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Pd-Catalyzed Borylative Cyclization of 1,6-Enynes

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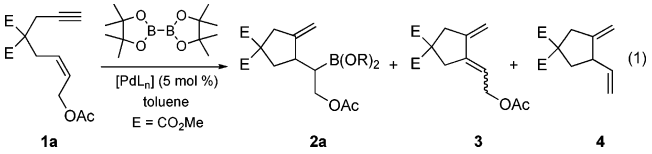
Enynes show a rich reactivity with many different metal catalysts and have been shown to evolve by different processes such as cycloisomerization,[1] skeletal rearrangements,[2] and alkoxy cyclization,[3] among others. Especially interesting are the cyclization reactions in which the dienes, diynes, or enynes react with bimetallic reagents of main group elements (M−M′; M, M′ = B, Si, Sn, etc.).[4] In these cases, the presence of carbon−heteroatom bonds is particularly useful for the further functionalization of the product. The formation of boron derivatives from unsaturated compounds provides more elaborated reagents that can be employed for synthetic purposes, with advantages due to low toxicity and high functional group compatibility. Herein we report a novel Pd-catalyzed cyclization reaction of 1,6-enynes in the presence of bis(pinacolato)diboron that provides homoallylic alkylboronates. Recent developments of the Suzuki−Miyaura cross-coupling reaction[5] allow the use of alkylboranes[6] or alkyltrifluoroborates[7] as nucleophilic partners. The synthesis of alkylboronates is usually performed by hydroboration of alkenes or reaction of main group organometallic derivatives with borate esters.[8,9] In the latter case, the reactions show low functional group compatibility. Recently, C−H activation of alkanes allows the preparation of primary alkylboronates.[10] The Pd-catalyzed reaction of bis(boron) compounds usually employed for the formation of aryl- and alkenylboron derivatives has not been applied to the preparation of alkylboronic acids or their derivatives to the best of our knowledge.

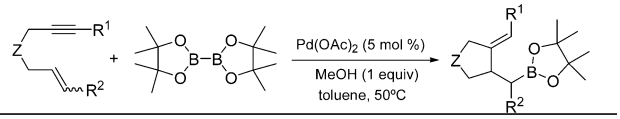
When enyne **1a** was reacted with bis(pinacolato)diboron in the presence of $Pd_2(dba)_3$·dba and PPh_3 in toluene, alkylboronate **2a** was obtained in low yield (ca. 20%), along with cycloisomerization derivative **3** and compound **4** in which the acetate group had been eliminated (eq 1). The formation of **2a** implies a formal 1,7-hydroboration of the enyne with concomitant carbocyclization, affording a C−C and a B−C bond in a single operation. Incorporation of H probably took place from traces of water contained in the solvent.

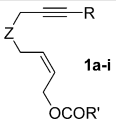
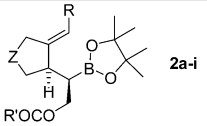
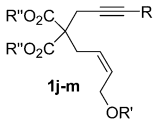
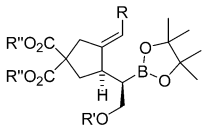
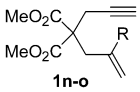
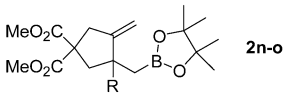
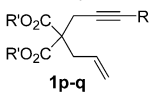
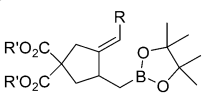


(1)

Optimization of the reaction conditions was performed by varying the solvent (toluene, dioxane, DMF), the precatalysts ($Pd_2(dba)_3$·dba, $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$), and some additives (NaOAc, *n*-Bu_4NF, or KF). It became apparent that the presence of phosphines or additives favored the formation of **3** and **4**. The best results for the formation of **2a** (65% yield) were obtained by using $Pd(OAc)_2$ (5 mol %) as precatalyst in dry toluene in the presence of 50 mol % of pinacol as a proton source. The use of MeOH (1 equiv) instead of pinacol led to similar yields and was preferred since separation is easier in the absence of free pinacol, and transesterification of the boronic ester does not take place. Compound **4** does not seem to form from **2a** since the latter did not decompose upon heating at 80 °C for 24 h in dry toluene even in the presence of $Pd(dba)_2$ (5%). In contrast, heating of **2a** in wet toluene gave diene **4**, probably by concerted elimination of the acetate and the boronic acid resulting from hydrolysis.

