DOI: 10.1002/adsc.201600356

Advanced Synthesis & Catalysis

A Palladium-Catalyzed Domino Approach to 2,3-Disubstituted Benzofurans *via* an Intermolecular Carbopalladation/C(sp^3)–H Functionalization/Isomerization Sequence

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Received: April 4, 2016; Revised: May 12, 2016; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600356.

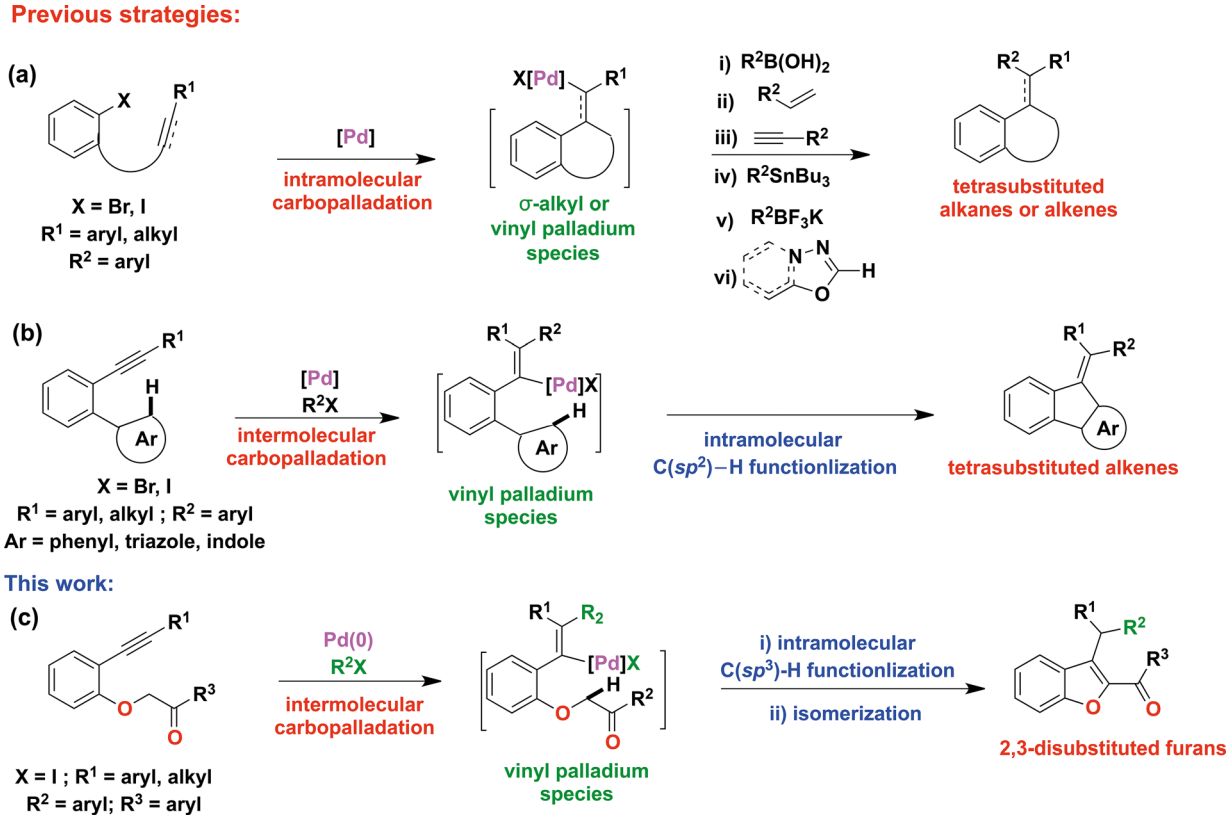
Abstract: A palladium-catalyzed domino strategy has been developed for the synthesis of 2,3-disubstituted benzofuran derivatives. This cascade reaction sequence involves intermolecular carbopalladation and C(sp^3)–H functionalization followed by isomerization.

