

# Design and Implementation of New, Silicon-Based, Cross-Coupling Reactions: Importance of Silicon–Oxygen Bonds

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## ABSTRACT

This Account chronicles the conceptual development, proof of principle, exploration of scope, and mechanistic investigations of a newly developed class of palladium-catalyzed cross-coupling reactions of silicon derivatives. Under the influence of fluoride activation a myriad of oxygen-containing silicon moieties undergo mild and stereospecific cross-coupling. The diversity of methods for introduction of silicon groupings into organic molecules and the range of organic electrophiles that can be used are outlined.

*“...The paths of research rarely lead in straightforward fashion from starting point to desired goal....Although intention predisposes the route, chance or occurrences along the way often enforce a change of course....Along the way, we come upon various points of interest which invite us to linger a while.”* — Georg Wittig (1979)<sup>1</sup>

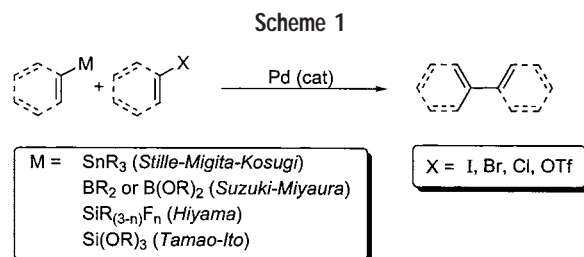
## Introduction

The preeminence of palladium-catalyzed, cross-coupling reactions among methods of carbon–carbon bond formation arises from the highly successful development of the Stille–Miyata–Kosugi reaction of organostannanes<sup>2</sup> and the Suzuki–Miyaura reaction of organoboranes (Scheme 1).<sup>3</sup> Both employ organometals that can be synthesized by several methods and are nonreactive in the absence of a catalyst. These characteristics are conducive to application in complex molecule synthesis wherein controlled bond construction and functional group compatibility are vital. However, certain drawbacks to these methods, including the toxicity and high molecular weight associated with tin and the limited stability and coupling

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efficiency of organoboranes, constitute important limitations. The pioneering work of Hiyama has demonstrated that organosilanes, when suitably functionalized and in the presence of a nucleophilic activator, can undergo similar cross-coupling reactions with palladium catalysis.<sup>4</sup> This discovery stimulated wide ranging investigations which revealed the utility of chloro- and fluorosilanes<sup>5</sup> and alkoxy-silanes<sup>6</sup> as versatile cross-coupling partners with a variety of electrophiles.



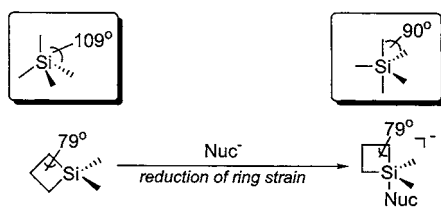
A common limitation of the aforementioned silicon-based coupling reactions is the harsh conditions (high temperatures and long reaction times) that are usually necessary. Because of the small electronegativity difference between silicon and carbon, the nucleophilic component in these reactions is relatively weak. Thus, under the reasonable assumption that transmetalation is the rate-determining step in these cross-couplings, our efforts focused on the design of a new silicon subunit with enhanced reactivity. In addition, the ideal silicon moiety would also embody characteristics that would make it superior to other organoelement-based donors; e.g., it should be (1) low molecular weight, (2) easily synthesized, (3) stable toward many reaction conditions, (4) readily activated, and (5) converted to harmless byproducts.

In view of Hiyama's findings that generation of a pentacoordinated silicon was a prerequisite to successful cross-coupling (assisted through his use of fluorosilanes), the initial proposal was to devise a more reactive organosilicon cross-coupling system by employing siletanes (silacyclobutanes) as the nucleophilic coupling partner. Previous work in these laboratories with siletanes in the aldol addition reaction illustrated their enhanced Lewis acidity compared to simple trialkylsilanes.<sup>7</sup> This property is a manifestation of “strain release Lewis acidity” which has its origins in the difference in coordination geometry between four-coordinate (tetrahedral) and five-coordinate (trigonal bipyramidal) silicon species (Scheme 2). Thus, the angle strain in a four-coordinate siletane (79° vs 109°) is partially relieved upon binding a fifth ligand to produce a trigonal bipyramidal species (79° vs 90°) in which the siletane bridges an apical and a basal position.<sup>8</sup> Thus, the propensity of the silane toward activation as the siliconate complex is enhanced and should facilitate transmetalation.

Thus, on this conceptual framework was launched a program to invent a new type of cross-coupling process.

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Scheme 2

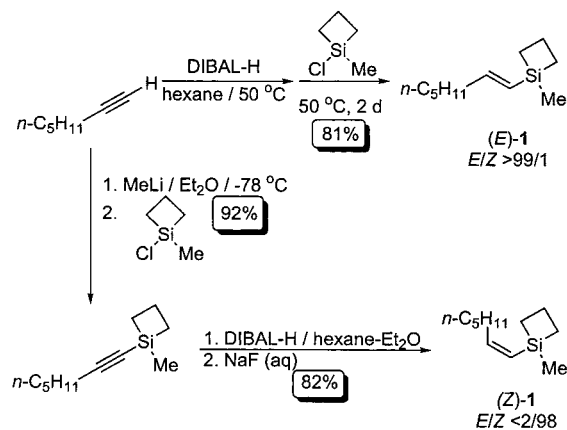


However, as is so often the case in scientific research, the outcome, albeit successful, was not what we anticipated but rather illuminated a detour which has led to a much richer and more interesting enterprise. This Account will chronicle the pathway from hypothesis to proof of principle to mechanistic investigations that ultimately led to new hypotheses and, most importantly, better synthetic methods.

## Siletane Cross-Coupling

**Alkenyl Siletanes.** The ease of synthesis of alkenyl siletanes allowed for the initial hypothesis to be readily tested. Silacyclobutanes (*E*-1 and (*Z*)-1 were synthesized in geometrically pure form in one or two steps from commercially available precursors (Scheme 3). Siletanes are easy to handle as they are air stable and can be purified by simple distillation.

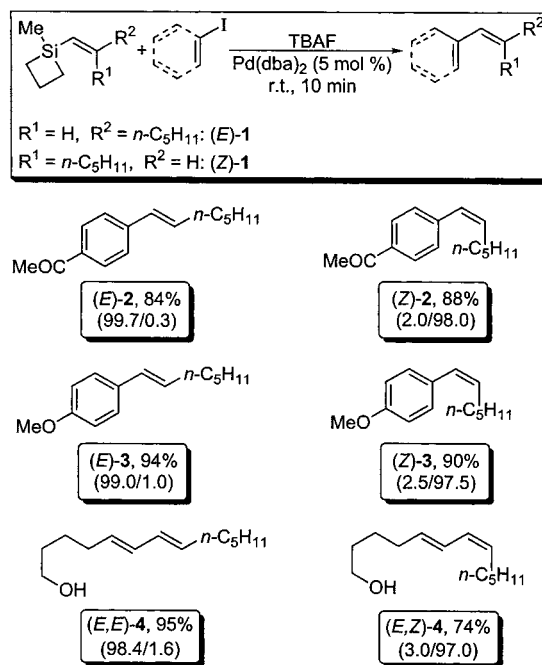
Scheme 3



To our delight, these substrates underwent cross-coupling reactions with aryl halides when promoted by an activator in the presence of a palladium catalyst (Scheme 4). Initial optimizations quickly maximized their efficiency. The use of TBAF as a nucleophilic activator was most effective, while other fluoride activators (TASF, TBAT, and KF) were incapable of promoting the reaction. A survey of catalysts revealed the “ligandless” palladium(0) as Pd(dba)<sub>2</sub> or Pd<sub>2</sub>(dba)<sub>3</sub> to be superior to other palladium sources. The reactions were remarkable for the extremely mild conditions (ca. 10 min at ambient temperature) of the TBAF promoted coupling of alkenyl siletanes (*E*-1 and (*Z*)-1 to a variety of alkenyl and aryl iodides.<sup>9</sup> This high reactivity was not affected by the electronic environment at the aryl iodides. In addition, the high stereospecificity with respect to the olefin geometry in the coupling is

