ORGANIC
LETTERS

2006
Vol. 8, No. 17
3733−3736

All-Carbon-Substituted Vinylsilane Stable to TBAF: Synthesis of Allyldimethylvinylsilane and Its Pd-Catalyzed Cross-Coupling under Mild Conditions

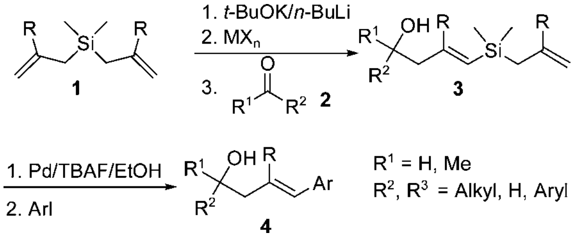
Lianhai Li* and Neenah Navasero

Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research,
P.O. Box 1005, Pointe-Claire-Dorval, Quebec, Canada H9R 4P8

lianhai_li@merck.com

Received May 26, 2006

ABSTRACT



Allyldimethylvinylsilanes 3 are easily synthesized by the reaction of silylallylmetals, generated from 1 by *n*-BuLi/*t*-BuOK, with carbonyl compounds in the absence or presence of metal halides. They can tolerate 2 equiv of TBAF in THF at room temperature for at least 6 h but can be easily activated in the presence of a palladium catalyst and TBAF to perform the cross-coupling reaction with aryl iodides at room temperature.

The Pd-catalyzed cross-coupling of vinylmetals[1] with aryl or vinyl halides/triflates is of great interest to synthetic chemists. However, in practice, the application of most vinylmetals as cross-coupling partners in complex synthesis is limited by the reactivity of the carbon−metal bond. Often, the vinylmetals are prepared in situ and used right away. In contrast, the silicon−carbon bond of silafunctional vinylsilane, which was recently demonstrated to undergo Pd-catalyzed cross-coupling under very mild conditions,[2] is highly stable. This makes it possible to carry the vinylsilane functionality through several steps in complex syntheses, making synthetic design more flexible. Optimally, the other substituents on the silicon atom of the vinylsilane should also be stable. Unfortunately, it has been found that at least one labile substituent is essential to carry out the coupling reaction under mild conditions.[2] One strategy that has proven effective in overcoming this issue is to develop a vinylsilane with an all-carbon-substituted silyl group, in which at least one carbon substituent could be easily activated to meet the requirement for a mild cross-coupling.[3] Several carbon substituents on the silicon of a vinylsilane, including 2-thiophenyl,[3a] 2-pyridyl,[3b] benzyl,[3c] and 1,3-propanediyl[3d] have been developed for this purpose.

We previously reported a convenient three-component synthesis of homoallylic alcohols (**4**) as shown in Scheme 1.[4] We intended to incorporate the sequence into a complicated multistep synthesis that requires the vinylsilane func-

---

[1] For a review, see: Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed, Cross-coupling Reactions*; Wiley-VCH: Weinheim, 1998.

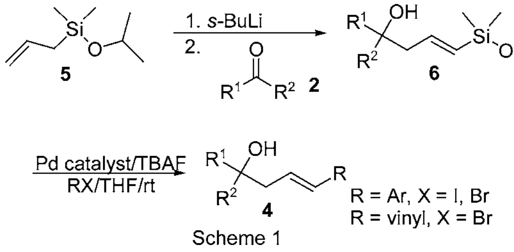
[2] For reviews, see: (a) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (c) Denmark, S. E.; Ober, M. E. *Aldrichimica Acta* **2003**, *36*, 75.

[3] (a) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, 138. (b) Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (c) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895. (d) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821.

[4] Li, L.; Navasero, N. *Org. Lett.* **2004**, *6*, 3091.

10.1021/ol061288l CCC: $33.50

Scheme 1



tional to be carried through several synthetic operations. However, this was confounded by the unstable Si−O bond in **6**, which readily hydrolyzed on silica gel. We now describe our efforts to identify a stable all-carbon replacement for the isopropoxy group we used previously.

