

Intramolecular Syn and Anti Hydrosilylation and Silicon-Assisted Cross-Coupling: Highly Regio- and Stereoselective Synthesis of Trisubstituted Allylic Alcohols

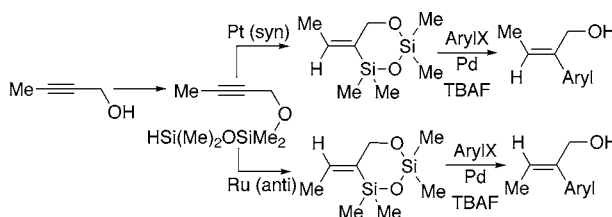
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ABSTRACT



The geometrical isomers of 6-ethylenedioxadisilacyclohexane were prepared by intramolecular hydrosilylation of an unsymmetrical disiloxane by the use of Pt (syn) and Ru (anti) catalysts. This new class organosilicon reagents underwent cross-coupling reactions with a range of aryl iodides to afford (*E*)- and (*Z*)-trisubstituted allylic alcohols in a highly stereospecific fashion.

Transition metal-catalyzed cross-coupling reactions between unsaturated organometallic agents and organo(pseudo)halides are one of the most powerful and versatile methods of carbon–carbon bond formation.¹ In recent years, organosilicon reagents have been extensively developed and now rival the more well-established organotin, organoboron, and organozinc reagents for generality, selectivity, and ease of handling.² As part of an ongoing program to establish the scope of organosilicon-based coupling reactions, we have demonstrated that a wide variety of unsaturated silafunctional groups such as simple silanols, cyclic siloxanes, disiloxanes, silacyclobutanes, and silyl hydrides are extremely reactive in cross-coupling with aryl and alkenyl halides.³

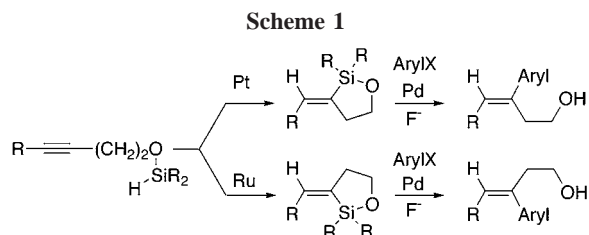
(1) (a) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985. (c) Tsuji, I. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Chichester, UK, 1995.

(2) (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 10. (b) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (c) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531.

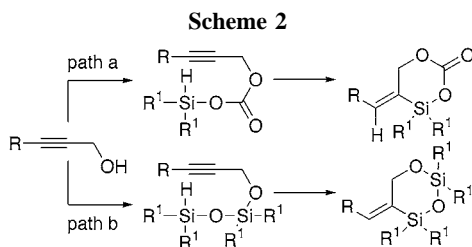
In addition to the nontoxicity, ease of handling, and excellent functional group compatibility of the substrates, the silicon-based cross-coupling approach greatly benefits from the wide variety of reactions for introduction of oxasilyl groups into organic structures with concomitant formation of defined alkene geometries. Three such reactions that have been documented in recent reports from these laboratories are (1) intramolecular hydrosilylation of homopropargyl alcohols,⁴ (2) intramolecular silylformylation of homopropargyl alcohols,⁵ and (3) ring-closing metathesis.⁶ All of these transformations create unsaturated siloxane units, which have been successfully engaged in fluoride-activated cross-coupling reactions. In the former cases, the configuration of the exo alkylidene unit was defined by the stereochemical

(3) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.
(4) (a) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61. (b) Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4163.
(5) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.*, in press.
(6) (a) Denmark, S. E.; Yang, S.-Y. *Org. Lett.* **2001**, *3*, 1749. (b) Denmark, S. E.; Yang, S.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 2102. (c) Denmark, S. E.; Yang, S.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15196.

course of the hydrosilylation. Both syn (platinum)^{4a} and anti (ruthenium)^{4b} hydrosilylations have been achieved, which in combination with stereospecific cross-coupling afford geometrically defined trisubstituted homoallylic alcohols (Scheme 1). The successful manipulation of homopropargylic alcohols stimulated the development of a cognate process for functionalization of propargylic alcohols. We report herein the successful realization of this strategy for the preparation of stereodefined, trisubstituted, allylic alcohols.



