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Selective carbon-carbon bond formation based on organosilicon reagents: origin and application*

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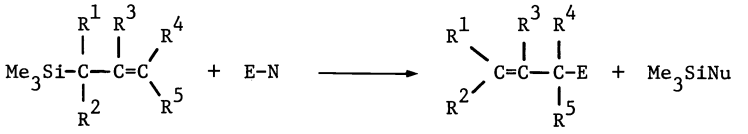
Abstract - Several new observations on the selective carbon-carbon bond forming reactions are described. Iodotrimethylsilane and trimethylsilyl triflate activate selectively the C-Cl bond rather than the C-O bond of α-chloro ethers and catalyze the allylation with allylsilanes to give the corresponding homoallyl ethers effectively in good yield. This reaction was successfully applied to the preparation of C-allylated sugars. Thus methyl α-D-glucopyranoside, methyl α-D-mannopyranoside and, in particular, the corresponding α-D-glycopyranosyl chlorides readily undergo allylation with allylsilanes in a highly stereoselective mode. The electronic effects on the diastereoselection in the reaction of allylsilanes with benzaldehyde acetals are then described. Cycloaddition reactions of 1-alkoxy- 3-trimethylsilyl-1,3-butadienes with various dienophiles including heterodienophiles were found to proceed very smoothly in a perfectly regiospecific mode. N-(Trimethylsilylmethyl)aminomethyl ethers, readily prepared from (trimethylsilylmethyl)amines, formaldehyde and an alcohol, react with electron deficient alkenes in the presence of iodosilane or silyl triflate in combination with cesium fluoride to give the corresponding pyrrolidine derivatives stereospecifically in excellent yield. 2-Dimethylaminomethyl-3-trimethylsilylmethyl-1,3-butadiene reacts with a variety of dienophiles involving heterodienophiles to give cycloadducts which are converted readily to 1,2-dimethylenecyclohexanes after successive treatments with methyl iodide and cesium fluoride in acetonitrile.

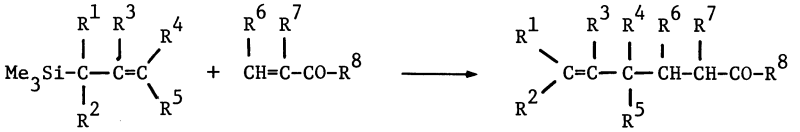
INTRODUCTION

Recently, organosilicon compounds have been used extensively for the selective carbon-carbon bond formation. Among them, allylsilanes are one of the most successful examples and we have developed the chemistry of allylsilanes as well as applications to organic synthesis in the last decade (ref. 1), since the first discovery of the regiospecific carbon-carbon bond formation (ref. 2).



(Type 1)

Regiospecific conjugate addition (ref. 3) is also one of the notable features of the reaction of allylsilanes and the reaction has been recognized now as a standard procedure (ref. 4).



(Type 2)

Cycloaddition reactions of allylsilane derivatives, especially of isoprenylsilanes, also open a way to natural product synthesis (ref. 5). Stereochemical studies on both type 1 (ref. 6) and 2 (ref. 7) reactions may be the most important additions to the jewel box.

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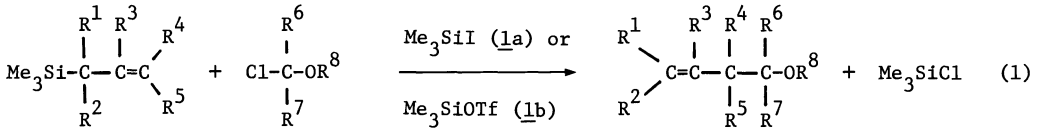
* Chemistry of Organosilicon Compounds. 220.

Conceptually, allylsilanes can be functionalized as desired and carbon and other hetero-atom electrophiles can enter the reaction. Therefore, many reactions of allylsilanes have been reported and numerous further applications will be recorded. After the recognition of regio- and stereo-specificity in the reactions, however, important things are to find the way of activation of carbon (or hetero-atom) electrophiles and/or allylsilanes (ref.1). In this paper, the author wishes to describe some recent observations on both selective activation of carbon electrophiles, and stereochemistry in the allylsilane chemistry. Additional application of isoprenyl silanes will be discussed also, and finally, a new chemistry related to selective 1, n-conjugate elimination will be described.

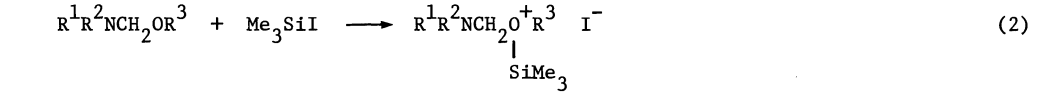
ACTIVATION OF CARBON-HETEROATOM BONDS BY ELECTROPHILIC CATALYSIS AND C-ALLYLATION OF PYRANOSIDES

Iodotrimethylsilane (1a) (ref. 8) and trimethylsilyl trifluoromethanesulfonate (2b) (ref. 9) can strongly interact especially with an oxygen atom among various heteroatoms in organic compounds to form a silyl oxonium ion and a variety of applications to organic synthesis using a stoichiometric and catalytic amount of these reagents have been developed. These reagents can also activate selectively a carbon-chlorine bond of α-chloroalkyl ethers (3), in which two kinds of heteroatom are involved in a molecule, and efficiently catalyze the reaction of 3 with allylsilanes (2) to give the substitution product of the allylsilane with an α-alkoxyalkyl, instead of an α-chloroalkyl group, at the γ-position in good yield (eq. 1) (ref. 10).

