

## Fluoride-Promoted Cross-Coupling Reactions of Alkenylsilanols. Elucidation of the Mechanism through Spectroscopic and Kinetic Analysis

Scott E. Denmark,\* Ramzi F. Sweis, and Daniel Wehrli

Contribution from the Roger Adams Laboratory, Department of Chemistry,  
University of Illinois, Urbana, Illinois 61801

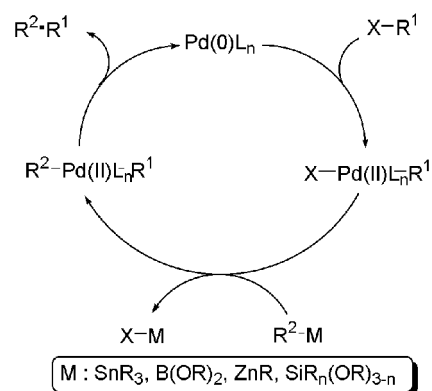
Received July 11, 2003; E-mail: denmark@scs.uiuc.edu

**Abstract:** The mechanism of the palladium-catalyzed cross-coupling reaction of (*E*)-dimethyl-(1-heptenyl)silanol ((*E*)-1) and of (*E*)-diisopropyl-(1-heptenyl)silanol ((*E*)-2) with 2-iodothiophene has been investigated through spectroscopic and kinetic analysis. A common intermediate in cross-coupling reactions of several types of organosilicon precursors has been identified as a hydrogen-bonded complex between tetrabutylammonium fluoride (TBAF) and a silanol. The order in each component has been determined by plotting the initial rates of the cross-coupling reaction at varying concentrations. These data provide a mechanistic picture that involves a fast and irreversible oxidative insertion of palladium into the aryl iodide and a subsequent turnover-limiting transmetalation step achieved through a fluoride-activated disiloxane derived from the particular silanol employed. The inverse order dependence of TBAF at high concentration is consistent with a pathway that proceeds through a hydrogen-bonded complex which is the lowest energy silicon species in solution.

### Introduction

The emergence of transition-metal-catalyzed cross-coupling reactions as one of the premier methods for general and selective carbon–carbon bond formation has been amply documented.<sup>1</sup> Since the discovery of this process independently by Kumada<sup>2a</sup> and Corriu,<sup>2b</sup> the primary focus of research has been the expansion of the scope of the reaction partners to incorporate a wide range of organic substrates (aromatic, heteroaromatic, olefinic, acetylenic, aliphatic, and functionalized derivatives of these) as well as different organometallic donors and organic acceptors. With some important exceptions noted below, detailed studies of the mechanism of this powerful process have lagged significantly behind the investment of effort on the preparative aspects. This constitutes one of the more striking examples of the disparity between synthetic utility and mechanistic understanding of a widely used transformation. As part of our own studies on the development of silicon-based cross-coupling reactions,<sup>3</sup> we were interested in understanding the differences from and similarities to the more well-established tin (Stille–Migita–Kosugi reaction<sup>4</sup>) and boron (Suzuki–Miyaura reaction<sup>5</sup>) cross-coupling methods (Figure 1).

The cross-coupling reactions of a wide variety of organofunctional silanes have been employed as mild and highly



**Figure 1.** Simplified catalytic cycle of commonly used palladium-catalyzed cross-coupling reactions.

efficient alternatives to the more widely known reactions of organotin and organoboron compounds. The organosilicon precursors are found to undergo highly efficient fluoride-promoted cross-coupling reactions in a stereospecific fashion and in excellent yields. Viable precursors for this process include siletanes, halosilanes, silanols, silyl ethers, polysiloxanes, and silyl hydrides. In view of their growing synthetic significance, the diversity of substrates that are capable of engaging in cross-coupling, and the range of reaction conditions that are employed, it was deemed prudent to examine the mechanistic features of silicon-based cross-coupling reactions.

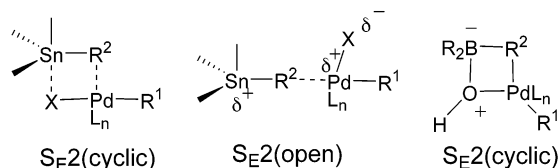
(1) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.  
 (2) (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.  
 (3) Reviews (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (b) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (c) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36* (3), 75.  
 (4) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1.

(5) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (d) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2.

In this and the following paper in this issue, the results of mechanistic studies of two organosilicon coupling reactions are presented through spectroscopic and kinetic analysis. The tetrabutylammonium fluoride (TBAF)-promoted cross-coupling reactions of silanes is described in this paper. The investigation commenced with spectroscopic studies to identify key reaction intermediates. This study was followed by a detailed kinetic analysis to deduce the overall rate equation and help explain the role of the reaction intermediates implicated in the spectroscopic studies. In the following paper, a fluoride-free cross-coupling reaction of unsaturated silanolates is analyzed through a comprehensive kinetic study. The selection of kinetic experiments allowed for both the elucidation of the rate equation and insight into the intermediates involved.

## Background

The impact of transition-metal-catalyzed cross-coupling reactions on synthetic organic chemistry over the last quarter century cannot be overstated. Synthetically useful variants such as the Stille–Miyaura–Kosugi reaction have been probed in great detail.<sup>4</sup> Early on, Stille conducted mechanistic studies on the cross-coupling reaction of organotin compounds with acyl chlorides and proposed an  $S_E2$  mechanism for transmetalation. Shortly thereafter, Farina provided a crucial kinetic analysis of palladium ligand effects on organotin cross-coupling reactions.<sup>6</sup> This study introduced a class of more effective ligands [ $\text{Ph}_3\text{As}$  and  $(2\text{-furyl})_3\text{P}$ ] that allowed for milder and more efficient reactions. Application of electrochemical techniques to investigate the function of palladium in the catalytic cycle has been demonstrated through the elegant and insightful work of Amatore and Jutand.<sup>7</sup> Their findings have significantly elaborated the simple “textbook” mechanism of the cross-coupling process by identifying important roles of anionic palladium intermediates in each step of the catalytic cycle. More recently, Espinet and co-workers have employed kinetic analysis to support an associative model for the key transmetalation step in organotin cross-coupling reaction and have studied the nature of this model [ $S_E2$  (cyclic) vs  $S_E2$  (open)] as well (Figure 2).<sup>8</sup>



**Figure 2.** Proposed mechanism of transmetalation steps of specific Stille and Suzuki cross-coupling reactions.

Despite its emergence as a powerful and general method for carbon–carbon bond formation, the Suzuki–Miyaura cross-coupling reaction of organoboron compounds is, mechanistically, a much less extensively studied system.<sup>5</sup> Surprisingly, insight into the reaction pathway is based mostly on speculation and a few detailed reports. The most thorough mechanistic investigations have focused on the stereochemical course of the reaction of saturated alkylboron compounds. Both Woerpel<sup>9</sup> and Soderquist<sup>10</sup> have reported that the transmetalation of alkyl-

boranes proceeds with retention of configuration. Studies by Soderquist employing  $^{11}\text{B}$  and  $^{31}\text{P}$  NMR spectroscopy as well as kinetic analysis suggest that transmetalation proceeds through a four-centered,  $\mu^2$ -hydroxyl complex between the borane and palladium. This proposal is similar to the  $S_E2$  (cyclic) transmetalation mechanism implicated for certain organotin cross-coupling reactions (Figure 2).

The aforementioned reports notwithstanding, there remains a dearth of experimentally supported mechanistic knowledge for many palladium-catalyzed, carbon–carbon bond forming reactions.<sup>11</sup> The advent of the organosilicon cross-coupling reaction as a widely applicable and synthetically viable method has, over the last 15 years, proceeded without a comprehensive mechanistic study.<sup>12</sup> Consequently, many questions about the mechanistic differences from and similarities to other coupling reactions remain unanswered.

The modest pace at which this reaction developed relative to organoboron and organotin cross-coupling reactions arises from the long-held notion that a carbon–silicon bond is not sufficiently polarized to participate as an effective donor. Hiyama successfully addressed this problem by the use of a nucleophilic fluoride source which he interpreted as the in situ generation of a reactive pentacoordinate silicate. Such silicates are believed to be sufficiently polarized to transfer the attached organic group to an organopalladium(II) halide.<sup>13,14</sup> This discovery stimulated active investigation with many types of fluoride donors as effective silicon cross-coupling reaction promoters. Still, there are no investigations on record that prove or disprove the existence of such silicates in these reactions.