Intramolecular hydrosilylation of propargylic alcohols by direct attachment to a silyl hydride has proved to be very challenging.⁷ In fact, attempts at the syn intramolecular hydrosilylation with propargylic hydridosilyl ethers result in polymerization,⁸ obviously arising from the instability of the oxasilacyclobutane ring.⁹ Clearly, a two-atom tether was needed to connect the oxygen of the propargyl alcohol with the silyl hydride;¹⁰ this would allow regioselective formation of a six-membered ring siloxane. (Scheme 2). We initially



considered the use of a carbonate as the tether (path a); however, the precursor proved to be very difficult to synthesize. A novel alternative that employed a disiloxane as the connecting tether (path b) was viewed with skepticism, but a catalytic method for silyl ether formation under mild conditions made this option more attractive.¹¹

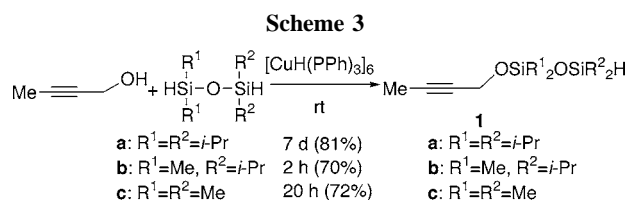
(7) For an excellent review of hydrosilylation, see: Ojima, I.; Li, Z.; Zhu, J. *In The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, UK, 1998; Vol. 2, Part 2, pp 1687–1792.

(8) (a) Tamao, K.; Maeda, K.; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, 29, 6955. (b) Ojima, I.; Vidal, E.; Tzamarioudaki, M.; Matsuda, I. *J. Am. Chem. Soc.* **1995**, 117, 6797.

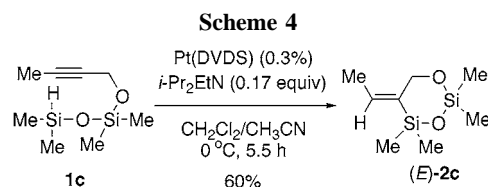
(9) Sugimoto, M.; Takama, A.; Ito, Y. *J. Am. Chem. Soc.* **1998**, 120, 1930.

(10) Use of disilanes as a one-atom tether was considered but then discarded in view of the incompatibility of the Si–Si bond with most hydrosilylation catalysts. Sugimoto, M.; Ito, Y. *Chem. Rev.* **2000**, 100, 3221.

At the outset, we were cognizant of the potential instability of the bis silyl ether, **1**, as well as the hydrosilylation products, **2** (Schemes 3 and 4). Thus, disiloxanes bearing bulky substituents were examined first. Tetraisopropylidisiloxylene is commonly used for protecting vicinal hydroxyl groups in sugars of nucleosides.¹² Thus, 2-butyne-1-ol was coupled with (commercially available) tetraisopropylidisiloxane using a catalytic amount of freshly prepared Stryker's catalyst¹³ to give alkynyldiisopropylidisiloxane **1a** in good chemical yield. Unfortunately, we were not able to find conditions that facilitated the desired hydrosilylation, so we turned to the dimethyldiisopropylidisiloxane **1b** prepared as described above from the unsymmetrical disiloxane precursor.¹⁴



With **1b** in hand, we examined the intramolecular hydrosilylation to form a six-membered cyclic disiloxane. Under the standard conditions with Pt(DVDS),^{4a,15} the desired syn hydrosilylation product (*E*)-**2b** was obtained as a stable compound (Scheme 4). However, the product also contained a regioisomer, as was anticipated from the literature precedent for the formation of six-membered rings by hydrosilylation.^{8b,16} Moreover, the sluggish and low-yielding cross-coupling of (*E*)-**2b** with a typical electrophile, iodobenzene, forced us to explore the synthesis and coupling of the most reactive analogue, tetramethyldisiloxane (*E*)-**2c**.



The precursor **1c** was prepared as describe above with minor modification (Scheme 3). It was found that the

(11) Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, 128, 1267.

(12) Markiewicz, W. T.; Padyukova, N. Sh.; Samek, Z.; Smrt, J. *Collect. Czech. Chem. Commun.* **1980**, 45, 1860.

(13) Stryker's catalyst was prepared (according to: Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, 29, 3749) and stored in a drybox. Commercial sources of Stryker's catalyst are significantly contaminated; see: Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, 56, 2779.

(14) Diisopropylidimethyldisiloxane was prepared from commercially available diisopropylchlorosilane by hydrolysis to the silanol followed by coupling with dimethylchlorosilane in 50% overall yield.

(15) Platinum(0)-1,3-divinyl-1,1,3,3,-tetramethyldisiloxane complex.

