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STUDIES ON THE SYNTHETIC REACTIONS VIA SILYL ETHERS

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JANUARY, 1978

Preface

This thesis deals with the studies completed by the author under the guidance of Professor Dr. Noboru Sonoda at Department of Petroleum Chemistry, Faculty of Engineering, Osaka University.

The author would like to express his sincere gratitude to Professor Dr. Noboru Sonoda for his invaluable guidance and constant encouragement throughout the course of this work since 1975.

The author wishes to make a grateful acknowledgement to Associate Professor Dr. Shinji Murai for his profound interest and helpful discussions. The author is also deeply grateful to the late Dr. Membo Ryang for his helpful suggestions which stimulated the author.

Grateful acknowledgements are also made to Dr. Ilsong Rhee, Dr. Kiyoshi Kondo, Mr. Noritaka Miyoshi for their helpful suggestions in stimulating discussions with the author.

It is a real pleasure for the author to express his gratitude to Mr. Shoji Otani, Mr. Tetsuro Horiike, Miss Akiko Shinonaga, and Mr. Isamu Niwa for their collaboration in the course of these experiments. He extends his thanks to Dr. Yoshio Seki and the other members in the Laboratory of Professor Sonoda for their occasional discussions and hearty cooperation with him.

Finally the author would like to thank his dear parents for their heartful encouragement which made possible the completion of this work.

Suita. Osaka
January, 1978

Ilhyong Ryu

List of Publications

The content of this thesis are composed of the following papers.

(1) An Unusual Simmons-Smith Reaction Affording Noncyclopropyl Compounds. A New Route to 2-Methylenecycloalkanols from Silyl Alkenyl Ethers
S. Murai, T. Aya, T. Renge, I. Ryu, and N. Sonoda,
J. Org. Chem., 39, 858 (1974).

(2) Synthesis of Cyclopropyl Esters from Silyl Enol Ethers
I. Ryu, S. Murai, S. Otani, and N. Sonoda,
Chem. Lett., 93 (1976).

(3) The Reaction of Enol Ethers with Simmmons-Smith Reagent. The Formation of Allylic Ethers
I. Ryu, S. Murai, and N. Sonoda,
Chem. Lett., 1049 (1976).

(4) Skeletal Rearrangement with Ring Expansion in the Simmons-Smith Reaction of Trimethylsiloxymethylenecyclopentanes
I. Ryu, S. Murai, S. Otani, and N. Sonoda,
Tetrahedron Lett., 1995 (1977).

(5) Two Types of Indirect Cyclodimerization of Biacetyl via Its Enol Silyl Ethers
S. Murai, I. Ryu, Y. Kadono, H. Katayama, K. Kondo, and N. Sonoda,
Chem. Lett., 1219 (1977).

(6) One-Pot-Conversion of 1-Siloxy-Cycloalkenes to 4-Siloxy-Spiro[n,2]alkanes with Diethylzinc-Methylene Iodide
I. Ryu, S. Murai, and N. Sonoda,
Tetrahedron Lett., 4611 (1977).

(7) A Convenient Synthesis of α-Phenylseleno Ketones and Aldehydes from Enol Silyl Ethers and Phenylselenenyl Bromide
I. Ryu, S. Murai, I. Niwa, and N. Sonoda,
Synthesis, in press.

(8) An Improved Procedure for Dimethyldicyanosilane and Trimethyl-Cyanosilane
I. Ryu, S. Murai, T. Horiike, A. Shinonaga, and N. Sonoda,
Synthesis, in press.

(9) Dimethyldicyanosilane. A New Reagent for Concurrent Silylation and Cyanosilylation of β-Diketones
I. Ryu, S. Murai, A. Shinonaga, T. Horiike, and N. Sonoda,
J. Org. Chem., in press.

(10) Cyclopropyl to Allylic Isomerization in the Simmons-Smith Reaction of Enol Ethers
I. Ryu, S. Murai, S. Otani, and N. Sonoda,
To be submitted.

Contents

Chapter 4 Synthetic Transformations of Cyclopropyl Silyl Ethers

Introduction

Until recently, there was nothing remarkable in the applications of silyl ethers to organic synthesis but the use as protecting groups of alcohols.

When one has an idea that one utilizes silyl ethers to various important synthetic reactions as intermediates, it seems intrinsically important to deal with silyl ethers equipped with a reactive C=C double bond or activated C-C single bonds adjacent to siloxy group. Enols and cyclopropanols which directly concerns the present studies have been known as such alcohols to posess reactive C=C double bond or strained cyclopropane rings adjacent to hydroxyl groups, respectively. Synthetic applications of these compounds, however, have never met with notable success despite the fact that much attention has been payed to them.

The main reason for this was due to their instability. As well known, enols can exist slightly under the tautomerism of the corresponding carbonyl compounds. Compared with enols, cyclopropanols seem fairly stable but not enough to be dealt with eaily, for instability both thermal and chemical often leads us to face some difficulties in dealing with such. In addition, the lack of a general and satisfactory method for preparation of cyclopropanols has often discouraged synthetic chemists to utilize cyclopropanols in various synthetic reactions.

To develop synthetically equivalent reactions of these 'reactive and unstable' alcohols by employing their silyl ethers is precisely the primary reason for the present studies.

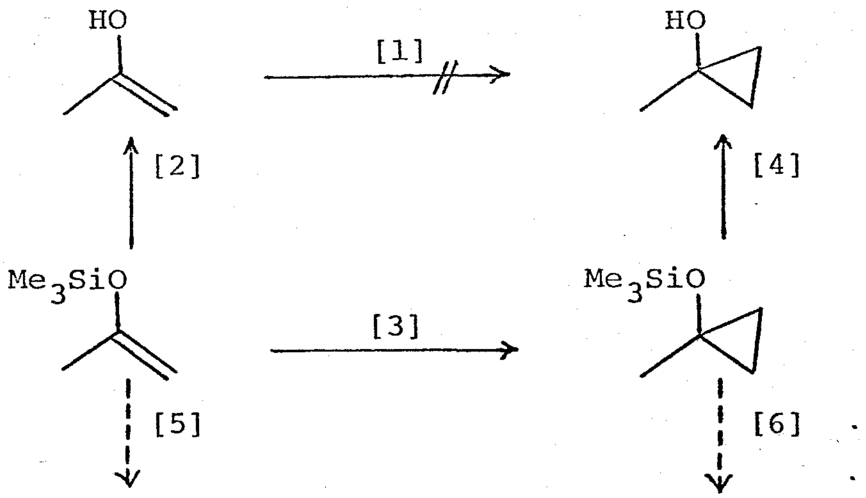
It seems significant to arrange each step consisting of such methodology utilizing silyl ethers as synthetic equivalent of enols. They are briefly summarized in the following way:

(1) Preparation of Silyl Ethers

(2) Transformation from Silyl Ethers

(3) Removal of Silyl Groups to Afford the Products

The envisaged example on cyclopropanol synthesis using enol silyl ethers may well account for these (see Scheme). Namely, for the preparation of cyclopropanols the direct cyclopropanation of enols (path [1]) is the shortest path but really impossible. However, the use of enol silyl ethers instead of enols for cyclopropanation (path [3]) followed by desilylation (path [4]) clearly led this synthesis to success.



In the present studies, transformations of path [3] in above scheme via the reaction with zinc carbenoid reagents were investigated in detail. The establishment of the synthetic method of cyclopropyl silyl ethers means not only that of useful precursors of cyclopropanols but also that of excellent synthetic equivalent of cyclopropanols, whose interesting chemistry has been drawn much attention.

Chapter 1 of this thesis deals with silylation of carbonyl compounds. This chapter involves the valid modification of previous silylating methods. In addition, the originally developed method for concurrent silylation and cyanosilylation of β-diketones is described.

In Chapter 2 is dealt with the synthesis of cyclopropyl silyl ethers by the reaction of enol silyl ethers with zinc carbenoid reagents. This chapter also involves the Simmons-Smith reaction of enol ethers, in which a new aspect that this reaction usually affords allylic isomers in addition to cyclopropyl ethers was described.

In Chapter 3 the observed cyclopropyl-allylic isomeriation in the reaction of enol silyl ethers with zinc carbenoid reagents is dealt with in detail.

In Chapter 4, a variety of transformations via cyclopropyl silyl ethers which reveal the potential utilities of them are noted

Though many attempts to develop the synthetic equivalent of enols have been undertaken (for example, enol ethers, enol acetates or enamines), enol silyl ethers seems to be the choice. This may be supported by the unique properties of organosilicon compounds: facile preparation of them; sufficient stability through most of transformation reactions; utilization of unique properties which organosilicon groups own; facile removal of silyl group.

Organosilicon chemistry has experienced a tremendous growth and wide interst in the past decade. It is a real pleasure for the author to have taken part in this through the present studies.

Chapter 1 Silylation of Carbonyl Compounds

1-1 Introduction

A great many methods exist for the synthesis of enol silyl ethers.[1] Maybe by classification of starting materials commonly available methods will be devided into the following three categories:

(1) via Silylation of Enolates of Corresponding Carbonyl Compounds

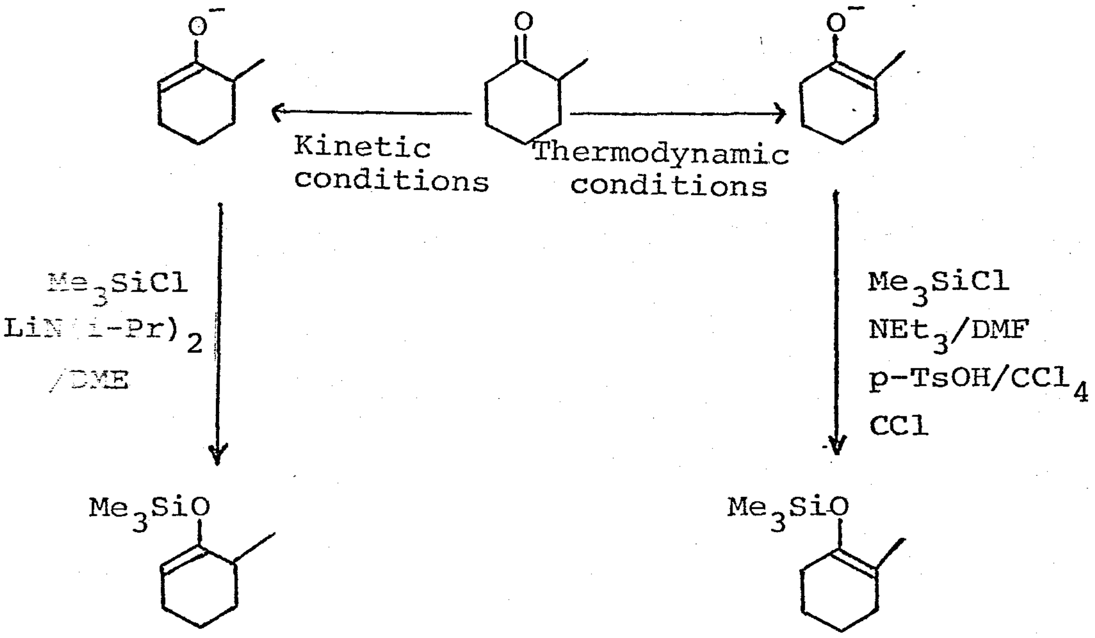
(2) via Hydrosilylation of α,β-Unsaturated Carbonyl Compounds

(3) via Reaction of Hydroformylation Analog of Silane from Olefins.[2]

All enol silyl ethers used for the present studies were prepared via silylation of corresponding carbonyl compounds. These synthesis were usually due to the procedure of H. O. House et al.,[3] or G. Stork and P. F. Hudrlik.[4] In some cases modification of these methods was employed.

One of the intrinsic features resultant from the use of enol silyl ethers for synthetic reactions as a synthetic equivalent of enols perhaps owes to the regiospecific synthesis of enol silyl ethers in the case of unsymmetrical ketones, such as 2-methylcyclohexanone shown in the following equation.

Either employment of these two isomers leads to regiospecific transformations and this was fully proven by various examples of α-substituted carbonyl compounds synthesis via the reactions with various electrophiles.[1]



(99 % purity)   (91 % purity)

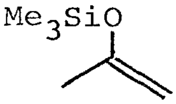
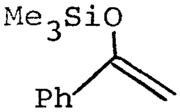
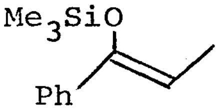
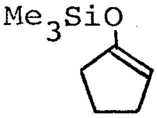
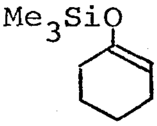
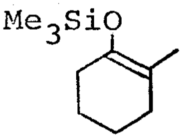
Mono-silylated β-diketones are viewed as enol silyl ethers having electron deficient C=C double bond. Masking of remained carbonyl group is assumed to lead to increasing the electron density of the C=C double bond. This chapter includes concurrent silylation and cyanosilylation of β-diketones with dimethyldicyanosilane.

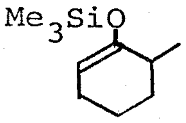
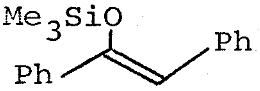
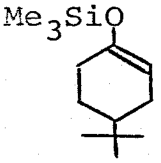
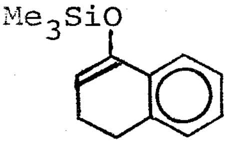
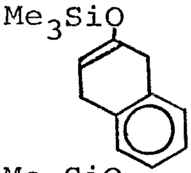
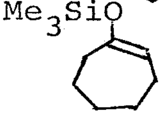
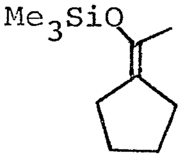
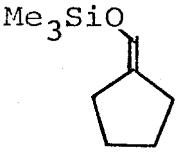
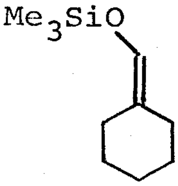
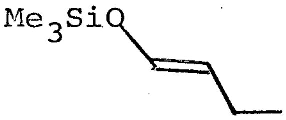
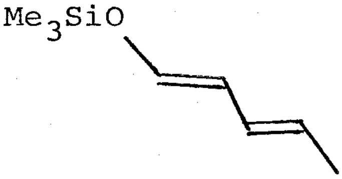
In addition, a convenient synthesis of α-phenylseleno ketones from enol silyl ethers and their silylation are described.

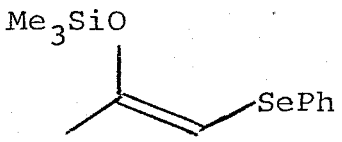
1-2 Silylation of Ketones and Aldehydes

Enol silyl ethers used in this study were prepared by silylation of corresponding enolates of carbonyl compounds. These carbonyl compounds are acetone, acetophenone, propiophenone, cyclopentanone, cyclohexanone, 2-methylcyclohexanone, 4-t-butylcyclohexanone,[5] 4,5-benzocyclohexanone, 3,4-benzocyclohexanone,[6] cycloheptanone, methyl cyclopentyl ketone,[7] cyclopentanecarboxaldehyde,[8] cyclohexanecarboxaldehyde,[9] n-butyraldehyde. Enol silyl ethers obtained from these carbonyl compounds by silylation are listed in the Table 1.

Table 1. Enol Silyl Ethers Obtained by Silylation of Carbonyl Compounds.

Enol Silyl Ether	B.p. °C (Torr)	Ref.
	93-94 (760)	10
	97-98 (19)	3
	140 (35)	3
	158-159(760)	3
	74-75 (20)	3
	101-102(45)	3,4

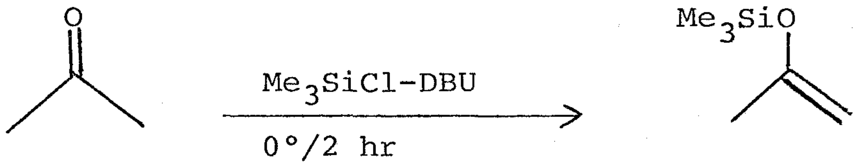
Enol Silyl Ether	B.p °C (Torr)	Ref.
	78-80 (20)	10
	130 (0.5)	10
	94-96 (3.9)	3
	132-133(13)	3
	89-91 (0.36)	3
	82-84 (25)	3
	72-74 (90)	3,4
	61-64 (14)	3
	91 (23)	3
	44-45 (50)	3
	82-84 (27)	3

	105 (0.85)	10

Procedures for silylation were mainly due to the methods of House[3] or Stork[4]. While in some cases modification or imprcved procedures were employed.

Silylation of acetone by the original method of House was not effective since it was hard to seperate silylated product from triethylamine, which was employed as base in the procedure.

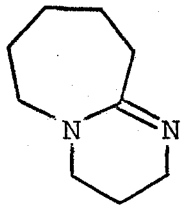
To overcome such difficulty, the use of DBU (1,8-diazabicyclo[5.4.0]undecene-7) has proved to be effective.



78 %

This method is simple and convenient for enol silyl ethers having lower boiling points or weak to aqueous treatment (direct distillation is possible).

DBU:



Silylation of kinetically controlled enolate of 2-methylcyclohexanone by lithium diisopropylamide was carried out in THF as a solvent, the use of such a popular solvent brought nothing inconvenient.[10]

1-3 Silylation and Cyanosilylation of β-Diketones

Many methods are already available for the synthesis of mono-silylated β-diketones.[11] From the point of view that one utilizes these compounds as synthetic intermediates of various transformations, some difficulties exist: weakness to hydrolysis (in the case of trimethylsilyl ethers); electron deficient C=C double bond; two reaction sites against the attack of electrophiles (carbon and oxygen). In order to overcome these difficulties some devices to mask the remained carbonyl group must be made, and methods with cyanosilylation were attempted.

For the present study, we started with the development of improved procedures for dimethyldicyanosilane and trimethylcyanosilane. There have been no satisfactory methods for the preparation of dimethyldicyanosilane[$Me_2Si(CN)_2$], proving to be useful for concurrent silylation and cyanosilylation of β-diketones. McBride et al. reported that a moderate yield of dimethyldicyanosilane was obtained by the reaction of silver cyanide with dimethyldibromosilane, which must be prepared from dimethyldichlorosilane via two steps.[12] The use of easily available dimethyldichlorosilane in the place of dimethyldibromosilane was reported to give a quite unsatisfactory result.[12] Hundeck prepared dimethyldicyanosilane from bis(diethylamino)-dimethylsilane[$(Et_2N)_2SiMe_2$], dimethyldichlorosilane, and hydrogen cyanide.[13] This method lacks convenience because bis(diethylamino)silane is not easily available and the use of hazardous hydrogen cyanide is not avoidable.

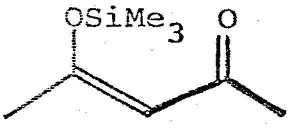
Here is described that dimethyldicyanosilane is conveniently prepared in a high yield by the reaction of silver cyanide with dimethyldichlorosilane using Soxhlet extractor. The procedure is essentially 'extraction' of silver cyanide with dimethyldichlorosilane. Silver cyanide, which was placed in cylindrical filter of Soxhlet apparatus, was 'extracted' with 2-3 molar excess of dimethyldichlorosilane at 120-140°(bath temperature) for 5-7 days. After removal of excess dimethyldichlorosilane, the residue was distilled under reduced pressure to give dimethyldicyanosilane in 76-85 % yield.

$$\mathrm{Me_2SiCl_2} + \mathrm{AgCN} \xrightarrow[\text{120-140°, 5-7 days}]{\text{Soxhlet extractor}} \underset{\text{76-85\%}}{\mathrm{Me_2Si(CN)_2}} + \mathrm{AgCl}$$

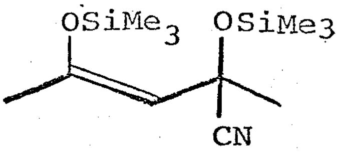
The use of Soxhlet apparatus is suitable for the preparation of moisture-sensitive silicon pseudohalides. The procedure of the filtration to remove silver chloride from the reaction mixture was made unnecessary by the use of Soxhlet apparatus. This is not only convenient but also prevents the product from contamination with siloxane oligomers arising from the hydrolysis of hygroscopic difunctional silanes($\mathrm{Me_2SiCl_2}$, $\mathrm{Me_2Si(CN)_2}$).

The present procedure is also applicable to the preparation of trimethylcyanosilane, a useful reagent in organic synthesis,[14] from trimethylchlorosilane and silver cyanide. Fractional distillation to seperate hexamethylsiloxane(b.p. 99-100°) from the product(b.p. 114-117°) was not necessary.[15]

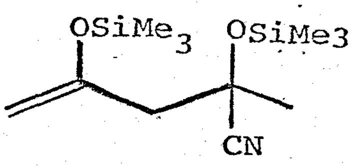
Nextly, we attempted the masking of carbonyl group of 1 by trimethylcyanosilane, prepared by above mentioned method. These reactions, however, always afforded significant amounts of isomeric product 3 in addition to desired 2.[17]



1 (E+Z)



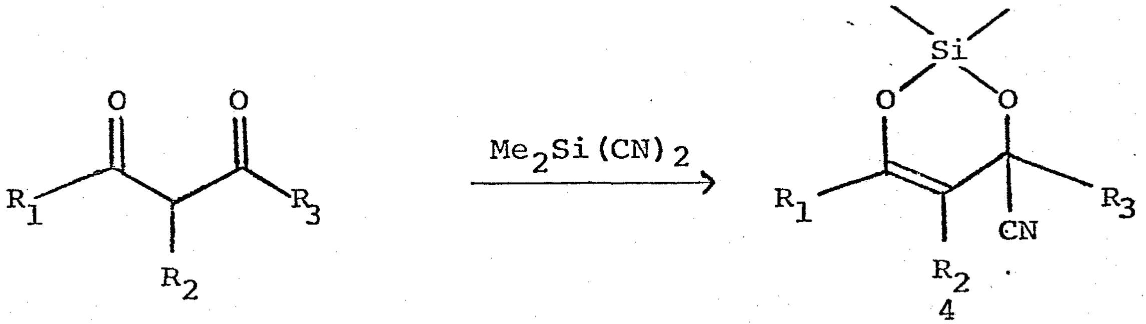
2 (E+Z)



3

To overcome this problem, the use of a bifunctional organosilicon reagent occurred to me, and we have developed a method for the preparation of analogs of 2 in an efficient and selective manner from β-diketones.

We made out that dimethyldicyanosilane[$Me_2Si(CN)_2$] readily reacts with β-diketones to give high yields of six-membered ring products, 4. The compounds 4 were the desired ones in which enol and carbonyl portions of β-diketones were concurrently silylated and cyanosilylated without generation of side products analogous to 3.



