

Borylation

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Palladium-Catalyzed Oxidative Carbocyclization–Borylation of Enallenes to Cyclobutenes

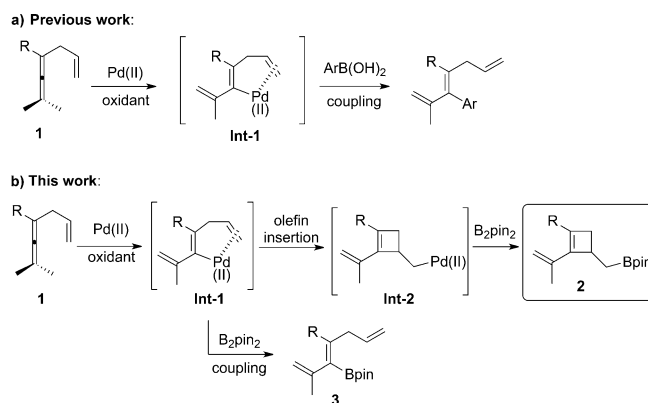
Youai Qiu, Bin Yang, Can Zhu,* and Jan-E. Bäckvall*

Abstract: A highly efficient palladium-catalyzed oxidative borylation of enallenes was developed for the selective formation of cyclobutene derivatives and fully-substituted alkenylboron compounds. Cyclobutenes are formed as the exclusive products in MeOH in the presence of H₂O and Et₃N, whereas the use of AcOH leads to alkenylboron compounds. Both reactions showed a broad substrate scope and good tolerance for various functional groups, including carboxylic acid ester, free hydroxy, imide, and alkyl groups. Furthermore, transformations of the borylated products were conducted to show their potential applications.

Cyclobutenes have attracted considerable attention owing to the fact that they are key structural elements in biologically relevant compounds, as well as in natural products.^[1] Moreover, because of the high strain of cyclobutenes, they participate in a number of useful synthetic transformations, such as electrocyclic ring-opening, metathesis-type reactions, and epoxidations.^[2] However, only a few methods have been developed for the construction of cyclobutenes.^[3] Therefore, the development of efficient methods for the preparation of these compounds is highly desirable.

We recently described an efficient olefin-directed palladium-catalyzed oxidative arylation of allenes (Scheme 1 a).^[4] The key intermediate **Int-1** is generated from enallene **1** through allene attack involving C–H bond cleavage. In the latter reaction, additional coordination of the olefin unit to palladium is crucial for activation of the allene attack to occur, and changing the allyl unit of **1** to an *n*-propyl unit completely shut down the reaction. The olefin was used only as an activating/directing group since it was argued that insertion of the olefin to give a cyclobutene is too slow compared to the aryl coupling observed.

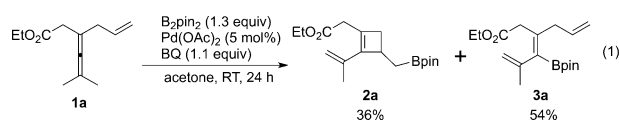
In continued work, we studied the extension of the reaction in Scheme 1 a to boron couplings of **1** (see **3** in Scheme 1 b) since organoboron compounds have been found to be convenient and versatile building blocks in organic



Scheme 1. Previous work and the current work.

synthesis and medicinal chemistry.^[5–12] During these studies, we observed that formation of cyclobutene **2**, presumably via intermediate **Int-2**, was highly favored under certain conditions (Scheme 1 b). To the best of our knowledge, there have been no reports on efficient cyclobutene formation through palladium-catalyzed olefin insertion to date.

