ORGANIC LETTERS

2007
Vol. 9, No. 10
2047−2049

Palladium-Catalyzed Carbene Insertion into Vinyl Halides and Trapping with Amines

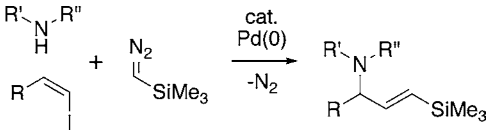
Sean K. J. Devine and David L. Van Vranken*

Department of Chemistry, 1102 Natural Sciences, University of California, Irvine, California 92697-2025

david.vv@uci.edu

Received March 28, 2007

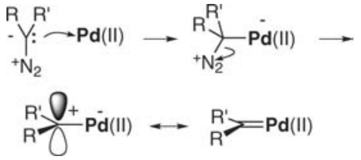
ABSTRACT



Palladium is shown to catalyze the three-component coupling of vinyl halides, trimethylsilyldiazomethane, and amines to generate allylamines. The mechanism is believed to involve formation of an $R{-}Pd{=}CHSiMe_3$ intermediate that undergoes migration of the vinyl ligand to the empty p-orbital of the carbene ligand. The resulting η^1-allylpalladium species forms an η^3-allylpalladium intermediate that is trapped by the amine nucleophile. Under the conditions tested, cyclic secondary amines and terminal vinyl iodides give the best results.

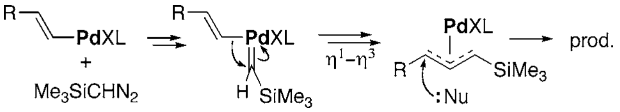
Palladium-catalyzed insertion of carbon monoxide and isonitriles into carbon−halogen bonds offers a powerful method for joining molecular fragments through one-carbon units.[1] There is growing interest in palladium-catalyzed reactions that stitch together organic fragments using carbene units.[2] Bröring and co-workers have shown that diazo compounds can serve as precursors of palladium−carbene complexes.[3] Carbene formation is likely to proceed through attack of the anionic diazo compound on a cationic Pd(II) species (Scheme 1).

Scheme 1. Mechanism for Pd−Carbene Formation from Diazo Compounds



In most palladium−carbene complexes with anionic ligands, R, cis to the carbene (e.g., $R{-}Pd{=}CX_2$), the Pd−R bonds tend to align with the empty p-orbital of the carbene—an orientation that facilitates donation and ultimately bond migration. The nitrogen lone pairs of N-heterocyclic carbene ligands donate into the empty orbital of the carbene, making them resistant to this type of bond migration. We set out to take advantage of migratory insertion of carbenes in $R{-}Pd{=}CHSiMe_3$ complexes as a way to effect three-component couplings of vinyl halides, trimethylsilylcarbenes, and amine nucleophiles (Scheme 2). 1-Trimethylsilyl substituents on η^3-allylpalladium complexes direct attack of nucleophiles to the opposite terminus, leading to vinylsilanes,

Scheme 2. Migration of Vinyl Groups Generates η^3-Allylpalladium Intermediates That Are Subject to Attack



---

[1] (a) Brunet, J. J.; Chauvin, R. *Chem. Soc. Rev.* **1995**, *24*, 89−95. (b) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417−6422. (c) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609−2612. (d) Ishiyama, T.; Oh-e, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1992**, *33*, 4465−4468.

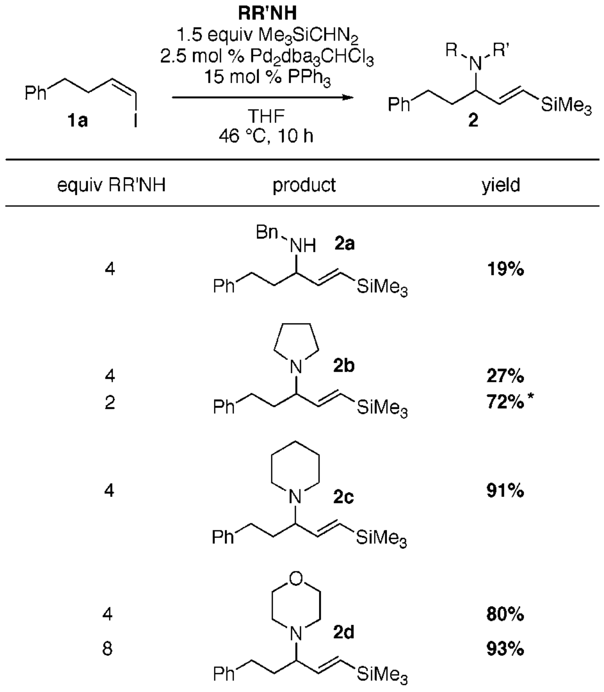
[2] (a) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219−5225. (b) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438−6441.

