

Organosilicon Reagents: Synthesis and Application to Palladium-Catalyzed Cross-Coupling Reactions

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Professor Scott E. Denmark (left) receiving the 2003 ACS Award for Creative Work in Synthetic Organic Chemistry from Dr. Chris D. Hewitt, Aldrich Vice President of Marketing and R&D. Photo © James Tkatch.



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1. Introduction

Transition-metal-catalyzed cross-coupling of organometallic reagents with organic halides has become a powerful method for carbon–carbon-bond formation. Organotin,¹ organoboron,² and organozinc³ reagents are well established as competent precursors for palladium-catalyzed cross-coupling

reactions, and have found wide application in synthetic organic chemistry. But, due to a number of drawbacks inherent to these substrates, organosilicon reagents have emerged as competitive alternatives. The lack of toxicity, high chemical stability, and low molecular weight of organosilanes make them ideal for use as nucleophilic partners in cross-coupling with organic halides and pseudohalides. Silicon-based reagents were originally considered to be insufficiently active toward palladium-catalyzed cross-coupling, but early work by Hiyama et al. showed that organosilanes could be activated by a nucleophilic promoter.⁴ Following this discovery, a multitude of organosilanes bearing a wide variety of substituents about the silicon center as well as an assortment of transferable groups have been identified.⁵ This review will concentrate on recent advances in the use of organosilanes in palladium-catalyzed cross-coupling reactions, with an emphasis on the preparative

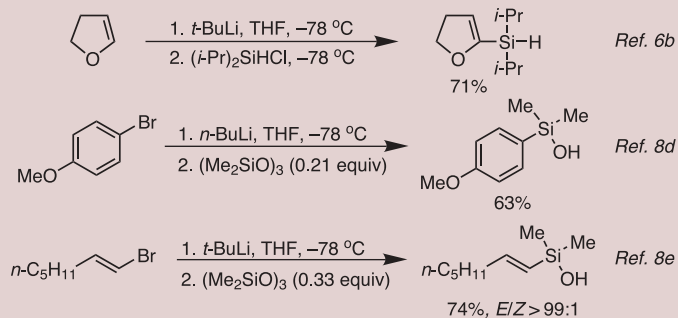


Figure 1. Preparation of Organosilanes by Reaction of Organometallic Reagents with Halosilanes or Cyclosiloxanes.

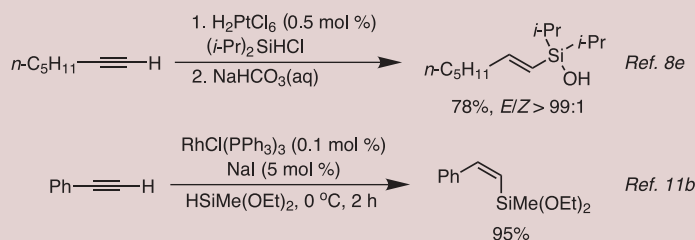


Figure 2. Preparation of Organosilanes by Hydrosilylation of Alkynes.

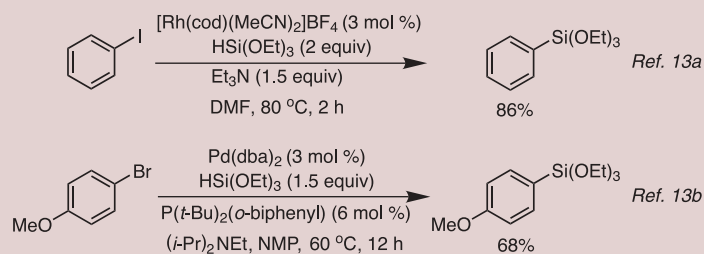


Figure 3. Preparation of Organosilanes by Transition-Metal-Catalyzed Coupling of Aryl Halides with Silyl Hydrides.

aspects of this chemistry and on the synthesis and applications of these substrates.

2. Synthesis of Organosilicon Reagents

In response to the growing interest in the palladium-catalyzed cross-coupling of organosilicon compounds, a number of methods to prepare a wide range of coupling precursors are now available. The preparations of these compounds are diverse, and are based on the type of organic moiety being employed as well as the substituents about the silicon atom. Of the methods described, most can be performed on a large scale to provide useful quantities of material thanks,

in large measure, to the relatively low cost and availability of the silicon-containing starting materials. Once synthesized, organosilanes are stable compounds that can be purified by chromatography or distillation and can be easily handled in most cases.

2.1. Reaction of Organometallic Reagents with Halosilanes or Cyclosiloxanes

The use of organolithium and organomagnesium reagents for the nucleophilic displacement of a leaving group at the silicon center is one of the simplest methods to introduce silicon into an organic molecule (**Figure 1**). The reaction of phenyllithium or

vinylmagnesium bromide with a dialkylchlorosilane⁶ readily provides the corresponding aryl- or vinylsilyl hydride. The newly formed silyl hydride can then be subjected to further manipulations to gain access to silyl ethers, silyl halides, and silanols.^{6,7} Direct formation of organosilanol can be similarly accomplished by addition of the organometallic reagent to a number of readily available and inexpensive cyclosiloxanes.⁸ Aqueous hydrolysis of the substituted polysiloxane formed in situ provides the organosilanol, which can then be easily purified by column chromatography or distillation. Although this method of synthesis is both straightforward and efficient, it is limited by substrate compatibility with the organometallic agent employed. This problem can be avoided by protection of the sensitive functional group or, better still, by use of one of the alternative methods described below.

2.2. Hydrosilylation of Alkynes and Alkenes

The metal-catalyzed hydrosilylation of alkynes and alkenes to provide substituted alkenylsilanes and alkylsilanes avoids the use of highly reactive organometallic reagents and the limitations associated with them.⁹ The insertion of a platinum,^{8c,10} rhodium,¹¹ or ruthenium¹² catalyst into an Si-H bond, provides an active metal hydride that undergoes addition across an unsaturated organic precursor generating an organosilyl halide or organosilyl ether (**Figure 2**). As with the previous method, the organosilicon compounds thus generated can be further manipulated to obtain organosilanol or other silicon species. The stereo- and regioselectivity of the hydrosilylation are dependent on the catalyst employed and the silicon precursor involved in the reaction, but a judicious choice of the two agents can lead to high levels of control in most cases.⁹ Obviously, this method is well suited for the preparation of alkenylsilanes and alkylsilanes. Other methods are needed to install the silicon functionality into aryl or heteroaryl subunits.

