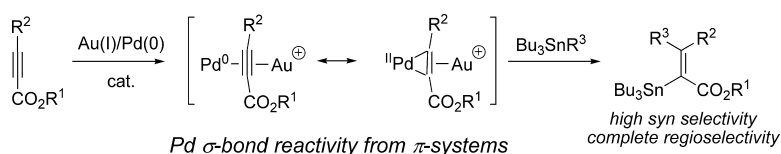


## Alkynes as Stille Reaction Pseudohalides: Gold- and Palladium-Cocatalyzed Synthesis of Tri- and Tetra-Substituted Olefins

Yili Shi, Sonja M. Peterson, Walter W. Haberaecker, and Suzanne A. Blum

*J. Am. Chem. Soc.*, **2008**, 130 (7), 2168-2169 • DOI: 10.1021/ja7110648b

Downloaded from <http://pubs.acs.org> on February 8, 2009



### More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 6 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



## Alkynes as Stille Reaction Pseudohalides: Gold- and Palladium-Cocatalyzed Synthesis of Tri- and Tetra-Substituted Olefins

Yili Shi, Sonja M. Peterson, Walter W. Haberaecker III, and Suzanne A. Blum\*

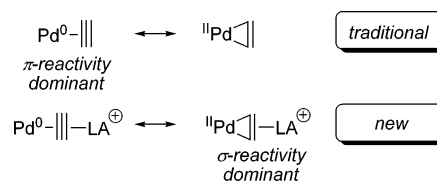
Department of Chemistry, University of California, Irvine, California 92697-2025

Received November 27, 2007; E-mail: blums@uci.edu

Palladium-catalyzed carbon–carbon cross-coupling reactions are a staple of modern synthetic chemistry due to the diverse products accessible and functional groups tolerated by these reactions. While powerful, these methods require initial oxidative addition into a carbon–halogen, –oxygen, or –hydrogen covalent (or ionic) bond (e.g., Stille,<sup>1</sup> Heck,<sup>2</sup> Suzuki,<sup>3</sup> Trost–Tsuji,<sup>4</sup> Buchwald–Hartwig,<sup>5</sup> and the ionic Arndtsen modification<sup>6</sup>). We now report extension of this chemistry from C–X bonds to C–C  $\pi$ -bonds through the employment of alkynes in the place of halides in a Stille-type vinylstannylation reaction. Carbometalation is a time-tested technique for the synthesis of olefins from alkynes;<sup>7</sup> however, compared to copper,<sup>8</sup> there are few palladium-catalyzed vinylstannylation reactions.<sup>9,10</sup> One limitation of Shirakawa and Hiyama's palladium-catalyzed vinylstannylation reaction is that double-addition products predominate. Our reaction provides an expedient route to the monoaddition products, yielding tri- and tetra-substituted olefins<sup>11,12</sup> from alkynes with absolute regioselectivity and high stereoselectivity via a Au(I)/Pd(0) bimetallic catalyst system that combines the characteristics of two metals to produce unique reactivity.<sup>13</sup>

We hypothesized that the alkynophilic<sup>14–16</sup> Lewis acid Au(I) would lower the LUMO of an alkyne fragment, promoting backbonding (i.e., oxidative addition) from Pd(0) into the alkyne,<sup>17–20</sup> which in turn increases palladium–carbon  $\sigma$ -bond character (Figure 1). Andersen reported a conceptually similar, structurally characterized  $\mu$ -ethylene bimetallic complex with Pt(0) as the Lewis base and Yb(II) as the Lewis acid.<sup>17–20</sup> To our knowledge, no employment of this structure class as a catalytic intermediate has been developed, despite the potential generality of such a method for accessing late-metal–carbon  $\sigma$ -bonds. With an alkyne as the oxidative addition partner, no C–X bond would be necessary for a cross-coupling reaction (i.e., the alkyne serves as a pseudohalide).<sup>21</sup>

