

Convergence of Mechanistic Pathways in the Palladium(0)-Catalyzed Cross-Coupling of Alkenylsilacyclobutanes and Alkenylsilanols

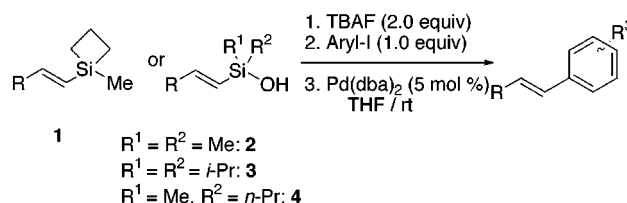
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ABSTRACT



Alkenylsilacyclobutanes and alkenylsilanols react in palladium-catalyzed cross-coupling reactions via the same intermediate, produced in situ upon treatment of either starting material with tetrabutylammonium fluoride.

Carbon–carbon bond formation via transition metal-catalyzed cross-coupling has emerged as a general and powerful reaction in organic synthesis.¹ Generally, this transformation involves the coupling of organo-(pseudo)-halides with organometallic compounds in the presence of a Ni(0)- or Pd(0)-catalyst. The most commonly employed organometallic nucleophiles are organostannanes (Stille), organoboranes (Suzuki), and organozincs (Negishi). Although these reagents have been proven to be very useful and have a very broad scope, there are some problems associated with these compounds, such as toxicity, ease of handling, functional group compatibility, or air-sensitivity.

Recent reports from these laboratories have introduced a new class of silicon-based nucleophiles which contain alkenylsilacyclobutanes.² This class of compounds undergo facile Pd(0)-catalyzed, cross-coupling reactions with a

multitude of aryl and alkenyl iodides in the presence of a nucleophilic activator such as tetra-*n*-butylammonium fluoride (TBAF) or hydroxide (TBAOH). Closer inspection of the reaction components revealed that silacyclobutanes suffered rapid ring-opening in the presence of nucleophiles. This observation ultimately led us to the demonstration that silanols and/or disiloxanes are also competent precursors for the cross-coupling process.³ We describe herein, detailed mechanistic investigations on the confluence of these reaction pathways.

In our initial investigations of silacyclobutanes² we noted

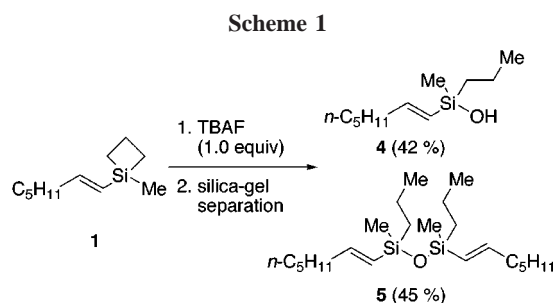
(2) (a) Denmark, S. E.; Choi, J.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495. (c) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999.

(3) (a) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (b) For previous studies on silicon-based cross-coupling reactions see: Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10.

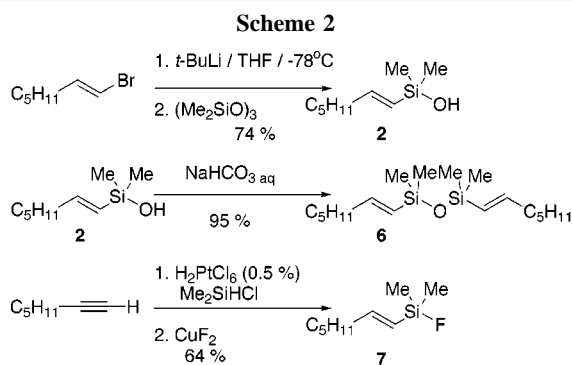
(4) Commercial TBAF is a crystalline trihydrate. Despite many reports on the dehydration of TBAF, this process primarily results in the formation of bifluoride. Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* **1998**, *63*, 9587.

(1) (a) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 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, U.K., 1995.

a significant exotherm upon treatment of **1** with TBAF. Controlled reaction of **1** with 1 equiv of TBAF yielded silanol **4** and disiloxane **5** in high yield, Scheme 1. This process was shown to require only catalytic quantities of TBAF; treatment of **1** with 5 mol % of TBAF in the presence of 50 mol % of water afforded disiloxane **5** instantaneously and quantitatively.⁴