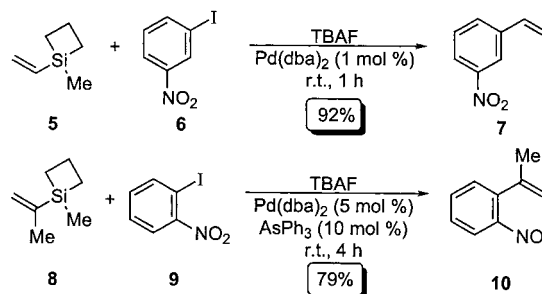
notable (greater than 98% in most cases). Even in coupling to alkenyl iodides to form (*E*)-4 and (*Z*)-4, the olefin geometry of both coupling partners is highly conserved.

Scheme 4



**Vinyl and Propenyl Siletanes.** The demonstration that alkenyl siletanes are competent coupling partners led to the extension of transferable groups to simple vinyl and propenyl moieties (Scheme 5).<sup>10</sup> In certain cases where the reaction times were longer, the use of triphenylarsine was found to prevent precipitation of the catalyst. The electrophile substrate generality was found to reflect that of the alkenylations in Scheme 4.

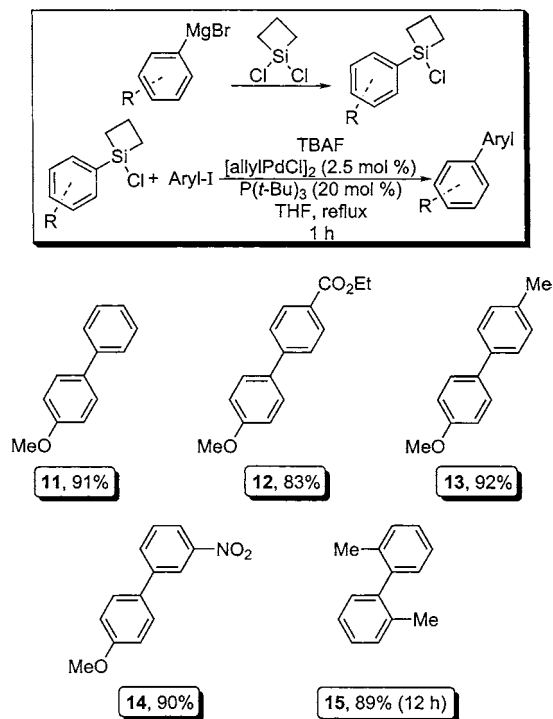
Scheme 5



**Aryl Siletanes.** The biaryl subunit is a commonly found motif in biologically active molecules as well as in novel materials such as organic semiconductors and liquid crystals.<sup>11</sup> Therefore, biaryl formation, particularly of unsymmetrical biaryls, remains an active area of organic synthesis.<sup>12</sup> Accordingly, mild biaryl coupling was also investigated using the siletane moiety (Scheme 6). It was found, however, that heteroatom substitution on the silicon atom of the siletane was necessary to enhance the polarity and thus reactivity of the sp<sup>2</sup> carbon–silicon bond. The starting siletanes are easily synthesized from aryl Grignard reagents and 1,1-dichlorosiletane. Unlike the

coupling with alkenyl siletanes, the biaryl couplings were slow at room temperature, and therefore, the reactions were run in THF at reflux. Addition of tri-*tert*-butylphosphine was necessary to suppress competing homo-coupling of the aryl iodide. Most of the biaryl couplings were complete within 1 h, independent of the electronic nature of the iodides. Steric factors reduced the rate of coupling, but even 2,2'-dimethylbiphenyl (**15**) was readily prepared by this method.

Scheme 6



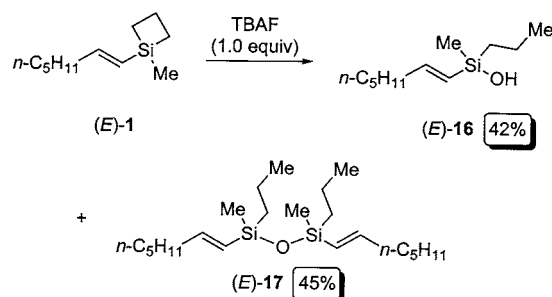
## Mechanistic Insights into the Reactive Intermediate

The unexpectedly high rate, selectivity, and generality of these coupling reactions were pleasing yet mystifying. Whether this enhanced reactivity was truly due to the "strain release Lewis acidity" of the siletane moiety was a subject of great curiosity and led to a search for the reactive silane intermediate in the reaction.

An early experimental observation of significant heat generation when combining the siletane with the TBAF solution was an important clue. Elucidating the origin of this exotherm was the first objective which was addressed by identifying the nature silicon species that resulted when (*E*)-**1** was mixed with TBAF (Scheme 7).<sup>13</sup> Two compounds were isolated following silica gel chromatography: the silanol (*E*)-**16** and disiloxane (*E*)-**17**. These products were clearly derived from ring opening of (*E*)-**1** by the combined action of TBAF and water (from the crystal hydrates in commercial TBAF·3H<sub>2</sub>O).

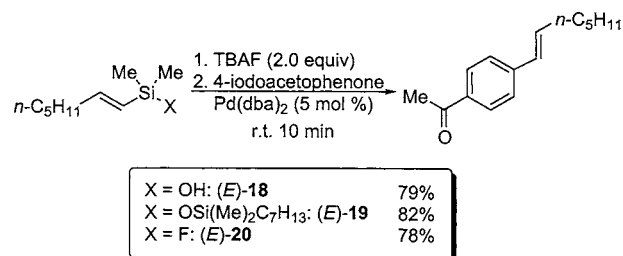
The destruction of the siletane ring upon exposure to TBAF clearly dismantled our original formulation of the process and compelled a thorough reevaluation of our mechanistic hypotheses. The primary question now became whether the silanol **16**, disiloxane **17**, or even a

Scheme 7



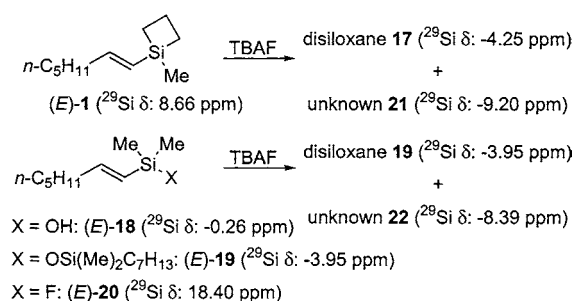
related fluorosilane was the actual species responsible for the cross-coupling. This question was addressed by independent synthesis of **18**–**20**, the dimethyl analogues of the three most likely candidates for that putative reactive intermediate. Strikingly, all three were shown to be competent coupling partners with 4-iodoacetophenone giving comparable yields after 10 min (Scheme 8).

