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Vinyldimethylphenylsilanes as Safety Catch Silanols in Fluoride-Free Palladium-Catalyzed Cross-Coupling Reactions

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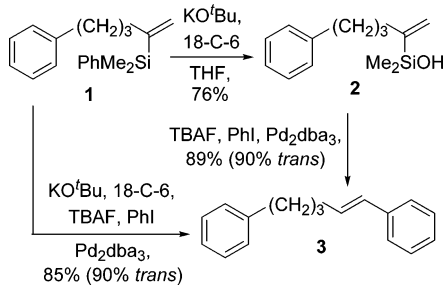
Abstract: A series of five structurally diverse vinyldimethylphenylsilanes have been shown to undergo a fluoride-free one-pot palladium-catalyzed cross-coupling reaction with phenyl iodide to give *ipso* coupled products in 62−86% yield. The limitations of this present protocol lie in the activation of Si−Ph vs protodesilylation by KOTMS/18-C-6, which seems sensitive to the sterics of cis substituents, but not geminal substituents.

Carbon−carbon bond formation by palladium-catalyzed cross-coupling reactions is now a general and powerful method in organic synthesis.[1] The most notable examples of cross coupling between organometallic nucleophiles and organic halides (or triflates) are the Suzuki coupling of organoboranes,[2] the Stille coupling of organostannanes,[3] and the Negishi coupling of organozincs.[4] Despite their wide utility these methods have specific disadvantages such as toxicity, ease of handling, functional group compatibility, or air sensitivity. Over the past decade the palladium-catalyzed cross coupling of organo silicon compounds with organic halides has been developed as an alternative cross-coupling procedure.[5] Organo silicon compounds are usually activated to cross coupling by addition of a fluoride source, which forms a silicon ate complex that is able to participate in transmetalation. Heteroatom-substituted alkenyl and aryl silanes such as haloorganosilanes, silanols, and silyl ethers are usually required for the reaction to take place.[6] However, these are sensitive to acidic and/or basic hydrolysis and are generally incompatible with silicon-based protecting group strategies. These limitations preempt the early stage incorporation of these silicon-based cross-coupling partners in multistep syntheses. A recent significant advance into the cross coupling of organo silicon compounds has been the advent of "safety catch" silanols.[7] These are derivatives that are, ideally, stable to a wide range of reaction conditions and workup procedures, but which can be selectively unmasked to give the more reactive Si−OH or Si−X coupling partner under specific conditions. Examples of these include methylsilacyclobutanes,[8] silyl hydrides,[9] 2-pyridylsilanes,[10] 2-thienylsilanes,[11] and benzyldimethylsilanes.[12] It has recently been shown that the vinylbenzyldimethylsilyl group is robust to acidic and basic hydrolysis and that standard silyl ethers can be deprotected in its presence.[12] Unmasking of the benzyldimethylsilane, to prepare for palladium-catalyzed coupling, takes place with fluoride ion which negates the possibility of using this coupling procedure in the presence of silyl ether protecting groups which are a prominent feature of many multistep syntheses. We had previously reported that treatment of vinyldimethylphenylsilanes with KO^{t}Bu and 18-C-6 in THF gives a vinyl silanol and have therefore been investigating the use of the robust dimethylphenylsilyl group as a safety catch silanol.[13] Here we report a one-pot fluoride-free cross-coupling procedure in which a range of vinyldimethylphenylsilanes have been unmasked and the resulting vinyl silanols coupled regioselectively with phenyl iodide in good yield. The use of the dimethylphenylsilyl group as an extremely stable cross-coupling partner under fluoride-free cross-coupling conditions offers the possibility of its use as a safety catch silanol in multistep syntheses with silyl ether protecting groups present.

