Synthetic Methods

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Palladium-Catalyzed Oxidative Borylative Carbocyclization of Enallenes**

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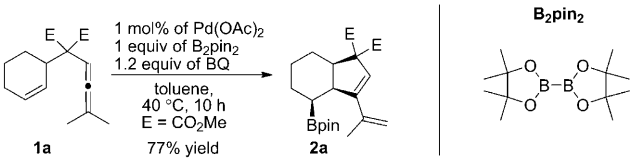
Carbocyclization reactions[1] constitute an important class of chemical transformations as there are many naturally occurring substances that contain a carbocyclic backbone.[2] New and efficient methods concerning carbocyclizations are greatly needed by the synthetic community. When constructing these new ring systems it is often desirable to generate appropriate chemical handles where subsequent chemical transformations can be achieved in a selective manner. Organoboronate compounds are versatile chemical handles and these functional groups can be used to create new valuable C–C bonds, for example through Suzuki–Miyaura cross-coupling procedures.[3] Formation of C–B bonds can be achieved through a variety of different routes,[4] a few of the more recognized approaches being the Brown hydroboration[5] and the palladium-catalyzed Miyaura borylation.[6] In addition there is a range of related and highly efficient transition-metal-catalyzed C–H borylation[7] processes based on palladium[8] and iridium.[9]

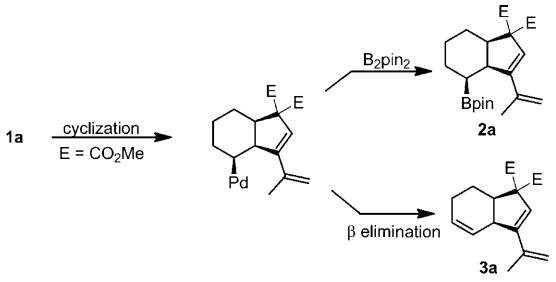
Oxidative C–C bond-forming reactions have recently attracted attention[10–12] and our research group has previously been involved in the development of various oxidative palladium-catalyzed carbocyclizations of ene- and diene-allenes.[12] In many of these carbocyclizations new C–C bonds are formed selectively using molecular oxygen as the terminal oxidant, thereby making the transformations more environmentally friendly.[13] Palladium-catalyzed carbocyclization in combination with borylation has so far attracted rather limited attention. The group of Cárdenas recently demonstrated an elegant non-oxidative palladium-catalyzed borylative cyclization of enynes and enallenes employing bis(pinacolato)diboron (B_2pin_2) as the borylating agent. In this case alkylboronate derivatives were obtained with high selectivity in good to high yields.[14]

Inspired by these results we envisioned a palladium-catalyzed oxidative carbocyclization/borylation procedure. Herein, we report that enallenes **1** undergo a stereoselective oxidative borylative carbocyclization to give products **2** (Scheme 1). In preliminary experiments we observed that treatment of **1a** with 5 mol% of $Pd(OAc)_2$, 1 equivalent of



Scheme 1. Oxidative borylative carbocyclization of enallene compounds. Yield of isolated product is shown.

B_2pin_2, and 1.5 equivalent of BQ in THF gave 40% yield (based on ^1H NMR analysis, with anisole as the internal standard) of the borylated carbocycle **2a** together with 8% of the side product **3a**, where β-hydride elimination from the σ-alkylpalladium intermediate had occurred (Scheme 2).[12e]



Scheme 2. Cleavage of the Pd–C bond by a boron-containing reagent vs. β elimination.

Encouraged by these results we set out to investigate the role of the solvent. These results clearly demonstrated that the solvent is crucial for the selectivity between **2a** and **3a**. Toluene is by far the most effective solvent for this transformation, resulting in 70% of **2a** and only 5% of **3a**.[15] Other solvents such as acetone and acetonitrile showed overall poor selectivities between **2a** and **3a**. Once toluene was established as the most effective solvent we briefly studied the influence of the palladium(II) source. Thus, $Pd(OAc)_2$ proved to be superior to $Pd(OOCCF_3)_2$ and most other Pd^{II} salts (e.g. $[PdCl_2(CH_3CN)_2]$ or $[Pd(acac)_2]$) showed none or little activity.