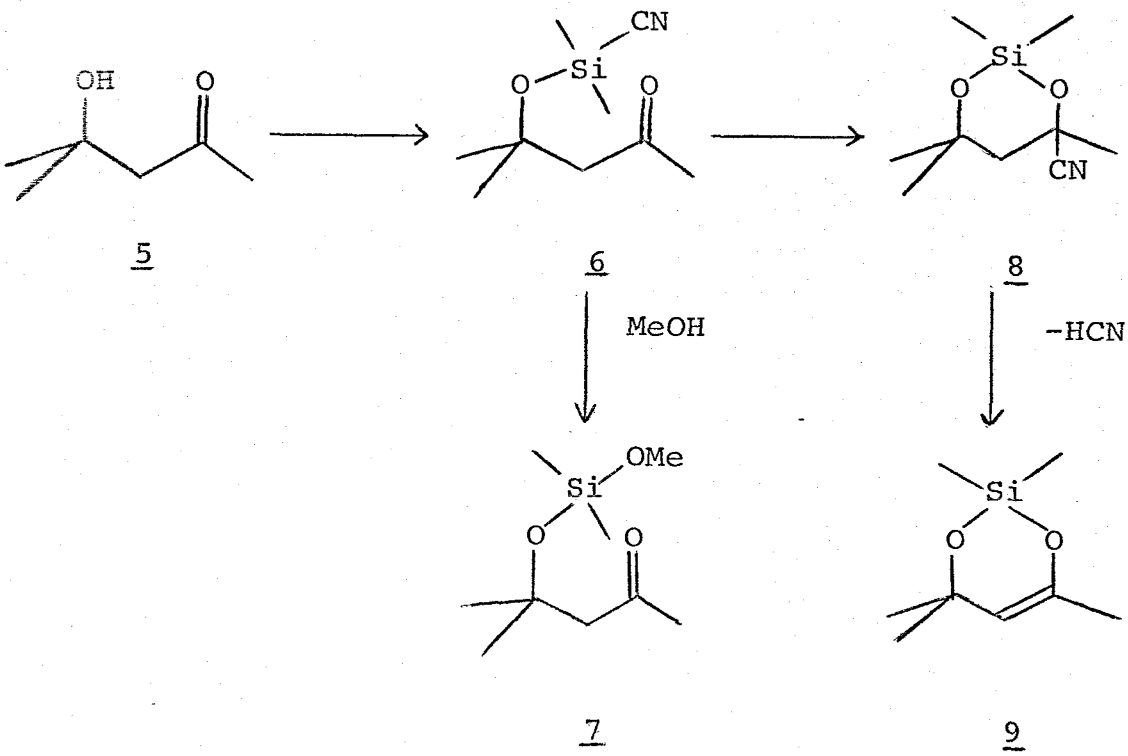
4

The reaction takes place exothermically with the evolution of hydrogen cyanide at room temperature to give 4. In a representative procedure dimethyldicyanosilane (12 mmol) is dissolved in dichloromethane (3 ml) and the solution is cooled to −40°C. The β-diketone (10 mmol) is slowly added to the solution by a hypodermic syringe, and the mixture is allowed to warm to room temperature over 1 hr. After removal of hydrogen cyanide and the solvent, purification is effected by distillation or recrystallization. The products obtained are very hygroscopic and should be manipulated under atomosphere of dry nitrogen. The results are summarized in Table I.

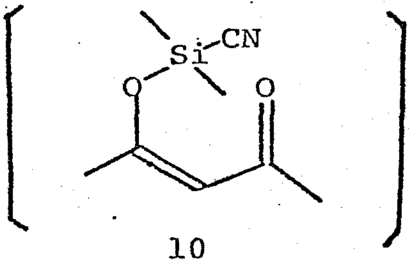
Except for the case of one difficultly enolized β-diketones[18] (entry 2 in Table I), the reaction proceeded immediately without any catalysts. The orientation of enolization in β-diketones is reflected in the structure of the products. In the case of β-diketones in which the orientation of enolization is ditinctly determined by conjugation, a single regioisomer was obtained (see entry 5 and also entries 7 and 8 in Table I).
It is noteworthy that the present reaction involves the silylation to give Z form product selectively, despite the fact that the other mathods for silylation of β-diketones give a mixture of E and Z isomers.[11]

The reaction of dimethyldicyanosilane with diacetone alcohol (5) in scheme 1 follows a path that may be consistent with that followed by the reaction described in this study. The major products of this reaction were 8 and 9.[19] The NMR spectrum of the reaction mixture after 1h showed the predominant formation of cyanoalkoxysilane 6, which seemed to be stable at low temperature (−30°C) and could be intercepted to afford dialkoxysilane 7 in 76 % yield upon treatment with methanol.[20]

Scheme 1



By analogy, the reaction of dimethyldicyanosilane with β-diketones may start with the silylation of enolic portion to give 10 followed by intramolecular cyanosilylation. However, we were unable to

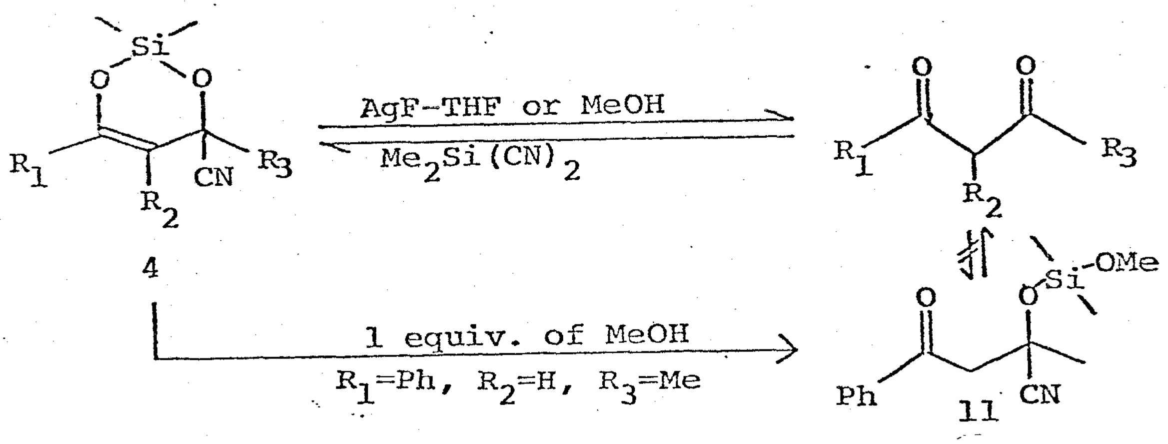


10

intercept the initial product 10 corresponding to 6. This suggests that the intramolecular cyanosilylation must be very fast in the case of 10.[21,22]

The six-membered ring products are moisture sensitive and can be easily converted to parent β-diketones on treatment with methanol or silver fluoride in THF (Scheme 2).[23]

Scheme 2

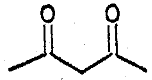
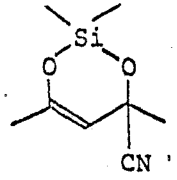
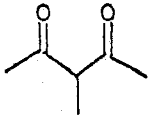
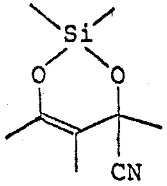
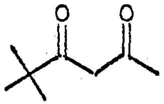
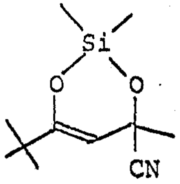
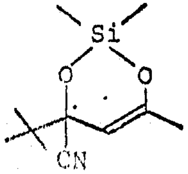


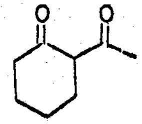
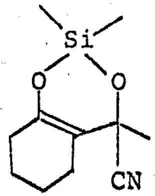
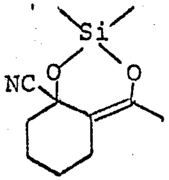
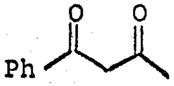
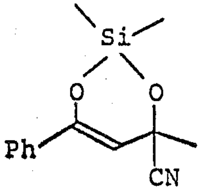
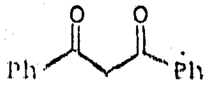
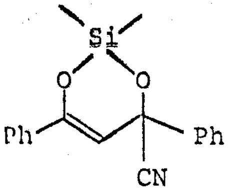
Interestingly, the reaction of the cyclic product of benzoyl acetone with one equivalent of methanol gave 11 in 76 % yield. This result implies that methanolysis proceeds stepwise (the enol silyl ether moiety was methanolized in the first stage). This partially methanolyzed product 11 has the structure of a mono-cyanosilylated β-diketone which appears to be otherwise inaccesible since the reaction of trimethylcyanosilane with β-diketones does not give mono-cyanosilylated products.[24]

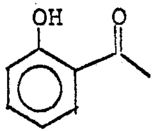
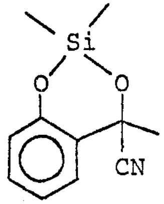
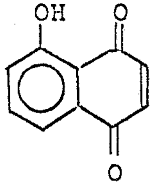
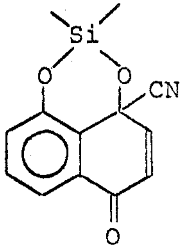
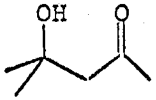
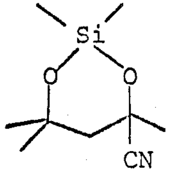
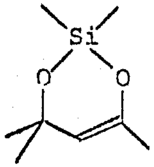
It should be noted that the present transformation may be useful for the protection of β-dicarbonyl or β-hydroxycarbonyl moieties. In addition, the results for juglone (entry 8) provides a new method of differentiation of one carbonyl group from the other.

Various synthetic applications of the product 4 may be envisaged.

Table 1 Concurrent Silylation and Cyanosilylation of β-Diketones and Related Compounds

Entry	β-Diketone	Products^{a}	Yield^{b} %	bp, °C (mp, °C)	IR, cm^{-1}	NMR (CCl_4), δ^{c}
1			91	87-90(20 mm)	1668	0.26 (s, 3H) 0.41 (s, 3H) 1.58 (s, 3H) 1.79 (s, 3H) 4.52 (s, 1H)
2^{d}			81	101-103(26 mm)	1663	0.24 (s, 3H) 0.35 (s, 3H) 1.66 (s, 3H) 1.70 (s, 3H) 1.85 (s, 3H)
3			86 (38:62)^{e}	108-110(23 mm)	1663	0.22 (s, 3H) 0.38 (s, 3H) 1.06 (s, 9H) 1.60 (s, 3H) 4.59 (s, 1H)
						0.22 (s, 3H) 0.38 (s, 3H) 1.01 (s, 9H) 1.84 (s, 3H) 4.55 (s, 1H)

4			98 (68:32)^{e}	109-111(7 mm)	1663	0.25 (s, 3H) 0.37 (s, 3H) 1.62 (s, 3H) 1.40- 2.50 (c, 8H)
						0.25 (s, 3H) 0.38 (s, 3H) 1.80 (s, 3H) 1.40- 2.50 (c, 8H)
5			97	101-104(0.3 mm)	1643	0.36 (s, 3H) 0.51 (s, 3H) 1.73 (s, 3H) 5.30 (s, 1H) 7.20- 7.58 (m, 5H)
6			95	(68.5-70.0)	1640	0.40 (s, 3H) 0.59 (s, 3H) 5.53 (s, 1H) 7.18- 7.80 (m,10H)

7^{f}			85	77-78(0.35 mm)	1610	0.32 (s, 3H) 0.43 (s, 3H) 1.89 (s, 3H) 6.70- 7.37 (m, 4H)
8^{f}			62	(132-134)	1637 1680	0.24 (s, 3H) 0.66 (s, 3H) 0.68 (d-d,2H) 7.09- 7.40 (m, 3H)
$9^{f,g}$		 8	7	63-64(8 mm)		0.14 (s, 3H) 0.26 (s, 3H) 1.28 (s, 3H) 1.59 (s, 3H) 1.61 (s, 3H) 1.99 (s, 1H) 2.03 (s, 1H)
		 9	41	56-58(38 mm)	1665	0.17 (s, 6H) 1.23 (s, 6H) 1.68 (s, 3H) 4.37 (s, 1H)

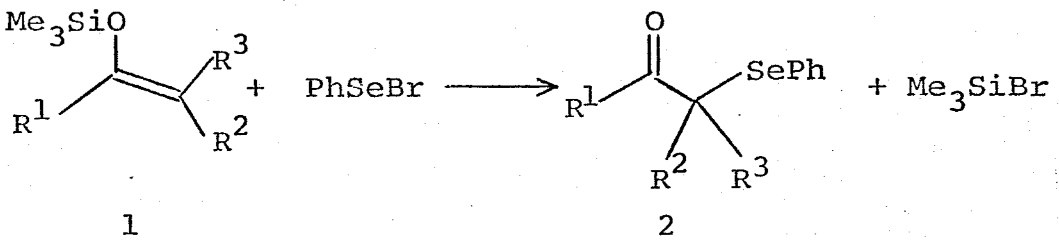
Footnotes of the Table 1

[a] All products except 8 gave satisfactory analytical data. [b] Isolated yields. [c] The assignment of structures is based on the fact that a methyl group on sp^3 carbon atom generally resonates at higher field than that on sp^2 carbon, for example, $(C\underline{H}_3)_2C(CN)OSiMe_3$: δ 1.54 (CCl_4) and $C\underline{H}_2{=}C(CH_3)OSiMe_3$: δ 1.67 (CCl_4). [d] Catalytic anount of zinc iodide was used. [e] Determined by NMR. [f] Two equivalents of dimethyldicyanosilane were used. [g] With one equivalent of Dimethyldicyanosilane, $(RO)_2SiMe_2$ (ROH=diacetone alcohol) was also formed: NMR(CCl_4) δ 0.12(s, 6H), 1.34(s, 12H), 2.11(s, 6H), 2.52(s, 4H).

1-4 Preparation and Silylation of α-Phenylseleno Ketones and Aldehydes

1-Siloxy-2-selenoalkenes are promising compounds to be utilized in synthetic reactions. Perhaps it seemed most popular to prepare these via silylation of α-seleno ketones. A convenient method for α-seleno ketones was developed. This method involves the reaction of enol silyl ethers with phenylselenenyl bromide. α-Phenylseleno carbonyl compounds are a useful precursor of α,β-unsaturated carbonyl compounds[25] and they have previously been prepared by either electrophilic reaction with $PhSe^+$, such as the reaction of enol esters with phenylselenenyl trifluoroacetate,[25c,25e,26] or by nucleophilic displacement represented by the reaction of ketone enolates with phenylselenenyl halides (PhSeCl, PhSeBr) or diphenyl diselenide.[25a,25c,27] From the viewpoint of convenience, direct α-phenylselenenylation of ketones and aldehydes with phenylselenenyl chloride (PhSeCl) is another attractive method. This reaction seems to have drawbacks with respect to generality or regiospecificity in the case of unsymmetrical ketones.[25c]

Described is the convenient method for the synthesis of α-phenylseleno ketones and aldehydes from the reaction of phenylselenenyl bromide and enol silyl ethers.[28]



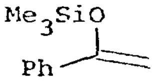
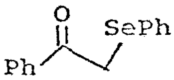
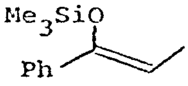
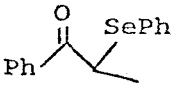
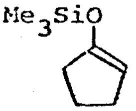
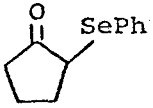
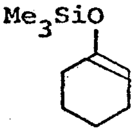
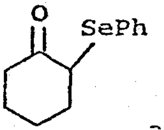
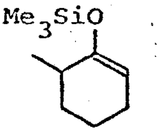
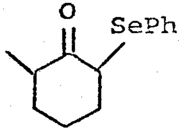
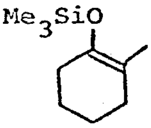
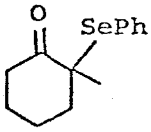
1 2

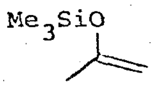
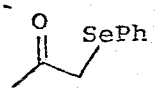
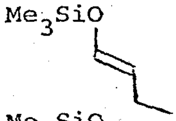
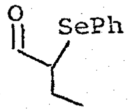
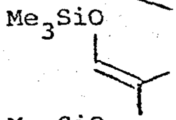
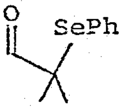
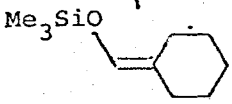
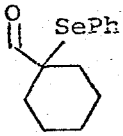
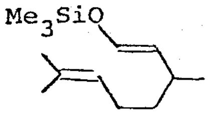
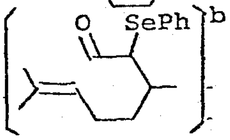
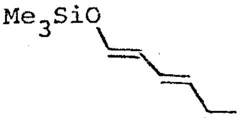
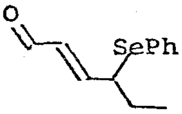
The present method has the following advantages; i) A wide variety of methods have been established for the synthesis of the starting enol silyl ethers. ii) Regiospecific introduction of phenylseleno groups can be attained (2e,2f). iii) Reaction conditions are very mild and essentially no side reaction has been observed. iv) The method is also suitable for the preparation of a large quantities of α-phenylseleno carbonyl compounds. v) The method can be applied to aldehydes (no condensation) (2h-2l). vi) Activation of PhSeBr (such as silver trifluoroacetate [25c,25e,26] is not necessary. The results are shown in Table 2 .

A typical experimental procedure for α-phenylseleno ketones is as follows. A solution of α-trimethylsiloxystyrene (10 mmol) in anhydorous ether (10 ml) was cooled to -70° with dry ice-acetone bath and then to this solution phenylselenenyl bromide (10 mmol) was added dropwise over 1 hr at the same temperature with stirring. After adding was completed, the mixture was allowed to warm to room temperature and subsequently solvent ether and trimethylbromosilane (b.p. 80°) were removed under reduced pressure (Method A). Recrystallization from n-pentane at 0° gave faint yellow needles of α-phenylselenoacetophenone in 91 % yield. Method A which uses nonaqueous work-up sometimes encountered the decomposition of the product accompanied with the formation of diphenyl diselenide.[29] Alternative procedure overcoming such difficulty was achieved by the use of aqueous treatment at -70°. After addition of PhSeBr, the reaction mixture was quickly poured into aqueous sodium bicarbonate solution (10 %). The mixture was extracted with ether, dried over sodium sulfate, and then evaporated in vacuo (Method B). The products obtained by the method B were sufficiently pure (N.M.R.) as not to require further purification. Traces of impurities (PhSeSePh, or hydrolysed ketone) were removed by either short path column chromatography or distillation. The reaction of silyl ether of citronellal (1k) afforded corresponding α-phenylseleno aldehyde with original double bond remained intact. The product, however, easily cyclized to 3 during work-up. Interestingly, in the case of silyl ether of trans-2-hexenal (1l), the selective introduction of phenylselenenyl group at γ-position of aldehyde could be attained (2l).

The silylation of α-phenylseleno ketones was carried out by the same procedure as described on that of kinetically controlled enolate of 2-methylcyclohexanone.

Table 2. α-Seleno Carbonyl Compounds from Enol Silyl Ethers and Phenylselenenyl Bromide.

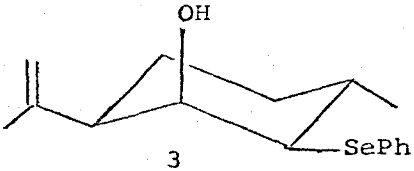
Substrate		Product		Yield(%)	Method
1a		2a		91	A
1b		2b		85	A
1c		2c		0-20 84	A B
1d		2d		69 91	A B
1e		2e	 [a]	35 77	A B
1f		2f		79	A

1g		2g		74	B
1h		2h		73	B
1i		2i		88	B
1j		2j		84	B
1k		2k		90[c]	B
1l		2l		80	B

[a] 1:1 of cis and trans isomers

[b] On treatment with column chromatography, 2k easily cyclized to give following β-phenylseleno alcohol.

N.M.R. (CCl_4); 1.08(d,3H) 1.69(s,3H)
2.10(s,1H) 2.89(dd,1H)
3.81(s,1H) 4.69(d,2H)
I.R. (cm^{-1}) 3470(OH) 1640(C=C)



3

c Yield which contained cyclized isomer 3.

Table 3. Physical Data for α-Phenylselenenyl Carbonyl Compounds

2	m.p. or b.p./torr (Lit,m.p.)	I.R.(cm^{-1}) νC=O	^{1}H-N.M.R.(CCl$_4$) δ(ppm)	Molecular formula[a]
a	31.5–33° (–)[3]	1660	4.21(s,2H)	–
b	34–35° (36.5–37°)[2a,2c,2d]	1675	4.59(q,1H,J=7Hz)	-
c	oil (oil)[2e]	1725	3.65(t,1H,J=7Hz)	-
d	53–54° (56–57.5°)[2e]	1695	3.80(t,1H,J=6Hz)	-
e	oil (oil)[2a,2c]	1700	3.82(br,1H) 4.01(dd,1H)	–
f	39–40°	1700	1.30(s,3H)	$C_{13}H_{16}OSe$ (267.2)
g	93–94°/4	1700	2.13(s,2H) 3.44(s,3H)	$C_9H_{10}OSe$ (213.1)
h	oil	1700	3.44(dt,2H,J=3, 7.5Hz) 9.42(d,1H,J=3Hz)	$C_{10}H_{12}OSe$ (227.2)
i	oil	1700	1.39(s,6H) 9.17(s,1H)	$C_{10}H_{12}OSe$ (227.2)
j	oil	1705	8.98(s,1H)	$C_{13}H_{16}OSe$ (267.2)
k	oil	1705	3.44(m,1H) 9.32(d,1H,J=4Hz)	$C_{15}H_{22}OSe$[b] (309.3)
l	oil	1680	3.71(dt,1H,J=8, 6Hz) 9.40(d,1H,J=8Hz)	$C_{12}H_{14}OSe$ (253.2)

a Compounds f-l are new and all gave satisfactory elemental analyses (C ±0.25 % H ±0.17 %).

elemental analyses

		C		H
f;	calc.	58.43		6.04
	found	58.65		5.95
g;	calc.	50.71		4.73
	found	50.56		4.76
h;	calc.	52.87		5.33
	found	52.87		5.50
i;	calc.	52.87		5.33
	found	52.86		5.20
j;	calc.	58.43		6.04
	found	58.43		6.17
k;	calc.	62.13		7.17
	found	62.24		7.23
l;	calc.	56.92		5.57
	found	56.67		5.55

b On standing 2k cyclizes to 3 easily, and therefore the sample measured might contained isomer 3.

1-5 Experimental

Silylation of Acetone

To a stirred solution of acetone (30 ml) and DBU (10 mmol) at 0° trimethylchlorosilane (10 mmol) was added dropwise over a period of 2 hr. Immediately DBU-HCl salt precipitated and the reaction was completed. Then distillation apparatus was fitted directly to the reaction vessel and the mixture was distilled. Fractional distillation with glass-packed vigreux column (25 cm) afforded 1-methyl-1-trimethylsiloxy-ethylene in 78 % yield (94-94°/760 torr). The use of DBU having high boiling point as base contributed to the simple isolation of enol silyl ether in this case. This method is also applicable to the silylation of acetaldehyde (final addition of acetaldehyde must be followed !).

Silylation of Kinetically Generated Enolate of 2-Methyl-Cyclohexanone[30]

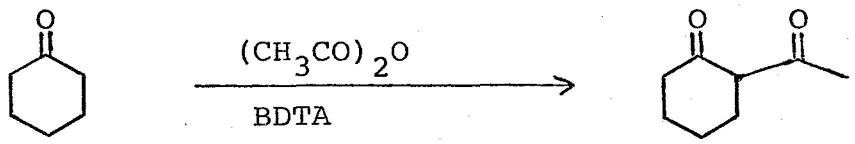
Diisopropylamine (31 g, 42 ml) in dry THF (160 ml) distilled from $LiAlH_4$ and deoxygenated prior to use was kept at 0° with Ice bath. Then, n-BuLi (0.3 mol) was added to it with a hypodermic syringe over a period of 10 min and stirred for 20 min at the same temperature (in situ preparation of $LiN(i\text{-}Pr)_2$). The mixture was cooled to -78 ° with Dry Ice-acetone bath and to the mixture were added dropwise 2-methylcyclohexanone (35.4 ml, 0.3 mol) and trimethylchlorosilane (44.4 ml). Then the mixture was allowed to warm to room temperature and stirring was continued for 30 min. The precipitated lithium chloride was filtered in dry nitrogen stream and the filtrate was evaporated under reduced pressure. The resultant residue was washed with dry ether (2×20 ml) and filtered again. Excess ether was evaporated under reduced pressure and the residue was distilled in vacuo to give 2-methyl-1-trimethylsiloxy-cyclohexene (93 %, b.p. 78-80°/20 torr).

