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Very Important Publication

The Synthesis of Benzofulvenes through Palladium-Catalyzed Sequential Three-Component Reactions

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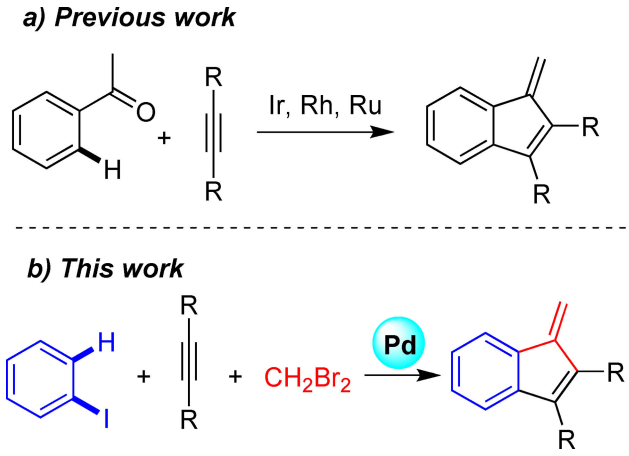
Abstract: An approach for the synthesis of benzofulvenes has been developed through palladium-catalyzed sequential three-component reactions. The reactions likely involve *C*,*C*-palladacycles as the key intermediates. The palladacycles are generated through cascade reactions of aryl halides and alkynes, and then reacted with CH_2Br_2 to form benzofulvenes as the final products.

Keywords: *C*,*C*-palladacycles; C–H activation; Alkylation; Palladium; Benzofulvenes

Benzofulvenes are key privileged scaffolds present in natural products and bioactive molecules and have found versatile applications in materials science, medicinal chemistry and organometallics.[1] In particular, benzofulvenes are important monomers in polymer chemistry, and polybenzofulvenes often show intriguing properties.[1e,f] A great number of methods have been developed for the synthesis of benzofulvenes.[2] The traditional methods often rely on the use of structurally complex starting materials. Notably, the synthesis of benzofulvenes through C–H activation has also been reported.[3] However, the reactions are limited to those using aryl ketones as starting materials. Therefore, continuous efforts should still be devoted to seeking new reactions for the synthesis of benzofulvenes.

As an important class of organometallic compounds, metallacycles are very common intermediates in transition-metal catalysis,[4] in particular in transition-metal-catalyzed C–H functionalization reactions.[5] In this context, *C*,*C*-palladacycles are particularly attractive.[6] *C*,*C*-Palladacycles consist of a C–Pd–C bonding motif and contain two C–Pd bonds. Due to their unique structures, *C*,*C*-palladacyclic intermediates may exhibit novel reactivity. More importantly, the presence of two C–Pd bonds offers opportunities to develop new transformations. *C*,*C*-Palladacycles are usually obtained by Pd-catalyzed intramolecular C–H activation of aryl halides as starting materials.[7] However, for this method, since *C*,*C*-palladacycles are synthesized directly from the Pd-mediated cyclization of the substrates, the substrates have complex structures and have to be presynthesized. Therefore, it is highly desirable to develop new methods for the synthesis of *C*,*C*-palladacycles by employing simple substrates.

It has been reported that *C*,*C*-palladacycles could be obtained from aryl halides and alkynes, which represents a straightforward method for the construction of *C*,*C*-palladacycles from relatively simple precursors.[8] However, the resulting palladacycles usually underwent intramolecular cyclization. Although the intermolecular arylation of *C*,*C*-palladacycles formed

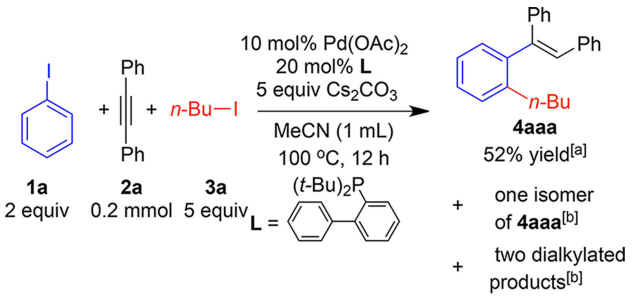


Scheme 1. Synthesis of benzofulvenes *via* transition-metal-catalyzed C–H activation.

via reactions of aryl iodides and alkynes has been developed, the aryl iodides were also the starting materials forming the *C*,*C*-palladacycles.[9] Actually, this reaction indicates that it should be quite a challenge to functionalize such *C*,*C*-palladacycles obtained from aryl halides and alkynes with other external reagents. Since multiple reactants, intermediates, and steps are involved in the reactions, each step should proceed in a well-defined sequence to make the reactions occur as desired. Herein, we report the alkylation reaction of *C*,*C*-palladacyclic intermediates obtained from aryl halides and alkynes. The transformation represents a novel method for the synthesis of benzofulvenes.

