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Pd(0)-Catalyzed Oxy- and Aminoalkynylation of Olefins for the Synthesis of Tetrahydrofurans and Pyrrolidines

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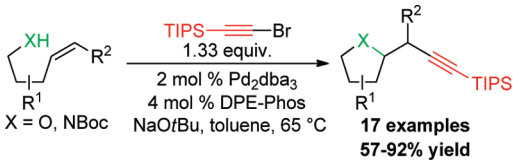
ABSTRACT



The first Pd(0)-catalyzed intramolecular oxy- and aminoalkynylation of nonactivated olefins is reported. The reaction gives access to important tetrahydrofuran and pyrrolidine heterocycles with high diastereoselectivity. The unique synthetic potential of acetylenes is further exploited to access key building blocks for the synthesis of bioactive natural products.

Heterocycles are essential structural elements for the bioactivity of natural and synthetic molecules. Among them, tetrahydrofurans and pyrrolidines are particularly important in natural products, such as the antitumoral annonaceous acetogenins gigantecin (**1**) and squamostatin C (**2**),[1] or the antibiotic alkaloid preussin (**3**) (Figure 1).[2] Consequently, the stereoselective synthesis of tetrahydrofurans and pyrrolidines has been extensively investigated.[3] Particularly interesting are methods using cyclization of alcohols or amines onto nonactivated olefins combined with a further bond forming event. Iodoetherification or amination reactions have been often used in the synthesis of heterocycles.[4] Recently, the power of metal catalysis has been harnessed to achieve multiple functionalizations of olefins[5] for the synthesis of tetrahydrofurans and pyrrolidines together with further C–N,[6] C–O,[7] or C–C bond formation.[8]

Impressive progress has been realized in Pd-catalyzed domino reactions involving cyclization on olefins to form a tetrahydrofuran or a pyrrolidine followed by carbonylation,[8a–c] vinylation,[8d,e] or arylation.[8f–j] Despite these recent breakthroughs, there are currently no examples of an oxy- or aminoalkynylation reaction for the synthesis of tetrahydrofurans or pyrrolidines.[9] Such a process would be highly useful, as the functionalization of alkynes through cross-coupling, reduction, addition, cyclization, cycloisomerization, or cycloaddition gives access to important building

(1) (a) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790. (b) Spurr, I. B.; Brown, R. C. D. *Molecules* **2010**, *15*, 460.

(2) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184.

(3) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.

(4) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814.

(5) For reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (e) Muniz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412.

(6) Using Pd catalysis: (a) Streuff, J.; Hovelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muniz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (c) Muniz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (d) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. (e) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. Selected examples for other methods: (f) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (g) Muniz, K.; Streuff, J.; Hoevelmann, C. H.; Nunez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125.

(7) Using Pd catalysis: (a) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. (b) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471. (c) Liskin, D. V.; Sibbald, P. A.; Rosewall, C. F.; Michael, F. E. *J. Org. Chem.* **2010**, *75*, 6294. (d) Kang, Y. B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. Selected examples for other methods: (e) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766. (f) Blanc, A.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 2096. (g) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (h) Cheng, H.; Stark, C. B. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1587. (i) de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 906.

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blocks used in synthetic chemistry, chemical biology, and material sciences.[10]

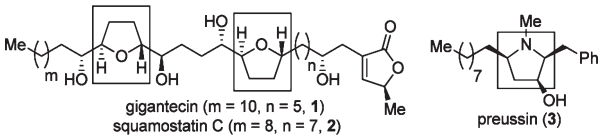
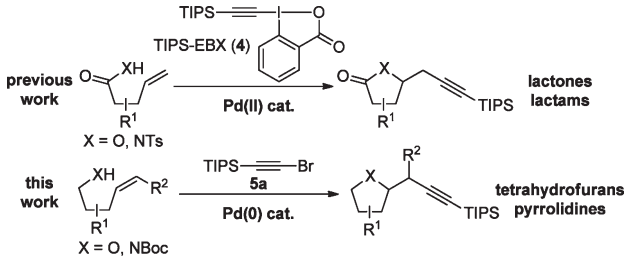


Figure 1. Tetrahydrofuran and pyrrolidine natural products.

