Silicon-Mediated Organic Synthesis

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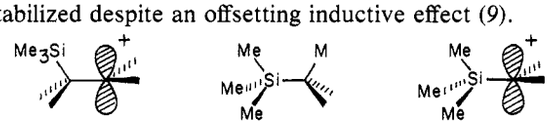
Summary. Organic chemists have used the chemical properties of tetracovalent silicon in a remarkable variety of new synthetic transformations. In carbon-functional silanes, exceptional stabilization is provided to a carbocation center in the beta position when the carbon-silicon bond lies in plane. This phenomenon directs electrophilic attack to the silicon-substituted carbon in aryl-, vinyl-, and alkynylsilanes and to carbon-3 in allylsilanes. For different reasons, silicon also stabilizes a carbon-metal bond in the alpha position. Consequently, access to many silicon-containing organometallics is readily available. The exceptional strength of silicon-oxygen and silicon-fluorine bonds is yet another factor that controls the chemical reactivity of silicon reagents. In recent developments, preparative chemists have taken advantage of these properties in imaginative and useful ways.

During the past 15 years, organosilicon chemistry has developed to the point where it is now a highly valued tool for the preparative organic chemist (*1–3*). From its early concerns primarily with silicone polymer fabrication (*4*), stereochemical phenomena (*5*), and functionalization of polar substances to enable gas chromatographic analysis (*6*), the field of organosilicon research has attained an increasingly important position in organic synthesis. The vigorous growth of this field has been due to the ever-increasing need for methods of forming carbon-carbon bonds under relatively controlled cationic and anionic conditions. Because it is the mildest metal, silicon fulfills this role and allows also for the implementation of additional reaction types. Furthermore, by the proper choice of reagents it is often possible to attain regioselectivity or stereoselectivity, that is, to obtain predominantly one positional or spatial isomer.

Some appreciation of the synthetic potential of silicon can be gained by comparing its properties with those of carbon, which is positioned above it in the periodic table. Chiefly because silicon is larger (atomic radius, 1.17 angstroms) and more electropositive (electronegativity, 1.74) than carbon (0.77 Å, 2.50), and possibly because silicon has empty 3*d* orbitals, Si–C bonds are weaker than C–C bonds (75 versus 83 kilocalories per mole, respectively). In contrast, single bonds from silicon to electronegative atoms such as oxygen (108 kcal/mole) and fluorine (129 kcal/mole) are notably strong. Consequently, while fluorine ion shows poor nucleophilicity for carbon, it readily attacks silicon.

In keeping with the position of silicon as a second-row element, bimolecular nucleophilic substitution in compounds of the type R_3SiX (where R is an aryl or alkyl group and X is the leaving group) occurs much more readily than in their carbon counterparts. This heightened reactivity carries over to carbon-functional silanes, where attack by oxygen and halogen nucleophiles is generally faster at silicon than at hydrogen. Also to be appreciated is the effect of silicon's greater electropositive character, which causes the sigma orbital associated with an Si–C bond to have a higher coefficient on carbon. Exceptional stabilization is therefore provided by overlap of such orbitals with the empty orbital of an adjacent carbocation center when an in-plane arrangement is adopted as in **1** (*7*). A carbon-metal (C–M) bond in the α position (**2**) is also favorably disposed for stabilization as the result of energy-lowering overlap of the filled C–M orbital with the *d* orbitals on silicon or the antibonding orbitals of the methyl-silicon (Me–Si) bond, both of which are empty (*8*). For related reasons, α-silyl cations of type **3** are appreciably destabilized despite an offsetting inductive effect (*9*).

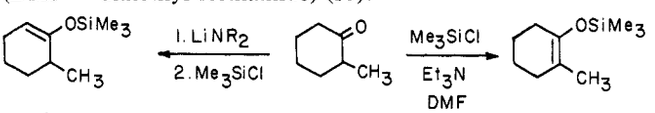


1 **2** **3**

These reactivity patterns, coupled with the low steric requirements of the trimethylsilyl group and the ability of Si–H bonds to add across olefinic and acetylenic linkages when appropriately catalyzed (hydrosilation), are the basis for the contributions of organosilicon chemistry to organic synthesis. The challenge has been to deploy the special chemical properties of silicon to achieve transformations heretofore more cumbersome or impossible to realize. In the following sections suitable examples of the power of this methodology are discussed.

Electrophilic Chemistry

The activation of carbonyl groups through conversion to silyl enol ethers has become a much utilized technique. Conditions have been developed to enable trapping of both kinetic and thermodynamic enolate anions such as **4** and **5** (DMF = dimethyl formamide) (*10*).



4 **5**

O-Silylation almost always predominates heavily (*11*). Regiospecificity in the generation of silyl enol ethers can also be attained by 1,4 addition to conjugated enones (*10, 12*), enone reduction by lithium in liquid ammonia (*13*), and reductive silylation of α-halo ketones (*14*); examples of these approaches are shown in the next group of reactions.

