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TRIMETHYSILYL TRIFLATE IN ORGANIC SYNTHESIS[1]

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Abstract—Trimethylsilyl triflate is a powerful silylating agent for organic compounds and acts as a catalyst which accelerates a variety of nucleophilic reactions in aprotic media. The reactions proceed via one-center, electrophilic coordination of the silyl group to hetero functional groups and exhibit unique selectivities.

The title compound (abbreviated to TMSOTf, **1**) is a readily accessible derivative of trifluoromethanesulfonic acid, a superacid.[2,3] It forms a colorless, fluid liquid boiling at 45–47° at 17 mm Hg and dissolves in aliphatic or aromatic hydrocarbons and haloalkanes without any reactions. Although the Si–O bond in **1** is covalent (rather than ionic) in nature, the Si atom is endowed with eminent electron deficiency by the presence of the electron-withdrawing trifluoromethanesulfonyl moiety attached to it. Indeed the NMR spectrum exhibits the ^{29}Si signal at the lowest field compared with those of any known trimethylsilyl derivatives.[2] As a consequence, the Si atom in **1** can interact strongly to various heteroatoms, particularly oxygen, in organic compounds to generate the corresponding silylated onium ions which have only feebly basic or nucleophilic triflate as the counter anion. Since Si atom in ordinary organosilicon compounds can accept only four ligands in the ground state, the silyl group tends to bind to a single hetero functional group. This lies in sharp contrast to conventional Lewis acids such as $AlCl_3$, $SnCl_4$, $TiCl_4$, etc., which are capable of assembling more than two functional groups onto the same metal center. In addition, **1** possesses three covalent Si–Me bonds and, in consequence, avoids complexities frequently encountered with ordinary Lewis acids, viz. aggregation and disproportionation or ligand exchange reaction arising from metal–halogen (or other heteroatom) bond rupture. Thus, organic substrates activated through such one-center, electrophilic coordination of the trimethylsilyl moiety can act as a supercationic species in hydrocarbon or haloalkane media, and may display unique chemical behavior not observable in reactions under conventional conditions. Described herein is utilization of such characteristics of **1** in organic synthesis

STOICHIOMETRIC USE OF TRIMETHYLSILYL TRIFLATE

Ring opening reactions of oxiranes

Silyl triflate **1** is a powerful silylating agent and a wide range of active hydrogen compounds are silylated in the presence of amines.[4] The reaction is initiated by coordination of the trimethylsilyl group to a heteroatom in the substrates. We have examined the reaction of **1** with a series of oxiranes which contain a highly basic O atom and found a variety of characteristic transformations.

A. Oxirane to allylic alcohol conversion.[5] Exposure of an oxirane **2** with equimolar amounts of **1** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (or a 1:1 mixture of **1** and 2,6-lutidine and then DBU) gives the isomeric allyl silyl ether **3**, deprotection of which by dil HCl or methanolic KF affords the allylic alcohol **4**. As shown in Table 1, tetra-, tri- and 2,2-disubstituted oxiranes and substrates derived from cyclic olefins of ordinary ring size can be used.

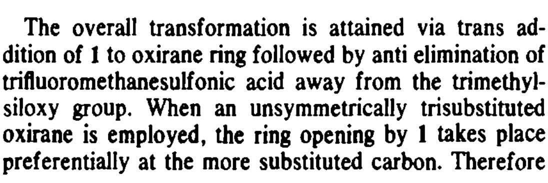


Fig. 1.

The overall transformation is attained via trans addition of **1** to oxirane ring followed by anti elimination of trifluoromethanesulfonic acid away from the trimethylsiloxy group. When an unsymmetrically trisubstituted oxirane is employed, the ring opening by **1** takes place preferentially at the more substituted carbon. Therefore

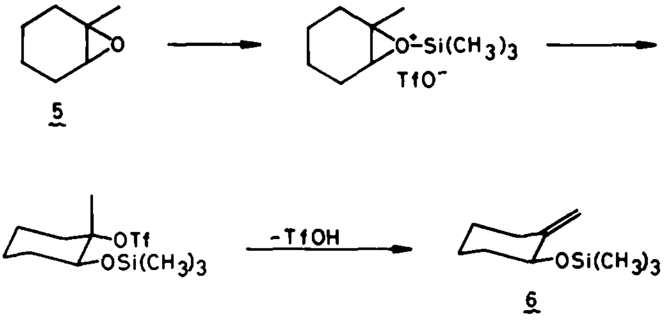


Fig. 2.

Table 1. Reaction of oxiranes and TMSOTf (1)[a]

oxirane	conditions (temp, °C/time, h)	product (% yield)
cyclopentene oxide	**1**, DBU (29/5)	3-trimethylsiloxycyclopentene (59)
cyclohexene oxide	**1**, DBU (22/20)	3-trimethylsiloxycyclohexene (87)
cycloheptene oxide	**1**, DBU (22/14)	3-trimethylsiloxycycloheptene (40, 100[b])
(E)-cyclododecene oxide	**1**, DBU (27/40)	3-trimethylsiloxycyclododecene (38)
2,3-dimethyl-2-butene oxide	1. **1**, Lu (-78/4) 2. DBU (15/5)	2,3-dimethyl-3-trimethylsiloxy-butene (87)
methylcyclohexene oxide	1. **1**, Lu (-78/3) 2. DBU (24/3)	1-methylene-2-trimethylsiloxy-cyclohexane (80)
methylenecyclohexane oxide	1. **1**, Lu (-78/3) 2. DBU (30/14)	1-trimethylsiloxymethylcyclohexene (72)
isobutene oxide	1. **1**, Lu (-78/10) 2. DBU (13/0.5)	2-methyl-3-trimethylsiloxypropene (62)
citronellol oxide	1. **1**[c], Lu[c] (-78/5) 2. DBU (28/4)	2,6-dimethyl-3,8-bis(trimethyl-siloxy)octene (71)
4,8-dimethyl-7-nonen-2-one oxide	1. **1**, Lu (-78/4) 2. DBU (20/0.5)	4,8-dimethyl-7-trimethylsiloxy-8-nonen-2-one (69)
methyl citronellate oxide	1. **1**, Lu (-78/4) 2. DBU (15/2)	methyl 3,7-dimethyl-6-trimethyl-siloxy-7-octanoate (79)
geraniol 2,3-oxide	1. **1**[c], Lu[c] (-78/5) 2. DBU (30/54)	(E)-2,6-dimethyl-7,8-bis(trimethyl-siloxy)-2,5-octadiene (66)
nerol 2,3-oxide	1. **1**[c], Lu[c] (-78/3) 2. DBU (32/14)	(E)-2,6-dimethyl-7,8-bis(trimethyl-siloxy)-2,5-octadiene (65) and 2-methy-6-methylene-7,8-bis(tri-methylsiloxy)-2-octene (16)