2.3. Transition-Metal-Catalyzed Coupling of Aryl Halides with Silyl Hydrides

Recently, investigations into the transition-metal-catalyzed coupling of organic halides with silyl hydrides have provided a powerful method for the synthesis of organosilanes. Base-activated insertion of a transition-metal complex into an Si-H bond

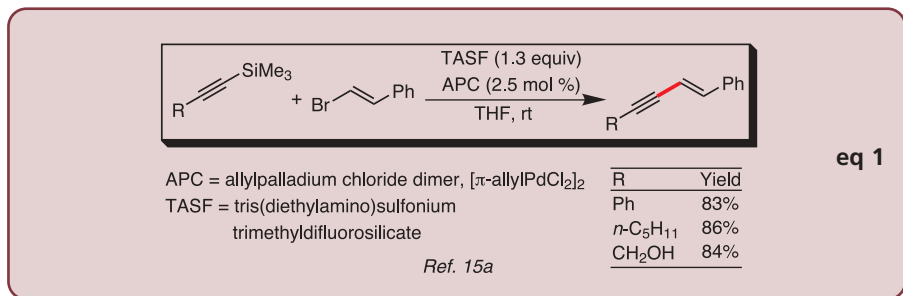
followed by transfer of the silyl group to an aryl or vinyl halide successfully provide the desired organosilane (**Figure 3**).¹³ This reaction is limited to the coupling of alkoxy-silanes, alkylsilanes, and halosilanes with electron-rich aryl iodides and bromides. The process is catalyzed by Pd(dba)₂^{13b,c} or [Rh(cod)(MeCN)₂]BF₄^{13a} in the presence of a stoichiometric amount of base, and is thought to proceed through Si–H/C–I bond exchange by oxidative addition of the hydrosilane followed by σ -bond metathesis of the Si–Pd/C–I bonds.^{13c}

3. Palladium-Catalyzed Cross-Coupling

The coupling of organosilicon reagents with organic halides and pseudohalides has evolved to be comparable in scope to other palladium-catalyzed coupling methods.^{4,5} Generally, the conditions for the palladium-catalyzed cross-coupling are mild, but do require a promoter [tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), tris(diethylamino)sulfonium trimethyldifluorosilicate (TASF), potassium trimethylsilylanolate (TMSOK), Ag₂O, Cs₂CO₃, etc.] to provide high yields of the desired cross-coupling products. The byproducts of the cross-coupling reaction are polysiloxanes, which can be removed by conventional methods such as chromatography (silica gel or reverse-phase) or distillation. Many types of organosilanes are competent coupling partners for the palladium-catalyzed reaction. The following survey of silicon-containing cross-coupling components is organized around three principal rubrics: (1) the type of transferable group on the organosilane, (2) the method of organosilane activation, and (3) the nontransferable substituents about the silicon center.

3.1. Alkynylsilanes

The palladium-catalyzed coupling reaction of terminal alkynes developed by Sonogashira and co-workers has been widely applied in many synthetic endeavors.¹⁴ Nevertheless, new general methods that employ mild conditions are still of great interest for the synthesis of substituted alkynes. Alkynyl(trialkyl)silanes and alkenylsilanols, which are easily synthesized by addition of alkynyllithium reagents to chlorosilanes, are competent reagents for the palladium-catalyzed cross-coupling reaction.¹⁵ The successful coupling of substituted trimethylsilylalkynes with aryl or vinyl iodides or with vinyl bromides requires the use of 1.3 equiv of TASF and 2.5 mol % of



$[\pi\text{-allylPdCl}_2]_2$ (APC) in THF at ambient temperature, to provide substituted alkynes in good yields (**eq 1**).^{15a} Catalytic amounts of CuCl or CuCl–Pd(PPh₃)₄ can also be used at elevated temperatures in DMF to effect the coupling of alkynyl(trialkyl)silanes with aryl chlorides or triflates.^{15b} Alternatively, dimethyl(phenylethynyl)silanol undergoes facile coupling with aryl iodides in THF at 60 °C in the presence of a stoichiometric amount of TBAF or Ag₂O and 5 mol % of Pd(PPh₃)₄.^{15c}

3.2. Alkenylsilanes

The palladium-catalyzed cross-coupling of alkenylsilanes with organic halides and pseudohalides has gained much attention because of the mild reaction conditions required and broad scope of olefinic products that can be obtained.^{4,5} In general, the cross-coupling reactions of alkenylsilanes are highly efficient, but several side processes can intervene under the reaction conditions. Of these undesirable processes, the most notable are the unproductive removal of the silicon moiety (protodesilylation) and the formation of undesired regioisomers. In most cases, manipulation of the reaction conditions (choice of promoter, palladium catalyst, and ligands) can avoid many of these pitfalls to provide high-yielding and selective reactions.

3.2.1. Fluoride Activation

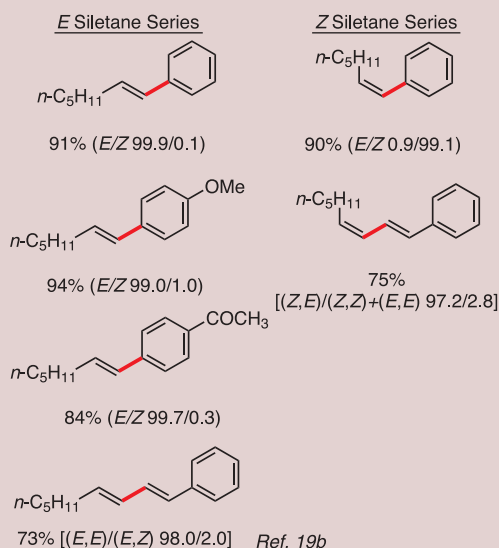
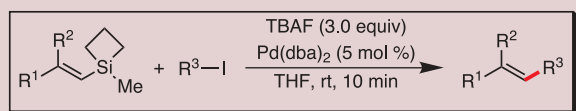
Because of the high affinity of fluoride for silicon (BDE Si–F = 135 kcal/mol),¹⁶ the use of a fluoride ion source (in the form of TBAF, TMAF, TASF, KF, or CsF) together with tetracoordinate silanes is believed to provide pentacoordinate fluorosilicate intermediates, which are considered to be the “active” species in the palladium-catalyzed cross-coupling reactions.⁴ Silicon-29 NMR spectroscopic studies on the use of TBAF as a promoter for the palladium-catalyzed cross-coupling of several types of alkenylsilanes (alkenylsilylanes, alkenylsilyl halides, alkenylalkoxy-silanes, alkenyldi-siloxanes, and alkenylsilanols) provide that

all of these precursors react via a common intermediate, hypothesized to be a hydrogen-bonded silanol–fluoride adduct.¹⁷ Because of this mechanistic commonality, a wide range of organosilanes, that display a similar reactivity yet provide a variety of precursor options, are competent reagents for the fluoride-activated cross-coupling reaction.

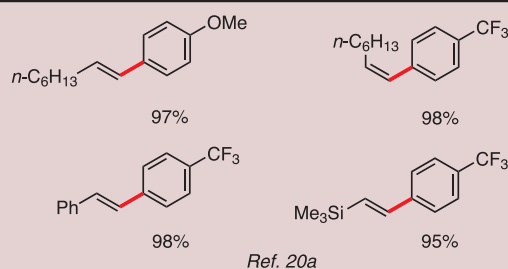
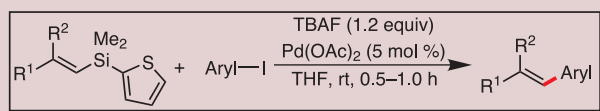
Three classes of alkenylsilanes undergo facile fluoride-promoted cross-coupling: (1) alkenylsilanes bearing alkyl groups on the silicon, (2) alkenylsilanes bearing fluoride-cleavable organic groups (alkenylsilanol surrogates), and (3) heteroatom-substituted alkenylsilanes. In general, alkyl-substituted alkenylsilanes are extremely stable to chemical manipulations prior to fluoride activation, but do not readily undergo productive cross-coupling. Alkenylsilanol surrogates are also stable under conditions for many reactions. However, these silanes contain a cleavable group that, in the presence of a fluoride activator, produces a heteroatom-substituted alkenylsilane in situ, which provides a compromise of stability and reactivity. Heteroatom-substituted alkenylsilanes are, of all the types identified here, the most reactive toward palladium-catalyzed cross-coupling due to the ease with which they can access an “active” species under fluoride promotion. Unfortunately, these silanes are also the most labile toward unproductive reactions including hydrolysis, protodesilylation, and dimerization and, therefore, must be promptly subjected to palladium-catalyzed cross-coupling without prior chemical manipulations. Thoughtful selection of the alkenylsilanes and the reactions in which they can be employed leads to a balanced combination of precursor and conditions, allowing for a wide range of olefinic cross-coupling products.