Although isomerically pure trimethylsilyl enol ethers can be transformed cleanly into structurally well-defined lithium enolates by reaction with methyl-lithium (for instance, in the replacement of Me_3Si in **6** as **6** → **7**) (*10, 15*), they are more often used directly with reagents that have reasonable electrophilicity. A valid assumption appears to be that silyl enol ethers have reactivities comparable to those of their derived enols. The key advantage to be gained is that one no longer deals with the complications which arise from keto-enol

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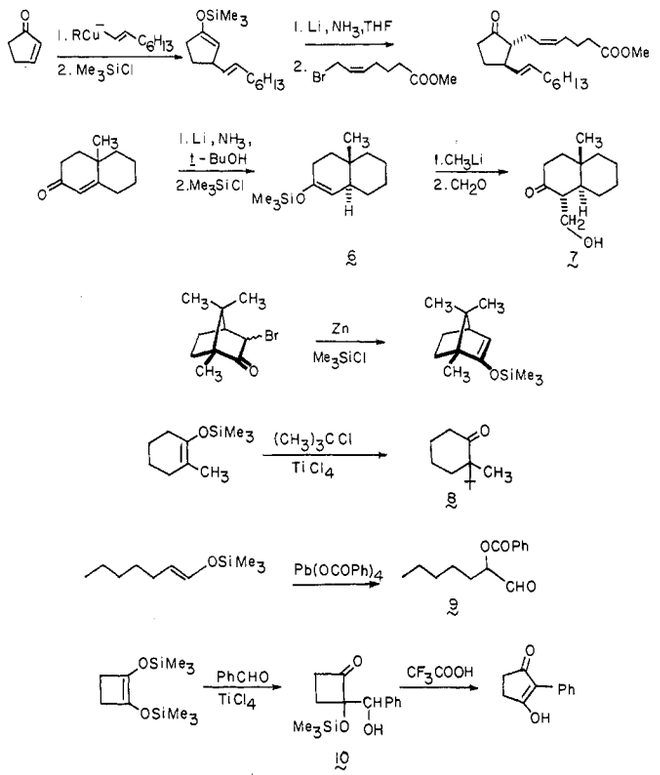
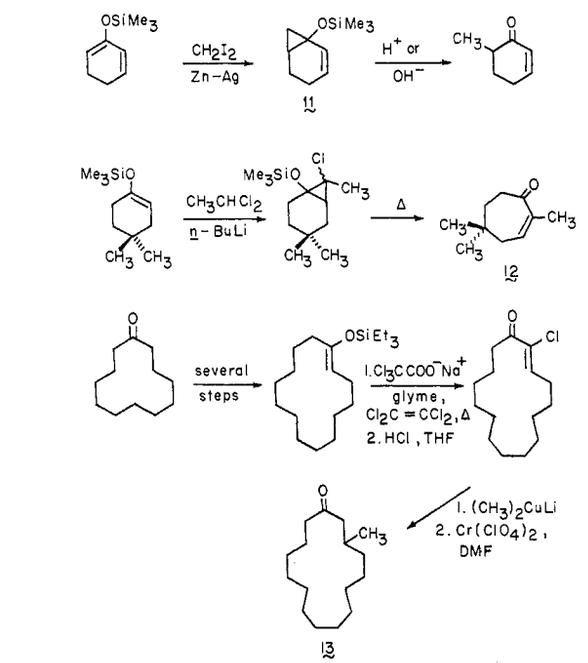
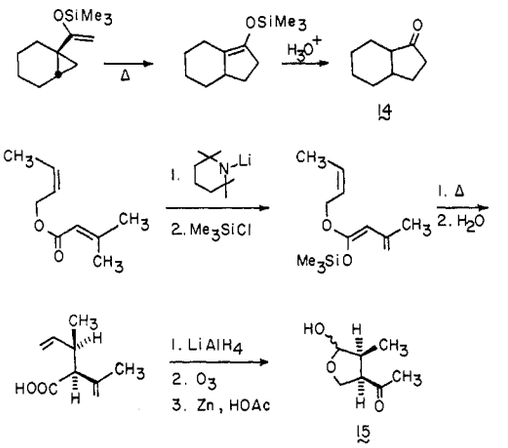
equilibria. A wider range of electrophilic processes is consequently made available; the formation of **8**, **9**, and **10** is exemplary (*16*). The facile generation of a quaternary center, as in **8**, is particularly noteworthy.



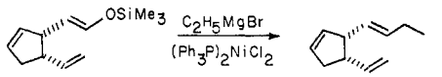
The double bond of silyl enol ethers can also be used advantageously. Following cyclopropanation, as in **11**, ring opening can be achieved in acid or base, or by using various electrophilic agents to achieve selective monoalkylation (*17*). Smooth ring expansions can be achieved, as in **12**, by halocarbene additions (*18*). The preparation of muscone (**13**) by this method is an example of a protocol by which an inexpensive starting material can be conveniently transformed into a valued commodity (*19*).



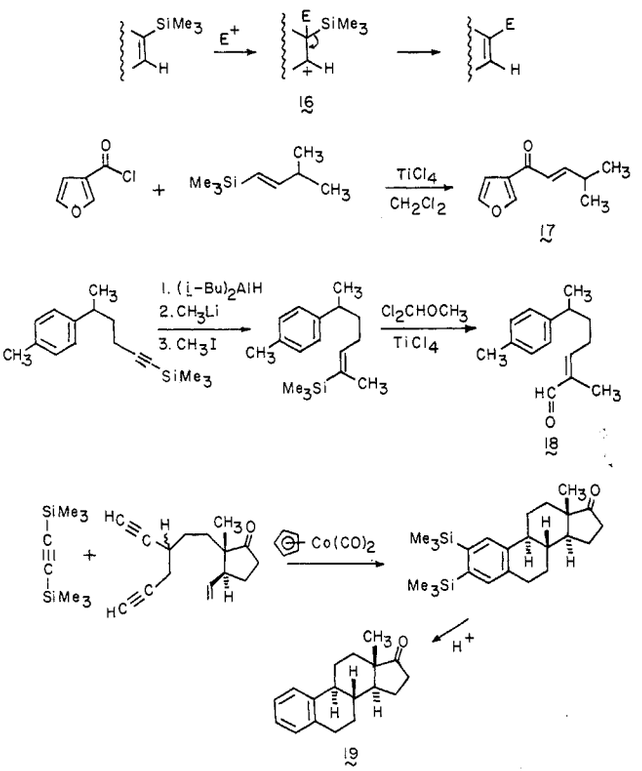
Upon thermal activation, silyl enol ethers can enter into vinylcyclopropane rearrangement, providing a useful means for cyclopentanone annulation, as in the formation of **14** (*20*). Through stereospecific Claisen rearrangement, olefinic acids have been produced which serve as precursors of insect pheromones, the antibiotic botryodiplodin (**15**), and other types of natural products (*21*).



