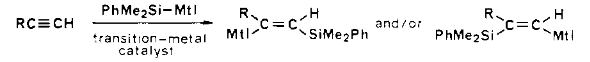
Transition-Metal-Catalyzed Silylmetalation of Acetylenes and Its Application to the Stereoselective Synthesis of Steroidal Side Chain

Hiroshi Hayami, Mitsuyoshi Sato, Shigekazu Kanemoto,
Yoshitomi Morizawa, Koichiro Oshima,* and Hitosi Nozaki

Department of Industrial Chemistry, Faculty of Engineering
Kyoto University, Yoshida, Kyoto 606, Japan

Received March 15, 1983

Much attention has been paid to the chemistry of vinylsilanes as useful intermediates for organic synthesis.[1] Despite the availability of many methods for the synthesis, there still exists a need for new selective and convenient procedures. Among many candidates, simultaneous addition of silyl group and metal to acetylenes with regioselectivity is certainly an attractive approach. Here we describe how PhMe$_2$SiMgMe or PhMe$_2$SiAlEt$_2$ adds easily to terminal acetylenes in the presence of a transition-metal catalyst with high regio- and stereoselectivities.



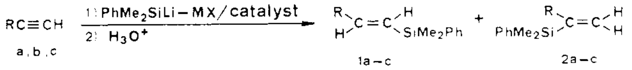
Platinum- or copper-catalyzed silylmagnesation followed by aqueous quenching provided exclusively (E)-1-silyl-1-alkenes, which have previously been produced by stoichiometric silylcupration[2] or silyltitanation.[3] On the other hand, palladium-catalyzed silylalumination afforded the regioisomer 2-silyl-1-alkenes with high regioselectivity. The results are summarized in Table I.

An ethereal solution of methylmagnesium iodide (1.1 M, 1.8 mL, 2.0 mmol) was added to a THF solution of dimethylphenylsilyllithium[4] (0.52 M, 3.8 mL, 2.0 mmol) at 0 °C under argon atmosphere. After this mixture stirred for 15 min, *cis*-PtCl$_2$(P-n-Bu$_3$)$_2$ (6.7 mg, 0.01 mmol) was added, and the resulting solution was stirred for an additional 15 min. A solution of 1-dodecyne (0.17 g, 1.0 mmol) in THF (3.0 mL) was added, and the whole was stirred for 30 min at 25 °C. Workup (ether, 1 N HCl) and purification by silica gel column chromatography gave (E)-1-(dimethylphenylsilyl)-1-dodecene (0.27 g) in 90% yield.

The regiochemistry of silylmetalation heavily depends on the transition-metal catalysts as well as metallic species of silyl–metal reagents employed. Ligands of the palladium catalysts also play the important role of controlling the product distributions. The reaction of 1-dodecyne with PhMe$_2$SiAlEt$_2$ in the presence of a variety of palladium catalysts was studied, ligand L of PdCl$_2$L$_2$ and the ratio of **1**/**2** being as follows: (m-MeOC$_6$H$_4$)$_3$P, 90/10; PPh$_2$CH$_2$CH$_2$PPh$_2$, 65/35; (2-(diphenylphosphino)ferrocenyl)-methyldimethylamine, 50/50; n-Bu$_3$P, 35/65; PPh$_3$, 30/70; (o-CH$_3$C$_6$H$_4$)$_3$P, 15/85.

The cis addition of a silyl–metal component was confirmed by the examination of the ^{1}H NMR spectrum of the product **1a** (J = 18.9 Hz) and also by the GLPC comparison with the authentic (Z) sample prepared from hydroalumination of 1-(dimethylphenylsilyl)-1-dodecyne.[5,6] Deuterolysis of the intermediate derived from silylmetalation gave the monodeuteriated alkenylsilanes. Thus, silyl reagents do not cause the acetylenic proton–metal exchange (see Scheme I).

