Aerobic Oxidation

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# Selective Cascade Reaction of Bisallenes via Palladium-Catalyzed Aerobic Oxidative Carbocyclization–Borylation and Aldehyde Trapping

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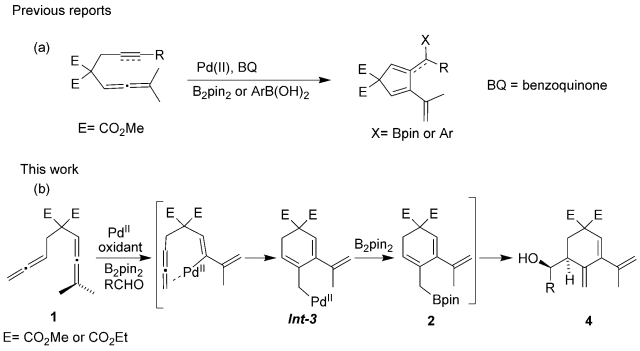
***Abstract:*** *A cascade reaction, consisting of a palladium-catalyzed regioselective aerobic oxidative carbocyclization–borylation of bisallenes and a final aldehyde trapping, afforded triene alcohols with high diastereoselectivity. The cascade reaction occurs under mild reaction conditions and proceeds via an allylboron intermediate that is trapped by the aldehyde in a stereoselective manner.*

In synthetic organic chemistry, cyclization of allenes is an important class of reactions that can be applied for the synthesis of a variety of carbocyclic and heterocyclic compounds.[1,2] In particular, transition metal-catalyzed cyclizations of conjugated and non-conjugated bisallenes provide efficient and atom-economical routes to polyunsaturated molecules.[3] In the synthesis of carbocyclic molecules, metal-catalyzed cascade reactions with C–C bond formation are of great interest for obtaining complex structures with high stereoselectivity.[4,5]

Organoboron compounds can be obtained through different routes such as Brown hydroboration and the palladium-catalyzed Miyaura borylation etc., and they are versatile building blocks in the synthesis of natural products and bioactive compounds.[6–8] In recent years, metal-catalyzed non-oxidative or oxidative carbocyclization studies with unsaturated systems have been well explored.[9,10,11] There are recent reports on non-oxidative palladium-catalyzed borylative cyclization of enynes and enallenes employing bis(pinacolato)diboron ($B_2pin_2$) as the borylating agent.[9]

In the past decade, our group has focused on the understanding of the mechanistic pathways in palladium-catalyzed oxidative carbocyclization reactions of enallenes, and allenynes (Scheme 1 a).[3b,c,10] These studies include palladium-catalyzed oxidative carbocyclization–borylation and carbocyclization–arylation of enallenes by the use of $B_2pin_2$ and arylboronic acids, respectively.[10b,c] In a similar fashion we have studied the palladium-catalyzed oxidative carbocyclization–borylation of allenynes in a regioselective manner.[10d] There is a demand of exploring these allene-based carbocyclizations towards new applications. Recently, we have developed a carbocyclization–arylation of bisallenes.[3c] It would be highly interesting to use a diboronate (e.g. $B_2pin_2$) instead of an arylboronic acid in the latter reaction of bisallene **1** leading to allylborane **2**, since the latter may undergo an additional C–C bond formation with an aldehyde (Scheme 1 b). It is expected that the reaction of the cyclic allylboron intermediate **2** with an aldehyde is highly stereoselective.[12] Here we report on a one-pot cascade reaction of bisallenes involving oxidative carbocyclization–borylation and final trapping with an aldehyde (Scheme 1 b).




