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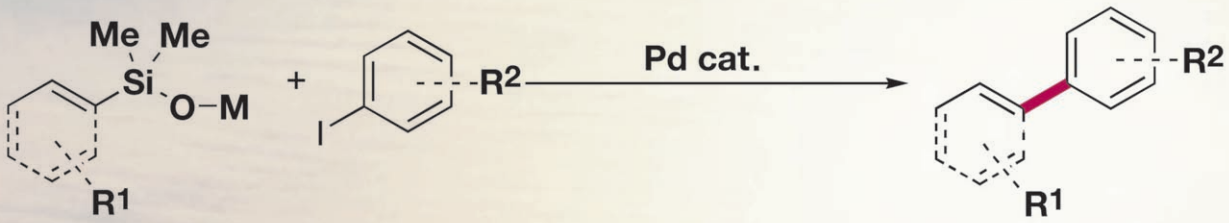
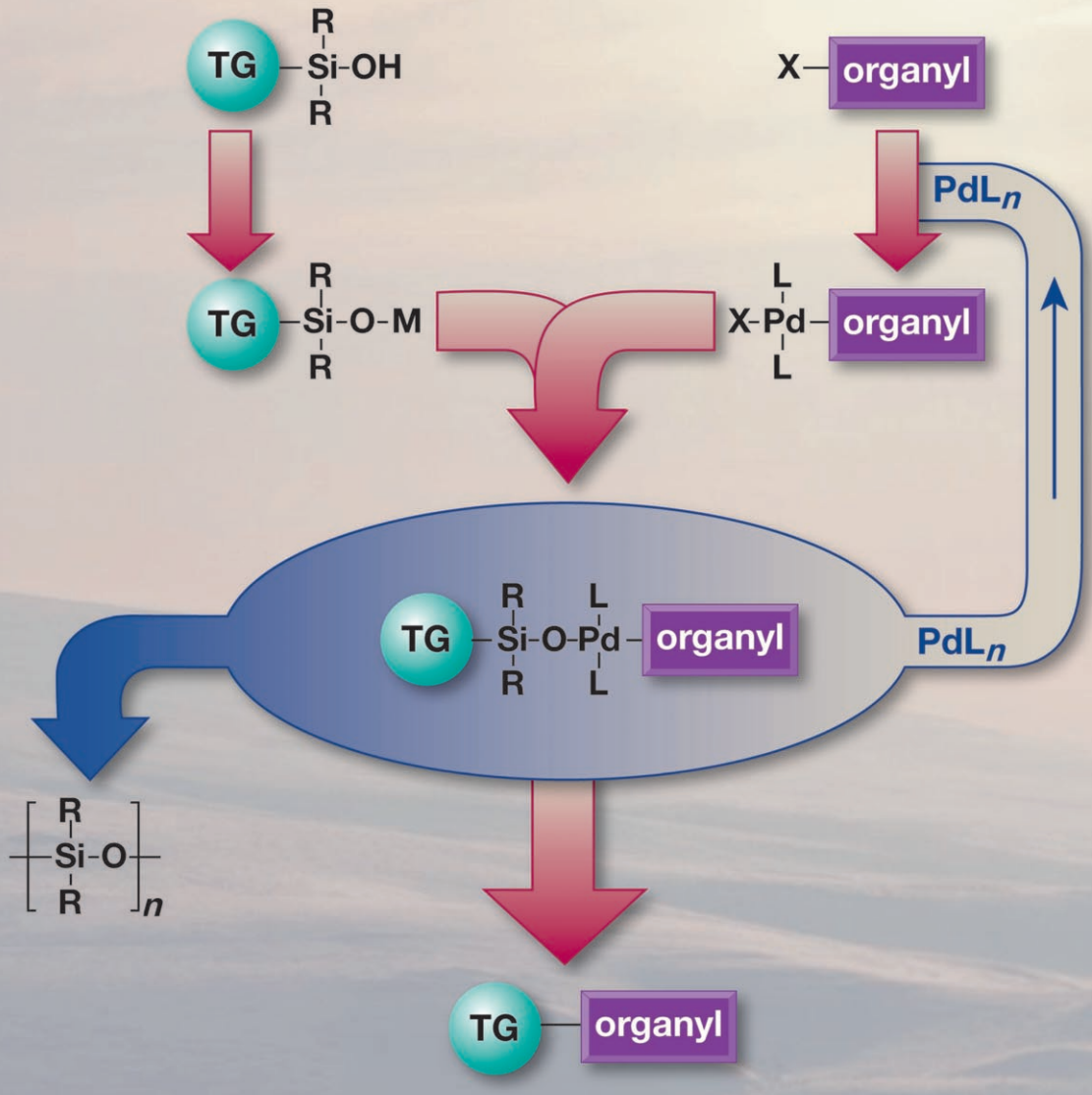


A Paradigm Shift in Silicon-Based Cross-Coupling Reactions



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Palladium-Catalyzed Cross-Coupling Reactions of Silanolates: A Paradigm Shift in Silicon-Based Cross-Coupling Reactions

Scott. E. Denmark* and John D. Baird[a]

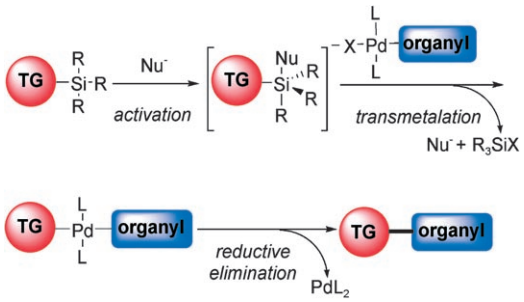
Abstract: This paper chronicles the conceptual development, proof of principle experiments, and recent advances in the palladium-catalyzed cross-coupling reactions of the conjugate bases of organosilanols. The discovery that led to the design and refinement of this process represents a classical illustration of how mechanistic studies can provide a fertile ground for the invention of new reactions. On the basis of a working hypothesis (which ultimately proved to be incorrect) and the desire to effect silicon-based cross-coupling without the agency of fluoride activation, a mild and practical palladium-catalyzed cross-coupling of alkenyl-, aryl-, and heteroaryl silanolates has been developed. The mechanistic underpinnings, methodological extensions, and the successful applications of this technology to the synthesis of complex molecules are described.

