



Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

Sample Contribution

Category		Organometallics
Volume	4	Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds
Product Subclass	4.4.27	α-Haloalkylsilanes
Written by		N. J. Lawrence



Science of Synthesis

Houben-Weyl Methods of Molecular Transformations

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Biographical Sketch



Nicholas Lawrence was born in 1963 in Chichester, West Sussex, UK. He graduated in Natural Sciences from Cambridge University in 1985. He remained at Cambridge to work with Professor Ian Fleming, FRS, gaining his Ph.D. in 1989, having investigated synthetic organosilicon chemistry and the synthesis of the pancreatic lipase inhibitor tetrahydrolipstatin (Orlistat). This was followed by postdoctoral research at Leicester University, UK, with Dr. Paul Jenkins, involving synthetic routes towards paclitaxel. He was appointed as a lecturer at UMIST in 1991 and Senior Lecturer in organic chemistry in 1997. He was appointed to a University Senior Research Fellowship at Cardiff University in 2000. His research interests include the development of new synthetic methods and the synthesis, design, and isolation (from medicinal herbs) of potential anticancer drugs. His fascination for organosilicon chemistry continues in the study of synthetic applications of polysiloxanes.

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	N. J. Lawrence	
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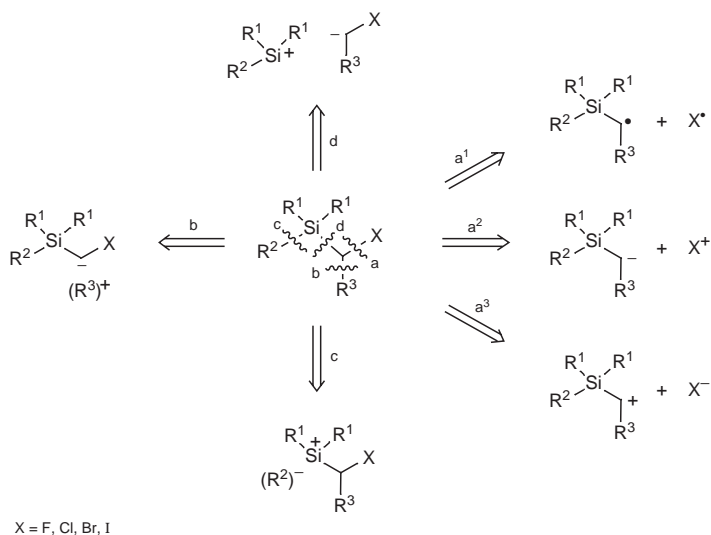
**4.4.27 Product Subclass 27:
 α -Haloalkylsilanes**

N. J. Lawrence

General Introduction

α -Haloalkylsilanes are primarily used in organic synthesis to prepare α -metalated silanes, which react with a variety of electrophiles. The nucleophilic substitution of the halogen atom provides a second important mode of reaction. The general patterns of reactivity and synthetic importance of α -haloalkylsilanes are revealed in the reviews of the use of the structurally simple examples of the class, such as (chloromethyl)trimethylsilane,^[1,2] (chloromethyl)(isopropoxy)dimethylsilane,^[3] and (1-chloroethyl)trimethylsilane.^[4] By far the most commonly encountered examples of the class are α -bromo- and α -chloroalkylsilanes. The use of iodides, such as (iodomethyl)trimethylsilane,^[5] is less common and fluorides rare with one important exception, trimethyl(trifluoromethyl)silane (Ruppert's reagent). Some of the most important applications of α -haloalkylsilanes are discussed in Applications of Product Subclass 27.

The general approaches to the synthesis of α -haloalkylsilanes are illustrated in [Scheme 1](#). Arguably the most important route (via disconnections a) involves the combination of an alkylsilane and the halogen. Often this is achieved using a radical reaction (a¹). Several α -bromo- and chloroalkylsilanes are prepared in this manner. The incorporation of a good leaving group at the α -position of the alkylsilane allows nucleophilic substitution using a halide (a³). Fluorides and iodides, in addition to chlorides and bromides, can be accessed using this method. The reaction of an electrophilic halogenating agent with an α -silyl anion is another method to form α -haloalkylsilanes (a²). Alkylation of the anion derived from a chloromethyl- or bromomethylsilane is an effective way of achieving the synthesis of α -haloalkylsilanes via disconnection b. Some simple haloalkylsilanes also bearing α -haloalkyl groups are transformed via reaction with nucleophiles to other α -haloalkylsilanes (disconnection c). Silylation of a carbenoid-type haloalkyl anion also offers a versatile method (disconnection d). The following methods (1–6) illustrate these approaches in more detail.

Scheme 1 General Approaches to α -Haloalkylsilanes

SAFETY: The α -haloalkylsilyl group does not bestow any great toxicity upon a molecule, and as such α -haloalkylsilanes do not require any special handling techniques. However, since they can function as alkylating agents in a synthetic sense, the more-reactive compounds, such as α -iodoalkylsilanes, should be treated with care. α -Haloalkylsilanes are stable at room temperature and can be purified by standard techniques; α -iodoalkylsilanes should be protected from sunlight.

