

Award Accounts

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Development of New Reagents Containing Silicon and Related Metals and Application to Practical Organic Syntheses

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Our research works in the last few decades are summarized. We have studied the synthetic use of organometallics, especially organosilicon compounds, and have developed a number of new reagents and reactions useful for efficient organic synthesis. In the first section, the allylation of carbon electrophiles with allylsilanes, the so-called Hosomi–Sakurai reaction, is described. We have demonstrated that the allylation reaction is valuable not only for highly regio- and stereoselective carbon–carbon bond formation but also for introduction of a variety of functionalities. The second section deals with synthetic reactions using highly coordinated organosilanes and other organometallics, including Cr, Mn, Fe, and Cu. Higher coordination by one or more extra anionic ligands brings about unique reactivities that enable synthetically useful transformations. As shown in the third section, we developed stable 1,3-dipole equivalents protected by a silyl group and their cycloadditions, leading to N, S, or O-containing heterocycles. The following section describes the stereoselective synthesis of cyclic ethers and amines by acid-catalyzed cyclizations of vinylsilanes bearing a hydroxy or amino group. These silicon-directed cyclizations have disclosed the synthetic utility of β-silylcarbenium ion species generated from vinylsilanes by protonation. The copper-catalyzed reactions of organosilanes via silicon–copper exchange are described in the fifth section. In the final section, our studies on homolytic carbometalation reactions are presented.

Silicon occurs abundantly in the earth's crust. It forms strong bonds with carbon; therefore organosilicon compounds are relatively stable and are easily handled compared with the other organometallics. The simultaneous discovery of the direct synthesis of organosilanes by Rochow and Müller made some functional organosilanes widely available. This contributed largely to the explosive growth of organosilicon chemistry.[1] A huge number of organosilicon compounds have so far been synthesized and utilized for organic synthesis. The great utility of organosilicon reagents is now well established.[2]

Since silicon is more electropositive than carbon, the covalent bond between silicon and carbon is negatively polarized at the carbon. This fact indicates that organosilicon compounds possess some potential as carbon nucleophiles. As a main subject of our research, we have pursued the development of efficient C–C bond-forming reactions directed by the nucleophilic character. In addition, our efforts have been directed to the design of new organosilicon reagents that function as stable synthetic equivalents of unstable carbon species. The directing effects of triorganosilyl groups as well as the polarization of Si–C bonds are important to understand the reactivities of organosilanes. We have focused our attention also on the use of the β-carbenium ion-stabilizing effect (β-effect) for regio- and stereoselective bond formation. As the result of these studies, a variety of new silicon reagents and new synthetic reactions utilizing the reactivities of organosilanes have been developed in this laboratory. Our research interest is not limited to organosilicon reagents, but covers the synthetic use of other organometallics. On the basis of our knowledge of organosilicon chemistry, we have studied new synthetic reactions with organometallic reagents containing Cr, Mn, Cu, Sn, and Sm. In this account, we describe the selected part of our research works over the last few decades.

1. Carbon–Carbon Bond Formation Using Allylsilanes

Allylation reactions of carbon electrophiles with allylmetals provide important tools for elongation of carbon chains and introduction of functional groups.[3] There are a lot of allylmetals that have been utilized for the nucleophilic allylation. Among these allylmetals, allyltriorganosilanes such as allyltrimethylsilane (**1a**) are thermally stable and considerably inert to water and oxygen. They are isolable and storable without special precautions. The strong Si–C bond suppresses the 1,3-shift of the silyl group, which enables a regiospecific allylation, although other allylmetals (M = Li, B, Mg, Al, Ti, Zn, Ga, Zr, Cd, In, etc.) undergo a rapid 1,3-shift of the metals even at low temperatures (Scheme 1).[4] In addition, it is possible to functionalize simple allylsilanes and to transfer the functionalized allyl groups onto carbon electrophiles with high regio-, stereo-, and chemoselectivities. Our studies disclosed these synthetic

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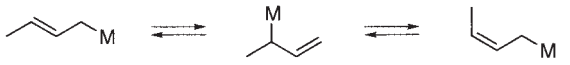
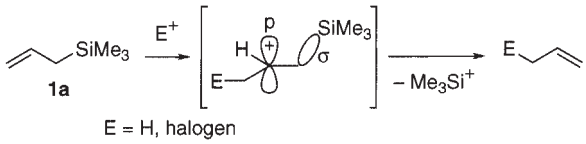


Scheme 1.



Scheme 2.

utilities of allylsilanes.

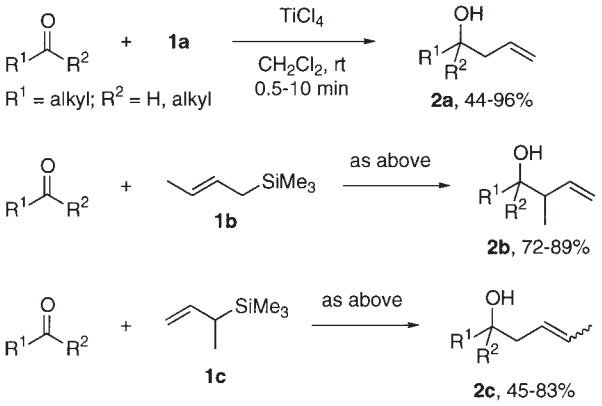
1.1 Early Studies on Reactions of Allylsilanes. In 1948, Sommer et al. reported that the allyl-Si σ bond of **1a** was easily cleaved by electrophiles such as halogens and Brønsted acids.[5] Later, Frainnet found that electrophiles reacted at the γ-carbon of allylsilanes.[6] The facile and regioselective reaction with allylsilanes is explained by the β-effect of the silyl group, the stabilization of the intermediary β-silylcarbenium ion by σ–π conjugation between the σ(Si–C) orbital and the vacant p orbital (Scheme 2).[7]

We introduced the first example of the C–C bond-forming reaction with **1a**, which was performed under radical conditions.[8] In the middle of the 1970s, uncatalyzed and Lewis acid-catalyzed allylations of carbonyl compounds with **1a** were reported by Calas', Abel's, and our groups.[9–11] Calas' and Abel's groups disclosed that **1a** added to activated carbonyl compounds such as perfluoroacetone and chloroacetone.[9,10] We believed in the high potential of allylsilanes as allylating agents on the basis of our spectroscopic studies[7c] and examined the allylation of carbonyl compounds independently. As a result, we found that, in the presence of $TiCl_4$, allylsilanes reacted smoothly with aldehydes and ketones in a regiospecific manner (vide infra).[11] Since this discovery, the Lewis acid-promoted allylation with allylsilanes (the Hosomi–Sakurai reaction) has been intensively studied by us and by other researchers.[12] These studies have demonstrated that allylsilanes are quite valuable for regio- and stereoselective allylation of a wide range of carbon electrophiles.

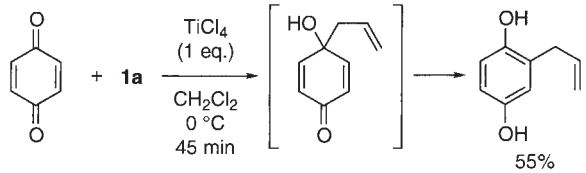
1.2 Lewis Acid-Promoted Allylation of Carbon Electrophiles. In the presence of a substoichiometric amount of $TiCl_4$ (0.5 equiv.), **1a** adds to aldehydes and ketones rapidly to give homoallyl alcohols **2a** in moderate to high yields (Scheme 3). The synthetic utility of this allylation is shown by its regiospecific allyl transfer. Thus the reactions of crotylsilane **1b** and (1-methylallyl)silane **1c** provide homoallyl alcohols **2b** and **2c**, respectively, by regiospecific allylation at the γ-position.[11] The original method of the carbonyl allylation developed by us requires a (sub)stoichiometric amount of a Lewis acid. At present, some Lewis acids are known to promote the allylation effectively with a catalytic quantity.[13]

The $TiCl_4$-promoted reaction of *p*-quinones with **1a** forms 2-allylhydroquinones via carbonyl allylation and the subsequent allyl migration (Scheme 4).[14]

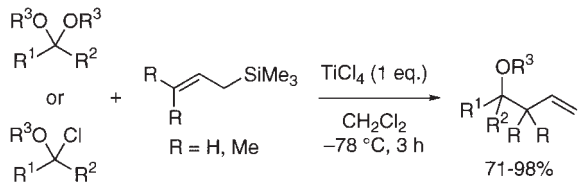
The Lewis acid-promoted allylation can be used for efficient synthesis of homoallyl ethers from acetals and α-chloro ethers (Scheme 5). Initially, we reported a method using a stoichiometric amount of $TiCl_4$;[15,16] however, it was found later that a catalytic amount of TMSI or TMS(OTf) was effective in



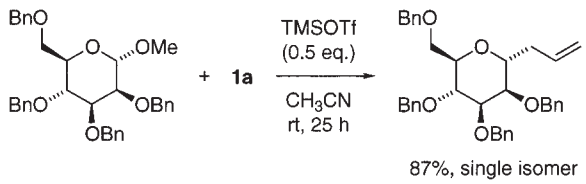
Scheme 3.



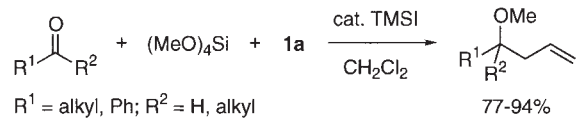
Scheme 4.



Scheme 5.



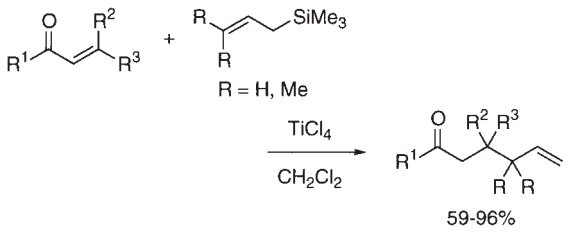
Scheme 6.