Our study began with the palladium-catalyzed reaction of 3,4-dienoate **1a** with B₂pin₂ using BQ (*p*-benzoquinone) as the oxidant. In analogy with the arylation in Scheme 1 a, the expected boron coupling product **3a** was obtained in 54 % yield. Surprisingly, the borylated cyclobutene compound **2a** was formed in 36 % yield [Eq. (1)].^[13]

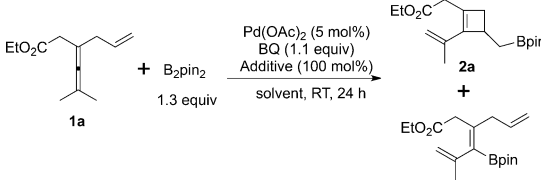


With these results in hand, we set out to optimize the reaction conditions for cyclobutene formation. Solvent screening showed that MeOH was the best solvent, in which the yield of **2a** was improved to 64 % (Table 1, entries 1–5). Interestingly, the addition of suitable amounts of H₂O favored the selective formation of cyclobutene **2a** (Table 1, entries 6–8), and with one equivalent of water, the yield of **2a** was 69 % (Table 1, entry 7). Furthermore, after investigation of different additives (Table 1, entries 9–12), we surprisingly found that the reaction in the presence of Et₃N (100 mol %) gave exclusive selectivity for the formation of cyclobutene **2a** in 51 % yield (Table 1, entry 12).^[14] The yield of **2a** could be further improved to 68 % when the amount of Et₃N was decreased to 20 mol % (Table 1, entry 13), and finally **2a** was

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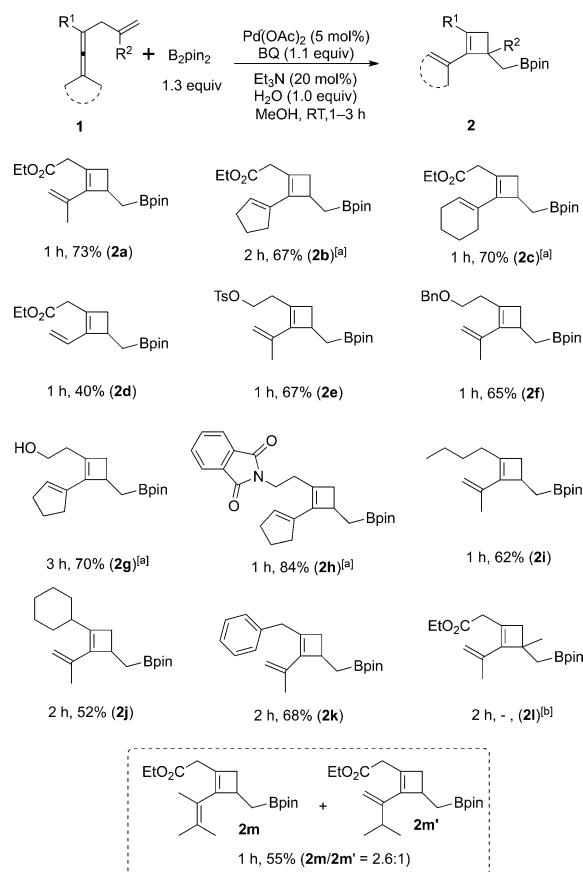
Table 1: Optimization of the reaction conditions.^[a]


Entry	Solvent	Additive [100 mol%]	Yield of 2a [%] ^[b]	Yield of 3a [%] ^[b]
1	Acetone	—	36	54
2	CH ₃ CN	—	40	53
3	DMF	—	32	55
4	EtOH	—	38	33
5	MeOH	—	64	25
6 ^[c]	MeOH/H ₂ O	—	65	27
7 ^[d]	MeOH/H ₂ O	—	69	16
8 ^[e]	MeOH/H ₂ O	—	65	20
9 ^[d,f]	MeOH/H ₂ O	DMSO	64	24
10 ^[d]	MeOH/H ₂ O	LiOAc·2 H ₂ O	44	35
11 ^[d]	MeOH/H ₂ O	Cu(OAc) ₂	34	41
12 ^[d]	MeOH/H ₂ O	Et ₃ N	51	0
13 ^[d,f]	MeOH/H ₂ O	Et ₃ N	68	0
14 ^[d,g]	MeOH/H ₂ O	Et ₃ N	68	3
15 ^[d,f,h]	MeOH/H ₂ O	Et ₃ N	75	0
16	AcOH	—	8	70
17 ^[i]	AcOH	—	0	78

