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Pd-Catalyzed Borylative Cyclization of Allenynes and Enallenes

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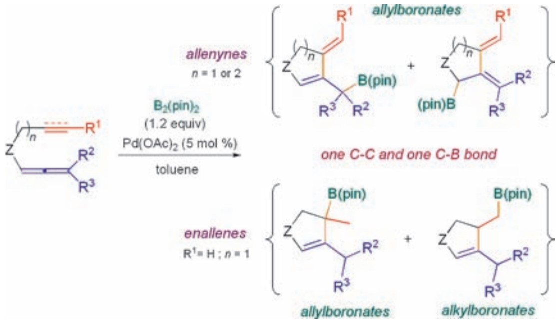
ABSTRACT



Pd-catalyzed cyclization of 1,5- and 1,6-allenynes and 1,5-enallenes with bis(pinacolato)diboron affords synthetically useful allylboronates and alkylboronates under smooth conditions in a formal hydroborylative carbocyclization reaction. One C−C and one C−B bond are formed in a single operation. The reaction outcome implies that different mechanisms operate for the reactions of allenynes and enallenes, respectively, the actual pathway depending on the relative reactivity of the alkyne or the alkene versus the allene moiety. The cyclized boronates obtained can be functionalized by oxidation or allylation reaction with aldehydes.

Transition-metal-catalyzed carbocyclization reactions of unsaturated species have provided useful methods for the preparation of a wide range of carbocycles or heterocycles with high efficiency and selectivity.[1] Compared with alkynes and alkenes, allenes have been much less studied as a component for the catalytic formation of carbon−carbon multiple bonds. However, allenes have proved to be versatile intermediates for organic synthesis in recent years.[2−6] Thus, transition-metal-catalyzed cycloisomerization and carbocyclization reactions of allenynes (Ti, Ru, Rh, Pd, Mo, Pt, Au)[2,3] and enallenes (Ru, Rh, Ni/Cr, Pd, Au)[4,5] have been reported in the literature. Thermal cycloadditions of allenynes and enallenes have also been described.[7]

Processes in which main group elements are introduced along the cyclization reaction are especially important since they allow the preparation of compounds which can be further functionalized. Thus, Shibata and co-workers reported the first hydrosilylative carbocyclization of allenynes,[8] and RajanBabu and co-workers the first silylstannylation−cy-

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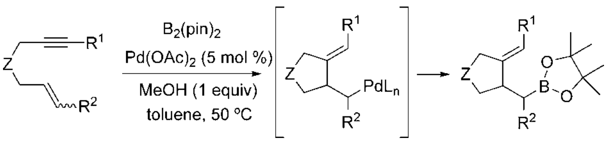
clization of allenynes.[9] We have recently reported a novel reaction for the formation of alkyl (homoallylic) boronates from enynes by a formal 1,7-hydroboration with concomitant carbocyclization (Scheme 1) and have extended the reaction to enediynes to obtain allylboronates.[10]

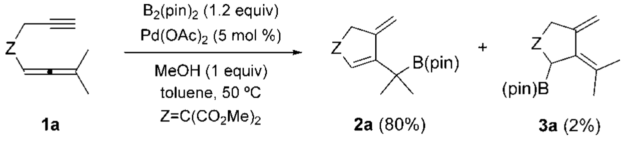
Scheme 1. Borylative Cyclization of 1,6-Enynes



Alkylboronates[11] and alkyltrifluoroborates[12] are useful nucleophilic partners in the Suzuki cross-coupling,[13] and allylboronates[14] are important in the stereoselective formation of C−C bonds from carbonyl compounds and derivatives.[15] Boronates are usually prepared by hydroboration of alkenes or by reaction of Li and Mg reagents with borate esters.[16] Herein, we report a novel Pd-catalyzed borylative cyclization reaction for the formation of allylboronates and alkylboronates from allenynes and enallenes, respectively, which avoids the use of highly nucleophilic or basic reagents. The resulting boronates have been used as substrates for subsequent oxidation and allylation reactions.

When 1,5-allenyne **1a** was subjected to reaction with bis(pinacolato)diboron in the presence of Pd(OAc)$_2$ and MeOH in toluene, a mixture of two five-membered ring allylboronates, **2a** and **3a**, was formed (Scheme 2). The formation of these two regioisomers implies a formal 1,7- and 1,5-hydroboration of the allenyne, respectively, with concomitant carbocyclization, affording one C−C and one B−C bond in a single operation. In all cases, i.e., both terminal and internal allenyne (referred to the alkyne moiety), the major regioisomer is that in which the boronate is located in the exocyclic position (**2**). Noteworthy, high yields are obtained despite the potential β-hydrogen elimination that could take place on the intermediates.