Scheme 8



The similarity of reaction rates and yields could be explained by either interconversion of these species to one another or conversion of each of them to a more advanced, common reactive intermediate. Interestingly, <sup>1</sup>H NMR analysis of a mixture of TBAF with either siletane **1**, silanol **18**, disiloxane **19**, or fluorosilane **20** showed only two species which were formed almost immediately. One was identified as the disiloxane of the corresponding silanol, and the other species as a mysterious compound **21** (or **22**) containing both silicon and fluorine as confirmed by <sup>29</sup>Si and <sup>19</sup>F NMR (Scheme 9). Moreover, the ratio of **21** (**22**) to disiloxane increased with TBAF stoichiometry; under typical conditions for cross-coupling the ratio is heavily in favor of **21** (**22**).

Scheme 9



The identity of unknowns **21** and **22** proved quite difficult to establish. All attempts to isolate this material provided only the silanols **16** or **18**. The sign and magni-

tude of the  $^{29}\text{Si}$  NMR chemical shift was indicative of tetracoordinate silicon species, yet it did not match any of the previously synthesized tetracoordinate silanes. The possibility that **21** and **22** could be oligomers was considered, but this possibility was ultimately eliminated by a novel  $^{29}\text{Si}$  NMR crossover experiment.<sup>12</sup> What structural possibilities remained for **21** and **22** if they are indeed monomeric and tetracoordinate? We considered two proposals, the tetrabutylammonium silyloxy salt (*E*)-**23** and a TBAF hydrogen bond complex (*E*)-**24** (Figure 1). The silyloxy salt could be immediately ruled out by independent synthesis of the corresponding *tetramethylammonium* salt, whose  $^{29}\text{Si}$  NMR chemical shift ( $-26.23$  ppm) did not correspond to that for **22**. Because compound (*E*)-**24** contains a hydrogen-bonded fluorine atom,  $^{19}\text{F}$  NMR analysis of a sample generated from (*E*)-**18** and TBAF should indicate the presence of a fluorine at a resonance different from that of TBAF. At room temperature, the spectrum displayed only a single resonance at  $-117.7$  ppm. Cooling the solution to  $-95$  °C, however, allowed the observation of two signals, one at  $-113.2$  ppm for TBAF and one at  $-150.8$  ppm which is very close to the chemical shift for bifluoride ( $\text{FHF}^-$ ) at  $-148$  ppm.<sup>14</sup>

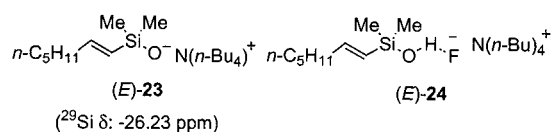


FIGURE 1. Tetrabutylammonium silyloxy salt (*E*)-**23** and the TBAF–silanol hydrogen-bonded complex (*E*)-**24**.

Although indirect, all of the available data are consistent with structure (*E*)-**24** (a hydrogen-bonded complex between an organosilanol and TBAF) as the fit best for the mystery reaction component. Subsequent kinetic analysis has revealed that even this species is not the ultimate reactive intermediate but that it is a low-energy resting state along the reaction pathway. Second-order dependence on silanol concentration suggests that this compound dimerizes prior to transfer of the alkenyl group to palladium.<sup>15</sup>

These mechanistic studies were extremely valuable because although they disproved the rationale for the ability of siletanes to couple so mildly, they uncovered an important structural clue that might underlie the special ability of these silicon derivatives to undergo such mild cross-coupling, namely the presence of an oxygen atom on the silyl moiety. Thus, on the basis these findings, a new program was initiated to probe the ability of alkenyl silanols, di- and polysiloxanes, and silyl ethers to participate in cross-coupling reactions (Figure 2).<sup>16,17</sup>

## Organosilanol Cross-Coupling

**Alkenyl Silanols.** The first studies to expand the scope of silicon cross-coupling encompassed alkenyl silanols (*E*)-**18** and (*Z*)-**18**, which were analogous to the products of the TBAF·3H<sub>2</sub>O-promoted ring opening of the previously employed siletanes.<sup>18</sup> The silanols immediately presented a number of advantages compared to the siletanes: (1)

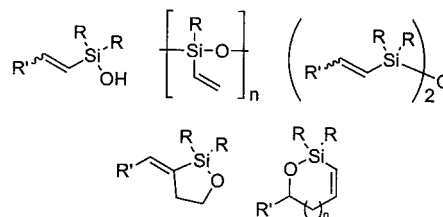
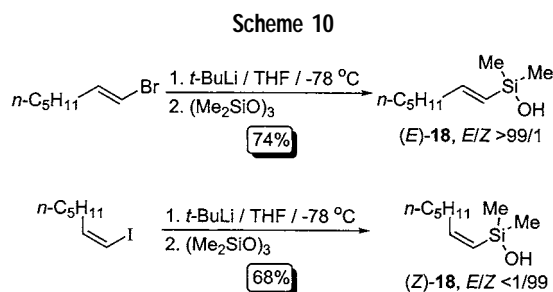
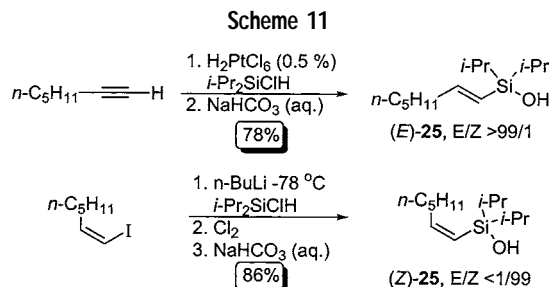


FIGURE 2. New organosilicon precursors for cross-coupling reactions.

the diversity of methods available to install the silanol group in geometrically defined form; (2) their stability and ease of handling; (3) the capability to modify the spectator group on the silicon to modulate reactivity and/or suppress side reactions. The heptenylsilanols (*E*)-**18** and (*Z*)-**18** were synthesized from established procedures as outlined in Scheme 10.<sup>19</sup> In both cases, reaction of the appropriate alkenyllithium agent with hexamethylcyclotrisiloxane ( $\text{D}_3$ ) produces the desired dimethylsilanol in good yield and high geometrical purity.



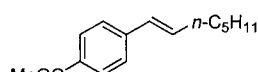
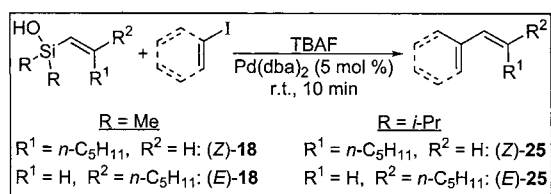
The preparation of 1-heptenyldiisopropylsilanols (*E*)-**25** and (*Z*)-**25** illustrated two other methods for synthesis of silanols both of which employ chlorodiisopropylsilane (Scheme 11). In the former case, the silicon group was installed by platinum-catalyzed hydrosilylation of 1-heptyne with followed by alkaline hydrolysis. In the latter case, chlorodiisopropylsilane serves as an electrophile in reaction with the lithioalkene to afford the intermediate (1-heptenyldiisopropylsilane in 95% yield. This, in turn, was converted to the (*Z*)-**25** by chlorination and mild hydrolysis.