General Informations for 1-2

Infrared spectra were recorded on Shimadzu IR-400. NMR spectra were taken on a Hitachi R-24B spectrometer or on a Japan Electron Optics JNM-PS-100 spectrometer (using Me_4Si as an internal standard in CCl_4 solution). Mass spectra were obtained on a Hitachi mass spectrometer Model RMU-6E. Elemental compositions were determined by high-resolution mass spectra (for gaschromatographically 100 % pure samples) which were measured using a Hitachi RMU-7M. GLC data were obtained with a Shimadzu GC-3BF equipped with a flame ionization detecter. Unless otherwise specified, the column used was a 3 mm × 3.8 m stainless steel column packed with 5 % OV-1 on Uniport KS.

β-Diketones were prepared according to the procedure of C. R. Hauser et al.[31] except commercially available acetyl acetone, benzoyl acetone, and dibenzoyl ketone.

Ex.



BDTA: Borontrifluoride-
diacetic acid complex

Dimethyldicyanosilane was prepared from silver cyanide and dimethyldichlorosilane and stored in dichloromethane solution.

Preparation of Dimethyldicyanosilane

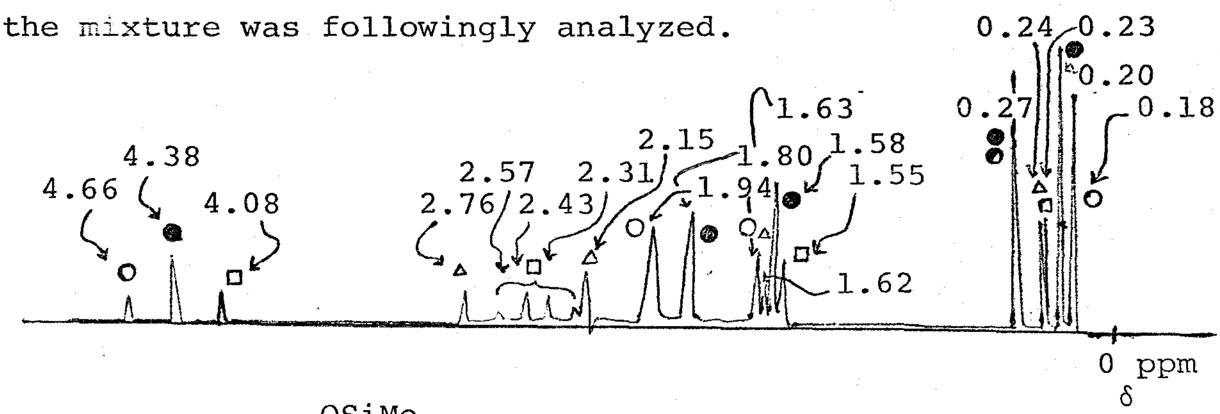
Dimethyldichlorosilane (90g, 0.7 mol) was placed in the bottom frask and silver cyanide (38g, 0.28 mol) in the cylindrical filter of the Soxhlet extracter, which was flame-dried under a dry nitrogen atomosphere prior to use. Then dimethyldichlorosilane was heated under reflux with an oil bath (120-140°) for 5 days. During the reaction, the upper part of the apparatus was wrapped with aluminium foil to protect silver cyanide from light. After excess dimethyldichlorosilane was recovered by distillation, the resultant hot residue was quickly transfered to a distillation apparatus having a wide-bore condenser. Distillation under reduced pressure gave a colorless liquid which immediately crystallized; yield: 13.1 g (85 %); m.p. 85-87° (Lit.[12] 80-83°); b.p. 108-109°/54 torr (Lit.[12] 165-170°/760 torr); IR(CH_2Cl_2) $\nu_{C\equiv N}$ 2180 cm^{-1}; NMR(CH_2Cl_2) δ 0.73 (s).

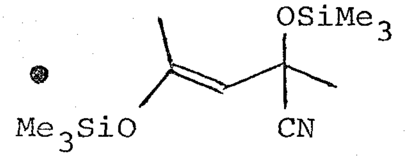
Preparation of Trimethylcyanosilane

Trimethylchlorosilane (80 g, 0.8 mol) and silver cyanide (33 g, 0.25 mol, in the cyrindrical filter) were placed in the flame-dried Soxhlet apparatus. Trimethylchlorosilane was heated under reflux for 4 days. The apparatus was protected from light by a cover of aluminium foil during the reaction. After removal of excess trimethylchlorosilane by distillation, trimethylcyanosilane was distilled; yield: 18.4 g (74 %); b.p. 114-117° (Lit.[15] b.p. 114-117°); IR(neat) $\nu_{C\equiv N}$ 2200 cm^{-1}; NMR(CCl_4) δ 0.37 (s).

Cyanosilylation of Monosilylated Acetyl Acetone in the Presence of Zinc Iodide

Unexpected contamination of isomer 3 was not reported by the other group. Monosilylated acetylacetone (E+Z) 1 (20 mmol) was treated with trimethylcyanosilane (22 mmol) in the presence of catalytic amount of zinc iodide at 100° (bath temperature) for 2.5 hr. Then the reaction mixture was distilled in vacuo to give a mixture of cyanosilylated products 2 (E+Z) and 3 in 83 % total yield (4.5 g, 58.5-60.0°/0.2 torr). Each product was isolated by preparative GLC (a Varian Aerograph Model 90-P using SF-96 at 180° (oven temp.)). NMR spectra of the mixture was followingly analyzed.



●


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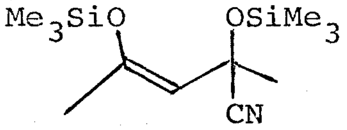
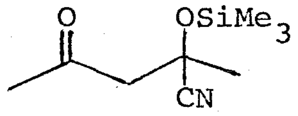
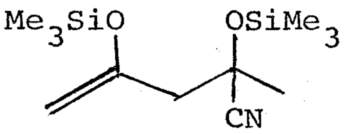


IR: 1670 cm^{-1} $(\nu_{C=C})$: m/e 271 (M^+), 256, 229, 157, 147, 84, 75, 73, 45, 43.

△


IR: 1730 cm^{-1} $(\nu_{C=O})$; m/e 184 (P-15), 166, 157, 147, 115, 94, 75, 73, 69, 47, 45, 43.

□


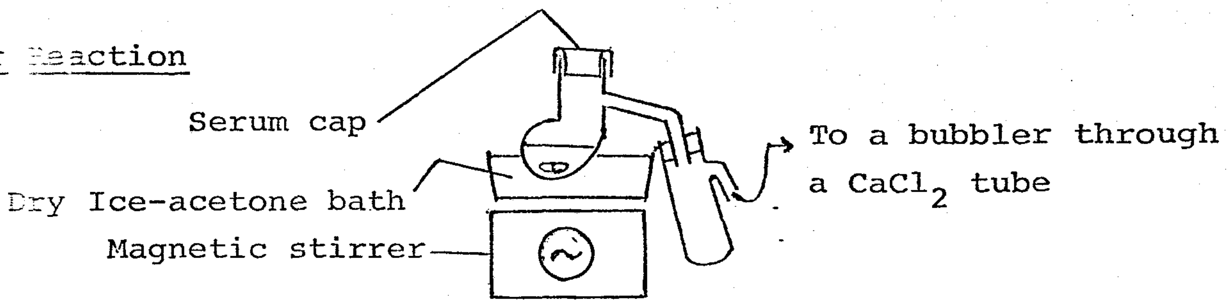
IR: 1640 cm^{-1} $(\nu_{C=C})$; m/e 271 (M^+) 256, 231, 157, 147, 115, 100, 75, 73, 45, 43.

Anal. Calcd for $C_{24}H_{25}OSiN$: C, 53.14; H, 9.23; N, 5.17. Found: C, 53.26; H, 8.97; N, 5.30.

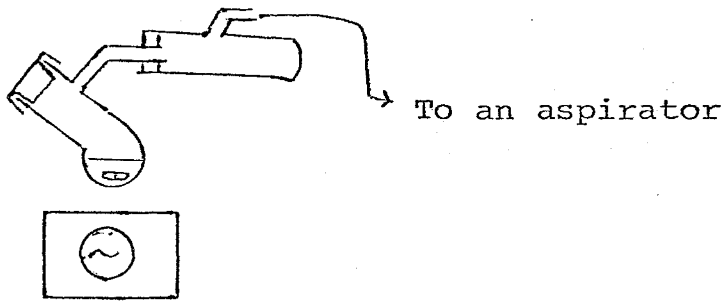
General Procedure for the Reaction of Dimethyldicyanosilane with β-Diketones

A reaction apparatus employed is displayed in the following. This apparatus can be used for reaction, evaporation of solvents, and distillation without transfer of the reaction product and the use of this contributed to the elevation in yields.

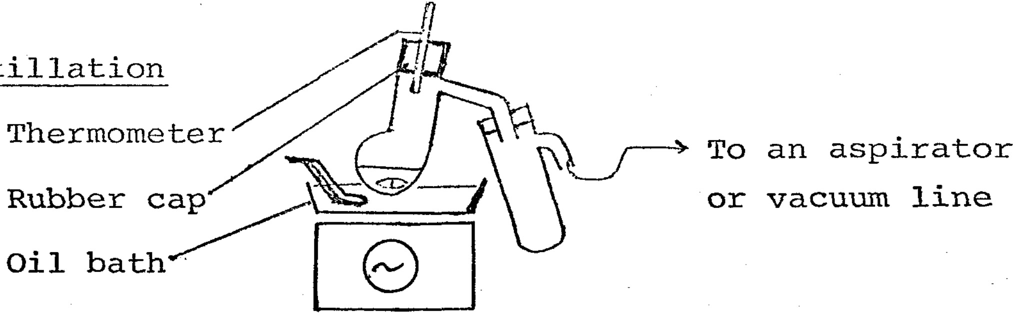
For Reaction



For Evaporation



For Distillation



Generally, to a magnetically stirred solution of dimethyldicyanosilane (1.32 g, 12 mmol) in methylene chloride (3 ml), β-diketone (10 mmol) (if necessary, dissolved in dichloromethane) with a hypodermic syringe under dry nitrogen atomosphere at -50° (Dry Ice-acetone bath). Stirring was continued till the temperature reached to room temperature over a period of 1 hr. Then the solvent was evaporated under reduced pressure by aspirater in which alkaline trap was attached. Vacuum distillation was undertaken using the same reaction vessel, as well as reaction and evaporation, to give six-membered ring products. Purity was checked by NMR. Purification was effected by distillation or recrystalization.

General Procedures for α-Phenylseleno Ketones and Aldehydes:

Method A.

In a 50 ml round bottomed flask fitted with a stirrer and a dropping funnel were placed the enol silyl ether (10 mmol) and anhydrous ether (10 ml). The solution was cooled to -70° with Dry Ice/acetone bath. Then phenylselenenyl bromide [(10 mmol); prepared in situ from equimolar of bromine and diphenyl diselenide,[25c] in anhydrous ether (20 ml) was added slowly (1 hr). The reddish brown color of phenylselenenyl bromide immediately diminishes upon addition. After the addition was completed, the reaction mixture was allowed to warm to room temperature. Ether and trimethylbromosilane (b.p. 80°) were removed under reduced pressure (20-0.5 torr). The resultant oily product was crystallized by the addition of pentane. Purification was achieved by recrystallization (pentane or hexane) or distillation.

Method B.

After the addition of phenylselenenyl bromide was completed as described above, the mixture was poured into 10 % aqueous sodium hydrogen carbonate solution (50 ml). The aqueous phase was extracted with ether (2 ×20 ml) and the combined ether extract was dried with sodium sulfate. After removal of the solvent, the residual oil was chromatographed on silica gel (Merck 60 mesh 35-70) using benzene as eluent or distilled.

1-6 References and Notes

(1) P.F. Hudrlik in "New Applications of Organometallic Reagents in Organic Synthesis," D. Seyferth Edi., Elsevier Scientific Publishing Company, Amsterdam, 1976, pp127-159; J. K. Rasmussen, Synthesis, 91 (1977).

(2) Y. Seki doctoral thesis, Osaka University, 1978.

(3) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 34, 2324 (1969).

(4) G. Stork and P. F. Hudrlik, J. Am. Chem. Soc., 90, 4462 (1968).

(5) L. T. Somdborn, Org. Syn. Coll. Vol. I, 340 (1932).

(6) M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. E. Stewart, Org. Syn. Coll. Vol. IV, 903 (1963).

(7) C. D. Nenitzescu and E. Cioršnescu, Chem. Ber., 69B, 1820 (1936).

(8) O. Grummit, J. Liska, and G. Greull, Org. Syn., Coll. Vol. V, 320 (1973).

(9) P. Pino and C. Botteghi, Org. Syn., 53, 1835 (1973).

(10) Improved procedure or modification. See experimental.

(11) S. Torkelson and C. Ainworth, Synthesis, 722 (1976) and refer-ences cited therein.

(12) J. J. McBride, Jr. and H. C. Beachell, J. Am. Chem. Soc., 74, 5247 (1952).

(13) J. Hundeck, Zeit. anorg. allgem. Chem., 345, 23 (1966).

(14) D. A. Evans and J. M. Hoffman, J. Am. Chem. Soc., 98, 1983 (1976); D. A. Evans, J. M. Hoffman, and L. K. Truesdale, ibid., 95, 5822 (1973); D. A. Evans, L. K. Truesdale, and G. L. Carroll, J. Chem. Soc., Chem. Commun., 55 (1973).

(15) Evans reported the preparation of trimethylcyanosilane from silver cyanide and trimethylchlorosilane by the modified method of MacDiarmid,[16] which required fractional distillation. D. A. Evans, G. L. Carrol, and L. K. Truesdale, J. Org. Chem., 39, 914 (1974).

(16) See reference 9 in (15).

(17) 3: ir(neat) 1640 cm^{-1}; NMR(CCl_4) δ 0.23(s, 18H), 1.55(s, 3H), 2.18-2.56(d-d, 2H), 4.08(s, 2H); MS m/e 271(M^+).

(18) For enolization of β-diketones see S. Forsen and M. Nilsson in "The Chemistry of the Carbonyl Group", Vol 2, J. Zabicky, Edi., Interscience Publishers, London, 1970, Chapter 3 and H. O. House, "Modern Synthetic Reactions" 2nd Ed., W. A. Benjamin, Menlo Park, Calif, 1972, pp 157-240.

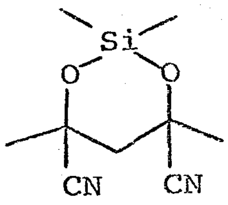
(19) It is not clear whether 9 was formed from dehydrocyanation of 8 or directly from 6.

(20) 6: NMR(CH_2Cl_2) δ 0.33(s, 6H), 1.34(s, 6H), 2.06(s, 3H), 2.56 (s, 2H). 7: ir 1720 cm^{-1}; NMR(CCl_4) δ 0.07(s, 6H), 1.33(s, 6H), 2.09(s, 3H), 2.48(s, 2H), 3.39(s, 3H); MS m/e 189 (P-15).

(21) Well accepted 1,6-interaction of silicon and oxygen may be responsible for this. See T. J. Pinnavaia and J. A. McClarin, J. Am. Chem. Soc., 96, 3012 (1974) and references cited therein.

(22) The possibility that the initial formation of doubly cyanosilylated product (i) followed by dehydrocyanation might afford 4 is not precluded at the present stage.

(i):



(23) For example, the parent β-diketone of 5-cyano-1,1,3,5-tetramethyl-2,6-dioxa-1-silacyclohex-3-ene was regenerated on treatment with methanol (2 ml for 4 mmol of 4) in 85 % (r.t., 20hr).

(24) The reaction of trimethylcyanosilane with one equivalent of acetyl acetone gave the enol silyl ether 1 (E+Z) in a high yield.

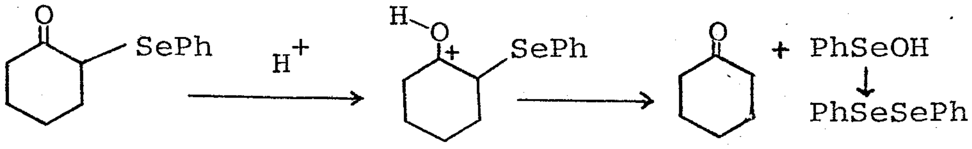
(25) (a) H. J. Reich, J. M. Lenga, and I. L. Reich, J. Am. Chem. Soc., 95, 5813 (1973); (b) idem., J. Org. Chem., 39, 2133 (1974); (c) idem., J. Am. Chem. Soc., 97, 5354 (1975); (d) K. B. Sharpless, R. F. Lauler, and A. Y. Teranishi, ibid., 95, 6137 (1975); (e) D. L. J. Clive, J. C. S. Chem., Commum., 659 (1973).

(26) H. J. Reich, J. Org. Chem., 39, 428 (1974).

(27) Various methods for α-seleno ketones are summarized in ref. 25c. Nucleophilic selenium reagent RSe^-Na^+ is also often used.

(28) Reich has mentioned briefly that the reaction of enol silyl ethers with PhSeBr may give α-seleno ketones. (see footnote 46 in ref. 25a). Neither details nor examples of the reaction have, however, been published, to the best of our knowledge.

(29) Under acidic conditions, α-phenylseleno ketones might decompose to give diphenyl diselenide.



(30) Ainworth used THF for silylation of esters with LiN(i-Pr)$_2$. C. Ainworth and Y. -N. KuO, J. Org. Metal. Chem., 46, 59 (1972).

(31) C-L. Mao, F. C. Frostick, Jr., E. H. Man, R. M. Manyik, R. L. Wells, and C. R. Hauser, J. Org. Chem., 34, 1425 (1969).

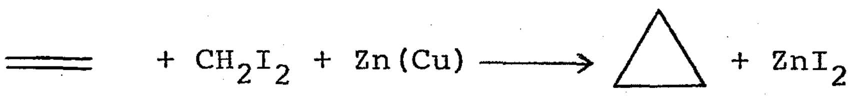
Chapter 2 Cyclopropanation of Enol Silyl Ethers

2-1 Introduction

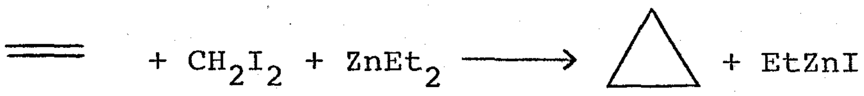
Cyclopropyl silyl ethers are potential precursors of cyclopropanols.[1] In addition, cyclopropyl silyl ethers have found a wide application in organic synthesis.[2] Therefore, the establishment of the convenient and general method for the preparation of these compounds must be intrinsically important and this ensures many synthetic applications still undeveloped. On the basis of the established method for the synthesis of cyclopropyl silyl ethers in this chapter, a variety of trials for developing new transformations of them will be further referred in Chapter 4.

The most common and useful method for the preparation of cyclopropyl silyl ethers must be cyclopropanation reaction of enol silyl ethers with zinc carbenoid reagents frequently used for the synthesis of cyclopropanes from olefins. The Simmons-Smith reaction developed by Simmons and Smith is the representative zinc carbenoid reagent available for cyclopropane synthesis.[3]

(1) Simmons-Smith reagent



(2) Furukawa reagent



This method has been known by having no side reaction which is observed with free carbenes. The only by-product in this reaction is zinc iodide(ZnI_2), which has been regarded as a substant of no importance or rather troublesome, since it occasionally lowers the yields by initiating the polymerization of starting olefins.

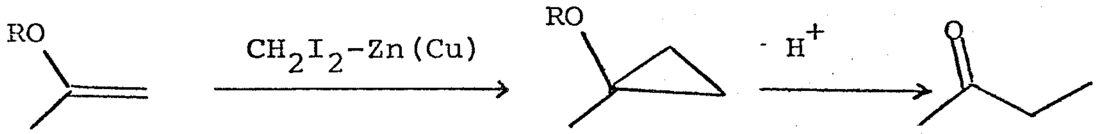
Diethylzinc-methylene iodide, called Furukawa reagent is another representative zinc carbenoid reagents.[4,5] This modificated method of Simmons-Smith reaction has various improved aspects: higher yields, milder reaction conditions, plural solvents being available, available for alkylidene transfer without decrease in yields, etc. Reactive species in this system seem to be fairly different from those in the Simmons-Smith reaction. Usually ethylzinciodide(EtZnI) is supposed to be a by-product of this reaction.

Many reports on the cyclopropanation of enol ethers using either zinc carbenoid reagent have been known up to now.[6] In principle the reaction of enol silyl ethers may be considered as analogous reaction of them. The purpose of this chapter involves the establishment of the reaction conditions for cyclopropyl silyl ethers, which can be expected as potential intermediates in organic synthesis.

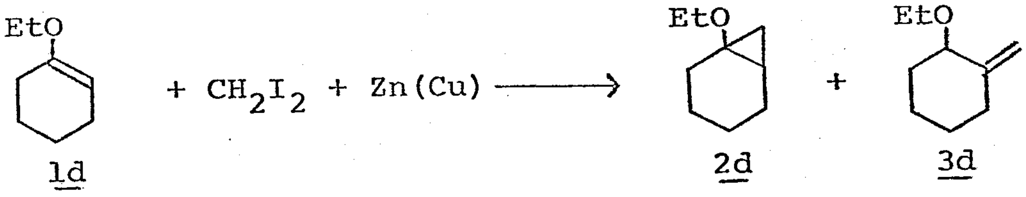
This chapter starts with the reinvestigtion of the Simmons-Smith reaction of cyclic enol ethers in which the reliability as general method for cyclopropanation seems to have been established by various previous works.

2-2 The Simmons-Smith Reaction of Enol Ethers

There have been many reports on the cyclopropanation of enol ethers with the Simmons-Smith reagent.[6] The cyclopropyl ethers obtained by this reaction can be converted to α-methyl ketones by hydrolysis,[7] and such a transformation has been utilized in the synthesis of steroids or terpens.[8] The reliability of this reaction in a sense that it gives cyclopropyl ethers without trouble seems to have been established by these previous works.

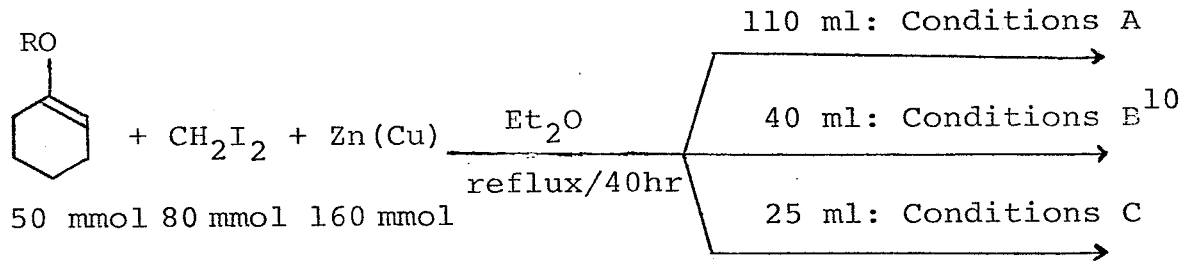


Contrary to the general understanding so for accepted, however, it has been found that the Simmons-Smith reaction of cyclic enol ethers usually gives two types of products, i. e., cyclopropyl ethers and their allylic isomers. For example, the Simmons-Smith reaction of 1-ethoxycyclohexene under a certain reaction conditions gave 1-ethoxy-2-methylene-cyclohexane (3d) besides an expected cyclopropanated product, 1-ethoxybicyclo-[4.1.0]heptane. (2d).