3.2.1.1. Alkenyl(trialkyl)silanes

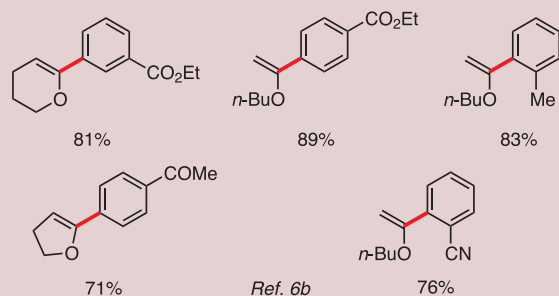
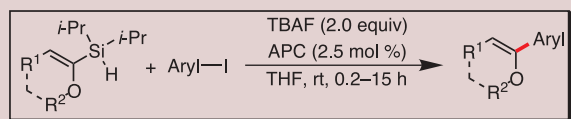
The combination of readily available trimethyl(vinyl)silane and an aryl iodide, under somewhat modified conditions to those developed for alkynyl(trialkyl)silanes mentioned previously (2.4 equiv of TASF and 5 mol % of Pd(PPh₃)₄ in THF at 50 °C),



eq 2



eq 3



eq 4

is effective for the production of vinylated products. The reaction is tolerant of diverse functionality on the aryl iodide, but substitution on the trimethyl(vinyl)silane inhibits productive cross-coupling. The failure to engage substituted alkenyl(trialkyl)silanes in this process is believed to arise from their inability to form the required pentacoordinate fluorosilicate species.¹⁸

3.2.1.2. Alkenylsilanol Surrogates

3.2.1.2.1. Alkenylsiletanes

Alkenylsilacyclobutanes represent a special class of alkenyl(trialkyl)silanes that can undergo facile palladium-catalyzed cross-coupling with aryl and vinyl iodides. These reactions proceed rapidly in the presence of 3 equiv of TBAF and 5 mol % of Pd(dba)₂ in THF at ambient temperature (eq 2).¹⁹ Alkenylsiletanes, which can be readily prepared from organometallic addition to 1-chloro-1-methylsilacyclobutane,^{19b} originally were thought to undergo cross-coupling this rapidly due to the enhanced Lewis acidity of the silicon center from strain release during the formation of the pentacoordinate fluorosilicate.^{19c} However, under the reaction conditions, the siletanes are observed to undergo a fast initial ring opening to form alkenyl(propyl)(methyl)silanols, which are most likely the active species for the cross-coupling reaction.¹⁷ Direct comparisons to alkenylsilanol, alkenylsilyl halides, and alkenylsilyl ethers reveal a similar reactivity, and corroborate the observation that these alkenylsilanes react via the same intermediate.¹⁷

3.2.1.2.2. Alkenyl(thienyl)- and Alkenyl(pyridyl)silanes

The observation that 2-thienyl and 2-pyridyl groups on silicon are not transferred to organic halides under standard palladium-catalyzed cross-coupling conditions, combined with the fact that at least one activating group or heteroatom is required on the silicon center to provide the coupling product, prompted the investigation of alkenyldimethyl(2-thienyl)silanes and alkenyldimethyl(2-pyridyl)silanes. These compounds are considered excellent cross-coupling substrates due to the enhanced stability provided by the heterocyclic groups toward moisture, acid, and base as compared to the corresponding halosilanes or other heteroatom-substituted silanes.^{20a} This allows for the alkenylsilane coupling precursors to resist some chemical manipulations prior to palladium-catalyzed cross-coupling. Alkenyldimethyl(2-thienyl)silanes undergo cross-

coupling with a number of aryl iodides and bromides in the presence of 1.2 equiv of TBAF and 5 mol % of Pd(OAc)₂ in THF at ambient temperature (eq 3).^{20a} Similarly, alkenyldimethyl(2-pyridyl)silanes afford cross-coupling products from aryl and vinyl iodides at slightly elevated temperatures.^{20b,c}

3.2.1.2.3. Alkenyl(benzyl)silanes

Benzyl dimethylsilyl-substituted alkenes are similar to the aforementioned 2-thienyl- and 2-pyridylsilanes in that the benzyl group is also considered non-transferable. In addition, it is stable to acid, buffered fluoride medium, and strong base. However, the benzyl substituent does suffer rapid cleavage with 2.2 equiv of TBAF in THF at 0 °C to provide the corresponding silanol. Accordingly, benzyldimethylsilanes are expected to possess enhanced chemical stability compared to heteroaryl-containing silanes and yet still be activated with TBAF for cross-coupling.²¹