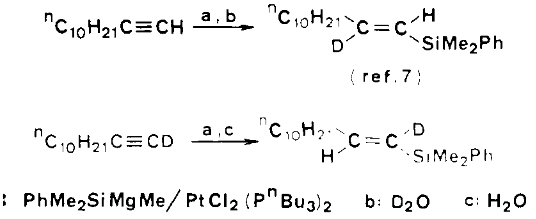
Table I. Transition-Metal-Catalyzed Silylmetalation[a]



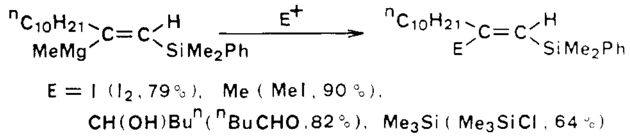
R	MX	catalyst	yield, %	1:2
a, n-C$_{10}$H$_{21}$	MeMgI	*cis*-PtCl$_2$(P-n-Bu$_3$)$_2$	90	>99:<1
		CuI[b]	86	>99:<1
		PdCl$_2$(PPh$_3$)$_2$	76	60:40
	Et$_2$AlCl	[c]	60	97:3
		RhCl(PPh$_3$)$_3$	70	91:9
		CuI[b]	78	55:45
		PdCl$_2$-(P(o-CH$_3$C$_6$H$_4$)$_3$)$_2$	85	15:85
	ZnBr$_2$[d]	*cis*-PtCl$_2$(P-n-Bu$_3$)$_2$	55	70:30
		PdCl$_2$(PPh$_3$)$_2$	71	30:70
		RuCl$_2$(PPh$_3$)$_3$	75	20:80
b, n-BuCH(OH)	MeMgI	CuI[b]	85	95:5
	Et$_2$AlCl	Pd(OAc)$_2$-P(o-CH$_3$C$_6$H$_4$)$_3$[e]	80	30:70
c, PhCH$_2$OCH$_2$CH$_2$	MeMgI	CuI[b]	90	>99:<1
	Et$_2$AlCl	PdCl$_2$(PPh$_3$)$_2$	88	30:70

[a] A mixture of the acetylene substrate, PhMe$_2$SiLi–MX reagent, and a catalyst (1:2:0.01 mol ratio) was employed. The reactions were performed at 25 °C in THF unless otherwise stated and completed within 1 h. [b] CuI (5 mol %) was used. [c] Pt or Ru catalysts did not accelerate the silylalumination reactions. The reaction mixture was heated at reflux for 8 h without catalyst. The reaction proceeded extremely slow at 25 °C. [d] A reagent was produced by mixing the silyllithium with ZnBr$_2$ in a 2:1 ratio. [e] See ref 10.

Scheme I

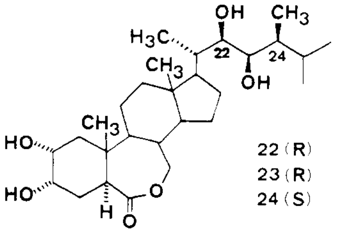


Scheme II



The present method provides not only simple silyl-substituted alkenes but also functionalized alkenylsilanes. Some electrophiles react with the alkenylmetal species without difficulty. For instance, treatment of the intermediate derived from PtCl$_2$(P-n-Bu$_3$)$_2$-catalyzed silylmagnesation of 1-dodecyne with iodine, methyl iodide, and valeraldehyde gave the corresponding silylalkenes carrying the electrophilic partner E (Scheme II). All these electrophiles reacted at 25 °C within 1 h.[8]

Combination of this new method with our previous findings provides an easy route to the stereoselective synthesis of the side chain of a plant growth steroidal hormone, brassinolide.[9]



brassinolide

---

(1) For recent reviews: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. Magnus, P. *Aldrichimica Acta* **1980**, *13*, 43.

(2) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2528.

(3) Tamao, K.; Akita, M.; Kanatani, R.; Ishida, N.; Kumada, M. *J. Organomet. Chem.* **1982**, *226*, C9.

(4) Gilman, H.; Lichtemwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 607.

(5) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215.

