

## Review

## Cross-Coupling Reactions of Organosilicon Compounds: New Concepts and Recent Advances

Scott Eric DENMARK\* and Ramzi Farah SWEIS

Roger Adams Laboratory, Department of Chemistry, University of Illinois; Urbana, Illinois 61801, U.S.A.

Received September 9, 2002

This review highlights the rapid evolution of the newly-developed class of palladium-catalyzed cross-coupling reactions of organosilicon compounds. A myriad of heteroatom-containing silicon moieties (silyl hydrides, siletanes, silanols, silyl ethers, orthosiliconates, di- and polysiloxanes and pyridylsilanes) undergo mild and stereospecific cross-coupling. The diversity of methods for introduction of silicon groups into organic molecules and the range of organic electrophiles that can be used are emphasized.

**Key words** cross-coupling; organosilicon; palladium

Palladium-catalyzed cross-coupling reactions occupy a unique status among methods for the construction of carbon–carbon bonds. The well-established Stille–Miyata–Kosugi coupling of organostannanes<sup>1–3</sup>) and the Suzuki–Miyaura coupling of organoboron compounds<sup>4,5</sup>) are two reactions that, until recently, have been the “gold-standard” among various palladium-catalyzed coupling reactions. Their wide use and extraordinary synthetic utility have provided the impetus to develop newer and more effective variants (Fig. 1). More recently organosilanes have also been shown to be competent coupling partners in those reactions that employ shelf-stable reagents. The early work of Hiyama demonstrated that in the presence of a nucleophilic promoter, fluorosilanes could undergo a variety of cross-coupling reactions whose scope rivaled that of organotin and organoboron cross-couplings.<sup>6–8</sup>) Since these reports, many variants of organosilicon cross-coupling have been developed that extend beyond the use of fluorosilanes and that possess many attractive features which now elevate this method to be a viable alternative to other types of cross-coupling. This report will outline recent advances in the development of organosilicon cross-coupling reactions and provide an overview of scope and applicability of this new technology.

Organosilanes were previously thought to be too unreactive to be effective cross-coupling partners. The small electronegativity difference between silicon and carbon resulted in a relatively weak nucleophilic reagent for the cross-coupling. The use of fluorosilanes was therefore a significant breakthrough, demonstrating that in the presence of a nucleophilic promoter, these compounds could access a pentacoordinate “ate” species, which was postulated to undergo the coupling reaction due to its enhanced polarization at the carbon–silicon bond. Because silicon-based compounds are generally non-toxic, have low molecular weight, and are easily incorporated into molecules by a variety of methods, the potential for developing other silicon-based cross-coupling systems superior to methods previously employed was recognized.

One of the first successful alternatives to fluorosilanes in organosilicon cross-coupling was achieved through the use of siletanes. Predicated on the necessity to generate a pentacoordinate silicon for the coupling process, it was hypothesized that the use of a siletane should enable generation of the pentacoordinate silicate more readily in the presence of a nucleo-

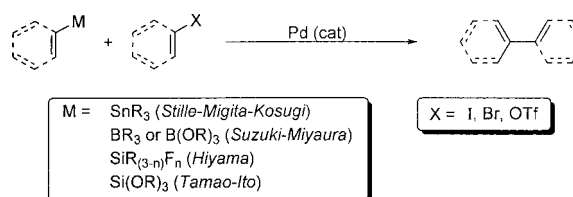


Fig. 1. Generalized Formulation of Palladium-Catalyzed Cross-Coupling Reaction

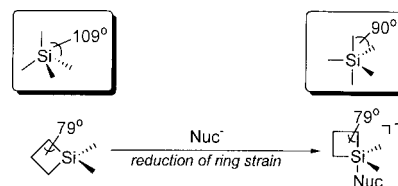


Fig. 2. Concept of “Strain-Release Lewis Acidity”

phile due to the enhanced Lewis acidity of the silicon. 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 (Fig. 2). Therefore, the angle strain in a four coordinate siletane ( $79^\circ$  vs.  $109^\circ$ ) is partially relieved upon binding a fifth ligand to produce a trigonal bipyramidal species ( $79^\circ$  vs.  $90^\circ$ ) in which the siletane bridges an apical and basal position.<sup>9,10</sup>)

On the basis of this conceptual framework, a cross-coupling system employing both alkenyl- and arylsiletanes was developed. Alkenylsiletanes (*E*)- and (*Z*)-**1** underwent facile, room temperature cross-coupling to both electron-rich and electron-deficient aryl iodides (Chart 1).<sup>11</sup>) In addition to the remarkable mildness and reactivity (*ca.* 10 min at ambient temperature), high stereospecificity with respect to alkene geometry in the coupling was observed (greater than 98% in most cases). Arylsiletane **4** underwent similarly facile cross-coupling to generate an unsymmetrical biaryl product.<sup>12</sup>) Unlike the alkenylsiletanes, this coupling required slightly elevated temperatures. In addition, heteroatom substitution on the silicon atom was necessary to enhance the polarity and thus reactivity of the *sp*<sup>2</sup> carbon–silicon bond.

The use of siletanes in organosilicon cross-coupling achieved many significant milestones that hinted at the po-

\* To whom correspondence should be addressed. e-mail: denmark@scs.uiuc.edu

tential superiority of organosilanes over other organo-element nucleophiles in cross-coupling chemistry. In addition to the previously mentioned advantages associated with organosilanes, these particular couplings exhibited mildness, high efficiency, excellent stereospecificity, and notable functional group compatibility. In addition, the substrates were easily synthesized in a few steps from commercially available precursors.

These attributes were later found to not be unique to the siletane moiety. Rather, a series of reports have since highlighted the use of different types of heteroatom-substituted organosilanes (*e.g.*, silanols, siloxanes, silyl ethers, and even pyridylsilanes) in similarly mild cross-coupling reactions. This remarkable expansion of scope with regard to the organosilicon moiety was not realized until recently, and will be detailed below according to the type of silane employed.

### Organosilanol Cross-Coupling

**Silver (I) Oxide-Promoted Coupling** Organosilanols are air-stable compounds that have recently found great use in silicon-based cross-coupling chemistry.<sup>13–16</sup> The first cross-couplings with organosilanols were independently published by two groups. The reaction systems are not similar, in

that different activators and catalysts are employed by each.

In the system developed by Mori *et al.*, both aryl- and alkenylsilanols undergo cross-coupling with aryl iodides in modest to good yields. In this study, the best activator was found to be silver (I) oxide, which promoted the coupling of aryl silanol **6** to a variety of aryl iodides (Chart 2).<sup>17,18</sup> The common silicon coupling promoter, tetrabutylammonium fluoride (TBAF), was ineffective in this method. Alkenylsilanols were also employed with similar success. The range of aryl iodides compatible under the reaction conditions is quite general, with electron poor iodides generally giving much lower yields (**10**). It is noteworthy that the iodide is exclusively preferred as the site of cross-coupling, even in the presence of a bromide and triflate (**11**, **12**).

The long reaction times and elevated temperatures required for this method, however, prompted further investigation into coupling partners other than a simple silanol. In light of the beneficial role of the hydroxyl group on silicon

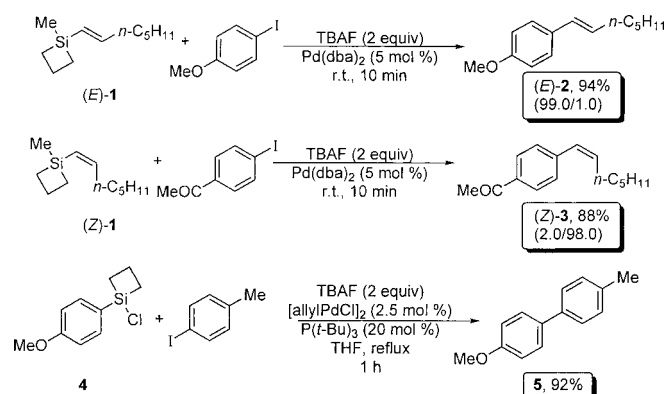
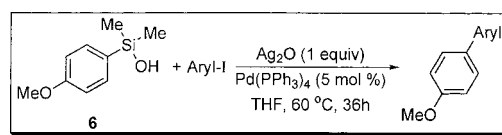


Chart 1. Cross-Coupling Reactions of Alkenyl- and Arylsiletanes

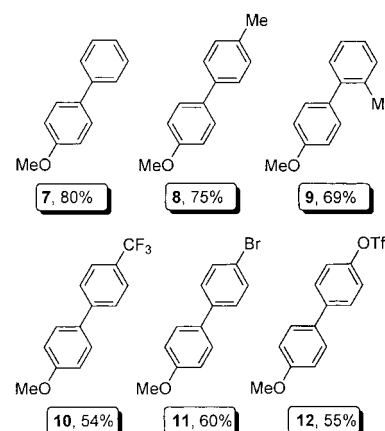


Chart 2. Cross-Coupling Reactions of Arylsilanols Promoted by  $\text{Ag}_2\text{O}$

Ramzi F. Sweis was born in Chicago, Illinois, on August 24, 1975. He graduated with a B.S. degree in chemistry from Northwestern University in 1997. In 1998 he began graduate studies at the University of Illinois working under the direction of Scott E. Denmark. During this time, he has been supported by a number of graduate fellowships and has received an R. C. Fuson Travel Award.

