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Pd-catalyzed borylative cyclisation of 1,7-enynes†‡

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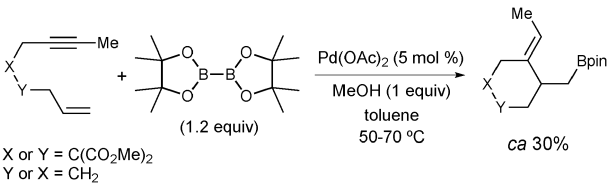
Reaction of a variety of 1,7-enynes with bis(pinacolato) diboron catalysed by Pd bis(trifluoroacetate) affords homoallylic and allylic boronates containing a six membered carbo- or heterocycle, by formation of C–C and C–B bonds

Enynes are versatile starting compounds for the metal-catalysed formation of carbocycles. Depending mainly on the catalyst, a wide variety of structures can be accessed. The reactivity of 1,6-enynes has been extensively studied during the last few years. In contrast, systematic studies on 1,7-enynes are not as abundant.[1] Cyclisation of 1,7-enynes can afford 5,[2] 6, 7,[3] and even 8[4] membered carbocycles. Reactions can be catalysed by complexes of several metals such as Pd,[5] Pt,[6] Au,[7] Ru,[8] Co,[9] Ga,[10] In,[11] Ti,[12] *etc.* In addition to the cycloisomerisation,[13] skeletal rearrangement,[14] and metathesis,[15] cascade reactions involving additional reagents can be powerful tools for the construction of complex molecules. Thus, 1,7-enynes have been described in processes involving alkoxycyclisation,[16] reaction with carbonyl compounds,[17] oxidation,[18] Pauson–Khand type reactions,[19] and carboxylation,[20] among others. We are especially interested in reactions in which the cyclisation is accompanied by the introduction of a main group element, in order to prepare carbon nucleophiles suitable for further functionalisation. In this respect, cyclisation of 1,7-enynes with concomitant silylation,[21] or borylstannylation,[22] has been reported.

Some years ago, we described a Pd-catalyzed borylative cyclisation of 1,6-enynes for the preparation of cyclopentane-derived homoallylic boronates in good yields, smooth conditions, and in the presence of functional groups, since there is no need to use highly nucleophilic and basic Li or Mg nucleophiles.[23] Cascade borylative polycyclisation of different enediynes,[24] and borylative cyclisation of enallenes and allenynes[25] allow the preparation of alkyl and allylboronates as well.

In this communication, we report the first borylative cyclisation of 1,7-enynes, which has remained elusive for years. Initial experiments under the optimised conditions for 1,6-enynes afforded the desired products in low yields.



This reaction leads to the formation of six-membered rings, and can be considered as a formal 1,8-hydroboration with concomitant cyclisation. Borylation takes place at the terminal alkene carbon of the starting enyne. The alkylboronate is prone to be used in subsequent transformations, what confers this reaction a high potential from a synthetic point of view. For this reason, we tried to find optimized conditions. An extensive study varying Pd catalysts, added ligands, solvents, reaction time and temperature led us to develop this reaction and to explore its scope. Interestingly, $Pd(TFA)_2$ resulted to be much more convenient compared with $Pd(OAc)_2$, and provided products in moderate to high yields. In general, reactions take place at higher temperature compared to 1,6-enynes, although they can be performed even at room temperature in some cases. Addition of different phosphines for the reaction of **1b** resulted in hydroboration of the alkyne in low yield.[26] As it can be seen in Table 1, the expected cyclic homoallylic boronates have been isolated for substrates containing a homopropargylic chain (**1a–1i**).

