

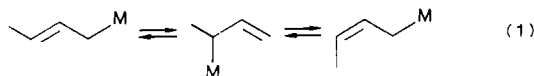
# Characteristics in the Reactions of Allylsilanes and Their Applications to Versatile Synthetic Equivalents

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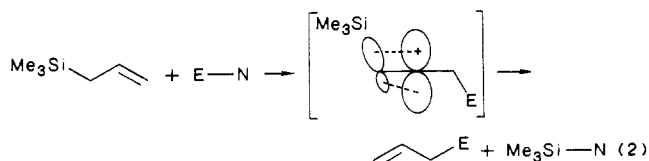
Although unstable reactive intermediates are of great importance in organic synthesis, they are generally hard to handle and are unstable under usual conditions. However, it is possible to obtain these species in the form of cryptic reactive intermediates by the chemical conversions of stable compounds that act as synthetic equivalents. Organosilicon compounds, extensively used for selective carbon-carbon bond formation, are particularly suitable for this purpose, since numerous stable reagents can be designed and synthesized. Much attention has been recently focused on syntheses and applications of allylsilanes to synthetic reagents.<sup>1</sup> Allylsilanes are thermally stable and relatively inert to water and oxygen. In addition, they are isolable and storable without special precautions, in contrast to other allylating reagents (M = Li, MgX, ZnX, CdX, BL<sub>n</sub>, AlL<sub>n</sub>, TiL<sub>n</sub>, ZrL<sub>n</sub>, CrL<sub>n</sub>, etc.) which undergo a rapid 1,3-shift of the metal group even at low temperature (eq 1).<sup>2</sup>



It is possible to functionalize simple allylsilanes and to transfer functionalized allyl groups onto carbon electrophiles with high regio-, stereo-, and chemoselectivity. Since allylsilanes have thermally stable and localized carbon-silicon  $\sigma$  bonds, control of regiochemistry in the allylation can be readily attained. In this Account we describe the characteristics of the reaction of allylsilanes and summarize their convenient and useful applications to production of versatile synthetic equivalents of a number of active species otherwise inaccessible. Major emphasis will be placed on the results obtained in our own laboratory.

## Characteristics in the Reactions of Allylsilanes

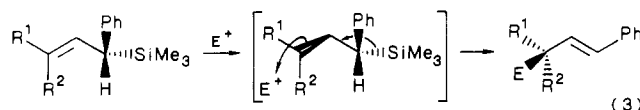
In 1948, Sommer et al. reported that the allyl-Si  $\sigma$  bond of allyltrimethylsilane easily underwent cleavage not only by electrophiles such as halogens and halogen acids but also by bases.<sup>3</sup> In general, electrophiles attack the terminal carbon of the allylic group regioselectively (eq 2).<sup>4</sup> The facile and regioselective reaction of elec-



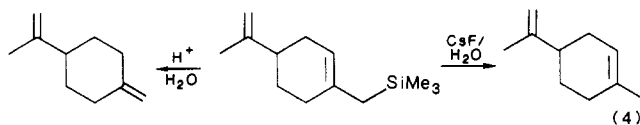
Akira Hosomi was born in Osaka, Japan, in 1943 and was educated at Kyoto University, where he received his Ph.D. degree under Professor Makoto Kumada in 1970. In 1970 he joined the faculty of the Department of Chemistry, Tohoku University, and became Professor of Pharmaceutical Sciences, Nagasaki University, in 1985. His research interests lie principally in the fields of organic synthesis using organometallic compounds and bio-organometallic chemistry.

trophiles with allylsilanes is explained by the  $\beta$  effect of the silyl group. The  $\beta$ -silyl carbocation is stabilized by the  $\sigma$ - $\pi$  conjugation between the  $\sigma$ (Si-C) orbital and the vacant  $p_{\pi}$  orbital.<sup>5</sup>

Hayashi and Kumada have prepared optically active allylsilanes and have demonstrated unambiguously that the reaction of allylsilanes with various electrophiles in the acyclic system proceeds with anti S<sub>E'</sub> stereochemistry due to stereoelectronic effects (eq 3).<sup>6</sup> The allylation proceeds with high enantioselectivity.<sup>7</sup>