Scott E. Denmark was born in Lynbrook, New York on 17 June 1953. He obtained an S.B. degree from MIT in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D. Sc. Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois. He was promoted to associate professor in 1986, to full professor in 1987 and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry and the origin of stereocontrol in fundamental carbon-carbon bond forming processes. Professor Denmark is currently on the Board of Editors of *Organic Reactions* and *Organic Syntheses*. He is an Associate Editor of *Organic Letters* and is the Editor of *Topics in Stereochemistry*.



Ramzi F. Sweis



Scott E. Denmark

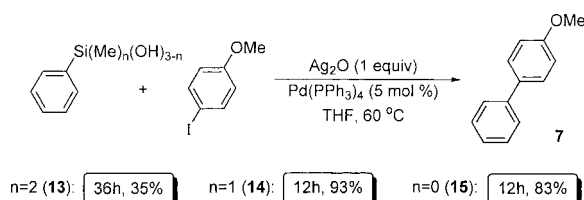


Chart 3. Cross-Coupling Reactions of Arylsilanediols and Arylsilanetriols Promoted by  $\text{Ag}_2\text{O}$

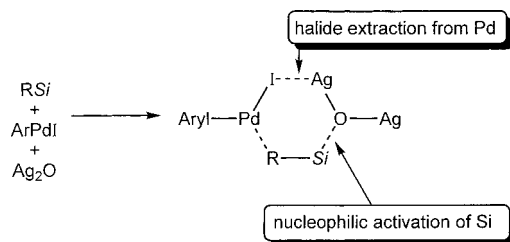


Fig. 3. Proposed Mechanism of Activation by  $\text{Ag}_2\text{O}$

for successful cross-coupling, a more active silicon precursor was sought that employed more than one hydroxyl group per silicon atom.<sup>19)</sup> Aryl- and alkenylsilanediols and -triols were easily synthesized from the corresponding chlorides and subjected to the similar cross-coupling reactions. The comparison of silanol **13**, silanediol **14**, and silanetriol **15** demonstrates the higher coupling efficiency associated with **14** and **15** relative to the simple silanol (Chart 3). The clean synthesis of such polyols, however, is not always possible. Many liquid silanediols and triols are used directly from the hydrolysis mixture of the corresponding chlorides since purification of these compounds is difficult to achieve.

The unique ability of silver oxide to effectively promote these coupling reactions arises from two properties (Fig. 3). First, the oxygen atom of the  $\text{Ag}_2\text{O}$  can serve as a nucleophile to activate the silicon, generating the necessary silicate intermediate. Second, the silver atom can promote halide extraction from the arylpalladium iodide intermediate. This would presumably generate a more reactive cationic palladium species. These hypotheses have yet to be proven experimentally. Nonetheless, the notable efficiency of  $\text{Ag}_2\text{O}$  as a promoter for silanol cross-coupling is clearly evident.

**Tetrabutylammonium Fluoride (TBAF)-Promoted Coupling Alkenylsilanols:** A slightly different silanol cross-coupling system, developed by Denmark *et al.*, employed  $\text{Pd}(\text{dba})_2$  as a catalyst for alkenylsilanol coupling.<sup>20)</sup> In this reaction, TBAF is an effective promoter, yielding reaction times of a few minutes at room temperature. Careful mechanistic work on the siletane cross-coupling revealed that upon mixing a siletane with TBAF, a silanol was recovered from reaction solution (formed from the water contained in the commercially available trihydrate of TBAF).<sup>21)</sup>

Accordingly, alkenyldimethylsilanols (*E*)-**16** and (*Z*)-**16**, along with two analogs, diisopropylsilanols (*E*)-**17** and (*Z*)-**17**, also undergo cross-coupling reactions with a variety of aryl and alkenyl iodides (Chart 4). A few unique advantages of these compounds are: (1) the ability to be synthesized by multiple methods in geometrically pure form, (2) their stability and ease of handling, and (3) the capability to modify the spectator group on the silicon to modulate reactivity and/or

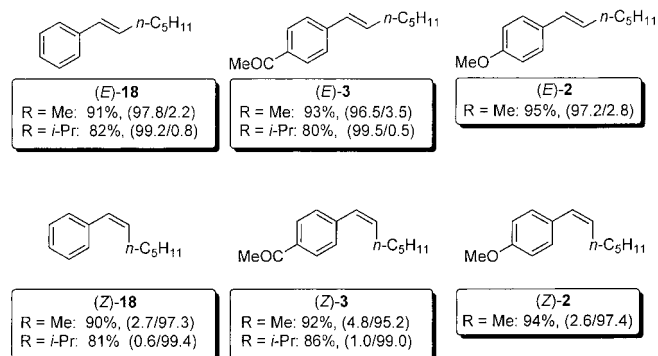
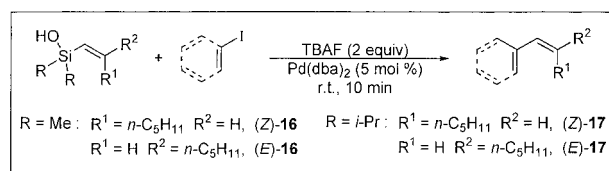


Chart 4. Cross-Coupling Reactions of Alkenylsilanols Promoted by TBAF

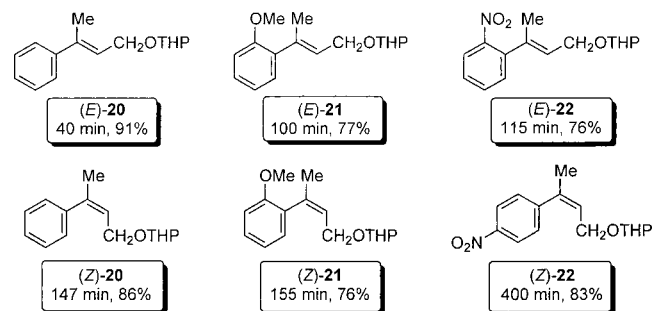
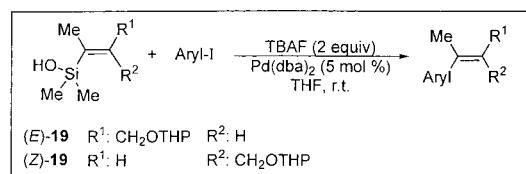


Chart 5. Cross-Coupling Reactions of Hindered Alkenylsilanols Promoted by TBAF

suppress side reactions.

It is notable that the reactions of (*E*)- and (*Z*)-**16** are just as rapid and high yielding as the previously reported siletane couplings albeit with marginally lower stereospecificity. Both electron-rich and electron-poor aryl iodides couple with equal facility. The cross-coupling of the isopropylsilanols (*E*)-**17** and (*Z*)-**17**, however, show higher stereospecificity and display similar reaction times, although in slightly lower yields.

In view of the success obtained with organosilanols, it is not surprising that extension to more highly substituted (and challenging) substrates is also profitable.

**Highly Substituted Alkenylsilanols:** Trisubstituted alkenylsilanols (*E*)-**19** and (*Z*)-**19**, could be synthesized in high yielding sequences and undergo cross-coupling with a variety of aryl iodides (Chart 5).<sup>22)</sup>

Most of the reactions proceed smoothly using the same mild conditions as previously employed in spite of the rates being generally lower than observed with silanols (*E*)-**16** and

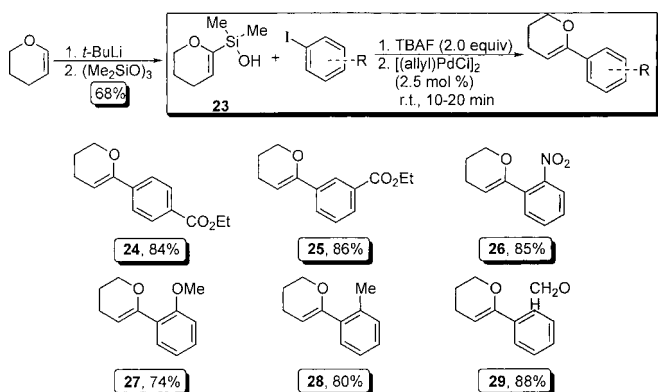


Chart 6. Cross-Coupling Reactions of 2-(Dihydropyranyl)dimethylsilanol Promoted by TBAF

(*Z*)-**16**. One noteworthy finding is that (*Z*)-**19** coupled at consistently lower rates than (*E*)-**19**. Clearly, then, increased substitution on the alkenylsilanols attenuated reactivity, but this is significant only in the cases involving the *Z*-isomers. Reactions with (*Z*)-**19** also produces small amounts of dimers arising from homocoupling of the aryl iodide. This problem is overcome by the portion-wise addition of the electrophile. In general, these couplings tolerate several functional groups and the rates are generally independent of steric and electronic factors (*cf.*, Chart 5 for the reaction times for (*E*)-**20**, (*E*)-**21**, and (*E*)-**22**). Overall, these reactions highlight the use of (*E*)-**19** and (*Z*)-**19** as useful stereo-defined prenylating agents. In addition, the products represent stereodefined trisubstituted allylic alcohols, whose syntheses are otherwise not trivial.

