Steric Influence of the Trimethylsilyl Group in Organic Reactions†

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Contents

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I. Introduction

The Me_3Si group is commonly used in organic reactions for the control of stereochemistry. There are two general ways to utilize this silyl group in order to obtain selectivity. The first is to locate the Me_3Si group in the skeleton of substrates at an appropriate position. After the desired transformation is accomplished, the Me_3Si group in products can then be removed by protodesilylation. The second is to replace the protons in reagents or catalysts by the Me_3Si group. Examples include $Me_3SiOCH_2CH_2OSiMe_3$ (from $HOCH_2CH_2OH$), $Me_3SiC{\equiv}CSiMe_3$ (from $HC{\equiv}CH$), $Me_3SiSiMe_3$ (from H_2), $(Me_3Si)_3N$ (from NH_3), $Me_3SiSSiMe_3$ (from H_2S), Me_3SiCl (from HCl), and $Me_3SiOSO_2CF_3$ (from $HOSO_2CF_3$). Both approaches involve the replacement of protons with the bulkier Me_3Si group. Thus the Me_3Si group is referred to as the "bulky proton".[1]

In this Review, we discuss the influence of the Me_3Si group on organic compounds and reactions. Topics are selected from papers published mainly between 1980 and mid-1988. During this period of time, several informative reviews on silicon-mediated stereochemically

† Dedicated to Professor Nien-Chu Yang on the occasion of his birthday.

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TABLE 1. **Order of the Size of Alkyl and Aryl Silyl Groups Based on Their Influence on Various Reactions**

reaction studied	selectivity basis	order of the size	ref
oxidation of trialkylsilanes	reaction rate	$Et_2MeSi < (n\text{-}Pr)_2MeSi < (n\text{-}Bu)_2MeSi < Et_3Si < (n\text{-}Pr)_3Si < (n\text{-}Bu)_3Si < (t\text{-}Bu)(cyclohexyl)_2Si < (cyclohexyl)_3Si$	12, 13, 14
alkylation of silylallyl anion with alkyl halides	α/γ site of alkylation	$Me_3Si < Et_3Si < (n\text{-}Pr)_3Si$	15
silylation of 1-silacyclopentenyl anion	reaction site	$Me_3Si < Et_3Si < (i\text{-}Pr)_3Si$	16
addition of α-silyl propargylic anion to aldehydes	ratio of E/Z configuration	$Me_3Si < Et_3Si < (t\text{-}Bu)Me_2Si$	17
Michael addition of enol silane to chiral α,β-unsaturated ketones	diastereofacial preference	$Me_3Si < (t\text{-}Bu)Me_2Si$	18
transmetalation and silyl migration	rate of silyl migration	$Me_3Si \sim Et_3Si < (t\text{-}Bu)Me_2Si$	19
reduction with trialkylsilanes	reduction rate	$EtMe_2Si < Et_2MeSi < (n\text{-}Pr)_3Si < (i\text{-}Pr)_2MeSi$	20
nitrodesilylation of disilylacetylenes	removal of silyl groups	$Me_3Si < (i\text{-}Pr)Me_2Si < (t\text{-}Bu)Me_2Si < (i\text{-}Pr)_3Si$	21
desilylation of silylphenylethynes	base-induced removal of silyl groups	$Me_3Si < EtMe_2Si < Ph_3Si < Et_2MeSi < Et_3Si$	22a
hydrolysis of silyl ethers	desilylation rate	$Me_3Si < Et_3Si < (t\text{-}Bu)Me_2Si$	23
desilylation of silyl ethers	hydrolysis rate	$Me_3Si < Et_3Si < (i\text{-}Pr)Me_2Si < (t\text{-}Bu)Me_2Si < (t\text{-}Bu)Ph_2Si$	22b, 24, 25
hydrolysis of silyl phenol ethers	hydrolysis rate (acidic)	$Me_3Si < (t\text{-}Bu)Me_2Si < Et_3Si < (n\text{-}Pr)_3Si < (n\text{-}Bu)_3Si$	26, 27
	hydrolysis rate (alkaline)	$Me_3Si < Et_3Si < (t\text{-}Bu)Me_2Si < (n\text{-}Pr)_3Si < (n\text{-}Bu)_3Si$	26, 27
hydrolysis of trialkylsilanes	hydrolysis rate (acidic)	$(n\text{-}Pr)Me_2Si < (n\text{-}Pr)_2MeSi < Et_3Si < (n\text{-}Pr)_3Si < (n\text{-}Bu)_3Si < (Me_2CHCH_2)_3Si < (i\text{-}Pr)_3Si$	12, 28, 29
	hydrolysis rate (alkaline)	$EtMe_2Si < (n\text{-}Pr)Me_2Si < Et_2MeSi < (n\text{-}Pr)_2MeSi < Et_3Si < (i\text{-}Pr)Me_2Si < (n\text{-}Pr)_3Si < (i\text{-}Pr)_2MeSi < (t\text{-}Bu)Me_2Si < (i\text{-}Pr)_3Si$	12, 30
hydrolysis of fluorotrialkylsilane	hydrolysis rate	$Et_2MeSi < Et_3Si < (n\text{-}Bu)(i\text{-}Pr)MeSi < (n\text{-}Bu)_3Si < (i\text{-}Pr)_3Si$	31a
hydrolysis of silyl ethers	hydrolysis rate (acidic)	$Me_3Si < PhMe_2Si < Et_3Si < (i\text{-}Pr)Me_2Si < Ph_3Si < (i\text{-}Pr)_3Si$	31b, 32
	hydrolysis rate (alkaline)	$PhMe_2Si < Me_3Si \sim Ph_3Si < (i\text{-}Pr)Me_2Si < Et_3Si < (i\text{-}Pr)_3Si$	31b, 32
hydrolysis of silyl ethers	hydrolysis rate	$(i\text{-}Pr)(CH_2CH_2CH_2CH_2)Si < (i\text{-}Pr)_2MeSi < (t\text{-}Bu)Me_2Si < (i\text{-}Pr)_3Si < (t\text{-}Bu)(CH_2CH_2CH_2CH_2)Si$	33, 34, 35
hydrolysis of silyl ethers	half-life of silyl ethers (acidic)	$(t\text{-}Bu)Me_2Si < (i\text{-}Pr)_3Si < (t\text{-}Bu)Ph_2Si$	36
	half-life of silyl ethers (alkaline)	$(t\text{-}Bu)Me_2Si \sim (t\text{-}Bu)Ph_2Si < (i\text{-}Pr)_3Si$	36
hydrolysis of silyl enol ethers	hydrolysis rate (acidic or alkaline)	$Me_3Si < (t\text{-}Bu)Me_2Si <$ (2,4,6-tri-*tert*-butylphenoxy)Me_2Si	37
ethanolysis of silyl chlorides	reactivity in solvolysis	$(t\text{-}Bu)_3Si < (Me_3Si)_3CMe_2Si$	38, 39
solvolysis of silyl iodides	reactivity in solvolysis	$(Me_3Si)_3CMe_2Si < (t\text{-}Bu)_3Si$	40
methanolysis of silyltriphenylgermanes	reaction rate	$Me_3Si < Et_3Si$	41

controlled reactions were revealed by Fleming[2,3] and Weidenbruch and Schäfer.[4]

The selectivity in reactions resulting from silicon groups can be attributed to a steric effect or an electronic effect or both. This Review will concentrate on the steric influence of the Me_3Si group.

II. Size of the Me_3Si Group

The Me_3Si group has been utilized more often than any other silyl group for the control of stereochemistry in organic reactions. Among the alkyl and aryl silyl groups, the Me_3Si is smaller than others. The steric effect of the Me_3Si group in organic compounds is thus less severe but can significantly change their chemical reactivity,[5-8] spectroscopic characteristics,[9] and physical properties.[10,11]

Table 1 shows the influence of many silyl groups on reaction rate or selectivity. Two types of influence are involved: (A) the effect of a silyl group on reactions occurring at the neighboring centers and (B) the effect of R groups attaching to Si on the nucleophilic attack at the Si atom. Our analysis of the results, which are obtained by other research groups, shows that both effects generally have a parallel trend. In order of smaller group (less influence) to bulkier group (greater influence), we generalize this trend as follows, which could be useful in the design of new reactions: $Me_3Si < PhMe_2Si < EtMe_2Si < (n\text{-}Pr)Me_2Si \sim Ph_3Si < Et_2MeSi < (n\text{-}Pr)_2MeSi < (n\text{-}Bu)_2MeSi < Et_3Si < (i\text{-}Pr)Me_2Si < (n\text{-}Bu)(i\text{-}Pr)MeSi \sim (n\text{-}Pr)_3Si < (i\text{-}Pr)(CH_2CH_2CH_2CH_2)Si < (t\text{-}Bu)Me_2Si \sim (i\text{-}Pr)_2MeSi < (n\text{-}Bu)_3Si < (Me_2CHCH_2)_3Si < (t\text{-}Bu)Ph_2Si \sim (i\text{-}Pr)_3Si < (t\text{-}Bu)(CH_2CH_2CH_2CH_2)Si < (t\text{-}Bu)_3Si < (t\text{-}Bu)(cyclohexyl)_2Si < (cyclohexyl)_3Si$.

Often the size of the Me_3Si group is compared with that of the *tert*-butyl group. The length of the C–Si bond is 1.89 Å in the Me_3Si group[42] and is 24% longer than that of the C–C bond (1.53 Å) in the *tert*-butyl group. Although the Me_3Si group occupies a bigger space in organic compounds (Figure 1), the *tert*-butyl group causes more steric congestion. Evidence was obtained from a variety of studies, which include investigations on ^{13}C and ^{29}Si NMR spectroscopic properties of Me_3Si- and *tert*-butyl-substituted benzenes,[43] on the deformation of $Me_3Si\text{–}CH_2\text{–}SiMe_3$ and $t\text{-}Bu\text{–}CH_2\text{–}t\text{-}Bu$,[44] on the silylating ability of $(Me_3Si)\text{-}RNCOMe$ (R = $SiMe_3$ and *t*-Bu),[45] on the competitive alkylation of an α-keto sulfone with trimethylsilyl and *tert*-butyl allylic iodides,[46] on the regioselective, nickel-catalyzed hydrocyanation of silylalkynes,[47] and on the substituent effect in the [3,3]-sigmatropic rearrangement of *O*-allyl silylketene acetals.[48]

Occasionally, reaction outcomes are the same resulting from the steric influence of the Me_3Si and the *tert*-butyl groups. An example is the addition of (3-

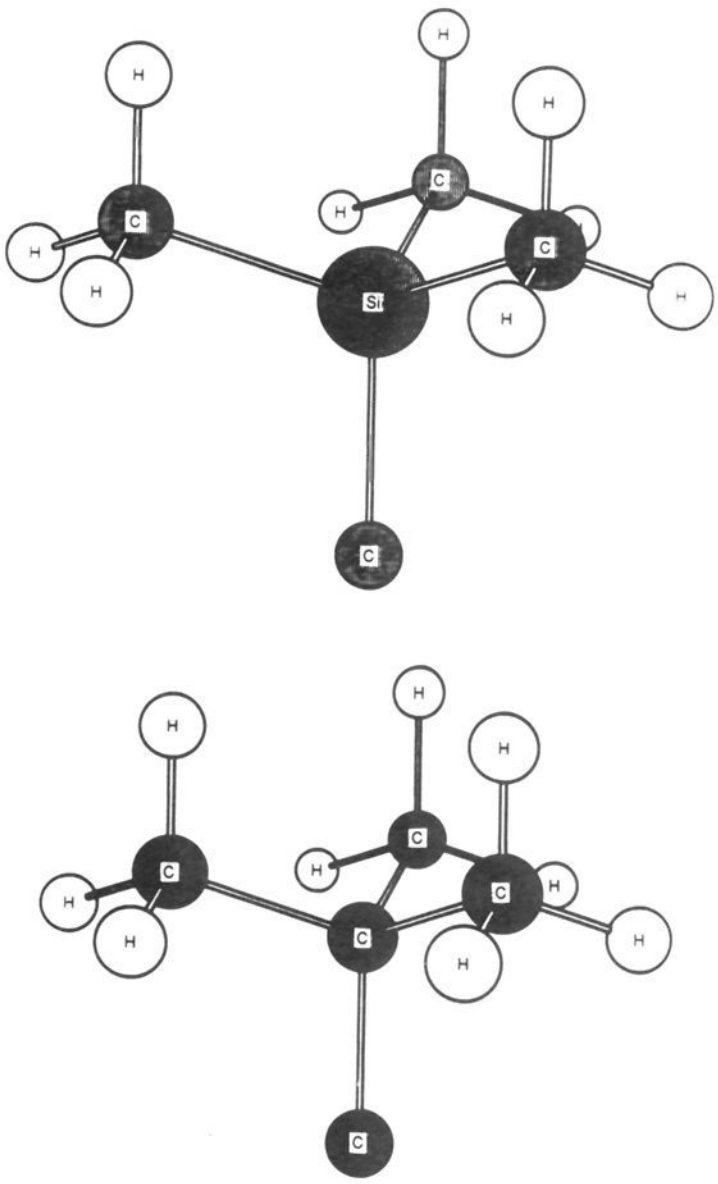


Figure 1. Visual comparison of the Me_3Si group (top) with the *tert*-butyl group (bottom). Both groups are attached to carbon atoms. The C–Si bonds are 1.89 Å in the Me_3Si group, and the C–C bonds are 1.53 Å in the *tert*-butyl group.

