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Ligand-controlled divergent formation of alkenyl- or allylboronates catalyzed by Pd, and synthetic applications

Alicia Martos-Redruejo, Ruth López-Durán, Elena Buñuel, and Diego J. Cárdenas[*a]

The use of different ligands allows the preparation of either allyl- or alkenylboronates by Pd-catalyzed borylation of allylic carbonates containing alkyne groups. Unprecedented borylative cyclisation to alkenylboronates takes place with 10 PCy₃. The difficult dissociation of NHC ligands allows borylation of carbonates in the presence of alkynes. Oxidation, regioselective Suzuki couplings, as well as Au-catalyzed cycloisomerisation of boronates illustrate the potential synthetic applications of these reactions.

15 Boronates are important synthetic reagents. They are stable, compatible with most functional groups and environmentally friendly, tolerating oxygen and water. A wide variety of boronates can be used as nucleophilic partners in Suzuki cross-coupling reactions; and allylboronates are reactive towards 20 aldehydes and imines, to cite just the most common uses of these compounds.[1] For that reason, the development of methods for the preparation of boronates, avoiding the use of highly nucleophilic and basic reagents is of main interest. On the other hand, enynes constitute versatile starting materials for the formation of carbo 25 and heterocycles,[2] skeletal rearrangements,[3] and alkoxy-cyclisation,[4] among other reactions. During the last few years, Pd-catalyzed borylative cyclisation reactions of polyunsaturated species have been developed by our group[5-9] and Bäckvall's,[10] with the aim of preparing cyclized boronates. Our seminal work 30 described an unprecedented preparation of homoallylic boronates starting with 1,6-enynes, in which esters substituting the allylic position were tolerated (Figure 1, top).[5,11] In our previous studies, addition of ligands precluded the incorporation of the boron substituent. Now, we have found conditions in which the choice 35 of the appropriate ligand allows control of the borylation of alkyne–containing allylcarbonates, affording simple Miyaura coupling to allylboronates, or unprecedented formation of *alkenylboronates* by borylative cyclisation, a method which is complimentary with alkyne hydroboration and the usual reactions 40 of strongly basic Li and Mg nucleophiles with B(OMe)₃.

Thus, we started our study by reacting enynes containing an allylic carbonate group (**1**). In our previous work mentioned above,[5] we reported that reactions of acetates or other ester derivatives, under ligandless conditions, took place without 45 activation of the C-O bond, leading to homoallylic boronates containing the unreacted ester group (Scheme 1, top). Reactions in the presence of phosphines led to simple cycloisomerisation
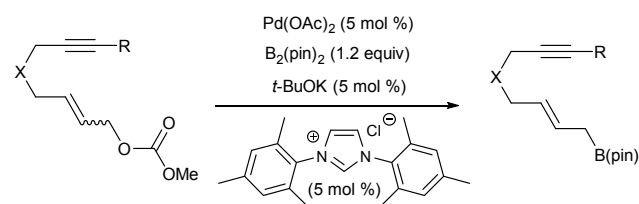
without incorporation of boryl group.
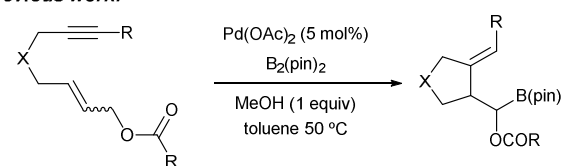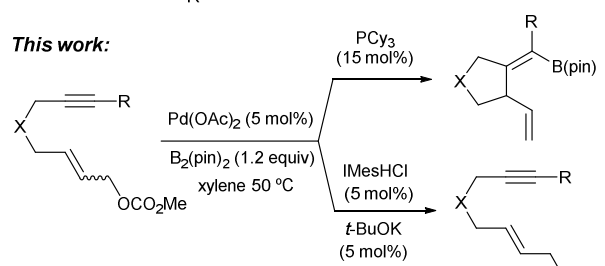
50 Scheme 1. Pd-catalyzed borylation reactions of substituted 1,6-enynes