Keywords: cross-coupling · green chemistry · organosilicon · palladium · silanolates

Introduction

The palladium-catalyzed cross-coupling of organometallic nucleophiles with organic electrophiles is among the most important in the panoply of modern synthetic methods for the formation of carbon–carbon bonds.[1] A variety of organometallic donors have been conscripted into useful service, the most common of which are organostannanes,[2] organoboranes,[3] and organozinc[4] reagents. Less commonly used, but synthetically promising, are silicon-bearing organic donors. The ground-breaking work of Hiyama[5] and Hatanaka has been extended and developed into a practical and versatile reaction.[6] The cross-coupling of organosilicon reagents features many advantages including the ease of preparation and purification of silanes, their low-molecular weight, and high stability. Moreover, the process generates environmentally benign byproducts.

Unlike the Stille and Negishi reactions, which require no activation, or the Suzuki reaction, which requires only heating with mild bases, silicon-based cross-coupling reactions often require heating in the presence a fluoride source. Because of the low polarizability of the C–Si bond the silicon function must undergo nucleophilic activation[5,6] to induce migration of a transferable group (TG) onto the organopalladium species (transmetalation). Under conditions of fluoride activation, the intermediacy of a pentacoordinate siliconate is proposed that is capable of transferring an unsaturated group in the transmetalation step (Scheme 1).



Scheme 1. The proposed mechanism of Pd-catalyzed cross-coupling.

Despite the absence of detailed mechanistic studies, the reigning dogma in the field posited that pentacoordinate siliconates were required for the transmetalation and that enhancing the ease or rate of formation of this intermediate should lead to enhanced reaction rates. This hypothesis led to the introduction of more electrophilic silane moieties as donors, such as polyhalosilanes[5] and polyalkoxysilanes.[7] An alternative strategy for enhancing the formation of pentacoordinate siliconates without making recourse to heteroatom-substituted silanes was introduced in these laborato-

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ries with the demonstration that silacyclobutanes are also competent precursors for silicon-based cross-coupling reactions under fluoride activation.[8] The design was based upon the concept of "strain release Lewis acidity"[9] to increase the equilibrium concentration of the hypercoordinate species. However, mechanistic studies demonstrated that the actual reaction precursor is a silanol generated in situ by fluoride-assisted ring cleavage.[10] Subsequently, it was shown that the oxygen atom (from hydrated TBAF·3H_2O) is crucial to the success of the reaction and fluoride-activation has been demonstrated for many types of organooxysilanes, including silanols, silyl ethers, polysiloxanes, as well as other all-carbon precursors (2-pyridyl-, 2-thienyl-, benzyl- and triallylsilanes).[11] Despite the generality and reaction scope of fluoride-activated cross-coupling reactions, these conditions still present many drawbacks, such as the high cost of organic soluble fluoride sources, the corrosive nature of fluoride which etches glass reaction vessels, and the evident incompatibility with silicon protecting groups. Consequently, the broad application of silicon-based cross-coupling reactions has not materialized.

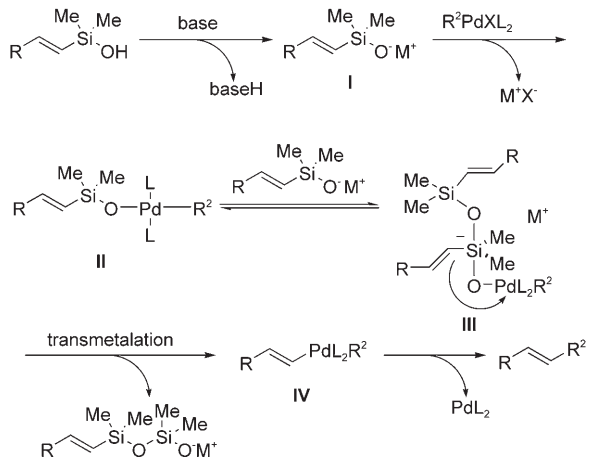
Fluoride-Free Activation

To overcome the limitations associated with fluoride, we sought to develop a cross-coupling process that possessed all the advantages of silicon-based donors, but which did not require a fluoride source for activation.[12] Following the Hiyama–Hatanaka paradigm that a pentacoordinate siliconate is required for the crucial transmetalation, we envisioned that simple deprotonation of the silanol might open a new pathway for activation (Scheme 2).

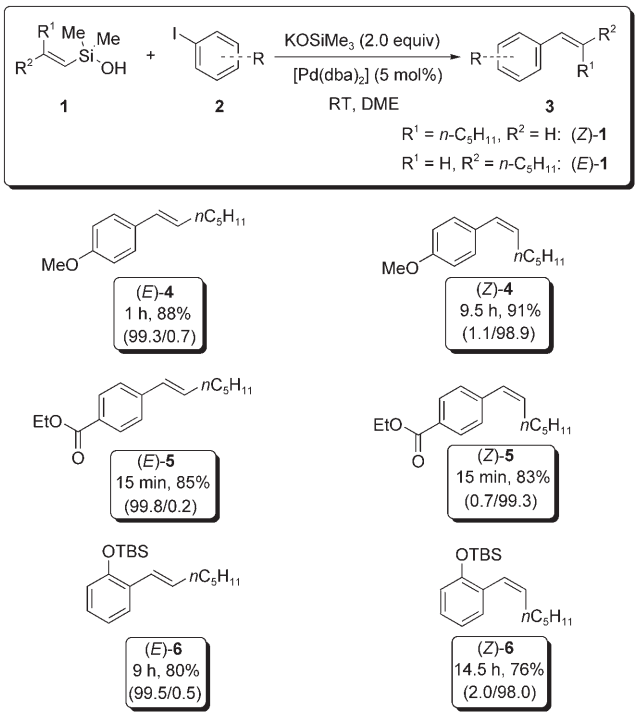
In this proposal, the conjugate base of the silanol serves two roles. First, the silanolate **I** could displace the halide on the organopalladium–X species to generate a palladium silanolate complex **II**. The crux of the new hypothesis is that another silanolate molecule might activate the palladium silanolate complex through the formation of a pentacoordinate siliconate **III**, which should be able to undergo transmetalation. With this mechanistic construct in mind, a variety of Brønsted bases (2.0 equiv) in different solvents were used to deprotonate (*E*)-1-heptenyldimethylsilanol (**1**) including MeLi, NaH, KH, and KO*t*Bu and the resulting silanolate was combined with 1-iodonaphthalene and [$Pd(dba)_2$] (0.05 equiv).[13] Of those bases surveyed, KH (in DME) proved optimal affording complete conversion of (*E*)-**1** in 15 min. However, with less reactive silanols the reduction of the aryl iodide is a competitive side process. Presumably, the excess KH is responsible, and it was thus hypothesized that a superior base would be strong enough to deprotonate the silanol ($pK_a = 9$–11), but not strong enough to induce undesirable base-promoted side reactions, bind palladium, and function as a competitive inhibitor, or serve as a hydride source.