We evaluated some simple and low molecular weight groups and found that an allyl group might serve our purpose.[5] First of all, an allyl group would be compatible with our method in synthesizing the vinylsilane from a silylallyl anion, which can be generated from the simple diallyldimethylsilane as an equivalent to the allyldimethyl(2-propoxy)silane (Scheme 2). Furthermore, the widely documented synthetic application as well as reactivity of allylsilane can provide the necessary information to facilitate the design in a complex synthesis.

Scheme 2

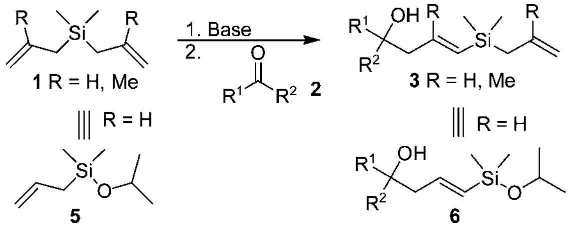
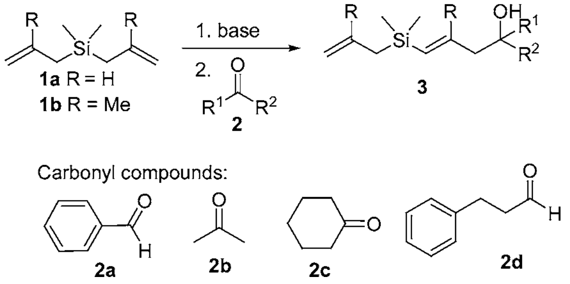
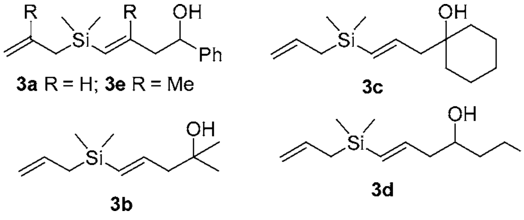


Table 1. Generation of an Allyl Anion and Addition to Carbonyls



entry	conditions[a]	diallylsilane	carbonyl compd	product (yield %)
1	A	**1a**	**2a**	**3a** (49)
2	B	**1a**	**2a**	**3a** (45)
3	C	**1a**	**2a**	**3a** (67)
4	C	**1a**	**2b**	**3b** (5)
5	C	**1a**	**2c**	**3c** (30)
6	D	**1a**	**2b**	**3b** (54)
7	D	**1a**	**2c**	**3c** (52)
8	C	**1a**	**2d**	**3d** (34)[b]
9	E	**1a**	**2d**	**3d** (58)
10	C	**1b**	**2d**	**3e** (33)
11	F	**1b**	**2a**	**3e** (63)

[a] **A**: s-BuLi (0.9 equiv)/TMEDA (0.9 equiv)/−78 °C/THF/1 h. **B**: n-BuLi (1.1 equiv)/t-BuOK (1.1 equiv)/−78 °C/THF/1 h. **C**: n-BuLi (0.9 equiv)/t-BuOK (0.9 equiv)/−78 °C/THF/1 h. **D**: Conditions **C**/$ZnCl_2$/1 h/room temperature. **E**: Conditions **C**/CuCN/1 h/−78 °C. **F**: n-BuLi (0.9 equiv)/t-BuOK (0.9 equiv)/−78 °C to room temperature/Et_2O/1 h [b] About an equal molar amount of the α-adduct obtained.



