			**K** (8, 83); **L** (114)			

Silicon groups ⇨ / **Functional groups** ⇩	$SiMe_2(O^iPr)$		$PhMe_2Si$ Ph_2MeSi Ph_3Si *p*-$TolMe_2Si$	$AllylMe_2Si$ 	 R = H, Me X = O, S Menthofuryl	α-silylthioether
lactone	**D** (19)		**K** (87); **L** (84a-c, 87); **M** (2b, 84a); **N** (82h, 120, 121)	**K** (130)		
lactam	**I** (67)		**K** (85a-d, 111, 113); **L** (2b, 84); **N** (2b)			
amine I, II, III			**K** (8, 87, 106a, 108, 109); **L** (87)			
amide			**K** (8, 85a, 99)			
nitrile	**F** (1a)	**G** (45b, 45g)	**K** (8)			
nitro						
cyano		**H** (53d)				
imide			**L** (2b)			
"isolated" hydroxy group		**H** (53d)	**K** (8, 93d); **L** (2a, 82g, 93b-c, 98, 123, 124); **N** (93a-b)			155[a]
α-hydroxy group	**G** (24); **H** (21, 25,156)		**L** (94); **N** (8, 37b, 96, 117)		**K** (135)	155[a], 156[a]
ether	**D** (1a)	**C** (49a); **H** (70); **J** (61b)	**K** (85a,c,d, 108, 112); **L** (84b, 90a-b); **N** (91a-b, 116)	**K** (126)	132[a], 134[a]	
thioether		**H** (53e)				
TBDMS	**G** (22)	**G** (55); **H** (62); **J** (63)	**K** (158); **N** (121)	**K** (126)	**K** (135)	
acetate		**H** (53b)	**K** (2a, 8, 82a, 111); **L** (2b, 8); **M** (2b, 8); **N** (2b, 8, 37b, 82h; 86a,c, 88, 96)	**K** (103,126)		
benzoate		**J** (62); **H** (62)	**K**, **L** (8); **N** (8; 86b, 89, 93b)	**K** (130)		

Silicon groups ⇨ / Functional groups ⇩	$SiMe_2(O^iPr)$		$PhMe_2Si$ Ph_2MeSi Ph_3Si *p*-$TolMe_2Si$	$AllylMe_2Si$ 	 R = H, Me X = O, S Menthofuryl	α-silylthioether
benzyl (BnO, BnN)			**K** (109); **L** (84a, 90a, 114, 118); **N** (37b, 91a-d, 116, 117)	**K** (103)		156[a]
carbonate			**M** (2b, 8)			
carbamate			**N** (116)	**K** (103)		
tosylate, mesylate			**K** (112, 157); **L** (158)		131[a]	
epoxide			**N** (89)		**K** (135)	
acetal acetonide	**H** (21)	**C** (52a); **G** (51, 55); **H** (53a-d; 54); **I** (57a); **J** (61b, 62)	**K** (101); **L** (98); **N** (37b, 88, 91a-d, 116, 117)		**K** (135)	155[a], 156[a]
pyridine	**D** (1a)		**K** (99)			
furan		**J** (61b)				
oxazoline			**K** (119)	**K** (126)		
azide			**L** (98)			
phosphorus compounds			**K** (97a); **L** (97b)			
halide					**K** (135)	

[a] Specific conditions slightly different from procedures A-N.

Table 6. Oxidation conditions A-J (Tamao-Kumada).

Conditions	Oxidant	Fluoride	Additive	Solvent	Reference
[OxA]	mCPBA	KF or KHF_2	-	DMF	9
[OxB]	mCPBA	-	Na_2HPO_4	MeOH	16
[OxC]	30% H_2O_2	KF or KHF_2	-	DMF	1b
[OxD]	90% H_2O_2	KF or KHF_2	-	DMF	1a
[OxE]	30% H_2O_2	KF or KHF_2	Ac_2O	DMF	1b
[OxF]	45% AcOOH	KF or KHF_2	-	DMF	1a
[OxG]	30% H_2O_2	-	$NaHCO_3$ or $KHCO_3$	MeOH, THF	1a
[OxH]	30% H_2O_2	KF or KHF_2	$NaHCO_3$ or $KHCO_3$	MeOH, THF	1a
[OxI]	30% H_2O_2	KF	$KHCO_3$	DMF	57b
[OxJ]	30% H_2O_2	-	KOH	MeOH, THF	61b

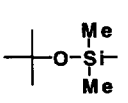
Table 7. Oxidation conditions K-N (Fleming).