To overcome these challenges, the soluble and inexpensive base $KOSiMe_3$ was investigated for the in situ formation of the requisite silanolate. The use of two equivalents of $KOSiMe_3$ in DME at room temperature effects the cross-coupling of both (*E*)-**1** as well as (*Z*)-**1** with a variety of aryl iodides in short reaction times and with high stereospecificity (Scheme 3). The mildness and synthetic potential of this method is exemplified in the cross-coupling of substrates bearing silicon protecting groups for the preparation of (*E*)- and (*Z*)-**6**.

Concurrent with our work, Hiyama, Mori et al. reported the fluoride-free cross-coupling of silanols in which silver(I) oxide effects the cross-coupling of a variety of aryl- and alkenylsilanols.[14] The need for heating and extended reaction



Scheme 2. Proposed mechanism for the fluoride-free cross-coupling of silanols.



Scheme 3. Fluoride-free cross-coupling of alkenyl silanols.

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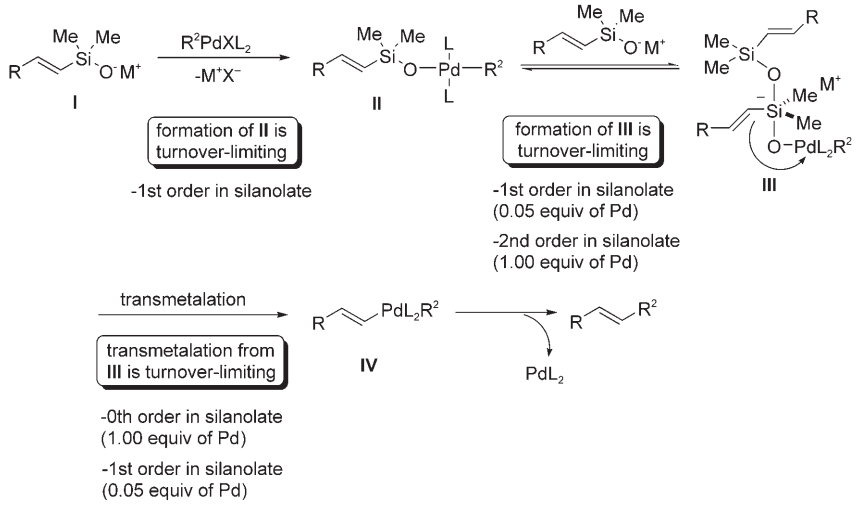
times prompted the examination of other silicon reagents. By the use of the more reactive silanediol or -triol, the reactions generally proceed to completion in 12 h to afford the desired cross-coupling products in good yields.[15] The mechanism of this reaction is proposed to involve nucleophilic activation of silicon by the oxygen atom of the Ag_2O, as well as silver-promoted halide extraction from the organopalladium halide.[16]



Scheme 4. Proposed mechanism and kinetic consequences for each step.

Mechanistic Interlude

Although the $KOSiMe_3$-based cross-coupling of alkenylsilanols proved to be synthetically useful, the mechanistic hypothesis for this mode of activation was by no means verified. To establish the proposed dual role of the silanolate, a series of kinetic experiments has been performed to elucidate the reaction order with respect to each component in the cross-coupling of (*E*)-**1** with 2-iodothiophene.[17]

The reaction displays the expected zeroth-order dependence on 2-iodothiophene and first-order dependence on palladium.[18] However, the rate dependence on silanolate concentration is more revealing.

The order in potassium silanolate (*E*)-**1** was determined under two conditions to rule out other possible kinetic scenarios; first under catalytic conditions in which 0.05 equivalents of palladium (with respect to iodide) was employed, and secondly, with a stoichiometric amount of palladium in which one equivalent (with respect to iodide) was used. Under catalytic conditions (0.05 equiv of palladium) two different regimes are seen. When the silanolate loading is below one equivalent (relative to iodide), the reaction exhibits first-order dependence in silanolate; however, when the silanolate loading is greater than one equivalent, zero-order behavior in silanolate is seen. This break in rate dependence is usually associated with a change in mechanism or rate-limiting step. Remarkably, when these experiments are conducted with one equivalent of palladium (relative to the aryl iodide) first-order behavior in silanolate is observed!

According to the proposed mechanism (Scheme 4), the turnover-limiting step of the catalytic cycle is one of the following three events: formation of complex **II**, formation of complex **III**, or transmetalation from **III**. The possibility that oxidative addition of the palladium catalyst into the aryl–iodide bond is turnover-limited is ruled out by the zeroth-order rate dependence on the 2-iodothiophene. Likewise, turnover-limiting reductive elimination is highly unlikely, since reductive elimination from dialkylpalladium(II) species are known to be fast and irreversible.[19] If formation of **II** is turnover-limiting, the expected kinetic consequence would be first-order silanolate dependence which is consistent with the observed results under catalytic palladium loading. If formation of **III** is turnover-limiting, under catalytic palladium loadings the reaction would exhibit first-order silanolate behavior, because the palladium is saturated in the form of **II**. However, when a stoichiometric amount of palladium (relative to aryl iodide) is employed the expected kinetic consequence would be second-order in silanolate (the palladium is saturated in the form of aryl-Pd-I). From the above experiments, the first-order behavior in silanolate under stoichiometric palladium loading clearly rules out the possibility that formation of **III** is turnover-limiting. Furthermore, this result eliminates the possibility that complex **III** is involved, because a second-order rate dependence on silanolate should be observed as the silanolate concentration is increased. The third possibility under the proposed mechanism would be transmetalation from **III**, but this possibility can be discounted because intermediate **III** does not lie on the reaction pathway.

