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Palladium-Catalyzed Oxidative Domino Carbocyclization−Arylation of Bisallenes

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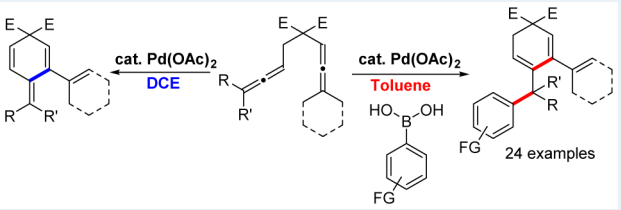
Supporting Information

ABSTRACT: Herein we report a highly efficient and site-selective palladium-catalyzed oxidative carbocyclization−arylation reaction of bisallenes and arylboronic acids under operationally simple conditions for the selective synthesis of cyclohexadiene derivatives. The palladium source and the solvent proved to be crucial for the selectivity and the reactivity displayed. Interestingly, in the absence of the nucleophile, an oxidative carbocyclization-β-elimination pathway predominates. The reaction conditions are compatible with a wide range of functional groups, and the reaction exhibits broad substrate scope. Furthermore, key information regarding the mechanism was obtained using control experiments and kinetic studies.

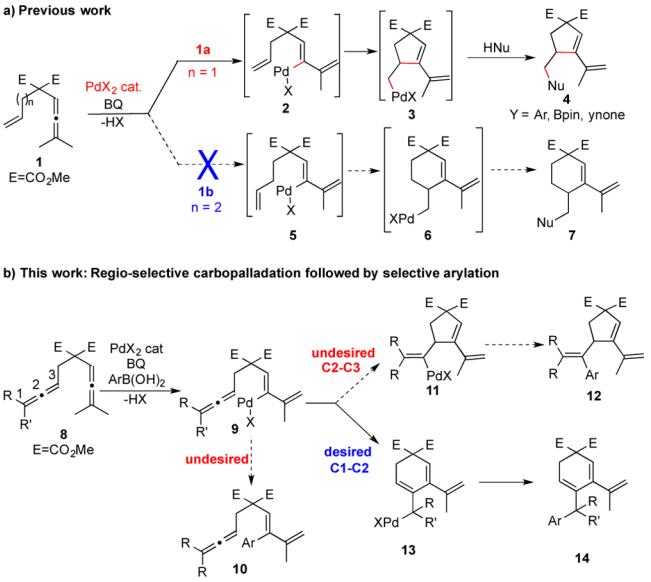


KEYWORDS: *bisallenes, palladium catalysis, carbocyclization, oxidation, arylation*

Carbocyclization reactions of allenes[1] have attracted considerable attention in the past few years, and the versatile reactivity of allenes has been exploited in the synthesis of a diverse range of natural products and biologically active compounds.[2] Various transition-metal-catalyzed cyclization reactions of allenes have been established for the preparation of a variety of carbo- and heterocyclic derivatives.[3] In particular, novel strategies based on palladium catalysis have been studied for the construction of complex molecular structures from simple starting materials.[4] Although allenes have been widely utilized in the carbocyclization reactions, more challenging bisallenes were largely ignored, and the state-of-the-art of the cyclization reactions of bisallenes is mostly limited to cycloaddition and cycloisomerization reactions.[5] Therefore, there is an increasing demand to develop novel and efficient carbocyclizations reaction of bisallenes.[6] In particular, transition-metal-catalyzed cascade carbocyclization reactions have attracted attention as they allow the construction of complex molecular structures from simple starting materials.[7,8]