Modulating the steric and electronic properties of ligands on palladium has long been recognized as the method of choice to enhance reactivity for certain organopalladium intermediates. Nowhere has this been more clearly demonstrated than in the newly developed ligands for mild Suzuki cross-coupling reactions with chloride electrophiles, substrates traditionally considered to react at prohibitively low rates.<sup>15</sup> Such ligands are believed to accelerate both oxidative addition and transmetalation steps of the palladium catalytic cycle.

The complexity of even the simplest mechanistic picture (Figure 1) poses many questions that can be answered through spectroscopic and kinetic analysis as well as elucidation of the turnover-limiting step. For example, if fluoride activation of an organosilane is turnover-limiting, then a more efficient activator

(9) Woerpel, K. A.; Ridgeway, B. H. *J. Org. Chem.* **1998**, *63*, 458.

(10) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

(11) The mechanism of palladium-catalyzed aminations has also been the focus of several in-depth mechanistic investigations. See: (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (b) Alcazar-Roman, L. M.; Hartwig, J. F.; Reingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618.

(12) Hiyama has interpreted regiochemical and stereochemical outcomes of palladium-catalyzed coupling of benzyl- and allyltrifluorosilanes as a result of  $S_E2$ - and  $S_E'$ -type transmetalations that can be influenced by solvent, catalyst ligands, and temperature. See: (a) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. (b) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511. Ohmura, H.; Matsuhashi, H.; Tanaka, M.; Kuroboshi, M.; Hiyama, T.; Hatanaka, Y.; Goda, G. *J. Organomet. Chem.* **1995**, *499*, 167.

(13) Isolable pentacoordinate fluorosilicates were demonstrated to undergo cross-coupling reactions prior to this breakthrough. Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542.

(14) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 270.

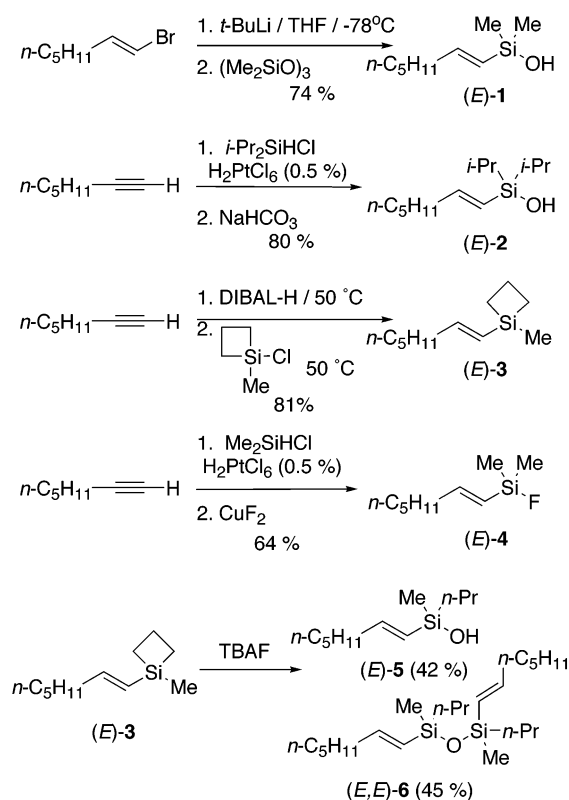
(15) For a review on advances in palladium-catalyzed coupling reaction to aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(6) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(7) (a) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(8) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. (b) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771.

Scheme 1



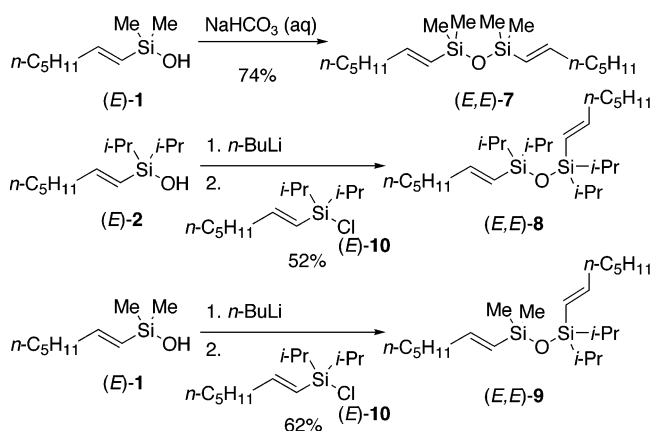
would have to be discovered before a significant effect of ligand modulation on palladium could be observed. Hence, the goal of a comprehensive kinetic analysis is to illuminate the role of every component in the reaction and piece together a complete picture of the overall mechanism.

The objectives of this mechanistic study were formulated as (1) the spectroscopic identification of intermediates in organosilanol cross-coupling reactions [similar experiments employing other silanes (siletanes, fluorosilanes, and disiloxanes) that have successfully been used in cross-coupling reactions should reveal the intervention of common intermediates among the different donors] and (2) the determination of the kinetic rate equation of this process to clarify the role of each of the components in the palladium-catalyzed cross-coupling reaction with an aryl iodide. With knowledge of reaction intermediates and the rate equation, it is reasoned that a more refined mechanistic picture could be generated that was consistent with all the data provided by these two avenues of investigation.

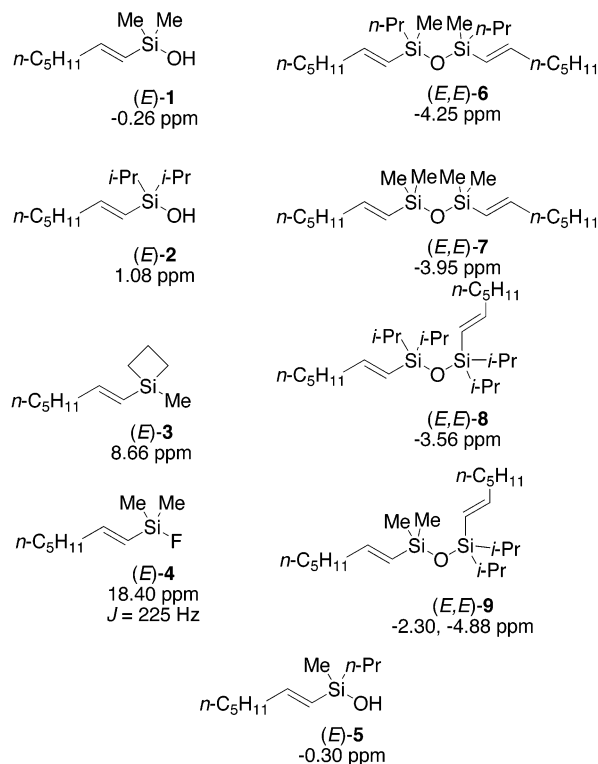
## Results

**1. Preparation of Organosilane Precursors and Reference Compounds.** All of the functional organosilicon coupling precursors are derivatives of the (*E*)-1-heptenylsilane unit and were all prepared from 1-heptyne directly or via (*E*)-1-bromoheptene (itself prepared from 1-heptyne) as outlined in Scheme 1. The two silanols (*E*)-1 and (*E*)-2 represent the two main methods of preparation, namely, capture of an organolithium reagent with hexamethylcyclotrisiloxane (D<sub>3</sub>) or platinum-catalyzed hydrosilylation.<sup>16</sup> Siletane (*E*)-3 could be prepared by direct silylation of the hydroalumination product of 1-heptyne.<sup>17</sup> Finally, silanol (*E*)-5 and its dimer disiloxane (*E,E*)-6 were generated by TBAF-promoted opening of (*E*)-3.<sup>18</sup> Reference

Scheme 2



samples of other disiloxanes, (*E,E*)-7, (*E,E*)-8, and (*E,E*)-9, were prepared as shown in Scheme 2. Simple dimerization sufficed for (*E,E*)-7, but the more sterically hindered disiloxanes were more efficiently prepared by nucleophilic substitution on (*E*)-10 with silanols. To aid in interpreting the spectroscopic analysis of the reactive intermediates, the <sup>29</sup>Si chemical shifts of all these compounds are compiled in Figure 3.



