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

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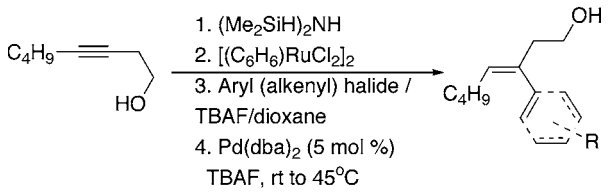
ABSTRACT



A highly regio- and stereoselective anti-intramolecular hydrosilylation of alkynyl silyl ethers catalyzed by a ruthenium arene complex has been developed. The resultant (*Z*)-alkylidenesilacyclopentanes are efficiently coupled with aryl or alkenyl halides in the presence of tetrabutylammonium fluoride and a palladium(0) catalyst. The yields are generally good, and the reaction is compatible with a wide range of functional groups. The overall transformation achieves the stereoselective conversion of homopropargyl alcohols to trisubstituted homoallylic alcohols.

Transition-metal-catalyzed cross-coupling reactions between (primarily) main-group organometallics and organo(pseudo)-halides are among of the most powerful carbon−carbon bond formation methods. In addition to the traditional organometallic donors,[1]namely organostannanes, organoboranes, and organozinc compounds, organosilicon reagents now represent an emerging class of useful nucleophiles.[2−4]

Recent developments in these laboratories have greatly expanded the scope of organosilicon compounds that can participate in cross-coupling processes.[5] We have established that unsaturated silanes containing functional units such as simple silanols,[5c,e,f,j,k] siloxanes,[5g,h] disiloxanes,[5i] silacyclobutanes,[5a,b,d] and silyl hydrides[5f] are extremely reactive in cross-coupling with aryl and alkenyl halides.

In addition to nontoxicity, ease of handling, and excellent functional group compatibility, another important advantage of this silicon-based method includes the ease and stereoselective introduction of functionalized silyl units. For example, syn hydrosilylation of alkynes has been extensively used to prepare (*E*)-alkenylsilanes. Thus, terminal alkynes

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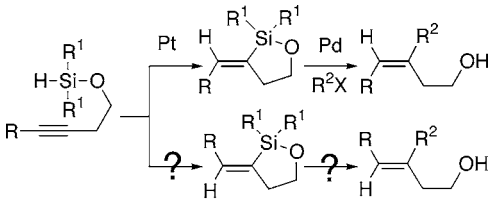
are efficiently transformed into (*E*)-alkenes via the corresponding silanols or siloxanes. Similarly, by harnessing the directing role of hydroxyl group, homopropargylic alcohols can be transformed into trisubstituted homoallylic alcohols through a syn-intramolecular hydrosilylation. The amalgamation of hydrosilylation and cross-coupling reactions clearly provides an unambiguous route to geometrically and stereochemically defined disubstituted (*E*)-alkenes[5i] and trisubstituted alkenes (Scheme 1).[5g] In view of the power of this transformation, we sought to develop a complimentary strategy to access the opposite geometrical isomers through an anti-hydrosilylation. We report herein the implementation of this strategy for the preparation of stereodefined, trisubstituted homoallylic alcohols.

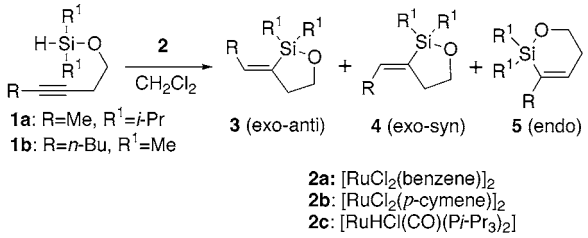
Scheme 1



The success of this strategy requires the development of an anti-intramolecular hydrosilylation. In sharp contrast to the well-established syn-hydrosilylation (in both inter- and intramolecular modes),[6] anti-intermolecular hydrosilylation is less well known,[6,7] and only one example of intramolecular anti-hydrosilylation of nonfunctionalized alkenylhydrosilanes has been reported. This transformation is catalyzed by strong Lewis acids and gives endo rather than exo products when the ring size is smaller than six.[8] We sought to develop an intramolecular anti-hydrosilylation that was compatible with labile Si−O bonds and which could provide the requisite alkylidene silacyclopentanes by exo hydrosilylation. Thus, the intramolecular closure of alkynyloxysilanes was investigated using those transition-metal catalyst/solvent systems that are known to give anti hydrosilylation products in intermolecular cases.

