

One-Pot, Three-Component Synthesis of Linearly Substituted Homoallylic Alcohols via Allyl(isopropoxy)dimethylsilane

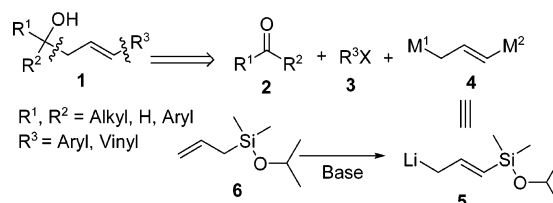
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ABSTRACT



A two-step approach that involves the synthesis of vinylsilane from allyl(isopropoxy)dimethylsilane (6) and the subsequent Pd-catalyzed cross-coupling of the resulting vinylsilane is applied in developing a novel diversity-oriented, three-component synthesis to homoallylic alcohols of common structure 1. Upon treatment of 6 with *s*-BuLi, the silylallylmetal 5 is generated and reacted with carbonyl compounds to produce functionalized vinylsilanes, which can couple with aryl/vinyl halides in the presence of palladium catalyst to afford 1.

Interest in using vinylsilanes to replace other vinylmetals¹ in Pd-catalyzed cross-coupling with aryl or vinyl halides/triflates was initiated by Hiyama² and Ito,³ who reported that vinyltrimethylsilane undergoes palladium-catalyzed cross-coupling under harsh conditions. It was later found that silafunctional vinylsilane undergoes the Pd-catalyzed cross-coupling under very mild conditions,⁴ drawing much attention as a new coupling partner owing to low cost, low toxicity, ease of handling, high functional group compatibilities, mild reaction conditions, and simplicity of byproduct removal.

Attracted by these advantages and the high stability of the silicon–carbon bond, we were interested in developing a

novel multicomponent diversity-oriented synthesis by executing this cross-coupling at the end. This would require a way of introducing a silafunctional vinylsilane moiety into a complex molecule along with the formation of at least one additional carbon–carbon (C–C) or carbon–heteroatom (C–X) bond. Many reported methods for the synthesis of silafunctional vinylsilanes based on the direct introduction of silyl substituents to a vinyl functional via reactions such as selective inter-⁵ or intramolecular⁶ hydrosilylation of a triple bond and the silafunctional silylation of a vinylmetal reagent⁷ would not meet the demand. However, it is possible to fulfill the purpose by synthesizing the desired vinylsilane from an organosilicon reagent; during the process the

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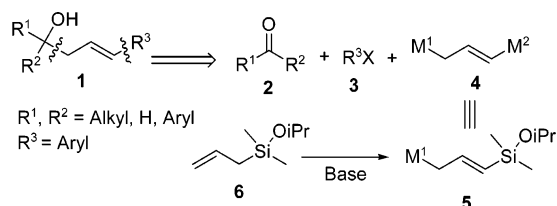
(4) For reviews, see: (a) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (c) Denmark, S. E.; Ober, M. E. *Aldrichimica Acta* **2003**, *35*, 75.

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Scheme 1



organosilicon reagent acts as one component to react with at least one other component through new C–C or C–X bond formation. By carrying out the Pd-catalyzed cross-coupling in the final step to introduce one more component, the organosilicon reagent would provide at least two reaction sites for new bond formation, thus securing a multicomponent synthesis.

Homoallylic alcohols of the common structure **1** (Scheme 1) are important intermediates in organic synthesis⁸ and frequently appear in natural products and bioactive compounds.⁹ Most literature preparations are based upon two-component approaches¹⁰ and have certain drawbacks to serve as a general and diversity-oriented synthesis. A three-component synthesis of **1** by using allyldiindium **4** (Scheme 1; $M^1, M^2 = \text{In}$)¹¹ is attractive because of easy access to

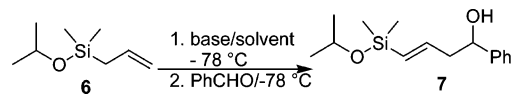
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Table 1. Generation of Allyl Anion and Addition to Benzaldehyde



entry	solvent	base	eq	¹ H NMR yield (%)
1	THF	<i>s</i> -BuLi/TMEDA	1.1	59
2	THF	<i>s</i> -BuLi	1.1	70 (65) ^c
3	THF	<i>n</i> -BuLi	1.1	<i>a</i>
4	THF	<i>t</i> -BuLi	1.1	<i>b</i>
5	THF	<i>s</i> -BuLi	1.0	65
6	THF	<i>s</i> -BuLi	1.2	67
7	Ether	<i>s</i> -BuLi	1.1	20

^a Multiple products: *n*-BuCH(OH)Ph and *n*-BuSi(Me)₂CH₂CH=CH₂.