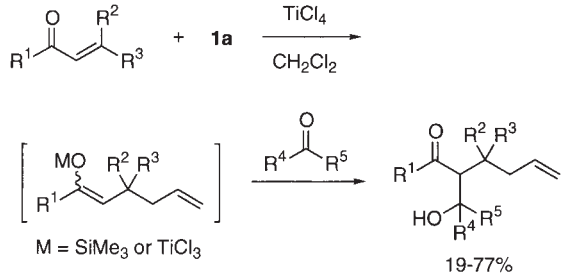
Scheme 7.

the acetal allylation.[17–19] The acetal allylation also proceeds in a regiospecific manner. Crotylation of aliphatic acetals with **1b** shows high *syn* diastereoselectivity, irrespective of the geometry.[20] *C*-Allylation of glycopyranosides with allylsilanes takes place with high diastereoface-stereoselectivity (Scheme 6).[21] Homoallyl ethers can be synthesized from aldehydes by the TMSI-catalyzed tandem acetalization–allylation reaction using silyl ethers and **1a** (Scheme 7).[22]

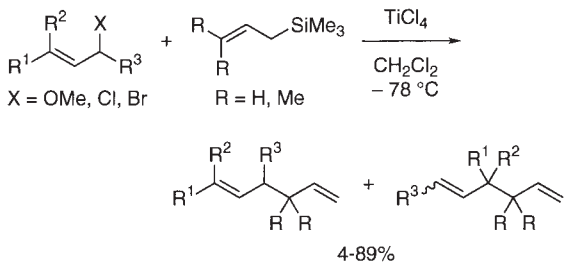
Conjugate allylation of α-enones also can be achieved efficiently by the $TiCl_4$-promoted reaction with allylsilanes (Scheme 8).[23] Various α-enones including sterically hindered ones undergo the conjugate allylation with high regioselectivi-



Scheme 8.



Scheme 9.



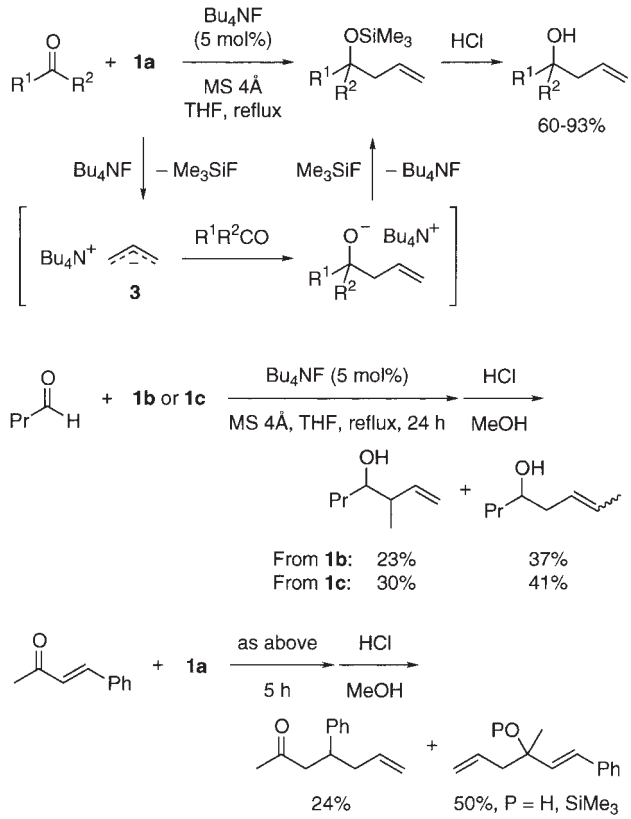
Scheme 10.

ty. The products are good precursors of 1,5-dicarbonyl compounds and 2-cyclohexenones.[24] The conjugate allylation with allylsilanes provides a powerful tool for total syntheses of natural products.[25]

The allylation of α-enones proceeds through nucleophilic attack of the allyl group and the subsequent hydrolysis of the enolate intermediates. Alkylation of the intermediates with aldehydes or acetals realizes "one-pot" double alkylation of α-enones (Scheme 9).[26]

Allyl halides and ethers also undergo the Lewis acid-promoted allylation to give 1,5-dienes, although the regioselectivity with respect to the reaction site of the allyl electrophiles is not necessarily good (Scheme 10).[27] The use of acetals derived from α-enals leads to double allylation products.[28]

1.3 Fluoride Ion-Catalyzed Allylation of Aldehydes, Ketones, and α-Enones. A fluoride ion shows high affinity to the silicon atom of certain organosilanes due to the high Si–F bond energy. In the reactions of organosilicon reagents, this characteristic has been frequently utilized for the activation of the Si–X (X = C, H, O) bonds.[29–31] We found that a fluoride ion source such as Bu_4NF catalyzed allylation of carbonyl compounds with allylsilanes (Scheme 11).[32] The fluoride ion-catalyzed allylation is different from the Lewis acid-promoted allylation in regio- and chemoselectivities. The allylation of an aldehyde with **1b** gives a regioisomeric mixture of allylation products.[33] A similar result is obtained with **1c**. In addition, the reaction of



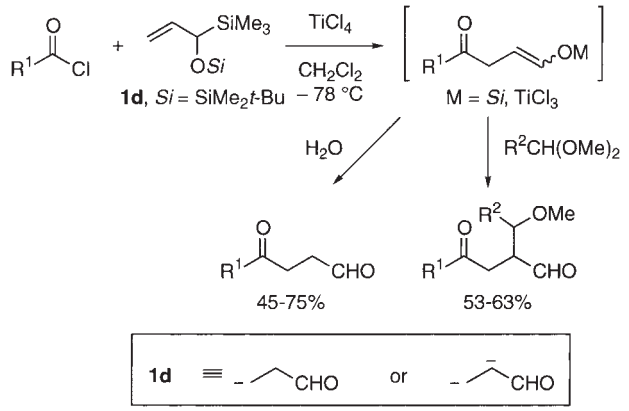
Scheme 11.

an α-enone with **1a** results in the competitive formation of 1,2- and 1,4-addition products. These results indicate the presence of a metal-free active allyl anion species such as **3**.

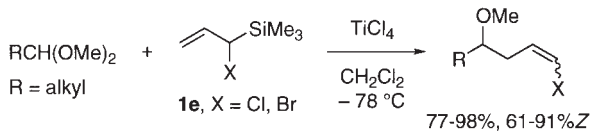
The fluoride ion-catalyzed method is available for intramolecular conjugate allylation of α-enones as well as inter- and intramolecular conjugate allylations of α-enoates and α-enamides.[34]

1.4 Allylation with Functionalized Allylsilanes. We developed several allylsilanes bearing a functional group at the α, β, or γ-position for efficient syntheses of highly functionalized synthetic intermediates and natural products. (1-Siloxyallyl)silane **1d**, easily prepared from allyl silyl ethers, reacts with acid chlorides to give β-formyl ketones.[35] When a second electrophile is added to the reaction mixture before protonolysis, "one-pot" double alkylation on the vicinal carbons occurs.[26] Thus **1d** serves as a homoenolate anion and vicinal dianion equivalent (Scheme 12). Allylation of carbon electrophiles with (1-haloallyl)silanes **1e** is useful for *Z*-selective preparation of functionalized vinyl halides (Scheme 13).[36] Since the halide products are available for further C–C bond formation by metal-catalyzed cross coupling reaction, **1e** can be viewed as a 1,3-zwitterion equivalent.

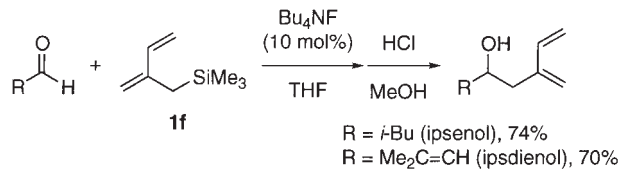
(2-Vinylallyl)silane (isoprenylsilane) **1f** is an important reagent for the introduction of an isoprene unit into carbon electrophiles such as aldehydes, ketones, acetals, and acid chlorides.[37–39] Ipsenol and ipsdienol (pheromones of a bark beetle) can be synthesized by acylation of **1f**, followed by carbonyl reduction, or by the fluoride ion-catalyzed isoprenylation of the corresponding aldehydes (Scheme 14). In the presence of a Lewis acid, (2-alkoxycarbonylallyl)silane **1g** reacts smoothly



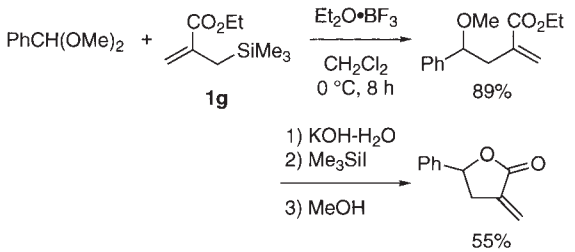
Scheme 12.



Scheme 13.



Scheme 14.

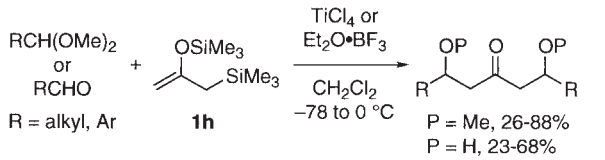


Scheme 15.

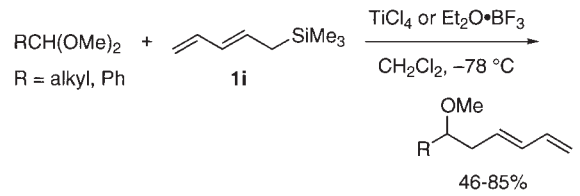
with acetals to give the corresponding homoallyl ethers, which are good precursors of α-methylene-γ-butyrolactones, key structures of a number of naturally occurring sesquiterpenes with potential cytotoxic activity (Scheme 15).[40] (2-Siloxyallyl)silane **1h**, a hybrid reagent containing an allylsilane unit and an enoxysilane unit, acts as an acetone α,α'-dianion equivalent to undergo double alkylation with aldehydes and acetals (Scheme 16).[41] Vinylcyclopropane and vinyloxirane units can be directly introduced by allylation with 2-cyclopropyl- and 2-oxiranyl-substituted allylsilanes.[42,43]

The Lewis acid-promoted reaction of acetals with 2,4-pentadienylsilane **1i**, a γ-substituted allylsilane, occurs only at the ε-position of **1i** to give the corresponding 1,3-dienes (Scheme 17).[44]

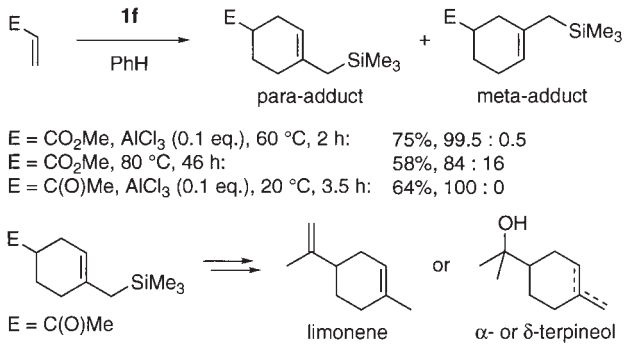
1.5 Cycloaddition of Allylsilanes. We studied not only electrophilic substitution reactions of allylsilanes but also their cycloadditions with electron-deficient unsaturated bonds and 1,3-dipolars that provide silyl-substituted products. Isoprenylsilane **1f** smoothly undergoes the Diels–Alder reaction with unsymmetrical dienophiles to give "para"-adducts with high regioselectivity (Scheme 18).[45,46] This fact is reasonably explained by the directing effect of the silyl groups. The extensive σ(Si–C)–π conjugation raises the HOMO of the diene unit as the coefficient of the atomic orbital at the position γ to the silyl group increases. The regioselectivity is improved dramatically by the addition of a catalytic amount of a Lewis acid.[47] The cycloadducts having an allylsilane moiety are obtained with almost 100% para selectivity. The Lewis acid-catalyzed cycloaddition of **1f** is quite valuable for the synthesis of terpenes such as limonenes, terpineols, bisabolenes, and cadinenes.