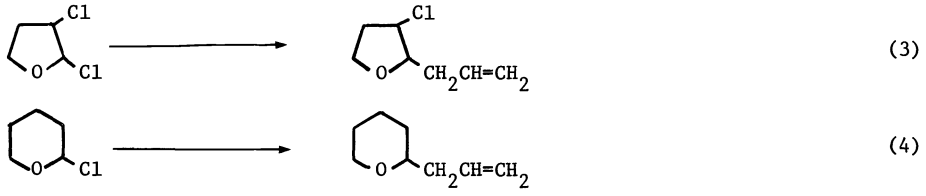


2 3 4

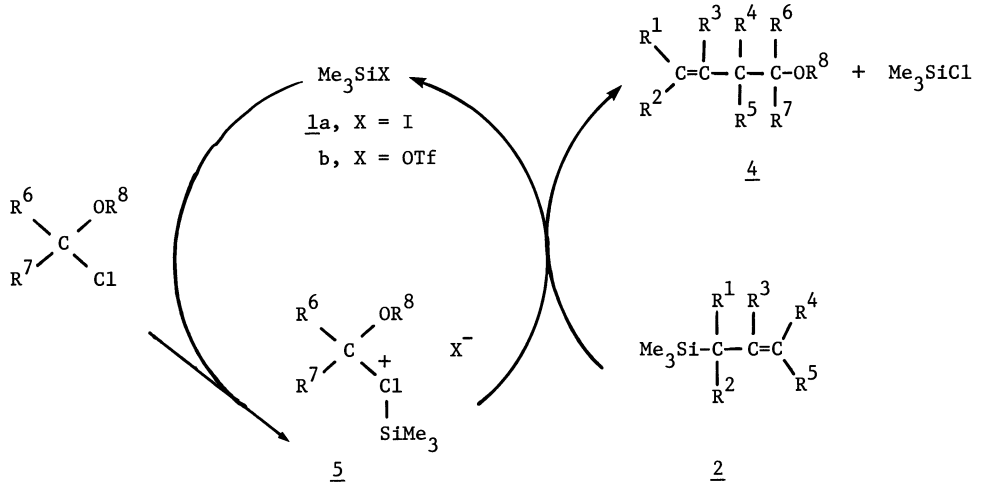
This is actually the first example of a catalytic use of 1 for the activation of a carbon-chlorine bond (ref. 11). Although the silyl triflate (1b) has been known as an activator of mostly oxygen-containing molecules, it is noteworthy that, in these cases, the activation occurred only at the carbon-chlorine bond rather than the carbon-oxygen bond of 3.
The regiospecific allyl transfer and the ability of 1 to govern the site of activation of α-chloro ethers represent the most fascinating facets of this α-alkoxyalkylation. The selectivity of the activation site by 1 depends mostly upon the stabilizing ability of the adjacent heteroatom toward an incipiently formed carbocation. It is well-known that the stabilizing effect of the MeO group to the cationic center is larger than that of the Cl group. The Brown-Okamoto's substituent constants σ^+ in the Hammett correlation are -0.78 for p-MeO and 0.11 for p-Cl (ref. 12). In addition, the driving force of the cleavage of the carbon-chlorine bond may be reasonably attributed to the strong silicon-chlorine bond (ref. 13). Accordingly, the catalytic reaction of aminomethyl ethers with 1a produces aminomethyl cation equivalents which undergo effective aminomethylation (ref. 14).



The reaction of 2 with 3 proceeds very smoothly in the presence of a catalytic amount of 1a or 1b at temperature lower than room temperature to give the corresponding homoallyl ethers (4) regiospecifically in good yields. Acetonitrile and dichloromethane were the most suitable solvent among examined. As an example, 1-chloro-3-methylbutyl methyl ether reacts with isoprenylsilane very smoothly with an aid of 1 to afford ipsenol methyl ether in 80 or 86% yield, respectively. It is noteworthy that cyclic α-chloro ethers such as 2,3-dichlorotetrahydrofuran and 2-chlorotetrahydropyran can also be readily allylated only at the α site of the ethers selectively with allyltrimethylsilane with concurrent activation of the carbon-chlorine bond to give the corresponding 2-allyl-3-chlorotetrahydrofuran and 2-allyltetrahydropyran in 90 and 78 % yield.

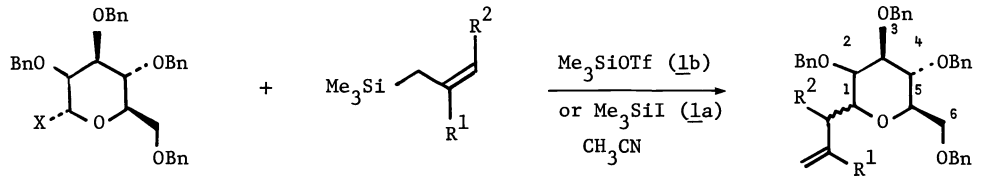


Although the mechanism of the present reaction should be elucidated by further experiments, the results can be rationalized as shown in Scheme 1, in which the initial formation of an silylhalonium ion (5), stabilized by an adjacent alkoxyalkyl group, takes place selectively at low temperature. An silyloxonium ion that is considered rather frequently as an active intermediate in the reactions of oxygen-containing substrates with 1, may not play an important role in the present case. The intermediate (5) thus undergoes either bimolecular or unimolecular nucleophilic displacement by the allylsilane (2).



Scheme 1. A catalytic cycle of the reaction of allylsilane with α-chloro ethers.

