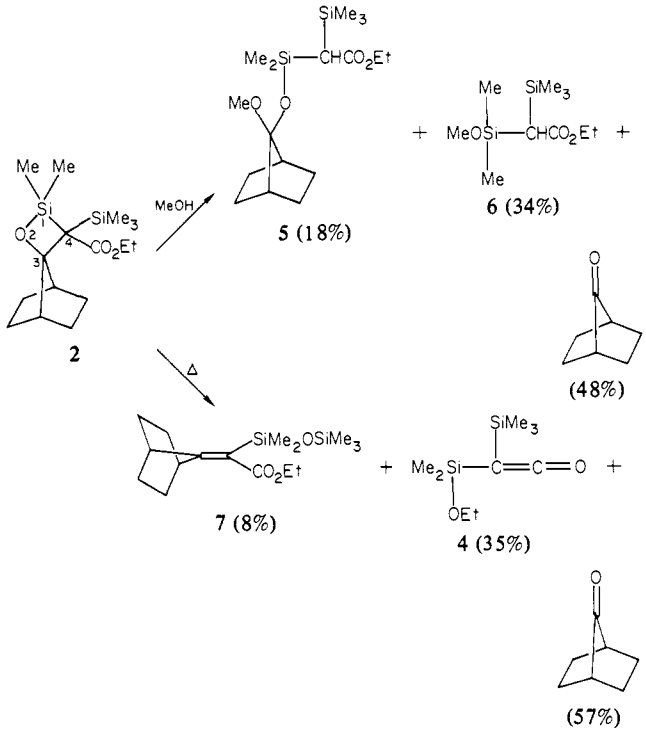
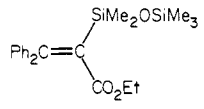
Scheme I



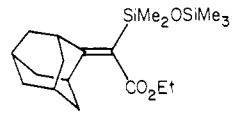
(q, $SiCH_3$), 2.3 (q, $SiCH_3$), 15.0 (q, $OCCH_3$), 27.2 (t, norbornyl CH_2), 27.4 (t, norbornyl CH_2), 40.5 (d, norbornyl CH), 58.9 (s, $SiCCO_2Et$), 62.2 (t, OCH_2), 113.8 (s, SiOC), 164.7 (s, C=O); IR (NaCl) $\nu(CO_2Et)$ 1560 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_3Si_2$: C, 58.84; H, 9.25. Found: C, 58.47; H, 9.20. An unusual chemical shift of ^{13}C at C_3 (113.8 ppm) and an abnormal stretching vibration of the ester carbonyl (1560 cm^{-1}) were observed. These unusual spectroscopic features of the silaoxetane may reflect a strong polarization of the C_3–C_4 bond ascribed to the strain of a four-membered ring and to interactions of the ester carbonyl with the proximate silicon. The high-resolution mass spectrum showed a relatively strong molecular ion at m/e 326.1737 (calcd for $C_{16}H_{30}O_3Si_2$ 326.1732) and fragmentation peak at 216.0994 (M^+ – norbornone, calcd for $C_9H_{20}O_2Si_2$ 216.1000), confirming that the silaoxetane was in hand. The silaoxetane **2** (Scheme I) is attacked by alcohols to break the bonds of C_3–C_4 and Si–O. For instance, when treated with methanol at room temperature, the silaoxetane **2** gave product **5** along with methoxysilane **6** and norbornone. Moreover, thermal decomposition of **2** at 185 °C for 5 h led to products of vinylsiloxane **7**, ketene **4**, and norbornone. Note that intramolecular migration of the trimethylsilyl group would give the product **7**. These results strongly support that the structure of **2** is 1,2-silaoxetane.