Scheme 16.



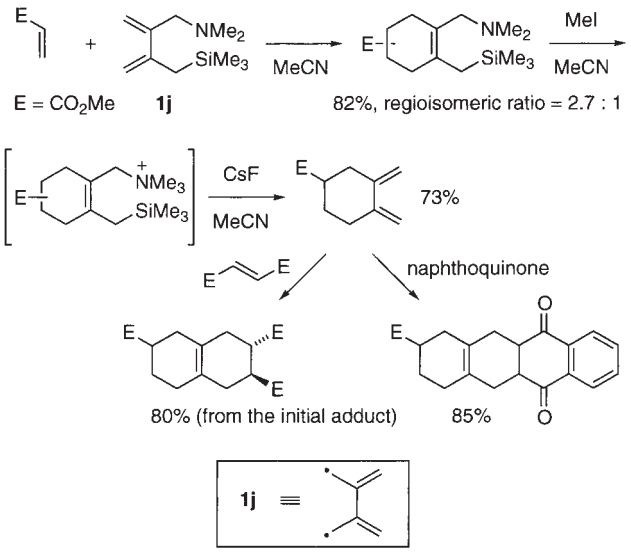
Scheme 17.



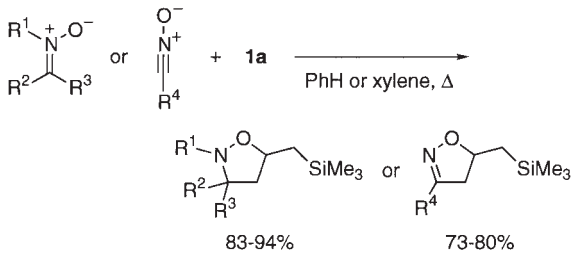
Scheme 18.

2-Dimethylaminomethyl-3-trimethylsilylmethyl-1,3-butadiene (**1j**) serves formally as a 2,2′-biallyl diradical synthon (Scheme 19).[48] The cycloaddition of **1j** with dienophiles provides 1-dimethylaminomethyl-2-(trimethylsilylmethyl)cyclohexenes, which can be converted into 1,2-dimethylenecyclohexanes efficiently by conjugate 1,4-elimination. The *s-cis* 1,3-dienes generated in situ undergo the second cycloadditions with electron-deficient unsaturated bonds and 1,3-dipolars to give bicyclic compounds in good to high total yields from the initial cycloadducts. The successive Diels–Alder reaction using **1j** is applicable to the synthesis of precursors of anthracyclinone antibiotics.

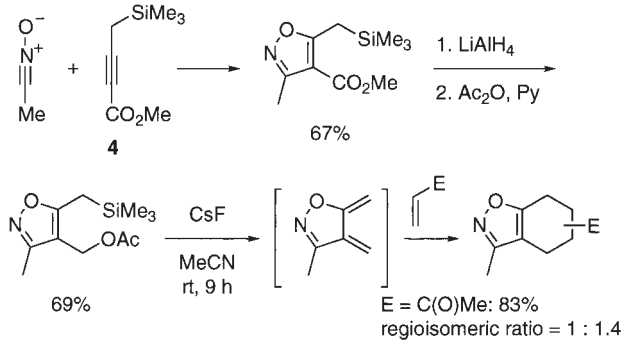
Allylsilane **1a** reacts with nitrones and nitrile oxides to give single regioisomers of isoxazolidines and isoxazolines, respectively, in good yields (Scheme 20).[49] The former [3 + 2] cycloadducts can be easily converted into homoallylamines by hydrogenolysis of the N–O bond, followed by β-elimination of



Scheme 19.



Scheme 20.

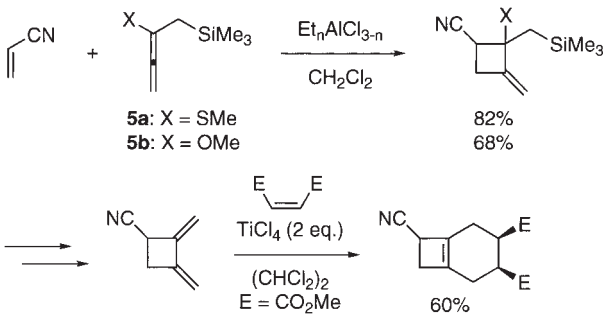


Scheme 21.

the neighboring silyl and hydroxy groups. Nitrile oxides also add to propargylsilane **4** to afford 5-(silylmethyl)isoxazoles (Scheme 21).[50] 4-(Acetoxymethyl)isoxazoles derived from the cycloadducts are useful as precursors of dimethyleneisoxazolines. The Lewis acid-promoted reaction of (allenylmethyl)silanes **5** with electron-deficient alkenes and alkynes affords methylene-cyclobutanes and -cyclobutenes, respectively (Scheme 22).[51] The [2 + 2] cycloadducts also can be utilized for further ring construction via dimethylenecyclobutanes.

2. Organic Synthesis Using Highly Coordinated Organometallics Including Silicon and Transition Metals

In the late 1970s, Kumada and co-workers introduced the synthetic use of highly coordinated organosilanes.[52] They disclosed that the carbon ligand of organopentafluorosilicates



Scheme 22.

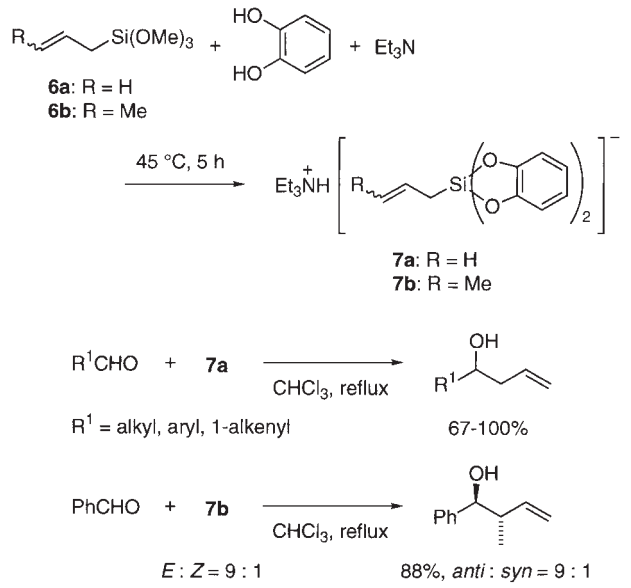
showed high reactivity to carbon and heteroatom electrophiles. Since their pioneering works, much attention has been paid to the use of organo- and hydrosilicates as carbon nucleophiles and reducing agents.[2a]

Highly coordinated organosilanes can be readily prepared, particularly when the silicon bears electronegative atoms and groups. Our attention was focused on higher coordination of organosilanes with oxygen ligands and its application to fine organic synthesis, because the high affinity of oxygen to silicon serves for the formation of relatively stable silicates, and the diversity of oxygen ligands enables fine adjustment of the reactivity of silicates toward highly selective synthetic reactions. As the result of our efforts, we found that allyl-, 1-alkenyl-, and hydrosilicates bearing oxygen ligands have unique and synthetically valuable reactivities that do not appear in the corresponding tetracoordinate silanes (Sections 2.1–2.2).[53]

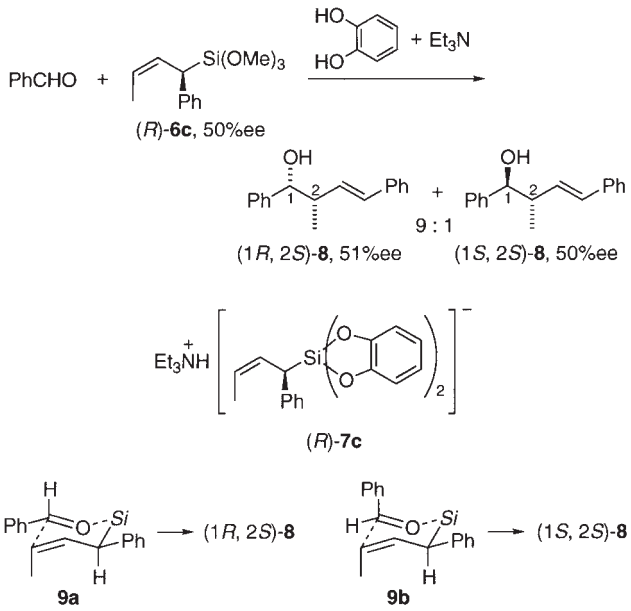
The formation of silicates by nucleophilic attack of an anionic ligand should be influenced by steric effects of the substituents on silicon. We envisioned that introduction of a small silyl group such as a dimethylsilyl (DMS) group might make organosilicon reagents more reactive, due to the ease of nucleophilic attack to the silicon center. On the basis of this working hypothesis, we investigated the reactivity and synthetic utility of DMS enolates (Section 2.3).

In connection with our studies on organosilicates, we were interested also in the reactivity of transition metal ate complexes bearing carbon ligands. Ate complexes such as organocuprates have frequently been utilized as carbon nucleophiles.[54] In contrast, we have disclosed that Cr, Mn, and Cu ate complexes bearing alkyl ligands are valuable for reductive metalation of alkyl halides and pseudohalides (Section 2.4).