In an extention of the study, it has been demonstrated that the reaction of methyl α-D-gluco- and mannopyranosides (6) and α-D-glycopyranosyl chlorides (7) with allylsilanes (2) can be effectively catalyzed by these reagents (1) to give the corresponding C-allylated glycopyranosides stereoselectively where the α anomer overwhelmingly dominates over the β anomer in excellent yields (ref. 15).



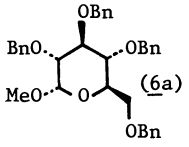
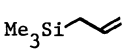
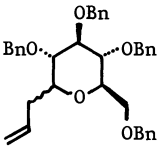
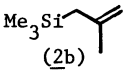
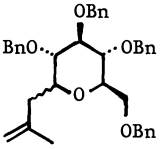
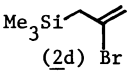
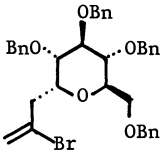
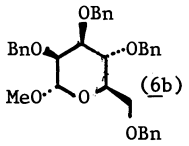
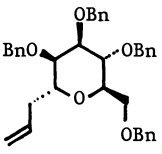
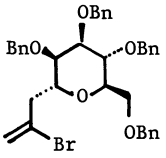
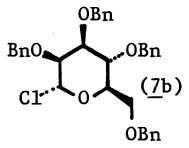
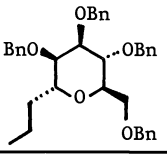
(5)

6a (2α), X = OMe
b (2β), X = OMe
7a (2α), X = Cl
b (2β), X = Cl

2a, $R^1 = R^2 = H$
b, R^1 = Me, $R^2 = H$
c, $R^1 = H$, R^2 = Me
d, R^1 = Br, $R^2 = H$

Methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (6a) reacts with allyltrimethylsilane (2a) very smoothly in the presence of a catalytic amount of silyl triflate (1b) in acetonitrile at room temperature to afford a ca. 10:1 (α:β) stereoisomeric mixture of C-allylated glucopyranosides in high yield. Iodotrimethylsilane (1a) also promotes the reaction, although less effectively. The yield of the reaction depends on the solvent and the amount of the catalyst employed. Acetonitrile is the most suitable solvent among examined for the present allylation of carbohydrates. Dichloromethane, the most commonly used solvent for the allylation with allylsilanes, does not bring satisfactory results. Although the reaction of 6 proceeds very slowly when promoted by less than 5 mol% of 1, the starting 6 being recovered along with a small amount of the product, the use of 50 mol% of 1 is enough to complete the reaction, giving an allylated glycopyranoside stereoselectively. Similarly, α- and β-methallyl groups can be introduced with 2-butenyltrimethylsilane (2c) and 2-methyl-2-propenyltrimethylsilane (2b), respectively. The allylation with 2-bromo-2-propenyltrimethylsilane (2d) proceeds very stereoselectively to afford the corresponding α anomer only. Both electronic and steric effects may account for the results, since the nucleophilicity of the double bond of 2d decreased in some extent owing to electron withdrawal of the bromine group. However, the latter effect seems to be important, since the reaction with 2b gave slightly lower selectivity than with 2a, presumably due to the sterically more hindered and more reactive β-methallyl group in 2b. Moreover, the reaction of methyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside (6b) whose benzyloxy group at 2 position orients to β with 2a

TABLE 1. Selected Examples of Stereoselective Synthesis of C-Allylated Glycopyranosides

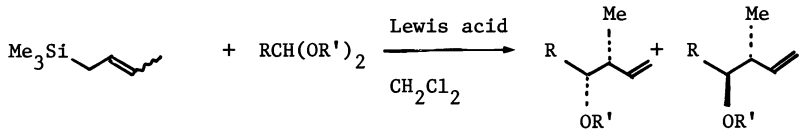
Pyranoside (6) or Pyranosyl Chloride (7)	Allylsilane (2)	Conditions	Product	% Yield	(α/β)
 (6a)	 (2a)	1b, 16 h		86	(10/ 1)
6a	 (2b)	1b, 10 h		87	(6/ 1)
6a	 (2d)	1b, 16 h		71	(1/ 0)
 (6b)	2a	1b, 25 h		87	(1/ 0)
6b	2d	1a, 12 h		45	(1/ 0)
 (7b)	2a	1b, 4 h		80	(1/ 0)

takes place more selectively to give the corresponding α-C-allylated compound exclusively. The β isomer could not be detected at all in this case. Perhaps more interestingly to note, glycopyranosyl chlorides (7), instead of 6, can be allylated more readily and mildly by the catalysis with 1, the similar stereochemical outcome being obtained. In these cases the use of 20 mol% of 1 is enough to promote the allylation. Furthermore 1a can activate the carbon-chlorine bond of 7 sufficiently in a similar way to the reaction of a variety of α-chloroalkyl ethers (ref. 10, 16). Thus the catalytic activity of 1 toward carbohydrates has been best exerted to the pyranosyl chloride.

The allyl group is useful as a masked functional group such as formyl, acetonyl and formylmethyl (ref. 17). In addition, the stereospecific introduction of β-bromoallyl group (ref. 18) that involved two functionalities could be useful for further transformation of the allylated pyranosides as a chiral building block.