While silyl enol ethers are usually inert toward Grignard reagents, coupling can be readily effected by the addition of a nickel catalyst (*22*). The technique represents a powerful cross-coupling method for olefin synthesis (*23*).

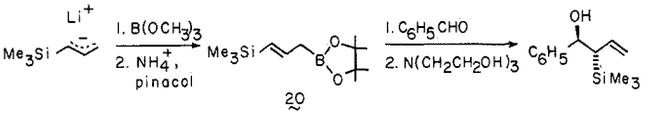


Aryl- and vinyl-silicon bonds are cleaved with unusual facility by electrophilic reagents because Si–C bonds stabilize a β-carbocation (see **1**) better than do C–H and C–C bonds. Attack by the electrophile (E^+) is consequently most often directed to the silicon-bearing carbon, as in **16**. With loss of the silyl functionality, a product is formed with net substitu-



tion by the electrophile. This type of intermolecular reaction has been widely employed; some examples from the area of natural products chemistry include the formation of isoegomaketone (**17**) (*24*), nuciferal (**18**) (*25*), and estra(10)-trien-17-one (**19**) (*26*).

A highly diastereoselective condensation reaction occurs when the vinylsilane also forms part of an allylic boronate moiety, such as **20** (*27*). Controlled deoxysilylation of the resulting *threo* hydroxy silanes (note preferential loss of the boron functionality) provides a convenient synthesis of either *Z* or *E* terminal dienes.



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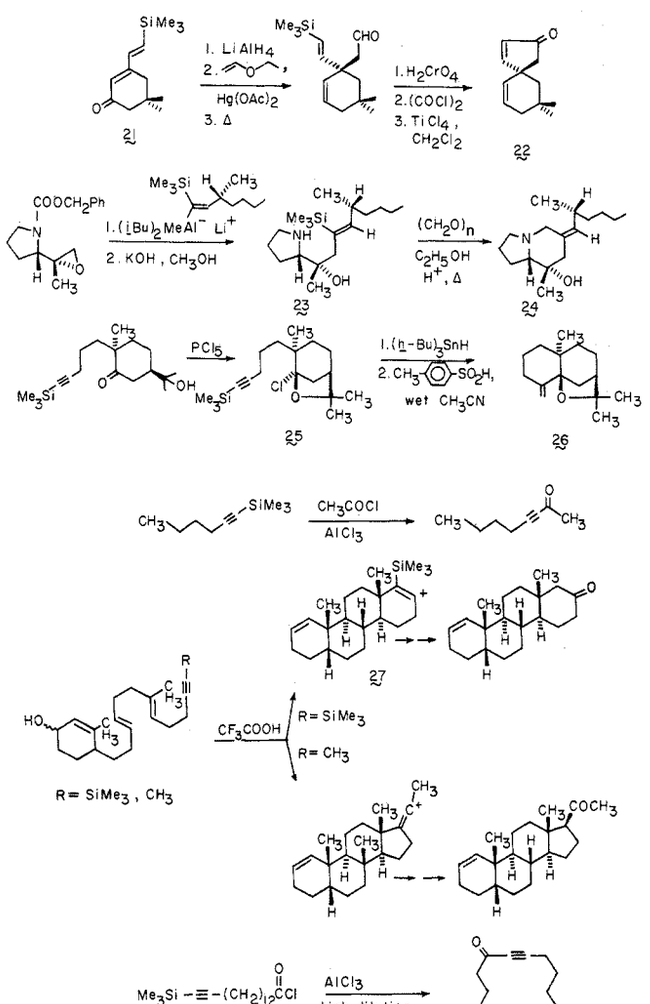
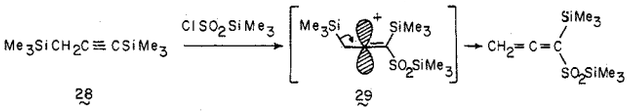
Still more impressive are the recent advances in organic synthesis which have as their basis intramolecular variants of this concept. The vinylsilane-mediated spiroannulation sequence which effects facile overall conversion of **21** to spirodienone **22** (*28*) and the iminium ion–vinylsilane cyclization **23** to **24** which stereospecifically assembles the (*Z*)-6-alkylideneindolizidine ring system known as dendrobatid toxin 251D are particularly noteworthy (*29*). Where silylacetylenes are concerned, free radical conditions can be applied to achieve addition across the triple bond. In the cyclization of **25**, the key step in a new synthesis of β-agarofuran (**26**), kinetically favored six-membered ring formation controls the regiochemistry of C–C bond formation (*30*).



