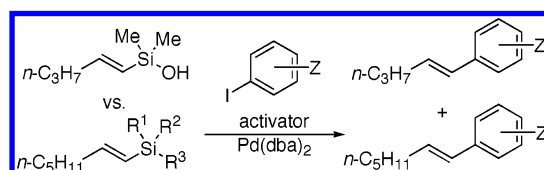# JOC*Article*

# A Qualitative Examination of the Effects of Silicon Substituents on the Efficiency of Cross-Coupling Reactions

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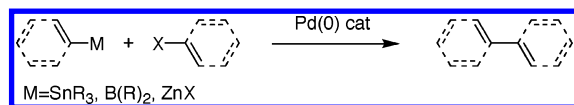
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A qualitative study of the effects of various substituents on the silicon atom in cross-coupling reactions of alkenylsilanes has been carried out. In intermolecular competition experiments, the influence of carbon-based groups (methyl, ethyl, isopropyl, *tert*-butyl, phenyl, and 3,3,3-trifluoropropyl) and alkoxy groups (monoethoxydimethyl-, diethoxymethyl-, and triethoxy) on the silicon have been evaluated under activation by two different methods, fluoride (TBAF) and silanolate (TMSOK). The influence of the substituents was highly dependent on the method of activation. In the presence of TBAF, there was only a modest steric effect (except for *tert*-butyl substituents), and the efficiency decreased slightly with increasing numbers of alkoxy groups. In the presence of TMSOK, a significant steric effect was noted, but the number of alkoxy groups had almost no influence. These trends were interpreted in terms of the divergent mechanisms for the cross-coupling process.

## Introduction

The transition-metal-catalyzed cross-coupling reaction has emerged as a powerful and general method for carbon–carbon and carbon–heteroatom bond formation. After initial independent reports from Kumada and Corriu on the reaction of organomagnesium reagents with alkenyl or aryl halides catalyzed by a Ni(II) complex, many other organometallic reagent have proven to be useful nucleophiles in this reaction. Among the most synthetically useful, organostannanes, organoboranes, and zinc reagents have become popular because of good functional group compatibility (Scheme 1).[1] Although these have found broad application, the search continues for reactions that proceed under milder conditions, with stable, readily available starting materials, and without toxic byproducts.

**SCHEME 1**



In recent years, the coupling reactions of organosilicon compounds have provided a viable alternative.[2] Following the pioneering work of Hiyama,[3] the utility of this method has been expanded significantly by the introduction of heteroatoms on the silicon species and by the use of additives to increase reactivity.[4] Reports from these laboratories have documented the use of silacyclobutanes, silanols, silyl hydrides, cyclic silyl ethers, disiloxanes, and even oligosiloxanes.[5] The reaction conditions employed for these couplings are mild, employing a

(1) For a recent review, see: (a) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (b) *Handbook of Organopalladium Chemistry*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002. (c) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Chichester, 1995.

(2) For reviews on silicon-based cross-coupling, see: Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10. (b) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61−85. (c) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapter 4. (d) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *3*, 211−226.

(3) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918−920.

(4) For other examples of silicon-based-cross coupling, see: (a) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 749−750. (b) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2055. (c) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309−1310. (d) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M.; DeShong, P.; Lark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600−7601. (e) Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, W. M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201−12225.

(5) (a) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. (c) Denmark, S. E.; Ober, M. H. *Aldrichim. Acta* **2003**, *36*, 75−85.

Pd(0) catalyst and a nucleophilic activator, generally fluoride anion. In addition, a method for activation that does not require fluoride ion has also been developed in recent years.[6] The more practical features of both of these processes are as follows: (1) efficiency and mildness of reaction conditions, (2) stereospecificity with respect to both of addends, (3) generally fast reaction rates, (4) broad functional group compatibility, and (5) ease of handling of starting materials and removal of byproducts.

In addition to our demonstration of the synthetic advantages of silicon-based cross-coupling, we are also interested in a deeper understanding of the elementary molecular events in the catalytic cycle. Preliminary mechanistic investigations revealed that the basic structural requirement for facile cross-coupling is the presence of one oxygen function on the silicon (alcohol, ether, disiloxane).[7] The remaining spectator groups on the silicon offer a unique opportunity to modulate the reactivity of the silyl moiety. The contributions of both steric and electronic effects on the rate of the coupling are of significant preparative and mechanistic interest and find limited parallels in the coupling reactions of other organoelement reagents. An additional feature is that variation of the spectator group can easily be accomplished from the large number of readily available silicon precursors. Thus, we report herein a detailed investigation on the steric and electronic contributions of the silicon substituents to the efficiency of the cross-coupling reactions.

## Background

**1. Organosilicon Nucleophiles in Cross-Coupling.** The use of organosilicon reagents to promote and control carbon−carbon bond formation in organic synthesis is increasingly exploited and remains an active area of research.[8] Because the carbon−silicon bond is much less polarized than other carbon−metal bonds, organosilicon compounds generally do not exhibit appreciable reactivity toward weak electrophiles. However, polarization of the carbon−silicon bond can be enhanced by formation of a siliconate complex through association with nucleophiles. Fluoride ion is particularly effective in view of the high enthalpy of Si−F bonds (159 kcal/mol).[9] In 1988, Hiyama and Hatanaka[3] capitalized on this feature and reported the first efficient palladium-catalyzed cross-coupling of vinyltrimethylsilane with and aryl halide in the presence of a fluoride source (Scheme 2).

**SCHEME 2**



In these examples, vinyltrimethylsilane reacts with a variety of alkenyl and aryl iodides in good to excellent yields in the presence of 2.5 mol % of allylpalladium chloride dimer (APC) and triethyl phosphite. The silicon moiety was activated by either of two readily available fluoride sources: tris(diethylamino)-

sulfonium difluorotrimethylsilicate (TASF) or tetrabutylammonium fluoride (TBAF).

However, this reaction works only with vinyltrimethylsilane, **1**, whereas no reaction was observed when, e.g., (*E*)-1-octenyltrimethylsilane was employed as the starting material. Thus, further activation of the silicon atom (polarization of C−Si-bond) was required. This has been achieved by using fluorosilanes as substrates, as illustrated in Scheme 3.[10] The monofluorosilane undergoes the cross-coupling reaction in high yield in the presence of APC catalyst and TASF. This method has wide scope proceeding smoothly with a variety of vinyl and aryl iodides in the presence of TASF or TBAF. The reaction of alkenylfluorosilanes with alkenyl iodides proceeded with retention of configuration to produce dienes of high isomeric purity.[2]
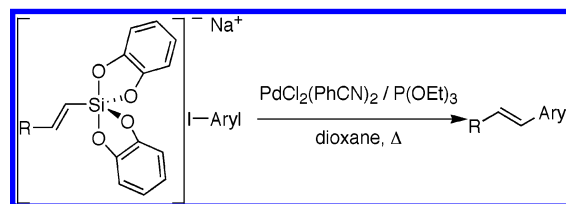
**SCHEME 3**
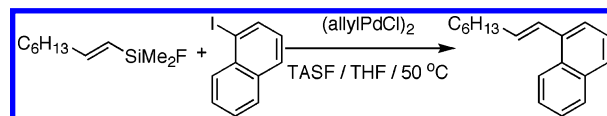


In 1989, it was found that alkenyl*fluoro*silanes could be replaced by alkenyl*alkoxy*silanes.[11] Thus, in the presence of a palladium catalyst and a fluoride activator, alkenylalkoxysilanes undergo cross-coupling reactions in a similar manner as fluorosilanes.

The assumption that a pentacoordinate siliconate[12] is a necessary intermediate was further supported by the synthesis of alkenylbis(catecholato)silicates by Hosomi and co-workers.[13] These compounds undergo cross-couplings without an additional activator, as outlined in Scheme 4. When combined with aryl iodides in the presence of a palladium catalyst, the corresponding styrenes are formed with moderate yields at slightly elevated temperatures.

**SCHEME 4**



The most recent and synthetically useful of the heteroatom-substituted silanes to be developed are the organosilanols (Scheme 5).[5] These agents can be readily synthesized from a number of precursors, are shelf stable and can be activated for coupling to iodides, bromides, and triflates[14] by both fluoride ion and Bronsted bases.

**SCHEME 5**
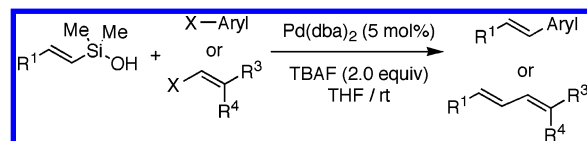
(6) For a review of the nonfluoride activated couplings, see: Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954−5963.