DIASTEREOSELECTIVE REACTION OF CROTYLSILANES. IMPORTANCE OF THE ELECTRONIC EFFECTS IN ACYCLIC STEREOSELECTION

Control of acyclic stereoselection is one of the most important targets in synthetic organic chemistry and therefore, currently much attention has been focused on the highly diastereoselective reaction of crotyl organometallics with aldehydes (ref. 19, 20). We have demonstrated recently that the diastereoselectivity in the reaction of crotylsilanes (2c) with aromatic acetals is controlled cleanly by the geometry of crotylsilanes and, in addition, by the substituent on the aromatic nucleus, contrary to the remarkable syn selectivity with aliphatic acetals irrespective of the geometry of crotylsilanes. To our knowledge, this is



(6)

2c 8 syn anti

the unprecedented example showing that the electronic effect, rather than the steric effect, plays an important role on diastereofacial control. At first, the stereochemistry in reactions of Z- and E-crotylsilanes with a variety of acetals (8) was examined and the results are listed in TABLE 2.

TABLE 2 Reactions of Z- and E-2c with Acetals Promoted by a Lewis Acid

Acetal	Activator	Z-2c % Yield	Z-2c (syn/anti)	E-2c % Yield	E-2c (syn/anti)
t-BuCH(OMe)$_2$ (8a)	$TiCl_4$	83	(93/ 7)	63	(96/ 4)
	10 mol% Me_3SiI	71	(92/ 8)		
	1 mol% Me_3SiOTf	70	(92/ 8)	66	(97/ 3)
$Me_2CHCH_2CH(OMe)_2$ (8b)	$TiCl_4$	99	(91/ 9)	90	(91/ 9)
PhCH(OMe)$_2$ (8c)	BF_3OEt_2	78	(28/72)	94	(75/25)
	10 mol% Me_3SiI	82	(28/72)	99	(69/31)
	1 mol% Me_3SiOTf	76	(20/80)	66	(79/21)
PhCH(OEt)$_2$ (8d)	BF_3OEt_2	82	(31/69)	75	(71/29)
PhCHCl(OMe) (8e)	1 mol% Me_3SiOTf	80	(29/71)	53	(84/16)

As can be seen from the results recorded in TABLE 2, reactions of crotylsilanes with aliphatic acetals such as pivalaldehyde dimethylacetal (8a) and isovaleraldehyde dimethylacetal (8b) proceed very smoothly in a regiospecific and highly syn selective mode, irrespective of the geometry of 2c. However aromatic acetals such as benzaldehyde dimethylacetal (8c) react with Z-2c with high anti preference, although the syn selectivity is observed with E-2c. α-Chloro ether (8e) also affords similar results. The stereoselectivity does not depend on the nature of Lewis acids or activators among examined such as titanium chloride, boron trifluoride etherate, iodotrimethylsilane, and trimethylsilyl trifluoromethanesulfonate.

TABLE 3 Reactions of Z- and E-Crotyltrimethylsilanes with Aromatic Acetals

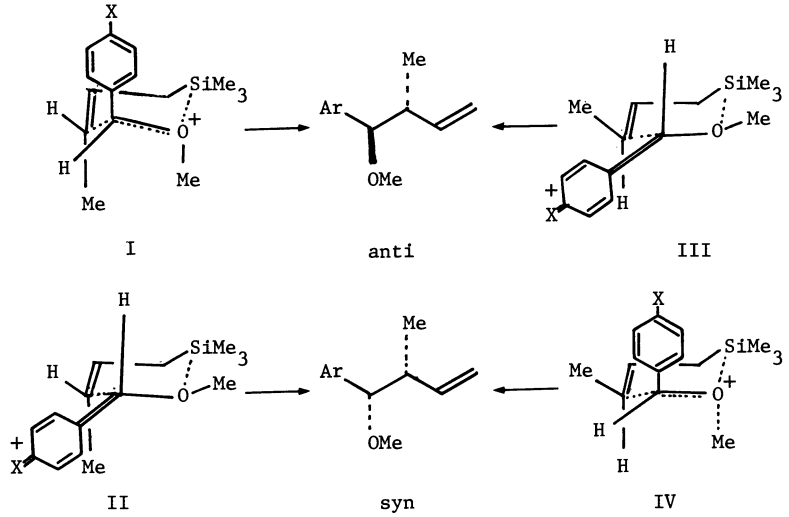
Acetal	Z-2c % Yield	Z-2c (syn/anti)	E-2c % Yield	E-2c (syn/anti)
p-MeO-C_6H_4-CH(OMe)$_2$	66	(46/54)	56	(45/55)
p-Me-C_6H_4-CH(OMe)$_2$	87	(32/68)	77	(65/35)
C_6H_5-CH(OMe)$_2$	78	(28/72)	94	(75/25)
p-NC-C_6H_4-CH(OMe)$_2$	92	(20/80)	84	(80/20)

Interestingly the stereoselectivity can be dramatically controlled by the substituent on the ring of aromatic acetals, the results being listed in TABLE 3. Thus, increasing antiselectivity is observed in the case of Z-2c with increasing electron-withdrawal due to the substituent in the order of p-CN>H>p-Me>p-MeO. On the other hand, with E-2c, syn selectivity increases with electron-withdrawing substituent. It is worth to note that a Hammett's plot between logarithms of the diastereomer ratio ln(syn/anti) and Brown-Okamoto's σ^+ reveals

good linear correlation (ρ = -1.25, r = 0.996 for Z-2c and ρ = 1.26, r = 0.988 for E-2c). Apparently the electronic effect plays an important role on the decision of the diastereoselectivity.

The observed selectivity in aromatic acetals is inconsistent with the mechanism proposed for the reactions of 2 with aldehydes involving an acyclic transition state. Furthermore, a simple six-membered cyclic transition state, in which the most stable conformation in the chair form is commonly considered, can not reasonably explain the results of the present reaction.