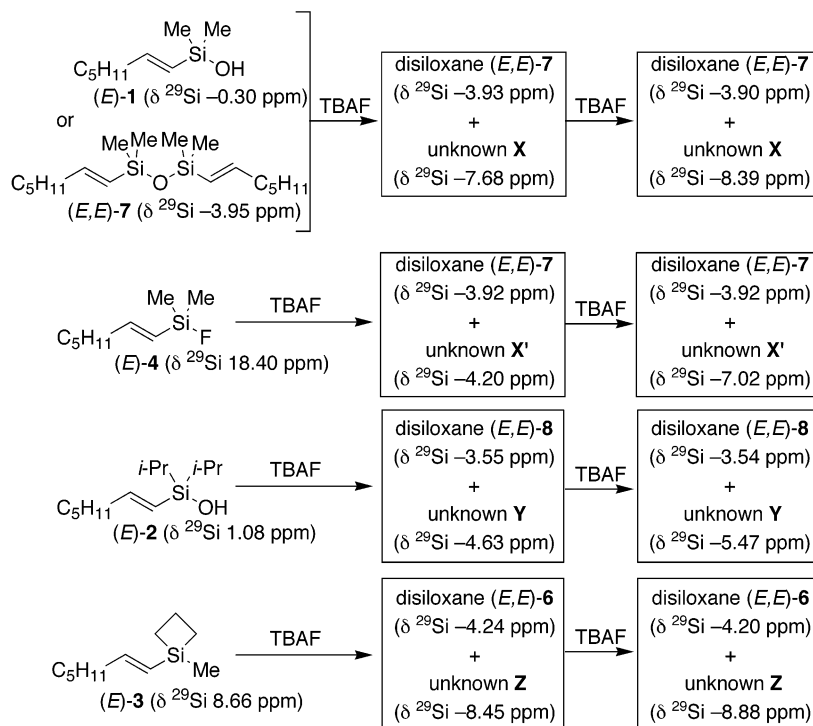
**Figure 3.** Silicon-29 NMR chemical shifts ( $\delta$ , ppm, in THF) for reference compounds.

**2. Nature of Reaction Intermediates.** Several types of heteroatom-substituted organosilanes are viable cross-coupling reaction partners. Because most of these organosilanes are activated by TBAF, an initial study was conducted to compare rates and yields of product obtained from the TBAF-promoted, palladium-catalyzed cross-coupling reaction of silanols (*E*)-1 and (*E*)-2, siletane (*E*)-3, fluorosilane (*E*)-4, and disiloxane

(16) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565.

(17) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821.

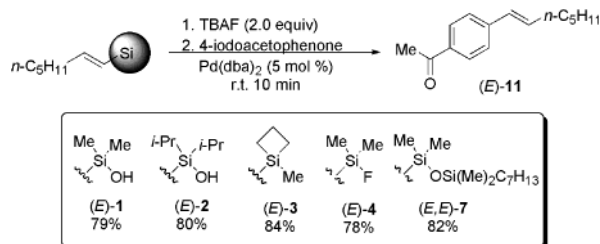
(18) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491.



**Figure 4.** Silicon-29 NMR analysis of treatment of organosilane precursors with TBAF.

$(E,E)$ -7 with 4-iodoacetophenone. Under the standard reaction conditions (5 mol %  $\text{Pd}(\text{dba})_2$ , 2.0 equiv of TBAF in THF at room temperature for 10 min), all of these precursors reacted qualitatively at the same rate and gave the same yield of the product styrene  $(E)$ -11 (Scheme 3).

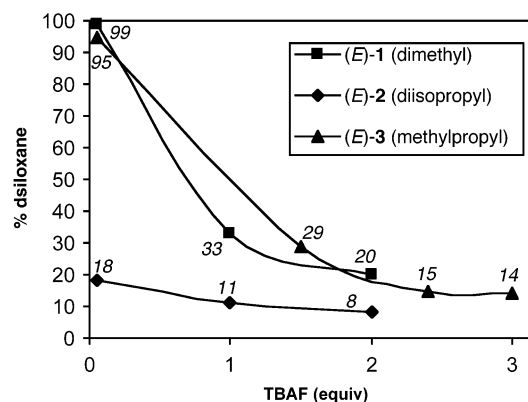
### Scheme 3



This outcome suggested the possible existence of a common reactive intermediate. To evaluate this possibility, the five organosilanes, silanols  $(E)$ -1 and  $(E)$ -2, siletane  $(E)$ -3, fluorosilane  $(E)$ -4, and disiloxane  $(E)$ -7 were treated with 1.0 equiv of TBAF in  $\text{THF}-d_8$ . Both  $^1\text{H}$  and  $^{29}\text{Si}$  NMR spectroscopic analysis of the reaction mixtures showed that, in each case, two new compounds were formed almost immediately (Figure 4). These two compounds are structurally related and differ only in the nature of the substituents on the starting organosilanes. One of the two was readily identified as the disiloxane of the corresponding silanol by comparison to an authentic sample. The other species (unknowns X, X', Y, and Z) were also silicon-containing compounds as confirmed by  $^{29}\text{Si}$  NMR analysis, but clearly different from any reference compounds available (Figures 3 and 4).<sup>19</sup>

Two important observations were made during the spectroscopic investigation. First, both the  $^{29}\text{Si}$  NMR chemical shift position of the unknowns X, Y, and Z and the ratio of these

species with their corresponding disiloxanes were dependent on the amount of TBAF present. The effects on the  $^{29}\text{Si}$  NMR chemical shifts upon the addition of a second equivalent of TBAF are clearly illustrated in Figure 4. Uniformly, all species X, X', Y, and Z are shifted to higher field, whereas the resonance positions of the disiloxanes remain effectively unchanged. This trend provides strong evidence that the unknown species are in equilibrium association with fluoride. Second, the disiloxanes and the unknown species must be in equilibrium because their ratio is dependent on the amount of TBAF employed. The results in Figure 5 show that for the three different substitution patterns on silicon this ratio increased steadily as more TBAF was employed.<sup>20</sup> However, a striking effect of steric demand on this ratio was also evident by comparison of the mixtures generated from the silanols  $(E)$ -1 and  $(E)$ -2 or siletane  $(E)$ -3. Whereas the dimethyl- and methylpropylsilanols rapidly and nearly quantitatively formed their disiloxanes  $(E,E)$ -7 and  $(E,E)$ -6 with 5 mol % TBAF, the diisopropylsilanol  $(E)$ -2 was much less prone to dimerization. This difference diminished as the amount of

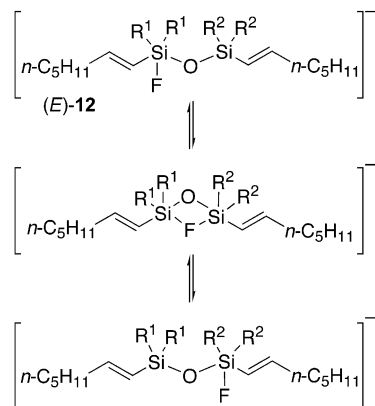


**Figure 5.** Equilibrium ratio of unknown to disiloxane detected in a mixture of  $(E)$ -1,  $(E)$ -2, or  $(E)$ -3 and TBAF in  $\text{THF}-d_8$ .

TBAF increased. Moreover, the difference in composition between silanols (*E*)-1 and (*E*)-2 became even smaller at extended times, suggesting a slow equilibration for the bulkier diisopropylsilanol. After 100 h in the presence of 2.0 equiv of TBAF, the ratios were  $X/(E,E)$ -7 = 78/22 and  $Y/(E,E)$ -8 = 85/15.

The identity of unknowns **X**, **Y**, and **Z** proved difficult to establish. The sign and magnitude of the  $^{29}\text{Si}$  NMR chemical shifts were indicative of tetracoordinate silicon species, yet they did not match any of the synthesized tetracoordinate silanes.<sup>21</sup> Having excluded simple, tetracoordinate silicon compounds as the unknown components, the possibility that **X**, **Y**, and **Z** could be dimers such as (*E,E*)-12 was investigated (Scheme 4). Although a pentacoordinate silicon is formally present, fast exchange of the fluorine atom between the two silicon atoms would explain a single signal in the  $^{29}\text{Si}$  NMR spectra. Furthermore, such a compound would display resonances further downfield than a pentacoordinate silicon atom but further upfield of the region where four-coordinated silicon atoms would usually be expected. The same would be true for higher order oligomers as well.