SCHEME 1



Results and Discussion. Our previous communication reported the one-pot cross-coupling procedure of vinyl silane **1** (Scheme 1).[13] Treatment of **1** with KO^{t}Bu and 18-C-6 in THF gave the corresponding silanol **2**, which could be isolated and coupled to give the *cine*

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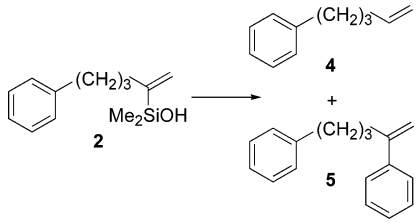
SCHEME 2[a]



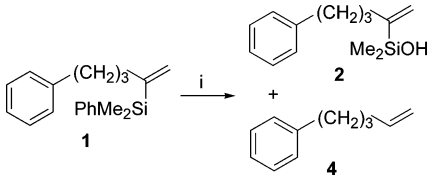
[a] Reagents: KO^{t}Bu or KO^{t}Bu and 18-C-6 or 18-C-6, TBAF, PhI, Pd_2dba_3, rt, 3 h. Product distribution of crude reaction mixture by ^{1}H NMR with KO^{t}Bu **2**:**4**, 10:1, KO^{t}Bu and 18-C-6 **2**:**4**, 13:1, 18-C-6 **5**.

substitution product **3**. Combining the two reactions to give a one-pot procedure gave an 85% yield of the same *cine* product (Scheme 1). The *cine* product presumably arises from a Heck-type process or Pd(0) carbene species rather than transmetalation from Si to Pd as Denmark observes in his silanol cross couplings.[6] We wished to investigate the generality of this procedure and the stereospecificity of the reaction with respect to *E*, *Z* and more substituted alkenes. We knew the reaction proceeds through the intermediacy of a silanol (**2**) and the use of these groups as a coupling handle with many different electrophilic coupling partners has been well documented.[7]

Before synthesizing a range of vinyl silanes we repeated our initial experiments with vinyl silane **1** and found the reaction to be very sensitive to small differences in reaction conditions. In addition to the previously observed *cine* coupled product **3** we observed silanol **2** and protodesilylated material **4**. From our previous work we had good evidence[13] that the reaction proceeded via a silanol intermediate and therefore carried out studies to maximize the conversion of phenyl silane to silanol. Treatment of vinyl silane **1** with 3 equiv of both KO^{t}Bu and 18-C-6 gave complete conversion to silanol **2** in ~30 min at room temperature. However, using these conditions in our one-pot procedure gave no coupled product, with only a 5:2 mixture of silanol **2**:protodesilylated material **4** (Scheme 2). Subjection of silanol **2**[14] to Denmark's cross-coupling conditions[15] gave complete conversion to *ipso* coupled product **5** (Scheme 2) rather than *cine* coupled product **3**. We reasoned that excess KO^{t}Bu or 18-C-6 could be inhibiting the one-pot reaction and indeed when we attempted to repeat the coupling of silanol **2** in the presence of KO^{t}Bu or KO^{t}Bu and 18-C-6 or 18-C-6 alone, we only observed coupled product in the absence of KO^{t}Bu (Scheme 2). It seemed that KO^{t}Bu was inhibiting the palladium catalyst either by competing with silyloxide for the palladium center, which Denmark had noted while developing fluoride-free cross-coupling conditions,[16] or by degradation of dba ligand. To develop a one-pot procedure we rationalized two possible protocols: use KO^{t}Bu to form silanol and then quench the excess base before adding reagents for coupling, or find another base to effect silanol formation which did not inhibit the coupling reaction.