Our group has been largely interested in the development of palladium-catalyzed oxidative carbocyclization reactions of various unsaturated systems such as enallenes,[9] dienallenes,[10] and allenynes.[11] In recent studies, we have described carbocyclization reactions of enallenes followed by arylation, borylation, or carbonylation.[12] In these carbocyclizations, we noticed that the cyclization was highly sensitive toward the size of the carbocycle being formed. Enallenes **1a** (n = 1) led to the functionalized cyclopentenes **4** via the intermediacy of **2** and **3** using catalytic amounts of Pd(II)-salt and oxidant (Scheme 1a). In sharp contrast, enallenes **1b** (n = 2) failed to provide the corresponding cyclohexene derivatives **7** under these oxidative conditions. Very recently, we reported that coordination of the pendent olefin with palladium is vital for the subsequent attack of the allene moiety to palladium for the formation of intermediate **2**.[13,14] Weaker coordination of enallene **1b** (n = 2) might be the reason for its limited reactivity, and we envisaged that replacing the alkene unit by an allene would resolve the coordination issues and would give access to the cyclohexene derivatives, which are found in many natural products (Scheme 1b).[15]

Scheme 1. Oxidative Pd-Catalyzed Carbocyclization of (a) Enallenes and (b) Bisallenes



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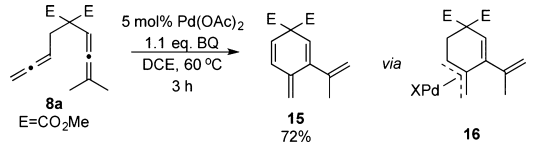
Controlling the chemoselectivity of insertion of organopalladium(II) intermediate with allenes is the key challenge associated with the envisioned project (Scheme 1b). Insertion of vinylpalladium(II) **9** with allene can take place either on C2−C3 or C1−C2 of the allene leading to either cyclopentene **11** or cyclohexene **13** intermediate.[16] Quenching these intermediates with a suitable nucleophile will give the corresponding carbocycle **12** or **14**. Arylboronic acids were chosen as coupling reagents as they are known to undergo fast transmetalation with Pd(II). In addition they are nontoxic, easily available, and stable.[17] A further challenge is to control the site-selectivity for the formation of dienylpalladium(II) intermediate (cf. **9**) when both the allene moieties are substituted in **8** (R and/or R′ = alkyl) as other cyclization pathways also compete.

In initial studies, bisallene **8a** was allowed to react with 5 mol % of $Pd(OAc)_2$ in DCE solvent at room temperature overnight. The reaction was sluggish and afforded a mixture of unidentified products along with starting material. However, we were pleased to find that the reaction proceeded smoothly at 60 °C and led to selective formation of methylencyclohexadiene **15** in 72% isolated yield after 3 h (Scheme 2). Isolation of **15** as the only product supports our initial proposal of insertion of dienylpalladium(II) intermediate **9** selectively at the C1−C2 of the allene.

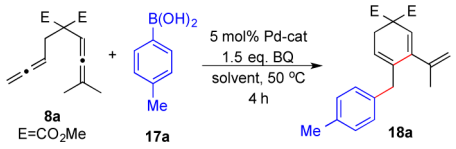
Scheme 2. Initial Studies for the Pd-Catalyzed Carbocyclization of Bisallenes

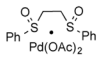


Intrigued by these initial results, we set out to achieve Pd(II)-catalyzed oxidative cascade carbocyclization−arylation of bisallenes (Table 1). For the initial studies, *p*-tolylboronic acid was used as the nucleophile in reaction with **8a**. We were pleased to find that 5 mol % of $Pd(OAc)_2$ and 1.5 equiv of BQ in DCE solvent at rt overnight afforded the envisioned product in 47% yield along with 12% of **8a** (Entry 1). At slightly higher temperature (50 °C), the reaction was completed in 4 h and selectively afforded **18a** in 65% NMR yield (Entry 2). No *β*-elimination product **15** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Various solvents were screened to improve the yield, and it was found that the reaction has a strong dependence on the solvent. Although no reaction was observed in polar solvents such as DMSO and acetonitrile (Entries 8 and 9), other solvents such as THF, acetone, methanol, and 1,4-dioxane led to the product in 51−71% yields (Entries 3−6). Gratifyingly, toluene provided cleanly the product **18b** in 81% NMR yield (79% isolated yield) at 50 °C after 4 h (Entry 7). Screening of the different Pd(II)-salts was done in toluene solvent (Entries 10−14), among which $Pd(OAc)_2$ was found to be the best catalyst.