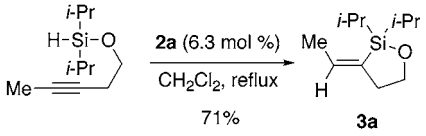
For orienting experiments, we selected 3-pentynyloxydiisopropylsilane (**1a)** to facilitate purification of the hydridosilanes and also to ensure that the cyclic siloxane products could be isolated and purified. This substrate (prepared by straightforward silylation of the alcohol) was subjected to initial screening under conditions known to promote anti-intermolecular hydrosilylation (Scheme 2). Of all the ruthenium catalysts employed,[9] only the ruthenium arene complexes (**2a** and **2b**) gave the exo,anti-hydrosilylation product

Scheme 2



3 as the major product along with a small amount of the exo,syn-hydrosilylation product **4**. In striking contrast, the ruthenium hydride complex **2c**[10] afforded exclusively **4** in 75% yield. The other catalysts shown gave low conversion and more complex mixtures. Further optimization with complexes **2a** and **2b** in CH_2Cl_2 revealed a positive dependence of selectivity on catalyst loading and concentration.[11] It was found that the loading of catalyst could be decreased by adding the silyl ether to catalyst through a syringe pump. Under these conditions, **2a** promoted the reactions faster and gave better yield than **2b**. Catalyst **2a** can also be easily removed from the reaction mixture by precipitation with pentane or hexane. Thus, cyclosiloxane (*Z*)-**3a** was obtained in good yield as a single isomer by adding a CH_2Cl_2 solution of **1a** by syringe pump to catalyst **2a** (6.3 mol %) in refluxing CH_2Cl_2 (Scheme 3).

Scheme 3



Initial cross-coupling experiments with **3a** were carried out using the standard conditions established for the silanol couplings with a simple aryl iodide.[5c] Thus, siloxane **3a** 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, but at an unacceptably slow rate and in poor yield. Even after extensive optimization, other electrophiles beyond iodobenzene failed to couple with **3a**, and the main product obtained was 3-penten-1-ol from protodesilylation of **3a**. Apparently, the steric hindrance from the diisopropyl group as well as the cis-configured methyl group diverted the siloxane into a less sterically demanding protodesilylation pathway.

To facilitate the coupling process, we replaced the offending isopropyl groups with methyl groups. Once again

(6) For an excellent review of hydrosilylation, see: Ojima, I.; Li, Z.; Zhu, J. In T*he chemistry of organic silicon compounds*; Rappoport, Z., Apeloig, Y., Eds.; John Wiley & Sons: Great Britain, 1998; Vol. 2, pp 1687−1792.

(7) For recent examples of anti-intermolecular hydrosilylations: (a) Mori, A.; Takahisa, E.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. *Chem. Lett.* **1998**, 443. (b) Na, Y.; Chang, S. *Org. Lett.* **2000**, *2*, 1887. (c) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726. (d) Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922.

(8) Sudo, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 8919.

(9) Other catalysts employed: $[RuCl_2(p\text{-cymene})Py]$, $[RuCl_2(p\text{-cymene})(PPh_3)]$, $[RuCl_2(C_6Me_6)]_2$, $[RhI(PPh_3)_3]$, $[Ru(PPh_3)_3Cl_2]_2$, $[RuCl_2(COD)]$.

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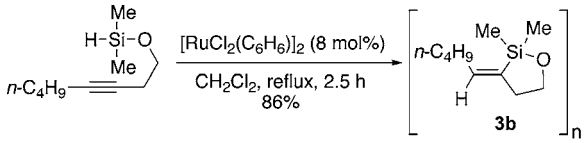
(11) This is in sharp contrast to the general belief that for anti-hydrosilylation low loading of catalyst give high selectivity.

for ease of purification and handling of volatile organosilicones, 3-octyn-1-ol was converted to the alkynyloxydimethylsilane **1b** by treatment with tetramethyldisilazane.[12] Unfortunately, the intramolecular hydrosilylation catalyzed by **2a** in CH_2Cl_2 was not nearly as selective, affording both stereoisomers **3b** and **4b** as well as endo-hydrosilylation product **5b**. Moreover, the optimization of this process was thwarted by the rapid oligomerization of **3b** upon concentration. Nevertheless, we could still employ the oligomers as cross-coupling precursors[5g] and evaluate the hydrosilylation selectivity at the level of the arylated product. In this way, it was possible to improve the stereo- and regioselectivity of the hydrosilylation process by slow (syringe pump) addition of **1b** to a refluxing solution of **2a** in dichloromethane. The siloxane could be isolated after purification by precipitation of the ruthenium catalyst and filtration of the suspension through charcoal (Scheme 4). The product thus obtained was used directly in the following cross-coupling reactions.

Scheme 4

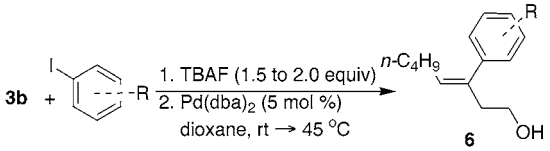


The first electrophile examined with **3b** was 2-iodianisole, which failed to couple with the more congested siloxane **3a**. A solvent survey revealed that dioxane gave the best results in terms of rate and cleanness of the reaction, though there was still a small amount of protodesilylation product detected. Ultimately, it was found that sequential addition of TBAF suppressed the protodesilylation, and the coupling rate was also enhanced. The beneficial effect of fewer equivalents of TBAF seemed to be substrate dependent; for example, in the case of iodobenzene, the use of 2 equiv of TBAF promoted the reactions faster than the use of 1 equiv. This suggested a sequential addition of TBAF when a slow reaction was encountered, which was employed subsequently.