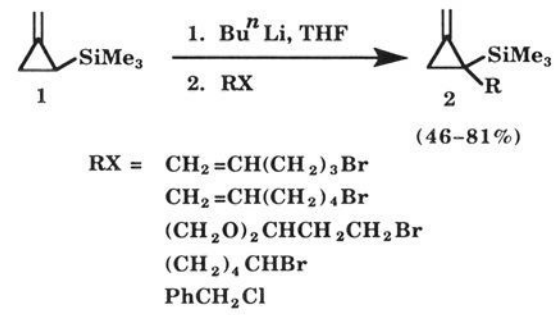
methyl-2,4-pentadienyl)lithium to $Me_3SiCOMe$ and Me_3CCOMe to give conjugated dienyl alcohols exclusively.[49] Both additions occur at the terminal carbon of the lithium reagent.

From a stereochemical point of view, the steric hindrance in or between organic compounds should not only depend upon the size of the substituents. The relative geometry of substituents to the reacting center also should be considered.[50–52] It is therefore reasonable to predict that, under certain circumstances, the influence of the Me_3Si group could be greater than that of the *tert*-butyl group. From the literature, we found one example belonging to this category:

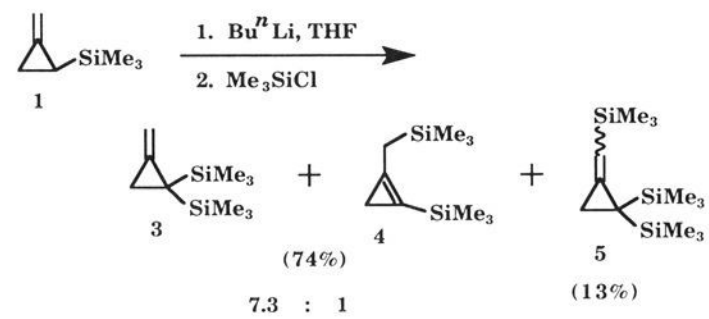
Taylor et al. measured the rates (k_{rel}) per β hydrogen of the pyrolysis of β-(trimethylsilyl)ethyl acetate[53] and β-*tert*-butylethyl acetate[54] in the gas phase at 327 °C. β-(Trimethylsilyl)ethyl acetate pyrolyzes 50 times faster than β-*tert*-butylethyl acetate (k_{rel} = 125 for $AcOCH_2CH_2SiMe_3$ and k_{rel} = 2.5 for $AcOCH_2CH_2CMe_3$). Results from control experiments showed that the steric environment in these compounds plays a part in governing the pyrolysis rate.

A different way to view the size of the Me_3Si group is to use the conformational free energy (i.e., the *A* value; $A = -\Delta G° = RT \ln K$ in kcal/mol for the equilibrium between the axial and equatorial conformers in a monosubstituted cyclohexane). Kitching et al.[55] determined the *A* value for the Me_3Si group to be 2.5 kcal/mol by NMR techniques. This number is significantly smaller than that of Me_3C (>4.5 kcal/mol),[56] comparable to that of CF_3 (2.4–2.6 kcal/mol),[57] and larger than those of Me_2HC (~2.15 kcal/mol),[58] C_2H_5 (1.75 kcal/mol),[58] and CH_3 (1.74 kcal/mol).[59]

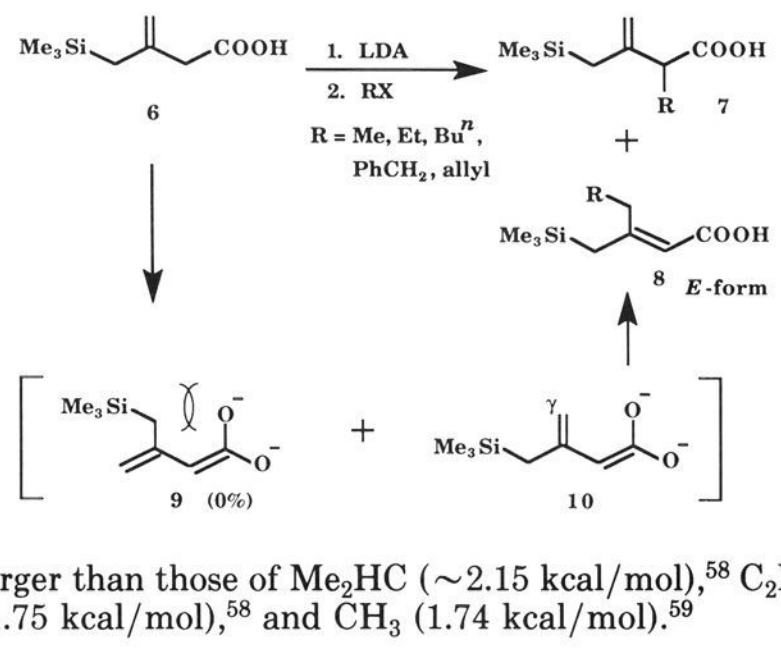
SCHEME 1



SCHEME 2



SCHEME 3



	CH_3	C_2H_5	Me_2HC	$Me_3Si \cong CF_3$	Me_3C
A value, kcal/mol	1.74	1.75	~2.15	2.4–2.6	>4.5

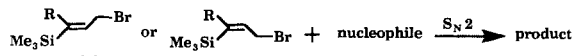
III. Me_3Si-Controlled Organic Reactions with Stereo- or Regioselectivity

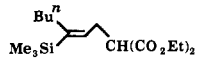
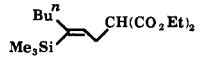
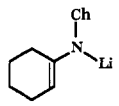
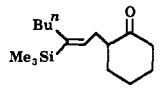
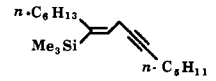
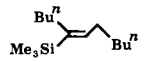
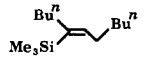
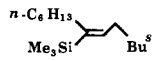
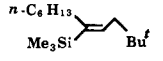
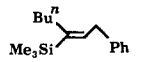
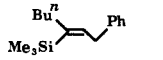
Many novel ways were reported involving the use of the Me_3Si group for the control of reactions. We divide them into 26 types and discuss them as follows.

A. Alkylation

Steric hindrance resulting from the Me_3Si group provides regioselectivity in alkylations. In general, alkylation of allylic trimethylsilanes under alkaline conditions occurs preferentially at the γ position (relative to the silicon atom) to give vinylsilanes as the major products.[15,60–62] Nevertheless, Sternberg and Binger treated (trimethylsilyl)methylenecyclopropane (**1**) with *n*-BuLi and then organic halides to give α-alkylated products **2** exclusively in 46–81% yields (Scheme 1).[63] The γ-alkylation is disfavored because it would give cyclopropene derivatives—compounds with high ring strains. When they silylated **1** with Me_3SiCl (Scheme 2), a mixture of disilylated products **3** and **4** (**3**/**4** = 7.3:1) was obtained in 74% yield, along

SCHEME 4



11 or 12 (R)	nucleophile	product 13	yield (%)
11 (Bu^n)	$NaCH(CO_2Et)_2$		60
12 (Bu^n)	$NaCH(CO_2Et)_2$		79
11 (Bu^n)			86
11 (n-C_6H_{13})	$Li_2(n\text{-}C_5H_{11}C{\equiv}C)_2CuCN$		85
11 (Bu^n)	$LiCuBu^n_2$		100
12 (Bu^n)	$LiCuBu^n_2$		100
11 (n-C_6H_{13})	Bu^sCu		100
11 (n-C_6H_{13})	Bu^tCu		100
11 (Bu^n)	$LiCuPh_2$		76
12 (Bu^n)	$LiCuPh_2$		85

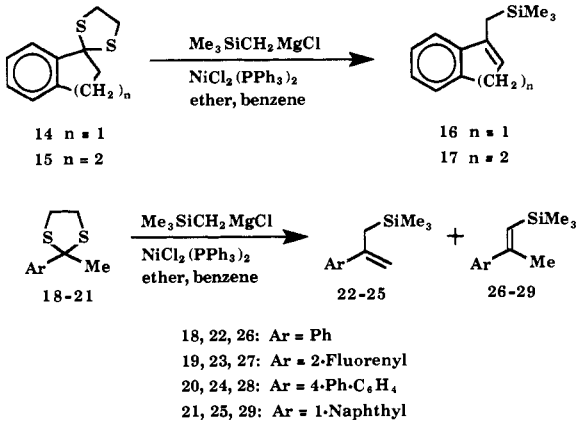
with trisilyl derivative **5** (13%). The formation of silyl cyclopropene **4** indicates the great steric influence of the Me_3Si group.

In the alkylation of 3-((trimethylsilyl)methyl)-3-butenoic acid (**6**) under alkaline conditions, Itoh et al. obtained two products **7** and **8** (Scheme 3).[64] Conjugated acids **8** are obtained (via intermediate **10**) in the *E* form only. They suggested that formation of intermediate **9**, leading to the corresponding *Z* isomers, is greatly disfavored because of the steric hindrance resulting from the bulky Me_3Si group. Coordination of the Li^+ counterion with both oxygen and carbon might also play a role in the regioselectivity.

By introducing a Me_3Si group at the vinylic position in allylic bromides, such as **11** and **12** (Scheme 4), Kang et al. controlled substitution to occur at the α position.[65] A variety of nucleophiles react with **11** and **12** by an S_N2 process to give **13** in 60–100% yields.

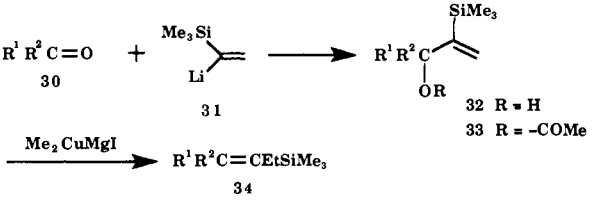
Dithioacetals $(RCH_2)ArC(SCH_2CH_2S)$ react with Grignard reagents in the presence of a nickel catalyst to give a regioisomeric mixture of alkenes.[66] Ni and Luh[67] considered that introduction of a bulky Me_3Si group in the starting Grignard reagent (i.e., Me_3SiCH_2MgCl) would give intermediates $(RCH_2)ArC(CH_2SiMe_3)[Ni]$. In order to release the steric congestion, these intermediates could undergo regioselective elimination to yield alkenylsilanes exclusively. On the basis of this design, they treated dithioacetals **14**, **15**, and **18–21** with Me_3SiCH_2MgCl and $NiCl_2(PPh_3)_2$ in ether and benzene to give alkylation products

SCHEME 5



dithioacetal	product	yield %
14	16	70
15	17	71
18	22 and 26 (5.7:1)	82
19	23 and 27 (9.0:1)	72
20	24 and 28 (8.1:1)	81
21	25 and 29 (1.6:1)	60

SCHEME 6



	isolated yield (%) of 34	selectivity *E* : *Z*
R^1 = Me, R^2 = Et	80	1.9 : 1
R^1 = Me, R^2 = Bu^i	70	4 : 1
R^1 = Me, R^2 = Pr^i	75	11.5 : 1
R^1 = Et, R^2 = CH_2Ph	75	3.2 : 1

16, **17**, and **22–29** in good yields (Scheme 5).