As it has been demonstrated that *C*,*C*-palladacycles have high reactivity towards alkyl halides,[7n] we first investigated alkylation reaction of *C*,*C*-palladacyclic intermediates obtained from aryl halides and alkynes. Therefore, iodobenzene **1a** and diphenylacetylene **2a** were selected for constructing *C*,*C*-palladacycle, and *n*-butyl iodide was used as the alkylating reagent. After extensive screening, alkylated product **4aaa** was obtained in 52% yield under the conditions as shown in Scheme 2. An isomer of **4aaa** and two dialkylated products were also observed by GC-MS. Although the structures of these minor isomers could not be identified due to insufficient quantities, the isomer of **4aaa** may result from the alkylation of the alkene moiety (for the mechanism of the alkylation reaction see the Supporting Information).

The greatest advantage of *C*,*C*-palladacycles is that they contain two C–Pd bonds. Although the above alkylation reaction demonstrates the feasibility of intermolecular functionalization of *C*,*C*-palladacycles obtained from aryl halides and alkynes, only one C–Pd bond was functionalized. Our aim is to develop synthetically useful reactions by functionalizing both C–Pd bonds of *C*,*C*-palladacycles. We found that *C*,*C*-palladacycles can react with CH_2Br_2, affording fluorenes as the products.[10] Therefore, we turned to investigate the reaction of the *C*,*C*-palladacycles



[a]Yields of the the isolated products.
[b]Observed by GC-MS.

Scheme 2. Alkylation of *C*,*C*-palladacyclic intermediate with alkyl iodides.

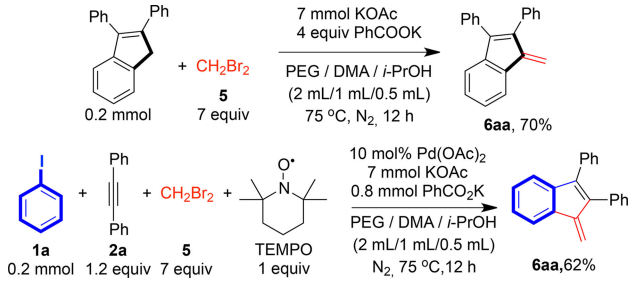
formed in situ from aryl halides and alkynes with CH_2Br_2. Unexpectedly, benzofulvene **6aa** was obtained in the reaction of **1a**, **2a**, and **5** in the presence of $Pd(OAc)_2$ and KOAc (Table 1, entry 1). Spurred by this exciting result, we continued to optimize the reaction conditions. The addition of $PhCO_2K$ promoted the yield to 21% (entry 2). The same amount of KOAc was less effective (entry 3). The yield was improved to 30% when 0.5 mL isopropanol was added. The isopropanol should act as a reductant, because the catalytic cycle is expected to start with Pd(0). Gratefully, a yield of 50% was obtained by replacing isopropanol with PEG (entry 5).[11] The yield increased when the reaction was carried out in a mixture of DMA, PEG, and isopropanol (entries 6 and 7). Finally, benzofulvene was formed in 90% yield when the amount of KOAc was enhanced to 7 mmol. While the role of KOAc is unknown, KOAc is a common base in the C–H activation reaction of aryl halides and can promote C–H activation.[12]

To gain insight into the mechanism of the benzofulvene-forming reaction, we first synthesized 2,3-diphenyl-1*H*-indene. When 2,3-diphenyl-1*H*-indene was allowed to react with CH_2Br_2, **6aa** was obtained in a yield of 70%. Furthermore, a small amount of 2,3-diphenyl-1*H*-indene was observed under some conditions that were tested during the course of reaction

Table 1. Optimization of reaction conditions for the benzofulvene-forming reaction.