The reason for this unprecedented stereochemistry in the aromatic acetals is not completely clear at this stage, but the mechanism of the reaction of 2 with aromatic acetals may be explained as follows. In marked contrast to aliphatic acetals, aromatic acetals can be activated by the Lewis acid to undergo the C-O bond cleavage, resulting in the intermediary formation of benzylic cationic species. If the six-membered cyclic transition states (I and IV) are involved as shown in Scheme 2, an electron-withdrawing p-cyano group on the aromatic ring produces the partial double bond nature between the benzylic carbon and the ether oxygen due to the donation of electrons from the oxygen where aryl and methyl groups occupy anti position each other.



X = p-CN: I > II, III < IV

X = p-MeO: I < II, III > IV

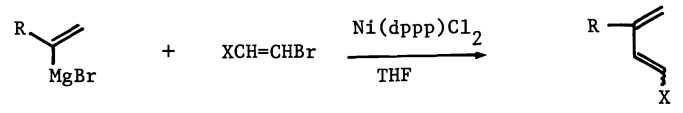
Scheme 2. Mechanism of Diastereoselection in the allylation

Therefore, anti and syn isomers are dominantly produced from Z- and E-2c, respectively. However such double bond nature between benzylic carbon and alkoxy oxygen atoms may disappear or decrease the extent by the introduction of electron-donating p-methoxy group, resulting in the formation of the transition states (II and III) predominantly. Thus E-2 increases the anti selectivity and the reverse selectivity is induced in Z-2. This might be the reason why reversal of the diastereoselectivity from reactions of the crotyl metallics (B, Al, Mg, Zn, Li, Ti, Zr,.....) with aldehydes is induced, where the six-membered cyclic transition state is similarly involved.

REGIOSPECIFIC CYCLOADDITION REACTIONS USING FUNCTIONALIZED ISOPRENYLSILANE AND RELATED DERIVATIVES

Previously, we have described that 2-trimethylsilylmethyl-1,3-butadiene (9a) is not only an efficient and convenient reagent for the nucleophilic isoprenylation, where the reaction of 9a proceeds as a substituted allylsilane, but also an excellent diene for the regio- and stereo-selective Diels-Alder reaction with unsymmetrical dienophiles (ref. 21). Introduction of a functionality into 9a is an interesting extention of the work, and recently we have prepared 1-methoxy- and 1-ethoxy-3-trimethylsilylmethyl-1,3-butadienes (9b and 9c, respectively) and 1-methoxy-3-trimethylsilyl-1,3-butadiene (9d). Perfectly regiospecific cycloaddition reactions of 9 with dienophiles involving heterodienophiles are observed.

Isoprenylsilanes (9a-9c) are prepared by the cross-coupling reaction of the Grignard reagent (10a) of β-bromoallyltrimethylsilane (2d) in the presence of a catalytic amount of dihalo(diphosphine)nickel(II) as a mixture of stereoisomers. The ratio of isomers depends on the geometry of the starting β-alkoxyvinyl bromide (11). Similarly, 9d is obtained from the



(7)

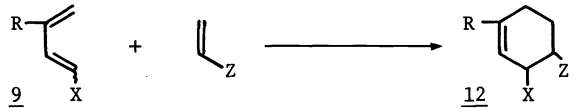
10a, R = CH_2SiMe_3
b, R = $SiMe_3$

11a, X = H
b, X = OMe
c, X = OEt

9a, R = CH_2SiMe_3; X = H
b, R = CH_2SiMe_3; X = OMe
c, R = CH_2SiMe_3; X = OEt
d, R = $SiMe_3$; X = OMe

dppp: $Ph_2P(CH_2)_3PPh_2$

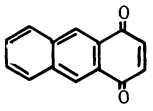
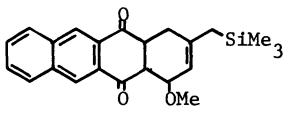
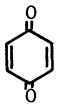
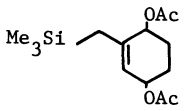
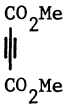
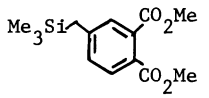
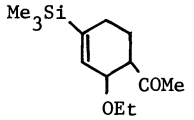
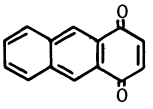
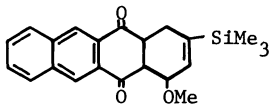
Grignard reagent (10b) of α-bromovinyltrimethylsilane.
Multi-functionalized 1,3-dienes (9b–9d), thus obtained, display high reactivity and regio- and stereo-specificity toward various dienophiles, selected examples of the representative results of which are listed in TABLE 4. In all cases, the thermal reaction proceeds very smoothly without any catalyst to afford the corresponding cycloadducts (12) in good yield, although the elimination of an alcohol from the cycloadduct with acetylenic dienophiles takes place readily, resulting in the formation of aromatic derivatives.



(8)

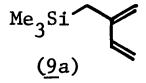
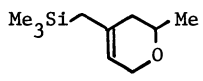
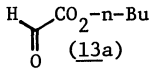
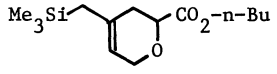
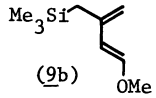
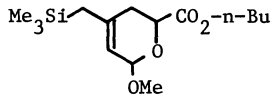
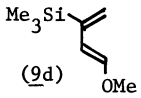
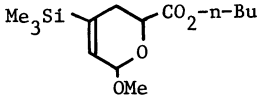
It is interesting to examine the reaction of 9 with aldehydes which can enter the reaction as electrophiles as well as heterodienophiles. In the presence of a Lewis acid catalyst, 9a reacts with a variety of aldehydes to give dihydropyran derivatives along with isoprenylated alcohols, the relative yields being dependent on the structure of aldehydes and a Lewis acid as a catalyst. The results are summarized in TABLE 5.