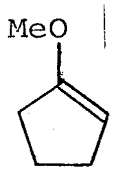


To my knowledge there has been almost no description of the formation of non-cyclopropyl compounds in the literature previously reported and this led us to reinvestigate the Simmons-Smith reaction of enol ethers in detail.

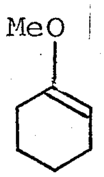
As the representative enol ethers, five and six membered, methoxy and ethoxy compounds (1a-1d) were prepared for the present systematic study.[9] Three kinds of reaction conditions (A, B, and C) were employed according to the concentration of reaction mixture, for preliminary experiments showed the notable dependence of product distribution on it. The differences in them are only those in the amounts of the solvent used as indicated in the following way.



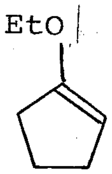
Generally, to a suspension of zinc-copper couple (160 mmol)[11] in anhydrous ether (reaction conditions A, 110 ml; reaction conditons B; 40 ml; reaction conditions C; 25 ml) were added an enol ether 1 (50 mmol) and methylene iodide (80 mmol) and then the mixture was refluxed for 40 hr. The results are give in the Table 1.



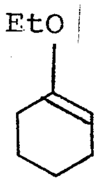
1a



1b

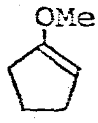
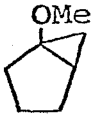
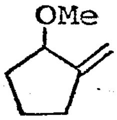
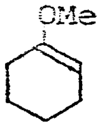
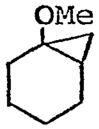
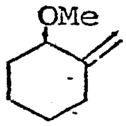
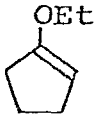
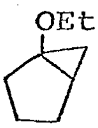
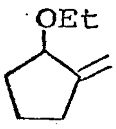
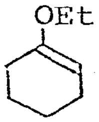
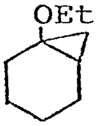
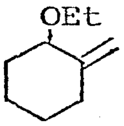


1c



1d

Table 1. The Simmons-Smith Reaction of Enol Ethers 1a-1d.

Enol Ether	Conditions[a]	Products[b] and Rel. %				Total yield[c] (%)
1		2		3		
 1a	A		99		1	73
	B		87		13	60
	C		29		71	62
 1b	A		98		2	72
	B		83		17	59
	C		2		98	66
 1c	A		86		14	69
	B		46		54	87
	C		4		96	63
 1d	A		86		14	66
	B		44		56	87
	C		2		98	79

[a] Reaction conditions: enol ether, 50 mmol; methylene iodide, 80 mmol; Zn(Cu), 160 mmol; ether, 110 ml(A), 40 ml(B), or 25 ml (C); ether reflux; 40 hr.

[b] Determined by GLC. [c] Isolated yields.

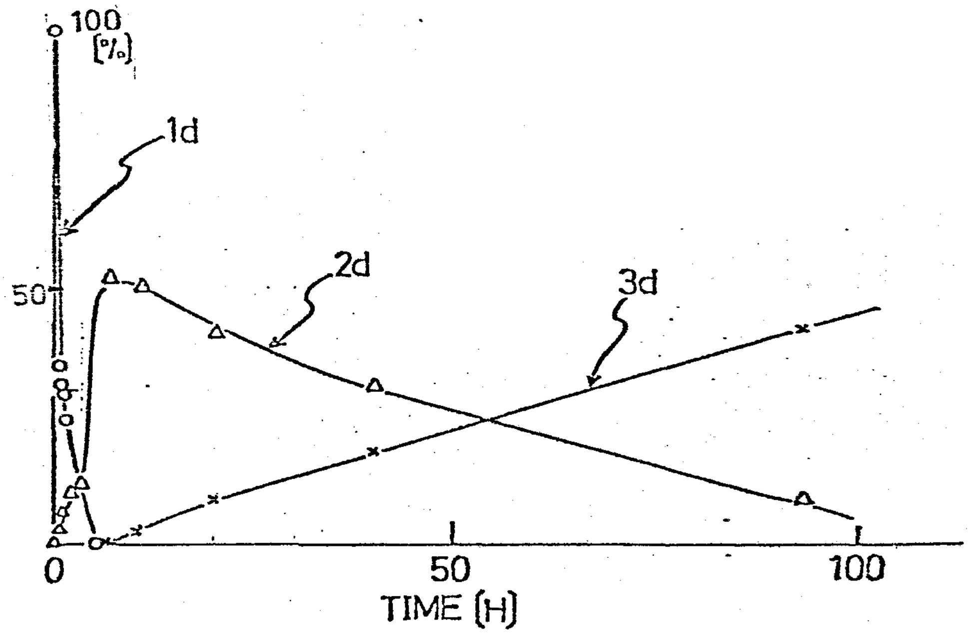
Formation of allylic ethers was observed in all cases studied (see the Table 1).[12] The results are reproducible. The assignment of the structure of allylic ethers (3) follows clearly from the spectral data, for example, 1-methoxy-2-methylene-cyclopentane 3a has following spectral properties: m/e 112 ($M^{\ddagger}$); i.r.(neat) 1650 cm^{-1} ($\nu_{C=C}$); N.M.R.(CCl_4) δ 4.95 ($=CH_2$).

Under the reaction conditions A, the normal products 2 were obtained as major ones, whereas the allylic products 3 predominated under the reaction conditions C. Thus, the selective formation of allylic ethers 3 was performed by merely adopting the reaction conditions of the highest concentration.

The forming process of unusual isomers 3 was ascertained to be resulted by the further isomerization of initially formed cyclopropyl ethers 2. A time course study of the Simmons-Smith reaction of 1-ethoxycyclohexene (1d) was undertaken (the reaction conditions employed fall in the range of 'standard' conditions). As clearly shown in the next Figure 1, the allylic isomer 3d was found to be obtained from the initially formed cyclopropyl ether 2d. Zinc iodide which was produced concomitantly (not shown in Figure 1) with the consumption of zinc carbenoid in this reaction system seemed to play an important role for the present cyclopropyl allylic isomerization. In fact, only in the presence of zinc iodide, isolated cyclopropyl ethers isomerized to allylic ethers in ether at 34°.

It seems important characteristic that one can obtain each product selectively by merely changing the amounts of the solvent.

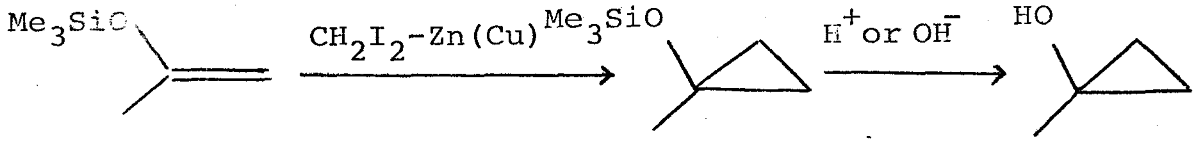
Figure 1. Time Course of the Simmons-Smith Reaction of 1d.



Reaction conditions: 1d (80 mmol), zinc-copper couple (160 mmol), methylene iodide (120 mmol), p-tolyl methyl ether (160 mmol), diethyl ether (40 ml), ether reflux.

2-3 Synthesis of Cyclopropyl Silyl Ethers by the Reaction of Enol Silyl Ethers with Simmons-Smith Reagent

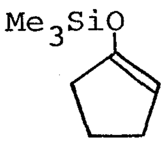
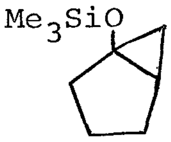
For the purpose of developing general and convenient method for the synthesis of cyclopropanols the Simmons-Smith reaction of enol silyl ethers was first carried out by this and the others.[2a-2d]

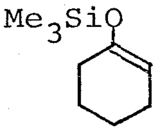
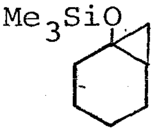
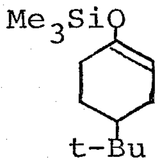
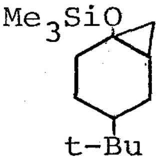
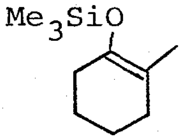
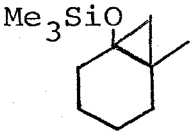
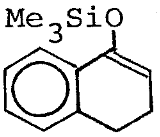
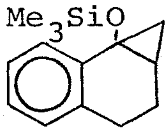
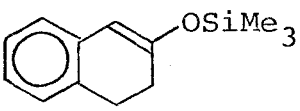
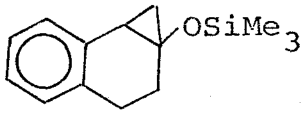
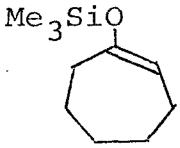
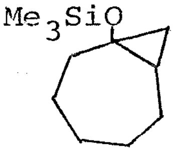
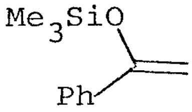
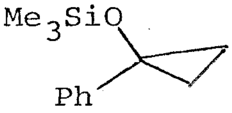
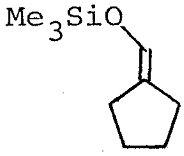
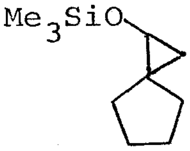
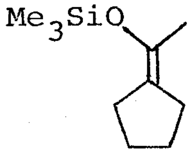
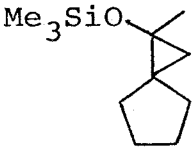
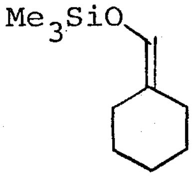
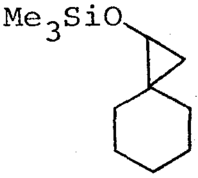


Importance of the establishment of the procedure for the cyclopropanation of enol silyl ethers is ascribed not only to cyclopropanol synthesis but to versatile availability of cyclopropyl silyl ethers as potential intermediates in organic synthesis. Cyclopropyl silyl ethers are more stable both chemically and thermally than corresponding cyclopropanols and there exists nothing troublesome in dealing with.

It was made out that good purities of cyclopropyl silyl ethers can be obtained through the Simmons-Smith reaction which employed 'diluted' reaction conditions A. Results are shown in the Table 2.

Table 2. The Simmons-Smith Reaction of Enol Silyl Ethers 1 under Reaction Conditions A.[a]

	Enol silyl ether 1	Cyclopropyl ether 2	Yield[b] %	(purity[c,d]) (%)
e			76	(97)

f			71	(92)
g			80[e]	(91)
h			73	(100)
i			65	(100)
j			64	(99)
k			61	(100)
l			43	((100)
m[f]			87[g]	(100)
n[f]			78[g]	(100)
o[f]			58[g]	(100)

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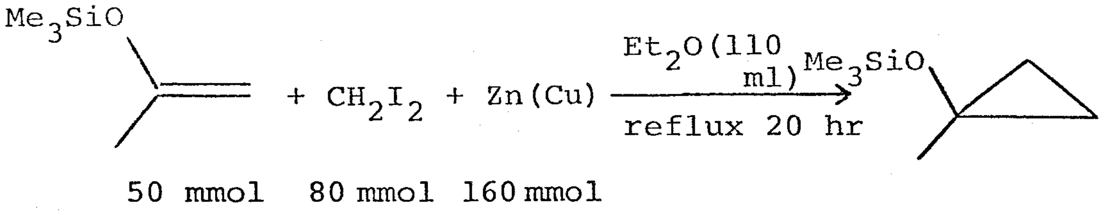
[a] See text. [b] Isolated yield. [c] Determined by GLC.
[d] Impurity was due to the corresponding allylic isomer.
[e] A mixture of stereo isomers(1:1). [f] One tenth reaction scale.
[g] Yield estimated from GLC.

The reactions were carried out for 40 hr under ether refluxing. Under these conditions, minor process involving isomerization cannot be entirely discounted in the case of 1e, 1f, 1g, and 1j in the Table 2.

As an improved method overcoming this difficulty, shortening the reaction time may be recommended. Namely, usually the Simmons-Smith reaction of enol silyl ethers completed within 20 hr, except for rare delayed cases because of occasional inefficiency of the generation of zinc carbenoid species.

Contamination by isomerized allylic isomers has never been detected in the case of runs 1h, 1i, 1l, and 1o even under the 'concentrated' conditions, and therefore attentions to reaction conditions need not be payed in these cases.

The established procedure summarized below offers the general methods for the preparation of cyclopropyl silyl ethers.



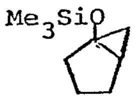
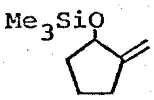
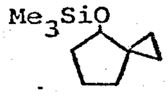
2-4 Synthesis of Cyclopropyl Silyl Ethers by the Reaction of Enol Silyl Ethers with Furukawa Reagent

As referred in the Introduction of this chapter, reaction species from diethylzinc and methylene iodide (Furukawa reagent) seems to be fairly different from those from Simmons-Smith reagent. A by-product of the reaction with this reagent can be tentatively regarded as ethylzinciodide (EtZnI). While, diethylzinc operates as divalent species to one equivalent of methylene iodide, the use of diethylzinc smaller to one equivalent of methylene iodide must bring the formation of zinc iodide as a by-product. Moreover, the postulation of the following equations between ethylzinciodide and zinc iodide has been accepted so far.[13]

$$\mathrm{EtZnI} \rightleftharpoons \mathrm{ZnI_2} + \mathrm{ZnEt_2}$$

All these strongly demonstrate the possibility of occurrence of isomerization in this reaction system as well as that of Simmons-Smith reaction. This proved to be the case. In the following is the results of 1-trimethylsiloxycyclopentene with diethylzinc-methylene iodide in benzene under several reaction conditions in which only the amounts of diethylzinc were differentiated while the others were unchanged. Interestingly, these reactions always afforded three kinds of products, i. e. cyclopropyl silyl ether, allyl silyl ether, and spiro-type of silyl ether. No doubt the formation of spiro ether is due to the cyclopropanation of allylic isomers. The obvious tendency that decrease in the amounts of diethylzinc used resulted in the increase in the product molar ratio of allylic ether and spiro ether was observed. This fact strongly demonstrated that the isomerization to allylic ethers in this reaction system may be ascribed to the formation of zinc iodide as a by-product.

Table 3. Molar ratio-dependent on Product Distribution.

$ZnEt_2$ (m mol)	 2e	 3e	 4e
15	92 %	8 %	
10	84	16	
5	55	45	

Reaction conditions: 1e (5 mmol), methylene iodide (6 mmol), benzene (3 ml), 20 °C, 20 hr.

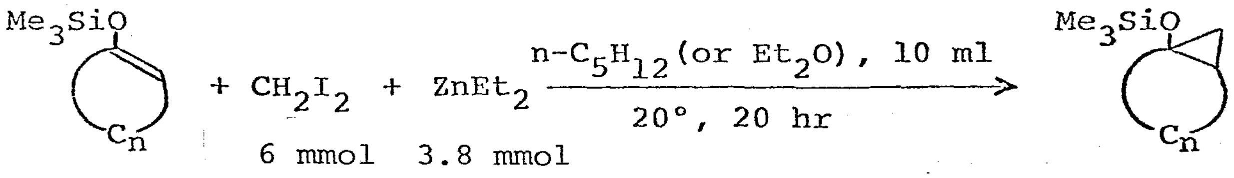
Nextly, changing the solvent (anisole, benzene, n-pantane, or diethyl ether), the reaction of 1-siloxycyclopentene with Furukawa reagent was carried out. The employed reaction conditions locates in the range of 'diluted' conditions. It is

Table 4. The Reaction of 1e with Diethylzinc-Methylene Iodide.[a]

Solvent	Product Distribution (rel %)[b]			Total Yield (%)[b]
	2e	3e	4e	
anisole	48	48	4	78
benzene	44	46	10	75
n-pentane	98	2	0	81
Et_2O	99	1	0	70

[a] Reaction conditions: 1e (5 mmol), methylene iodide (6 mmol), diethylzinc (3.8 mmol), solvent (10 ml), 20 °C, 40 hr.
[b] Determined by GLC

turned out from the result that the use of ether, or n-pentane as a solvent is the most suitable for the selective preparation of cyclopropyl silyl ethers, while the use of aromatic solvent brings a contamination of allylic ether and spiro ether (see Table 4). And this led to the establishment of the reaction conditions for the selective synthesis of cyclopropyl silyl ethers using these solvents (n-pentane or diethyle ether). Established conditions for five, six, or seven membered cyclopropyl silyl ethers are summarized in the next equation.



n=3,4,5
5 mmol

purity 98-100 %

Yield in n-C_5H_{12} (Et_2O)

n=3	81 (70) %
n=4	82 (78) %
n=5	75 (79) %

2-5 Experimental

General Informations.

Boiling poins are not corrected. Infrared spectra were recorded on a Shimadzu IR-400 as neat liquids. NMR spectra (100 MHz) were recorded on a Japan Electron Optics JNM-PS-100 spectrometer (using Me_4Si as an internal standard in CCl_4 solution). Mass spectra were obtained on a Hitachi mass spectrometer Model RMU-6E. Elemental compositions were determined by high-resolution mass spectra (for gaschromatographically ~100 % pure samples) which were measured using a Hitachi RMU-7M or by elemental analyses which were performed by the analytical center of this department. GLC data were obtained with a Shimadzu GC-3BF equipped with a flame ionization detecter. Unless otherwise specified, the column used was a 3 mm × 3.8 m stainless steel column packed with 5 % OV-1 on Uniport KS or 10 % SE-30 on Chromosorb W. The purification of analytical samples in preparative scales was made with a Varian Aerograph Model 90-P.

General Procedure of the Simmons-Smith Reaction of Enol Ethers 1a-1d.

Enol ethers 1a-1d were prepared by the method of Wohl. Diethyl ether was dried with DRYNAP^R(Na-Pb alloy, Wako Chem. Co.) and distilled prior to use. Zinc-copper couple was made in situ by the procedure of Rawson.

Zinc powder(10.4 g, 0.16 g-atom) and cuprous chloride(1.60 g, 16 mmol) in anhydrous ether(A: 110 ml; B: 40 ml; C: 25 ml) was stirred under reflux maintaining anhydrous conditions. After 2 hr an enol ether (0.05 mol) and methylene iodide(21.4 g, 0.08 mol) were added successively, the mixture was heated at reflux filtrate was washed twice with 50 ml of cold saturated ammonium chloride and the aqueous layer was extracted twice with two 20 ml portions of ether. Combined extract was washed with cold saturated sodium bicarbonate solution (50 ml), then with cold water (2×50 ml). The ether extract was dried over magnesium sulfate and the solvent was removed at reduced pressure, then the residual oil was distilled. When necessary, pure samples were obtained by preparative GLC.

Spectral data for cyclopropyl ethers. 2a: b.p. 74°C/114 mm; IR 3020 cm^{-1}; NMR δ 0.50(d-d, 1H), 0.70(d-d, 1H), 0.90-2.10(m, 7H), 3.25(s, 3H); MS *m/e* 112(m^+). (Found: m^+ *m/e* 112.0889. Calc. for $C_7H_{12}O$: 112.0887).

2b: b.p. 104°C/134 mm; IR 3030 cm^{-1}; NMR δ 0.03(d-d, 1H), 0.17 (d-d, 1H), 0.50-2.30(m, 9H), 3.12(s, 3H); MS *m/e* 126(m^+). (Found: C, 75.96; H, 11.48. Calc. for $C_8H_{14}O$: C, 76.14; H, 11.18)

2c: b.p. 74-75°C/75 mm; IR 3020 cm^{-1}; NMR δ 0.45(d-d, 1H), 0.70 (d-d, 1H), 0.90-2.10(m, 7H), 1.12(t, 3H), 3.45(q, 2H); MS *m/e* 126(m^+). (Found: m^+ *m/e* 126.1014. Calc. for $C_8H_{14}O$: 126.1043).

2d: b.p. 59°C/18 mm; IR 3030 cm^{-1}; NMR δ 0.14(d-d, 1H), 0.75 (d-d, 1H), 0.75-2.20(m, 9H), 1.19(t, 3H), 3.39(q, 2H); MS *m/e* 140 (m^+). (Found: C, 76.96; H, 11.61. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.43).

Spectral data for allylic ethers. 3a: b.p. 104°C/134 mm; IR 1650 cm^{-1}; NMR δ 0.90-2.45(m, 6H), 3.24(s, 3H), 3.65-3.85(c, 1H), 4.95(s, 2H);;MS *m/e* 112(m^+). (Found: m^+ *m/e* 112.0877. Calc. for $C_7H_{12}O$: 112.0886).

3b: b.p. 72-73°C/48 mm; IR 1660 cm^{-1}; NMR δ 1.20-2.30(m, 8H), 3.15(s, 3H), 3.50(c, 1H), 4.72(s, 2H); MS *m/e* 126(m^+). (Found: C, 76.26; H, 11.49. Calc. for $C_8H_{14}O$: C, 76.14; H, 11.18).

3c: b.p. 53-54°C/28 mm; IR 1650 cm^{-1}; NMR δ 1.15(t, 3H), 1.40-2.55(m, 6H), 3.28(d-q, 2H), 3.85(c, 1H), 4.90(s, 2H); MS *m/e* 126(m^+). (Found: m^+ *m/e* 126.1034. Calc. for $C_8H_{14}O$: 126.1043).

3d: b.p. 87-88°C/ 73 mm; IR 1658 cm^{-1}; NMR δ 0.90-2.55(m, 8H), 1.15(t, 3H), 3.32(d-q, 2H), 3.60(c, 1H), 4.72(s, 2H); MS *m/e* 140(m^+). (Found: C, 76.72; H, 11.19. Calc. for $C_9H_{16}O$: C, 77.09; H, 11.43).

A Time Course of the Simmons-Smith Reaction of 1-Ethoxycyclohexene (1d).

To a stirred suspension of zinc-copper couple(10.4 g, 0.16 g-atom) in anhydrous ether(40 ml) were added 1d(10.24 g, 0.08 mol) and p-tollyl methyl ether(19.52 g, 0.16 mol) to serve as the internal standard.

Methylene iodide(32.16 g, 0.12 mol) was added to the mixture and then the mixture was heated at reflux. A small aliquot of the mixture was withdrawn occasionally by a syringe, treated with cold saturated ammonium chloride solution, and analyzed by GLC (10 % PEG 20M on Chromosorb W, 3 mm × 3m). The results are shown in the Figure 1.

Synthesis of Cyclopropyl Silyl Ethers by Simmons-Smith Reaction. The procedure is the same as the Simmons-Smith reaction of enol ethers under the reaction conditions A ('diluted'). Zinc powder (10.4 g, 0.16 g-atom) and cuprous chloride (1.60 g, 16 mmol) in anhydrous ether (110 ml) was stirred under reflux for 2 hr. Then an enol silyl ether (0.05 mol) and methylene iodide (21.4 g, 0.08 mol) were added dropwise. The reflux was continued for 40 hr. The cooled mixture was filtered and the filtrate was washed with cold saturated ammonium chloride solution (2×50 ml), cold saturated sodium bicarbonate (50 ml), and water (2×50 ml). The combined extact was dried over magnesium sulfate. After removal of the solvent, the residue was distilled in vacuo to give cyclopropyl silyl ether 2.

