

Palladium-Catalyzed [3 + 2] Annulation of Alkynes with Concomitant Aromatic Ring Expansion: A Concise Approach to (Pseudo)azulenes

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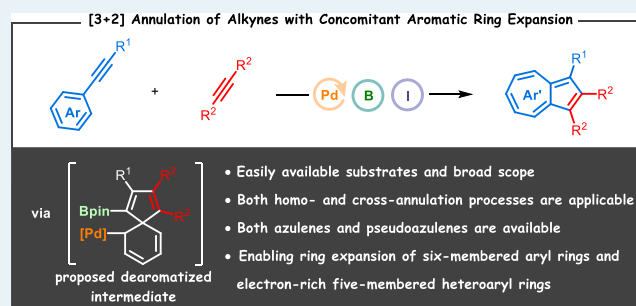
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Supporting Information

ABSTRACT: The construction of (pseudo)azulenes represents an appealing yet challenging task in organic synthetic chemistry. Herein, we disclose a palladium-catalyzed [3 + 2] annulation technique of alkynes with concomitant aromatic ring expansion driven by a diboron reagent and iodide, affording a concise approach to azulenes (7-fused-5 bicycle) and pseudoazulenes (6-fused-5 bicycle). Compared with the documented synthetic strategies, the route to (pseudo)azulenes developed herein is applicable for both homo- and cross-annulation processes and exhibits a broad substrate scope. It is worth noting that this transformation is not only suitable for the ring expansion of the phenyl moiety to afford azulenes but also applicable to the ring expansion of the electron-rich five-membered heterocycles to deliver pseudoazulenes. Experimental and computational investigations on the mechanism support the formal trans-palladium-boration across the alkyne, cis-addition of the alkyne, dearomative spiroannulation, and aromatic ring expansion process.

KEYWORDS: alkyne dimerization, [3 + 2] annulation, ring expansion, (pseudo)azulenes, dearomative spiroannulation



INTRODUCTION

Azulene, which features a fused bicyclic structure of a cyclopentadienyl anion and a tropylium cation, represents the most known nonbenzenoid aromatic hydrocarbon. The unique structure configuration endows it with optical, electronic, and biological properties distinct from those of the isoelectronic isomer naphthalene.¹ To date, azulenes and their analogues have been used for many applications such as pharmaceuticals, fluorescence switching, and organic electronic materials (Scheme 1).^{2–4} Therefore, many efforts have been focused on the development of concise synthetic approaches to azulene derivatives,^{5–9} such as Ziegler–Hafner’s azulene synthesis,⁵ Danheiser’s ring expansion,⁶ Nozoe’s azulene synthesis,⁷ and cycloaddition with fulvenes.⁸ The annulation of diaryl alkynes has also been documented as an efficient route to prepare azulenes in one step. In the early precedents, stoichiometric amounts of palladium salts were typically required, and the yields were rather low.¹⁰ In 2013, Matsuda and Murakami et al. disclosed a π -acidic platinum and gold complex-catalyzed skeletal rearrangement of 2,2-di-(arylethynyl)biphenyls for the synthesis of azulenophenanthrenes (Scheme 2a).¹¹ In 2018, Hashmi and co-workers described the synthesis of substituted azulenes by the homoannulation of diarylalkynes in the presence of a cationic gold catalyst (Scheme 2b).¹² The success of this Lewis acid catalysis procedure is based on the generation of a vinyl cation, which is then attacked by the less electron-rich aromatic ring

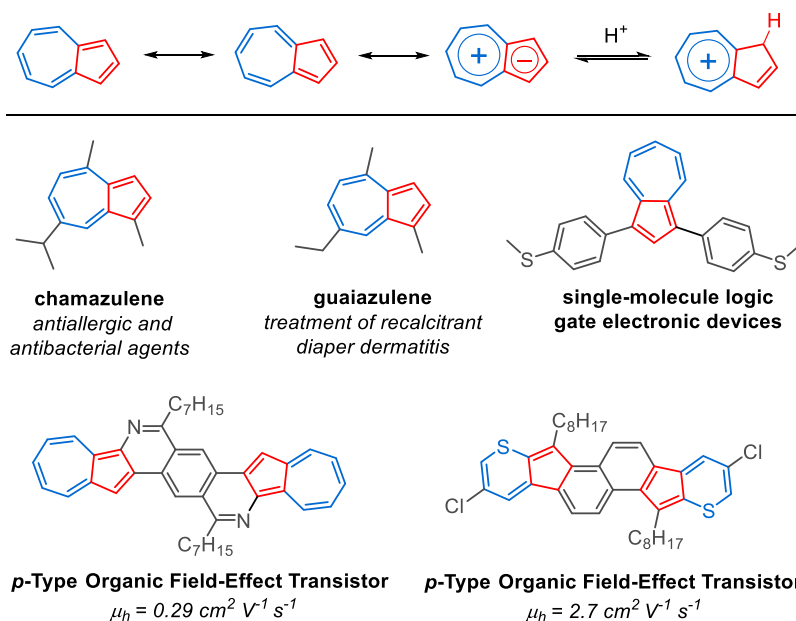
bearing a fluorine substituent to deliver a cationic spirocyclic intermediate via a strong +M effect.^{12,13} However, in the pioneering examples, the cross-annulation between two different alkynes has not been disclosed to construct the azulene skeletons, and diheteroaryl acetylenes have not been used as annulation reagents to deliver 6-fused-5 pseudoazulenes.