Our group has developed the Pd(II)-catalyzed oxy- and aminoalkynylation of olefins with EBX (ethynyl benziodoxolone) reagent **4** for the synthesis of lactones and lactams (Scheme 1).[11] However, the developed methods could not be used to access tetrahydrofurans or pyrrolidines, and C−C bond formation was limited to primary positions. Herein, we report a different approach for the oxy- and aminoalkynylation of olefins using Pd(0) catalysis and triisopropylsilyl ethynyl bromide (**5a**), which allowed us to override both limitations (Scheme 1). To the best of our knowledge, this is the first example of Pd(0) catalysis for the oxy- and aminoalkynylation of olefins or for any $C-X/C_{(SP^3)}-C_{(SP)}$ domino sequence on alkenes. Tetrahydrofurans and pyrrolidines were obtained in good yields and diastereoselectivities, and examples of alkynylation at secondary positions are also reported. The synthetic potential of the obtained acetylenes is demonstrated in further transformations giving access to the core structures of acetogenin natural products.

The oxyalkynylation of penten-5-ol (**6a**) with TIPS-EBX (**4**) as reagent and a Pd(II) catalyst gave only low yields (<25%), and no conversion was observed with

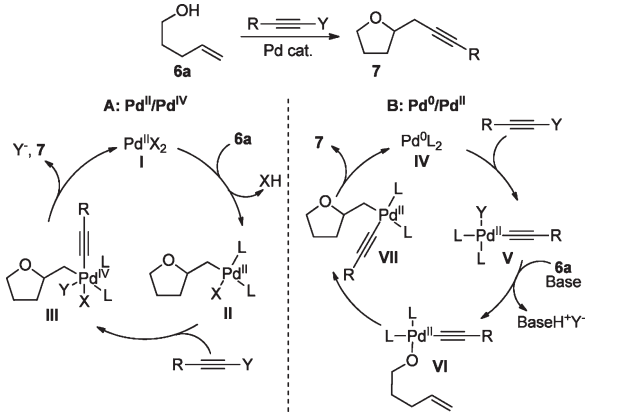
Scheme 1. Oxy- and Aminoalkynylation of Alkenes



halogeno acetylenes. At this point, we decided to reconsider our working model for the reaction (Scheme 2). For lactonization[11a] we had used an electron-poor Pd(II) catalyst **I**, which would react with the strong oxidant **4** to form a putative Pd(IV) intermediate **III** only after oxypalladation to give **II** had occurred. However, the use of a Pd(0) catalyst **IV** with **4** led to fast formation of a diyne product and to silylation of alcohol **6a** (Table 1, entry 1).[12] We speculated that a weaker and less electrophilic oxidant, such as a halogeno acetylene, should be less prone to the observed side reactions. Instead, oxypalladation and reductive elimination via **VI** and **VII** would give the product **7**, opening a new Pd(0)/Pd(II) manifold for the reaction.

When Wolfe's conditions[8f−j] were used with phenyl- or phenylethyl-ethynyl bromides (**5b** and **5c**) (Table 1, entries 2−3), complex mixtures of products were obtained. At this point, we decided to turn toward triisopropylsilyl acetylenes derivatives, which had demonstrated exceptional properties in metal catalysis.[11,13] Gratifyingly, whereas chloroacetylene **5d** displayed only low conversion (entry 4) and iodoacetylene **5e** lead to dimerization (entry 5),[14] a promising 69% of yield was obtained using 2 mol % $Pd_2(dba)_3$ and DPE-Phos as a ligand with bromoacetylene **5a** (entry 6).

Scheme 2. Working Models for the Oxyalkynylation of Penten-5-ol (**6a**)



Further optimization studies allowed us to identify toluene as the optimal solvent and confirmed DPE-Phos as the ideal ligand (entry 7).[15] Under these conditions, **7a**

(8) Using Pd catalysis: Carbonylation: (a) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583. (b) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483. (c) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124. Vinylation: (d) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205. (e) Ney, J. E.; Hay, M. B.; Yang, Q. F.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614. Arylation: (f) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (g) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (h) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (i) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157. (j) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276. Synthesis of epoxides or aziridines: (k) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052. (l) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7224. Selected examples for other methods: (m) Zhang, G. Z.; Cui, L.; Wang, Y. Z.; Zhang, L. M. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (n) Brenzovich, W. E.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5519.