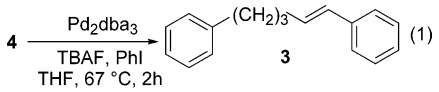
A brief study showed that addition of a slight molar excess of AcOH (1.1 equiv), to KO^{t}Bu, after silanol formation was complete (TLC, silica, 2% EtOAc/petrol), followed by addition of TBAF, Pd_2dba_3, and PhI allowed coupling to proceed and gave a 3:1 mixture of *ipso* coupled product **5**:starting material **1**. Silanol formation was then investigated with a range of other bases in combination with an equimolar amount of 18-C-6 as this had been found to be necessary when investigating silanol formation with KO^{t}Bu (Scheme 3). The success of KOTMS to promote silanol formation was of particular interest as Denmark had used this base as an activator in fluoride-free cross-coupling reactions of silanols.[15] We inferred that this base would not inhibit the palladium chemistry of the coupling reaction and could also lead to the development of a one-pot cross-coupling reaction using the dimethylphenylsilyl group as a "safety catch silanol" without the need for TBAF. Treatment of dimethylphenylsilane **1** with KOTMS and 18-C-6 at room temperature for 30 min followed by addition of Pd_2dba_3 and PhI and the mixture heated to reflux for 2 h gave 86% of *ipso* coupled product **5**. Performing the reaction at room temperature alone led to a mixture of silanol **2**, disiloxane, and *ipso* coupled product **5**, even with continued stirring for several days or addition of TBAF.

SCHEME 3[a]



[a] Reagents: (i) base (3 equiv), 18-C-6 (3 equiv), THF, rt. Product distribution of crude reaction mixture by ^{1}H NMR when base is KOH, **2**:**4**, 4:1 after 7 h; KOTMS, **2** after 2 h; KOAc, **1** after 14 h.

With a protocol for a one-pot coupling established we returned to our original reaction,[13] which had originally given *cine* coupled product **3** (Scheme 1), but with varying equivalents of KO^{t}Bu and 18-C-6 and slight alterations of reaction conditions gave variable ratios of **3**, silanol **2**, and protodesilylated material **4**. A possible explanation for the formation of *cine* coupled product **3** could be a Heck reaction of protodesilylated material **4**, the formation of the latter we knew from other work was susceptible to moisture and the quality of reagents.[17] Submitting alkene **4**, formed via protodesilylation of the vinyl silane **1**, to conditions used to cross-couple silanol **2** gave almost quantitative conversion to *cine* product **3** with heating (eq 1).[18] Therefore a possible explanation for the results obtained previously by us was that protodesilylation was rapid with consumption of most of the base that then allowed a Heck reaction to proceed.



To investigate the scope and limitations of our one-pot coupling procedure we synthesized four representative alkenes **6**–**9** (Figure 1). Vinyldimethylphenylsilanes **6** and **7** were chosen to ascertain whether double bond geometry was conserved during coupling. Alkenes **8** and **9** were chosen to probe whether more hindered trisubstituted alkenes could be prepared stereoselectively. The

(14) Prepared by analogy to: Hirabayashi, K.; Takahisa, E.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 2409.
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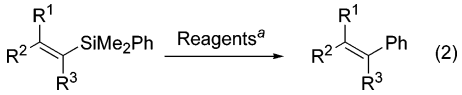
TABLE 1. Scope of Safety Catch Silane with Respect to Alkene



entry	alkene	R^1	R^2	R^3	conversion[b]	yield,[c] %
1	**1**	H	H	$(CH_2)_3Ph$	>95% *ipso*	86
2	**6**	H	$(CH_2)_3Ph$	$(CH_2)_3Ph$	10:1 *ipso*: desilylated	82
3	**7**	$(CH_2)_3Ph$	H	H	3:1 *ipso*: desilylated	62[d]
4	**8**	$(CH_2)_3Ph$	H	Me	2:1 *ipso*: desilylated	67[d]
5	**9**	H	Me	$(CH_2)_3Ph$	100% *ipso*	76[d,e]

[a] Reagents: KOTMS (2.0 equiv), 18-C-6 (2.0 equiv), THF, rt, 30 min; PhI (1.1 equiv), Pd_2dba_3 (5 mol %), 67 °C, 2 h. [b] Measured from crude ^1H NMR. [c] Isolated yield of pure *ipso* coupled product. [d] Structure of product confirmed by nOe (see the Supporting Information). [e] Reaction mixture heated to 67 °C during silanol formation.