In contrast, reaction of carbonates **1a-l** with B₂(pin)₂ in the presence of Pd(OAc)₂ and IMes ligand (formed in situ by deprotonation of the imidazolium chloride with *t*-BuOK) in 55 xylene, afforded the corresponding allylboronates (Table 1). The reaction is fast (less than 30 min) and takes place under smooth conditions (50 °C) in the absence of added base, as usual for carbonates. A variety of starting compounds showing different tethering groups between the alkene and the alkyne (malonate 60 and NTs) were used. The allylboronate product always shows (*E*) configuration on the alkene, regardless the configuration of the double C-C bond on the starting material (see Table 1: entries 1-2, 3-4, and 5-6). Terminal alkynes gave complex reaction mixtures, probably for the occurrence of other reactions, but the 65 reaction could be extended to alkyl, aryl and TMS substituted alkynes. Phenyl substituted alkynes provided lower yields (entries 3 and 4), but *p*-MeO-phenyl derivative **1i** gave the corresponding boronate **2i** in high yield (entry 9). The presence of the triple bond is compatible with these reaction conditions, the alkyne 70 remaining unreacted. Finally, compounds **1k** and **1l** also afforded the desired products, as expected for these simpler reagents. In summary, this constitutes a Miyaura reaction for the formation of allylboronates in smooth conditions and in the presence of internal alkynes.[12]
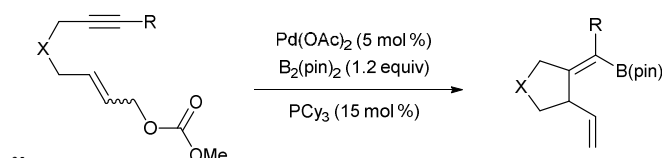
Table 1. Pd-Catalyzed formation of allylboronates

Pd(OAc)₂ (5 mol %)
B₂(pin)₂ (1.2 equiv)
t-BuOK (5 mol %)
(5 mol %)

detected in low yields in mixtures that could not be separated. A TMS-substituted product (**3q**) could be obtained again, in spite of the presence of alkoxide in the reaction medium.
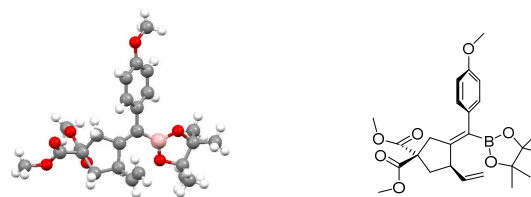
Table 2. Pd-Catalyzed borylative cyclisation to alkenylboronates

Pd(OAc)₂ (5 mol %)
B₂(pin)₂ (1.2 equiv)
PCy₃ (15 mol %)

Entry	Reagent	Product	(%)
1	**1a** : (*E*) X = C(CO₂Me)₂, R = Me	**2ab**	54
2	**1b** : (*Z*) X = C(CO₂Me)₂, R = Me	**2ab**	71
3	**1c** : (*E*) X = C(CO₂Me)₂, R = Ph	**2cd**	30
4	**1d** : (*Z*) X = C(CO₂Me)₂, R = Ph	**2cd**	47
5	**1e** : (*E*) X = NTs, R = Me	**2ef**	78
6	**1f** : (*Z:E*; 1:1.4) X = NTs, R = Me	**2ef**	63
7	**1g**[a] : (*E*) X =NTs, R = TMS	**2gh**	69
8	**1h** : (*Z:E*; 0.4:1) X = NTs, R = TMS	**2gh**	67
9	**1i** : (*Z*) X = NTs, R = *p*-MeO(C₆H₄)	**2i**	72
10	**1j**	**2j**	37
11	**1k**	**2k**	70
12	**1l**	**2l**	59

Reaction conditions: xylene mixture, 50℃, 25 min. a) Contains 9% of *Z* isomer.

entry	Reagent	Product	(%)
1	**1a** : (*E*) X = C(CO₂Me)₂, R = Me	**3ab**	72[a]
2	**1b** : (*Z*) X = C(CO₂Me)₂, R = Me	**3ab**	71[b]
3	**1c** : (*E*) X = C(CO₂Me)₂, R = Ph	**3cd**	26
4	**1d** : (*Z*) X = C(CO₂Me)₂, R = Ph	**3cd**	18
5	**1e** : (*E*) X = NTs, R = Me	**3ef**	71
6	**1f** : (*Z*) X = NTs, R = Me	**3ef**	61
7	**1m** : (*E*) X = C(CO₂Me)₂, R = *p*-MeO(C₆H₄)	**3mn**	68[a]
8	**1n** : (*Z*) X = C(CO₂Me)₂, R = *p*-MeO(C₆H₄)	**3mn**	37[a]
9	**1o** : (*Z*) X = NTs, R = H	**3o**	53
10	**1p** : (*E*) X = C(SO₂Ph)₂, R = Me	**3p**	73[c]
11	**1q** : (*E*) X = C(SO₂Ph)₂, R = TMS	**3q**	56[d]