Organoboron compounds are versatile reagents and synthetic intermediates enabling many valuable chemical transformations in organic synthesis.¹⁴ Recently, transition-metal-catalyzed borylative difunctionalization of alkynes has emerged as a powerful tool to provide diverse functionalized alkenyl boron compounds. In these processes, the borylmetallic species are typically added on the same side of the carbon–carbon triple bond to give the cis-borated alkenylmetallic species, followed by capturing another electrophile (Scheme 2c).¹⁵ Undoubtedly, the significance of this chemistry could be further highlighted by participation of the *in situ* produced reactive borylmetallic alkenyl intermediates in the assembly of

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Scheme 1. Dipolar Structural Features and Selected Examples on (Pseudo)azulene Derivatives



more complex structures. Herein, we wish to describe the palladium-catalyzed [3 + 2] reaction between (hetero)aryl alkyne (3C synthon) and alkyne (2C synthon) accompanied by ring expansion, providing a unique approach to substituted azulenes and pseudoazulenes (Scheme 2d). Diaryl alkynes, diheteroaryl alkynes, and aryl alkyl alkynes can undergo both the homo- and cross-annulation reactions with alkynes. The reaction is proposed to involve the formal trans-palladium-boration of the internal alkyne, cis-addition of an alkyne, dearomatization spiroannulation, and ring expansion process, in which iodide is proposed to act as a pivotal ligand to trigger the reaction and drive the cis–trans isomerization of boroalkenyl palladium species. This reaction is impressive considering that the following challenges encountered can be overcome: (a) while much success has been achieved on transition-metal-catalyzed cis-selective borylative 1,2-difunctionalization of alkynes, relatively fewer reports have been disclosed on such reactions involving a trans-selective mode;¹⁶ (b) the dearomatization process is thermodynamically disfavored owing to the high aromatic stabilization energy of planar arenes;^{17,18} and (c) a number of possible side reactions have to be avoided such as the protonation of highly reactive organopalladium intermediates, diborylative addition, and protodeborylation and cyclopolymerization of alkynes.^{15,19} In the present paper, we report our synthesis together with study of the reaction mechanism.

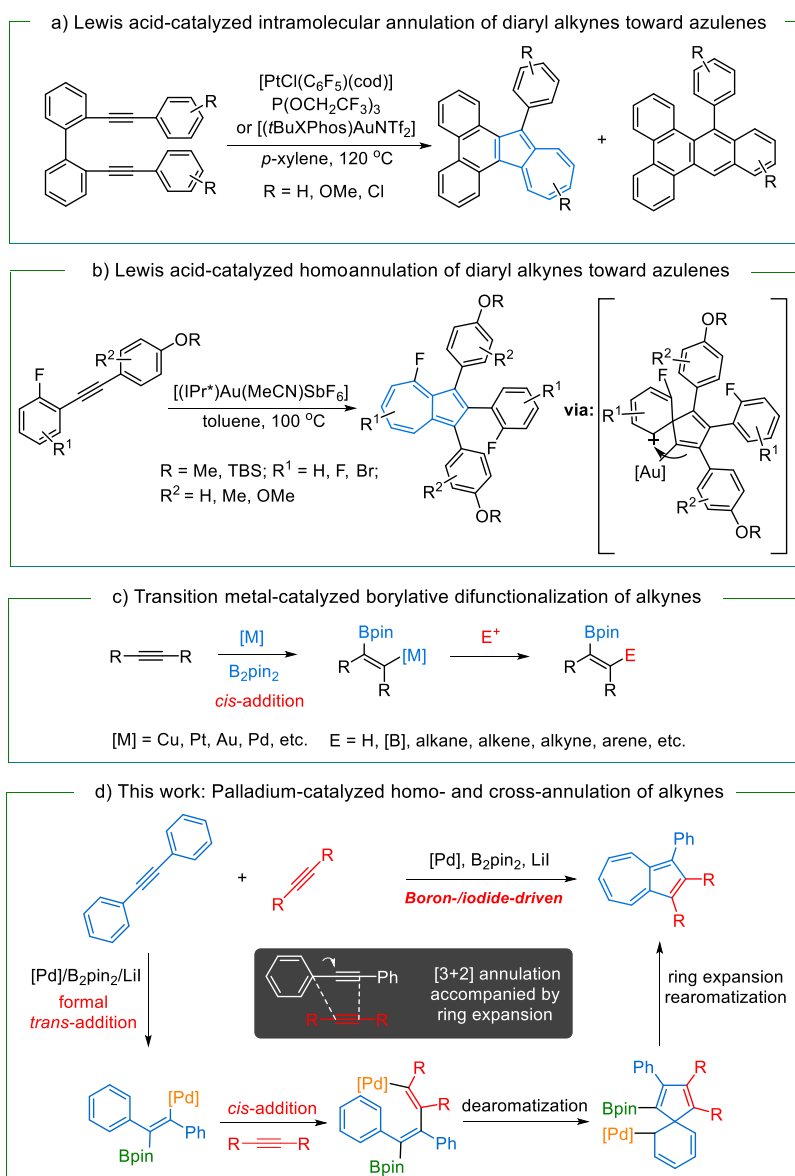
RESULTS AND DISCUSSION

Reaction Discovery and Development. During our investigation on the palladium-catalyzed carboborylation of alkynes with aryl iodides, we surprisingly found that 1,2,3-triphenyl azulene **3a** rather than triphenyl alkenylborate²⁰ was formed in 14% yield when diphenyl acetylene **1a** reacted with phenyl iodide in the presence of Pd(acac)₂ (10 mol %) and B₂Pin₂ (2.0 equiv) in 2-methyl tetrahydrofuran (2-Me-THF) (Scheme 3). The structure of the azulene product **3a** was confirmed by single-crystal X-ray diffraction analysis (Scheme 4). This unexpected observation encouraged us to further study this chemistry. When phenyl bromide or chloride instead

