

# Palladium-Catalyzed Oxidative Allylic C–H Silylation

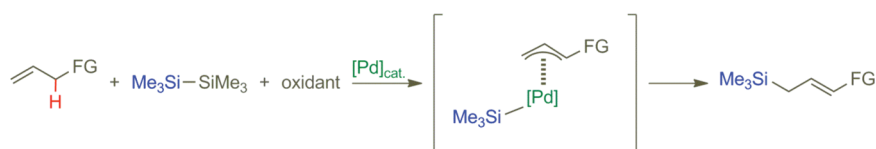
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## ABSTRACT



Palladium-catalyzed allylic C–H silylation was performed with use of hexamethyldisilane as the silyl source. These C–H functionalization reactions occur only in the presence of hypervalent iodine reagents or other strong oxidants and proceed with excellent regioselectivity, providing the linear allylic isomer of the allylsilane products. In demonstrating the first oxidative allylic C–H silylation of alkenes, this study marks an important advance for the catalytic C–H functionalization method.

Catalytic C–H functionalization provides a simple, atom-economical alternative to some of the classical functional group transformation based procedures.<sup>1–11</sup> Currently, further development of this potentially very powerful method faces two important challenges: (i) finding selective functionalization techniques for the transformation of only a single C–H bond in the substrate to avoid formation of complex isomeric mixtures of products and (ii) extending the synthetic scope of the C–H bond activation based methods to create a wide variety of C–X bonds.

Although the most developed areas involve replacing C–H with C–C and C–O bonds,<sup>4–9</sup> the functionalization

of alkenes and arenes with main group reagents is emerging as a powerful tool for the synthesis of organometallic reagents.<sup>3,10,11</sup> For example, C–H borylation has become a useful approach for obtaining organoboronate reagents from alkenes and arenes.<sup>3</sup> Catalytic C–H silylation, however, is much less developed than the corresponding borylation<sup>2,10</sup> processes, probably because of the lower reactivity of commonly employed organometallic silyl sources compared to the borane sources.

Previously reported C–H silylation reactions include aromatic,<sup>12–14</sup> benzylic,<sup>15</sup> vinylic,<sup>16–18</sup> and alkyl<sup>19,20</sup> substrates. However, in contrast to allylic C–H borylation,<sup>21–24</sup> catalytic allylic C–H silylation has remained almost entirely undeveloped. To date, catalytic allylic silylations have entirely relied on the conversion of preinstalled functional

(1) Dyker, G. *Handbook of C–H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.

(2) Hartwig, J. *Organotransition Metal Chemistry*; University Science Books: Sausalito, CA, 2010.

(3) Mkhali, I. A. I.; Murphy, J. M.; Barnard, J. H.; Marder, T. B.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(4) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(5) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

(6) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(7) Lewis, J. C.; Bergman, R.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(8) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824.

(9) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(10) Marciniak, B. *Coord. Chem. Rev.* **2005**, *249*, 2374.

(11) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.

(12) Tsukada, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5022.

(13) Lu, B.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 7508.

(14) Ihara, H.; Sugimoto, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502.

(15) Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, B.; Chatani, N. *J. Am. Chem. Soc.* **2004**, *126*, 12792.

(16) LaPointe, A. M.; Rix, F. C.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 906.

(17) Lu, B.; Falck, J. R. *J. Org. Chem.* **2010**, *75*, 1701.

(18) Jiang, Y.; Blacque, O.; Fox, T.; Frech, C. M.; Berke, H. *Chem.—Eur. J.* **2009**, *15*, 2121.

(19) Sadow, A. D.; Tilley, T. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 803.

(20) Sadow, A. D.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 643.

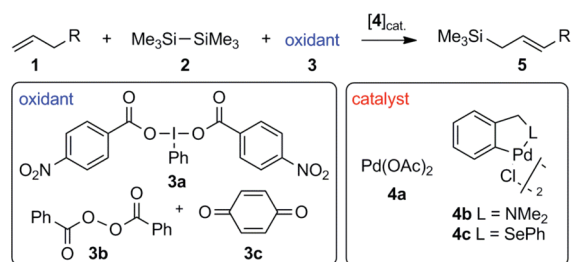
(21) Caballero, A.; Sabo-Etienne, S. *Organometallics* **2007**, *26*, 1191.

(22) Olsson, V. J.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6891.

(23) Olsson, V. J.; Szabó, K. J. *J. Org. Chem.* **2009**, *74*, 7715.

(24) Kondoh, A.; Jamison, T. F. *Chem. Commun.* **2010**, *46*, 907.