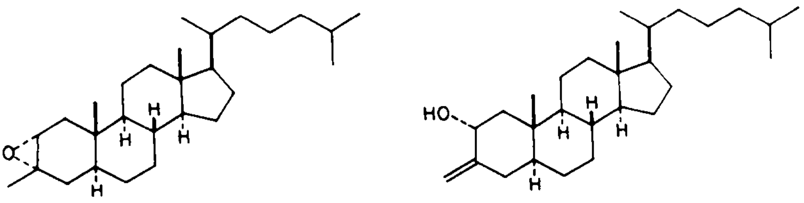
[a] Lu = 2,6-lutidine. Py = pyridine. Unless otherwise stated, the reaction was carried out in benzene (room temperature) or toluene (low temperature) using 1 equiv of TMSOTf, Lu, and DBU. [b] Conversion was 40%. [c] Two equivalents. [d] Total yield.

the reaction of the oxirane **5** affords regioselectively the product **6**. In a like manner, the reaction of the steroidal substrate **7** with **1** and 2,6-di-t-butylpyridine at – 78° gives after deprotection the alcohol **8** exclusively.[6] The regio- and stereochemical outcome observed with geraniol and nerol 2,3-oxide (Table 1) also agrees with this mechanism.

Simple 2,3-dialkylated and monoalkylated oxiranes are inert to the standard reaction conditions. These substrates under forcing conditions produce enol silyl ethers via carbocation intermediates. Cyclooctene oxide undergoes transannular reaction giving *endo-cis*-2-trimethylsiloxy-bicyclo[3.3.0]octane.

3-*Trimethylsiloxycyclohexene*. To TMSOTf (10.2 mmol) dissolved in benzene (20 ml) was added a mixture of cyclohexene oxide (10.7 mmol) and DBU (2 ml) in benzene (5 ml). After being stirred at 22° for 20 hr, the mixture was poured onto a silica gel column and eluted (2 : 1 hexane/ether mixture as eluant). The eluates were concentrated (200 mmHg) and distilled to give the desired allylic silyl ether, bp 50–60°/50 mm Hg, 87% yield.

1-*Methylene*-2-*trimethylsiloxycyclohexane*. To a mixture of TMSOTf (3.17 mmol) and 2,6-lutidine (0.37 ml) in toluene (5 ml) was added methylcyclohexene oxide (3.28 mmol) at – 78°. After stirring at – 78° for 2 hr, DBU (0.55 ml) was added. The resulting mixture was stirred at 24° for an additional 3 hr, poured into 0.1 N HCl, and extracted with hexane. The extracts were chromoatographed on silica gel (2 : 3 benzene/hexane mixture as



7 **8**

Fig. 3.

eluant) to give the product having an exocyclic double bond in 80% yield.

B. Neighboring-atom or -bond participation in the ring opening.[6] The isomerization giving allyl silyl ethers is not the sole pathway of the TMSOTf promoted reaction of oxiranes. If the oxirane substrate contains some nucleophilic atom or bond at the suitable position, the ring opening may be facilitated by electron release from such moiety.

The oxirane **9** undergoes clean cyclization via neighboring CO group participation to give **10** in 80% yield. Certain C-C σ bonds also participate in the skeletal transformation accompanying the oxirane ring opening. For instance, trans addition of **1** to the steroidal oxirane **11** is quite difficult because of the steric hindrance by the 13 Me. Instead, by assistance of **1**, this angular Me group undergoes 1,2-migration to form after desilylation the alcoholic product **12** in 86% yield. α-Pinene oxide (**13**) suffers ready cleavage of the 4-membered ring, resulting in *trans*-carveol (**14**) in 72% yield.

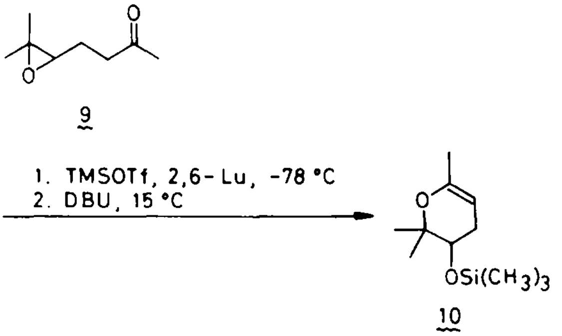
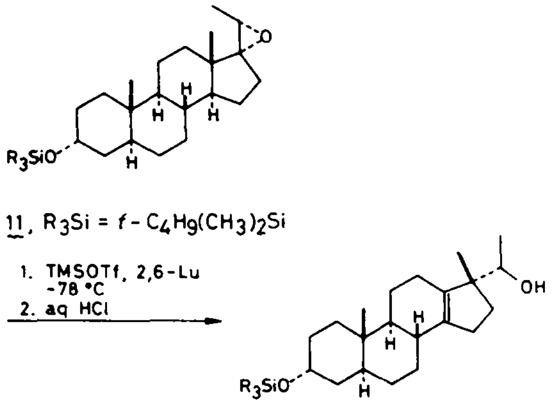


Fig. 4.



11, $R_3Si = t\text{-}C_4H_9(CH_3)_2Si$

12, $R_3Si = t\text{-}C_4H_9(CH_3)_2Si$

Fig. 5.

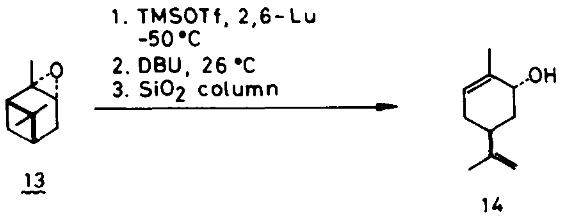


Fig. 6.