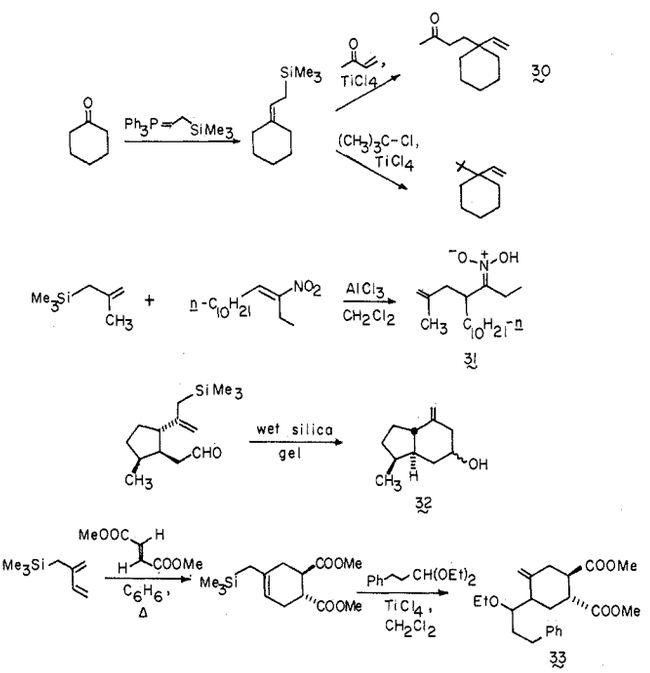
Like vinylsilanes, alkynylsilanes generally react with electrophiles to give substitution products (*31*). When alkynylsilanes are used as terminator groups in polyolefin cyclization, stabilization provided by the C–Si bond in **27** gives rise to a regioselectivity opposite to that provided by alkyl substituents (*32*). In intramolecular cyclization reactions, addition rather than substitution will be forced on the alkynylsilane if the ring being formed is small (compare **25** → **26**). When factors of this type are not at issue, normal reactivity returns (*33*).

The bifunctional acetylene **28** reacts with electrophiles in the sense shown in intermediate **29** (*34*). This reactivity



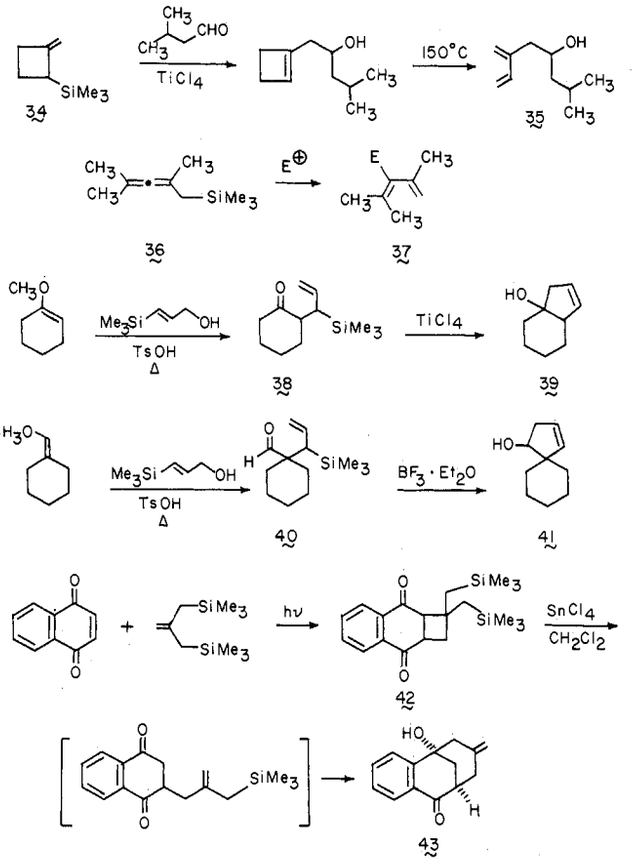
28 29

pattern indicates that cationic stability as in **1** is more favorable than that found, for example, in **27**. An identical pattern of behavior is followed by allylsilanes, loss of the silicon substituent occurring rapidly. As suggested by examples **30** to **33**, the range of electrophiles toward which allylsilanes are reactive is large (*35*). As a rule, allylsilanes are somewhat more nucleophilic than the corresponding hydrocarbons, while vinylsilanes usually show comparable reactivity.



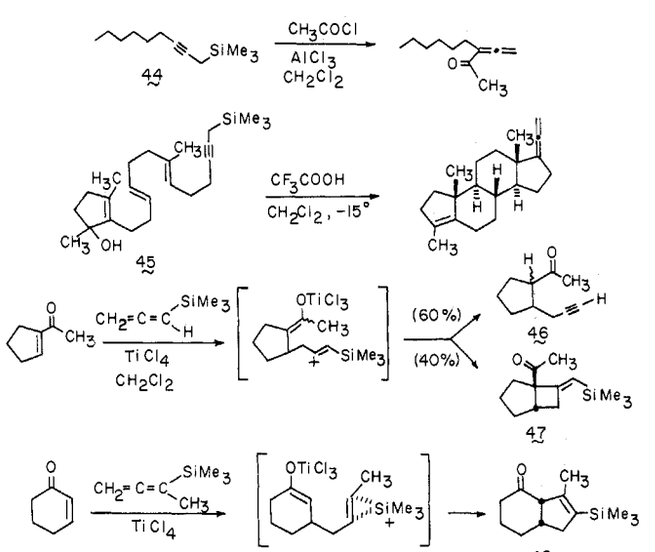
As a consequence of their chemical versatility, allylsilanes have been applied in a broad spectrum of imaginative synthetic protocols. In the methylenecyclobutane **34**, reaction with electrophiles proceeds exclusively in the expected way with allyl shift to give a 1-substituted cyclobutene. Subsequent thermal ring opening provides a functionalized isoprene; the terpenoid tagetol (*35*) is an example (*36*). Comparable mechanistic considerations lead one to view silane **36** as an immediate precursor of 2,3-disubstituted butadienes. Because the reactivity of **36** is comparable to that of simpler allylsilanes, an efficient and simple route has been opened to such compounds as **37** (*37*). The in situ Claisen rearrangement which transforms enol ethers into 2-substituted 3-trimethylsilyl enones—for instance, **38** and **40**—provides a new and richly variable technique for the synthesis of annulated (**39**) and spirocyclic (**41**) systems (*38*). In one of the more elegant applications of this chemistry, disilane **42** was prepared by [2 + 2] photocyclization and treated with stannic chloride. Following Lewis

acid–promoted elimination of one silyl substituent, which yields an allylsilane, cyclization to tricyclic hydroxy ketone **43** takes place (*39*).