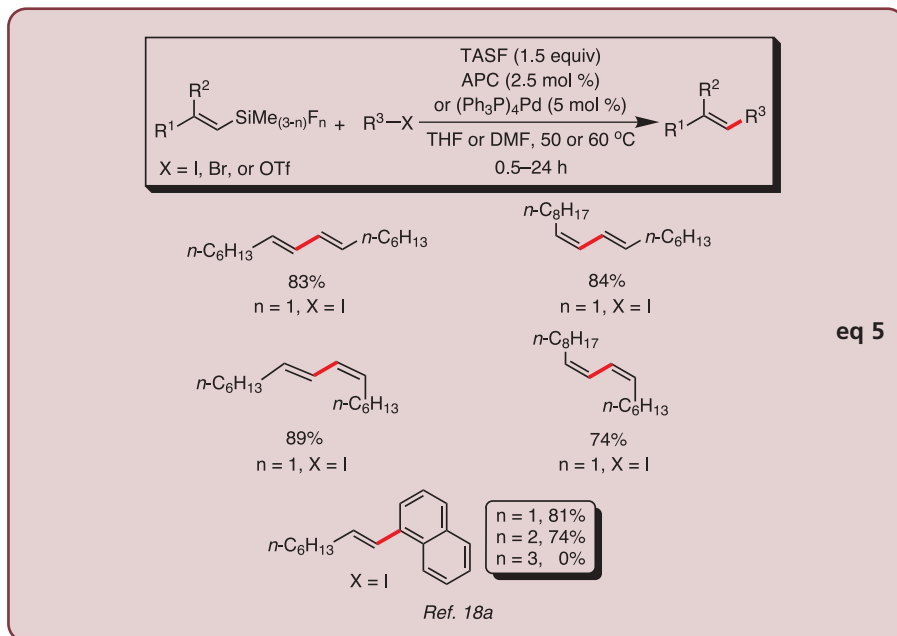
3.2.1.2.4. Alkenylsilyl Hydrides

Silyl hydrides, which are easily synthesized through organometallic addition to dialkylchlorosilanes, are more stable to hydrolysis than are the heteroaryl-substituted organosilanes. In addition, they have lower molecular weights compared to other non-heteroaryl-substituted organosilanes and are thus ideal for use with sensitive or precious substrates. These characteristics are illustrated in the palladium-catalyzed cross-coupling of 2-(4,5-dihydrofuranyl)-diisopropylsilane and 2-(5,6-dihydro-4H-pyridyl)diisopropylsilane. These alkenylsilyl hydrides undergo oxidative hydrolysis when combined with TBAF·3H₂O, producing the alkenylsilanol in situ.²² Indeed, the corresponding silanols give similar results under identical conditions. A number of (α-alkoxyvinyl)silyl hydrides are effective cross-coupling agents when combined with aryl iodides in the presence of 2 equiv of TBAF and 2.5 mol % of APC in THF at room temperature (eq 4).^{6b} The reaction is compatible with a broad range of functional groups, and manipulation of the intermediate alkoxy vinyl ethers with 1 N HCl provides the corresponding ketones directly.^{6b}

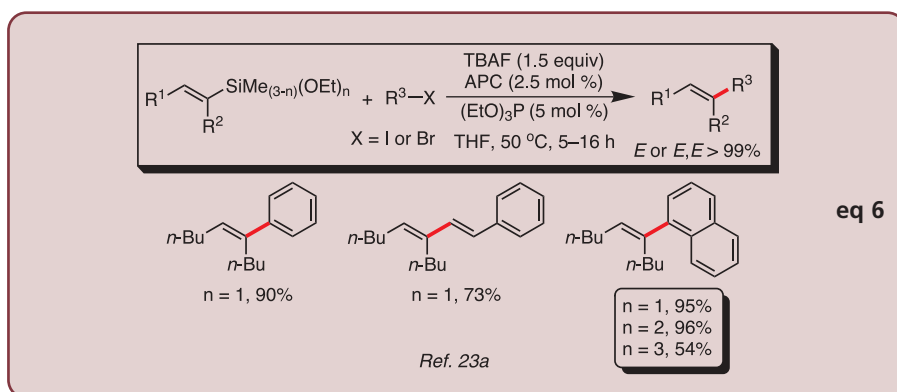
3.2.1.3. Heteroatom-Substituted Alkenylsilanes

3.2.1.3.1. Alkenylsilyl Halides

Alkenylsilyl chlorides and fluorides were among the first alkenylsilanes to act as effective and general substrates in the



eq 5



eq 6

palladium-catalyzed cross-coupling reaction.⁴ The combination of halo(alkyl)silanes or dihalo(alkyl)silanes with organic halides in the presence of 1.5 equiv of TASF and 2.5 mol % of APC in THF at 50 °C or, alternatively, with 5 mol % of (Ph₃P)₄Pd in DMF at 60 °C provides the desired cross-coupling products in good yields (eq 5).^{18a} Many organic halides and pseudohalides are suitable as coupling partners, and the reaction is highly stereo- and regioselective in the case of (*E*- and (*Z*-)fluoro(dimethyl)silyl-1-alkenes. Interestingly, trihalosilanes are ineffective in the cross-coupling reaction of 1-iodonaphthalene, but do function in the coupling with an alkenyl triflate.^{18b}

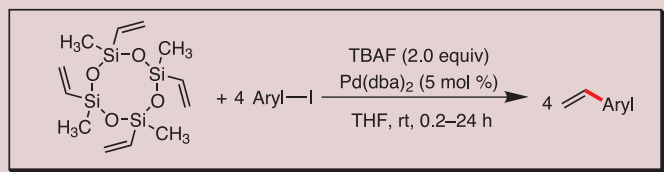
3.2.1.3.2. Alkenyl(alkoxy)silanes

Alkenyl(alkoxy)silanes (silyl ethers) react at rates comparable to those of alkenylsilanol and alkenylsilyl halides with similar numbers of heteroatoms about the silicon center, but are less prone to hydrolysis

or oligomerization. Alkenylmono-, di-, and trialkoxysilanes—in the presence of 1.5 equiv of TBAF, 2.5 mol % of APC, and 5 mol % of (EtO)₃P in THF at 50 °C—undergo cross-coupling with a number of organic halides (eq 6).^{23a} Vinyltrimethylsiloxane has also proved useful as a vinyl transfer agent for aryl iodides.^{23b}

3.2.1.3.3. Alkenyldisiloxanes and Poly(alkenyldisiloxanes)

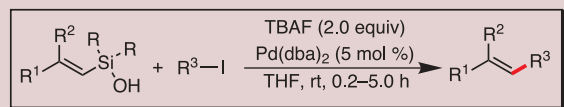
Alkenyldisiloxanes are readily formed by dehydrative dimerization of their parent alkenylsilanols with a catalytic amount of base.¹⁷ The disiloxane moiety is thermodynamically stable, making alkenyldisiloxanes one of the more easily handled types of organosilicon compound. Because they converge to the same intermediate in the presence of TBAF as the corresponding alkenylsilanol, alkenyldisiloxanes undergo cross-coupling with the same outcome.¹⁷ Similarly, the readily available siloxane oligomers also provide productive cross-coupling with



eq 7

Aryl: 2-MeOC₆H₄ 4-MeOC₆H₄ 3-NO₂C₆H₄ 4-CH₃COC₆H₄ 4-EtO₂CC₆H₄
Yield: 72% 63% 87% 88% 85%

Ref. 24b

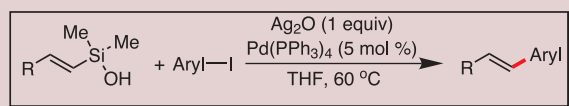


eq 8

R = Me, R⁴ = MeO: 95% (*E/Z* 97.2/2.8) R = Me, R⁴ = MeO: 94% (*E/Z* 2.6/97.4)
R = *i*-Pr, R⁴ = Ac: 80% (*E/Z* 99.5/0.5) R = *i*-Pr, R⁴ = Ac: 86% (*E/Z* 1.0/99.0)

R = Me: 91% [(*E,E*)/(*E,Z*) 95.8/4.2] R = Me: 64% [(*Z,Z*)/AOI 87.8/12.2]
R = *i*-Pr: 87% [(*E,E*)/ α -isomer 97.8/2.2] R = *i*-Pr: 68% [(*Z,Z*)/AOI 92.4/7.6]
 α -isomer = cine-rearranged product AOI = all other isomers