α -Haloalkylsilanes have no special spectroscopic properties. However, representative NMR shifts^[6–8] and coupling data for the series of (halomethyl)trimethylsilanes are summarized in Table 1. The analysis of α -fluoroalkylsilanes via ^{19}F NMR clearly presents an additional method of characterization.

Table 1 NMR Spectroscopic Data of (Halomethyl)trimethylsilanes^[6–8]

	^1H (δ)	^{13}C (δ) ^d	^{29}Si (δ)
$\text{Me}_3\text{SiCH}_2\text{F}$	0.15, 4.4 ^a	80.0 ^b	-1.8 ^c
$\text{Me}_3\text{SiCH}_2\text{Cl}$	0.11, 2.72	30.3	3.5
$\text{Me}_3\text{SiCH}_2\text{Br}$	0.13, 2.42	17.4	2.3
$\text{Me}_3\text{SiCH}_2\text{I}$	0.03, 1.93	-11.9	2.3

^a $^2J_{(\text{H}-\text{F})}$ 47 Hz.

^b $^1J_{(\text{F}-\text{C})}$ 124 Hz.

^c $^2J_{(\text{F}-\text{Si})}$ 27 Hz.

^d Methylene signal.

Synthesis of Product Subclass 27

4.4.27.1

Method 1: Direct Halogenation of Alkylsilanes

The direct halogenation of alkylsilanes, via the radical substitution of a hydrogen atom at the α -carbon, sometimes gives α -haloalkylsilanes in acceptable yields. This approach has been used mostly for the preparation of simple derivatives.^[9–11] The reaction is considerably less selective for silanes of higher complexity, unless the radical generated at the α -

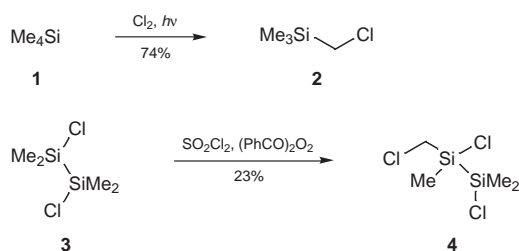
for references see p 19

position is stabilized. It is therefore not surprising that the method has found use for the preparation of α -aryl- α -haloalkylsilanes. There are no examples of the synthesis of α -iodoalkylsilanes by direct combination of a silane with iodine. There is one example of the synthesis of α -fluoromethylsilanes from the reaction of tetramethylsilane and fluorine.^[12] This is unlikely to be a useful method with any general applicability. However, the Grignard reagents derived from chloromethyl-substituted silanes react with the electrophilic fluorinating agent *N*-fluoropyridinium triflate to give fluoromethyl-substituted silanes.^[13]

4.4.27.1.1 Variation 1: Chlorination of Alkylsilanes

There are many reports of the chlorination of simple alkylsilanes. For example, the transformation of tetramethylsilane (**1**) into (chloromethyl)trimethylsilane (**2**) is effected by the action of chlorine under photochemical conditions.^[14] The yield of the reaction in carbon tetrachloride is not high, in common with other examples of this type of reaction. However, significantly higher yields are obtained when the photochemical reaction is performed in the gas phase.^[15] The reaction has been used for the synthesis of (α -chloroethyl)triethylsilane from tetraethylsilane.^[16] The radical chlorination of alkylsilanes is also effected by sulfuryl chloride in the presence of a peroxide initiator (usually dibenzoyl peroxide). The reaction is mostly limited to tetraalkylsilanes and triarylsilanes or those only bearing a methyl group.^[17] Disilanes also undergo the reaction (e.g., **3** \rightarrow **4**) (Scheme 2). The reaction of trihaloalkylsilanes^[14] and dihaloalkylsilanes^[18] is complicated by substitution at other positions in the alkyl chain. Indeed, trichloroalkylsilanes undergo substitution preferentially at the β -position. As expected for a radical reaction, an α -aryl group accelerates the reaction and allows selective α -chlorination of benzylic silanes.^[14,19]

Scheme 2 Chlorination of Alkylsilanes^[11,14]



1,2-Dichloro-1-(chloromethyl)-1,2,2-trimethyldisilane (**4**); Typical Procedure:^[11]

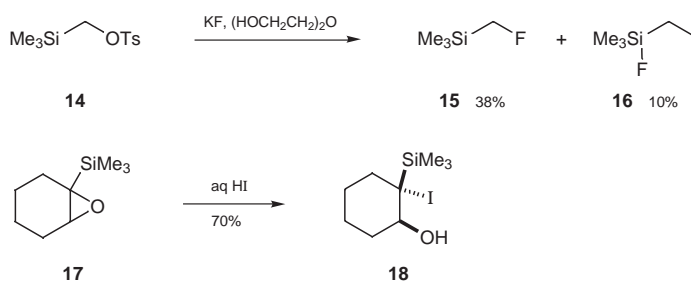
1,2-Dichloro-1,1,2,2-tetramethyldisilane (**3**; 40 g, 214 mmol) and benzoyl peroxide (0.1 g) were placed in a 100-mL three-necked flask equipped with a reflux condenser and pressure-equalizing dropping funnel. The mixture was heated to 80–85 °C and SO_2Cl_2 (43.5 g, 320 mmol) added dropwise through the funnel over a period of 30 min. The mixture was heated for a further 3 h. Additional SO_2Cl_2 (20 g, 150 mmol) was added and the mixture was heated for another 5 h. After flash distillation, fractionation through a short column packed with glass helices gave, in addition to unchanged starting material **3** (yield: 14 g; bp 68–69 °C/50 Torr), the α -chlorodisilane **4**; yield: 11 g (23%); bp 84–85 °C/20 Torr.

