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Palladium-Catalyzed Carbene Insertion and Trapping with Carbon Nucleophiles

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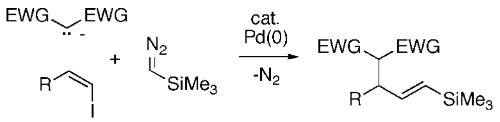
ABSTRACT



Palladium catalysts are shown to catalyze the three-component coupling of vinyl halides, trimethylsilyldiazomethane, and stabilized carbon nucleophiles. The reaction is believed to proceed through a palladium-carbene intermediate LX(R)Pd═CHSiMe$_3$ that undergoes migration of the vinyl substituent to the electrophilic carbene center to generate an η^3-allylpalladium intermediate. The allylpalladium intermediate is attacked by the carbon nucleophile to generate a vinylsilane product.

Vinylsilanes are versatile functional groups for electrophilic substitution reactions. 5-Silyl-4-pentenoic acid derivatives can be cyclized to give butyrolactones[1] or extended to generate precursors to polyene cyclizations.[2] In the past, 5-trimethylsilyl-δ,γ-unsaturated carboxylic acid derivatives have been made through either Ireland−Claisen rearrangements[3] or palladium-catalyzed allylic alkylation reaction.[4,5] When beta hydrogens are present next to the η^3-allylic moiety, formation of dienes through elimination often competes with allylic alkylation.

Diazo compounds can serve as carbene precursors in palladium-catalyzed reactions.[6–9] Previously, we showed that the migration of vinyl groups to carbene ligands generated η^3-allylpalladium intermediates that could be trapped with cyclic secondary amines.[6a] In this work we show that a related three-component coupling using stabilized carbon nucleophiles can be used to construct 5-silyl-4-pentenoic acid derivatives with two new carbon−carbon bonds.

Our mechanistic model for the reaction (Scheme 1) starts with oxidative addition of palladium to the vinyl halide to generate vinylpalladium complex ***a***, followed by formation of a palladium carbene ***b***.[10] Migration of the vinyl ligand to the empty p orbital of the carbene ligand generates the η^1-allylpalladium complex ***c***. Presumably, the η^1-allylpalladium complex generates an η^3-allylpalladium intermediate ***d***, that is then attacked by the carbon nucleophile.

Our initial attempt to realize this transformation using styryl bromide **1** was met with a surprising palladium-catalyzed transformation. When trimethylsilyl-diazomethane and phenyl tri-*n*-butylstannane were added slowly to styryl bromide **1** none of the desired vinylsilane was generated. Instead, *E*,*Z*-diene **2**[11] was isolated in 60% yield (Scheme

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(1) Miura, K.; Hayashida, J.; Takahashi, T.; Nishikori, H.; Hosomi, A. *J. Organomet. Chem.* **2003**, *686*, 242–250.

(2) Burke, S. D.; Saunders, J. O.; Oplinger, J. A.; Murtiashaw, C. W. *Tetrahedron Lett.* **1985**, *26*, 1131–1134.

(3) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668–3670.

(4) Tsuji, J.; Yuhara, M.; Minato, M.; Yamada, H.; Sato, F.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 343–346.

(5) Sakaguchi, K.; Yamada, T.; Ohfune, Y. *Tetrahedron Lett.* **2005**, *46*, 5009–5012.

(6) (a) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047–2049. (b) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438–6441. (c) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219–5225.

(7) (a) Peng, C.; Cheng, J. J.; Wang, J. B. *J. Am. Chem. Soc.* **2007**, *129*, 8708–8709. (b) Peng, C.; Wang, Y.; Wang, J. J. *Am. Chem. Soc.* **2008**, *130*, 1566–1567.

(8) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587–5590.

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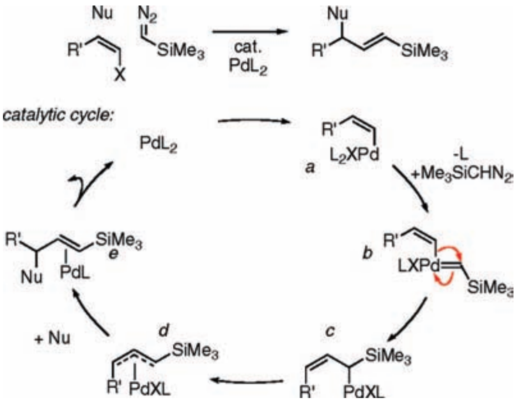
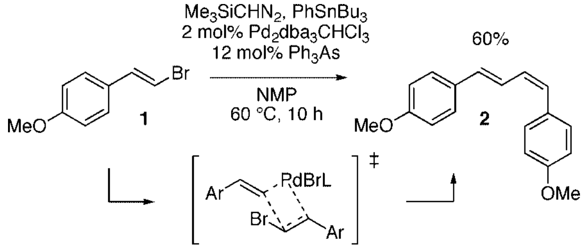
10.1021/ol800431w CCC: $40.75