With the elimination of complex **III** as an intermediate, it follows that the transmetalation must occur directly from the breakdown of **II**. The fact that transmetalation occurs through a tetracoordinate, covalently bound palladium silanolate is a surprise and introduces an unprecedented mechanism. This conclusion deviates from the Hiyama–Hatanaka paradigm, and clearly contradicts the dogma in silicon-based cross-coupling reactions that the reaction must proceed through a pentacoordinate siliconate.[20] The revised mechanism involves formation of the palladium silanolate complex **V**, *direct intramolecular transmetalation* to the palladium(II) species **VI**, and reductive elimination to afford the product (*E*)-**7** (Scheme 5).

That the reaction proceeds through the formation of a palladium silanolate complex **V**, and *not* through the formation of a pentacoordinate siliconate not only violates the

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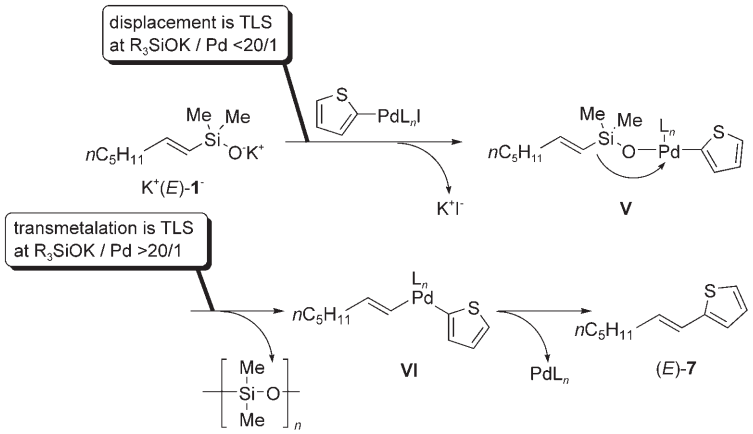


Scheme 5. Experimentally derived mechanism of silanolate cross-coupling.

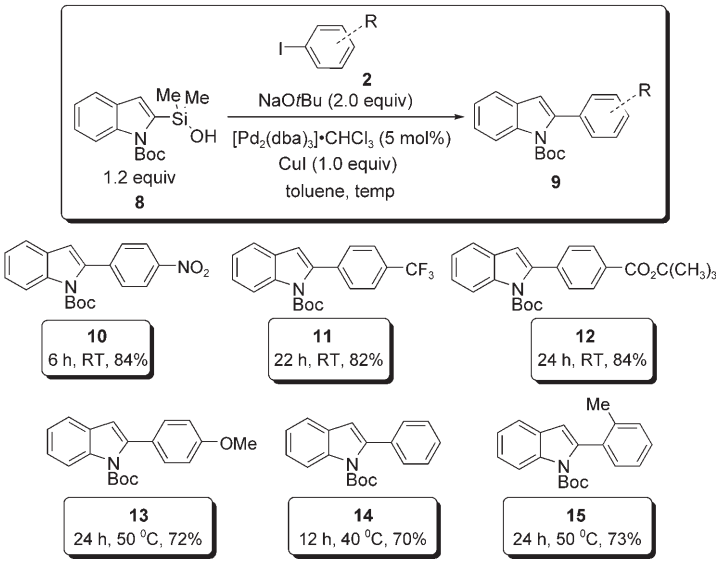
tenet that a pentacoordinate siliconate is required for transmetalation, but also implicates a key role for the Si-O-Pd linkage.[21] The remarkable rate of the transmetalation from **V** is most likely entropic in origin, as the Si-O-Pd moiety connects both the migrating unsaturated group and the arylpalladium species and renders the process *intramolecular*. This observation is also surprising in light of the mechanism of the fluoride-promoted cross-coupling of silanols, in which the turnover-limiting step is an *intermolecular* transmetalation from a fluoride-complexed disiloxane (pentacoordinate silicon species).[22]

This watershed discovery enabled a fundamental rethinking of the mechanism and provided opportunities for reaction design. First, the discovery that a metal silanolate is the active species implies that the reactivity and solubility of the silanolate will depend strongly on the identity of the cation. Second, this finding also stimulated a reevaluation of the nature and amount of the Brønsted base used to form the metal silanolate. A suitable base for the reaction need only generate the desired metal silanolate, and several simple bases have been demonstrated as successful activators for silanols, including NaO*t*Bu, NaH, Cs_2CO_3, and $KOSiMe_3$. The applications of these bases in various coupling processes is summarized below.

Activation by Sodium *tert*-Butoxide

The formation of sodium silanolates by treatment of silanols with NaO*t*Bu is a general method for the cross-coupling of many types of silanols. This Brønsted base has been particularly useful for the cross-coupling of heterocyclic silanolates, such as indolyl-2-silanols.[23] Indoles are well represented within the fields of pharmaceutical, materials, and natural products chemistry; however, the use of 2-indolylmetals in cross-coupling reactions suffers from rather harsh conditions (stannanes[24]) or competitive protiodeborylation (boronic acids[25]).

N-Boc(2-indolyl)dimethylsilanol (**8**) is easily prepared[26] and suitable conditions for the cross-coupling of **8** with 4-nitroiodobenzene are the use of NaO*t*Bu (2.0 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%), and CuI (1.0 equiv).[23] The cross-coupling reactions proceed faster and more cleanly in the presence of CuI. Interestingly, initial reactions with TBAF or $KOSiMe_3$ led to rapid protiodesilylation. A variety of substrates including electron-rich, electron-poor, and 2-substituted aryl iodides react smoothly under these conditions (Scheme 6).



Scheme 6. Cross-coupling of *N*-Boc(2-indolyl)silanol.

The more electron-rich *N*-methyl(2-indolyl)dimethylsilanol (**16**) illustrates the effect of other nitrogen substituents. Under the same conditions used for the cross-coupling of **8**, a variety of electron-donor-substituted aryl iodides react smoothly with **16** at room temperature (Scheme 7). However, iodides bearing electron-withdrawing groups afford the desired products in lower yields. By changing to aryl bromides and employing 1,4-bis(diphenylphosphino)butane (dppb) the desired products are formed in good yields from these substrates.