As previously reported, the reaction of **1** involves a silaethylene intermediate which produces the silaoxetane **2** with norbornone, and which rearranges to the ketene **4**.[3]

Vinylsiloxanes **8** and **9** were also obtained in 13% yields together



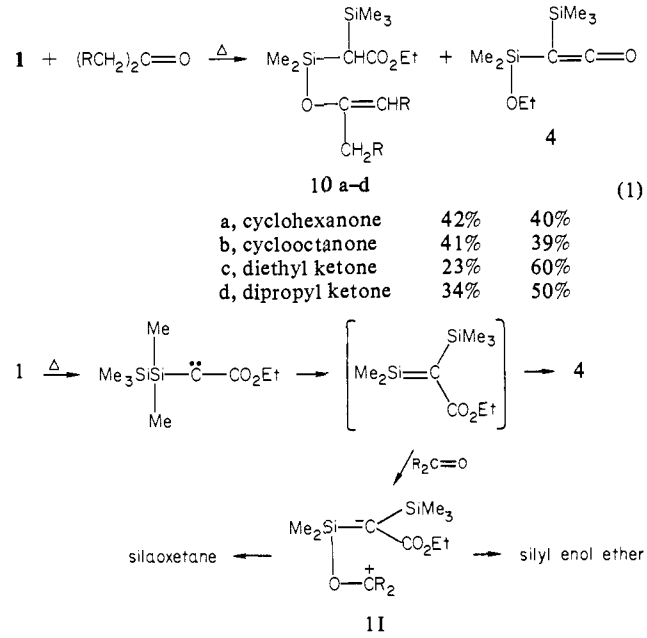
8



9

with the ketene **4** (78% and 86% yields, respectively) when thermolyses of **1** were carried out in the presence of benzophenone or adamantanone.

However, thermolysis of **1** (eq 1) in ketones having α hydrogens such as cyclohexanone, cyclooctanone, diethyl ketone, or dipropyl ketone led to the corresponding silyl enol ethers **10** and the ketene



a, cyclohexanone	42%	40%
b, cyclooctanone	41%	39%
c, diethyl ketone	23%	60%
d, dipropyl ketone	34%	50%

(1)

4 but gave neither silaoxetanes nor the corresponding vinylsiloxanes.

Silyl enol ethers **10** may be formed by simultaneous hydrogen migration in zwitterion **11** (eq 2), and 1,2-silaoxetane may not be involved in the reaction of such ketones having α hydrogens.

It is essential therefore that the stable silaoxetane is isolated from 7-norbornone, and it seems to be sterically stabilized by the presence of trimethylsilyl and norbornyl groups.

Acknowledgment. We acknowledge partial support by the Shinetsu Chemical Co.

Registry No. 1, 79251-24-4; **2**, 83547-74-4; **3**, 83547-75-5; **4**, 79251-25-5; **5**, 83547-76-6; **6**, 79251-30-2; **7**, 83547-77-7; **8**, 83547-78-8; **9**, 83547-79-9; **10a**, 79251-31-3; **10b**, 83547-80-2; **10c**, 83547-81-3; **10d**, 83547-82-4; 7-norbornone, 10218-02-7; benzophenone, 119-61-9; adamantanone, 700-58-3; cyclohexanone, 108-94-1; cyclooctanone, 502-49-8; diethyl ketone, 96-22-0; dipropyl ketone, 123-19-3.

(3) Ando, W.; Sekiguchi, A.; Sato, T. *J. Am. Chem. Soc.* **1981**, *103*, 5573.

Regioselective Arylation of Silyl Enol Ethers of Methyl Ketones with Aryl Bromides

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Although there have been a lot of precedents on arylation of ketones or their equivalents, they all require special reagents, a large excess of substrates, drastic reaction conditions, or multistep operations. Regiochemical aspects of these arylation reactions have not yet been fully elucidated up to now.[1] Even in several examples that have been described with use of silyl enol ethers, neither nucleophilic character nor regiochemical integrity of the enol ether has been directly utilized for this transformation.[2] In

(1) Caine, D. "Carbon–Carbon Bond Formation"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, pp 152–157.