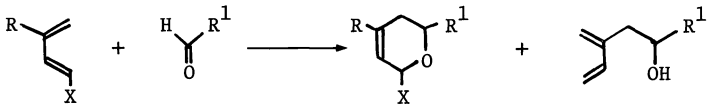
TABLE 4. Selected Examples of Thermal reactions of 1,3-dienes with dienophiles

1,3-Diene	Dienophile	Cycloadduct	% Yield (cis/trans)
Me_3Si (9b) OMe			82
Me_3Si (9c) OEt			80
9c			85
Me_3Si (9d) OMe			60 (86/14)
9d			90

Interestingly the perfect regiospecificity of the thermal reaction can be achieved with unsymmetrical dienophiles, only one regioisomer being obtained. Cycloaddition of 2-triethylsilyl-1,3-butadiene is known not to give regioselective products (ref. 22).
It is worth to note that carbonyl compounds such as glyoxylate (13a) and oxomalonate reveal high reactivity toward 9, giving the corresponding cycloadduct (14) exclusively under the thermal conditions. The reaction proceeds in a perfectly regiospecific mode even without a Lewis acid catalyst.

TABLE 5. Selected Examples of Reactions of 1,3-dienes with heterodienophiles

1,3-Diene	Heterodienophile	Cycloadduct	% Yield
 (9a)			46
9a	 (13a)		74
 (9b)	13a		93
 (9d)	13a		73



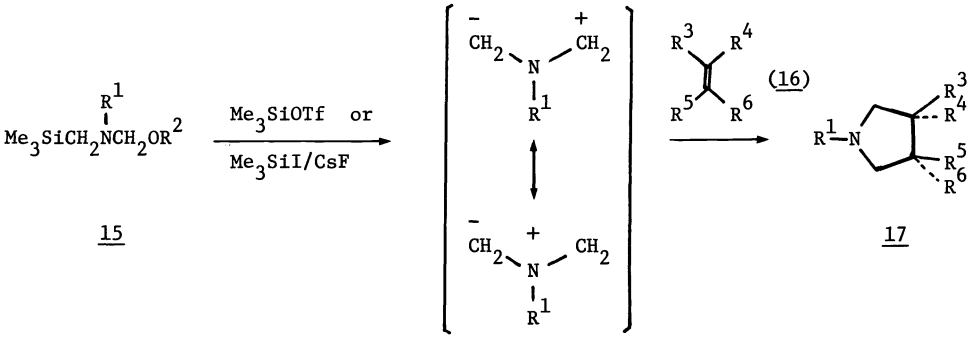
9 13 14 (from 9a) (9)

The cycloadducts, containing an allylsilane or vinylsilane structure, may be further transformed to a variety of functionalized compounds by an easy process. For example, the facile availability of pyran and tetracene derivatives is of particular interest with respect to glycoside, anthracycline antibiotics and antitumor agents.

CONCERTED 1,3-ELIMINATION: N-(TRIMETHYLSILYLMETHYL)AMINOMETHYL ETHERS AS AZOMETHINE YLIDE SYNTHONS. A NEW ACCESS TO PYRROLIDINE DERIVATIVES

In the previous section, it has been demonstrated that α-heteroatom-substituted ethers and related compounds (RR'CXY; X, Y = R_2N, RO, RS and halogen) are activated chemoselectively by iodosilane or silyl triflate to undergo efficient reactions for regiospecific introduction of α-heteroatom-substituted alkyl group to silyl enol ethers (ref. 16) and allylsilanes (ref. 10). In an extension of the study, we have found that N-(trimethylsilylmethyl)aminomethyl ethers (15) activated by trimethylsilyl trifluoromethanesulfonate (1b) or iodotrimethylsilane (1a) and cesium fluoride readily react with electron deficient alkenes (16) to give the corresponding pyrrolidine derivatives (17) stereospecifically in good yield (ref. 23). This constitutes an unprecedented and expedient route to non-stabilized azomethine ylides. Azomethine ylides are one of the most important 1,3-dipoles from both synthetic and theoretical point of view. However, either electron-withdrawing or conjugating substituents are required inevitably for stabilizing the dipoles in the generation of azomethine ylides through thermally induced ring-opening of aziridines. Therefore, generation of non-stabilized azomethine ylides, especially by fluoride ion-promoted desilylation of immonium salts, has been a current interest.

The requisite aminomethyl ethers (15) were prepared quite easily from (aminomethyl)silanes (18) in good yield.



15 (16) 17 (10)

$$Me_3SiCH_2NHR^1 + (CH_2O)_n + R^2OH \longrightarrow Me_3SiCH_2\underset{\displaystyle R^1}{N}CH_2OR^2 \qquad (11)$$

18a, R^1=cyclo-C_6H_{11}
b, R^1=$PhCH_2$

19a, R^2=Me
b, R^2=n-Bu

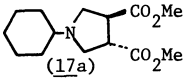
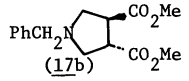
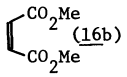
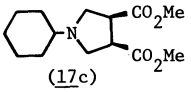
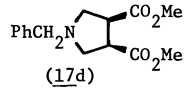
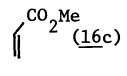
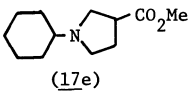
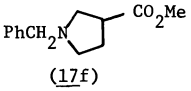
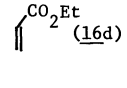
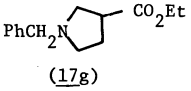
15a, R^1=cyclo-C_6H_{11}; R^2=Me
b, R^1=$PhCH_2$; R^2=Me
c, R^1=$PhCH_2$; R^2=n-Bu

Aminomethyl ether (15a), catalyzed by 1b, undergoes 1,3-elimination of methoxytrimethylsilane in the presence of electron deficient alkenes (16) to afford the corresponding pyrrolidine derivatives (17, R^1=cyclo-C_6H_{11}) in considerably high yield. Addition of a small amount of cesium fluoride accelerates the reaction and improves the yield of 17. Nevertheless, it is worth to note that the reaction proceeds sufficiently even without cesium fluoride. The selected examples of results are listed in TABLE 6.

