ORGANIC
LETTERS

2008
Vol. 10, No. 16
3619−3621

Pd-Catalyzed Borylative Polycyclization of Enediynes to Allylboronates

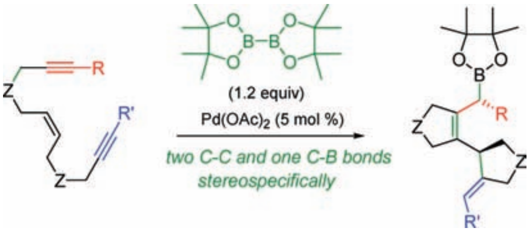
Juan Marco-Martínez, Elena Buñuel, Rebeca Muñoz-Rodríguez, and Diego J. Cárdenas*

Departamento de Química Orgánica, Universidad Autónoma de Madrid,
Cantoblanco, 28049 Madrid, Spain

diego.cardenas@uam.es

Received June 24, 2008

ABSTRACT



Pd-catalyzed dicyclization of 6-ene-1,11-diynes with bis(pinacolato)diboron affords synthetically useful allylboronates under smooth conditions. Two new C−C and one C−B bonds are stereospecifically formed in a single operation. The stereochemical outcome depends on the starting alkene configuration. The reaction is general and has been applied to differently substituted enediynes. Isolation of intermediate 1,3-dienes suggests a regioselective β-hydrogen elimination along the reaction pathway.

Alkylboronates and alkyltrifluoroborates are becoming more and more important intermediates for synthetic purposes,[1,2] since they can be used as nucleophilic partners in the Suzuki cross-coupling[3] and other C−C bond-forming reactions. 1,2-Diborylated alkanes prepared by diboration of C═C bonds have been recently used for the enantioselective synthesis of 1,2-diols.[4] Alkyl- and allylboronates are usually prepared by hydroboration of alkenes or reaction of main-group organometallic derivatives with borate esters.[5] C−H activation of alkanes is a promising alternative for the preparation of primary alkylboronates.[6] We have recently developed a novel reaction for the formation of alkyl (homoallylic) boronates from enynes by a formal 1,7-hydroboration with concomitant carbocyclization (Scheme 1).[7]

The success of this reaction relies on the absence of β-hydrogen elimination on the putative alkylpalladium intermediate **I**. In our aim to exploit the synthetic utility of this process, we explored the reaction of 6-ene-1,11-diynes.

---

(1) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (b) Netherton, M.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.

(2) Recent examples of synthetic applications of alkyltrifluoroborates: (a) Molander, G. A.; Yokoyama, Y *J. Org. Chem.* **2006**, *71*, 2493–2498. (b) Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75–78. (c) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396. (d) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534–5539. (e) Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153–2155. (f) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357–360.

(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

(4) Diboration of allenes: (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328–16329. Diboration of alkenes: (b) Morgan, J. B.; Miller, S. P.; Morken, J. P *J. Am. Chem. Soc.* **2003**, *125*, 8702–8703.

(5) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; pp 1−99.

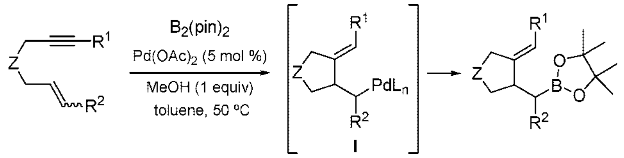
(6) (a) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684–13685. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997. (c) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 15334–15335. (d) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C.; Fan, Y.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 2538–2552.

(7) Marco-Martínez, J.; López-Carrillo, V.; Buñuel, E.; Simancas, R.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1874–1875.

(8) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576–12583. Metal-catalyzed synthesis of allylboronates: (a) Ishiyama, T.; Ahiko, T.; Miyaura, N *Tetrahedron Lett.* **1996**, *37*, 6889–6992. Enantioselective synthesis: (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857. See references cited therein.

10.1021/ol801424m CCC: $40.75

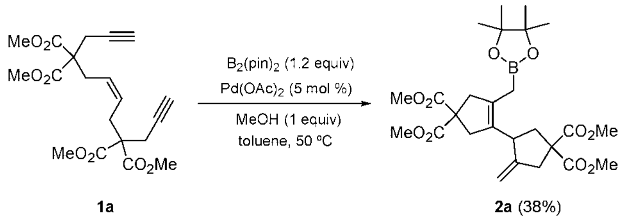
Scheme 1. Borylative Cyclization of 1,6-Enynes



In this paper, we wish to report the formation of *allylboronates* from enediynes by a Pd-catalyzed cascade reaction with bis(pinacolato)diboron. Allylboronates[8] are useful reagents involved in the stereoselective formation of C−C bonds especially by reaction with carbonyl compounds and derivatives.[9]

We considered the possibility of trapping the intermediate alkylpalladium complexes by intramolecular reaction with a second alkyne. This would give rise to alkenylpalladium complexes and, eventually, to alkenylboronates. Instead, when 6-ene-1,11-diyne **1a** was subjected to reaction with bis(pinacolato)diboron in the presence of Pd(OAc)$_2$ and MeOH in toluene, allylboronate **2a** was formed (Scheme 2).[10]