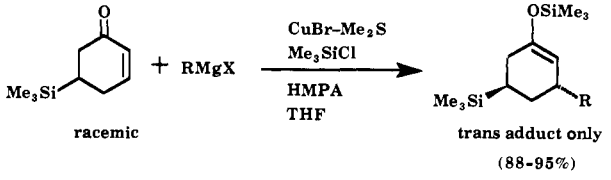
B. Substitution

In the synthesis of (*E*)- and (*Z*)-(trimethylsilyl)alkenes, the geometry can be controlled by the Me_3Si group. Scheme 6 shows a new method developed by Amouroux and Chan.[68] Reaction of ketones **30** with [α-(trimethylsilyl)vinyl]lithium (**31**) gives alcohols **32** in good yields. By use of acetyl chloride and silver cyanide,[69] alcohols **32** are converted to the corresponding acetates **33** in ~80% yield. Reaction of acetates **33** with Me_2CuMgI gives a mixture of (*E*)- and (*Z*)-**34**. The major isomers (i.e., (*E*)-**34**) have the bulky Me_3Si group trans to the larger substituent between R^1 and R^2.

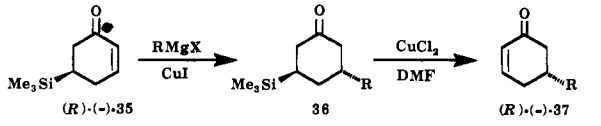
C. Michael Addition

The bulky Me_3Si group enables 5-(trimethylsilyl)-2-cyclohexen-1-one to react as a Michael acceptor in a highly stereoselective manner. Asaoka et al.[70] obtained 1,4-adducts in high yields (88–95%) by reacting 5-(trimethylsilyl)-2-cyclohexen-1-one with Grignard reagents in the presence of CuBr·Me_2S, Me_3SiCl, HMPA, and THF (Scheme 7). The Grignard reagents

SCHEME 7

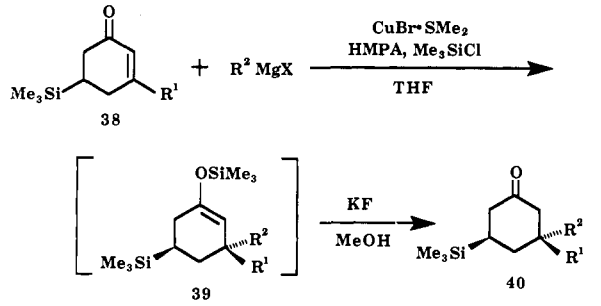


SCHEME 8



	yield(%)	yield(%)	% e.e.
R = Ph	94	82	98
R = *p*-MeC$_6$H$_4$	96	83	98
R = Bu^t	86	92	96

SCHEME 9



R^1	R^2	X	yield 40 (%)
Me	Ph	Br	94
Ph	Me	I	56
Me	Bu^n	Br	91
Bu^n	Me	I	80
Me	$PhCH_2CH_2$	Br	86
$PhCH_2CH_2$	Me	I	90
Me	*p*-Tol	Br	90

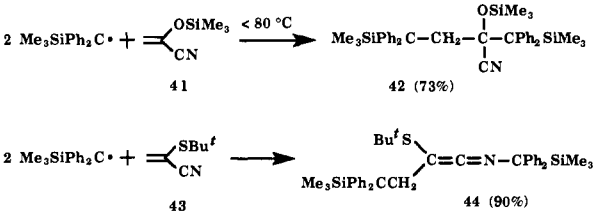
include phenyl-, (*p*-tolylsulfonyl)-, (2-phenylethyl)-, methyl-, *tert*-butyl-, and hexylmagnesium halides. These 1,4-adducts are generated in the trans form exclusively. They applied this strategy to a total synthesis of (+)-α-curcumene.[70]

Asaoka et al. also synthesized highly optically pure cyclohexenones (*R*)-(-)-**37** from (*R*)-(-)-**35** via **31** (Scheme 8).[71] 1,4-Addition of Grignard reagents to (-)-**35**, in the presence of Cu^I catalyst, gives adducts **36** as the only products in high yields. Adducts **36** then are converted to (*R*)-(-)-**37** with $CuCl_2$ in DMF.

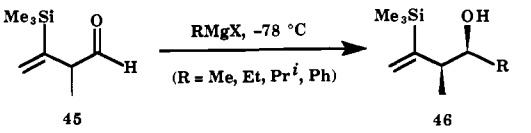
By applying the same strategy to 3-substituted 5-(trimethylsilyl)-2-cyclohexen-1-ones (**38**), Asaoka et al.[72] were able to generate a quaternary carbon center in the ring of cyclohexanones stereoselectively (Scheme 9). 1,4-Addition of Grignard reagents to **38** gives silyl enol ethers **39**. Subsequent hydrolysis of **39** in methanol with a catalytic amount of KF affords cyclohexanones **40**. When substituents R^1 in **38** are alkyl or aralkyl groups, adducts **40** are obtained in high yields as the exclusive diastereomer. Only one cyclohexenone (i.e., **38**; R^1 = Ph) gives a mixture of diastereomers (ratio = 97:3).

Reaction of radical $Me_3SiPh_2C^•$ with siloxy nitrile **41** proceeds in a 1,2-fashion to give adduct **42** in 73% yield (Scheme 10), as reported by Neumann and Stapel.[73]

SCHEME 10



SCHEME 11



SCHEME 12

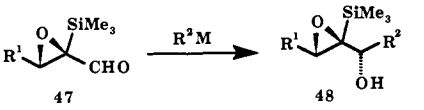


TABLE 2. Diastereoselective Addition of Grignard Reagents to Aldehyde 45

Grignard reagent	major product R	diastereoselectivity	yield of **46**, %
MeMgI	Me	10:1	84
EtMgBr	Et	>99:1	92
i-PrMgBr	*i*-Pr	>99:1	91
PhMgBr	Ph	>99:1	94
CH_2=C(SiMe$_3$)MgBr	CH_2=C(SiMe$_3$)	>99:1	93

TABLE 3. Diastereoselective Addition of Organometallic Reagents (R^2M) to Aldehydes 47

aldehyde **47** R^1	R^2M	diastereoselectivity	total yield of **48**, %
n-Bu	MeMgBr	7:1	89
n-Bu	MeLi	5.4:1	89
n-amyl	EtMgBr	26:1	86
n-amyl	*i*-PrMgBr	23:1	81
n-Bu	CH_2=$CHCH_2$MgBr	5.6:1	90
n-amyl	PhMgBr	7.9:1	97
n-amyl	*n*-BuC≡CLi	9.8:1	93

When $Me_3SiPh_2C^•$ reacts with acceptor **43** with a bulky *tert*-butyl group, 1,4-adduct **44** is obtained exclusively in 90% yield.

D. 1,2-Addition

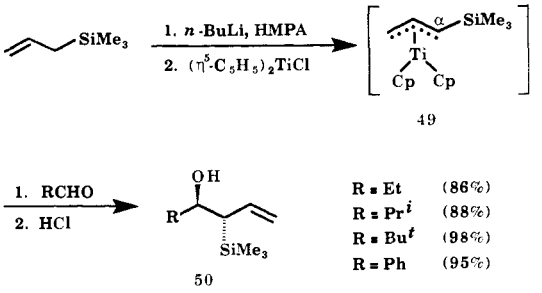
Highly diastereoselective 1,2-additions can be accomplished by placement of the bulky Me_3Si group either in substrates or in reagents. Sato et al.[74,75] treated β-trimethylsilyl aldehyde **45** with Grignard reagents to give 1,2-adducts **46** as the major diastereomers in good to excellent yields (Scheme 11 and Table 2). The diastereoselectivity is better than 99:1 in most cases. Similarly, trimethylsilyl epoxy aldehydes **47** react with various Grignard or lithium reagents to give the corresponding alcohols **48** as the major diastereomers (Scheme 12).[76] The diastereoselectivity varies from 5.4:1 to 26:1 and the yields of the reactions are 81–97% (Table 3). In contrast, a related epoxy aldehyde without the Me_3Si group (i.e., detrimethylsilyl-**47** with R^1 = *n*-amyl) reacts with EtMgBr or *n*-BuC≡CLi to produce almost an equal amount of diastereomers.

Corriu et al.[77] found that vinyltrimethylsilanes can be prepared by addition of (Me_3SiCH=$CHCH_2$)Cu(CN)Li to carbonyl compounds, such as MeCHO, Me-

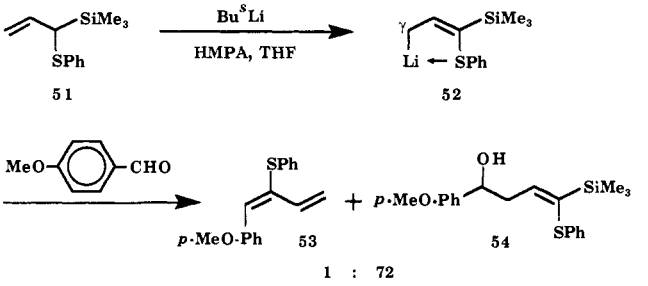
TABLE 4. Diastereomer Ratios in the Reactions of Nucleophiles (NuM) with Acylsilanes 55 at −78 °C

R^2 in 55	NuM	conditions	yield of 56 + 57, %	α-hydroxy silane ratio 56:57	yield of 59 + 60, %
Ph	*n*-BuLi	THF	92	>100:1	89
Ph	MeLi	THF	96	>40:1	76
Ph	(allyl)$SiMe_3$	CH_2Cl_2, $TiCl_4$	68	>100:1	56
Ph	(allyl)MgBr	THF	96	>11:1	85
1-cyclohexenyl	*n*-BuLi	THF	56	>30:1	40
1-cyclohexenyl	MeLi	THF	69	>100:1	69
1-cyclohexenyl	(allyl)$SiMe_3$	CH_2Cl_2, $TiCl_4$	50	>30:1	40
1-cyclohexenyl	(allyl)MgBr	THF	69	11:1	39
cyclohexyl	*n*-BuLi	THF	98	15:1	80
cyclohexyl	MeLi	THF	77	21:1	61
cyclohexyl	(allyl)$SiMe_3$	CH_2Cl_2, $TiCl_4$	96	>100:1	79
cyclohexyl	(allyl)MgBr	THF	93	3.5:1	75

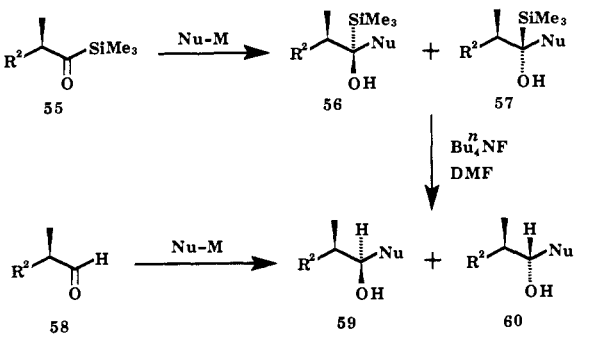
SCHEME 13



SCHEME 14



SCHEME 15



COCl, MeCH=CHCHO, and PhCH=CHCHO. Reagent $(Me_3SiCH{=}CHCH_2)Cu(CN)Li$ reacts regioselectively at the γ position (relative to the Me_3Si group) to give 1,2-adducts in 45–75% yields.

In contrast, Sato et al. reported that (trimethylsilyl)allyl anion reacts at the α position with aldehydes in the presence of $(\eta^5\text{-}C_5H_5)_2Ti[\eta^3\text{-}1\text{-}(trimethylsilyl)allyl]$ (**49**, Scheme 13).[78] This Ti complex is prepared from [(trimethylsilyl)allyl]lithium and $(\eta^5\text{-}C_5H_5)_2TiCl$, which can be generated in situ by reaction of $(\eta^5\text{-}C_5H_5)_2TiCl_2$ with isobutylmagnesium chloride. Treatment of **49** with EtCHO, *i*-PrCHO, *t*-BuCHO, and PhCHO gives the corresponding (*R,S*)-(±)-4-hydroxy-3-(trimethylsilyl)-alkenes (**50**) in good to excellent yields. Triethylaluminum ate complex $Me_3SiCH{=}CHCH_2AlEt_3Li$ also reacts with carbonyl compounds predominantly at the α position (relative to the Me_3Si group).[79] Yamamoto et al. obtained 1,2-adducts with α/γ ratios of 16:1 from EtCHO, 5.7:1 from *i*-PrCHO, and 2.4:1 from PhCHO.

