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Intramolecular Hydrosilylation and Silicon-Assisted Cross-Coupling: An Efficient Route to Trisubstituted Homoallylic Alcohols

Scott E. Denmark* and Weitao Pan

245 Roger Adams Laboratory, Department of Chemistry, University of Illinois,
600 South Mathews Avenue, Urbana, Illinois 61801

denmark@scs.uiuc.edu

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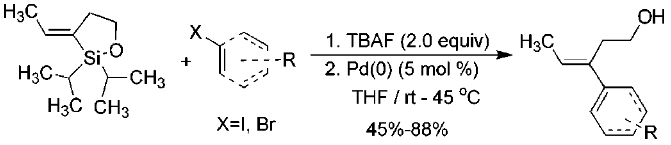
ABSTRACT



Alkylidenesilacyclopentanes (formed by intramolecular hydrosilylation of homopropargyl alcohols) are efficiently coupled with aryl or alkenyl halides in the presence of tetrabutylammonium fluoride and a palladium(0) catalyst. Yields of cross-coupling were generally high, and the reaction is compatible with a wide range of functional groups. The overall transformation achieves the conversion of homopropargyl alcohols to trisubstituted homoallylic alcohols in a highly stereoselective fashion.

The invention and development of efficient and stereospecific carbon−carbon bond-forming reactions remains among the central missions of synthetic organic chemistry. One of the most powerful reactions to emerge in the past quarter century is the transition metal-catalyzed cross-coupling between (primarily) main-group organometallic species and organo(pseudo)halides. Witness the impact of the Stille coupling of organostannanes, the Suzuki coupling of organoboranes, or the Negishi coupling of organozinc reagents and the case is easily made for the stature of these transformations in the armamentarium of organic synthesis.[1]

We have recently set out to elevate the implementation of organosilicon reagents in palladium-catalyzed cross-coupling to a similar rank. The pioneering work of Hiyama,[2] Ito,[3] and DeShong[4] established that organosilicon compounds with heteroatom(s) attached at the silicon can be used as the donors in cross-coupling reactions, thus eliminating some of the problems associated with the aforementioned methods: toxicity, handling of reagents, and lack of functional group compatibility. Disclosures from these laboratories have established that silacyclobutanes[5a,b,d] and simple silanols[5c] or silyl hydrides[5f] are extremely reactive in cross-coupling with aryl and alkenyl halides. Preliminary mechanistic investigations[5e] reveal that the basic structural requirement for facile cross-coupling is the presence of an oxygen function on the silicon (alcohol, ether, disiloxane). Accordingly, we recognized the opportunities for installing a fresh carbon−silicon bond via intramolecular hydrosilylation of a pendant silyl ether.[6] This process would provide an unambiguous route to geometrically defined vinylic silanes necessarily bearing

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[1] (a) Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 1995.

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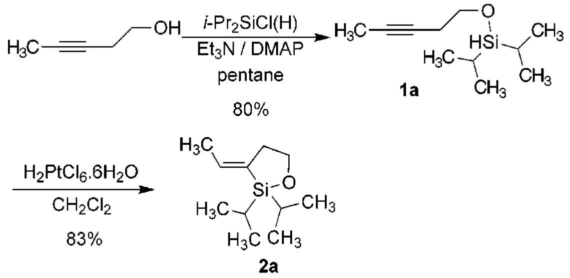
an oxygen function. We report herein the successful realization of this strategy for the preparation of stereodefined homoallylic alcohols.[7]

To test the feasibility of the overall transformation, we chose to examine each stage independently and therefore selected a substrate that would allow isolation and characterization of both intermediates. The cyclic siloxane, **2a**, derived from 3-pentyn-1-ol, was chosen for ease of handling (low molecular weight) and the diisopropylsilyl group was chosen to facilitate purification (stability of the silyl ethers).[5f] Thus, silylation of 3-pentyn-1-ol with diisopropylchlorosilane provided the silyl ether **1a** in good yield, Scheme 1. Intramolecular hydrosilylation of **1a** was effected with a catalytic amount of Speier's catalyst to afford **2a** cleanly and in high yield.