Reaction conditions (unless otherwise stated): xylene mixture, 50℃, 8 h. a) Reaction performed in 1,4-dioxane; b) 1,4-dioxane, 110℃, 2.5 h; c) Pd(OAc)₂, 15 mol % (65 % with 5 mol%); d) 130℃, 40 min


Figure 1. Crystal structure of **3mn**

Interestingly, when the reaction was performed in the presence of Pd(OAc)₂ and PCy₃ as ligand, a completely different outcome was observed. A novel borylative cyclisation led to alkenylboronates **3**, isomers of the above mentioned allylboronates (Table 2). The reaction gives rise to the formation of one C-C and one C-B bond in a single operation with formation of five member carbo- or heterocycles.[13] This process is stereoselective, affording a single configurational isomer of the alkenylboronate. Crystal structures of **3mn** (Figure 1) and **3p** (ESI) confirmed the stereochemistry of the new C-C double bond. Again, the reaction shows a broad scope, and more interestingly, terminal alkyne **1o** also gave the corresponding product. Bis(phenylsulfonyl)methane derivatives also afforded the expected compounds in good yields, in contrast to the observed in the conditions in Table 1: allylboronates from bis(sulfonyl) were

A mechanistic rationale for the formation of allyl- or alkenylboronates is depicted in Scheme 2. We propose reduction of the precatalyst to Pd(0) followed by oxidative addition of the allyl carbonate and decarboxylation to give allyl complex **A**. If a fast transmetalation process takes place, boryl-Pd intermediate **B** would evolve to the allylboronate by regioselective C-B reductive elimination, and a catalytically active Pd(0) species. Alternatively, coordination of the alkyne of complex **A** to give **C**, followed by carbometallation would provide alkenyl-Pd derivative **D**. Subsequent transmetalation leading to **E** and reductive elimination would generate the alkenylboronates. Noteworthy, hindered trialkylphosphines and NHC ligands usually confer similar properties to Pd complexes. Thus, activation of aryl chlorides, and inhibition of β–hydrogen elimination of alkyl-Pd intermediates in couplings can be achieved with both kinds of ligands.[14,15]
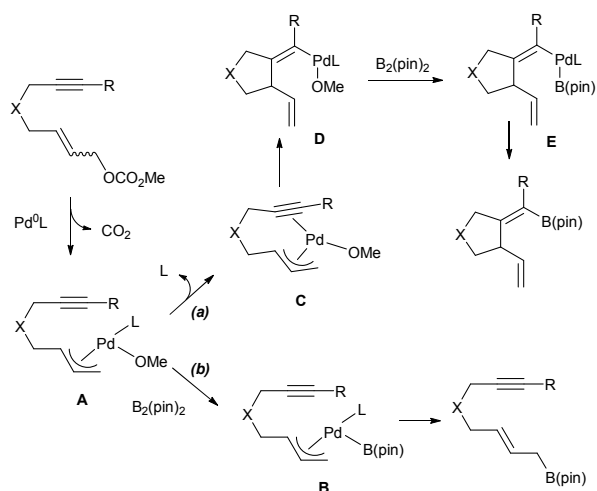
Scheme 2. Proposed reaction pathway for both reactions.

We hypothesised that the reason for the differential behavior observed for these ligands in the formation of boronates could be related to the ability to coordinate the alkyne to the allyl-Pd intermediate **A**. Thus, formation of **C** can only take place when a vacant coordination site is available. Therefore, dissociation of PCy$_3$ is necessary for this reaction to occur. In the presence of a highly stronger coordinating IMes, alkyne could not entry into the coordination sphere, and the carbometallation could not take place. DFT calculations on model complexes support this idea. As expected, NHC ligand dissociation is far more difficult and may hamper the insertion of the alkyne into the allyl-Pd complex (Scheme 3).

L	ΔG
IMes	18.7
PCy$_3$	4.2
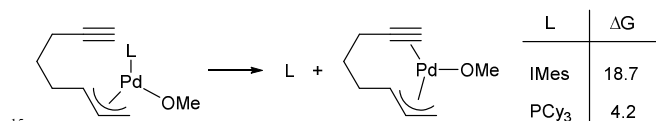
Scheme 3. Calculated ΔG of dissociation (kcal mol^{-1}). M06/6-31G(d) (C,N,O,H) LANL2DZ (Pd), PCM (xylenes mixture).