The regioselective synthesis of alkenes is possible from the same allylsilane by the choice of hydrolysis conditions. Thus, whereas allylsilanes readily undergo regioselective protonolysis at the  $\gamma$  position under acidic conditions, accompanied by a shift of the double bond, they are protonated regioselectively at the  $\alpha$  carbon via an allylic anion when treated with cesium fluoride in DMF and DMSO (eq 4).<sup>8</sup>



Organosilyl groups are frequently used for protecting active hydrogens of alcohols, carboxylic acids, and

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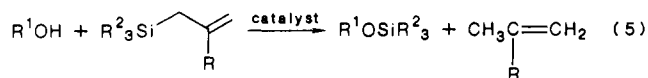
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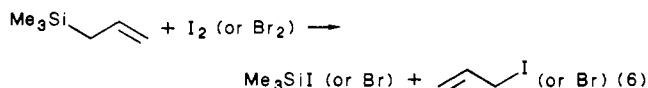
(7) Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* 1983, 24, 2865.

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amines. Allylsilanes and  $\beta$ -methallylsilanes are convenient silylating reagents because volatile propene and isobutene are the sole byproducts. *p*-Toluenesulfonic acid, trifluoromethanesulfonic acid, iodine, and iodo-trimethylsilane have been found to be good catalysts for the silylation (eq 5).<sup>9</sup>

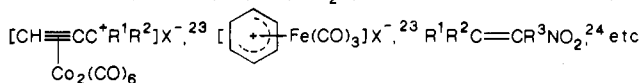
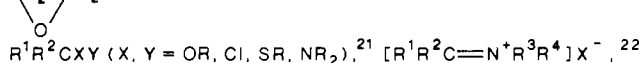
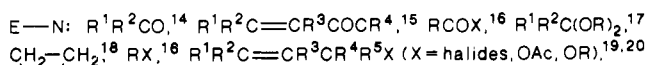
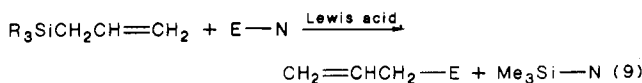
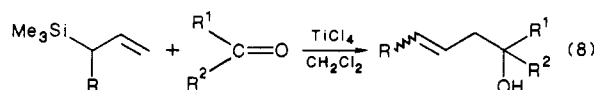
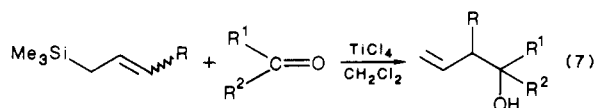


Allylsilanes readily react with halogens to give the corresponding bromosilanes and iodides, which are useful for cleavage of a carbon-oxygen bond of esters and ethers (eq 6).<sup>10</sup>



### Reactions of Allylsilanes with Carbon Electrophiles

We reported the first example of the carbon-carbon bond-forming reaction of allyltrimethylsilane with bromotrichloromethane under free radical conditions.<sup>11</sup> In the mid-1970s, Lewis acid catalyzed and uncatalyzed reactions of allyltrimethylsilane with carbonyl compounds were found by Calas's,<sup>12</sup> Abel's,<sup>13</sup> and our group.<sup>14</sup> Since the initial scope of the allylations was limited to activated carbonyl compounds such as perfluoroacetone and chloroacetone, allylsilanes did not have a strong impact in the field of organic synthesis.<sup>12,13</sup> However, we have found that, in the presence of titanium chloride, allylsilanes do react with aldehydes and ketones very smoothly in a regioselective fashion (eq 7 and 8).<sup>14</sup> After this discovery, a number of other Lewis acid mediated reactions of allylsilanes with various carbon electrophiles were found (eq 9).



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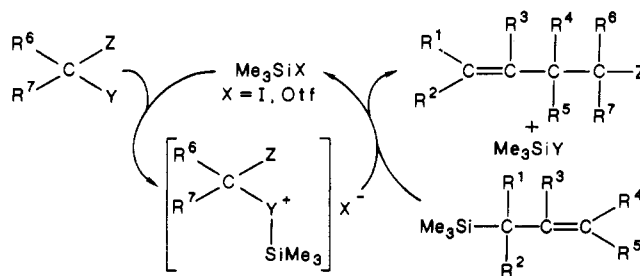
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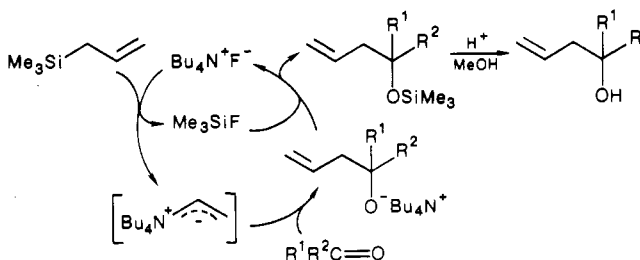
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### Scheme I A Catalytic Cycle for the Allylation