In order to explore this hypothesis, dimethyl acetylenedicarboxylate (DMAD) was treated with 20 mol % of PPh<sub>3</sub>AuCl/AgSbF<sub>6</sub> and 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub> in the presence of 1 equiv of tri-*n*-butylvinylstannane. Gratifyingly, these conditions produced tetrasubstituted olefin **1a** in 51% <sup>1</sup>H NMR yield<sup>22</sup> (Table 1, entry 2). Optimization of the Lewis acid catalyst revealed that a weakly coordinating anion for the gold complex, such as SbF<sub>6</sub> or PF<sub>6</sub>, was required for high reactivity (entries 1, 2, and 5). Employment of the less alkynophilic<sup>14</sup> Lewis and Brønsted acids AgSbF<sub>6</sub>, BF<sub>3</sub>, and benzoic acid resulted in zero or poor conversion (entries 8–10). More than 1 equiv of silver inhibited the reaction (entry 3). Consistent with this inhibitory effect, isolation of the cationic Au(I) catalyst resulted in significantly higher conversion than the catalyst generated in situ (entries 2 and 4). The observation of an inhibitory effect of silver in our reaction is of particular note given the current interest in developing efficient cationic Au(I) catalysts via silver salt metathesis.<sup>14,23</sup> Both Au(I) and Pd(0) were required for conversion (entries 6 and 7). Supporting Pd(0)'s role as an oxidative addition partner to the alkyne, Pd(II) is significantly less active (entry 12).



**Figure 1.** Proposed Lewis acid activation of alkynes leads to an increase in backbonding from Pd(0), permitting Pd(II)–C  $\sigma$ -bond reactivity.

**Table 1.** Effect of Catalyst Composition on Product <sup>1</sup>H NMR Yield

entry	Lewis acid	Pd cat.	<sup>1</sup> H NMR yield (%)
1	PPh <sub>3</sub> AuCl	Pd <sub>2</sub> (dba) <sub>3</sub>	24
2	PPh <sub>3</sub> AuCl/AgSbF <sub>6</sub> (1:1)	Pd <sub>2</sub> (dba) <sub>3</sub>	51
3	PPh <sub>3</sub> AuCl/AgSbF <sub>6</sub> (1:2)	Pd <sub>2</sub> (dba) <sub>3</sub>	33
4	PPh <sub>3</sub> AuSbF <sub>6</sub> ·CH <sub>3</sub> CN	Pd <sub>2</sub> (dba) <sub>3</sub>	62
5	PPh <sub>3</sub> AuPF <sub>6</sub>	Pd <sub>2</sub> (dba) <sub>3</sub>	73
6	PPh <sub>3</sub> AuPF <sub>6</sub>	none	0
7	none	Pd <sub>2</sub> (dba) <sub>3</sub>	0
8	BF <sub>3</sub> ·(OMe) <sub>2</sub>	Pd <sub>2</sub> (dba) <sub>3</sub>	25
9	AgSbF <sub>6</sub>	Pd <sub>2</sub> (dba) <sub>3</sub>	0
10	PhCO <sub>2</sub> H	Pd <sub>2</sub> (dba) <sub>3</sub>	0
11	PPh <sub>3</sub> AuCl/AgSbF <sub>6</sub> (1:1)	Pd(Pf-Bu <sub>3</sub> ) <sub>2</sub>	39
12	PPh <sub>3</sub> AuCl/AgSbF <sub>6</sub> (1:1)	(PPh <sub>3</sub> ) <sub>2</sub> PdCl <sub>2</sub>	trace

A probable competing alkyne oligomerization reaction, detected by <sup>1</sup>H NMR spectroscopy, was circumvented by slow addition of the alkyne. Accordingly, reaction of tri-*n*-butylvinylstannane with slowly added DMAD produces **1** in 96% <sup>1</sup>H NMR yield, with a 95:5 selectivity for the syn addition product (Table 2, entry 1).