The substituent on the nitrogen atom could be changed widely since 18 can be prepared by the reaction of chloromethyltrimethylsilane and a variety of primary amines. For example, N-benzyl-N-(trimethylsilylmethyl)aminomethyl ethers (15b and 15c) were prepared from benzylamine in good yield. The reactivity of 15b and 15c toward 1,3-dipolarophiles seems to be quite similar to 15a and the corresponding 1-benzylpyrrolidines that are easily deprotected under mild conditions are obtained in good yield.

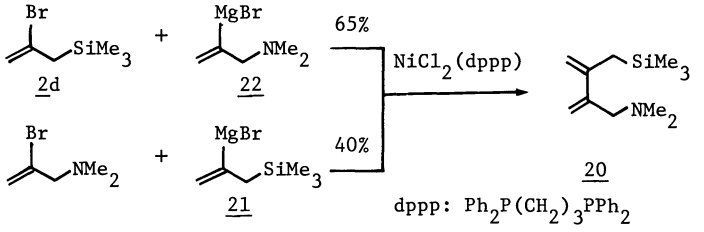
This methodology can be applied to the generation of other non-stabilized heteroatom 1,3-dipoles such as carbonyl ylides and thiocarbonyl ylides.

TABLE 6 Selected Examples of Reactions of N-(trimethylsilylmethyl)aminomethyl ethers with dipolarophiles

Aminomethyl ether (15)	Dipolarophile (16)	Conditions	Product	% Yield
$Me_3SiCH_2\underset{\displaystyle}{N}(CH_2OMe)$ (15a)	MeO_2C, CO_2Me (16a)	Me_3SiOTf (1b) 60°C, 26 h, THF	 (17a)	58
15a	16a	1b, CsF, THF 60 °C, 18 h	17a	90
$Me_3SiCH_2\underset{\displaystyle PhCH_2}{N}CH_2OMe$ (15b)	16a	1b, CH_3CN 60 °C, 15 h	 (17b)	74
15b	16a	1b, CsF, THF 60 °C, 25 h	17b	83
$Me_3SiCH_2\underset{\displaystyle PhCH_2}{N}CH_2O\text{-n-Bu}$ (15c)	16a	1a, CsF, CH_3CN 50 °C, 10 h	17b	75
15a	 (16b)	1b, CsF, THF 60 °C, 36 h	 (17c)	72
15b	16b	1b, CsF, THF 60 °C, 25 h	 (17d)	83
15a	 (16c)	1b, CsF, THF 60 °C, 18 h	 (17e)	80
15c	16c	1a, CsF, CH_3CN 60 °C, 15 h	 (17f)	91
15b	 (16d)	1b, CsF, THF 60 °C, 25 h	 (17g)	85

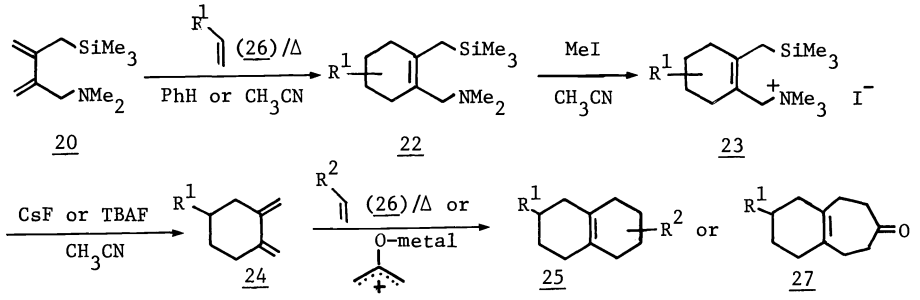
CONCERTED 1,4-ELIMINATION: 2-DIMETHYLAMINOMETHYL-3-TRIMETHYLSILYLMETHYL-1,3-BUTADIENE. A NEW AND FACILE ENTRY TO 1,2-DIMETHYLENECYCLOHEXANES

As an extension of the chemistry of isoprenylsilanes (vide supra), we have developed a method of preparation and tandem cycloaddition reactions of 2-dimethyl-aminomethyl-3-trimethylsilylmethyl-1,3-butadiene (20) that serves as an effective 2,2'-biallyl synthon.
The requisite 1,3-diene can be prepared conveniently by the nickel complex-catalyzed cross-coupling reaction between an excess amount of the Grignard reagent (21) prepared from (2-bromo-2-propenyl)trimethylsilane (2d) and (2-bromo-2-propenyl)dimethylamine. Similarly, combination of the Grignard reagent 21 and the bromide 2d is another favorable access to 20.



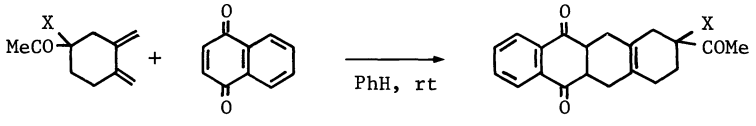
(12)

Tandem cycloaddition reactions of 20 provide a novel and interesting route to [6.6] and [6.7] ring systems, the whole sequences of which are shown in the following scheme.