[a] The reaction was conducted with 0.20 mmol of **1a**, B₂pin₂ (1.3 equiv), BQ (1.1 equiv), and 5 mol% of Pd(OAc)₂ in 1 mL of solvent. [b] Determined by ¹H NMR with anisole as the internal standard. [c] H₂O (0.5 equiv) was added. [d] H₂O (1.0 equiv) was added. [e] H₂O (2.0 equiv) was added. [f] 20 mol% of additive was added. [g] 10 mol% of Et₃N was added. [h] The reaction was run in MeOH (4 mL) for 1 h. [i] 2,6-Dimethyl-BQ (1.5 equiv) was used instead of BQ and the reaction time was 4 h.

obtained exclusively in 75 % yield in a diluted solution within 1 h (Table 1, entry 15). Interestingly, reversed selectivity for the formation of **3a** was observed when AcOH was used as the solvent (Table 1, entry 16). The exclusive formation of alkenylboron compound **3a** was achieved in 78 % yield within 4 h when 2,6-dimethylbenzoquinone was used as the oxidant (Table 1, entry 17).

The substrate scope for the formation of cyclobutenes **2** was then studied under the optimized reaction conditions (Scheme 2). In addition to two methyl substituents on the enallene moiety, cyclopentylidene and cyclohexylidene enallenes (**1b** and **1c**) also afforded the corresponding products (**2b** and **2c**) in good yields. Trisubstituted allene **1d** also underwent the carbocyclization and afforded product **2d**, although in moderate yield. Tosyl and benzyl 3,4-dienol derivatives **1e** and **1f** worked well under the standard conditions. To our delight, enallene substrates with functional groups such as a free hydroxy group in **1g** and imide in **1h** furnished cyclobutene derivatives **2g** and **2h** in 70 % and 84 % yield, respectively. Furthermore, the reaction tolerated different alkyl groups as R¹ in the oxidative carbocyclization to cyclobutene, for example, R¹ = *n*-butyl (**1i**), cyclohexyl (**1j**), or benzyl (**1k**). However, only a complex mixture was obtained with enallene **1l** (R² = methyl) under the standard

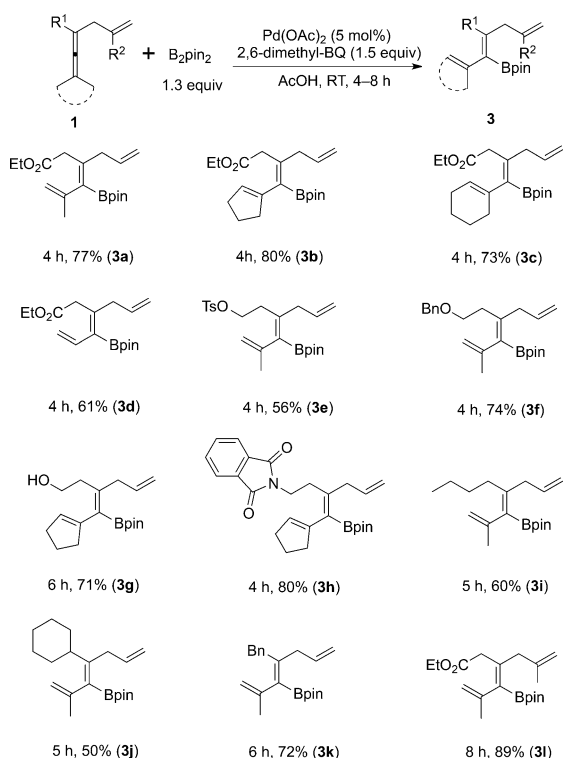


Scheme 2. Palladium-catalyzed oxidative borylating carbocyclization for the formation of cyclobutenes **2**. [a] Et₃N (40 mol%) was used. [b] Complex mixture.