Other heterocyclic silanols are viable substrates for cross-coupling under NaO*t*Bu activation. For example, 3,4,5-trisubstituted isoxazoles can be prepared by a sequential process involving a [3+2] cycloaddition and subsequent cross-coupling of the isoxazolyl silanol (Scheme 8).[27] The isoxazole core is constructed by a cycloaddition between an alkynyldimethylsilyl ether and an in situ prepared aryl nitrile oxide. The silicon function plays two roles in that it controls the regioselectivity of the [3+2] cycloaddition,[28] and it enables further functionalization through the cross-coupling

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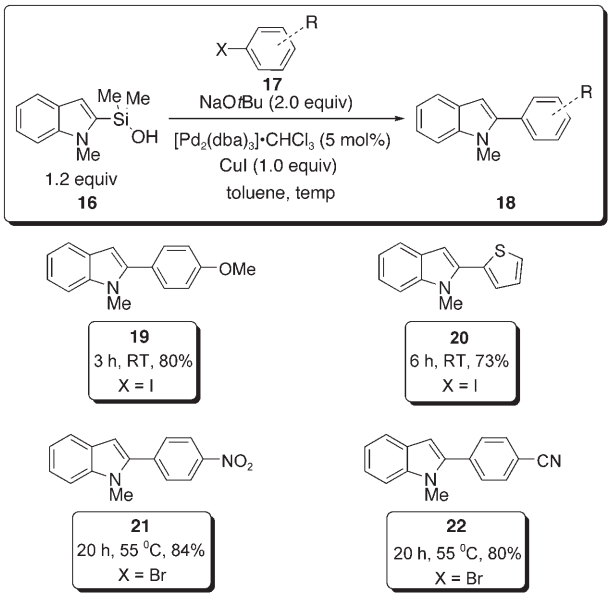
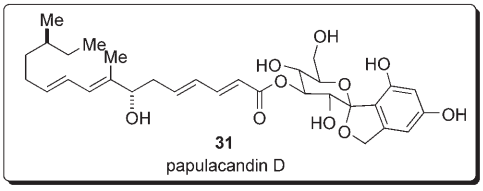


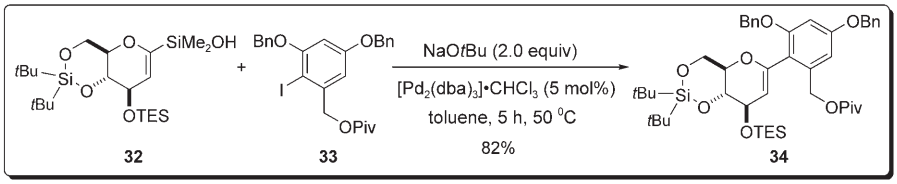
Scheme 7. Cross-coupling of *N*-methyl(2-indolyl)silanol (**16**).

reaction. Optimal conditions for the coupling employ 2.5 equivalents of NaO*t*Bu, 5 mol% of $[Pd_2(dba)_3]\cdot CHCl_3$ in either toluene or dioxane at 80°C. Other activators such as $KOSiMe_3$, Cs_2CO_3, or K_3PO_4 give significant amounts of protiodesilylation.

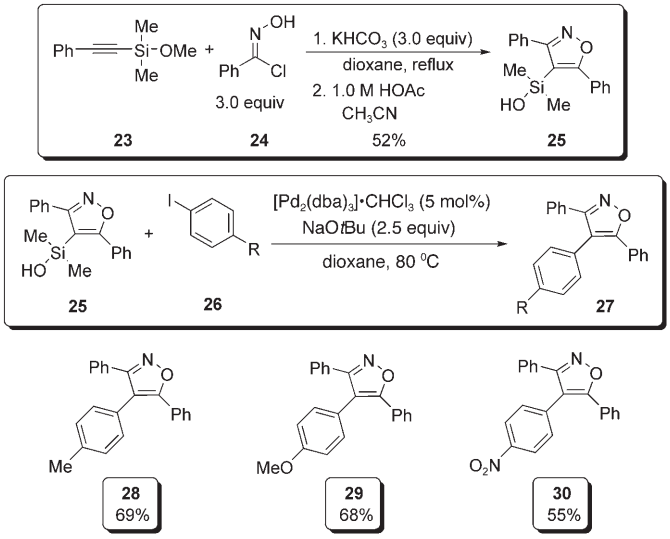
The cross-coupling of sodium silanolates generated with NaO*t*Bu is illustrated in a recently completed total synthesis of the antifungal agent papulacandin D (**31**).[29] Cross-coupling between the sterically hindered glucal-2-silanol **32** and aryl iodide **33** was envisioned for the construction of the C-aryl glycoside core (Scheme 9). This cross-coupling reaction poses significant synthetic challenges, because the aryl iodide is electron-rich and bears substituents at both *ortho*-positions and the sterically encumbered glucal silanol **32** is expected to be a sluggish coupling partner.[30] Further, the cross-coupling conditions must enable activation of the silanol function without affecting either of two silicon protecting groups in **32**. Treatment of the protected silanol with NaO*t*Bu, $[Pd_2(dba)_3]\cdot CHCl_3$ and the aryl iodide affords the 2-arylglucal **34** in 82% yield.[31] The compatibility of the sodium silanolate with delicate functionality and different silicon protecting groups highlights the mildness of this method.

The observation that competing protiodesilylation is attenuated under NaO*t*Bu activation (compared to, for example, $KOSiMe_3$) led to the examination of the stability of the sodium silanolate as well as alternative methods for its preparation.





Scheme 9. Preparation of the sugar core of papulacandin D.



Scheme 8. Synthesis and cross-coupling of isoxazolylsilanols.

Activation by Sodium Hydride

The demonstration that a strong base such as NaO*t*Bu serves only to deprotonate the silanol led to the reinvestigation of NaH to generate the metal silanolate irreversibly. Although NaH had been tested in initial studies, the inadvertent use of two equivalents of NaH promoted the reduction of the aryl iodide.[13] Accordingly, the sodium silanolate of *N*-Boc(2-indolyl)dimethylsilanol (**8**) was generated with a stoichiometric amount of NaH and then was tested in a cross-coupling reaction. In situ generated $Na^+\mathbf{8}^-$ couples smoothly with 4-iodoanisole in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ in toluene at 80°C in the *absence* of CuI.[32] Other aryl iodides that were problematic under NaO*t*Bu activation, such as those containing esters and nitriles, proved to be excellent substrates (Scheme 10).