Entry	Base (mmol)	Solvent (mL)	Yield (%)[a]
1	KOAc (2.4)	DMA (2)	11
2	$KOAc/PhCO_2K$ (2.4/0.8)	DMA (2)	21
3	KOAc (3.2)	DMA (2)	15
4	$KOAc/PhCO_2K$ (2.4/0.8)	DMA/*i*-PrOH (2/0.5)	30
5	$KOAc/PhCO_2K$ (2.4/0.8)	DMA/PEG (2/0.5)	50
6	$KOAc/PhCO_2K$ (2.4/0.8)	DMA/PEG/*i*-PrOH (2/0.5/0.5)	61
7	$KOAc/PhCO_2K$ (2.4/0.8)	DMA/PEG/*i*-PrOH (1/2/0.5)	72
8	$KOAc/PhCO_2K$ (7/0.8)	PEG/DMA/*i*-PrOH (2/1/0.5)	90 (85[b])

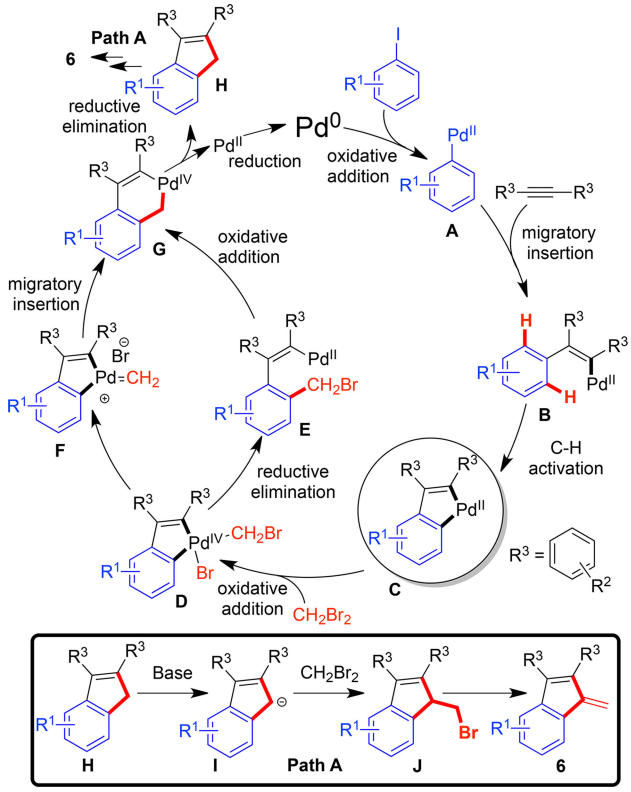
[a] The yields were determined by ^1H NMR analysis of the crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard.
[b] Isolated yield. PEG = poly(ethylene glycol) 400. DMA = *N*,*N*-dimethylacetamide.



Scheme 3. Mechanistic studies.

optimization. These outcomes indicate that 2,3-diphenyl-1*H*-indene should be formed as the intermediate in the reaction. The benzofulvene was formed in good yields when the reaction was performed in the presence of TEMPO, which is against a SET process.

On the basis of these experimental results and previous reports,[9a,10, 13] a mechanism is proposed as shown in Scheme 4. The catalytic cycle starts with the oxidative addition of iodobenzenes to Pd(0). The resulting arylPd(II) species **A** undergo migratory insertion to form vinylPd(II) species **B**. The subsequent intramolecular C–H activation generates *C*,*C*-palladacycle **C.** **C** may undergo oxidative addition of CH_2Br_2 to form Pd(IV) complex **D**. The reductive elimination and intramolecular oxidative addition



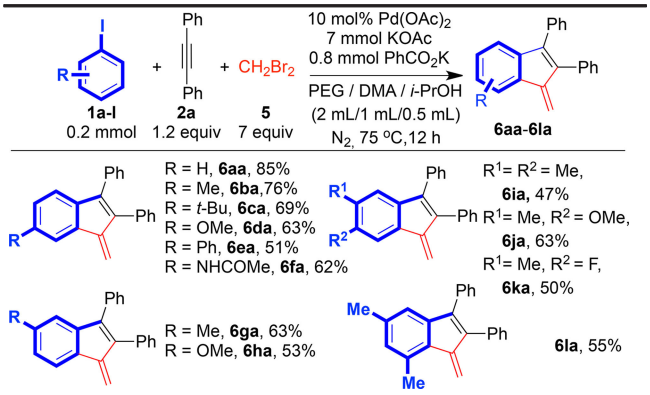
Scheme 4. Proposed mechanism.

yield six-membered palladacycle **G**. Alternatively, **G** could also be formed *via* a carbene complex **F**. The reductive elimination of **G** generates intermediate 2, 3-diphenyl-1*H*-indene **H** and releases Pd(II), which is reduced to Pd(0) to close the catalytic cycle. Under the basic conditions, **H** can react with CH_2Br_2 to form alkylated products **J**. The subsequent elimination reaction yields final benzofulvene products **6**.