We first attempted to generate the silylallyl anion from **1a** with a s-BuLi/TMEDA complex[6] in THF. The addition of the resulting anion to PhCHO only afforded **3a** in 49% yield (entry 1, Table 1). We then turned our attention to Schlosser's base[7] and found that when a stirred solution of **1a** with 1.1 equiv of t-BuOK in THF was treated with 1.1 equiv of n-BuLi at −78 °C for 1 h and then reacted with benzaldehyde the desired product **3a** was obtained in 45% yield along with the formation of 10% of the divinylsilane, which resulted from the addition of both metalated allyl groups to benzaldehyde (entry 2, Table 1). To avoid this byproduct, we decided to use 0.9 equiv of t-BuOK and 0.9 equiv of n-BuLi to perform the reaction; this improved the reaction yield to 67% with no formation of the byproduct being observed (entry 3, Table 1). However, when acetone or cyclohexanone was employed as a representative aliphatic ketone, the yield decreased to 5% and 30%, respectively (entries 4 and 5, Table 1). We thought that this was due to the presence of t-BuOK, a strong base which might cause the enolization of the carbonyl compounds employed. To avoid it, $ZnCl_2$ was added to modify the reactivity of the generated anion complex. By this modification,[8] vinylsilanes **3b** and **3c** were obtained in 54% and 52% yields, respectively (entries 6 and 7, Table 1). It is worth noting that in all cases only the trans-substituted γ-adduct was observed. The direct addition of the silylallyl anion generated by Schlosser's base to 3-phenylpropanal produced the desired product in 29% yield (entry 8, Table 1). In this case, the low yield was caused by the generation of an equal amount of α-adduct. The modification by $ZnCl_2$ and some other metal halides such

---

(5) For a previous application of the allyldimethylsilyl group as a latent stable silafunctional group that enables the Tamao oxidation, see: Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.

(6) Tamao, K.; Nakajo, E.; Ito, Y. *Synth. Commun.* **1987**, *17*, 1637.

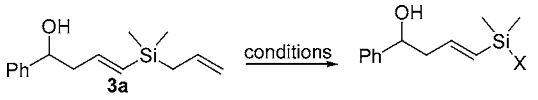
(7) Schlosser, M.; Franzini, L. *Synthesis* **1998**, 707.

(8) For a previous application of $ZnCl_2$ in modifying the reactivity of silylallylmetal, see: Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004.

as $CeCl_3$ resulted in no change to the reaction results. Fortunately, we found that the problem could be solved by the use of CuCN;[9] the desired product was obtained in 58% yield without the detection of an α-adduct (entry 9, Table 1). The addition of the anion generated from diallylsilane **1b** by using Schlosser's base in THF at −78 °C to benzaldehyde was found to afford the desired vinylsilane in 33% yield (entry 10, Table 1), but the yield was improved to 63% when the anion was generated in ether (entry 11, Table 1).

We then used **3a** to investigate the activation of the allyl group by TBAF in THF and found that when **3a** was treated with 2 equiv of TBAF in THF for 6 h at room temperature 95% of **3a** was recovered (entry 1, Table 2). The presence of 6 equiv of ethanol in the above reaction resulted in no change of the reaction result; 96% of **3a** could be recovered after 6 h of reaction (entry 2, Table 2). However, when 2 equiv of TBAF, 6 equiv of EtOH, and 5% of $Pd_2(dba)_3$ were employed together, TLC showed that **3a** was consumed in less than 30 min. After workup, ^{1}H NMR characterization of the crude product indicated that the distinctive signals associated with the allyl group had completely disappeared whereas those of the vinyl functionality were intact (entry 3, Table 2). As a comparison, we only recovered the starting **3a** from the reaction run with $Pd_2(dba)_3$ and 6 equiv of EtOH (entry 4, Table 2). These results suggest that the TBAF and the Pd catalyst worked together to activate the allyl group. A plausible explanation for this is that the interactions of the Pd species with the double bonds (either with allyl or with the vinyl or even with both) enhance the affinity of the fluoride anion with silicon, thus accelerating the reaction.