Keywords: benzofurans; C(sp^3)–H functionalization; domino reaction; palladium; vinyl palladium species

The development of simple and straightforward synthetic methodologies towards the construction of valuable heterocycles has an essential role in organic synthesis. In recent years, the domino reaction has received significant attention due to its convenience in assembling multiple bonds in a one-pot process, thus providing an efficient and step-economical route for the synthesis of complex heterocycles.[1] One representative strategy is the generation of transient vinyl palladium(II) species from the intermolecular or intramolecular carbopalladation of alkynes (or alkenes) and aryl halides, which can be further captured by any nucleophile in a cascade sequence.[2] The seminal work describes the trapping of *in situ* vinyl palladium species with alkenes,[3] or boronic acids[4] and leads to tetrasubstituted alkenes. Inspired by these works, substantial advances have been made by capturing this active species with anions, nucleophiles,[5] organometallic reagents,[6] and C(sp^2)–H/(*sp*)-H functionalization reactions[7] [Scheme 1, Eqs. (a) and (b)]. Recently, our group has also developed the Pd/Ni-catalyzed stereoselective synthesis of tetrasubstituted olefins *via* intermolecular carbopalladation followed by triazole C(sp^2)–H activation.[8] Despite the significant progress made in this field, this active palladium species has not yet been intercepted with C(sp^3)–H bonds. Encouraged by our continuing interest on metal-catalyzed cascade reactions,[9] we envisioned that the active vinyl Pd(II) species from intermolecular carbopalladation could be trapped with C(sp^3)–H bonds to construct 2,3-disubstituted benzofurans [Scheme 1, Eq. (c)].

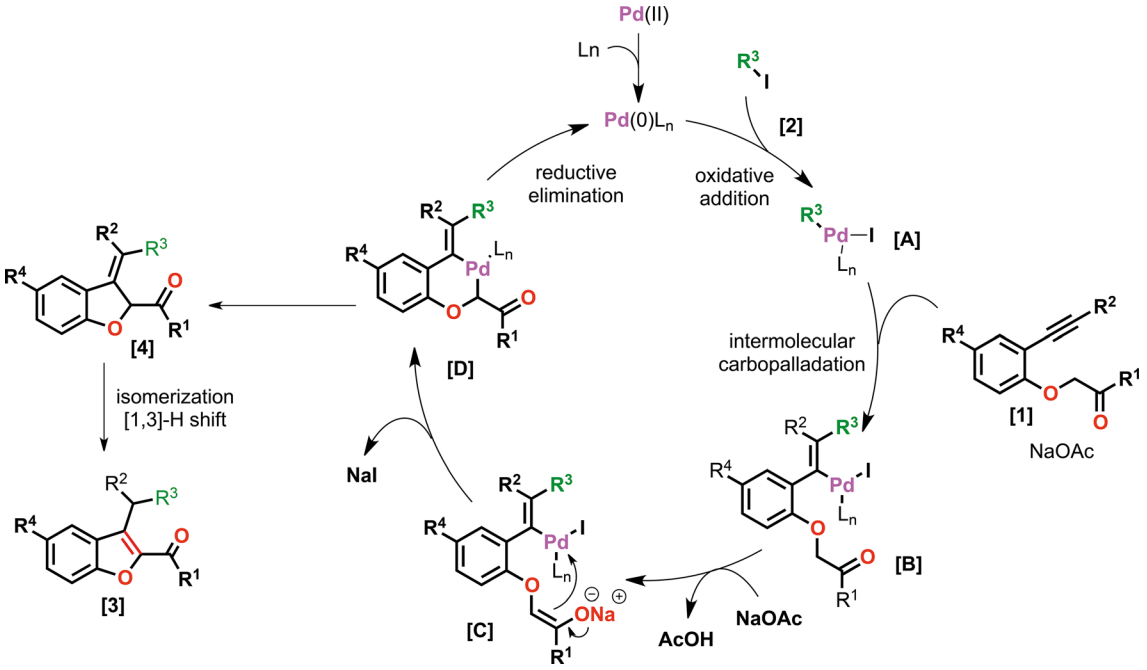
Benzofurans are a ubiquitous class of heterocycles, which are embedded in numerous pharmaceuticals, natural products, unnatural compounds possessing bio-activity and materials.[10] Consequently, tremendous efforts have been made towards the synthesis of benzofuran and its derivatives.[11] The reported methods to prepare the 2,3-disubstituted benzo[*b*]furans are less represented in the literature. The available methods are frequently suffering from multistep synthesis and harsh reaction conditions. The scope of the present cascade reaction involves simple starting materials and relatively tolerable reaction conditions.