Conformationally selective transannular cyclization of humulene oxides is also a subject of interest. Reaction of **1** and humulene 9,10-oxide (**15**) which exists in the CT conformer (toluene, 2,6-lutidine, −20 to −10°) leads smoothly to the tricyclic structure **16** (two isomers, 80% combined yield) via intramolecular C=C bond participation. This product is convertible to (±)-africanol.[7] The 6,7-oxide **17** gives rise to the tricyclic alcohol **18** in 76% yield.[8]

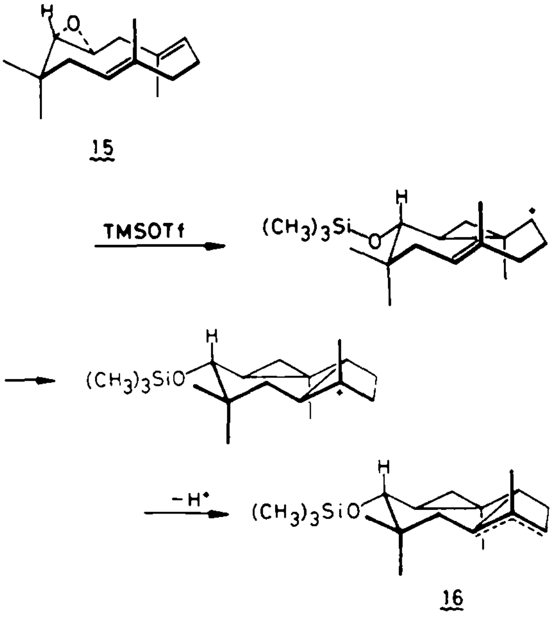


Fig. 7.

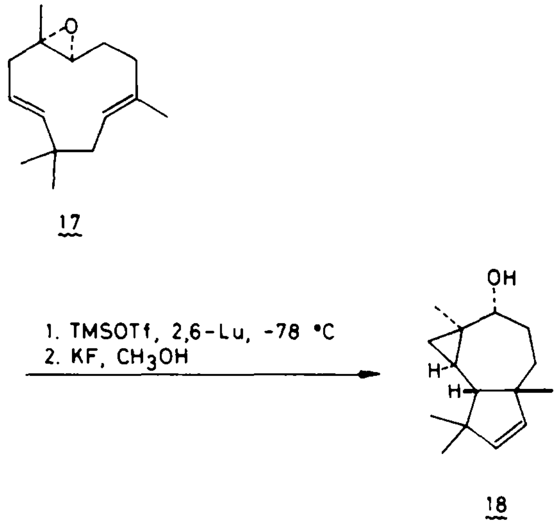


Fig. 8.

Ring opening of some epoxy nitrones with **1** is known to generate reactive alkenyl nitrosonium ions which undergo cycloaddition across olefinic substrates.[9]

C. Deoxygenation of oxiranes.[6] Squalene 2,3-oxide (**19**) is deoxygenated in 70% yield under the above described conditions. The mechanism has not yet been elucidated, however.

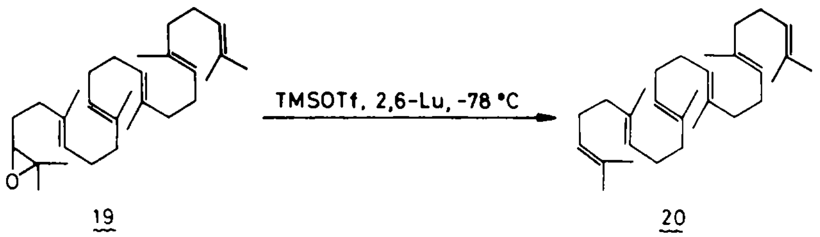


Fig. 9.

Penam to cephem skeletal conversion[6]

The sulfenic acid trimethylsilyl ester **21** is readily available from the corresponding penicillin sulfoxide. When **21** is exposed ot 1.5 equiv of **1** in dichloromethane (15°, 12 hr), the disacetoxycephalosporin **22** is obtained in 58% yield under elimination of a trimethylsilanol element.

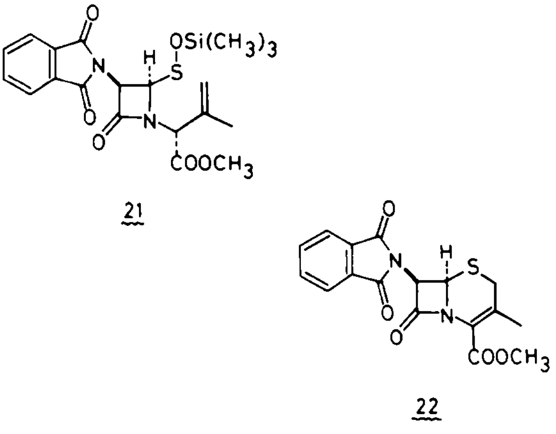


Fig. 10.

CATALYTIC USE OF TRIMETHYLSILYL TRIFLATE

Certain O-containing compounds such as aldehydes, ketones, ortho esters, some t-alkyl esters or ethers, are viewed as latent carbocations masked by an O atom(s). The highly oxophilic agent **1** can activate these substances to allow the electron-deficient center reacting with various nucleophiles, as generally recognized in acid promoted polar reactions. Here if the nucleophilic reagents are bound to trimethylsilyl group, the reaction can be made catalytic, where the silyl moiety serves as the chain carrier. Described below are some versatile reactions realized under very mild, aprotic conditions.

A. Reactions with heteroatom-centered nucleophiles. Tertiary (but not primary or secondary) alkyl or aralkyl trimethylsilyl ethers react with a variety of silylated oxygen nucleophiles with the aid of catalytic amount of **1**.[1,10] As exemplified in Table 2, alkyl trimethylsilyl ethers, phenyl trimethylsilyl ether, trimethylsilyl carboxylates are employable as the nucleophilic agents. This reaction provides a convenient tool for tritylation of carboxylic acids.

$$R_3COSi(CH_3)_3 + (CH_3)_3SiOR' \xrightarrow[-[(CH_3)_3Si]_2O]{\text{cat TMSOTf}} R_3COR'$$

Trityl methacrylate. To a mixture of trityloxytrimethylsilane (10 mmol) and trimethylsilyl methacrylate (10 mmol) in CH_2Cl_2 (50 ml) was added a CH_2Cl_2 soln of TMSOTf (0.1 mmol) at 0°. After the mixture was stirred at 0° for 6 hr, a few drops of pyridine was added. Quenching with saturated $NaHCO_3$ aq was followed by extraction with CH_2Cl_2. The extracts were dried over K_2CO_3 and chromatographed on silica gel (15 : 1 petroleum ether/ether mixture as eluant) to afford the trityl ester, m.p. 98–99°, 73% yield.