The Reaction of 1-Trimethylsiloxycyclopentene (1e) with Diethylzinc-Methylene Iodide in Benzene. ——Molar Ratio Dependence on Product Distribution.

The reaction was carried out in a round bottom 30 ml flask equipped with a magnetic stirrer, reflux condenser with calcium chloride drying tube, gas-inlet with 3-way cock under N_2 atom. To the stirred solution of 1-trimethylsiloxycyclopentene (1e) (0.78 g, 5 mmol) and dry benzene (3 ml) was added diethylzinc (5, 10, 15 mmol) by the use of hypodermic syringe in dry nitrogen stream. Then, methylene iodide (1.61 g, 6 mmol) was added dropwise with hypodermic syringe through 3-way cock at room temperature (caution to exotherm!). Stirring was continued for 20 hr. Then the mixture was treated with NH_4Cl, $NaHCO_3$, and H_2O, and dried over magnesium sulfate. After evaporation, the residual oil was analyzed by GLC (OV-1, 100°).

The Reaction of 1-Trimethylsiloxycyclopentene (1e) with Diethylzinc-Methylene Iodide.

To a stirred solution of 1e (0.78 g, 5 mmol) and diethylzinc (0.38 ml, 3.8 mmol) in 10 ml of solvent (arisole, benzene, n-pentane, or ether) was added methylene iodide (1.61 g, 6 mmol) dropwise (caution to exothermic!). The mixture was stirred at 20° for 40 hr. Then the mixture was washed with cold saturated ammonium chloride (2×5 ml), cold saturated sodium bicarbonate (5 ml), and water (2×5 ml). Combined ether extract was dried over magnesium sulfate and distilled under reduced pressure. Products were identified by GLC(10 % SE-30 on Chromosorb W) with authentic samples. Product distribution and yields were also determined by GLC using n-dodecane as an internal standard.

Synthesis of Cyclopropyl Silyl Ethers by the Reaction of Enol Silyl Ethers with Diethylzinc-Methylene Iodide in n-Pentane or Ether:

General Procedure.

Methylene iodide (1.61 g. 6 mmol) was added dropwise during about 20 min to a stirred mixture of enol silyl ether (2) (5 mmol), diethylzinc (0.38 ml, 3.8 mmol), and solvent (n-pentane or ether, 10 ml) at room temperature. After stirring for 20 hr at room temperature, the reaction mixture was worked up in the usual manner. Yields and purity was determined by GLC(OV-1), comparing with the authentic samples.

Spectral Data of Cyclopropyl Silyl Ethers 2e-2o.

2e: bp 66-68°C(13 mm); ir 3030 cm^{-1}, NMR(CCl_4) 0.09(s, 9H), 0.33-2.05(c, 9H); MS m/e 170 (M^+).

Anal. Calcd for $C_9H_{18}OSi$: C,63.46; H,10.65. Found: C,63.59; H, 10.99.

2f: bp 70-71°C(24 mm); ir 3030 cm^{-1}; NMR(CCl_4) δ 0.07(s, 9H), 0.00-0.26(c, 9H); MS m/e 184 (M^+).

Anal. Calcd for $C_{10}H_{20}OSi$: C,65.15; H, 10.94. Found: C,65.39; H, 11.14.

2g: bp 120-123°C(17mm); ir 3040 cm^{-1}; NMR(CCl_4) δ 0.06(s, 9H), 0.00-2.40(c, s, 0.79, s, 0.81, 19H); MS m/e 240 (M^+).

Anal. Calcd for $C_{13}H_{28}OSi$: C,69.93;H,11.74. Found: C,69.96; H, 11.83.

2h: bp 72-75°C(7 mm); ir 3040 cm^{-1}; NMR(CCl_4) δ 0.09(s, 9H),0.35 (s, 2H), 0.85-2.10(c, 11H); MS m/e 198 (M^+).

Anal. Calcd for $C_{11}H_{22}OSi$: C,66.60; H,11.18. Found: C,66.12; H, 11.40.

2i: bp 139-143°C(16mm); ir 3061, 3027 cm^{-1}; NMR(CCl_4) δ 0.09 (s, 9H), 0.75-1.23(c, 2H), 1.46-2.79(c, 5H), 6.74-7.68(c, 4H); MS m/e 232 (M^+).

Anal. Calcd for $C_{14}H_{20}OSi$: C, 72.35; H, 8.67. Found: C,72.40; H,8.84.

2j: bp 82-86°C(0.2 mm); ir 3020, 3050 cm^{-1}; NMR(CCl_4) δ 0.13 (s, 9H), 0.97-1.27 (c, 2H), 1.77-2.74 (c, 5H), 6.76-7.15 (c, 4H); MS m/e 232 (M^+).

Anal. Calcd for $C_{14}H_{20}OSi$: C,72.35; H,8.57. Found: C,72.29; H, 8.83.

2k: bp 97-99°C (16 mm); ir 3020 cm^{-1}; NMR(CCl_4) δ 0.10 (s, 9H), 0.15-2.45 (c, 13H); MS m/e 198 (M^+).

Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.87; H, 11.39.

2l: bp 90-95°C (10 mm); NMR(CCl_4) δ 0.02 (s, 9H), 0.86-1.09 (c, 6H), 7.2 (c, 5H); MS m/e 206 (M^+).

Anal. Calcd for $C_{11}H_{18}OSi$: C, 69.84; H, 8.79. Found: C, 69.80; H, 8.58.

2m: bp 63-65°C (13 mm); ir 3020 cm^{-1}; NMR(CCl_4) δ 0.08 (s, 9H), 0.24-0.64 (m, 2H), 0.88-1.88 (c, 8H), 2.94-3.08 (d-d, 1H); MS m/e 184 (M^+).

High-Resolution MS. Calcd for $C_{10}H_{20}OSi$: 184.1282. Found: 184.1269.

2n: bp 74°C (14 mm); ir 3020 cm^{-1}; NMR(CCl_4) δ 0.12 (s, 9H), 0.28-0.60 (c, 2H), 1.33 (s, 3H), 1.30-2.04 (c, 8H); MS m/e 198 (M^+).

High-Resolution MS. Calcd for $C_{11}H_{22}OSi$: 198.1438. Found: 198.1421.

2o: bp 93-95°C (23 mm); ir 3100 cm^{-1}; NMR(CCl_4) δ 0.10 (s, 9H), 0.15-0.42 (m, 2H), 1.05 (c, 4H), 1.40 (c, 4H), 2.92 (d-d, 1H); MS m/e 198 (M^+).

High-Resolution MS. Calcd for $C_{11}H_{22}OSi$: 198.1438. Found: 198.1427.

2-6 References and Notes

(1) D. H. Gibson and C. H. DePuy, Chem. Rev., 74, 605 (1974).

(2)(a) S. Murai, T. Aya, and N. Sonoda, J. Org. Chem., 38, 4354 (1973); (b) J. M. Conia and C. Girard, Tetrahedron Lett., 2767 (1973); (c) G. M. Rubottom and M. I. Lopez, J. Org. Chem., 38, 2097 (1973); (d) C. R. LeGoaller and J. -L. Pierre, Bull. Soc. Chim. Fr., 1531 (1973); (e) S. Murai, Y. Seki, and N. Sonoda, Chem. Comm., 1032 (1974); (f) I. Ryu, S. Murai, S. Otani, and N. Sonoda, Chem. Lett., 93 (1976); (g) Y. Itoh, S. Fujii, and T. Saegusa, J. Org. Chem., 41, 2073 (1976); (h) S. A. Monti, F. G. Cowherd, and T. W. McAinch, ibid., 40, 858 (1975); (i) S. R. Wilson, M. E. Walters, and B. Orbaugh, ibid., 41, 378 (1976); (j) C. Girard and J. M. Conia, Tetrahedron Lett., 3327, 3333 (1974); (k) C. Girard, P. Amice, J. P. Barnier, and J. M. Conia, Tetrahedron Lett., 3329 (1974); (l) M. Audibrand, R. LeGoaller, and P. Arnaud, C. R. Acad. Sci. Paris, 268, 2322 (1969); (m) R. LeGoaller and J. -L. Pierre, ibid., 276, 193 (1973); (n) B. M. Trost and M. J. Bogdanowicz, J. Am. Chem. Soc., 95, 289 (1973); idem, ibid., 95, 5311 (1973); (o) J. P. Barnier, B. Carnier, C. Girald, J. M. Denis, J. Sakum, and J. M. Conia, Tetrahedron Lett., 1747 (1973).

(3) H. E. Simmons, T. L. Cairns, and S. A. Vladuchick, Organic Reactions, 20, 1 (1973).

(4) J. Furukawa, N. Kawabata, and N. Nishimura, Tetrahedron, 24, 53 (1968).

(5) J. Furukawa and N. Kawabata, Adv. Organometal. Chem., 12, 83 (1974).

(6) (a) E. Wenkert and D. A. Bergs, J. Am. Chem. Soc., 89, 2507 (1967); (b) R. E. Ireland, D. R. Marshall, and J. W. Tilley, ibid., 92, 4754 (1970); (c) J. F. Templeton and C. W. Wie, Tetrahedron Lett., 3955 (1971); (d) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr, S. S. Sathe, D. J. Scharf, and G. Toshi, J. Am. Chem. Soc., 92, 7428 (1970); (e) W. F. Johns and K. W. Salamon, J. Org. Chem., 36, 1952 (1975); (f) M. E. Kuehne and G. DiVincenzo, ibid., 37, 1023 (1972).

(7) For example, see ref. 6a.

(8) For example, see ref. 6b and ref. 6c.

(9) Prepared from corresponding ketones and orthoesters.
R. A. Wohl, Synthesis, 38 (1974).

(10) In our preliminary communications we had termed such reaction conditions 'concentrated'. However, in many works of Simmons-Smith reaction such conditions were popularly used so far.

(11) R. J. Rawsson and I. T. Harrison, J. Org. Chem., 35, 2057 (1970).

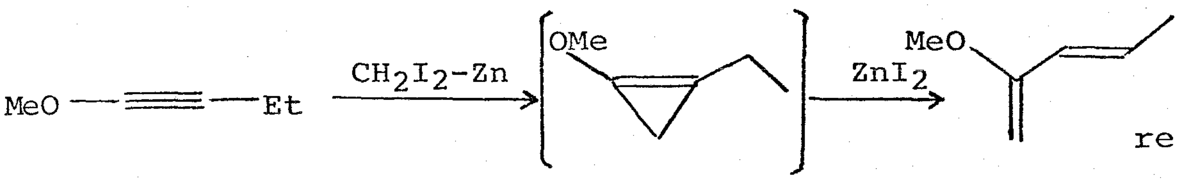
(12) The Simmons-Smith reaction of 1b was previously reported by Chan et al. without experimental detail.
J. H. -H. Chan and B. Rickborn, J. Am. Chem. Soc., 90, 6406 (1968).

(13) M. H. Abraham and P. H. Rolfe, J. C. S. Chem. Comm., 325 (1965) and refs cited therein.

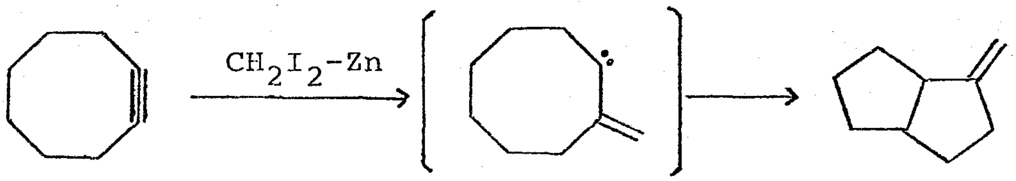
Chapter 3 Cyclopropyl to Allylic Isomerization in the Reaction of Enol Silyl Ethers with Zinc Carbenoid Reagents

3-1 Introduction

To my knowledge, in the reaction of olefins with zinc carbenoid reagents, few cases affording noncyclopropyl compounds has been known. Restricted examples of those are found in the Simmons-Smith reaction of acetylenenic compounds, of which typical examples are shown in the following:

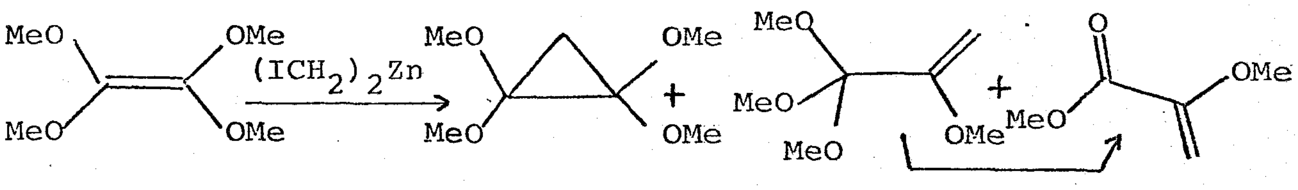


ref. (1)

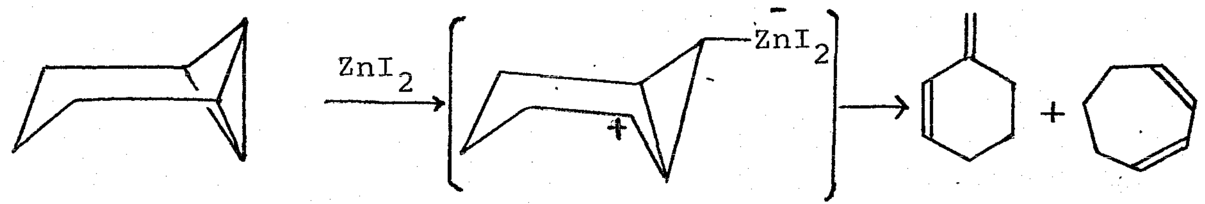


ref. (2)

The formation and partial isomerization of 1,1,2,2-tetramethoxy-cyclopropane by the reaction of bis(iodomethyl)zinc with tetramethoxy-ethylene, specially designed olefin, has been reported by Hoffman and coworkers.[3]



Zinc iodide promoted isomerization of highly strained compounds carried out in a discriminated system has been reported in some cases.



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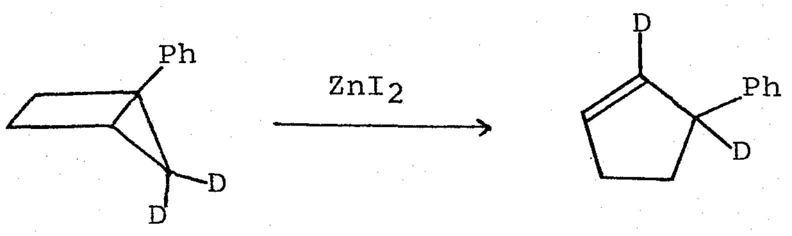

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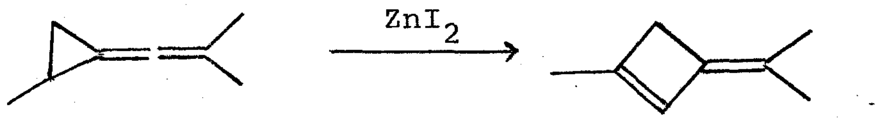
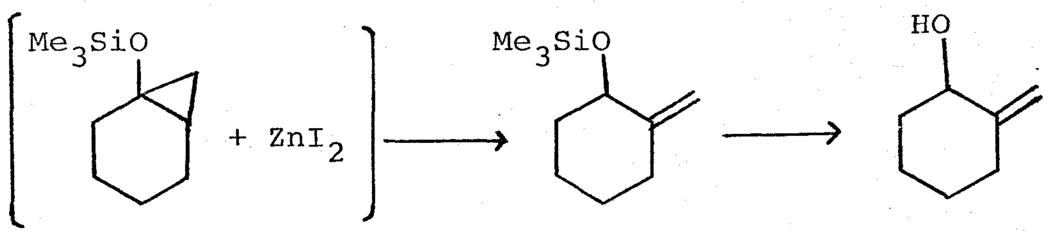


ref. (6)

Most cases of these examples were accompanied with a good many amounts of deduction of strain energy, for example, even the isomerization of bicyclo[2.1.0]pentane to cyclopentene results in the 47 kcal/mol of strain release.[7]

The zinc iodide promoted cyclopropyl to allylic isomerization reaction refered in the prerious chapter may be discerned from above mentioned examples by two aspects: the isomerization is accompanied with relatively low strain release; when enol silyl ethers were employed in place of enol ethers, the present in situ isomerization is directly combined with the synthetic applications by subsequent desilylation.

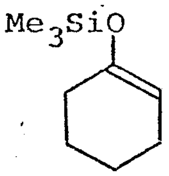


In this chapter, is dealt with cyclopropyl to allylic isomerization in the Simmons-Smith reaction of enol silyl ethers in detail. One pot synthesis of 4-siloxy-spiroalkanes from the reaction of enol silyl ethers and Furukawa reagent is also described.

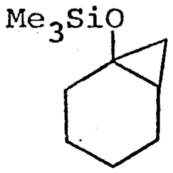
3-2 Cyclopropyl to Allylic Isomerization in the Simmons-Smith Reaction of Enol Silyl Ethers.

Isomerization observed in the Simmons-Smith reaction of enol ethers (see Chapter 2) was more notably found in that of enol silyl ethers. The results of the Simmons-Smith reaction of enol silyl ethers under a variety of reaction conditions are summarized in the Table 1.

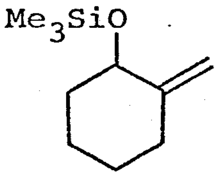
All procedures gave reproducible results and worked well on larger (fourfold) and smaller (one fifth) reaction scales. In most cases under these 'standard' or 'concentrated' conditions, the Simmons-Smith reaction of 1 gave no trace of spiro compounds 4, which would be resulted from further cyclopropanation of allylic isomers.



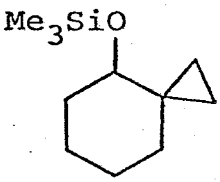
1f



2f



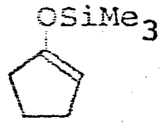
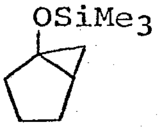
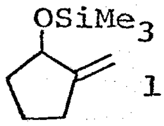
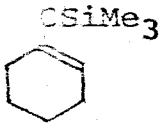
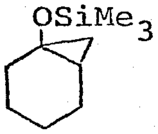
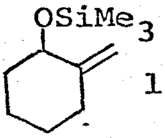
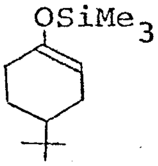
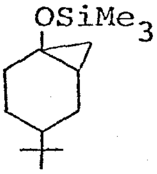
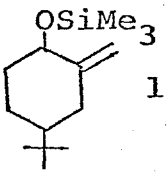
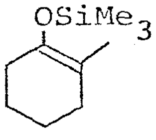
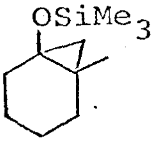
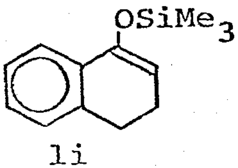
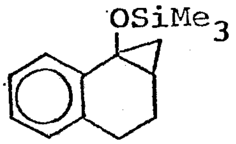
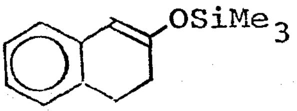
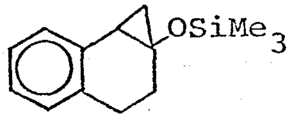
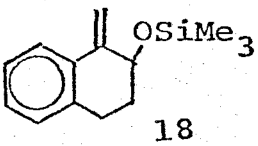
3f

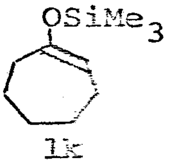
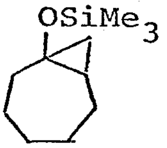
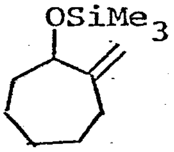
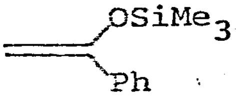
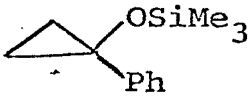
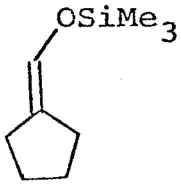
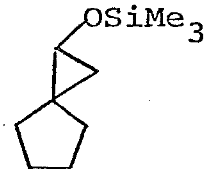
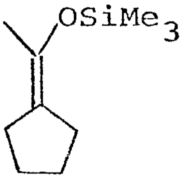
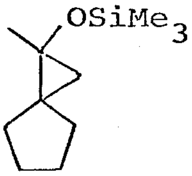
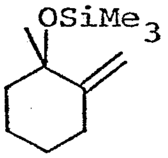
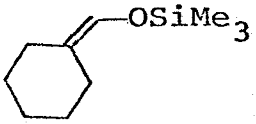
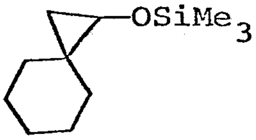


4f

The 'standard' conditions B gave exclusively noncyclopropyl ethers 3, in the reactions of 1e, 1f, and 1g. The reaction of 1-trimethylsiloxy-3,4-benzocyclohexene (1j) or 1-trimethylsiloxy-

Table 1. The Simmons-Smith Reaction of Enol Silyl Ethers.