After having the optimized reaction conditions in hand for the cascade carbocyclization−arylation of bisallenes, we investigated the scope of the reaction using bisallene **8a**. As can be seen from Scheme 3, various functionalized arylboronic acids reacted efficiently with **8a** to give the corresponding products in good to high yields (**18a**−**18p**). Both electron-donating and electron-withdrawing substituted arylboronic

Table 1. Optimization of Reaction Conditions



No.	Pd-catalyst	Solvent	Yield[a] (**18a**)	Yield[a] (**8a**)
1	$Pd(OAc)_2$	DCE[b]	47%	12%
2	$Pd(OAc)_2$	DCE	65%	-
3	$Pd(OAc)_2$	THF	69%	9%
4	$Pd(OAc)_2$	Acetone	51%	
5	$Pd(OAc)_2$	MeOH	52%	-
6	$Pd(OAc)_2$	1,4-dioxane	71%	-
7	$Pd(OAc)_2$	Toluene	81% (79%)[c]	-
8	$Pd(OAc)_2$	DMSO	-	79%
9	$Pd(OAc)_2$	Acetonitrile	-	86%
10		Toluene	74%	-
11	$Pd(TFA)_2$	Toluene	51%	40%
12	$Pd(acac)_2$	Toluene	40%	54%
13	$PdCl_2$	Toluene	-	87%
14	$Pd(BF_4)_2(CH_3CN)_4$	Toluene	-	85%

[a]Yield was detected by ^{1}H NMR using mesitylene as an external standard. [b]Reaction was done at room temperature for overnight. [c]Yield in parentheses refers to the isolated yield.

acids resulted in full conversion in reaction with **8a** after 4−5 h. Arylboronic acids with electron-donating substituents such as alkyl or methoxy groups on the aromatic ring resulted in slightly higher yields (**18a**, **18c**−**18f**) compared to those with electron-withdrawing groups (**18g**−**18m**). Halogen substituents such as F, Cl, Br, and I at different positions of the aromatic ring are compatible with the reaction conditions to afford the corresponding derivatives **18g**−**18j** in good yields (60−78%).

The reaction also tolerates different functional groups such as formyl, acetyl, nitro, and vinyl on the aromatic ring of the arylboronic acids providing the corresponding products **18k**−**18n** in 71%, 79%, 69%, and 77% respectively. Interestingly, *trans*-2-phenylvinylboronic acid also reacted with bisallene **8a** to afford the product **18p** in 45% yield.

The optimized reaction conditions established for the reaction of bisallene **8a** were also tested with other bisallenes **8b**−**8f** (Table 2). When the dimethyl groups of the allene moiety were replaced by more bulky groups such as pentamethylene **8b** or diethyl **8c**, the corresponding products **18q** and **18r** were isolated in 74% and 69% yields, respectively (Entries 2−3). Unsymmetrical allene **8d** also showed a similar reactivity to provide a mixture of **18s** and **18s′** in a 2.7:1 ratio (Entry 4). Deuterated cyclohexadiene derivative $[\mathbf{d}]_5$-**18b** was obtained in 68% yield using bisallene $[\mathbf{d}]_6$-**8a** (Entry 5). Despite the possibility of cross-carbocyclization reaction with substituted bisallenes **8e** and **8f**, we were pleased to find that the reaction gave selectively the carbocyclic products **18t**−**18v** in 57−74% yields under the optimized conditions (Entries 6−8).