^b Main product was *t*-BuCH(OH)Ph. ^c Isolated yield by flash chromatography over Florisil.

various carbonyl compounds and aryl/vinyl halides. Its drawback is the poor stereochemical control of the resulting double bond and the lack of flexibility due to the instability of the carbon–indium bond. Later, Hiyama and co-workers reported that the synthesis of the corresponding alkyl ether of **1** could be achieved by a two-step sequence that involves the allylation of acetals with 1-silyl-1-boryl-2-alkenes and the subsequent Pd-catalyzed cross-coupling of the resulting vinylborate.¹² Denmark's recent synthesis of (*Z*)-isomers of **1** by a RCM and Pd-catalyzed cross-coupling sequence represents another interesting example.¹³ Inspired by these works and the synthetic potential of the synthesis of vinylsilane from organosilicon reagents, we thought that if a highly regio- and stereoselective γ -addition¹⁴ of silylallylmatal **5** to carbonyl compounds could be achieved, a three-component diversity-oriented synthesis of homoallylic alcohols **1** could be realized (Scheme 1). Treatment of **6** with a base to generate **5** as an equivalent to allyldimetal **4** provides the first reaction site to carry out the synthesis of vinylsilane. By taking advantage of the high stability of the Si–C bond, we expected the sequence could be performed stepwise as well as in a one-pot fashion.

Allylsilane **6** was prepared by silylation of 2-propanol with commercially available allylchlorodimethylsilane. We first tested the generation of **5** from **6** with LDA¹⁵ or Schlosser's base^{13d,16} by following literature procedure in ether or THF. Unfortunately, its addition to PhCHO only afforded **7** in less than 50% yield when determined by using ¹H NMR of the crude with toluene as an internal standard. This prompted us to test other bases. We were pleased to find that when **6** was treated with 1.1 equiv of *s*-BuLi/TMEDA complex in THF for 1 h at –78 °C, followed by reaction with PhCHO for 1 h at –78 °C, **7** was obtained in 59% yield (entry 1, Table 1). The yield was further improved to 70% when *s*-BuLi was used alone (entry 2, Table 1). With *n*-BuLi as base, nucleophilic replacement of the isopropoxy group on

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Table 2. Pd-Catalyzed Cross-Coupling of **7** with RX

entry	R-X	Pd cat. ^a	time (h)	product R	isolated yield (%)
1	Ph-I	A	4	Ph	1a (97)
2	4-EtO ₂ CC ₆ H ₄ I	A	3	4-EtO ₂ CC ₆ H ₄	1b (98) ^c
3	4-AcC ₆ H ₄ I	A	4	4-AcC ₆ H ₄	1c (96)
4	4-MeOC ₆ H ₄ I	A	4	4-MeOC ₆ H ₄	1d (90)
5	2-MeC ₆ H ₄ I	A	3.4	2-MeC ₆ H ₄	1e (80)
6	2-MeOC ₆ H ₄ I	A	4	2-MeOC ₆ H ₄	1f (0)
7	2-MeOC ₆ H ₄ I	B	1.5	2-MeOC ₆ H ₄	1f (93)
8	2-MeC ₆ H ₄ I	B	3	2-MeC ₆ H ₄	1e (99)
9	PhBr	B	24 ^b	Ph	1a (82)
10		B	24 ^b		1g (38)
11		B	2 ^b		1h (66)

^a Catalyst: A = Pd₂(dba)₃; B = (Allyl)PdCl₂. ^b Reaction done at 50 °C instead of room temperature. ^c Same yield obtained when equal molar of crude **7** was used.

silicon by *n*-Bu dominated (entry 3, Table 1).¹⁴ To avoid this, *t*-BuLi was tested, but no formation of **7** was observed (entry 4, Table 1). The predominant formation of *t*-BuCH(OH)Ph suggested that no metalation of **6** had occurred. Slight alteration of the amount of *s*-BuLi to 1.0 or 1.2 equiv did not affect the yield (entries 5 and 6, Table 1). Using Et₂O instead of THF as solvent had a negative impact (entry 7, Table 1).¹⁷ Thus, the conditions described in entry 2 of Table 1 were selected as standard conditions for vinylsilane preparation.¹⁶ It is worth noting that in all cases only the trans substituted γ -adduct was observed.

