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Palladium-Catalyzed Domino Mizoroki–Heck/Intermolecular C(sp^3)–H Activation Sequence: An Approach to the Formation of C(sp^3)–C(sp^3) Bonds

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A palladium-catalyzed domino Mizoroki–Heck/intermolecular unactivated C(sp^3)–H alkylation reaction has been developed. This simple palladium nanoparticle catalytic system shows good activity and affords the dimeric dihydrobenzofuran derivatives in moderate to good yields. Furthermore, this reaction provides a new method for the elaboration of domino reactions involving a C(sp^3)–C(sp^3) bond-forming process.

Introduction

The rapid construction of complex heteroatom-containing molecular skeletons has become an attractive challenge in the past years. For this reason, domino reactions have proven to be an appealing and highly efficient strategy for the rapid formation of multiple bonds in organic synthesis.[1] In recent years, the transition-metal-catalyzed transformation of C–H bonds has emerged as one of the most promising and powerful methods for the construction of C–C bond frameworks.[2] In contrast with the better developed cross-dehydrogenative-coupling (CDC) reactions of C(sp)–H[3] and C(sp^2)–H[4] bonds, the alkylation of unactivated and nonacidic C(sp^3)–H[5] bonds remains one of the most challenging tasks in the field of C–H activation.[6]

In connection with more interest in the development of domino processes involving C–H activation as a key step, an impressive series of efficient procedures and novel methodologies have been devised and successfully applied to the synthesis of a variety of structures including dihydrobenzofurans,[7] indolines,[7] isoindoles,[8] spirooxindoles,[9] spirohydroquinolins,[10] and spiropentacyclic compounds.[11] For example, the (alkyl)Pd^{II} halide intermediate in the intramolecular Mizoroki–Heck (MH) reaction can undergo an intramolecular or intermolecular direct arylation to form a second new bond (Scheme 1a and b).[7,9a,10] More recently, Zhu et al. reported the first example of a palladium(0)-catalyzed domino carbopalladation/intramolecular C(sp^3)–C(sp^3) bond-forming process by an alkylpalladium(II) intermediate (Scheme 1c).[9b] To the best of our knowledge, no reports have appeared where domino processes involving a challenging intermolecular C(sp^3)–H activation has been used.

Results and Discussion

Herein, we report the first simple and efficient palladium-catalyzed domino cyclization involving carbopalladation and the subsequent intermolecular functionalization of an unactivated C(sp^3)–H bond for the preparation of dimeric dihydrobenzofuran derivatives. The underlying principle is shown in Scheme 2. Intramolecular MH reaction of arene **1** would give 2,3-dihydrobenzofuran **2a** and (alkyl)-Pd^{II} intermediate **A**. The intermediate **A**, being sufficiently stable and ideally positioned, should be able to activate the C(sp^3)–H bond of **2a** by the auxiliary coordination of the oxygen atom on the furan ring, thus leading to a dimeric dihydrobenzofuran product **3aa** by the sequential CDC reaction.

Particular interest in palladium-catalyzed MH reactions[12] prompted us to study the domino cyclization reaction involving the CDC transformation of C(sp^3)–H bonds by using palladium nanoparticle catalysts. To test our strategy, we tried to synthesize 3,3-dimethyl-2,3-dihydrobenzofuran (**2a**) and dimer **3aa** from 1-iodo-2-(2-methylprop-2-enyloxy)benzene (**1a**) by a domino reaction, where the MH and CDC reactions took place sequentially (Table 1). Product **3aa** was a crystalline solid, and single-crystal X-ray diffraction confirmed the exact structure.[13] Initial screening of palladium sources was carried out by treating 0.5 mmol of **1a** with 2 mol-% of palladium, 1 equiv. of (nBu)$_4$NBr (TBAB) and 2 equiv. of K_3PO_4 in *N*,*N*-dimethylacetamide (DMA) at 120 °C under nitrogen for 24 h. To our delight, all of palladium precursors exhibited good activity and afforded a mixture of **2a** and **3aa** in 55–90% yields (Table 1,