We commenced our optimization studies using 1-phenyl-2-(2-(phenylethynyl)phenoxy)ethan-1-one (**1a**) with iodobenzene (**2a**) in the presence of various palladium catalysts, ligands, and bases as shown in Table 1. We were pleased to obtain an encouraging outcome of desired product with $Pd(PPh_3)_4$ and NaOAc in DMF (Table 1; entry 1). With the initial success, we evaluated different Pd(II) and Pd(0) sources with or without ligands and among them $Pd(OAc)_2$ in combination with PPh_3 furnished the maximum yield of 55% (Table 1; entries 2–7). Inferior performance was observed, when the reaction was screened with other phosphine ligands (entries 8–11). Next, the feasibility of the reaction was investigated with several inorganic bases (entries 12–17). With the strong bases such as LiO-*t*-Bu and KO-*t*-Bu it under-



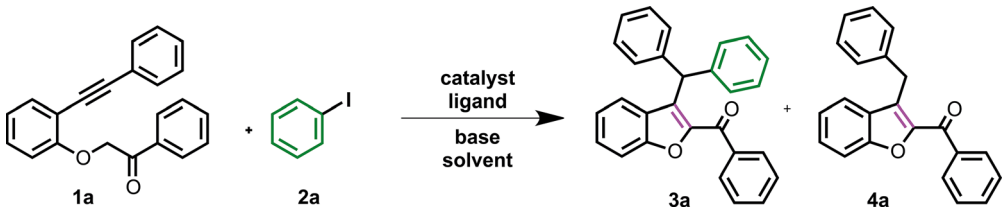
Scheme 1. Domino reactions *via* vinyl palladium species: previous and present approaches.

goes the intramolecular carbanion-yne cyclization to give undesired compound **4a** predominantly (entries 12 and 13)[12] and relatively mild bases were inefficient (entries 14–17). These results indicated that the base plays a crucial role and NaOAc was found to be the optimum base in this transformation. Changing the solvent did not improve the reaction yield (entries 18–22). Reactions were performed at different



Scheme 2. Proposed reaction mechanism.

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



Entry	Catalyst	Ligand	Base	Solvent	Time/Temp. [°C]	Yield [%] **3a**/**4a**
1	$Pd(PPh_3)_4$	–	NaOAc	DMF	16/100	26/traces
2	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	16/100	55/traces
3	$Pd_2(dba)_3$	–	NaOAc	DMF	16/100	35/traces
4	$Pd(dba)_2$	–	NaOAc	DMF	16/100	40/traces
5	$PdCl_2$	PPh_3	NaOAc	DMF	16/100	–
6	$Pd(TFA)_2$	PPh_3	NaOAc	DMF	16/100	–
7	$Pd(PPh_3)_2Cl_2$	PPh_3	NaOAc	DMF	16/100	–
8	$Pd(OAc)_2$	TFP	NaOAc	DMF	16/100	28/10
9	$Pd(OAc)_2$	dppf	NaOAc	DMF	16/100	40/–
10	$Pd(OAc)_2$	$P(cy)_3$	NaOAc	DMF	16/100	–
11	$Pd(OAc)_2$	$P(n\text{Bu})_3$	NaOAc	DMF	16/100	–
12	$Pd(OAc)_2$	PPh_3	LiO-*t*-Bu	DMF	16/100	–/85
13	$Pd(OAc)_2$	PPh_3	KO-*t*-Bu	DMF	16/100	–/78
14	$Pd(OAc)_2$	PPh_3	KOPiv	DMF	16/100	15/60
15	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	16/100	–
16	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	16/100	traces/25
17	$Pd(OAc)_2$	PPh_3	KOAc	DMF	16/100	28/traces
18	$Pd(OAc)_2$	PPh_3	NaOAc	DMSO	16/100	50/traces
19	$Pd(OAc)_2$	PPh_3	NaOAc	ACN	16/reflux	15/–
20	$Pd(OAc)_2$	PPh_3	NaOAc	toluene	16/reflux	–/traces
21	$Pd(OAc)_2$	PPh_3	NaOAc	dioxane	16/reflux	–/traces
22	$Pd(OAc)_2$	PPh_3	NaOAc	DMA	16/120	38
23	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	20/80	72/traces
24	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	20/60	–
25[b]	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	30/80	65/traces
26[c]	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	20/80	76/traces