Ref. 8e



eq 9

67%, 3 h 95%, 4 h
Ref. 26a

TBAF activation. Poly(alkenylsiloxanes) are easily synthesized by hydrosilylation of terminal alkynes with poly(methylhydro)siloxane (PMHS) and a catalytic amount of (Bu₄N)₂PtCl₆. Cross-coupling of poly(alkenylsiloxanes) with a number of aryl iodides proceeds smoothly with 5 equiv of the polysiloxane, 1.2 equiv of TBAF, and 2.5 mol % of Pd₂(dba)₃•CHCl₃ in THF at 60 °C.^{24a} Several commercially available cyclo-oligodisiloxanes, orthosiliconates, and disiloxanes are extremely efficient vinyl transfer agents for a broad range of aryl iodides with 2–3 equiv of TBAF and 1–5 mol % of Pd(dba)₂ in THF at ambient temperature.^{24b} 1,3,5,7-Tetravinyl-1,3,5,7-tetramethylcyclotetrasiloxane is the most competent of the vinyl transfer agents under these conditions, allowing all of the possible

vinyl groups to transfer during the cross-coupling reaction (eq 7). This reaction is general and, due to the inexpensive and nontoxic nature of the starting materials, amenable to large-scale preparations.^{24b}

3.2.1.3.4. Alkenylsilanols

Alkenylsilanols are excellent substrates for the palladium-catalyzed cross-coupling reaction when activated by TBAF. Alkenyl(dimethyl)silanols and alkenyl(diisopropyl)silanols couple rapidly with a large number of aryl and vinyl iodides in the presence of 2 equiv of TBAF and 5 mol % of Pd(dba)₂ in THF at ambient temperature (eq 8).^{3c} Highly substituted and functionalized (*E*- and *Z*-)alkenyl(dialkyl)silanols also undergo facile coupling, with good efficiency

and high stereospecificity.^{25a} The palladium-catalyzed cross-coupling of alkenyl(dimethyl)silanols with aryl and vinyl triflates and nonaflates can also be accomplished at ambient temperature by the use of a hydrated TBAF (TBAF•3–10H₂O) in 1,4-dioxane solution in the presence of 5 mol % of PdBr₂ and 10 mol % of 2-[di(*tert*-butyl)phosphino]-1,1'-biphenyl. Under these conditions, the undesired cleavage of the pseudohalide to the corresponding phenol or ketone is minimized by the increased hydration level of the TBAF solution.^{25b}

3.2.2. Fluoride-Free Activation of Alkenylsilanols, Diols, and Triols

Tetrabutylammonium fluoride (TBAF) and other fluoride-containing reagents are highly effective for promoting the palladium-catalyzed cross-coupling of a range of organosilanes. However, the widespread use of silicon protecting groups in complex-molecule synthesis precludes the application of a fluoride-activated coupling that may jeopardize the integrity of the silicon protecting groups. Thus, a non-fluoride promoter that would facilitate the silicon-based couplings with equal efficiency and selectivity is highly desirable. The first such promoter that has been identified is silver oxide (Ag₂O), which can activate alkenylsilanols, diols, and triols in the presence of a palladium catalyst in THF at 60 °C (eq 9).^{26a,b} Silver oxide is thought to act as a nucleophilic activator for the silanol to form a pentacoordinate silicate species, and to assist in halide abstraction from the palladium center thus facilitating transmetalation.^{26a}

Alternatively, the inexpensive salt, potassium trimethylsilanolate (TMSOK), can also be employed for the activation of alkenyl(dimethyl)silanols.^{26c,d} For example, the cross-coupling of (*E*- and *Z*-)1-heptenyl(dimethyl)silanols with a variety of aryl and vinyl iodides is efficiently promoted by 2 equiv of TMSOK and 5 mol % Pd(dba)₂ in DME at ambient temperature (eq 10).^{26c} When activated by TMSOK, silanols are as reactive as when activated by TBAF and give rise to cross-coupling products in high yields and with excellent regio- and stereoselectivities. Direct comparison of the palladium-catalyzed cross-coupling of alkenyl(dialkyl)silanols under activation by TBAF or TMSOK reveals a striking difference in the sensitivity of the coupling rate to steric effects at the silicon center.^{26d} For example, whereas under TBAF activation both alkenyldimethyl- and alkenyldiisopropylsilanols couple at the same rate, under TMSOK activation the

dimethylsilanol react nearly 20 times faster! This and other observations suggest that a different mechanism may be operating under the fluoride-free conditions. It is possible to employ other bases (e.g., KH, NaH, KO t -Bu, NaO t -Bu, or NaOH) for the palladium-catalyzed cross-coupling of alkenyl(dialkyl)silanol, but they are not as effective nor as well studied as those already mentioned.^{26b-d}

3.3. Arylsilanes

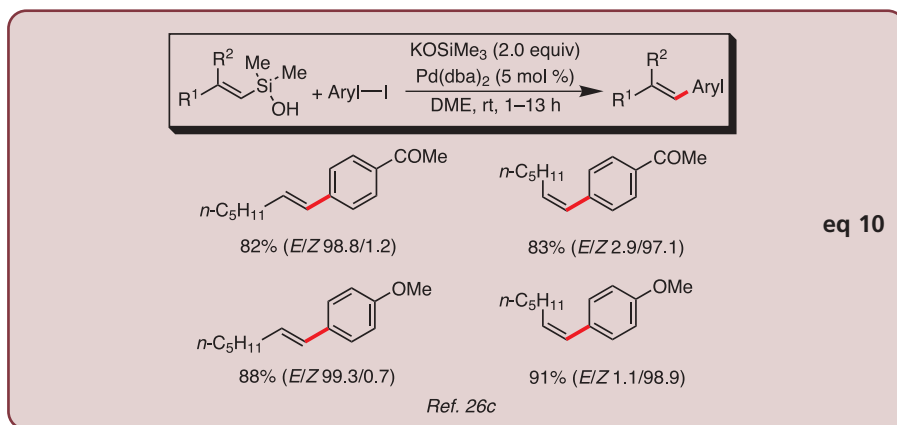
Compared to alkenylsilanes, arylsilanes have similar physical and chemical properties and may be prepared through similar synthetic routes. Unlike their alkenyl counterparts, however, arylsilanes require more forcing conditions to undergo palladium-catalyzed cross-coupling with aryl and vinyl halides. These harsher conditions often lead to undesirable side reactions such as protodesilylation and homocoupling of the organic halide.^{4,5} A number of protocols have been developed to suppress or minimize the unproductive pathways and maximize the formation of the desired cross-coupling products.