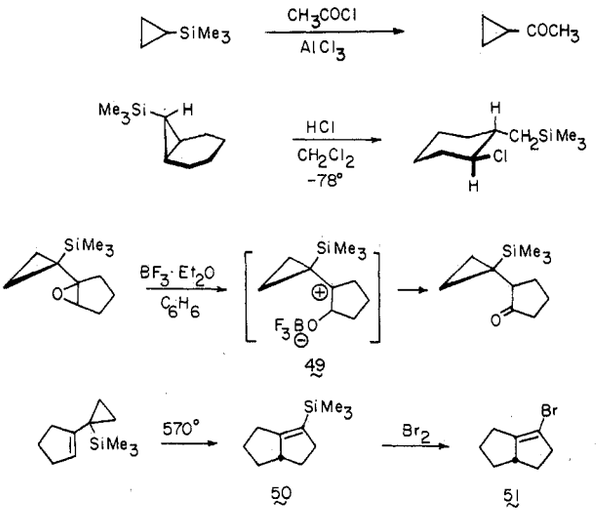


As foreshadowed by **28**, propargylsilanes are readily transformed to allenes by electrophilic reagents. The chemical reactivity of **44** and **45** is prototypical (*40*). Allenylsilanes experience electrophilic attack regiospecifically at C-3, initially providing a vinyl cation. This species may lose the silyl substituent to yield an acetylene (**46**), undergo intramolecular capture with retention of the silane residue (**47**), or be sufficiently stabilized by interaction with the adjacent C–Si bond to be subject to 1,2-silyl migration (**48**) (*41*).

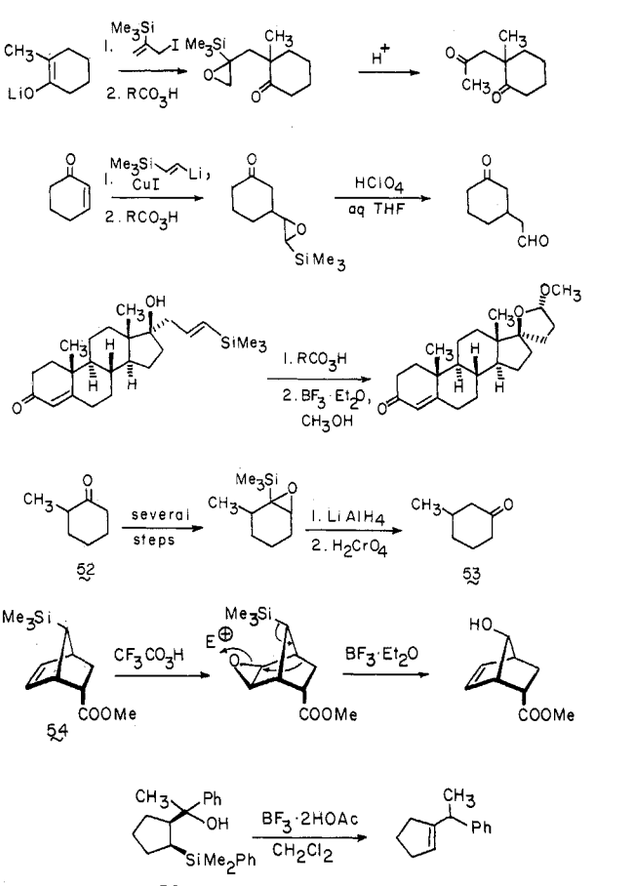
Although silylcyclopropanes show appreciable stability in the presence of a variety of chemical reagents, they are known to be subject to electrophilic substitution (*42*) and ring opening



(*43*). Recent studies have shown that α-trimethylsilylcyclopropylcarbinyl cations, such as **49**, are unwilling to undergo elimination to the methylenecyclopropane (*44*). The pyrolysis of structurally related vinylcyclopropanes does, however, lead smoothly to annulated vinylsilanes (**50**), which can be transformed under electrophilic conditions to functionalized cyclopentenes (**51**) (*45*).



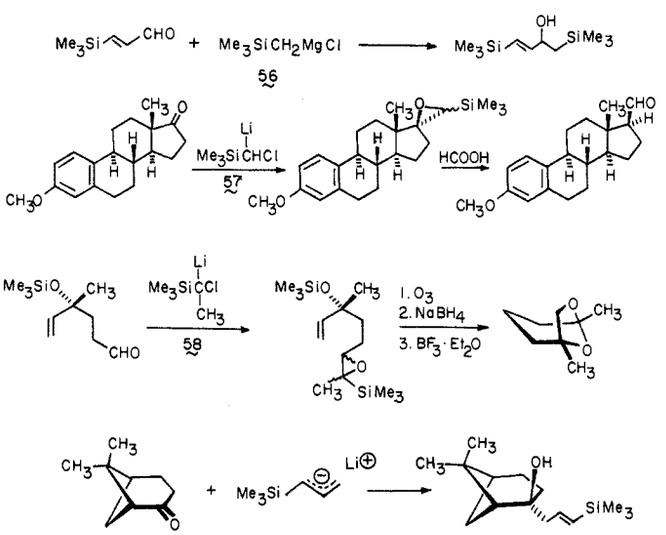
Open-chain epoxysilanes are hydrolyzed in aqueous acid to aldehydes and ketones. When used in this manner, a vinylsilane can conveniently serve as a masked carbonyl group (*46*). In these reactions the carbonyl group appears on the carbon atom that originally carried the silicon substituent. This process can be cleanly reversed in cyclic epoxysilanes. A useful method for achieving 1,2-carbonyl migration—for instance, **52** → **53**—has stemmed from this chemistry (*47*). Singlet oxygen can act on vinylsilanes with similar results (*48*).



