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The direct use of phenyldimethylsilanes in silicon assisted palladium catalysed cross coupling†

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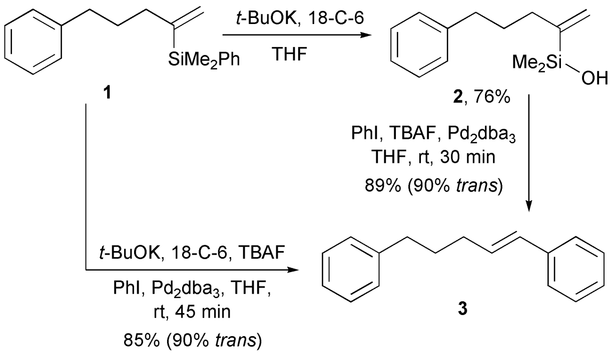
A vinyl-phenylsilane has been used as a masked vinyl organometallic for a cross coupling reaction with phenyl iodide to provide the cine substitution product in high yield.

Carbon–carbon bond formation by palladium catalysed cross coupling reactions are now a general and powerful method in organic synthesis.[1] Arguably the most notable examples of cross coupling between organometallic nucleophiles and organic halide (or triflate) are the Suzuki–Miyaura coupling of organoboranes,[2] Stille–Migita–Kosugi coupling of organostannanes[3] and Negishi coupling of organozincs.[4] These methods have gained popularity amongst the synthetic community, in part, as they employ isolatable or easily prepared organometallics that are weak nucleophiles with good functional group stability. However these methods have specific disadvantages such as toxicity, ease of handling, functional group compatibility or air sensitivity. This has led to the development of complimentary methods which have tried to address one or more of these drawbacks.[1a] Over the past decade the palladium catalysed cross coupling of organo silicon compounds to organic halides has been developed as an alternative cross coupling procedure.[5] Pioneering studies by Hiyama have shown that activation of organofuctional silicon compounds is possible by addition of a fluoride source to promote the palladium-catalysed, cross-coupling reactions to various organic halides.[6] The activation of functionalised organo silicon compounds by a fluoride source to form a reactive siliconate complex that participates in transmetallation has been investigated by a number of other research groups.[7] More recent developments have developed the use of silanols in cross coupling reactions.[7h,i,8] A characteristic of all these methods is the use of more reactive organo silicons such as haloorganosilanes, orthosiliconates silyl ethers, silacyclobutanes and silyl hydrides. Functionality which could be tempremental in a multi step synthesis. We wish to report here our preliminary observations that the robust phenyldimethylsilyl group can be used directly in a palladium catalysed cross coupling reaction.

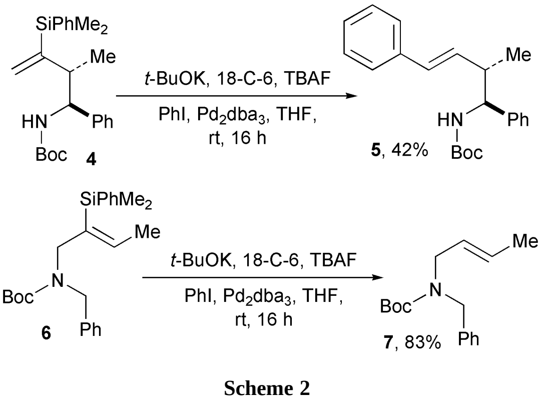
We have recently reported a mild method for the protodesilylation of C-2 phenyldimethylsilyl terminal alkenes using a mixture of *t*-BuOK-18-C-6-TBAF.[9] In this work we found that the intermediate in the protodesilylation reaction sequence is a silanol. The formation of silanols from the treatment of phenylsilanes with *t*-BuOK is not unprecedented, but it was reported that the proposed mechanism required DMSO.[10] Treatment of model compound **1** with *t*-BuOK (2 equiv.) and 18-C-6 (1.5 equiv.) in undried THF for 2 h at room temperature gave a 76% yield of silanol **2** (Scheme 1). The extensive optimisation of reaction conditions (Pd cat., fluoride source, stoichiometry, solvent and temperature) already carried out by Denmark *et al.*[6h–j,8] provided ideal cross coupling conditions with phenyl iodide to give cross coupled product **3** in 89% yield. The key transformation by combining these two reactions was carried out by treatment of **1** with a mixture of *t*-BuOK (2.5 equiv.), 18-C-6 (1.5 equiv.), TBAF (2 equiv) and Pd_2dba_3 (10 mol %) with PhI (1 equiv.) in undried THF[11] at room temperature for 45 min and gave a 85% yield of **3**. We believe this is a significant advance as the phenyldimethylsilyl group is resistant to most chemical reagents and so could be carried through a multistep synthesis with more confidence than any of the more reactive functionalised organosilanes presently used for palladium catalysed cross coupling reactions. Our mild conditions for the liberation of a silanol from the phenylsilane precursor coupled with standard cross coupling conditions[6h–j,8] provides an excellent benign organometallic nucleophile for multi step syntheses.

Of course the striking observation with this particular substrate is the high yield of cine substitution. The alkene **3** is isolated as a ~90% pure *trans* stereoisomer contaminated with a mixture of other alkene isomers.[12] This product presumably arises from a Heck type process or Pd(0)-carbene species previously reported in organoborane[2] and organostannane[13] cross couplings, but not to the efficiency here. It is worth noting that in the work developing the use of silanols in cross coupling reactions only terminal silanols have been reported.[6h–j,8]

Preliminary investigations into the stereoselectivity and generality of this cross coupling protocol has relied upon other phenyldimethyl silanes we have generated from our aza-[2,3]-Wittig sigmatropic rearrangement project. Treatment of the more complex C-2 phenyldimethylsilyl terminal alkene **4** under identical reaction conditions gave a 42% yield of cine



Scheme 1



Scheme 2

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† Electronic supplementary information (ESI) available: further experimental details. See http://www.rsc.org/suppdata/cc/b2/b205765d/

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substitution product **5** (Scheme 2). Treatment of phenyldimethylsilyl alkene **6** under identical silanol forming/cross coupling reaction conditions, but stirring overnight, led to protodesilylation and gave **7** in 83% yield. Termination of the reaction after 45 min gave the corresponding silanol (44%) and **7** (44%).

We are currently investigating the substrate tolerance and stereoselectivity of this protocol which will form the basis of a full publication in the near future. The preliminary results presented here suggest that this mild procedure holds particular promise for the use of phenyldimethylsilyl groups in direct cross coupling reactions for complex molecule synthesis.

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Notes and references

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13 See ref 3*b*, pp. 48–49.