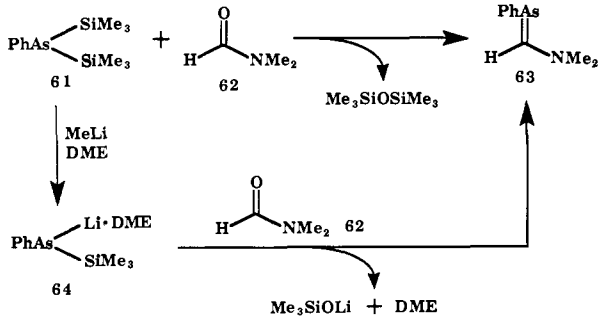
(Alkylthio)- and (arylthio)allyl metal reagents react with electrophiles with a high degree of regioselectivity. The regiochemistry of the products depends upon the metals and electrophiles.[80,81] Kyler and Watt found that the bulky Me_3Si group in 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**51**) makes the γ site more reactive.[82] Treatment of *p*-anisaldehyde with alkenyllithium **52**, prepared from **51** and *sec*-BuLi in HMPA/THF, gives diene **53** (by α addition) and alkenol **54** (by γ addition, 72% isolated yield) in a ratio of 1:72 (Scheme 14). Reagent **52** also reacts with a variety of aldehydes and ketones at the γ center.

Recently, Ohno et al. reported that acyltrimethylsilanes **55** undergo nucleophilic addition to afford α-hydroxy silanes **56** and **57** in a highly selective manner (Scheme 15 and Table 4).[83] The stereoconfiguration of the major product **56** can be predicted by use of Cram's rule. Desilylation of **56** and **57** with $n\text{-}Bu_4NF$ in DMF affords alcohols **59** and **60**; these alcohols can also be obtained from aldehydes **58** and nucleophiles NuM. The ratio of **59** to **60** from **55** is much larger than that from the corresponding aldehydes **58**. For example, treatment of **55** (R^2 = Ph) with *n*-BuLi in THF at −78 °C gives a mixture of **56** and **57** (R^2 = Ph, Nu = *n*-Bu). This mixture is desilylated to yield **59** and **60** (R^2 = Ph, Nu = *n*-Bu) with a ratio >100:1. The ratio of **59** to **60**, however, drops to 5:1 when they are prepared directly from **58** (R^2 = Ph) and *n*-BuLi.

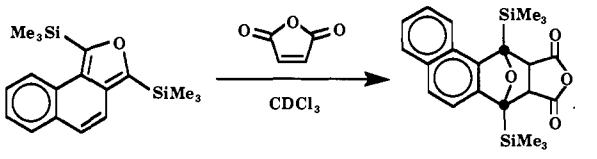
Formation of ate complexes is a potential problem in the nucleophilic additions involving boron-activated olefins.[84] Cooke and Widener introduced a bulky Me_3Si group at the α position of vinyldimesitylborane ($Mes_2BCH{=}CH_2$ (Mes = mesityl)) to suppress the complexation.[85] Thus $Mes_2B(Me_3Si)C{=}CH_2$ reacts with a variety of nucleophiles, as listed below, to give the corresponding adducts $Mes_2B(Me_3Si)CHCH_2Nu$ in good to excellent yields: *n*-BuLi (96%), BuMgCl (in the presence of $CuBr{\cdot}Me_2S$, 51%), $Bu_2Cu(CN)Li_2$ (66%), PhLi (95%), *t*-BuLi (86%), $CH_2{=}CH(CH_2)_4Li$ (91%), $(SCH_2CH_2CH_2S)CHLi$ (97%), and $t\text{-}BuOOCCH_2Li$ (96%).

Phenylbis(trimethylsilyl)arsine (**61**) reacts very slowly (3 weeks) with excess dimethylformamide (**62**) to give ((dimethylamino)methylidene)phenylarsine (**63**) in 33% yield and byproduct $Me_3SiOSiMe_3$ (Scheme 16), as reported by Becker et al.[86] This reaction can be accelerated by addition of a small amount of solid sodium hydroxide. Thus a 93% yield of **63** is obtained after 4

SCHEME 16



SCHEME 17

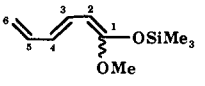


time	*endo* : *exo*
initial	9 : 1
0.3 h	2.2 : 1
3.5 h	1 : 2.1

days. Alternatively, they removed one Me_3Si group from **61** with MeLi in 1,2-dimethoxyethane (DME) to afford intermediate **64**. This intermediate reacts with **62** to give **63** (85%) and Me_3SiOLi in 24 h. These results indicate that two Me_3Si groups in reagent **61** reduce its reactivity.

E. Diels–Alder Reaction

In the Diels–Alder reaction, steric effects resulting from the Me_3Si group can prevail over orbital effects. Eguchi et al. studied the reactivity of 1-methoxy-1-(trimethylsiloxy)-1,3,5-hexatriene (**65**) toward dienophiles.[87] The results from the CNDO/2 calculations show that the HOMO coefficient is the largest at C-4. If the Diels–Alder reaction of **65** is controlled by the orbital effect, C-1 and C-4 should be the reactive centers.

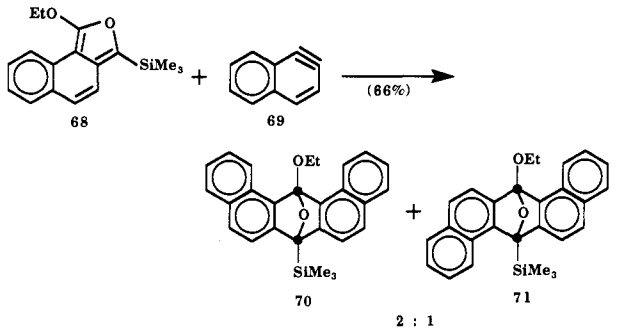


65

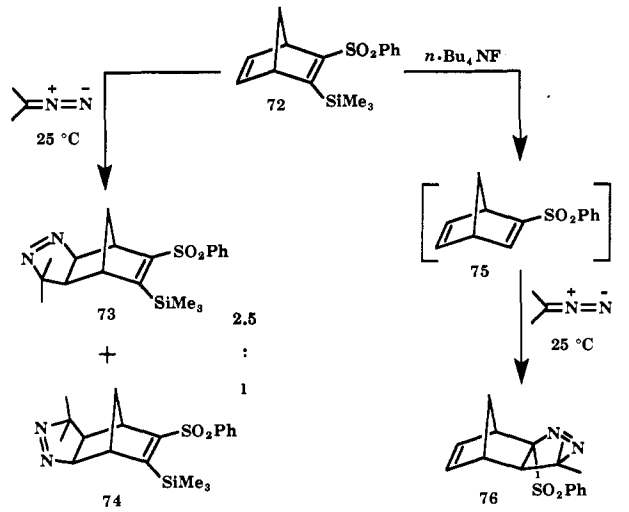
Nevertheless, Eguchi et al. found that dienophiles react with **65** at the C-3 and C-6 positions to give cycloadducts at room temperature to 110 °C. These adducts are desilylated during chromatographic separation to afford the corresponding methyl carboxylates.[87] The dienophiles and the yields of the methyl carboxylates are maleic anhydride (76%), *N*-phenylmaleimide (100%), methyl vinyl ketone (98%), methacrolein (36%), methyl acrylate (89%), ethyl propiolate (35%), dimethyl acetylenedicarboxylate (62%), and nitrosobenzene (82%). They concluded that the steric hindrance from the trimethylsiloxyl group or the methoxy group or both significantly reduces the reactivity of C-1.

Rickborn et al.[88] found that 1,3-bis(trimethylsilyl)-naphtho[1,2-*c*]furan (**66**) reacts with maleic anhydride in $CDCl_3$ at room temperature to give cycloadducts **67** as a mixture of endo and exo isomers (Scheme 17). The initial endo/exo ratio is 9:1; the ratio drops to 2.2:1 after 0.3 h and 1:2.1 after 3.5 h. They suggested that the steric interactions between the Me_3Si groups and dienophiles could be responsible for kinetic preference for the formation of the endo cycloadduct and thermodynamic preference for the exo cycloadduct. The steric factor of the Me_3Si group also plays a role in the control of the stereoselectivity in the Diels–Alder reaction of 1-ethoxy-3-(trimethylsilyl)naphtho[1,2-*c*]furan (**68**) with 1,2-naphthalyne (**69**). The adducts **70** and **71** are obtained within a ratio of 2:1 in 66% total yield (Scheme 18).[88]

SCHEME 18



SCHEME 19



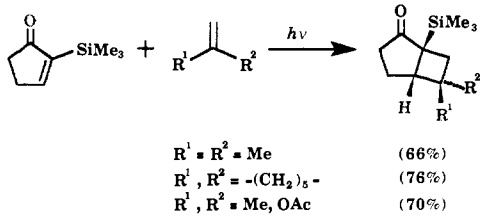
F. 1,3-Dipolar Cycloaddition

The Me_3Si group can govern the regioselectivity in a 1,3-dipolar cycloaddition. In 1987, Padwa et al.[89] reported that (trimethylsilyl)bicycloheptadiene **72** reacts with diazopropane at 25 °C to give regioisomers **73** and **74** in a ratio of 2.5:1 (Scheme 19). Diazopropane preferentially adds to the sterically less encumbered C–C double bond in **72**. In contrast, diazopropane reacts with sulfonylated bicycloheptadiene **75**, obtained by desilylation of **72** with *n*-Bu_4NF, at the substituted C–C double bond to give adduct **76** exclusively.[89] In the same year, Williams et al.[90] reported that cyclopentadiene reacts with **72** at the sterically less hindered C–C double bond to give the corresponding exo [4 + 2] cycloadduct in 98% yield.

G. [2 + 2] Cycloaddition

The steric effect of the Me_3Si group can direct photochemical reactions.[91] Swenton et al. obtained regioselectivity in the photocycloaddition of 2-(trimethylsilyl)cyclopentenone to isobutylene, methylenecyclohexane, and isopropenyl acetate in the presence

SCHEME 20



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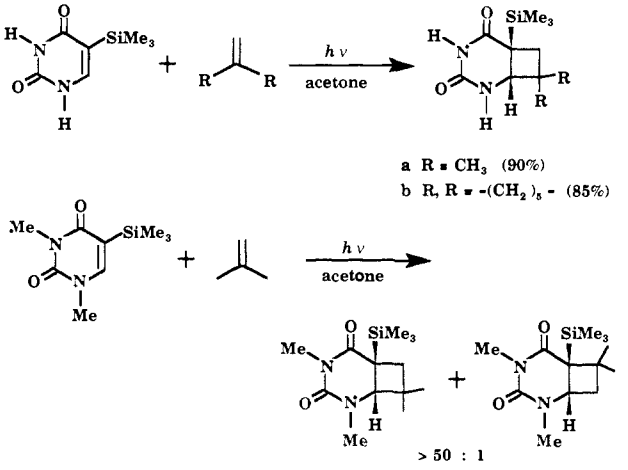
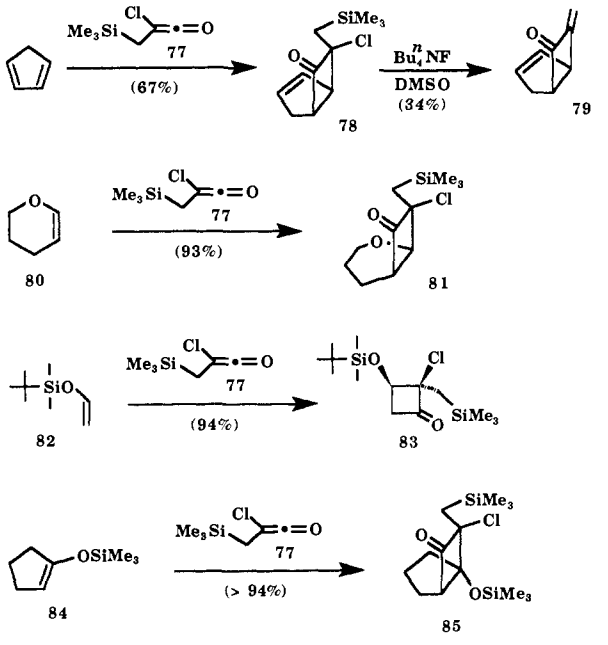