The scope of the cross-coupling reaction was next examined 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). Interestingly, methyl 2-iodobenzoate, which did not react with the corresponding (*E*)-silacyclopentane,[5g] reacted with **3b** to give a reasonable yield of desired product. For all aryl iodides examined, the reaction proceeded generally in good yield and under mild conditions. Noteworthy features of this process are as follows: (1) electron-rich and -deficient aryl halides exhibit similar reactivity, (2) ortho substituents on the aryl iodide do not affect the reaction rate significantly, (3) the coupling process tolerates diverse functional groups such as ester, nitro, cyano, ether, and even a free hydroxyl group, (4) all of the reactions were highly stereoselective. The small amount of stereoisomers observed most likely reflect some leakage in the hydrosilylation step.

(12) We noted that traces of residual tetramethyldisilazane caused the cross-coupling to become capricious.[5g] It was also observed that certain volatile silicon compounds such as tetramethyldisiloxane have adverse effects on the ruthenium catalyst.

Table 1. Palladium-Catalyzed Cross-Coupling of **3a** with Aryl Iodides[a]

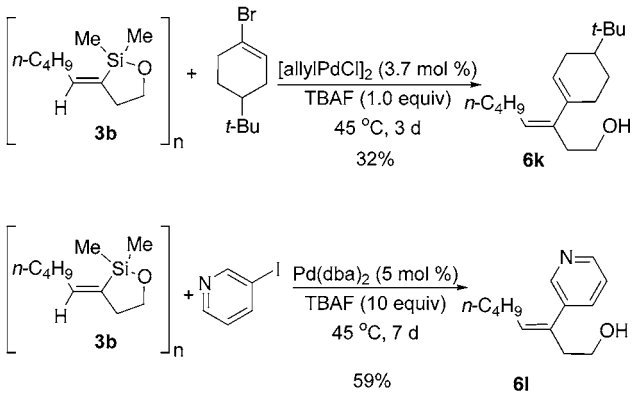


entry	R	time, h/*T*, °C	product	yield,[b] %
1	H	8.1/45	**6a**	65[c] (95.3/4.7)[d]
2	2-MeO	27/rt; 21/35	**6b**	68[b] (97/3)[e]
3	2-COOMe	43/35	**6c**	64[b] (95/5)[e]
4	2-NO_2	7/rt, 47/35	**6d**	66[b] (96.2/3.8)[d]
5	3-$HOCH_2$	13.5/rt, 33/45	**6e**	59[c] (98.4/1.6)[d]
6	4-CH_3O	41/rt	**6f**	60[b] (99.3/0.7)[d]
7	4-MeCO	46/rt	**6g**	66[b] (97.4/2.6)[e]
8	4-NO_2	7.6/45	**6h**	68[b] (96.4/3.6)[e]
9	4-CN	25.5/45	**6i**	64[c]
10	4-COOEt	15.5/40	**6j**	72[b] (96.5/3.5)[e]

[a] Reaction conditions: 1.1 equiv of **3b**, 1.52−2.0 equiv of TBAF, and 5 mol % of $Pd(dba)_2$ were employed for 1.0 equiv of iodide in dioxane at designated temperature. [b] Yields of analytically pure materials. [c] Yield of chromatographed and distilled homogeneous materials. [d] Isomeric ratio determined by ^1H NMR analysis. [e] Isomeric ratio determined by capillary GC analysis.

Coupling reactions of **3b** are not limited to benzene derivatives. For instance, 1-bromo-4-*tert*-butyl-1-cyclohexene (an unactivated vinyl bromide) as well as 3-iodopyridine reacted with **2b** to give the expected products **6k** and **6l**, respectively (Scheme 5). Stereo- and regioselective functionalization of unactivated internal alkynes other than propargylic alcohols proved to be difficult and rare.[13] The newly developed, silicon-based, carbon−carbon bond forma-

Scheme 5



tion reaction, in combination with stereochemically complimentary hydrosilylation, allows for selective and mild additions to alkynes. In doing so, the multiple roles of silicon atom provide a general and predictable means to functionalize homopropargylic alcohols at the 3-position with access to either double-bond geometry. These subunits are often encountered in natural products and are themselves useful synthetic intermediates.[14] It is also noteworthy that the siloxane itself is a versatile subunit for further synthetic manipulation;[15] for example, it can be converted stereospecifically to a vinyl halide which is an important building block.

The ability to introduce silafunctional units in a controlled and stereoselective fashion by intramolecular hydrosilylation bodes well for the functionalization of propargylic alcohols as well. These studies along with applications in synthesis will be disclosed in due course.

(13) For a recent example see: Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621.

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 **3a**, **3b** and all new 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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(14) 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. *Heterocycles* **1997**, *45*, 1385. (c) Crousse, B.; Alami, M.; Linstrumelle, G. *Synlett* **1997**, 922.

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