Aldehydes and ketones are readily acetalized by a stoichiometric amount (2 equiv) of alkyl trimethylsilyl ethers in the presence of **1**.[11] The reaction is achievable in dichloromethane at temperatures as low as −78°. Some examples are given in Table 3. 2-Cyclohexenone, a typical α,β-unsaturated ketone, is acetalyzed without concomitant double-bond migration; the double bond in 3-cyclohexenone or 3-cyclopentenone does not shift either.

$$R_2C{=}O + 2(CH_3)_3SiOR' \xrightarrow[-[(CH_3)_3Si]_2O]{\text{cat TMSOTf}} R_2C(OR')_2$$

Benzaldehyde dimethyl acetal. To a CH_2Cl_2 soln (1 ml) containing TMSOTf (0.1 mmol) were successively added methoxytrimethylsilane (20 mmol) and benzaldehyde (10 mmol) at −78°. The mixture was stirred at this temperature for 3 hr, quenched with dry pyridine (0.2 ml), poured into saturated $NaHCO_3$ aq, extracted with ether, dried over a 1 : 1 mixture of Na_2CO_3 and

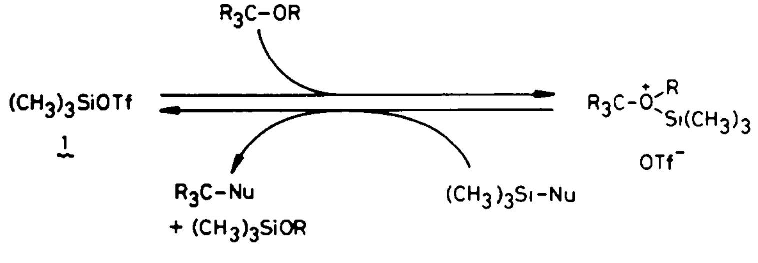


Fig. 11.

Table 2. *O*-tritylation and -*tert*-Butylation Catalyzed by TMSOTf (1)[a]

$R_3COSi(CH_3)_3$	$R'OSi(CH_3)_3$	conditions temp, °C/time, h	% yield of product
trityloxytrimethylsilane	ethoxytrimethylsilane	0/0.5	97
trityloxytrimethylsilane	2,3,5-tris(*O*-trimethylsilyl)-*O*-methyl-β-*D*-ribofuranose	0/0.5	85[b]
trityloxytrimethylsilane	phenoxytrimethylsilane	14/18	98
trityloxytrimethylsilane	trimethylsilyl decanoate	15/4	78
trityloxytrimethylsilane	trimethylsilyl methacrylate	0/6	73
trityloxytrimethylsilane	trimethylsilyl benzoate	0/2	86
tert-butoxytrimethylsilane	trimethylsilyl decanoate	14/70	37

[a] The reaction was carried out in dichloromethane using $R_3COSi(CH_3)_3$, $R'OSi(CH_3)_3$, and TMSOTf in 1:1:0.01 mol ratio. [b] A 1:3 mixture of α and β isomers.

Table 3. Acetalization of carbonyl compounds with alkoxysilanes catalyzed by TMSOTf (1)[a]

carbonyl substance	alkoxysilane	conditions temp, °C/time, h	% yield of acetal product
cyclohexanone	$(CH_3)_3SiOCH_3$	-78/3	89
cyclohexanone	$[(CH_3)_3SiOCH_2]_2$	-78/4	96
cyclohexanone	$(CH_3)_3SiOCH_2C_6H_5$	-78/20	99
cyclopentanone	$(CH_3)_3SiOCH_3$	-78/3	90
benzaldehyde	$(CH_3)_3SiOCH_3$	-78/3	94
2-cyclohexenone	$[(CH_3)_3SiOCH_2]_2$	-78/20	92
3-cyclohexenone	$[(CH_3)_3SiOCH_2]_2$	-78/3 and -20/0.2	99
3-cyclopentenone	$[(CH_3)_3SiOCH_2]_2$	-78/4	94

[a] Reaction was carried out in dichloromethane using stoichiometric amounts of a carbonyl compound and an alkoxysilane and 1 mol % of 1.

Na_2SO_4, and evaporated. Bulb-to-bulb distillation gave the acetal, b.p. 125–135°/51 mmHg, 94%.

Thioacetalization can be performed in a similar manner.[6] For instance, reaction of cyclohexanone and 2 equiv of ethylthiotrimethylsilane with 1 mol % of 1 (CH_2Cl_2, − 78°, 10 hr) forms the thioacetal 23 in 84% yield.

N-centered nucleophiles also enter into the catalytic reaction. Thus the reaction of butanal dimethyl acetal reacts with 2-trimethylsiloxpyridine in the presence of 1 (CH_2Cl_2, − 78°, 3 hr) to give the pyridine 24 in 99% yield.[12] This type of displacement reactions have been utilized successfully in nucleoside synthesis.[13] Trimethylsilyl azide is usable as a nucleophile as well.[14]

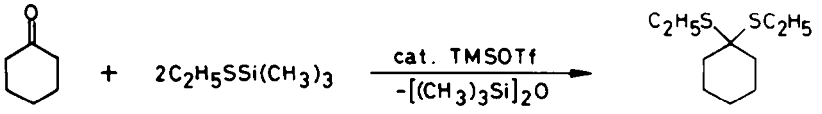


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Fig. 12.

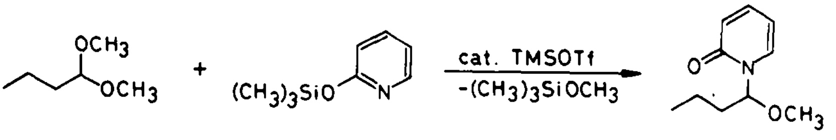

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Fig. 13.