# Scheme 1. Synthesis of Allylsilanes by Catalytic C–H Silylation



groups.<sup>25–32</sup> We have found only a single reaction reported by Ishikawa and co-workers,<sup>33</sup> which is based on palladium-catalyzed C–H activation of a single substrate using a highly reactive disilacyclobutene derivative as the silyl source. However, the poor accessibility of disilacyclobutenes and the low chemoselectivity of this process limits the practical use of the method.

Our efforts were directed toward the development of palladium-catalyzed allylic C–H silylation using readily accessible starting materials, including commercially available hexamethyldisilane as the silyl source. We have now found that such reactions can be performed in the presence of hypervalent iodine reagents<sup>34</sup> (or other strong oxidants), which have been successfully employed in many recently reported C–H functionalization processes.<sup>8,9,35–37</sup> For example, we have shown that palladium-catalyzed allylic C–H acyloxylation<sup>36</sup> and vinylic C–H borylation<sup>37</sup> can be performed with iodine(III) reagents. In a typical reaction (Scheme 1) the alkene (**1**), hexamethyldisilane (**2**), and the appropriate oxidant (**3**) were reacted in the presence of palladium catalyst **4** at 80 °C for 18 h.

These reaction conditions are relatively mild compared to the conditions for the aromatic<sup>12–14</sup> or benzylic<sup>15</sup> C–H silylation reactions, and because of the oxidative conditions sacrificial hydrogen acceptors (such as norbornene) are not needed. A high level of functional group tolerance was achieved even in the presence of strong oxidants (such as **3a,b**); ester (**1a–c**), amide (**1d,e,g**), and benzyl (**1a,d**) functional groups remained unchanged. The regioselectivity

**Table 1.** Oxidative Silylation of Allylic C–H Bonds<sup>a</sup>

entry	substrate	method <sup>b</sup>	catalyst	product	E:Z <sup>c</sup>	yield <sup>d</sup>
1		A	<b>4a</b>		5:1	69%
2	<b>1a</b>	B	<b>4a</b>	<b>5a</b>	8:1	77%
3	<b>1a</b>	B	<b>4b</b>	<b>5a</b>	8:1	75%
4		A <sup>e</sup>	<b>4a</b>		4:1	70%
5		A	<b>4a</b>		10:1	58%
6		A <sup>f</sup>	<b>4a</b>		10:1	60%
7		A	<b>4b</b>		>95:1	52%
8		B	<b>4a</b>		1:6	45%
9		B	<b>4a</b>		1:3	52%
10		A <sup>g</sup>	<b>4c</b>		>95:1	59%

<sup>a</sup> Unless otherwise stated, a mixture of **1** (0.2 mmol), **2** (0.4 mmol), the oxidant, and the palladium catalyst **4** (5 mol %) was stirred for 18 h at 80 °C. <sup>b</sup> Method A: **3a** (0.4 mmol) was used as oxidant in DME (0.5 mL). Method B: **3b** (0.4 mmol) and **3c** (0.2 mmol) were used as oxidants in THF (0.5 mL) in the presence of **6** (0.2 mmol). <sup>c</sup> E/Z ratio determined by <sup>1</sup>H NMR from the crude reaction mixture. <sup>d</sup> Isolated yield of both isomers. <sup>e</sup> THF was used as a solvent. <sup>f</sup> **6** (0.1 mmol) was added. <sup>g</sup> At 60 °C.

of the silylation reaction was excellent with only linear isomers forming. A high stereoselectivity was achieved for most substrates. Typically, the trans isomer was formed as the major (entries 1–6) or the only product (entries 7 and 10). However, for sulfone **1f** and sulfonamide **1g** the selectivity was changed and the cis isomer became the major product (entries 8 and 9). With the exception of **5f** and **5g**, the trans and cis allylsilanes could easily be separated by column chromatography and isolated as single isomers.

In the absence of alkene substrate (**1**) iodane **3a** and disilane **2** underwent degradation even without palladium catalyst. When the reaction was conducted under standard catalytic conditions, but without oxidants (**3**), formation of allylsilane products could not be observed. We found that hypervalent iodine reagent **3a** proved efficient for most of