2.1 Carbon–Carbon Bond Formation with Allylsilicates and 1-Alkenylsilicates. The synthetic use of allylsilicates bearing fluorine and/or oxygen ligands was independently reported by three research groups including ours in the late 1980s.[55–57] We investigated carbonyl allylation with triethylammonium bis(catecholato)allylsilicates **7**, which can be readily prepared from allyltrimethoxysilanes **6**, catechol, and triethylamine (Scheme 23).[58] Allylsilicate **7a** reacts smoothly with aliphatic and aromatic aldehydes to furnish the corresponding homoallyl alcohols. The carbonyl allylation is achieved efficiently also by in situ generation of **7a** from **6a**. The reaction with *E*-rich crotylsilicate **7b** takes place at the position γ to silicon, and crotylated products are obtained with high *anti* diastereoselectivity. This fact implies that the allylation proceeds via a cyclic transition state. As shown below, such a reaction mechanism is strongly supported by stereochemical outcomes



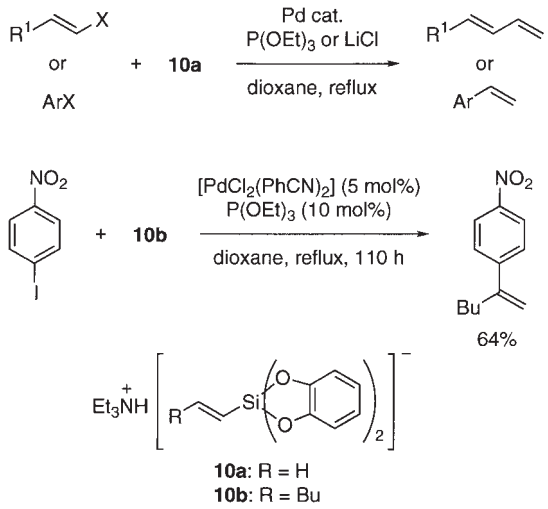
Scheme 23.



Scheme 24.

in asymmetric allylation with optically active allylsilicates.

The allylation of benzaldehyde with allylsilicate (*R*)-**7c**, generated in situ from optically active allyltrimethoxysilane **6c** (50% ee), provides a 9:1 diastereomeric mixture of allylated products **8** with *syn* selectivity (Scheme 24).[59] High levels of asymmetric transfer are observed in both diastereomers, whose major enantiomers have (1*R*,2*S*)- and (1*S*,2*S*)-configurations. The 2*S* configuration clearly indicates that the γ-carbon of (*R*)-**7c** attacks the aldehyde on the same side as the silyl group occupies. Judging from the relative position of the silyl group to the incoming aldehyde, (1*R*,2*S*)- and (1*S*,2*S*)-**8** would arise from six-membered cyclic transition states **9a** and **9b**, respectively. The predominant formation of *syn*-**8** is attributable to nonbonding interactions of the pseudoaxial phenyl group of **9b**, which destabilizes **9b** to suppress the formation of *anti*-**8**.



Scheme 25.

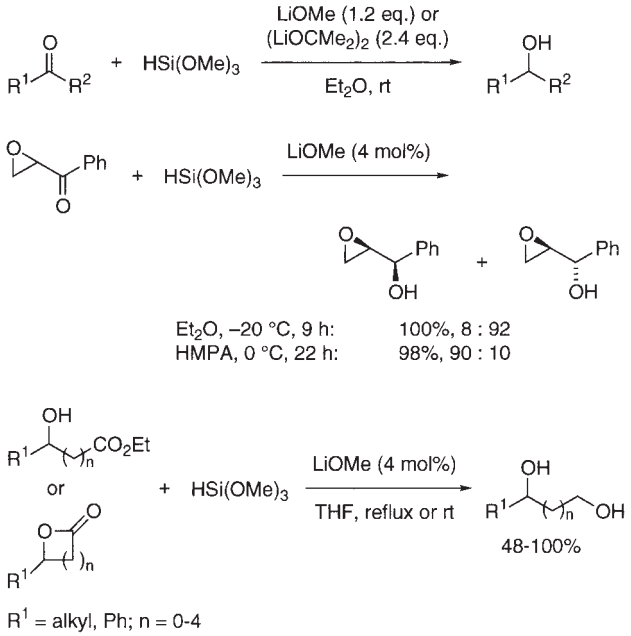
1-Alkenylsilicates **10** as well as **7** can be readily obtained from the corresponding trimethoxysilanes by the same method. They are available for cross-coupling reactions between sp^2-carbon centers (Scheme 25).[60] In the presence of a palladium catalyst and an additive ($P(OEt)_3$ or LiCl), **10a** reacts smoothly with 1-alkenyl halides and aryl halides (triflates) to give 1,3-dienes and styrenes, respectively. Interestingly, the Pd-catalyzed reaction of 1-hexenylsilicates **10b** with 1-iodo-4-nitrobenzene forms an α-substituted styrene (a *cine*-substitution product).[29,61]

2.2 Reduction with Hydrosilicates. Initially, we found that alkoxyhydrosilanes such as trimethoxysilane are useful for reduction of aldehydes and ketones in the presence of alkali metal alkoxides.[62] Then the reduction of α,β-epoxy ketones, hydroxy esters, lactones, and *N*-tosylimines with trimethoxysilane was realized by a catalytic amount of lithium methoxide (Scheme 26).[63,64] In the catalytic reduction of α,β-epoxy ketones, both diastereomers of the alcohol products can be obtained selectively by the proper choice of solvent.[63] The use of diethyl ether as solvent gives *anti*-isomers selectively by chelation control, while the reduction in HMPA shows *syn*-selectivity by Felkin–Anh control. The reduction of hydroxy esters and lactones with trimethoxysilane leads to diols in moderate to good yields.[64] This method is unsuitable for the conversion of simple non-functionalized esters into alcohols. Various *N*-tosylimines including aromatic and aliphatic ones can be reduced to *N*-tosylamines under similar conditions.[64]

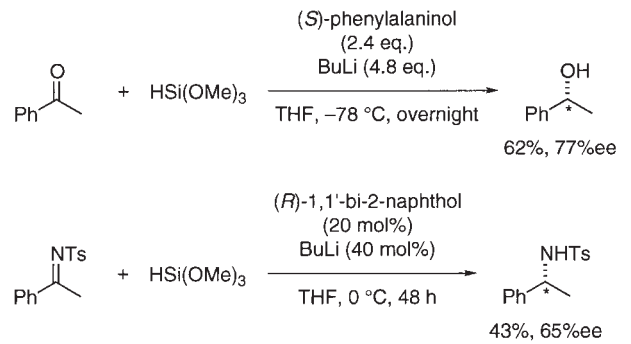
The use of lithium salts of homochiral diols and amino alcohols as silaphilic activators enables the asymmetric reduction of ketones and imines (Scheme 27).[65]

2.3 Nucleophilic Addition of DMS Enolates. The aldol reaction of triorganosilyl enolates usually requires a promoter such as a Lewis acid.[66] Recently, it has turned out that the elaboration of the substituent on silicon enables an uncatalyzed aldol reaction of silyl enolates.[67] We have demonstrated that DMS enolates add efficiently to aldehydes in DMF without any promoter. The corresponding TMS enolate shows much lower reactivity under the same conditions (Scheme 28).[68]

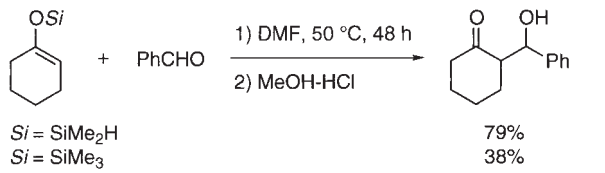
Chloride ion sources such as $CaCl_2$ and LiCl effectively promote the aldol reaction of DMS enolates under milder condi-



Scheme 26.



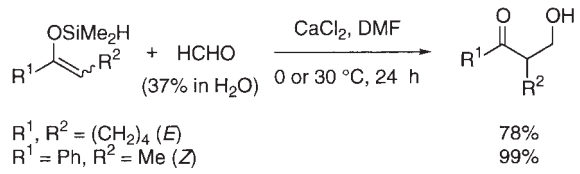
Scheme 27.



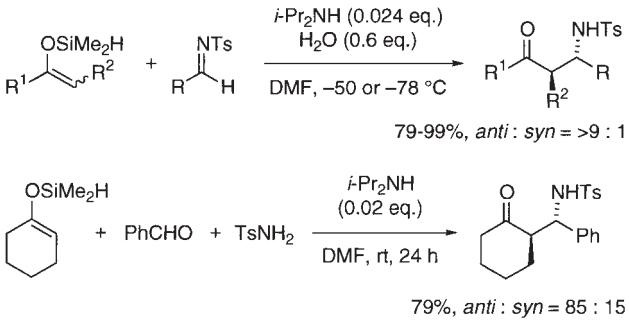
Scheme 28.

tions.[69] The rate-accelerating ability of $CaCl_2$ is higher than those of $CaBr_2$ and CaI_2. Chloride ion would activate DMS enolates by nucleophilic attack to the silicon. Interestingly, the $CaCl_2$-promoted aldol reaction proceed efficiently even in the presence of water. Hydroxymethylation of DMS enolates can be achieved by using an aqueous solution of formaldehyde (Scheme 29).

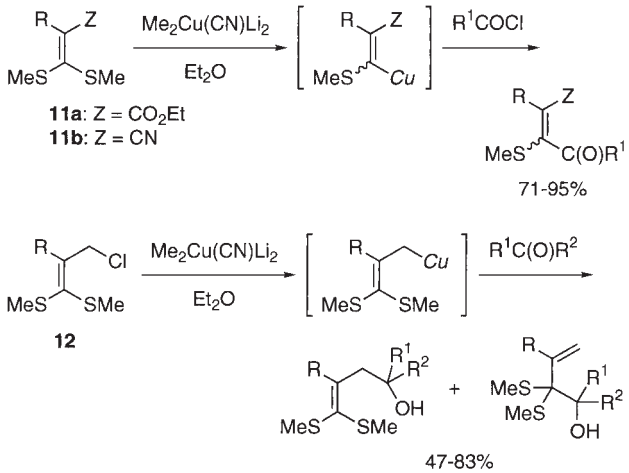
In the presence of water and a catalytic amount of an amine, DMS enolates react smoothly with aromatic and α,β-unsaturated *N*-tosylimines to give β-amino ketones with high *anti*-diastereoselectivity (Scheme 30).[70] The Mannich-type reaction would also involve nucleophilic activation of DMS enolates. The base-catalyzed system is applicable to the three-component coupling reaction of aromatic aldehydes, $TsNH_2$, and



Scheme 29.



Scheme 30.

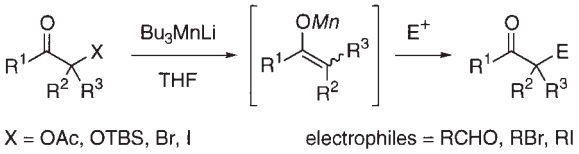


Scheme 31.

