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Fluoride-free cross coupling using vinyldisiloxanes†

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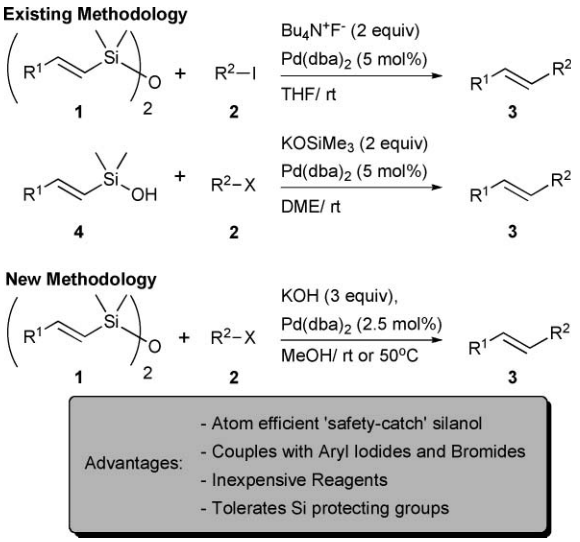
Vinyldisiloxanes equilibrate with the corresponding silanolates under basic conditions and subsequently undergo palladium catalysed cross coupling with aryl/heteroaryl iodides and bromides.

The transition metal catalysed formation of C–C bonds is arguably one of the most utilized transformations in academic and industrial synthetic organic chemistry.[1] Organotin (Stille),[1,2] organoboron (Suzuki–Miyaura),[1,3] organozinc (Negishi)[1,4] and Grignard reagents (Kumada)[5] are well established organometallics employed in transition metal catalysed cross couplings. The development of alternative, cost effective organometallics, which are easier to handle and less toxic, remains an active area of research. Consequently organosilanes aroused interest. Pioneering work by Hiyama and Hatanaka established the cross coupling of organosilanes with aryl and vinyl halides *via* activation of the Si–C bond with fluoride (F^-) to facilitate transmetallation.[6] Since this early discovery there have been numerous advances, one of the most notable being the development of fluoride-free palladium catalysed cross coupling of organosilanols and silanolates with various organic halides.[7] Due to the increased reactivity of silanols and silanolates relative to alkyl silanes, masked forms known as 'safety-catch' silanols were developed; examples include silacyclobutanes, 2-pyridylsilanes, 2-thienylsilanes, phenyldimethylsilanes and benzyldimethylsilanes.[8,9] The masked silanols could be carried through multi-step syntheses but when subjected to specific reaction conditions the silanol intermediate would be formed and undergo the desired cross coupling reaction.

Herein, we describe the development of new methodology for fluoride-free cross coupling using aryl substituted vinyldisiloxanes as masked silanolate precursors. We report that under basic conditions, disiloxanes (**1**) are in an equilibrium with the active silanolate (**6**). In the presence of an aryl/heteroaryl halide (**2**) and a base, disiloxanes readily participate in fluoride-free palladium catalysed cross coupling, which presumably proceeds *via* the *in situ* formation and subsequent reaction of the corresponding silanolate species.

The use of disiloxanes has several advantages in the context of silicon-based coupling processes. For example, vinyl disiloxanes can be readily obtained from inexpensive starting materials (*vide infra*). Consequently they provide an attractive atom efficient alternative to existing 'safety-catch' silanols, which are generally more costly or difficult to prepare or can require the use of a fluoride source. In addition, disiloxanes exhibit good levels of functional group tolerance relative to the more reactive silanols and silanolates. Thus disiloxane-based protocols may prove to be more flexible in the context of multi-step syntheses, as the disiloxane functionality could potentially be installed at an early stage in the synthesis and carried through several synthetic steps.

Though the use of disiloxanes as silanolate precursors in cross coupling reactions with aryl halides is known, such protocols generally require either the use of a fluoride activator or have typically focused upon the synthesis of functionalised styrene derivatives (*i.e.* the introduction of a terminal olefin group, $R^1 = H$, $R^2 =$ aryl/heteroaryl in Scheme 1 & 2).[10] The methodology described in this report allows the fluoride-free cross coupling of a range of readily synthesised aryl substituted vinyldisiloxanes. In addition, silicon protecting groups, which are commonly employed in organic synthesis, were tolerated under the new fluoride-free reaction conditions.[11] Furthermore, aryl bromides could be cross coupled with disiloxanes in a comparable yield and selectivity to aryl iodides, a noteworthy result considering aryl bromides are more readily available and typically easier to synthesise than aryl iodides (Scheme 1 & 2).[12]



Scheme 1 Conventional methodology and new methodology.