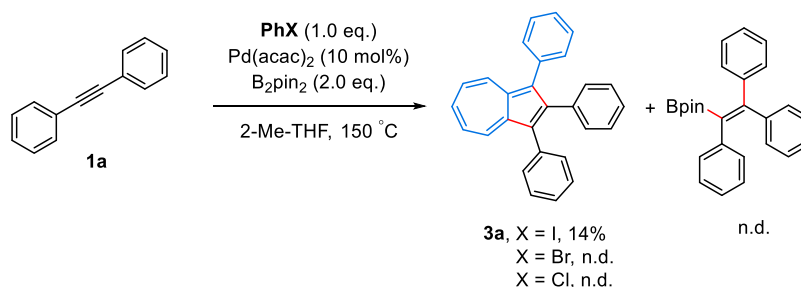
of phenyl iodide was subjected to the above catalytic system, no azulene **3a** was detected. Based on these results, we conjectured that iodide may play an important role in this reaction.

When KI (3.0 equiv) was used instead of aryl iodide, a 12% yield of **3a** was obtained under the otherwise identical conditions (Table 1, entry 1). Other non-iodide additives such as Cs₂CO₃, KO^tBu, and LiO^tBu could not promote this reaction (Table 1, entries 2–4). After extensive screening of the common iodides including I₂, Bu₄NI, iodotrimethylsilane (TMSI), NiI₂, and LiI, the reaction yield could be improved to be 62% along with the generation of 6% yield of (*E*)-hydroborated diphenyl alkene **5a** and 17% yield of the recovered starting material **1a** using LiI as the additive (Table 1, entries 5 and 6, and Table S1, entry 9, and Scheme S1 in the Supporting Information). Next, the palladium catalyst precursors were examined. While Pd(CH₃CN)Cl₂ gave the desired product **3a** in a diminished yield of 21% (Table 1, entry 7), other common palladium sources such as PdCl₂ and Pd(OAc)₂ almost did not promote this transformation (Table 1, entries 8 and 9). Palladium(II) complexes with other 1,3-diketone ligands such as hexafluoropentane-2,4-dione, 1,3-diphenylpropane-1,3-dione, and methyl isobutyrylacetate provided **3a** in decreased yields (Table 1, entries 10–12). The palladium salt with steric hindered 2,2,6,6-tetramethylheptane-3,5-dione as the ligand only gave a trace amount of **3a** (Table 1, entry 13). The addition of ligands such as 1,10-phenanthroline (**L1**), 2,2'-bipyridine (**L2**), triphenylphosphine (**L3**), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos, **L4**), and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr-HCl, **L5**) was detrimental to the described annulation reaction (Table 1, entry 14). While B₂neop₂ gave the desired product **3a** in 12% yield (Table 1, entry 15), other common boron reagents such as B₂(NMe₂)₄, B₂cat₂, and HBpin could not promote the annulation reaction (Table 1, entry 16). Ether-type solvents such as THF and 1,4-dioxane as well as nitrile solvents such as acetonitrile were also suitable for this reaction, albeit in lower efficiency (Table 1, entries 17–19). No azulene product was detected in the