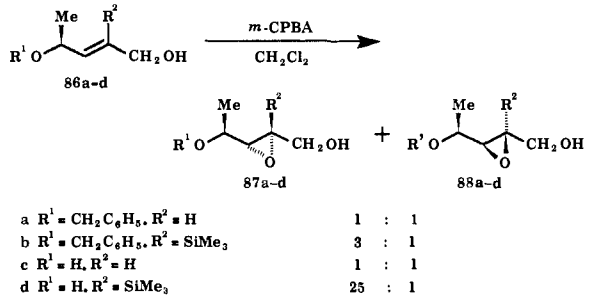
SCHEME 22



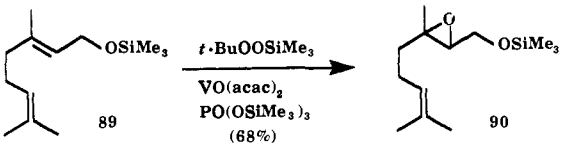
of stannous chloride (Scheme 20).[92] These reactions give head-to-tail adducts as the major products. Similarly, the acetone-sensitized photocycloaddition of 5-(trimethylsilyl)uracils to isobutylene and methylenecyclohexane gives predominantly head-to-tail adducts in very good yields (Scheme 21).[91,93]

The instability of methyleneketene (CH_2=C=C=O) limits its applicability in organic synthesis.[94] Paquette et al.[95] prepared chloro[(trimethylsilyl)methyl]ketene (77) as the synthon for methyleneketene. Cyclopentadiene reacts with 77 in dry pentane at 0 °C to give [2 + 2] adduct 78 in 67% yield (Scheme 22). The large Me_3Si group governs the stereochemical outcome. Treatment of 78 with n-Bu_4NF in DMSO produces enone 79 in 34% yield. Similarly, 77 reacts with di-

SCHEME 23



SCHEME 24



hydropyran (80), silyl enol ether 82, and silyl cyclopentenol 84 to afford adducts 81 (93%), 83 (94%), and 85 (>94%), respectively. Sterically congested olefins, however, do not react with 77.

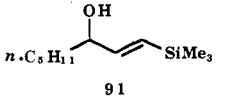
H. Epoxidation

The Me_3Si group attached to an allylic position of alkenes provides remarkable stereoselectivity in the epoxidation of C–C double bonds. In 1980, Hasan and Kishi[96] reported that the reaction of allylic alcohol **86a** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 produces a 1:1 mixture of diastereomeric epoxy alcohols **87a** and **88a** (Scheme 23). Similarly, **86c** gives a mixture of **87c** and **88c** also in a 1:1 ratio. In order to improve the stereoselectivity, they introduced a Me_3Si group at the β sp^2 carbon. This bulky group significantly changes the ratio of diastereomeric epoxides. Thus **86b** gives **87b** and **88b** in a ratio of 3:1; **86d** affords **87d** and **88d** in a ratio >25:1. Protodesilylation of **87d** with n-Bu_4NF in DMF gives **87c** with complete retention of the stereoconfiguration at the oxirane carbon.

In 1982, Narula[97] reported a similar strategy for the epoxidation of trimethylsilylated allylic alcohols by using $VO(acac)_2$ and *t*-BuOOH. For most substrates, Narula obtained excellent selectivity—only one diastereomer is generated in the epoxidation.

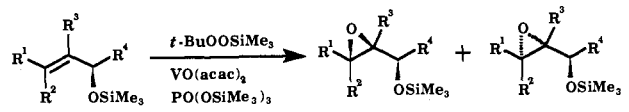
Hiyama and Obayashi[98] found that *t*-$BuOOSiMe_3$ can epoxidize allylic and homoallylic trimethylsilyl ethers in CH_2Cl_2 with $VO(acac)_2$ and $PO(OSiMe_3)_3$ as catalysts. Thus geranyl trimethylsilyl ether (**89**) undergoes oxidation to give the corresponding monoepoxide **90** in 68% yield (Scheme 24). The other C–C double bond in **89** remains unchanged. They further applied this method to the epoxidation of alkenes with a trimethylsiloxyl group attached to a chiral carbon in the allylic or in the homoallylic position (Scheme 25). Diastereomeric mixtures are obtained with ratios from 1:1.9 to 9:1. Thus Me_3Si groups provide a modest directing effect on the stereoselective epoxidation of allylic and homoallylic trimethylsilyl ethers.

In the study of kinetic resolution of allylic alcohols, Sato et al.[99,100] found that γ-trimethylsilyl species **91** can

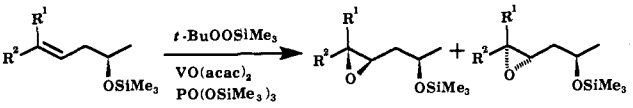


91

SCHEME 25

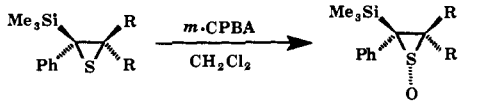


	yield	
a $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Me$	(85%)	9 : 1
b $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Me$	(78%)	1 : 1.2
c $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Bu$	(21%)	1 : 1.9



	yield	
a $R^1 = Et$, $R^2 = H$	(60%)	6.7 : 1
b $R^1 = R^2 = Me$	(56%)	8.1 : 1

SCHEME 26



92 R = Ph
93 R = C_6H_4-*p*-OMe
94 R = Ph
95 R = C_6H_4-*p*-OMe

be resolved more efficiently than any other secondary allylic alcohols by chemical means. Reagents used in the resolution include *t*-BuOOH, L-(+)-diisopropyl tartrate, and Ti(O-*i*-Pr)$_4$. Recently, Sharpless et al.[101] measured the k_f/k_s value of **91** to be 700, where k_f and k_s are the epoxidation rates of the fast and the slow enantiomers, respectively. The high resolution comes from the steric bulk of the Me_3Si group at the olefinic terminus. Introduction of the Me_3Si group makes the epoxidation rate increase for one enantiomer and decrease for the other.[101]

I. S-Oxidation

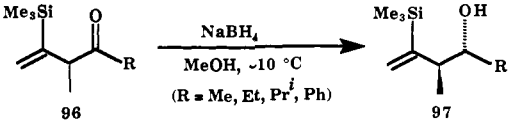
In the oxidation of tetrasubstituted thiiranes **92** and **93** with *m*-CPBA, Bonini et al.[102] obtained the corresponding episulfoxides **94** and **95** in 32% and 58% yields, respectively (Scheme 26). No products were observed with the sulfoxide moiety syn to the Me_3Si group. The configuration of anti episulfoxide **95** is confirmed by X-ray structural analysis. They considered that the steric hindrance resulting from the Me_3Si group prevented *m*-CPBA from approaching the S center on the same side of the thiirane.

J. Reduction

The bulky Me_3Si group can direct the reduction of β-trimethylsilyl ketones to the corresponding alcohols with high diastereoselectivity. In 1984, Sato et al.[74,75] reported that ketones **96** react with $NaBH_4$ in methanol to produce alcohols **97** as the major diastereomers in 92–98% yields (Scheme 27). The stereoselectivity is >99:1 in most cases. The configuration of the products can be predicted by use of Cram's rule. Protodesilylation of trimethylsilyl alcohols **97** with NaH or KH in HMPA gives the corresponding homoallylic alcohols, which are useful in the synthesis of macrolide and ionophore antibiotics.[75]

The Me_3Si-directed reduction was also applied to the conversion of β-trimethylsilyl epoxy ketones **98** and **100** to alcohols **99** and **101**, respectively (Scheme 28).[103]

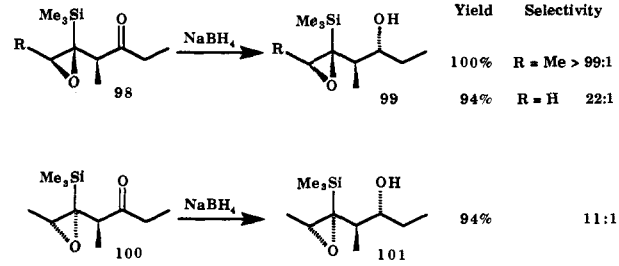
SCHEME 27



major product

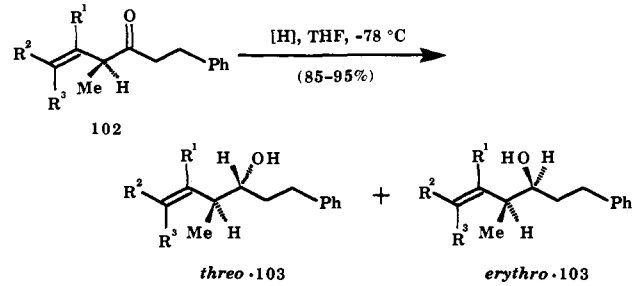
R	diastereoselectivity major : minor
Me	19 : 1
Et	> 99 : 1
Pr^i	> 99 : 1
Ph	> 99 : 1

SCHEME 28



	Yield	Selectivity
98 → 99	100%	R = Me > 99:1
	94%	R = H 22:1
100 → 101	94%	11:1

SCHEME 29



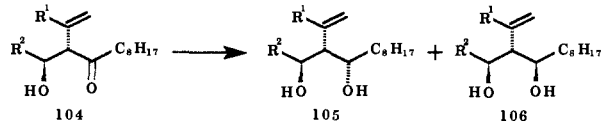
			103: *threo*/*erythro*	
R^1	R^2	R^3	DIBAL	L-Selectride
H	H	H	0.89 : 1	24 : 1
H	Bu	H	1.1 : 1	13 : 1
H	H	Bu	1.5 : 1	> 99 : 1
Me_3Si	H	H	8.1 : 1	> 99 : 1
Me_3Si	Bu	H	16 : 1	> 99 : 1
Me_3Si	H	Bu	> 99 : 1	> 99 : 1

The stereoselectivity varies from 11:1 to >99:1.

Tsuchihashi et al. reported a highly stereoselective reduction of optically pure α-methyl-β,γ-enones **102** to give the corresponding alcohols **103**.[104] Treatment of **102** with diisobutylaluminum hydride (DIBAL-H) or lithium tri-*sec*-butylborohydride (L-Selectride) in THF at −78 °C gives a mixture of *threo*- and *erythro*-**103** in 85–95% yield (Scheme 29). A bulky Me_3Si group at the β position increases the *threo*-**103**/*erythro*-**103** ratio. This strategy was further applied to convert some trimethylsilyl alkynyl ketones to the corresponding alkynols.[105]

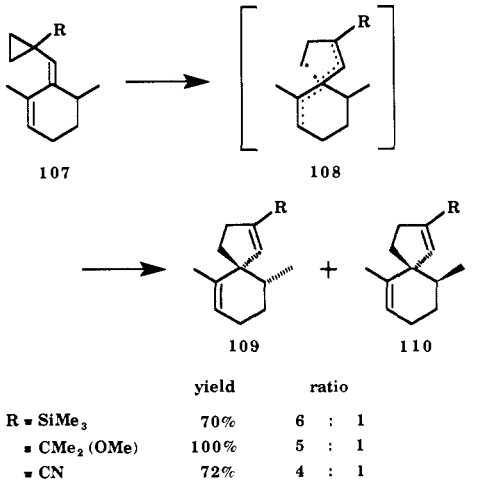
In the reduction of (trimethylsilyl)vinyl aldols **104a** and **104b** with $LiBEt_3H$ or DIBAL-H in THF at −78 °C, Tsuchihashi et al.[106] obtained a mixture of diastereomeric diols **105a** + **106a** and **105b** + **106b**, respectively (Scheme 30). Use of $LiBEt_3H$ gives excellent selectivity (>99:1) for both **105a**/**106a** and **105b**/**106b**. This re-

SCHEME 30



a	R^1 = $SiMe_3$, R^2 = H	$LiBEt_3H$	> 99 : 1
		DIBAL	4 : 1
b	R^1 = $SiMe_3$, R^2 = CH_2OCH_2Ph	$LiBEt_3H$	> 99 : 1
		DIBAL	1 : 1.5
c	R^1 = H, R^2 = CH_2OCH_2Ph	$LiBEt_3H$	1 : 49