(7) (a) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865−4875. (b) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876−4882.

(8) For a recent monograph on organosilicon chemistry, see: Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*; Wiley-Interscience: New York, 2000.

(9) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246−252.

(10) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268−270.

(11) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051−6054.

(12) Damrauer, R., Danahey, S. E. *Organometallics* **1986**, *5*, 1490−1494.

Clearly, organofunctional silicon compounds (substituted by heteroatoms) are viable precursors for transition-metal-catalyzed cross-coupling reactions. However, all of these reactions require a nucleophilic activator to promote the coupling process, presumably to access the reactive pentacoordinate siliconate for the crucial transmetalation. The nature of this activator is considered next.[15]

**2. Activation.** Because of the high bond energy of the silicon fluorine bond, the formation of a siliconate is expected to be possible using fluoride ion as the nucleophile. Tris(diethyl-amino)sulfonium difluorotrimethylsilicate (TASF) was successfully used in cross-coupling reactions, but in some cases transfer of a methyl group from this reagent to the aryl iodide was observed. Also, this reagent is not easily handled and has limited solubility. These problems were overcome by the use of TBAF, which was found to be the most general source of fluoride ion.[3]

Successful fluoride-free coupling reactions with other promoters have also been reported. Potassium hydroxide[16] as well as tetrabutylammonium hydroxide (TBAOH) have been shown to activate the reaction. These bases are generally less efficient than TBAF; however, as weaker silicon nucleophiles they can help to overcome problems associated with protiodesilylation. Silver oxide has also shown potential as an activator for silanol couplings.[17] Reports from these laboratories have demonstrated the effectiveness of potassium trimethylsilanolate, sodium and potassium hydride, sodium *tert*-butoxide, and cesium carbonate to effect the cross-coupling of silanols. Indeed, even the preformed silanolates are useful reagents.[18]

**3. Silicon Substituents.** In most of the studies reported to date, the effect of the silicon substituent has not been addressed. However, examination of the type and number of heteroatom substituents has been studied. Hiyama has shown that mono-fluorosilanes and difluorosilanes but not trifluorosilanes undergo cross-coupling reactions in the presence of a palladium catalyst and TBAF.[3,19] A similar trend was observed for ethoxysilanes; mono- and dimethoxysilanes exhibit the same reactivity, whereas the trimethoxysilane was less reactive although a quantitative comparison was not reported.[10]

Silanediols and -triols have also proven to be competent donors in the reaction.[17] Aryl- and alkenylsilanediols and -triols are easily synthesized from the corresponding chlorides and subjected to similar cross-coupling reactions. The comparison of the alkenylsilanol, silanediol, and silanetriol demonstrates the higher coupling efficiency associated with increasing numbers of hydroxyl groups. Here again, quantitative comparisons are not reported.

In early studies of fluoride-promoted coupling of acyclic alkenylsilanols, it was reported that the size of the alkyl

substituent (methyl vs isopropyl) had little effect on the efficiency of coupling.[20] Although this trend is generally true for acyclic substrates, subsequent investigation with exo alkyl-idene siloxanes revealed a dramatic difference favoring the less sterically demanding dimethylsiloxane.

Our goal was to systematically examine the contribution of the steric and the electronic effects of the substituents on the efficiency of the cross-coupling reaction. We sought to establish a qualitative scale based on the comparison of various coupling partners under different conditions. The study will address four components of this process: (1) the steric contribution of various alkyl/aryl substituents in the diorganosilanol couplings, (2) the contribution of multiple heteroatom substitution on silicon, (3) the importance of the aryl electrophile in modulating steric and electronic effects at silicon, and (4) the importance of the reaction conditions, specifically activator, in manifesting effects at the silicon.

To establish such a scale, we developed a simple competition experiment between silanols (or silyl ethers) so that the relative efficiencies of reaction could be determined. A schematic illustration of the competition is presented in Figure 1. The experiment will consist of pairwise combination of two silanols (or silyl ethers) bearing different substituents R and R′ in the presence of *a limiting amount* of an aryl iodide. The silyl groups will be attached to transferable groups G and G′ which are nearly identical so as to have no influence on the efficiency of the coupling, but still differentiable by an analytical method. Thus, the dependence of the efficiency of coupling on R and R′ can easily be determined by the ratio of coupling products ArylG and ArylG′. After complete disappearance of the iodide, the respective ratio of the coupling product arriving from each silicon precursor will be determined $(1 - x/1 - y)$. Given that each silicon precursor reacted at a defined rate, a correlation between the product ratio and the relative rates $(k_1/k_2)$ can be established.[21]
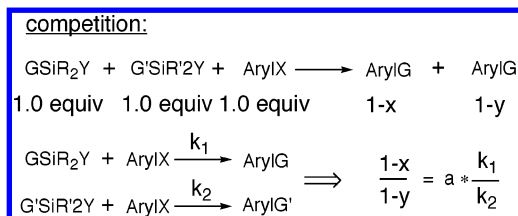


FIGURE 1. Design of competition experiments.

## Results

**1. Preparation of Starting Materials.** For these studies, we chose to examine the coupling of a diverse set of silicon substituents with representative electrophiles. The geometrically

(13) Hosomi, A., Kohra, S., Tominaga, Y. *Chem. Pharm. Bull. Jpn.* **1988**, *36*, 4622−4625.

(14) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771−3774.

(15) For a novel illustration of intramolecular activation of a tetracoordinate silane, see: Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952−6953.

(16) Hagiawara, E.; Gouda, K.-I.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439−442.

(17) (a) Hirabayashi L., Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T.; *Org. Lett.* **1999**, *1*, 299−302. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, 65, 5342−5349.

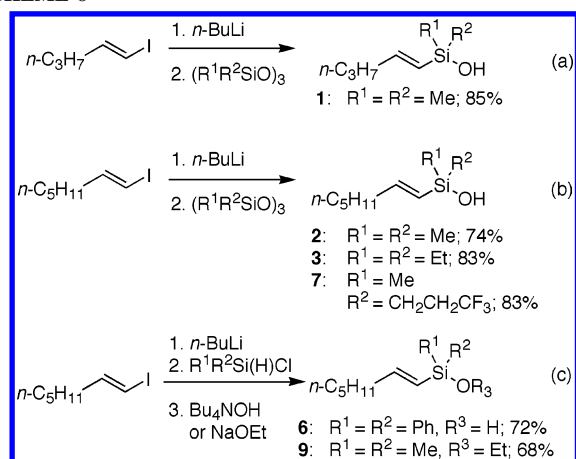(18) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793−795.

(19) Qualitatively, Hiyama has established the following series: for allyl and alkyl transfers (SiF₃), for aryl transfers (SiMeF₂ or SiMe₂F), and for alkenyl transfers (SiMe₂F).[2b]

(20) (a) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491−2494. (b) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61−64.
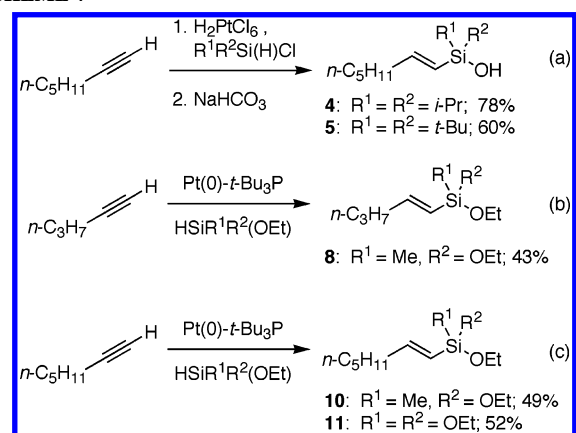
(21) Although it is obvious that product ratios at complete conversion do not reflect true rate ratios, we will demonstrate the viability of this approach in a qualitative sense by comparing the results of experiments that employ stoichiometric and super-stoichiometric amounts of the nucleophile (pseudo-order conditions). It should be pointed out, however, that even with stoichiometric amounts of the silane or a halide, the actual reactive intermediate (aryl-PdL$_n$I) is limited in concentration to the amount of catalyst employed (0.05 equiv). Thus, even at the most simplistic stoichiometry for completion of reactants (1.0 equiv of each silane for 1.0 equiv of iodide as shown in Figure 1) the actual competition between the silanes for the true reactive intermediate is 40/1 at the outset and 20/1 near the completion of the reaction, clearly in the first-order regime.