B. Reaction with trialkylsilanes (hydrogen nucleophiles).[15] Trialkylsilanes act as a hydride transfer agent toward acetals. Thus various ethers are derived from acetals in dichloromethane under mild conditions, as shown in Table 4. When a ketone is used in place of acetals, a significant amount of dimeric ether is produced. For instance, reaction of cyclohexanone with trimethylsilane under the standard conditions gives dicyclohexyl ether in 86% yield.

$$R_2C(OCH_3)_2 + R'_3SiH \xrightarrow[-R'_3SiOCH_3]{\text{cat TMSOTf}} R_2CHOCH_3$$

Benzyl methyl ether. To a CH_2Cl_2 soln (0.5 ml) of TMSOTf (0.05 mmol) were added successively trimethylsilane (5.7 mmol) and benzaldehyde dimethyl acetal (5.1 mmol) at 0°. The mixture was stirred at 0° for 30 min and then at 28° for 13 hr, poured into saturated $NaHCO_3$ aq, extracted with ether, and dried over Na_2SO_4. Evaporation gave the ethereal product in 96% yield.

C. Reaction with carbon-centered nucleophiles. Cyanohydrin trimethylsilyl ethers are readily formed by the TMSOTf catalyzed reaction of ketones and cyanotrimethylsilane in dichloromethane.[6] Some examples are listed in Table 5.

$$R_2C{=}O + (CH_3)_3SiCN \xrightarrow{\text{cat. TMSOTf}} R_2C(CN)OSi(CH_3)_3$$

Table 4. Reaction of acetals and trialkylsilanes in the presence of TMSOTf (1)[a]

acetal	trialkysilane	% yield of ether product
butyraldehyde dimethyl acetal	$(CH_3)_3SiH$	100
benzaldehyde dimethyl acetal	$(CH_3)_3SiH$	96
benzaldehyde dimethyl acetal	$(C_2H_5)_3SiH$[b]	90
3-pentanone dimethyl acetal	$(CH_3)_3SiH$	100
cyclohexanone dimethyl acetal	$(CH_3)_3SiH$	100
4-tert-butylcyclohexanone dimethyl acetal	$(CH_3)_3SiH$	89[c]

[a] The reaction was conducted in dichloromethane using an acetal, trialkylsilane, and 1 (1:1:0.01–0.03 mol ratio) at 0 °C for 30 min and then 24–28 °C for 12–14 h. [b] Reaction at 29 °C for 16 h. [c] cis/trans = 44:56.

Table 5. Reaction of ketones and cyanotrimethylsilane catalyzed by TMSOTf (1)[a]

ketone	conditions temp, °C/time, h	% yield of cyanohydrin trimethylsilyl ether
cyclohexanone	-78/2	90
cyclooctanone	-30/10	94
2-adamantanone	-78/14	99
acetophenone	10/10	88
α-tetralone	-30/10	88
2-cyclohexenone	-20/12	73[b]
p-benzoquinone	15/60	0

[a] The reaction was carried out in dichloromethane using a ketone, cyanotrimethylsilane, and TMSOTf (1:1:0.01 ratio). [b] 3-Cyano-1-trimethylsiloxycyclohexene as by-product in 6% yield.

The actual nucleophilic species involved in the reaction may be trimethylsilyl isocyanide. The reaction of 4-t-butylcyclohexanone leads to a mixture of **25** and **26** with the former predominating (**25** : **26** = 91 : 9). The catalyzed reaction with the dimethyl acetal derivative exhibits a similar stereoselectivity, giving the cyanohydrin methyl ether **27** and **28** in 88 : 12 ratio.

25, R = $(CH_3)_3Si$
27, R = CH_3

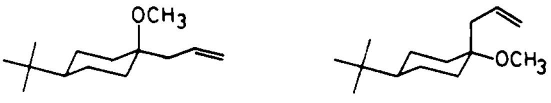
26, R = $(CH_3)_3Si$
28 R = CH_3

Fig. 14.

1-*Cyano*-1-*trimethylsiloxycyclohexane*. To a mixture of cyclohexanone (10.5 mmol) and cyanotrimethylsilane (11.1 mmol) in CH_2Cl_2 (20 ml) was added a CH_2Cl_2 soln of TMSOTf (0.1 mmol) at −78°. After the mixture was stirred at −78° for 2 hr, a few drops of pyridine was added. The resulting mixture was poured into sat $NaHCO_3$ aq. Extraction with CH_2Cl_2 followed by bulb-to-bulb distillation gave the cyanohydrin trimethylsilyl ether, b.p. 90° (bath)/6 mmHg, 90% yield.

In the presence of a catalytic amount of **1**, allyltrimethylsilane reacts with acetals at low temperatures leading to the corresponding homoallylic ethers in high yield (Table 6).[16] The reaction with 4-t-butylcyclohexanone dimethyl acetal as substrate −40° produced a mixture of **29** and **30** in favor of the equatorial-allyl isomer **29** (**29**:**30** = 97:3, 89% yield).

$$R_2C(OR')_2 + (CH_3)_3SiCH_2CH{=}CH_2 \xrightarrow[-(CH_3)_3SiOR']{\text{cat. TMSOTf}} R_2C(OR')CH_2CH{=}CH_2$$



29

30

Fig. 15.

Carbonyl compounds such as benzaldehyde, benzophenone, acetophenone, 4-t-butylcyclohexanone fail to give the allylation products. Thus the acetal function acts as an activating group, rather than a protecting group, of CO function under these conditions.

4-*Phenyl*-4-*methoxy*-1-*butene*. To a mixture of TMSOTf (0.1 mmol) and allyltrimethylsilane (11.5 mmol) in CH_2Cl_2 (1 ml) was added a soln of benzaldehyde dimethyl acetal (10.5 mmol) in CH_2Cl_2 (4 ml). The mixture was stirred at −78° for 6 hr and poured into sat $NaHCO_3$ aq. Extractive workup with ether followed by chromatography on silica gel (1 : 20 ether/hexane mixture as eluant) gave the allylated product in 88% yield.