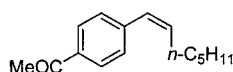
With these silanols in hand, their cross-coupling with a series of aryl and alkenyl iodides was conducted (Scheme 12).<sup>20</sup> It is notable that the reactions of (*E*)- and (*Z*)-**18** were just as rapid and high yielding as those previously reported for siletanes. Both electron-rich and electron-poor aryl iodides coupled with equal facility. The slightly lower stereospecificities compared to those for the

siletanes were remedied in the cross-coupling of the isopropylsilanols (*E*)-**25** and (*Z*)-**25**, which displayed higher stereospecificity and similar reaction times.<sup>21</sup> The effect of the spectator alkyl group was also evident in alkenyl-alkenyl couplings. The cross-coupling of (*E*)-**18** with (*E*)-6-iodo-5-hexenol gave product (*E,E*)-**4** in good yield but accompanied by a small amount of cine rearrangement product. The use of (*E*)-**25** gave better selectivities for the (*E,E*) product and significantly reduced the amount of cine rearrangement.<sup>22</sup>

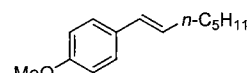
Scheme 12



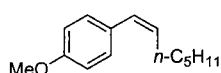
R = Me: 93%, (96.5/3.5)  
R = *i*-Pr: 80%, (99.5/0.5)



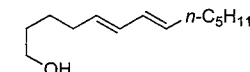
R = Me: 92%, (4.8/95.2)  
R = *i*-Pr: 86%, (1.0/99.0)



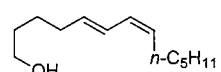
R = Me: 95%, (97.2/2.8)



R = Me: 94%, (2.6/97.4)



R = Me: 91%, (95.8/4.2)  
R = *i*-Pr: 87%, (97.8/2.2)



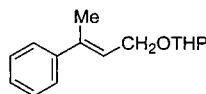
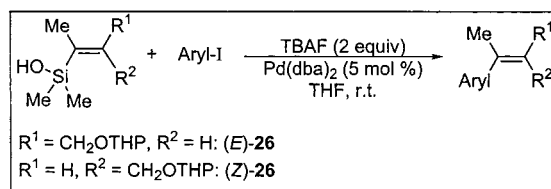
R = Me: 72%, (4.6/95.4)

Prompted by the success obtained with organosilanols, we sought to extend these couplings to prepare more highly substituted alkenes.

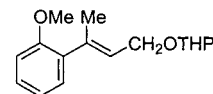
**Highly Substituted Alkenyl Silanols.** Trisubstituted alkenyl silanols have been prepared in geometrically defined form and subjected to the same cross-coupling reaction to gauge the effect of higher substitution on the alkene. Prior studies comparing vinyl and propenyl siletanes showed relative reactivity was variable and substrate dependent.<sup>9</sup> By analogy, we selected two silanols (*E*)-**26** and (*Z*)-**26**, to study the rate and selectivity of cross-coupling with a variety of aryl iodides (Scheme 13).<sup>23</sup>

Most of the reactions were successful using the same mild conditions as previously employed despite the rates being generally lower than previously observed with silanol (*E*)-**26** and (*Z*)-**26**. One noteworthy finding was that (*Z*)-**26** coupled at consistently lower rates compared to (*E*)-**26**. In general, these couplings tolerated several types of functional groups, and the rates were generally independent of steric and electronic factors. Overall, these reactions highlight the use of substituted alkenyl silanols to produce stereodefined trisubstituted allylic alcohols, whose syntheses are generally not trivial.

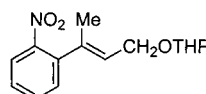
Scheme 13



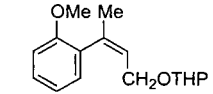
40 min, 91%



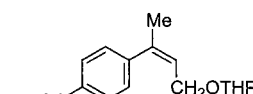
100 min, 77%



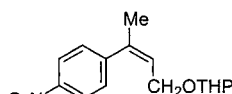
115 min, 76%



155 min, 76%



125 min, 86%

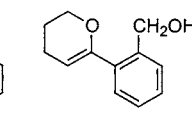
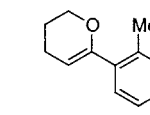
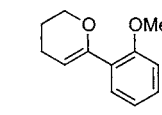
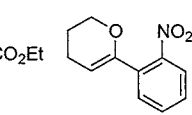
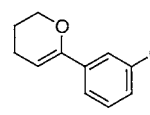
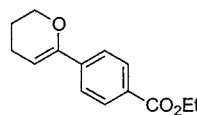
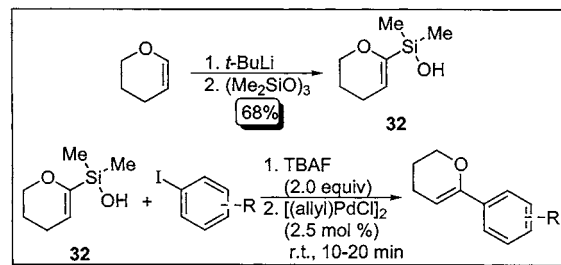


400 min, 83%

The preceding study revealed the rate-retarding effect of an  $\alpha$ -methyl substituent on the alkenyl silanol. Because we were interested in the possibility of using this reaction as a nucleophilic acylation method, we were concerned about the effect of a heteroatom substituent at the same position.

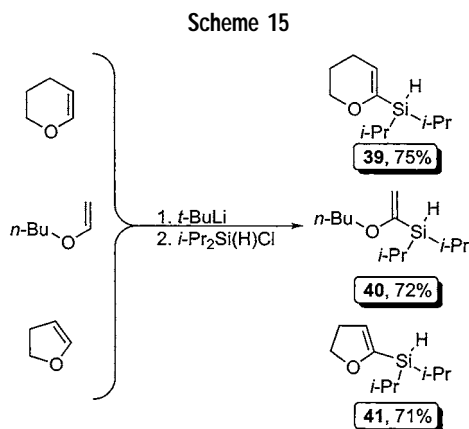
**$\alpha$ -Alkoxy-Alkenyl Silanols and Silyl Hydrides.** To investigate the effects of substituents on the coupling process we next examined silanols containing an  $\alpha$ -alkoxy group.<sup>24</sup> For example, 2-(5,6-dihydro-4*H*-pyran-2-yl)dimethylsilanol (**32**) was easily produced by lithiation of

Scheme 14

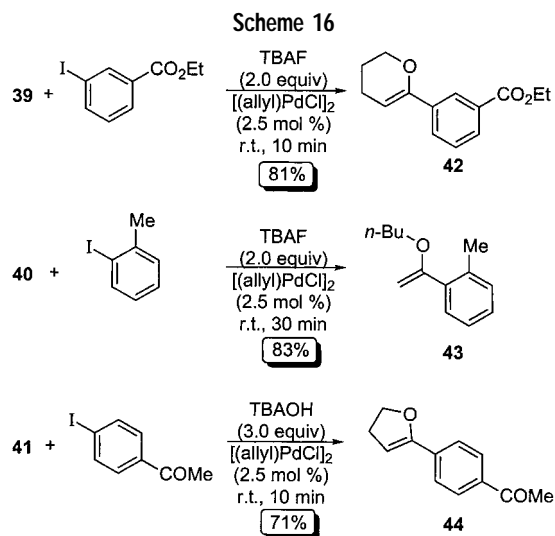


pyran followed by trapping with hexamethylcyclotrisiloxane (Scheme 14). Gratifyingly, **32** underwent cross-coupling with several aryl and alkenyl iodides with the same facility, mildness, and functional group compatibility as the silanols previously mentioned. In all these cases, however,  $[(\text{allyl})\text{PdCl}]_2$  was used as the catalyst instead of  $\text{Pd}(\text{dba})_2$ . The higher reactivity of the silicon- compared to tin-based cross-coupling was illustrated by the synthesis of **37**. This compound was made previously by a Stille coupling and required 2 h in refluxing acetonitrile to give the same final yield.<sup>25</sup>

Unlike **32**, the synthesis of other  $\alpha$ -alkoxydimethylsilanols by the same method proved more difficult than expected. For example, the lithiation/ $\text{D}_3$  trapping sequence of *n*-butyl vinyl ether and dihydrofuran did not furnish the dimethylsilanols cleanly. Making recourse to the corresponding diisopropylsilanols involved capture of the lithio anion with diisopropylsilane (Scheme 15).