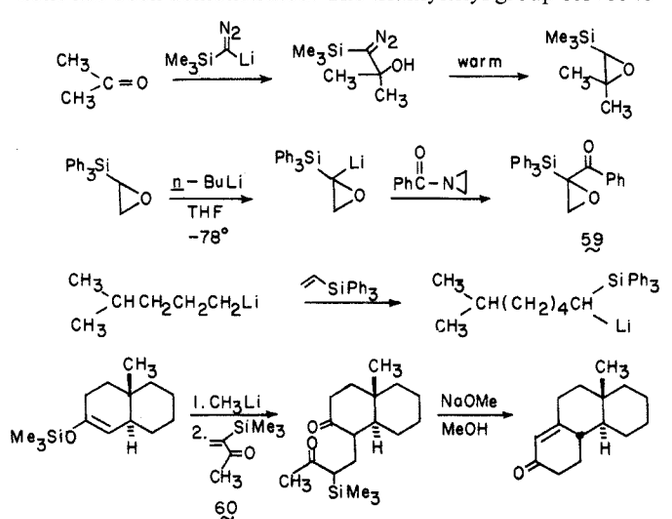
Finally, it is important to recognize that silicon substituents can direct the course of carbonium ion rearrangements from distal positions (*49*). The manner in which a silyl group can control the outcome of these reactions is illustrated for two examples (**54** and **55**).

Nucleophilic Chemistry

As noted earlier, silicon is able to stabilize adjacent carbon-metal bonds even though it is more electropositive than carbon. For this reason, formation of the Grignard reagent **56** (*50*) and α-deprotonation of a host of functionalized silanes to produce α-lithiosilanes are now commonplace (*51*). Among reagents of this class, **57** and **58** have so far commanded the greatest attention because of their usefulness as nucleophilic carboxaldehyde and methyl ketone equivalents (*52*). Since allylsilanes are easily metallated, their anions have also found broad use in synthesis (*53*).

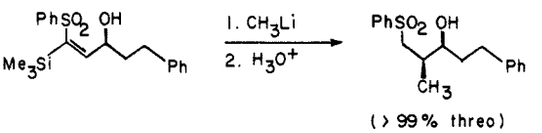


The ease with which (trimethylsilyl)diazomethane is deprotonated is noteworthy since the resulting carbonyl addition products are transformed readily into epoxysilanes (*54*). Alkyllithium reagents also remove the proton α to silicon in epoxysilanes and provide for convenient nucleophilic transfer of this heterocyclic moiety (see **59**) (*55*). Triphenylvinylsilane and related compounds enter into 1,2 addition with alkyllithiums to generate α-lithio-α-silyl nucleophiles (*56*). The utility of silylated vinyl ketones (**60**) in Robinson annulation reactions has been demonstrated. The trialkylsilyl group serves to

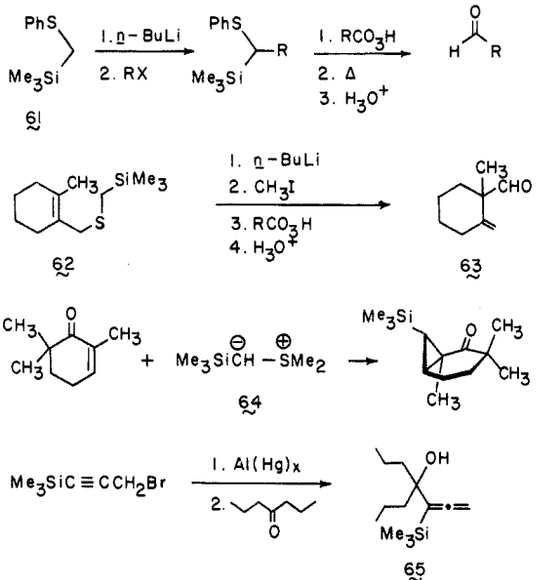


retard enone polymerization and allow use of these building blocks under aprotic conditions with regiospecifically generated enolates (*10, 13, 57*).

High levels of 1,2-asymmetric induction are attained when methyllithium is added to a vinylsilane which is further activated by a phenylsulfonyl group and has an allylic alkoxide as an existing chiral center (*58*).



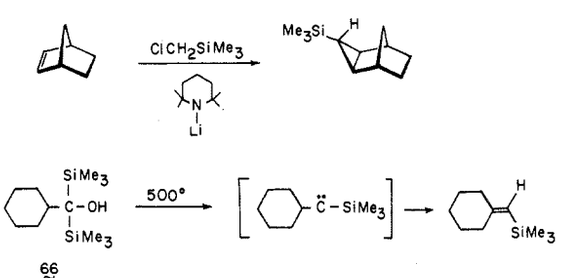
The ease with which **61** can be deprotonated and alkylated is valued because the adducts are convertible to aldehydes by sequential oxidation, thermal rearrangement, and hydrolysis (*59*). This methodology and anionic sigmatropy were elegantly coupled in the formation of aldehyde **63** from **62** (*60*). The



silicon-substituted ylide **64** undergoes conjugate addition to enones to give silylcyclopropanes (*61*). The organometallic produced by reaction of (trimethylsilyl)propargyl bromide with aluminum amalgam condenses with carbonyl compounds to give allenic products **65** (*62*).