The cross-coupling of other in situ prepared heterocyclic silanolates such as *N*-Boc(2-pyrrolyl)-, 2-thienyl-, and 2-fur-

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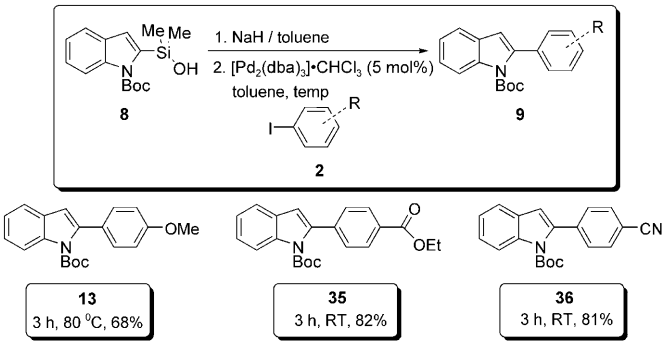
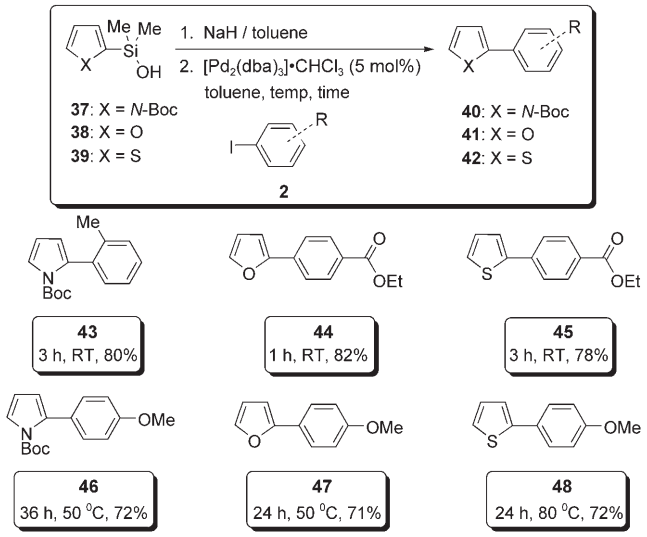


Scheme 10. Cross-coupling of in situ prepared indolyl-2-silanolate.

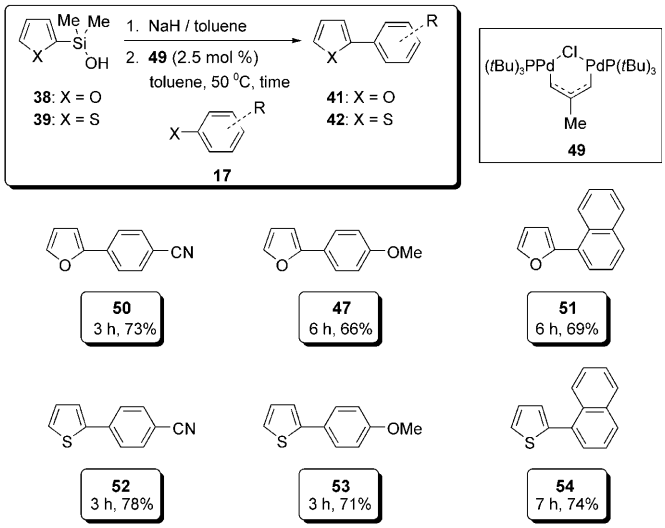


Scheme 11. Cross-coupling of in situ generated heterocyclic silanolates with aryl iodides.

yldimethylsilanolate proceed smoothly at room temperature with electron-poor aryl iodides, while those bearing electron-donating groups generally require mild heating (Scheme 11).[32] It is worth noting that the cross-coupling of *N*-Boc(2-pyrrolyl)boronic acids is known to suffer from protiodeborylation as well as a competing homodimerization side process not observed in this reaction.[25]

Aryl bromides are also suitable substrates for the cross-coupling of 2-thienyl- and 2-furylsilanolates under catalysis by the palladacycle **49**[33] (Scheme 12). The reactions proceed to completion within 3 h at 50 °C in toluene.

Because the sodium silanolate is believed to be the active silicon species in the reaction, $Na^{+}\mathbf{8}^{-}$ was independently prepared, isolated, and characterized as a white solid by treating the silanol with a stoichiometric quantity of NaH. The independently prepared silanolate reacted with comparable rate and yield to the in situ prepared silanolate. Storing the silanol as its active sodium salt also provides two distinct advantages: 1) the reaction procedure is simplified by simply charging the reaction vessel with silanolate for the



Scheme 12. Cross-coupling heterocyclic silanolates with aryl bromides.

cross-coupling reaction, and 2) silanols are known to dimerize to their corresponding (unreactive) disiloxanes in the presence of acid or base, and storage as the salt inhibits this process.

Activation by Cesium Carbonate

The use of the mild, inorganic base, Cs_2CO_3 has been developed for the cross-coupling of aryl silanols via their cesium silanolates.[34] In contrast to the cross-coupling of alkenyl and heteroaryl silanolates, aryl silanolates are less reactive partners and typically require more forcing conditions. The cross-coupling of electron-rich arylsilanols with aryl iodides is accomplished using $Cs_2CO_3 \cdot 3H_2O$ (2.0 equiv) in toluene at 90 °C in the presence of allylpalladium chloride dimer (APC; 5 mol %) and Ph_3As (10 mol %) (Scheme 13). The analogous cross-coupling of aryl bromides proceeds with 10 mol % of dppb instead of Ph_3As.[35]

The effect of the metal counterion in the cross-coupling of the (4-methoxyphenyl)dimethyl silanolate is negligible.[36] The Na, K, Rb, and Cs salts reacted at similar rates under the standard conditions with bromobenzene (conversion after 1 h: Na, 55 %; K, 80 %; Rb, 81 %; Cs, 88 %). The slower rate of the sodium salt, is due to poor solubility of the silanolate in toluene.