***Scheme 1.*** Previous work and proposal for this work.

In palladium-catalyzed oxidative carbocyclizations, the use of an aerobic biomimetic oxidation system is an environmentally benign procedure associated with high atom economy.[10a,11] We have applied an aerobic oxidation process via multistep electron transfer involving three redox systems: $Pd^{II}/Pd^0$-benzoquinone (BQ)/hydroquinone (HQ)-Co(salophen)$^{ox}$/Co(salophen). In the carbocyclization reaction the substrate is oxidized to the desired product by the substrate-selective catalyst[11a] $Pd(OAc)_2$, which becomes reduced to $Pd^0$. The $Pd^0$ is subsequently reoxidized to $Pd^{II}$ by catalytic amounts of BQ, which is reduced to HQ. The HQ is reoxidized to BQ by the catalytic electron transfer mediator (i.e. Co(salophen)) with molecular oxygen as the oxidant.[10a,11,13–15]

Bisallenes **1a**–**1g** were prepared according to literature procedures.[16] In an initial investigation to optimize the reaction, we employed bisallene **1a** (Table 1) as a model substrate, and a series of experiments were performed in combination with $B_2pin_2$ to examine the oxidative palladium-catalyzed reactions for carbocyclization and borylation using $Pd(OAc)_2$ (5 mol%) and BQ. Different amounts of BQ and $B_2pin_2$ were employed in the Pd-catalyzed carbocyclization of **1a**. The use of 1.5 equiv of BQ in the absence of $B_2pin_2$ at

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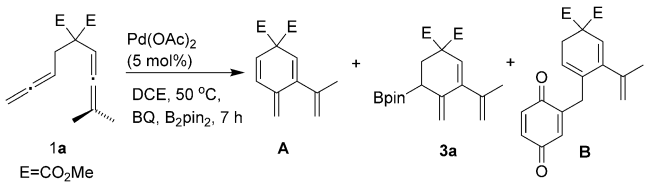
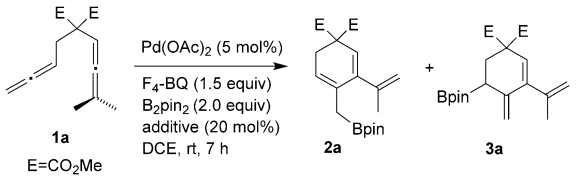
***Table 1:*** Results of initial study.[a]




| Entry | BQ (equiv) | $B_2pin_2$ (equiv) | Yield [%][b,c] A | 3a | B |
|---|---|---|---|---|---|
| 1 | 1.5 | – | 72(70) | – | – |
| 2 | 2.5 | 1.5 | Traces | 25 | 62 |
| 3 | 3 | 1.0 | Traces | Traces | 75(71) |
| 4 | 3 | 0.1 | 60 | 5 | 10 |

[a] Reaction conditions: **1a** (1.0 equiv) (0.2 mmol), 5 mol% of $Pd(OAc)_2$, anhydrous DCE (2.0 mL). [b] Yield determined by $^1H$ NMR using mesitylene as an internal standard. [c] Isolated yield in parenthesis.

***Table 2:*** Optimization of the reaction conditions.




| Entry | Additives | Ratio of 2a:3a | Yield [%][a] |
|---|---|---|---|
| 1 | – | 74:26 | 99 |
| 2 | PTSA | NR[b] | 0 |
| 3 | $Et_3B$ | Decompose | 0 |
| 4 | AcOH | 70:30 | 44 |
| 5 | $BF_3{\cdot}Et_2O$ | 100:0 | 34 |
| 6 | $LiOAc{\cdot}H_2O$ | 79:21 | 97 |
| 7 | NaOAc | 74:26 | 99 |
| 8 | $Na_2CO_3$ | 84:16 | 99 |
| 9[c] | $Na_2CO_3$ | 79:21 | 99 |

[a] Yield determined by $^1H$ NMR analysis using mesitylene as an internal standard. [b] NR: no reaction. [c] 50 mol% of additive.

50 °C for 7 h in DCE (1,2-dichloroethane), afforded product **A** in 72% yield (Table 1, entry 1) most likely via isomerization of ***Int*-3** (Scheme 1b) to the secondary σ-allyl-Pd complex followed by β-hydride elimination. Surprisingly, with an increased amount of BQ (2.5 to 3 equiv) in the presence of $B_2pin_2$ (1.5 to 1 equiv), BQ derivative **B** was obtained in 62 to 75% yield (Table 1, entries 2 and 3). Interestingly, when $B_2pin_2$ was reduced to 0.1 equiv in the presence of BQ (3 equiv), compound **A** (60%) was formed as the main product together with small amounts of secondary boronic ester triene derivative **3a** (5%) and quinone derivative **B** (10%) (Table 1, entry 4). In this initial study, we were not able to obtain the desired carbocyclic primary boron compound **2a**, probably because of its reaction with BQ.