## Scheme 4

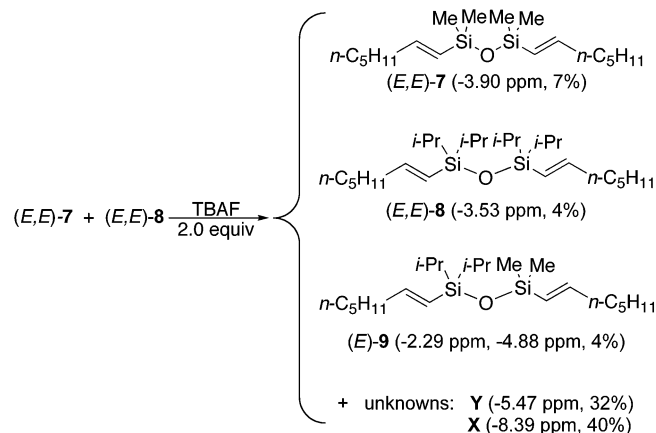


To test this possibility, an equimolar mixture of disiloxanes (*E*)-7 and (*E*)-8 was treated with 1 equiv of TBAF. Analysis of the mixture by  $^{29}\text{Si}$  NMR revealed six signals (Scheme 5). The smaller signals corresponded to the starting disiloxanes (*E*)-7 (−3.95 ppm, 7%) and (*E*)-8 (−3.56 ppm, 4%). Two more were from the mixed disiloxane (*E*)-9 at −2.30 and −4.88 ppm, clearly demonstrating that crossover between 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 were in exact agreement with the unknown

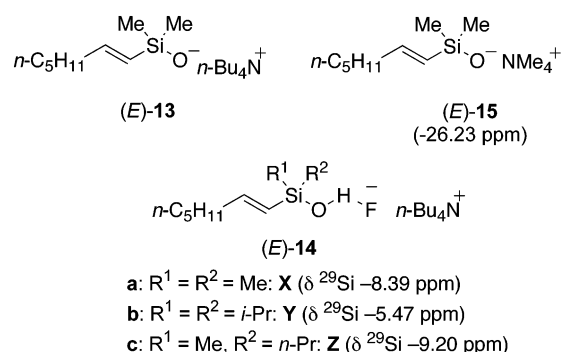
- (19) Treatment of fluorosilane (*E*)-4 with TBAF clearly generated the same two species ((*E,E*)-7 and **X**) as are formed from either silanol (*E*)-1 or disiloxane (*E,E*)-7 by  $^1\text{H}$  NMR analysis. However, the unknown species **X** formed from (*E*)-4 displayed a different  $^{29}\text{Si}$  chemical shift. We believe that the chemical structures of **X** and **X'** are the same, but because of the different amount of fluoride ion in the different samples (from (*E*)-4 vs (*E*)-1), the  $^{29}\text{Si}$  chemical shifts are influenced. Indeed, all the species **X**, **Y**, and **Z** change their  $^{29}\text{Si}$  resonance position upon addition of TBAF; see Figure 4.
- (20) It should be pointed out that the ratios of disiloxane and “unknowns” in Figure 5 represent equilibrium values obtained by independent NMR analysis. Under normal conditions, the rate of reaction is competitive with the rate of establishing these equilibria, so that the actual ratios may not reflect the ratios during a cross-coupling reaction.
- (21) The typical chemical shift range for tetracoordinate silicon is  $\delta$  +30 to −30 ppm, and for pentacoordinate silicon it is  $\delta$  −75 to −130 ppm. Takeuchi, Y.; Takayama, T. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; John Wiley: Chichester, U.K., 1998; Chapter 6, Vol. 2, Part 1.

compounds formed from silanols (*E*)-1 and (*E*)-2 (**X** and **Y**), respectively. The absence of a third crossover peak indicates that these compounds are monomeric species, in which a silicon atom is attached to two alkyl groups, one (*E*)-1-heptenyl group, and a heteroatom. Thus, the possibility that species such as (*E*)-12 were the unknowns was ruled out.

## Scheme 5



Since **X** and **Y** were monomeric and tetracoordinate, two possibilities for their identity were considered: the tetrabutylammonium silyloxy salt (*E*)-13 and a TBAF hydrogen bond complex, (*E*)-14 (Figure 6). The silyl oxide salt was ruled out by independent synthesis of the tetramethylammonium salt (*E*)-15 whose  $^{29}\text{Si}$  NMR chemical shift (−26.23 ppm) is not in the correct range to be compound **X**. Because compound (*E*)-14 contains a hydrogen-bonded fluorine atom, an  $^{19}\text{F}$  NMR spectrum was taken of a sample of **X** generated from silanol (*E*)-1 and TBAF. If a complex such as (*E*)-14 were present, the spectrum should indicate the presence of a fluoride at a resonance different from that of TBAF. At room temperature, the  $^{19}\text{F}$  NMR spectrum displayed only a single resonance at −117.7 ppm for TBAF (literature values −109 to −120).<sup>22</sup> However, cooling the solution to −95 °C allowed the observation of a second signal at −150.8 ppm. No such signal was observed upon cooling the TBAF itself. This signal is very similar to that for  $n\text{-Bu}_4\text{N}^+\text{HF}_2^-$ , which displays a  $^{19}\text{F}$  NMR chemical shift at ca. −148 ppm.<sup>22–25</sup> Thus, all of the data provide evidence, albeit indirectly, that the structures for **X**, **Y**, and **Z** (the unknown intermediates of the various organosilane cross-coupling reactions) fit best to hydrogen-bonded complexes

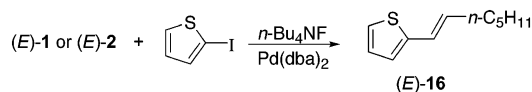


**Figure 6.** Tetra-*n*-butylammonium silyl oxide (*E*)-13, TBAF–silanol hydrogen-bonded complex (*E*)-14, and tetramethylammonium silyl oxide (*E*)-15.

between an organosilanol and TBAF (Figure 6). Further evidence would be forthcoming from kinetic studies outlined below.

**3. Kinetics.** The order for each component of the TBAF-promoted reaction of (*E*)-1-heptyldimethylsilanol ((*E*)-1) to 2-iodothiophene, catalyzed by bis(dibenzylideneacetone)palladium(0), was determined by varying the concentration of each component individually and monitoring the progression of this reaction at room temperature by GC (Scheme 6). The  $t_o$  of each kinetic run corresponded to the addition of the catalyst to the mixture. Throughout the course of the reaction, aliquots were removed and quenched by addition into a 20% aqueous solution of 2-diethylaminoethanethiol, which was shown in preliminary studies to quench the reaction instantaneously by sequestering the palladium catalyst completely. The samples were then filtered through a small prepacked column of silica gel and eluted with diethyl ether. The resultant eluent was injected into the gas chromatograph three times. The chromatograms were analyzed for the formation of the product as a function of time. The conversion of the reaction was determined by integrating the product peak relative to that of an internal standard, biphenyl, after correction for their predetermined relative response factors. 2-Iodothiophene was chosen as the electrophile because its lower rate of coupling conveniently allowed for accurate manual kinetic analysis. This coupling system reached completion within a few hours rather than a few minutes, which enabled a larger number of data points to be taken at the onset of the reaction so that accurate initial-rate fits could be obtained.

#### Scheme 6



The order in 2-iodothiophene was determined by plotting the initial rate versus concentration (Figure 7). The concentrations of the reaction components were as follows: (*E*)-1, 50 mM; TBAF, 188 mM; Pd(dba)<sub>2</sub>, 2.5 mM. The three data points of the aryl iodide concentrations correspond to 25, 50, and 100 mM. A slope of 0.068 indicates an absence of any effect of the aryl iodide concentration on the rate, establishing zeroth-order behavior in this system.