The preceding study revealed the rate-retarding effect of an  $\alpha$ -methyl substituent on the alkenylsilanol. The effect of heteroatom substituents in the same position is important for extending the generality of the reaction. If successful, this would constitute a useful method for nucleophilic acylation.

( $\alpha$ -Alkoxyalkenyl)silanols and Silyl Hydrides: Silanols containing an  $\alpha$ -alkoxyalkenyl group are readily synthesized from the corresponding enol ethers.<sup>23)</sup> For example, 2-(5,6-dihydro-4*H*-pyran-2-yl)dimethylsilanol **25** is produced by lithiation of pyran and trapping with hexamethylcyclotrisiloxane ( $D_3$ ) (Chart 6). This silanol undergoes 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, though, the catalyst used is [(allyl)PdCl]<sub>2</sub> instead of Pd(dba)<sub>2</sub> primarily for ease of product purification. The higher reactivity of the silicon compared to tin-based cross-coupling is illustrated by the synthesis of **28**. This compound was made previously by a Stille coupling which required 2 h in refluxing acetonitrile to give the same final yield.<sup>24)</sup>

Unlike **23**, other  $\alpha$ -alkoxydimethylsilanols are not readily prepared by the same method. Making recourse to the corresponding diisopropylsilanols involves capture of the lithio anion with diisopropylchlorosilane to give silyl hydrides **30**–**32**. These silyl hydrides themselves couple quite readily without the need for a difficult prior oxidation step (Chart 7). 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>25)</sup>

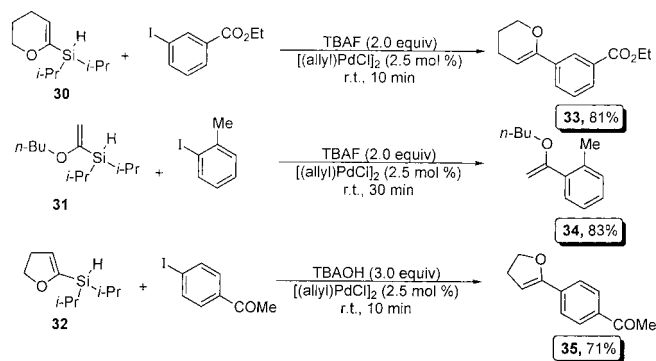


Chart 7. Cross-Coupling Reactions of  $\alpha$ -Alkoxyalkenylsilanes

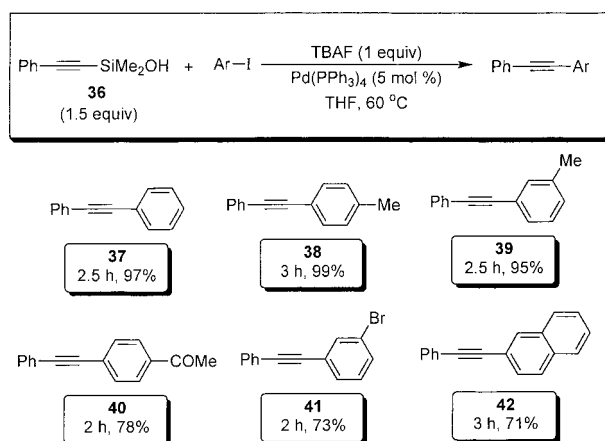


Chart 8. Cross-Coupling (Sonogashira) Reactions of Alkynylsilanols Promoted by TBAF

Unlike **30** and **31**, silyl hydride **32** suffered rapid protio-desilylation in the presence of the TBAF, releasing dihydrofuran. Replacement of the TBAF solution with tetrabutylammonium hydroxide (3.0 eq) solution in MeOH allows the coupling reaction to proceed smoothly to **35**.

The cross-coupling reactions of aryl- and alkenylsilanols are adequate replacements for the analogous Stille and Suzuki reactions. Yet the scope of organosilanols coupling extends beyond this. It has also been shown that the use of alkynylsilanols presents a viable alternative to the classic Sonogashira-type couplings of alkynes.

Alkynylsilanols: The coupling reaction of alkynyltrimethylsilanes using a palladium/copper(I) co-catalyst system has been reported and studied quite thoroughly.<sup>26)</sup> However, the cross-coupling of alkynylsilanols in the presence of TBAF proceeds under still milder conditions (Chart 8).<sup>27)</sup> Dimethyl(phenylethynyl)silanol, **36**, experiences successful cross-coupling with a variety of aryl iodides. Using only one equivalent of TBAF at 60 °C, the reactions are generally high yielding and complete within a few hours. This method is quite general, in that other alkynylsilanols containing a variety of pendent groups also successfully coupled in the same fashion.

Heck-type Coupling of Arylsilanols: All of the cross-coupling reactions described thus far require nucleophilic promoter such as Ag<sub>2</sub>O or TBAF. In the absence of such a promoter, however, a Heck-type process has recently been observed between aryl- and alkenylsilanols and a series of elec-

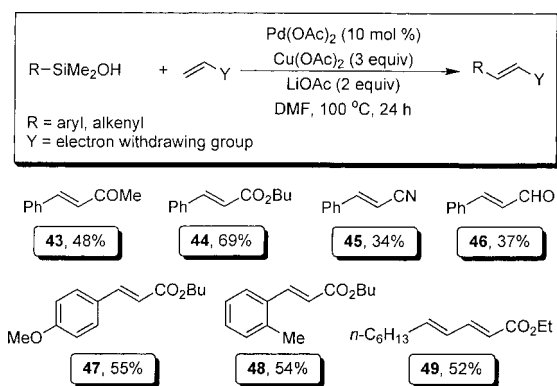
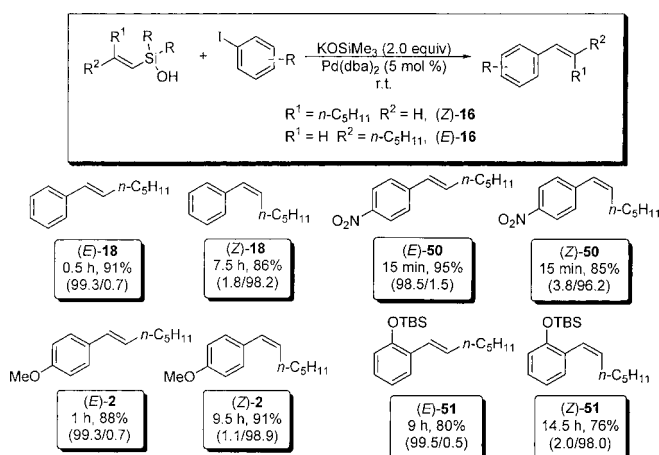


Chart 9. Mirozoki-Heck Reactions of Alkenyl- and Arylsilanols

Chart 10. Cross-Coupling Reactions of Alkenylsilanols Promoted by  $\text{KOSiMe}_3$ 

tron deficient alkenes.<sup>28</sup>) This system employs  $\text{Pd(OAc)}_2$  (10 mol%) as the catalyst. In addition,  $\text{Cu(OAc)}_2$  with  $\text{LiOAc}$  were used to re-oxidize the resultant  $\text{Pd(0)}$  species, which is a necessary byproduct of the coupling (Chart 9). This halogen-free, Heck-type process works best with silanols;  $\text{PhMe}_2\text{SiOMe}$ ,  $\text{PhSiMe}_3$ , and  $\text{PhMe}_2\text{SiCl}$  are much less effective than  $\text{PhSiMe}_2\text{OH}$ , **45**, in direct comparisons.<sup>29</sup>) It is intriguing to note that phenyltrifluorosilane exhibits similar reactivity to the silanol, thereby demonstrating that a single hydroxy group on the silicon atom is as effective as three fluorine atoms in activating the Si-C bond for cleavage.