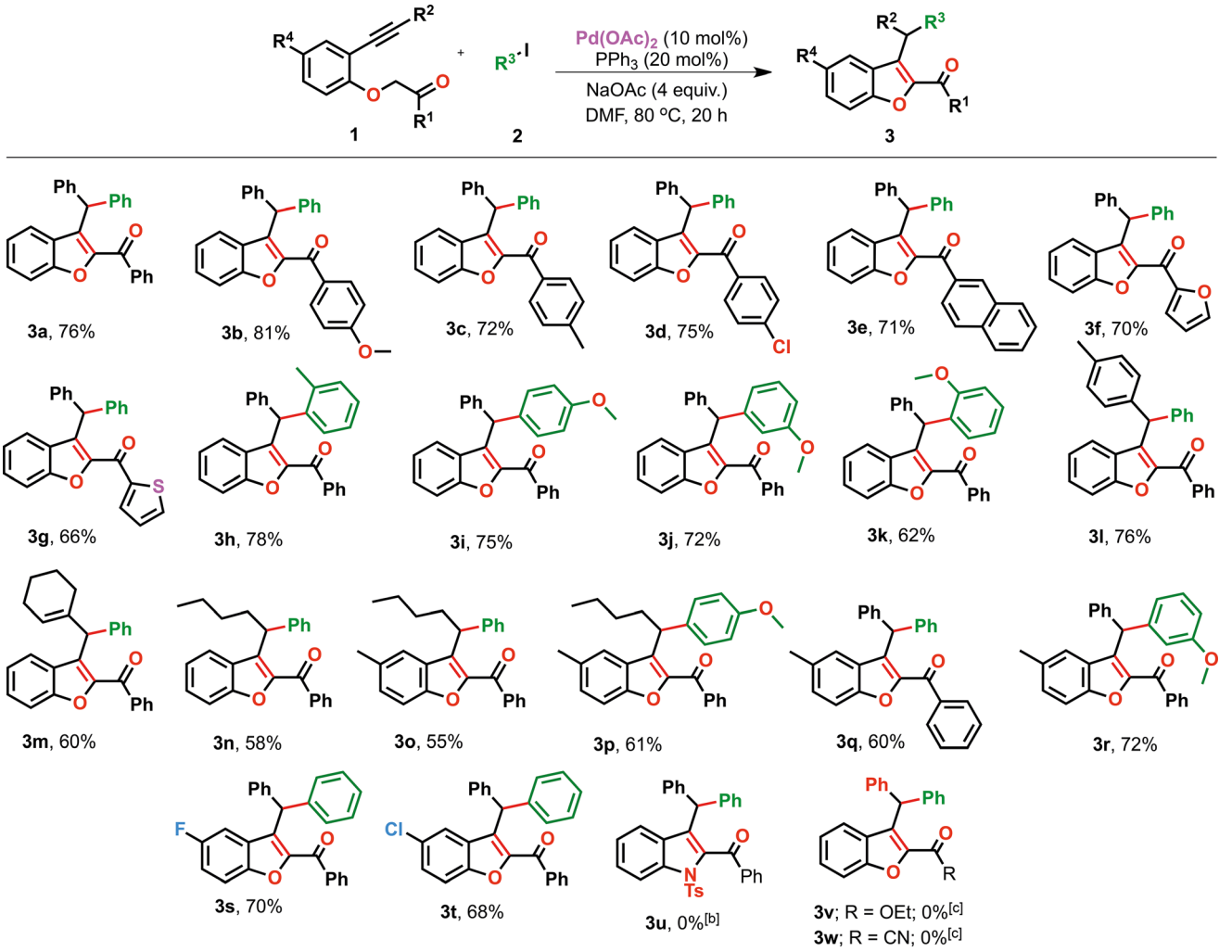
[a] *Reaction conditions:* **1a** (0.29 mmol), **2a** (0.43 mmol), catalyst (0.1 equiv.), ligand (0.2 equiv.), base (3 equiv.), solvent (1.5 mL).
[b] Catalyst (0.05 equiv.) and ligand (0.1 equiv.) used.
[c] 4 equiv. of base.