Oxidation of the resulting silyl hydrides to the silanols was a daunting prospect in view of the sensitive vinyl ether functionality. To our surprise, however, silyl hydrides **39**–**41** themselves coupled quite readily (Scheme 16). Most likely, the hydrides are converted to silanols in situ by the fluoride-catalyzed “oxidative hydrolysis” which generates hydrogen from the water in TBAF.<sup>26</sup>



Unfortunately, the coupling of **41** was unsuccessful. Unlike **39** and **40**, silyl hydride **41** suffered rapid protodesilylation in the presence of the TBAF, releasing dihydrofuran. Fortunately, replacement of the TBAF solution with tetrabutylammonium hydroxide (3.0 equiv) solution in MeOH allowed the coupling reaction to proceed smoothly to yield furan **44**.

The survey of coupling reactions employing several classes of alkenyl silanols has been largely quite successful. The facile, room-temperature coupling of disubstituted, trisubstituted, and heteroatom-substituted silanols clearly illustrates the structural generality of silanols in this type of reaction. To further expand the scope of oxygenated silicon functionalities that can be used as substrates, we next turned to organo di- and polysiloxanes. Our early mechanistic work suggested that these compounds should be equivalent to silanols, and we investigated both commercially available as well as in-situ prepared specimens.

## Organosiloxane Cross-Coupling

**Commercially Available Vinylating Agents.** The early observation that disiloxanes and silanols coupled at identical rates under the same conditions (see Scheme 8) encouraged us to explore the use of several commercially available, inexpensive vinylpolysiloxanes to carry out simple vinylation of aryl and alkenyl halides.<sup>27</sup> Three classes of such siloxanes were examined, cyclooligo-disiloxanes (**45** and **46**), an orthosiliconate (**47**), and hexavinylidisiloxane (**48**), to gauge their ability to deliver each of their vinyl groups (Figure 3).

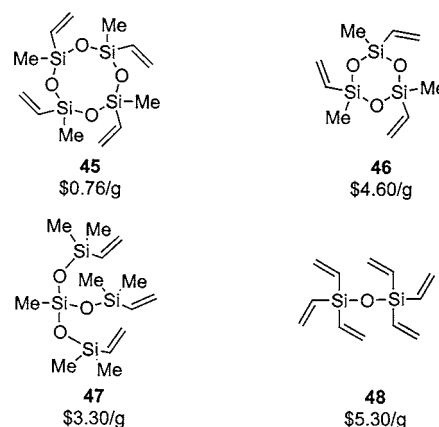
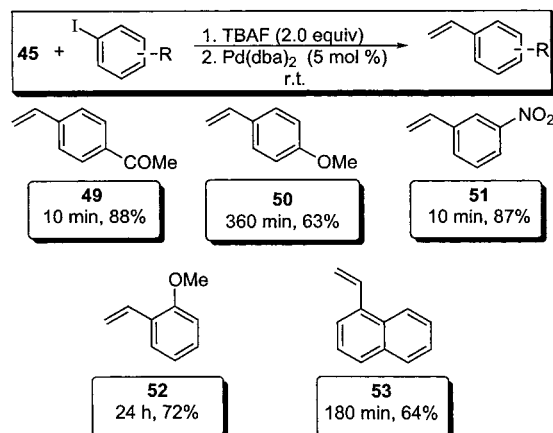


FIGURE 3. Commercially available vinylpolysiloxanes.

In optimization studies, **45**–**47** all underwent efficient cross-coupling to 4-iodoacetophenone within 10 min (using standard conditions: 2 equiv of TBAF, 5 mol %  $\text{Pd}(\text{dba})_2$ , at room temperature). Disiloxane **48**, however, did not couple as well, giving incomplete transfer of the available vinyl groups. In view of the low cost of **45**, this polysiloxane was employed in a survey of vinylation using a range of aryl and alkenyl electrophiles. The products span of range of electronically rich and poor aryl iodides (Scheme 17). Unlike previous examples with silanols, this reaction was slower with electron-rich iodides and required 3 equiv of TBAF (with **50** and **52**). In addition, steric

effects were apparent, with the reaction times significantly longer for the synthesis of **52** and **53**. Finally, vinylations of alkenyl iodides also progressed efficiently and with high stereospecificity at room temperature. The low cost combined with the high facility of these vinylations clearly demonstrate their superiority over other methods, particularly on a large scale.

Scheme 17



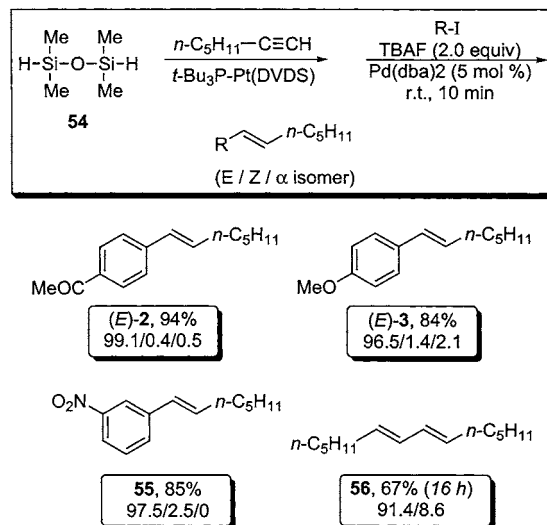
Although the preparative advantages of commercially available siloxanes were clearly demonstrated, the number of structurally diverse precursors is obviously limited. In view of the facility of these couplings, we sought to develop a general method for the custom preparation of alkenyl disiloxanes from simple starting materials to expand the scope of the alkenyl–aryl coupling process.

**One-Pot Hydrosilylation/Cross-Coupling.** To extend the realm of siloxane coupling beyond simple vinyl precursors, a facile and high-yielding approach to synthesize a variety of alkenyl siloxanes was needed. The synthesis of (*E*)-**25** from 1-heptyne via platinum-catalyzed hydrosilylation (Scheme 11) suggested a suitable approach, by substituting a readily available hydrido-disiloxane as the precursor. Furthermore, if the hydrosilylation were rapid and high yielding, then the subsequent coupling might also be conducted without the need to isolate the intermediate disiloxane. Such a “one-pot” hydrosilylation/cross-coupling protocol would provide hydroarylation products directly from alkynes.<sup>28</sup> For this plan to be successful, the hydrosilylation precursor and catalyst would have to be compatible with the coupling conditions and the regio- and stereoselectivity of the hydrosilylation would have to be extremely well controlled.

The initial survey of hydrosilylation with 1-heptyne revealed a significant sensitivity of reaction stereochemistry on the hydrosilanes and transition metal catalysts. Although the use of Speier’s catalyst (H<sub>2</sub>PtCl<sub>6</sub>) with diisopropylchlorosilane was successful for the synthesis of (*E*)-**25**, the chlorosilane was not a viable partner for the cross-coupling step. Room-temperature hydrosilylation of alkynes with hydridodisiloxanes could also be achieved using other platinum sources, particularly (*t*-Bu<sub>3</sub>P)Pt(0)(DVDS).<sup>29</sup> Tetramethyldisiloxane (**54**) was found to give complete conversion to the coupling product with the highest regio-

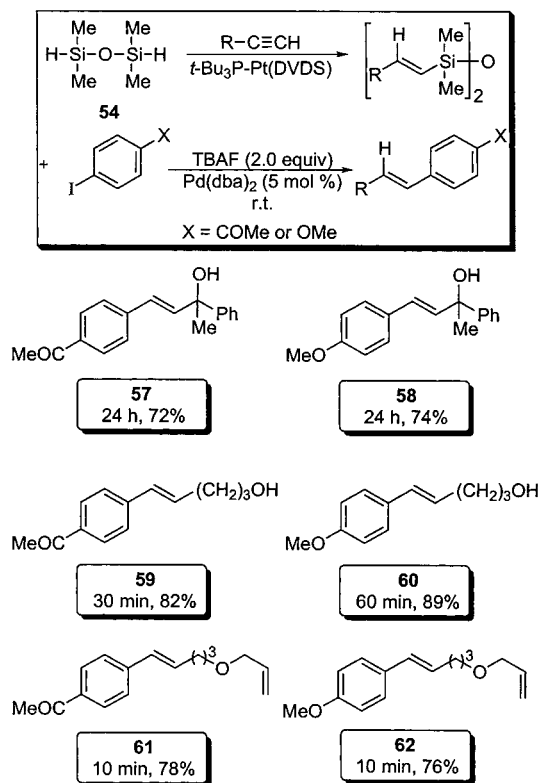
and stereoselectivity (Scheme 18).<sup>30</sup> The hydrosilylation required only 30 min at room temperature, followed by a 10 min coupling in all cases except the alkenyl–alkenyl coupling (**56**), which required a significantly longer reaction time. As little as 1 mol % loadings of palladium catalyst were also sufficient in this system.