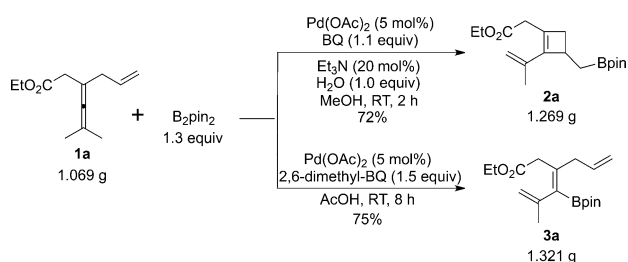
conditions, probably owing to steric effects disfavoring olefin insertion to give the four-membered ring. Finally, the reaction of the dissymmetric allene **1m**, which bears methyl and isopropyl groups, afforded **2m** and **2m'** in a combined 55 % yield. The **2m/2m'** ratio was 2.6:1 owing to selective allenic C–H cleavage, which occurred during allene attack to form **Int-1** (see Scheme 1 a).

We next explored the substrate scope under the optimal reaction conditions for the formation of fully-substituted alkenylboron compounds **3** (reversed selectivity; Scheme 3).^[15,16] The reaction of substrates with two methyl groups, cyclopentylidene, cyclohexylidene, or even one methyl group on the allene moiety all worked well, affording the corresponding products **3a–3d** in good yields. Tosyl 3,4-dienol **1e** produced **3e** in a slightly lower yield, while benzyl 3,4-dienol **1f** gave **3f** in 74 % yield. Surprisingly, substrates containing a free hydroxy or imide group could also be employed. Alkyl substituents on the allene unit (R¹), such as *n*-butyl, cyclohexyl, or benzyl groups, were tolerated. It is noteworthy that the reaction of enallene **1l**, which bears a methyl group at the internal position of the olefin (R² = Me), produced **3l** in 89 % yield.

To demonstrate the synthetic potential of the current methods, the reactions of enallene **1a** were conducted on a one-gram scale. Notably, the reaction could be easily extended to a scale of 5.5 mmol of **1a** to afford the



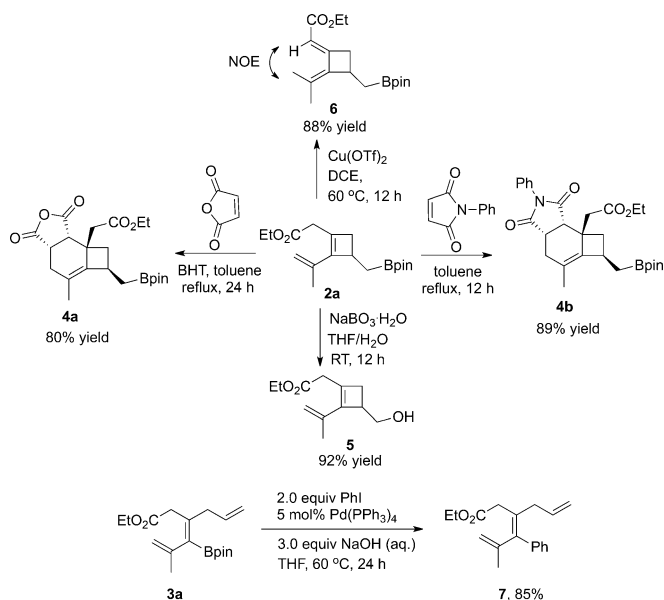
Scheme 3. Palladium-catalyzed oxidative borylation for the formation of alkenylboron compounds **3**. [a] The reaction was conducted in AcOH (1 mL) at room temperature with **1** (0.20 mmol), B_2pin_2 (1.3 equiv), and 2,6-dimethyl-BQ (1.5 equiv) in the presence of $\text{Pd}(\text{OAc})_2$ (5 mol %).