temperatures and the best yield was accomplished at 80 °C (entries 23 and 24). Decreasing the catalyst loading results in a longer time to complete the reaction and slightly decreased the reaction yield (entry 25). Increasing the equivalents of base improved the reaction yield to 76% and we fixed this as optimized conditions for further studies (entry 26).

After establishing the suitable set of reaction conditions, we probed the scope and limitations of this cascade reaction and summarized the results in Table 2. A variety of different aryl-substituted groups at the R^1 position such as phenyl, *p*-anisyl, *p*-tolyl, and 4-chlorophenyl were successfully converted into desired products in moderate to good yields (Table 2; **3a–3d**). Interestingly, the R^1 replaced with naphthyl, furan and thiophene substrates were smoothly converted into corresponding benzofurans (**3e–g**). The scope of the reaction was demonstrated with different aryl iodides (R^3) and the respective compounds were isolated (**3h–k**). Of note, substrates in which R^2 substituted with aryl, alkyl, or cycloalkyl groups, the reaction generally worked well (**3l–3p**). The scope of the reaction at R^4 was also examined with different groups such as methyl, chloro and fluoro, the corresponding benzofurans were obtained in good yields (**3q–t**). However, the attempts to extend the strategy to indole derivatives were failed (**3u**). The carbonyl groups replaced with ester and cyano groups did not provide the expected molecules (**3v–w**). The structure of the compound **3g** was confirmed by X-ray analysis.[13]

On the basis of observed results and literature precedence,[6,7,8] a plausible mechanistic pathway has been proposed in Scheme 2. Initially the aryl iodide undergoes oxidative addition with *in situ* generated Pd(0) catalyst and subsequently react with compound **1** *via* intermolecular carbopalladation gives complex **B**.[14]

Table 2. Substrate scope and limitations.[a]



[a] *General reaction conditions:* **1** (0.29 mmol), **2** (0.43 mmol), $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.2 equiv.), NaOAc (4 equiv.), DMF (1.5 mL) at 80 °C for 20 h.
[b] Reaction mixture decomposed.
[c] No reaction.

Then the complex **B** activates the sp^3 carbon with the assistance of base gives six-membered palladacycle **C**. The reductive elimination of complex **C** delivers alkene intermediate **4** and expels catalyst for the next cycle. Finally, the intermediate **D** isomerize *via* [1,3]-H shift to desired 2,3-disubstituted benzofurans (**3**).