Scheme 1. Mechanistic Model for Three-Component Coupling with Carbon Nucleophiles



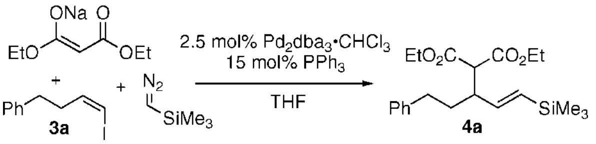
2) along with a 73% yield of biphenyl. Palladium catalyzed homocouplings of *E*-styrylbromides have been observed before,[12] and can be attributed to the carbapalladation of the highly reactive styryl bromide by the vinylpalladium bromide, followed by *β*-elimination of $PdBr_2$, which is reduced back to Pd(0) by the arylstannane. With this problem in mind, we turned our attention away from aryl-substituted alkenes and arylstannane nucleophiles to vinyl halides with aliphatic substituents and enolate nucleophiles. Indeed, this combination of starting materials is expected to give a much more interesting class of products.

Scheme 2. Heck Dimerization Outcompetes Carbene Insertion



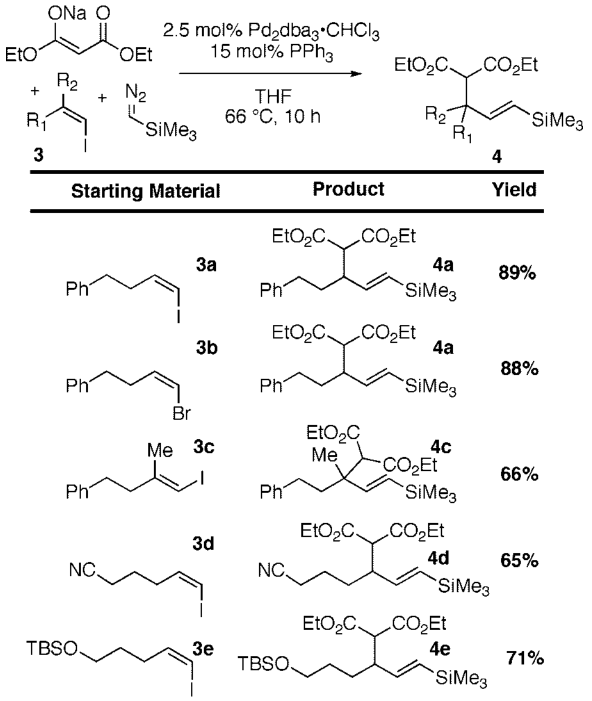
We turned to a three-component coupling of vinyl iodide **3a**, 2 equiv of sodium diethylmalonate, and 1.5 equiv trimethylsilyldiazomethane, added by syringe pump. The malonate anion is generated by treatment of diethyl malonate with sodium hydride. Excess sodium malonate anion helps to neutralize the equivalent of hydroiodic acid that is generated in the reaction. The yield for this initial reaction was poor 24% and 30% of the vinyl iodide starting material was present in the final reaction mixture (Scheme 3). Other products present in the crude product mixture were consistent with addition of the diazo compound, which is also a stabilized carbanion, to the η^3-allylpalladium intermediate to generate a mixture of dienes. Other bases were ineffective. DBU gave none of the desired vinylsilane. With *O*,*N*-bis(trimethylsilyl)acetamide as the base the yield of vinylsilane was 2%. By increasing the amount of malonate, addition of malonate to the η^3-allylpalladium intermediate was favored over competitive addition of the diazo compound. When the addition of trimethylsilyldiazomethane was stretched out over 17 h, instead of 10 h, the yield of the desired vinylsilane was decreased, and diene products akin to those formed in Scheme 2 were apparent by NMR. Yields increased progressively with the inclusion of more malonate, which is the least expensive component of the reaction mixture (Scheme 3). Ultimately, our isolated yields reached 89.5% through a judicious choice of temperature and stoichiometry.