Scheme 2. Annulation and Addition Reactions of Alkynes

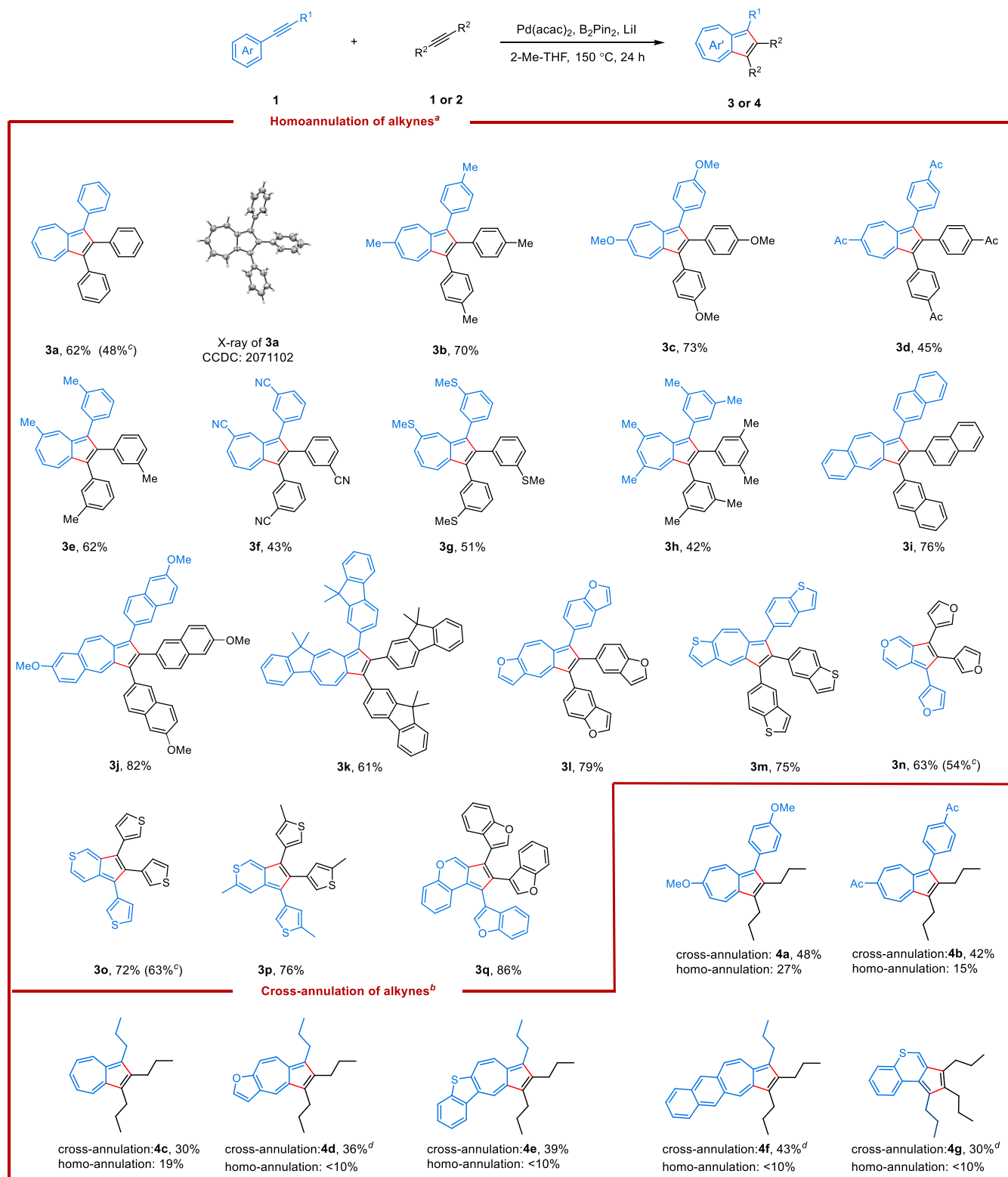


Scheme 3. Reaction Discovery



absence of either the palladium catalyst, LiI, or the boron reagent, indicating the essential role of these reagents (Table 1, entries 20–22). In addition, decreased yields of **3a** were obtained when the dosage of B₂pin₂ or LiI was reduced (Table S2 in the Supporting Information). Therefore, we chose the conditions in entry 6 as the optimal conditions to investigate the scope of the present reaction.

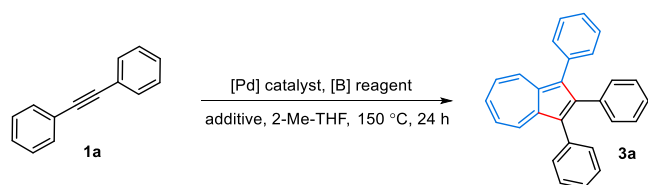
Substrate Scope. With the optimized reaction condition in hands, we investigated the substrate scope of this reaction (Scheme 4). Diaryl acetylenes with electron-neutral, -donating, or -withdrawing groups such as methyl, methoxy, methylthio, acetyl, and cyano could undergo the [3 + 2] annulation accompanied by aromatic ring expansion to afford the corresponding azulenes in 42–73% yield (**3a–3h**). The position of substituents on the phenyl ring exhibited an

Scheme 4. Substrate Scope^a

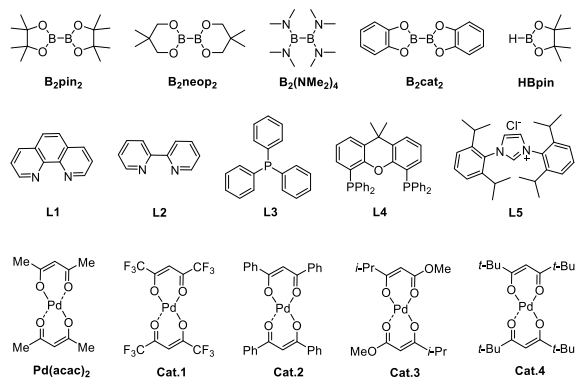
^aReaction conditions: **1** (0.2 mmol), Pd(acac)₂ (10 mol %), B₂pin₂ (2.0 equiv), and LiI (3.0 equiv) in 2-Me-THF (1 mL) at 150 °C under N₂ for 24 h. ^bReaction conditions: **1** (0.1 mmol), 4-octyne **2a** (0.3 mmol), Pd(acac)₂ (20 mol %), B₂pin₂ (4.0 equiv), and LiI (6.0 equiv) in 2-Me-THF (1 mL) at 150 °C under N₂ for 24 h. ^cReaction was performed in a 2 mmol scale. ^dReaction for 48 h.

obvious influence on the yields. Generally, the *para* substitution led to a better yield than the *meta* substitution (**3b** vs **3e**). No azulene products were detected when diaryl acetylenes with *ortho* substituents were used. Instead, a trans-

hydroborylative adduct was obtained along with large amounts of intact substrates (Scheme 5, eq 6). Besides diphenyl acetylenes, internal alkynes with the fused aryl rings such as 2-naphthyl and 9,9-dimethyl-9H-fluoren-2-yl were also suitable