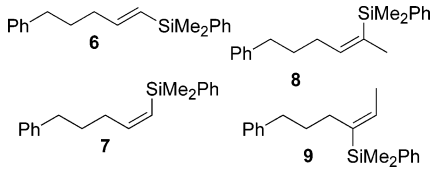


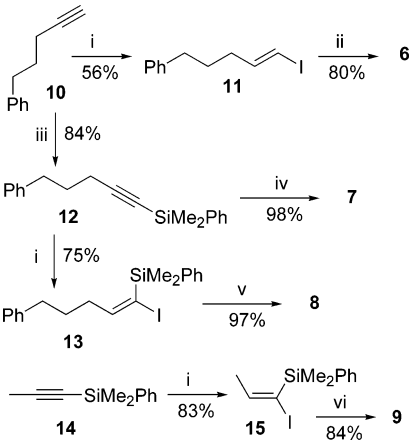
FIGURE 1.

diastereoisomers of **8** and **9** could not be prepared in pure form and so were not investigated.

A conventional route was used to convert alkyne **10** into both *E*-vinyl silane **6** and *Z*-vinyl silane **7**, although the stereoselective ruthenium catalyzed hydrosilylation of terminal alkynes with dimethylphenylsilane is known.[19] Treatment of **10** with DIBAL and I_2[20] gave *E*-vinyl iodide **11**,[21] which was subsequently metalated and quenched with dimethylphenylsilyl chloride in good yield to give **6** (Scheme 4). Conversely, treatment of the silyl alkyne **12**, derived from **10**, with DIBAL and then H_2O[22] gave **7** in excellent yield. Trisubstituted alkene **8** was accessed from acetylene **12** by hydroalumination with DIBAL and quenching with iodine.[23] Stereospecific metalation and alkylation with methyl iodide gave **8** in good yield.[24] Similarly **14**[25] was stereospecifically converted into **15** and the resultant vinyl anion isomerized[26] and converted into **9** in good yield (Scheme 4).[18]

The four vinyl silanes **6**−**9** were then submitted to the optimized one-pot cross-coupling procedure developed for **1** (eq 2, Table 1). Phenyl-vinyl silanes **1**, **6**, and **9** without substituents cis to the silyl group gave excellent yields of *ipso* coupled products under these fluoride-free one-pot reaction conditions (entries 1, 2, and 5). Substrates

SCHEME 4[a]



[a] Reagents: (i) DIBAL, I_2; (ii) *t*-BuLi, $PhMe_2SiCl$; (iii) *n*-BuLi, $PhMe_2SiCl$; (iv) DIBAL, H_2O; (v) *s*-BuLi, MeI; (vi) *s*-BuLi, $Ph(CH_2)_3I$.

with cis substituents **7** and **8** were more likely to undergo protodesilylation, but still gave synthetically useful isolated yields of *ipso* coupled products (entries 3 and 4). From these results it would seem that the limitations of this present protocol lie in the activation of Si−Ph vs protodesilylation by KOTMS/18-C-6, which seems sensitive to the sterics of cis substituents, but not geminal substituents. We can conclude that the phenyldimethylsilyl group is a viable safety catch silanol for use in fluoride-free palladium-catalyzed cross-coupling reactions and should be of use in multistep organic syntheses in the presence of silyl ether protecting groups.

Experimental Section

General Procedure for Cross Coupling. To a solution of vinyldimethylphenylsilane (0.20 mmol) in THF (1.5 mL) was added KOTMS (2.0 equiv) and 18-C-6 (2.0 equiv) at room temperature and the solution was stirred for 30 min. PhI (1.1 equiv) was added and after a further 10 min Pd_2dba_3 (5 mol %) was added and the mixture was then heated at reflux for 2 h. The reaction mixture was purified by filtering through a silica plug and eluting with Et_2O, column chromatography (petrol), and where necessary bulb-to-bulb distillation to give the coupled product.

Acknowledgment. This work is part of the Ph.D. Thesis of R.H.M., University of Nottingham. We thank

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(24) Structure confirmed by nOe, details in the Supporting Information.
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Supporting Information Available: Experimental details for the synthesis of vinyl silanes, full characterization data for all compounds, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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