4.4.27.1.2 Variation 2: Bromination of Alkylsilanes

The bromination of alkylsilanes has not found widespread use as a general route to α -bromoalkylsilanes. A rare example is the efficient bromination of (isopropyl)trimethylsilane (**5** \rightarrow **6**).^[20] The related bromination of (isopropyl)dimethylsilane clearly shows that a hy-

of Product Subclass 27) is also produced (Scheme 4). The reaction of (trimethylsilyl)methyl trifluoromethanesulfonate with sodium iodide is a good method for the synthesis of (iodomethyl)trimethylsilane.^[32] A siloxy group has been used as the leaving group in the synthesis of 9-chloro-3-methoxy-9-(trimethylsilyl)fluorene derivatives.^[33] α -Alkoxytrimethylsilanes can be transformed into α -bromomethyl- and α -iodomethylsilanes by the action of triphenylphosphine/bromine and potassium iodide/phosphoric acid, respectively.^[34] A more widely used, and related, reaction involves the ring opening of α,β -epoxysilanes (see Section 4.4.29) by halide. In this way, α -halo- β -hydroxyalkylsilanes are obtained with high regioselectivity by treatment of the epoxide with hydrochloric,^[35] hydrobromic,^[36] and hydriodic acids (e.g., **17** \rightarrow **18**)^[37] or tetrafluorosilane/water/diethylisopropylamine.^[38] The silyl group accelerates the substitution at the α -position, even when it is more sterically hindered than the β -position.

Scheme 4 α -Haloalkylsilanes by Nucleophilic Substitution of a Hydroxy-Derived Leaving Group and Ring Opening of an α,β -Epoxysilane by Halide Ion^[31,37]



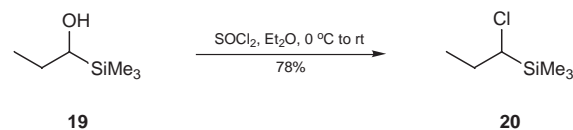
4.4.27.2.1

Variation 1:

Substitution with Chloride Using Thionyl Chloride

Early examples of the substitution of α -hydroxysilanes with chloride employ thionyl chloride as the reagent.^[39] The transformation is achieved simply by mixing the alcohol with thionyl chloride in diethyl ether (**19** \rightarrow **20**, Scheme 5). A benzylsilyl group is not cleaved by the hydrochloric acid produced under these conditions. The reaction has not seen many applications, probably because the yields are not generally high. This has prompted the development of other methods (Sections 4.4.27.2.2 and 4.4.27.2.3).

Scheme 5 α -Chloroalkylsilanes from α -Hydroxyalkylsilanes and Thionyl Chloride^[39]



(1-Chloropropyl)trimethylsilane (20); Typical Procedure:^[39]

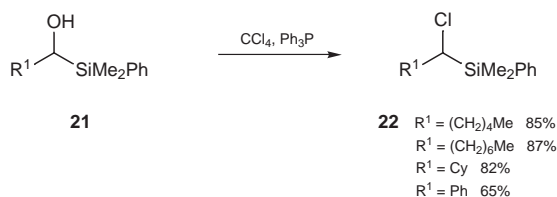
(1-Hydroxypropyl)trimethylsilane (**19**; 0.75 g, 5.8 mmol) in dry Et_2O (5 mL) was added dropwise at 0°C to a stirred soln of SOCl_2 (0.76 g, 6.4 mmol) in dry Et_2O (5 mL). The resulting soln was stirred at 0°C for 20 min and at 25°C for a further 20 min and then heated under reflux for 1 h. Evaporation produced the α -chloropropylsilane **20** as a crude light brown oil; yield: 0.68 g (78%).

4.4.27.2.2

Variation 2:**Chlorination of α -Hydroxyalkylsilanes with Triphenylphosphine and Carbon Tetrachloride**

Significant improvements to the method were accomplished by Barrett and co-workers. They found that conversion of α -hydroxyalkylsilanes **21** {prepared by the addition of [(dimethyl)(phenyl)silyl]lithium to aldehydes}^[40] into the α -chloroalkylsilanes **22** is effected by reaction with carbon tetrachloride and triphenylphosphine without complication (Scheme 6). The Grignard reagent derived from **22** proved to be excellent for the synthesis of α -ketosilanes, used in the synthesis of alkenes via the Peterson reaction (see Applications of Product Subclass 27). The reaction and subsequent purification of **22** is not complicated by competing Brook rearrangement. α -Bromoalkylsilanes can be prepared in a similar fashion from α -hydroxyalkylsilanes by treatment with carbon tetrabromide and triphenylphosphine,^[41] phosphorus tribromide,^[42] or dibromotriphenylphosphorane.^[43]

Scheme 6 α -Chloroalkylsilanes from α -Hydroxysilanes with Carbon Tetrachloride and Triphenylphosphine^[40]