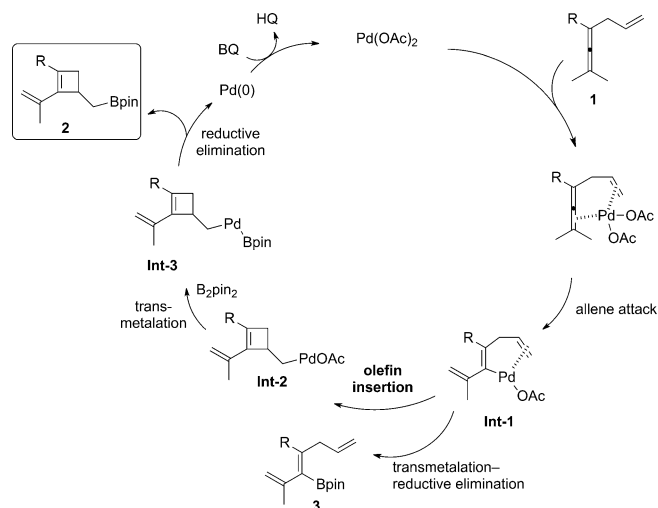
Scheme 4. Gram-scale reactions of **1a**.

corresponding cyclobutene **2a** (1.269 g, 72%) and alkenylboron **3a** (1.321 g, 75%; Scheme 4).

Transformations of cyclobutenes **2a** were also studied. Considering the conjugated diene moiety in cyclobutenes **2**, these compounds may undergo [4+2]-cycloadditions^[17] to provide a simple and direct route towards polycyclic compounds. The reaction of **2a** with maleic anhydride or *N*-phenylmaleimide afforded fused tricycles **4a** or **4b**, respectively, in both cases as single diastereoisomers.^[18,19] Oxidation of **2a** was easily conducted to give the free hydroxylated product **5** in 92% yield with $\text{NaBO}_3 \cdot \text{H}_2\text{O}$ as the oxidant.^[21] Furthermore, an interesting [1,5]-*H* migration of **2a** occurred under the catalysis of copper(II) to give diene product **6** in 88% yield. The configuration of the C=C double bond was confirmed by NOE measurements. Suzuki coupling of vinyl boronate **3a** with iodobenzene afforded product **7** in 80% yield (Scheme 5).^[12]



Scheme 5. Transformations of **2a** and **3a**.



Scheme 6. Proposed mechanism.

A possible mechanism for the palladium-catalyzed oxidative carbocyclization-borylation of enallenes is given in Scheme 6. The reaction of $\text{Pd}(\text{OAc})_2$ with **1** could form vinylpalladium intermediate **Int-1** through allene attack involving allenic C–H bond cleavage, which is promoted by the coordination of allene and olefin to Pd^{II} .^[4,22] Then, vinylpalladium **Int-1** could undergo an olefin insertion to form cyclobutene intermediate **Int-2**.^[3] Subsequent transmetalation of **Int-2** with B_2pin_2 would produce **Int-3**, which upon reductive elimination would give the target cyclobutene derivative **2**. Transmetalation of **Int-1** with B_2pin_2 , followed by reductive elimination would give product **3**. Insertion of an olefin into the C–Pd bond in **Int-1** to give **Int-2** is highly favored in MeOH with a catalytic amount of Et_3N , finally giving cyclobutenes **2**.^[23] The reaction in MeOH is faster than that in HOAc. However, the selective formation of alkenylboron compounds **3** is most likely due to a favored trans-

metalation of vinylpalladium **Int-1** with B₂pin₂ under acidic conditions.

In conclusion, we have developed an efficient palladium-catalyzed oxidative carbocyclization–borylation of enallenes for the selective formation of cyclobutenes **2**. By changing the reaction conditions, fully substituted alkenylboron compounds **3** were selectively obtained. The formation of cyclobutenes **2** through olefin insertion into the C–Pd bond is rarely reported. Both borylation reactions showed a broad substrate scope and good tolerance for various functional groups, including carboxylic acid ester, free hydroxy, imide, and alkyl groups. Furthermore, the reactions could be easily extended to the gram scale. Further studies on the scope, synthetic application, and asymmetric variants of the new reactions are currently underway in our laboratory.

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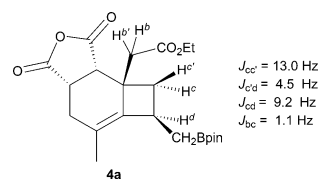
Keywords: allenes · borylation · cyclobutenes · oxidation · palladium

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(*trans*) $> ^4J_{\text{HH}}(\text{cis})$ was reported by Widmalm.^[20] For details, see the Supporting Information.



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