### Scheme II A Catalytic Cycle of the F<sup>-</sup> Ion Catalyzed Allylation



Titanium tetrachloride among various Lewis acids usually gives satisfactory results. Other promoters such as  $SnCl_4$ ,  $AlCl_3$ ,  $BF_3 \cdot Et_2O$ ,  $Me_3SiOTf$ ,  $Me_3SiI$ ,  $Me_3O^+BF_4^-$ , and  $Ph_3CClO_4$  have also been used frequently, depending upon the electrophile. Although a stoichiometric amount of a Lewis acid is generally required for the activation of electrophiles, a catalytic amount of  $Me_3SiOTf$ ,<sup>25</sup>  $Me_3SiI$ ,<sup>26</sup> and  $Ph_3CClO_4$ <sup>27</sup> can induce allylation of acetals and geminal diheteroatom-substituted alkanes. The catalytic cycle is shown in Scheme I.

Fluoride ion displays a strong nucleophilic affinity for a silicon atom owing to the high silicon-fluorine bond energy (ca. 140 kcal/mol) and produces a functionalized carbanion if the  $pK_a$  of the conjugate acid is relatively small. Therefore the allyl-Si bond of allylsilanes is readily cleaved by  $Bu_4NF$  (TBAF) to give an allylic anion species that is free from a metal cation. The resulting allylic species adds to a carbonyl compound

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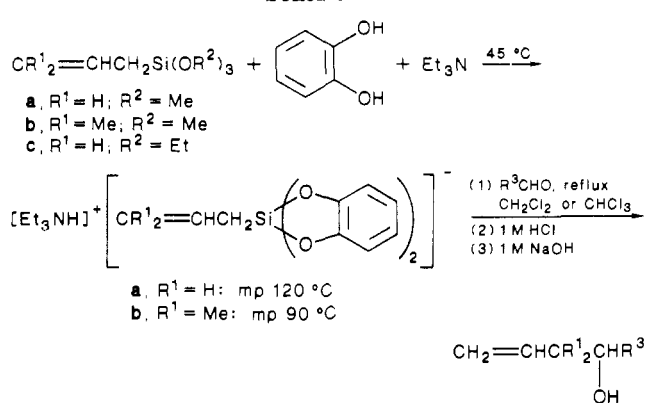
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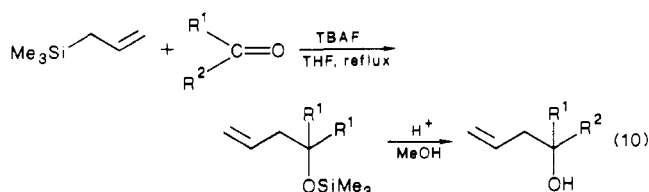
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Scheme III



chemoselectively to afford a homoallyl silyl ether (eq 10).<sup>28</sup> The catalytic cycle by TBAF is shown by Scheme II.



In contrast to the Lewis acid promoted reaction under strongly acidic conditions, the fluoride ion catalyzed reaction proceeds under almost neutral conditions. However, the lack of regioselectivity in the allylation is pointed out as a sole drawback, due to the generation of an allyl anionic species as the intermediate. Nevertheless, a variety of 2-substituted allylsilanes, e.g., (2-haloallyl)-, (2-(trifluoromethyl)allyl)-, and (2-vinyl-substituted allyl)trimethylsilane (isoprenylsilane) can be conveniently used.

Although tetracoordinate allylsilanes require nucleophilic activators such as fluoride ion or electrophilic activators for allylations, we have recently found that pentacoordinate triethylammonium bis(catecholato)-allylsilicate, readily prepared from allyltrimethoxysilane, catechol, and triethylamine, reacts with aldehydes smoothly in dichloromethane or chloroform at reflux temperature or under neat conditions *without catalyst* to give the corresponding homoallyl alcohols in high yield (Scheme III).<sup>30</sup> Allylation takes place regioselectively. To our knowledge, this provides the first example of direct transfer of an organic ligand from an organosilicon compound to a carbon electrophile *without catalyst*. The reaction can also be achieved by mixing of an aldehyde, allyltrimethoxysilane, catechol, and triethylamine without isolation of the in situ generated pentacoordinate allylsilicate.<sup>31</sup>