**(1-Chlorohexyl)dimethylphenylsilane [22, R¹ = (CH₂)₄Me]; Typical Procedure:^[40]**

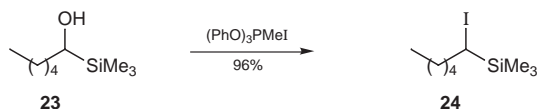
A soln of the α -hydroxysilane **21** [R¹ = (CH₂)₄Me; 18.77 g, 80 mmol] and Ph₃P (27 g, 100 mmol) in THF (300 mL) and CCl₄ (50 mL) (**CAUTION**) was heated under reflux for 6 h in a flask under an atmosphere of argon. After cooling the solvent was removed by vacuum distillation. The residue was extracted with hexanes (3 × 300 mL). Evaporation and chromatography (silica gel, hexanes) of the residue gave the α -chlorosilane **22** as a colorless oil; yield: 17.2 g (85%).

4.4.27.2.3

Variation 3:**Iodination of α -Hydroxyalkylsilanes with Methyl(triphenoxy)phosphonium Iodide**

Barrett and co-workers also found that α -iodoalkylsilanes can be prepared by reaction with methyl(triphenoxy)phosphonium iodide (e.g., **23** → **24**, Scheme 7).^[44] These compounds are of limited synthetic value in the Peterson reaction, since iodine/metal exchange is difficult. Nevertheless the method for their preparation is a rare and potentially important one.

Scheme 7 α -Iodoalkylsilanes from α -Hydroxyalkylsilanes^[44]

**(1-Iodoheptyl)trimethylsilane [24, R = (CH₂)₄Me]; Typical Procedure:^[44]**

DMF (20 mL) was added to the crude alcohol **23** [R = (CH₂)₄Me; 5 mmol] under dry N₂. To this soln was added (PhO)₃PMeI (3.39 g, 7.5 mmol) and the mixture stirred for 12 h in the dark. MeOH (2 mL) and sat. aq Na₂S₂O₃ (1 mL) were added successively. The resulting mix-

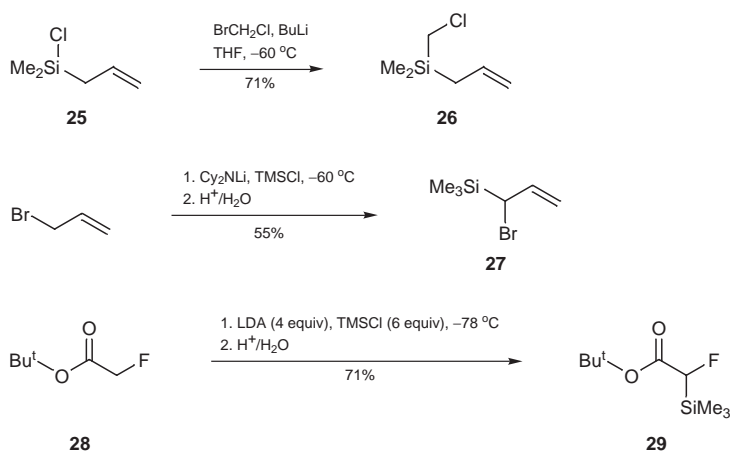
for references see p 19

ture was extracted with Et₂O (3 × 30 mL). The combined Et₂O extracts were washed with sat. aq. NH₄Cl and brine, dried (MgSO₄), and evaporated. The residue was purified by flash chromatography (silica gel, hexanes) followed by Kugelrohr distillation (110 °C, 0.7 Torr) to give the stable α-iodoalkylsilane **24**; yield 1.36 g (96%).

4.4.27.3 Method 3: Haloalkylation of Halosilanes

The haloalkylation of chlorosilanes by the reaction of a (α-haloalkyl)metal species is a useful and reasonably general method for the preparation of α-haloalkylsilanes (disconnection d, **Scheme 1**). Generally, the (chloroalkyl)lithium reagents are prepared in situ by the deprotonation of the corresponding alkyl halide.^[45] For example, (chloromethyl)lithium is conveniently prepared in situ by the treatment of bromochloromethane with butyllithium at temperatures between –70 and –60 °C, in the presence of the chlorosilane (**25** → **26**).^[45] Under these conditions butyllithium does not react with the chlorosilane. The method is applicable to the synthesis of a wide variety of silanes including disilanes and allylsilanes. Bromomethyl and iodomethyl derivatives can be prepared with increasing difficulty by the use of dibromomethane and diiodomethane. 3-Haloprop-1-enes react in the same way with chlorotrimethylsilane and lithium dicyclohexylamide efficiently producing α-haloallylsilanes (allyl bromide → **27**, **Scheme 8**).^[46] (Halomethyl)aryl compounds react in the same way when lithium diisopropylamide is used as the base.^[47–49] Several heterocyclic derivatives have been prepared by this method. [Chloro(pyridin-3-yl)methyl]lithium [prepared from lithium diisopropylamide and 3-(chloromethyl)pyridine] reacts well with chlorotrimethylsilane.^[50] Similar processes can be used to silylate the lithio derivatives of 4-(chloromethyl)pyridine,^[51] 4-(fluoromethyl)pyridine,^[51] and 2-(chloromethyl)benzothiazole.^[52] (Dihalomethyl)trialkylsilanes are prepared efficiently from dihalomethanes, lithium diisopropylamide, and chlorosilanes.^[53] Deprotonation of trihalomethanes with butyllithium at low temperature, followed by reaction with chlorosilanes, generates trihalomethylsilanes.^[54] Similar processes can be effected by formation of the Grignard reagent derived from polybromo- or polyiodomethane.^[55] 1-Bromo-1-(trimethylsilyl)cyclopropanes^[56] can be prepared by the treatment of 1,1-dibromocyclopropanes, magnesium, and chlorotrimethylsilane under ultrasonic irradiation.^[57]