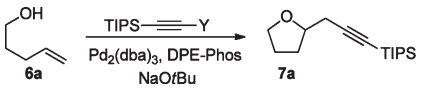
(9) With the exception of conjugate addition of alkynes on Michael acceptors, the alkynylation of olefins has only been achieved in a few rare cases in the past. See for a few selected examples: (a) Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1982**, *23*, 4517. (b) Larock, R. C.; Narayanan, K. *Tetrahedron* **1988**, *44*, 6995. (c) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (d) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060. (e) Kohno, K.; Nakagawa, K.; Yahagi, T.; Choi, J. C.; Yasuda, H.; Sakakura, T. *J. Am. Chem. Soc.* **2009**, *131*, 2784. (f) Li, Y. B.; Liu, X. H.; Jiang, H. F.; Liu, B. F.; Chen, Z. W.; Zhou, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 6341.

(10) Diederich, F.; Stang, P. J.; Tykwinski, R. R.; *Acetylene Chemistry: Chemistry, Biology and Material Science*; Wiley-VCH: Weinheim, 2005.

(11) (a) Nicolai, S.; Erard, S.; González Fernández, D.; Waser, J. *Org. Lett.* **2010**, *12*, 384. (b) Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4680.

could be isolated in 92% yield using only 1.33 equiv of bromide **5a** (Table 2, entry 1).

Table 1. Optimization of the Oxyalkynylation Reaction



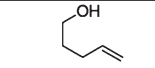
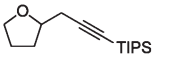
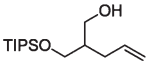
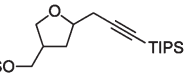
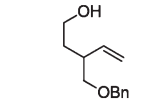
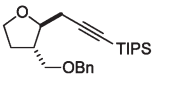
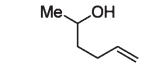
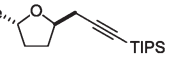
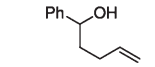
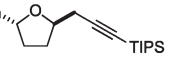
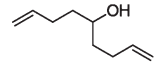
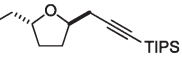
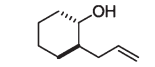
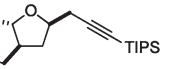
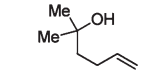
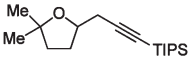
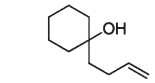
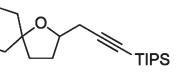
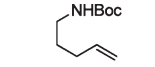
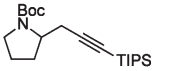
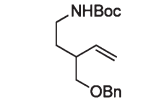
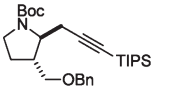
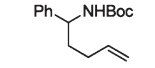
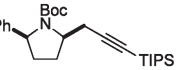
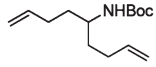
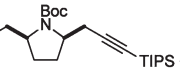
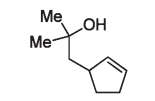
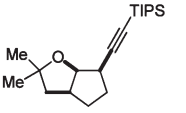
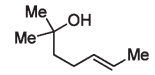
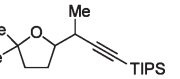
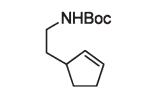
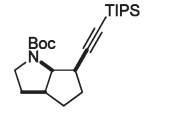
entry	reagent	ligand	solvent	yield[a]
1	TIPS-EBX	DPE-Phos	THF	<5%
2	Ph—≡—Br (**5b**)	DPE-Phos	THF	-[b]
3	$PhCH_2CH_2$—≡—Br (**5c**)	DPE-Phos	THF	-[b]
4	TIPS—≡—Cl (**5d**)	DPE-Phos	THF	22%
5	TIPS—≡—I (**5e**)	DPE-Phos	THF	31%
6	TIPS—≡—Br (**5a**)	DPE-Phos	THF	69%
7	TIPS—≡—Br (**5a**)	DPE-Phos	toluene	87%

[a] Reaction conditions: 0.15 mmol of **6a**, 0.20 mmol of **5**, 0.20 mmol of NaO*t*Bu, 0.003 mmol of $Pd_2(dba)_3$, 0.006 mmol of ligand, 0.8 mL of dry solvent under N_2 at 65−70 °C. Yield determined via GC-MS. [b] Complex mixture of nonseparable products.