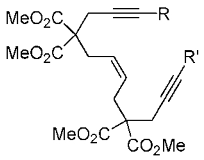
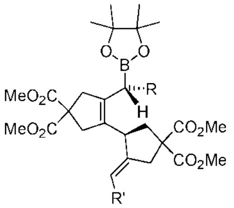
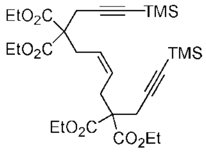
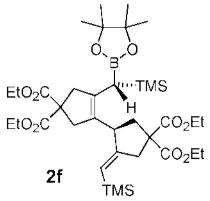
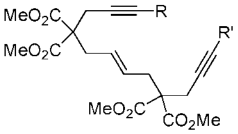
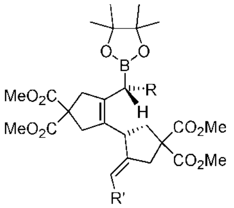
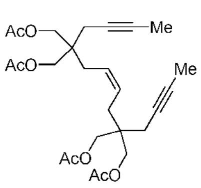
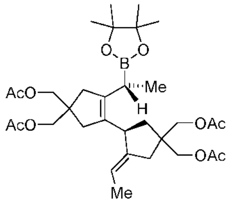
Scheme 2. Pd-Catalyzed Borylative Cyclization of an Enediyne



This result is in sharp contrast with that of Ojima, who obtained alkenyl silanes in the Rh-catalyzed cyclative hydrosilylation of the same kind of enediynes.[10b]

This cascade reaction provides two C−C and one C−B bond in a single operation and stereoselectively. Internal alkynes afford the corresponding boronates in higher yields (Table 1, entries 2, 3, 6, and 7). Nonsymmetrical **1d** and **1e** afford borylation of the terminal alkynes (entries 4 and 5), in a fully regioselective process. Instead, compound **1g** gives a 1:1 mixture of the two possible regioisomers. We were pleased to confirm the stereospecificity of the reaction by using (*E*)-alkenes (entries 8−10) which provide different stereoisomers of the final products. Yields are lower in this case due to the presence of unseparable dienes or tricycles (see below).[11,12] The relative stereochemistry was determined for compound **2b** by single-crystal X-ray diffraction (see the Supporting Information).

Table 1. Pd-Catalyzed Borylative Cyclization of Enediynes

	substrate	t(h)	product	yield(%)
				
1	**1a**	5.5	**2a** : R = R′ = H	38
2	**1b**	7.5	**2b** : R = R′ = Me	83
3	**1c**	7	**2c** : R = R′ = Ph	65
4	**1d**	4	**2d** : R = H, R′ = Me	59
5	**1e**	6	**2e** : R = H, R′ = Ph	53
6	 **1f**	24	 **2f**	74
7	**1g**	22	**2g** : R, R′ = Ph, Me	72[a]
				
8	**1h**	18	**2a** : R = R′ = H	36[b]
9	**1i**	6	**2i** : R = R′ = Me	70[b]
10	**1j**	7.5	**2j** : R = R′ = Ph	46[b]
11	 **1k**	15	 **2k**	80

[a] Mixture of the two possible regioisomers (60:40). Major isomer: R = Ph, R′ = Me (see the Supporting Information). [b] NMR yields in mixtures with dienes or tricycles.

---

(9) (a) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415. (b) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587.

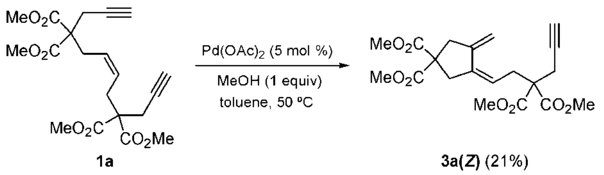
(10) Silylcarbocyclization of enynes: (a) Lee, S.-Y.; Ojima, I *J. Am. Chem. Soc.* **2000**, *122*, 2385–2386. (b) Ojima, I.; McCullagh, J. V.; Shay, W. R. *J. Organomet. Chem.* **1996**, *521*, 421–423. (c) Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc.* **2005**, *127*, 17756–17767.

(11) Boronates tend to decompose in column chromatography when longer retention times are used, which precludes isolation of pure compounds in some cases.

(12) Related enediynes containg terminal alkynes with bis(sulfonyl)methane or NTs as tethers did not afford the desired compunds.

With the aim of obtaining some evidence about the mechanism, enediynes were subjected to the reaction conditions in the absence of $B_2(pin)_2$. Diene **3a(*Z*)** (R = H) was obtained stereoselectively from **1a** (Scheme 3).[13,14]

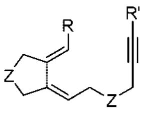
Scheme 3. Reaction in the Absence of $B_2(pin)_2$ Affords 1,3-Dienes



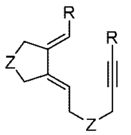
Compound **3a(*Z*)** led to **2a** when treated with $B_2(pin)_2$ and $Pd(OAc)_2$ under the above-mentioned conditions in ca. 25% yield,[15] which suggests the intermediacy of 1,3-dienes in the reaction pathway. In contrast, the only product that could be isolated from the reaction of **1i** under the same conditions was the corresponding (*E*)-alkene **3b(*E*)** (R = Me), which is consistent with a regio- and stereoselective β-hydrogen elimination.