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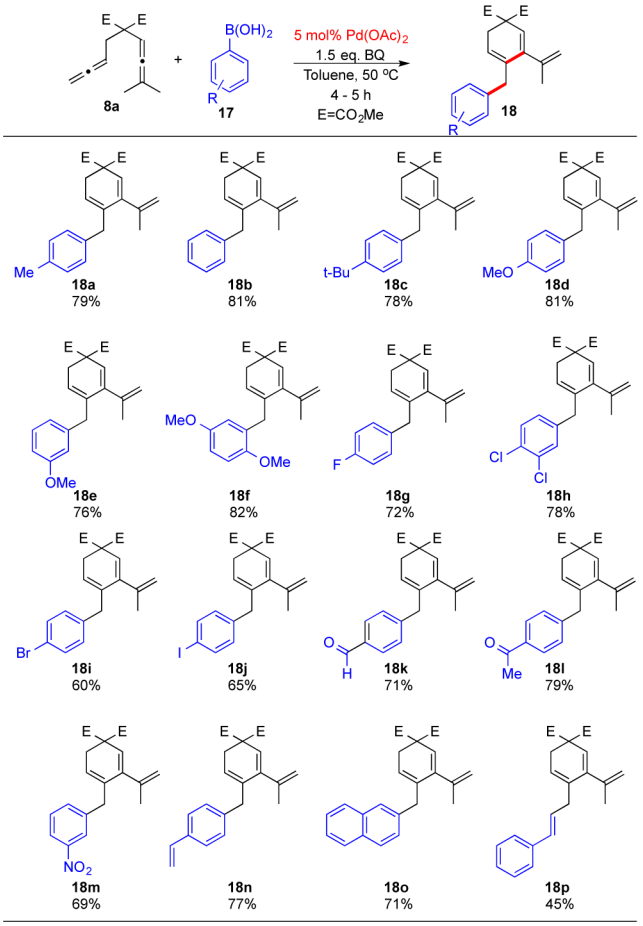
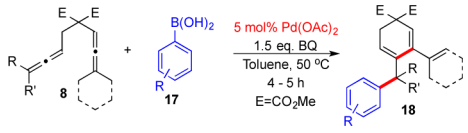
Scheme 3. Scope of the Reaction with Various Boronic Acids

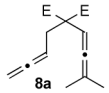
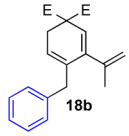
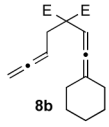
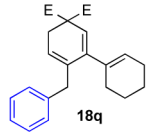
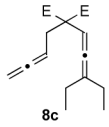
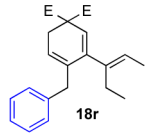
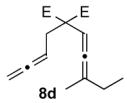
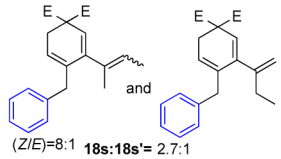
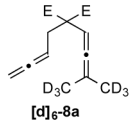
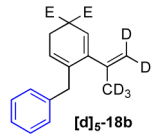
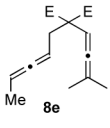
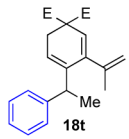
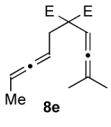
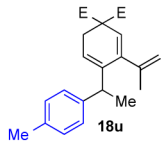
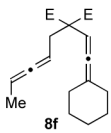
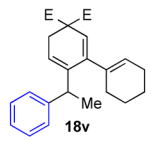


Tetramethyl-substituted bisallene **8g** required a slightly higher temperature (70 °C) for completion and provided the product **18w** in 46% yield along with a cyclopentene byproduct **19** in 18% (Scheme 4). These results indicate the high selectivity of the methodology to form the dienylpalladium(II)-intermediate (cf. **9**) by the nucleophilic attack of the more substituted allene moiety selectively on the palladium(II) center. Nucleophilic attack of the second allene moiety of **18w** onto Pd(II) affords **Int**, which after carbopalladation onto C2−C3 of allene and arylation leads to **19**.

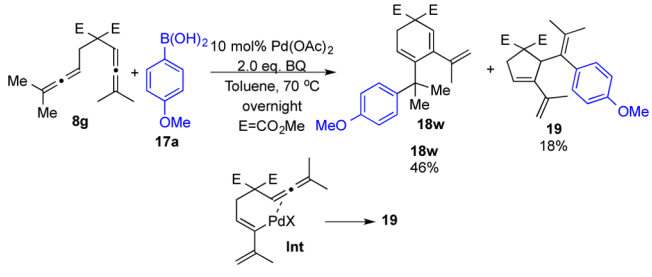
To gain some insight into the reaction mechanism, several control experiments were performed. In the absence of benzoquinone, only traces of the product were observed using 1.0 equiv of $Pd(OAc)_2$ in reaction with **8a**, suggesting that BQ is playing a more pivotal role than acting only as a simple oxidant for this transformation. Enallene **20** was treated with phenylboronic acid (Scheme 5a) under the standard conditions. No formation of the corresponding cyclized product **21** was observed, suggesting that the allene moiety was crucial for the successful Pd(II)-catalyzed carbocyclization. In another control experiment, differently substituted enallene **22** was treated with phenyboronic acid under the optimized conditions (Scheme 5b). Even at a higher temperature with prolonged reaction time, no product was observed. Comparison of this outcome with the isolation of **19** as a byproduct in reaction with **8g** (Scheme 4), clearly suggests the importance of the formation of π-complex between Pd(II) and the allene unit of bisallene for the nucleophilic addition of the allene moiety to