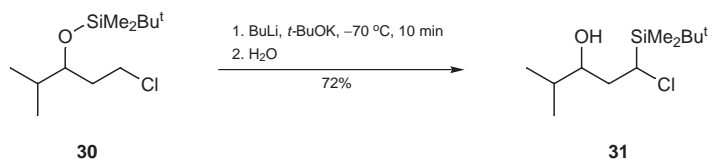
Scheme 8 Reaction of Halosilanes with (α-Haloalkyl)lithium Reagents^[45,46,60]



In general, the approach works when electron-withdrawing groups are present at the α -position. For example, α -haloesters are easily deprotonated with lithium diisopropylamide and silylated to give α -haloalkylsilanes.^[58,59] The reactions are often complicated by competing O-silylation. An excess of both lithium diisopropylamide and chlorosilane ensures a good yield of *tert*-butyl α -fluoro- α -(trimethylsilyl)acetate (**29**) from *tert*-butyl α -fluoroacetate (**28**).^[60]

The treatment of silyl ethers of type **30** yields α -chloroalkylsilanes effectively by an in situ method of (α -haloalkyl)metal formation (Scheme 9). In this case the silyl group undergoes intramolecular transfer from the nearby silyl ether group.^[61] Elimination of hydrochloric acid from the α -chloroalkylsilane **31** is a competing reaction producing alkenylsilanes as byproducts.

Scheme 9 Intramolecular Reaction of a Silyl Ether with a (Haloalkyl)lithium Species^[61]



Allyl(chloromethyl)dimethylsilane (**26**); Typical Procedure:^[45]

Allyl(chloro)dimethylsilane (**25**; 9.7 g, 70 mmol), BrCH_2Cl (9.3 g, 70 mmol) and dry THF (150 mL) were added to a 500-mL three-necked flask equipped with a magnetic stirrer bar, N_2 inlet tube, and thermometer. The mixture was cooled to $-70\text{ }^\circ\text{C}$ and 1.6 M BuLi in hexanes (45 mL, 70 mmol) added down the cold wall of the flask via a syringe over 40 min. During the addition the temperature of the mixture was maintained between -70 and $-60\text{ }^\circ\text{C}$. The soln was then warmed to rt and H_2O (50 mL) was added. The mixture was extracted with hexanes (3×100 mL). The combined extracts were dried (CaCl_2) and evaporated under reduced pressure. The residue was distilled to give the α -chloromethylsilane **26**; yield: 7.6 g (71%); bp $77\text{ }^\circ\text{C}/80$ Torr.

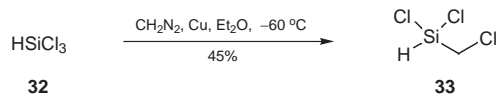
4.4.27.4

Method 4:

Reaction of Halosilanes with Diazomethane

Halosilanes react with diazoalkanes to form α -haloalkylsilanes (**32** \rightarrow **33**, Scheme 10). The reaction is facilitated by copper powder or copper(II) salts.^[62–64] Fluorosilanes are the least reactive of the halides in this type of reaction and effectively do not react in this manner. The reaction is most efficient with di-, tri-, and tetrachlorosilanes. The reaction between tetrachlorosilane and diazomethane is violent at room temperature, but can be controlled at low temperature. In polyhalosilanes, the introduction of one halomethyl group generally retards the introduction of another. Nevertheless, the method is useful for the synthesis of dichloro[bis(chloromethyl)]silane from trichloro(chloromethyl)silane.^[65] Bromosilanes are more reactive than chlorosilanes. The method is applicable to halodisilanes.^[66] The reaction of iodotrimethylsilane or trimethylsilyl trifluoromethanesulfonate with diazomethane does not require catalysis, whereas that of bromotrimethylsilane proceeds conveniently in the presence of zinc dibromide.^[67]

Scheme 10 Reaction of Halosilanes with Diazomethane^[64]



for references see p 19

Dichloro(chloromethyl)silane (33):^[64]

CAUTION: Diazomethane is highly toxic and irritating. It is also a detonator and appropriate safety precautions should be taken when using this reagent (e.g., special glassware, use of a blast shield, etc.). For further details on the safe handling of diazomethane see refs^[68,69].