A similar plot was constructed from the results of varying the concentrations of the silanol. Because previous work in these laboratories demonstrated the synthetic utility of both dimethylsilanol (*E*)-1 and its isopropyl analogue (*E*)-2, kinetic data were acquired for both of these substrates in the aforementioned reaction (Figures 8 and 9). In the study employing silanol (*E*)-1, data were acquired for silanol concentrations of 25, 38, 50, 64, and 100 mM. The concentrations of TBAF and palladium were the same as employed previously, with the aryl iodide at

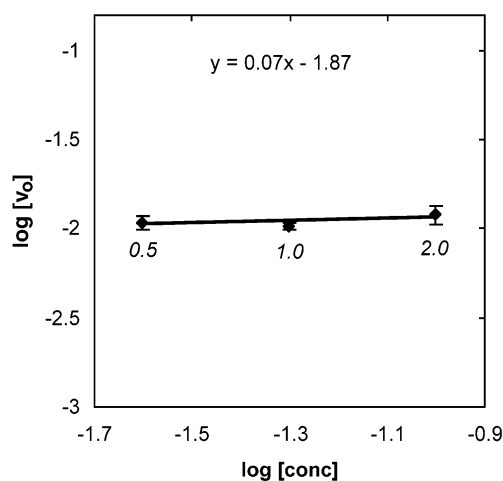


Figure 7. Reaction order of 2-iodothiophene in the cross-coupling to (*E*)-1.

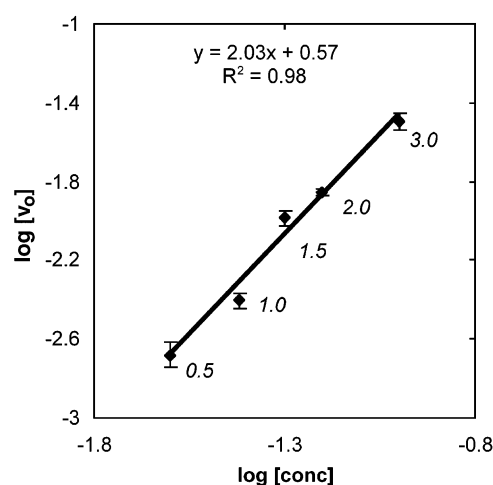


Figure 8. Reaction order of (*E*)-1 in the cross-coupling reaction with 2-iodothiophene.

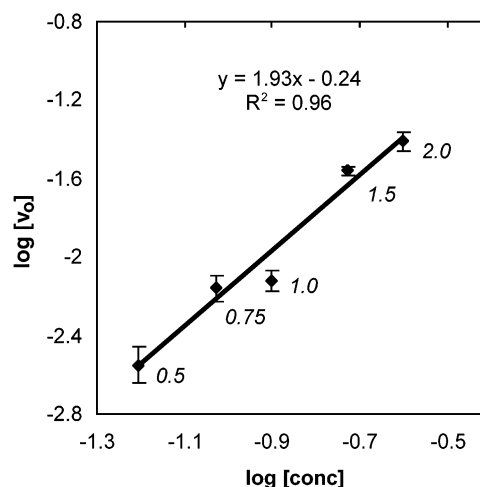


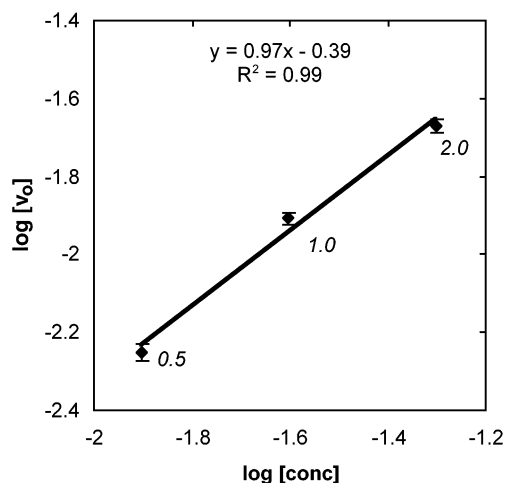
Figure 9. Reaction order in (*E*)-2 in the cross-coupling reaction with 2-iodothiophene.

a fixed concentration of 50 mM. In the analysis with silanol (*E*)-2, data were obtained with silanol concentrations of 63, 94, 125, 188, and 250 mM. The aryl iodide, palladium, and TBAF concentrations were 125, 6.25, and 250 mM, respectively. Slopes of 2.03 and 1.93 were obtained for (*E*)-1 and (*E*)-2, respectively; consistent with second-order behavior.<sup>26,27</sup> In light of the

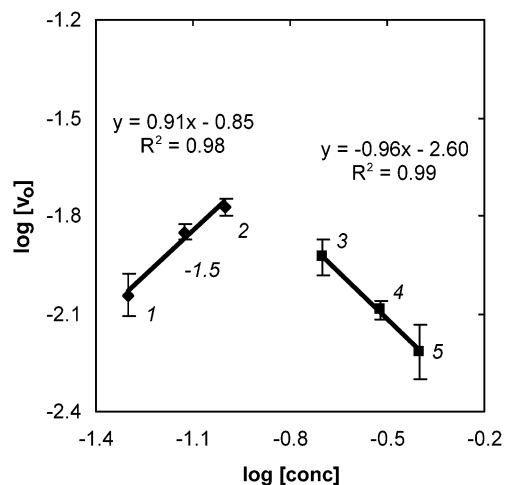
- (22) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.  
 (23) (a) Fujiwara, F. Y.; Martin, J. S. *J. Am. Chem. Soc.* **1974**, *96*, 7625. (b) Fujiwara, F. Y.; Martin, J. S. *J. Am. Chem. Soc.* **1974**, *96*, 7632. (c) Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A. *Synthesis* **1988**, 953. (d) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.  
 (24) Unfortunately, cooling the solution to  $-95\text{ }^\circ\text{C}$  did not reveal  $^1\text{J}_{\text{HF}}$  splitting, as is observed for  $\text{HF}_2^-$  at  $-80\text{ }^\circ\text{C}$ , ref 22.  
 (25) Further attempts to provide spectroscopic support for (*E*)-14 as the structure of **X** involved heteronuclear NOE experiments between the hydrogen resonance at 5.05 ppm and the fluorine resonances for TBAF (ca. 117 ppm) and **X** (ca. 150 ppm). Although weak NOE signals could be detected, the interpretation was ambiguous due to the water of hydration from the TBAF sample.

foregoing spectroscopic studies, which revealed rapid disiloxane formation in a mixture of silanol and TBAF, this striking result supports the hypothesis that it is a disiloxane that undergoes the cross-coupling reaction and not the silanol itself.

This assertion was verified by determination of the reaction order beginning with disiloxane (*E*)-7 (Figure 10). Three concentrations of (*E*)-7 were employed, 12.5, 25, and 50 mM, with all other components at the same concentration as employed in the silanol studies. The data in Figure 10 clearly show a slope of nearly unity (0.97). Taken together, the first-order behavior of disiloxane (*E*)-7, its known formation from the corresponding silanol in the presence of TBAF, and the second-order behavior in silanol clearly suggest that a disiloxane, not a silanol, is on the pathway toward the product when either silanol (*E*)-1 or silanol (*E*)-2 is employed as the donor.