Scheme 18



The range of alkynes which participated in this process was also surveyed, and despite highly variable reaction times, the yields and stereospecificities were exceptional (Scheme 19). The hydrosilylation of alkynes could be cleanly conducted in the presence of a free hydroxyl group (**57–60**) and even in the presence of a pendant alkene

Scheme 19



(**61**, **62**), thereby demonstrating high chemoselectivity as well. In all cases, the major stereo- and regioisomer was formed in greater than 99% purity.

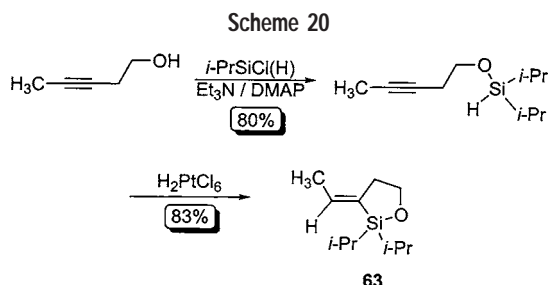
This one-pot hydrosilylation/cross-coupling procedure provides the ability to prepare styrenes starting from commercially available alkynes and silanes without isolation of intermediates. The benchmark for high efficiency, stereoselectivity, and mild conditions previously set with alkenyl silanols is again achieved in this case, even with the extra step of hydrosilylation. In addition, the ability of different siloxanes to be synthesized and coupled highlights that the scope of siloxanes in cross-coupling is similar to that for silanols.

The recognition that silanes with an oxygen substituent, either in the form of a silanol or siloxane, couple with similar ease suggested the use of simple silyl ethers in cross-coupling. This new domain introduces new avenues by which silicon can be introduced into a molecule to preordain the site of the coupling reaction.

## Silyl Ether Coupling

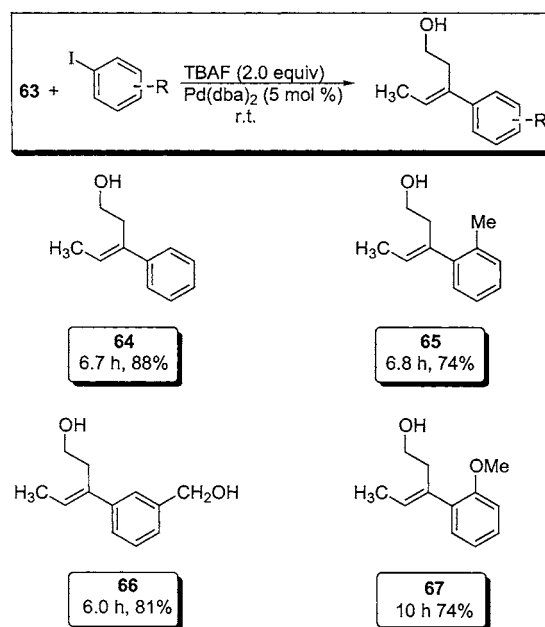
### Cyclic Silyl Ethers from Intramolecular Hydrosilylation.

Cyclic silyl ethers represented an intriguing possibility because there were several general methods for their preparation, and by virtue of the oxygen substituent, they should be similar in reactivity to siloxanes and silanols. The hydrosilylation of alkynes to form vinyl silanes as described above could be easily rendered intramolecular by attachment of the silane as, e.g., a homopropargylic silyl ether to form an oxasilacyclopentane **63** (Scheme 20).<sup>31</sup> In this structure, the double-bond geometry is defined by the stereochemical course of hydrosilylation (syn using platinum(0)) and the ether tether defines the location of the silicon while also providing the requisite heteroatom activation.



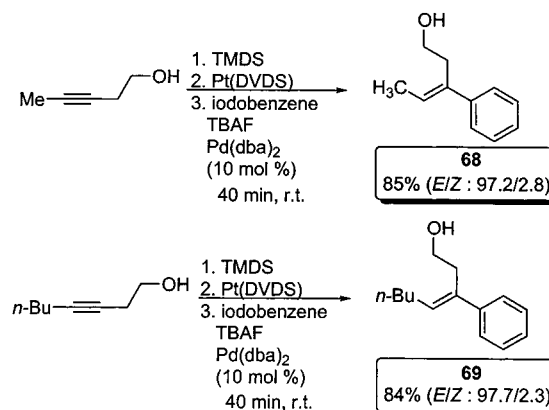
Silyl ether **63** underwent cross-coupling with a range of aryl iodides after careful optimization of reaction conditions (Scheme 21). The reaction times were generally longer than those observed with simple alkenyl silanols and siloxanes but were similar to the trisubstituted alkenyl silanols previously described. The slower rate of cross-coupling often led to formation of homocoupling products. To eliminate homocoupling of the aryl iodides, the electrophile was added portionwise to afford good yields for the desired products at room temperature. Two noteworthy features of these reactions are the absence of any significant electronic or steric effect on the rate of coupling and the high stereospecificity of the process.<sup>32</sup>

Scheme 21



The rate of cross-coupling of the corresponding dimethylsilyl silyl ethers was much greater. However, because of their sensitivity to oligomerization and hydrolysis, an in-situ preparation and coupling was developed. In this procedure, tetramethyldisilazane (TMDS) was used as the silylating agent to streamline the procedure and minimize the formation of potentially deleterious byproducts (Scheme 22). Despite the need for higher catalyst loadings (10 mol %), the hydrosilylation and coupling reactions proceeded smoothly in most cases, with excellent yield and stereospecificity.<sup>33</sup>

