Palladium-Catalyzed Regio- and Stereoselective Hydrosilylation of Electron-Deficient Alkynes
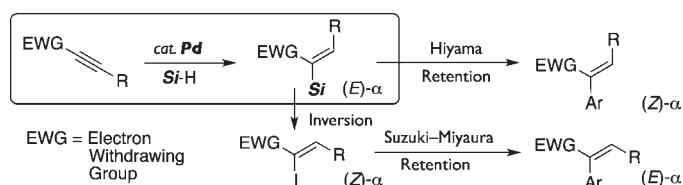
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ABSTRACT

Highly regio- and stereoselective hydrosilylation applicable to a broad range of electron-deficient alkynes has been established using palladium catalysis. The synthetic utility of the method has been demonstrated by further transformations of α-silylalkenes, particularly Hiyama coupling and stereoinverting iododesilylation followed by Suzuki−Miyaura coupling, which enables stereodivergent syntheses of α-arylenoates.

Silylalkenes serve as a powerful building block in organic synthesis owing to diverse types of valuable transformations, such as protodesilylation providing the corresponding alkene, Tamao−Fleming oxidation producing the carbonyl compound, and Hiyama coupling enabling new carbon−carbon bond formations.[1] Silylalkene also offers advantages over other metal alkenes in terms of stability, cost, and low toxicity. Although transition-metal-catalyzed hydrosilylation of alkynes is one of the most straightforward and popular methods of preparing silylalkenes,[2] it often results in regio- and/or stereoisomeric mixtures that are usually difficult to separate. To address this, enormous efforts have been made to regulate the regio- and stereochemistry, particularly for the reaction of internal alkynes. Accordingly, some successful methods

have been developed, including systems employing cationic ruthenium[3] and platinum[4] catalyses as well as a smart approach using a well-designed substrate appended with a regioregulatory metal-coordinating group.[5] Despite these outstanding studies, however, establishing a method capable of providing a specific isomer with a broader substrate scope remains a challenge. Here we describe highly regio- and stereoselective hydrosilylation achieved by the use of palladium catalysis,[6] generally applicable to alkynes activated by an adjacent electron-withdrawing group, as well

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(2) (a) Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1989; Vol. 1, Chapter 25. (b) Hiyama, T.; Kusumoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 3.12. (c) *Comprehensive Handbook on Hydrosilylation*; Marciniec, B., Ed.; Pergamon Press: Oxford, 1992. (d) Marciniec, B.; Maciejewski, H.; Pietraszuk, C.; Pawluć, P. In *Hydrosilylation: A Comprehensive Review on Recent Advances*; Marciniec, B., Ed.; Advances in Silicon Science; Springer: Berlin, 2009; Vol. 1, Chapters 2 and 3.

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(4) (a) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928. (b) After submission of this paper, Pt-catalyzed hydrosilylation of internal alkynes including ynoates was reported: Rooke, D. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2012**, DOI: 10.1002/anie.201108714.

(5) Kawasaki, Y.; Ishikawa, Y.; Igawa, K.; Tomooka, K. *J. Am. Chem. Soc.* **2011**, *133*, 20712–20715.

(6) For Pd-catalyzed hydrostannylation of electron-deficient alkynes, see: (a) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips, H. K. *Tetrahedron Lett.* **1990**, *31*, 6621–6624. (b) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867. (c) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron Lett.* **1992**, *33*, 4495–4498. (d) Dodero, V. I.; Koll, L. C.; Faraoni, M. B.; Mitchell, T. N.; Podestá, J. C. *J. Org. Chem.* **2003**, *68*, 10087–10091.

as some practical derivatizations of the hydrosilylated products.

Initially, we explored the optimized conditions for E-α-selective hydrosilylation of methyl 2-hexynoate (**1a**) with PhMe$_2$SiH (**2a**) (1.2 equiv). The reaction in toluene at room temperature using PtCl$_2$ (5 mol %), the effective catalyst reported for E-α-selective hydrosilylation of alkynyl ketones,[4] proceeded with high efficiency but in diminished regioselectivity (Table 1, entry 1). Adding a phosphine ligand to this system was rather detrimental to the reaction rate (entry 2). Other widely used catalysts, such as the Speier, Karstedt, and Wilkinson catalysts, also gave unsatisfying results (entries 3−5). The reaction with a cationic ruthenium catalyst afforded (Z)-β-isomer (Z)-**4a** selectively, as reported (entry 6).[3] After extensive screening, we found that a palladium(0) catalyst, particularly the combination of Pd(dba)$_2$ and PCy$_3$,[7,8] worked ideally, providing the desired (E)-α-isomer (E)-**3a** in an excellent yield with extremely high regio- and stereoselectivity (entry 7).[9] When PhMe$_2$SiD (**2a-D**, >99% D)[10] was used instead of **2a**, deuterium was introduced completely and exclusively to the β-position of the product. This result indicates that the reaction proceeds in accordance with the Chalk−Harrod mechanism, which involves oxidative addition of silane to Pd(0), regio- and stereoselective hydropalladation to the alkyne, and then reductive elimination to afford the product.[11]