**Figure 10.** Reaction order in disiloxane (*E*)-7 in the cross-coupling reaction with 2-iodothiophene.

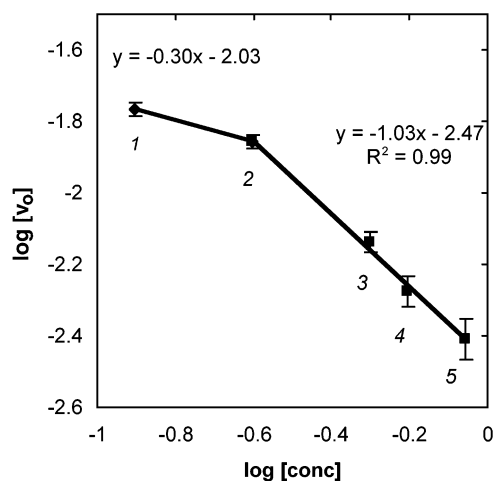


**Figure 11.** Reaction order of TBAF in the cross-coupling reaction of silanol (*E*)-1 with 2-iodothiophene.

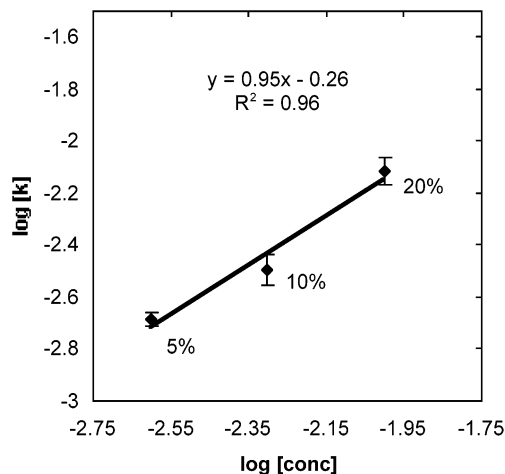
The order of TBAF in this reaction was similarly acquired. A plot of initial rate versus concentration in the cross-coupling reaction of silanol (*E*)-1 to 2-iodothiophene (both at 50 mM) was obtained for TBAF concentrations of 50, 75, 100, 150, 200,

and 250 mM. The palladium concentration was 2.5 mM as before. This plot shows two discrete behaviors (Figure 11). At 2 equiv of TBAF or below, a slope of 0.91 is consistent with first-order behavior. Beyond 2 equiv of fluoride, however, the rate of reaction actually *decreases*, displaying an inverse order in fluoride. In fact, the slope of  $-0.96$  between 3 and 5 equiv of TBAF indicates an order of  $-1$  in this region.

When the effect of TBAF concentration on initial rate was examined in the same cross-coupling reaction of silanol (*E*)-2, this switch in order was not observed (Figure 12). Rather a negative slope was obtained throughout, consistent with an inverse order in TBAF to as little as 1 equiv.



**Figure 12.** Reaction order of TBAF in the cross-coupling reaction of silanol (*E*)-2 with 2-iodothiophene.



**Figure 13.** Rate-constant dependence on the concentration of Pd(dba)<sub>2</sub> in the cross-coupling reaction of silanol (*E*)-1 to 2-iodothiophene.

Finally, with the overall order in reactants obtained, the rate constant dependence on catalyst loading was determined by plotting the calculated first-order rate constant versus concentration for palladium loadings of 5, 10, and 20 mol % (Figure 13).<sup>28</sup> This order was determined with respect to the silanol and

(26) Clearly, the reaction order is not affected by the steric demand of the pendant alkyl groups on the silanol. Quantitative studies also have shown that, under fluoride activation, (*E*)-1 and (*E*)-2 have nearly identical coupling rates. Denmark, S. E.; Neuville, L.; Christy, M. E. L. Unpublished results from these laboratories.

(27) A reviewer has suggested that higher order behavior in silanol may be masked by carrying out reactions at high substrate-to-catalyst ratios. We have also determined the kinetic order in (*E*)-1 with a stoichiometric amount of Pd(dba)<sub>2</sub> and substoichiometric amounts of silanol (0.5, 0.75, and 1.00 equiv), and the reaction still showed second-order dependence on silanol concentration (slope 2.1018,  $R^2 = 0.96701$ ).

(28) The first-order rate constant was obtained by fitting to the slope of a plot of log[conversion] against time.

aryl iodide concentrations of 50 mM and the TBAF concentration of 188 mM. A slope of 0.95 was obtained, which is consistent with a first-order dependence of the observed rate constant on the concentration of palladium.

The higher order behavior in silanol and inverse order in TBAF provided critical information for the determination of the mechanism of this reaction. A detailed picture of the alkenylorganosilanol cross-coupling reaction under fluoride activation could be formulated by interpretation of both the spectroscopic and kinetic data.<sup>29</sup>

## Discussion

**1. Spectroscopy.** The spectroscopic studies in the initial phase of this investigation provided the first evidence for a similar reaction pathway for silanes, silanols, fluorosilanes, and disiloxanes. The existence of a common intermediate, as detected by <sup>1</sup>H and <sup>29</sup>Si NMR spectroscopic analysis, and, in particular, the similarity in rates and yield of the reactions of these silanes, suggested a common mechanism. It is intriguing to note that such an intermediate is likely involved in the original processes with fluorosilanes pioneered by Hiyama and Hatanaka wherein the intermediacy of monomeric polyfluorosilanes was postulated.<sup>30</sup>

The use of <sup>29</sup>Si NMR spectroscopy provided the most compelling evidence for the proposed hydrogen-bonded TBAF–silanol complex (*E*)-**14** as the unknown intermediate. The large difference in chemical shifts of silicon atoms in different chemical environments convincingly eliminated the possibility that this unknown ( $\delta(^{29}\text{Si}) -8.39$  ppm) exists as a silanolate ( $\delta(^{29}\text{Si}) -26$  ppm), a disiloxane ( $\delta(^{29}\text{Si}) -3.95$  ppm), or a silicate ( $\delta(^{29}\text{Si})$  ca.  $-75$  to  $-130$  ppm). The <sup>29</sup>Si NMR chemical shifts of **X**, **Y**, and **Z** were in the range for tetracoordinate silicon species, and the crossover experiment with silanols (*E*)-**1** and (*E*)-**2** and TBAF clearly established that the unknowns **X** and **Y** are *monomeric tetracoordinate silanes*. The combined evidence pointed to hydrogen-bonded complex (*E*)-**14** by the process of elimination. Such a complex is not unlikely, particularly in light of the strong hydrogen bonds formed between TBAF and proton sources.<sup>31</sup> The identification of this intermediate was even more significant in formulating a rational interpretation of the kinetic data for this cross-coupling reaction.

**2. Kinetics.** Although the spectroscopic studies revealed that a silanol is in equilibrium with its corresponding disiloxane and a hydrogen-bonded complex to TBAF, only the results of the kinetic analysis shed light on which of these species are actually intermediates in the cross-coupling reaction pathway. On the basis of the reigning dogma of silicon-based cross-coupling reactions, we assumed that TBAF activation of some silicon species is required to promote transmetalation to palladium. Under that assumption, several mechanistic scenarios can be formulated that involve a silanol ((*E*)-**1** or (*E*)-**2**), disiloxane ((*E,E*)-**7** or (*E,E*)-**8**), or TBAF–silanol hydrogen-bonded com-

**Table 1.** Correlation of Possible Turnover-Limiting Steps with the Expected Order in Silanol, TBAF, and Palladium Catalyst

scenario	turnover-limiting step	kinetic consequence
1	fluoride activation of silanol	first-order in silanol first-order in TBAF zeroth-order palladium
2	fluoride activation of disiloxane	second-order in silanol first-order in TBAF zeroth-order palladium
3	transmetalation of a fluoride-activated silanol	first-order in silanol first-order in TBAF first-order palladium
4	transmetalation of a fluoride-activated disiloxane	second-order in silanol first-order in TBAF first-order palladium

plex ((*E*)-**14**) as the resting state of the silicon species. Likely possibilities for the turnover-limiting step along with the kinetic consequences are outlined in Table 1. This analysis, in turn, provides the framework for interpretation of the kinetic data acquired because the reaction order reflects the reaction pathway from the lowest energy resting state to the transition state of the rate-determining or turnover-limiting step.

Some of the results from the kinetic analysis were straightforward to interpret because of similarities to other well-studied systems. For example, the first-order rate-constant dependence on palladium concentration is consistent with a single molecule of the palladium catalyst participating in each turnover of the catalytic cycle. This behavior is similar to the results obtained for organotin cross-coupling reactions.<sup>6</sup> It is noteworthy that the rate dependence on the catalyst concentration, manifested in the rate constant, eliminates the possibility that simple fluoride activation of the silanol (which does not involve palladium) could be turnover-limiting (Table 1, scenarios 1 and 2).