(13)

Preparation of octalines 25 can be attained readily in a stepwise manner, the products 22-25 being isolated cleanly at any step. Indeed 20 reveals high reactivity toward a variety of dienophiles bearing electron-withdrawing groups to give the corresponding stable cycloadducts 22 as a regioisomeric mixture in good yield. After the cycloadducts 22 are quaternized with methyl iodide, treatment of a system containing ammonium salts 23 that are also isolable, with cesium fluoride or tetra-n-butylammonium fluoride (TBAF) even at temperature lower than 25 °C provides smoothly 1,2-dimethylenecyclohexane derivatives 24 by the conjugate 1,4-elimination. 24, otherwise difficult to prepare, can be either isolated cleanly or, without isolation, trapped efficiently with electron deficient alkenes as second dienophiles to afford octalines 25 in excellent yield. The selected results are illustrated in TABLE 7.
It should be pointed out that 1,2-dimethylenecyclohexanes 24 are expedient reagents for the cycloaddition reactions as highly reactive dienes, presumably due to the rigid s-cis structure. In facts, tetracyclic derivatives 25f and 25g, that may be important key intermediates for synthesis of anthracycline antibiotics, are obtained by the tandem Diels-Alder reaction of 20 with methyl vinyl ketone or methyl α-acetoxyvinyl ketone as the first dienophile and naphthoquinone as the second one.



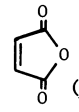
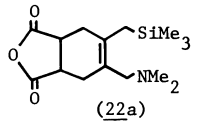
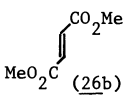
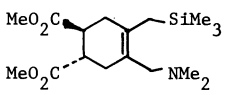
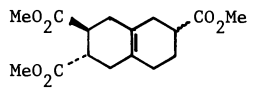
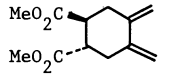
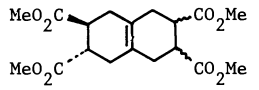
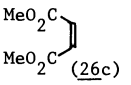
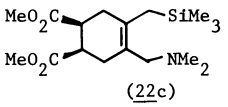
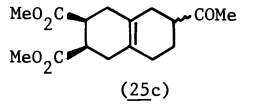
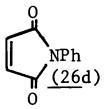
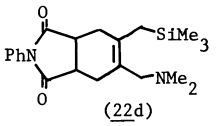
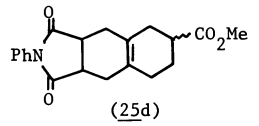
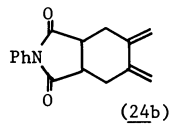
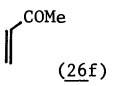
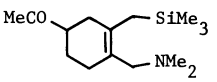
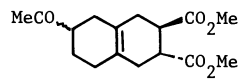
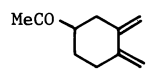
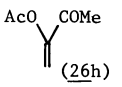
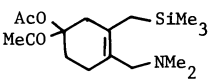
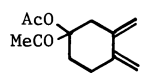
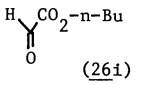
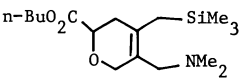
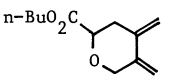
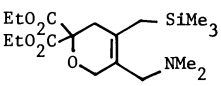
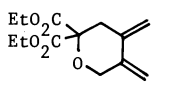
(14)

24c, X = H
d, X = OAc

25f, X = H, 85%
g, X = OAc, 80%

Moreover the [3 + 4] cycloaddition reaction of 24 with 2-oxyallyl cations (ref. 24) proceeds smoothly to give the corresponding [6.7] ring compounds (27).
Reaction of 20 with heterodienophiles 26i and 26j yield the corresponding cycloadducts 22i and 22j in 90 and 73% yield, which are converted to 1,2-dimethylene-4-oxocyclohexanes 24e

TABLE 7. Selected Examples of Tandem Diels-Alder Reactions of 20

First Dienophile	Product (22)	(% Yield)	Second Dienophile	Product (24) or (25)	(% yield)
 (26a)	 (22a)	(89)			
 (26b)	 (22b)	(86)	 (26e)	 (25a)	(85)
26b				 (24a)	(97)
26b			26b	 (25b)	(80)
 (26c)	 (22c)	(71)	26f	 (25c)	(66)
 (26d)	 (22d)	(85)	26e	 (25d)	(66)
26d				 (24b)	(63)
 (26f)	 (22f)	(82)	26b	 (25e)	(80)
26f				 (24c)	(73)
 (26h)	 (22h)	(70)		 (24d)	(82)
 (26i)	 (22i)	(90)		 (24e)	(94)
O=C(CO$_2$Et)$_2$ (26j)	 (22j)	(73)		 (24f)	(91)

and 24f quantitatively by treatment with fluoride ion after quaternization. Cycloaddition of 24f, in situ generated from 22j, to dimethyl fumarate affords the corresponding bicyclic compounds 25j in 76% yield.

It is noteworthy to state that 22-25 can be prepared by the "one pot" operation without isolation of each product during all sequences. Apparently the overall yields are improved considerably rather than those in the stepwise manner. In this case acetonitrile is utilized conveniently as a solvent in the reactions.

The present reaction in which 20 is regarded as a novel 2,2'-biallyl synthon opens a convenient route to [6.6] and [6.7] ring systems which are important intermediates to a variety of cyclic naturally occurring products.

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