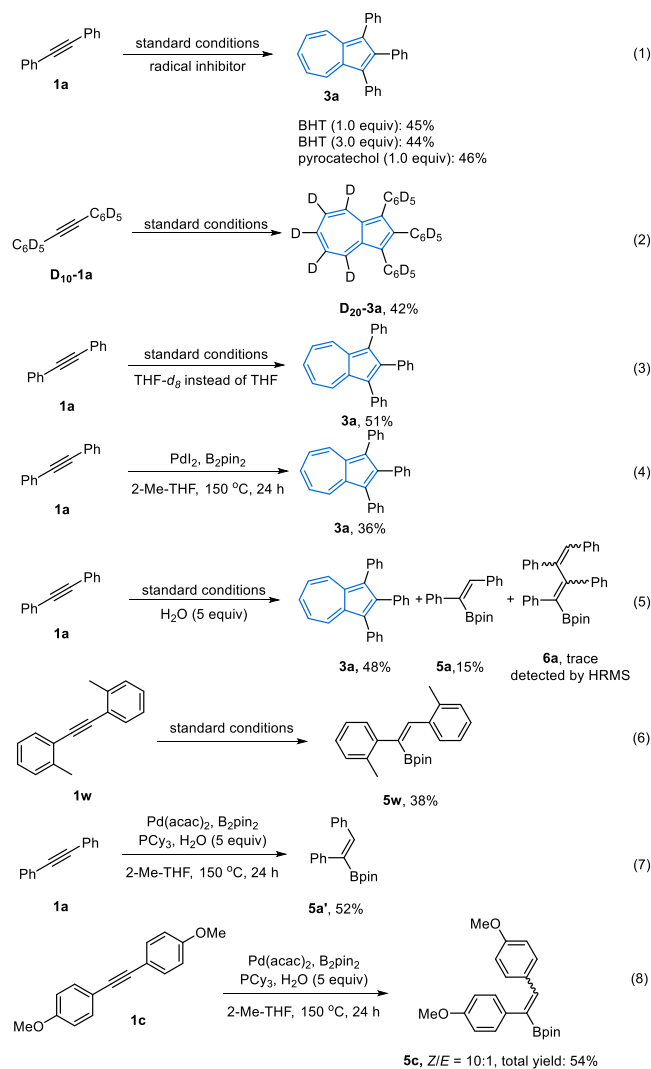
Table 1. Optimization of the Reaction Conditions^a

Entry	Catalyst	[B]	Additive	Yield (%)
1	Pd(acac) ₂	B ₂ pin ₂	KI	12
2	Pd(acac) ₂	B ₂ pin ₂	Cs ₂ CO ₃	n.d.
3	Pd(acac) ₂	B ₂ pin ₂	KO ^t Bu	n.d.
4	Pd(acac) ₂	B ₂ pin ₂	LiO ^t Bu	n.d.
5	Pd(acac) ₂	B ₂ pin ₂	I ₂	n.d.
6	Pd(acac) ₂	B ₂ pin ₂	LiI	62
7	Pd(CH ₃ CN)Cl ₂	B ₂ pin ₂	LiI	21
8	PdCl ₂	B ₂ pin ₂	LiI	trace
9	Pd(OAc) ₂	B ₂ pin ₂	LiI	n.d.
10	Cat. 1	B ₂ pin ₂	LiI	51
11	Cat. 2	B ₂ pin ₂	LiI	46
12	Cat. 3	B ₂ pin ₂	LiI	42
13	Cat. 4	B ₂ pin ₂	LiI	trace
14	PdCl ₂ +L1, L2, L3, L4 or L5	B ₂ pin ₂	LiI	n.d.
15	Pd(acac) ₂	B ₂ neop ₂ B ₂ (NMe ₂) ₄	LiI	12
16	Pd(acac) ₂	B ₂ cat ₂ or HBpin	LiI	n.d.
17 ^b	Pd(acac) ₂	B ₂ pin ₂	LiI	52
18 ^c	Pd(acac) ₂	B ₂ pin ₂	LiI	28
19 ^d	Pd(acac) ₂	B ₂ pin ₂	LiI	50
20	-	B ₂ pin ₂	LiI	n.d.
21	Pd(acac) ₂	-	LiI	n.d.
22	Pd(acac) ₂	B ₂ pin ₂	-	n.d.



^aReaction conditions: alkyne **1a** (0.2 mmol), catalyst (10 mol %), boron reagent [B] (2.0 equiv), and additive (3.0 equiv) in 2-Me-THF (1 mL) at 150 °C under N₂ for 24 h. ^bTHF was used as the solvent. ^c1,4-Dioxane was used as the solvent. ^dCH₃CN was used as the solvent. n.d.: not detected.