defined (*E*)-(1-heptenyl)silanols and (*E*)-(1-pentenyl)silanols (or their corresponding silyl ethers) were selected as test substrates to investigate the influence of the nontransferable groups on the silicon atom. These alkenylsilanes were chosen to allow for direct comparison to previously described cross-coupling reactions and because the aliphatic groups should not influence the efficiency of the coupling process. The preparation of various silane derivatives can be readily achieved by two synthetic approaches: (1) lithium−halogen exchange of an alkenyl iodide and subsequent reaction with an appropriate silicon electrophile (Scheme 6) and (2) hydrosilylation of an alkyne (Scheme 7).[22] The first method is particularly efficient when the intermediate alkenyllithium species is reacted with cyclic siloxanes or with a chlorosilane.[23] Indeed, (*E*)-dimethyl(1-pentenyl)silanol (**1**), (*E*)-dimethyl(1-heptenyl)silanol (**2**), (*E*)-diethyl(1-heptenyl)silanol (**3**), and (*E*)-methyl(1-heptenyl)trifluoropropylsilanol (**7**)[4a] could be obtained from their corresponding trisiloxane precursor in 85, 74, 83, and 83% yields, respectively. The use of diphenylchlorosilane and dimethylchlorosilane with subsequent hydrolysis to the silanol or etherification leads to (*E*)-diphenyl(1-heptenyl)silanol (**6**) and (*E*)-dimethyl(1-heptenyl)-ethoxysilane (**9**) in 72 and 68% yields, respectively.

**SCHEME 6**



**SCHEME 7**

(22) For a review on hydrosilylation, see: Ojima, I.; Li, Z.; Zhu, J. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, Part 2, Chapter 29, p 1687.

(23) Hirabayashi, K.; Takahisa, E.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2409−2417.

Alternatively, hydrosilylation of alkynes was employed to prepare (*E*)-diisopropyl(1-heptenyl)silanol (**4**) and (*E*)-di-*tert*-butyl-(1-heptenyl)silanol (**5**) in 78% and 60% yields, respectively, after subsequent hydrolysis of the intermediate chlorosilanes (Scheme 7).

The synthesis of diethoxy- and triethoxyalkenylsilanes proved to be more challenging. Because clean monosubstitution of only one leaving group on a di- or trichlorosilane or ethoxysilane is rather difficult, we chose once again to use hydrosilylation (Scheme 7). However, in this case, the reaction led to both the desired product as well as an appreciable amount of 1,1-disubstitued alkenylsilane (10−20%). Efforts to suppress the formation of this isomer by the use of a different catalyst (H$_2$PtCl$_6$, Pt(0)-DVDS, RhI(PPh$_3$)$_3$) or by varying the reaction conditions (inverse addition order of reactant, solvent, or temperature) were unsuccessful. Ultimately, sacrificial radial chromatography was used to remove the undesired isomer and allowed access to pure samples of (*E*)-diethoxy(1-pentenyl)-methylsilane (**8**, 43%), (*E*)-diethoxy(1-heptenyl)methylsilane (**10**, 49%), and (*E*)-(1-heptenyl)triethoxysilane (**11**, 52%).

With the requisite silyl precursors in hand, we next investigated their relative reactivities in the palladium(0)-catalyzed cross-couplings.

**2. Competition Experiments.** Because our primary objective was to establish a quantitative scale of reactivities, we chose to use capillary gas chromatographic analysis of the reaction mixtures as the analytical tool. For accurate determination of the conversion (yield) and product ratios (relative reactivities), response factors for all of the substrates and products were carefully determined against an internal standard (naphthalene, see the Supporting Information). All experiments were performed minimally in duplicate.

The competition experiments were conducted with (*E*)-dimethyl(1-pentenyl)silanol (**1**), which was chosen as the standard with variously substituted (*E*)-(1-heptenyl)silanols in the presence of a limiting amount of aryl iodide and a substoichiometric amount of Pd(dba)$_2$. In addition, the competition experiments were conducted under activation with both TBAF and TMSOK to reveal if the reactivity trends were dependent on reaction conditions.[7] After complete consumption of the iodide, the product ratio was determined quantitatively by GC analysis of the 1-pentenyl and 1-heptenyl products calibrated against the internal standard. 4-Iodoacetophenone, 4-iodoanisole, and 2-iodotoluene, which represent electron-poor, electron-rich, and sterically encumbered iodides, were employed as electrophiles in the coupling.

**A. Carbon Substituents Effects.** The first parameter investigated was the effect of alkyl and aryl substituents on the silicon. To establish the validity of the method and a control experiment to calibrate the analysis, we performed the competition between **1** and **2** with each of the aryl iodides. The product ratios obtained, which are almost exactly 50/50 (entries 1, 6, and 12, Table 1), allowed us to conclude that no spurious contribution due to different lengths of the side chains in the transferable group (1-pentenyl vs 1-heptenyl) was observed.

First, silanol **1** was set in competition with various dialkyl/diaryl(1-heptenyl)silanols (**2−7**) in the coupling either to 4-iodoacetophenone, 4-iodoanisol, or 2-iodotoluene. The results compiled in Table 1 clearly demonstrate that the nature of aryl iodide has little influence on the efficiency of the reaction. Thus, it is possible to discuss the carbon substitution contribution to the relative efficiencies in general across all three substrate classes. Comparison of entries 1−3, 6−8, and 12−14 reveals a

**TABLE 1. Competition Experiments: Carbon Substituents**[a]
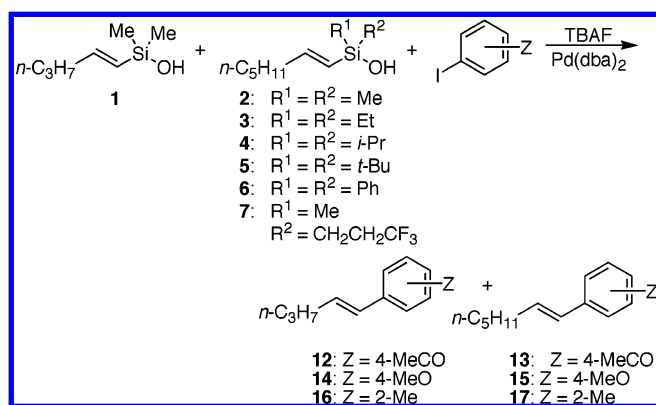


| entry | aryl (Z) | C3 vs C5 | products | ratio[b] |
|-------|----------|----------|----------|----------|
| 1 | 4-MeCO | **1** vs **2** | **12/13** | 50.8/49.2[c] |
| 2 | 4-MeCO | **1** vs **3** | **12/13** | 56.7/43.3 |
| 3 | 4-MeCO | **1** vs **4** | **12/13** | 59.9/40.1 |
| 4 | 4-MeCO | **1** vs **5** | **12/13** | 96.4/3.6 |
| 5 | 4-MeCO | **1** vs **6** | **12/13** | 49.5/50.5[c] |
| 6 | 4-MeO | **1** vs **2** | **14/15** | 50.7/49.3[d] |
| 7 | 4-MeO | **1** vs **3** | **14/15** | 53.3/46.7[d] |
| 8 | 4-MeO | **1** vs **4** | **14/15** | 61.6/38.4[d] |
| 9 | 4-MeO | **1** vs **5** | **14/15** | 96.1/3.9[d] |
| 10 | 4-MeO | **1** vs **6** | **14/15** | 56.3/43.7[d] |
| 11 | 4-MeO | **1** vs **7** | **14/15** | 44.6/55.4 |
| 12 | 2-Me | **1** vs **2** | **16/17** | 50.2/49.8 |
| 13 | 2-Me | **1** vs **3** | **16/17** | 58.6/41.4 |
| 14 | 2-Me | **1** vs **4** | **16/17** | 60.5/39.5 |
| 15 | 2-Me | **1** vs **5** | **16/17** | 100.0/0.0 |
| 16 | 2-Me | **1** vs **6** | **16/17** | 50.1/49.9 |

[a] Reactions were run on a 0.5 mmol scale with 1.0 equiv of **1**, 1 equiv of **2−7**, 1.0 equiv of aryl iodide, 4.0 equiv of TBAF, and 5 mol % of Pd(dba)$_2$. [b] Average product ratio of two separate reactions unless noted. [c] Average product ratio of four separate reactions. [d] Reactions were run on a 0.2 mmol scale with 1.0 equiv of **1**, 1.0 equiv of **2−7**, 1.0 equiv of aryl iodide, 4.0 equiv of TBAF, and 5 mol % of Pd(dba)$_2$.

consistent, but strikingly weak, steric effect on the efficiency in the expected order where dimethyl reacts faster than diethyl which is marginally faster than diisopropyl. By contrast, the di-*tert*-butyl-substituted silanol (**5**) was significantly less reactive than the dimethyl (**1**) (entries 4, 9, and 15). Indeed in the case of 2-iodotoluene, none of the coupling product (**17**) was detected. Surprisingly, the efficiency of the reaction of the diphenylsilanol (**6**) was nearly indistinguishable from that of the dimethylsilanol standard (cf. entries 5, 10, and 16) possibly suggesting a combination of opposing steric and electronic factors. Finally, the remote effect of a trifluoromethyl group, investigated in the (1-heptenyl)methyltrifluoropropylsilanol (**7**), was found to be weakly accelerating (entry 11) compared to the reference dimethylsilanol. Thus, taking the average of the results for the three series and normalizing the efficiency of dimethylsilanol substrate (**1**) to 1.0 we can establish a relative reactivity order of: (Me)CF$_3$CH$_2$CH$_2$Si ≥ Me$_2$Si ≈ Ph$_2$Si > Et$_2$Si > *i*-Pr$_2$Si ≫ *t*-Bu$_2$Si following **7/1/6/3/4/5** = 1.24/1.00/0.92/0.78/0.65/0.025.