We then examined the scope of the reaction (Table 2). The cyclization of primary alcohols proceeded in 80−92% yield (entries 1−3). We then turned to the use of secondary alcohols in the cyclization reaction (entries 4−7). This class of substrates is particularly interesting, as *trans* 2,5-disubstituted tetrahydrofurans are often represented in natural products, such as acetogenins (Figure 1). The reaction worked in 60−80% yield and excellent *trans* diastereoselectivity (>95:5) (entries 5−7), with the exception of the small Me substituent (entry 4). The reaction tolerated a second double bond in the molecule (entry 6) and gave access to bicyclic heterocycles (entry 7). Useful yields could be obtained with tertiary alcohols (entries 8−9), including for the formation of a spiro-bicyclic heterocycle **7i** (entry 9).

In our previous work, completely different conditions had to be used when going from lactonization to lactamization.[11] However, this was not the case when using

Table 2. Scope of the Alkynylation Reaction

entry	substrate	product	yield[a]
1	 **6a**	 **7a**	92%
2	 **6b**	 **7b**	88% (67:33 dr)
3	 **6c**	 **7c**	80% (85:15 dr)
4	 **6d**	 **7d**	80% (87:13 dr)
5	 **6e**	 **7e**	60% (>95:5 dr)
6	 **6f**	 **7f**	65% (>95:5 dr)
7	 **6g**	 **7g**	79% (>95:5 dr)
8	 **6h**	 **7h**	69%
9	 **6i**	 **7i**	57%[b]
10	 **6j**	 **7j**	81%
11	 **6k**	 **7k**	76% (87:13 dr)
12	 **6l**	 **7l**	80% (94:6 dr)
13	 **6m**	 **7m**	57% (>95:5 dr)
14	 **6n**	 **7n**	86% (>95:5 dr)
15	 **6o**	 **7o**	71%[b] (>95:5 dr)
16	 **6p**	 **7p**	86% (>95:5 dr)

[a] Reaction conditions: 0.40 mmol of **6**, 0.53 mmol of alkyne **5a**, 0.53 mmol of NaO*t*Bu, 0.008 mmol of $Pd_2(dba)_3$, 0.016 mmol of DPE-Phos, 2.1 mL of toluene under N_2 at 65−70 °C for 3 h. Isolated yield after column chromatography. [b] At 110 °C.

Pd(0) catalysis, and no further optimization was required in the case of Boc-protected amines as substrates (entries 10−13). Excellent *cis* selectivity was observed in the formation of 2,5-disubstituted pyrrolidines (entries 12−13), which is the same relative stereochemistry as observed in preussin (**3**) (Figure 1). Up to now, we had examined only

(12) On a 0.40 mmol scale, 1,4-bis(triisopropylsilyl)buta-1,3-diyne and triisopropyl(pent-4-enyloxy)silane were obtained in 8 and 84% yield respectively using the conditions of entry 1, Table 1. See Supporting Information.

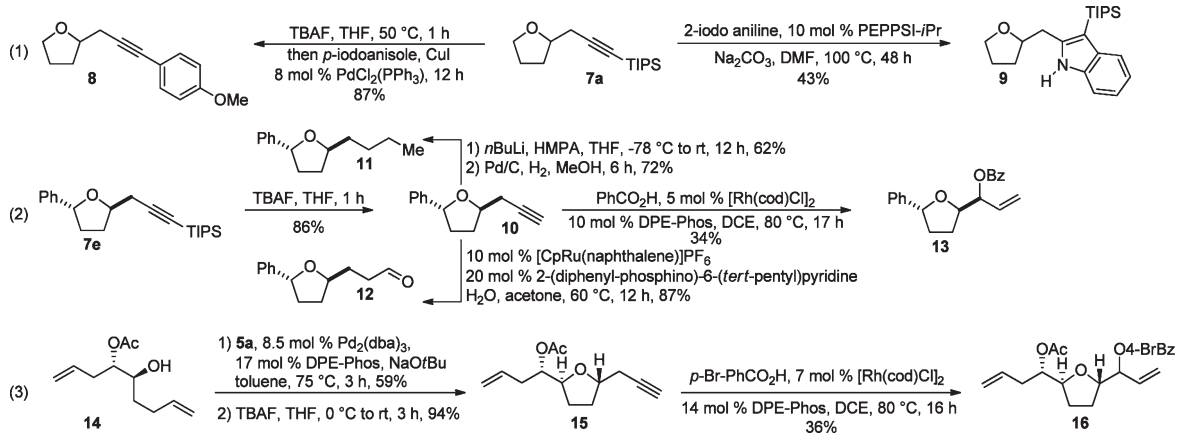
(13) (a) Rucker, C. *Chem. Rev.* **1995**, *95*, 1009. (b) Nishimura, T.; Sawano, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8057. (c) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (d) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (e) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (f) Brand, J. P.; González Fernández, D.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102.