The stereochemical outcome (threo selectivity) of this allylation using an (*E*)-crotylsilane reveals that the reaction may proceed via a cyclic transition state, in sharp contrast to the Lewis acid catalyzed allylation where an acyclic linear transition state is considered (Scheme IV).<sup>6,7</sup>

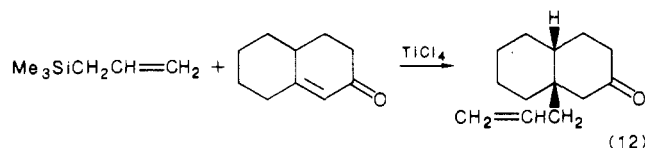
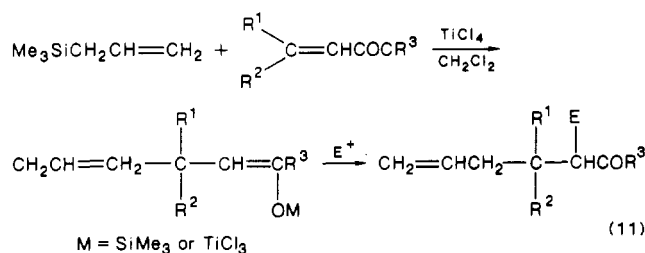
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Another remarkable and important feature associated with the reactions of allylsilanes is their conjugate addition to  $\alpha,\beta$ -unsaturated ketones.<sup>15</sup> In general, conjugate allylation is useful and important in organic synthesis because the allyl group can be readily converted to other functional groups. Before we found a novel conjugate allylation in 1977, copper ate complexes had usually been employed for this purpose.<sup>32</sup> However, allylic copper reagents are unstable and do not always give satisfactory results. In contrast to other allyl organometallic reagents, which reveal a more ionic nature, allylsilanes are covalently bonded and are soft allylating reagents. Therefore allylsilanes smoothly react with  $\alpha,\beta$ -enones preferentially in a conjugate mode, leading to  $\delta,\epsilon$ -enones by simple protonolysis. The reaction is regioselective with respect to the allylic group. The intermediary enolates can be trapped by another carbon electrophile to undergo double alkylations at both  $\alpha$  and  $\beta$  positions of  $\alpha,\beta$ -enones (eq 11). Further advantages of this reaction can be manifested by the stereoselective introduction of the allyl group at the angular position of the fused cyclic  $\alpha,\beta$ -enones in a *cis* fashion (eq 12).<sup>15</sup>



Conjugate allylation of  $\alpha,\beta$ -unsaturated esters, nitriles, and amides has been attained by the fluoride ion catalyzed reaction.<sup>33</sup> Cyclization reactions using the intramolecular 1,4-addition of allylsilanes are applied to the stereoselective synthesis of bicyclic compounds.<sup>34</sup>

Stereochemical control in acyclic systems is an important goal in modern synthetic organic chemistry and much attention has been focused on the diastereoselective reaction of crotyl metallic reagents with aldehydes.<sup>35</sup> Whereas  $\alpha$ -alkyl- and  $\alpha$ -aryl-substituted allylsilanes displayed high *E* selectivity in the allylation,<sup>14</sup> reactions of ( $\alpha$ -haloallyl)silanes (R = Cl, Br) proceed with high *Z* preference.<sup>36</sup> Moreover, a highly erythro selective allylation is observed in the reaction of crotyltrimethylsilane with an aldehyde, although the (*Z*)-crotylsilanes do not reveal good selectivity.<sup>37</sup>

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Table I  
Allylsilanes as Synthetic Equivalents of Reactive Intermediates

Allylsilane	Synthetic Equivalent	Allylsilane	Synthetic Equivalent

The diastereoselectivity of aromatic acetals is not parallel to that of aldehydes.<sup>38</sup> In this case the electronic effect due to the aromatic substituent plays an important role in the diastereofacial control, rather than the steric effect. Thus, with increasing electron withdrawal of the aromatic substituent, increasing anti (threo) selectivity is observed in the case of (*Z*)-crotylsilane. On the other hand, with (*E*)-crotylsilane, the syn selectivity increases with the electron-withdrawing substituent.