To confirm the conclusions of relative efficiencies from product ratios, we examined the loading dependence of silanol precursor on the outcome. Two substrates were selected for this comparison, **1** vs **4** and **1** vs **6**, using 2.0, 4.0, and 6.0 equiv of the combined silanols (and 2.0 equiv of TBAF per silanol) with respect to the iodide (4-iodoanisole). The results in entries 1−3 and 4−6 (Table 2) show clearly that the product ratios are

largely independent of the stoichiometry, thus supporting the conclusion that these numbers indeed represent the relative reactivities of the silanols under these conditions.

**TABLE 2. Competition Experiments: Carbon Substituents**[a]
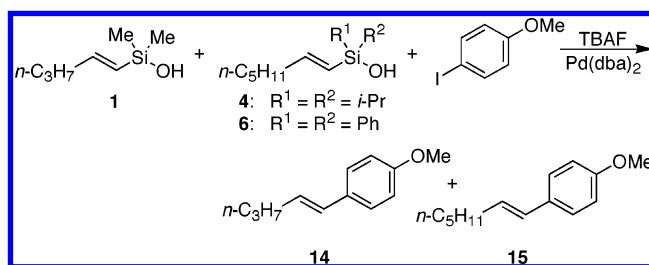


| entry | C3 vs C5 | 1/4 (equiv)[b] | TBAF (equiv)[b] | 14/15 ratio[c] |
|-------|----------|----------------|-----------------|----------------|
| 1 | **1** vs **4** | 1.0/1.0 | 4.0 | 66.1/33.9 |
| 2 | **1** vs **4** | 2.0/2.0 | 8.0 | 67.0/33.0 |
| 3 | **1** vs **4** | 3.0/3.0 | 12.0 | 69.4/30.6 |
| 4 | **1** vs **6** | 1.0/1.0 | 4.0 | 59.6/40.4 |
| 5 | **1** vs **6** | 2.0/2.0 | 8.0 | 59.6/40.4 |
| 6 | **1** vs **6** | 3.0/3.0 | 12.0 | 58.2/41.8 |
| 7 | **1** vs **4** | 1.0/1.0 | 1.0 | 54.5/45.5[d] |
| 8 | **1** vs **4** | 1.0/1.0 | 2.0 | 58.5/41.5 |
| 9 | **1** vs **4** | 1.0/1.0 | 4.0 | 66.1/33.9 |
| 10 | **1** vs **4** | 1.0/1.0 | 8.0 | 66.6/33.4 |
| 11 | **1** vs **6** | 1.0/1.0 | 1.0 | 41.3/58.7[e] |
| 12 | **1** vs **6** | 1.0/1.0 | 2.0 | 50.2/49.8 |
| 13 | **1** vs **6** | 1.0/1.0 | 4.0 | 59.6/40.4 |
| 14 | **1** vs **6** | 1.0/1.0 | 8.0 | 50.0/50.0 |

[a] Reactions were run on a 0.2 mmol scale with 2.5 mol % of Pd$_2$(dba)$_3$. [b] With respect to 4-iodoanisole. [c] Average product ratio of two separate reactions. [d] Stalled at 65% conversion. [e] Stalled at 88% conversion.

In addition, we have examined the effect of TBAF stoichiometry on the product ratio. Here again (entries 7−10 and 11−14, Table 2) there are small variations that, although interpretable in the context of our mechanistic picture (see the Discussion), they do not meaningfully change the relative ordering of the substituent effects.

Because di-*tert*-butyl(1-heptenyl)silanol (**5**) gave only a trace amount of coupling product in the competition experiments, its reactivity was established in an independent coupling experiment. The cross-coupling to 4-iodoacetophenone, with 5 mol % of Pd(dba)$_2$ and 2.0 equiv of TBAF reached full conversion after 19 h at 50 °C and (*E*)-4-(1-heptenyl)acetophenone (**13**) was isolated in 59% yield along with 12% of a homocoupling product arising from the iodide.

**B. Heteroatom Substituents Effects.** The effect of varying the number of heteroatom substituents around the silicon was probed next (Table 3). The competition experiments were set up to compare the reference dimethylsilanol (**1**) with either diethoxymethyl(1-heptenyl)silane (**10**) or triethoxy(1-heptenyl)-silane (**11**). Competition between diethoxymethyl(1-pentenyl)-silane (**8**) and triethoxy(1-heptenyl)silane (**11**), was also performed. As before, a control experiment in the competition between **1** and **9** (Table 3, entry 10) showed that silanol and silyl ether functions behave as equivalents in the coupling reaction under TBAF activation. The nature of the aryl iodide again had no significant effect on the ratios obtained, as was previously observed with the carbon substituents.

The influence of increasing numbers of oxygen substituents is readily apparent. Comparison of entries 1, 4, and 7 reveals almost identical efficiencies of reaction for the dimethylsilanol **1** compared to the diethoxymethylsilane **10** affording an average

**TABLE 3. Competition Experiments: Heteroatom Substituents**[a]
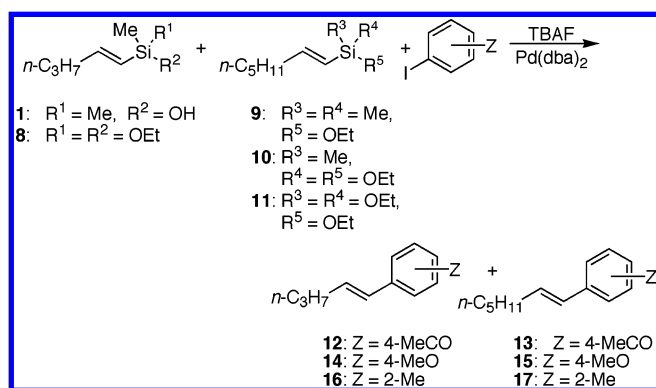


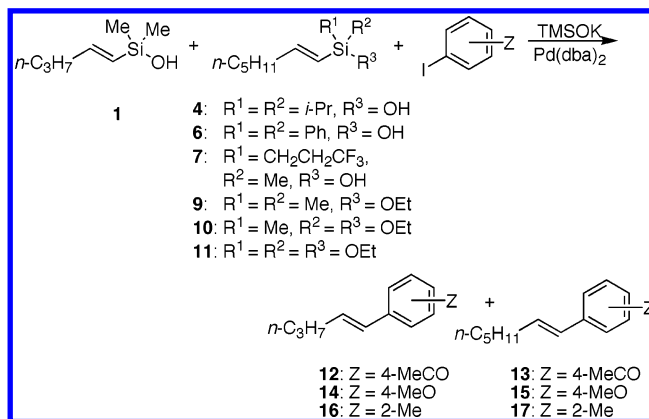| entry | aryl (Z) | C3 vs C5 | products | ratio[b] |
|-------|----------|----------|----------|----------|
| 1 | 4-MeCO | **1** vs **10** | **12/13** | 49.2/50.8 |
| 2 | 4-MeCO | **1** vs **11** | **12/13** | 73.9/26.1 |
| 3 | 4-MeCO | **8** vs **11** | **12/13** | 73.1/26.8 |
| 4 | 4-MeO | **1** vs **10** | **14/15** | 56.6/43.4 |
| 5 | 4-MeO | **1** vs **11** | **14/15** | 81.5/18.5 |
| 6 | 4-MeO | **8** vs **11** | **14/15** | 76.4/23.6 |
| 7 | 2-Me | **1** vs **10** | **16/17** | 51.4/48.6 |
| 8 | 2-Me | **1** vs **11** | **16/17** | 81.1/18.9 |
| 9 | 2-Me | **8** vs **11** | **16/17** | 74.4/25.6 |
| 10 | 4-MeO | **1** vs **9** | **14/15** | 49.4/50.6 |