Scheme 2. Pd-Catalyzed Borylative Cyclization of an Allenyne



Terminal allenynes afford the corresponding boronates with moderate to good yields (Table 1).[17,18] The best results

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(3) Alternative mechanisms for allenyne cycloisomerization: For Co: (a) Llerena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027–7030. For Ga: (b) Lee, S. I.; Sim, S. H.; Kim, S. M.; Kim, K.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 7120–7123. For Hg: (c) Sim, S. H.; Lee, S. I.; Seo, J.; Chung, Y. K. *J. Org. Chem.* **2007**, *72*, 9818–9821. For Mo-catalyzed allenyne metathesis: (d) Murakami, M.; Kadowaki, S.; Matsuda, T. *Org. Lett.* **2005**, *7*, 3953–3956. For Rh-catalyzed reactions not involving cycloisomerization: (e) Miura, T.; Ueda, K.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2008**, 5366–5368.

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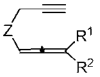
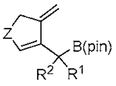
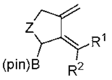
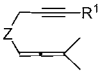
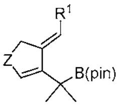
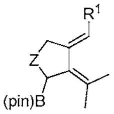
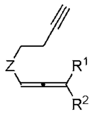
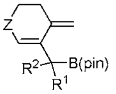
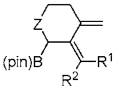
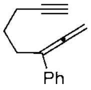
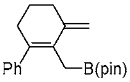
(17) Endocyclic allylboronates **6b** and **6c** were obtained as a mixture of geometric isomers. The crystal structure of the *E*-isomer of **6c** was determined using a pure sample from a chromatographic partial separation.

(18) Boronates tend to decompose in column chromatography when longer retention times are used, which precludes isolation of pure compounds in some cases. Derivatives **3a**, **3b**, **3d**, and **3f** could not be fully characterized due to their instability and fast decomposition in solution.

Table 1. Pd-Catalyzed Borylative Cyclization of Allenynes[a]

	substrate		temp (°C)	t(h)	isolated yield(%) /ratio[b]	
			Z=C(CO$_2$Me)$_2$			
1	**1a**	R^1 = R^2 = Me	50	4	82[c]	**2a**:**3a** (97: 3)
2	**1b**	R^1 = Me, R^2 = Et	50	4	67	**2b**:**3b** (89:11)
3	**1c**	R^1 = Me, R^2 = ^{i}Pr	-20	14	60	**2c**:**3c** (67:33)
4	**1d**	R^1 = R^2 = -(CH$_2$)$_5$	50	4	80	**2d**:**3d** (91: 9)
			Z=C(CO$_2$Me)$_2$			
5	**1e**	R^1 = Me	50	51	36[d]	**2e**:**3e** (100:0)
6	**1f**	R^1 = Ph	rt	1.5	42	**2f**:**3f** (88:12)
			Z=C(CO$_2$Me)$_2$			
7	**4a**	R^1 = R^2 = Me	rt	22	45[e]	**5a**:**6a** (100:0)
8	**4b**	R^1 = Me, R^2 = Et	50	4	43	**5b**:**6b** (100:0)
9			rt	3	33	(88:12)
10	**4c**	R^1 = Me, R^2 = ^{i}Pr	rt	24	53	**5c**:**6c** (23:77)
11	**4d**	R^1 = R^2 = -(CH$_2$)$_5$	rt	1	97	**5d**:**6d** (59:41)
12	**4e**			24	12 **5e**	

