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Silicon-Induced Ene-Type Reaction in the Thermal Conversion of Enolates to β-Silyl Enones with Molecular Dioxygen

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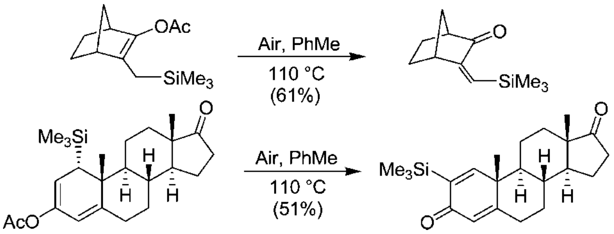
ABSTRACT



Reaction of alkyl, acetoxy, and silyl enol ethers of 3-(organosilyl)cyclohexanone with molecular dioxygen in toluene at 110 °C produced the corresponding conjugated enones in yields up to 88% yield. The reaction of the same type failed on replacement of the silyl group at the C-3 position with an isopropyl group. These results indicate the existence of an unprecedented silicon-induced ene-type reaction. Its reaction mechanism, generality, limitations, and exceptions are discussed.

Electronic effects due to silicon can direct organic reactions of various types:[1] because a silyl group is present at an appropriate position of the reactants, some reactions that do not otherwise proceed become feasible; some reactions that otherwise generate a mixture of products then yield an exclusive product, and some reactions that otherwise afford a desired product in a low yield then generate it efficiently. Examples involving photochemical[2–5] and electrochemical[6–9] processes include photodecarbonylation of trimethylsilyl β,γ-enals and formyl octalins,[10,11] Norrish type-I cleavage of β-trimethylsilyl cycloalkanones,[12–14] electrochemical aldol condensation,[15] and electrochemical oxidation of enol acetates to enones.[16]

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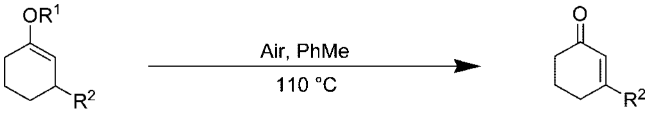
Continuing our research on silicon-induced, -directed, and -promoted reactions, we sought to develop a synthetically valuable reaction that is induced by silicon under thermal conditions. Herein, we report our success in utilizing the electronic effect of silicon to induce an ene-type reaction. Our design in placing a silyl group at the C-3 position of enol ethers or acetates proved to be an essential factor that allowed these compounds to react with molecular dioxygen in toluene upon heating to give the corresponding α,β-unsaturated ketones in attractive yields up to 88% (see Table 1).

Table 1. Oxidation of Silyl Enol Ethers of 3-(Organosilyl)Cyclohexanone to the Corresponding Conjugated Enones

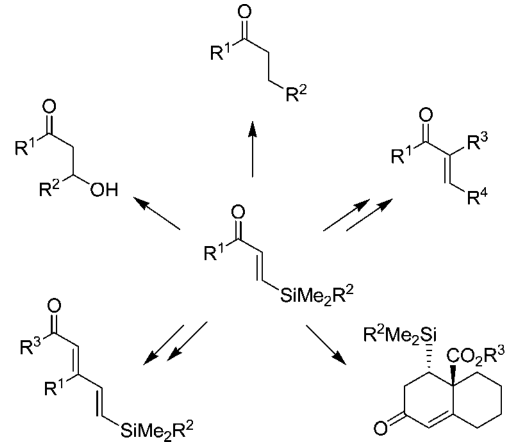


substrate	R^1	R^2	time (h)	yield(%)	product
1	SiMe$_3$	SiMe$_3$	4.0	61	**12**
2	SiMe$_2$(*t*-Bu)	SiMe$_3$	4.0	88	**12**
3	SiPh$_3$	SiMe$_3$	10	40	**12**
4	Ac	SiMe$_3$	4.0	82	**12**
5	Me	SiMe$_3$	4.0	71	**12**
6	PO(OPh)$_2$	SiMe$_3$	48	0	**12**
7	SiMe$_3$	SiMe$_2$Ph	10	31	**13**
8	SiMe$_3$	SiMePh$_2$	10	15	**14**
9	SiMe$_3$	SiPh$_3$	10	0	**15**
10	Ac	isopropyl	4.0	0	–
11	Ac	H	4.0	0	–