We therefore decided to carry out the carbocyclization/borylation reaction with different oxidants with the aim of isolating **2a**. After trying various oxidants, it was finally found that tetrafluoro-1,4-benzoquinone ($F_4$-BQ) (1.5 equiv) with bisallene **1a** using catalytic amount of $Pd(OAc)_2$ (5 mol%) in the presence of $B_2pin_2$ (2 equiv) at room temperature in DCE provided allylic primary and secondary carbocyclic boronic esters **2a** (74%) and **3a** (26%) as major and minor products, respectively (Table 2, entry 1).

We then turned our attention towards optimizing the yield of the primary boronic ester **2a** by addition of various additives. It was found that addition of base substantially improved the yield of allylic primary carbocyclic boronic ester **2a**. The employment of *p*-toluenesulfonic acid (PTSA) or $Et_3B$ additives was ineffective as well as the addition of catalytic amounts of AcOH (Table 2, entries 2–4). Addition of $BF_3{\cdot}Et_2O$ gave a high selectivity (100:0) but the yield was low. With $LiOAc{\cdot}H_2O$ the yield was high and the selectivity **2a**:**3a** was 79:21 (Table 2, entry 6). NaOAc decreased the ratio **2a**:**3a** (entry 7). Finally, with 20 mol% of $Na_2CO_3$, **2a** was formed with good selectivity (84/16 ratio) and yield (entry 8). Increasing the amount of $Na_2CO_3$ to 50 mol% decreased the selectivity (79:21 ratio, entry 9). Moreover, the use of various $Pd^{II}$ catalysts did not improve the regioselectivity (see Supporting Information).

With these improved reaction conditions for obtaining **2a** as the major isomer, we studied various substrates **1a**–**1g** for the borylative carbocyclization (Table 3). The corresponding allylboronic compounds **2a**–**2g** were obtained in good yields (64–84%). It was desirable to apply an aerobic oxidative carbocyclization–borylation process. Pd-catalyzed reaction of **1a** with $B_2pin_2$ (2 equiv) at room temperature using catalytic amounts of $F_4$-BQ (20 mol%) and Co(salophen) (5 mol%) as electron transfer mediators (ETMs) under 1 atm of molecular oxygen ($O_2$) in DCE (Table 3, entry 1, method B) afforded **2a** in 83% yield. A similar yield (Table 3, entry 1, method A, 84%) was obtained in the non-aerobic oxidative reaction.

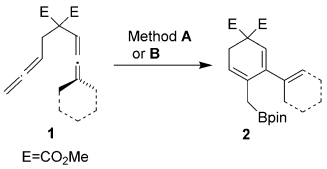
In the aerobic oxidative carbocyclization–borylation reaction, Co(salophen) was the best ETM for obtaining product **2a** in high yield. Similar results were obtained for substrates **1a** and **1b**, with either stoichiometric amounts of $F_4$-BQ (method A) or under aerobic conditions (method B) affording products **2a** and **2b**, respectively, in good yields (Table 3, entries 1 and 2).

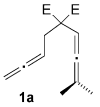
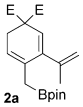
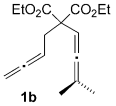
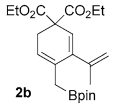
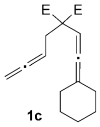
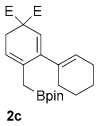
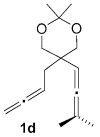
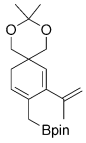
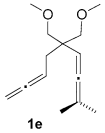
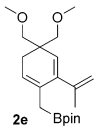
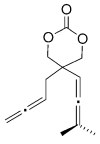
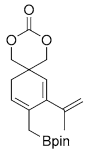
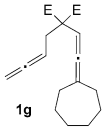
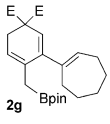
With the results in Table 3, we now can provide an explanation for the formation of carbocyclic benzoquinone derivative **B** (Table 1, entry 3). In this case the allylboron compound **2a** generated will react with the carbonyl group of the quinone followed by a [3,3′] rearrangement (Scheme 2).[17] Subsequent tautomerization and oxidation lead to derivative **B**. This cascade reaction inspired us to develop a cascade reaction where the generated allylboron compound is continuously trapped by a carbonyl compound (such as an aldehyde) present in the reaction mixture.