Reaction of acetals or certain ortho esters and enol trimethylsilyl ethers, leading to the aldol type product, is achieved in dichloromethane with the aid of **1**.[17] The condensation reaction exhibits various characteristic features.

$$R_2C(OR')_2 + (CH_3)_3SiOCR^1{=}CR^2_2 \xrightarrow[-(CH_3)_3SiOR']{\text{cat. TMSOTf}} R_2C(OR')CR^2_2COR^1$$

The lack of double-bond migration in the enol silyl ether

Table 6. Reaction of acetals with allytrimethylsilane in the presence of TMSOTf (1)[a]

acetal	conditions 1, mol %	temp, °C/time, h	% yield of homoallyl ether
butanal dimethyl acetal	10	-78/1	95
benzaldehyde dimethyl acetal	10	-78/2	90
3-pentanone dimethyl acetal	10	-78/0.2, -50/1, and -30/1	89
acetophenone dimethyl acetal	10	-78/0.2 and -50/2	79
cyclohexanone dimethyl acetal	1	-60--45/18	81
cyclododecanone dimethyl acetal	10	-78/0.2 and -40/1	83
adamantanone dimethyl acetal	10	-78/0.2 and -40/1	98[b]
2-methoxytetrahydropyran	10	-50/0.2, -40/2, and 0/0.5	87[c,d]
cinnamaldehyde dimethyl acetal	10	-78--70/3	78[e]

[a] The reaction was performed in dichloromethane using an acetal and allyltrimethylsilane in 1:1 mol ratio. [b] Conversion was 59%. [c] 2-Allyltetrahydropyran. [d] Conversion was 78%. [e] (*E*)-3-Methoxy-1-phenyl-1,5-hexadiene.

under these conditions allows the regiospecific aldol reaction. Combination of an aldehyde enolate and a ketonic carbonyl, in a formal sense, is also possible by this directed condensation method. The enol silyl ethers derived from carboxylic esters or thioesters are equally employable. The structures of the products are kinetically determined and erythro-selective[18] regardless of the geometry of starting enolates, in sharp contrast to the stereoselection observed in ordinary aldol reaction involving Lewis acidic metal enolates. The erythro-directed displacement is understood in terms of the acyclic extended transition states of type 31. In the reaction with the (*E*)-enol silyl ethers, the transition state 32 giving the erythro adduct is sterically favored over the diastereoisomeric transition state 33 affording the threo adduct because the latter suffers repulsive gauche R/R^2 interaction. In a like manner, the erythro transition state 34 arising from (*Z*)-enol silyl ethers is preferable to the threo transition state 35.

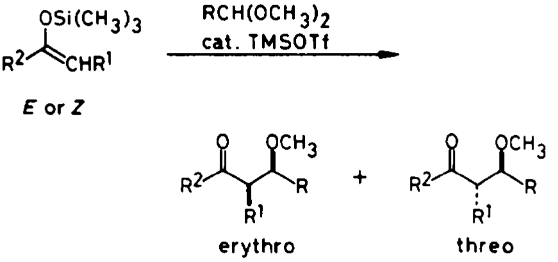
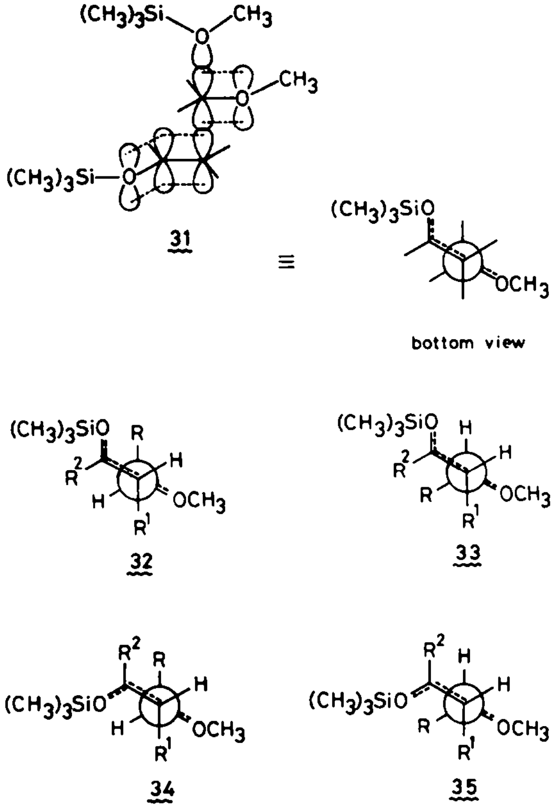


Fig. 16.



31 32 33 34 35

Fig. 17.

Table 7. Condensation of acetals or ortho esters with enol silyl ethers catalyzed by TMSOTf (1)[a]

acetal or ortho ester	enol silyl ether	conditions temp, °C/ time, h	% yield of product (erythro/threo)
butanal dimethyl acetal	1-phenyl-1-trimethylsiloxyethene	-78/10	75
butanal dimethyl acetal	1-trimethylsiloxycyclohexene	-78/12	91 (89:11)
butanal dimethyl acetal	2-methyl-1-trimethylsiloxypropene	-78/4	89
2-methylpropanal dimethyl acetal	1-trimethylsiloxycyclohexene	-78/10	95 (86:14)
2-methylpropanal dibenzyl acetal	1-phenyl-1-trimethylsiloxyethene	-30/19	73
2-methylpropanal dibenzyl acetal	3,3-dimethyl-2-trimethylsiloxybutene	-30/12	20
4-methyl-6-oxoheptanal dimethyl acetal	1-trimethylsiloxycyclohexene	-78/12	92[b]
benzaldehyde dimethyl acetal	(Z)-4,4-dimethyl-3-trimethylsiloxy-2-pentene	-78/4	94 (95:5)
benzaldehyde dimethyl acetal	(E)-1-phenyl-1-trimethylsiloxypropene	-78/5	83 (71:29)
benzaldehyde dimethyl acetal	(Z)-1-phenyl-1-trimethylsiloxypropene	-78/4	97 (84:16)
benzaldehyde dimethyl acetal	1-trimethylsiloxycyclohexene	-78/10	89 (93:7)
benzaldehyde dimethyl acetal	1-trimethylsiloxycyclohexene	-90/8	86 (92:8)

Table 7(*Contd*).