*a* Reactions were run on a 0.2 mmol scale with 1.0 equiv of **1** or **8**, 1.0 equiv of **9**, **10**, or **11**, 1.0 equiv OF aryl iodide, 4.0 equiv of TBAF, and 5 mol % of Pd(dba)$_2$. *b* Average product ratio of two separate reactions.

product ratio of 52.8/47.2. The triethoxysilane **11**, however, was markedly less reactive compared to the reference standard **1** (entries 2, 5, and 8) with a average ratio of 78.8/21.2. The average of the results for the three series furnishes the relative order of Me$_2$SiOH ∼ Me$_2$SiOEt ≥ MeSi(OEt)$_2$ > Si(OEt)$_3$ following **1/9/10/11** = 1.00/1.02/0.92/0.27. The results from entries 3, 6, and 9 which directly compare the di- and triethoxylsilanes **8** and **11** exclude any unknown contribution of the silyl ether functionality and also allow for an integrated scale to be composed. The relative order (normalized to 1.0 for) is MeSi(OEt)$_2$ > Si(OEt)$_3$ following **8/11** = 1.0/0.34. The equivalence of **8** and **9** can be established from this number and comparison of **1/9** with **1/11**. Thus, we can now formulate the scale (normalizing to 1.0 for Me$_2$SiOEt) as: Me$_2$SiOEt ≥ MeSi(OEt)$_2$ > Si(OEt)$_3$ following **9/10/11** = 1.00/0.89/0.26 in good agreement with the scale based on **1**.

**C. Substituents Effects with TMSOK.** The effect of various carbon or heteroatom substituents on the silicon was investigated in potassium trimethylsilanoate (TMSOK) activated cross-coupling. For this comparison, a limited set of compounds was chosen. To probe the effects of carbon-based substituents, the diisopropyl- (**4**), diphenyl- (**6**) and methyltrifluoropropylsilanols (**7**) were tested. In this series, only substrate **4** would be tested with all three aryl iodides. For evaluation of heteroatom substituents, the homologous series of mono-, di-, and triethoxysilanes (**9**, **10**, and **11**) were chosen for coupling but only with 4-iodoanisole.

The results from these studies (Table 4) stand in striking contrast to those from competitions under TBAF activation. Results from entries 1−3 reveal a strong steric effect wherein the diisopropylsilanol reacts much more slowly than the dimethylsilanol. This effect was consistently retained over the three aromatic iodides and in the case of iodoacetophenone, complete selectivity was obtained. Interestingly, the efficiencies of the reaction of the diphenylsilanol **6** and the (methyl)-

trifluoropropylsilanol **7** were both clearly higher than that of the dimethylsilanol reference (entries 4 and 5) suggesting a contribution of factors other than a purely steric are beneficial under TMSOK activation. By contrast the efficiencies of the reaction of the ethoxy-substituted silanes (**9**, **10**, and **11**) showed no significant differences compared to that of silanol **1**.

**TABLE 4. Competition Experiments: TMSOK Activation**[a]



| entry | aryl (Z) | C3 vs C5 | products | ratio[b] |
|-------|----------|----------|----------|----------|
| 1 | 4-MeCO | **1** vs **4** | **12/13** | 100.0/0.0 |
| 2 | 4-MeO | **1** vs **4** | **14/15** | 95.0/5.0 |
| 3 | 2-Me | **1** vs **4** | **16/17** | 93.7/6.3 |
| 4 | 4-MeO | **1** vs **6** | **14/15** | 20.6/79.4 |
| 5 | 4-MeO | **1** vs **7** | **14/15** | 34.9/65.1 |
| 6 | 4-MeO | **1** vs **9** | **14/15** | 48.1/51.9 |
| 7 | 4-MeO | **1** vs **10** | **14/15** | 45.2/54.8 |
| 8 | 4-MeO | **1** vs **11** | **14/15** | 51.6/48.4 |

*a* Reactions were run on a 0.2 mmol scale with 1.0 equiv of **1**, 1.0 equiv of **4**, **6**, **7**, and **9**−**11**, 1.0 equiv of aryl iodide, 4.0 equiv of TMSOK, and 5 mol % of Pd(dba)$_2$. *b* Average product ratio of two separate reactions.

Normalizing the efficiency of the dimethylsilanol substrate **1** to 1.0, the relative order was established as Ph$_2$SiOH > (Me)-CF$_3$CH$_2$CH$_2$SiOH > MeSi(OEt)$_2$ ≥ Me$_2$SiOH ≈ Si(OEt)$_3$ ≈ Me$_2$SiOEt ≫ (i-Pr)$_2$SiOH following **6/7/10/1/11/9/4** = 3.85/1.86/1.21/1.00/0.94/0.93/0.04.

For activation by TMSOK we also examined the dependence of product ratios on the stoichiometry of both the silanols and the activator. Because there was effectively no reaction of **4** under these conditions we only examined the competition between **1** and **6** again at 2.0, 4.0, and 6.0 equiv of combined silanols (with 4.0 equiv of TMSOK) with respect to iodide (4-iodoanisole). The results in entries 1−3, Table 5, show clearly that as in the case of TBAF activation, the product ratios are independent of the stoichiometry. However, as seen in entries 4−7, the ratios are significantly influenced by the amount of TMSOK employed in strong contrast to the behavior under TBAF activation. Although this outcome does influence the relative ordering we found that increasing the amount of TMSOK in the competition between **1** and **4** had no effect on the ratio. The origin of the TMSOK loading effect can also be understood in view of the mechanistic differences in the two processes and will be discussed later.

**3. Tandem Cross-Coupling of an Unsymmetrical Bis-(silane).** Having established the relative rates of cross-coupling of various silafunctional groups, the feasibility of sequential coupling of a bis(silyl)diene through selective activation of different silyl groups was identified as a proof of concept experiment.[24] We selected the 1,4-(bis(1-silyl)ethenyl)benzene[25]

**TABLE 5. Competition Experiments: TMSOK Activation**[a]
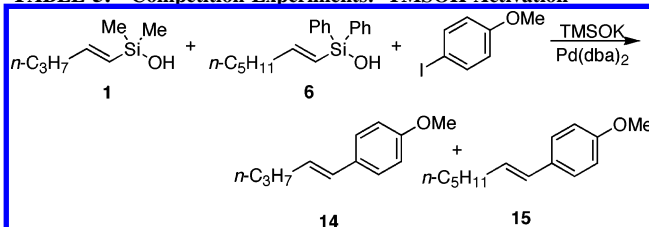


| entry | silanols (equiv)[b] | TMSOK (equiv)[b] | 14/15 ratio[c] |
|-------|---------------------|------------------|----------------|
| 1 | 1.0/1.0 | 4.0 | 35.6/64.4 |
| 2 | 2.0/2.0 | 8.0 | 34.6/65.4 |
| 3 | 3.0/3.0 | 12.0 | 37.9/62.1 |
| 4 | 1.0/1.0 | 1.0 | 14.1/85.9 |
| 5 | 1.0/1.0 | 2.0 | 16.0/84.0 |
| 6 | 1.0/1.0 | 4.0 | 35.6/64.4 |
| 7 | 1.0/1.0 | 8.0 | 58.8/41.2 |

[a] Reactions were run on a 0.2 mmol scale with 2.5 mol % of $Pd_2(dba)_3$. [b] With respect to 4-iodoanisole. [c] Average product ratio of two separate reactions.

**19** as a test substrate bearing two spatially isolated alkenylsilane functions. To achieve a synthetically useful differentiation of the individual coupling events, dimethyl and diisopropylsilyl ethers were chosen in view of their disparate coupling rates under TMSOK activation. Consideration of entries 1−3, Table 4, suggested that there should be a roughly 20-fold difference in the coupling rates of these groups.

The synthesis of **19** is outlined in Scheme 8. Hydrosilylation of 4-ethynylstyrene[26] with subsequent etherification gave the ethoxy-diisopropylsilane **18**. Dehydrosilylation was effected by combining **18** with dimethylethoxyvinylsilane in the presence of a Ru(II) catalyst.[27] Overall, the three-step sequence, hydrosilylation, etherification, and dehydrosilylation, afforded **19** in 58% yield.