In general, internal alkynes afford higher reactions yields (entries 2, 4, 5, 11, 14 and 16) compared with terminal ones, and homoallylic boronates containing exclusively *E* alkenes are formed, as determined by NOESY experiments. Configuration of the double bond was confirmed in the crystal structure of compounds **2i** and **4g** (see ESI‡ for details). Substrates containing terminal alkenes, on the other hand, provide better results. The absence of substituents containing hydrogen atoms susceptible of being eliminated in the intermediate complexes is probably the reason for this behaviour. Thus, for substituted alkenes on the distal carbon (entries 6 and 7), more complex crude reaction mixtures, containing non-borylated cyclic products, were obtained. For homoallylic alkenes, sulfones afford better results compared with malonate derivatives, probably due to the lower coordinating ability of the former, as we will discuss below. Interestingly, the tether group has an influence on the reaction outcome when homoallylic substrates (**3a–h**) are subjected to the reaction conditions. Thus, sulfone derivatives **3f–g** experience again the regioselective formation of the expected cyclic boronates (**4f–g**). In contrast, malonate and tosylamide derivatives (**3a–e**) showed the formation of mixtures of

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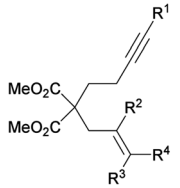
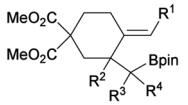
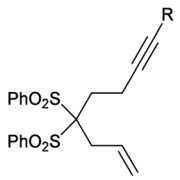
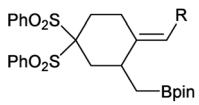
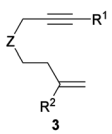
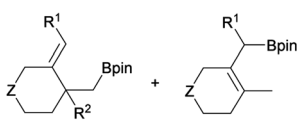
† Dedicated to the memory of our friend and colleague Dr G. Christian Claessens, who regretfully passed away last June 2012.

‡ Electronic supplementary information (ESI) available: Experimental procedures, data and computational details. CCDC 888322 and 888323. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc34468h

Table 1 Pd-catalyzed borylative cyclisation of 1,7-enynes (reaction conditions: $B_2(pin)_2$ (1.05 equiv.), $Pd(TFA)_2$ 5 mol%, MeOH (1 equiv.), toluene, [substrate] = 0.2 M, reaction times to completion are shown)

	Substrate	t(h)	T(°C)	Products	Yield (%)
					
1	**1a**	5	80	**2a** : $R^1 = R^2 = R^3 = R^4 = H$	44
2	**1b**	6		**2b** : R^1 = Me, $R^2 = R^3 = R^4 = H$	70
3	**1c**	4		**2c** : R^1 = Ph, $R^2 = R^3 = R^4 = H$	34[a,b]
4	**1d**	2		**2d** : R^1 = TMS, $R^2 = R^3 = R^4 = H$	70
5	**1e**	2		**2e** : $R^1 = R^2$ = Me, $R^3 = R^4 = H$	55
6	**1f**	26		**2f** : $R^1 = R^4$ = Me, $R^2 = R^3 = H$	13[b]
7	**1g**	21		**2g** : R^1 = Me, $R^2 = R^4 = H$, R^3 = = CH_2OAc	22[c]
					
8	**1h**	18	80	**2h** : $R^1 = R^2 = R^3 = R^4 = H$	47
9	**1i**	2		**2i** : R^1 = Me, $R^2 = R^3 = R^4 = H$	59
	 **3**			 **4** **5**	
10	**3a**	1	50	**4a** : **5a** (67:33) Z = $C(CO_2Me)_2$, R^1 = = $R^2 = H$	55
11	**3b**	2	50	**4b** : **5b** (65:35) Z = $C(CO_2Me)_2$, R^1 = Me, $R^2 = H$	75
12	**3c**	30	80	**4c** : **5c** (67:33) Z = $C(CO_2Me)_2$, R^1 = Ph, $R^2 = H$	38[d]
13	**3d**	6	50	**4d** : **5d** (77:23) Z = NTs, $R^1 = R^2 = H$	20
14	**3e**	24	50	**4e** : **5e** (90:10) Z = NTs, R^1 = Me, $R^2 = H$	59
15	**3f**	7	20	**4f** Z = $C(SO_2Ph)_2$, $R^1 = R^2$ = H	60
16	**3g**	4	20	**4g** Z = $C(SO_2Ph)_2$, R^1 = Me, $R^2 = H$	77[a,e]
17	**3h**	22	50	**4h** Z = NTs, $R^1 = R^2$ = Me	51