#### Allylsilanes as Synthetic Equivalents

Allylsilanes are versatile synthetic reagents for the regioselective introduction of the allyl group into elec-

trophiles. Therefore various reactive intermediates, otherwise inaccessible, can be obtained as synthetic equivalents by the functionalization of the allylic group in allylsilanes. Allylsilanes prepared for this purpose are listed in Table I.

**Regiocontrolled Allyl Anion Equivalents.** Although tetracoordinate allylsilanes are inert toward various carbon electrophiles without a promoter at ambient temperature as described above, they react regioselectively with carbonyl compounds at the  $\gamma$  carbon of the allyl group in the presence of titanium tetrachloride.<sup>14</sup>

To take an example, we have found that the regioselective prenylation at the primary and tertiary carbons of the prenyl group is easily attained by the introduction of two methyl groups onto the  $\alpha$  and  $\gamma$

(38) Hosomi, A.; Ando, M.; Sakurai, H. *Chem. Lett.* 1986, 365.

carbons of the allyl group (eq 13 and 14). Thus primary allylsilanes react with electrophiles to give the  $\alpha$ -allyl silane:

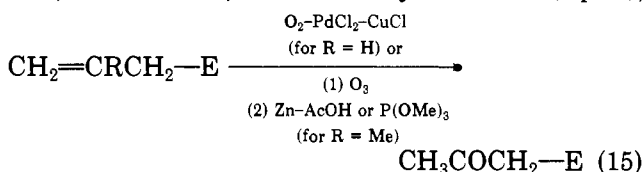
$$\text{Me}_3\text{SiCH}_2\text{CH}=\text{CMe}_2 + \text{E}-\text{N} \rightarrow \text{CH}_2=\text{CHCMe}_2-\text{E} + \text{Me}_3\text{Si}-\text{N} \quad (13)$$

or the  $\beta$ -allyl silane:

$$\text{Me}_3\text{SiCMe}_2\text{CH}=\text{CH}_2 + \text{E}-\text{N} \rightarrow \text{Me}_2\text{C}=\text{CHCH}_2-\text{E} + \text{Me}_3\text{Si}-\text{N} \quad (14)$$

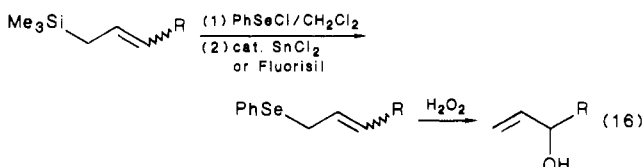
primary and tertiary prenyl crypto anions, which are important for terpene syntheses, are obtained. The starting ( $\alpha,\alpha$ -dimethylallyl)- and ( $\gamma,\gamma$ -dimethylallyl)-silanes are readily prepared regioselectively from the reaction of common prenyl Grignard reagent with trichlorosilane (followed by methylation) and chlorotrimethylsilane, respectively.<sup>39</sup> Artemisia ketone, a monoterpene ketone, is synthesized cleanly by use of ( $\gamma,\gamma$ -dimethylallyl)trimethylsilane.<sup>16</sup>

**Acetyl Anion Equivalents.** The olefinic part of allylation products can be subject to functional group transformations.<sup>40</sup> Terminal olefins are easily oxidized to afford methyl ketones by the Wacker process or by ozonization followed by reductive workup. Since the allyl and  $\beta$ -methallyl groups are converted to an acetyl group, allyl- and ( $\beta$ -methallyl)trimethylsilanes are viewed as acetyl anion equivalents. The conversion of  $\delta,\epsilon$ -enones to 1,5-diketones by oxidation (eq 15),



followed by base-catalyzed annelation to yield fused cyclic  $\alpha,\beta$ -enones, has been applied to the synthesis of nootkatone, the flavor of banana.<sup>41</sup> Total synthesis of Lycopodium alkaloids was also attained by use of this reaction, and perhydroazulenone was prepared by conjugate allylation with the allylsilane as a key reaction.<sup>42</sup>

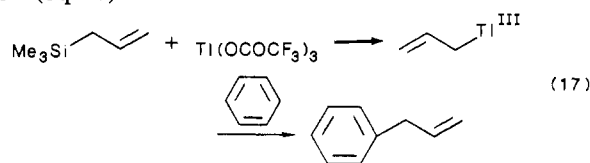
**Synthetic Equivalents of Allyl Cations.** Phenylselenation of allylsilanes with PhSeCl is accompanied by cleavage of the silicon-allyl bond (eq 16).<sup>43</sup> The



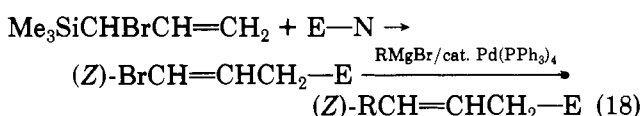
organoselenyl group adds to the less substituted site of the allylic group, which can be readily converted to a hydroxy group by oxidation with hydrogen peroxide. Thus the allylsilane should be regarded as a hydroxy-allyl synthon.