Enol Ether 1	Conditions[a]	Products[b] 2	and Rel. %	3		Total yield[c] (%)
 1e	B		0		100	71
 1f	B		0		100	68
 1g	B		0		100	71[d]
 1h	B C		100 100			78 70
 1i	B C		100 100			58 63
 1j	B C		82 52		18 48	66 56

 1k	B		99		1	77
	C		16		84	65
	C*[k]		0		100	50
 1l	B		100			40
	C		100			51
 1m[f]	B		99		1	73[e]
	C		80	3m=3f	20	73[e]
	C"[j]		15		85	80[e]
 1n[f]	A'[g]		99		1	65[e]
	B		97		3	80[e]
	B'[h]		91		9	82[e]
	C		25		75	77[e]
	C'[i]		8		92	66[e]
 1o[f]	B		100			66[e]
	C		100			86[e]

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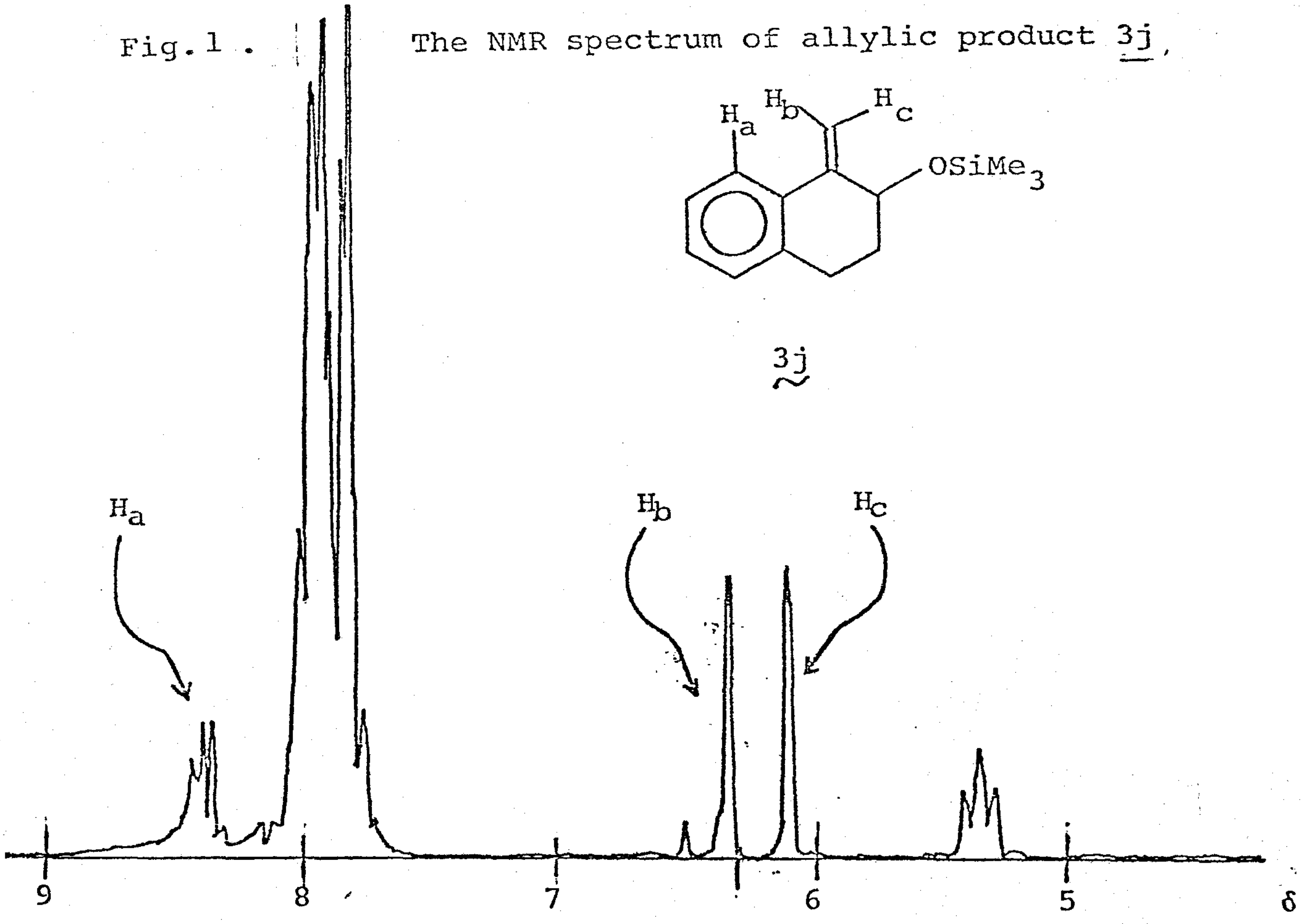
[a] See text. [b] Determined by GLC. [c] By isolation and weighing unless otherwise noted. [d] A mixture of stereo isomers(1:1). [e] Yield estimated from GLC. [f] One tenth reaction scale. [g] For 5 mmol of 1n 5.5 ml of ether. [h] For 5 mmol of 1n 3.2 ml of ether. [i] For 5 mmol of 1n 2.0 ml of ether was used. [j] For 5mmol of 1m 0.5 ml of ether. [k] 21 ml of ether was used for 50 mmol of 1k.

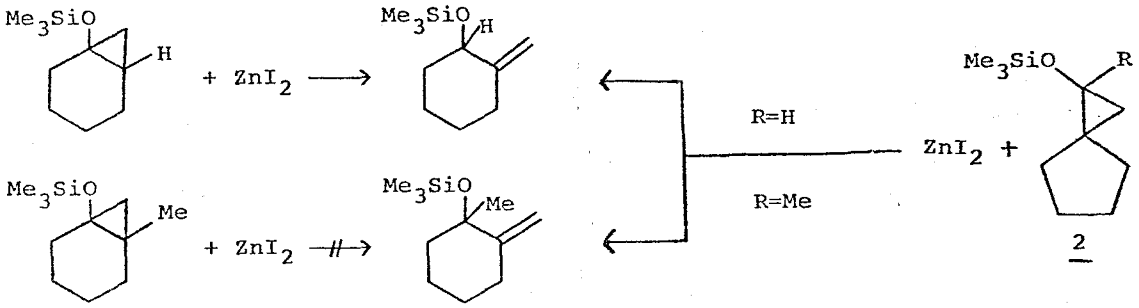
cycloheptene (1k)[8] also gave the corresponding allylic ether 3k or 3j respectively, in addition to cyclopropyl silyl ethers. In these cases, however, the predominant formation of each allylic ether required 'more concentrated' conditions. High dependence of concentration upon product distribution (the more the conditions became concentrated, the more allylic isomers were obtained) was well understood by the results of trimethylsiloxymethylenecyclopentane (1m). The conditions C" in this case are the most concentrated ones which afforded products without decrease in yields.[9]

The structure of 3j was determined by NMR (NOE measurement).[10] Irradiation at H_a in Fig 1 showed 17 % area increase of H_b. This confirmed the position of exomethylene group of 3j.

Fig. 1 . The NMR spectrum of allylic product 3j,



The present isomerization reaction involes the cleavage of cyclopropane ring and consecutive 1,2-migration of hydrogen. The corresponding 1,2-migration of methyl group, however, could not be achieved so far. For example, in the system of the Simmons-Smith reaction of 1-trimethylsiloxy-2-methylcyclohex-1-ene (1o), 1,2-methyl migration has not been observed at all even under 'concentrated' conditions C. The definite example of skeletal rearrangement accompanying 1,2-migration of carbon in the Simmons-Smith reaction of 1m or 1n. These compounds give rise to strained spiro[4,2]heptane adducts (2m and 2n) as initial products.



2

The most 'concentrated' conditions (C' or C") yielded ring expanded allylic isomer 3m or 3n as major product. The unusual product 3l or 3m may be formed by the cleavage of cyclopropane ring of 2m or 2n by zinc iodide followed by ring expansion with 1,2-migration of the carbon skeleton.

The Simmons-Smith reaction of trimethylsiloxymethylene-cyclohexane gave nothing but normally expected spiro[5,2]-octane adduct, even when 'concentrated' conditions were adopted. This suggests that the strain release from spiro[4,2]heptane system to methylenecyclohexane system may be the essential driving force in the isomerization of 2m or 2n.

Strain release may be essential factor for the performance of the present isomerization accompanied with either H migration or C migration.[11]

Observations from these above results were briefly summarized as follows:

(1) Usually two kinds of products are obtained.

(2) Product ratios are highly dependent on the concentration of the reaction mixture.

(3) Selective synthesis of each product is possible by (2).

(4) Strain release to some extent is indispensable for the present isomerization.

(5) Isomerizations with both H-migration and C-migration occurr (the latter requires more strain release).

(6) RO-group plays an important role for isomerization (siloxy group is the most suitable for it).

(7) In this isomerization, sterically less hindered expheral C-C bond of cyclopropanes cleaves in selective manner.[12]

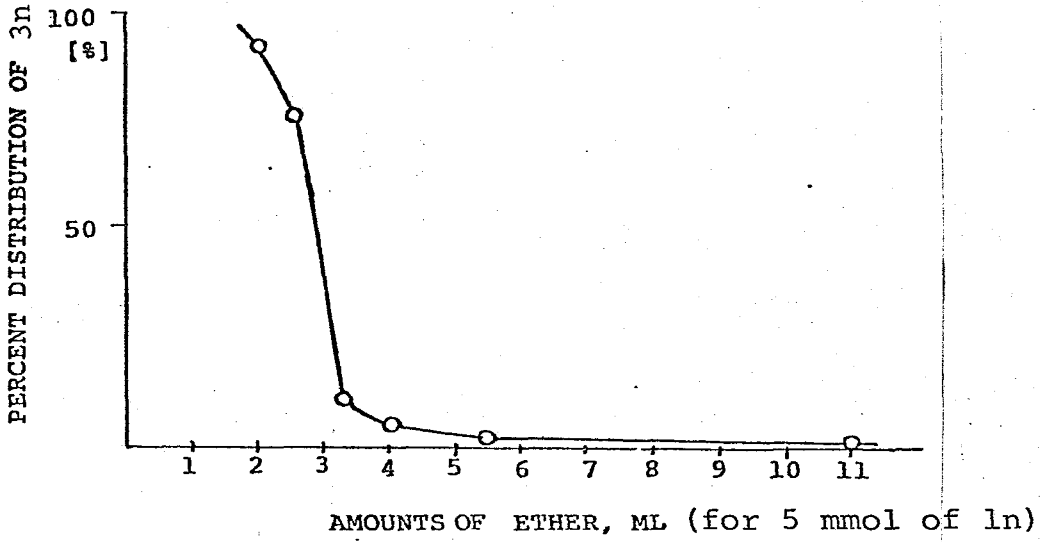
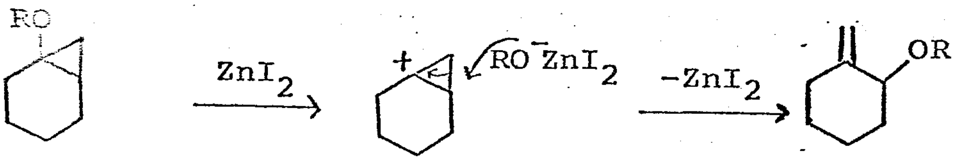


Figure 2. The Simmons-Smith Reaction of 1n in Several Concentrations.

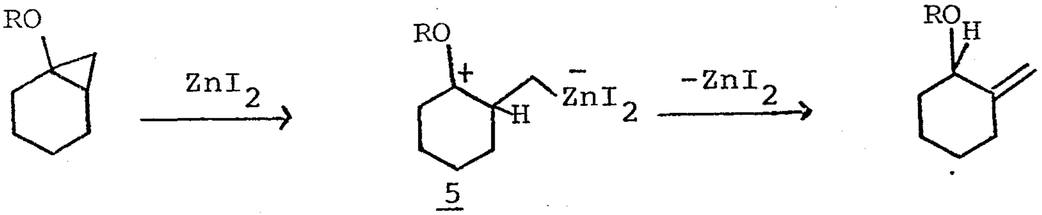
3-3 Reaction Path for Allylic Ethers

Zinc iodide often causes the heterolytic cleavage of RO-C bond by the abstraction of RO$^-$ anion to form carbocation.[13] The anologous role of zinc iodide in the present isomerization was clearly precluded.by the structural determination of the isomerized product 3j from 3,4-benzo-derivative of bicyclo[4.1.0]-1-trimethylsiloxyheptane 2j (no rearrangement of siloxy group).

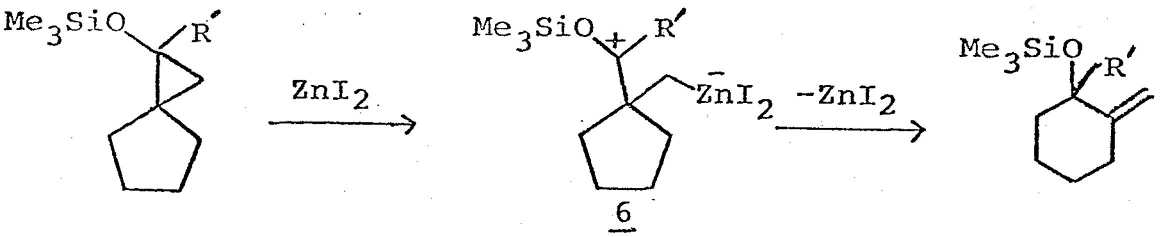


The role of zinc iodide in the present reaction is to promote isomerization of with 1,2-migration.

The author proposes the ionic reaction path which well accounts for both isomerizations with H-migration and C-migration.



(eq 1)



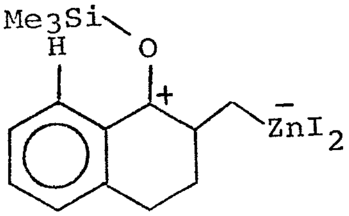
(eq 2)

Compared with the results for the siloxyalkenes, alkoxyalkenes showed a reluctant tendency to isomerize. The relative yields of 3 which may approximate the relative facility of the cyclopropyl ethers to isomerize, were in the order; MeO- EtO- Me_3SiO- . For example, under the same reaction conditions B, the methoxy compound 1b gave 17 % of the allylic isomer 3b, the ethoxy compound 1d gave 56 % of the allylic isomer 3d and the trimethylsiloxy compound 1f gave exclusively the allylic isomer 3f. The differences observed in reactivities may be accounted for by the different abilities of RO groups to stabilize the positive charge in the transition state leading to 5. The recently provocated β-effect of silicon well explains the most facile isomerization in the case of siloxy compounds.[14]

The results of methyl substituted substrate 1n showed that the formation of allylic isomer 3n was easier than that of 3m. The observed enhancement of rearrangement by the methyl group may be explained by assuming an above ionic intermediate 6. The failure of ring expansion to methylenecycloheptane derivative in case of 1l may be due to the lack of sufficient strain, as well as the case of 1o.[12]

Fig. 2 ~~(p-64)~~ shows relation between product distribution of the Simmons-Smith reaction of 1n and the amounts of the solvent used. Remarkable change in product distribution was observed near the point of 3 ml. It seems likely that some interaction between zinc iodide and cyclopropyl ethers under concentrated conditions, which ensures the subsequent isomerization. Namely, when coordination sites of zinc iodide are fully occupied by the solvent ether as under the diluted conditions, further isomerization may be difficult to take place, and under higher concentrated conditions cyclopropyl ethers placed by diethyl ether on the coordination sites of zinc iodide may result in the isomerization to allylic isomers. The notable effect resultant from the concentration seems not to be interpretted simply in terms of reaction rate.

Curiously, the Simmons-Smith reaction of the trimethylsilyl ether of α-tetralone enolate gave no trace of isomerized product. Though it seems rather hard to account for this, the resistance to isomerization in this case may be attributed to the steric repulsion between bulky trimethylsilyl group and perihydrogen, which may cause the prohibition of required inversion of carbon linked with trimethylsiloxy group (see 7).



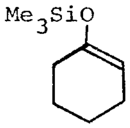
7

The cleavage of cyclopropane ring took place at the C-C bond between carbon atom having RO group and methylene carbon. Both the favorable attack of zinc iodide at less hindered site and the formation of more stable carbanion having a bonding character with zinc iodide may be consisted with this selectivity.

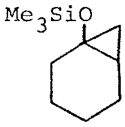
In recent years metal promoted isomerization of highly strained compounds meets much interest and in them several examples of isomerization by zinc iodide have been reported.[15] As compared with these examples, the present isomerization proceeded with relatively small strain release. For example, transformation of bicyclo[4.1.0]heptyl system to methylenecyclohexyl system results in the release of ca. 25 kcal/mol of strain, which locates in the smallest class.[7,16]

3-4 One-Pot-Conversion of 1-Siloxycycloalkene to 4-Siloxy-Spiro[n,2]alkanes with Diethylzinc-Methylene Iodide

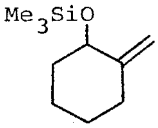
It was dealt with in Chapter 2 that cyclopropanation of 1 with the Simmons-Smith reagent (CH_2I_2-Zn(Cu)) gave 2. It was also dealt with in the previous section that the usual product 3 was obtained when a smaller amount of the solvent (Et_2O) was used for this reaction. The exomethylene compound 3 has been ascertained to be formed through the isomerization of 2 by zinc iodide which is generated during the course of the Simmons-Smith reaction. Notably, under the reaction conditions to give 3, no trace of a spiro-ether 4 which could arise by further cyclopropanation of the C=C bond of 3 has been obtained. Several attempts for the selective synthesis of spiro-ethers of the type 4 directly from 1 using Simmons-Smith reaction have never met with satisfactory results.[17]



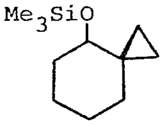
1f



2f



3f

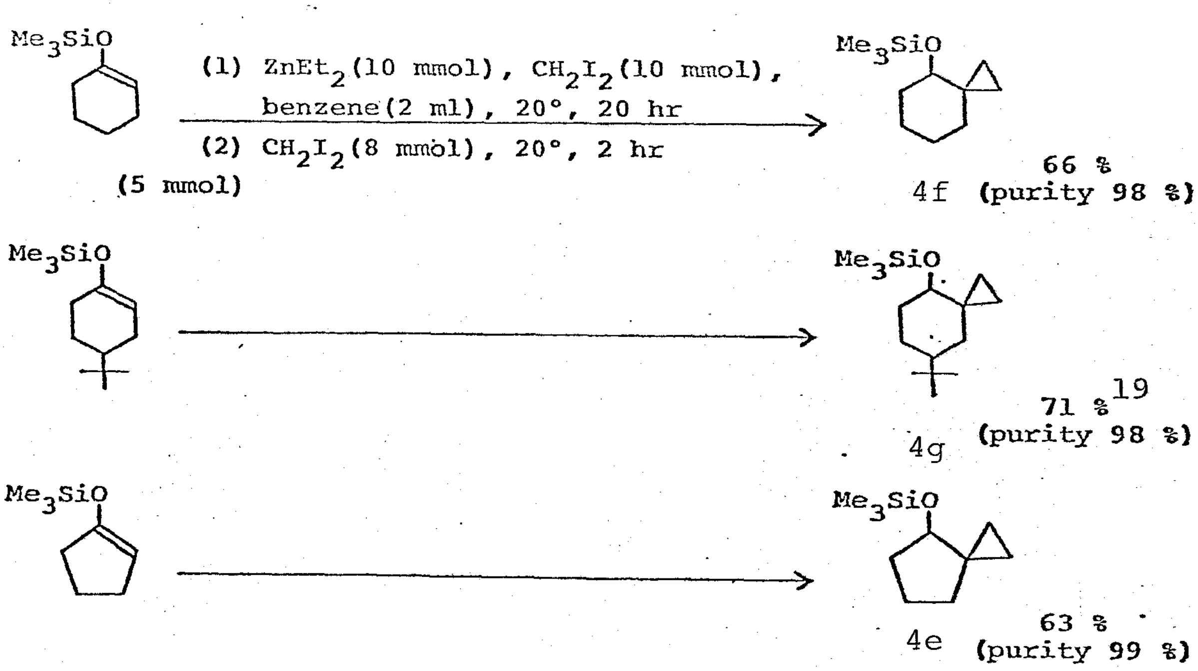


4f

In this section are described the one-pot-synthesis of spiro-ethers of the type 4 by the reaction of enol silyl ethers 1 with diethylzinc-methylene iodide.[18] Results are shown in Scheme . The present spiro-ether synthesis is remarkable in the sense that the three sequential reactions (1→2, 2→3, and 3→4) take place in the same reaction vessel to give the desired spiro-ethers 4 exclusively.

For the selective synthesis of spiro-ethers, it is important to use an aromatic solvent (benzene or anisole) in a smaller amount relative to the substrates as in the ratio shown in Scheme (see Section 3 in Chapter 2). When the reaction was carried out using a relatively large amount of benzene, a mixture of three products were obtained because of slower and incomplete conversion of 2 to 3. For example, the reaction of 1 (3.3 mmol) with $ZnEt_2$ (2.5 mmol) and CH_2I_2 (3.7 mmol) in benzene (10 ml, a larger amount) at 20° for 24 hr gave a mixture of 2 (20 %), 3 (74%), and 4 (6%).

Scheme. One-Pot-Synthesis of 4-Siloxyspiro[n,2]alkanes by the Reaction of Enol Silyl Ethers with Diethylzinc and Methylene Iodide.



Zinc iodide may play an important role for cyclopropyl-allylic isomerization in the present system as well as in the case of Simmons-Smith reaction.

Spiro-ethers thus obtained directly from enol silyl ethers can be easily converted to corresponding spiroalkanols or spiro-alkanones. For example, treatment of the spiro-ether 4 with 0.1N-NaOH/MeOH gave spiro[5,2]octan-4-ol (7) in 94 % yield, whereas pyridinium chlorochromate/CH_2Cl_2[20] gave spiro[5,2]octan-4-one (8) in 76 % yield. Since the enol silyl ether 1 can be prepared in high yield from cyclohexanone, the present reaction provides an efficient method for the conversion of the cyclohexanone to 7 or 8. Multistep and low overall yield syntheses of 7[21] or 8[22] have been reported. For example, Crandall and Seidewand prepared spiroalkanone 8 via three steps from 2-carboethoxycyclohexanone(9 % overall yield).[22a]

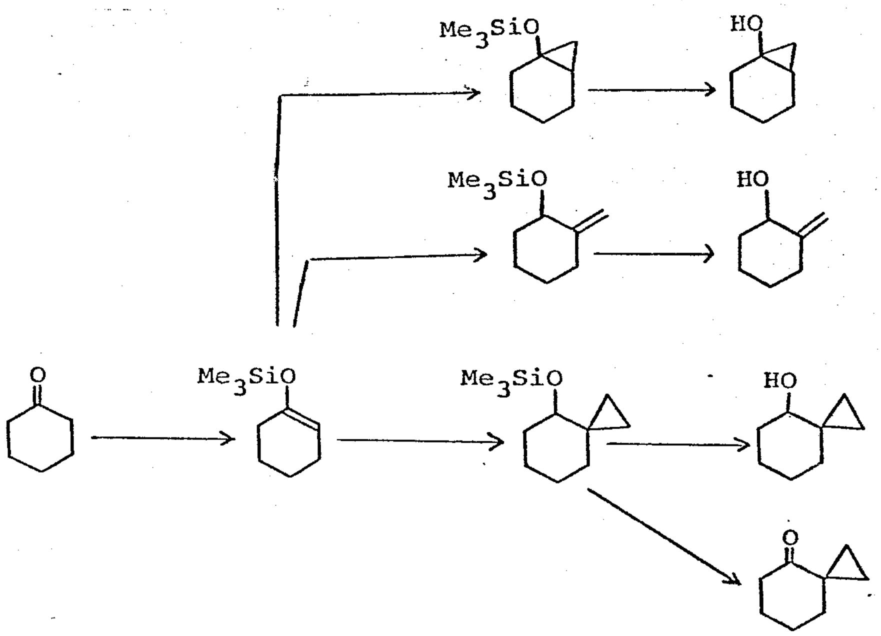
3-5 Synthetic Aspects of the Reaction of Enol Silyl Ethers with Zinc Carbenoid Reagents

Much interest has been directed to the properties of cyclopropanols.[23] Cyclopropyl silyl ethers whose synthesis was established in the previous chapter, can be quite easily converted to corresponding cyclopropanols in quantitative yields upon treatment with 0.1N-NaOH in MeOH.[24] This method is of value especially for the synthesis of 1-hydroxy[n.1.0]alkanes, which are an unique class of cyclopropanols having a hydroxy group at bridgehead carbon and have been rather inaccesible.

The establishment of the reaction conditions for selective formation of allyl silyl ethers provides a new excellent route to 2-methylene-cycloalkanols by subsequent hydrolysis. Such structures are frequently found in the structural units of terpenoids. Previous methods affording them via several steps from corresponding ketones are not somewhat satisfying.[21,22]

4-Siloxyspiro[n,2]alkanes selectively obtained in the reaction system of enol silyl ethers and Furukawa reagent can be converted to 4-hydroxyspiroalkanes quantitatively by the same procedure of hydrolysis. Moreover, it should be noted that this can be also converted to 4-spiro[n,2]alkanones by direct oxidation with pyridinium chlorochromate. This transformation clearly shows the novel efficient method for α,α'-ethylenation of cyclic ketones.

Above three transformations performed in the reaction system of enol silyl ethers with zinc carbenoid reagents operate as excellent routes to combine all these valuable products with ketones.



3-6 Experimental

The Simmons-Smith Reaction of Enol Silyl Ethers under Reaction Conditions B or C.

The same procedure as the reaction of enol ethers, which was indicated in the Chapter 2 was employed.

Spectral Data of Allylic Silyl Ethers 3.