The amount of catalyst could be lowered to as little as 1 mol% without any loss in yield or selectivity simply by

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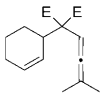
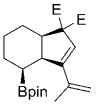
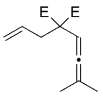
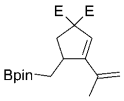
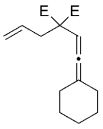
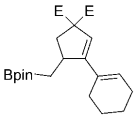
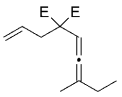
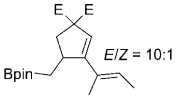
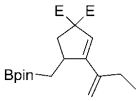
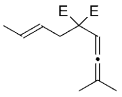
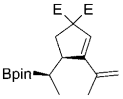
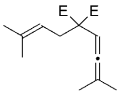
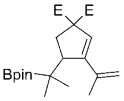
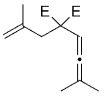
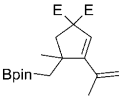
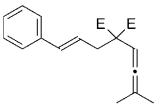
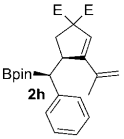
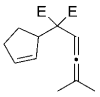
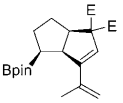
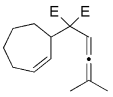
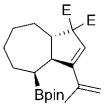
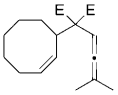
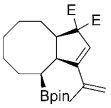
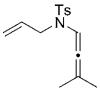
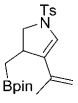
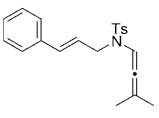
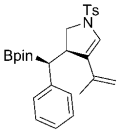
extending the reaction time to 10 hours. In an attempt to further suppress the formation of the β-elimination product (**3a**) the reaction was conducted at different temperatures with 1 mol% of $Pd(OAc)_2$ in toluene. At 80°C, a mixture of **2a**/**3a** was obtained in a 1:1 ratio. Lower temperatures produced significantly less **3a** but at room temperature the reaction was too slow and it proved difficult to obtain full conversion. Finally, 40°C was found to be the optimal temperature both with respect to by-product formation and conversion (Scheme 1).

During the course of our optimization we consistently used 1 equivalent of B_2pin_2 as this must be considered a relatively valuable reactant.[15] Addition of excess BQ (1.5 equiv) did not improve the reaction as the yields were slightly lower or comparable to when 1.2 equivalent was used. In a final attempt to improve the reaction, 1 equivalent of various additives were introduced: NaOAc, HOAc, and H_2O. Of these additives only water resulted in a minor increase of the reaction rate, whereas the other additives did not have any significant effect on the transformation. This outcome also demonstrates that the reaction is relatively robust, thus allowing it to be carried out without tedious exclusion of air and/or moisture.[16]

Once suitable reaction conditions were found we investigated the scope of the reaction (Table 1). Enallenes **1a**–**1k** were prepared according to literature procedures[12b,e] and subjected to the optimal conditions: 1 mol% of $Pd(OAc)_2$, 1.2 equivalent of BQ and 1.0 equivalent of B_2pin_2 in toluene at 40°C for 10 hours. In most cases the reactions proceeded smoothly. However, introduction of a second substituent on the olefin (**1f**) had a negative effect on the reaction outcome and only around 25% conversion was achieved after 36 hours and the β-elimination product (**3f**, see the Supporting Information) was obtained as the major product. Also, despite our best efforts we were unable to purify the desired product (**2f**) by column chromatography on silica gel.