With optimized conditions in hand, we continued to explore the stereochemistry of the vinylstannylation reaction. Seven of eight substrates exhibit excellent syn:anti addition selectivities ( $\geq$ 95:5; exception entry 2, 89:11 syn:anti). As expected for a Stille-type reaction, the addition is stereospecific with respect to the vinylstannane: (*Z*)-propenyltri-*n*-butylstannane and (*E*)-propenyltri-*n*-butylstannane couple with preference for retention of configuration. Some stereochemical leakage to *E* occurs with the sterically bulky *Z* stannane (60:40 *Z*:*E*, entry 6).

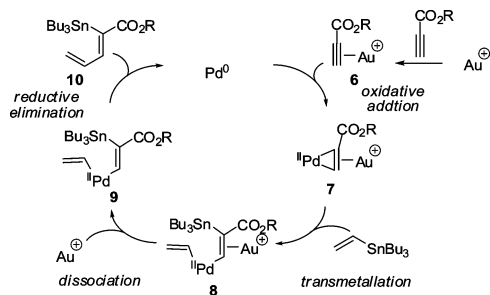
The utility of the Pd/Au-catalyzed method for formation of tri- and tetra-substituted olefins is illustrated by a range of stannane partners (i.e., sp<sup>2</sup>, sp, secondary, oxygenated,  $\beta$ -substituted; Table 2).<sup>24</sup> Complete regioselectivity is maintained even in the presence of a sterically bulky *tert*-butyl ester. Interestingly, no evidence for reentry into the catalytic cycle by the product vinylstannanes is observed. Presumably, this is because of the increased steric hindrance provided by  $\alpha$ -branching and  $\beta$ -substitution.

A proposed mechanism for the Au- and Pd-cocatalyzed vinylstannylation of alkynes is detailed in Scheme 1. Coordination of

**Table 2.** Scope of Au- and Pd-Catalyzed Alkyne Stille Reaction<sup>a</sup>

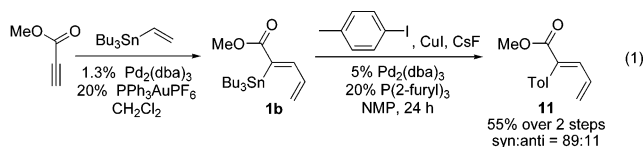
entry	alkyne	stannane	product	( <sup>1</sup> H NMR yield) isolated yield	
$R^1O_2C-C\equiv C-R^2 + Bu_3SnR^3 \xrightarrow[1.3-2.6\% Pd_2(dba)_3]{20\% PPh_3AuPF_6} R^1O_2C-C(R^2)=C(R^3)-Bu_3Sn \geq 95:5 \text{ syn:anti}^b$					
1				(96) 87	<b>1a</b>
2	R <sup>1</sup> = Me, R <sup>2</sup> = CO <sub>2</sub> Me			(75) 73 <sup>b</sup>	<b>1b</b>
3	R <sup>1</sup> = Me, R <sup>2</sup> = H			(49) 40	<b>1c</b>
4				(73) 61 <sup>c</sup>	<b>2</b>
5				(62) 51 <sup>c,d</sup>	<b>3</b>
6	R <sup>2</sup> = CO <sub>2</sub> Me			(89) 81	<b>4a</b>
7	R <sup>2</sup> = H			(57) 49 <sup>c</sup>	<b>4b</b>
8				(58) 52 <sup>c</sup>	<b>5</b>

<sup>a</sup> Conditions: CH<sub>2</sub>Cl<sub>2</sub>, slow addition of alkyne over 6 h, then 24–48 h, 23 °C, 2.0 equiv of stannane. <sup>b</sup> Exception: entry 2, 89:11 syn:anti. <sup>c</sup> With 4.0 equiv of stannane. <sup>d</sup> A ratio of 60:40 syn Z:syn E was isolated.