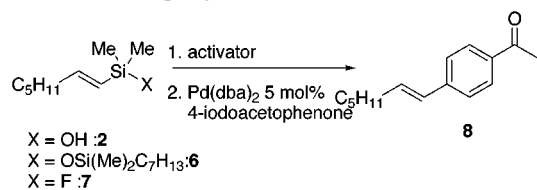
It was thus clear that silacyclobutanes were not involved in the cross-coupling under these conditions, but the reactions were nonetheless remarkably facile. To determine what other potential precursors would be competent for the cross-coupling, several organosilicon compounds (silanol **2**, disiloxane **6**, and fluorosilane **7**) were chosen, Scheme 2. In these compounds the dimethylsilyl group was employed to simplify their synthesis without changing their chemical properties. The three candidates were subjected to standard coupling conditions (5 mol % Pd(dba)₂, 1.1 equiv of 4-iodoacetophenone, 0.3 M in THF, rt) with different amounts of fluoride and hydroxide activators, Table 1.



The results in the first column clearly show that no reaction takes place in the absence of activator and starting materials could be recovered. With 1.0 equiv of TBAF, full conversion of all three precursors was achieved after 1 h, and the coupling product **8** was isolated in good yields. Closer investigation revealed that, although the reactions were initially fast (75% conversion after 10 min), complete

(5) We surmise that this is due to the accumulation of a silicon-containing byproduct which scavenges some of the fluoride activator.

Table 1. Cross-Coupling Reactions of **2**, **6**, and **7**

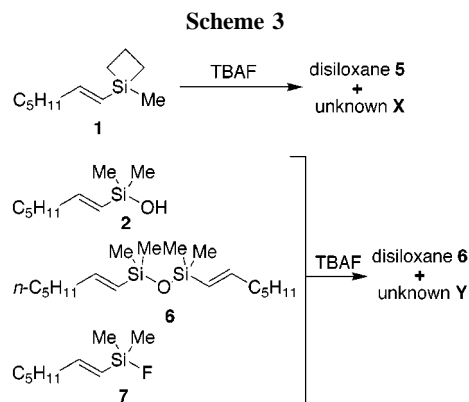


	no activator	yield, % (time)		
		TBAF ^a	TBAF ^b	TBAOH ^b
2	NR	82 (1 h)	79 (10 min)	75 (3 h)
6	NR	82 (1 h)	82 (10 min)	78 (3h)
7	NR	79 (1 h)	78 (10 min)	22 (24 h)

^a 1 equiv. ^b 2 equiv.

conversion required 1 h.⁵ This drawback was easily overcome by the simple expedient of a second equivalent of TBAF. For all three precursors, full conversion was achieved in less than 10 min, and the product **8** was isolated in high yields in all cases. With TBAOH as the activator, the reaction of both silanol **2** and disiloxane **6** were substantially slower; however, the product could be isolated after 3 h. In the case of the fluorosilane **7**, the reaction was sluggish, and only 22% of the product could be isolated after 24 h. Thus, we had established that all of the above compounds are competent precursors for the Pd(0)-catalyzed cross-coupling-reaction in the presence of TBAF.

Since all of the above silicon compounds reacted with comparable rates and yields, the presence of a common intermediate was suspected. To shed light on this possibility, the four compounds shown in Scheme 3 were treated with



1.0 equiv of TBAF in THF-*d*₈. ¹H NMR analysis of the reaction mixtures showed that in each case two compounds were formed, the disiloxane (**5** or **6**) and a second compound which could not be assigned to any previously prepared compound. The unknown compound **Y** was seen from all three precursors **2**, **6**, and **7** but was different from **X** formed from **1**. Moreover, the ratio of unknown (**X** or **Y**) and

disiloxane (**5** or **6**) in solution was highly dependent on the amount of TBAF present. The results in Table 2 show that the portion of **X** increased steadily as more TBAF was used with silacyclobutane **1**.

Table 2. Ratio of Disiloxane **5**/Unknown **X**

TBAF (equiv)	ratio 5 / X	TBAF (equiv)	ratio 5 / X
0.05	>19/1	3.5	1/7.2
1.5	1/2.5	4.5	1/8.3
2.4	1/5.8	4.8	1/9.2
3.0	1/6.3	6.6	1/15.8

The identity of the unknown species proved challenging to establish. Inspection of the ^1H NMR spectrum of **Y** showed that the silicon-atom is attached to two methyl groups and an (*E*)-1-heptenyl group. Furthermore, ^{29}Si NMR analysis of **Y** showed a sharp singlet at -8.39 ppm, which is clearly different from **2**, **6**, or **7**, Figure 1. Similar conclusions can be drawn for **X**. Finally, the sign and magnitude of the chemical shifts indicate that both **X** and **Y** are tetravalent silicon species.⁶