***KOSiMe<sub>3</sub>-Promoted Cross-Coupling:*** Although significant progress has been achieved with the TBAF-promoted coupling of organosilanes, it was recognized that certain incompatibilities can arise from the use of a fluoride promoter. For example, the fluoride ion would be incompatible in complex molecule synthesis wherein one of the coupling partners might contain silyl protective groups. In addition, while the use of a stoichiometric amount of silver oxide to promote organosilanols coupling reactions allows for a fluoride-free system, the conditions generally require elevated temperatures and long reaction times (cost notwithstanding). As a result, the development of a mild and convenient, non-fluoride-promoted system is desirable.

An alternate promoter could be a nucleophilic silyloxide, which is capable of generating an active pentacoordinate silicate in much the same manner as TBAF. The inexpensive and

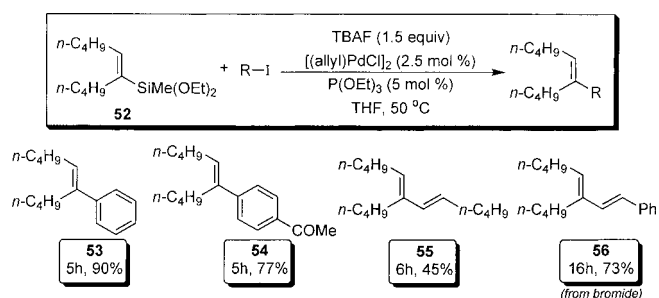


Chart 11. Cross-Coupling Reactions of Alkenyldiethoxysilanes Promoted by TBAF

soluble agent,  $\text{KOSiMe}_3$ , effectively promotes the coupling of both silanols (*E*)-**16** and (*Z*)-**16** at acceptable rates to a variety of aryl iodides at room temperature (Chart 10).<sup>30,31</sup>)

A survey of coupling partners shows this to be a very general method, which tolerates several functionalities and proceeds readily at room temperature. Unlike most TBAF-promoted reactions however, the *Z* isomer of the silanol reacts at a much lower rate than the *E* isomer. In general, electron deficient aryl iodides couple faster than their electron rich counterparts. The synthetic potential of this new method of activation is clearly demonstrated in the synthesis of (*E*)- and (*Z*)-**53**. The coupling reaction occurs 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 a silanolate as an activator has been achieved through this fluoride-free method.

Whereas many examples of organosilanols coupling can now be found, the appeal of organosilanes in cross-coupling has also benefited greatly from progress in organosilyl ether cross-coupling. Novel approaches to incorporating this moiety into molecules as well as the impact of these substrates on biaryl synthesis are the two main highlights of this subset.

### Organosilyl Ether Cross-Coupling

**Alkenylsilyl Ethers** The use of alkenylsilyl ethers in palladium catalyzed cross-coupling reactions has long been known. In fact, it was only a year after Hiyama's landmark report on the TBAF-promoted vinyltrimethylsilane coupling reactions that Tamao and Ito capitalized on the use of alkoxy-substituted silanes as component for such reactions.<sup>32</sup>) Successful palladium-catalyzed coupling reactions of diethoxysilane **52** are demonstrated with a series of aryl and alkenyl halides (Chart 11). Either mono- or diethoxysilanes are useful substrates for such a reaction with TBAF as the promoter. It is noteworthy that the corresponding triethoxysilanes give much lower yields under similar reaction times. The generality of this silyl ether coupling adds a useful class of organosilicon substrates that are complementary to the fluoro-silanes developed by Hiyama.

**Cyclic Silyl Ethers via Intramolecular Hydrosilylation:** A main advantage of using silyl ethers in cross-coupling reactions lies in the ability to incorporate them into molecules by a diverse array of methods. Cyclic silyl ethers, as a class, nicely illustrate this attribute. The well-known hydrosilylation of alkynes to form vinylsilanes could be easily rendered intramolecular by attachment of the silane as, e.g., a homo-

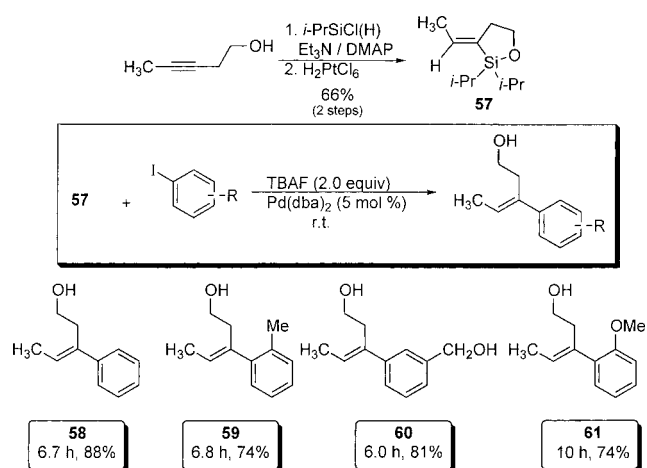


Chart 12. Intramolecular Hydrosilylation/Cross-Coupling of 3-Pentyn-1-ol

propargylic silyl ether to form an oxasilacyclopentane **57** (Chart 12).<sup>33</sup> In this structure, the double-bond geometry is defined by the stereochemical course of hydrosilylation and the ether tether defines the location of the silicon atom with respect to the alkene.

Silyl ether **57** undergoes cross-coupling with a range of aryl iodides (Chart 12). The reaction times are generally longer than those observed with simple alkenylsilanols and -siloxanes but are similar to the trisubstituted alkenylsilanols previously described. The slower rate of cross coupling often leads to formation of homocoupling byproducts, which can be minimized by the portionwise addition of the electrophile. 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>34</sup> The facile formation and high reactivity of these silicon-containing substrates bodes well for the use of other methods of synthesizing cyclic silyl ethers for incorporation into designed cross-coupling partners.

**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 are ample testimony to its utility.<sup>35–38</sup> Silyl ethers **63–67** of various ring sizes can be prepared by the RCM reaction (Chart 13).<sup>39</sup> Only the sterically less sensitive and more reactive molybdenum-based catalyst,  $[(CF_3)_2MeCO]_2Mo(=CHCMe_2Ph)(=NC_6H_3-2,6-i-Pr_2)$ , effects the ring closure for these silyl ethers.

The cross coupling of the cyclic silyl ethers **63–67** to aryl iodides with various functionalities and electronic properties is successful (Chart 14). Aryl halides bearing electron-withdrawing and electron-donating groups exhibit similar reactivity. In addition, the absence of other isomers in the coupling products illustrates the high selectivity of the cyclic silyl ether approach in the synthesis of cross-coupling products with *Z* alkene 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. A substituent at the  $\alpha$ -position of silyl ether (**68**) retards the rate significantly, but the

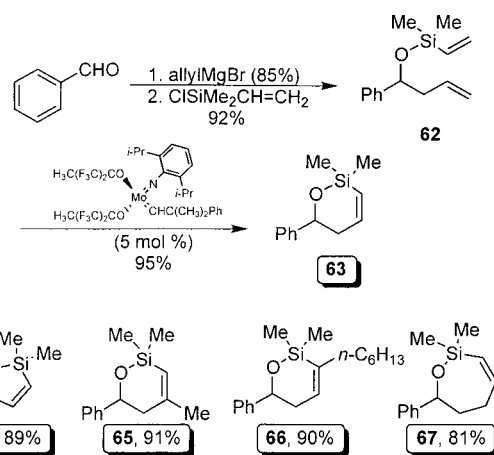


Chart 13. Formation of Unsaturated, Cyclic Silyl Ethers by Ring-Closing Metathesis

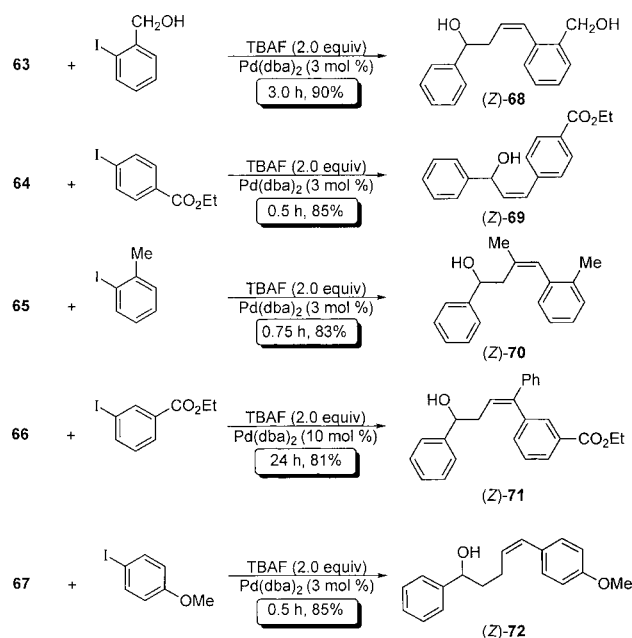


Chart 14. Cross-Coupling Reactions of Unsaturated, Cyclic Silyl Ethers Promoted by TBAF

yields of all these reactions are satisfactory.