Importantly, we did not detect any side products arising from palladium(0) catalysis;[17] such processes have been reported previously by the research groups of Morken[18] and Cárdenas.[14] Cyclic enallenes **1a**, **1i**, **1j**, and **1k** afforded products with stereospecific *cis* addition of the elements of carbon and boron to the alkene bond (Table 1, entries 1, 9–11). The stereochemistry of these compounds was established by coupling-constant analysis in combination with NOE interactions. The structure of **2a** was also confirmed by X-ray crystallographic analysis and the structure is illustrated in Figure 1.[19] Substrates containing monosubstituted olefins (**1b**–**1d**) gave primary alkylboronates (**2b**–**2d**) in fair to good yields. When the two alkyl groups on the allene are different (e.g. **1d**) there is a moderate selectivity in the formation of the conjugated diene (3:1 for **2d**, entry 4) owing to the low regioselectivity in the activation of the allene. Notably, the procedure appears to be most effective with olefins having a substituent at the internal carbon atom. For example, enallene **1g** cyclized to produce carbocyclic alkylboronate **2g** with one new quaternary carbon atom in 86% yield (entry 7). This result is easily rationalized by the fact that the σ-palladium(II) intermediate lacks the presence of a β-hydrogen atom, hence transmetalation can proceed smoothly without this competing

Table 1: Palladium-catalyzed oxidative borylative carbocyclization.[a]

Entry	Enallene	Product	Yield [%][b]
1	**1a** 	**2a** 	77
2	**1b** 	**2b** 	78
3	**1c** 	**2c** 	68
4	**1d** 	**2d**[c]  *E*/*Z* = 10:1 **2d′** 	60[d]
5	**1e** 	**2e** 	58
6	**1f** 	**2f** 	5[e,f]
7	**1g** 	**2g** 	86
8	**1h** 	**2h** 	64[g]
9	**1i** 	**2i** 	89
10	**1j** 	**2j** 	63[h]
11	**1k** 	**2k** 	62[h]
12	**5a** 	**6a** 	71[i]
13	**5b** 	**6b** 	60[i]

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol%), B_2pin_2 (1.0 equiv), BQ (1.2 equiv), toluene (0.1 mmol mL^{-1}), 40°C, 10 h. [b] Yield of isolated product after column chromatography on silica gel. [c] *E*/*Z* = 10:1. [d] **2d**/**2d′** = 3:1. [e] Full conversion could not be achieved within 36 h. [f] Determined by ^{1}H NMR analysis of the crude reaction mixture. [g] **1h** consists of an inseparable mixture of allene/alkyne (1:1.6) where the alkyne does not react during catalysis. [h] 20 h reaction time. [i] For reaction parameters see Scheme 4. Ts = 4-toluenesulfonyl.

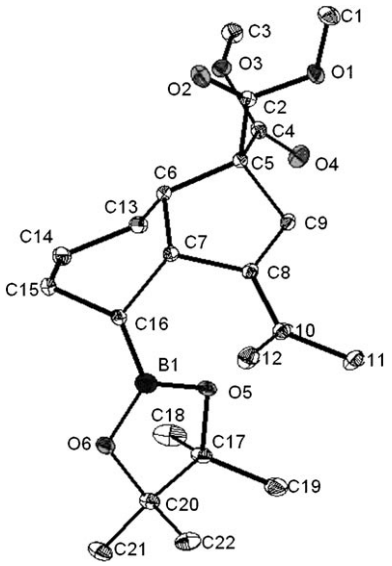
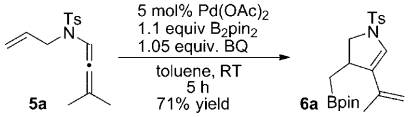


Figure 1. DIAMOND drawing of **2a**.[21] The thermal ellipsoids are drawn at 30% probability and hydrogen atoms are omitted for clarity.



Scheme 3. Borylative carbocyclization of aza-enallene compounds. Yield of isolated product is shown.