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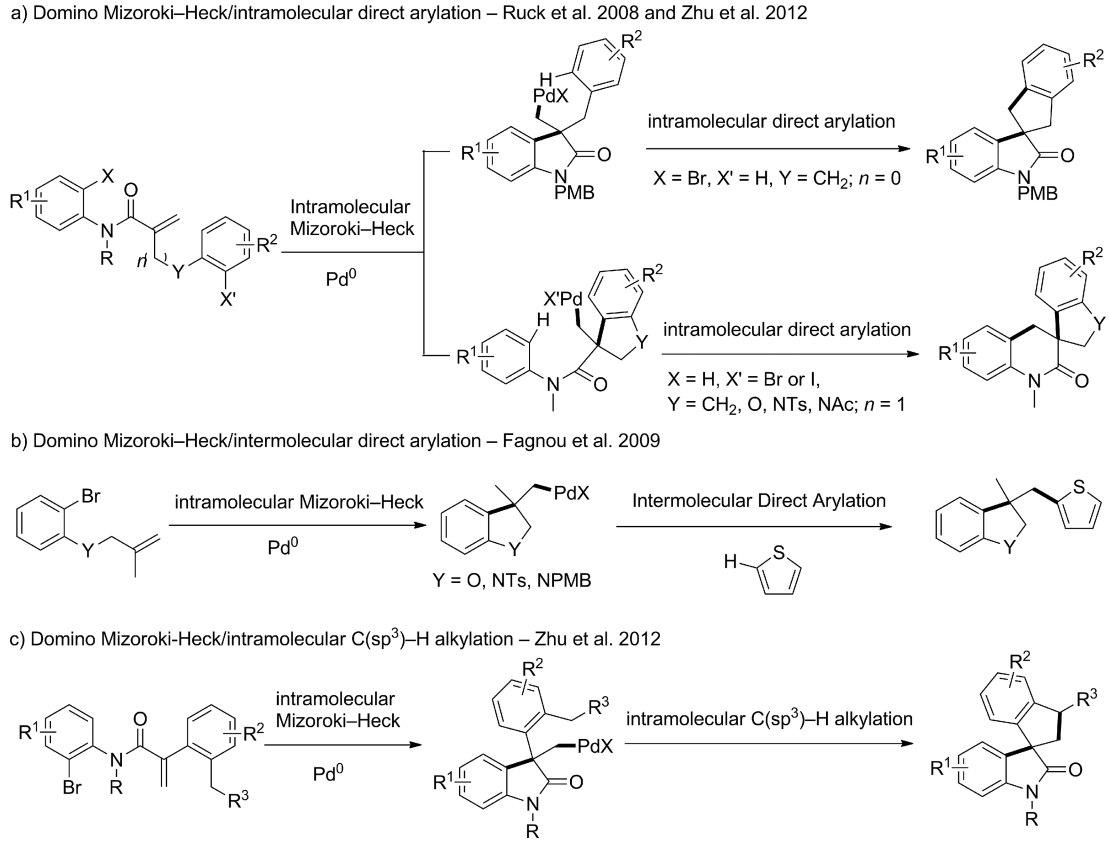
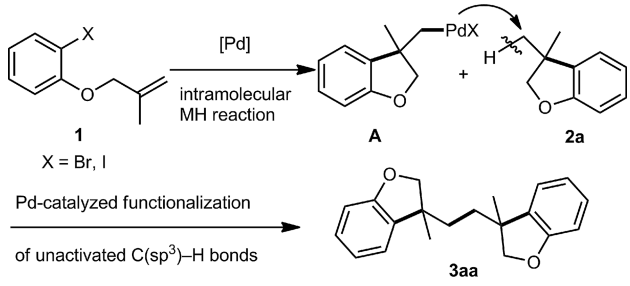


Scheme 1. Precedent in domino Mizoroki–Heck/C–H activation involving alkylpalladium(II) intermediates and the formation of new C–C bonds.



Scheme 2. Proposed domino reaction involving a C(sp^3)–H bond activation.

