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Palladium-Catalyzed Allylic C−OH Functionalization for Efficient Synthesis of Functionalized Allylsilanes

Nicklas Selander, Jennifer R. Paasch, and Kálmán J. Szabó*

Department of Organic Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden

Received October 27, 2010; E-mail: kalman@organ.su.se

Abstract: A new method is described for palladium-catalyzed allylic silylation using allylic alcohols and disilanes as precursors. The reactions proceed smoothly under mild and neutral conditions, and this method is suitable for synthesis of regio- and stereodefined allylsilanes. The presented silylation reaction can be easily extended to include synthesis of allylboronates by change of the dimetallic reagent. The presented synthetic procedure offers a broad platform for the selective synthesis of functionalized allyl metal reagents, which are useful precursors in advanced organic chemistry and natural product synthesis.

Allylsilanes encompass the reactivity of both alkenes and metal-allyl reagents, which renders these compounds as one of the most important building blocks in modern organic synthesis.[1,2] The silyl group in allylsilane reagents has a hyperconjugative[3] directing effect (β-silyl effect) enabling a highly selective transformation of the sp^2 carbons. The versatile scope of the reactions includes allylations, such as the Hosomi−Sakurai reaction;[4,5] transition-metal-catalyzed processes, such as the Hiyama coupling;[6,7] and even selective synthesis of functionalized allylic fluorides.[8,9] The widespread use of these useful synthetic applications demands development of new effective synthetic methods to obtain regio- and stereodefined allylsilanes. In this respect transition-metal-catalyzed processes proved to be the most successful procedures.[9−24] In particular, palladium-catalyzed synthesis of allylsilanes by substitution of allylic esters[12,13,23,25] and ethers[14] using disilanes[26] as a silyl source proved to be very useful, because of the relatively easy access to the precursors and the broad synthetic scope of the reactions. The cost efficiency and the environmental benefits of these processes could be substantially increased, if allylic alcohols (**1**) were used directly as substrates[27,28] without using any additives. This is a highly challenging task as the hydroxy group is one of the most reluctant leaving groups, which usually has to be activated in substitution reactions.

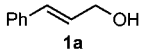
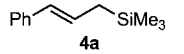
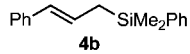
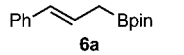
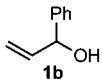
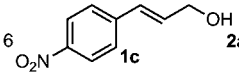
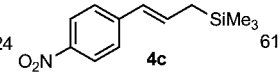
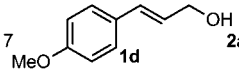
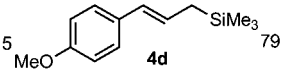
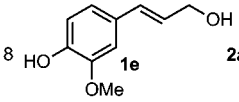
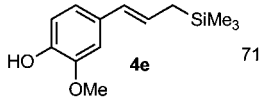
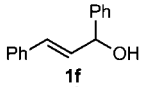
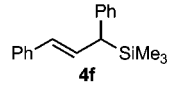
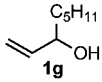
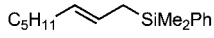
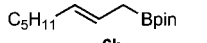
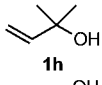
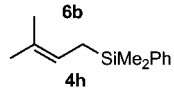
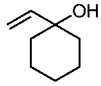
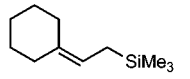
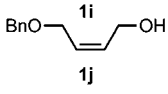
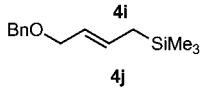
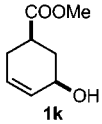
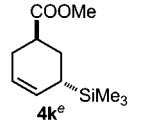
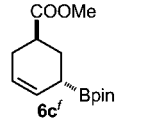
Our group has successfully developed several related catalytic methods for the use of allylic alcohols as precursors for the synthesis of allylboronates.[29−37] We have now devised a new, inexpensive, and mild procedure for the preparation of functionalized allylsilanes from allylic alcohols (Figure 1). Our best conditions (Table 1) involve the use of hexamethyldisilane (**2a**) as a silyl source and $Pd(BF_4)_2(MeCN)_4$ **3** as a catalyst (5 mol %) in a DMSO/MeOH 1:1 mixture for smooth conversion of various allylic alcohols (**1**) to allylsilanes (**4**). The reactions were conducted under mild conditions (typically at 50 °C) without an inert atmosphere and without addition of any acids, chloride/acetate salts, or other additives, which are commonly used in analog palladium-catalyzed substitution reactions of allylic esters and ethers.[12−14] Due to the mild and neutral reaction conditions many functional groups, such as aromatic OH, NO_2, OR, and COOMe substituents, are tolerated in the silylation reactions. The reactions proceeded very cleanly, as in most cases the desired allylsilane was the only product formed with a full conversion of the applied allylic alcohol. The reaction time required for the full conversion of the substrate was longer in the presence of electron-withdrawing groups (such as **1c**) compared to electron-donating substituents (**1a**, **1d**−**e**); cf. entries 6 and 1, 7, 8. Primary (such as **1a**, **1c**−**e**, **1j**), secondary (**1b**, **1f**−**g**, **1k**), tertiary (**1h**−**i**), and cyclic (**1j**, **k**) alcohols could easily be converted to the corresponding allylsilanes.