3e: b.p. 60-61°C/18 mm; IR 1665 cm^{-1}; NMR δ 0.04(s, 9H), 1.34-2.47(c, 6H), 4.11-4.47(c, 1H), 4.72-5.41(c, 2H); MS *m/e* 170(m$^+$). (Found: C, 63.16; H, 10.84. Calc. for $C_9H_{18}OSi$: C, 63.46; H, 10.65).

3f: b.p. 60-65°C/10 mm; IR 1660 cm^{-1}; NMR δ 0.09(s, 9H), 0.97-2.74(m, 8H), 3.86-4.19(c, 1H), 4.62(s, 1H), 4.75(s, 1H); MS *m/e* 184(m$^+$). (Found: C, 64.87; H, 10.65. Calc. for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94).

3g: obtained as 1:1 mixture of stereo isomers: b.p. 108-115°C /6 mm; IR 1655 cm^{-1}; NMR δ 0.06(s, 9H), 0.88(s, 9H), 0.98-2.19 (m, 7H), 4.11(c, 1H), 4.62(c, 1H), 4.80(c, 1H); MS *m/e* 240(m$^+$). (Found: C, 69.82; H, 11.85. Calc. for $C_{13}H_{26}OSi$: C, 69.93, H, 11.74).

3j: b.p. 82-83°C/0.35 mm; IR 1630 cm^{-1}; NMR δ 0.09(s, 9H), 1.70-3.14(m, 4H), 4.40(m, 1H), 5.16(s, 1H), 5.42(s, 1H), 6.70-7.20(c, 3H), 7.36-7.58(c, 1H); MS *m/e* 232(m$^+$). (Found: m$^+$ *m/e* 232,1293. Calc. for $C_{14}H_{24}OSi$: 232.1282).

3k: b.p. 74-78°C/10 mm; IR 1650 cm^{-1}; NMR δ 0.07(s, 9H), 1.00-2.45(m, 10H), 4.10-4.35(c, 1H), 4.20-5.00(c, 2H); MS *m/e* 198(m$^+$). (Found: m$^+$ *m/e* 198.1450. Calc. for $C_{11}H_{22}OSi$: 198.1438).

3n: b.p. 76°C/14 mm; IR 1642 cm^{-1}; NMR δ 0.09(s, 9H), 1.35 (s, 3H), 1.55(c, 8H), 4.10-4.35(c, 1H), 4.76(c, 1H); MS *m/e* 198(m$^+$). (Found: m$^+$ *m/e* 198.1466. Calc. for $C_{11}H_{22}OSi$:198.1438).

One-Pot-Procedure for 4-Trimethylsiloxyspiro[5,2]octane (4): A Typical Procedure.

Under a dry nitrogen atomosphere, to a stirred solution of 1-trimethylsiloxy-cyclohexene (1) (0.85 g, 5 mmol), diethylzine (1.0 ml, 10 mmol), and dry benzene (2 ml) was added methylene iodide (2.68 g, 10 mmol) during 20 min at 20°C. After stirring for 20 hr, and additional methylene iodide (2.14 g, 8 mmol) was added in one portion (slightly exothermic, temperature reached to 40°) for the completion of the reaction. Then the mixture was stirred for an additional 2 hr, diluted with diethyl ether (20 ml) and poured into cold saturated aq NH_4Cl (50 ml). The aqueous layer was extracted twice with diethyl ether (2×10 ml). The combined ether extract was washed with aq $NaHCO_3$ and water and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give 0.65 g (66 %) of 4-trimethylsiloxy-spiro[5,2]octane, bp 83-85° (20 mm).

Spectral Data of Spiro Ethers 4.

	Bp(°/torr)	IR(neat)	NMR(CCl_4)δ	Mass * m/e	High Res. Mass** Found(Calcd)
4e	80-81.5 /19	3055	0.04(s,9H) 0.0-0.86 (m,4H) 1.14-2.12 (m,6H) 3.63(d-d,1H)	184(M^+) 169(P-15) 156(P-C_2H_4) 141 75 73	$C_9H_{17}OSi$ 169.1017 (169.1047)
4f	74-76 /8	3055	0.05(s,9H) 0.0-0.50 (m,4H) 1.0-2.0 (m,8H) 3.14-3.36 (c,1H)	198(M^+) 183(P-15) 170(P-C_2H_4) 155 75 73	$C_{10}H_{19}OSi$ 183.1211 183.1204

4g***	78-79 /0.4	3060	0.6(s) 0.8(s) (9H) 0.0-0.80 (m,4H) 0.84(s) 0.86(s) (9H) 2.88(c) 3.64(d-d) (1H)	254(M^+) 239(P-15) 226(P-C_2H_4) 169 75 73	$C_{14}H_{27}OSi$ 239.1836 (239.1830)

* A trace of parent peak was observed.
** P-15. *** A mixture of 1:1 stereo isomers

Spiro[5,2]octan-4-ol.

To a solution of 0.1N-NaOH and 10 ml of MeOH was added 4f (0.597 g, 3 mmol) at room temperature. After stirring for 30 min at 25°C MeOH was evaporated in vacuo. Then, to the resulting oil was added 20 ml of ether and the solution was washed with 20 ml of water. The aqueous layer was extracted four times with 5 ml portions of ether and the combined extract was dried over $MgSO_4$. After removal of ether, the vacuum distillation gave 0.355 g (94 %) of spiro[5,2]-octan-4-ol, bp 90-94° (23 mm), whose spectral data (IR, NMR, MS) were identical with those of an authentic sample.[21a]

Spiro[5,2]octan-4-one.

To a stirred suspension of pyridinium chrolochlomate (1.62 g, 7.5 mmol) in CH_2Cl_2 (10 ml),[20] 4-trimethylsiloxyspiro[5,2]octane (4f) (0.99 g, 5 mmol) in 1 ml of CH_2Cl_2 was added in one portion. After 1.5 hr, 10 ml of dry ether was added and the supernatant decanted from the black gum. The residue was washed four times with 3 ml portions of dry ether. The combined solution was passed through a short pad of Kieselgel 60. After removal of the solvent, the vacuum distillation gave 0.471 g (76 %) of spiro[5,2]octan-4-one, bp 80-81° (28 mm); ir(neat) 1693 cm^{-1}; NMR(CCl_4) δ 0.59 (d-d, 2H), 1.40-2.64 (m, 8H); MS, m/e 124, 96.

2-Methylenecyclohexanol.

To a stirred solution of 3 ml of 1N-NaOH and 30 ml of MeOH was added 3f (10 mmol) at room temperature. After stirring for 3 hr, the mixture was neutralized by 1N-HCl and MeOH was evaporated. Then, the resulting oil was dissolved in 20 ml of ether and washed with 20 ml of water. The aqueous layer was extracted four times with 10 ml portions of ether and the combined extract was dried over $MgSO_4$. After removal of the solvent, a quantative yield of 2-methylenecyclohexanol was obtained. Spectral data (IR, NMR) were identical with those of the authentic sample.[21a]

3-7 References and Notes

(1) M. Jauterat and V. Schwarz, Tetrahedron Lett., 5101 (1966).

(2) G. Wittig and J. J. Hatchison, Annal. Chem., 741, 79 (1970).

(3) R. W. Hoffman, U. Bressel, and G. Mühl, Chem. Ber., 105, 2104 (1972).

(4) P. G. Gassman and T. J. Atkins, J. Am. Chem. Soc., 94, 7748 (1972).

(5) M. A. Mckinney and S. K. Chou, Tetrahedron Lett., 1145 (1974).

(6) L. Fitjer, Angew. Chem. Int. Ed. Engl., 14, 360 (1975).

(7) S. Chang, D. McNally, S. Shary-Tehrany, S. M. J. Hickey, and R. H. Boyd, J. Am. Chem. Soc., 92, 3109 (1970); N. L. Allinger, and J. T. Sprague, ibid., 94, 5734 (1972).

(8) The author thanks to Mr. Yoshio Hatayama for his collaboration in this experimental.

(9) The Simmons-Smith reaction without solvent was unsuccesful (non reproducible results).

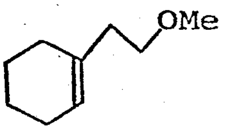
(10) G. E. Bachers and T. Schaefer, Chem. Rev., 71, 617 (1971); R. A. Bell and J. K. Saunders, Can. J. Chem., 46, 3421 (1968).

(11) Allylic isomers have not been obtained in the Simmons-Smith reaction of linear enol silyl ethers. For example, the reaction of enol silyl ethers of propiophenone or pinacolone gave only cyclopropyl ethers under concentrated conditions.

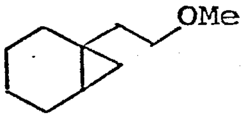
(12) Contrastly nonselective ring cleavage of bicyclo[n.1.0]-alkanes (n=3,4) with acetic acid was reported: K. B. Wiberg, K. C. Bishop, III and R. B. Davidson, Tetrahedron Lett., 3169 (1973).

(13) E. J. Corey, J. L. Gras, and P. Ulrich, Tetrahedron Lett., 809 (1976); B. Fraser-Reid and B. Radatus, Can. J. Chem., 50, 2919 (1972).

Under the vigorous reaction conditions (with a large excess of Simmons-Smith reagent, with smaller amounts of solvent), the Simmons-Smith reaction of 1b yielded unusual two products i and ii, which could not be obtained without C-O bond fission. The compound i seemed to be obtained via the isomerization of the spiro adduct (resulted by cyclopropanation, isomerization, cyclopropanation), and ii via further cyclopropanation of i.



i



ii

(14) For β-effect of silicon: T. G. Traylor, W. Hanstein, H. J.

Berwin, N. A. Clinton, and R. S. Brown, J. Am. Chem. Soc., 93, 5715 (1971) and references cited therein. Also see M. E. Yung, J. Org. Chem., 41, 1479 (1976).

(15) See refs 4, 5, and 6.

(16) This fact may support the proposed ionic intermediates 5 and 6, in which the role of RO-group is essential.

(17) S. Murai, T, Aya, T. Renge, I. Ryu, and N. Sonoda, J. Org. Chem., 39, 859 (1974).

(18) J. Furukawa and N. Kawabata, Adv. Organometal. Chem., 12, 83 (1974).

(19) A mixture of 1:1 stereo isomers.

(20) E. J. Corey, and J. W. Suggs, Tetrahedron Lett., 4481 (1975).

(21) (a) T. Tsuji, I. Moritani, and S. Nishida, Bull. Chem. Soc. Jap., 40, 2338 (1967); (b) W. G. Dauben and G. H. Berezin, j. Am. Chem. Soc., 85, 468 (1963).

(22) (a) J. K. Crandall and R. J. Seidewand, J. Org. Chem., 35, 697 (1970); (b) P. Bravo, G. Graudiano, C. Ticozzi, and A. U-Ronchi, Tetrahedron Lett., 4481 (1968); (c) E. L-Ruff and P. Khazanie, Can. J. Chem., 45, 225 (1975).

(23) D. H. Gibson and C. H. DePuy, Chem. Rev., 74, 605 (1974).

(24) S. Murai, T. Aya, and N. Sonoda, J. Org. Chem., 38, 4354 (1973).

Chapter 4 Synthetic Transformation of Cyclopropyl Silyl Ethers

4-1 Introduction

Cyclopropyl silyl ethers are versatile synthetic intermediates available for many interesting transformations.[1] A part of them has been done on a basis of the numerous accumulation in the chemistry of cyclopropanols.[2] Cyclopropyl silyl ethers are enough stable to deal with both thermally and chemically, compared with corresponding cyclopropanols.

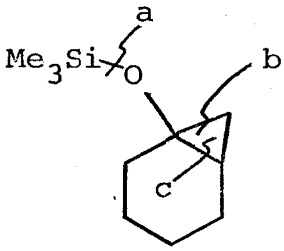
For the purpose of this introduction, it is convenient to divide the envisaged transformations of cyclopropyl silyl ethers according to the following reaction types:

(1) Electrophilic substitution reaction at oxggen (a cleavage)

(2) Cleavage reaction of C-C bond of cyclopropane by electrophilic attack at carbon (b cleavage)

(3) Base induced ring cleavage reaction

(4) Oxidative cleavage reaction (c cleavage)



In the first section of this chapter, the synthesis of cyclopropyl esters by the reaction of cyclopropyl silyl ethers with acid halides activated by zinc iodide are shown.

Attempts to utilize base induced ring cleavage reaction of cyclopropyl ethers to 1-carbon-homologation of ketones are described in the subsequent section.

Finally, bond forming reactions at β-position of carbonyl group, which are resulted from the reaction of cyclopropyl silyl ethers with some metal salts, are also described.

4-2 One-Pot-Synthesis of Cyclopropyl Esters from Enol Silyl Ethers. The Reaction of Cyclopropyl Silyl Ethers with Electrophilic Carbon Moieties.

Two reaction sites are possible to the electrophilic attack to cyclopropyl silyl ether. They are at oxygen and at carbons of cyclopropane ring at β-position from oxygen. In this section, is described the reaction of cyclopropyl silyl ethers with electrophilic carbon moieties, such as acid halides, ethyl chloroformate, allyl bromide, ethyl orthoformate, or benzaldehyde.

At first it occurred to us that zinc iodide, a by-product of Simmons-Smith reaction might be utilized to activate these electrophilic carbon moieties.

Positive results are included in the synthesis of cyclopropyl esters resultant from the predominant attack of zinc iodide activated acid halides at oxygen.

Cyclopropyl esters are the fundamental derivative of cyclopropanols.[2] Several methods previously known for them are quite unsatisfactory since these suffer from a lack of convenience or relatively low yields.

Here is described a novel synthesis of cyclopropyl esters **3** from enol silyl ethers **1**, Simmons-Smith reagent, and acid halides It has been shown that the direct addition of acid halides to the reaction mixture of Simmons-Smith reagent and **1** gave good yields of **3**. The Table shows the results of the one-pot-synthesis of a variety of cyclopropyl esters **3** from the corresponding enol silyl ethers **1**.

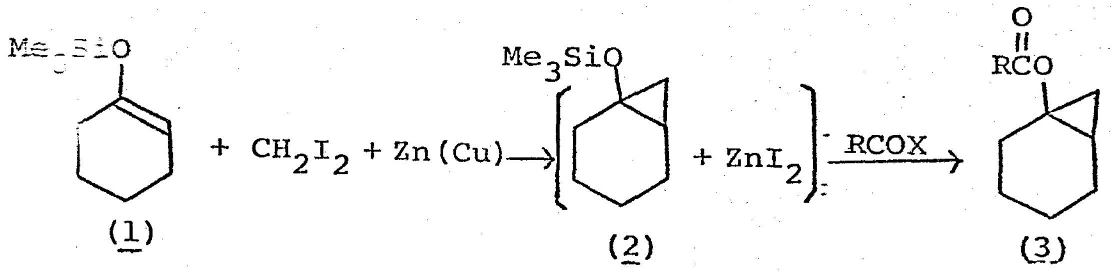


Table. Reaction of RCOCl with the reaction mixture of Simmons-Smith reagent and silyl enol ethers (1).

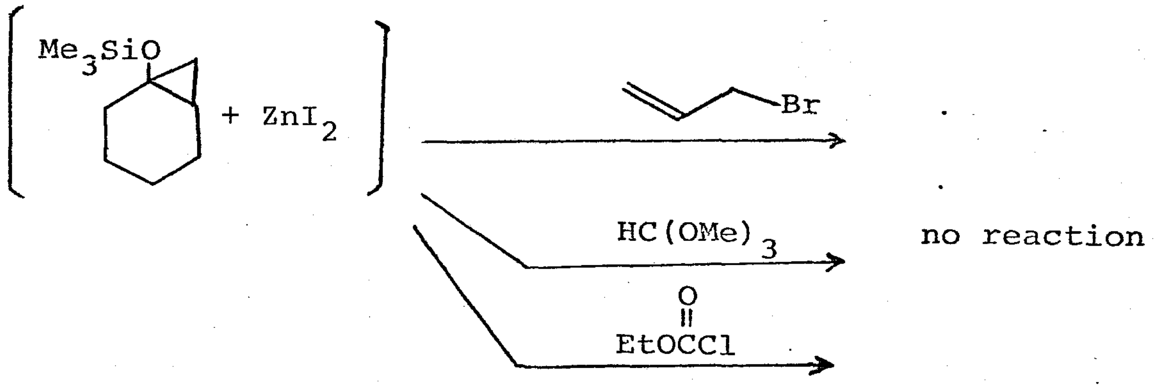
Entry	Enol Ethers (**1**)	Acid Halides	Yields of (**3**)$^{a)}$
1	1-Trimethylsiloxycyclohexene	CH_3COCl	65%
2		PhCOCl	43%$^{b)}$
3		PhCOCl$^{c)}$	70%
4		$CH_3CH=CHCOCl$	58%
5	1-Trimethylsiloxycyclopentene	CH_3COCl	70%
6	α-Trimethylsiloxystyrene	CH_3COCl	48%
7	1-Ethoxycyclohexene	CH_3COCl	—$^{d)}$

a) Isolated yields are given. b) The formation of ethyl benzoate due to the benzoylation of the solvent was observed. c) Two equivalents of benzoyl chloride were used. d) Cyclopropyl acetate was not formed, but 1-ethoxy-bicyclo[4.1.0]heptane which was the product of the Simmons-Smith reaction was obtained in 56% yield.

Zinc iodide, which is the by-product of Simmons-Smith reaction, seems to play an important role for the activation of acid halides in the present synthesis. Treatment of an isolated silyl cyclopropyl ether, 1-trimethylisiloxybicyclo[4.1.0]heptane, with acetyl chloride in ether at 38°C gave no cyclopropyl ester without the presence of zinc iodide.[3] It should be also noted that the formation of cyclopropyl esters was restricted to the case of siloxy compounds (see entry 7 in Table). This synthesis of cyclopropyl esters may be of value, especially for the bicyclic ones which are hardly accessible by previous methods.

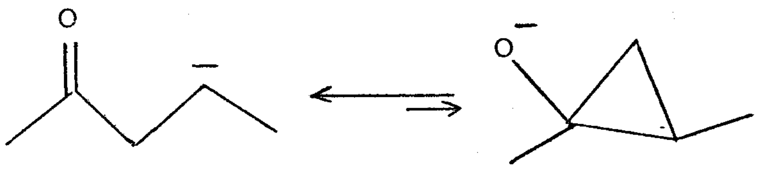
Hart et al. previously reported that AcCl-$AlCl_3$ immediately reacted with cyclopropane to give a mixture of various acetylated products.[5] While, in this case, the AcCl-ZnI_2 gave no carbon acetylated products even when excessive amounts of acetyl chloride was employed. Consequently, the success of the present synthesis can be attributed to the moderate activity of zinc iodide as Lewis acid, which is enough to cause the electrophilic substitution at oxygen and enough weak not to cause the acetylation of cyclopropane.

While, the reaction of allyl bromide, trimethyl orthoformate, or ethyl chloroformate with the reaction mixture of Simmons-Smith reagent and enol silyl ethers did not take place.



If the attack of electrophilic carbon moieties takes place at the carbon of cyclopropane ring, cyclopropyl silyl ether is to behave as synthetic equivalent of homoenolate anion to form new C-C bond at β-position from carbonyl carbon.

Homoenolate anion first invoked by Nickon[6] has so-called 'reversed' polarity, and therefore the C-C bond formation by this process is the current matter of importance and attention.[7]



From the point of view dereloping such transformation using cyclopropyl silyl ethers, the exclusive O-attack of acid halides activated by zinc iodide offer the rather pessimistic results and this suggested the requirement of some devices.

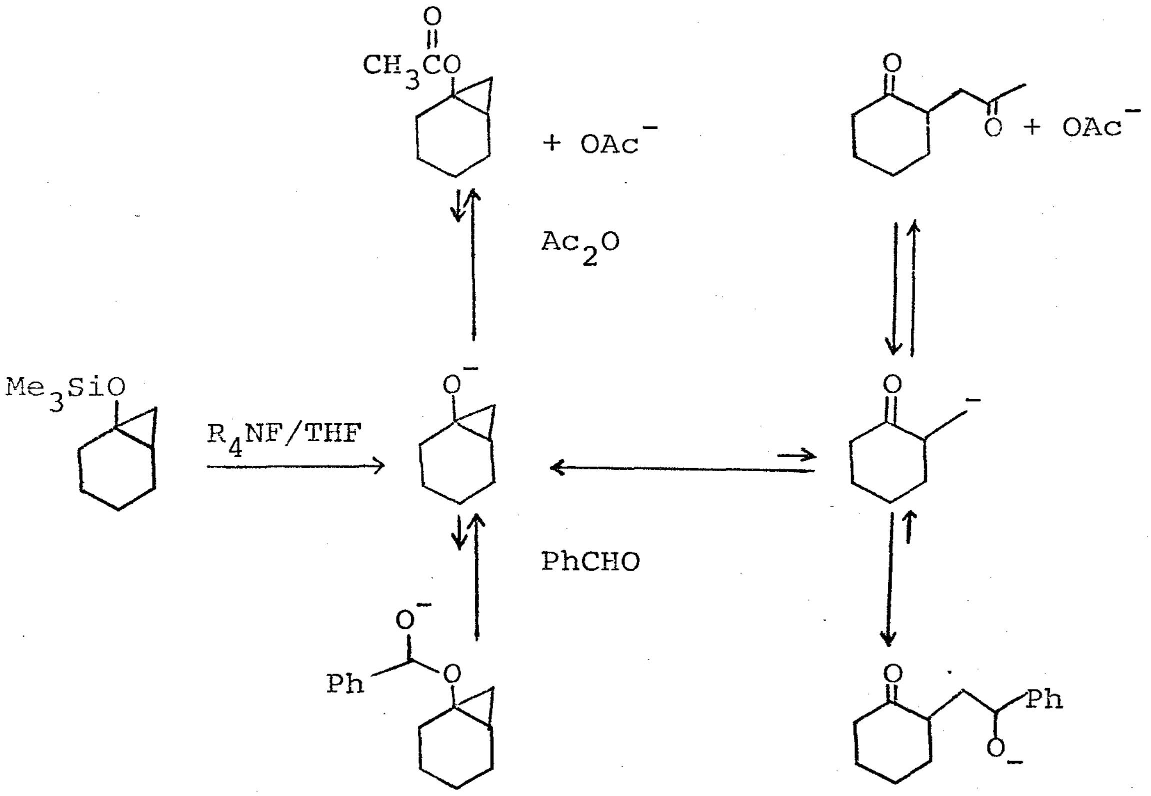
Some trials for C-attack were undertaken employing 'an improved idea': employment of stronger Lewis acid; avoidance of such elctrophilic carbon moieties as to cause the formation of stable product led by direct attack at oxygen. Benzaldehyde was employed as such an electrophilic carbon moiety, which seems to be reluctant to form products via O-attack.[8]

Recently, Mukaiyama et al. showed that that use of titanium tetrachloride was very effective to activate various electrophilic carbon moieties.[9] They reported that the titanium tetrachloride catalyzed reaction of enol silyl ethers with benzaldehyde took place smoothly to give the corresponding Aldol type products, even under -78°.[9c]

Employing titanium tetrachloride as Lewis acid, the reaction of cyclopropyl silyl ethers with benzaldehyde was carried out, while the coupled product could not be obtained even under the refluxing conditions of dichloromethane.

Similar attempts by basic approach using tetra-n-butylammonium fluoride[10] in which the direct formation of homoenolate anion was envisaged were also unsuccessful.[11] These resuts clearly show the contrastive reactivity of cyclopropane ring to C=C double bonds against the attack of electrophilic carbon moieties.