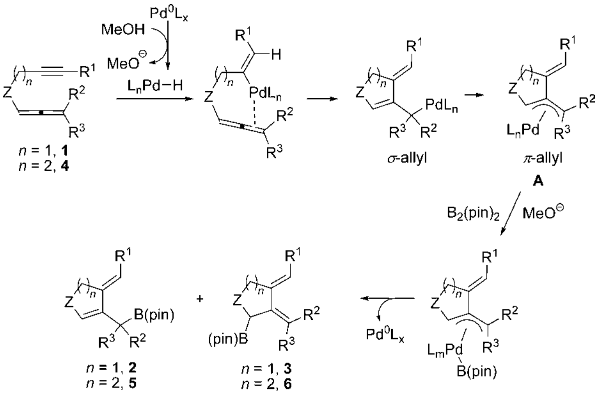
[a] Standard conditions: allenyne **1** or **4** (1 equiv), B$_2$(pin)$_2$ (1.2 equiv), Pd(OAc)$_2$ (5 mol %), MeOH (1 equiv) in dry toluene (1 mL) were stirred at the indicated temperature under Ar atmosphere. [b] Isomers **2** and **3** were completely separated in most cases. See Supporting Information for details. [c] Pd(OAc)$_2$ (10 mol %) was added. [d] Additional B$_2$(pin)$_2$ (1 equiv) and Pd(OAc)$_2$ (5 mol %) were added after 48 h with no reaction at rt and then heated at 50 °C. [e] A mixture of nonseparable β-elimination products was obtained in additional 16% yield.

were obtained for allenynes **1a** and **1d** (ca. 80% yield). The lower yields obtained for the internal allenynes, **1e**−**f**, could be due to the lower reactivity of the internal alkyne with respect to the allene moiety and the potential competition of the allene in the early stages of the reaction pathway (see below).

When the reaction was performed with the 1,6-allenynes (**4**), homologues of **1**, six-membered ring allylboronates **5** and **6** were obtained in formal 1,8- and 1,6-hydroborylative carbocyclizations, respectively. Reactions of **4a** and **4b** afforded a single regioisomer in each case, **5a** and **5b**, respectively, with moderate yields (Table 1). However, allenyne **4d** provides an excellent yield (97%), with a significant increase in the endocyclic boronate proportion (**5d**:**6d**, 59:41), and **4c** affords the mixture of allylboronates with the endocyclic boronate as the major regioisomer (**6c**).[19] Finally, the methylene-bridged allenyne **4e** gave **5e** in lower yield. Low yields are probably due to decomposition of starting materials since conversion was complete in all cases.

A reasonable reaction pathway for the formation of the observed products is shown in Scheme 3. The reaction probably starts with the formation of a Pd−hydride complex by protonation of Pd(0) intermediates with the alcohol, which promotes the hydropalladation of the alkyne.[20] Subsequent carbometalation of the allene by the alkenylpalladium intermediate would take place regioselectively with formation of the new C−C bond onto the central carbon of the allene and would give rise to allyl−Pd intermediate **A** (Scheme 3). Methoxide-promoted transmetalation of **A** with bis(pinacolato)diboron, followed by reductive elimination, would lead to the observed final products **2** and **3**. Therefore, we propose that the regioselective outcome of the reaction is a consequence of the relative feasibility of both possible C−B reductive eliminations on the allylpalladium intermediate.

Scheme 3. Proposed Reaction Pathway for Allenynes



On the other hand, when 1,5-enallenes **7a**,**b** were subjected to the same reaction conditions, the following mixtures of alkyl- and allylboronates, **8a**,**b** and **9a**,**b**, were obtained in moderate yields (ca. 60%) (Table 2).

The reaction outcome indicates the occurrence of a different mechanism. In this case, the mechanistic pathway probably starts with the hydropalladation of the terminal double bond of the allene resulting in a vinyl−Pd intermediate.[4f] Then, insertion of the alkene into the C−Pd bond would give **B** (Scheme 4). Finally, transmetalation of **B** with the boron reagent and reductive elimination would lead to alkylboronate **8**. The formation of the regioisomer **9** could be explained by a β-hydrogen elimination in the alkylpalladium intermediate **B** and subsequent hydropalladation of the exocyclic alkene with the opposite regioselectivity to give **C**. Transmetalation and reductive elimination would afford compound **9**. This proposal is consistent with the isolation of cycloisomerization com-

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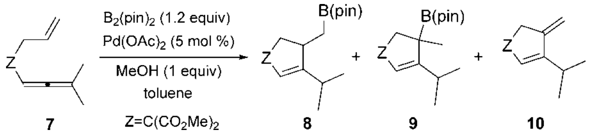
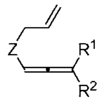
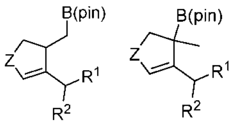
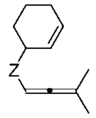
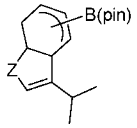
(19) Probably, the steric hindrance exerted by the ^{i}Pr and Cy substituents hampers the transmetalation on the exocyclic allylpalladium intermediate, being more favorable on the endocyclic species.