The transmetalation of allylsilanes with a thallium(III) salt produces highly active allylthallium(III) species that act as allyl cations toward various nucleophiles. Moreover, treatment of allyltrimethylsilane with iodosobenzene in the presence of boron trifluoride

etherate yields a hypervalent allylthallium(III) species. Since this reacts with various nucleophiles, the allylsilanes work as the synthetic equivalent of an allyl cation (eq 17).<sup>44</sup>

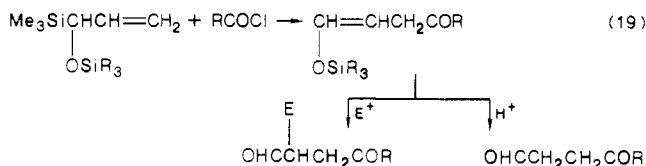


**Halogen-Substituted Allylsilanes.** Isomerically pure ( $\alpha$ -haloallyl)silanes, prepared conveniently from metalated allylic halides and chlorotrimethylsilane, provide a stereoselective and facile entry to synthetically useful vinylic halides with high *Z* preference.<sup>37</sup> Since the *Z*-vinylic halides thus obtained are alkylated further by the stereoselective Grignard cross-coupling reaction, ( $\alpha$ -haloallyl)silanes can be viewed as the zwitterion equivalent of a vinyl cation and an allyl anion (eq 18).



( $\gamma$ -Chloroallyl)trimethylsilane can be used as an  $\alpha$ -chloroallyl anion equivalent.<sup>45</sup> Moreover, the regioselective transformation of allylsilanes to allylic alcohols via conversion to allyl selenides followed by oxidative workup with SnCl<sub>2</sub> can be achieved by the phenylselenodesilylation of allylsilanes. Thus (3-bromoallyl)trimethylsilane is utilized as the synthetic equivalent of a 3-hydroxypropen-3-yl synthon or a 3-hydroxypropen-1-yl synthon.

**(1-Siloxyallyl)silanes.** (1-Siloxyallyl)silanes, prepared regioselectively by metalation of (allyloxy)silanes with *sec*-butyllithium followed by silylation with chlorosilanes, react with electrophiles such as acid halides to give 3-keto aldehydes.<sup>46</sup> When a second electrophile is added to the reaction mixture before protonolysis, "one-pot" double alkylations on the neighboring carbon atoms occur.<sup>47</sup> Thus, (1-siloxyallyl)silanes act as homoenolate anion and dianion equivalents (eq 19).



**(2-(Alkoxy carbonyl)allyl)silanes.** The introduction of an alkoxy carbonyl group into the  $\beta$  position of the allyl group of allylsilanes has led to reagents for 2-(alkoxy carbonyl)allylation of various electrophiles.<sup>48</sup> ( $\beta$ -(Alkoxy carbonyl)allyl)silanes give  $\alpha$ -methylene- $\gamma$ -butyrolactones, important key structures of a number of naturally occurring sesquiterpenes with potential cytotoxic activity (eq 20).

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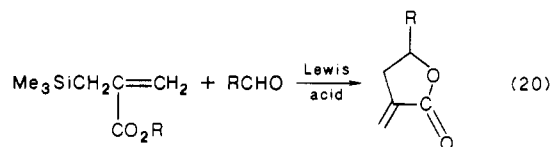
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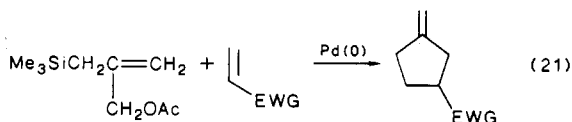
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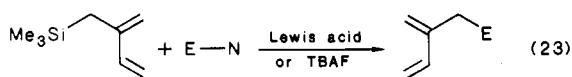
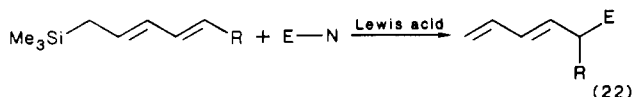
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**2-((Trimethylsilyl)methyl)allyl Acetate and Related Compounds.** The title compounds are versatile synthetic reagents for the introduction of a trimethylenemethane unit via the [3 + 2] cycloaddition (eq 21). These interesting reagents have elegantly been reviewed by Trost.<sup>49</sup>