Table 1. Optimization toward E-α-Selective Hydrosilylation of α,β-Ynoate
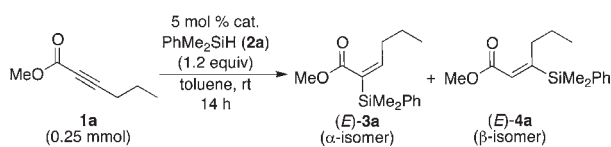
entry	catalyst	yield (%)[a]	ratio of **3a/4a**[a]
1	PtCl$_2$	87	82/18
2[b]	PtCl$_2$/PCy$_3$	8[c]	ND
3	H$_2$PtCl$_6$·4H$_2$O	89	83/17
4	Pt(dvds)	27	79/21
5	RhCl(PPh$_3$)$_3$	15	44/56
6[d]	[Cp*Ru(MeCN)$_3$]PF$_6$	96	2/98[e]
7[b]	**Pd(dba)$_2$/PCy$_3$**	**96 (90)**[f]	**>99/1**

[a] Combined yields and ratio of hydrosilylated products determined by ^{1}H NMR. In terms of stereochemistry, unless otherwise noted, (E)-isomer (E/Z = >99:1) was obtained. ND = not determined. [b] Phosphine (10 mol %) was used. [c] Unreacted **1a** (87%) remained. [d] Reaction performed using 3 mol % of the catalyst in acetone for 2 h. [e] The E/Z ratio of β-isomer was 6/94. [f] Isolated yield in parentheses.

The optimized conditions were commonly applicable to various hydrosilanes, with a few exceptions. Most trialkylsilanes tested in the reaction with ynoate **1a** similarly afforded the desired adduct in excellent yield and selectivities (Table 2, entries 1−3), whereas the highly sterically hindered silane showed poor reactivity (entry 4). Chlorohydrosilane tended to deactivate the palladium catalyst, leaving the alkyne intact (entry 5). Silanes substituted with 2-pyridyl or alkoxy groups, the products of which are expected to be readily transformable (vide infra), reacted more rapidly (entries 6−8). Among the dihydrosilanes examined, t-Bu$_2$SiH$_2$ afforded a monohydrosilylated product in high yield without forming an over-reacted product (entry 10).

Table 2. Scope of Hydrosilanes
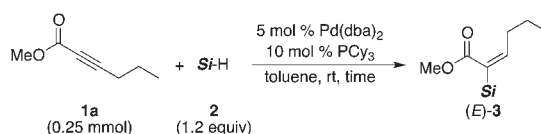
entry	**Si**-H	time (h)	product	yield (%)[a]
1	BnMe$_2$SiH (**2b**)	14	**3b**	99
2	Et$_3$SiH (**2c**)	14	**3c**	86
3	t-BuMe$_2$SiH (**2d**)	14	**3d**	99
4[b]	i-Pr$_3$SiH (**2e**)	48	**3e**	(27)[c]
5	t-Bu$_2$ClSiH (**2f**)	2	**3f**	0
6	2-PyMe$_2$SiH (**2g**)	14	**3g**	76
7	(MeO)$_2$MeSiH (**2h**)	3	**3h**	90
8	(EtO)$_3$SiH (**2i**)	1	**3i**	73 (95)[c]
9	PhMeSiH$_2$ (**2j**)	2	**3j**	CM
10	t-Bu$_2$SiH$_2$ (**2k**)	2	**3k**	85

[a] Isolated yields; α/β = >99:1; E/Z = >99:1. CM = complex mixture. [b] Reaction conducted at 80 °C. [c] ^{1}H NMR yields in parentheses.