Reaction of trans derivative **1h** in the absence of $B_2(pin)_2$ led to tricycle **4a** (R = H) in 30% yield (no 1,3-diene was detected). Tricyclic compounds seem to be formed from compounds **3** by Diels−Alder intramolecular cycloaddition,[16] rather than coming from Pd-catalyzed reactions, since heating of **3a(*Z*)** led to aromatized **4a** through the likely intermediacy of **5a** (R = H). Diphenyl derivative **5b** (R = Ph) was isolated from **1j** from the reaction in the absence of $B_2(pin)_2$. This compound also aromatizes upon heating a solution in the presence of oxygen, although more slowly.[17] Higher cycloaddition ability of **3(*E*)** compared with **3(*Z*)** due to the configuration of the disubstituted alkene explains why the former are not detected in some cases.

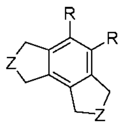
Z = $C(CO_2R)_2$



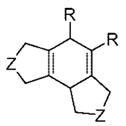
3(*Z*)



3(*E*)



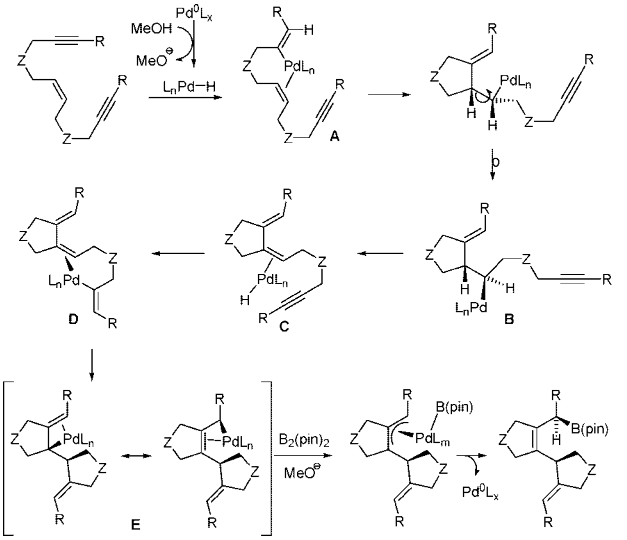
4



5

The reaction probably takes place by formation of a Pd hydride complex which promotes hydropalladation of the terminal alkyne. After 1,2-insertion of the alkene into alkenyl-Pd intermediate **A** (Scheme 4) a regioselective β-hydrogen elimination would afford 1,3-diene **C**.

Scheme 4. Proposed Reaction Pathway



Although related intermediates involved in the Oppolzer reaction usually evolve through elimination of the exocyclic H atoms,[18] the stereospecificity of the overall process suggests the opposite regioselectivity in this case.[19] Insertion of the other alkyne into the Pd−H bond in **C** to give **D** stereoselectively, followed by carbometalation of the diene would give rise to allyl-Pd intermediate **E**. This 1,2-insertion explains the relative stereochemistry observed in the final products. Methoxide-promoted transmetalation of **E** with the boron reagent and reductive elimination would lead to the observed final products.

In summary, we have developed a cascade reaction in which formation of two C−C and one C−B bonds affords allylboronates in smooth conditions. The stereochemical information contained in the starting double bond travels along the multistep reaction pathway giving rise to the stereospecific formation of two asymmetric centers.

Acknowledgment. We thank César Pastor (SIdI-UAM) for the X-ray studies We gratefully acknowledge the MEC (projects CTQ2004-02040/BQU and CTQ2007-60494/BQU) for financial support and for a FPU fellowship to J.M.-M.

Supporting Information Available: Experimental details, spectra for new compounds, and crystal structure determination of **2b**.This material is available free of charge via the Internet at http://pubs.acs.org.

OL801424M

---

[13] The same double-bond configuration was observed in dienes obtained from **1b** and **1c** (NOESY), although low yields (<15%) were observed in these cases. Partial decomposition of these compounds precludes isolating them in higher yields.

[14] Related carbocycles by Rh-catalyzed reactions: Shibata, T.; Kurokawa, H.; Kanda, K *J. Org. Chem.* **2007**, *72*, 6521–6525.

[15] Approximate yield since starting diene **3a(Z)** was not pure. These compounds tend to decompose and are difficult to purify.

[16] Cycloisomerization of enynes and enediynes: (a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491–12509. (b) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255–4267.

[17] Probably, the steric hindrance between the phenyl rings precludes oxidation of the benzylic position in **4j**.

[18] Reviews: (a) Oppolzer, W. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, Chapter 8.3. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38–52.

[19] A β-hydrogen elimination involving the exocyclic chain would destroy the stereochemical information contained in the starting alkene.