SCHEME 31



	yield	ratio
R = $SiMe_3$	70%	6 : 1
= CMe_2(OMe)	100%	5 : 1
= CN	72%	4 : 1

ducing agent has weak chelating ability; the selectivity comes from the great steric bias posed by the Me_3Si group. On the other hand, DIBAL-H gives poorer selectivity (**105a**/**106a** = 4:1 and **105b**/**106b** = 1:1.5) because both the chelating and the steric effects are involved. Furthermore, they obtained reverse selectivity (**105c**/**106c** = 1:49) in the reduction of vinyl aldol **104c**, which does not have a Me_3Si group.[107]

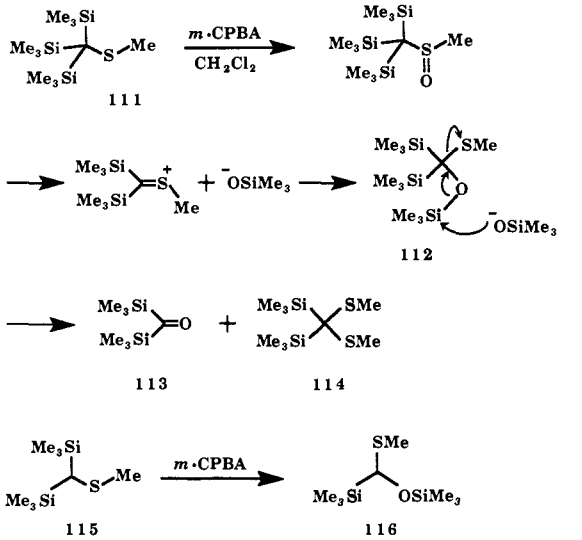
K. Elimination

Replacement of a proton with the Me_3Si group in some organic compounds can increase the rate of pyrolysis. Taylor et al.[53] studied the pyrolysis of β-substituted ethyl acetates $AcOCH_2CH_2X$ (X = H, CMe_3, SiR_3, and $GeEt_3$) to AcX and ethylene in the gas phase. At 327 °C, the reaction $AcOCH_2CH_2SiMe_3 \rightarrow AcOSiMe_3 + CH_2{=}CH_2$ is 125 times faster than the reaction $AcOCH_2CH_3 \rightarrow AcOH + CH_2{=}CH_2$. It is believed that the steric factor of the Me_3Si group plays a part in acceleration of the fragmentation.

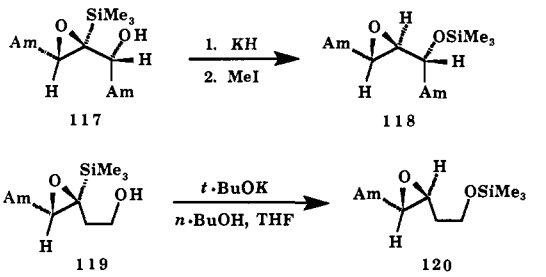
L. Sigmatropic Rearrangement

Paquette et al. developed a new method for the synthesis of spiro[4.5] sesquiterpenes (Scheme 31).[108] By heating trimethylsilyl vinylcyclopropane **107** at 560 °C, they obtained a 70% yield of diastereomeric spiro vinylsilanes **109** and **110** (R = $SiMe_3$) in a ratio of 6:1. The selectivity comes from the steric influence of the Me_3Si group in intermediate **108** (R = $SiMe_3$) during the combination of radical centers. In the thermolysis of vinylcyclopropane **107** with a CMe_2(OMe) group at 440 °C, two isomeric products **109** and **110** (R = CMe_2(OMe)) are obtained in quantitative yield. The ratio of **109** to **110**, however, drops to 5:1. Thermolysis of vinylcyclopropane **107** with a CN group at 470 °C gives a mixture of rearrangement products **109** and **110** (R = CN) in a ratio of 4:1. Thus the steric influence in this pyrolytic spiroannulation follows the order Me_3Si > CMe_2(OMe) > CN.

SCHEME 32



SCHEME 33



M. Sila-Pummerer Rearrangement

Reaction of tris(trimethylsilyl)(methylthio)methane (**111**) with *m*-CPBA in dichloromethane gives a mixture of silyl ketone **113** (45%) and thioketal **114** as main products in a 1:1 ratio (Scheme 32), as reported by Ricci et al.[109] For this transformation, they proposed a mechanism involving sila-Pummerer rearrangement. Silyl ether intermediate **112**, containing three Me_3Si groups nearby, was detected. Oxidation of bis(trimethylsilyl)(methylthio)methane (**115**) with *m*-CPBA, however, affords stable silyl ether **116**, in which less steric compression exists between the Me_3Si groups.

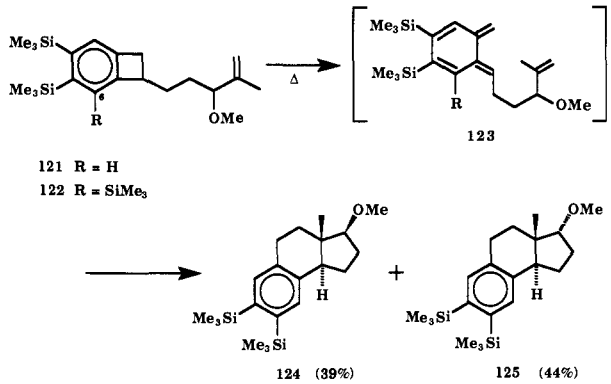
N. Migration

In an attempt to methylate epoxy alcohol **117**, Yamamoto et al.[110] obtained silyl ether **118** exclusively by 1,3-silyl migration (Scheme 33). Similarly, treatment of epoxy alcohol **119** with *t*-BuOK in *t*-BuOH and THF gives **120**. The steric hindrance between the Me_3Si and the amyl groups provides the major driving force for the migration to occur.

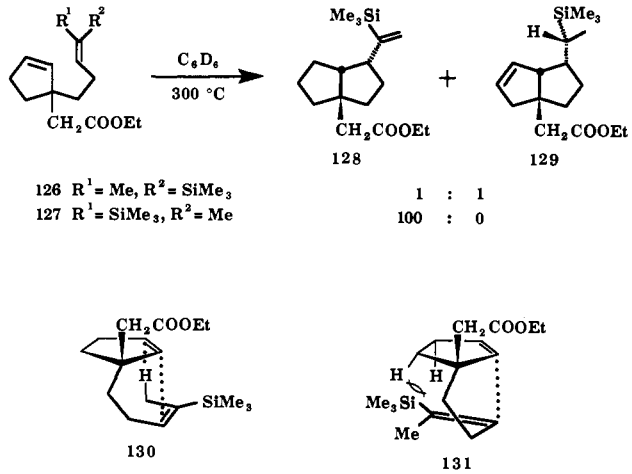
O. Ring Opening

Vollhardt et al.[111] pyrolyzed a diastereomeric mixture of bis(trimethylsilyl)benzocyclobutenes **121** at 175 °C to give **124** (39%) and **125** (44%). The entire trans-

SCHEME 34



SCHEME 35



formation involves a ring opening and an intramolecular Diels–Alder reaction (Scheme 34). Under the same reaction conditions, tris(trimethylsilyl)benzocyclobutene **122** remains unchanged for 22 h. It is believed that the Me_3Si group at the C-6 position in **122** sterically (and perhaps also electronically) blocks the ring opening. Intermediate **123** (R = $SiMe_3$) thus cannot be generated.

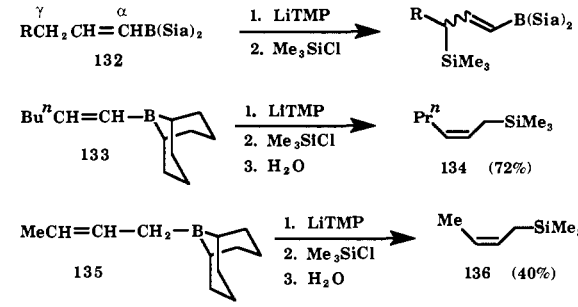
P. Ene Reaction

The Me_3Si group in organic compounds can control the regio- and stereochemistry of the ene reaction. Ziegler et al. reported that pyrolysis of vinylsilane **126** at 300 °C in benzene-d_6 gives a 1:1 ratio of bicyclooctanes **128** and **129** (Scheme 35).[112] Under the same conditions, vinylsilane **127** provides bicyclooctane **128** exclusively. Conversion of **127** to **128** involves transition state **130**, which is thermodynamically more favorable than transition state **131**. Steric interactions exist between the Me_3Si group and hydrogens on the cyclopentene ring in **131**, which leads to **129**.

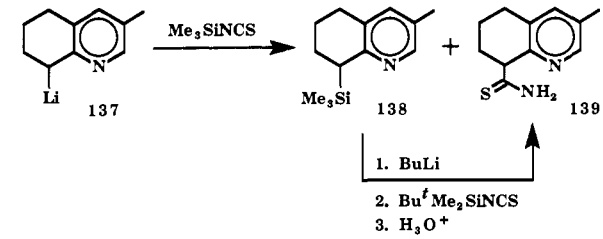
Q. Silylation

Regioselectivity and feasibility of trimethylsilylations are influenced by the Me_3Si group in silylating agents. Silylation occurs at the γ position when alkenyldisiamylboranes **132** are treated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and then Me_3SiCl (Scheme 36).[113] The regioselectivity comes from the steric repulsion between the bulky siamyl (Sia) and the Me_3Si groups. By replacing the siamyl group with a less bulky borane-containing substituent, 9-borabicyclo-

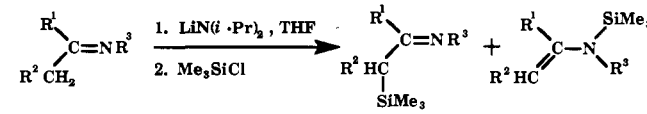
SCHEME 36



SCHEME 37



SCHEME 38



	yield (%)	
$R^1, R^2 = -(CH_2)_4-$, R^3 = cyclohexyl	70	0
$R^1 = Bu^t$, R^2 = H, R^3 = cyclohexyl	0	0
$R^1 = Bu^t$, R^2 = H, $R^3 = Bu^n$	50	0
$R^1 = Bu^t$, R^2 = H, R^3 = Ph	0	65
R^1 = Ph, R^2 = H, R^3 = Ph	45	30

[3.3.1]nonane, Yamamoto et al.[114] were able to silylate **133** and **135** at the α position. After protonolysis, allylic silanes **134** (72% from **133**) and **136** (40% from **135**) are obtained in the *Z* form.

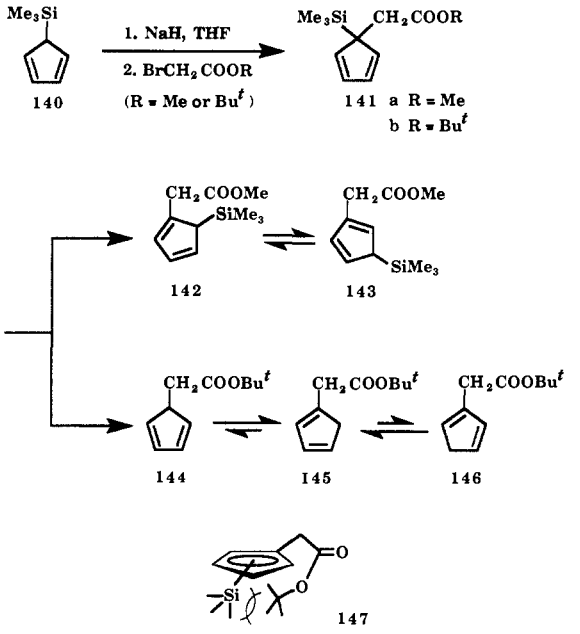
Crossley and Shepherd[115] studied the reaction of 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline (**137**) with trimethylsilyl isothiocyanate (Scheme 37). Trimethylsilyl tetrahydroquinoline **138** and thioamide **139** are generated; the ratio of **138**/**139** is solvent dependent. A mixture of toluene and hexane gives **139** as the main product (35–40%). More polar solvents, such as ether/hexane and THF/hexane, afford **138** almost exclusively. A modest increment of steric hindrance in silicon reagents however suppresses the silylation completely. They also found that treatment of **138** with BuLi and then *tert*-butyldimethylsilyl isothiocyanate gives thioamide **139** in almost quantitative yield upon aqueous acidic workup.