Activation by Potassium Trimethylsilanolate

The base $KOSiMe_3$ is one of the mildest activators in that it effects the cross-coupling of silyl moieties already containing an oxygen function, such as silanols, silyl ethers and disiloxanes. Accordingly, a strategy for the sequential cross-coupling of differentially functionalized 1,4-bissilylbutadienes that relies on the two distinct mechanisms for silicon based cross-coupling could be developed (Scheme 14).[37] One end

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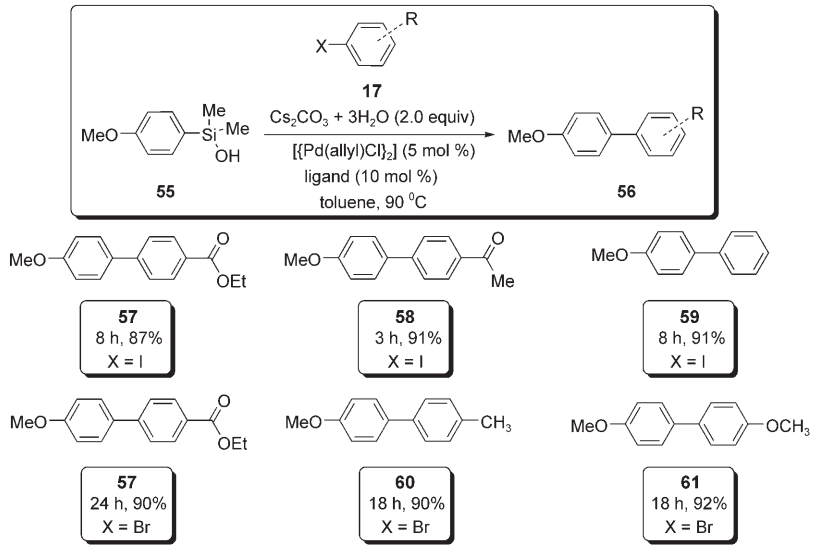
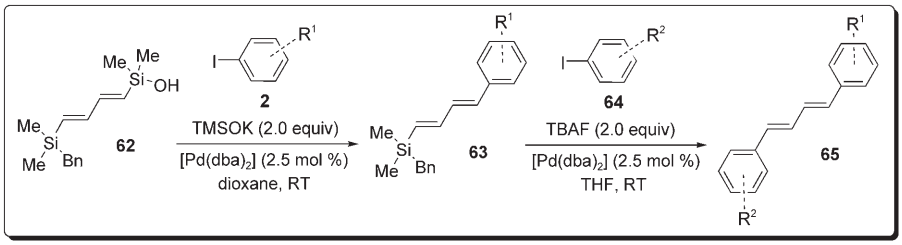


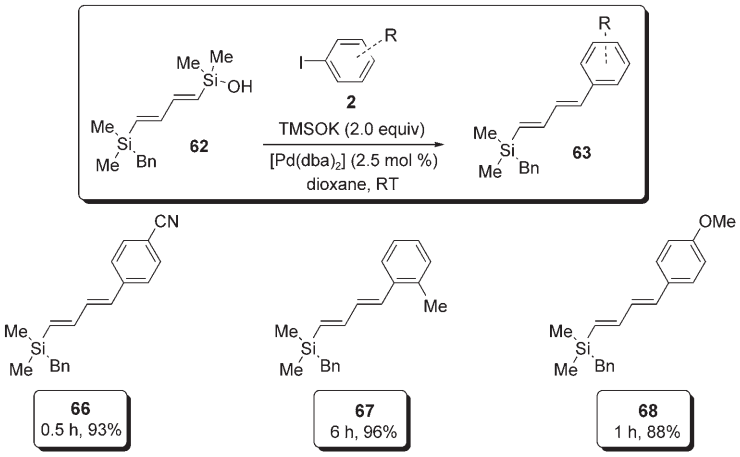
Scheme 13. Aryl silanolate cross-coupling with aryl iodides and bromides.



Scheme 14. Sequential cross-coupling of 1,4-bissilylbutadienes.

of the 1,4-bissilylbutadiene bears a silanol that is converted to the active potassium silanolate with $KOSiMe_3$. The other end bears a benzyl silane which is inert under these conditions, but which can be activated upon exposure to fluoride.[38]

Under activation by $KOSiMe_3$, the silanol exhibits reactivity of typical alkenyl silanols and couples smoothly with a wide range of substituted aryl iodides in the presence of $[Pd(dba)_2]$ in dioxane at room temperature to afford the dienylsilane products in good yields (Scheme 15). The presence of electron-withdrawing or -donating groups on the aryl iodide have little effect on the rate of the reaction, but aryl iodides bearing *ortho*-substituents react more slowly.



Scheme 15. TMSOK activation of silanol unit in 1,4-bissilylbutadienes.

Under fluoride activation the silanol is unmasked from the benzyl silane and the subsequent cross-coupling proceeds smoothly with various aryl iodides in good yields (Scheme 16). For some problematic substrates, a 2-thienyl[39] group can be used in place of the benzyl group on the silane as well. This synthetic strategy underscores the importance of mechanistic understanding in reaction design, as the two distinct mechanisms are complementary and further highlight the versatility of silicon cross-coupling reagents.

The synthetic utility of 1,4-bissilylbutadienes has been demonstrated in the total synthesis of RK-397, a member of a large family of polyene macrolides exhibiting antifungal activity.[40] Retrosynthetic analysis revealed that the polyene chain could be accessed rapidly through the sequential cross-coupling of a 1,4-bissilylbutadiene to prepare the tetraene portion of the known polyene phosphonate **74** (Scheme 17).

In situ preparation of the sodium silanolate by stoichiometric deprotonation with NaH and treatment with the THP-protected ether **77** in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ provided the desired product in 77% yield (Scheme 18).[41] Unmasking the silanol under TBAF activation and cross-coupling with ethyl (*E*)-3-iodopropenoate **75** and $[Pd(dba)_2]$ afforded the key tetraene **79** in 79% yield.