Oxygenation of olefins through an ene reaction typically occurs through a photochemical pathway and requires a dye as sensitizer.[17] These reactions and their mechanisms have been extensively investigated and applied in organic synthesis.[18] We undertook to broaden its applicability by modifying the basic ene reaction for the preparation of α,β-unsaturated β-silyl ketones. Some intriguing examples in the literature that utilize these organosilicon compounds in synthesis are illustrated in Scheme 1.[19–23]

To realize the possibility of an ene-type reaction between a silicon-containing enolate with molecular dioxygen, we first synthesized substrates **1**−**9** by a Michael addition of R$_3$SiLi (R = Me or Ph) to 2-cyclohexen-1-one. The resultant enolates were then treated with an appropriate organic chloride in situ. Second, we dissolved 3-silylenol trimethylsilyl ether **1** in toluene (0.11 M) and heated the solution at reflux (i.e., 110 °C) in the presence of O$_2$ from air for 4.0 h. Pure 3-silyl enone **12** was isolated in 61% yield from the reaction mixture through chromatography. Replacing toluene with other solvents having lower boiling points, including benzene, *p*-dioxane, diethyl ether, and THF, furnished product **12** in lower yields.

Scheme 1. Synthetic Applicability of α,β-Unsaturated β-Silyl Ketones



By replacing the SiMe$_3$ group attached to the enol moiety with a bulkier SiMe$_2$(*t*-Bu) group (see Table 1), we improved the efficiency of the transformation. Under the same conditions, substrate **2** was converted to **12** in 88% yield. Reactions of the same type also proceeded on replacement of the silyl group with an acetoxy or methyl group in the enolates. For example, we obtained 82% and 71% yields for **12** from enol acetate **4** and methyl enol ether **5**, respectively. This transformation failed, however, on replacement of the acetoxy group in **4** with a phosphoryl group (cf. **6**).

Furthermore, replacement of the SiMe$_3$ group at position C-3 with a bulkier silyl group,[24,25] including SiMe$_2$Ph, SiMePh$_2$, and SiPh$_3$, gave the corresponding 3-silyl-2-cyclohexen-1-ones **13**−**15** in 31%, 15%, and 0% yields, respectively. These results indicate that a smaller C-3 silyl group in the substrate provided a greater yield; the SiMe$_3$ group was the most effective one among various silyl groups tested.

As first control experiments, we applied the same oxygenation conditions to 3-(isopropyl)-1-cyclohexenyl acetate (**10**) and the parent cyclohexenyl acetate (**11**). Although the isopropyl group in **10** and the trimethylsilyl group in **4** might

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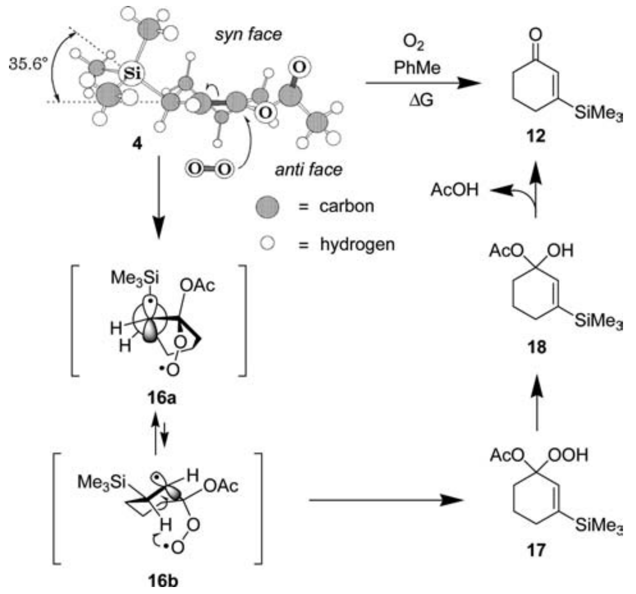
exert a similar steric effect,[25] the smooth oxidation of **10** with molecular dioxygen occurred to a negligible extent, as for the unsuccessful oxygenation of **11**. The thermal oxidation shown in Table 1 was therefore induced by a silicon atom through its electronic effect. As second control experiments, we irradiated toluene solutions of **1** and **4**, separately, with UV light ($\lambda > 300$ nm) near 23 °C instead of 110 °C; enone **12** was not detectably generated. We conclude accordingly that 3-silyl-1-cyclohexenyl ethers or acetates (i.e., **1** or **4)** react with molecular dioxygen to produce the corresponding enones through a thermal, rather than a photochemical, process.