Figure 1. Palladium-catalyzed direct silylation and borylation of allylic alcohols.

We have found that not only **2a** but also its diphenyl analog **2b** could also be used as a silyl source (entries 2, 10, 12). This is particularly advantageous when the low boiling point of the desired trimethylsilanes (TMS) encumbers the isolation of the product, as in the case of the TMS analog of **4g** or **4h**. In addition, variation of the silyl group offers several synthetic advantages, when allylsilanes are applied as substrates.[2] The reaction is also very robust and easily scalable without further optimization of the reaction conditions. For example, a 20 times scale up to 3 mmol of **1a** could be carried out without a significant change of the isolated yield (entry 1).

The regio- and stereoselectivity of the reaction is very high. The regioselectivity is excellent as the linear allylic product is formed exclusively. For example, isomeric allylic alcohols **1a** and **1b** gave only the linear allylsilane **4a** (cf. entries 1 and 5) indicating a possible allyl-palladium mechanism for the transformation. The double bond geometry was selectively *trans* in all acyclic allylsilane products. Even by starting with *cis*-alcohol **1j** we obtained *trans*-allylsilane **4j** in high selectivity, which is also a typical signature of the allyl-palladium mechanism. Starting from stereodefined allylic alcohol **1k**, in which the leaving hydroxy group and the COOMe substituent are in a *cis* relationship, the major product is **4k** with a *trans* configuration of the silyl and COOMe groups. Although the diastereoselectivity is not completely clean (the *trans*/*cis* ratio is 3:1), the major formation of the inversion product **4k** suggests that the silyl group is coordinated to palladium prior to a nucleophilic attack.[12,13] As mentioned above additives were not required to obtain a high activity and selectivity using our catalytic system. In fact additives, which are able to coordinate strongly to palladium, inhibited the reaction. For example, the addition of only 10 mol % of LiCl to our catalyst system (at 50 °C for 15 h) led to an incomplete reaction for silylation of **1a** and the isolated yield was

Table 1. Palladium-Catalyzed Allylic C−OH Functionalization for the Synthesis of Organosilanes and Boronates[a]

Entry	Substrates		Cond.[b]	Product	Yield[c]
1	 **1a**	$(Me_3Si)_2$ **2a**	50/15	 **4a**	84/77[d]
2	**1a**	$(Me_2PhSi)_2$ **2b**	50/15	 **4b**	79
3	**1a**	$(Bpin)_2$ **5**	50/0.25	 **6a**	77
4	**1a**	**5**	20/1.5	**6a**	78
5	 **1b**	**2a**	50/15	**4a**	82
6	 **1c**	**2a**	50/24	 **4c**	61
7	 **1d**	**2a**	50/15	 **4d**	79
8	 **1e**	**2a**	50/15	 **4e**	71
9	 **1f**	**2a**	50/15	 **4f**	69
10	 **1g**	**2b**	50/15	 **4g**	78
11	**1g**	**5**	20/1.5	 **6b**	76
12	 **1h**	**2b**	50/15	 **4h**	78
13	 **1i**	**2a**	65/15	 **4i**	72
14	 **1j**	**2a**	50/15	 **4j**	69
15	 **1k**	**2a**	60/15	 **4k**[e]	52
16	**1k**	**5**	20/1.5	 **6c**[f]	70

[a] Unless otherwise stated allylic alcohol **1** (0.15 mmol), dimetal reagent **2** or **5** (0.18 mmol), and catalyst **3** (5 mol %) were dissolved in a DMSO (0.2 mL)/MeOH (0.2 mL) mixture and stirred for the indicated times and temperatures. [b] Reaction conditions: temperature/time = °C/h. [c] Isolated yield (%). [d] The reaction is scaled up to 3.0 mmol of **1a**. [e] Product isolated in a 3:1 *trans*/*cis* mixture. [f] Product isolated in a 5:1 *trans*/*cis* mixture.

