

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 fluoridefree 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 SCHEME 1



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 palladiumcatalyzed 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 vinyldimethvlphenylsilanes with KO^tBu 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 silvl ether protecting groups present.

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^tBu 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^tBu or KO^tBu and 18-C-6 or 18-C-6, TBAF, PhI, Pd₂dba₃, rt, 3 h. Product distribution of crude reaction mixture by ¹H NMR with KO^tBu **2:4**, 10:1, KO^tBu 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 evidence¹³ 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^tBu and 18-C-6 gave complete conversion to silanol $\mathbf{2}$ 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:protodesilvlated material 4 (Scheme 2). Subjection of silanol 2^{14} to Denmark's cross-coupling conditions¹⁵ gave complete conversion to *ipso* coupled product 5 (Scheme 2) rather than *cine* coupled product 3. We reasoned that excess KO'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^tBu or KO^tBu and 18-C-6 or 18-C-6 alone, we only observed coupled product in the absence of KO^tBu (Scheme 2). It seemed that KO^tBu was inhibiting the palladium catalyst either by competing with silvloxide 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^tBu 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'Bu, after silanol

SCHEME 3^a



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

formation was complete (TLC, silica, 2% EtOAc/petrol), followed by addition of TBAF, Pd₂dba₃, 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^tBu (Scheme 3). The success of KOTMS to promote silanol formation was of particular interest as Denmark had used this base as an activator in fluoridefree 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 Pd₂dba₃ 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.

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^tBu 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 onepot 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

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TABLE 1. Scope of Safety Catch Silane with Respect to Alkene

$R^{2} \xrightarrow[R^{3}]{\text{SiMe}_{2}\text{Ph}} \xrightarrow[R^{3}]{\text{Reagents}^{a}} R^{2} \xrightarrow[R^{3}]{\text{Ph}} (2)$						
entry	alkene	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	$conversion^b$	yield, ^c %
1	1	Н	Н	$(CH_2)_3Ph$	>95% ipso	86
2	6	Н	$(CH_2)_3Ph$	$(CH_2)_3Ph$	10:1 <i>ipso</i> : desilylated	82
3	7	$(CH_2)_3Ph$	Н	Н	3:1 <i>ipso</i> : desilylated	62^d
4	8	$(CH_2)_3Ph$	Н	Me	2:1 <i>ipso</i> : desilylated	67^d
5	9	Н	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), Pd₂dba₃ (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 guenched with dimethylphenylsilvl chloride in good yield to give 6 (Scheme 4). Conversely, treatment of the silvl 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 14²⁵ was stereospecifically converted into 15 and the resultant vinyl anion isomerized²⁶ 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

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^a Reagents: (i) DIBAL, I₂; (ii) *t*-BuLi, PhMe₂SiCl; (iii) *n*-BuLi, PhMe₂SiCl; (iv) DIBAL, H₂O; (v) *s*-BuLi, MeI; (vi) *s*-BuLi, Ph(CH₂)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 Pd₂dba₃ (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 Et₂O, column chromatography (petrol), and where necessary bulb-to-bulb distillation to give the coupled product.

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Supporting Information Available: Experimental details for the synthesis of vinyl silanes, full characterization

data for all compounds, and $^1\mathrm{H}$ and $^{13}\mathrm{C}$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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