Scheme 22

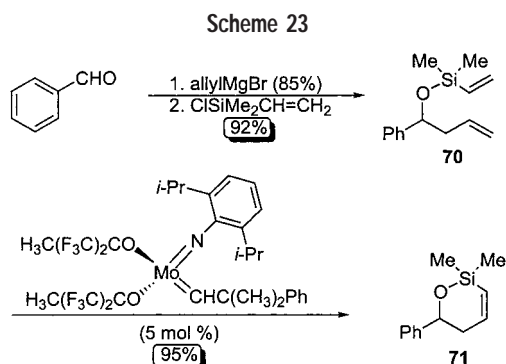


### Cyclic Silyl Ethers from Ring-Closing Metathesis.

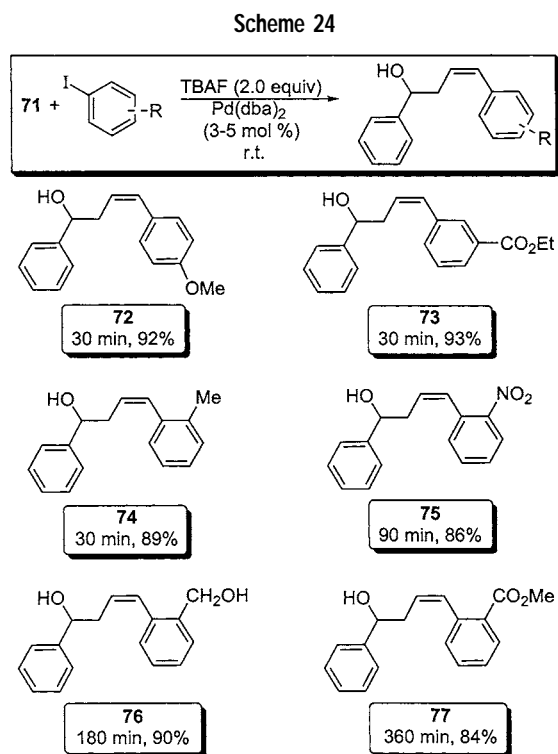
In recent years, the use of ring closing metathesis (RCM) has emerged as one of the most powerful new reactions in organic synthesis. The ease of operation and mild conditions by which carbo- and heterocyclic rings of various sizes can be accessed is a testament to its utility.<sup>34</sup> Given the number of methods to incorporate a silicon moiety into a molecule, and based on the previous success in cross-coupling with cyclic silyl ethers, the prospect of constructing cyclic unsaturated silyl ethers by the RCM approach



was very intriguing.<sup>35</sup> Thus, silyl ether **70** was prepared and tested for the ability to undergo RCM (Scheme 23). Interestingly, only the less sterically sensitive Schrock's catalyst,  $[(CF_3)_2MeCO]_2Mo(=CHCMe_2Ph)(=NC_6H_3-2,6-i-Pr_2)$ , effected the ring closure giving cyclic silyl ether **71** in 95% yield.



With **71** in hand, the cross-coupling to aryl iodides with various functionalities and electronic properties was examined (Scheme 24). Aryl halides bearing electron-withdrawing and electron-donating groups exhibited similar reactivity. No significant steric effects were noted except in cases where coordination to the palladium may be inhibitory (**75–77**). The absence of other stereo- or regioisomers in the coupling products illustrates the high selectivity of the cyclic silyl ether approach in the synthesis of cross-coupling products with *Z* olefin geometry.



This process exhibits excellent scope with regard to the tether length (i.e. silyl ether ring size) and substituents on the alkene both in the RCM step and the subsequent cross-coupling step. Five-, six-, and seven-membered silyl

ether rings were prepared by RCM as were six-membered rings bearing an additional substituent (Figure 4).

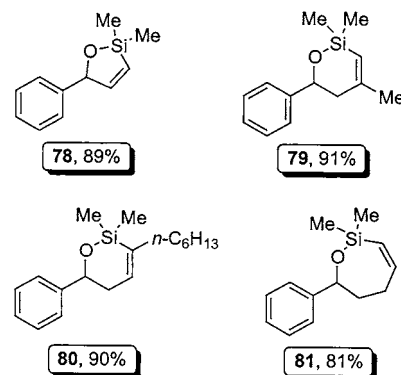
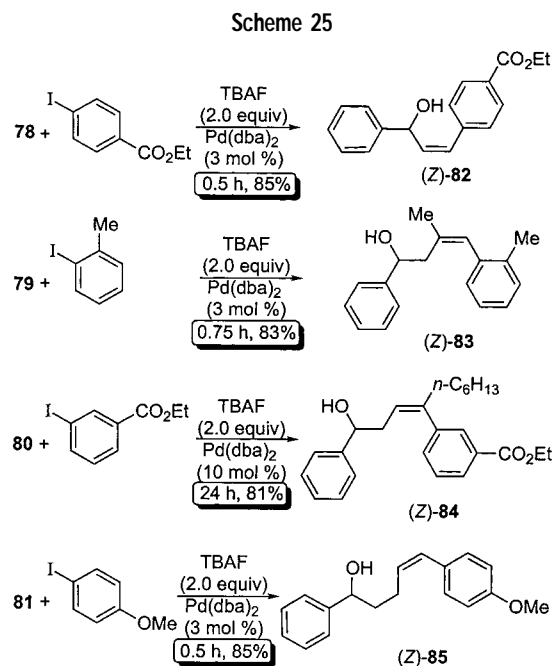


FIGURE 4. Cyclic silyl ethers of various ring sizes.

The cross-coupling reactions of compounds **78**, **79**, and **81**, containing five-, six-, and seven-membered rings, respectively, were very rapid with a variety of aryl iodides (Scheme 25). A substituent at the  $\alpha$ -position of silyl ether (**80**) retarded the rate significantly, but the yields of all these reactions were satisfactory.

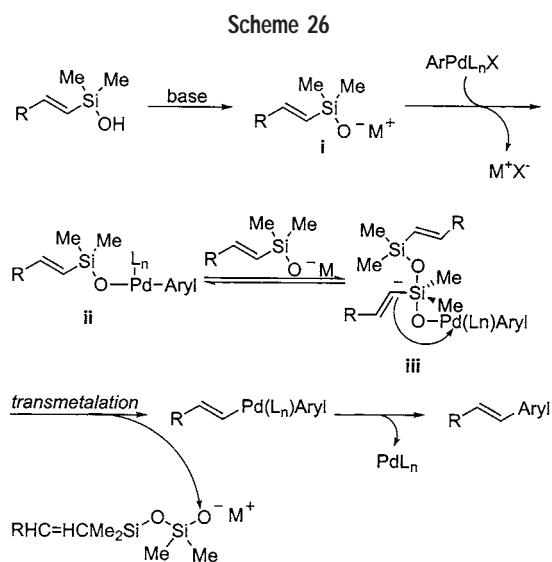


The application of the RCM approach to create a diverse array of cyclic silyl ethers successfully expands the scope of reactions utilizing the temporary silicon tether approach and the novel concept of heteroatom activation of the silicon from the coupling substrate itself. Thus, in cases where homoallylic alcohols are the desired coupling products, the aforementioned methods are a convenient alternative to synthesizing the analogous silanols.

## Non-Fluoride-Promoted Coupling of Organosilanols

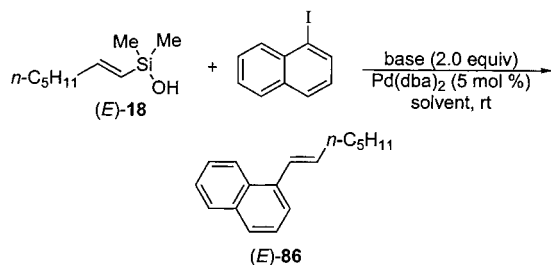
Although significant progress has been achieved with the TBAF-promoted coupling of organosilanes, it was recognized that certain incompatibilities can arise from the

necessity of a fluoride promoter. For example, its use would be incompatible in a complex molecule synthesis wherein one of the coupling partners might contain silyl protective groups. As a result, the development of a convenient, non-fluoride-promoted system employing organosilanols as coupling partners was sought.<sup>36,37</sup> On the basis of a new mechanistic model, an intriguing proposal was formulated that identified the deprotonation of the silanol as a key event (Scheme 26). The resultant silyloxide **i** was proposed to displace the iodide on the arylpalladium halide to form complex **ii**. If the prerequisite for transmetalation is to generate a pentacoordinate siliconate, then this should be easily accessible by attachment of a second molecule of the silyloxide onto the arylpalladium-silicon complex (**iii**). The key step, transmetalation, should then be facilitated as an intramolecular reaction.