Table 2. Allyl Group Activation

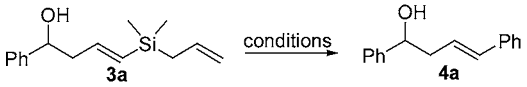


entry	conditions	time (h)	results
1	TBAF (2 equiv)/THF/rt	6	95% **3a** recovered[a]
2	TBAF (2 equiv)/THF/rt EtOH (6 equiv)	6	96% **3a** recovered[a]
3	TBAF (2 equiv)/EtOH (6 equiv) $Pd_2(dba)_3$ (5%)/THF/rt	0.5	100% **3a** consumed[b]
4	EtOH (6 equiv) $Pd_2(dba)_3$ (5%)/THF/rt	6	98% **3a** recovered[a]

[a] Isolated by flash chromatography. [b] TLC and crude ^{1}H NMR.

Having demonstrated that the allyl group could serve as a preactivation group under the coupling conditions, we proceeded to test the Pd-catalyzed cross-coupling of **3a** with iodobenzene. We first performed the coupling reaction without preactivation of the allyl group, under which conditions the desired coupling product **4a** was obtained in 74% yield (entry 1, Table 3). The yield was relatively lower than the coupling of the 2-propoxy-substituted vinylsilane in a previous study.[4] We suspected the lower yield in this case was caused by the coupling of the allyl group with iodobenzene. We found that the yield was improved to 91% by running the activation for 30 min as described above (entry 3, Table 2) and then adding iodobenzene to accomplish the cross-coupling.

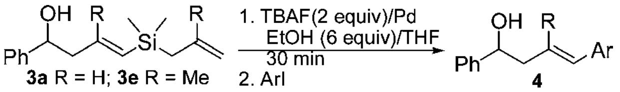
Table 3. Optimization of Cross-Coupling



entry	conditions	yield % **4a**
1	PhI/TBAF (2 equiv)/EtOH (6 equiv) $Pd_2(dba)_3$ (5%)/THF/rt/4 h	74
2	1. TBAF (2 equiv)/EtOH (6 equiv) $Pd_2(dba)_3$ (5%)/THF/rt/0.5 h 2. PhI/4 h	91

Being satisfied with the results obtained in entry 2 of Table 3, we moved on to test the variation of aryl iodide in this Pd-catalyzed cross-coupling by using **3a** and **3e** as representative vinylsilanes under these conditions. When para-substituted aryl iodides were employed, the coupling reaction consistently afforded the coupling product in good yields (70−91%, entries 1−4 and 6−9, Table 4). The reaction was compatible with functional groups such as ketone and ester. When 2-iodoanisole was employed and the coupling was done by using $(allylPdCl)_2$ as the catalyst, we found that **3a** acted as an efficient coupling partner (entry 5, Table 4), but **3e** did not (entry 10, Table 4). The difference might be due to the increased steric hindrance from the methyl group in **3e**.

Table 4. Variation of ArI in the Pd-Catalyzed Cross-Coupling



entry	ArI[a]	vinylsilane	product (Ar, R)	isolated yield (%)
1	PhI	**3a**	Ph	**4a** (91)
2	$4\text{-}EtO_2CC_6H_4I$	**3a**	$4\text{-}EtO_2CC_6H_4$, H	**4b** (85)
3	$4\text{-}AcC_6H_4I$	**3a**	$4\text{-}AcC_6H_4$, H	**4c** (84)
4	$4\text{-}MeOC_6H_4I$	**3a**	$4\text{-}MeOC_6H_4$, H	**4d** (78)
5	$2\text{-}MeOC_6H_4I$[b]	**3a**	$2\text{-}MeOC_6H_4$, H	**4e** (63)
6	PhI	**3e**	Ph, Me	**4f** (74)
7	$4\text{-}EtO_2CC_6H_4I$	**3e**	$4\text{-}EtO_2CC_6H_4$, Me	**4g** (82)
8	$4\text{-}AcC_6H_4I$	**3e**	$4\text{-}AcC_6H_4$, Me	**4h** (83)
9	$4\text{-}MeOC_6H_4I$	**3e**	$4\text{-}MeOC_6H_4$, Me	**4i** (70)
10	$2\text{-}MeOC_6H_4I$[b]	**3e**	$2\text{-}MeOC_6H_4$, Me	**4j** (11)

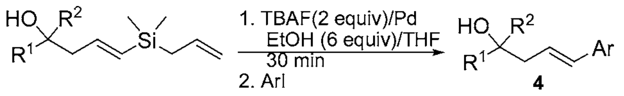
[a] Catalyst: $Pd_2(dba)_3$/4 h. [b] Catalyst: $(allylPdCl)_2$/24 h.