**Scheme 1.** Proposed Catalytic Mechanism, Showing Analogy to the Traditional Stille Reaction

cationic Au(I) to the alkyne promotes nucleophilic addition/oxidative addition of Pd(0). Transmetalation of tri-*n*-butylvinylstannane across one of the palladium–carbon  $\sigma$ -bonds of **7** results in vinyl transfer to palladium and tin transfer to the nascent olefin. Dissociation of Au(I) followed by reductive elimination forms the observed vinylstannylated product, **10**, and regenerates Pd(0). An alternative mechanism that cannot be ruled out at this time involves Au(I) activation of the vinylstannane toward C–Sn oxidative addition or oxidative cyclization, providing entry into the reaction pathway previously proposed for acyl and allyl stannanes but inaccessible for vinylstannanes.<sup>25</sup>

We next investigated the ability of the stannyldiene products to participate in traditional cross-coupling reactions with aryl halides. Reaction of crude stannyldiene **1b** with iodotoluene in the presence of 5% additional Pd<sub>2</sub>(dba)<sub>3</sub> yields the all-carbon trisubstituted olefin **11** in 78% yield (55% over two steps) (eq 1). This two-step procedure affects an aryl vinylation of the starting alkyne with absolute regioselectivity and high stereoselectivity for the syn addition product. The successful derivatization of crude product **1b** demonstrates synthetic access to the full amount of material represented by the <sup>1</sup>H NMR yield.<sup>9</sup>



In conclusion, we have developed a palladium- and gold-cocatalyzed vinylstannylation of alkynes to form tri- and tetra-substituted olefins with excellent regio- and stereocontrol. The reactions are postulated to proceed via Au(I) activation of the alkynes toward nucleophilic metalation/oxidative addition to Pd(0). In this mechanism, the alkyne serves as a pseudohalide in a Stille-type cross-coupling reaction. In a broader sense, the reactions reported herein provide an entry into the extensive catalytic chemistry of palladium–carbon  $\sigma$ -bonds starting from  $\pi$ -systems.

We are currently exploring the mechanism of this reaction and developing additional functionalization reactions of these activated  $\pi$ -systems. These investigations are part of ongoing research in our group to explore the use of Lewis acids to activate organic substrates toward metalation.

**Acknowledgment.** We thank The Petroleum Research Fund (46285-G1) and the University of California at Irvine for funding, and Dr. John Greaves for mass spectrometry assistance.

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

## References

- Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.
- de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.
- Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
- Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.
- Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590.
- Knochel, P. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 4, pp 841–870.
- For a review, see: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
- Shirakawa, E.; Yoshida, H.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 4290.
- Yoshida, H.; Shirakawa, E.; Nakao, Y.; Honda, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn* **2001**, *74*, 637.
- Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670.
- Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.
- For a review on bimetallic catalysis by late transition metals, see: van den Beuken, E. K.; Feringa, B. L. *Tetrahedron* **1998**, *54*, 12985.
- Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.
- Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.
- Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.
- Burns, C. J.; Andersen, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 915.
- For a recent example of Lewis acid catalyzed formation of a transition metal aldehyde  $\pi$ -complex, see: Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 201.
- Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Sausalito, CA, 1987; pp 155, 645–647.
- Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Am. Chem. Soc.* **1983**, *105*, 1690.
- The importance of backbonding from palladium(0) to alkenes was recently highlighted by the work of Stahl and Landis, who showed that palladium(0) has a kinetic preference for binding to electron-poor olefins. Popp, B. V.; Thorman, J. L.; Morales, C. M.; Landis, C. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 14832.
- Measured by <sup>1</sup>H NMR spectroscopy as a ratio of product to an internal standard (mesitylene). No side products of a reaction with mesitylene were observed.
- Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.
- Under our standard conditions, <sup>1</sup>H NMR spectroscopy data suggest that terminal alkynylketones polymerize rapidly. Sulfonylketones and alkynylcarboxylic acids do not react.
- Nakao, Y.; Satoh, J.; Shirakawa, E.; Hiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2271.

JA710648B