Scheme 3. Optimization of Reaction Conditions for Three-Component Coupling



Equiv. Nu	Temp.	Time	Yield
2	46 °C	10 h	**24%**
4	66 °C	10 h	**63%**
4	66 °C	17 h	**39%**
8	66 °C	10 h	**84%**
12	66 °C	10 h	**89%**

Scheme 4. Substrate Variation



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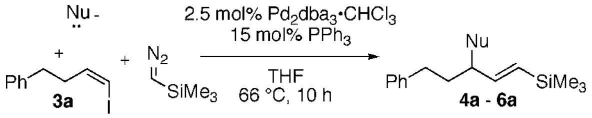
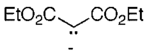
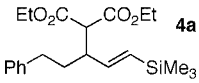
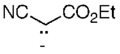
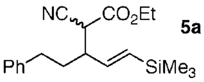
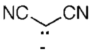
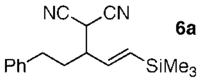
(12) (a) Tietze, L. F.; Petersen, S. *J. Org. Chem.* **2000**, *9*, 1827–1830. (b) Wakioka, M.; Nagao, M.; Ozawa, F. *Organometallics* **2008**, *27*, 602–608.

We next set out to explore the functional group tolerance of the reaction. The reaction seems to require the *Z* vinyl halide. When the reaction was attempted using *E*-**3a**, the desired vinylsilane was produced in only 11% yield and most of the vinyl iodide was recovered. One explanation for the superiority of *Z* vinyl halides is that steric compression accelerates the migration of the vinyl group to the carbene. Vinyl bromides appear to be as effective as vinyl iodides. The reaction even works with disubstituted vinyl iodide **3c** to generate a highly congested quaternary center. Nitriles and silyl ethers are well tolerated as indicated by the formation of adducts **4d** and **4e**, respectively (Scheme 4). In no case did we observe products resulting from further alkylation of the malonate product. Indeed, when diethyl 2-methylmalonate was employed none of the desired products were generated under the standard conditions. Bromostyrene **1** was still a poor substrate under the optimized conditions due to formation of diene products.

Scheme 5. Application of Other Stabilized Carbon Nucleophiles

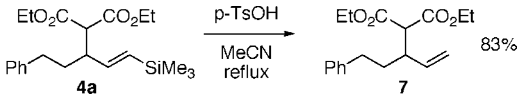


Nucleophile	Product	Yield
12 equiv. 	 **4a**	**89%**
6 equiv. 	 **5a**	**47%**
4 equiv. 	 **6a**	**61%**

We next explored the ability of other stabilized carbanions, similar to diethyl malonate, to participate in the reaction (Scheme 5). Solubility limited the number of equivalents that could be employed in the reaction without changing the concentration of the other reagents. Thus, with only 6 equiv of nucleophile/base, ethyl cyanoacetate gave only 47% yield of vinylsilane **5a** as a 1.2:1 mixture of diastereomers. Surprisingly, malononitrile gave an even higher yield of vinylsilane **6a** with fewer equivalents of the nucleophile.

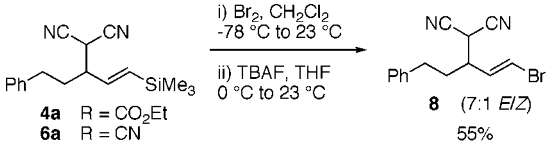
Vinylsilanes are valuable synthetic intermediates. For example, they can be protodesilylated to reveal the parent olefin, or stereospecifically halodesilylated to produce the haloalkene.[13] To favor protodesilylation of the vinylslane over cyclization of the ester carbonyl,[1] 1 equiv of pTsOH•H_2O was used (Scheme 6).

Scheme 6. Protodesilylation Reveals a Terminal Olefin



Bromodesilylation of vinylsilane **4a** was attempted under the two-step conditions of Kobayashi.[14] However, bromolactonization competed with bromine addition even in the presence of 1 equiv of *n*-$Bu_4N^+Br^-$. When malononitrile derivative **6a** was used as a substrate the desired vinyl bromide was isolated as a 7:1 ratio of *E* and *Z* isomers (Scheme 7). The ability to start with a vinyl halide and, through a two-step sequence of carbene insertion/bromodesilylation, regenerate a vinyl halide holds particular promise for iterative carbene insertions.

Scheme 7. Halodesilylation Regenerates a Vinyl Halide



In conclusion, we have developed a new three-component coupling using *Z* vinyl halides, trimethylsilyldiazomethane, and stabilized carbon nucleophiles to generate vinylsilanes.

Acknowledgment. This work was supported by ACS PRF 42780-AC1.

Supporting Information Available: Experimental procedures and spectral data for compounds **2**, **3a**−**e**, and **4a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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