We considered whether the newly developed reaction produces radical intermediates. Repeating the conversion **2** → **12** under conditions similar to those described above, we added 4-methyl-2,6-di(*tert*-butyl)phen-1-ol (1.0 equiv) to the reaction mixture. This phenol functions as an efficient scavenger of peroxyl radical.[26] After 4.0 h, we recovered the starting material **2** in 17% yield and detected no enone **12** by GC−mass spectrometry. These results indicate that peroxyl radical intermediates were likely generated in the reactions shown in Table 1.

The enol acetate moiety is known to be stable[27] and cannot be oxidized to the corresponding enone with air at 110 °C (see **10** and **11** in Table 1). Oxidation of enol ethers to the corresponding enones can be accomplished; however, it requires a catalyst Pd^0/SiO_2.[28] On the other hand, a silyl group at the allylic position acts as an activating group for alkene toward oxidation.[29] The effect of silyl groups can be attributed to the orbital interaction between the π-orbital of the carbon to carbon double bond and the C−Si σ bond.[30] The allylsilane moiety can be oxidized with easy because of the electron-donating ability of β-silyl group.[31] Combining this information and our experimental results, we propose a plausible mechanism shown in Scheme 2, in which the conversion **4** → **12** serves as a representative example.

Through computation with the CVFF force field, we obtained the thermodynamically most stable conformation of **4** by energy minimization. Addition of molecular dioxygen to enol acetate **4** might occur at an elevated temperature from the anti face of the activating $SiMe_3$ group to give peroxyl radical **16a**. Because of the possible coplanarity exerted by the radical orbital, the C−C bond, and the C−Si bond in the moiety $^{\bullet}$C−C−Si of **16a**, the carboradical center can become stabilized by a β silyl group, predominantly through "$\sigma-\pi$ hyperconjugation."[1c] This stabilization was absent from the corresponding radical intermediate generated on oxygenation of nonsilylated enol acetates **10** and **11**.

Scheme 2. Proposed Mechanism for the Conversion of Enol Acetate **4** to 3-Silyl Enone **12**



After the energy barrier of the step **4** → **16a** was overcome, the resultant intermediate **16a** could alter its conformation to **16b**. Although the former is thermodynamically more stable than the latter, equilibrium exists between these two conformational isomers. The isomer **16b** allows an intramolecular transfer of hydrogen to take place from a carbon atom to an oxygen atom. Monodeoxygenation[32] subsequently occurs in the resultant peroxide **17** to afford hydroxy acetate **18**; extrusion of acetic acid in situ then furnishes final product **12**. The entire process has the same outcome as an ene-type reaction. For a typical ene reaction involving molecular dioxygen as an enophile,[33] the reactive species is molecular dioxygen in its first excited singlet state, O_2 ($^1\Delta_g$), which requires UV light and a dye as a sensitizer. In contrast, we found that the reactions shown in Table 1 proceeded in the dark; they thus conform to an "ene type" reaction.

Molecular dioxygen might abstract the hydrogen α to the $SiMe_3$ group in **4** to generate an allylic carboradical center that becomes stabilized by the silyl group through an α effect.[34] Pioneering works reported by Nickon,[35] Schenck,[36] Foote,[37] and co-workers indicate that the double bond in the hydroperoxide product is invariably shifted to a position adjacent to the original double bond in an ene reaction. A