3.3.1. Arylsiletanes

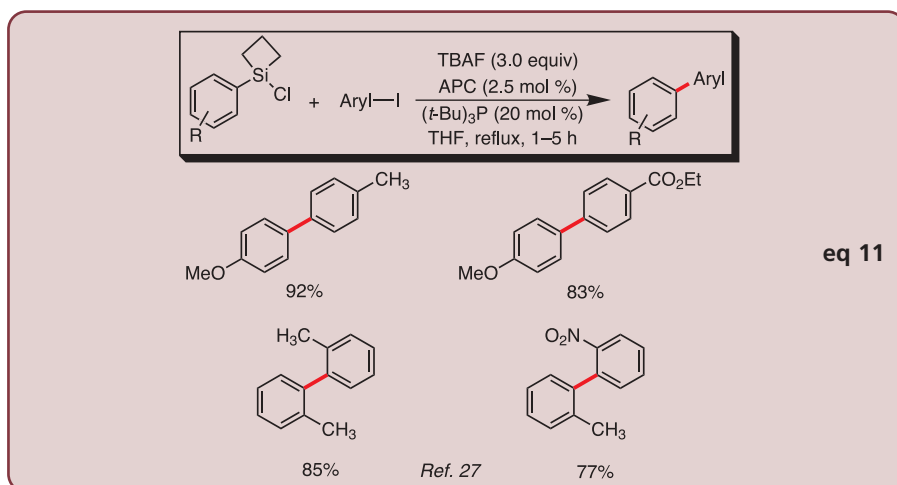
Unlike alkenylsilacyclobutanes, the palladium-catalyzed cross-coupling of methyl(phenyl)silacyclobutane with aryl iodides in the presence of 3 equiv of TBAF and 5 mol % of APC in refluxing THF provides no desired cross-coupling products. However, activation of the siletane by substituting a chloride or fluoride for the methyl group on the silicon allows these halo(aryl)silacyclobutanes to couple readily with aryl iodides under somewhat modified conditions (eq 11).²⁷ These conditions also provide a moderate amount of undesired homocoupling product, which can be minimized by the addition of 20 mol % of (t -Bu)₃P to the reaction mixture. The addition of the phosphine ligand to the reaction retards both the homocoupling and cross-coupling pathways, but overall provides a more favorable ratio of the two observed products. Under these conditions, both aryl(chloro)silacyclobutanes and aryl(fluoro)silacyclobutanes are competent coupling precursors, with aryl(chloro)silacyclobutanes providing biaryl cross-coupling products with slightly extended reaction times.²⁷

3.3.2. Arylsilyl Halides

Palladium-catalyzed phenyl transfer to aryl iodides, bromides, and triflates can



eq 10



eq 11

be performed with tetrabutylammonium triphenyldifluorosilicate (TBAT), an active difluorosilicate, in the presence of 10 mol % of Pd(dba)₂ in DMF at 95 °C to afford unsymmetrical biaryls in good yields.^{28a} The cross-coupling of substituted aryl(alkyl)difluorosilanes with aryl iodides, bromides, and triflates takes place smoothly to provide a number of biaryls in high yields.^{18b,28b,c} Aryl(alkyl)dichlorosilanes can also be employed as cross-coupling partners with aryl halides under activation with fluoride [KF, APC (5 mol %), DMF, 120 °C],^{28c} or with sodium hydroxide [Pd(OAc)₂, Ph₃P, THF, 60 °C].^{28d} Application to solid-phase synthesis can also be accomplished using iodobenzoic acid tethered to Wang resin.^{28e}

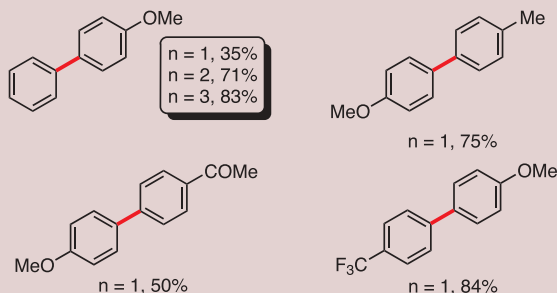
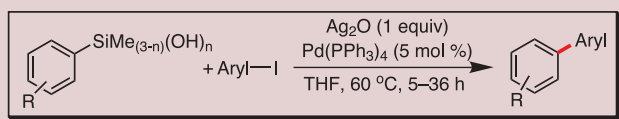
3.3.3. Aryl(alkoxy)silanes

Compared to the corresponding halides, aryl(alkoxy)silanes are more stable and, in some cases, readily available. Phenyltrimethoxysilane undergoes facile palladium-catalyzed cross-coupling with aryl iodides and bromides. In the presence of 2 equiv of TBAF and 10 mol % of Pd(dba)₂ in DMF at 95 °C, the desired substituted benzene products are formed with little or no

homocoupling byproduct observed.^{23b} The cross-coupling of phenyltrimethoxysilane with aryl chlorides can also be accomplished with the addition of phosphine^{29a} or N-heterocyclic carbene^{29b} ligands to the reaction mixture. Alkyl halides can also be subjected to the palladium-catalyzed cross-coupling with substituted aryltrimethoxysilanes in the presence of 2.4 equiv of TBAF, 4 mol % of PdBr₂, and 10 mol % of (t -Bu)₂MeP in THF. Both alkyl iodides and bromides are competent coupling partners, and the reaction is performed at ambient temperature to provide alkyl-substituted arenes in good yields.^{29c}

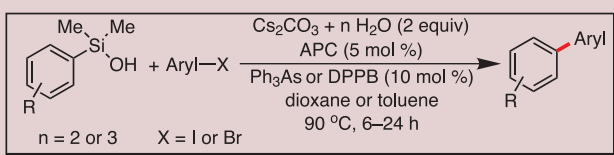
3.3.4. Arylsilanol, Diols, and Triols

The preparation of arylsilanol is discussed in Section 2.1. Arylsilane diols and triols can easily be synthesized by addition of aryllithium reagents to chlorosilanes followed by careful hydrolysis of the corresponding di- and trihalosilanes. As with their alkenyl counterparts, all three types can be activated with 1 equiv of Ag₂O in the presence of a palladium catalyst in THF at 60 °C to give cross-coupling products with



Ref. 26a,b

eq 12

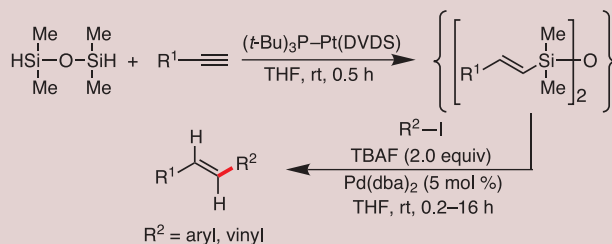


DPPPB = 1,4-bis(diphenylphosphino)butane

X	R	Aryl	Yield
I	4-MeO	4-MeC ₆ H ₄	90%
I	4-MeO	2-MeC ₆ H ₄	85%
I	4-MeO	4-EtO ₂ CC ₆ H ₄	87%

Ref. 30

eq 13



R ¹	R ²	Yield
<i>n</i> -C ₅ H ₁₁	4-MeOC ₆ H ₄	84%
<i>n</i> -C ₅ H ₁₁	4-AcC ₆ H ₄	94%
<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁ CH=CH	67%
Ph	4-MeOC ₆ H ₄	74%
HO(CH ₂) ₃	4-MeOC ₆ H ₄	89%

DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane

Ref. 32

Scheme 1. One-Pot, *Intermolecular Tandem Hydrosilylation/Cross-Coupling Reaction.*

aryl iodides (eq 12).^{26a,b} The coupling of arylsilanols with aryl iodides can also be achieved at 90 °C in dioxane by the action of 2 equiv of Cs₂CO₃·2H₂O in the presence of 5 mol % of APC and 10 mol % of Ph₃As. The corresponding reaction of aryl bromides requires the use of 10 mol % of 1,4-bis(diphenylphosphino)butane (DPPB) instead of Ph₃As and is carried out at 90 °C in

toluene (eq 13).³⁰ Both methods provide high yields of biaryls and little or no homocoupling byproduct.