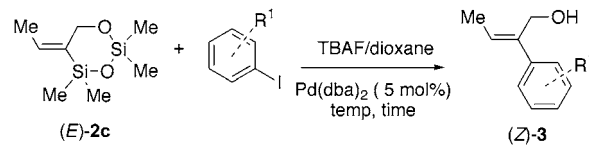
(16) Steinmetz, M. G.; Udayakumar, B. S. *J. Organomet. Chem.* **1989**, 378, 1.

oxidative coupling of 2-butyne-1-ol with tetramethyldisiloxane was not selective; the ratio of mono to bis silyl ether was nearly statistical. Fortunately, using a large excess of tetramethyldisiloxane (26 equiv) almost completely suppressed the formation of the bis silyl ether.¹⁷ The formation of silicon-containing byproducts also complicated purification of **1c**, but thorough drying of the reagents greatly reduced this problem.¹⁸ Direct distillation of the product after removal of the excess disiloxane provided **1c** in good yield and of sufficient purity for subsequent reactions.

The syn hydrosilylation of **1c** was first attempted with a catalytic amount of Pt(DVDS)^{4a} which led to a significant amount of oligomerization. After a brief optimization it was found that addition of Hünig's base suppressed the formation of oligomers. As shown in Scheme 4, the desired hydrosilylation product (*E*)-**2c** could be formed and, much to our surprise, isolated in good yield under mild conditions.

Whereas the stability of (*E*)-**2c** was unexpected, its high reactivity in cross-coupling was anticipated. The results of reaction of (*E*)-**2c** with a selection of aryl iodides under the standard conditions (TBAF (2.0 equiv), Pd(dba)₂ (5 mol %)) are collected in Table 1. As was seen with other siloxane nucleophiles, the scope of reaction of (*E*)-**2c** with aryl iodides bearing many common functional groups (ester, ketone, alcohol, ether) was good. In all cases, the corresponding (*Z*)-allylic alcohols were formed in high yield and excellent stereospecificity. When methyl 2-iodobenzoate was used, a lactone, (*Z*)-**3f** was obtained (Scheme 5).

Table 1. Facile Synthesis of (*Z*)-Trisubstituted Allylic Alcohols^a



entry	R ¹	time, h (temp, °C)	product	yield ^b , % (ratio, <i>Z/E</i>) ^c
1	H	3.3 (rt)/1.4 (45)	(<i>Z</i>)- 3a	79 (100) ^d
2	2-MeO	12.9 (rt)/13 (40)	(<i>Z</i>)- 3b	81 (100)
3	3-HOCH ₂	5.4 (rt)/1.9 (40)	(<i>Z</i>)- 3c	81 (100) ^d
4	4-CH ₃ O	3.2 (rt)/2 (35)	(<i>Z</i>)- 3d	71 (100)
5	4-MeCO	10.1 (rt)	(<i>Z</i>)- 3e	82 (100)

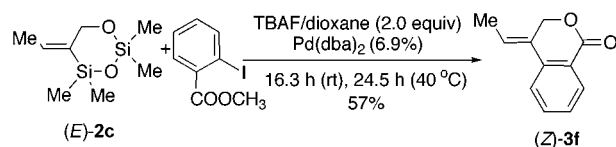
^a All reactions employed 1.05 equiv of (*E*)-**2c**, 2.0 equiv of TBAF, and 5 mol % Pd(dba)₂ for 1.0 mmol of iodide in dioxane at the designated temperature. The iodide was added in portions (see Supporting Information). ^b Yields of analytically pure materials. ^c Determined by capillary GC analysis. ^d Yields of chromatographed and distilled materials.

Following our previous experience with the anti-selective hydrosilylation of homopropargylic silyl ethers, we examined the reaction of **1c** with [RuCl₂(C₆H₆)₂].^{4b} The conditions

(17) Tetramethyldisiloxane is an inexpensive, commercially available material and can be reused. In fact, for most preparations of **1c**, recovered tetramethyldisiloxane was used.

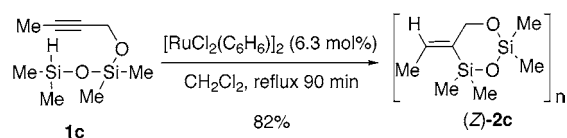
(18) These silicon impurities were found to have adverse effects on the ruthenium-catalyzed hydrosilylation reaction.