[a] 10 mol% of $Pd(TFA)_2$. [b] Yield from the ^1H NMR spectrum. [c] Non-borylated cyclic compounds were also formed. [d] 1.05 equiv. of $B_2(pin)_2$ and 5 mol% of $Pd(TFA)_2$ were additionally added after 22.5 h. [e] When 5 mol% of $Pd(TFA)_2$ was used, conversion was 92% and the product was isolated in 74% yield.

two different isomers (**4** and **5**) in a 3 : 1 to 9 : 1 ratio depending on the substrate. Compounds **5** are again cyclic boronates, and in this case the boryl group binds to the alkyne terminal carbon of the starting enyne, and the newly formed C–C double bond is endocyclic. Lower temperature favours the formation of derivatives **4a–e**, but conversion is not complete. Although isomers could not be separated by column chromatography, GC-MS analysis allowed us to obtain separate mass spectra. For the formation of compounds **2** and **4**, we propose the pathway outlined in Fig. 1. The reaction probably starts by reduction of precatalyst to Pd(0) and formation of a Pd hydride by protonation with the alcohol.

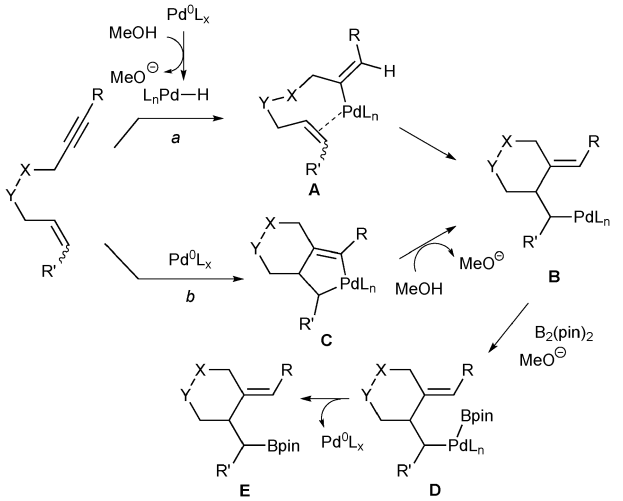


Fig. 1 Proposed reaction pathway for the borylative cyclisation.

The hydride evolves by insertion of the alkyne into the Pd–H bond, which would account for the observed alkene configuration. Alternatively, intermediate **B** could be formed by oxidative cyclometalation of the enyne to give **A**, followed by protonolysis of the alkenyl–Pd bond. Transmetalation reaction with $B_2(pin)_2$, which could be assisted by methoxide released upon Pd–H formation, and subsequent reductive elimination lead to the final product. β-Hydrogen elimination involving the side chain R′ in intermediate **D** is in accord with the lower yields observed in some cases. Elimination of the hydrogen of methyne groups is not observed for intermediates with X = CH_2.

Formation of derivatives **5** can be explained by β-elimination of H from intermediates of type **F** to give **G** (Fig. 2). Subsequent hydrometalation from **G** with the opposite regioselectivity would afford allyl complex **H**. In the absence of added ligands, η^3-allyl complexes **I** are probably formed. Again, transmetalation with the diboron reagent followed by reductive elimination would give rise to the final product.