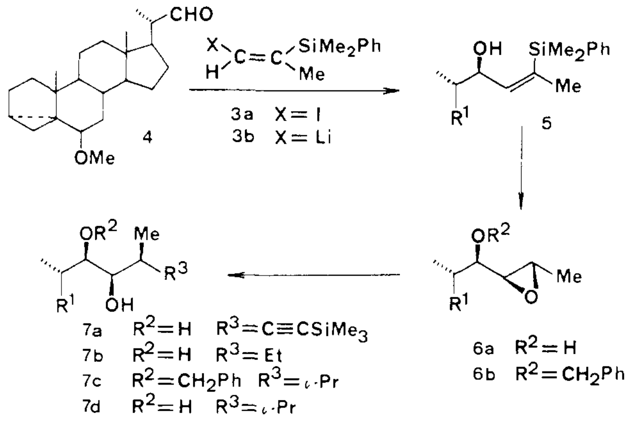
(6) Silylalumination has been also proved to proceed in a cis fashion by the examination of ^{1}H NMR of (E)-1-deutero-1-dodecene prepared by palladium-catalyzed silylalumination of 1-dodecyne followed by quenching with D$_2$O and successive desilylation.

(7) Bp 104–108 °C (0.1 torr, bath temperature); IR (neat) 2930, 2860, 1605, 1430, 1250, 1115, 808, 692 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 0.30 (s, 6 H), 0.7–1.9 (m, 19 H), 1.9–2.2 (m, 2 H), 5.8–6.1 (m, 1 H), 7.1–7.5 (m, 5 H). Anal. Calcd for C$_{20}$H$_{33}$DSi: C, 79.13; H, 11.62. Found: C, 78.98; H, 11.79.

(8) In the case of Me$_3$SiCl, the addition of CuI (5 mol %) was necessary for the reaction.

0002-7863/83/1505-4491$01.50/0

Scheme III



Palladium-catalyzed silylalumination of propyne followed by addition of iodine provided an 88:12 mixture of 2-(dimethylphenylsilyl)-1-iodo-1-propene (**3a**)[10] and its regioisomer. The desired 2-silylalkene **3a** was obtained in pure form by column chromatography. Treatment of a mixture of the aldehyde **4**[11] and iodoalkene **3a** with butyllithium at -78 °C gave, after chromatography, the (22*S*)-allylic alcohol **5**[12] *in* 48% *yield along with* the (22*R*) isomer (16% yield; Scheme III). Silyl-group-assisted stereoselective epoxidation[13] (VO(acac)$_2$-*t*-BuOOH) followed by elimination of PhMe$_2$Si group with *n*-Bu$_4$NF gave the key intermediate *threo*-α,β-epoxy alcohol **6a**[14] exclusively (65% yield). Regio- and stereoselective ring opening of epoxy alcohol with the organoaluminum compound Et$_2$AlC≡CSiMe$_3$[15] proceeded with *inversion at the reacting center to give* 1,2-diol **7a**[16] *in* 60% *yield.* Removal of Me$_3$Si group (KF, Me$_2$SO) and hydrogenation (H$_2$, PtO$_2$) provided **7b**.[17] Reaction of benzyl ether **6b** with the higher order mixed cuprate[18] (Me$_2$CH)$_2$Cu(CN)Li$_2$ afforded **7c**[19] (63% yield), which was transformed into **7d** (Li in liquid NH$_3$).[9b,20-22]

---

[9] (a) Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D., Jr.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C. *Nature* (*London*) **1979**, *281*, 216. (b) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6581. (c) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962. (d) Wada, K.; Marumo, S.; Ikekawa, N.; Morisaki, M.; Mori, K. *Plant Cell Physiol.* **1981**, *22*, 323.