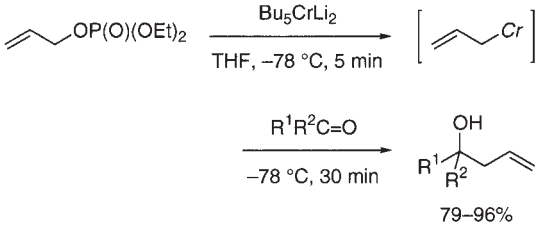
DMS enolates. In this case, addition of water is not necessary because the condensation between aldehydes and $TsNH_2$ yields *N*-tosylimines along with water.

2.4 Reductive Metalation with Transition Metal Ate Complexes. We have shown that dilithium cyanodimethylcuprate ($Me_2Cu(CN)Li_2$) is valuable for preparation of functionalized copper reagents by reductive metalation.[71,72] For example, the reactions of vinyl sulfides **11** and allyl chlorides **12** with the cuprate provide the corresponding vinyl- and allylcopper reagents, respectively. These copper reagents are usable for C–C bond-forming reactions with carbon electrophiles (Scheme 31). The reductive metalation of **11a** forms mainly the (*Z*)-vinylcopper species, while the cyano-substituted substrates **11b** are metalated with *E*-selectivity.

Lithium tributylmanganate (Bu_3MnLi) is effective in reductive metalation of α-oxy and α-halo ketones. The manganese enolates formed are alkylated efficiently with aldehydes and haloalkanes in a regiospecific manner (Scheme 32). The reductive generation of the enolates may involve a kind of oxidative addition of the substrate to the ate complex.[73] Similarly allyl-,



Scheme 32.



Scheme 33.

propargyl-, and phenylthiomethyl-manganese reagents can be prepared from the corresponding halides by reductive metalation with $Bu_{2+n}MnLi_n$ ($n = 1, 2$).[74,75]

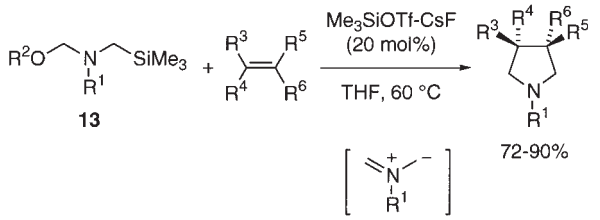
Similar to Bu_3MnLi, the alkylchromium(III) ate complex (Bu_6CrLi_3) prepared from $CrCl_3$ and six equivalents of BuLi has enough reducing ability for metalation of α-bromo- and α-acetoxy-substituted ketones and esters. The chromium enolates formed react with various carbon electrophiles such as aldehydes, ketones, haloalkanes, and oxiranes.[76,77] Reductive metalations of allylic and propargylic phosphates with Bu_5CrLi_2 provide a convenient route to allyl- and propargylchromium reagents (Scheme 33).[78]

3. Efficient Synthesis of Heterocycles by [3 + 2] Cycloaddition of 1,3-Dipoles

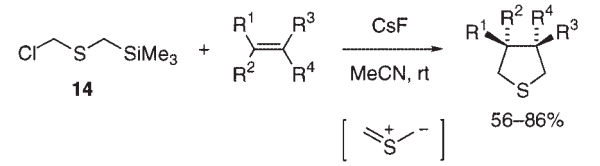
[3 + 2] Cycloadditions of 1,3-dipoles are valuable for the construction of 5-membered heterocycles containing one or more heteroatoms such as nitrogen, oxygen, or sulfur.[79] Particularly, azomethine and carbonyl ylides are synthetically important 1,3-dipoles, since their cycloadditions enable easy introduction of pyrrolidine and tetrahydrofuran units, which are frequently found in biologically active natural products. The conventional method for the generation of these active species is thermolysis of certain aziridines and oxiranes. However, this method requires either electron-withdrawing or conjugating substituents for stabilizing these 1,3-dipoles. We succeeded in the generation and cycloadditions of non-stabilized azomethine and thiocarbonyl ylides by using newly designed organosilicon reagents.[80] In addition, we have recently introduced new access to non-stabilized carbonyl ylides via reductive metalation.[81]

3.1 Cycloaddition of Silicon-Based 1,3-Dipole Synthons. *N*-(Silylmethyl)iminium salts serve as precursors of electronically stabilized azomethine ylides.[79a] We showed that *N*-(trimethylsilylmethyl)aminomethyl ethers **13** undergo 1,3-elimination under dual catalysis by a Lewis acid and a fluoride source to form non-stabilized parent azomethine ylides efficiently.[82,83] The in situ-generated ylides react smoothly with electron-deficient alkenes in a stereospecific manner (Scheme 34).

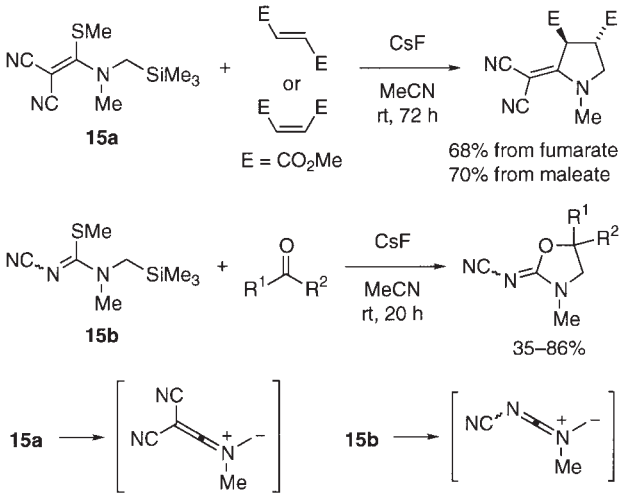
Chloromethyl trimethylsilylmethyl sulfide (**14**) is a good precursor of the parent thiocarbonyl ylide.[84,85] In the presence of CsF, the sulfide adds to electron-deficient alkenes and alkynes to afford the corresponding tetrahydro- and dihydrothiophenes, respectively, in good yields (Scheme 35). The use of carbonyl compounds as dipolarophiles leads to the formation of 1,3-oxathiolanes.[86]



Scheme 34.



Scheme 35.

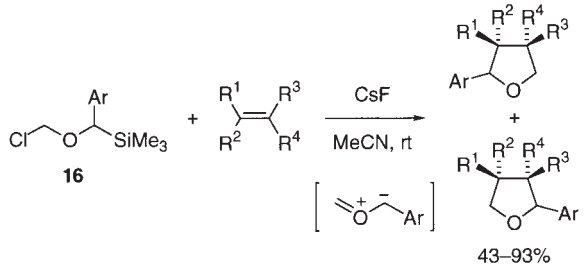


Scheme 36.

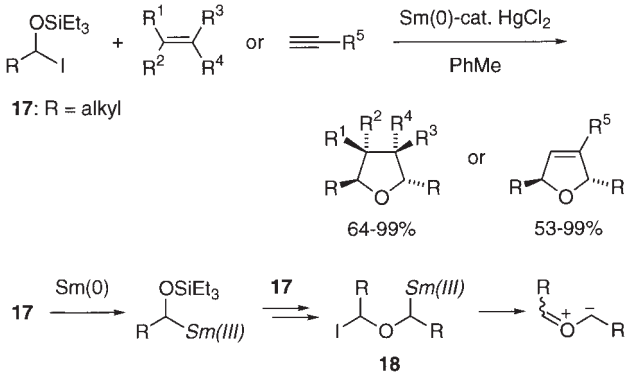
Silicon-based reagent **15a** works as a synthetic equivalent of the alkylideneazomethine ylide, although it is not clear whether the reaction mechanism involves the formation of a dipolar intermediate (Scheme 36).[87] The related reagent **15b** acts as an iminoazomethine ylide in the cycloaddition to aldehydes and ketones.[88]

Chloromethyl silylmethyl ethers **16** as well as **14** undergo efficient 1,3-elimination in the presence of CsF. The carbonyl ylides in situ-generated from **16** add to a variety of dipolarophiles including both activated and nonactivated alkenes (Scheme 37), alkynes, allenes, aldehydes, ketones, and imines.[89] The reactivity of carbonyl ylides stands in sharp contrast to that of azomethine and thiocarbonyl ylides. Unfortunately, this method is not applicable to the generation of non-stabilized carbonyl ylides.

3.2 Generation and Cycloaddition of Nonstabilized Carbonyl Ylides. In the course of our studies on reductive metalation of organic compounds, we incidentally found that treatment of iodohydrin triethylsilyl ethers **17** with a samarium re-



Scheme 37.

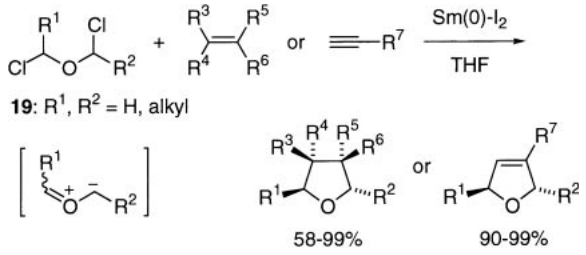


Scheme 38.

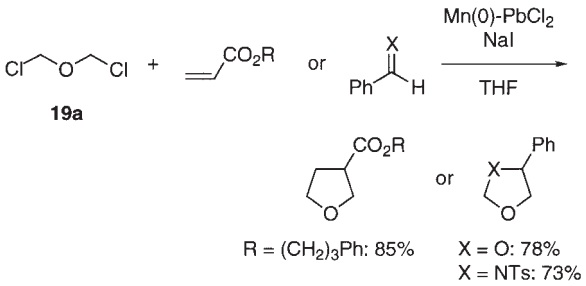
agent formed symmetrical non-stabilized carbonyl ylides by reductive dimerization.[90] The [3 + 2] cycloaddition of the carbonyl ylides thus generated provides a rapid and stereoselective route to multi-substituted tetrahydro- and dihydrofurans (Scheme 38). The configurations of alkene dipolarophiles are retained in the cycloadducts. In addition, all major isomers possess 2,5-*trans* stereochemistry. This observation is consistent with our understanding of the ab initio calculation which shows that the most stable conformation of the 1,3-disubstituted carbonyl ylide is a sickle form. The ylide formation from **17** is presumed to involve α-samaroalkyl α'-iodoalkyl ether **18** as an intermediate.