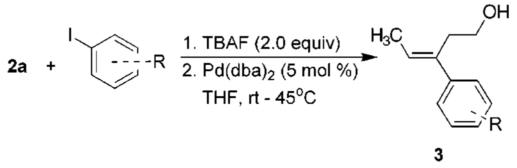
Scheme 1



Orienting experiments were carried out using the standard conditions established for the silanol couplings with a simple aryl iodide.[5c] Thus, siloxane, **2a**, was dissolved in 2.0 equiv of a 1.0 M solution of TBAF in THF, followed by the addition of iodobenzene and 5 mol % of Pd(dba)$_2$. Gratifyingly, the siloxane did undergo the coupling process, however, at a significantly reduced reaction rate compared to the related silanols. Moreover, the reaction mixture was contaminated with a substantial amount of biphenyl (the product of self-coupling of iodobenzene), and thus the yield of the cross-coupling product was attenuated. The addition of various ligands[5b] or decreasing the amount of Pd(0) did not meaningfully improve the results. Fortunately, we found that adding the iodide in portions satisfactorily suppressed the formation of biphenyl and correspondingly improved the yield of the desired coupling product. The portionwise addition of the iodide proved to be effective in reducing the amount of homocoupling byproduct in most cases. For a few, very slow reacting substrates, even this expedient was not helpful (vide infra).

With a reproducible procedure in hand, we next explored the scope of the reaction with regard to the nature and position of substituents on the aromatic ring. The results compiled in Table 1 reveal good compatibility with all common functional groups tested (ester, ketone, nitro, alcohol, nitrile, ether). For all aryl iodides examined, the reaction proved to be mild and high yielding except in the case of 2-nitroiodobenzene (entry 4) which was very slow and gave a substantial amount of nitrobenzene as a byproduct. Noteworthy features of this process are that (1) electron-withdrawing or -donating groups exhibit similar reactivity, (2) ortho substituents on the aryl iodide do not affect the reactivity significantly, (3) the reaction tolerates diverse functional groups such as ester, nitro, cyano, ether, and even free hydroxy group, and (4) the reactions of all halides were stereospecific, with the exception of 4-nitroiodobenzene and 1-iodonaphthalene, which gave a small amount of the geometrical isomer.

Table 1. Palladium-Catalyzed Cross-Coupling of **2** with Aryl Iodides[a]



entry	R	time, h/temperature, °C	product	yield,[b] %
1	H	6.66/rt	**3a**	88
2	2-Me	6.83/rt	**3b**	74
3	2-MeO	10.0/35	**3c**	74
4	2-NO$_2$	23/35	**3d**	56
5	3-HOCH$_2$	6.0/rt	**3e**	81
6	4-CH$_{3O}$	6.50/rt	**3f**	72
7	4-MeCO	6.0/rt	**3g**	70
8	4-NO$_2$	6.25/rt	**3h**	67[c]
9	4-CN	46/45	**3i**	70
10	4-COOEt	16/45	**3j**	86

[a] Reaction conditions: 1.1 equiv of **2a**, 2.0 equiv of TBAF, and 5 mol % of Pd(dba)$_2$ were employed for 1.0 equiv of iodide in THF at rt. The iodide was added in portions as specified (see Supporting Information). [b] Yields of analytically pure materials. [c] Isomeric ratio 95.2/4.8 by capillary GC analysis.

This variant of the coupling reaction is not limited to benzene derivatives. For instance, 1-iodonaphthalene, 1-bromo-4-*tert*-butyl-1-cyclohexene (an unactivated vinyl bromide), and 3-iodopyridine reacted with **2a** to give the expected products **3k, 3l**, and **3m**, respectively, in reasonable to good yield (Figure 1).

The optimization of this process next turned to the investigation of the importance of the silicon substituents. It was of interest to see whether and how the size of the substituents on the silicon would affect the rate and selectivity of the reaction. Additional benefits such as improved mass efficiency and ease of byproduct removal could be realized with a smaller group in place of an isopropyl group. We thus focused our attention on the corresponding dimethylsiloxane. However, the synthesis of the siloxanes was problematic. The intramolecular hydrosilylation of dimethylsilyl ethers with chloroplatinic acid resulted in polymeric materials. Though the platinum(0)−1,3-divinyl-1,1,3,3-tet-

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(6) 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.; John Wiley & Sons: Great Britain, 1998; Vol. 2; pp 1687−1792.