A broad substrate scope of alkynes was represented, as well (Table 3). Not only β-alkylated ynoates but also β-aryl- and trimethylsilyl-substituted compounds performed well as substrates (entries 1−4). A siloxymethyl group, which could give a low selectivity because of the electronic effect, did not interfere with the regioselectivity, in sharp contrast with the platinum catalytic system (entry 5).[4] A substrate without a β-substituent as well as one having another terminal alkynyl group could also be employed, although the isolated yields of these products were moderate on account of their instability (entries 6 and 7). Moreover, our system was widely applicable to alkynes activated by other electron-withdrawing groups including ynones, ynal, and ynamide (entries 8−11). Alkynyl sulfone also acted as a good substrate, although the product was hard to isolate because protodesilylation occurred easily during purification on silica gel (entry 12). Unfortunately,

(7) Pd$_2$(dba)$_3$/PCy$_3$-catalyzed hydrosilylation of terminal alkynes: Motoda, D.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 1529–1531.

(8) Other electron-rich ligands such as P(n-Bu)$_3$, P(c-C$_5$H$_9$)$_3$, and IMes·HCl were also effective. See Supporting Information for details.

(9) See Supporting Information for characterization of the isomers.

(10) PhMe$_2$SiD (**2a-D**) was prepared according to: Caseri, W.; Pregosin, P. S. *J. Organomet. Chem.* **1988**, *356*, 259–269.

(11) (a) Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 16–21. (b) Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 1133–1135. (c) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441–1449.

the reaction of dimethyl acetylene dicarboxylate, which has an extra electron-withdrawing group, resulted in a complex mixture even though the reaction was carried out at 0 °C.[12]

Table 3. Scope of Electron-Deficient Alkynes

entry	alkyne	Si-H		time (h)	product		yield (%)[a]
1	(EtO₂C–C≡C–Me)	1b	2a	14	(E)-3l		93
2	(MeO₂C–C≡C–Ph)	1c	2a	14	(E)-3m		99
3[b]	(EtO₂C–C≡C–Ph)	1d	2i	0.5	(E)-3n		97
4	(EtO₂C–C≡C–SiMe₃)	1e	2a	16	(E)-3o		99
5	(EtO₂C–C≡C–CH₂OTBS)	1f	2a	16	(E)-3p		88[c]
6	(EtO₂C–C≡CH)	1g	2i	3	(E)-3q		59 (78)[d]
7	1h	1h	2i	14	(E)-3r		42 (98)[d]
8	(Me–CO–C≡C–SiMe₃)	1i	2a	14	(E)-3s		94
9	(Ph–CO–C≡C–CH₂OTBS)	1j	2a	14	(E)-3t		99
10	1k	1k	2a	16	(E)-3u		(74)[d] (65)[e]
11	(Me₂N–CO–C≡C–Ph)	1l	2i[f]	2	(E)-3v		88
12	(p-tol–SO₂–C≡C–SiMe₃)	1m	2i[f]	1	(Z)-3w		(92)[d]

[a] Isolated yields unless otherwise noted; α/β = >99:1; E/Z = >99:1. [b] Reaction performed with 5 mmol of **1d** using Pd(OAc)₂ instead of Pd(dba)₂. [c] Product contained a small amount of protodesilylated product. [d] Yields determined by ¹H NMR in parentheses. [e] Isolated yield after derivatization to the corresponding allyl alcohol by Luche reduction. [f] 1.0 equiv of **2i** was used.

(12) The reaction of 1-phenyl-1-propyne, an unactivated alkyne, with triethoxysilane (**2i**) afforded the product in poor regioselectivity (66% yield, α/β = 74/26, determined by ¹H NMR).

As we attempted to prepare silylalkenes in larger amounts, we encountered a problem: low reproducibility in stereoselectivity of the product was observed in certain cases.[13] After careful studies, we found that silylalkene (E)-**3i** could be partially isomerized by treatment with triethoxysilane (**2i**) under the same conditions as those used for hydrosilylation of alkynes.[14] This result suggests that the undesired isomerization is triggered by the second hydrosilylation of initially formed silylalkene with redundant hydrosilane, followed by β-hydride elimination (Scheme 1).[15] On the basis of this observation, we succeeded in preparing a sufficient amount of stereoisomerically pure silylalkenes with high reproducibility, merely by using an equimolar amount of hydrosilane.