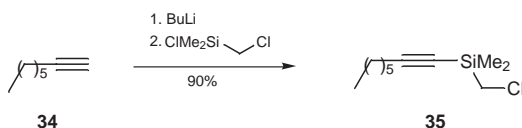
Trichlorosilane (**32**; 40 g, 0.296 mol) in anhyd Et₂O (100 mL) in a 1-L three-necked flask equipped with a mechanical stirrer, a Y-joint holding a thermometer and a drying tube filled with Drierite, and a dropping funnel was cooled to –60 °C and Cu powder (0.5 g) added. A cold soln of CH₂N₂ (0.194 mol) in Et₂O (350 mL) was added slowly through the dropping funnel, with vigorous stirring of the mixture. N₂ evolution began immediately. After the addition was complete the mixture was stirred for 2 h between –65 to –60 °C under dry N₂. The mixture was allowed to warm to rt and stirred for a further 2 h. The Et₂O was removed by distillation through an 18-inch column packed with glass helixes. Another preparation of the same scale was performed and the residues combined and fractionally distilled to give dichloro(chloromethyl)silane (**33**); yield: 40 g (45% based on **32**); bp 97.0–97.4 °C/773 Torr.

4.4.27.5

Method 5:
Nucleophilic Substitution of Halo(haloalkyl)silanes

Substitution at silicon of silanes already bearing bromomethyl or chloromethyl groups is a common process for preparing α -halomethylsilanes. The principle reason for the popularity of the method is the availability of chloro(chloromethyl)dimethylsilane and (bromomethyl)(chloro)dimethylsilane.^[70] Nevertheless the reaction does work well with other halo(α -haloalkyl)silanes.^[14,71] Addition of Grignard^[14,72] and organolithium reagents occurs without the complication of substitution of the halogen at the α -position (e.g., **34** → **35**, Scheme 11). The method has been used to prepare α -halomethyl-substituted vinylsilanes from vinyl Grignard^[73] and vinyl lithium reagents.^[74] Allyl,^[75] alkynyl,^[76] aryl,^[77] and benzyl organometallic reagents also work well. Reaction of (bromomethyl)(chloro)dimethylsilane with alcohols and triethylamine [and sometimes 4-(dimethylamino)pyridine] is commonly used to prepare (bromomethyl)silyl ethers for radical cyclization.

Scheme 11 Reaction of an Alkynyllithium Reagent with Chloro(chloromethyl)dimethylsilane^[76]



(Chloromethyl)(dimethyl)oct-1-ynylsilane (35); Typical Procedure:^[76]

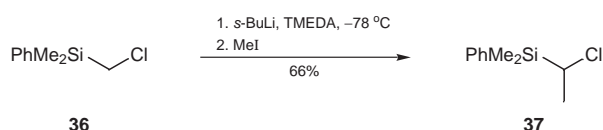
1.5 M BuLi in hexanes (37.3 mL, 55.9 mmol) was added at –78 °C to oct-1-yne (**34**; 6.15 g, 55.9 mmol) in THF (60 mL). The mixture was allowed to warm to 0 °C and stirred for 1 h, and then at rt for a further 15 min. The mixture was cooled to –78 °C. Chloro(chloromethyl)dimethylsilane (8.0 g, 55.9 mmol) in THF (20 mL) was added dropwise to the mixture over 1 h. The resulting mixture was stirred overnight at –78 °C. The mixture was allowed to warm to rt and sat. aq NH₄Cl (50 mL) was added and the mixture extracted with EtOAc (2 × 100 mL). The organic extracts were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The residue was distilled to give (chloromethyl)(dimethyl)oct-1-ynylsilane (**35**) as an oil; yield: 10.9 g (90%); bp 54–57 °C/3 Torr.

4.4.27.6

Method 6: Alkylation of α -Haloalkylsilanes

α -Haloalkylsilanes are deprotonated to provide an anion that reacts readily with haloalkanes (disconnection b, [Scheme 1](#)). The carbanion derived from (chloromethyl)trimethylsilane is stable at low temperature (decomposing slowly over 1 h at -40°C) and reacts with a variety of electrophiles. Similar stability is evident for other members of the product class (**36** \rightarrow **37**, [Scheme 12](#)). α -Haloalkylsilanes are most commonly deprotonated with *sec*-butyllithium at -78°C in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA).^[78–80] Under these conditions α -elimination is not a competing reaction.

Scheme 12 Alkylation of (Chloromethyl)silanes^[78]



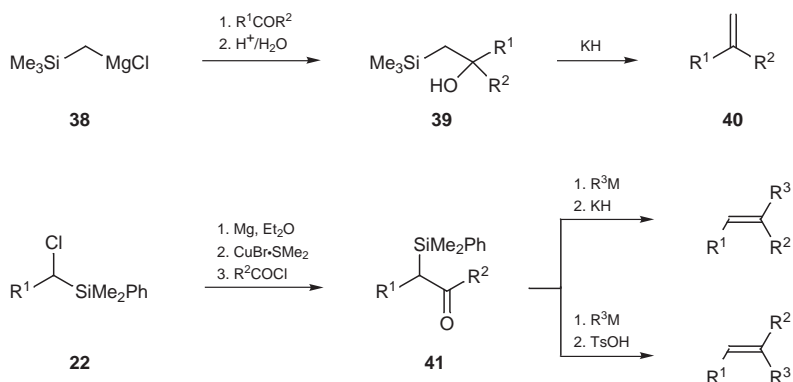
(1-Chloroethyl)(dimethyl)phenylsilane (**37**); Typical Procedure:^[78]