(2) Two-step arylation of silyl enol ether via alkylation with a tricarbonyl(cyclohexadienylium)iron salt: Kelly, L. F.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1980**, *21*, 2455. Arylation of silyl enol ether possessing a leaving group such as halogen or an oxirane with organometallic species: Tamao, K.; Zembayashi, M.; Kumada, M. *Chem. Lett.* **1976**, 1239. Sakurai, H.; Shirahata, A.; Araki, Y.; Hosomi, A. *Tetrahedron Lett.* **1980**, *21*, 2325. Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

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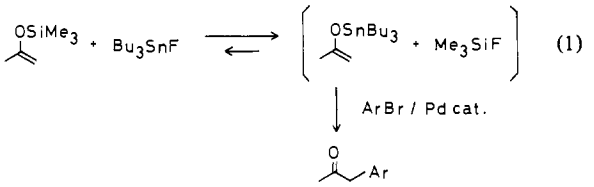
the present paper, we describe regioselective arylation of silyl enol ethers of methyl ketones with aryl bromides.

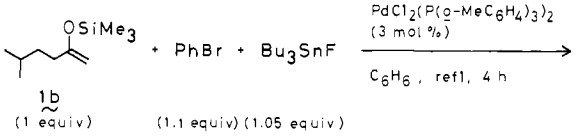
A survey of transition-metal-catalyzed cross-coupling reactions[3] suggested that the use of α-stannyl ketones would effect such arylation reactions. Accordingly, we undertook a one-pot reaction of a silyl enol ether with an aryl bromide in the presence of a trialkyltin fluoride[4] and a palladium catalyst, in which we postulated the following two sequential reactions: (i) in situ generation of an α-stannyl ketone via silyl/stannyl exchange[5] and (ii) its arylation with the aryl bromide.[6] An appropriate choice of combination of reagents is demonstrated to allow just such sequence to occur.

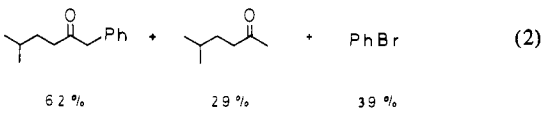


(1)

As fluorides, we examined trimethyl-,[7] triethyl-,[7] tributyl-,[8] and triphenyltin fluorides,[9] and the third one usually gave satisfactory results probably because of its relatively high solubility. Practically no reaction took place when this fluoride was replaced with another one. Tributyltin chloride or methoxide also failed to react with silyl enol ethers. Among the following four palladium catalysts examined, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(Ph_2PCH_2CH_2PPh_2)$, and $PdCl_2(P(o\text{-}CH_3C_6H_4)_3)_2$, use of ca. 3 mol % of the last one proved to be most effective. The representative procedure is as follows (run 6 in Table I). A mixture of the silyl enol either **1b** (74.5 mg, 0.4 mmol), bromobenzene (0.046 mL, 0.44 mmol), tributyltin fluoride (130 mg, 0.42 mmol), and $PdCl_2(P(o\text{-}CH_3C_6H_4)_3)_2$ (9.5 mg, 0.012 mmol) in benzene (0.9 mL) was heated to reflux for 3 h under nitrogen. The reaction mixture was diluted with ether, treated briefly with 1 N NaOH under vigorous stirring, and extracted with ether. Drying and removal of the solvent from the combined extracts followed by silica gel column chromatography afforded the arylated ketone (45 mg, 60%).

The results are listed in Table I. The product yields fall in a range of 50–65% in equimolar reactions with various aryl bromides. Besides the recovered bromide, a major side product is the desilylated ketone (see eq 1). The use of 1.5 equiv of a silyl enol

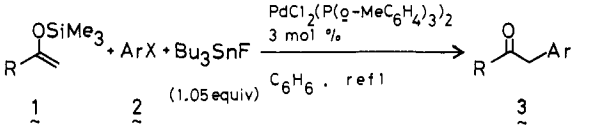


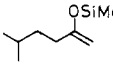
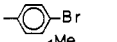
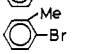
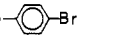
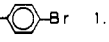
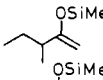
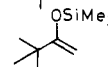
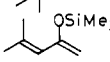
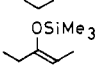


(2)

ether to an aryl bromide raises the product yield remarkably up to 86% (run 11), whereas an excess use of aryl bromide does not result in any improvement (see runs 1 and 5).