In the planned cascade reaction, an allyl-Bpin intermediate **2a** is generated via an in situ carbocyclization–borylation and this intermediate can continuously be trapped by an aldehyde present in solution. Normally, it is difficult to control the relative configuration at two adjacent stereocenters in a single reaction but the cascade reaction sequence proceeded in a highly stereoselective manner. This high stereoselectivity is due to the fact that the reaction between the allylboron intermediate and the aldehyde involves a Zimmerman–Trax-

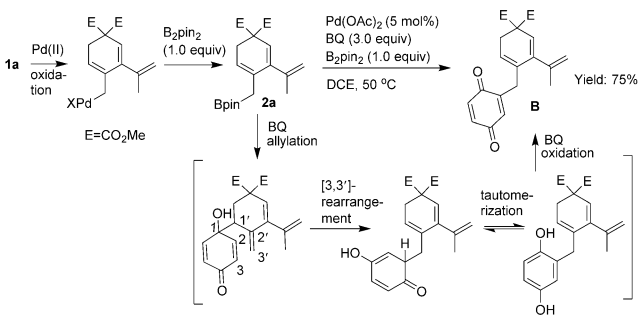
  

***Table 3:*** Scope of substrates.



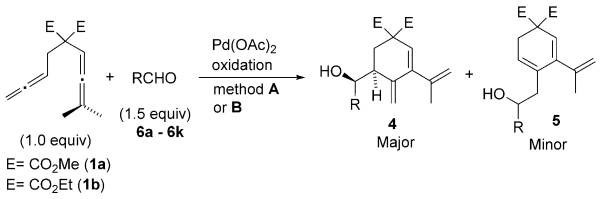

| Entry | Substrate (E = $CO_2$Me) | Product | Yield of **2** [%][a] (method A/B) |
|---|---|---|---|
| 1 |  **1a** |  **2a** | A:84<br>B:83 |
| 2 |  **1b** |  **2b** | A:84<br>B:82 |
| 3 |  **1c** |  **2c** | A:81 |
| 4 |  **1d** |  **2d** | A:80 |
| 5 |  **1e** |  **2e** | A:85 |
| 6 |  **1f** |  **2f** | A:78 |
| 7 |  **1g** |  **2g** | A:64 |

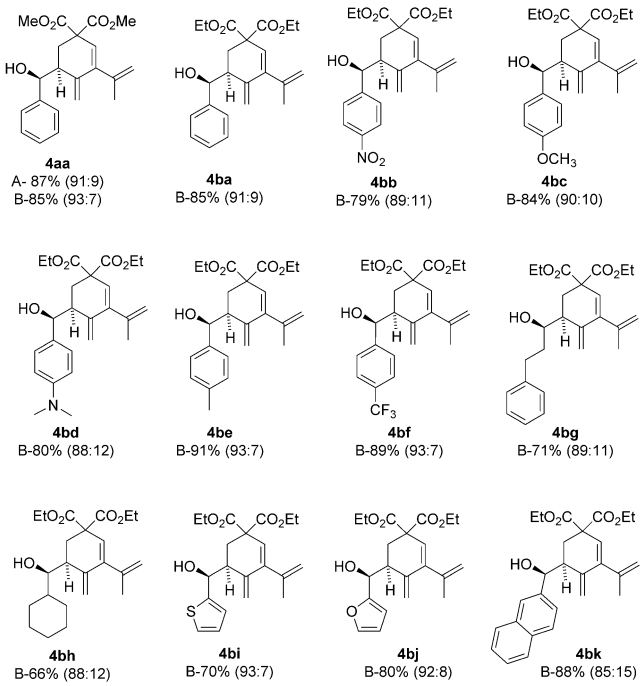
[a] Isolated yield after column chromatography. Method A: $Pd(OAc)_2$ (5 mol%), $F_4$-BQ (1.5 equiv), $B_2pin_2$ (2 equiv), $Na_2CO_3$ (20 mol%), DCE, rt, 7 h. Method B: $Pd(OAc)_2$ (5 mol%), $F_4$-BQ (20 mol%), Co(salophen) (5 mol%), $B_2pin_2$ (2 equiv), $Na_2CO_3$ (20 mol%), DCE, rt, $O_2$ balloon, 7 h.