3.4. Alkylsilanes

Protocols for the palladium-catalyzed cross-coupling of alkylsilanes with organic halides include highly activated organo-

silicon reagents which allow for methyl, allyl, or alkyl cross-coupling. Methyl transfer to aryl iodides is accomplished with 2 equiv of TASF and 1.3 mol % of APC in THF at 50 °C to provide methylated cross-coupling products in good yields.^{31a} More interestingly, alkyltrifluorosilanes yield cross-coupling products with aryl iodides and bromides when activated with 4 equiv of TBAF and 5 mol % of (PPh₃)₄Pd in refluxing THF.^{31b} Allyltrifluorosilanes couple with aryl iodides and triflates under the action of TBAF or TASF and 5 mol % of a palladium catalyst.^{31c} Overall, the cross-coupling of alkylsilanes is not as well established as those of alkynyl-, alkenyl-, or arylsilanes, and few general procedures have been identified.

4. Tandem Reactions of Organosilicon Compounds

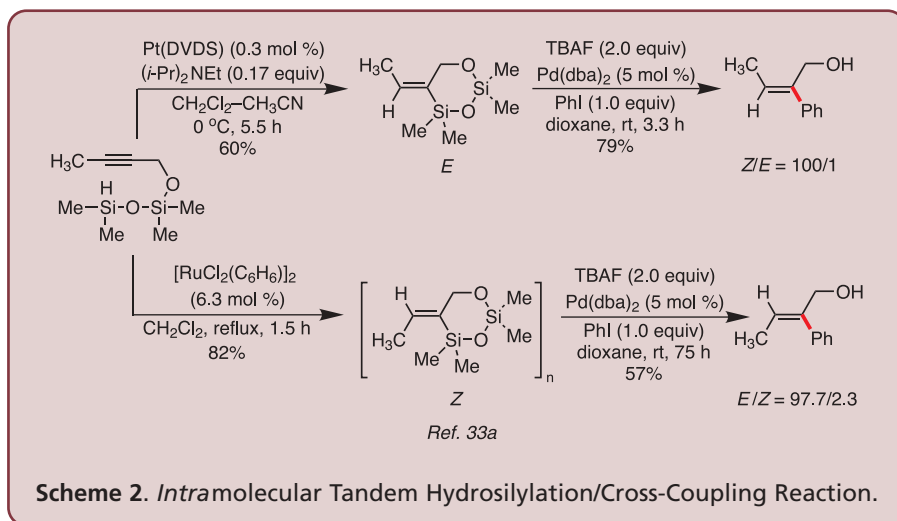
The diversity of organosilicon compounds that undergo palladium-catalyzed cross-coupling, as well as the different methods by which they can be synthesized enable a wide range of synthetic applications. Multistep or tandem reactions that harness the power of the organosilicon moiety can be effectively applied to create complex structures rapidly. These tandem reactions, terminating with palladium-catalyzed cross-coupling, highlight the advantages that silicon-based carbon-carbon bond formation can offer to the realm of synthetic organic chemistry.

4.1. Intermolecular Hydrosilylation/Cross-Coupling

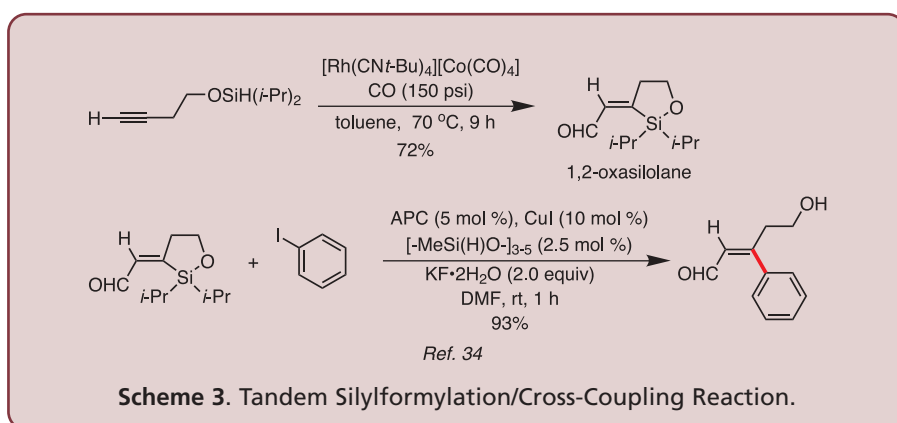
The hydrosilylation of terminal alkynes, followed by palladium-catalyzed cross-coupling of the alkenylsilane product, affords 1,2-disubstituted *E* alkenes in high yields and with high stereoselectivities. For example, a symmetrical alkenyldisiloxane can be generated by reaction of 0.5 equiv of tetramethyldisiloxane, (*t*-Bu)₃P-Pt(DVDS) with a terminal alkyne. The hydrosilylation is highly regio- and stereoselective for the production of the *E* 1-alkenyldisiloxane. The subsequent cross-coupling reaction can be performed directly on the in situ generated alkenyldisiloxane with aryl or vinyl iodide under the action of 2 equiv of TBAF and 5 mol % of Pd(dba)₂ to yield the desired products (Scheme 1).³² This efficient Pt-Pd system effects the net hydroarylation of terminal alkynes.

4.2. Intramolecular Hydrosilylation/Cross-Coupling

Starting from simple propargylic and homopropargylic alcohols, highly functionalized trisubstituted allylic and homoallylic alcohols are obtainable through an intramolecular hydrosilylation followed by a rapid palladium-catalyzed cross-coupling of the intermediate cyclosiloxanes with aryl iodides. Propargylic alcohols can easily be converted to *E* or *Z* alkenylcyclo-disiloxanes under Pt(DVDS) or [RuCl₂(C₆H₆)₂] catalysis, respectively, in high yields and with excellent stereo- and regioselectivities. The palladium-catalyzed cross-coupling of these cyclo-disiloxanes with a number of aryl iodides (in the presence of 2 equiv of TBAF and 5 mol % of Pd(dba)₂ in 1,4-dioxane at ambient temperature) leads to trisubstituted *Z* or *E* allylic alcohols (Scheme 2).^{33a} The one-pot synthesis of trisubstituted homoallylic alcohols is accomplished by treating the corresponding homopropargylic alcohol with 1 equiv of tetramethyldisilazane (TMDS), and 0.3 mol % of Pt(DVDS) in THF at ambient temperature. This provides the intermediate alkyldiene-1,2-oxasilolanes, which are then treated with aryl iodides, 2.2 equiv of TBAF, and 10 mol % of Pd(dba)₂ to afford the trisubstituted homoallylic alcohols.^{33b}



Scheme 2. Intramolecular Tandem Hydrosilylation/Cross-Coupling Reaction.



Scheme 3. Tandem Silylformylation/Cross-Coupling Reaction.