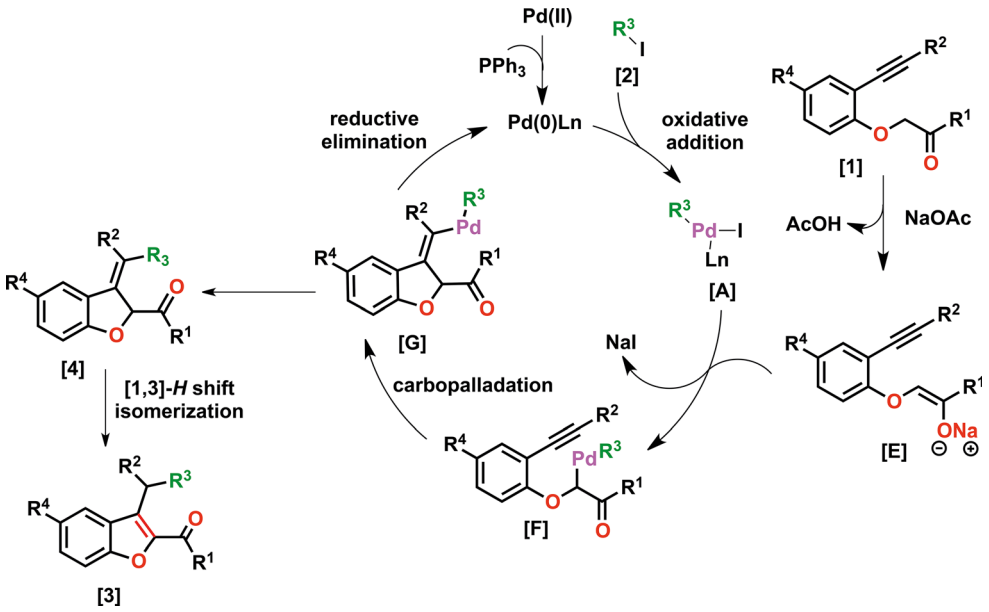
An alternative reaction mechanism *via* deprotonative palladation of methylene carbon has been outlined in Scheme 3.[15] Initially the starting material **1** will convert into corresponding enolate **E** with the aid of base. Next the enolate **E** reacts with the arylated palladium species **A** to give intermediate **F**. Subsequently, it undergoes intramolecular carbopalladation with alkynes followed by reductive elimination to give the intermediate **4** which then isomerizes into **3**.

In conclusion, a palladium-catalyzed domino approach to the synthesis of 2,3-disubstituted benzofurans has been developed. This method can provide a synthetic route to disubstituted benzofurans in an efficient manner. The cascade reaction proceeds *via* an intermolecular carbopalladation, C(sp^3)–H functionalization and isomerization sequence. The salient features of this work include mild reaction conditions, good substrate scope and moderate to high yields.

Experimental Section

General Procedure for the Synthesis 2,3-Disubstituted Benzofurans (3a–t)

An oven-dried 15-mL glass tube with screw cap was charged with **1a** (0.29 mmol) in DMF (1.5 mL) and then **2a** (0.43 mmol), $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.2 equiv.), and



Scheme 3. Alternative reaction pathway.

NaOAc (4 equiv.) were added. The reaction mixture was heated to 80 °C for 20 h. After the reaction was completed (monitored by TLC), the reaction mass was partitioned between water and ethyl acetate, then the combined organic phases washed with brine solution, dried over sodium sulfate and evaporated under vacuum. The resulting crude material was purified by flash column chromatography on silica gel (100–200 mesh) with suitable ratios of hexane and ethyl acetate to afford the desired product (**3**). The identity and purity of the compounds were determined by ^{1}HNMR, ^{13}CNMR, DEPT and HR-MS data.

Acknowledgements

We gratefully acknowledge the financial support from the Ministry of Science and Technology (MOST), Taiwan and thank the Centre for Research Resources and Development of Kaohsiung Medical University for NMR analyses.

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[12] a) P.-Y. Chen, T.-P. Wang, K.-S. Huang, C.-L. Kao, J.-C. Tsai, E.-C. Wang, *Tetrahedron* **2011**, *67*, 9291–9297; b) The structure of **4a** was confirmed by X-ray analysis (CCDC 1471981; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).

[13] CCDC 1471975 (**3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[14] The rationalization for the regioselective insertion of aryl palladium species into alkynes has been explained in the Supporting Information.

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