This report focuses upon the application of this new disiloxane-based methodology to the synthesis of a wide range of (*E*)-stilbenes; these natural product scaffolds have a number of

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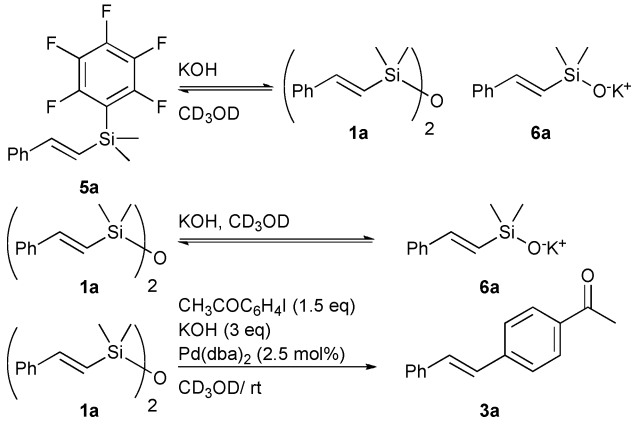
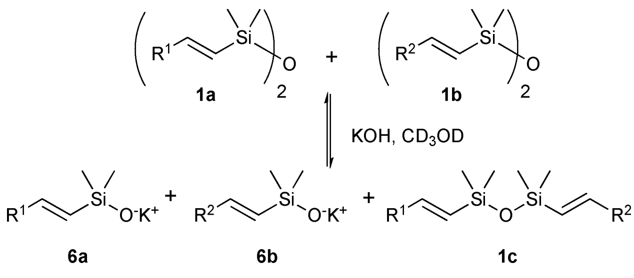
† Electronic supplementary information (ESI) available: Experimental procedures and full characterisation data. See DOI: 10.1039/b900852g



Scheme 2 Initial NMR Experiments.

therapeutic indications including prevention of cardiovascular disease, effects on metabolism, anti-inflammatory activity along with anticancer properties.[13]

Our research began with investigating the use of pentafluorophenylsilane as a 'safety-catch' silane (Scheme 2, **5a**). In the development of fluoride-free cross coupling conditions, initial NMR studies revealed that the Si–C bond was cleaved rapidly, forming a mixture of the disiloxane (**1a**) and silanolate (**6a**). Further NMR studies using phenylvinyldisiloxane (**1a**) and potassium hydroxide in deuterated methanol, revealed that the disiloxane was in an equilibrium with the silanolate (**6a**). When the corresponding silanol (**4**, R^1 = Ph) was treated with base, a mixture of the disiloxane (**1a**) and silanolate (**6a**) were both visible, by ^1H and ^{13}C NMR and liquid chromatography mass spectrometry (LCMS). These early encouraging results led us to investigate the Pd-catalysed cross coupling of disiloxane **1a** with 4-iodoacetophenone using potassium hydroxide. The consumption of the aryl iodide and formation of coupled product (**3a**) was observed by NMR in real time. As further evidence of this disiloxane/silanolate equilibrium, an exchange experiment was carried out (Scheme 3). When disiloxanes **1a** and **1b** were treated with base, the corresponding silanolates (**6a** & **6b**) and the starting disiloxanes (**1a** & **1b**), along with the mixed disiloxane (**1c**), were all observed by LCMS. The mixed disiloxane (**1c**) was isolated and characterised.

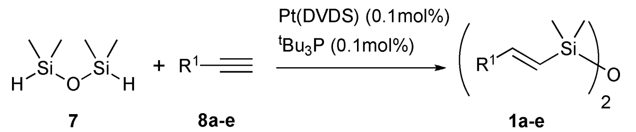


R^1 = Phenyl; R^2 = *p*-tolyl

Scheme 3 Disiloxane/silanolate exchange.

Excellent (*E*)-selectivity can be obtained for the hydrosilylation of alkynes using the catalyst Pt(0)-1,2-divinyl-1,1,3,3-tetramethyldisiloxane (Pt(DVDS)) in a complex with $^tBu_3P$.[9] In accordance with a previous report by Denmark[14] we found that the hydrosilylation of terminal alkynes (**8a–e**) using 1,1,3,3-tetramethyldisiloxane (**7**) as the silane and the catalytic complex Pt(DVDS)/$^tBu_3P$ yielded a variety of (*E*)-vinyldisiloxanes (**1a–b** & **1d–f**) in excellent yields (Table 1). The selectivity and yields for the hydrosilylation were consistently high when electron rich (**8d**), electron poor (**8c**) and heterocyclic (**8e**) terminal alkynes were investigated.