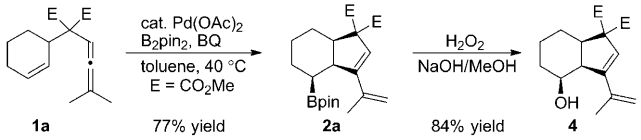
pathway. Enallenes substituted at the end (*E*) of the olefin (entries 5 and 8) also gave a stereospecific *cis* carboborylation of the double bond. Increasing the ring sizes of the olefin did seem to have a slightly negative effect on the yield (entries 10 and 11). The seven- and eight-membered ring, **1j** and **1k**, resulted in borylated products in 63% and 62% yield, respectively. Also, we again observed that **2j** formed as the *trans*-5,7-fused bicyclic ring. This outcome is consistent with our previous findings.[12e,20]

In most cases studied, the borylated carbocycles **2a**–**2k** (with the exception of **2f**) were isolated using standard chromatography techniques without any substantial (if any) degradation.[22]

Finally, to further increase the scope of this novel transformation we attempted to adapt this reaction to include aza-enallenes,[23] a substrate class previously used in effective oxidative carbocyclizations.[12a] Indeed these substrates also proved suitable for a borylative carbocylization (entries 12 and 13).

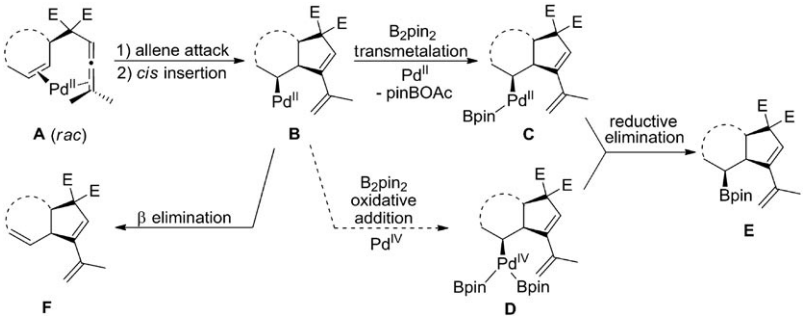
Treatment of **5a** with 5 mol% of $Pd(OAc)_2$ together with 1.1 equivalents of B_2pin_2 and 1.05 equivalents of BQ at room temperature gave the cyclized hydropyrrole **6a** in 71% yield (entry 12 and Scheme 3). When this reaction was run under the standard conditions outlined in Table 1 large amounts of Diels–Alder product (**7**, see the Supporting information) was formed between **6a** and unreacted BQ. By lowering the temperature of the reaction and decreasing the amount of BQ to 1.1 equivalent this side product could be depressed and **6a** was isolated in 71% yield. In the same manner aza-allene **5b** afforded **6b** (entry 13).

To demonstrate the usefulness of alkylboronate compounds we conducted an oxidation of **2a** to give the free alcohol **4**, which was isolated in 84% yield (Scheme 4).[14a] Another interesting application would be to conduct a Suzuki–Miyaura coupling reaction that would tolerate alkylboronates as the coupling partner.[24]



Scheme 4. Formation and oxidative cleavage of alkylboronate compounds. Yield of isolated product is shown.

Mechanistically we can speculate about two possible pathways. Previously suggested mechanisms would account for the transformation of **A** into **B** through allene attack on palladium and subsequent *cis* insertion of the alkene into the generated vinylpalladium bond (Scheme 5, additional ligands are omitted for clarity).[12a,b,e] The most likely pathway from **B** into **C** would be transmetalation with B_2pin_2, in which one boron atom replaces the acetate group on palladium and the other boron atom forms pinBOAc. One referee suggested that transmetalation might occur already at intermediate **A**, thus avoiding transmetalation of a σ-palladium(II) intermediate **B**, which is prone to undergo *syn* β-hydride elimination. We consider this pathway less likely because of the lower electrophilicity of (pin)BPdOAc compared to $Pd(OAc)_2$, which would lead to a very slow allene attack. Previous studies indicate that allene attack on $Pd(OAc)_2$ is fast.[12c,25] Subsequent reductive elimination of **C** (with retention of configuration) would give the desired product **E** (**2a**) and Pd^0. The latter is reoxidized by *p*-benzoquinone. Formation of the known side product **F** would be explained by *syn* β-hydride elimination from intermediate **B**. There is also another possible pathway involving oxidative addition of B_2pin_2 to the σ-palladium(II) intermediate **B** resulting in a palladi-