Scheme 1. Plausible Mechanism for Partial Isomerization of Silylalkene via Second Hydrosilylation
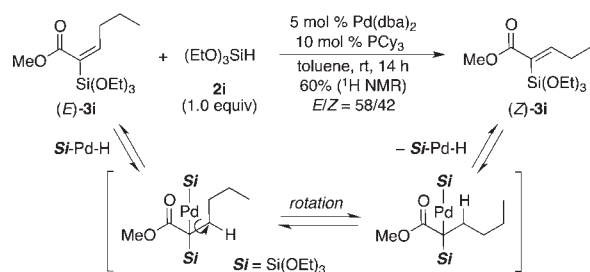
Silylalkenes were demonstrated to be capable of conversion to alkene derivatives by forming a new C−H or C−C bond with a high degree of stereochemical retention. For example, ethyl cis-cinnamate (**5**) was obtained efficiently from (E)-α-silylalkene (E)-**3n** by protodesilylation using TBAF in water-containing THF (Figure 1, eq 1). Moreover, after the conditions were fine-tuned, Hiyama coupling[16] was accomplished under mild conditions without decreasing the E/Z ratio: adding (E)-**3n** slowly to a mixture of 4-iodoanisole, PdCl₂(PPh₃)₂, AgF,[17] and K₂CO₃ in MeCN afforded α-arylated cinnamate (Z)-**6** in high yield (eq 2). To our knowledge, this is the first example of Hiyama coupling at the α-position of α,β-unsaturated carbonyl compounds. The dimethoxysilyl group worked as well as the triethoxysilyl

(13) Low reproducibility was also observed in 0.25 mmol scale. The reactions of ynoate **1a** (0.25−5 mmol) with 1.2 equiv of **2i** under the optimized conditions always gave the product in high yields (>90% by ¹H NMR), but the E/Z ratio randomly oscillated between 64/36 and >99/1. Partial isomerization was frequently observed particularly when electron-deficient hydrosilane was used and/or the hydrosilylated product was highly reactive, such as triethoxysilylalkenyl sulfone **3w**.

(14) No isomerization of (E)-**3i** was observed when any one of the reagents among Pd(dba)₂, PCy₃, or triethoxysilane was absent.

(15) (a) Mori, A.; Takahisa, E.; Kajiro, H.; Nishihara, Y.; Hiyama, T. Polyhedron **2000**, 19, 567−568. (b) Mori, A.; Takahisa, E.; Yamamura, Y.; Kato, T.; Mudalige, A. P.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. Organometallics **2004**, 23, 1755−1765.

(16) (a) Hiyama, T. In Metal Catalyzed Cross-Coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 10. (b) Denmark, S. E.; Sweis, R. F. In Metal Catalyzed Cross-Coupling Reactions; 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 4.

(17) Using AgF as a F⁻ source was crucial. All attempts to use TBAF, which is generally used in Hiyama coupling, under various palladium/phosphine ligand systems were unsuccessful.

group: the alkene (*E*)-**3h** was successfully coupled with an electron-deficient aryl iodide, 1-iodo-2-nitrobenzene, furnishing the desired product (*Z*)-**7**, which was reported to be readily convertible to indole derivatives (eq 3).[18] In addition, the coupling reaction of silylalkene (*E*)-**3i** with phenyl acetylene also proceeded smoothly under almost the same conditions providing eneyne (*Z*)-**8** efficiently (eq 4).[19]
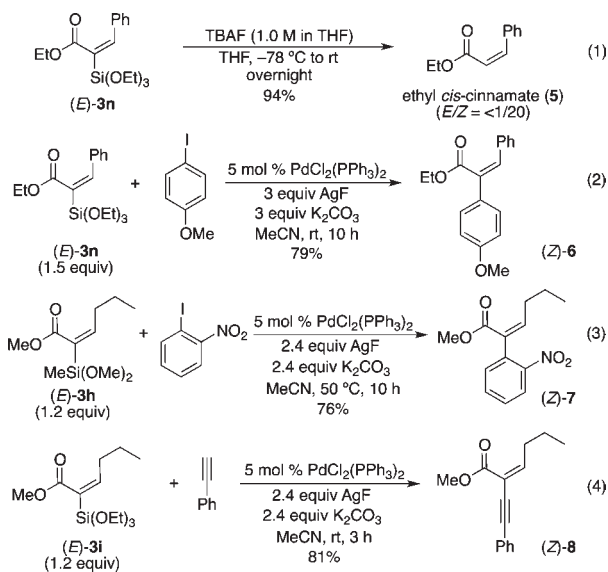
Figure 1. Stereoretaining transformations of silylalkenes.