[10] Pd(OAc)$_2$–phosphine combination was catalytically as effective as PdCl$_2$L$_2$ [L: phosphine ligand such as PPh$_3$, (o-CH$_3$C$_6$H$_4$)$_3$P]. Palladium(II) acetate (40 mg, 0.18 mmol) and (o-CH$_3$C$_6$H$_4$)$_3$P (0.16 g, 0.54 mmol) were combined in THF (3.0 mL). A solution of PhMe$_2$SiAlEt$_2$ derived from PhMe$_2$SiLi (12.5 mmol) and Et$_2$AlCl (12.5 mmol) in THF (20 mL) was added at 0 °C, and the whole was stirred for 10 min at 0 °C. The resulting mixture was added to propyne (neat, 4.0 mL) at -78 °C, and the mixture was stirred for 5 min at −78 °C, 2 h at 0 °C, then 30 min at 25 °C. A solution of iodine (3.2 g, 12.5 mmol) in THF (10 mL) was added dropwise at 0 °C, and the mixture was stirred for another 10 min at this temperature and poured into hexane (100 mL) containing NaF (2.0 g). Water (10 mL) was added, and the precipitate was filtered. The filtrate was washed with aqueous NaHSO$_3$ and brine and dried over Na$_2$SO$_4$. Purification by silica gel column chromatography (hexane) gave **3a** (2.8 g, 73% yield) as a clear oil: bp 85 °C (0.01 torr, bath temperature); IR (neat) 2960, 1555, 1430, 1250, 1110, 832, 814, 695 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.52 (s, 6 H), 1.80 (d, J = 1.5 Hz, 3 H), 6.72 (d, J = 1.5 Hz, 1 H), 7.07–7.61 (m, 5 H); MS, m/e (relative intensity) 302 (M$^+$, 2), 175 (19), 135 (100), 105 (47), 43 (76).

[11] Wiersig, J. R.; Waespe-Sarcevic, N.; Djerassi, C. *J. Org. Chem.* **1979**, *44*, 3374.

[12] ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.34 (s, 3 H), 0.38 (s, 3 H), 0.50 (s, 3 H), 0.88 (d, J = 6.0 Hz, 3 H), 0.97 (s, 3 H), 1.87 (d, J = 1.8 Hz, 3 H), 2.72 (m, 1 H), 3.29 (s, 3 H), 4.08 (d, J = 9.2 Hz, 1 H), 6.26 (dd, J = 9.2, 1.8 Hz, 1 H), 7.32 (m, 3 H), 7.50 (m, 2 H).

[13] Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3387.

[14] ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.70 (s, 3 H), 0.98 (s, 3 H), 1.29 (d, J = 5.2 Hz, 3 H), 2.72 (m, 2 H), 2.88 (dq, J = 5.2, 2.3 Hz, 1 H), 3.29 (s, 3 H), 3.62 (dd, J = 7.5, 2.3 Hz, 1 H).

[15] Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.

[16] ^{1}H NMR (200 HMz, CDCl$_3$) δ 0.09 (s, 9 H), 0.69 (s, 3 H), 0.98 (s, 3 H), 1.15 (d, J = 8.0 Hz, 3 H), 2.57 (m, 1 H), 2.63 (m, 1 H), 2.74 (m, 1 H), 3.30 (s, 3 H), 3.48 (dd, J = 5.0, 5.0 Hz, 1 H), 3.80 (m, 1 H).

[17] ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.69 (s, 3 H), 0.80 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.0 Hz, 3 H), 0.93 (d, J = 7.5 Hz, 3 H), 0.98 (s, 3 H), 2.74 (m, 1 H), 3.29 (s, 3 H), 3.54 (m, 2 H); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 11.9, 12.0, 12.2, 12.3, 13.0, 19.3, 21.4, 22.8, 24.0, 24.9, 27.2, 27.9, 30.6, 33.3, 35.0, 35.2, 35.7, 37.0, 40.3, 42.6, 43.3, 47.9, 52.5, 56.4, 56.6, 74,6, 74.9, 82.4.

[18] Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.

[19] ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.68 (s, 3 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.0 Hz, 3 H), 0.97 (s, 3 H), 2.72 (m, 1 H), 3.26 (s, 3 H), 3.40 (d, J = 8,0 Hz, 1 H), 3.68 (m, 1 H), 4.67 (dd, J = 17.5, 6.5 Hz, 2 H), 7.31 (m, 5 H). The regioisomer, 1,3-diol monobenzyl ether, could not be detected in the reaction mixture. The 23-oxo compound generated by the isomerization of epoxide **6b** was obtained (10% yield) as a byproduct.