Having developed an efficient synthetic protocol for benzofulvenes, we then investigated the substrate scope of the method. We first examined the compatibility of various substituted iodobenzenes. As shown in Table 2, a variety of functional groups at the *para* positions, including methyl, *tert*-butyl, methoxy, phenyl, and acetamido, were compatible (**6ba–6fa**), and substrates bearing a *meta*-substituent were also suitable (**6ga** and **6ha**). The reactivity of disubstituted iodobenzenes was also investigated. A range of iodobenzene derivatives were transformed into the corresponding benzofulvenes in moderate yields (**6ia–6la**). It should be mentioned that a trace amount of isomers were observed by GC-MS in most of the reactions. However, the structures of the isomers could not be identified due to insufficient amount, and they may result from the *cis-trans* isomerization of the vinyl palladium complexes (for the possible structures of the isomers and the formation processes see the supporting information).[9a]

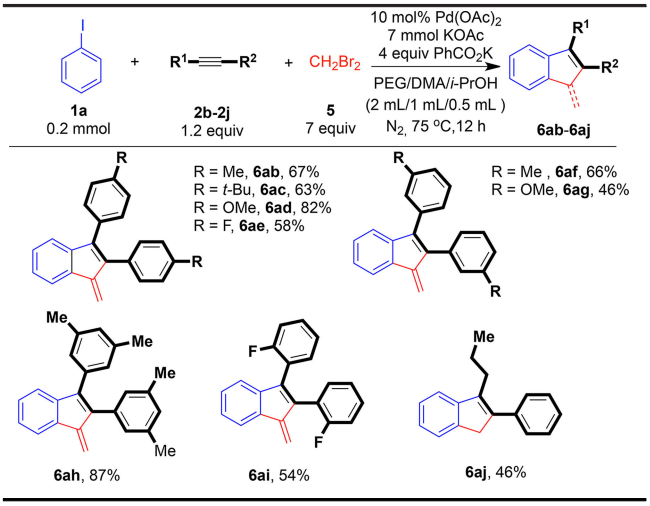
Next, we examined the performance of substituted diphenylacetylenes. A variety of symmetrical diphenylacetylenes bearing two methyl, *tert*-butyl, methoxy, or fluoro groups at the *para* positions reacted with iodobenzene and CH_2Br_2 to afford various benzofulvene derivatives in moderate or good yields (Table 3, **6ab–6ae**). The *meta*-substituted diphenylacetylenes also underwent the cascade reaction (**6af–6ah**), and even the substrate bearing two *ortho*-fluoro groups was compatible (**6ai**). The unsymmetrical alkynes was

Table 2. Iodobenzene scope of the benzofulvene-forming reaction.[a]



[a] Yields of the isolated products.

Table 3. Diarylacetylene scope of the benzofulvene-forming reaction.[a]



[a] Yields of the isolated products.

also examined. 2-Propyl phenylacetylenes was subjected to the standard conditions. The indene **6aj** was obtained instead of the expected benzofulvene. The reason might be that the benzylic C–H bond is less acidic and cannot be deprotonated under the conditions. It should be noted that the reaction exhibit high regioselectivity and **6aj** was the sole product.[14]

In conclusion, we have developed a new approach for the synthesis of benzofulvenes through palladium-catalyzed sequential three-component reactions. The reactions involve putative *C*,*C*-palladacycles as the key intermediates. Unlike the common methods for accessing such species from structurally complex starting materials, in this case the palladacycles were accessed from simple aryl halides and alkynes. The resulting *C*,*C*-palladacycles then react with CH_2Br_2 to form benzofulvenes as the final products. Further studies towards understanding the detailed mechanism and exploring other reactions of *C*,*C*-palladacycles generated in this way are underway in our lab.

Experimental Section

A 35 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with diphenylacetylenes **2** (0.24 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $PhCO_2K$ (128.2 mg, 0.8 mmol) and KOAc (687.0 mg, 7.0 mmol). Then the mixture was first stirred at room temperature for 1 minute followed by the addition of DMA (1 mL), *i*-PrOH (0.5 mL), aryl iodides **1** (0.2 mmol), CH_2Br_2 **5** (98.2 μL, 1.4 mmol) and PEG (Mn 400, 2 mL). The reaction was frozen with liquid nitrogen, and the tube was then evacuated and backfilled with nitrogen (10 times).The reaction was stirred at 75 °C for 12 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (15 mL) and washed with brine (2×15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative silica gel TLC to afford the corresponding products.

Acknowledgements

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