decreased from 84% to 35%. It is even more interesting that addition of LiOAc completely inhibited the process. We could not find any trace of **4a** in the reaction mixture, when **1a** was reacted under our usual conditions (entry 1) in the presence of 10 mol % LiOAc. With PPh_3 (10 mol %) a very complex reaction mixture was obtained with low conversion of **1a**. The silylation of **1a** with $Pd(OCOCF_3)_2$ proceeded with a similar yield (70%) as with **3** (84%) under identical conditions (entry 1). However, the yield was decreased when $PdCl_2$ was used as the catalyst (50%), and no silylated product **4a** was formed at all using $Pd(OAc)_2$ as the catalyst source. Surprisingly, $Pd_2(dba)_3$, which was efficiently used as the catalyst in the silylation of allylic esters,[12,13,23] was completely inefficient for the silylation of allylic alcohols. The application of a DMSO/MeOH mixture was also important to obtain a fast and clean silylation reaction. In pure DMSO the conversion of **1** to **4** is extremely slow, while in pure methanol byproducts appear in the reaction mixture. Application of DMSO is probably important to keep the palladium, in particular Pd(0), species in solution during the catalysis. The reaction can also be conducted in chloroform; however the yield of the transformation drops because of the formation of byproducts. For example the isolated yield for the silylation of **1a** decreased from 84% to 55% when the DMSO/MeOH mixture (entry 1) was replaced by chloroform.

To our delight, a very fast and very selective borylation reaction occurred when disilane **2** was replaced with bis(pinacolato)diboron (**5**) (entries 3, 4, 11, 16) using otherwise identical conditions. It was found that the borylation was much faster than the silylation reaction. Thus, the silylation of **1a** had to be conducted for 15 h at 50 °C to obtain a complete conversion, while formation of allylboronate **6a** required only 15 min under the same reaction conditions (cf. entries 1 and 3). In fact the C−OH borylation of **1a** could be completed under neutral conditions in 90 min at room temperature (entry 4). Likewise, alkyl substituted allylic alcohol **1g** reacted rapidly under mild conditions affording linear allylic boronate **6b**. The stereoselectivity of the borylation of **1k** (*trans*/*cis* 5:1) is somewhat higher than that of the silylation reaction providing the inversion product **6c** as the major diastereomer. When silaborane reagent $PhMe_2Si$-Bpin was used in place of **2** or **5** under the standard conditions, an intractable mixture was obtained along with rapid precipitation of palladium-black.

In order to obtain more insights into the mechanism of the reactions we compared the rate of formation of the organometallic products as a function of the substituent effects in the allylic precursor, the nature of the leaving group, and the source of the organometallic functionality (see Supporting Information for the diagram). One of the most interesting findings is that, under identical reaction conditions, cinnamyl alcohol **1a** is silylated faster than cinnamyl acetate **8**. In the presence of a nitro group in the para position of the phenyl ring (**1c**), the rate of silylation is slower than that for the parent compound **1a**, while with a methoxy substituent the rate is practically unchanged. On the other hand the borylation reaction of **1a** is much faster (about 10 times) than the corresponding silylation reaction.

The mechanism of the above rapid and selective silylation of allylic alcohols has not been understood in every detail; however on the basis of the above studies (Table 1) at least a plausible catalytic cycle can be constructed (Figure 2). Our assumption is that the catalytic process starts from a Pd(0) species, which may be generated from **3** by reduction by either **2** or methanol under our standard conditions. In either case, the formation of a "naked" Pd(0) species is supposed to form in which the ligands are very loosely coordinated. The activation of the hydroxy group is probably the most intriguing reaction step of the catalytic cycle. Although, allylic alcohols are employed in several transition-metal-catalyzed processes,[27,28] very few reactions proceed under mild conditions,[30,38] without external activators, as in the above presented process. Possibly, the high oxophilicity of silicon leads to the formation of ate-complex **10**. Structurally related hypervalent silylsilicate species have been previously reported in the literature.[39,40] Formation of

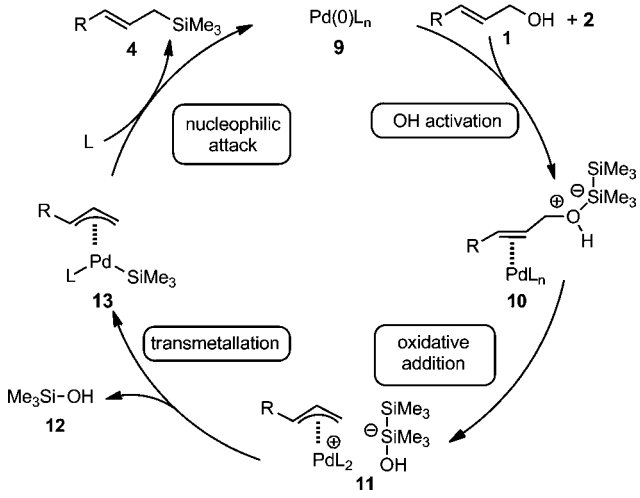


Figure 2. Proposed catalytic cycle for silylation of allylic alcohols.

such a species is also promoted by electron donation from Pd(0) to the π^*-MO of the double bond, which increases the nucleophilicity of the oxygen atom. In complex **10** the C−O bond is sufficiently weakened for an oxidative addition of Pd(0) to generate allyl-palladium complex **11**.