We anticipated that reductive 1,3-elimination of α-chloroalkyl α'-chloroalkyl ethers **19** with a samarium reagent would form carbonyl ylides via an alkylsamarium(III) intermediate similar to **18**. Thus we found that the samarium-mediated reaction of **19** with alkenes and alkynes gave the corresponding [3 + 2] cycloadducts (Scheme 39).[91] This protocol realizes the generation and cycloaddition of the parent carbonyl ylide (R^1, R^2 = H) and discloses its high reactivity.

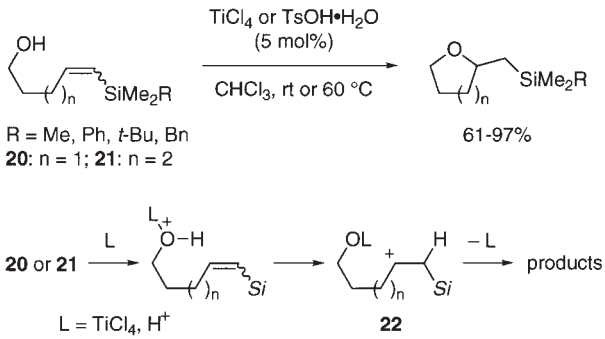
The samarium-mediated generation of carbonyl ylides from **19** is not suitable for cycloaddition to electron-deficient dipolarophiles because the samarium reagent causes the competitive direct reduction of these dipolarophiles. However, the use of manganese metal as the reductant solves this problem.[92] The manganese-mediated method enables efficient cycloaddition of **19a** to acrylates and hetero-dipolarophiles (Scheme 40).



Scheme 39.



Scheme 40.

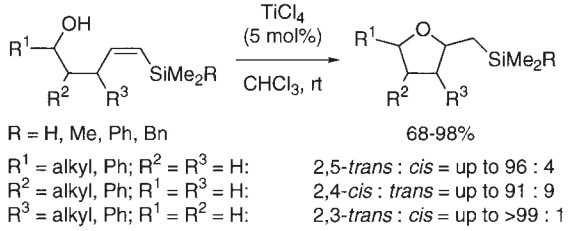


Scheme 41.

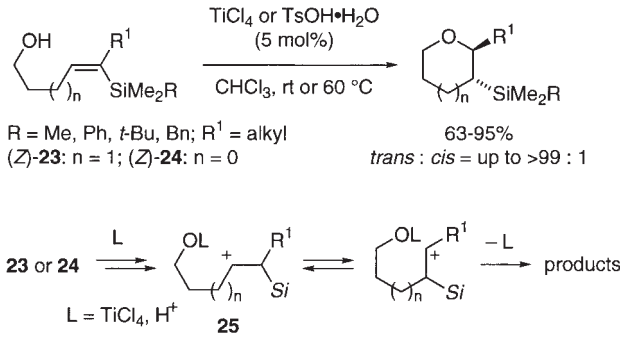
4. Acid-Catalyzed Cyclization of Vinylsilanes Bearing a Nucleophilic Functionality: Synthetic Use of β-Silylcarbenium Ions

β-Silylcarbenium ions, which are thermodynamically stable due to the β-effect of the silyl group, readily undergo β-elimination of the silyl group by nucleophilic attack of a counter anion or a solvent molecule to afford the corresponding alkenes (Scheme 2). For this reason, the active carbon species had not been considered to be useful for bond-forming reactions. In the last decade, however, it has turned out that internal carbon and heteroatom nucleophiles efficiently add to the β-silylcarbenium ions arising from allylsilanes.[93] Synthetic reactions via this bond-forming process are quite valuable for highly stereoselective construction of carbocycles and heterocycles. On the other hand, our attention was focused on the potential of vinylsilanes as precursors of β-silylcarbenium ions. We have found that intramolecular addition of a hydroxy or amino group to vinylsilanes proceeds efficiently under catalysis by an acid, and this silicon-directed cyclization serves for the stereoselective synthesis of substituted cyclic ethers and amines.[94]

4.1 Cyclization of Vinylsilanes Bearing a Hydroxy Group. In the presence of a catalytic amount of $TsOH \cdot H_2O$ or $TiCl_4$, vinylsilanes **20** and **21** are smoothly cyclized to 2-silylmethyl-substituted tetrahydrofurans (THFs) and tetrahydropyrans (THPs) (Scheme 41).[95] The silyl group is essential to this cyclization. Thus the replacement of the silyl group by an alkyl group results in no reaction. The use of a relatively electron-donative and bulky silyl group such as $SiMe_2t$-Bu



Scheme 42.



Scheme 43.

and $SiMe_2Bn$ accelerates the cyclization. (*Z*)-Vinylsilanes are more reactive than the *E*-isomers. A plausible reaction mechanism involves the formation of β-silylcarbenium ion **22** by an intramolecular proton transfer.

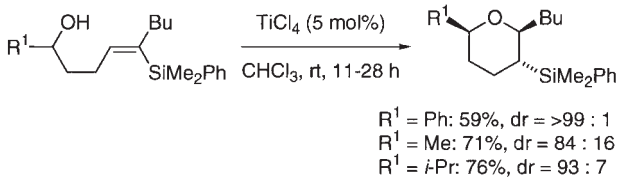
This cyclization is useful for highly stereoselective synthesis of disubstituted THFs.[96] When an alkyl or phenyl group is introduced into the 1-, 2-, or 3-position of (*Z*)-**20**, *trans*-2,5-, *cis*-2,4-, or *trans*-2,3-disubstituted THFs are formed as the major isomers, respectively (Scheme 42).

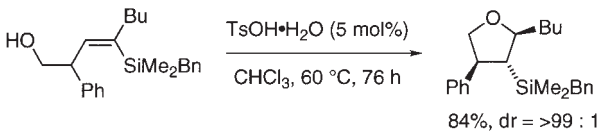
Under catalysis by an acid, vinylsilanes **23**, bearing an alkyl group at the α-position, undergo 1,2-silyl-migrative cyclization to give 2-alkyl-3-silyl-THPs, in marked contrast with **20** (Scheme 43).[97] The cyclization of (*Z*)-**23** proceeds efficiently with high *trans*-diastereoselectivity, while the use of (*E*)-**23** results in lower yields and poor *cis*-selectivity. Vinylsilanes **24**, whose methylene tether is shorter by one carbon, are cyclized to 2-alkyl-3-silyl-THPs via 1,2-silyl migration. The reaction mechanism for these cyclizations probably involves 1,2-silyl migration of β-silylcarbenium ion **25**, which would be facilitated by the inductive effect of the α-alkyl substituent.

Introduction of an alkyl or phenyl group into the methylene tether of (*Z*)-**23** and (*Z*)-**24** enables highly stereoselective synthesis of tri-substituted THPs and THFs, respectively (Scheme 44).[98]

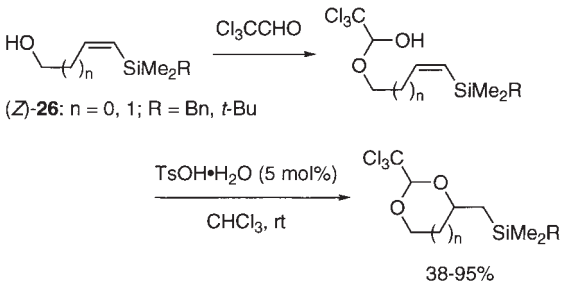
The silicon-directed cyclization using vinylsilanes is applicable to the synthesis of cyclic acetals.[99] Hemiacetals prepared from vinylsilanes (*Z*)-**26** and chloral lead to 1,3-dioxolanes and 1,3-dioxanes by treatment of $TsOH \cdot H_2O$ (Scheme 45).

4.2 Cyclization of Vinylsilanes Bearing an Amino Group. Vinylsilanes (*Z*)-**27** and (*Z*)-**28**, bearing an amino group protected by an electron-withdrawing group, are smoothly cyclized to pyrrolidines and piperidines, respectively, in the presence of an acid catalyst (Scheme 46).[100] This cyclization provides a highly stereoselective route to 2,4- and 2,3-disubstituted pyrrolidines.

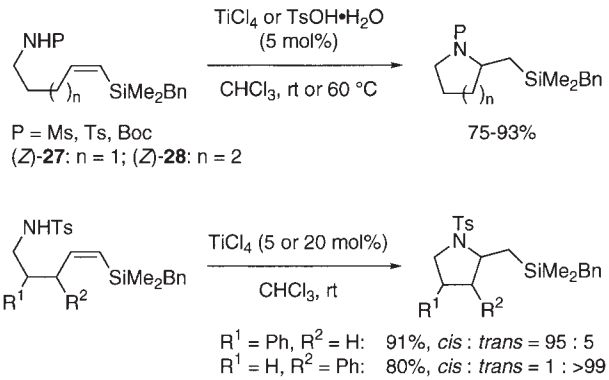




Scheme 44.



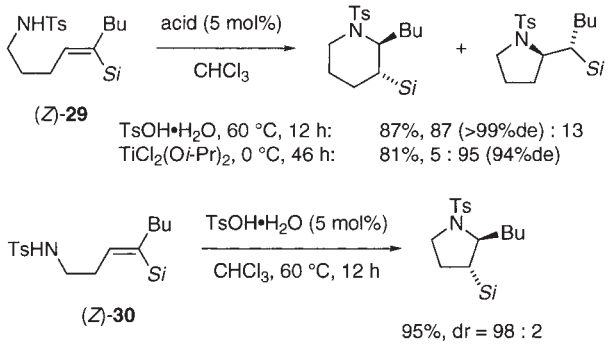
Scheme 45.



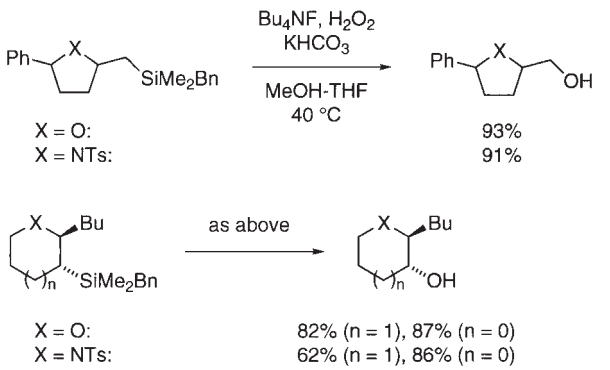
Scheme 46.