An intramolecular version of this process has also recently been developed.<sup>40</sup> A series of cyclic silyl ether substrates bearing a tethered electrophile undergo the cross coupling reaction to produce medium-size rings (Chart 15). The results demonstrate that 9-, 10-, 11-, and 12-membered cycloalkadienes could easily be synthesized by this method. This is significant because the synthesis of rings of this size, particularly with a 1,3-*cis-cis* diene unit is quite challenging due to the unfavorable entropic and enthalpic factors associated with such a transformation.<sup>41,42</sup>

The application of the RCM approach to create a range 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 or medium-sized rings are the desired products, the aforementioned methods offer a facile and direct way for

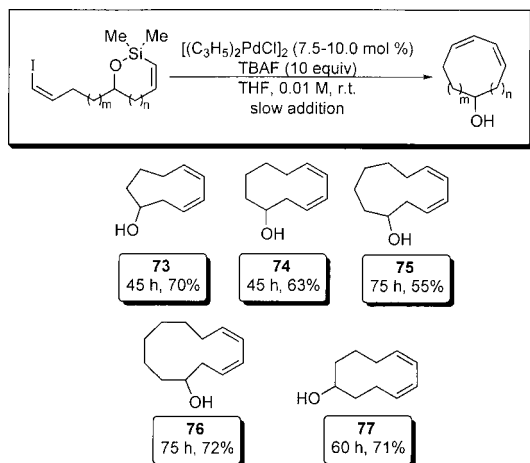


Chart 15. Intramolecular Cross-Coupling of Unsaturated, Cyclic Silyl Ethers Promoted by TBAF

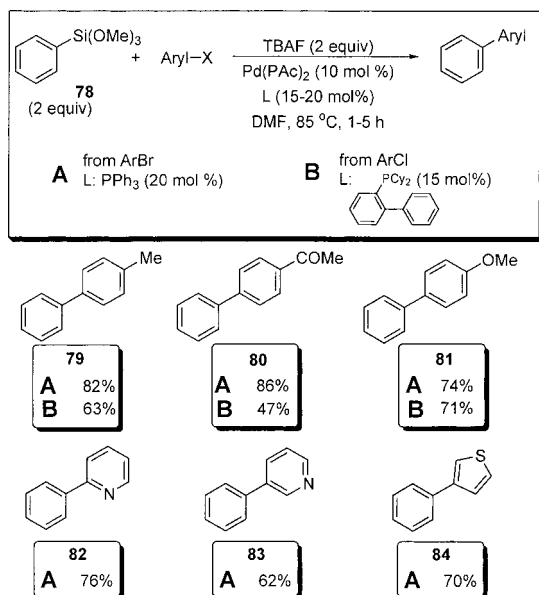


Chart 16. Cross-Coupling Reactions of Phenyltrimethoxysilane with Aryl Bromides and Chlorides Promoted by TBAF

their synthesis.

Despite what seems to be a diverse collection of organosilyl ether cross-coupling systems, all the aforementioned examples are similar in one aspect: they employ *alkenyl*silyl ethers. More recently, however, arylsilyl ethers have played a significant role in the realm of biaryl synthesis.

**Arylsilyl Ethers** One of the first general studies of arylsilyl ethers in cross-coupling was reported by DeShong.<sup>43,44</sup> Phenyltrimethoxysilane, **78**, efficiently reacts with several aryl halides in the presence of Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> (Chart 16). In general, the coupling to aryl bromides is high yielding for both electron rich and electron-deficient arenes (**80**, **81**).<sup>45</sup> Heterocyclic bromides are also viable substrates for this reaction (**82**–**84**).

The cross-coupling of arylsilyl ethers with aryl chlorides has also been possible, albeit in much lower yield than the corresponding reactions with aryl bromides (**B**, Chart 16). For this reaction, it is necessary to employ a different phos-

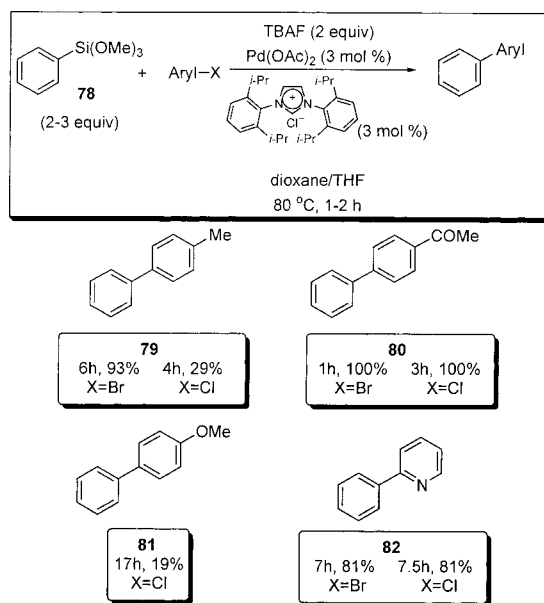


Chart 17. Cross-Coupling Reactions of Phenyltrimethoxysilane with Aryl Bromides and Chlorides Promoted by TBAF

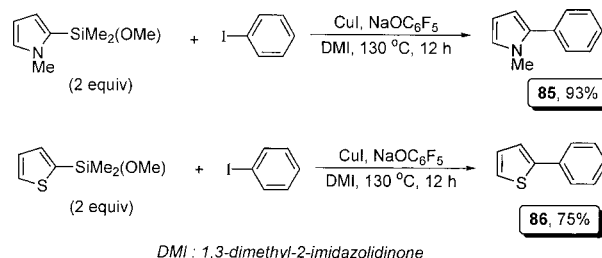


Chart 18. Copper-Promoted Cross-Coupling of Arylsilyl Ethers

phine ligand, 2-(dicyclohexylphosphino)biphenyl which is well known to activate aryl chlorides in other palladium-catalyzed coupling reactions.<sup>46,47</sup> Despite the use of siloxane in excess (*ca.* 2 eq) and relatively high catalyst loadings, the coupling of **78** proceeds rapidly with several different types of aryl halides in good yields thereby exhibiting broad functional group compatibility.

Soon after DeShong's report on the use of aryl silyl ethers, Nolan reported a much more effective system consisting of Pd(OAc)<sub>2</sub> and an imadazolium carbene as the ligand (Chart 17).<sup>48</sup> In this system, **78** couples both with aryl bromides as well as electron-deficient and heterocyclic aryl chlorides (**80**, **82**). Unfortunately, the coupling to electron rich aryl chlorides was generally low yielding (**79**, **81**). The substrate scope is comparable to previous reports and generally, two or more equivalents of silyl ether are needed. A key advantage of this system, however, is the low catalyst loadings used (3% Pd and ligand).

*Palladium and Fluoride-Free Aryl Silyl Ether Cross-Coupling:* A problem that has occasionally been encountered when employing arylsilanes for coupling reactions in the presence of a nucleophilic promoter is the protio-desilylation of the starting material. This issue is solved by the use of a stoichiometric amount of copper to promote the cross-coupling of arylsilyl ethers with iodoarenes (Chart 18).<sup>49</sup> It is necessary to use Cu(OC<sub>6</sub>H<sub>5</sub>)<sub>2</sub>, generated *in situ* by mixing CuI

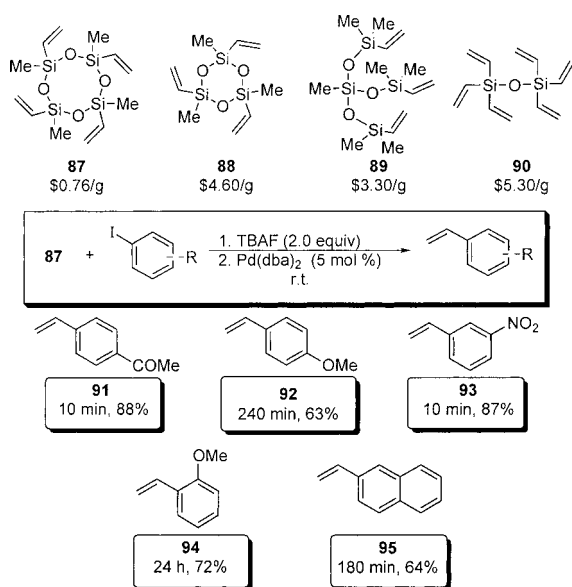


Chart 19. Vinylation of Aryl Halides with Commercially Available Di- and Polyvinylsiloxanes

and  $\text{NaOC}_6\text{H}_5$ , to effectively promote this coupling. Unlike other arylsilyl ether couplings, wherein a trialkoxysilane is used, the *mono*-methoxysilane reacted much more efficiently than either the di- or trimethoxysilane. Despite the harsh conditions used, this is an impressive reaction in that it is both fluoride- and palladium free.