1.4 M *s*-BuLi in cyclohexane/isopentane (92:8) (164 mL, 0.230 mol) was added dropwise over 1.5 h to (chloromethyl)(dimethyl)phenylsilane (**36**; 40.0 g, 0.217 mol) in THF (260 mL) at -78°C . TMEDA (24.1 g, 0.21 mol) was added dropwise to the resulting mixture over 20 min, maintaining the temperature at -78°C . The soln was stirred for 1 h at -78°C and then allowed to warm to -55°C . MeI (41.2 g, 0.29 mol) in THF (70 mL) was added dropwise over 1 h, and the mixture stirred for a further 40 min at -40°C and then 16 h at rt. The mixture was added carefully to cold sat. aq NH_4Cl (700 mL) and extracted with Et_2O (3×350 mL). The combined organic extracts were washed with H_2O , dried (Na_2SO_4), and evaporated under reduced pressure. The residue was distilled to give the silane **37** as an oil; yield: 28.3 g (66%); bp $76^\circ\text{C}/6$ Torr.

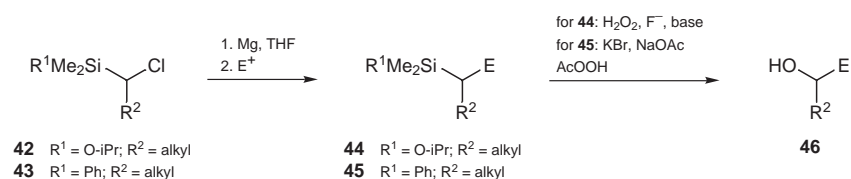
Applications of Product Subclass 27 in Organic Synthesis

The Grignard reagents derived from α -haloalkylsilanes have found widespread use in organic synthesis. Perhaps the most common application of (chloromethyl)trimethylsilane^[14] is as a methylenating agent in the Peterson reaction.^[81] In this reaction addition of the Grignard reagent **38** to carbonyl compounds generates an alcohol **39**, from which an alkene **40** is produced by base-catalyzed elimination ([Scheme 13](#)). The process offers a useful alternative to the Wittig reaction. The Grignard reagents derived from α -haloalkylsilanes are particularly useful for preparing β -ketosilanes, which are themselves useful in the stereoselective version of the Peterson alkenation reaction.^[82] For example, the Grignard reagent derived from (α -chloroalkyl)(dimethyl)phenylsilane **22** reacts with acyl chlorides [with copper(I) catalysis] to give the ketone **41**. Reaction of this ketone with an organometallic reagent (R^3M) followed by potassium hydride or 4-toluenesulfonic acid yields either stereoisomer of the trisubstituted alkene ([Scheme 13](#)). A related process has shown that (iodomethyl)trimethylsilane generates alkenes directly from ketones by the use of samarium(II) trifluoromethanesulfonate.^[83] (α -Silylalkyl)lithiums are produced from α -haloalkylsilanes via transmetalation by reaction with an alkylolithium^[42] or by direct reaction with lithium metal.^[19,84]

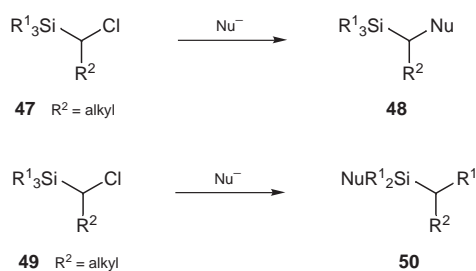
for references see p 19

Scheme 13 α -Haloalkylsilanes in the Peterson Reaction^[81,82]

The Grignard reagents of (chloroalkyl)(isopropoxy)dimethylsilane (**42**, $\text{R}^1 = \text{O-iPr}$) and (chloroalkyl)(dimethyl)phenylsilane (**43**, $\text{R}^1 = \text{Ph}$) provide excellent hydroxyalkyl anion equivalents, which react with electrophiles such as aldehydes, imines,^[80] ketones and epoxides to give the adducts **44** and **45**, respectively (Scheme 14). The hydroxyalkyl group **46** is revealed using the standard silyl-to-hydroxy protocols.

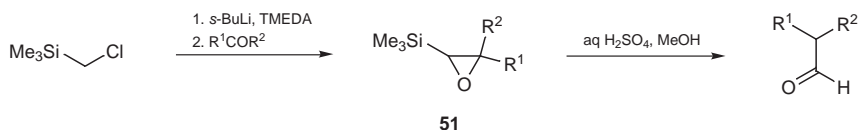
Scheme 14 Hydroxymethylation with α -Haloalkylsilanes^[80]

α -Haloalkylsilanes readily undergo halogen substitution (e.g., **47** \rightarrow **48**) by a wide range of nucleophiles such as iodide,^[85] ammonia,^[86] azide,^[87] amines,^[87] diethyl phosphonacetate,^[88] and phosphorus ylides^[89] (Scheme 15). The use of iodide and fluoride as nucleophiles provides a useful method for the preparation of α -iodo- and α -fluoroalkylsilanes from α -bromo- and α -chloroalkylsilanes. Fluoromethyl-substituted silanes are prepared in moderate yield by the reaction of the corresponding chloromethyl compound with cesium fluoride in the presence of 18-crown-6.^[90] A variation of the substitution reaction is the nucleophile-induced 1,2-transfer of a group bound to the silicon atom (e.g., **49** \rightarrow **50**), which can interfere sometimes with the direct displacement (e.g., **47** \rightarrow **48**).