This hypothesis was tested by subjecting silanol (*E*)-**18** to the coupling conditions with a variety of bases (Table 1). Sodium hydride proved to be an effective base, and rates were much higher in DMF and DME than in THF. The superior base in terms of rate, however, was potassium hydride. It exhibited the same solvent dependence

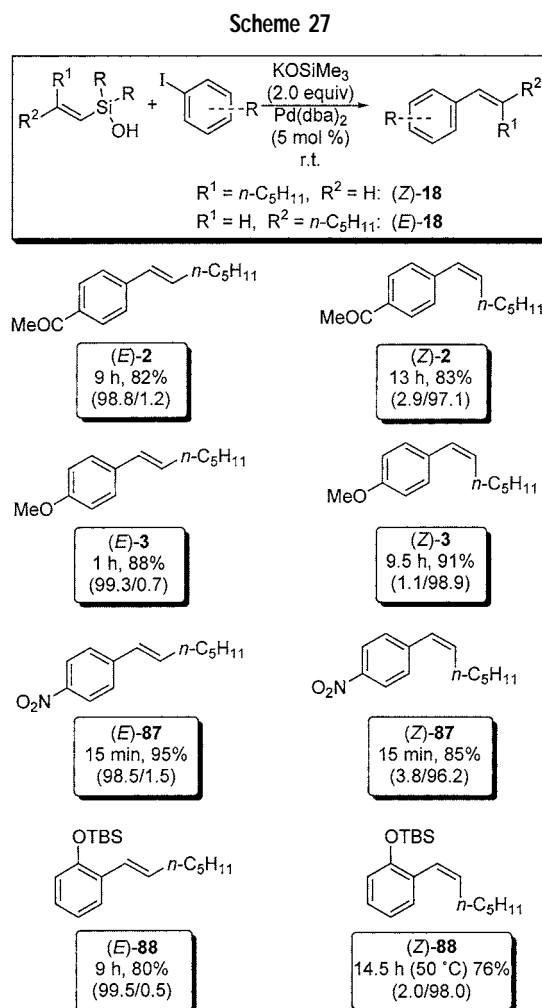
**Table 1. Effect of Base and Solvent on the Fluoride-Free-Promoted Cross-Coupling of (*E*)-**18****



base	solvent	time, h	yield (%)
NaH	THF	4	85
NaH	DMF	1.5	78
NaH	DME	1	81
KH	THF	2	85
KH	DME	0.25	82

on rate, but the coupling in DME was complete within 15 min. Other bases such as *KOt*-Bu were less effective, and MeLi gave no coupling product at all.

Subjecting (*Z*)-**18** to the same conditions with KH gave only 48% yield of product (*Z*)-**86**. The problem was shown to be competitive reduction of the aryl iodide as evidenced by the isolation of naphthalene in 30% yield. Other bases such as *KOt*-Bu were inferior to KH. It was reasoned that an ideal base need only be strong enough to produce a measurable concentration of the silyloxide, be capable of associating with and activating a species such as **ii**, and not be a competitive inhibitor by unproductively binding the palladium. Logically, the first choice would be another silyloxide such as the inexpensive and soluble agent,  $\text{KOSiMe}_3$ .<sup>38</sup> Gratifyingly, this mild base effectively promoted the coupling of both (*E*)- and (*Z*)-**18** at acceptable rates without evidence of the competing reduction pathway (Scheme 27).



This method displayed excellent generality; reactions proceeded readily at room temperature and tolerated a range of aryl functional groups. Unlike most TBAF-promoted reactions, however, the *Z* isomer of the silanol reacted at a much lower rate than the *E* isomer. In general, electron-deficient aryl iodides coupled faster than their electron-rich counterparts, except 4-iodoacetophenone,

which reacted quite sluggishly, although the yields were still high. The synthetic potential of this new method of activation was clearly demonstrated in the synthesis of (*E*)- and (*Z*)-**88**. The coupling reaction occurred cleanly in the presence of a TBS-protected alcohol without any observable deprotection. Thus, not only has the compatibility with silyl protective groups been established, the concept of employing the silanol moiety as a prosthetic group for controlled carbon-carbon bond formation and as an activator has also been achieved through this fluoride-free method.

## Conclusion and Outlook

The initial foray into the field of organosilicon cross-coupling chemistry began with the simple testing of the siletane, strain-release Lewis acidity concept. Unbeknown at the time, was the fruitful journey that lay ahead initiated by early mechanistic studies to identify the common intermediate organosilicon species. Since then, the room-temperature couplings of silanols, silyl hydrides, di- and polysiloxanes, and cyclic silyl ethers have been documented. In addition, these couplings have become even more appealing through the use of commercially available starting materials for vinylation as well as one-pot procedures for hydroarylation of terminal alkynes. The use of other popular methods such as RCM in conjunction with silyl ether coupling has further expanded the scope of the process. Finally, the extension of this method to non-fluoride activators illustrates another important dimension in the use of silanols.

Work in this field has been quite active since the initial disclosure of siletane cross-coupling from these laboratories 3 years ago. Future studies are focused on several fronts, including the extension of scope to incorporate less reactive substrates such as chlorides and triflates, further optimization of alkenyl/alkenyl couplings, and creation of an efficient biaryl (and heteroaryl) synthesis using silanols. In addition, synthetic endeavors are underway that highlight the power of this cross-coupling through key steps in the total synthesis of natural products. It must also be noted that the mechanistic work is still at its infancy, and more detailed analysis of the reaction through kinetics and reactive-intermediate isolation is underway. Such studies should provide an even better understanding of these reactions and aid in finding solutions to the many interesting challenges and unexpected opportunities that lie ahead.

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- (22) Cine refers to the product arising from coupling at the  $\beta$ -position to silicon.
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- (31) Denmark, S. E.; Pan, W. Intramolecular Hydrosilylation and Silicon-Assisted Cross-Coupling: An Efficient Route to Trisubstituted Homoallylic Alcohols. *Org. Lett.* **2001**, *3*, 61–64.
- (32) A complementary anti hydrosilylation/cross-coupling process that uses a ruthenium-based catalyst has recently been developed. Denmark, S. E.; Pan, W. Manuscript submitted for publication.
- (33) Extension of this approach to the synthesis of allylic alcohols has also been achieved using a novel class of unsymmetrical disiloxanes. Denmark, S. E.; Pan, W. Manuscript in preparation.
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- (35) (a) Denmark, S. E.; Yang, S.-M. Sequential Ring-Closing Metathesis and Silicon-Assisted Cross-Coupling Reactions: Stereocontrolled Synthesis of Highly Substituted Unsaturated Alcohols. *Org. Lett.* **2001**, *3*, 1749–1752. (b) Denmark, S. E.; Yang, S.-M. Intramolecular Silicon-Assisted Cross Coupling Reactions: General Synthesis of Medium-Sized Rings Containing a 1,3-*cis-cis* Diene Unit. *J. Am. Chem. Soc.* **2002**, *124*, 2102–2103.
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- (37) Hiyama and Mori have reported the use of stoichiometric amounts of Ag<sub>2</sub>O as a coupling activator, though at elevated temperatures: (a) Hirabayashi, L.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. A New Transformation of Silanols. Palladium-Catalyzed Cross-Coupling with Organic Halides in the Presence of Silver(I) Oxide. *Org. Lett.* **1999**, *1*, 299–301. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. Palladium-Catalyzed Cross-Coupling of Silanols, Silanediols, and Silanetriols Promoted by Silver(I) Oxide. *J. Org. Chem.* **2000**, *65*, 5342–5349.
- (38) Potassium trimethylsilanolate (Aldrich), \$63/mol. Tetrabutylammonium fluoride trihydrate (Fluka), \$624/mol.

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