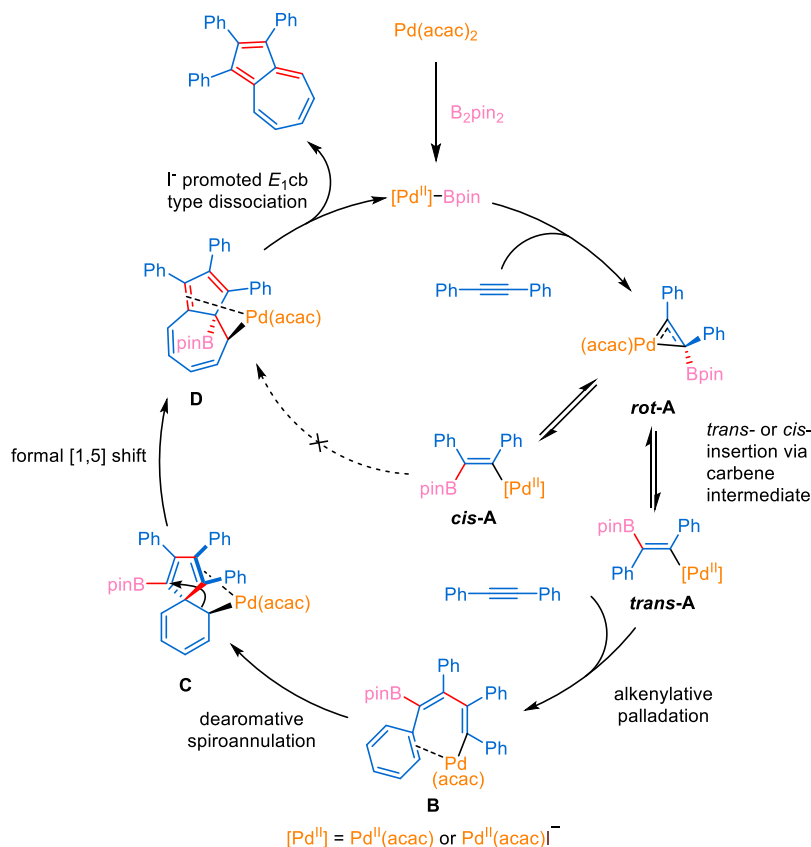
substrates, providing the π -extended azulenes in good yields (76% yield for **3i**, 82% yield for **3j**, and 61% yield for **3k**). Furthermore, benzoheteroarenes such as 1,2-di(benzofuran-5-yl)ethyne and 1,2-bis(benzothiophen-5-yl)ethyne could be smoothly converted to the corresponding heteroaryl-fused azulenes through the expansion of the phenyl ring (**3l** and **3m**). Very interestingly, di(β -furanyl) and di(β -thienyl)-acetylenes gave the pseudoazulenes through the ring expansion of the five-membered heterocycle in moderate to high yields

Scheme 5. Mechanism Investigation^a

^aStandard conditions: **1a** (0.2 mmol), Pd(acac)₂ (10 mol %), B₂pin₂ (2.0 equiv), and LiI (3.0 equiv) in 2-Me-THF (1 mL) at 150 °C under N₂ for 24 h.

(**3n–3p**). In contrast to the reaction with 1,2-di(benzofuran-5-yl)ethyne, the reaction of 1,2-di(benzofuran-3-yl)ethyne produced pseudoazulene **3q** in 86% yield. This is quite remarkable considering that the previously reported transition-metal-mediated dimerizations of diarylacetylenes toward azulenes were incompatible with diheteroaryl acetylene substrates. When the nonsymmetrical diaryl alkynes such as 1-methoxy-4-(phenylethynyl)benzene **1x** were subjected to the present catalytic system, a mixture of azulenes consisting of four isomers was generated with a total yield of 36% (see the Supporting Information, Scheme S2). To further examine the substrate scope, the cross-annulation of diaryl alkynes or aryl alkyl alkynes with alkyl alkynes was attempted (Scheme 4). To our delight, with a substrate molar ratio of 1:3, diaryl acetylenes and dialkyl acetylenes could engage in the transformation under the standard conditions, albeit in lower yields (**4a** and **4b**). Notably, unsymmetrical aryl alkyl alkynes could also work under the described catalytic system to deliver a variety of 1,2,3-trialkyl-substituted azulenes (**4c–4g**). The homoannulating products of the arylalkynes were also generated as the side products in these reactions (Schemes

Scheme 6. Proposed Catalytic Cycle



S3–S9). It should be mentioned that the obtained homoannulation byproducts (less than 10% yield) in the synthesis of azulenes **4d–4g** always involved unseparated uncertain impurities. The competition reaction with two electronically different diaryl alkynes (**1c** and **1d**) gave a mixture of cross-annulation and homoannulation products in low yields, in which electronic-rich **1c** delivers a slightly higher yield than electronic-poor **1d** in the homoannulation (**3c/3d** = 5:3, see the [Supporting Information](#), Scheme S10).

Mechanism Investigation. To shed light on the reaction mechanism of this annulation reaction, preliminary experimental investigations were carried out (Scheme 5). Under the standard conditions, the reaction of diphenyl acetylene **1a** in the presence of common radical inhibitors such as butylated hydroxytoluene (BHT) and pyrocatechol gave a moderately decreased yield. The reaction could not be completely inhibited even in the presence of 3.0 equiv of BHT (eq 1). In addition, no obvious signal was detected in the electron paramagnetic resonance (EPR) experiment. These results suggested that a single-electron transfer process may not be involved in the present azulene synthesis reaction. The reaction with the deuterated substrate D_{10} -**1a** under the standard conditions gave D_{20} -**3a** in 42% yield, and the reaction of **1a** in D_8 -THF furnished **3a** in 51% yield, indicating that no H–D scrambling took place in the annulation reaction (eqs 2 and 3). The replacement of $Pd(acac)_2$ and LiI with PdI_2 could afford the substituted azulene **3a** in 36% yield (eq 4). In contrast, in the absence of an iodide, no desired reaction was detected, and most of alkyne **1a** remained intact (Table 1, entries 2–4). These results demonstrated the pivotal role of iodide in the aromatic ring expansion accompanied by the [3 +