acetal or ortho ester	enol silyl ether	conditions temp, °C/ time, h	% yield of product (erythro/threo)
benzaldehyde dimethyl acetal	(E)-1-methoxy-1-trimethylsiloxypropene	-78/6	74 (50:50)
benzaldehyde dimethyl acetal	(E)-t-butylthio-1-trimethylsiloxy propene	-78/4	92 (78:22)
benzaldehyde dibenzyl acetal	(Z)-1-phenyl-1-trimethylsiloxypropene	-78/1	98[b]
acetone dimethyl acetal	1-phenyl-1-trimethylsiloxyethene	-78/12	96
acetone dimethyl acetal	1-trimethylsiloxycyclopentene	-78/10	87
acetone dimethyl acetal	1-trimethylsiloxycyclohexene	-78/10	87
acetone dimethyl acetal	6-methyl-1-trimethylsiloxycyclohexene	-78/12	89[c]
acetone dimethyl acetal	2-methyl-1-trimethylsiloxypropene	-78/4	85
acetone dimethyl acetal	3-methyl-2-trimethylsiloxy-2-butene	-78/4	87
methyl ortho formate	1-trimethylsiloxy cyclohexene	-78/12	89
2-acetoxytetrahydropyran	1-phenyl-1-trimethylsiloxyethene	-78/4	81
2-acetoxytetrahydropyran	(Z)-1-phenyl-1-trimethylsiloxypropene	-78/10	91 (62:38)
dimethoxymethane	1-trimethylsiloxycyclohexene	16/10[d]	48
dibenzyloxymethane	1-phenyl-1-trimethylsiloxyethene	17/12[d]	92
dibenzyloxymethane	(Z)-1-phenyl-1-trimethylsiloxypropene	18/12[d]	77
dibenzyloxymethane	1-trimethylsiloxycyclopentene	12/10[d]	76
dibenzyloxymethane	1-trimethylsiloxycyclopentene	12/100[e]	65
dibenzyloxymethane	1-trimethylsiloxycyclohexene	18/12[d]	87
dibenzyloxymethane	6-methyl-1-trimethylsiloxycyclohexene	14/12[d]	78[c]

[a] Unless otherwise stated, the reaction was carried out in dichloromethane using acetal or ortho ester, enol silyl ether, and TMSOTf in 1:1:0.01—0.1 mol ratio. [b] A mixture of diastereomers. [c] A mixture of cis- and trans-isomers. [d] A 1:1 mixture of TMSOTf and 2,6-di-tert-butylpyridine (5—10 mol %) was used as the catalyst system. [e] A 1:1 mixture of TMSOTf and dicyclohexylmethylamine (10 mol %) was used as the catalyst system.

The reaction using simple dialkoxymethanes as the electrophilic agent requires the addition of a catalytic amount of a hindered base such as 2,6-di-t-butylpyridine or dicyclohexylmethylamine.[19]

Carbonyl compounds are much less reactive compared with the corresponding acetal derivatives and exhibits a lower degree of stereoselectivity. For instance, the TMSOTf catalyzed reaction of benzaldehyde dimethyl acetal and 1-trimethylsiloxycyclohexene proceeds smoothly in dichloromethane at −90° to give a diastereomeric mixture of aldol methyl ethers in 86% yield and in erythro/threo ratio of 92 : 8. Whereas the corresponding reaction of benzaldehyde takes place only at room temperature; in dichloromethane only 2-benzylidenecyclohexanone is obtained (85%) and the reaction in toluene produces a 49 : 51 mixture of erythro and threo aldols as trimethylsilyl ethers (60%). Ordinary alkanals do not enter the aldol reaction.

2-Methoxybenzylcyclohexanone. To a soln of 1-trimethylsilocycyclohexane (5.12 mmol) and benzaldehyde dimethyl acetal (5.47 mmol) in CH_2Cl_2 (15 ml) was added a CH_2Cl_2 soln of TMSOTf (0.05 mmol) at −78°. After the mixture was stirred at −78° for 8 hr, water was added. The product was extracted with ether and chromatographed on silica gel (10 : 1 petroleum ether/ether mixture as eluant) to give *erythro*-2-methoxybenzylcyclohexane (less polar, 82% yield) and its threo isomer (more polar, 6.7% yield).

2-Benzyloxymethylcyclopentanone. To a soln of 1-trimethylsiloxycyclopentene (3.1 mmol), dibenzyloxymethane (3.1 mmol), and 2,6-di-t-butylpyridine (0.33 mmol) in CH_2Cl_2 (7 ml) was added a CH_2Cl_2 soln of TMSOTf (0.33 mmol) at 12°. The mixture was stirred at 12° for 10 hr and quenched by saturated $NaHCO_3$ aq. Extraction with CH_2Cl_2 followed by chromatography on silica gel (3 : 1 petroleum ether/ether mixture as eluant) gave the desired adduct in 76% yield.

When a mixture of propionic anhydride and 1-trimethylsiloxycyclohexene is treated with **1** (10 mol%) dissolved in CH_2Cl_2 (17°, 12 hr), the C-acylated product **36** is formed in 61% yield.[12]

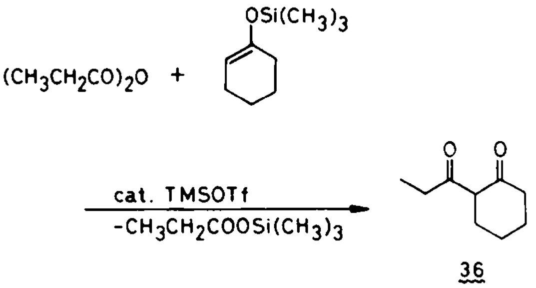


Fig. 18.

D. Reaction with a selenium nucleophile. Phenyl trimethylsilyl selenide, unlike silyl ethers or thioethers, undergoes conjugate addition toward α,β-unsaturated ketones in dichloromethane containing a catalytic amount of **1** (−78°), 0.5 hr), resulting in the formation of positionally defined enol silyl ethers. Subsequent reaction with acetals or ortho esters (−50 to −20°, 0.5 to 1 hr), followed by oxidative removal of the phenylseleno group by 30% H_2O_2 (0 to 40°) furnishes the α-alkoxy- or dialkoxylalkylated products.[20] The overall transformation is accomplished in one pot without isolation of the intermediates. Several examples are listed in Table 8. This procedure when coupled with the organocopper conjugate addition method,[21] provides a new tool for regiospecific vicinal carba-condensation of enones.

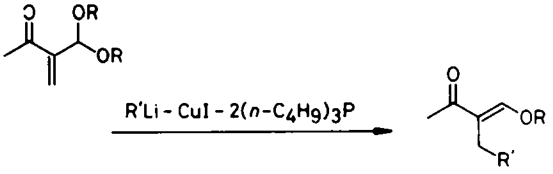


Fig. 20.