With **7** prepared, we started to investigate its cross-coupling with aryl halides and vinyl bromides (Table 2). We found that the coupling between **7** and PhI proceeded smoothly at room temperature in THF to afford **1a** in 97% yield with 5 mol % of Pd₂(dba)₃ and 2 equiv of TBAF (entry 1, Table 2).¹⁸ *para*-Substituted aryl iodides were also good coupling partners with **7** to produce alcohols **1b–d** in excellent yields (entries 2–4, Table 2). Pd₂(dba)₃ is efficient in catalyzing the coupling of **7** with 2-iodotoluene to afford **1e** in 80% yield (entry 5, Table 2) but failed to catalyze the cross-coupling of **7** with 2-iodoanisole to form **1f**; instead, the homo-coupling of 2-iodoanisole dominated (entry 6, Table 2).¹⁹ We solved the problem by using (allyl)PdCl₂,

(14) Examples of γ -addition of various silylallylmetals to carbonyl compounds: (a) Corriu, R. J. P.; Guerin, C.; M'Boula, J. *Tetrahedron Lett.* **1981**, 22, 2985. (b) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, 102, 5004. (c) Chan, T. H.; Labrecque, D. *Tetrahedron Lett.* **1992**, 33, 7997. (d) Liu, L.; Wang, D. *J. Chem. Res., Synop.* **1998**, 612.

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(17) Various reaction temperatures and reaction times were tested; no better yield of **7** was obtained.

(18) By using 3% and 4% of the catalyst, **1a** was obtained in 89% and 95% yield, respectively.

Table 3. One-Pot Synthesis: Variation of ArI

entry	Ar-I	Pd cat. ^a	equiv of TBAF	product Ar	isolated yield (%) ^b
1	Ph-I	A	2	Ph	1a (85)
2	Ph-I	A	2.4	Ph	1a (90)
3	Ph-I	A	3	Ph	1a (89)
4	4-EtO ₂ CC ₆ H ₄ I	A	2.4	4-EtO ₂ CC ₆ H ₄	1b (89)
5	4-AcC ₆ H ₄ I	A	2.4	4-AcC ₆ H ₄	1c (91)
6	4-MeOC ₆ H ₄ I	A	2.4	4-MeOC ₆ H ₄	1d (86)
7	2-MeC ₆ H ₄ I	B	2.4	2-MeC ₆ H ₄	1e (63)
8	2-MeOC ₆ H ₄ I	B	2.4	2-MeOC ₆ H ₄	1f (65)
9	2-MeO ₂ CC ₆ H ₄ I	B	2.4	2-MeO ₂ CC ₆ H ₄	1i (56)

^a Catalyst: A = 5% Pd₂(dba)₃; B = 5% (Allyl)PdCl₂. ^b The product yields were calculated on the basis of the limiting reagents aryl iodides used.

which effected the coupling to give **1f** in 93% yield (entry 7, Table 2). Using (allyl)PdCl₂ instead of Pd₂(dba)₃ also improved the coupling yield between **7** and 2-iodotoluene from 80% to 99% (entries 5 and 8, Table 2).

By running the reaction at 50 °C for 24 h and with (allyl)PdCl₂ as catalyst, PhBr coupled with **7** to produce **1a** in 82% yield (entry 9, Table 2). Under similar conditions, 2-bromopropene also coupled with **7** to give **1g** in 38% yield (entry 10, Table 2).²⁰ The coupling between **7** and 2-bromostyrene²¹ went smoothly, and **1h** was obtained in 66% yield in 2 h (entry 11, Table 2).

Our findings above demonstrate that the sequence can be carried out stepwise and also set a stage for further investigation of performing the sequence in a one-pot fashion. We first prepared vinylsilane **7** as described in entry 2 of Table 1. Without workup, the resulting mixture was neutralized with 1.1 equiv of AcOH, and 0.7 equiv²² of iodobenzene and 5 mol % of Pd₂(dba)₃ were added. The reaction was stirred at room temperature for 24 h²³ after the addition of TBAF. We found that by using 2 equiv of TBAF, **1a** was obtained in 85% yield (entry 1, Table 3). The yield was slightly improved to 90% with 2.4 equiv of TBAF (entry 2, Table 3), and no further improvement was observed with 3.0 equiv of TBAF (entry 3, Table 3).