**Vinyl-Substituted Allylsilanes.** Pentadienylsilanes, prepared from pentadienylpotassium and chlorotrimethylsilane, as regiocontrolled pentadienyl anion equivalents (eq 22).<sup>50</sup> Moreover, we have found



that 2-((trimethylsilyl)methyl)-1,3-butadiene (isoprenylsilane) is an important reagent for the introduction of an isoprene unit by substitution and cycloaddition reactions.<sup>51</sup> Thus isoprenylsilane reacts with various electrophilic species such as acetals, acid chlorides, and carbonyl compounds with the aid of a Lewis acid to give the corresponding isoprenylated products (eq 23). Isoprenylation of carbonyl compounds is also carried out satisfactorily by fluoride ion catalysis. Thus an effective and relatively weak basic route to the isoprenyl anion (or its equivalent) has been attained. The allyl anion species in this case is symmetric, so that there is no problem of regioselectivity of the allylation.

Syntheses of ipsenol and ipsdienol (pheromones of a bark beetle, *Ips paraconfusus*) have been achieved by acylation of isoprenylsilane followed by hydride reduction of the resulting monoterpene ketones or by one-step operation between isoprenylsilane and the corresponding aldehyde catalyzed by fluoride ion (eq 24).<sup>29</sup>

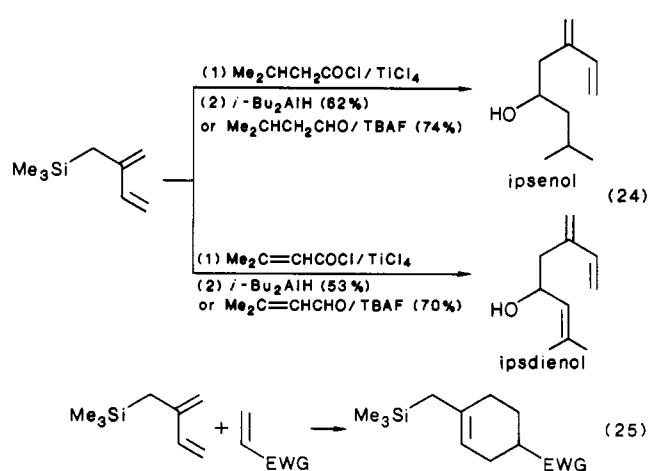
Isoprenylsilane and its tin analogue undergo cycloaddition reaction with unsymmetrical dienophiles in a highly regioselective mode (eq 25).<sup>51</sup> These results are reasonably explained by the HOMO-LUMO interaction in the Diels-Alder reaction.<sup>52</sup> The extensive  $\sigma(\text{M}-\text{C})-\pi$  conjugation in the isoprenylsilane and isoprenyltin raises the HOMO of the dienes with increasing coefficients of atomic orbitals at the 1-position of the HOMO.

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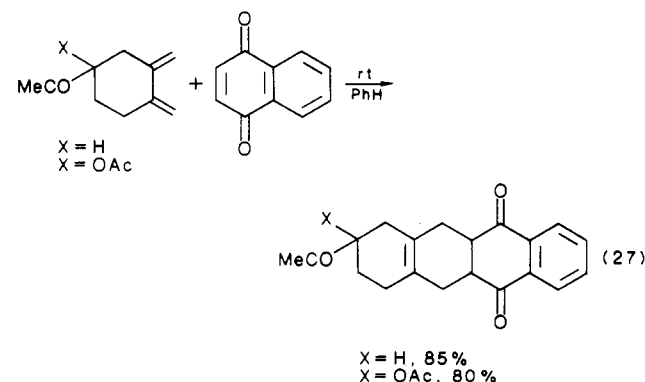
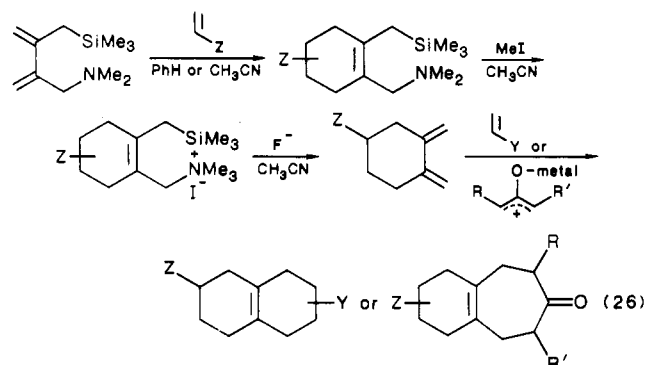
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The regioselectivity has been improved dramatically by the addition of a catalytic amount of a Lewis acid. The cycloadducts having an allylsilane skeleton again are obtained with 100% para selectivity. Therefore the isoprenylsilane acts as an excellent building block for the synthesis of terpenes such as terpineols, limonenes, bisabolones, and cadinenes.<sup>51</sup>