The breadth of organosilyl ether cross-coupling now rivals that of organosilanols. The ease of synthesis of many of the precursors, as well as the stability and high reactivity associated with many of the silyl ethers, are alluring features of this class of substrates. In spite of this, there is still need for improvement, particularly in designing systems that do not require a large excess of organosilane relative to the electrophile employed.

The theme of oxygen substitution on the silicon atom for enhancing reactivity has been extended to polysiloxanes. These organosilicon compounds constitute dimers and oligomers of silanols. The commercial availability and low cost of polysiloxanes render this class of organosilicon donors highly attractive, particularly for large-scale cross-couplings.

### Polysiloxane Cross-Coupling

**Commercially Available Vinyllating Agents** The commercial availability of several inexpensive polyvinylsiloxanes makes these reagents ideal for simple vinylation of aryl and alkenyl halides. Three classes of such siloxanes, cyclooligo-disiloxanes (**87**, **88**), an orthosiliconate (**89**), and hexavinylid-siloxane (**90**), are suitable for the delivery of vinyl groups (Chart 19).<sup>50)</sup>

In optimization studies, **87**–**89** all undergo efficient cross-coupling to 4-iodoacetophenone within 10 min. Polysiloxane **87** displayed good reactivity and generality with a wide range of aryl and alkenyl electrophiles. Unlike the reactions of alkenylsilanols, this coupling is slower with electron-rich iodides and requires 3 eq of TBAF for completion (with **92**, **94**). In addition, steric effects were apparent, with the reaction times significantly longer for the synthesis of **94** and **95**.

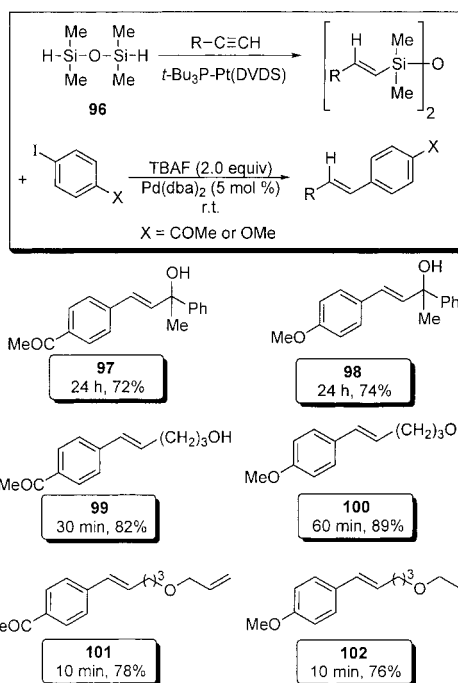


Chart 20. Intermolecular Hydrosilylation/Cross-Coupling of Terminal Alkynes

Nevertheless, the low cost combined with the high facility of these vinyllations clearly demonstrate their superiority over tin-based methods.<sup>51,52)</sup>

Although the preparative advantages of commercially available siloxanes are clearly demonstrated, the number of structurally diverse precursors is obviously limited. This shortcoming of such facile coupling reactions is addressed through the development of a general method for the custom preparation of alkenyl disiloxanes from simple starting materials.

**One-Pot Hydrosilylation/Cross-Coupling** The custom synthesis of alkenyl disiloxanes is achieved in a manner analogous to the synthesis of *E*-alkenylsilanols by a well-established, platinum-catalyzed hydrosilylation of alkynes. In this case, however, a readily available hydridodisiloxane is employed as the precursor. The combination of the hydrosilylation step with a subsequent, cross-coupling step avoids the need to isolate the intermediate disiloxane. This newly developed “one-pot” hydrosilylation/cross-coupling hence provides hydroarylation products directly from alkynes.

Two general methods employing this “one-pot” procedure have been developed. The first employs (*t*-Bu<sub>3</sub>P)Pt(0)(DVDS)<sup>53)</sup> as a hydrosilylation catalyst in combination with tetramethyldisiloxane (**96**) and a variety of alkynes (Chart 20).<sup>54)</sup> The hydrosilylation and subsequent cross-coupling reaction promoted by TBAF proceeds at room temperature. In addition, despite highly variable reaction times, the yields and stereospecificities are exceptional. The hydrosilylation of alkynes can be cleanly conducted in the presence of a free hydroxyl group (**97**–**100**) and even in the presence of a pendant alkene (**101**, **102**). In all cases, the major isomer is formed in greater than 99% purity.

The second general method consists of using various cyclic and non-cyclic polysiloxanes with either TBAF or Ag<sub>2</sub>O as the activator.<sup>55)</sup> The use of poly(phenylmethylsilox-



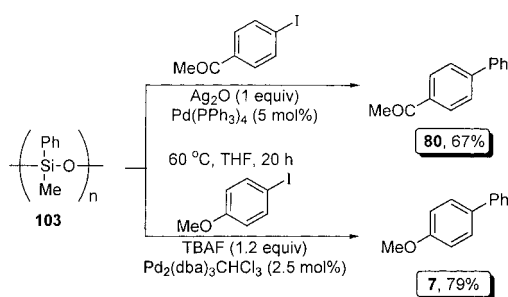


Chart 21. Phenylation of Aryl Halides with Poly(phenylmethyl)siloxane

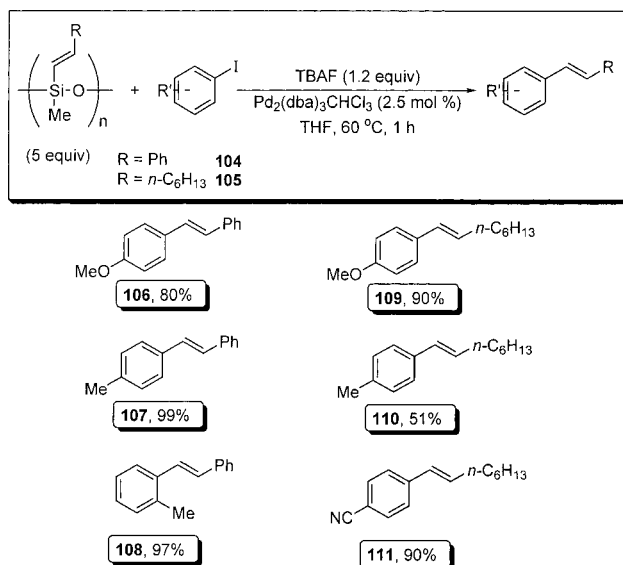


Chart 22. Cross-Coupling of Aryl Halides with Poly(alkenylmethyl)siloxanes Promoted by TBAF

ane) (**103**) serves as a very convenient phenylating source when promoted by  $\text{Ag}_2\text{O}$  for biaryl synthesis (Chart 21). TBAF is also an effective promoter and works well with a phosphine-free catalyst,  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ . The reaction is quite general and comparable in yield to silanol cross-coupling.

In addition, poly(alkenylmethylsiloxanes) can be customized by the hydrosilylation of alkynes with poly(methylhydroxysilane) (PMHS) in the presence of  $(\text{Bu}_4\text{N})_2\text{PtCl}_6$  in quantitative yields (Chart 22).<sup>55</sup> It is impressive that the resultant polysiloxanes are stable at room temperature under aerobic conditions for months and can be used for the subsequent cross-coupling reaction without further purification. The coupling of siloxanes **104** and **105** with several different aryl iodides provides convenient access to products previously synthesized from silanols. Electron rich (**106**, **109**), electron deficient (**114**) and even sterically encumbered aryl iodides (**108**) couple equally well. In general, the use of polysiloxanes in this fashion streamlines intermediate purification steps involved when employing other silicon reagents.

The recognition of effective vinylating reagents that are commercially available, in combination with novel one-pot approaches to synthesize coupling products from alkynes, render the use of polysiloxanes in cross-coupling chemistry very attractive. This is particularly applicable in synthesis on large scale or where intermediate steps of purification can be

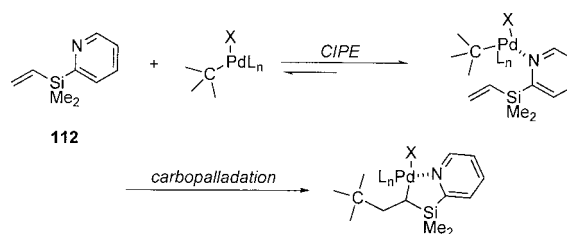


Fig. 4. Mechanism of Directed Carbopalladation of 2-Pyridyldimethyl(vinyl)silane

cumbersome. This class of organosilane coupling partners clearly shows a unique superiority both in cost and efficiency when compared to other non-silicon coupling reactions.