Carbenoid Chemistry

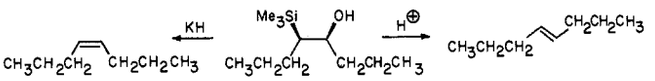
Cuprous chloride–promoted decomposition of (trimethylsilyl)diazomethane in olefins produces silylcyclopropanes with retention of alkene stereochemistry (*63*). More recently, the combination of lithium 2,2,6,6-tetramethylpiperidide and (chloromethyl)trimethylsilane has evolved as a functionally similar (*64*) but not identical (*43*) carbene source. Other known routes to silylcarbenes involve the decomposition of organomercury reagents such as $(Me_3SiCCl_2)Hg$ (*65*) and insertion of



atomic carbon into Si–H bonds (*66*). Detailed studies of (trimethylsilyl)(carboethoxy)carbene (*67*), (trimethylsilyl)-phenylcarbene (*68*), (trimethylsilyl)carbene (*69*), and bis(trimethylsilyl)carbene (*70*) have also been reported. The pyrolysis of 1-(trimethylsilyl)-1-alkanols (such as **66**) as a method of carbene formation holds considerable promise (*71*).

Elimination Reactions

Although alkene-forming 1,2-elimination reactions of β-functional organosilanes have been known for more than three decades, applications to organic synthesis have appeared only recently. The rapid development of this area appears to be due principally to (i) the demonstration that these eliminations can proceed under very mild conditions with fluoride ion (*72, 73*); (ii) the discovery that β-hydroxyalkylsilanes undergo elimination under both acidic and basic conditions (*74*), most notably with high and opposite stereoselectivities (see **67**) (*75*); and (iii) the realization that 1,3- and 1,4-elimination reactions are feasible.



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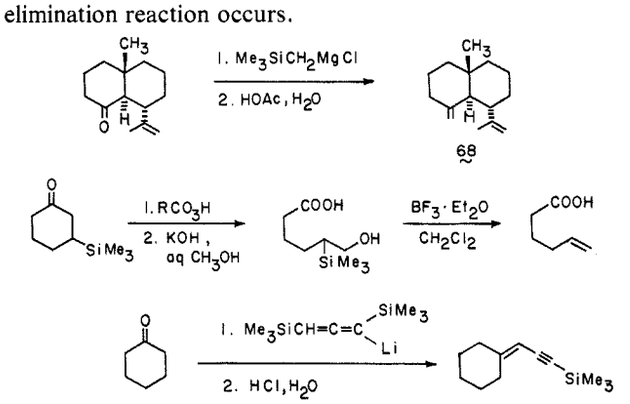
The most useful alkene-forming process is the Peterson olefination reaction, which involves the condensation of carbonyl compounds with α-silyl organometallics (*76*). As exemplified by the preparation of β-gorgonene (**68**), the scheme is closely allied to the Wittig reaction but is more powerful because of the higher nucleophilicity and smaller bulk of the silicon reagent relative to a phosphorus ylide. If the silicon-bearing carbon does not also carry a carbanion-stabilizing group, β-hydroxysilanes are generally isolated and must be separately treated with acid (*77*) or base (*78*). Otherwise, a fast elimination reaction occurs.



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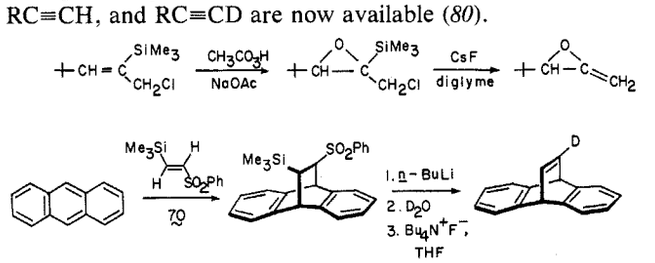
The usefulness of fluoride ion–promoted β-dehalosilylation has been amply demonstrated. Allenes, allene oxides, and cyclopropenes have been prepared (*73*). The smooth elimination of β-silylsulfones in the presence of F^- (*79*) has been applied to cycloadducts of **70** with the result that synthetic dienophile equivalents of HC≡CH, HC≡CD, DC≡CD, RC≡CH, and RC≡CD are now available (*80*).



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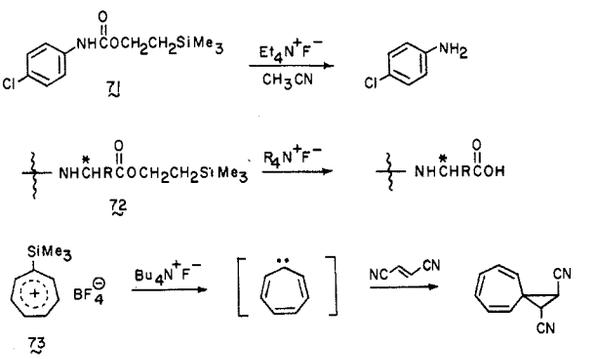
Special attention has been given to β-(trimethylsilyl)ethoxy protecting groups for both amines (*81*) and carboxylic acids (*82*). Derivatives such as **71** and **72** are stable under a wide variety of conditions, but may be readily cleaved by fluoride ion without racemization occurring. The exceptional strength of the Si–F bond has been used to advantage in converting the silyl-substituted tropylium ion **73** to cycloheptatrienylidene (*83*).