4.3. Silylformylation/Cross-Coupling

In the preceding two cases, hydrosilylation provided olefinic coupling precursors containing a newly formed carbon–silicon bond. Silylformylation, on the other hand, gives rise to new, vicinal carbon–silicon and carbon–carbon bonds to create an aldehyde-containing alkenylsilane. These compounds provide functionalized α,β -unsaturated aldehydes when subjected to the palladium-catalyzed cross-coupling. The realization of this tandem silylformylation/cross-coupling process begins with the intramolecular silylformylation of homopropargylic silyl ethers with 0.5 mol % of [Rh(CN*t*-Bu)₄][Co(CO)₄] under 150 psi of carbon monoxide in toluene at 70 °C. The newly formed, aldehyde-containing, cyclic silyl ethers are competent cross-coupling partners with aryl iodides in the presence of 2 equiv of KF·2H₂O, 5 mol % of APC, 10 mol % of CuI, and 2.5 mol % of methylhydrocyclo-siloxane in DMF at ambient temperature (Scheme 3). The use of both CuI and the hydrosilane are essential for the efficiency of the cross-coupling reaction

and are thought to mediate the formation of the key reactive catalytic species.³⁴

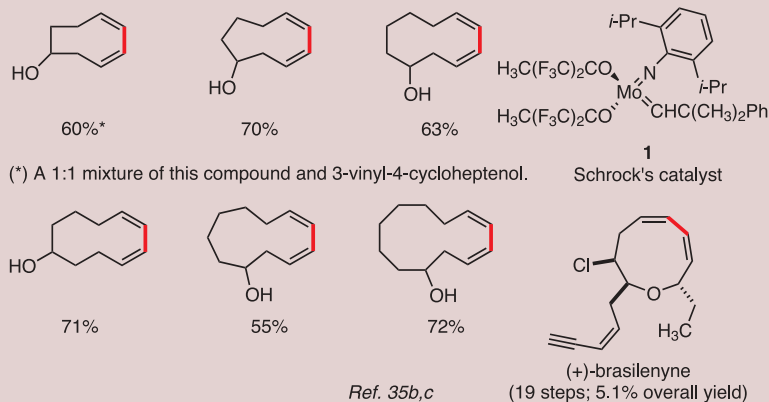
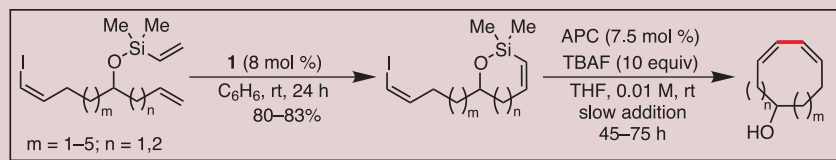
4.4. Mizoroki–Heck Reaction/Cross-Coupling

As mentioned in Section 3.2.1.2.2, the use of 2-pyridylsilanes as cross-coupling agents allows for the preservation of the silicon moiety through chemical manipulations prior to the palladium-catalyzed cross-coupling. A secondary property of the pyridyl group is that it can be employed as a directing group for the Mizoroki–Heck reaction. These two assets allow for a tandem Heck reaction/palladium-catalyzed cross-coupling reaction to afford highly substituted alkenes efficiently and in good yields. Exposure of dimethyl(hexenyl)-(2-pyridyl)silane to 0.5 mol % of Pd₂(dba)₃·CHCl₃, 2 mol % of tri(2-furyl)phosphine (TFP), 1 equiv of Et₃N, and an aryl iodide in THF at 60 °C produces in situ the Mizoroki–Heck coupling product with retention of the 2-pyridylsilane unit. This intermediate, aryl-substituted dimethyl-(hexenyl)(2-pyridyl)silane can then undergo a subsequent cross-coupling reaction upon

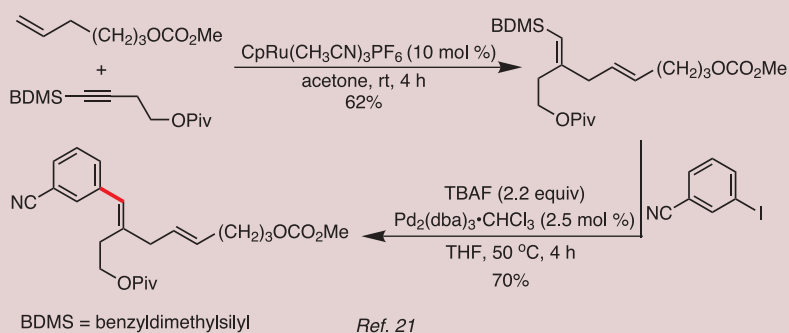
addition of 1 equiv of TBAF and a second aryl iodide to provide the olefinic products in good yields and excellent stereo- and regioselectivities.^{20b,c} The selectivity of the Mizoroki–Heck process is proposed to be enhanced by the 2-pyridylsilane functionality, which directs the carbopalladation across the double bond of the alkenyl-dimethyl(2-pyridyl)silane.^{20b}

4.5. Ring-Closing Metathesis/Cross-Coupling

The combination of ring-closing metathesis (RCM) and palladium-catalyzed cross-coupling constitutes a powerful sequence for the synthesis of substituted, unsaturated alcohols and medium-size rings with *cis,cis*-1,3-diene units. Alkenyl-(dimethyl)silyl ethers containing terminal alkenes undergo efficient ring closure in the presence of Schrock's catalyst to afford cycloalkenylsiloxanes of varying sizes. These siloxanes couple with aryl iodides in the presence of 2 equiv of TBAF and 5 mol % of Pd(dba)₂ in THF at room temperature to provide highly substituted styrenes in high yields.^{35a} The intramolecular



Scheme 4. Tandem Ring-Closing Metathesis/Cross-Coupling Reaction (Yields Shown Are for the Cross-Coupling Step).



Scheme 5. Tandem Alder-Ene/Cross-Coupling Reaction.

variant of this reaction provides access to a number of medium-size rings,^{35b} and has been exemplified in the synthesis of (+)-brasilenyne, an antifeedant isolated from *Aplysia brasiliensis* (Scheme 4).^{35c}

4.6. Alder-Ene/Cross-Coupling

The intermolecular Alder-ene reaction of benzyldimethylsilylalkynes, catalyzed by 10 mol % of $\text{CpRu}(\text{CH}_3\text{CN})_3\text{PF}_6$, provides trisubstituted vinylsilanes in good yields and regioselectivities. These benzyldimethylsilyl-substituted alkenes can then be further functionalized through palladium-catalyzed cross-coupling with aryl iodides or bromides in the presence of 2.2 equiv of TBAF and 2.5 mol % of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ in THF at 25 or 50 °C (Scheme 5).²¹ Both the Alder-ene and

cross-coupling reactions proceed efficiently to provide highly functionalized alkenes in good yields.

5. Summary and Outlook

The scope and generality of synthetic applications for which organosilanes can be employed in palladium-catalyzed cross-coupling reactions have grown substantially in the past five years. Nonetheless, the palladium-catalyzed cross-coupling of organosilanes with organic halides and pseudohalides is still an evolving field. Some of the major challenges that appear on the horizon are the development of (1) new, more reactive and more functional-group-tolerant organosilicon species, (2) new methods for activation of the cross-coupling

process, (3) new methods for the introduction of organosilicon moieties into cross-coupling precursors, and (4) a better understanding of the mechanistic details^{4,17,26c} of the activation and transmetalation steps in the process. Ongoing and future studies are certain to broaden the potential of these reactions and their applications in complex-molecule synthesis. We are confident that the burst in activity in this area over the past few years will continue unabated, and bring with it new and exciting advances in organosilicon chemistry.

6. Acknowledgements

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