All of the aforementioned variants of silicon cross-coupling have highlighted the activating ability of an oxygen atom substitution on silicon. The advantages of silanols, silyl ethers, and siloxanes over other classes of organosilicon precursors such as chloro- and fluorosilanes is apparent in their stability, reactivity, and ease and low cost of synthesis. These advantages, however, have not halted investigation into other classes of reactive silane precursors for cross-coupling. The use of pyridyl-substituted silanes, while not a member of the general class of oxygen substituted silanes, has revealed new avenues of cross-coupling chemistry previously not available.

### Pyridylsilane Cross-Coupling

The utility of alkenyl-pyridylsilanes in palladium-catalyzed reactions was first recognized in a slightly different arena. 2-Pyridyldimethyl(vinyl)silane (**112**), was found to be quite effective for the Heck reaction with aryl and alkenyl iodides.<sup>56</sup> The process of carbopalladation of vinylsilanes under typical Heck reaction conditions generally leads to silicon-carbon bond cleavage. However, pyridylsilane **112** is stable under such reaction conditions. It is believed that the nitrogen of the pyridine ring engages in complex induced proximity effect (CIPE) by coordinating to the palladium to promote the carbopalladation step (Fig. 4).<sup>57–59</sup>

The Heck coupling to a variety of aryl iodides is achieved under mild conditions using  $\text{Et}_3\text{N}$ , and  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ /tri-(2-furyl)phosphine as the catalyst system (Chart 23). In all cases, the yields are exceptional and the preference for the trans product is quite high (>99%). The Heck coupling proceeds with only 1 mol% of catalyst, even for sterically demanding substrates such as **115**. Most noteworthy, however, is that the coupling to a 1,2-disubstituted vinylsilane proceeds with high regioselectivity, and geometrical selectivity for the trans isomer. This lends much support to the hypothesis of a CIPE effect of the pendent pyridine.

When TBAF was added to the reaction mixture, only cross-coupling products were observed where a new carbon-carbon bond is formed in place of the carbon-silicon bond.<sup>60,61</sup> Mixing TBAF with pyridyldimethyl(alkenyl)silanes results in cleavage of the pyridyl group and formation of the corresponding silanol presumably from the water contained in commercial TBAF. Therefore, the pyridyl group can also serve as a masked silanol. The TBAF-promoted, cross-coupling of several pyridyldimethyl(alkenyl)silanes has been reported, thereby showing two different coupling pathways that are accessible when using these types of silanes (Chart 24).

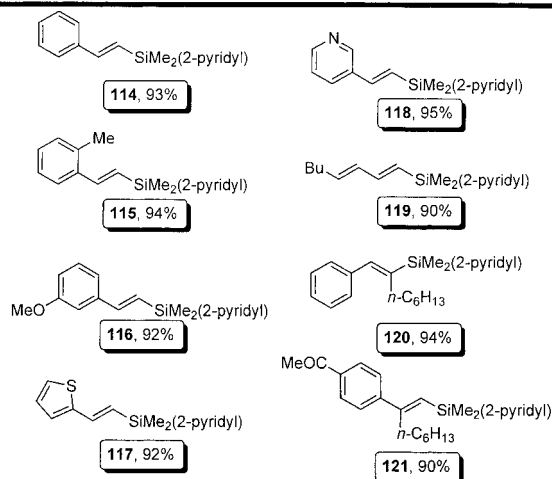
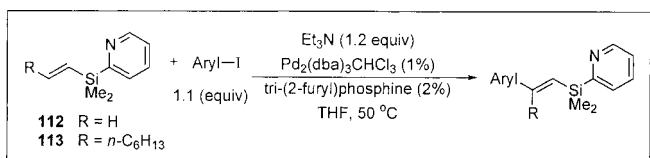


Chart 23. Heck Reactions of 2-Pyridyldimethyl(alkenyl)silanes

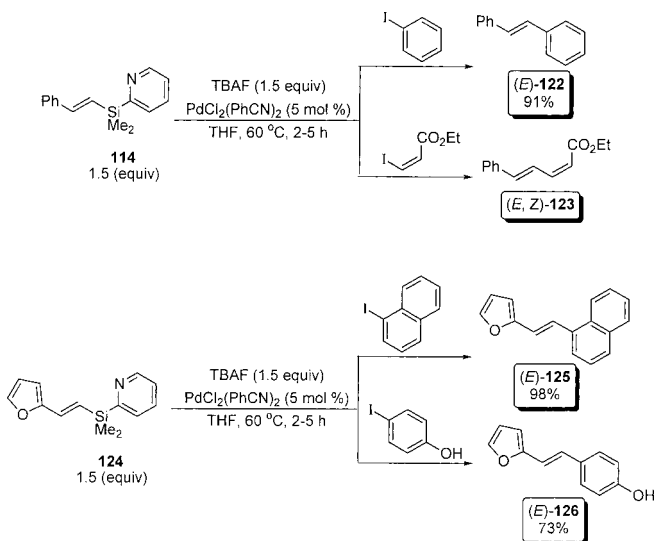


Chart 24. Cross-Coupling Reactions of 2-Pyridyldimethyl(alkenyl)silanes Promoted by TBAF

The TBAF-promoted coupling to alkenyl and aryl iodides works equally well (*(E)*-**122** and *(E,Z)*-**124**). As with previously-reported coupling reactions with silanols, the reactions employing pyridylsilanes are also compatible with several functional groups including an ester (*(E,Z)*-**123**) and a phenol (*(E)*-**126**).

The successful implementation of two distinct cross-coupling pathways from a single starting material clearly makes possible their combination in a one-pot procedure. The sequential carbometallation/transmetalation/cross-coupling of alkenylpyridyl(butenyl)silane (*(E)*-**127**) generates, in a complete regio- and stereoselective fashion, two new carbon-carbon bonds (Chart 25). This impressive sequence provides access to extended conjugated systems consisting of trisubstituted olefins in a simple one-pot/two-step procedure.

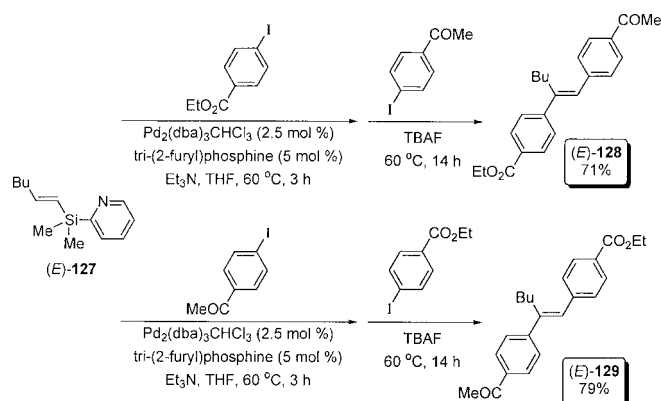


Chart 25. Tandem Heck/Cross-Coupling Reactions of 2-Pyridyldimethyl(alkenyl)silanes

The effectiveness of pyridylsilanes to direct two types of coupling reactions widens the scope of organosilicon cross-coupling both experimentally and conceptually since it represents a new class of organosilanes that are not dependent on the more common methods of simple heteroatom substitution.

## Conclusions and Outlook

Palladium-catalyzed cross-coupling of organosilicon compounds has emerged as a powerful, adaptable, and often superior method for carbon-carbon bond formation. The substrate scope that is currently available, particularly with regard to the nature of the organosilicon group used, has expanded tremendously over the last few years. This is due, in no small part, to many beneficial features that are common to all major oxygen-substituted organosilanes, not the least of which is their uniformly high reactivity. Each member of this class of organosilanes: silanols, silyl ethers, and polysiloxanes, possesses unique advantages. These include (1) the variety of methods to synthesize different silanols, (2) the unique approach of incorporating silyl ethers into molecules through intramolecular tethers, (3) and the cost-effectiveness of using commercially available polysiloxanes as vinylating sources or as substrates for one-pot processes with alkynes. Although current efforts are heavily focused on oxygen-substituted silanes, this is by no means an exclusive path to progress as exemplified by the effective use of siletanes, silyl hydrides, and pyridylsilanes as well.

In conclusion, the sheer volume of diverse, commercially-available silanes, the numerous methods to incorporate silicon into organic molecules, the low toxicity and molecular weight of organosilicon compounds, as well as the continuing evolution of new, active, coupling partners lends little doubt that organosilanes will soon occupy a premier status among palladium-catalyzed cross-coupling systems.