The reactive site of ketimines in trimethylsilylation depends upon their steric environment. Sarma[116,117] found that both C- and N-silylations occur in ketimines under alkaline conditions (Scheme 38).

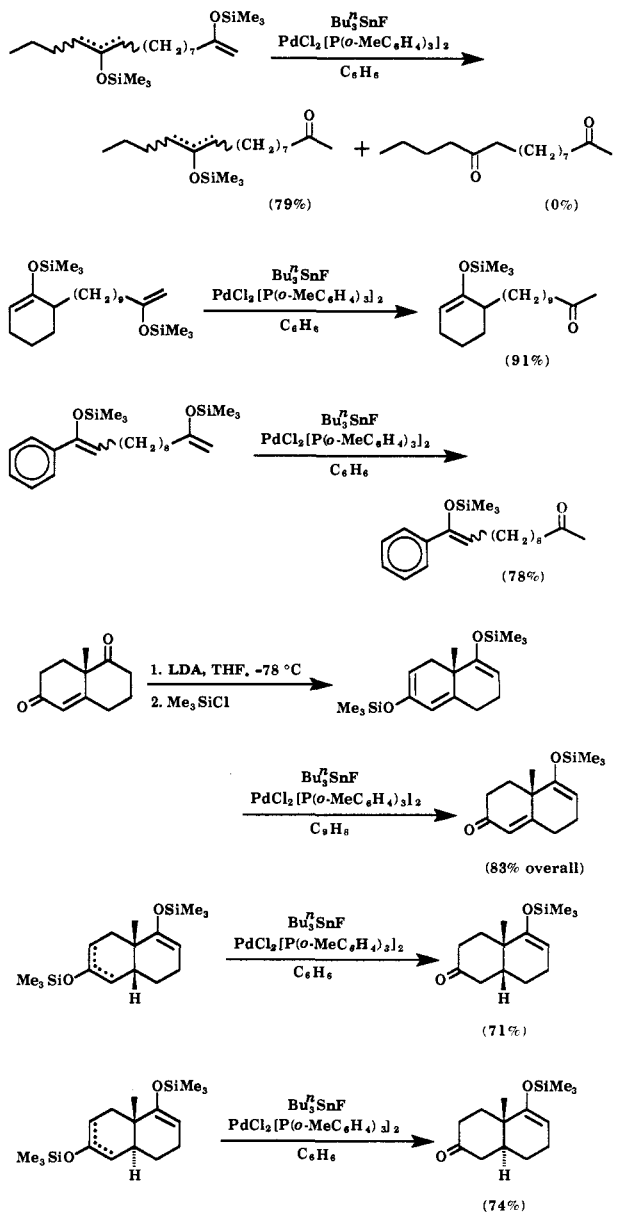
R. Desilylation

Steric congestion in compounds created by the Me_3Si group may provide the driving force for desilylation to occur. Vilarrasa et al. reacted (trimethylsilyl)cyclopentadiene (**140**) with methyl bromoacetate in the presence of NaH in THF to give a methyl ester (i.e., **141a**, **142**, or **143**) in good yield (Scheme 39).[118] Under

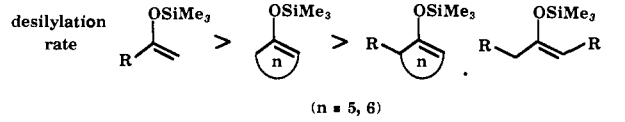
SCHEME 39



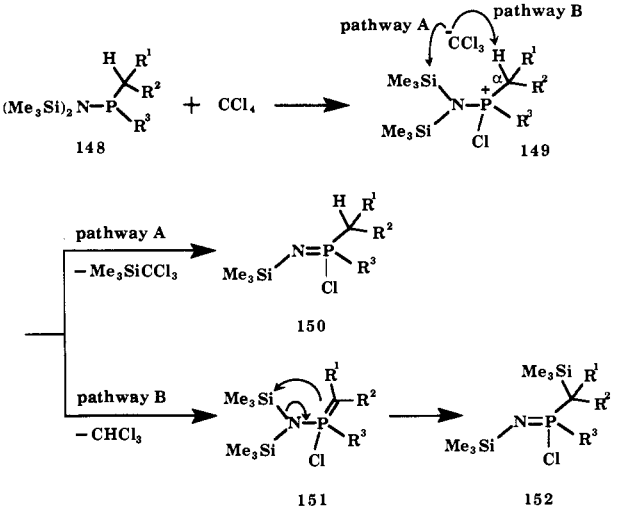
SCHEME 40



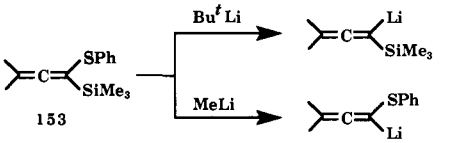
SCHEME 41



SCHEME 42



SCHEME 43



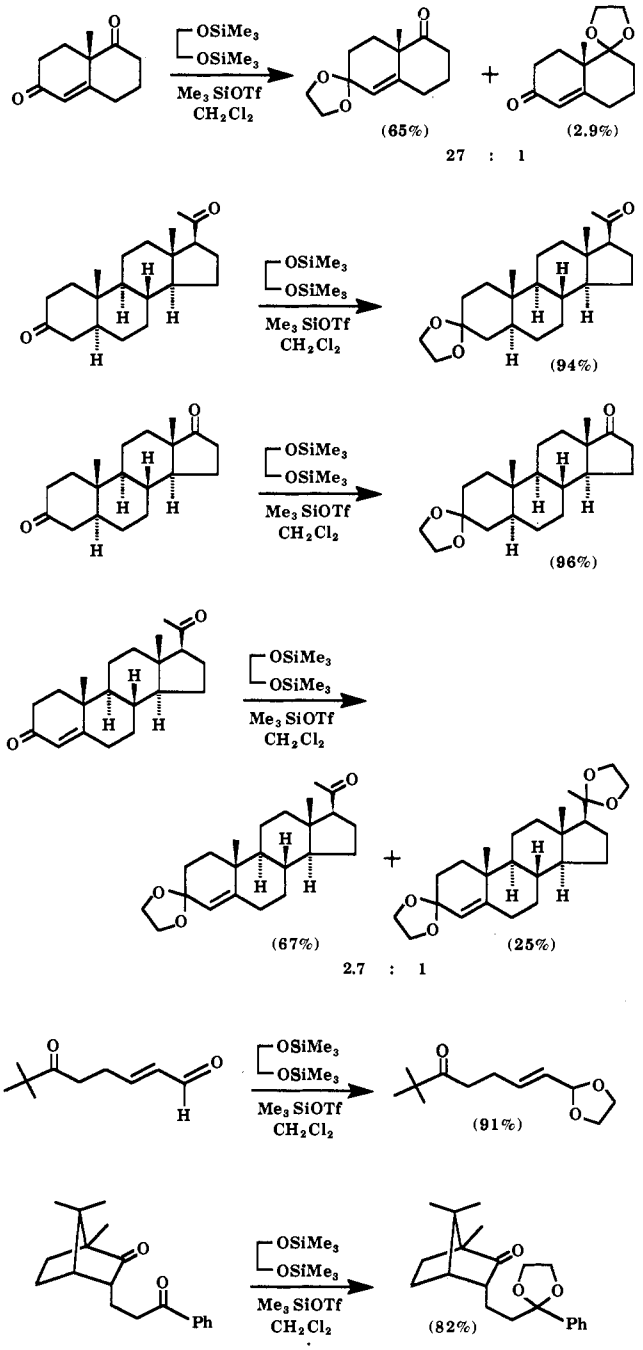
the same conditions, alkylation of **140** with *tert*-butyl bromoacetate produces desilylated species **144–146** in 95% yield. They indicated that steric hindrance exists between the Me_3Si and the *tert*-butyl groups in intermediate **141b** (cf. **147**).

The steric environment of the Me_3Si group in substrates may dominate selective detrimethylsilylations. By using *n*-Bu_3SnF and a catalytic amount of $PdCl_2[P(o\text{-}MeC_6H_4)_3]_2$, Kuwajima et al.[119] obtained high regioselectivity in monodesilylation of bis(silyl enol) ethers (Scheme 40). Reagent *n*-Bu_3SnF, instead of $PdCl_2[P(o\text{-}MeC_6H_4)_3]_2$, is responsible for the selectivity. The desilylation rate depends upon the steric congestion around the double bonds of silyl enol ether moieties. The rate decreases in the order shown in Scheme 41.

Wisian-Neilson et al.[120] reported that reaction of [bis(trimethylsilyl)amino]phosphines (**148**, R^1, R^2, R^3 = H, Me, *i*-Pr, *t*-Bu, Ph) with CCl_4 gives *P*-chloro-*N*-silylphosphoranimines **150** and **152** (via **151**, Scheme 42). These products are generated through desilylation (pathway A) and deprotonation (pathway B). The competition between these two pathways depends upon the steric bulk of the substituents at phosphorus as well as solvent polarity and an electronic effect resulting from R^1 and R^2. Desilylation of **149** by Cl_3C^- to liberate Me_3SiCCl_3 is favorable when the α hydrogen has a sterically congested environment, such as $R^1 = R^2$ = Me, R^3 = *i*-Pr, *t*-Bu, or Ph.

Bridges et al. reported that cleavage of the carbon–sulfur bond occurs when allene **153** reacts with *t*-BuLi at −25 °C (Scheme 43).[121] Nevertheless, desilylation takes place at 25 °C when MeLi is employed. The change of reaction pathway reflects the large steric

SCHEME 44



hindrance to attack at silicon by *t*-BuLi and its great thiophilicity.

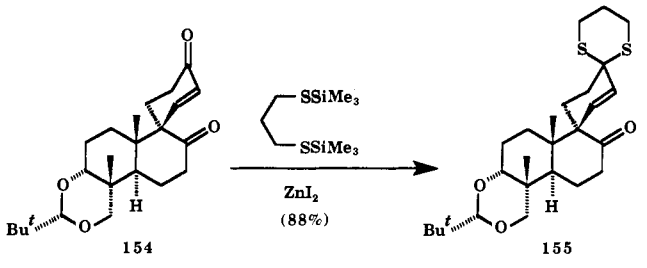
S. Ketalization

Selective monodioxolanation of dicarbonyl compounds can be accomplished by use of $Me_3SiOCH_2CH_2OSiMe_3$ in the presence of catalyst $Me_3SiOSO_2CF_3$ (Scheme 44).[1] These silicon-containing reagents preferentially react with the sterically less congested carbonyl group under conditions of kinetic control. Results from control experiments indicate that the selectivity comes from the steric, instead of the electronic, effect resulting from Me_3Si groups.

T. Thioketalization

Evans et al.[122] found that thiotrimethylsilanes ($RSSiMe_3$) react with aldehydes and ketones with ZnI_2

SCHEME 45



SCHEME 46

as the catalyst to give the corresponding thioacetals in good to excellent yields (70–98%). Corey et al.[123] adopted this procedure for the selective protection of a less sterically hindered α,β-enone moiety in the presence of a more hindered saturated carbonyl group in **154**. By use of bis(trimethylsilyl)propane-1,3-dithiol and ZnI_2 in chloroform, **154** is converted to **155** in 88% yield (Scheme 45). Conversion of **154** to **155** serves as a key step in a total synthesis of (±)-aphidicolin.

U. Nitration

Speier[124] found that the ortho, meta, and para positions in (trimethylsilyl)benzene possess different reactivities toward nitration. The reactivity of the para position is normal; the ortho/para ratio is 0.42.[125] Glyde and Taylor[126] suggested that the ratio was affected by the steric hindrance resulting from the Me_3Si group. This steric influence, however, is weaker on the meta position (meta/para ratio = 0.75).