**SCHEME 8**
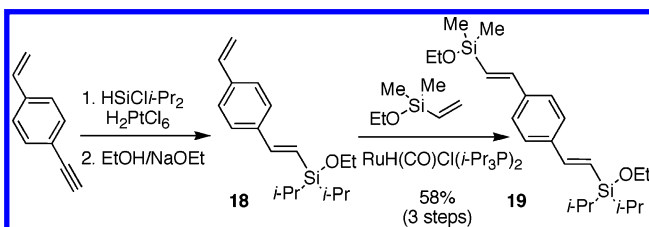


With the bis(alkenylsilyl) ether **19** in hand, the sequential cross-coupling was examined (Scheme 9). Compound **19** was treated with 4-iodobenzonitrile in the presence of 2.5 mol % of [allylPdCl]$_2$ (APC) and 4.0 equiv of TMSOK in THF at room temperature. After completion of the reaction, the mixture was filtered through a silica plug and the residue was subjected to the second coupling. Treatment of the intermediate with

(24) For a different solution to the problem of selective activation of bis(silanes), see: Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004−8005.

(25) (a) Symmetrical 1,4-(bis(1-silyl)ethenyl)benzenes have use recently as cross-linkers during polymerizations: Chen, R.-M.; Chien, K.-M.; Wong, K.-T.; Jin, B.-Y.; Luth, T.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 11321−11322. (b) *Silicon-Containing Polymers*; Jones, R. G., Ando, A., Chojnowski, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2000.

(26) Prepared from the known 4-(trimethylsilylethynyl)benzaldehyde: Austin, W. B.; Bilow, N.; Kelleghan, J.; Lau, J. S. Y. *J. Org. Chem.* **1981**, *46*, 2280−2286. See the Supporting Information for details.

(27) Yi, C. S.; He, Z.; Lee, D. W. *Organometallics* **2000**, *19*, 2036−2039.

2-iodotoluene, in the presence of 2.5 mol % of APC and 4.0 equiv of TBAF, afforded the unsymmetrical 1,4-bis(styryl)-benzene **20** in 76% overall yield. A sample of the symmetrical 1,4-bis(2-(4-cyanophenyl)ethenyl)benzene (**21**) was obtained under TBAF activation with 2.0 equiv of 4-iodobenzonitrile (Scheme 9).[28] This was prepared to ensure that the symmetrical product was not formed in the coupling with TMSOK.

**SCHEME 9**
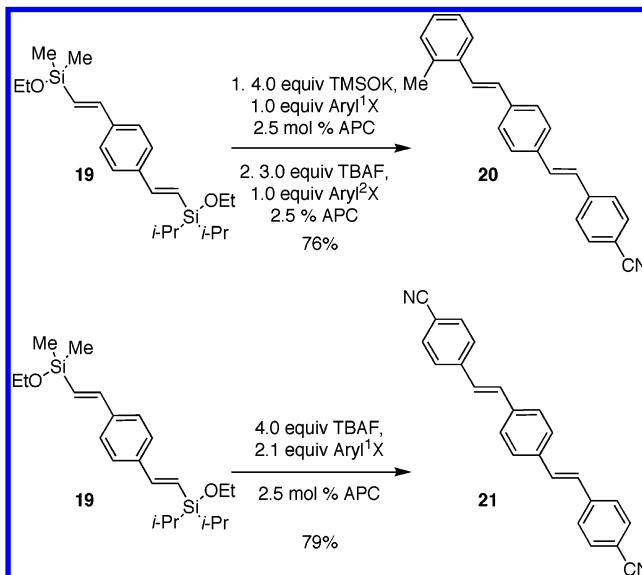


## Discussion

The results of the competition experiments between alkenyl-silanes bearing various silafunctional groups with different aryl iodides provided qualitative measures of substituent effects that can be summarized in a number of significant trends. First, the nature of the electrophile has little influence on the relative efficiencies of the coupling. Second, both steric and electronic factors of the silicon substituent are important influences on the efficiency of coupling. Third, the behavior of the different silicon directing groups is strongly dependent on the activator used for the coupling. To understand the origin of these effects requires discussion of our current understanding of the mechanism of silicon-based cross-coupling.[7]

The generally accepted, three-step catalytic cycle proposed for cross-coupling reaction, involving oxidative addition (2), transmetalation (3), and reductive elimination (4), is shown in Figure 2. For reactions involving aryl iodides wherein oxidative
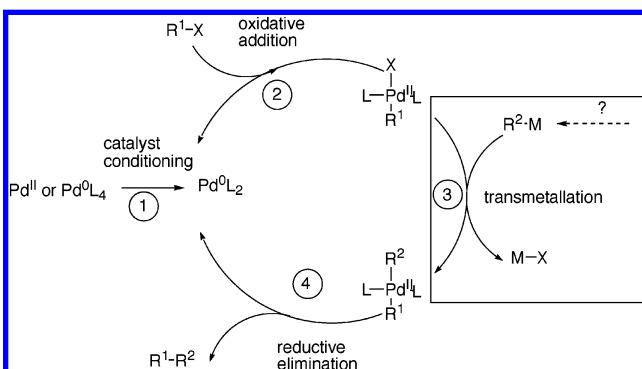


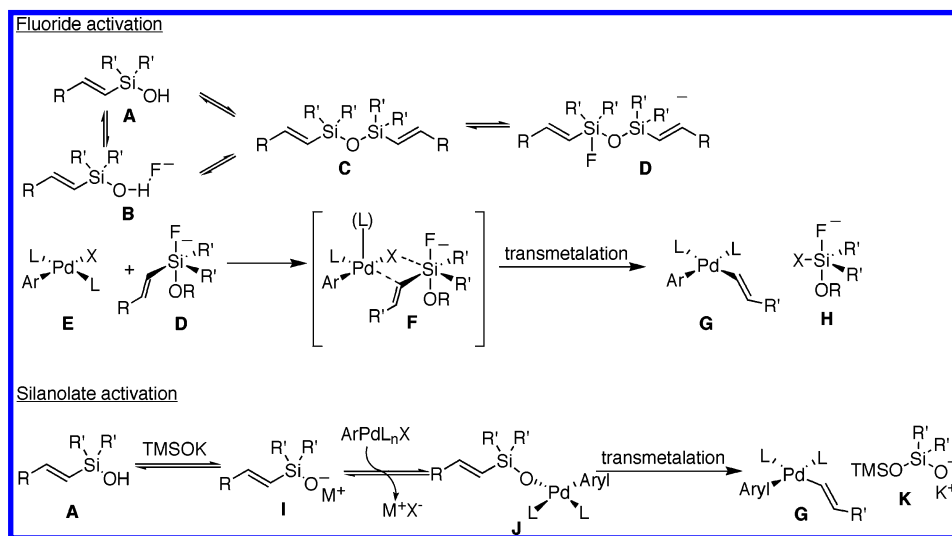**FIGURE 2.** Catalytic cycle for cross-coupling.

**FIGURE 3.** Hypotheses for the generation of activated species for transmetalation.

addition is fast and irreversible, transmetalation is believed to be the rate-determining step.

Since a silanol by itself is not a competent participant, additional steps leading to a reactive species able to undergo transmetalation must be added to the cycle. Our current view, supported by kinetic and spectroscopic studies, is that these steps are dependent on the activation.[7] The pathways for fluoride and for silanoate activation are summarized in Figure 3.

Spectroscopic studies[7] have shown that in upon treatment with TBAF·3H$_2$O, silanols (as well as silyl ethers, hydrides, fluorides, etc.) are converted to disiloxanes and a second species currently assigned as the structure **B**, which is believed to be an unproductive "resting state". In the presence of fluoride ions, disiloxanes can access a pentacoordinate state, leading to intermediate **D**. This intermediate can then undergo transmetalation with **E** through an as yet to be established mechanism (depicted here as a σ bond metathesis as has been postulated by Hiyama).[29]

In the case of silanoate activation, kinetic studies reveal an initial, preequilibrium deprotonation of the silanol **A**; the silanoate **I** then displaces the anionic ligand on the palladium forming complex **J** containing a palladium−oxygen−silicon bond.[30] Transmetalation then ensues directly from **J** without additional activation. The different experimental influences on efficiency will be discussed in view of these mechanistic scenarios.

**1. Nature of the Electrophile.** In previous studies on the scope of the cross-coupling process, we found that both steric and electronic contributions from substituents on the aryl iodide affected the efficiency of alkenylsilanol coupling.[5] In general, electron-rich aryl iodides are less reactive than electron-deficient iodides. This observation may simply reflect the charge affinity of the rate-determining transmetalation step.