Scheme 5



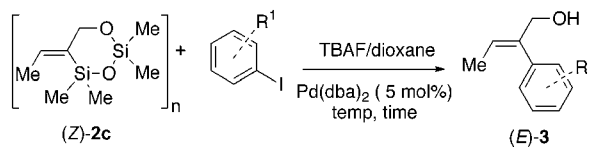
developed for this process required refluxing a dichloromethane solution of **1c** with the catalyst (Scheme 6). The hydrosilylation proceeded as expected, but the elevated temperatures caused the oligomerization of the product. Fortunately, after removal of the ruthenium catalyst, crude polymeric [(*Z*)-**2c**]_n was shown to couple with iodobenzene in dioxane highly stereospecifically, albeit more slowly than (*E*)-**2c**.

Scheme 6



The results of a survey of the cross-coupling of [(*Z*)-**2c**]_n with a few representative aryl iodides are collected in Table 2. As with (*E*)-**2c**, the polymeric [(*Z*)-**2c**]_n exhibited good

Table 2. Facile Synthesis of (*E*)-Trisubstituted Allylic Alcohols^a

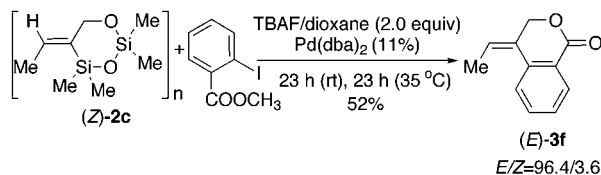


entry	R ¹	time, h (temp, °C)	product	yield ^b , % (<i>E/Z</i> ratio) ^c
1	H	75 (rt)	(<i>E</i>)- 3a	57 (97.7/2.3)
2	2-MeO	67 (rt)/3 (40)	(<i>E</i>)- 3b	65 (98.5/1.5)
3	4-CH ₃ O	20 (rt)/3.5 (40)	(<i>E</i>)- 3d	50 (97.3/2.7)
4	4-MeCO	22.5 (rt)/10 (40)	(<i>E</i>)- 3e	64 (98.5/1.5)

^a All reactions employed 1.5–1.8 equiv of [(*Z*)-**2c**]_n, 2.0–2.5 equiv of TBAF, and 5–11 mol % Pd(dba)₂ with 1.0 mmol of iodide in dioxane at the designated temperature. ^b Yields of chromatographed and distilled materials. ^c Determined by capillary GC analysis.

compatibility with many common functional groups tested (ester, ketone, ether). The attenuated yield might be due to the presence of other silyloxy nucleophiles. The reactions of all halides were highly stereospecific. Again, when methyl 2-iodobenzoate was used, a lactone (*E*)-**3f** was obtained (Scheme 7). It is interesting to note that this lactone was formed at the later stages of reaction, unlike the (*Z*)-isomer, which was visible already at the beginning of the reaction.

Scheme 7



The success and utility of this method can be appreciated by comparison to the problems associated with the coupling reactions of the corresponding vinylstannane, (*Z*)-2-tributylstannyl-2-butenol ((*Z*)-4), which proceed in low yield (with 4-iodoanisole) and also give a substantial amount of cine rearrangement product.¹⁹ In fact, the observation of cine rearrangement products has been a problem for crowded vinylstannanes in general.^{19b} In comparison, neither (*E*)-2c nor [(*Z*)-2c]_n gave detectable amounts of the cine product. The slight erosion in stereospecificity with [(*Z*)-2c]_n might arise from imperfect stereocontrol in the hydrosilylation.

This method highlights the directing effect of the hydroxyl group for the regioselective and stereoselective introduction of aromatic moieties at the 2-position of propargylic alcohols. Whereas Ensley reported the selective preparation of (*Z*)-4 by radical hydrosilylation of 2-butenol, the (*E*)-isomer is not

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available.²⁰ Other methods of hydrostannylation of propargylic alcohol derivatives give variable regio- and stereoselectivities.²¹

In summary, we have demonstrated that propargylic alcohols can be highly regio- and stereoselectively functionalized at the 2-position by intramolecular hydrosilylation/cross-coupling to afford both (*E*)- and (*Z*)-2,3-disubstituted allylic alcohols. Together with our recently reported cross-coupling of 3-silyl-2-butenols to afford (*E*)- and (*Z*)-3,3-disubstituted allylic alcohols,²² we have been able to control the introduction of aryl and alkenyl substituents selectively on a propargylic alcohol. Studies on the carbosilylation/cross-coupling of propargylic alcohols to access tetrasubstituted products are in progress.

Acknowledgment. We are grateful to the National Institutes of Health (GM 63167) for generous financial support.

Supporting Information Available: Procedures for the preparation and characterization of **1**, (*E*)- and (*Z*)-2c, and all coupling products, as well as representative procedures for coupling reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) Denmark, S. E.; Pan, W. J. *Organomet. Chem.* **2002**, 653, 98.