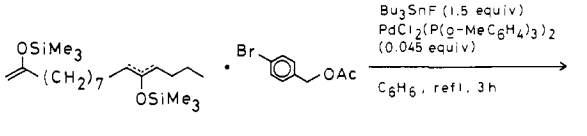
Table I. Arylation of Silyl Enol Ethers

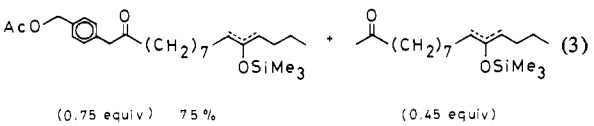


Run	1	2	Molar ratio 1 : 2	Period (h)	Yield 3 (%)[a,b]	Yield 1 (%)[c]
1	 1a	PhBr	1 : 2	4	65[c]	0
2	1a	PhBr	1 : 1.1	7	61[c]	0
3	1a		1 : 1.1	3	62	0
4	 1b	PhI	1 : 1.1	3.5	22[c]	trace
5	1b	PhBr	1 : 2	4	65[c]	0
6	1b	PhBr	1 : 1.1	3	60	0
7	1b	PhBr	1.5 : 1	3	84[d]	0
8	1b		1 : 1.1	3	62	0
9	1b		1 : 1.1	3	59	0
10	1b		1 : 1.1	3	58	0
11	1b	"	1.5 : 1	3	86[d]	0
12	1b		1.5 : 1	3	70[d]	0
13		PhBr	1 : 1.1	10	47[e]	trace
14		PhBr	1 : 1.1	24	29[c]	37
15		PhBr	1.5 : 1	3	56[d]	0
16		PhBr	1 : 2	5	35[c]	0
17		PhBr	1 : 1.1	3	<15	55
18		PhBr	1 : 1.1	7	0	66

[a] Isolated yields based on 1. [b] No contamination with the regioisomer and the diarylated product was observed by NMR in each case where the product was isolated. [c] Determined by NMR. [d] Isolated yields based on 2. [e] Bu_3SnF (1.6 equiv) was used.

Chemoselectivity observed in this reaction is quite interesting. Silyl enol ethers of methyl *n*-alkyl and methyl *sec*-alkyl ketones undergo arylation in good yields, while higher homologues such as those of diethyl ketone and a methyl *tert*-alkyl ketone survive the reaction conditions to be recovered. The remarkable difference of reactivities may arise from the steric repulsion between the alkyl group(s) attached to the olefinic moiety and the approaching tributyltin fluoride. This feature should account for selective arylation of a bis-silyl enol ether as depicted in eq 3.





(3)

Here are other noteworthy points, too. First, a careful examination of a crude reaction mixture of **1a** and bromobenzene (run 2 in Table I) revealed that this arylation reaction is highly re-

(3) For review: Kumada, M. *J. Pure Appl. Chem.* **1980**, *52*, 669. For transition-metal-catalyzed coupling of organotin compounds: Kosugi, M.; Migita, T. *J. Synth. Org. Chem. Jpn.* **1980**, *38*, 1142.

(4) For fluoride-mediated metathesis of silyl enol ethers: Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025.

(5) The silyl/stannyl group exchange should be performed in the presence of aryl bromide and the palladium catalyst. Otherwise, the product yield was considerably decreased presumably due to hydrolysis.

(6) After this paper had been submitted, Kosugi and Migita et al. reported a palladium-catalyzed arylation of acetonyltributylstannane: Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Migita, T. *Chem. Lett.* **1982**, 939.

(7) Licht, K.; Geissler, H.; Koehler, P.; Schnorr, H.; Kriegsmann, H. *Z. Anorg. Allg. Chem.* **1971**, *385*, 287. Krause, E. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 1447.

(8) This reagent was purchased from Tokyo Kasei Kogyo Co. (Japan) and was used after drying in vacuo (ca. 0.1 mmHg) for 6 h at 100–110 °C (bath temperature) without further purification. The use of purified material did not improve the yield.