***Scheme 2.*** Reaction of allylboron derivative **2a** with BQ.

***Table 4:*** Palladium-catalyzed cascade reaction.[a,b]



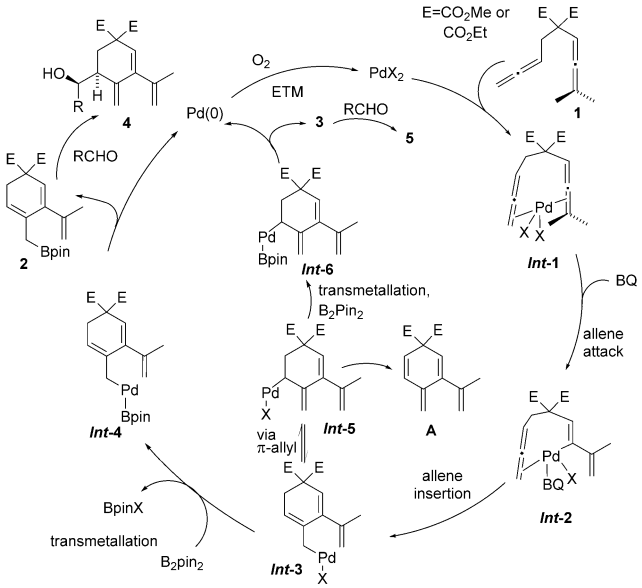




[a] Isolated yield after column chromatography. [b] The ratio in parenthesis is the ratio **4**:**5**. Method A: Same as in Table 3 but with 1.5 equiv of an aldehyde. Method B: Same as in Table 3 but with 1.5 equiv of an aldehyde.

ler (ZT) transition state[12a,b,18] (see Supporting Information). The cascade reaction of **1a** with benzaldehyde by method A or B afforded **4aa** (Table 4) as the major product in a mixture with small amounts of regioisomers **5**.

In the one-pot reaction using method A or B, **1b** was allowed to react with various substituted benzaldehydes (**6a**–**6f**) with electron-rich or electron-deficient substituents to give of **4bb**–**4bf**, in good yields (79–91%) with minor amounts of regioisomers **5** (Table 4). Under biomimetic oxidative conditions (method B), aliphatic aldehydes such as phenylpropionaldehyde (**6g**) and cyclohexylcarboxaldehyde (**6h**) with **1b** gave the corresponding derivatives **4bg** and **4bh** in 71% and 66% yields, respectively. Similarly, heterocyclic aldehydes, for example 2-thiophenecarboxaldehyde (**6i**) and furfural (**6j**), were also allowed to react under aerobic conditions (method B) producing the corresponding derivatives **4bi** and **4bj** in 70% and 80% yields, respectively, with small amounts of regioisomers **5bi** and **5bj** (**4bi**:**5bi** = 93:7 and **4bj**:**5bj** = 92:8). In all these cases two stereocenters were created in the reaction that gave isomer **4** but only one diastereomer of **4** was observed (> 99% d.r.).