2] annulation of aryl alkynes. When 5.0 equiv of H_2O (employed to capture the organometallic intermediate) was added to the catalytic system, **3a** was formed in 48% yield along with 15% yield of (*E*)-hydroborated diphenyl alkene **5a** and a trace amount of the borylated 1,3-diene adduct **6a** (eq 5). The reaction of 1,2-di-*o*-tolylethyne delivered hydroborated (*E*)-1,2-di-*o*-tolylethene **5w** rather than the corresponding azulene product in 38% yield (eq 6). These results indicated that the reaction might involve a cascade formal trans-addition of Pd–Bpin species on the C–C triple bond and an alkenylative palladation of another alkyne moiety. Moreover, when the reaction of **1a** was conducted in the presence of tricyclohexyl phosphine (PCy_3) without LiI, (*Z*)-hydroborated diphenyl alkene **5a'** was obtained in 52% yield (eq 7). Furthermore, the reaction of 1,2-bis(4-methoxyphenyl)ethyne **1c** in the absence of LiI gave the corresponding hydroborated alkene isomers **5c** in 54% yield (*Z/E* = 10:1). These results suggested that iodide is important to enable the trans-palladium-boration across the alkyne and following the azulene formation process (eqs 5–8).

Proposed Mechanism. Based on the preliminary mechanistic experiments and density functional theory (DFT) calculations (*vide infra*), a proposed mechanism is shown in Scheme 6 to explain the reaction. The reaction starts from the addition of the boryl palladium to diphenylacetylene, yielding a carbene-type intermediate, *rot-A*,^{22e} which could be in equilibrium with *trans-A* and *cis-A*. However, only *trans-A* can lead to the final product (*vide infra*). Such step is followed by another diphenylacetylene insertion to the palladium–carbon bond, giving intermediate **B**, which then undergoes a C–Pd bond insertion to the terminal phenyl ring, giving rise to

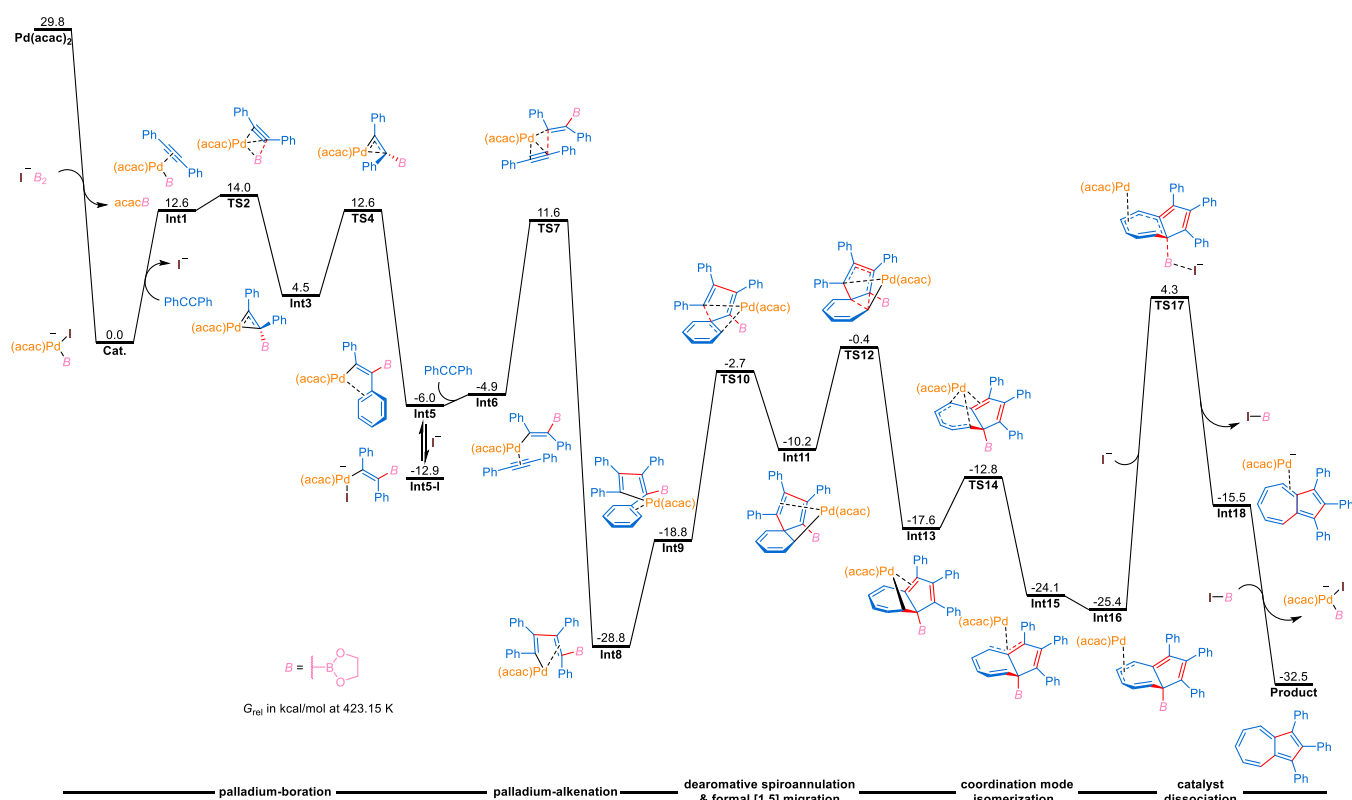


Figure 1. Gibbs free energy surface of the main reaction process at the SMD(THF)/*w*B97M-V/def2-QZVP//IEFPCM(THF)/PBE0-D3(BJ)/def2-SVP(-p) level.

a spiral intermediate, **C**, with a cyclopentadiene unit.²¹ After that, the [1,5]-alkyl migration for the cyclopentadiene part generates intermediate **D**, a complex formed between the boronized azulene and Pd(II). Finally, I⁻-assisted Pd–B elimination converts **D** to the final product and simultaneously releases the Pd–Bin catalyst. In what follows, we present the whole process with the DFT-computed kinetic and thermodynamic data (see the [Supporting Information](#) for the detailed computational settings).