Conditions	Electrophile	Oxidant	Additive	Solvent	Reference
[OxK]	HBF_4 or BF_3-2AcOH	AcOOH or m-CPBA or H_2O_2	NEt_3 or KF	ether	2a, 8
[OxL]	$Hg(OAc)_2$	AcOOH in AcOH	-	neat	2b, 8
[OxM]	Br_2	AcOOH in AcOH	-	neat	2b, 8
[OxN]	Br_2 (from KBr)	AcOOH in AcOH	AcONa (buffer)	neat	2b, 8

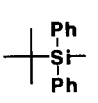
VI. STERIC HINDRANCE IN THE OXIDATION OF THE C-Si BOND

Throughout this review there have been various examples when the C-Si bond oxidation was either slowed down considerably or was simply not possible because of the steric hindrance. Tamao and Kumada first mentioned that the (^{t}BuO)Me_2Si group **114** was oxidised slower and requires more drastic conditions than (^{i}PrO)Me_2Si.[1,20] Brückner[124] showed that although the Ph_3Si is sterically very hindered, it can still be oxidised in mild conditions, however, just changing one of the phenyl groups for a *tert*-butyl prevented oxidation (Scheme 92).

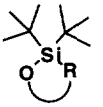
This aspect is particularly important in the light of recent studies by Danheiser,[160] Knölker,[13,161] and Malacria,[162] amongst others, who have demonstrated that sterically hindered silicon groups can favour rearrangements or reaction pathways which are not possible with smaller silicon groups. Therefore, in these strategies, the main challenge is to find a silicon group which is bulky enough to drive the reaction along the desired pathway, but which will be oxidisable using mild conditions. We have summarised below, some sterically hindered silicon groups which are known to be slowly or non-oxidisable using the classical oxidation procedures A to N (Scheme 125). These silicon groups have been shown to enhance the stereoselectivity in various processes and also the stability of the silicon intermediates compared to smaller analogues. This is the case with **115** which gives much better selectivity than Ph_2MeSi or $PhMe_2$Si, in [1,4]-retro-Brook rearrangement, but which is also oxidised in very low yield (11%).[124] Interestingly, Palomo,[85a] showed that treatment of **115** with HBF_4-OEt_2 produced the corresponding fluorosilane which then refused to be oxidised. Clive[41] observed a similar behaviour with **116**. Finally going from a *tert*-butyl substituent on silicon to a *tert*-butoxy (or *iso*-propoxy) group generally favours the oxidation. However, **114** and **117a-b** still require forcing oxidation conditions to be unmasked.[1] These few examples do not represent an exhaustive list but only indicate the influence that steric hindrance around the silicon centre has on the oxidation process. This also suggests that one of the challenges in the future will be the design of silicon groups having the specific steric requirements to allow the transformations mentioned above.[160-162]



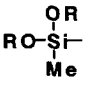
114[1b,20]



115[85a,124]



116[41]



117a R = ^{i}Pr[1b]
117b R = ^{t}Bu[1b]

Scheme 125

VII. CONCLUSION

This review has covered the wide range of oxidisable silicon groups and the compatibility of the various oxidation conditions with other functionality. Recent reports have begun to extend this methodology to the oxidation of C-Sn bonds.[93a,163,164] Clearly this subject has now reached a level of maturity which makes it readily accessible and convenient for the use in synthesis.

The challenges for the future are numerous, the synthesis of sterically demanding organosilicon groups that are easily oxidisable being just one example. As demonstrated the total synthesis of highly complex natural products using a minimum of alcohol protection is already feasible using this technology and the goal of the selective oxidation of different silicon groups within the same molecule will be reached in the not too distant future.

Acknowledgements. We gratefully acknowledge Dr. N. Abd. Rahman (University of Malaya, Kuala-Lumpur) for hepful suggestions. We also thank Prof. J. Dunoguès and Prof. P. Babin (University of Bordeaux) for stimulating discussions. Prof. van Boom (University of Leiden) and Prof. K. Krohn (University of Paderborn) are acknowledged for providing us with a preprint of their work. Finally, we would like to thank Dr. I. Eggleston, Dr. S. Ainge and Mr. R. Angelaud for proof-reading this article.

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(*Received* 8 *January* 1996)