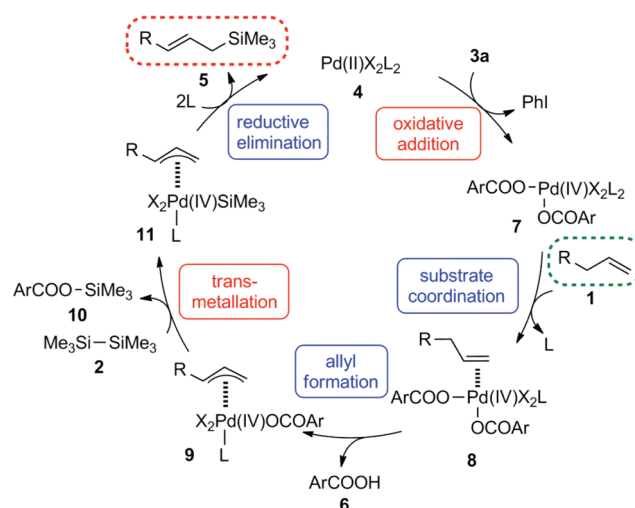
- (25) Sugimoto, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221.
- (26) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317.
- (27) Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5779.
- (28) Macsári, I.; Hupe, E.; Szabó, K. J. *J. Org. Chem.* **1999**, *64*, 9547.
- (29) Sugimoto, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174.
- (30) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 12650.
- (31) Moser, R.; Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 28.
- (32) Selander, N.; Paasch, J. R.; Szabó, K. J. *J. Am. Chem. Soc.* **2011**, *133*, 409.
- (33) Naka, A.; Hayashi, M.; Okazaki, S.; Ishikawa, M. *Organometallics* **1994**, *13*, 4994.
- (34) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
- (35) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
- (36) Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 5518.
- (37) Selander, N.; Willy, B.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4051.

the substrates, providing good yields and selectivities. Other iodine(III) reagents, such as  $\text{PhI}(\text{OAc})_2$ ,  $\text{PhI}(\text{OCOCF}_3)_2$ , or  $\text{PhI}(\text{OBz})_2$ , could also be applied, but the use of these oxidants resulted in lower yields of the silylated product. Iodonium reagent **3a** could be replaced by peroxide **3b**. However, to achieve as high yields and selectivities with **3b** as with **3a**, additives such as benzoquinone, BQ (**3c**) and 4-nitrobenzoic acid (**6**) also had to be used (cf., entries 1 and 2). BQ (**3c**) may both act as a co-oxidant<sup>38,39</sup> and facilitate<sup>40</sup> the coordination of the alkene to the palladium catalyst. Inclusion of **6** is required to ensure protic conditions necessary for the redox process of BQ. Although the **3b,c** oxidation system is less powerful than **3a**, it does not produce PhI as a byproduct, and therefore Heck-type<sup>41</sup> side reactions could be suppressed. These side reactions were particularly problematic for C–H silylation of sulfones **1f,g**, for which formation of the Heck-type product with PhI decreased the yield of silanes **5f,g** (Table 1).

We have previously shown that alkenes undergo palladium-catalyzed C–H acyloxylation in the presence of hypervalent iodine reagents.<sup>36</sup> This reaction could compete with the silylation under our reaction conditions. Choice of solvent and oxidant was important to decrease or even completely avoid the formation of the acyloxylation products.  $\text{Pd}(\text{OAc})_2$  (**4a**) proved to be an efficient catalyst for most of the reactions. However, for some substrates the chemoselectivity was low. For example, the transformation of amide **1e** to **5e** was accompanied by considerable amounts of acyloxylation products. The chemoselectivity of the reaction could be shifted to formation of allylsilane **5e** by employing palladacycle **4b** as catalyst (entry 7). The same catalyst also gave high yield and selectivity for C–H silylation of **1a** using the **3b,c** oxidant system (entry 3). C–H silylation of allylbenzene derivative **1h** under our typical conditions (at 80 °C) using **4a** gave a complex reaction mixture and a low yield of silylated product **5h**.

However, we have found that the reactivity could be increased and the formation of Heck-type and other by-products reduced by decreasing the temperature to 60 °C and using selenium-based<sup>42</sup> palladium catalyst **4c**. The substrate scope of the present C–H silylation method is limited to terminal alkenes with electron-withdrawing functional groups.

Although the mechanistic details have yet to be elucidated, the observed regioselectivity is consistent with an allylpalladium mechanism. It is well documented that palladium complexes with an unsymmetrically substituted allyl moiety undergo attack at the least substituted terminus, affording the linear allylic regioisomers.<sup>2,27,28</sup> On the basis of this and our previous experience with oxidative C–H borylation<sup>37</sup> and C–H acetoxylation<sup>36</sup> reactions, we suggest a plausible catalytic cycle in Figure 1.