Computational Investigation. In order to save computational time, a model system, in which the boron–pinacol (Bpin) groups were simplified by boron–glycol groups, was utilized ([Figure 1](#)). The calculated Gibbs energy surface is shown in [Figure 1](#). The reaction was proposed to be initiated by the ligand exchange between Pd(acac)₂, diborate, and iodine anions to give **Cat** as the catalytic active species. Then, the iodine anion can be further replaced by diphenylacetylene. These two steps give **Int1**, which then undergoes alkyne insertion, with a computed ΔG^\ddagger of 14.0 kcal/mol (from **Cat** and diphenylacetylene to **TS2**). **TS2** leads to neither the cis-adduct nor the trans-adduct but an unexpected twisted intermediate **Int3**.^{16a,22} It is noteworthy that such a structure is more frequently found to be a transition state, but here, this is an intermediate. This fact could be attributed to the stabilization of the sp³ C–Pd bond in this species through the hyperconjugation effect of the Bpin group. **Int3** may isomerize via the rotation of the C–C bond through **TS4** to give a formal trans-adduct, namely, **Int5**. Then, **Int5** can combine with iodide to form **Int5-I**, which is an off-cycle species. To continue the reaction, **Int5** then undergoes a second palladium–carbonation reaction with diphenyl acetylene, via **TS7**, to give **Int8**, an intramolecular olefin–Pd complex. Such

insertion requires a ΔG^\ddagger of 24.5 kcal/mol (from **Int5-I** to **TS7**). After that, **Int8** can be converted to **Int9** by changing its coordination pattern, from the Pd–alkene coordination to a Pd–aryl ring coordination. Then, the C–Pd bond in **Int9** undergoes a dearomative addition toward the phenyl ring through **TS10**, forming a five-membered spiral species, **Int11**. Such a step has a ΔG^\ddagger of 26.1 kcal/mol (from **Int8** to **TS10**). Calculations indicate that **Int11** undergoes a rapid formal [1,5] carbon migration^{11,12,23} on the cyclopentadiene ring via **TS12**. This rearrangement changes the cyclohexadienyl palladium structure to a palladium–cycloheptadiene complex, **Int13**. Then, **Int13** isomerizes into the allyl–palladium(II) complex **Int15** via **TS14** in a formal [1,5] palladium shift process. The geometry organization of **Int15** by changing the coordination type of Pd gives a more stable complex, **Int16**. The boron ester group was eliminated from **Int16** by excess iodide anions in a E₁cb pattern via **TS17**, and a Pd(0) anionic complex, **Int18**, is generated with a computed ΔG^\ddagger of 33.1 kcal/mol (**Int8** to **TS17**), which is the rate-limiting step of the whole catalytic cycle. The high activation free energy of this step is also consistent with the required temperature for this reaction (150 °C). Finally, the triphenylazulene product dissociates from Pd(0) through the oxidative addition of the B–I bond to the palladium center, which is accompanied by the regeneration of **Cat**.

Origin of the Observed Cis-/Trans-Selectivity. The selectivity during the main reaction scheme mainly results in the spatial requirement of the dearomative addition step. Only **Int8** from the initial trans-adduct has a stereoaccessible δ -phenyl ring, while the cis-adduct may only insert into the γ -phenyl ring and leads to a strained cyclobutene product, which is highly disfavored both thermodynamically and kinetically.

absence of iodide (Scheme 5, eqs 7 and 8), Int5-cis-Me4 with a B–O··Pd chelating interaction becomes the most stable intermediate and is quenched to give (Z)-vinylborate as a separated product.

CONCLUSIONS

In summary, we have demonstrated a unique catalytic system composed of a Pd complex, B₂pin₂, and LiI to trigger a [3 + 2] annulation process of alkynes accompanied by ring expansion. This reaction provides an efficient and convenient access to 1,2,3-trisubstituted (pseudo)azulenes. A mechanism involving the oxidative addition of the I–B bond to the palladium center, followed by the sequential formal trans-palladium boration on alkyne/cis-addition of alkyne/dearomative spiroannulation/aromatic ring expansion. The origin of the observed formal trans-selectivity in the borylative palladation is actually due to the spatial requirement of the subsequent dearomatization step and the Curtin–Hammett principle since fast swap between the cis- and trans-intermediates occurs. The simple operation procedure and product diversity render this method potentially applicable in the exploitation of functional materials and pharmaceuticals based on substituted azulene scaffolds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.1c04549>.

Detailed experimental procedures, characterization data, copies of ¹H and ¹³C NMR spectra of final products, UV–vis and fluorescence spectra, single-crystal X-ray diffraction analysis of **3a**, computational details, and Cartesian structures (PDF)

X-ray crystallographic Information of **3a** (CCDC-2071102) (CIF)

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Notes

The authors declare no competing financial interest.

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