We tried to get insight into the reasons for the different behaviour observed for substrates containing a homoallylic chain with malonate as tether. In these cases, β-hydrogen elimination seems to take place easily, in contrast to those substrates containing a homopropargyl chain, and/or sulfone as a connecting group between both unsaturated moieties. We hypothesised that the different coordinating ability of malonate and sulfone, and the relative position to Pd in intermediates **B** could be the reason. DFT calculations have been used to determine the relative energies of intermediates formed by

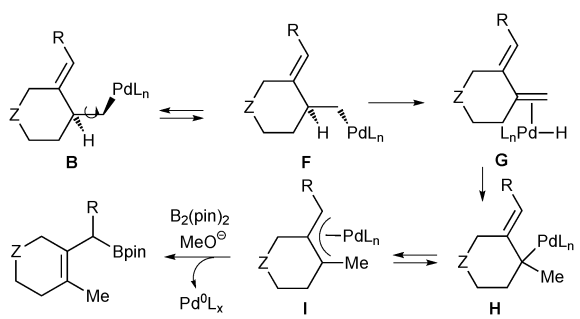


Fig. 2 A feasible reaction pathway for the formation of compounds **5**.

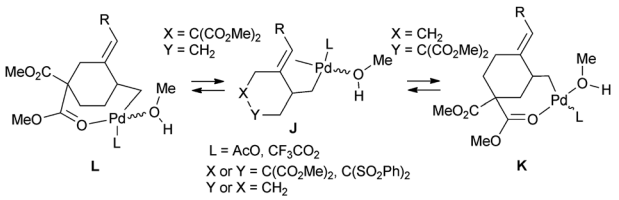


Fig. 3 Intermediate Pd complexes studied by DFT calculations.

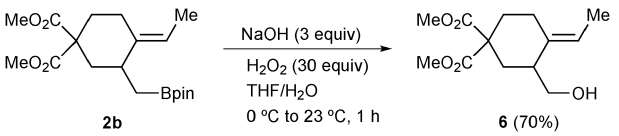


Fig. 4 Oxidation of boronate **2b** to the corresponding alcohol.

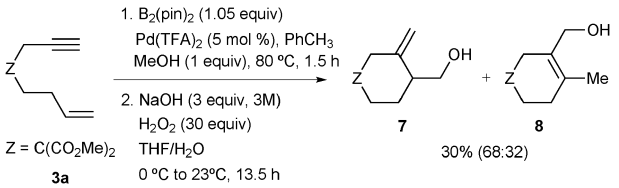


Fig. 5 Borylative cyclisation and oxidation of **3a**.

cyclisation in which either the new alkene or the substituent group (sulfone or malonate) coordinates to Pd (Fig. 3, see ESI‡ for details). After alkene carbometalation, intermediates **J** are expected to be formed. Ligand exchange processes should be associative, involving external ligand attack. Assuming fast ligand exchange, activation energies are not relevant.

We have found that intermediates **J** are the most stable ones for sulfones, whereas malonate groups in either two possible positions are able to displace the alkene to give complexes **K** or **L**. Once the alkene is dissociated, a free vacant site necessary for the elimination can be generated. Sulfones cannot give this process and therefore are stable enough and afford a single isomer. On the other hand, intermediates **K** (from homopropargyl substrates) are far more stable than **L**, compared to the respective alkene complexes **J**, and may constitute a thermodynamic sink precluding formation of coordinatively unsaturated intermediates. Lability of intermediates **L** would explain β-hydrogen elimination for those substrates and the formation of compounds **5**.

The boronates we have obtained can be used for synthetic purposes. As an example, oxidation of **2b** afforded primary alcohol **6**, which could not be prepared from enynes by hydroxycyclisation (Fig. 4).

Oxidation can be performed on the reaction crude without previous isolation of boronates. Thus, the following sequence afforded the expected mixture of alcohols **7** and **8** in the same ratio observed for the borylative cyclisation (Fig. 5).

In conclusion, we have developed a general borylative cyclisation of 1,7-enynes to homoallylic and allylic boronates containing six-membered ring under smooth conditions compatible with the presence of functional groups. The products can be further functionalised and constitute useful synthetic intermediates.

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