The zeroth-order dependence on the aryl iodide also finds analogy in the mechanism of organotin cross-coupling reactions.<sup>6</sup> This behavior is interpreted as a fast and irreversible oxidative insertion step of the palladium under the reaction conditions. The facility of this process has been well documented, and the predominant use of iodides in many of the early reports of cross-coupling chemistry has its origin in this feature.<sup>32</sup>

Thus, assuming that the generally accepted mechanism for cross-coupling reactions is in operation, the remaining possibilities are that either transmetalation or product-forming reductive elimination is the turnover-limiting step of this reaction. The positive correlation between the rate and silanol concentration strongly supports the conclusion that transmetalation is turnover-limiting, as it is in organotin coupling reactions. In addition, the second-order dependence on silanol concentration indicates that two molecules of the substrate participate in the transmetalation step. This unusual behavior, however, is confluent with the rapid formation of disiloxane from two molecules of silanol in the presence of TBAF, as revealed by the spectroscopic studies. *Therefore, the second-order dependence on silanol (and first-order dependence on disiloxane) is interpreted as indicating that a disiloxane, not a*

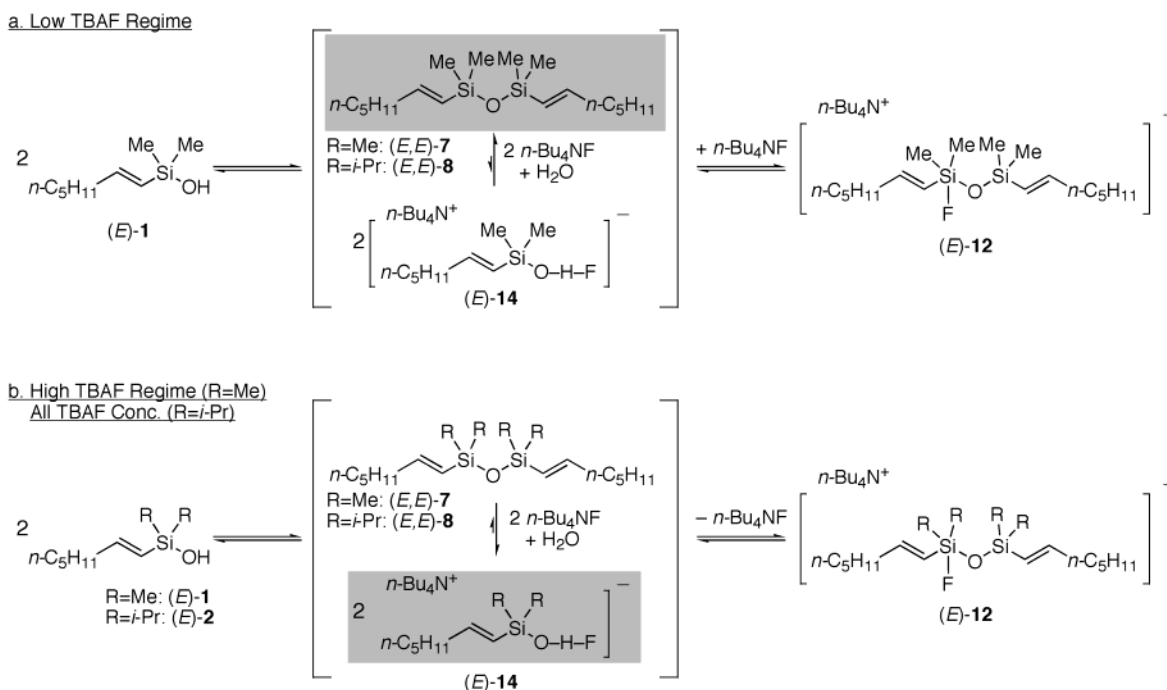
(29) For completeness, we have determined the Arrhenius activation parameters by studying the reaction over a 40 °C temperature range.  $E_a = 15.45$  kcal/mol,  $A = 22.19$  mol<sup>-1</sup> s<sup>-1</sup>,  $\Delta H^\ddagger = 14.87$  kcal/mol,  $\Delta S^\ddagger = -5.14$  eu, and  $\Delta G^\ddagger = 16.38$  kcal/mol.

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**Figure 14.** Preequilibrium dependence on TBAF concentration.

silanol, is undergoing turnover-limiting transmetalation (thus eliminating scenario 3, Table 1). The data thus far indicate that oxidative insertion of the palladium into the aryl iodide and disiloxane formation both precede a turnover-limiting transmetalation step.

The striking divergence of rate dependence on fluoride concentration in the coupling with silanol (*E*)-1 simultaneously provided a fascinating insight and a difficult challenge to interpret as it did not fit with any single mechanistic scenario we could imagine. A change in slope of this nature is usually indicative of a change in mechanism. However, the uniform inverse order dependence for diisopropylsilanol (*E*)-2 showed that, if true, the change in mechanism was dependent on the bulk of the substrate. Rather than propose a fundamental change in the mechanism, we interpret this unusual behavior as a consequence of different resting states in the preequilibrium association of the silicon precursors with TBAF. The spectroscopic studies clearly showed that, independent of the starting silicon moiety (silanol, disiloxane, fluorosilane, siletane), the only silicon-containing species observed upon treatment with TBAF·3H<sub>2</sub>O are the disiloxane and a hydrogen-bonded, silanol–TBAF complex, (*E*)-14 (Figure 4). Moreover, the equilibrium composition of this mixture was shown to be dependent on the structure of the silane precursor and the amount of TBAF·3H<sub>2</sub>O added (Figure 5). Thus, we can define two limiting scenarios in which the reaction proceeds either via the disiloxane as the resting state (i.e., low TBAF regime, Figure 14a) or via (*E*)-14 (i.e., high TBAF regime (R = Me) or all TBAF concentrations (R = *i*-Pr), Figure 14b).

From these pictures, it can now be understood how the dual function of TBAF (in creating the resting state (*E*)-14 and in activating the transmetalation) gives rise to reciprocal behavior in the kinetic scheme. To fully analyze the consequences, it must be first assumed that the rate-determining, transmetalation step involves interaction of a fluoride-activated disiloxane such as (*E*)-12 (Scheme 4) with an arylpalladium halide species. This

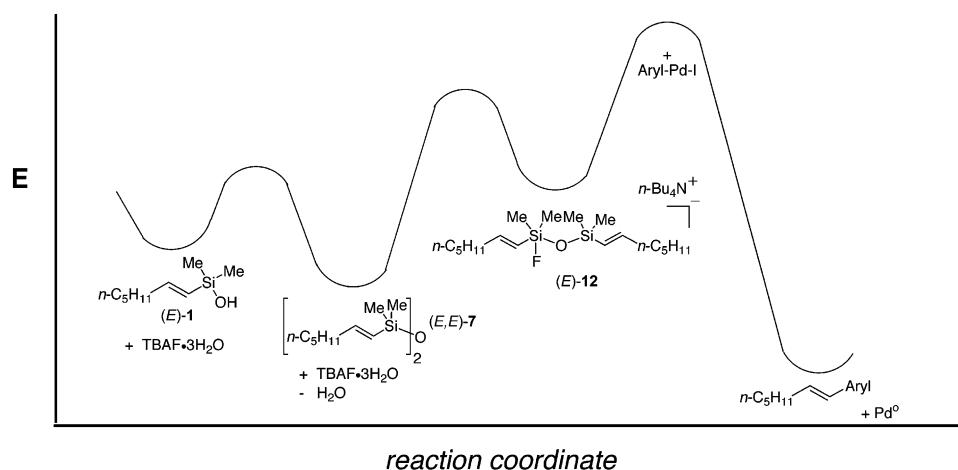
assumption is consistent with the second-order dependence on silanol (first-order dependence on disiloxane) and first-order rate-constant dependence on palladium concentration. Now, to understand the fluoride concentration dependence, recall that the composition of the preequilibrium resting state is also dependent on fluoride concentration and silanol structure. With (*E*)-1, first-order dependence on TBAF is observed at low fluoride concentrations (less than 2.0 equiv, Figure 11). By spectroscopic analysis, with less than 1.0 equiv of TBAF, silicon is mostly in the form of (*E,E*)-7 (Figure 5). Direct formation of (*E*)-12 from disiloxane (*E,E*)-7 would be consistent with second-order behavior in silanol, and first-order behavior in TBAF (“low TBAF regime”, Figure 14).