Table 1. Pd-Catalyzed Cyclization−Borylation of Enynes



	substrate	t (h)	product	yield (%)
	 **1a-i**		 **2a-i**	
1	**1a**	2.5	**2a :** Z = $C(CO_2Me)_2$, R = H, R' = Me	59
2	**1b**	3	**2b :** Z = $C(CO_2Me)_2$, R = H, R' = Ph	76
3	**1c**	3	**2c :** Z = $C(SO_2Ph)_2$, R = H, R' = Me	47
4	**1d**	5	**2d :** Z = $C(SO_2Ph)_2$, R = H, R' = Ph	47
5	**1e**	2.5	**2e :** Z = NTs, R = H, R' = Me	30
6	**1f**	4	**2f :** Z = $C(CO_2Et)_2$, R = Me, R' = Me	95
7	**1g**	84[a]	**2g :** Z = O, R = Me, R' = Me	21[b]
8	**1h**	3.5	**2h :** Z = $C(CO_2Me)_2$, R = Ph, R' = Me	81
9	**1i**	50[a]	**2i :** Z = $C(CO_2Et)_2$, R = $SiMe_3$, R' = Me	79
	 **1j-m**		 **2j-m**	
10	**1j**	24[c]	**2j :** R = Me, R' = Me, R'' = Et	80
11	**1k**	4	**2k :** R = Me, R' = CH_2Ph, R'' = Et	93
12	**1l**	3	**2l :** R = Ph, R' = Me, R'' = Me	77
13	**1m**	3	**2m :** R = Ph, R'= CH_2Ph, R '' = Me	71
	 **1n-o**		 **2n-o**	
14	**1n**	3	**2n :** R = Me	75
15	**1o**	3.5	**2o :** R = H	78
	 **1p-q**		 **2p-q**	
16	**1p**	6	**2p :** R = Me, R' = Et	93
17	**1q**	70[a]	**2q :** R = Ph, R' = Me	86

[a] Additional $Pd(OAc)_2$ (5 mol %) and MeOH (1 equiv) were added after 24 h (for entry 7, no MeOH was added). [b] Only 68% conversion was observed. Oligomers from **1g** seem to be formed. [c] As in footnote *a* but after 9 h.

We reasoned that the presence of a coordinating group on the allylic position and the presence of the exocyclic alkene would hamper *β*-hydride elimination in the putative intermediates, and we extended the reaction to related substrates. Thus, acetates and benzoates **1a**−**i** gave the corresponding alkylboronates in good to excellent yields, except for ether **1g** and amide **1e**. Single crystals

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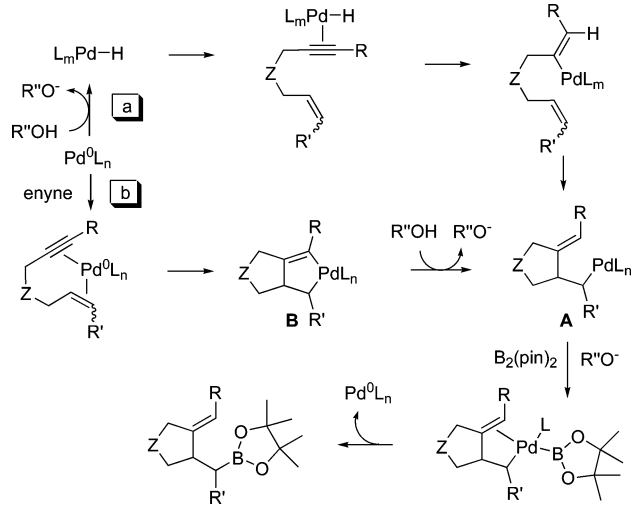
Scheme 1. Possible Mechanistic Pathways