(14) On a 0.40 mmol scale, 1,4-bis(triisopropylsilyl)buta-1,3-diyne and tetrahydrofuran **7a** were both obtained in 34% yield using the conditions of entry 5, Table 1. See Supporting Information.

(15) See Supporting Information for further tested conditions.

(16) (a) Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925. (b) de Carne-Carnavalet, B.; Archambeau, A.; Meyer, C.; Cossy, J.; Folleas, B.; Brayer, J. L.; Demoute, J. P. *Org. Lett.* **2011**, *13*, 956. (c) Thaler, T.; Guo, L. N.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 2174.

Scheme 3. Functionalization of the Products



monosubstituted olefins involving most probably a primary Pd-alkyl intermediate. The use of 1,2 disubstituted olefins would require a challenging SP^3-SP reductive elimination at a secondary position. Such processes are difficult in Pd catalysis.[16] Gratifyingly, the reaction also worked well for disubstituted olefins, in the case of both alcohols and amines (entries 14–16). Preorganization through rigidification was not required, and even simple acyclic substrate **6o** could be used (entry 15). In the case of bicyclic products **7n** and **7p**, an all-*cis* relationship of the substituents was observed. This is in accordance with the mechanism we proposed in our working model (Scheme 2) involving binding of the heteroatom to Pd, followed by *syn* oxypalladation and reductive elimination.

We then shortly investigated the transformation of the obtained acetylenes into important building blocks (Scheme 3). TIPS deprotection and Sonogashira coupling on **7a** can be done in one pot to give aryl acetylene **8** in 87% yield (Scheme 3, (1)).[17] A Larock annulation[18] gave indole **9** with perfect regioselectivity, albeit in moderate yield (43%). With **7e**, deprotection proceeded in good yield, and the terminal alkyne could be converted in two steps to known **11**,[19] which allowed us to confirm definitively the *trans* relationship of the substituents (Scheme 3, (2)). Hydration using the method developed by Hintermann[20] gave access to versatile aldehyde **12** in 87% yield, resulting in an overall addition of an oxygen atom and acetaldehyde to an olefin. We then introduced an oxygen group in the propargylic position using Breit's method.[21] The desired allylic ester **13** was obtained in 34% yield and 73:27 dr. This preliminary result is highly interesting, especially when considering that the reaction had been reported for the acid as a limiting agent, and no effort has yet been done to improve the reaction with only 1 equiv of alkyne. Building blocks for the synthesis of acetogenins were accessed starting from enantioenriched alcohol **14** (Scheme 3, (3)).[22] High diastereoselectivity for the desired *trans* product **15** was observed, giving an asymmetric entry to the α-monohydroxylated tetrahydrofuran ring of gigantecin (**1**) or squamostatin C (**2**) (Figure 1). A second hydroxy group could be introduced using Breit's method to access the bis α-hydroxylated tetrahydrofuran ring.

In summary, we have reported the first oxy- and aminoalkynylation reactions of alkenes catalyzed by a Pd(0) catalyst. Tetrahydrofurans and pyrrolidines were obtained in good yield and diastereoselectivity with simultaneous installation of a triple bond. The utility of the alkyne was demonstrated through its transformation in other functional groups and into key building blocks for the synthesis of acetogenin natural products. Principles applied in arylation chemistry could be transferred to alkynylation reactions if a triisopropylsilyl protecting group was present. This discovery will probably be of broad use in the development of other reactions involving acetylenes. Further investigations along this line, as well as the development of asymmetric methods, are currently ongoing in our group.

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Supporting Information Available. Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Sun, J.; Conley, M. P.; Zhang, C.; Kosmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705.

(18) Grunenthal GMBH, Patent: US2009/247505 A1, 2009.

(19) Shi, H.; Liu, H.; Bloch, R.; Mandville, G. *Tetrahedron* **2001**, *57*, 9335.

(20) Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* **2006**, *8*, 5853.

(21) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386.

(22) Zhao, H.; Gorman, J. T.; Pagenkopf, B. L. *Org. Lett.* **2006**, *8*, 4379.