The results compiled in Tables 1, 3, and 4 show clearly that the efficiency of the reaction is not significantly influenced by

the nature of the electrophile (aryl iodide). In the competition experiments, the palladium species are the same for both silanols. The lack of a change in the product composition suggests that the contribution of the substituent on the silicon is insensitive to the structure of the iodide.

**2. Steric Factors.** Steric effects on silicon have been well documented and exploited.[31] Indeed, the size of various silicon substituents has been used to control the reactivity of a neighboring group and the rate of nucleophilic substitution at the silicon. Shimizu[32] has developed a steric factor ($E_s^{Si}$) for silicon that allows the rate of reaction to be plotted against steric bulk in nucleophilic substitution. A good correlation is observed for the solvolysis of triorganochlorosilanes. As the steric bulk around the silicon atom increases, the reaction rate decreases because substitution involves an increase in the coordination number of the silicon atom.

**A. TBAF Activation.** The results of silanol cross-coupling obtained under TBAF activation, where steric factors were tested, showed decreasing reaction rates in the following order: Me$_2$Si ≈ Ph$_2$Si > Et$_2$Si > $i$-Pr$_2$Si ≫ $t$-Bu$_2$Si. The higher reactivity obtained with (1-heptenyl)methyltrifluoropropyl silanol (**7**) compared to the dimethylsilanol **1** excludes a purely steric contribution since the diethyl- (**2**) and the dimethylsilanol **1** exhibit a close reactivity *favoring* **1**. The order of reactivity follows the expected steric contribution;[32] however, the relative efficiencies are surprisingly low. Only di-*tert*-butyl-substituted silanol **5** was found to be significantly less reactive than the dimethylsilanol **1**. This suggests that steric factors are not a major contributor to the rate-determining step, a conclusion that is consistent with transmetalation as the turnover-limiting event but not consistent with σ bond metathesis as the mechanism of transmetalation. Even though the equatorial bond angles in pentacoordinate siliconate complexes[33] increase to 120°, the approach of an arylpalladium halide to the silicon center as

(28) Stammel, C.; Frohlich, R.; Wolff, C.; Wenck, H.; de Meijere, A.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 1709−1718.

(29) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**. *113*, 7075−7076. (b) A similar four-center process is believed to be operative in the Stille reaction: Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978−8993.

(30) For a discussion of Pd−O−Si bonds, see: Fukuoka, A.; Sato, A.; Kodama, K.-Y.; Hirano, M.; Komiya, S. *Inorg. Chim. Acta* **1999**, *294*, 266−274.

(31) For a review of steric effects at silicon, see: Hwu, R. J.-R.; Tsay, S.-C.; Cheng, B.-L. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, Part 1, Chapter 8, p 431.

(32) (a) Shimizu, N.; Takesue, N.; Yamamoto, A.; Tsutsumi, T.; Yasuhara, S.; Tsuno, Y. *Chem. Lett.* **1992**, 1263−1266. (b) Shimizu, N.; Takesue, N.; Yasuhara, S.; Inazu, T. *Chem. Lett.* **1993**, 1807−1810.

(33) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448.

depicted in Figure 3 should be more strongly influenced by the size of the R groups. The steric insensitivity of the reactions points to a transmetalation mechanism that may not bring the arylpalladium halide close to the silyl group. Only in the case of the di-*tert*-butyl-substituted silanol **5** does the steric hindrance become so extreme that activation by fluoride is disfavored. The lack of reactivity could also arise from the inability to form a disiloxane. Less sterically demanding dimethylsilanol and diisopropylsilanol were found to readily form disiloxanes.[7a]

The interesting observation that the relative reactivity of **1** and **4** or **6** showed a slight dependence on the fluoride stoichiometry is consistent with the mechanistic picture presented in Figure 3.[7] Our studies showed that the rate of cross-coupling of a dimethylsilanol shows a different dependence on fluoride concentration than a diisopropylsilanol. The dimethylsilanol shows two regimes, first order up to 2.0 equiv of TBAF then changes to inverse first order at higher loadings. The diisopropylsilanol showed inverse order dependence throughout. The increase in the relative amount of product arising from **1** as the loading of TBAF increases (Table 2, entries 7−10) is consistent with an early first-order dependence superimposed on an inverse order for **4**. A similar trend for **1** vs **6** (entries 11−14) can be interpreted this way as well, but we do not know the TBAF dependence for the diphenylsilanol **6**.

**B. TMSOK Activation.** In striking contrast to the lack of a steric effect under TBAF activation, the cross-coupling reactions promoted by TMSOK showed a dramatic steric effect on rate. As was already demonstrated in our kinetic studies, the mechanism differs from that involving TBAF. We found that at low loadings of $K^+\mathbf{1}^-$ or $K^+\mathbf{4}^-$ with respect to palladium, the reaction showed first-order dependence on silanolate, whereas at higher loadings (>20/1) the reaction order in silanolate changed to zero. Control experiments showed that the first-order regime represents a rate-limiting irreversible displacement of halide on palladium by the silanolate, whereas the zero-order region represents rate-limiting transmetalation from the intermediate **J** under saturation conditions. Steric effects will obviously manifest their influences during the addition of the silanoate to the palladium, potentially as well in the transmetalation. Thus, in both mechanistic regimes, the steric contribution of silicon substituents is anticipated to be large under TMSOK activation because of the nature and proximity of events that take place at the silicon atom.

**3. Electronic Factors.** Although the origin of the effect is unknown, the presence of one fluoro, ethoxy, or hydroxy substituent dramatically increases the reactivity of the silicon-bearing nucleophile compared to an alkyl subsistent. It was therefore expected that electronic factors could be of considerable influence on the relative efficiency of coupling.

**A. TBAF Activation.** The competition experiments run in the presence of TBAF revealed the following integrated reactivity order $(Me)CF_3CH_2CH_2SiOH \geq Me_2SiOH \geq Me_2SiOEt \geq MeSi(OEt)_2 > Si(OEt)_3$. The higher reactivity obtained with the methyltrifluoropropylsilanol (**7**) compared to the dimethylsilanol is in agreement with an electronic factor. Trifluoropropyl, as a weakly electron-withdrawing group, is better able to support the additional charge on the siliconate complex. The fact that the trifluoropropyl group is two carbon removed from the silicon should however explain it low contribution.

For the ethoxy series, the order is reversed from what might be expected based on the foregoing electronic argument. Several

hypotheses can be proposed to account for this order of reactivity. Hiyama has suggested that the formation of the hexacoordinate intermediate **M** shown in Figure 4 could explain the lower reactivity of tris-heteroatom-substituted silane.[3] Because these compounds are coordinatively saturated and hindered, they cannot attain the four-center transition structures required for the transmetalation (Figure 3, **F**).
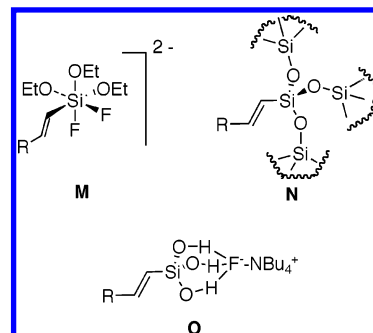


**FIGURE 4.** Hypothetical intermediates from polyalkoxysilanes in the presence of TBAF.

We propose that other arguments should also be considered. Because the fluoride source used (TBAF·3H$_2$O) contains three water molecules per fluoride, the silyl ethers can be hydrolyzed to silanols, subsequently leading to polysiloxanes. In the case of triethoxy- and to lesser extent diethoxysilanes, the hydrolysis of the ether can lead to polymeric network (**N**, Figure 4). Accessibility of the alkenyl group in the polymeric matrix or its solubility could become an issue. A third hypothesis focuses on the nature of fluoride solvation by silanols. The mechanism outlined in Figure 3 identifies an preequilibrium, preceding the transmetalation, in which a species (**B**) containing an SiOH−F bond is present in an unproductive "resting state". In a similar manner it is conceivable that a silanediol or -triol can give an analogous resting state (**O**, Figure 4), which would be even more stable.

**B. TMSOK Activation.** As before, reactions under silanolate activation gave completely different results from those using TBAF. The reactivity order follows: $Ph_2SiOH > (Me)CF_3CH_2$-$CH_2SiOH > MeSi(OEt)_2 \geq Me_2SiOH \approx Si(OEt)_3 \approx (Me)_2SiOEt$. The number of heteroatoms about the silicon had no effect on the efficiency of coupling. Although interesting in view of the expected difference in reactivity among the various alkoxysilanes, it is difficult to explain the lack of an effect. One can speculate about the possibility of offsetting steric and electronic influences, or the operation of yet an alternative mechanism. Given the similarity of efficiencies for **1** and **9** under these conditions, it is reasonable to assume that the silyl ethers react via a mechanism akin to either of those in Figure 3 through TMSOK cleavage of the ethers. Accordingly the similarity of ratios may reflect the insensitivity of the transmetalation to the nature of the groups around the silicon atom in species **J**.