However, (*E*)-1 also displays inverse first-order dependence on TBAF at high fluoride concentrations (greater than 3.0 equiv, Figure 11). Once again, spectroscopic analysis shows that now the predominant species in solution is (*E*)-14a (Figure 5). Assuming that the rate-determining, transmetalation step is the same, then formation of (*E*)-12 from (*E*)-14a would require the release of one molecule of TBAF for every two molecules of (*E*)-14a (“high TBAF regime”, Figure 14), thus leading to the observed overall inverse first-order dependence on TBAF.<sup>33,34</sup>

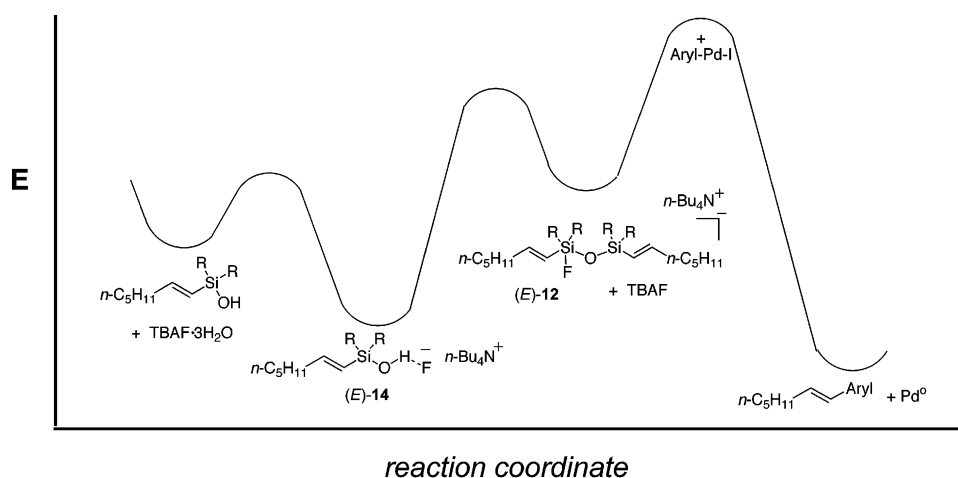
The situation with the diisopropylsilanol (*E*)-2 nicely illustrates the effect of steric bulk on the position of the same equilibrium. As was shown in Figure 5, even at low TBAF loadings, (*E*)-2 is not prone to dimerization and thus exists primarily as the hydrogen-bonded complex (*E*)-14b. Thus, at all TBAF loadings studied, reaction of silanol (*E*)-2 proceeds primarily via (*E*)-14b and thus shows uniform inverse order

(33) It is important to note that a rate equation reveals information regarding the mechanistic pathway from the lowest energy species to the highest transition state. Hence, the inverse order dependence of TBAF lends further support to the existence of (*E*)-14.

(34) It should be clear that, if the disiloxane were the resting state throughout, that eventually a saturation regime in the TBAF dependence would be reached and zeroth-order behavior would be displayed.



**Figure 15.** Mechanistic pathway of the palladium-catalyzed TBAF-promoted coupling reaction of (*E*)-1 and (*E*)-2 to 2-iodothiophene consistent with first-order rate dependence of fluoride.



**Figure 16.** Mechanistic pathway of the palladium-catalyzed TBAF-promoted coupling reaction of (*E*)-1 and (*E*)-2 to 2-iodothiophene consistent with inverse order rate dependence of fluoride.

dependence. It is worthy of note that, despite the reluctance of (*E*)-2 to dimerize to (*E,E*)-7, it still exhibited clean second-order dependence, indicating that a fluoride-activated disiloxane, (*E*)-12 ( $R^1 = R^2 = i\text{-Pr}$ ), is the key intermediate involved in the turnover-limiting step.

These two limiting scenarios can now be combined with the full catalytic cycle for fluoride-promoted, palladium-catalyzed cross-coupling reactions (Figures 15 and 16). In both of these schemes, the starting point is given as the dimethylsilanol (*E*)-1, but it should be noted that these scenarios are equally valid for the siletane (*E*)-3, fluorosilane (*E*)-4, and disiloxane (*E,E*)-7. Figure 15 depicts the process in the low TBAF regime wherein the silicon resting state is a disiloxane. Coordination of fluoride to form the complex (*E*)-12 provides sufficient activation to transfer the 1-heptenyl group to an arylpalladium(II) electrophile in the rate-limiting transmetalation. Figure 16 depicts the process in the high TBAF regime for smaller silicon moieties ( $R = \text{Me}$ ) or for bulkier species that do not dimerize readily. Here the generation of the activated complex (*E*)-12 (either by direct dehydration or via the disiloxane) requires loss of a molecule of TBAF. The catalytic cycle then proceeds analogously as outlined in Figure 15.

The mechanistic information obtained, summarized in Figures 14 and 15, is a pictorial presentation of the mechanism derived

by determining the order of each of the reaction components to derive an overall kinetic equation (eq 1).

$$\text{rate} = k_{\text{obs}}[\text{SiOH}]^2[\text{TBAF}]^n \quad (1)$$

$$k_{\text{obs}} = k[\text{Pd}]$$

for (*E*)-1,  $n = 1$  at  $\text{TBAF}/\text{SiOH} < 2$  and  
 $n = -1$  at  $\text{TBAF}/\text{SiOH} > 2$

for (*E*)-2,  $n = -1$

The equation is consistent with a fast and irreversible oxidative insertion of the palladium into the aryl iodide, as well as a turnover-limiting transmetalation step from a silane to the palladium. The change in fluoride order for the reaction of silanol (*E*)-1 indicates that two pathways are available for the silanol to participate in the transmetalation step: one proceeding through the corresponding disiloxane (*E,E*)-7 and the other through complex (*E*)-14a. The prevalent pathway depends on the relative amounts of the two species in solution, which in turn is dependent on the structure of the silanol and the TBAF/silanol ratio. In the coupling of silanol (*E*)-2, the main pathway is always through a complex such as (*E*)-14b as inverse order is observed throughout.

Finally, it is imperative to emphasize that this mechanistic picture involving both disiloxanes and hydrogen-bonded intermediate (*E*)-**14** is applicable for siletane-, silanol-, fluorosilane-, and disiloxane-based cross-coupling reactions (Figure 4). Therefore, it is reasonable to assert that the mechanism proposed in Figures 14 and 15 is also applicable to hydridosilanes<sup>35</sup> and for the newly developed surrogates for silanols such as the thienyldimethylsilyl,<sup>36</sup> pyridyldimethylsilyl,<sup>37</sup> and benzyl-dimethylsilyl<sup>38</sup> derivatives under the action of TBAF.

## Conclusions

The combination of spectroscopic studies to identify reaction intermediates and kinetic analysis to obtain a rate equation provided a clear mechanistic picture of the TBAF-promoted cross-coupling reactions of alkenylsilanols, -siletanes, -fluorosilanes, and -disiloxanes with aryl iodides. A common mechanistic pathway for these substrates was revealed that involves a turnover-limiting transmetalation with a fluoride-activated disiloxane. The formation of this key intermediate is dependent on the structure of the silicon precursor and the amount of TBAF employed.

Although these studies clarify a significant portion of the mechanistic pathway, there are still important components that remain ill-defined. Most importantly, the detailed process by which transmetalation proceeds and the orientation of the reacting partners need to be elucidated. These issues will be

probed by other techniques as well as by further kinetic studies on analogues. It should be noted that the mechanism forwarded herein may not apply to the coupling of arylsilanols or related systems in which different palladium catalysts, ligands, and fluoride activators are involved. Similar studies are planned for other commonly employed organosilicon systems to identify such potential divergences. By systematically studying variables such as temperature, solvent, transferable group, and catalyst, the factors that most strongly direct a particular pathway taken by different organosilanes in palladium-catalyzed cross-coupling reactions can be gauged. The outcome of these studies may provide insights for devising new silicon cross-coupling processes with even greater efficiency and generality.

Finally, the insights provided by this work have stimulated the investigation into fluoride-free activation methods for these reactions,<sup>39</sup> and the mechanistic analysis of one such system is discussed in the accompanying paper in this issue.

**Acknowledgment.** We are grateful for the National Institutes of Health for generous financial support (Grant R01 GM63167-01A1). D.W. thanks the Swiss National Science Foundation and the Novartis-Stiftung for postdoctoral fellowships.

**Supporting Information Available:** Procedures for the kinetic analysis including determination of response factors and raw GC data for all kinetic experiments along with preparation and characterization of all compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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