In allyl-palladium complex **11** the counterion is possibly a hypervalent silylsilane arising from the C−O bond cleavage of **10**. This silane may easily transmetalate with palladium to give complex **13**. The transmetalation delivers the silyl group to palladium, which subsequently may undergo reductive elimination without any further activation.[13] Our previous studies[13] have shown that transmetalation of disilanes to allyl-palladium complexes and the subsequent reductive elimination proceed very fast, with the high regioselectivity affording the linear allylic isomer. In the reductive elimination mechanism, the silyl group attacks the allyl moiety from the direction of palladium via a *syn* mechanism. Supposing that the allyl-palladium complex (**11**) forms mainly by the usual *anti* stereochemistry and the nucleophilic attack proceeds by a *syn* mechanism,[41,42] a predominant inversion found for silylation of **1k** to **4k** can be easily explained. We do not exclude the possibility that the mechanism of the presented borylation reaction (Figure 1) is the same. Probably, the OH-activation[29] and/or transmetalation is more efficient for the borylation process than for the silylation reaction, which may explain a faster formation of allylboronate **6a** than that of allylsilane **4a**. Exploration of the exact mechanism requires further experimental and modeling studies.

In summary, we have presented a new, efficient procedure for the inexpensive and environmentally benign selective synthesis of allylsilanes from allylic alcohols. The synthetic scope involves a wide range of substituted allylic alcohols with internal and external double bonds and even cyclic substrates. The applied reaction conditions provide an easy access to allylic boronates as well. By this study we have created a common platform for the synthesis of functionalized allylsilanes and allylboronates from allylic alcohols and the corresponding dimetallic reagents under identical reaction conditions. Thus, here we provide a simple and efficient route to a broad variety of building blocks for the synthesis of complex organic molecules including natural products.[2,43−45]

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Supporting Information Available: Detailed experimental procedures; characterization and ^{1}H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley: Chichester, 2000.
(2) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
(3) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496.
(4) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835.
(5) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *33*, 3043.
(6) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 16382.
(7) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.
(8) Hazari, A.; Gouverneur, V.; Brown, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1296.
(9) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891.
(10) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221.
(11) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317.
(12) Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5779.
(13) Macsári, I.; Hupe, E.; Szabó, K. J. *J. Org. Chem.* **1999**, *64*, 9547.
(14) Moser, R.; Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 28.
(15) Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174.
(16) Wu, J. Y.; Stanzl, B. N.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 13214.
(17) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 12650.
(18) Simon, M. O.; Martinez, R.; Genêt, J. P.; Darses, S. *Adv. Synth. Catal.* **2009**, *351*, 153.
(19) Shintani, R.; Ichikawa, Y.; Hayashi, T.; Chen, J.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2007**, *9*, 4643.
(20) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964.
(21) Terao, J.; Watabe, H.; Watanabe, H.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 1674.
(22) Bourque, L. E.; Cleary, P. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 12602.
(23) Tsuji, Y.; Kajita, S.; Isobe, S.; Funato, M. *J. Org. Chem.* **1993**, *58*, 3607.
(24) Oestreich, M.; Auer, G. *Adv. Synth. Catal.* **2005**, *347*, 637.
(25) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Organometallics* **2005**, *24*, 762.
(26) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320.
(27) Muzart, J. *Tetrahedron* **2005**, *61*, 4179.
(28) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.
(29) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723.
(30) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150.
(31) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588.
(32) Selander, N.; Szabó, K. J. *J. Org. Chem.* **2009**, *74*, 5695.
(33) Selander, N.; Szabó, K. J. *Dalton Trans.* **2009**, 6267.
(34) Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, 2293.
(35) Sebelius, S.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2003**, *5*, 3065.
(36) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, 2539.
(37) Selander, N.; Sebelius, S.; Estay, C.; Szabó, K. J. *Eur. J. Org. Chem.* **2006**, 4085.
(38) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.
(39) Kira, M.; Sato, K.; Kabuto, C.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 3747.
(40) Kano, N.; Nakagawa, N.; Shinozaki, Y.; Kawashima, T.; Sato, Y.; Naruse, Y.; Inagaki, S. *Organometallics* **2005**, *24*, 2823.
(41) Hartwig, J. *Organotransition Metal Chemistry*; University Science Books: Sausalito, CA, 2010.
(42) Kurosawa, H.; Ogoshi, S.; Kawasaki, Y.; Murai, S.; Miyoshi, M.; Ikeda, I. J. *J. Am. Chem. Soc.* **1990**, *112*, 2813.
(43) Gawronski, J.; Wascinska, N.; Gajewy, J. *Chem. Rev.* **2008**, *108*, 5227.
(44) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732.
(45) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

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