Scheme 15 Halide Substitution in α -Haloalkylsilanes^[85–90]

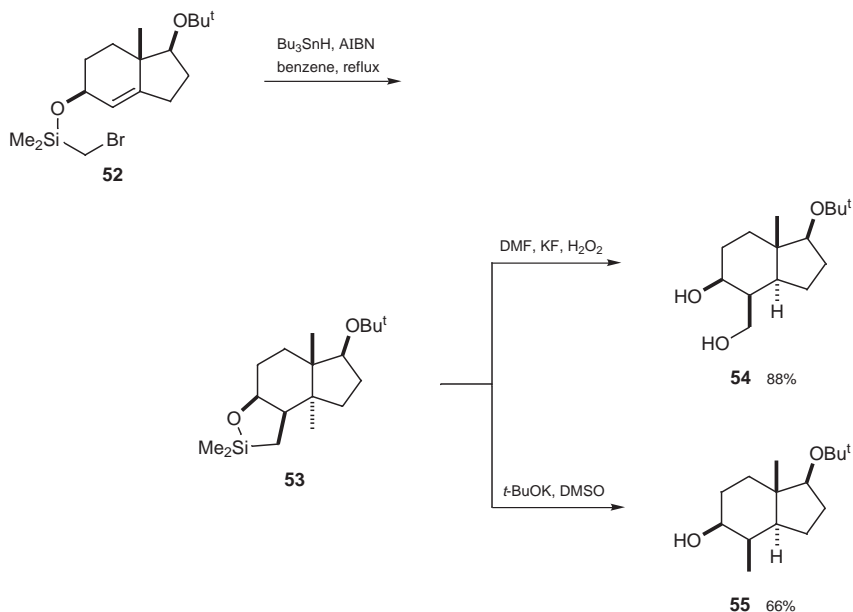
α -Haloalkylsilanes are deprotonated with lithium diisopropylamide or alkyllithium reagents^[55,91] to generate an organolithium reagent which reacts readily with electrophiles such as aldehydes and ketones (Scheme 16). This reaction is incorporated into a useful protocol for the homologation of ketones and aldehydes, by acid-catalyzed transformation of the first formed α,β -epoxysilanes **51** (see Section 4.4.29).^[79,92] The reaction does not work well with aldehydes or ketones that are either hindered or readily enolizable. Other electrophiles are compatible with the process. For example, the use of haloalkanes or deuterium oxide provides chain-extended α -haloalkylsilanes and α -halo- α -deuteroalkylsilanes, respectively.^[93]

Scheme 16 Alkylation of α -Haloalkylsilanes^[79,92]

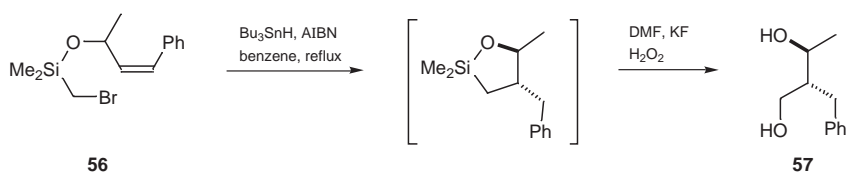


Silyl ethers incorporating an α -haloalkylsilyl moiety have been used to generate α -silyl radicals for radical cyclization (Scheme 17). Recent progress in the radical cyclization of (allyloxy)(bromomethyl)silanes, pioneered by Stork^[94] and Nishiyama,^[95] is summarized in an excellent review.^[96] The initial product **53** of the reaction of silyl ether **52** is oxidatively cleaved to give a diol **54**. Alternatively, treatment of **53** with potassium *tert*-butoxide in dimethyl sulfoxide gives the methyl-substituted alcohol **55**.^[97] Exceptional levels of stereocontrol are obtained in the acyclic series (e.g., **56** \rightarrow **57**).^[95] The reaction is usually performed with silyl ethers possessing a bromomethyl group as (bromomethyl)halo(dimethyl)silanes are commercially available. Nevertheless, α -alkyl- α -bromosilanes undergo the same type of reaction.^[43] The use of intramolecular radical traps facilitates tandem radical cyclizations in a similar fashion.^[98,99] (Chloromethyl)silanes and (bromomethyl)silanes are reduced under similar radical conditions to the corresponding trialkylmethylsilanes.^[7,39,100]

Scheme 17 Radical Cyclization of (Allyloxy)(bromomethyl)silanes^[94–97]

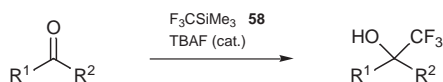


for references see p 19



Finally, no consideration of the chemistry of α -haloalkylsilanes would be complete without mention of Ruppert's reagent^[101,102] (**58**). In the presence of a source of fluoride (usually tetrabutylammonium fluoride), the reagent will deliver a trifluoromethyl group to carbonyl groups of aldehydes and ketones,^[103,104] esters,^[105] and a variety of other functional groups (Scheme 18). The exceptional versatility of the reagent is revealed in an excellent review from Prakash and Yudin.^[102]

Scheme 18 Trifluoromethylation of Carbonyl Compounds with Ruppert's Reagent^[101–104]



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