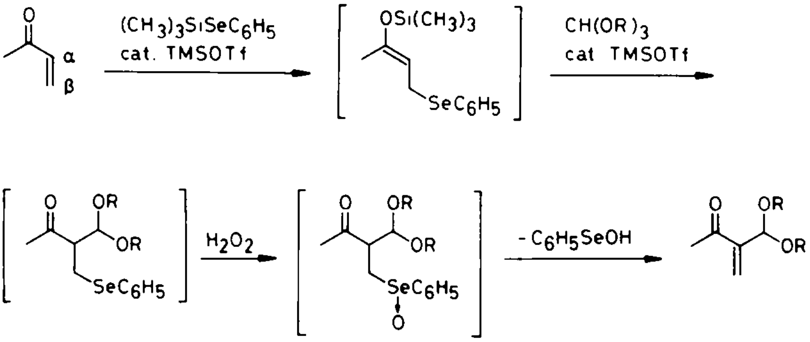


Fig. 19.

Table 8. α-Alkoxy- or dialkoxylation of α,β-unsaturated ketones[a]

enone	trapping acetal or ortho ester	product (% yield)
methyl vinyl ketone	benzaldehyde dimethyl acetal	3-methoxybenzyl-3-buten-2-one (57)
methyl vinyl ketone	ethyl ortho formate	3-diethoxymethyl-3-buten-2-one (53)
2-cyclopentenone	methyl ortho formate	2-dimethoxymethyl-2-cyclopentenone (58)
2-cyclohexenone	benzaldehyde dimethyl acetal	2-methoxybenzyl-2-cyclohexenone (75)
2-cyclohexenone	acetophenone dimethyl acetal	2-methoxymethylbenzyl-2-cyclohexenone (30)
2-cyclohexenone	cinnamaldehyde dimethyl acetal	2-α-methoxycinnamyl-2-cyclohexenone (83)
2-cyclohexenone	ethyl ortho formate	2-diethoxymethyl-2-cyclohexenone (76)

[a] The one-pot conversion was accomplished using an enone, phenyl trimethylsilyl selenide, an acetal or ortho ester, and **1** in 1:1:1:0.02–0.04 mol ratio in dichloromethane.

2-Methoxyphenylmethyl-2-cyclohexenone. To a CH_2Cl_2 (20 ml) containing TMSOTf (0.2 mmol) were successively added phenyl trimethylsilyl selenide (10 mmol) and 2-cyclohexenone (10 mmol) at −78°. After the mixture was stirred at −78° for 30 min, benzaldehyde dimethyl acetal (10 mmol) was added. Then the mixture was warmed to −25° and kept for 40 min. Pyridine (50 mg) and 30% H_2O_2 (3 ml) were added successively and the mixture was warmed slowly to 15°. After vigorous exothermic reaction ceased, the mixture was quenched with water and extracted with CH_2Cl_2. Concentration of the dried extracts followed by chromatography on silica gel (15 : 1 benzene/ethyl acetate mixture as eluant) gave the methoxybenzylated product in 75% yield.

IMMOBILIZATION OF TRIMETHYLSILYL TRIFLATE[22]

As illustrated above the silyl triflate 1 serves as an efficient silylating agent and as a promoter of a variety of nucleophilic reactions. Immobilization of this moisture-sensitive compound on a polymer supporting framework offers great operational simplicity and increases its synthetic utility. Preparation of such reagent is accomplished by silylation of Nafion-H, a perfluorinated resin-sulfonic acid, with chlorotrimethylsilane. The trimethylsilyl ester, Nafion-TMS (37), possesses considerable moisture-stability and reasonable chemical reactivity. Some examples of the silylation reaction with or without added bases are given in Table 9. Nafion-TMS can be utilized for certain catalytic reactions as well.[6]

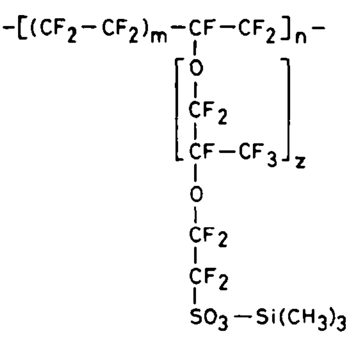


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Fig. 21.

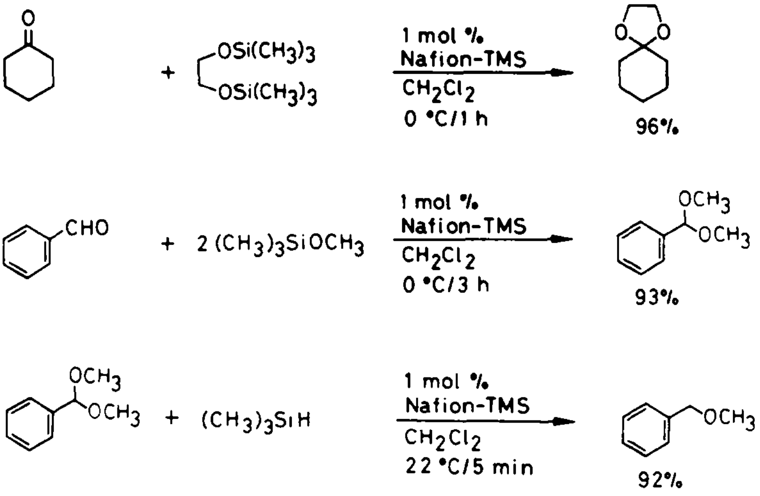

Fig. 22.

Table 9. Silylation by Nafion-TMS[a]

substrate	base	conditions temp, °C/time, h	product (% yield)
ethanol	none	29/12	ethoxytrimethylsilane (100)
ethanol	triethylamine	27/3	ethoxytrimethylsilane (100)
phenol	triethylamine	23/18	phenoxytrimethylsilane (86)
acetic acid	triethylamine	25/3	acetoxytrimethylsilane (54)
ethanethiol	triethylamine	29/2	ethylthiotrimethylsilane (91)
diethylamine[b]	none	28/6	diethylaminotrimethylsilane (94)

[a] The reaction was carried out in dichloromethane using substrate, Nafion-TMS, and triethylamine (if necessary) in 1:1:1.2 mol ratio. [b] Substrate/Nafion-TMS = 2.4:1.

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