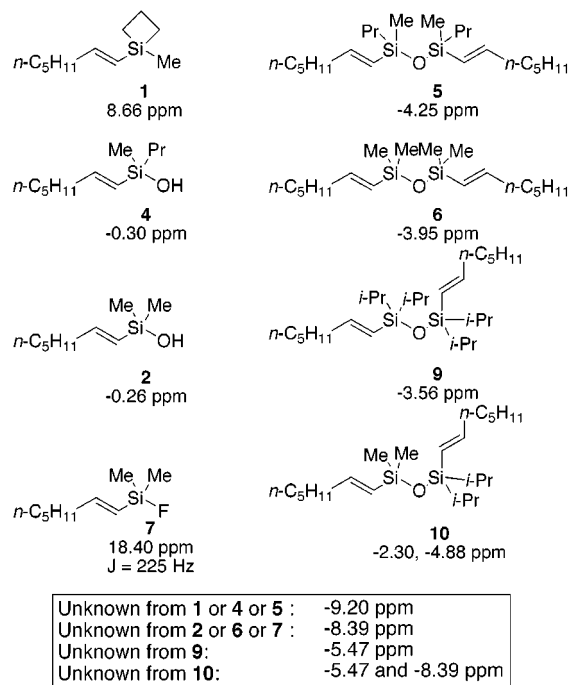


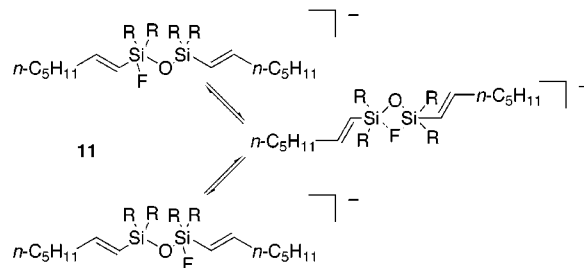
Figure 1. ^{29}Si NMR chemical shifts.

Having excluded simple, tetravalent silicon-compounds as the unknown components, we next investigated whether **X**

(6) The typical chemical shift range for tetracoordinate silicon is δ 30 to -30 ppm, for pentacoordinate silicon is δ -75 to -130 ppm. Takeuchi, Y.; Takayama, T. In *The Chemistry of Organic Silicon Compounds*; Rappaport, Z., Apeloig, Y., Eds.; John Wiley: Chichester, 1998; Chapter 6, Vol. 2, Part 1.

or **Y** could be an oligomer such as the dimeric compound **11** in Scheme 4. Although a pentavalent silicon atom is formally present, fast exchange of the fluorine atom between the two silicon atoms would explain the single signal in the ^{29}Si NMR. Furthermore, such a compound is expected to display ^{29}Si NMR resonances further downfield than a pentacoordinated silicon atom but further upfield of the region where four coordinated silicon atoms would usually be expected. This would hold also for trimeric, tetrameric, or higher oligomers.

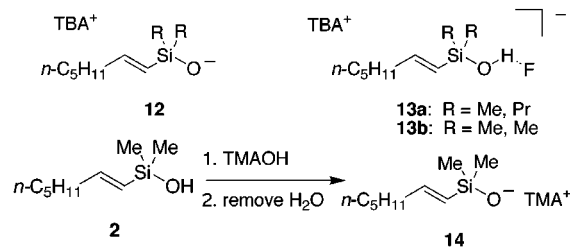
Scheme 4



To test this hypothesis, an equimolar mixture of disiloxanes **6** and **9** was treated with 1 equiv of TBAF. ^{29}Si NMR analysis of the mixture revealed six signals which could be assigned as follows. The smaller signals corresponded to disiloxanes **6** (-3.95 ppm, 7%), **9** (-3.56 ppm, 4%), and **10** (-2.30 ppm and -4.88 ppm, 4%), clearly demonstrating that crossover between the different disiloxanes is taking place.

The main two signals, however, were observed at -5.47 ppm (32%) and -8.39 ppm (40%). These chemical shifts are in exact agreement with the unknown compounds formed from disiloxanes **9** and **6**, respectively. The absence of a third (crossover) peak clearly indicates that the unknowns **X** and **Y** are monomeric species, in which the silicon atom is attached to two alkyl groups, one (*E*)-1-heptenyl group, and a heteroatom. Two candidates that fulfill these requirements are silyloxy **12** and silanol-fluoride adduct **13**, Scheme 5.