[3] Bröring, M.; Brandt, C. D.; Stellwag, S. *Chem. Commun.* **2003**, 2344−2345.

10.1021/ol070758o CCC: $37.00

which are useful intermediates for stereospecific organic transformations.[4]

Scheme 3. Three-Component Coupling of Vinyl Iodide **1a**, Trimethylsilyldiazomethane, and Amines

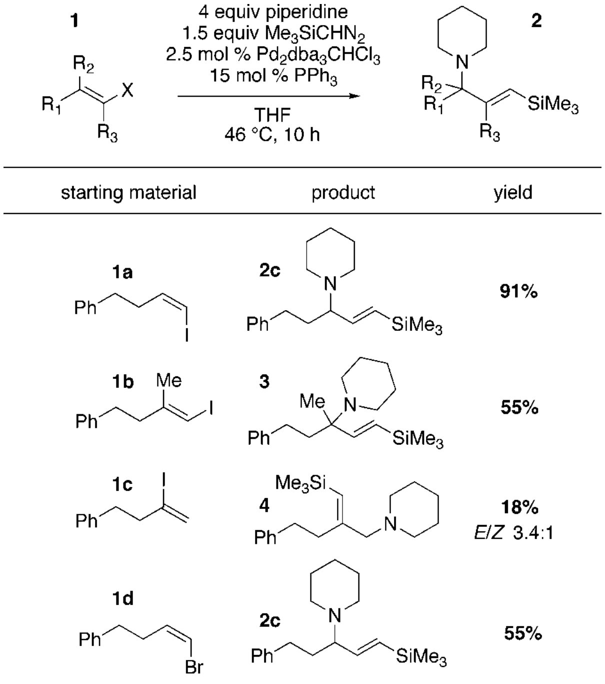


* 1 equiv K_2CO_3, 1 equiv $PhB(OH)_2$

Initially, we explored the three-component coupling of various amines with a readily synthesized vinyl iodide, 1-((*Z*)-4-iodobut-3-enyl)benzene (**1a**), and trimethylsilyldiazomethane using $Pd_2dba_3{\bullet}CHCl_3$ as the catalyst precursor (Scheme 3) and adding the diazo compound by syringe pump over 10 h. The results using benzylamine as a nucleophile gave the desired vinylsilane **2a** in 19% yield; about half of the starting material remained unreacted, implying low catalyst turnover.

Cyclic, secondary amines such as pyrrolidine and piperidine gave better results than benzylamine. The yield of allylamine **2b** was dramatically improved by addition of potassium carbonate and addition of phenylboronic acid to reduce any PdX_2 salts that might be degrading the diazo compound. However, the improved yield did not extend to other amines. Piperidine generated high yields of the desired vinylsilane **2c**. Morpholine (pK_a' 8.4) gave a lower yield of vinylsilane than piperidine (pK_a' 11.2), but good results were achieved by doubling the stoichiometry of morpholine. Higher stoichiometries of amine did not lead to better results with benzylamine. Instead, the yield of vinylsilane **2a** increased to 30% by dropping to 2 equiv of benzylamine and increasing the temperature to 66 °C. In general, the variation in yields does not correlate with the basicity of the amines in organic solvents. This lack of correlation has been observed in other palladium-catalyzed reactions of amines, such as arylation,[5] CO insertion,[6] and allylic alkylations.[7]

Scheme 4. Three-Component Coupling of Vinyl Halides, Trimethylsilyldiazomethane, and Piperidine



A number of different haloalkenes were subjected to the palladium-catalyzed three-component coupling with piperidine and trimethylsilyldiazomethane to generate the corresponding allylamines in varying yields (Scheme 4). Terminal vinyl iodides give the best results. Surprisingly, the vinyl iodide **1b** effectively generated tertiary allylic amine **3** in 55% yield. Unfortunately, the yield of allylamine **4** generated from the internal vinyl iodide **1c** was low, although these achiral products are arguably less interesting than the chiral amines generated from terminal vinyl halides. The vinyl bromide **1d** gave a lower yield of the corresponding allylamine **2c**. An attempt to perform the reaction on oct-1-enyl triflate gave none of the desired allylamine, implying that halide is important for the reaction. At present, the role of the halide ion is unclear.