Table 2. Scope of the Various Bisallenes in the Pd-Catalyzed Carbocyclization



No	SM	Product	Yield
1	 8a	 18b	81%
2	 8b	 18q	74%
3	 8c	 18r	69%
4	 8d	 (*Z*/*E*)=8:1 **18s:18s'=** 2.7:1	67%
5	 [d]$_6$-8a	 [d]$_5$-18b	68%
6	 8e	 18t	57%
7	 8e	 18u	74%
8	 8f	 18v	62%

Scheme 4. Pd-Catalyzed Carbocyclization−Arylation Cascade with Bisallene 8g



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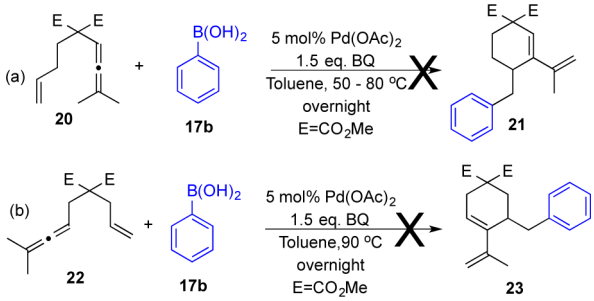
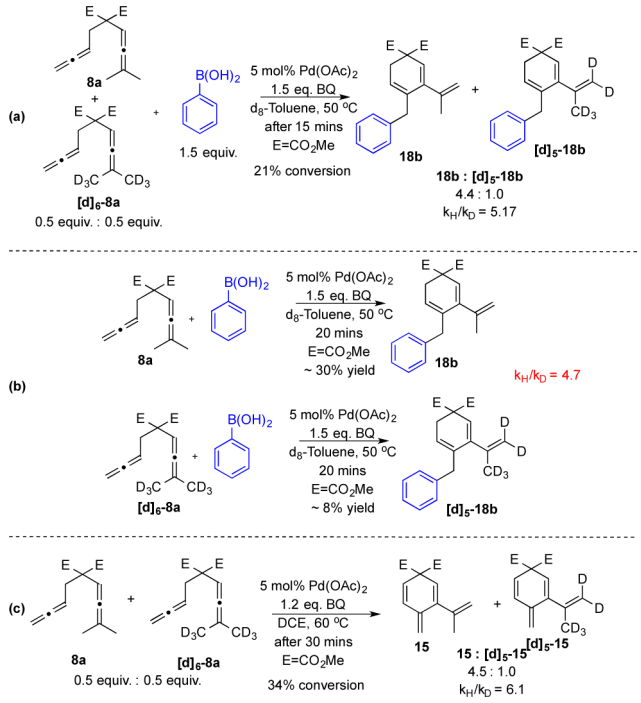
Scheme 5. Attempted Pd-Catalyzed Carbocyclization Reactions with Enallenes



the palladium center to form the required dienylpalladium(II)-complex.