The boronates we have prepared can be used for a number of synthetic applications. Thus, **3ef** was subjected to oxidation conditions to give the corresponding ketone **4** (Scheme 4).[16]
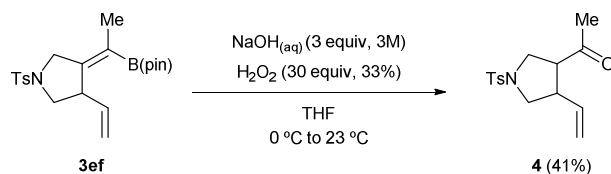
Scheme 4. Oxidation of an alkylboronate.

Some of the alkenylboronates (**3ab**, **3ef**, **3p**) were assayed in Suzuki reactions, affording the expected tetrasubstituted alkenes **5** in good yields, stereoselectively (Scheme 5).[17] No isomerisation to conjugated dienes was observed. Compound **5ab** could be more efficiently prepared by one-pot cyclisation of **1a** (Table 2), followed by cross-coupling in 63% yield over two steps.

On the other hand, Suzuki coupling of allylboronates **2** led to the regioselective formation of the branched derivatives **6** (Scheme 6), albeit in lower yields.[18,19]

3ab : X = C(CO$_2$Me)$_2$
3ef : X = NTs
3p : X = C(SO$_2$Ph)$_2$

**5ab** (72%)
5ef (57%)
5p (73%)
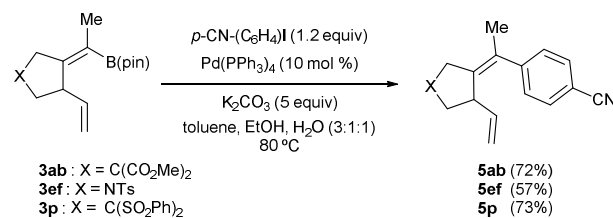
Scheme 5. Suzuki-Miyaura cross-coupling of alkenylboronates

The resulting compounds are 1,7-enynes, which have proved to be valuable synthetic intermediates.[20] Crystal structure of **6ef** can be found in the Supporting Information. The observed regioselectivity matches the observed for related couplings on allylboronates obtained by Pd-catalyzed cyclisation of dienynes. Buchwald has recently reported control on the regioselectivity of similar reactions by subtle differences on the ligands used.[21]

2ab : X = C(CO$_2$Me)$_2$, R = Me
2cd : X = C(CO$_2$Me)$_2$, R = Ph
2ef : X = NTs, R = Me

6ab (52%)
6cd (51%)
6ef (33%)
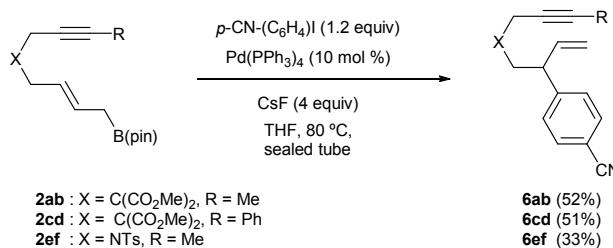
Scheme 6. Regioselective Suzuki coupling of allylboronates.

Finally, we would like to illustrate a potential interesting application of allylboronates. Terminal alkyne **7** was prepared by a different route, involving propargylation of allylboronate derived from malonate. Au-catalyzed cycloisomerisation afforded a mixture of two new isomeric allylboronates, which could not be separated. The observed mixture was expected, according to the previous work by Hall.[22] Regioselectivity is dependent on the reaction temperature. The high reactivity of cationic Au complexes in these processes allows lowering temperature to -78 °C, which favours formation of the six-member derivative (**8**:**9**, 1:3, Scheme 7). Useful reactions for the formation of allylboronates are expected to be developed with this approach.[23]

7 : X = C(CO$_2$Me)$_2$

8

9

(**8**:**9**)
72% (1:1), 23 °C
68% (1:3), -78 °C
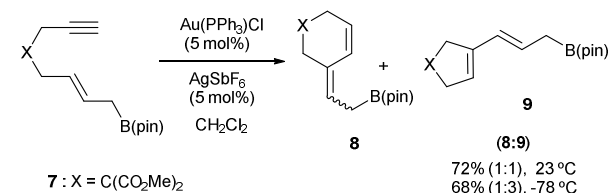
Scheme 7. Au-catalyzed cycloisomerisation reaction

In summary, a borylative cyclisation leading to alkenylboronates has been developed. The appropriate choice of ligand allows formation of allylboronates. Synthetic utility of these compounds has been illustrated, suggesting potential future applications.

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a Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Campus de Cantoblanco, 28049-Madrid, Spain. Fax: +34 914973966; Tel: +34 914974358; E-mail: diego.cardenas@uam.es

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