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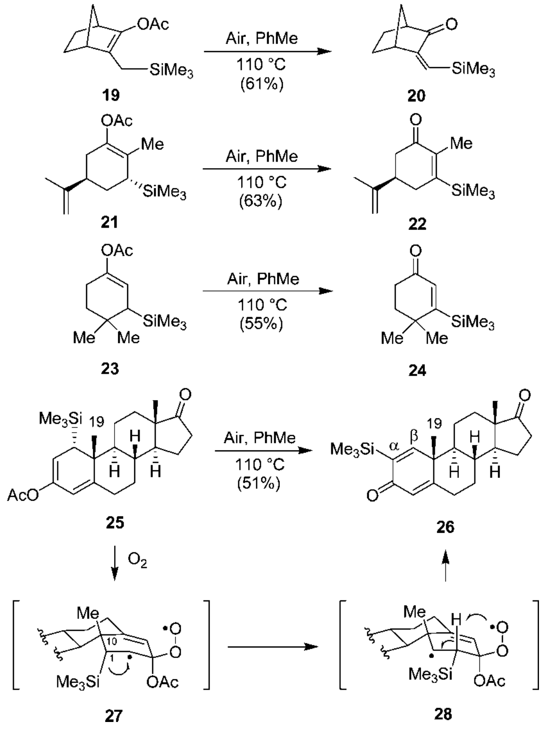
mechanism involving an initial hydrogen abstraction followed by radical recombination thereby explains how the smaller silyl groups gave greater yields (cf. entries 1 and 7−9 of Table 1).

After understanding the intrinsic properties of this silicon-induced ene-type reaction, we validated its applicability using substrates with varied structural complexity; these included a bridged bicyclic **19**, 1,2-substituted enol acetate **21**, hindered organosilane **23**, and polycyclic **25**. All four such enolate substrates with an $SiMe_3$ group at the position C-3 listed in Scheme 3 were successfully oxidized to the corresponding enones **20**, **22**, **24**, and **26** in satisfactory yields (51−63%) under the same conditions as the conversion **4** → **12**. The *Z* configuration of **20** was assigned on the basis of the nuclear Overhauser enhancement (NOE) between the =CH (3.6%) and the bridgehead =CCH (4.0%).

Scheme 3. Oxidation of Various 3-Silyl Enol Acetates to the Corresponding Conjugated Enones



In the conversion **25** → **26**, the $SiMe_3$ group resided notably at the α, instead of the *β*, position in product **26**. This 1,2-silyl migration[38–40] in intermediate **27** might reflect severe steric hindrance around the C-1 $SiMe_3$ group and the C-10 quaternary center. Hydrogen transfer via a transition structure with a five-membered ring in **28** would then be followed by formation of a double bond to give α-silyl cross dienone **26**.

The two singlets at *δ* 6.02 and 7.13 ppm associated with vinylic protons of cross dienone **26** in its ^1H NMR spectrum disclosed a clue about its structure. The peak at *δ* 7.13 ppm is expected to indicate a *β*, not an α, proton of the $H_\beta{-}C{=}C{-}C{=}O$ group. To realize the neighboring environment around the $SiMe_3$ group, the *β* vinylic proton and the C-19 angular methyl group, we irradiated them individually and observed the possible NOE. Mutual enhancements existed between the pair of $SiMe_3$ protons (7.6%) and the vinylic proton (7.7%) as well as the pair of vinylic proton (5.1%) and angular methyl protons (3.9%). In contrast, no enhancement was detected between the pair of $SiMe_3$ protons and angular methyl protons. These data clearly support our assignment that the vinylic proton at *δ* 7.13 ppm is adjacent to the C-19 angular methyl group and the $SiMe_3$ group, but these two groups are far apart. The $SiMe_3$ group in dienone **26** must hence reside at the C-2, not the C-1, position.

In conclusion, according to a silicon-induced reaction of ene type, the oxidation of 3-silyl-1-cyclohexenyl ethers or acetates with molecular dioxygen at 110 °C produced the corresponding *β*-silyl enones. Synthetically appealing yields are obtained upon an appropriately chosen C-3 silyl group and a cross substituent attached to the enol functionality. Mechanistic experiments indicate that the electronic stabilizing effect of silicon (α or *β* effect) on a carboradical intermediate likely plays a vital role in the induction of this new ene-type reaction.

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Supporting Information Available: Synthetic procedures and spectral data for compounds **2**−**14** and **19**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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