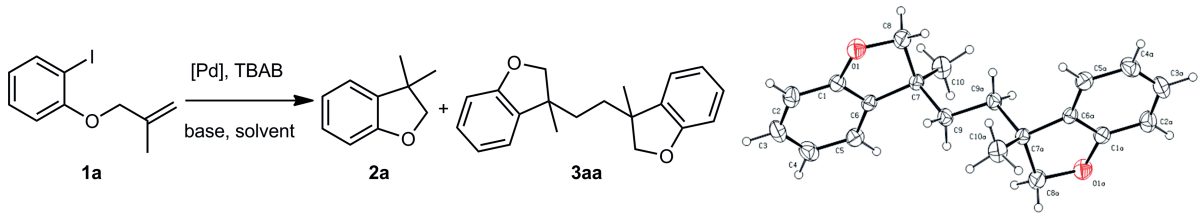
Entries 1–6). Moreover, using [Pd(COD)Cl_2] as the catalyst, we obtained the desired CDC product **3aa** in the best yield (54%). It is noteworthy that TBAB is not essential to the C(sp^3)–H activation, but its presence could improve the yield of **3aa** (Table 1, Entry 7). No product **3aa** was observed in the absence of the palladium precursor (Table 1, Entry 8). Furthermore, transmission electron microscopy (TEM) imaging demonstrated that palladium is present in the form of nanoparticles with an average particle size of 5.6 nm (Figure 1).

Having identified the optimal palladium source, we screened a wide range of bases and solvents (Table 2). K_3PO_4 was found to be the most efficient, and the product yield was significantly affected by the nature and amount of the base (Table 2, Entries 1–9). Solvent screening (Table 2, Entries 10–16) showed that cyclizing compound **2a** could be achieved in up to 100% yield in *n*-butanol,[14] and DMA was a best solvent with regard to the yield of **3aa**. Based on these optimization studies, further reactions were performed at 120 °C under nitrogen using [Pd(COD)Cl_2] (2 mol-%), TBAB (1 equiv.), and K_3PO_4 (3 equiv.) in DMA.

The scope and generality of this method was investigated using a variety of substrates **1a**–**f** (Scheme 3). The method tolerates various electronic and substitution patterns on the aromatic moieties, affording dimeric dihydrobenzofuran derivatives **3aa**–**ee**[15] in moderate to good yields (Scheme 3). Exceptions are reactions involving substrates having an *ortho*-substituted aryl halide fragment (e.g. **1f**). To our delight, the domino reaction with less active aryl bromides also gave the corresponding products under our optimized reaction conditions.

An interesting question is whether two different dihydrobenzofurans can be connected by C(sp^3)–H bond activation, which could broaden the scope and utility of this domino processes. To address this issue, aryl iodide **1a** was

Table 1. Effect of catalyst precursors on the domino reaction.[a]



Entry	[Pd]	TBAB [mmol]	Yield of **2a** [%][b]	Yield of **3aa** [%][b]
1	$PdCl_2$	0.5	45	43
2	$Pd(OAc)_2$	0.5	45	44
3	$[Pd(C_3H_5)Cl]_2$	0.5	44	47
4	$Pd_2(dba)_3$	0.5	31	33
5	$[Pd(PhCN)_2Cl_2]$	0.5	21	34
6	$[Pd(COD)Cl_2]$	0.5	36	54
7	$[Pd(COD)Cl_2]$	0	14	45
8	none	0.5	7	0

[a] Reaction conditions: **1a** (0.5 mmol), K_3PO_4 (1 mmol), DMA (1.5 mL), [Pd] (2 mol-%) at 120 °C under nitrogen for 24 h. [b] Yields are determined by GC–MS and ^{1}H NMR spectroscopy.