(9) Krause, E.; Becker, R. *Ber. Dtsch. Chem. Ges.* **1920**, *53*, 173.

gioselective. Formation of neither the regioisomer nor the diarylated product could be detected by NMR analysis. Second, a variety of aryl bromides, rather than iodides, bearing an electron-donating, an electron-withdrawing, or an ortho substituent can be employed with almost equal success. Mildness of the reaction conditions tolerates the presence of a ketone or an ester functionality in the substrate, which is one of the most striking features of this method. Finally, the simplicity of the procedure, e.g., one-pot conversion of easily available silyl enol ethers to arylated ketones, is another advantage over other methods.

Registry No. 1a, 83511-78-8; **1b**, 73503-97-6; **1** (R = $CH(CH_3)CH_2CH_3$), 83511-79-9; **1** (R = $C(CH_3)_3$), 17510-46-2; **1** (R = $CH=C(CH_3)_2$), 6651-46-3; **1** (R = Ph), 13735-81-4; **2** (Ar = Ph; X = Br), 108-86-1; **2** (Ar = C_6H_4-*p*-OMe; X = Br), 104-92-7; **2** (Ar = Ph; X = I), 591-50-4; **2** (Ar = C_6H_4-*p*-Me; X = Br), 106-38-7; **2** (Ar = C_6H_4-*o*-Me; X = Br), 95-46-5; **2** (Ar = C_6H_4-*p*-Ac; X = Br), 99-90-1; **3** (Ar = Ph; R = C_7H_{15}), 32508-90-0; **3** (Ar = C_6H_4-*p*-OMe; R = C_7H_5), 66164-34-9; **3** (Ar = Ph; R = $CH_2CH_2CH(CH_3)_2$), 27993--43-7; **3** (Ar = C_6H_4-*p*-Me; R = $CH_2CH_2CH(CH_3)_2$), 83511-80-2; **3** (Ar = C_6H_4-*o*-Me; R = $CH_2CH_2CH(CH_3)_2$), 83511-81-3; **3** (Ar = C_6H_4-*p*-OMe; R = $CH_2CH_2CH(CH_3)_2$), 83511-82-4; **3** (Ar = C_6H_4-*p*-Ac; R = $CH_2CH_2CH(CH_3)_2$), 83511-83-5; **3** (Ar = Ph; R = $CH(CH_3)CH_2CH_3$), 27993-42-6; **3** (Ar = Ph; R = $C(CH_3)_3$), 6721-67-1; **3** (Ar = Ph; R = $CH=C(CH_3)_2$), 61799-54-0; **3** (Ar = Ph; R = Ph), 451-40-1; Bu_3SnF, 1983-10-4; $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$, 40691-33-6; (1-cyclohexen-1-yloxy)trimethylsilane, 6651-36-1; [(1-ethyl-1-propenyl)oxy]trimethylsilane, 17510-47-3; 2-phenylcyclohexanone, 1444-65-1.

High-Pressure NMR Studies of Hemoproteins. Pressure-Induced Structural Changes in the Heme Environments of Cyanometmyoglobin

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Faculty of Engineering
Kyoto University, Kyoto 606, Japan
Received June 1, 1982

We are currently interested in the NMR of proteins under pressure with the aim to gaining an insight into details of protein structure in solution. We have previously studied the effects of high pressure on the spin states of heme iron[1] and on the ligand-exchange phenomena such as the acid–alkaline transition[2] of hemoproteins by the use of high-pressure high-resolution proton NMR at high field. We report here direct evidences for structural changes of the protein in the heme environments of cyanometmyoglobin (Figure 1) when subjected to high hydrostatic pressures.

A simple device for high-pressure NMR measurements and experimental details are described in our previous reports.[1] We followed the proton NMR spectrum of cyanometmyoglobin in H_2O solution[3] at various pH's and pressures with a special attention to exchangeable NH signals in the paramagnetically shifted region.