Reaction process envisaged are as follows:



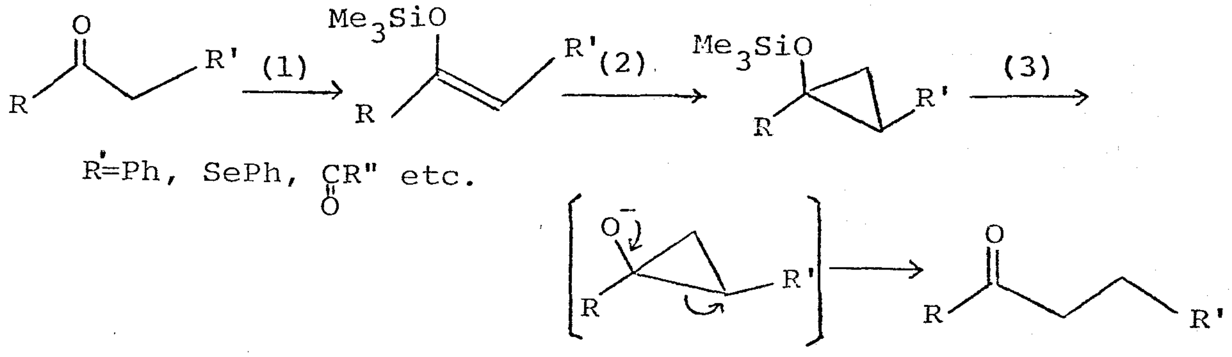
It may be the subject matter to make out better designed systems on either or both of substrate and reactant.[12]

4-3 One-Carbon-Homologation Reaction of Ketones via Basic Cleavage of Cyclopropyl Silyl Ethers

Carbon-homologation reactions have provided almost seductive attraction for synthetic organic chemists.[13]

Starting with an idea that one carbon number increased by cyclopropanation of enol silyl ethers might be utilized for one carbon-homologation of ketones, the following attempts were undertaken. Previously, some reports which dealt with cyclopropyl silyl ethers as intermediates of one-carbon-homologation have been known.[14]

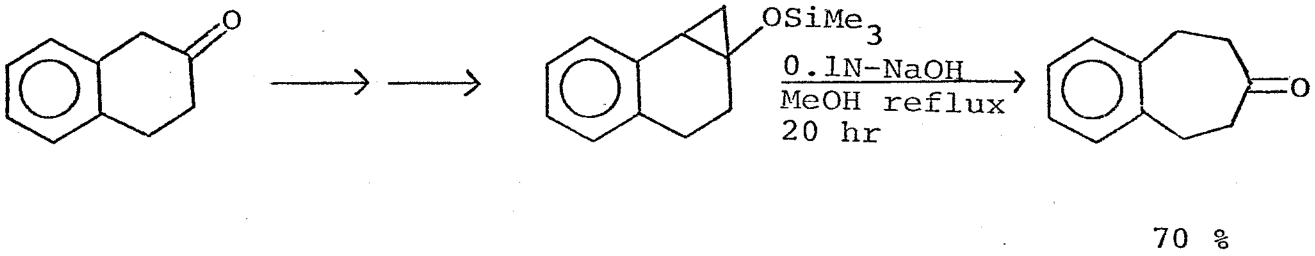
A strategy for this in the present study is illustrated as shown below:



$R' = Ph, SePh, \underset{\overset{\|}{O}}{C}R''$ etc.

If one employs R' substituent having an ability of anion stabilizing, the above strategy involving regiospecific base induced cleavage may be attained. The step 3 is an established reaction exemplified with many undertaken works.[15] The first silylating step also seems to have nothing difficult, that is, the direction of enol silylation in most cases can be attained to the direction desirable. Suffering step proved to exist in the cyclopropanation of these enol silyl ethers.

Consequently, when phenyl group was employed as R' substituent, 1-carbon-homologation reaction was clearly performed. 1-Trimethylsiloxy-3,4-benzo-bicyclo[4.1.0]heptane was treated with 0.1N-NaOH/MeOH under reflux conditions to yield 4,5-benzocycloheptanone in 70 % yield. This transformation showed regiospecific base induced ring cleavage reaction as illustrated in the following way:



This base induced cleavage was interpretted by the generation of O anion followed by transformation to C anion with strain release of cyclopropane ring, And regiospecific ring cleavage was led by anion stabilization by phenyl group adjacent to the C anion.

While, phenylseleno group was employed as R' substituent, the reaction of corresponding enol silyl ether with zinc carbenoid reagent gave rather complex results. Products obtained included isomerized one and this seemed to be unavoidable in case of the reaction with zinc carbenoid reagents.

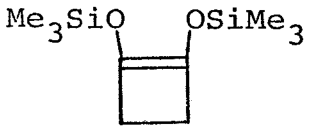
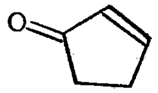
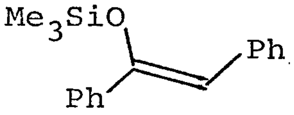
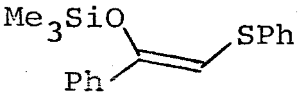
Moreover, the reaction of enol silyl ether of acetyl acetone with zinc carbenoid was unsuccessful, this reaction seemed to be accompanied by desilylation.

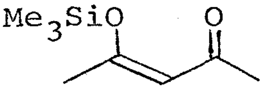
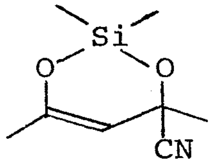
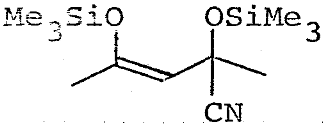
As a reason of this, it is easy to consider that the electron deficiency of the enol silyl ether made this reaction interfere. And this led me to attempt the reaction of 5-cyano-2,6-dioxa-1-silacyclohex-3-enes, in which carbonyl group was masked by cyanosilylation, with zinc carbenoid reagents. However, this reaction faced to the predominant desilylation reaction of starting silyl compounds. This perhaps is due to the facile interaction of 1,3-dioxa moieties with zinc salts which would cause desilylation and condensation of β-diketones.

Further investigation based on these observations cannot be apart from examining more improved procedure of cyclopropanation. As for the reaction of enol silyl ethers of β-diketones, the employment of more bulky silyl group in the place of trimethylsilyl group may be one of the choice.

The brief results of the attempted cyclopropanations are listed in the following Table.

Table. Attempted Cyclopropanation of Enol Silyl Ethers.

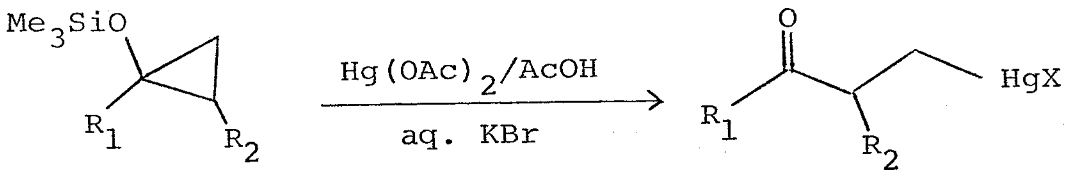
Enol Silyl Ethers	Zinc Carbenoids	Results
	$ZnEt_2$-CH_2I_2	 as a major product (30 %).
	$ZnEt_2$-CH_2I_2	no reaction (recovering substrate)
	$ZnEt_2$-CH_2I_2	complex (including isomerization product)

	Zn(Cu)-CH_2I_2[16] Zn(Ag)-CH_2I_2[17] $ZnEt_2$ -CH_2I_2	complex or a quite low yield
	Zn(Cu)-CH_2I_2 Zn(Ag)-CH_2I_2[17] $ZnEt_2$ -CH_2I_2	complex
	Zn(Cu)-CH_2I_2 Zn(Ag)-CH_2I_2[17] $ZnEt_2$ -CH_2I_2	complex or a quite low yield

4-4 Reaction of Cyclopropyl Silyl Ethers with Metal Salts

A variety of reactions of cyclopropanols with metal salts have been previously known.[2] It seems interesting to make a short comment on them here.

DePuy et al. have reported the reaction of cyclopropanols with ferric chloride or mercuric acetate in detail with respect to ring cleavage patterns.[18] Ring cleavage reaction induced by these two metal salts seems completely comparable. The chlorination reaction by ferric chloride takes place regiospecific ring cleavage between hydroxy-carbon and adjacent higher substituted carbon (C_1-C_2 cleavage). On the other hand, the reaction with mercuric acetate takes place in high regiospecific manner to give β-mercuro ketones which are resultant from the attack of mercury ion (II) to the less-substituted carbon atom of cyclopropane ring (C_1-C_3) cleavage).



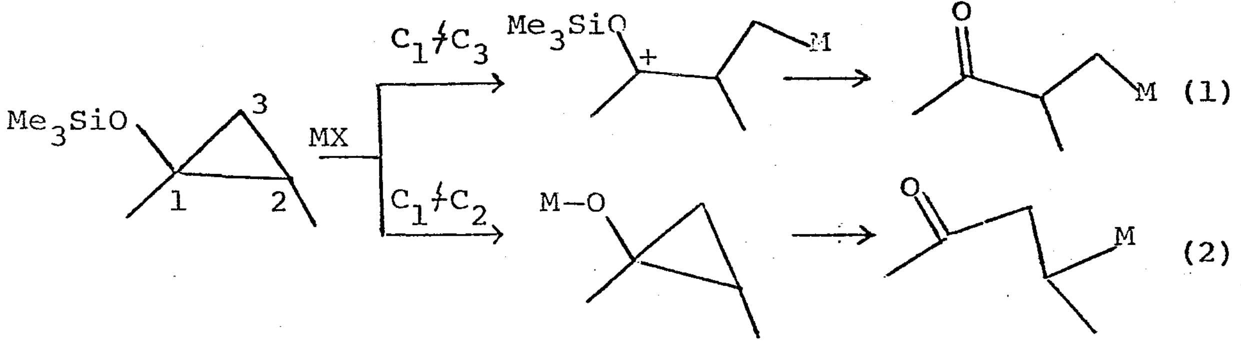
R_1=Ph, R_2=H 87% (X=Br)
R_1=Ph, R_2=Me 86%

Above fascinating results were enabled to combine with synthetic applications by adopting cyclopropyl silyl ethers as 'stable' synthetic equivalent of cyclopropanols.

The reaction of cyclopropyl silyl ether with ferric chloride in DMF was recently reported by Ito, Saegusa, et al.[19] This method followed by dehydrogen chlorination showed a excellent synthesis of α,β-unsaturated ketones from cyclopropyl silyl ethers. It seems notable that in bicyclic systems the ring cleavage at central bond with ring expansion occurrs to lead the formation of carbon-halogen bond formation at β-position of carbonyl group.[20]

The reaction of cyclopropyl silyl ethers with mercuric acetate was undertaken by this, and the results showed the selective cleavage of expheral C-C bond cleavage and the carbon-metal bond formation at β-position of carbonyl group (see p.89).

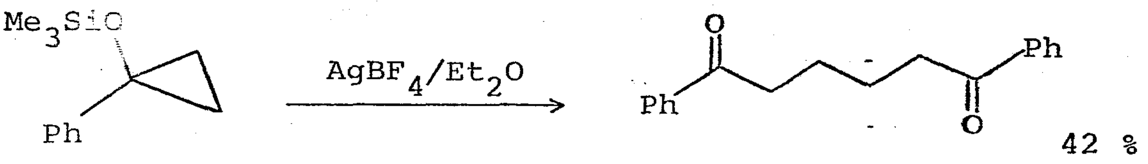
It is not hard to assume the tentative reaction path which well accounts for the differences of cleavage pattern by changing the metal salts.



The reaction with ferric chloride may be understood in terms of equation (2), and that with mercuric acetate in terms of equation (1).

The reaction tentavely classified into equation (2) was found with various types of metal salts which have an oxidazing ability. Palladium chloride, palladium acetate, cerric ammonium nitrate, chromium trioxide, etc. may be mentioned as such metal salts.[21]The reaction of 1-trimethylsiloxybicyclo[3.1.0]hexane with these metal salts yielded directly cyclohexenone (20-60 %), though improvement in both yield and selectivity should be necessary.

While, the reaction of cyclopropyl silyl ethers with silver tetrafluoroborate gave especially notable results. In the reaction of 1-trimethylsiloxy-1-phenyl-cyclopropane with silver tetrafluoroborate, oxidative cleavage of cyclopropane ring accompanied by C-C coupling took place to give 1,6-diketone in 42 % yield. To the best knowledge, this is the first example of the C-C coupling reaction at β-position from carbonyl carbon starting from cyclopropyl silyl ethers.[22]



The reaction mechanism for the present C-C coupling reaction must wait for more accumulations of data.[23,24]

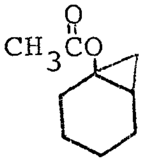
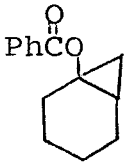
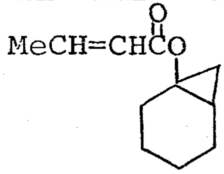
4-5 Experimental

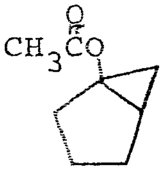
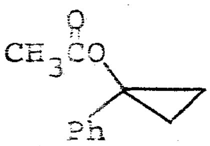
Cyclopropyl Esters:

General Procedure.

To a stirred suspension of zinc-copper couple (0.16 mol) and anhydrous ether (110 ml) were added enol silyl ether (0.05 mol) and methylene iodide (0.08 mol), and the mixture was refluxed for 21 hr. Then acid halide (0.05 mol) was slowly added to the reaction mixture, which contained zinc iodide as well as cyclopropyl silyl ether, and the mixture was refluxed for another 3 hr. After usual work-up (NH_4Cl, $NaHCO_3$, H_2O), the vacuum distillation of the ethereal solution gave cyclopropyl acetate.

Spectral and Analytical Data of Cyclopropyl Esters.

Cyclopropyl Ester	IR(neat) cm^{-1}	Mass m/e	NMR(CCl_4) δ	Anal. Found(Calcd)
	3050 1750	154(M^+)	0.25-0.9 (c,2H) 1.90(s,3H) 0.90-2.25 (m,9H)	C:69.78 (70.10) H: 9.17 (9.15)
	3050 1735 1458 1280 710	216(M^+) 111 (P-PhCO) 105 (PhCO)	0.52(apparent t, 1H) 0.80-2.40 (c,10H) 7.05-8.10 (m, 5H)	C:77.47 (77.25) H: 7.49 (7.46)
	3050 1736 1175	180(M^+) 165(P-Me) 111	0.36(apparent t, 1H) 0.67-2.78 (c,10H) 1.80(d,3H) 5.58(d-d,1H) 6.51-6.98 (m,1H)	C:73.05 (73.30) H: 8.68 (8.95)

	3050 1754 1209	140 (M^+) 125 (P-Me) 97 (P-MeCO)	0.70 (apparent s, 1H) 0.81 (apparent s, 1H) 0.85-2.38 (c, 7H) 1.92 (s, 3H)	C:68.18 (68.54) H: 8.73 (8.63)
	3060 1760 1450	176 (M^+) 161 (P-Me) 133 (P-MeCO)	1.55 (s, 4H) 1.88 (s, 3H) 6.90-7.40 (m, 5H)	C:74.83 (74.97) H: 6.96 (6.86)

<u>Basic Hydrolysis of 3,4-Benzo-1-Trimethylsiloxybicyclo[4.1.0]-heptane——Conversion to 4,5-Benzocycloheptanone.</u>

3,4-Benzo-1-trimethylsiloxybicyclo[4.1.0]heptane (0.928 g, 4 mmol) was treated with 0.1N-NaOH (1.5 ml) in MeOH (10 ml) under reflux for 20 hr. After neutralization with 1N-HCl, the mixture was concentrated, diluted with 20 ml of ether, and washed with 20 ml of water. The aqueous layer was extracted four times with 15 ml portions of ether and the combined extract was dried over $MgSO_4$. After removal of the solvent, the resulting oil was distilled in vacuo to give 0.45 g (70 %) of 4,5-benzocycloheptanone, bp 83-85° (0.6 torr); IR(neat) 1695 cm^{-1}; NMR(CCl_4) δ 2.30-3.10 (symmetric m, 6H), 7.24 (s, 4H); Mass(m/e) 160(M^+), 118, 117.

<u>The Reaction of 1-Phenyl-1-Trimethylsiloxycyclopropane with Mercuric Acetate.</u>

Mercuric acetate (1.59 g, 5 mmol) was dissolved in 16 ml of gracial acetic acid. 1-Phenyl-1-trimethylsiloxycyclopropane (1.03 g, 5 mmol) was added to the stirred solution with a hypodermic syringe. After stirring for 1 hr, the solvent was removed on a rotary evaporator at 50°. The resulting cloudy oil was taken up in CH_2Cl_2 and filtered to remove some of the unreacted mercuric acetate. Removal of the solvent yielded an semi-solid of β-acetoxymercuro propiophenone. The crude organomercurial acetate was placed in a erlenmeyer flask with 7.5 ml of saturated KBr solution to form a solid of corresponding β-bromomercuro propiophenone. The solid was crystalized from ethanol.

β-Bromomercuro propiophenone: mp 90.0-90.6°(Lit. 90.0-90.5°[18]); Ir (KBr) 1680 cm^{-1}; NMR($CDCl_3$) δ 1.97 (t, 2H), 3.58 (t, 2H), 7.59 (m,3H), 8.00(m, 2H).

The Reaction of 1-Phenyl-1-Trimethylsiloxycyclopropane with Silver Tetrafluoroborate.

Silver tetrafluoroborate (6 mmol) was treated with Molecular Sieve 5A in diethyl ether (30 ml) overnight. The mixture was cooled to -30° with Dry Ice-acetone bath and then 1-phenyl-1-trimethylsiloxycyclopropane (1.03 g, 5 mmol) was added to the mixture with hypodermic syringe. The stirred mixture was gradually allowed to warm up to room temperature over a period of 2 hr. Silver mirror appeared on the surface of reaction vessel as the reaction proceeded. Then, K_2CO_3 (0.35 g, 2.5 mmol) was added to the mixture, and the mixture was stirred for another 1 hr. After filtration followed by ether washing, the filtrate was concentrated and chromatographed on silica gel (Kieselgel 60, Merck) with n-pentane, benzene, or ether as eluent. The second elute in benzene was concentrated under reduced pressure to give an oily residue, which readily crystalized. Recrystalization from MeOH gave 1,6-diphenyl-1,6-hexadione(42 %). This elute also contained unidentified two by-products.

1,6-Diphenyl-1,6-hexadione: mp 110-112° (106-108°, Aldrich), IR($CDCl_3$) 1675 cm^{-1}($\nu_{C=O}$) [identical with the authentic chart

632E from "The Aldrich Library of Infrared Spectra"]; NMR ($CDCl_3$) δ 1.65-2.00 (m, 4H), 2.85-3.20 (m, 4H), 7.20-7.65 (m, 6H), 7.70-8.10 (m, 4H) [identical with the authentic chart 10c from "The Aldrich Library of NMR Spectra Vol. VI".

4-6 References and Notes

(1) See reference (2) in Chapter 2.

(2) C. H. DePuy, Acc. Chem. Res., <u>1</u>, 33 (1968); D. H. Gibson and C. H. DePuy, Chem. Rev., <u>74</u>, 605 (1974).

(3) There have been some reports on the formation of esters from alkoxysilanes and acid halides (in drastic conditions or poor yields[ref. (4)].

(4) R. O. Sauer and W. Patnode, J. Am. Chem. Soc., <u>67</u>, 1548 (1945); A. F. Reilly and H. W. Post, J. Org. Chem., <u>16</u>, 387 (1951); R. LeGoaller and P. Amaud, C. R. Acad. Sci., Paris, Ser. C, 1364 (1967).

(5) H. Hart and R. H. Schlosberg, J. Am. Chem. Soc., <u>90</u>, 5189 (1968). Also see M. P. Doyle and T. R. Bade, Tetrahedron Lett., 2727 (1973).

(6) A. Nickon and J. L. Lambert, S. J., J. Am. Chem. Soc., <u>88</u>, 1905 (1966). Also see ref. (2).

(7) As one of synthetic equivalents of homoenolate anion, oxy-allylic anion has been known.

D. A. Evans, G. C. Andrews, and B. Buckwalter, J. Am. Chem. Soc., 96, 5560 (1974); W. C. Still and T. L. Macdonald, ibid., 96, 5561 (1974).

(8) For example, the reaction of benzoyl chloride with mono-enol silyl ether of carboethoxy-acetone gave both C-benzoylated and O-benzoylated products, whereas the reaction of benzaldehyde with mono-enol silyl ether of acetyl acetone yielded only C-alkylated product.
U. Schmidt and M. Schwachau, Monatsh Chem., 98, 1492 (1967); idem., Tetrahedron Lett., 4491 (1967).

(9) (a) T. Mukaiyama and K. Saigo, Chem. Lett., 479 (1973).
(b) T. Mukaiyama, T. Izawa, and K. Saigo, ibid, 323 (1974).
(c) T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96, 7503 (1974).

(10) J. Pless, J. Org. Chem., 39, 2644 (1974).

(11) Generation of ammonium enolate by treatment of enol silyl ether with tetra-n-butyl ammonium fluoride has been known.
I. Kuwajima and E. Nakamura, J. Am. Chem. Soc., 97, 3257 (1975).

(12) It might be one of choices to employ 3,4-benzo-derivative of 1-trimethylsiloxy-bicyclo[4.1.0]heptane as starting cyclopropyl silyl ether.

(13) K. Sato and S. Inoue, J. Syn. Org. Chem. Jap., 35, 950 (1977).

(14) Dihalocarbene adduct of enol silyl ethers of cyclic ketones undergo facile ring expansion.
G. Stork and T. L. Macdonald, J. Am. Chem. Soc., 97, 1264 (1975); P. Amice, L. Blanco, and J. M. Conia, Synthesis,

196 (1975).

(15) J. E. McMurry and T. E. Glass, Tetrahedron Lett., 2575 (1971); R. M. Coates, L. O. Saundefur, and R. D. Smille, J. Am. Chem. Soc., 97, 1620(1975).

(16) J. -C. Limasset, P. Amice, and J. M. Conia, Bull. Soc. Chim. Fr., 3981 (1969).

(17) J. M. Denis, C. Girard and J. M. Conia, Synthesis, 549 (1972).

(18) C. H. DePuy and R. J. Van Lanen, J. Org. Chem., 39, 3360 (1974).

(19) Y. Ito, S. Fujii, and T. Saegusa, J. Org. Chem., 41, 2073 (1976); Y. Ito and T. Saegusa, ibid., 42, 2326 (1977).

(20) Recently oxidative cleavage reaction by lead (IV) acetate was reported. G. M. Rubottom, R. Marrer, D. S. Krueger, and J. L. Schreiner, Tetrahedron Lett., 4013 (1977).

(21) The oxidation of cyclopropanol with chromic acid has been reported by Rocek et al.
J. Rocek, A. M. Martinez, and G. E. Cushmac, J. Am. Chem. Soc., 95, 5425 (1973).

(22) 1,4-Diketone synthesis by C-C coupling at α-position of carbonyl group, which was resulted from the reaction of enol silyl ethers with Ag_2O.
Y. Ito, T. Konoike, and T. Saegusa, J. Am. Chem. Soc., 97, 649 (1975).

(23) It is not clear at the present time whether the reaction was initiated by O-attack or C-attack of Ag(I).

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