(7) For a single previous example of this concept see ref 3a.

ramethyldisiloxane complex (Pt(DVDS)) gave clean intramolecular hydrosilylation, any attempts to obtain the siloxane in a pure state or to scale-up the preparation of the siloxane led to oligomerization.[8]

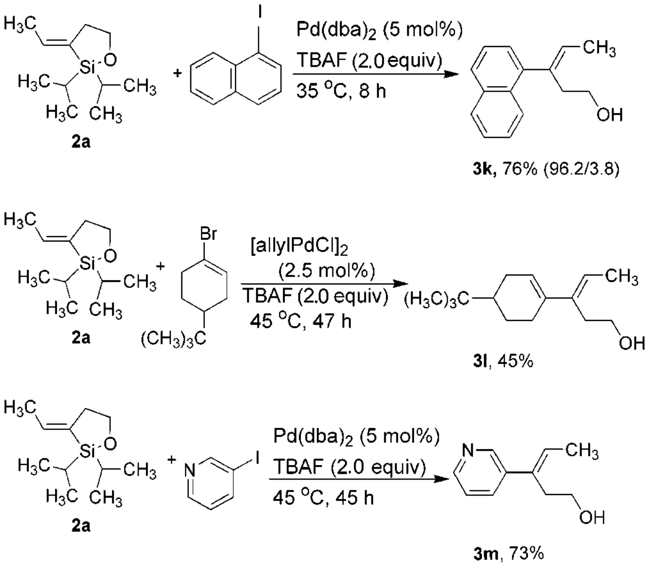


Figure 1. Cross-coupling of **2a** with nonbenzenoid halides.

A practical solution to this problem was conceived in the form of a one-pot protocol that would (1) obviate the need to isolate and purify the delicate silyl ether and siloxane and (2) improve the overall efficiency of the process. Thus, to streamline the procedure and minimize the formation of potentially deleterious byproducts, we employed tetramethyldisilazane (TMDS) as the silylating agent. Treatment of 3-pentyn-1-ol (**1b**) with 0.77 equiv of TMDS (neat) followed by dissolution in THF and closure under the action of Pt(DVDS) produced the siloxane **2b** efficiently by GC/MS analysis (Scheme 2). Unfortunately, the subsequent cross-coupling reactions were not reproducible and often stalled. Varying the amount of fluoride, reaction concentration, and palladium source resulted in no significant improvement. Fortunately, it was found that by increasing the loading of $Pd(dba)_2$ to 10%, the complete consumption of iodobenzene was achieved within 40 min, giving the desired product in 85% yield. The results for this and other iodides are collected in Table 2. Thus, 2-iodoanisole and 4-iodobenzonitrile also coupled smoothly with **2b** (formed in situ from 3-pentyn-1-ol) using the one-pot procedure (10 mol % of $Pd(dba)_2$), affording good yields of cross-coupling products. In these cases as well, 5% $Pd(dba)_2$ failed to promote the reactions efficiently.

Scheme 2

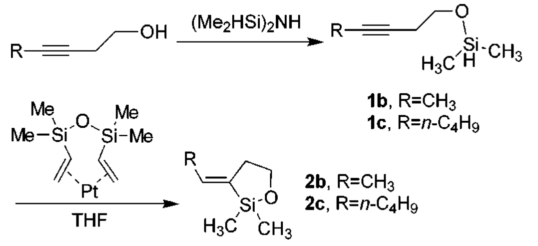
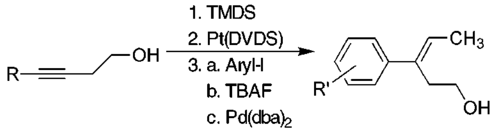


Table 2. One-Pot Arylation of Homopropargylic Alcohols



entry	R	R′	Pd, %	time, min/ emp, °C	product	yield,[c] % (isomeric ratio)
1[a]	Me	H	10	40/rt	**3a**	85 (97.2/2.8)
2[a]	Me	2-OMe	10	480/35	**3c**	75 (98.3/1.7)
3[a]	Me	4-CN	10	300/rt	**3i**	74 (96.7/3.3)
4[b]	*n*-Bu	H	10	40/rt	**4**	84 (97.7/2.3)
5[b]	*n*-Bu	H	5	90/rt	**4**	85 (98.3/1.7)

[a] Reaction conditions: (1) homopropargylic alcohols (1.3 equiv), TMDS (1.0−1.2 equiv), (2) 0.30−0.37% Pt(DVDS) in THF (1.5 mL/mmol alcohol). (3) TBAF (2.2 equiv), aryl iodide (1.0 equiv). [b] Reaction conditions: (1) homopropargylic alcohol (1.3 equiv), TMDS (1.0 equiv); (2) remove TMDS in vacuo, (3) 0.30−0.37% Pt(DVDS) in THF (1.5 mL/mmol alcohol), (4) TBAF (2.2 equiv), aryl iodide (1.0 equiv). [c] Yields of analytically pure materials.