**Figure 1.** Plausible catalytic cycle (Ar = *p*-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>).

We<sup>36,37</sup> and others<sup>9,43–46</sup> have shown that hypervalent iodine reagents easily oxidize Pd(II). The catalytic cycle is proposed to start with oxidation of the Pd(II) catalyst resulting in complex **7**. After coordination of the alkene substrate (**1**), complex **8** may undergo internal deprotonation to form allylpalladium complex **9**.

Although allylpalladium(IV) species are not commonly invoked as catalytic intermediates, Canty and co-workers have reported synthesis and characterization of such complexes.<sup>47</sup> Furthermore, the mechanistic studies reported by Liu<sup>40</sup> and by our group<sup>36</sup> indicated that allylpalladium(IV) intermediates may occur in palladium-catalyzed allylic C–H functionalization reactions performed in the presence of hypervalent iodines. The deprotonation of **8** may proceed via a so-called concerted metalation deprotonation (CMD) mechanism, which was proposed by Fagnou and co-workers for aromatic C–H activation reactions.<sup>48</sup> According to the CMD mechanism the deprotonation of the substrate occurs by an acyloxy ion (acetate, benzoate, etc.).

It should be noted that the oxidative addition and the allyl formation step could also happen in reverse order, and the order of these two processes can also be substrate dependent. Complex **9** may undergo two different reactions. Transmetalation with disilane **2** would provide **10** and complex **11**, which subsequently would undergo reductive elimination, affording the allylsilane product (**5**).

(43) Lagunas, M. C.; Gossage, R. A.; Spek, A. L.; van Koten, G. *Organometallics* **1998**, *17*, 731.

(44) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Organometallics* **2006**, *25*, 3996.

(45) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974.

(46) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050.

(47) Byers, P. K.; Canty, A. J. *J. Chem. Soc., Chem. Commun.* **1988**, 639.

(48) (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (b) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.

(38) Grennberg, H.; Simon, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1994**, 265.

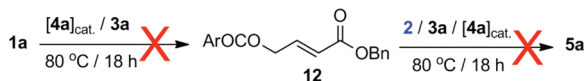
(39) Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *22*, 149.

(40) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978.

(41) Aydin, J.; Larsson, J. M.; Selander, N.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 2852.

(42) Yao, Q.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997.

**Scheme 2.** The Reaction Cannot Be Carried out As a Tandem Sequence via Intermediate Formation of Acyloxy Compound **12**



Alternatively, **9** may undergo reductive elimination providing an acyloxyated product (such as **12**, Scheme 2). Our previous studies have shown that allyl-Pd(II) acetate complexes are relatively stable to reductive elimination.<sup>28</sup> However, after transmetalation with disilanes they undergo very fast reductive elimination to give allylsilanes.<sup>28</sup> We believe that the same difference in reactivity applies for the corresponding allyl-Pd(IV) complexes, such as **9**. A possible reason for the formation of both *cis* and *trans* forms of the allylsilane products **5** could be an  $\eta^3$ - $\eta^1$ - $\eta^3$  isomerization of the allyl moiety in **9**.<sup>2,49</sup>

An alternative to the above mechanism (Figure 1) could be that palladium performs a tandem C–H acyloxylation<sup>36</sup>–allylic substitution<sup>27,28</sup> sequence in the transformation of the alkenes to allylsilanes. We have also considered this possibility (Scheme 2) for transformation of **1a** to **5a**. Thus, we attempted to perform C–H acyloxylation under our standard reaction conditions (entry 1) in the absence of **2**. However, this reaction did not give any acyloxy product **12**. To double check this alternative mechanistic pathway, we

prepared **12** via an alternative synthetic route and attempted to perform the silylation using **12** instead of **1a** (Scheme 2). In this process we could not observe formation of allylsilane **5a** at all. Thus, even if acyloxyated byproducts are formed under our reaction conditions (by reductive elimination from **9**) these types of compounds are not intermediates in the present allylic C–H silylation reaction.

In the case of using a mixture of **3b** and **3c** as oxidant the reaction may follow the above Pd(II)/Pd(IV) pathway; however, we cannot discount a classical Pd(0)/Pd(II) redox cycle. Mechanistic studies including DFT modeling are underway to explore the mechanistic aspects of this novel allylic C–H silylation mechanism.

In summary, we have presented the first oxidative allylic C–H silylation reaction. Our procedure is suitable for the completely regioselective and highly stereoselective synthesis of functionalized allylsilanes from alkenes. Notable features include the strongly oxidative conditions and that, unusually, palladium catalyzes the C–H silylation process.<sup>2</sup> Thus, our method constitutes an important new C–H functionalization approach and complements existing methods for the synthesis of allylsilanes.

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

(49) Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464.