Gratifyingly, the stereodivergent syntheses of α-arylenoates were achieved with the aid of iododesilylation of α-silylenoate, providing α-iodoenoate, the geometry of which is almost completely inverted. Thus, treating (*E*)-**3i** with 2.0 equiv of ICl (1.0 M solution in CH$_2$Cl$_2$), which is the general condition previously reported for stereoconvergent iododesilylation of α-trimethylsilylenones,[20] afforded the desired product (*Z*)-**9** with inverted geometry and high stereoselectivity (*E*/*Z* = 3/97) (Scheme 2). When only an equimolar amount of ICl was employed at a lower temperature, iodochlorinated ester **10** was unexpectedly obtained as a single diastereomer, along with a small amount of (*E*)-**9**. Compound **10** was more stable than anticipated and, by treating with TBAF at −78 °C, could also be converted into (*Z*)-**9** also in a highly regiocontrolled manner. This result indicates that **10** is a possible intermediate of the stereoinverting iododesilylation. Although the precise

(18) Söderberg, B. C. G.; Banini, S. R.; Turner, M. R.; Minter, A. R.; Arrington, A. K. *Synthesis* **2008**, 903–912.
(19) For Pd-catalyzed cross-coupling of ArSi(OMe)$_3$ with terminal alkyne in the presence of AgF and base, see: Ye, Z.; Liu, M.; Lin, B.; Wu, H.; Ding, J.; Cheng, J. *Tetrahedron Lett.* **2009**, *50*, 530–532.
(20) Alimardanov, A.; Negishi, E.-i. *Tetrahedron Lett.* **1999**, *40*, 3839–3842.
(21) When α-triethylsilylenoate **3c** was treated with 2.0 equiv of ICl, the α-iodoenoate was obtained as a mixture of stereoisomers (*E*/*Z* = 40/60) in 98% yield (^{1}H NMR).
(22) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

Scheme 2. Stereodivergent Syntheses of α-Arylenoates from the Same α-Silylenoate
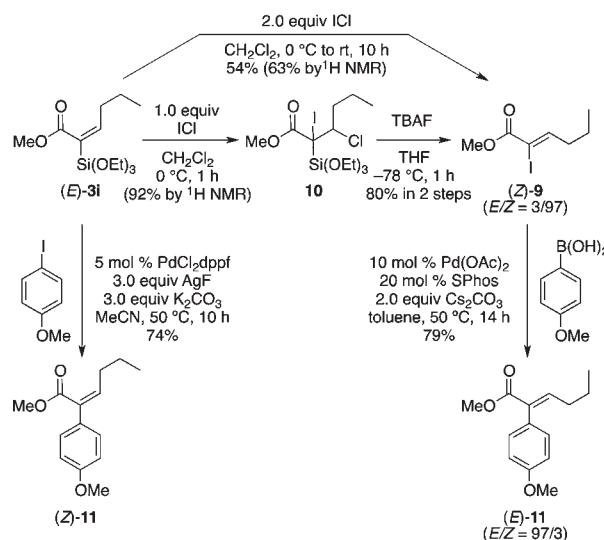
mechanism is unclear, the characteristics of the triethoxysilyl group are presumed to contribute greatly to the high levels of stereoinversion.[21] Stereoinverted α-iodoenoate served as a good substrate in Suzuki−Miyaura coupling: Pd/SPhos[22]-catalyzed reaction of (*Z*)-**9** with *p*-anisylboronic acid afforded (*E*)-α-arylenoate (*E*)-**11** stereospecifically. Meanwhile, as described above, the counterpart (*Z*)-isomer (*Z*)-**11** could be obtained directly by Hiyama coupling of silylalkene (*E*)-**3i** with 4-iodoanisole. Considering that both (*E*)-**11** and (*Z*)-**11** originate from the same starting material, this approach offers a rational method of preparing both stereoisomers of an α-arylenoate expeditiously.

In summary, we found an efficient palladium catalytic system for highly regio- and stereoselective hydrosilylation applicable to a broad range of electron-deficient alkynes and hydrosilanes. Highly stereocontrolled transformations of the hydrosilylated products clearly demonstrated the utility of the method. Specifically, Pd-catalyzed coupling reactions in combination with stereoinverting iododesilylation of silylalkene offers a great advantage in preparing both stereoisomers of α-substituted α,β-unsaturated carbonyl compounds.

Supporting Information Available. Experimental procedures and characterization data, including copies of ^{1}H and ^{13}C NMR spectra, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.