To gain more insight into the reaction mechanism, deuterium kinetic isotopic effect studies were performed. To investigate whether there is any competitive kinetic isotopic effect, a 1:1 mixture of **8a** and $[\mathbf{d}]_6$-**8a** was allowed to react with phenylboronic acid under optimized reaction conditions. A ratio of 4.4:1.0 between **18b** and $[\mathbf{d}]_5$-**18b** was observed (21% conversion, 15 min), from which the KIE (k_H/k_D) was determined to be 5.17 (Scheme 6a). The large KIE value in

Scheme 6. (a) Competitive Kinetic Isotopic Effect; (b) Parallel Kinetic Experiments; (c) Kinetic Isotopic Effect for β-Elimination

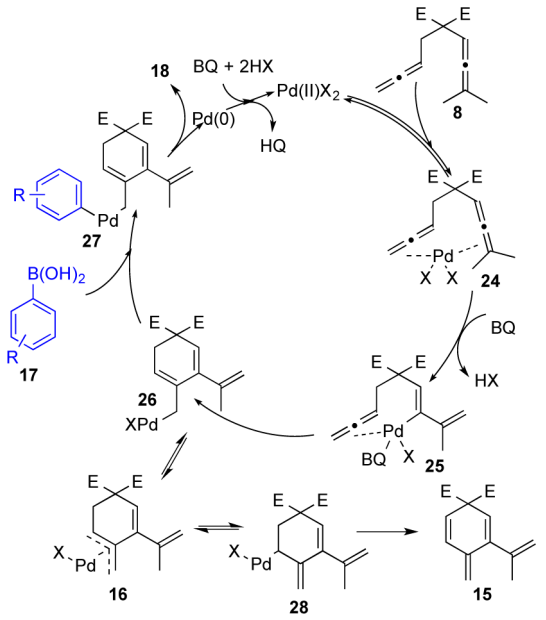


the competitive experiment requires that the C−H bond cleavage has to occur prior to any irreversible step of the reaction. Furthermore, parallel kinetic experiments were also performed where phenylboronic acid was allowed to react with **8a** and $[\mathbf{d}]_6$-**8a** in separate experiments. The progress of both the reactions was monitored by ^{1}H NMR at different time intervals (Scheme 6b). From these parallel kinetic experiments, an intermolecular KIE (k_H/k_D from initial rate) of 4.7 was obtained. The large KIE value of 4.7 indicates that the allylic C−H bond cleavage is involved in the rate-determining step.

In addition, competitive deuterated kinetic studies were also performed for the Pd(II)-catalyzed oxidative carbocyclization-β-elimination process leading to **15** (Scheme 6c). A mixture of **8a** and $[\mathbf{d}]_6$-**8a** was subjected to the conditions that favored the formation of **15**, which afforded a competitive kinetic isotope effect of k_H/k_D = 6.1.

On the basis of the control experiments in Scheme 5 and the deuterium kinetic isotopic experiments, the mechanism in Scheme 7 is proposed. $Pd(OAc)_2$ forms a π-complex (**24**), in

Scheme 7. Proposed Mechanism



which both allene units are coordinated to Pd(II). Nucleophilic attack of the more substituted allene moiety on the palladium center followed by rate-determining allylic C−H bond cleavage leads to the selective formation of dienylpalladium(II) species **25** co-ordinatinated with BQ. The intermediate **25** undergoes intramolecular carbopalladation of the C1−C2 double bond of the second allene generating the (σ-allyl)palladium(II)-intermediate **26**. Subsequent transmetalation with arylboronic acid **17** leads to the formation of **27**. Reductive elimination from **27** affords the product **18**. Competing rearrangement of (σ-allyl)palladium(II) intermediate **26** to the other (σ-allyl)-palladium(II)-intermediate **28** proceeds through the (π-allyl)-palladium(II) complex **16**, which gives **15** after β-elimination.

In conclusion, we have developed a novel palladium(II)-catalyzed oxidatative carbocyclization−arylation cascade reaction of bisallenes and arylboronic acids, providing access to a wide range of functionalized cyclohexadiene derivatives. Despite the possibility of various side reactions, the reaction conditions allowed the selective formation of the carbocyclic products under operationally simple reaction conditions. We propose that the facile formation of six-membered rings is due to the fact that the carbocyclization of the allene is geometrically favored due to perpendicular π-systems of the allene. The selectivity for six-membered rings and the compatibility of the various functional groups are highlights of the current reaction. Further studies to increase the scope of this carbocyclization beyond arylation and the synthetic application of this protocol are underway in our group.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02070.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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