The acid-catalyzed reaction of vinylsilane (*Z*)-**29**, bearing an alkyl group at the α-position, gives a mixture of direct and 1,2-silyl-migrative cyclization products.[101] Each cyclization proceeds with high levels of diastereoselectivity. The product ratio can be controlled by the reaction conditions used. Vinylsilane (*Z*)-**30**, which has a shorter methylene tether, undergoes only 1,2-silyl-migrative cyclization to afford the corresponding 2,3-disubstituted pyrrolidine with high *trans*-selectivity (Scheme 47).

4.3 Oxidative Cleavage of Si–C Bond of Silylated Products. It is well known that some silyl groups are valuable as hydroxy surrogates.[102,103] From the viewpoint of synthetic utility, the silyl groups of the products formed by the above cyclizations should be easily convertible to a hydroxy group. Indeed, the cyclized products bearing a dimethylsilyl, dimethylphenylsilyl, or benzyldimethylsilyl group can be converted into the corresponding alcohols with stereochemical retention by the original and modified Tamao methods.[103] A benzyldimethylsilyl group not only effectively promotes the silicon-di-



Scheme 47.



Scheme 48.

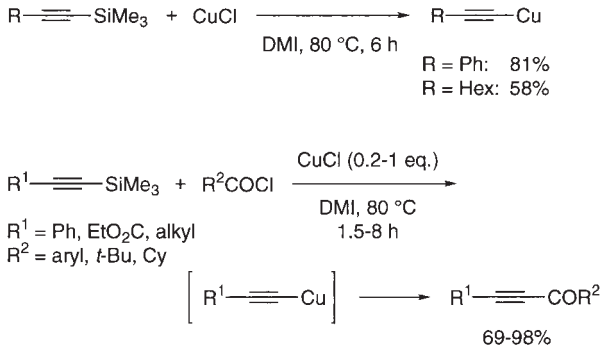
rected cyclizations but also serves as an efficient latent hydroxy group (Scheme 48).[104]

5. Copper(I)-Promoted Reactions of Organosilanes with Carbon Electrophiles

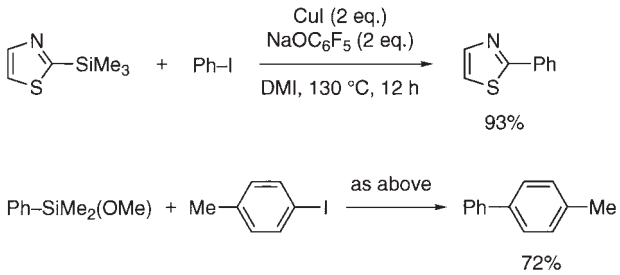
Organocopper reagents are useful for highly selective C–C bond formation.[54] They are usually prepared by treatment of copper salts with reactive organometallics such as organolithium and -magnesium. In contrast, we showed the first example of an alkynyl group transfer from silicon to copper, although alkynylsilanes are relatively stable.[105] This initial finding induced us to investigate transmetalation of some organosilicon compounds with copper salts and the synthetic use of the copper reagents formed. As a result, we have developed several Cu(I)-promoted reactions of organosilanes with carbon electrophiles.[106]

5.1 Reactions of Alkynylsilanes, Arylsilanes, and Silyl Enolates. Alkynylsilanes are convertible into alkynylcopper reagents by treatment with CuCl in 1,3-dimehyl-2-imidazolidinone (DMI) (Scheme 49). The alkynyl group transfer enables acylation of alkynylsilanes with acyl chlorides.[105] Thus, in the presence of a catalytic or stoichiometric amount of CuCl, simple and functionalized alkynylsilanes can be acylated to alkynyl ketones in good to high yields.

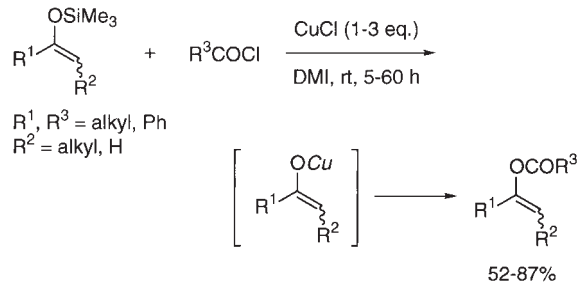
It is well-established that palladium complexes work as effective catalysts for the cross-coupling between organic halides (or triflates) and organosilanes.[29,107] On the other hand, we have developed the copper(I)-promoted cross-coupling reaction of aryl- or heteroarylsilanes with aryl halides.[108] Copper(I) pentafluorophenoxide ($CuOC_6F_5$) in situ-generated from CuI and $NaOC_6F_5$ promotes this coupling effectively even in the absence of an activator of organosilanes such as a fluoride ion source (Scheme 50).



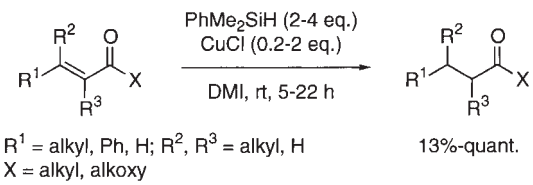
Scheme 49.



Scheme 50.



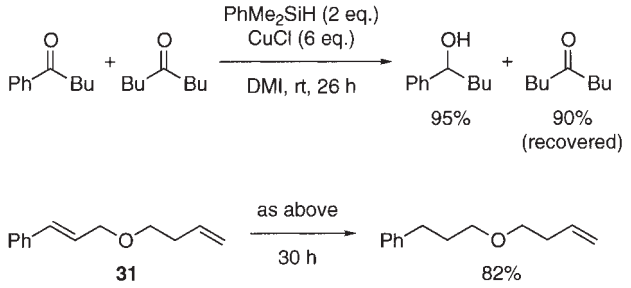
Scheme 51.



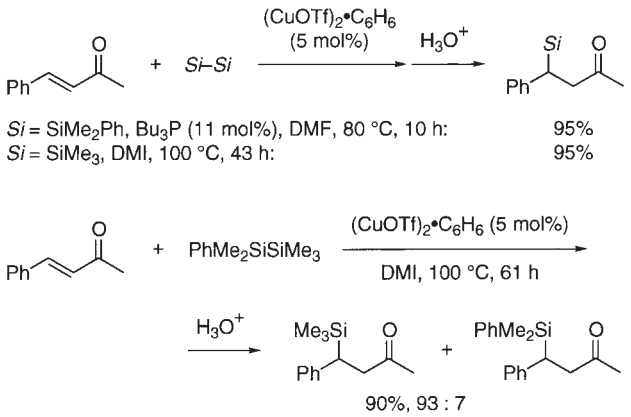
Scheme 52.

In the presence of CuCl, ketone silyl enolates undergo *O*-acylation with acyl chlorides to give vinyl esters (Scheme 51).[109] A plausible mechanism for this acylation involves the formation of a copper enolate intermediate by Si–Cu exchange.[110]

5.2 Reduction of Carbonyl Compounds and Alkenes with Hydrosilanes. Copper hydride complexes are available for stereo- and chemoselective conjugate reduction of α,β-unsaturated carbonyl compounds.[111] We have introduced a new method for the preparation of a copper hydride complex from CuCl and a hydrosilane by Si–Cu exchange.[112] The copper reagent generated in situ can be successfully utilized for the conjugate reduction (Scheme 52).



Scheme 53.

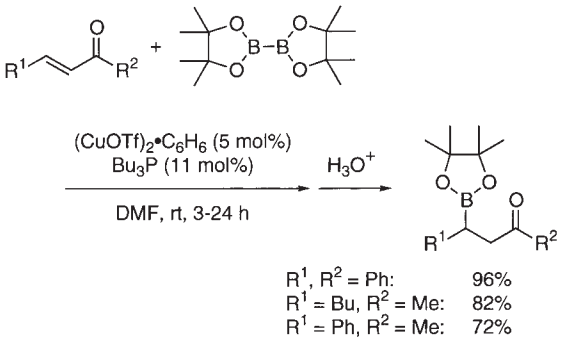


Scheme 54.

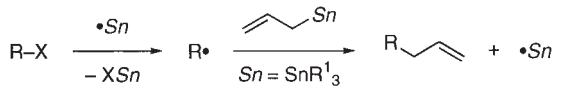
Selective reduction of ketones and alkenes conjugated with an aromatic group is achieved by a similar reduction system using a 1:3 mixture of CuCl and dimethylphenylsilane.[113] In competitive reduction of an aromatic ketone vs an aliphatic one, only the former is converted into the corresponding alcohol (Scheme 53). Additionally, diene **31** undergoes partial reduction of the styrene moiety.

5.3 Silylation and Borylation of α-Enones. Palladium complexes have frequently been used for catalytic activation of the Si–Si bond of disilanes and its application to Si–C bond formation.[114] We have disclosed that a copper(I) salt catalyzes 1,4-bis-silylation of α-enones with disilanes to give β-silylated ketones after protonolysis (Scheme 54).[115] The conjugate silylation of α-enones can be successfully carried out with hexamethyldisilane, which is relatively less reactive toward the Pd-catalyzed Si–Si bond cleavage.[116] Interestingly, the use of phenylpentamethyldisilane, an unsymmetrical disilane, leads to predominant introduction of the TMS group.

The Cu(I)-catalyzed system is applicable to conjugate borylation of α-enones with bis(pinacolato)diboron (Scheme 55).[117,118] In the presence of Bu_3P, the Cu(I)-catalyzed borylation proceeds efficiently at room temperature.



Scheme 55.



Scheme 56.

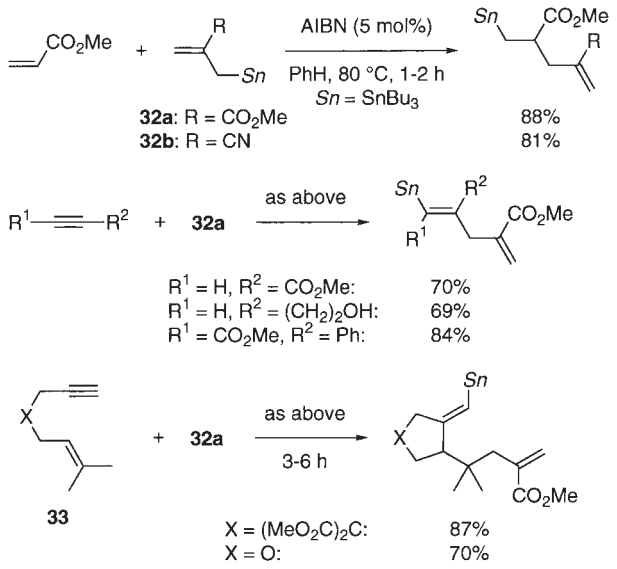
6. Homolytic Carbometalation Reactions

Carbometalation reactions of alkenes and alkynes are convenient for the stereocontrolled construction of organic molecules, because they usually proceed with high regio- and stereoselectivity and because the resultant organometallics react with various electrophiles with retention of the stereochemical integrity.[119] Recently, much attention has been focused on the carbometalation using relatively stable organometallics such as organosilanes and organostannanes in view of their unique reactivities, the ease of preparation, and the synthetically useful products.[120–123] These organometallics are known to add to the C–C unsaturated bonds under catalysis by a transition metal complex or a Lewis acid. In contrast, we have developed a novel type of carbometalation via a radical chain mechanism.