The capriciousness of the one-pot process is believed to be rooted in the residual tetramethyldisilazane (TMDS) which may poison the $Pd(dba)_2$. We were unable to remove the excesses of this reagent owing to the volatility of the silyl ether **1b**. To test this hypothesis, we made recourse to a higher molecular weight homopropargylic alcohol, 3-octyn-1-ol. When this alcohol was employed, the excess TMDS was easily removed by evacuation upon the completion of silylation. Intramolecular hydrosilylation with Pt(DVDS) proceeded normally, but now, the cross-coupling reaction could be effectively promoted with only 5 mol % of $Pd(dba)_2$ to give the expected products in 85% yield within 2 h. If 10 mol % of $Pd(dba)_2$ was used, the reaction was complete within 40 min, affording the desired product in 85% yield.[9]

Comparison of the results in Tables 1 and 2 clearly shows the advantages of the one-pot procedure: (1) ease of experimental protocol, (2) aryl iodide need not be added portionwise to avoid homocoupling, (3) intermediate silyl ethers need not be isolated (one step versus three), and (4) superior overall yields. However, in one important category

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(8) We ascribe this to the strain of the silacyclopentane ring and the low energy barrier to silyl ether exchange.

(9) Without removing the TMDS, the reaction gave a 63% yield of the product (72% conversion) over 44 h on a small scale, with 10 mol % catalyst loading.

the multistage procedure employing **2a** was superior, namely, stereospecificity. In all cases involving the dimethylsiloxane, a small amount of the *Z*-isomer was observed (1.7−2.3%). All attempts to suppress the formation of this isomer were unsuccessful. For instance, this minor product was not eliminated by decreasing the reaction concentration for hydrosilylation. Changing the hydrosilylation catalyst also failed to remedy the situation.[10]

The effect of the silicon substituent on the rate and selectivity of the cross-coupling had been addressed previously with silanols.[5c] In that study the size of the substituent (methyl versus isopropyl) had little effect on the rate of coupling. In the case at hand, the dimethylsiloxanes reacted faster than the corresponding diisopropylsiloxanes. Interestingly, this fact may also explain why it was not necessary to add the aryl iodide portionwise, given the competitive rate of cross-coupling compared to homocoupling of the aryl iodides. However, as was observed with silanols,[5c] the stereospecificity was dependent on substituent. The dimethyl derivatives tended to give a small amount of the isomeric products, whereas the diisopropyl analogues gave the coupling products with near perfect stereochemical fidelity.

In conclusion, we have demonstrated the expanded synthetic potential of our newly invented silicon-based cross-coupling. In this incarnation, the silicon atom has served in the following capacities: (1) as a temporary protecting group for the hydroxyl function, (2) as a temporary tether to fix the geometry of the vinylsilane, and (3) as the locus for directing the formation of a new carbon−carbon bond. In a very mild and environmentally friendly manner, homopropargyl alcohols were elaborated stereospecifically to trisubstituted homoallylic alcohols in good yields. These structures are often encountered in natural products and also are useful synthetic intermediates.[11] It has not been lost on the authors that the siloxane itself is a very versatile subunit for further synthetic manipulation.[12]

The ability to introduce silafunctional units in a controlled and stereoselective fashion by, inter alia, intramolecular hydrosilylation, silylformylation, and disilylation bodes well for the manifold applications of this methodology. These studies will be disclosed in due course.

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Supporting Information Available: Procedures for the preparation and full characterization of **1a**, **2a**, **3a−m**, and **4** along with representative procedures for coupling reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] It is conceivable that a competitive *intermolecular* hydrosilylation competes to form the undesired isomer.

[11] See the following and references therein: (a)Takeda, T.; Kabasawa, Y.; Fujiwara, T. *Tetrahedron* **1995**, *51*, 2515. (b) Okuma, K.; Tanaka, Y.-i; Hirabayashi, S.-i; Shioji, K.; Matsuyama, H. *Hereocycles* **1997**, *45*, 1385. (c) Crousse, B.; Alami, M.; Linstrumelle, G. *Synlett* **1997**, 922.

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