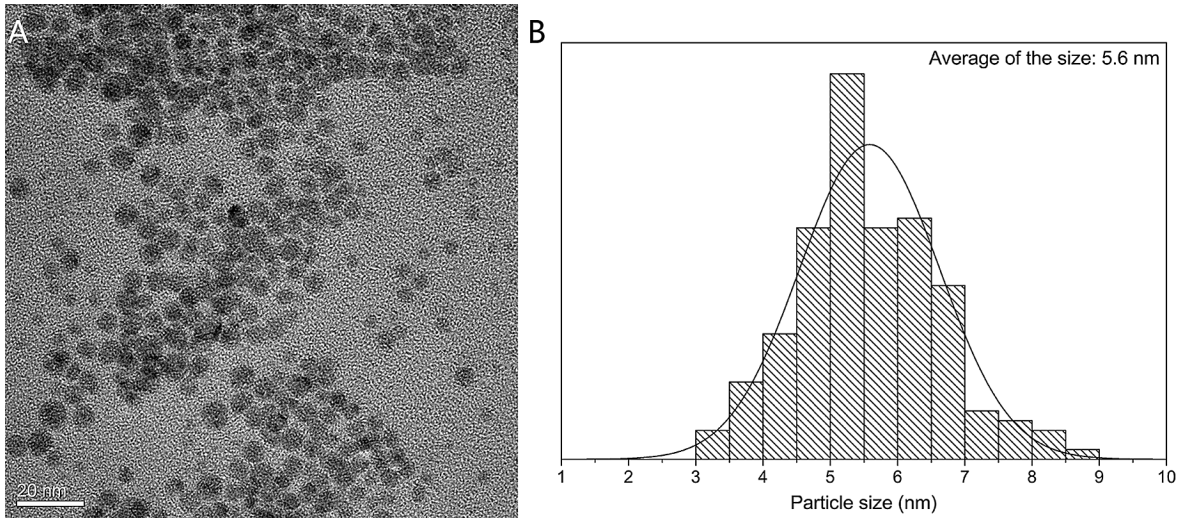


Figure 1. TEM micrographs and nanoparticle size distributions: $[Pd(COD)Cl_2]$ as catalyst precursor and reaction for 1 h. Reaction conditions: **1a** (0.5 mmol), $[Pd(COD)Cl_2]$ (0.01 mmol), K_3PO_4 (1.5 mmol), DMA (1.5 mL), TBAB (0.5 mmol), under nitrogen, 100 °C.

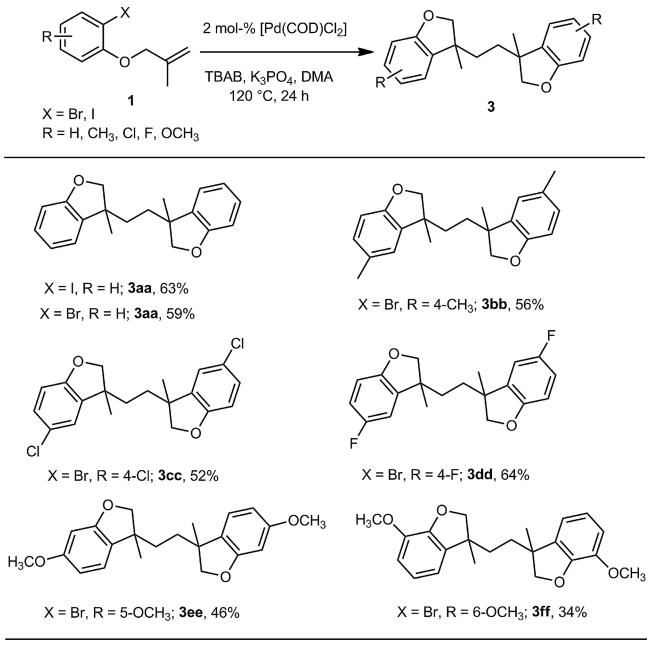
allowed to react with aryl bromides **1b–d** under the optimized conditions. The desired products **4ab–ad** were generated in moderate yields (Table 3, Entries 1–3). Meanwhile, the homocoupling products **3aa–dd** were also generated under our conditions. We were pleased to note that two less active aryl bromides **1b–d** also reacted well to afford the desired products **4bc–cd** in moderate yields (Table 3, Entries 4–6). To further illustrate the generality of our method, we applied this strategy to the domino reaction of 1-iodo-2-(3-methylbut-3-enyloxy)benzene (Scheme 4). To our surprise, the desired dimer was not observed, and tetracyclic compound **5** resulting from twofold C–H functionalizations was obtained in 70% yield.[16]

To gain insight into the palladium-catalyzed domino reaction, several control experiments were carried out to elucidate the process. Adding the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) did not inhibit the reaction, and the product **3aa** was obtained in 65% yield. Importantly, the system also worked well when the reaction was conducted in the dark (see the Supporting Information). These results indicated that a radical mechanism[6c–6e] was not involved in these transformations. Furthermore, according to the curve of conversion vs. time, the content of **2a** increased gradually at the beginning of the reaction and decreased after 12 h, while the amount of **3aa** increased sharply (Figure 2). The total content of **2a** and **3aa** did not change after 12 h, indicating that **2a** may participate in this reaction. What is more, the yield of **3aa** increased to 85% when **2a** (0.5 mmol) reacted with **1a** (0.5 mmol) under otherwise identical conditions. In addition, attempts to achieve the desired product **3aa** failed by using **2a** as reaction substrate, whereas the products **4ab** (4%) and **3bb** (57%) were obtained when **2a** reacted with **1b** (**3aa** was not observed). An increase in the yield of cross-