In the cascade reaction described in Table 4, we noticed that triene alcohol derivatives **4** undergo lactone formation on prolonged reaction times. This lactonization was faster when dimethyl malonate derivative **1a** was used. When **1a** was used together with 4-(trifluoromethyl)benzaldehyde (**6f**) a crystalline bicyclic lactone product **7** (see Ref. [19]) was obtained on prolonged reaction time. The bicyclic lactone product was submitted to X-ray crystallography analysis, which allowed stereochemical assignment of the trienol product **4** from the cascade reaction.[19]




***Scheme 3.*** Proposed mechanism for the formation of **4** and **5**.

A possible mechanism for the carbocyclization–borylation–aldehyde trapping is given in Scheme 3. Previous studies in our group have shown that carbocyclization involving 1,1-dimethyl allenes is initiated by an allene attack on $Pd^{II}$.[10] Formation of chelate complex ***Int*-1** from bisallene **1** and subsequent allene attack on the $Pd^{II}$ would generate vinylpalladium intermediate (***Int*-2**). The latter complex reacts via insertion of allene into the Pd-vinyl bond affording (σ-allyl)$Pd^{II}$ species ***Int*-3**, which can rearrange to ***Int*-5** via the more stable π-allyl complex (not shown). The σ-allyl intermediates with primary or secondary carbon-Pd bonds can undergo transmetallation with $B_2pin_2$ to produce complexes ***Int*-4** or ***Int*-6**, respectively. Subsequent reductive elimination from ***Int*-4** and ***Int*-6** results in the formation of boron compounds **2** and **3**, respectively, with concomitant formation of $Pd^0$. The latter species is reoxidized to $Pd^{II}$ by either BQ or by the $O_2$/ETM system. Subsequent reaction of the allylboron compound **2** with the aldehyde present in the mixture gives product **4**. Similarly, reaction of **3** with the aldehyde gives the minor product **5**.[16] In the absence of $B_2pin_2$, β-hydride elimination from ***Int*-5** occurs to furnish **A** as the sole product.

In conclusion, we have developed a $Pd^{II}$-catalyzed aerobic oxidative carbocyclization–borylation–aldehyde trapping cascade reaction of bisallenes to give triene alcohols with high diastereoselectivity. A wide range of bisallenes having different functionality and aldehydes with various functional groups are tolerated under biomimetic or nonaerobic conditions. The efficient construction of stereoselective complex structures via cyclic allylboronates and their applications in a one-pot reaction should be useful in natural product synthesis. Further investigations directed towards synthetic applications and asymmetric variants of this one-pot cascade reaction are underway in our laboratory.

## Acknowledgements

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** biomimetic oxidation · bisallene · cascade reaction · catalysis · palladium

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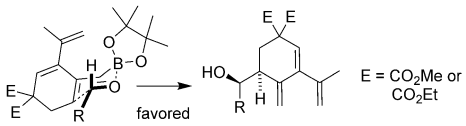
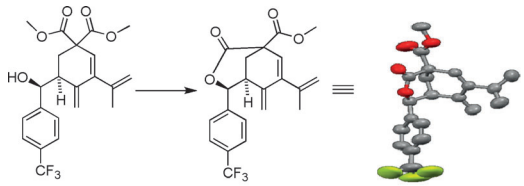



**4**

[19] Lactone formation of **4af** gives a crystalline lactone **7**. (CCDC 1486074).



**4af** **7** crystalline **7** X-ray

Manuscript received: October 27, 2016
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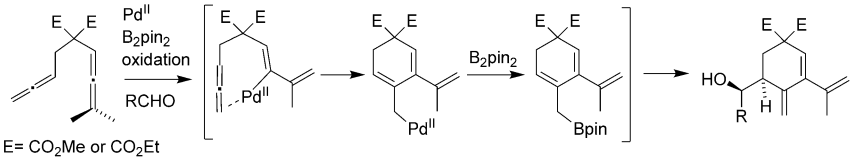
# Communications

**Aerobic Oxidation**

V. R. Naidu, D. Posevins, C. M. R. Volla, J.-E. Bäckvall* ——— ■■■–■■■

Selective Cascade Reaction of Bisallenes via Palladium-Catalyzed Aerobic Oxidative Carbocyclization–Borylation and Aldehyde Trapping




**Efficient cascade**: A palladium-catalyzed regioselective aerobic oxidative carbocyclization–borylation of bisallenes generates a reactive allylboron intermediate that is trapped by aldehyde present in the reaction mixture. The cascade reaction proceeds with high diastereoselectivity.