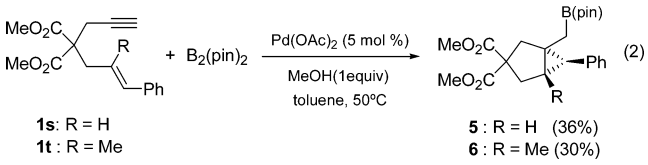


of benzoate derivative **2b** suitable for X-ray diffraction allowed us to assign the relative configuration for the new stereogenic centers. The reaction of (*E*)-**1a** and (*E*)-**1b** showed the process to be stereospecific. Internal alkynes afforded the best results (entries 6, 8, 10, 11, 16, and 17) even for the hindered **1i**, regardless of the substitution in the allylic position. The reaction gives exclusively *E* alkenes. Allyl ethers **1j**−**m** gave very good yields. To our delight, substrates containing hydrogens susceptible of elimination but not coordinating groups also afforded the expected boronates in high yields (entries 15−17). This significantly widens the reaction scope.[11]

We propose that the reaction takes place through the pathway outlined in Scheme 1. Reduction of precatalyst affords catalytically active Pd(0) species.[12] Oxidative addition of bis(boronates) to Pd(0) or metathesis with Pd−alkyne complexes has been calculated to be disfavored[13] and does not seem probable. Instead, formation of a Pd hydride by protonation with the alcohol followed by insertion of the alkyne into de Pd−H bond would account for the observed alkene stereochemistry (pathway a).[14] Alternatively, intermediate **A** could be formed by sequential coordination of the enyne to Pd(0), oxidative cyclometalation to give metalacycle **B**, and subsequent protonolysis of the Pd−C(sp^2) bond (pathway b).[15] Both mechanistic possibilities are consistent with the stereochemistry of the new stereogenic centers.[16] Nevertheless, previous calculations showed a high activation energy for the oxidative cyclometalation of enynes.[17] Transmetalation of **A** with bis(pinacolato)diboron promoted by alkoxide followed by reductive elimination would give the final product and regenerate the Pd(0) catalyst. It is important to note that transmetalation seems to be faster than β-hydride and β-oxygen eliminations. Probably, in the "ligandless" conditions in which the reaction takes place, intramolecular coordination of the alkene in intermediate **A** prevents the adoption of the required conformation for this elimination to take place. This fact contrasts with Suzuki cross-coupling reactions of substrates containing β-hydrogens which have been achieved by a precise control of the electronic and steric properties of phosphine ligands.[6b]

Interestingly, aryl alkenes **1s** and **1t** gave cyclopropyl derivatives **5** and **6**, respectively, although in low yields (eq 2). Migration of the metal atom in the homoallylic system by 1,2-insertion in intermediate **A** would explain this result.[18]

In summary, we have developed a new cyclization reaction for the stereoselective synthesis of homoallylic alkylboronates with a wide scope, in smooth conditions, and compatible with a wide variety of functional groups. Studies on the functionalization of these derivatives are currently in progress.



1s: R = H
1t : R = Me

5 : R = H (36%)
6 : R = Me (30%)

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Note Added after ASAP Publication: An author's surname and eq 1 were corrected on February 6, 2007.

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.

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(11) Moreover, crotyl derivative related to **1a** (with H instead of AcO) afforded the corresponding alkylboronate in ca. 75% yield (^{1}H NMR), but the presence of inseparable byproducts prevented purification.
(12) Reduction of $Pd(OAc)_2$ to Pd(0) is a facile process that may be promoted by β-elimination from the acetate ligand or the alcohol or by double transmetalation from bis(pinacolato)diboron.
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(18) Cyclopropyl derivatives could be involved in the formation of compounds **2**. Mechanistic studies are in progress.

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