Being satisfied with the results obtained in entry 2 of Table 3, we moved on to test the variation of aryl iodide in this one-pot synthesis under similar conditions by using benzaldehyde as a representative carbonyl compound. We found that the *para*-substituted aryl iodides worked well and afforded **1b–d** in excellent yields (86–91%, entries 4–6, Table 3). The *ortho*-substituted aryl iodides were less

(19) Literature example of Pd-catalyzed homocoupling in the presence Bu₄NBr: Dyker, G. J. *Org. Chem.* **1993**, 58, 234.


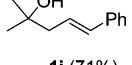
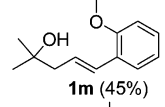

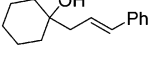
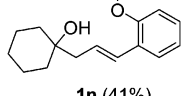

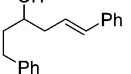
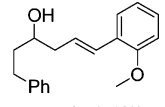
(20) Low yield seemed caused by instability of **1g** under the conditions.

(21) *E* and *Z* ratio about 6:1 of 2-bromostyrene was reflected in **1h** accordingly.

(22) This amount was used to match the yield of vinylsilane **7**; the product yields were calculated on the basis of the limiting reagent aryl iodides used.

(23) No attempt was done to optimize the reaction time.

Table 4. One-Pot Synthesis: Variation of ArI and Carbonyls

$ \begin{array}{c} \text{1. } s\text{-BuLi (1.1 eq) (-78 } ^\circ\text{C)} \\ \text{2. } \text{R}^1\text{COR}^2 \text{ (1.1 eq) (-78 } ^\circ\text{C)} \\ \text{3. } \text{AcOH (1.1 eq) (0 } ^\circ\text{C)} \\ \text{4. } \text{ArI/Pd/TBAF (rt)} \\ \text{(THF)} \end{array} \rightarrow $		
R^1COR^2	ArI Pd	PhI $\text{Pd}_2(\text{dba})_3$
		2-MeOPh-I $[\text{allylPdCl}]_2$
product (isolated yield) ^a		
	 1j (71%)	 1m (45%)
	 1k (62%)	 1n (41%)
	 1l (87%)	 1o (71%)

^a The product yields were calculated on the basis of the limiting reagents aryl iodides used.

efficient coupling partners than the *para*-substituted ones, and **1e–f** and **1i** were obtained in 56–65% yields (entries 7–9, Table 3).

This one-pot process was also extended to synthesize homoallylic alcohols from other carbonyl compounds (Table 4). Here we chose acetone, cyclohexanone, and 3-phenylpropanal as representative aliphatic ketone, aliphatic cyclic ketone, and aliphatic aldehyde, respectively, to replace

benzaldehyde in the preparation of vinylsilanes²⁴ and then performed the cross-coupling with aryl iodides. When iodobenzene was used with $\text{Pd}_2(\text{dba})_3$ as catalyst, alcohols **1j–l** were afforded in 71%, 62%, and 87% yield, respectively. With 2-iodoanisole as a representative *ortho*-substituted aryl iodide and with $(\text{allylPdCl})_2$ as catalyst, alcohols **1m–o** were obtained in 45%, 41%, and 71% yield, respectively.

In summary, we have developed a two-step sequence, including the synthesis of silafunctional vinylsilane from allyl(isopropoxy)dimethylsilane (**6**) and the subsequent Pd-catalyzed cross-coupling of the resulting vinylsilane, to achieve a diversity-oriented, three-component synthesis to linearly substituted homoallylic alcohols of common structure **1** (Scheme 1). Upon treatment of **6** with *s*-BuLi, the corresponding silylallylmetal **5**, which serves as an equivalent to allyldimetal **4**, was generated and further reacted with carbonyl compounds to produce functionalized vinylsilanes. In the presence of $(\text{allylPdCl})_2$ or $\text{Pd}_2(\text{dba})_3$ as catalyst, the vinylsilanes thus formed can couple with aryl/vinyl halides to afford **1**. The whole sequence can be performed stepwise as well as in a one-pot fashion.

Acknowledgment. We would like to extend our great thanks to Dr. Zhaoyin Wang, Dr. Claudio Sturino, and Mr. Carl Berthelette for proof-reading the manuscript.

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

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(24) Conditions were not modified for different carbonyl compounds.