A mechanistic model that is consistent with our results and observations involves initial oxidative addition to form a vinylpalladium halide complex *a* (Scheme 5). Addition of the diazo compound to this electrophilic complex would generate a vinylpalladium carbene *b*. Migration of the vinyl group to the carbene center, which is now precedented in a number of stoichiometric transformations,[8] would generate an η^1-allylpalladium complex *c*. Importantly, for chiral

---

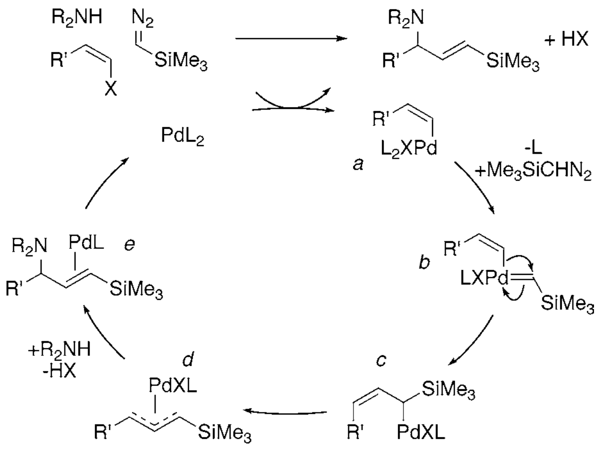
[4] Inami, H.; Ito, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1993**, *34*, 5919−5922.

[5] Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.

[6] Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235−3245.

[7] Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M. *Tetrahedron* **2005**, *61*, 9759−9766.

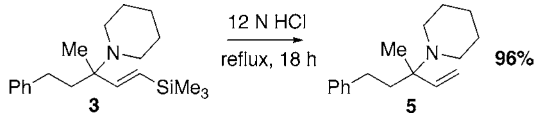
Scheme 5. Proposed Catalytic Cycle



products such as **2c**, **3**, and **4**, the stereochemistry is set in this migratory insertion step and cannot be lost through η^1-η^3-η^1 interconversions. Control of this key migration step represents an attractive target for asymmetric induction. Isomerization to the more stable η^3-allylpalladium complex *d*, with anti substituents, may precede nucleophilic attack to give the *E* vinylsilanes **2** and **3** that are observed as products.

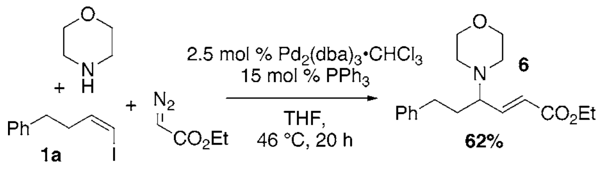
Vinylsilanes are valuable intermediates for stereospecific electrophilic substitution reactions; even protodesilylation generates a useful terminal olefin. After the trimethylsilyl group directs attack of the nucleophile to the more hindered position of the η^3-allylpalladium complex, it can be removed from the product (Scheme 6). Other recently developed palladium-catalyzed reactions for generating hindered α,α-disubstituted allylic amines from achiral substrates have not yet been shown to proceed with high levels of enantioselection.[9] This new approach combines the power of allylic fragment assembly, generation of chiral centers through carbene insertion, and regiocontrolled allylic alkylation.

Scheme 6. Access to α,α-Disubstituted Tertiary Allylic Amines



Simple palladium(II) salts are active catalysts for polymerization of ethyl diazoacetate with loss of nitrogen.[10] While not optimized for ethyl diazoacetate, the three-component coupling seems to work well (Scheme 7), in spite of the potential for polymerization. Clearly, as long as the Pd(II) complex has a migratable alkyl ligand, migratory insertion can win out over polymerization of the diazo compound. These results suggest that other diazo compounds might be effective in related palladium-catalyzed processes.

Scheme 7. Synthesis of γ-Amino Acids through Carbene Insertion



This communication shows the exciting potential for palladium-catalyzed carbene insertions to generate allylamines using vinyl halides and diazo compounds. While there is strong analogy with palladium-catalyzed CO insertion processes, the potential for complex molecule synthesis and asymmetric induction adds new dimensions to these processes.

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

Supporting Information Available: Experimental procedures and spectral data for compounds **2**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070758O

---

(8) (a) Danopoulos, A. A.; Tsoureas, N.; Green, J. C.; Hursthouse, M. B. *Chem. Commun.* **2003**, 756−757. (b) Albèniz, A. C.; Espinet, P.; Manrique, R.; Perez-Mateo, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2363−2366. (c) Sole, D.; Vallverdu, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *Organometallics* **2004**, *23*, 1438−1447.

(9) (a) Faller, J. W.; Wilt, J. C. *Organometallics* **2005**, *24*, 5076−5083. (b) Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633−636. (c) Watson, L. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516−17529.

(10) Ihara, E.; Haida, N.; Iio, M.; Inoue, K. *Macromolecules* **2003**, *36*, 36−41.