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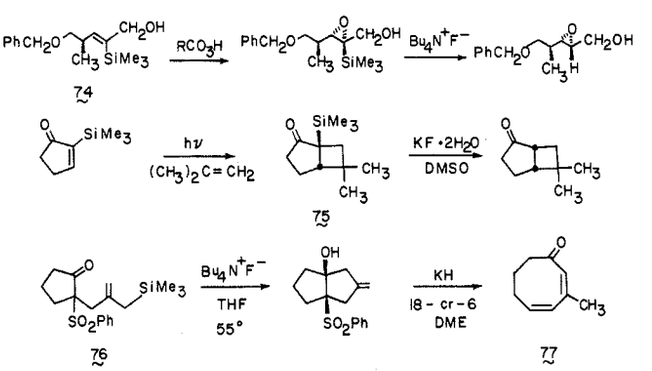
Imaginative applications of this synthetic methodology have recently appeared. Use of the trimethylsilyl group as a vinyl substituent in **74** allows for stereoselective epoxidation. Subsequent removal of the silicon residue with fluoride ion proceeds with retention of stereochemistry (*84*). Whereas photocycloaddition reactions of 2-cyclopentenone to terminal olefins show virtually no regioselectivity, this complication is nicely circumvented through incorporation of a trimethylsilyl group at C-2. Desilylation of the head-to-tail cycloadducts (such as **75**) delivers isomerically clean bicyclic ketones (*85*). The first stage of a general three-carbon ring expansion sequence illustrated by the conversion of **76** to **77** involves silane-mediated allyl anion generation (*86*).



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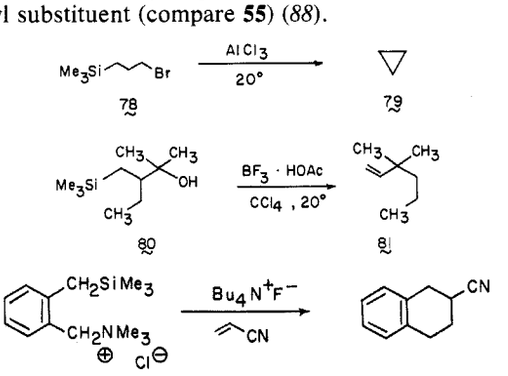
Although several 1,3 eliminations of a silyl group are known—for example, **78** → **79** (*87*)—the more common observation is β-alkyl or hydrogen migration with ultimate loss of the silyl substituent (compare **55**) (*88*).



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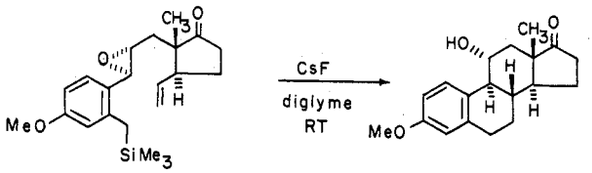
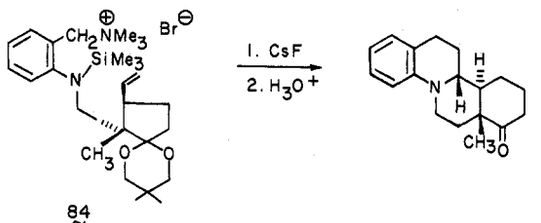
82

Fluoride ion–induced 1,4 eliminations of activated benzylic systems such as **82, 83,** and **84** proceed under very mild conditions to liberate highly reactive *o*-quinonemethides, which, under the proper conditions, can be trapped inter- or intramolecularly (*89*). This strategem now serves as the basis for the stereoselective synthesis of carbocyclic and heterocyclic natural products.



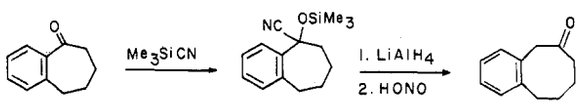
83



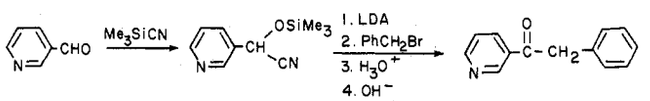
84

Synthetic Applications of Me_3SiX Reagents

Monofunctionalized trimethylsilyl compounds have emerged as utilitarian reagents for effecting a diverse array of chemical transformations. Cyanotrimethylsilane, for example, condenses readily with aldehydes and ketones to produce silylated cyanohydrins (**85**) (*90*). When the nitrile group in such adducts is reduced, β-aminoethanols result and Tiffeneau-Demjanov ring expansions become possible (*91*). Since conversion to the corresponding anion (in aldehyde derivatives) can also be accomplished, these nucleophiles serve well as acyl anion equivalents (*92*).

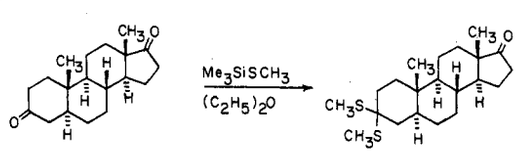


85



Iodotrimethylsilane, an equally versatile reagent, readily cleaves esters (*93*), lactones (*94*), carbamates (*95*), and aryl ethers (*96*) under conditions presumed to be neutral. Furthermore, alcohols are converted to alkyl iodides (*97*), sulfoxides to sulfides (*98*), and epoxides to silylated iodohydrins (*99*) in its presence. If the latter reaction is performed in the presence of a tertiary amine base, allylic alcohols result (*100*). There are also conditions that lead directly from epoxide to alkene with an exceptionally high yield (*101*).

Azidotrimethylsilane behaves analogously (*102*), primary amines being produced if the adducts are treated with lithium aluminum hydride (*103*). The condensation of methylthiotrimethylsilane with aldehydes and ketones likewise proceeds readily to deliver dithioacetals, regioselectively if desired (*104*).



The foregoing examples should give some idea of the exciting and highly promising nature of organosilicon-mediated organic synthesis. This field of research has been rapidly gaining momentum and its continued growth can be confidently forecast.

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