Table 1 (*E*)-Hydrosilylation of terminal alkynes[a]



Entry	Acetylene, R^1	Product	(*E*), [b]%	Yield, [c]%
1	C_6H_5 (**8a**)	**1a**	≥ 99	96
2	4-$(CH_3)C_6H_4$ (**8b**)	**1b**	≥ 99	82
3	4-$(NO_2)C_6H_4$ (**8c**)	**1d**	≥ 99	90
4	4-$(CH_3O)C_6H_4$ (**8d**)	**1e**	≥ 99	91
5[d]	3-Pyridyl (**8e**)	**1f**	≥ 99	94

[a] *Reagents and conditions:* 1,1,3,3-tetramethyldisiloxane (**7**) (1 equiv.), acetylene (**8**) (2 equiv.), Pt(DVDS) (0.1 mol%), $^tBu_3P$ (0.1 mol%), toluene, rt, 16 h. [b] Percentage calculated from isolated isomer. [c] Isolated yield. [d] Reaction heated at 60 °C.

The scope of the fluoride-free cross coupling of disiloxanes with aryl iodides was first investigated with **1a** (Table 2). Electron deficient aryl iodides (entries 1, 3 & 7), including those with *ortho*-substituents (entry 8), coupled in excellent yields. At room temperature, good selectivity was achieved for aryl iodide *versus* bromide functionality (entry 9). Interestingly, it was also possible to cross couple heteroaromatic iodides (entries 11 & 12).

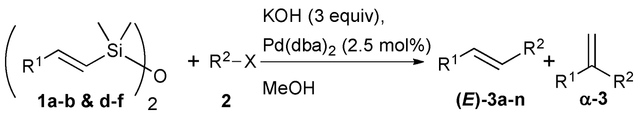
The coupling of electron rich aryl iodides proved to be more challenging (Table 2, entries 5 & 10). Under the standard conditions, a mixture of the desired (*E*)-stilbene and undesired α-substituted product was observed in a ratio of 1.5:1. To improve the selectivity for the desired product, an optimisation of the reaction conditions was carried out.

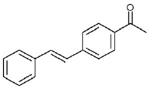
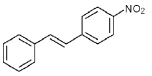
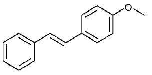
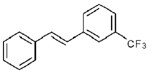
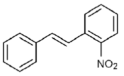
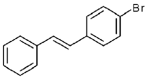
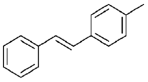
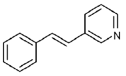
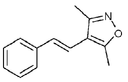
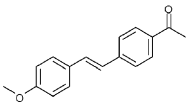
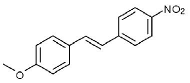
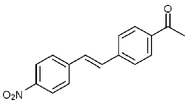
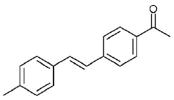
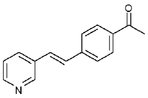
Elevated reaction temperatures were found to be unfavourable, resulting in a lower ratio of the desired (*E*)-product, as well as an increased percentage of reduced aryl iodide and homo-coupled product (Ullmann coupling of the aryl iodide starting material). A total of ten ligands were also investigated to see if a reduced cone angle around the palladium would improve the selectivity for (*E*) over α products. Tri(*ortho*-tolyl)phosphine was found to give the cleanest profile and the best (*E*):α ratio (50:1) when heating with 4-iodoanisole (1.5 equiv.), potassium hydroxide (7 equiv.) and disiloxane (**1a**, 1 equiv.) in methanol at 70 °C for 7 hours (entry 5). Under these optimal conditions for selectivity, the main side products of the reaction were the reduced aryl iodide (<13%) and homo-coupled product (<1%).

Pleasingly, electron deficient aryl bromides also cross coupled in excellent yields by simply elevating the temperature to 50 °C (Table 2, entries 2, 4 & 14). As with the corresponding aryl iodides, the cross coupling with electron rich aryl bromides was more problematic. This was overcome by the addition of X-Phos (5 mol%) to the reaction mixture. Under these conditions the cross coupling of 4-bromoanisole proceeded in a moderate yield with excellent (*E*)-selectivity (Table 2, entry 6).

The electronic nature of the vinyldisiloxane (**1a–b** & **1d–f**) did not appear to affect the reactivity or selectivity of the cross

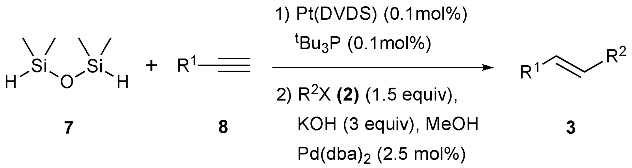
Table 2 Fluoride-free cross coupling of vinyldisiloxanes with aryl and heteroaryl iodides and bromides[a]