Scheme 5



We were not able to prepare silyloxy **12** for comparison purposes, due to the instability of the counterion under anhydrous conditions. However, when silanol **2** was treated with *tetramethylammonium* hydroxide and the water was

azeotropically removed, the corresponding silyloxy **14** could be isolated (Scheme 5). However, neither the ^1H NMR nor the ^{29}Si NMR ($\text{DMF-}d_7$, -26.23 ppm) spectra of this compound corresponded to the those for unknown **Y**; all diagnostic resonances were shifted to higher field compared to those for **Y**.⁷ Furthermore, when the silyloxy **14** was subjected to the reaction conditions in the presence or absence of dry fluoride activator (TMAF),⁸ no reaction was observed.

With all other reasonable hypotheses excluded, it remained to obtain support for structure **13b** as the unknown **Y**. Because compound **13b** contains a hydrogen-bonded fluorine atom, ^{19}F NMR should indicate the presence of a fluorine at a resonance different from TBAF. ^{19}F NMR analysis (rt) of a sample of **Y** generated from **2** and TBAF (1.0 equiv, THF) displayed only a single resonance at -117.7 ppm for TBAF. Cooling the solution to -95 °C, however, allowed the observation of a second signal at -150.8 ppm along with the signal for TBAF at -113.2 ppm. No such signal was observed upon cooling TBAF itself.

With compelling, albeit indirect support for the structure of the unknown as **13** we sought to demonstrate its intermediacy in the palladium-catalyzed cross-coupling reaction. ^1H NMR observation of a typical reaction mixture is shown in Figure 2. Following the standard protocol, TBAF

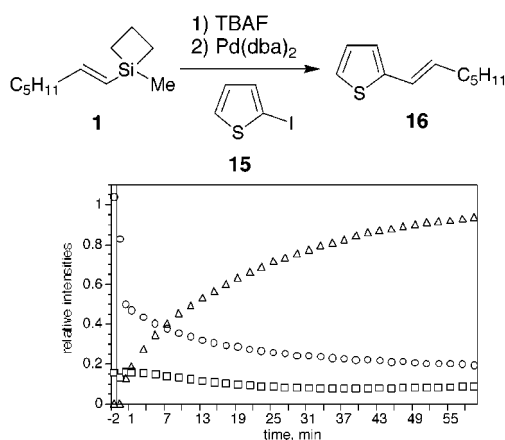


Figure 2. Reaction profile for opening and coupling of **1**.

and **1** were combined to give the initial mixture of **X** (○) and **5** (□) in a 5.6/1 ratio. Addition of $\text{Pd}(\text{dba})_2$ and iodothiophene (**15**) led to a fast consumption of **X** and the

(7) For direct comparison, the TMA salt of the unknown **Y** was generated in DMF which gave two signals, δ ^{29}Si NMR, -13.9 and -15.2 ppm, neither of which corresponded to **14**.

(8) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R. Feng, J. J. *Am. Chem. Soc.* **1990**, *112*, 7619.

production of **16** (△). Disiloxane **5** was also consumed but at a rate lower than unknown **X**. Clearly, **X** is consumed, but detailed kinetic analysis will be necessary to establish if it is directly on the reaction pathway.

An important implication of the intermediacy **13** is that reactions can be performed from the silanols under anhydrous conditions. Starting from **2**, the reaction proceeded to form **17** without the loss in yield or selectivity using the anhydrous fluoride source TMAF (Table 3). The coupling reaction proceeded smoothly with either TBAF, wet TMAF, or dry TMAF.

Table 3. Cross-Coupling with Various Fluoride Sources^a

entry	fluoride	time, min	yield, %	E/Z-ratio
1	TBAF·3H ₂ O	30	82	98.9/1.1
2	TMAF·3H ₂ O	30	84	98.6/1.4
3	TMAF	30	80	99.0/1.0

^a All reactions done in DMF due to the insolubility of TMAF in THF.

The similarity of rate, yield, and stereoselectivity for cross-couplings of **1** and **2** has its origin in the generation of the same kind of reactive intermediate. In the presence of TBAF·3H₂O, **1** suffers ring opening with formation of **5** and thus may enter the same manifold as is accessed from **2** and related silanol derivatives. On the basis of spectroscopic and reactivity data, the structure **13a/b** has been proposed for the common reactive intermediate formed from either **1** or **2** and TBAF.

Determination of the kinetic equation for the cross-coupling as well as elucidation of the detailed role fluoride ion in promoting the reaction are in progress.

Acknowledgment. We are grateful to the National Science Foundation for financial support (NSF CHE 9803124). D.W. thanks the Swiss National Science Foundation and the Novartis-Stiftung and J. Y. C. thanks the Korea Research Foundation (KRF) for postdoctoral fellowships.

Supporting Information Available: Experimental procedures and full characterization for all new compounds along with description of the experiments in Tables 1 and 3 and the NMR kinetics. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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