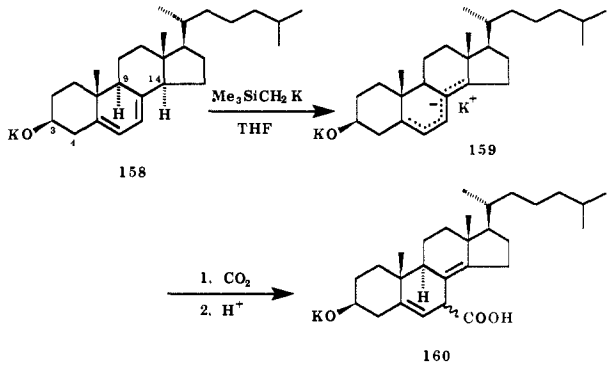
V. Solvolysis

Steric hindrance from the Me_3Si groups can retard nucleophilic attacks at the silicon atom attached to the $(Me_3Si)_3C$ moiety. Eaborn and Safa[127] found that $(Me_3Si)_3CSiMe_2OSiMe_3$ has low chemical reactivity. It is stable toward 2.5 M HCl in methanol at room temperature, 1 M NaOMe in refluxing methanol, KF/18-crown-6 in refluxing CH_2Cl_2, and KF in refluxing methanol. It is possible, however, to break the O–$SiMe_3$ bond in $(Me_3Si)_3CSiMe_2OSiMe_3$ to give $(Me_3Si)_3CSiMe_2OH$ by anhydrous CF_3COOH or KOH in water/DMSO.

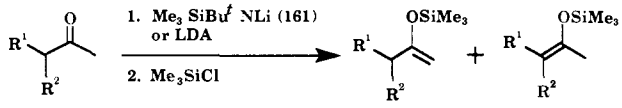
The highly sterically hindered silanol $(Me_3Si)_3CSiMe_2OH$ can also be obtained by solvolysis of the corresponding silyl perchlorate and silyl halides. Thus $(Me_3Si)_3CSiMe_2OClO_3$ is solvolyzed by water/methanol,[128] $(Me_3Si)_3CSiMe_2X$ (X = Cl or Br) by water/*n*-Bu_4PCl/KCl/CCl_4,[129] and $(Me_3Si)_3CSiMe_2I$ by methanol ($t_{1/2}$ = 13 days),[130] water/dioxane, and water/DMSO.[131,132]

In a meticulous study on trifluoroacetolysis of (trimethylsilyl)cyclohexenes, Wickham and Kitching[133] reacted *cis*- and *trans*-3,6-bis(trimethylsilyl)cyclohexenes (**156** and **157**) with CF_3COOD in chloroform (Scheme 46). By analyzing the ratio of products *cis*- and *trans*-3-deuterio-4-(trimethylsilyl)cyclohexenes, they concluded that cis isomer **156** undergoes prefer-

SCHEME 47



SCHEME 48



2-heptanone	161	49 : 1
	LDA	13 : 1
3-methyl-2-pentanone	161	24 : 1
	LDA	> 99 : 1
4-methyl-2-pentanone	161	32 : 1
	LDA	32 : 1
2-methylcyclohexanone	161	99 : 1
	LDA	49 : 1
trimethylsilyl acetone	161	49 : 1
	LDA	4 : 1

entially the anti mode of attack by CF_3COOD. The anti/syn ratio is 1.14 for trans isomer **157**; steric congestion by the Me_3Si group in the γ-carbon region hinders the anti approach by CF_3COOD.

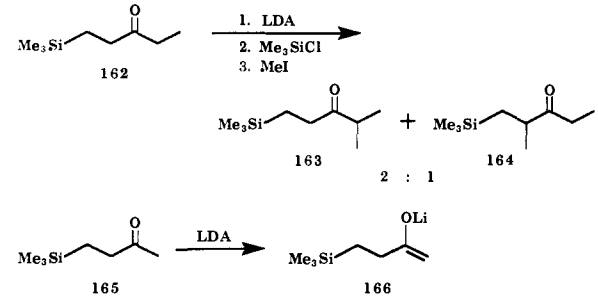
W. Deprotonation

Selective deprotonation is extremely important to organic synthesis. The selectivity can be obtained by use of Me_3Si-containing bases or by placement of the Me_3Si group in substrates. Moret and Schlosser utilized Me_3SiCH_2K to remove the C-14 proton of potassium alkoxide of 5,7-cholestadien-3β-ol (**158**) in a highly regioselective manner (Scheme 47).[134] The resulting dianion **159** reacts with dry ice to give diastereomeric carboxylic acids **160** in 43% yield upon acidic workup. The methylene protons at the C-4 position are not abstracted because of the electronic and the steric effects resulting from the C-3 oxide aggregation. The methine proton at the C-9 position is not readily accessible either; it is located in a sterically congested area.

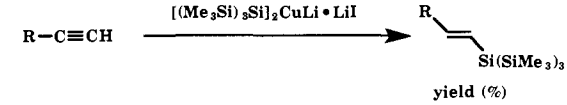
Larson et al.[135] developed several hindered, strong bases, such as lithium *tert*-butyl(trimethylsilyl)amide (**161**). Reagent **161** can deprotonate unsymmetric ketones regioselectively. The selectivity is comparable with or better than that offered by lithium diisopropylamide (LDA), as indicated in Scheme 48.

Fleming et al. found that the Me_3Si and the Me_2PhSi groups in the β position of ketones can direct enolization to occur on the side away from the silyl groups.[136] β-Trimethylsilyl ketone **162** reacts with lithium diisopropylamide, Me_3SiCl, and then MeI to give α-methylated ketones **163** and **164** in a 2:1 ratio (Scheme 49). β-Trimethylsilyl ketone **165** can also be enolized completely to terminal enolate **166**. The directing effect comes from the steric influence of the bulky silyl groups.

SCHEME 49

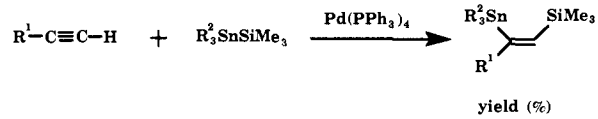


SCHEME 50



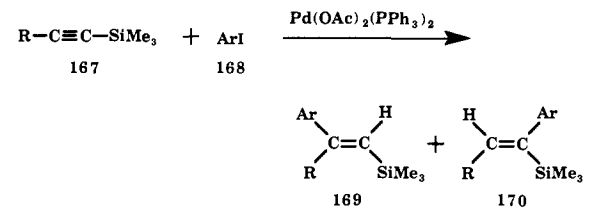
	yield (%)
R = Bu^n	80
R = Bu^t	72
R = Ph	63

SCHEME 51



		yield (%)
R^1 = Ph	R^2 = Bu	91
R^1 = $NC(CH_2)_3$-	R^2 = Bu	90
R^1 = Me_3Si	R^2 = Bu	85
R^1 = $THPOCH_2CH_2$-	R^2 = Bu	92
R^1 = $HO(CH_2)_3$-	R^2 = Bu	87
R^1 = Ph	R^2 = Ph	66

SCHEME 52



X. Silylmetalation

In the study of silylcuprate reagents, Chen and Oliver[137] reacted $((Me_3Si)_3Si)_2CuLi\cdot LiI$ with terminal acetylenes to give trans olefins exclusively (Scheme 50). The steric hindrance around silicon atoms prevents addition of the $(Me_3Si)_3Si$ group to the more crowded sp carbon. The regioselectivity of this silylcupration is opposite to that in the corresponding carbocupration.[138,139]

Terminal acetylenes also react with silylstannanes in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give silyl tin olefins in good to excellent yields (Scheme 51).[140] Chenard and Van Zyl found that this silylstannylation is highly stereo- and regioselective: only *cis* adducts are obtained, and the Me_3Si group always adds to the terminal carbon. Nonterminal acetylenes, however, do not react with silylstannanes under the same conditions; this is presumably due to the steric hindrance.

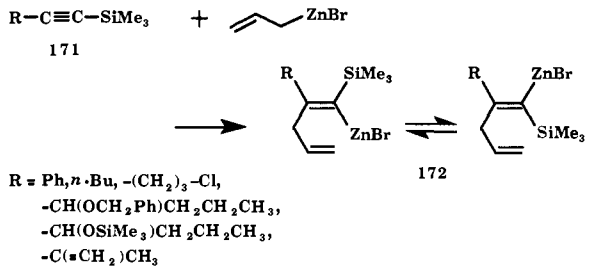
Y. Carbometalation

(Trimethylsilyl)acetylenes **167** react with aryl iodides **168** in the presence of $Pd(OAc)_2(PPh_3)_2$, piperidine, and formic acid to give 2,2-disubstituted vinylsilanes **169**

TABLE 5. Addition of 168 to 167 Giving 169 and 170

alkyne 167 R	aryl iodide 168 Ar	yield, % 169	170
4-$H_2NC_6H_4$	4-$MeOC_6H_4$	48	
4-HOC_6H_4	4-$MeOC_6H_4$	60	
4-ClC_6H_4	4-HOC_6H_4	56	11
3-$MeOOCC_6H_4$	4-HOC_6H_4	60	11
4-$MeCONHC_6H_4$	C_6H_5	50	10
3-$H_2NC_6H_4$	3-MeC_6H_4	41	
2-MeC_6H_4	4-HOC_6H_4	71	
4-$MeOC_6H_4$	4-$MeOC_6H_4$	55	
4-$MeOOCC_6H_4$	4-HOC_6H_4	47	18
4-$MeCOC_6H_4$	4-$MeOC_6H_4$	44	10
Me	4-MeC_6H_4	43	12

SCHEME 53

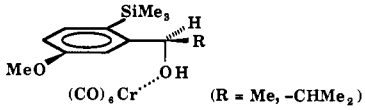


and **170** (Scheme 52 and Table 5), as reported by Cacchi et al.[141] The bulky Me_3Si group controls the carbopalladation step,[141-143] which favors the formation of **169**.

The regioselectivity is also observed in the allylzincation of ethynylsilanes **171** with allyzinc bromide (Scheme 53), as reported by Molander.[144] Whether products **172** are cis or trans highly depends upon the structure of **171** and the reaction conditions. The GC yields of **172** vary from 52 to 88%.

Z. Complexation

By introducing the Me_3Si group temporarily at an ortho position in benzyl alcohol derivatives, Uemura et al. accomplished a highly diastereoselective chromium complexation (Scheme 54).[145] The Me_3Si group can be easily removed later. Silyl alcohols **173** react with $Cr(CO)_6$ (130 °C) or tricarbonyl(naphthalene)chromium ($Nap{\cdot}Cr(CO)_3$, 70 °C) and then with n-Bu_4NF to give predominantly (S^*,R^*)-(η^6-arene)$\cdot Cr(CO)_3$ complex **174**. They proposed that these reactions proceed via a transition state such as **177**, in which the chromium



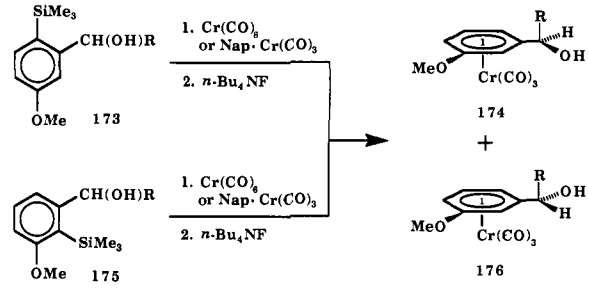
177

reagent coordinates with the hydroxyl group. The selectivity comes from the steric influence of the Me_3Si moiety. This moiety forces the R group (R = Me, $CHMe_2$) to stay on the farther side, as indicated in **177**. Similarly, silyl alcohols **175** afford the other diastereomeric complexes (S^*,S^*)-**176**.

IV. Conclusion

This Review presents many examples to show that the bulky Me_3Si group can control stereochemistry in organic reactions. By placement of the Me_3Si group at an appropriate position in substrates or by use of Me_3Si-containing reagents, products usually can be

SCHEME 54



compound	chromium reagent	ratio of 174 to 176	yield (%)
173 (R = Me)	$Cr(CO)_6$	19 : 1	66
173 (R = $CHMe_2$)	$Cr(CO)_6$	24 : 1	77
175 (R = Me)	$Cr(CO)_6$	1 : 49	69
173 (R = Me)	$Nap{\cdot}Cr(CO)_3$	49 : 1	82
173 (R = $CHMe_2$)	$Nap{\cdot}Cr(CO)_3$	100 : 0	85
175 (R = Me)	$Nap{\cdot}Cr(CO)_3$	0 : 100	97
175 (R = $CHMe_2$)	$Nap{\cdot}Cr(CO)_3$	0 : 100	88

obtained with the desired configuration. The steric hindrance resulting from the Me_3Si group is expected to continue to play an important role in organic chemistry.

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