Table 2. Optimization of palladium-catalyzed domino reaction of **1a**.[a]

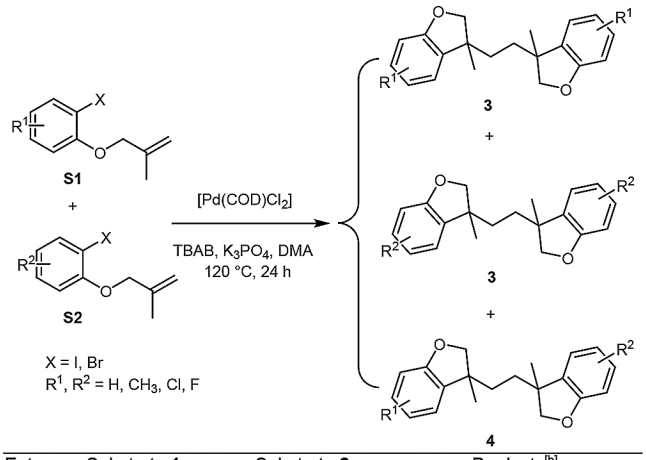
Entry	Base	Solvent	Temp. [°C]	Yield of **2a** [%][b]	Yield of **3aa** [%][b]
1	Na_2CO_3	DMA	120	13	0
2	K_2CO_3	DMA	120	24	5
3	Cs_2CO_3	DMA	120	25	4
4	CsF	DMA	120	39	12
5	K_3PO_4	DMA	120	36	54
6[c]	K_3PO_4	DMA	120	38	55
7[d]	K_3PO_4	DMA	120	23	66
8	NaOH	DMA	120	11	6
9	*t*BuOLi	DMA	120	27	37
10	K_3PO_4	toluene	100	21	17
11	K_3PO_4	1,4-dioxane	100	31	18
12	K_3PO_4	*n*-butanol	100	100	0
13	K_3PO_4	DMF	100	30	25
14	K_3PO_4	DMA	100	23	27
15	K_3PO_4	DMA	130	38	54
16	K_3PO_4	NMP	130	48	42

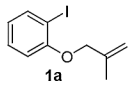
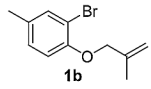
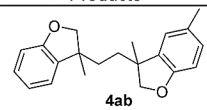
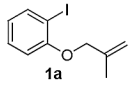
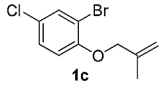
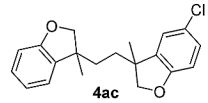
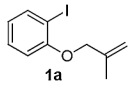
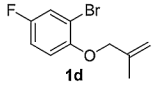
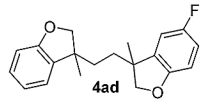
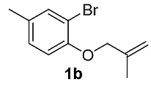
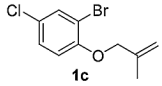
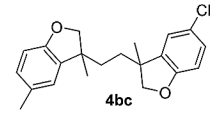
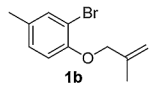
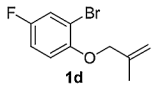
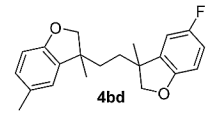
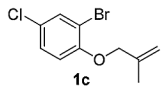
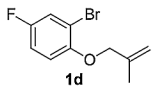
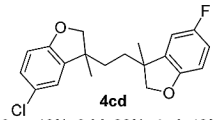
[a] Reaction conditions: **1a** (0.5 mmol), TBAB (0.5 mmol), base (1 mmol), solvent (1.5 mL), $[Pd(COD)Cl_2]$ (2 mol-%) under nitrogen for 24 h. [b] Yields are determined by GC–MS and ^1H NMR spectroscopy. [c] 48 h. [d] K_3PO_4 (1.5 mmol).



Scheme 3. Scope of the palladium-catalyzed domino reaction involving C(sp^3)–H activation. Reaction conditions: see Table 2, Entry 7. Yields of isolated products.