[20] ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.66 (s, 3 H), 0.78 (d, J = 7.0 Hz, 3 H), 0.83 (d, J = 6.3 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.96 (s, 3 H), 2.72 (m, 1 H), 3.26 (s, 3 H), 3.51 (d, J = 8.9 Hz, 1 H), 3.67 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 10.2, 11.9, 12.1, 13.1, 19.3, 20.7, 20.9, 21.4, 22.8, 24.0, 24.9, 27.9, 30.5, 30.7, 33.3, 35.0, 35.1, 36.8, 40,0, 40,3, 42.6, 43.3, 47.9, 52.5, 56.4, 56.5, 73.4, 74.9, 82.3.

[21] Alternatively **7d** was obtained in 42% yield from **7a** by the following series of procedures: acetylation of diol, hydration of silylacetylene (HgSO$_4$) to ketone, Wittig methylenation (Ph$_3$P=CH$_2$), hydrogenation, and final deacetylation.

[22] Financial support by the Ministry of Education, Science, and Culture, Japanese Government (Grant-in-Aid for Special Project Research 57118006) is acknowledged.

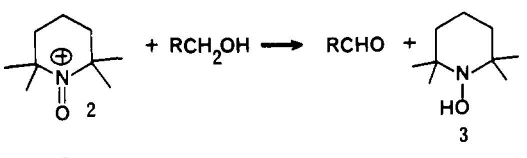
Nitroxyl-Mediated Electrooxidation of Alcohols to Aldehydes and Ketones

M. F. Semmelhack,* Chuen S. Chou, and David A. Cortes

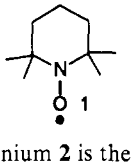
Department of Chemistry, Princeton University
Princeton, New Jersey 08544

Received March 7, 1983

Chemically mediated[1,2] electrooxidation of alcohols can be achieved with 2,2,6,6-tetramethylpiperidine nitroxyl (**1**); oxoammonium **2** is the active oxidizing agent and hydroxylamine **3** is the byproduct.[3] The process occurs at low potential (ca. +0.4



3



1

---

[1] Direct electrooxidation of alcohols cannot be achieved because of the high overpotential of the hydroxyl group. Simple alcohols do not show oxidation waves under polarographic analysis in neutral solution at a platinum electrode out to +2.0 V vs. the saturated calomel electrode.

[2] Mediators previously reported required +1.0–1.3 V to recycle. (a) Thioanisole: Shono, T. *Tetrahedron Lett.* **1979**, *20*, 3861–3864. (b) Bromide anion: Shono, T.; Matsumura, Y.; Hayashi, J. *Ibid.* **1980**, *21*, 1867–1870. (c) Iodide anion: Shono, T.; Matsumura, Y.; Hayashi, J.; Mizoguchi, M. *Ibid.* **1979**, *20*, 164–168. (d) nitrate: Leonard, J. E.; Scholl, P. C.; Steckel, T. P.; Lentsch, S. E.; van de Mark, M. R. *Ibid.* **1980**, *21*, 4695–4699. (e) Poly(4-vinylpyridine): Yoshida, J.-I.; Nakai, R.; Kawabata, N. *J. Org. Chem.* **1980**, *45*, 5269.

[3] Cation **2** is easily formed by oxidation of the readily available nitroxyl **1** with, for example, chlorine,[4] peracid,[5] and electrooxidation.[6] The hydroxylamine intermediate, **3**, is known,[7] but neither preparative electrolysis nor voltammetric studies have appeared. We have now shown that the cyclic voltammetry oxidation peak potential for **3** in acetonitrile is ca. +0.8 V vs. Ag/AgNO$_3$; direct recycling would require high positive potential. However, **3** reacts with **2** to generate **1** and a proton, and **1** reenters the cycle. Therefore, the catalytic cycle can be set up at potentials just sufficient for conversion of **1** to **2** (+0.4 V vs. Ag/AgNO$_3$).

0002-7863/83/1505-4492$01.50/0