Scheme 5. Palladium(II)-catalyzed oxidative carboborylation.

um(IV) intermediate **D**, which would undergo fast reductive elimination to give **E**.[26] The pinBPdOAc formed would then eliminate pinBOAc with formation of Pd^0. Although we favor the pathway via Pd^{II}/Pd^0 we cannot rule out a Pd^{IV}/Pd^{II} pathway at present.[27]

In conclusion, we have developed a palladium(II)-catalyzed oxidative borylative carbocyclization of enallene compounds. The protocol gives alkylboronates in good yields and requires only minimal amounts of reactants. Formally this reaction constitutes a 1,2-carboborylation of olefins under oxidative conditions and it occurs with *cis* addition to the olefin. We believe that this approach can be applied to other similar palladium(II)-catalyzed oxidation processes. Current studies are focused on extending the use of diboronates in palladium-catalyzed oxidations with the purpose to quench organopalladium intermediates.

Experimental Section

Catalytic oxidative carboborylation: $Pd(OAc)_2$ (0.45 mg, 0.002 mmol, 1 mol%), B_2pin_2 (51 mg, 0.20 mmol), and BQ (26 mg, 0.24 mmol) were added to a solution of enallene **1a** (0.1M, 56 mg, 0.20 mmol) in toluene. The reaction mixture was then heated at 40°C for 10 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluent: pentane/diethyl ether (v/v) 50:1) to give the alkylboronate **2a** as a white solid (62 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.60$ (d, $J = 2.6$ Hz, 1H), 4.92 (m, 1H), 4.87 (brs, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.54 (ddd, $J = 7.1$, 6.3, 2.6 Hz, 1H), 3.03 (m, 1H), 1.91 (s, 3H), 1.62 (m, 2H), 1.45–1.26 (m, 5H), 1.17 (s, 6H), 1.16 ppm (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 170.8, 170.3, 151.8, 140.7, 123.6, 114.1, 82.8 (2C), 68.5, 52.5, 52.0, 46.1, 43.7, 24.8 (2C), 24.6 (2C), 23.2, 23.0, 22.8, 22.3 ppm. HRMS (ESI): *m/z* calcd for $C_{22}H_{33}BO_6Na$ $[M+Na]+$: 427.2262; found: 427.2267.

Oxidation of borylated carbocycle **2a**: H_2O_2 (35% aq, 0.64 mmol, 56 μL), and NaOH (3M aq, 0.39 mmol, 0.13 mL) were added to a solution of alkylboronate **2a** (52 mg, 0.13 mmol) in THF (3 mL). The reaction mixture was stirred at RT for 3 h and was subsequently extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed by brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: pentane/ethyl acetate (v/v) 5:1) to give the product **4** as a white solid (32 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.85$ (brs, 1H), 5.14 (brs, 1H), 5.10 (brs, 1H), 4.15 (brs, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.22 (m, 1H), 3.12 (dd, $J = 8.5$, 4.0 Hz, 1H), 2.46 (d, $J = 5.0$ Hz, 1H), 1.96 (s, 3H), 1.99–1.92 (m, 1H), 1.87–1.83 (m, 1H), 1.74–1.65 (m, 1H), 1.46–1.36 (m, 2H), 1.34–1.28 ppm (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.4$, 171.0, 149.1, 137.7, 127.0, 115.7, 68.2, 65.2, 52.9 (2C), 48.2, 41.2, 30.6, 23.1, 20.8, 15.6 ppm. HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$: 317.1359; found: 317.1358.

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