Table 3. Scope of the palladium-catalyzed domino reaction of different substrates.[a]

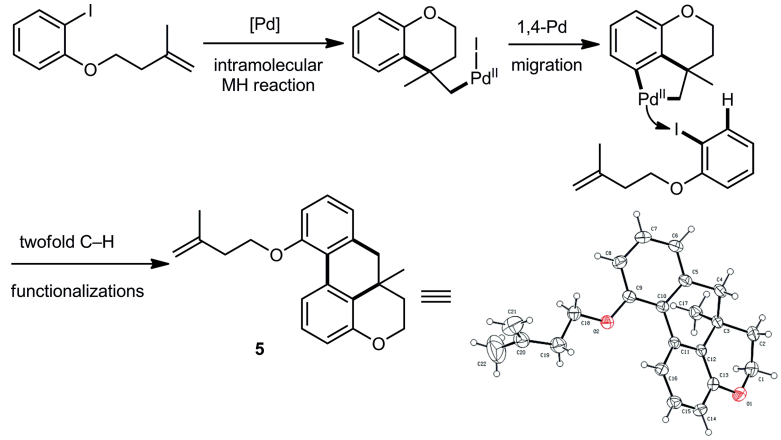


Entry	Substrate **1**	Substrate **2**	Products[b]
1			
	1a	**1b**	**4ab**
			3aa: 43%; **3bb**: 28%; **4ab**: 29%
2			
	1a	**1c**	**4ac**
			3aa: 32%; **3cc**: 14%; **4ac**: 46%
3			
	1a	**1d**	**4ad**
			3aa: 28%; **3dd**: 18%; **4ad**: 55%
4[c]			
	1b	**1c**	**4bc**
			3bb: 41%; **3cc**: 20%; **4bc**: 34%
5[c]			
	1b	**1d**	**4bd**
			3bb: 34%; **3dd**: 32%; **4bd**: 45%
6[c]			
	1c	**1d**	**4cd**
			3cc: 19%; **3dd**: 28%; **4cd**: 46%

[a] Reaction conditions: Substrate **1** (0.5 mmol), substrate **2** (0.5 mmol), TBAB (1 mmol), K_3PO_4 (2.5 mmol), DMA (2.5 mL), $[Pd(COD)Cl_2]$ (4 mol-%) at 120 °C under nitrogen for 24 h. [b] Isolated yields (yield of **4** is reported with respect to 0.5 mmol of **1**). [c] $[Pd(COD)Cl_2]$ (5 mol-%).

coupling products **4ac** (14%) or **4ad** (16%) was observed when **2a** reacted with **1c** or **1d**.[17] These results suggest that **2a** indeed participated in the step of C(sp^3)–H activation, and the alkylpalladium halide intermediate may be crucial to this domino reaction.

The exact mechanism of this reaction is not clear at present. However, on the basis of these preliminary results and the literature reports,[9b,18,19] a plausible pathway for this domino reaction was proposed (Scheme 5). The (alkyl)Pd^{II} halide intermediate **A**, generated from intramolecular MH reaction, coordinates with the product **2a**. The resulting complex **B** undergoes reversible cyclometalation to give **C**, probably by a concerted metalation deprotonation mechanism. The Pd^{II} intermediate **C** readily should undergo a reductive elimination to regenerate the Pd^0 complex and concomitantly release the desired product **3aa**. Gratifyingly, ESI-MS studies indicated that the alkylpalladium complexes **A** and **C** were formed (for details, see the Supporting Information).



Scheme 4. Palladium-catalyzed domino reaction involving two C–H functionalizations. Reaction conditions: iodoarene (0.5 mmol), TBAB (1 equiv.), K_3PO_4 (3 equiv.), DMA (1.5 mL), [Pd(COD)Cl_2] (2 mol-%) at 120 °C under nitrogen for 24 h.