(20) We cannot rule out the presence of heterogeneous hydride-containing catalytic species in this step, due to the absence of stabilizing ligands and the formation of Pd-black during the reaction performance.

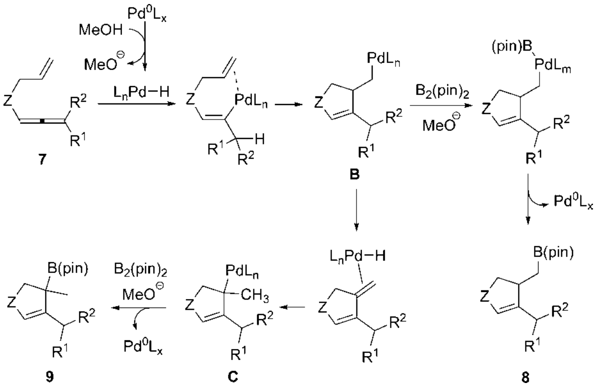
Table 2. Pd-Catalyzed Borylative Cyclization of Enallenes



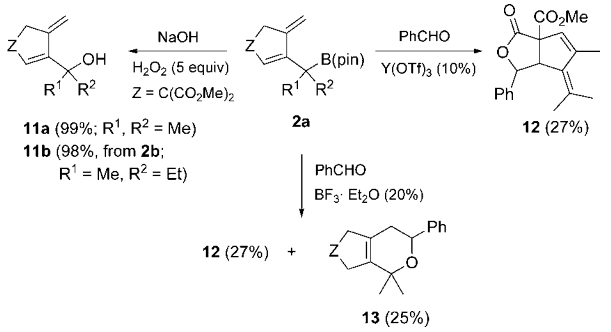
	substrate	temp (°C)	t(h)	isolated yield (%)[a] /ratio
		Z=C(CO$_2$Me)$_2$		
1	**7a** R^1 = R^2 = Me	70	3	63[b] **8a**:**9a**[c] (82:18)
2	**7b** R^1 = Me, R^2 = Et	50	16	61[b] **8b**:**9b**[c] (49:51)
3	**7c** 	50	7	60[d] **8c** 

[a] β-Elimination products **10a** and **10b** (see Supporting Information) were obtained in additional 20% yield each. [b] Yields calculated by NMR. [c] Approximate yield since these compounds contain pinacol resulting from decomposition. [d] The three regioisomers indicated were separated by column chromatography (see Supporting Information for yields and details).

Scheme 4. Proposed Reaction Pathway for Enallenes



Scheme 5. Oxidation and Allylboration Reactions of Allylboronates



pounds **10a**,**b**. The case of **7c** is special since the desired product **8c** is obtained along with regioisomeric alkylboronates located around the initial cyclohexene moiety, due to the possibility of consecutive β-hydrogen eliminations and reinsertions in this ring.

These results show the different reactivity between alkyne, allene, and alkene moieties regarding the hydropalladation process since alkynes are more reactive than allenes, and the latter are more reactive than alkenes.

With the aim of demonstrating the utility of these boronate compounds in further functionalizations, allylboronates **2a**,**b** were subjected to oxidation and to reaction with aldehydes in the presence of Lewis acids[21] (Scheme 5).

Thereby, alcohols **11a**,**b** were obtained in almost quantitative yields. Allylation reaction of benzaldehyde with **2a** in the presence of different Lewis acids [Y(OTf)$_3$ or BF$_3$•Et$_2$O] provided lactone **12** in low yields (ca. 27%) as a result of the intramolecular transesterification between the alcohol resulting from the allylation and one of the ester groups. Heterocyclic derivative **13** is also obtained when BF$_3$•Et$_2$O is used. This compound could be the result of a Lewis acid catalyzed hetero Diels−Alder reaction of the aldehyde with a conjugated diene formed by decomposition of the boronate. The optimization of this allylation reaction and other C−C bond-forming reactions with these allylboronates and alkylboronates is currently under active investigation.

In summary, we have developed a formal hydroborylative carbocyclization reaction of allenynes and enallenes in which formation of one C−C and one C−B bond affords allylboronates and alkylboronates under smooth conditions. In general, the process is regioselective. Oxidation of allylboronates and allylation of aldehydes can be performed on the boronates to obtain functionalized derivatives. The development of other applications of these boronates are currently in progress.

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Supporting Information Available: Experimental details, spectra for new compounds, and crystal structure determination of **2f** and **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Kennedy, J. W. J. Hall, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732–4739. See also ref 15.