Figure 2 illustrates an example of the proton NMR spectra of cyanometmyoglobin (horse) in Tris·HCl buffer[4] pH 7.8 in H_2O at various pressures. Paramagnetically shifted resonances are shown in the spectra. It is of particular interest to note that the exchangeable proton signal at 18.6 ppm, which has been assigned[6]

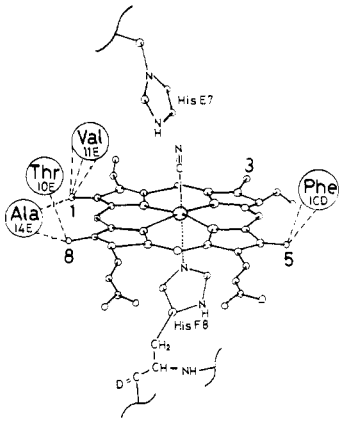

Figure 1. Heme environmental structure of cyanometmyoglobin based on the X-ray structure analysis. The dotted lines stand for the interatomic contacts within 3.9 Å.[10]

to the N_3H proton of distal histidyl (E7) imidazole, moves upfield upon pressurization, while the proximal histidyl (F8) NH proton resonance[6] at 16.4 ppm exhibits no pressure effect. The exchangeable proton peak e at 8.7 ppm, which was also assigned to the proximal histidine F8 peptide NH proton (Figure 1),[6] is also insensitive to pressure. These findings suggest that the distal region is more compressible than the proximal region in cyanometmyoglobin.

Another interesting feature in Figure 2 is the specific shift of the heme peripheral proton resonances, especially the 8- and 5-methyl signals[7] at 22.2 and 8.7 ppm, respectively, upon pressurization. With raising pressure from 1 to 900 atm, the 8- and 5-methyl peaks exhibit sizable upfield shifts accompanied by broadening, while the 1-methyl signal position remains at 13.4 ppm. When pressure is further increased above 1000 atm, these spectral changes for two methyl resonances appear to go back to those for lower pressures, with the distal histidyl N_3H proton peak exhibiting a continuous upfield shift. The single proton peak c at 13.1 ppm, previously assigned to the vinyl $C_\alpha H$,[8] shows noticeable downfield shift upon pressurization up to 900 atm, and beyond this pressure seems to move upfield toward the signal position at 1 atm. These spectral features of the heme peripheral proton groups at high pressures may allow us to expect that a pressure-induced structural change is proportional to pressure, as is manifested as a continuous shift of the distal histidyl N_3H peak, while this effect of a structural change could be exerted discontinuously on the heme peripheral proton groups. Nonbonded interactions between the heme periphery and amino acid residues in the heme vicinity may be modulated by pressure-induced local structural changes. These van der Waals contacts, which are presumably responsible for specific shift for the methyl and vinyl proton resonances, appear to be released at a specific pressure, say 1000 atm. It can be, at least, said that the pressure effects are localized to a particular region of the protein.

We have also examined high-pressure NMR of cyanide complexes of sperm whale myoglobin and its derivatives reconstituted with deuterioheme (the vinyl groups at the 2- and 4-positions are replaced by protons). Pressure-induced spectral changes for these cyanometmyoglobins at pH 7.5–8.1 were almost the same as those mentioned above for horse cyanomyoglobin. For the cyanide complex of deuteriomyoglobin, the distal histidyl N_3H signal at 18.3 ppm shifted 1.0 ppm upfield at 750 atm, and the pyrrole proton resonances located in the upfield region at −19.5 and −25.0 ppm experienced noticeable pressure-induced shifts of 0.5 ppm

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(3) Proton NMR spectra were recorded at 300 MHz on a Nicolet NT-300 spectrometer equipped with a 1180E computer system. Typical spectra of cyanomyoglobin consisted of 40000 trasients with 8K data points and a 5.8-μs 90° pulse after the strong solvent resonance in H_2O solution was suppressed by a 500-μs low-power 180° pulse.

(4) The pH of Tris·HCl buffer has been shown[5] to be independent of pressure up to 2000 atm, while the pH of phosphate buffer was shown to be decreased by 0.4 upon pressurization to 1000 atm. Therefore, we used Tris·HCl buffer throughout the present study unless otherwise noted.

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