---

(9) For a previous application of CuCN in modifying the reactivity of silylallylmetal, see: Corriu, R. J. P.; Guerin, C.; M'Boula, J. *Tetrahedron Lett.* **1981**, *22*, 2985.

We then chose three aryl iodides, which were iodobenzene, 4-iodo-acetophenone, and 2-iodoanisole to test the coupling reaction with vinylsilanes **3b**−**d**. We found that the coupling of these vinylsilanes with iodobenzene or 4-iodo-acetophenone proceeded smoothly to afford the coupling products in high yields (83−97%, entries 1, 2, 4, 5, 7, and 8, Table 5). However, their coupling with 2-iodoanisole in the presence of $\mathrm{(allylPdCl)_2}$ as the catalyst was less efficient with the coupled products obtained in moderate yields (63−65%, entries 3, 6, and 9, Table 5).

Table 5. Variation of ArI and Silane in the Pd-Catalyzed Cross-Coupling



entry	ArI[a]	vinyl-silane	product **4** Ar; R¹, R²	isolated yield (%)
1	PhI	**3b**	Ph; Me, Me	**4k** (85)
2	$\mathrm{4\text{-}AcC_6H_4I}$	**3b**	$\mathrm{4\text{-}AcC_6H_4}$; Me, Me	**4l** (87)
3	$\mathrm{2\text{-}MeOC_6H_4I}$[b]	**3b**	$\mathrm{2\text{-}MeOC_6H_4}$; Me, Me	**4m** (65)
4	PhI	**3c**	Ph; $\mathrm{-(CH_2)_5-}$	**4n** (83)
5	$\mathrm{4\text{-}AcC_6H_4I}$	**3c**	$\mathrm{4\text{-}AcC_6H_4}$; $\mathrm{-(CH_2)_5-}$	**4o** (83)
6	$\mathrm{2\text{-}MeOC_6H_4I}$[b]	**3c**	$\mathrm{2\text{-}MeOC_6H_4}$; $\mathrm{-(CH_2)_5-}$	**4p** (60)
7	PhI	**3d**	Ph; $\mathrm{Ph(CH_2)^2}$, H	**4q** (97)
8	$\mathrm{4\text{-}AcC_6H_4I}$	**3d**	$\mathrm{4\text{-}AcC_6H_4}$; $\mathrm{Ph(CH_2)_2}$, H	**4r** (85)
9	$\mathrm{2\text{-}MeOC_6H_4I}$[b]	**3d**	$\mathrm{2\text{-}MeOC_6H_4}$; $\mathrm{Ph(CH_2)_2}$, H	**4s** (63)

[a] Catalyst: $\mathrm{Pd_2(dba)_3}$/4 h. [b] Catalyst: $\mathrm{(allylPdCl)_2}$/24 h.

To conclude, we have found that silylallylmetals can be generated upon treatment of diallyldimethylsilanes **1** with *n*-BuLi/*t*-BuOK. These silylallylmetals react readily with benzaldehyde to generate the desired vinylsilanes **3**. They also react smoothly with other carbonyl compounds to form **3** by using metal halides to modify their reactivity. Vinylsilanes **3** can tolerate 2 equiv of TBAF in THF at room temperature for at least 6 h but can be easily activated if a palladium catalyst and TBAF are both present. Being activated, they can perform the cross-coupling reaction with aryl iodides to give substituted homoallylic alcohols at room temperature. Such reactivity makes this type of vinylsilanes a unique member in the all-carbon-substituted vinylsilane family.

Acknowledgment. We would like to extend our great thanks to Dr. Zhaoyin Wang for proofreading the manuscript.

Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061288L