Beneficial effects on efficiency are observed when diphenyl or trifluoropropyl groups are introduced. The result can be explained in terms of an increase in the acidity of the silanol, Scheme 10. Substituents such as phenyl, methoxy, fluoro and chloro enhance the acidity of silanols.[34] Therefore, the rates differences could reflect an increased concentration of the deprotonated conjugate base necessary to form the key intermediate **J**, Figure 3.

**SCHEME 10**
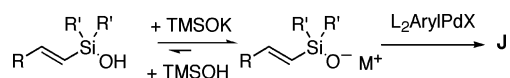


The results of varying the silanolate stoichiometry in Table 5 provide strong support for this interpretation. The enhanced efficiency of coupling of **6** compared to **1** with only 1.0 equiv of TMSOK likely represents the higher equilibrium concentration of K$^+$**6**$^-$ given the greater acidity of **6**.[34b] However, this advantage disappears in the intrinsic nucleophilicities of K$^+$**1**$^-$ and K$^+$**6**$^-$ become important with superstoichiometric amounts of TMSOK wherein the silanols are more fully deprotonated.

## Conclusion

Through systematic examination of the steric and the electronic effects on the efficiencies of the cross-coupling reaction, we have established a qualitative scale of reactivity that was found to be highly dependent on the method of activation. The integrated reactivity order for fluoride activation is (Me)CF$_3$CH$_2$CH$_2$SiOH ≥ Me$_2$SiOEt ≈ Me$_2$SiOH ≥ Ph$_2$SiOH ≥ Et$_2$SiOH > MeSi(OEt)$_2$ > *i*-Pr$_2$SiOH > Si(OEt)$_3$ ≫ *t*-Bu$_2$-SiOH following **7/9/1/6/3/10/4/11/5** = 1.24/1.02/1.00/0.92/0.89/0.78/0.65/0.27/0.025. The integrated order for silanoate activation is Ph$_2$SiOH > (Me)CF$_3$CH$_2$CH$_2$SiOH > MeSi(OEt)$_2$ ≥ Me$_2$SiOH ≈ Si(OEt)$_3$ ≈ Me$_2$SiOEt ≫ *i*-Pr$_2$ following **6/7/10/1/11/9/4** = 3.85/1.86/1.21/1.00/0.94/0.93/0.04. This study reveals that a dimethylsilanol and a diisopropylsilanol are comparable precursors for alkenyl transfer under fluoride activation where as a dimethylsilanol is a more efficient precursor than a diisopropylsilanol for alkenyl transfer under silanolate activation. Analysis of the reactivity trends provided additional support into the operation of different mechanistic pathways for the different modes of activation.

From a preparative point of view, barring incompatibilities with fluoride ion, reactions with this activator tend to be faster and less sensitive to structural and electronic features of the reactants. However, recent advances that employ preformed metal silanolates stoichiometrically[18] have made the nonfluoride coupling reactions the method of first choice.

## Experimental Section

**General Experimental Procedures.** See the Supporting Information.

**(*E*,*E*)-4,4′-(1,4-Phenylenediethendiyl)bisbenzonitrile (23).**[28] Bis-silane **22** (390 mg, 1.0 mmol), 4-iodobenzonitrile (458 mg, 2.0 mmol, 2.0 equiv), and (allylPdCl)$_2$ (9.3 mg. 0.025 mmol, 0.025 equiv) were dissolved in a solution of TBAF (4.0 mL, 1.0 mmol, 1 M in THF, 4 equiv). The reaction mixture was stirred for 6 h at room temperature. The solution was quenched with water (20 mL) and extracted with EtOAc (5 × 20 mL), and the combined organic phases were washed with brine (20 mL). The organic layer was dried with MgSO$_4$ (anhydrous) and filtered. The solvent was then evaporated in vacuo to give a solid which was purified by column chromatography (silica gel, CH$_2$Cl$_2$/hexane, 2/1) to afford 262 mg (79%) of **23** as yellow solid. Data for **23**: mp 288 °C; $^1$H NMR (500 MHz, CDCl$_3$) 7.65 (d, *J* = 8.4, 4 H, HC(4)), 7.60 (d, *J* = 8.4, 4 H, HC(3)), 7.56 (s, 4 H, HC(9)), 7.21 (d, *J* = 16.3, 2 H, HC(6)), 7.13 (d, *J* = 16.3, 2 H, HC(7)); $^{13}$C NMR (126 MHz, CDCl3) 141.8 (C(5)), 136.8 (C(8)), 132.7 (C(3)), 131.9 (C(6)), 127.6 (C(4)), 127.4 (C(7)), 127.1 (C(9)), 119.2 (C(1)), 110.9 (C(2)); TLC $R_f$ 0.26 (CH$_2$Cl$_2$/hexane, 2/1) [UV + KMnO$_4$].

**4-[2-[4-[2-(2-Methylphenyl)ethenyl]phenyl]ethenyl]-benzonitrile (24).** A solution of bis-silane **22** (390 mg, 1.0 mmol), 4-iodobenzonitrile (229 mg, 1.0 mmol, 1.0 equiv), and (allylPdCl)$_2$ (9.3 mg, 0.025 mmol, 0.025 equiv) in DME (4 mL) was stirred at room temperature for 5 min, and then TMSOK (512 mg, 4.0 mmol, 4.0 equiv) was added. The reaction mixture was stirred at room temperature for 6 h, whereupon EtOAc (20 mL) was added and the reaction was stirred for 10 min further. The reaction mixture was then filtered through a short silica gel column (20 g), the plug was washed with EtOAc (100 mL), and the solvent was evaporated in vacuo. To the crude product were added 2-iodotoluene (128 μL, 1.0 mmol, 1.0 equiv), (allylPdCl)$_2$ (9.3 mg. 0.025 mmol, 0.025), and a solution of TBAF (3.0 mL, 1 M in THF, 3.0 mmol, 3.0 equiv). The reaction mixture was stirred for 4 h at room temperature, and then EtOAc (25 mL) was added. After being stirred 10 min further, the reaction was quenched with water (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried over MgSO$_4$ (anhydrous) and filtered. After evaporation of the solvent, the residue was purified by column chromatography (silica gel, hexane/CH$_2$Cl$_2$, 2/1) and sublimed to afford 244 mg (76%) of **24** as a yellow solid. Data for **24**: mp 294 °C (subl); $^1$H NMR (500 MHz, CDCl$_3$) 7.64 (d, *J* = 8.5, 2 H, HC-(4)), 7.60 (m, 3 H, HC(3) and HC(15)), 7.54 (s, 4 H, HC(9) and HC(10)), 7.38 (d, *J* = 16.4, 1 H, HC(13)), 7.21 (m, 4 H, HC(6), HC(16), HC(17), and HC(18)), 7.11 (d, *J* = 16.3, 1 H, HC(7)), 7.01 (d, *J* = 16.1, 1 H, HC(12)), 2.45 (s, 3 H, HC20)); $^{13}$C NMR (126 MHz, CDCl3) 142.1 (C(5)), 138.3 (C(14)), 136.4 (C(8)), 136.1 (C(11)), 135.8 (C(19)), 132.7 (C(3)), 132.2 (C(6)), 130.7 (C(18)), 129.5 (C(17)), 127.9 (C(15)), 127.5 (C(4)), 127.3 (C(7)), 127.2 (C(9)), 127.0 (C(10)), 126.7 (C(16)), 126.5 (C(12)), 125.5 (C(13)), 119.3 (C(1)), 110.7 (C(2)), 20.1 (C(20)); IR (CHCl$_3$) 3021 (m), 2227 (s), 1600 (s), 1514 (w), 1460 (w), 1214 (w), 1174 (w), 964 (s); MS (EI, 70 eV) 321 (M$^+$, 100), 203 (13), 157 (16); TLC $R_f$ 0.21 (hexane/CH$_2$Cl$_2$, 2/1) [UV + KMnO$_4$]; GC $t_R$ 31.24 min (100%) (HP5, injector 225 °C, column 275 °C, 15 psi); HRMS calcd for C$_{24}$H$_{19}$N$_1$ 331.1518, found 321.1517.

**Supporting Information Available:** Full experimental details for the preparation and characterization of all substrates and products. Determination of response factors and raw GC data for all competition experiments is also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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