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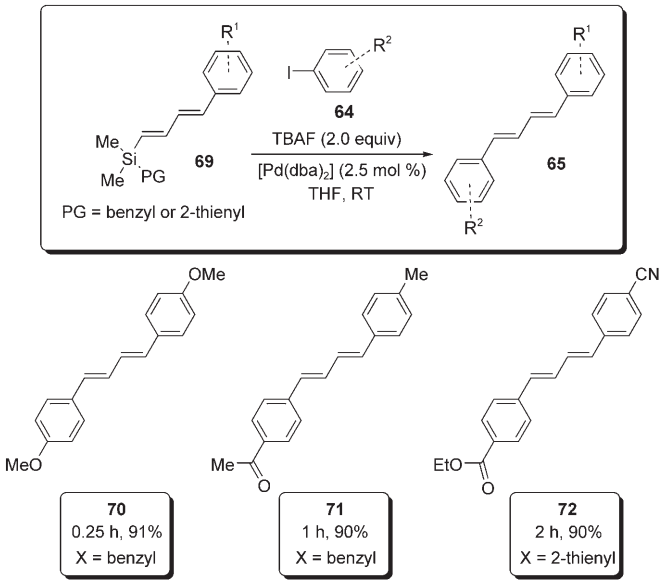
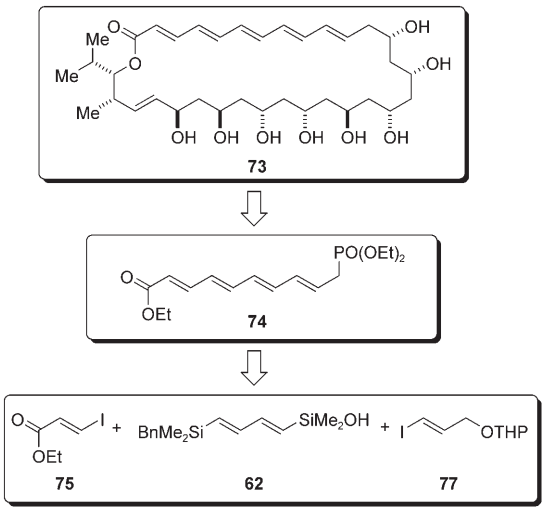
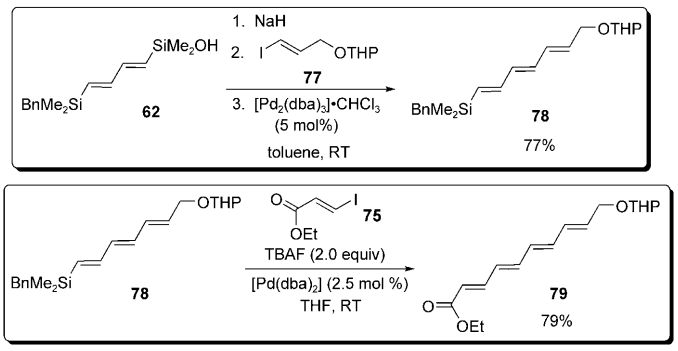


Scheme 16. Fluoride-activated cross-coupling of 1-silylbutadienes.



Scheme 17. Retrosynthetic analysis for the tetraene portion of RK-397.



Scheme 18. Sequential cross-coupling for the preparation of tetraene ester **79**.

Conclusion and Outlook

Although the development of silicon-based cross-coupling reagents has lagged behind the initially more successful tin-, zinc-, and boron-based reagents, the cross-coupling of organosilanes has proven to be a viable, synthetically useful, and, in some cases, superior alternative to the more traditional cross-coupling methods. Harnessing the utility of silanols in cross-coupling reactions has enabled the mild preparation of a diverse array of products. Their ease of synthesis, stability, and low molecular weight make silanols an ideal class of reagents for cross-coupling reactions. Key milestones in the development of the fluoride-free cross-coupling of silanols include the discovery of Ag_2O and $KOSiMe_3$ as activators, elucidation of the new mechanism, the use of sodium alkoxide bases to solve the problem of protiodesilylation of heterocyclic silanolates, and the use of metal silanolates directly by stoichiometric deprotonation. Mechanistic studies on the fluoride-free cross-coupling of silanols have revealed a new pathway for the activation of silanols which usurps the longstanding notion that pentacoordinate silicates are required for successful cross-coupling of organosilanes. Understanding these advances through mechanistic insight, and placing them within the context of this new paradigm in silicon cross-coupling has enabled new reactions and synthetic strategies. The amalgamation of the original Hiyama–Hatanaka paradigm for fluoride-promoted reactions (proceeding through a pentacoordinate silicate) coupled with the new non-fluoride activation paradigm (tetracoordinate palladium-silanolate) has enabled the sequential cross-coupling of 1,4-bissilylbutadienes by exploiting the two distinct methods of silane activation. Furthermore, the ability to use the stable, storable silanolates directly in the reaction simplifies the reaction protocol and eliminates the problem of disiloxane formation sometimes observed upon long-term storage of silanols.

Although the initial efforts to develop a non-fluoride method of activation were predicated on an intriguing proposal that ultimately proved to be incorrect, the results have provided a far more interesting and promising direction for further research. With a clearer picture of the detailed mechanism for this process, a new vista in the cross-coupling of organosilicon reagents is emerging. Future studies include the design of more active metal silanolates used to form the palladium silanolate intermediate that can more easily undergo group transfer in the key transmetalation step. This goal may be realized by tuning the electronic nature of the nontransferable groups on the silicon atom to enhance the polarizability of the C–Si bond. Clearly the role of the oxygen atom on the silanol is crucial to the success of the reaction. Mechanistic elucidation has revealed that the transmetalation event is an *intramolecular* process orchestrated through the formation of a covalent Si-O-Pd linkage. The design of ligands for palladium that take advantage of the intramolecularity of the transmetalation and assist in this process are currently being studied. Moreover, detailed mechanistic studies aimed at understanding the elemental

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steps in the transmetalation of palladium silanolates as well as the potential similarities to the transmetalation process for organoboranes are under way.

Still more exploratory directions are envisioned in the use of silanolates as precursors for the generation of organometallic species derived from other elements. Efforts directed toward understanding and developing the migration of the transferable groups from silicon to other (transition) metals such as copper, nickel, rhodium, gold, and mercury are under active study. Other limitations that need to be addressed are the scope of transferable group and the electrophile in this reaction. The cross-coupling of aliphatic silanolates has yet to be realized and the use of aryl triflates and aryl chlorides remains underdeveloped. Nonetheless, the cross-coupling of silanolates has emerged as a powerful synthetic method and this new paradigm holds great promise for further study and development.

Acknowledgements

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