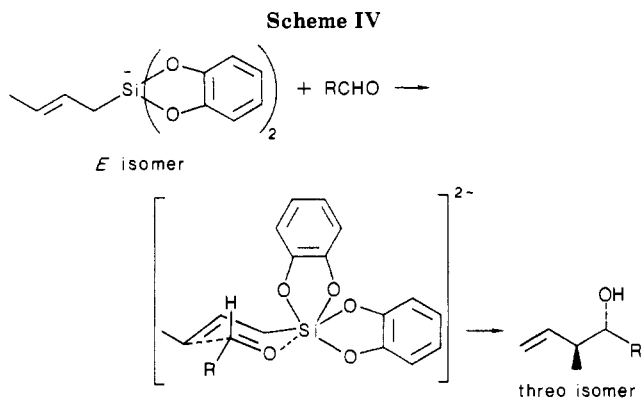
2-((Dimethylamino)methyl)-3-((trimethylsilyl)methyl)-1,3-butadiene<sup>53</sup> has been found to serve as equally convenient precursor of a 2,2'-biallyl diradical synthon as 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene reported by Trost,<sup>54</sup> the diradical undergoing tandem Diels-Alder reactions (eq 26). Isolable 1,2-dimethylenecyclohexanes are good reagents for synthesis of precursors of anthracyclone antibiotics (eq 27).<sup>53</sup>



Moreover, both 2-((dimethylamino)methyl)-3-((trimethylsilyl)methyl)-1,3-butadiene<sup>53</sup> and 2-(bromo-

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methyl)-3-((trimethylsilyl)methyl)-1,3-butadiene<sup>54</sup> have been used as a synthetic equivalent of a 2,2'-biallyl zwitterionic species. 4-Alkoxy-substituted isoprenylsilanes are more active and regioselective for the cycloaddition and give the corresponding cycloadducts without catalyst. Cycloadditions of this reagent to carbonyl compounds give precursors of deoxy sugar derivatives.

Allylsilanes containing a leaving group at the  $\delta$  position become a synthetic equivalent of 1,3-dienes by conjugate 1,4-elimination.<sup>55</sup>

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## Concluding Remarks

Allylsilanes, stable in air and moisture, storable, and easy to handle, can be readily functionalized. Synthetic methods using these allylsilanes have developed rapidly, and allylsilanes are now having a strong impact upon the field of organic synthesis. Much more remains to be discovered in the area of allylsilanes as reagents in organic synthesis.

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# A Critical Evaluation of Studies Employing Alkenyl Halide "Mechanistic Probes" as Indicators of Single-Electron-Transfer Processes

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Chemical reactions come about through the reorganization of valence electrons. The notion that organic reactions proceed via either polar or single-electron-transfer (SET) processes is widespread in organic

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chemistry. If one considers an associative polar process versus an outer-sphere electron-transfer process that gives a radical species, then the two pathways are quite different. However, the distinction need not be so dramatic; for example, there is only a subtle difference between an inner-sphere SET process resulting in a substitution reaction and a polar  $S_N2$  reaction.<sup>1</sup> For organic reactions, there has been some lack of appreciation of the details of outer-sphere (nonbonding) and inner-sphere (bonding) electron-transfer reactions, and most qualitative studies searching for SET pathways have sought evidence of radical or radical anion products. In other words, whether stated or not, these studies have been directed at uncovering outer-sphere

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