Entry	Disiloxane	X	Product		(*E*), [b]%	Yield, [c]%
1	**1a**	I		**3a**	≥99	91
2[d]	**1a**	Br		**3a**	≥99	96
3	**1a**	I		**3b**	≥99	88
4[d]	**1a**	Br		**3b**	≥99	94
5[e]	**1a**	I		**3c**	≥98	66
6[f]	**1a**	Br		**3c**	≥98	56
7	**1a**	I		**3d**	≥99	91
8	**1a**	I		**3e**	≥99	75
9	**1a**	I		**3f**	≥99	61
10[e]	**1a**	I		**3g**	≥99	72
11[g]	**1a**	I		**3h**	≥99	56
12	**1a**	I		**3i**	≥99	53
13	**1e**	I		**3j**	≥99	83
14[d]	**1e**	Br		**3k**	≥99	79
15	**1d**	I		**3l**	≥99	70
16	**1b**	I		**3m**	≥99	73
17[d]	**1f**	I		**3n**	≥99	61

[a] *Reagents and conditions:* **1** (1 equiv.), **2** (1.5 equiv.), KOH (3 equiv.), Pd(dba)$_2$ (2.5 mol%), MeOH, rt, 2–16 h. [b] Percentage calculated from isolated isomer. [c] Isolated yield. [d] Heated at 50 °C, 4–16 h. [e] P(*o*-tolyl)$_3$ (5 mol%), KOH (7 equiv.), 70 °C, 16 h. [f] X-Phos (5 mol%), 70 °C, 4 h. [g] Heated at 70 °C for 16 h.

Table 3 One pot hydrosilylation and fluoride-free cross coupling of terminal acetylenes to form substituted (*E*)-stilbenes[a]



Entry	Acetylene	R^2X (**2**)	Product	Yield, [b]%
1	**8a**	4-$(CH_3CO)C_6H_4I$	**3a**	89
2[c]	**8a**	4-$(CH_3CO)C_6H_4Br$	**3a**	82
3	**8a**	4-$(NO_2)C_6H_4I$	**3b**	86
4[c]	**8d**	4-$(NO_2)C_6H_4Br$	**3k**	98

[a] *Reagents and conditions:* 1,1,3,3-tetramethyldisiloxane (**7**) (1 equiv.), acetylene (**8**) (2 equiv.), Pt(DVDS) (0.1 mol%), $^tBu_3P$ (0.1 mol%), toluene, rt, 16 h, followed by aryl halide (**2**) (1.5 equiv.), KOH (3 equiv.), $Pd(dba)_2$ (2.5 mol%), MeOH, rt, 2–16 h. [b] Isolated yield. [c] Cross coupling reaction heated to 50 °C.

coupling as good conversion to the (*E*)-stilbene products was achieved for all the disiloxanes synthesised (Table 2, entries 13–17).

With the individual steps in hand, we then explored the possibility of a 'one-pot' hydrosilylation followed by fluoride-free cross coupling (Table 3). Pleasingly, excellent yields of the isolated (*E*)-stilbenes were obtained for both aryl iodides (entries 1 & 3) and bromides (entries 2 & 4). Significantly, the yields for the 'one-pot' procedures were comparable to those for the individual steps.

In summary, we have demonstrated that disiloxanes cross couple under fluoride-free conditions as a result of their equilibrium with the active silanolates under basic conditions. An operationally simple protocol for the synthesis of a range of substituted (*E*)-stilbene derivatives in good to excellent yields with excellent levels of geometrical purity from inexpensive starting materials was developed. This method provides an attractive, cost-effective alternative to the transition metal catalysed routes traditionally used to generate molecules containing this privileged scaffold. Though this study was limited in scope to the formation of stilbene derivatives, it is hoped that the disiloxane-mediated cross coupling methodology will find application in the synthesis of other classes of compounds. For example, preliminary work on the cross coupling of aryl halides with aryl, vinyl and alkyl substituted disiloxanes has yielded promising results. Another area for further study is the use of disiloxanes as stable silanol/silanolate equivalents in multi-step synthetic procedures which could offer new disconnection strategies in the synthesis of complex molecular architectures. Further exploration into the scope and diversity of cross coupling with disiloxanes is under current investigation and results will be reported in due course.

Acknowledgements

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10 For example, Denmark has recently reported the fluoride-free cross coupling of dimethylvinylsilanolate, generated *in situ* from divinyltetramethyldisiloxane (DVDS), with aromatic halides. This methodology was exploited in the vinylation of a range of aryl iodides and bromides (see ref. 8(a) and S. E. Denmark and C. R. Butler, *J. Am. Chem. Soc.*, 2008, **130**, 3690–3704). See also ref. 14.

11 Triisopropylsilyl-protected alcohol was found to be stable under the cross coupling reaction conditions.

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14 S. E. Denmark and Z. Wang, *Org. Lett.*, 2001, **3**, 1073–1076. In this report, vinyldisiloxanes were used in Pd-catalysed cross coupling reactions with aryl iodides; however, fluoride was required as the activation source.