**Acknowledgments** We are pleased to acknowledge the support of the National Science Foundation (CHE0105205), the National Institutes of Health (GM63167-01A1), and Pharmacia Corporation. R.F.S. thanks Johnson and Johnson for a graduate fellowship.

## References and Notes

- Stille J. K., *Angew. Chem., Int. Ed.*, **25**, 508–524 (1986).
- Mitchell T. N., "Metal Catalyzed Cross-Coupling Reactions," Chapter 4, ed. by Diederich F., Stang P. J., Wiley-VCH, Weinheim, 1998.
- Farina V., Krishnamurthy V., Scott W. J., *Org. React.*, **50**, 1–657

- (1998).
- 4) Miyaura N., Suzuki A., *Chem. Rev.*, **95**, 2457—2483 (1995).
  - 5) Suzuki A., *J. Organomet. Chem.*, **576**, 147—168 (1999).
  - 6) Hiyama T., “Metal Catalyzed Cross-Coupling Reactions,” Chapter 10, ed. by Diederich F., Stang P. J., Wiley-VCH, Weinheim, 1998.
  - 7) Hiyama T., Shirakawa E., *Topics in Current Chemistry*, **219**, 61—88 (2002).
  - 8) Denmark S. E., Sweis R. F., *Acc. Chem. Res.*, **35**, 835—846 (2002).
  - 9) Denmark S. E., Griedel B. D., Coe D. M., Schnute M. E., *J. Am. Chem. Soc.*, **116**, 7026—7043 (1994).
  - 10) Denmark S. E., Griedel B. D., *J. Org. Chem.*, **59**, 5136—5138 (1994).
  - 11) Denmark S. E., Choi J. Y., *J. Am. Chem. Soc.*, **121**, 5821—5822 (1999).
  - 12) Denmark S. E., Wu Z., *Org. Lett.*, **1**, 1495—1498 (1999).
  - 13) For general methods on the synthesis of organosilanols, see: Hirabayashi K., Takahisa E., Nishihara Y., Mori A., Hiyama T., *Bull. Chem. Soc. Jpn.*, **71**, 2409—2417 (1998).
  - 14) Sieburth S. McN., Fensterbank L., *J. Org. Chem.*, **58**, 6314—6318 (1993).
  - 15) Sieburth S. McN., Mu W., *J. Org. Chem.*, **58**, 7584—7586 (1993).
  - 16) Lickiss P. D., *Advances in Inorganic Chemistry*, **42**, 147—262 (1995).
  - 17) Hirabayashi L., Kawashima J., Nishihara Y., Mori A., Hiyama T., *Org. Lett.*, **1**, 299—301 (1999).
  - 18) Hirabayashi K. Mori A., Kawashima J., Suguro M., Nishihara Y., Hiyama T., *J. Org. Chem.*, **65**, 5342—5349 (2000).
  - 19) The cross-coupling of disiloxanes and trimethylsilyl derivatives was attempted under optimized conditions and found unsuccessful.<sup>18)</sup>
  - 20) Denmark S. E., Wehrli D., *Org. Lett.*, **2**, 565—568 (2000).
  - 21) Denmark S. E., Wehrli D., Choi J. Y., *Org. Lett.*, **2**, 2491—2494 (2000).
  - 22) Denmark S. E., Pan W., *J. Organomet. Chem.*, **653**, 98—104 (2002).
  - 23) Denmark S. E., Neuville L., *Org. Lett.*, **2**, 3221—3224 (2000).
  - 24) Macleod D., Moorcroft D., Quayle P., Dorrity M. R. J., Malone J. F., Davies G. M., *Tetrahedron Lett.*, **31**, 6077—6080 (1990).
  - 25) Deneux M., Akhrem I. C., Avetissian D. V., Myssoff E. I., Vol'pin M. E., *Bull. Soc. Chim. Fr.*, **1973**, 2638—2642 (1973).
  - 26) Nishihara Y., Ikegashira K., Hirabayashi K., Ando J., Mori A., Hiyama T., *J. Org. Chem.*, **65**, 1780—1787 (2000).
  - 27) Chang S., Yang S. H., Lee P. H., *Tetrahedron Lett.*, **42**, 4833—4835 (2001).
  - 28) Hirabayashi K., Nishihara Y., Mori A., Hiyama T., *Tetrahedron Lett.*, **39**, 7893—7896 (1998).
  - 29) These comparisons were conducted with a stoichiometric amount of Pd(OAc)<sub>2</sub> and therefore without Cu(OAc)<sub>2</sub> or LiOAc as stoichiometric oxidants.
  - 30) Denmark S. E., Sweis R. F., *J. Am. Chem. Soc.*, **123**, 6439—6440 (2001).
  - 31) Potassium trimethylsilanolate (Aldrich) \$63/mole. Tetrabutylammonium fluoride trihydrate (Fluka) \$624/mole.
  - 32) Tamao K., Kobayashi K., Ito Y., *Tetrahedron Lett.*, **30**, 6051—6054 (1989).
  - 33) Denmark S. E., Pan W., *Org. Lett.*, **3**, 61—64 (2001).
  - 34) A complimentary anti hydrosilylation/cross-coupling process that uses a ruthenium-based catalyst has recently been developed: Denmark S. E., Pan W., *Org. Lett.*, **4**, (2002) in press.
  - 35) Furstner A., *Angew. Chem., Int. Ed.*, **39**, 3012—3043 (2000).
  - 36) Grubbs R. H., Chang S., *Tetrahedron*, **54**, 4413—4450 (1998).
  - 37) Schuster M., Blechert S., *Angew. Chem. Int. Ed.*, **36**, 2036—2056 (1997).
  - 38) “Alkene Metathesis in Organic Synthesis,” ed by Furstner A., Springer, Berlin, 1998.
  - 39) Denmark S. E., Yang S-M., *Org. Lett.*, **3**, 1749—1752 (2001).
  - 40) Denmark S. E., Yang S-M., *J. Am. Chem. Soc.*, **124**, 2102—2103 (2002).
  - 41) Illuminati G., Madnolini L., *Acc. Chem. Res.*, **14**, 95—102 (1981).
  - 42) Liebman J. F., Greenberg A., *Chem. Rev.*, **76**, 311—365 (1976).
  - 43) Mowery M. E., DeShong P., *J. Org. Chem.*, **64**, 1684—1688 (1999).
  - 44) Mowery M. E., DeShong P., *Org. Lett.*, **1**, 2137—2140 (1999).
  - 45) In cases where homocoupling of the aryl halide could be problematic, the use of tri-*o*-tolylphosphine in place of triphenylphosphine is suggested.
  - 46) Wolfe J. P., Singer R. A., Yang B. H., Buchwald S. L., *J. Am. Chem. Soc.*, **121**, 9550—9561 (1999).
  - 47) Wolfe J. P., Buchwald S. L., *Angew. Chem. Int. Ed.*, **38**, 2413—2416 (1999).
  - 48) Lee H. M., Nolan S. P., *Org. Lett.*, **2**, 2053—2055 (2000).
  - 49) Ito H., Sensui H., Arimoto K., Miura K., Hosomi A., *Chem. Lett.*, **1997**, 639—640 (1997).
  - 50) Denmark S. E., Wang Z., *J. Organomet. Chem.*, **624**, 372—375 (2001).
  - 51) McKean D. R., Parrinello G., Renaldo A. F., Stille J. K., *J. Org. Chem.*, **52**, 422—424 (1987).
  - 52) Stille J. K., Groh B. L., *J. Am. Chem. Soc.*, **109**, 813—817 (1987).
  - 53) DVDS: 1,3-divinyl-1,1,3,3-tetramethyldisiloxane.
  - 54) Denmark S. E., Wang Z., *Org. Lett.*, **3**, 1073—1076 (2001).
  - 55) Mori A., Suguro M., *Synlett*, **2001**, 845—847 (2001).
  - 56) Itami K., Mitsudo K., Kamei T., Koike T., Nokami T., Yoshida J., *J. Am. Chem. Soc.*, **122**, 12013—12014 (2000).
  - 57) Beak P., Meyers A. I., *Acc. Chem. Res.*, **19**, 356—363 (1986).
  - 58) Snieckus V., *Chem. Rev.*, **90**, 879—933 (1990).
  - 59) Beak P., Basu A., Gallagher D. J., Park Y. S., Thayumanavan S., *Acc. Chem. Res.*, **29**, 552—560 (1996).
  - 60) Itami K., Nokami T., Yoshida J., *J. Am. Chem. Soc.*, **123**, 5600—5601 (2001).
  - 61) Itami K., Nokami T., Ishimura Y., Mitsudo K., Kamei T., Yoshida J., *J. Am. Chem. Soc.*, **123**, 11577—11585 (2001).