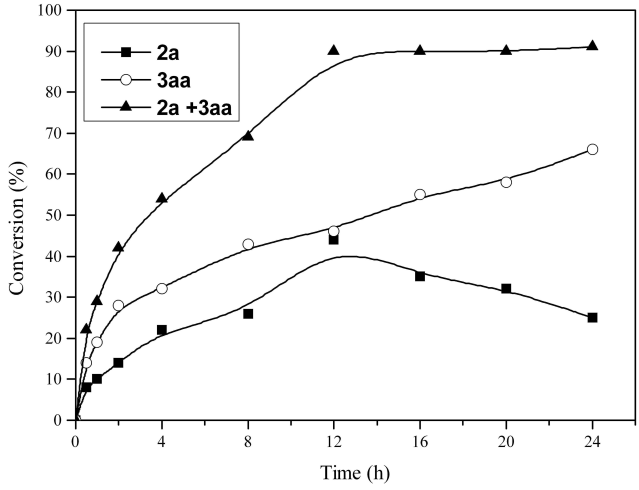
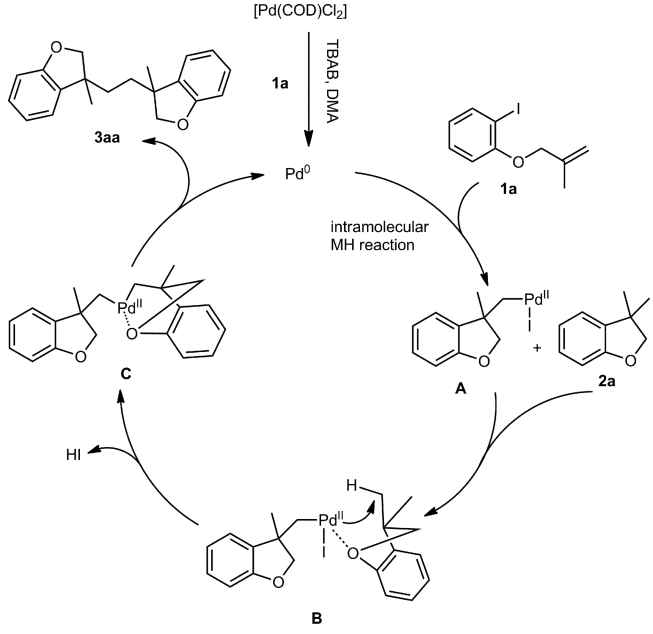


Figure 2. Conversion vs. time plot for the domino reaction of **1a**. Reaction conditions: see Table 2, Entry 7. Yields are determined by GC–MS, and biphenyl is an internal standard.



Scheme 5. Proposed mechanism.

Conclusions

We have reported a simple and efficient palladium-catalyzed domino reaction involving the functionalization of C(sp^3)–H bonds. This catalytic reaction provides an efficient method for the synthesis of dimeric dihydrobenzofurans from simple starting materials. Importantly, this strategy first realizes a domino process involving a challenging intermolecular unactivated C(sp^3)–H alkylation.

Experimental Section

Representative Procedure for 3aa: K_3PO_4 (1.5 mmol), TBAB (0.5 mmol), and [Pd(COD)Cl_2] (2.85 mg, 0.01 mmol) were added into a dried Schlenk tube with a magnetic bar, which was subjected to evacuation/flushing with dry nitrogen five times, and then **1a** (0.5 mmol) and DMA (1.5 mL) were added successively to it. The reaction mixture was heated at 120 °C for 24 h with stirring. After standard workup procedures (see the Supporting Information), the crude product was purified by silica gel chromatography, and **3aa** was isolated as white solid (46.3 mg, 0.158 mmol, 63%).

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

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[13] See the Supporting Information. CCDC-999259 (**3aa**) 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. The dimeric **3aa** (*meso* and *d*/*l* pair) may be formed according to ^{1}H NMR spectra and crystallographic data.

[14] Olefin insertion was shown to be fast by running the reaction under reductive MH conditions, with 100% conversion to compound **2a**. See ref.[2b] Further deuterated experiments to explain the source of the hydrogen of **2a** are shown in the Supporting Information.

[15] X-ray structures of **3bb** and **3cc** are shown in the Supporting Information. CCDC-1013559 (**3cc**) and -1013560 (**3bb**) contain 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.

[16] CCDC-999260 (**5**) 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. A similar reaction was reported by Lautens et al. just now; see: M. Sickert, H. Weinstabl, B. Peters, X. Hou, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 5147; *Angew. Chem.* **2014**, *126*, 5247. The process provides a very efficient way to synthesize fused ring systems. Further studies to extend the scope and clarify the mechanism are currently underway.

[17] **2a** (0.25 mmol), TBAB (1 equiv.), K_3PO_4 (2 equiv.), DMA (1 mL), [Pd(COD)Cl_2] (2 mol-%) at 120 °C for 24 h; **1b**–**d** (0.25 mmol), **2a** (1 equiv.), TBAB (2 equiv.), K_3PO_4 (6 equiv.), DMA (1.5 mL), [Pd(COD)Cl_2] (4 mol-%) at 120 °C for 24 h.

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