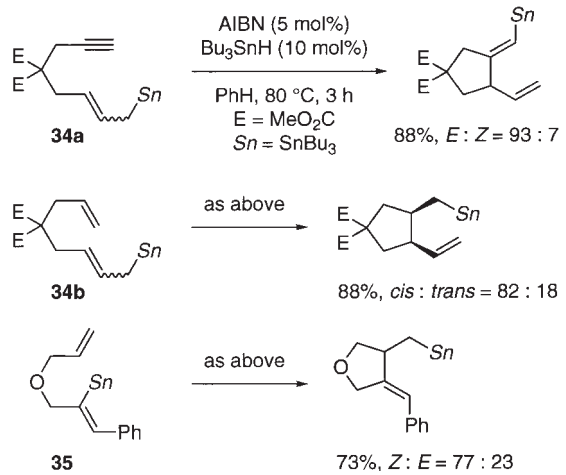
6.1 Carbostannylation. Allylstannanes are important reagents for allylation of various carbon radical precursors.[124] In the homolytic allylation, an allylstannane plays two roles as a radical transfer agent (Scheme 56). One is to generate a stannyl radical, which abstracts an atom or group from the precursor to provide an alkyl radical, and the other is to allylate the alkyl radical with regeneration of the stannyl radical. It is also well-established that a stannyl radical easily adds to an alkene to form a β-stannylalkyl radical.[124a] On the basis of these facts, we expected that a radical-initiated reaction of an alkene with an allylstannane would realize homolytic allylstannylation by the stannyl radical addition to the alkene and the subsequent allylation with the allylstannane.

We initially found that methyl acrylate actually underwent the expected allylstannylation in the presence of AIBN.[125] The reaction efficiency is strongly affected by the allylstannane employed. The use of allylstannanes **32**, bearing an electron-withdrawing group at the β-position, leads to efficient allylstannylation (Scheme 57). The allylstannylation with **32a** is applicable to electron-deficient alkenes and various alkynes except nonactivated internal ones.[125–127] It tolerates the presence of a hydroxy group, as shown in some other radical reactions. The reaction of alkynes proceeds in a *trans* addition mode. The AIBN-initiated reaction of enynes **33** with **32** provides the cyclized products incorporated with the stannyl and allyl groups.[128]

Allylstannanes **34**, bearing an alkenyl or alkynyl group, can be cyclized by intramolecular allylstannylation via a radical chain process (Scheme 58).[129] The combined use of AIBN and tributylstannane is effective in improving the reaction efficiency. In sharp contrast with the intermolecular allylstannylation, the intramolecular version does not require an electron-withdrawing group at the position β to the stannyl group. Under the same conditions, vinylstannane **35** also undergoes intramolecular vinylstannylation to give the corresponding cyclized



Scheme 57.

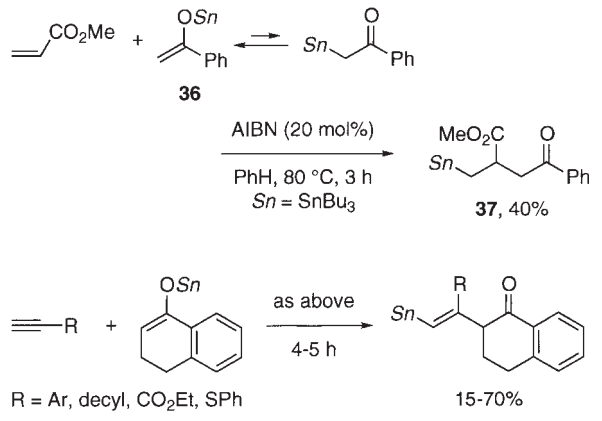


Scheme 58.

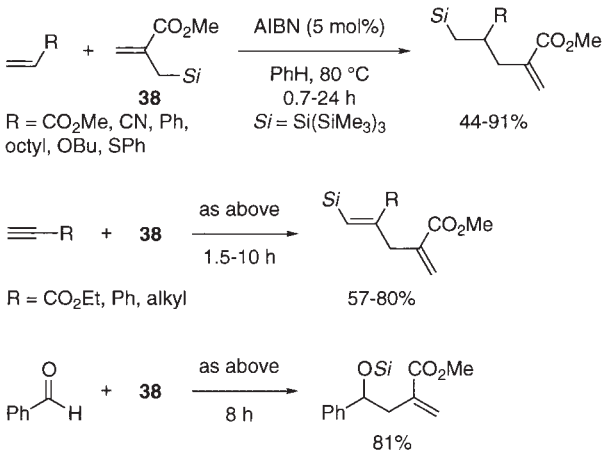
product.

Stannyl enolates serve for stannyl radical-mediated alkylation of haloalkanes.[130] Particularly, stannyl enolates derived from aromatic ketones have high ability as radical transfer agents.[131] We have found that these enolates also are usable for homolytic carbostannylation of alkenes and alkynes (Scheme 59).[132] According to the report by Baba et al., in the presence of Bu_4NBr, stannyl enolate **36** (a tautomeric mixture of keto and enol forms) reacts with methyl acrylate to give a Michael adduct (δ-keto ester).[133] In contrast, the radical-initiated reaction of **36** with methyl acrylate forms β-stannyl ester **37**.

6.2 Allylsilylation. Allyltris(trimethylsilyl)silanes as well as allylstannanes are available for homolytic allylation of haloalkanes.[134] The radical chain process involves the S_H2' reaction of allyltris(trimethylsilyl)silanes with carbon radical species. The reactivity of allyltris(trimethylsilyl)silane **38** as a radical transfer agent can be utilized for allylsilylation of alkenes, alkynes, and aldehydes (Scheme 60).[135] Interestingly, the radical-initiated allylsilylation is applicable to simple and electron-rich alkenes. The allylsilylation of alkynes affords *trans*-addition products exclusively as the above carbostannylations.



Scheme 59.



Scheme 60.

7. Conclusions

We have studied organic syntheses using organosilanes and the related organometallics over the last few decades. Particularly, our studies on the synthetic use of allylsilanes captured the world's attention. The allylation reactions of carbon electrophiles with allylsilanes have been frequently used for highly stereo- and regioselective C–C bond formation.[2,3,93b,136] The discovery of the so-called Hosomi–Sakurai reaction not only provided an efficient and versatile allylation method tolerant of various functionalities but also contributed to the development of other synthetically important reactions using allylsilanes and some related reagents, such as allenylsilanes and propargylsilanes. Among such reactions, [3 + 2] and [2 + 2] cycloadditions of these β,γ-unsaturated organosilanes to electron-deficient unsaturated bonds are valuable for the stereoselective construction of carbocycles and O- or N-containing heterocycles.[93,137] Thus the importance of allylsilanes as synthetic reagents is well recognized nowadays.

We have disclosed that highly coordinated organosilanes bearing oxygen ligands show synthetically valuable reactivities that do not appear in the corresponding tetracoordinate silanes.[53] For instance, allylation of aldehydes with allylsilicates bearing catecholate ligands spontaneously occurs in a regio- and stereospecific manner. The diversity of oxygen ligands enables enantioselective reduction of ketones and ketimines with

homochiral hydrosilicates. In connection with the synthetic use of highly coordinated species, we have recently introduced the base-catalyzed addition of DMS enolates to carbon electrophiles and the reductive metalation of alkyl halides and pseudohalides with Cr, Mn, and Cu ate complexes bearing alkyl ligands.

Cycloadditions of 1,3-dipoles provide convenient and straightforward routes to 5-membered heterocycles.[79] The 1,3-elimination reaction of the silicon-based 1,3-dipole reagents developed by us is highly important as a practical method for the generation of non-stabilized azomethine and thiocarbonyl ylides that are inaccessible by the conventional methods.[80] Aryl-substituted carbonyl ylides can be generated efficiently by a similar method. We have also developed novel access to non-stabilized carbonyl ylides by utilizing the reducing ability of samarium reagents.[81] These studies contributed greatly toward widening the applicability of 1,3-dipoles and revealing the reactivities of non-stabilized 1,3-dipoles.

β-Silylcarbenium ions are subject to nucleophile-induced desilylation to form the corresponding alkenes (Scheme 2). We have disclosed that β-silylcarbenium ions generated from vinylsilanes by protonation are valuable for efficient and stereoselective intramolecular bond formation. The acid-catalyzed cyclizations of vinylsilanes bearing a hydroxy or amino group not only reveal the utility of vinylsilanes as precursors of β-silylcarbenium ions but also serve for highly stereoselective synthesis of 5- and 6-membered cyclic ethers and amines.[94]

Palladium and platinum complexes are frequently used for the formation of C–C and C–Si bonds via catalytic activation of organosilanes.[2,29,107,114] The behaviors of these transition metal catalysts are well recognized. We have developed several Cu(I)-promoted reactions of organosilanes, and have demonstrated that Cu(I) salts are effective in the activation of Si–C, Si–H, and Si–Si bonds.[106] Our studies bring important insights for the development of more practical synthetic methods using Cu(I) salts instead of expensive transition metal complexes.

Carbometalation reactions of organometallics with alkenes and alkynes generally proceed via a concerted or ionic mechanism.[119] In contrast, we have found the radical-initiated carbometalations of certain allylstannanes, stannyl enolates, and allylsilanes with C–C unsaturated bonds. The homolytic reactions show high regio- and stereoselectivities, and tolerate polar functionalities. Such novel types of carbometalation give a new route to highly functionalized organostannanes and organosilanes.

In summary, we have developed a variety of new synthetically useful reagents and reactions on the basis of the unique reactivities of organosilanes and the related organometallics. Our studies made a significant contribution toward clarifying the reactivities of organometallic reagents and unstable carbon species such as 1,3-dipoles and β-silylcarbenium ions. Organosilicon reagents are easily accessible, relatively stable, and less toxic compared with other organometallic reagents. Therefore, we believe that the development of synthetic reactions using organosilicon reagents will become more significant for environmentally benign organic synthesis.

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