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An aerobic [2 + 2 + 2] Cyclization via Chloropalladation: From 1,6-Diynes and Acrylates to Substituted Aromatic Carbocycles

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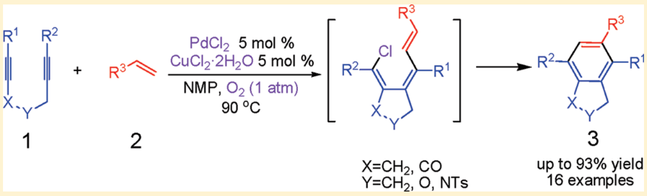
S Supporting Information

ABSTRACT: A Pd-catalyzed aerobic [2 + 2 + 2] cyclization of 1,6-diynes and acrylates proceeding through a chloropalladation process has been developed. Polysubstituted five-membered aromatic carbocycles/heterocycles were obtained in good to excellent yields. The results of the mechanistic study are consistent with the proposed reaction mechanism.



Polysubstituted aromatic carbocycles/heterocycles are ubiquitously found in biologically interesting molecules and therapeutic agents. One of the most versatile and efficient approaches to synthesize functionalized aromatic carbocycles is the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction, which involves multiple bond formation processes in a single transformation.[1] In particular, Rh-, Ru-, Pd-, Ni-, and Co-catalyzed [2 + 2 + 2] cycloaddition reactions have been reported to afford arene scaffolds bearing diverse functional groups.[2] Generally, these reactions proceed via a common metallacyclopentadiene intermediate **A** (Scheme 1), which is presumably generated from the oxidative addition of alkynes to metal catalysts, and subsequent reductive elimination reaction would afford aromatic carbocycle/heterocycle products. However, precious ligands are often required to improve the turnover numbers of these catalytic processes. Plus, the reaction scope is limited, and only certain types of substrates could afford respectful yields of the desired products. Herein, we report a ligand-free, Pd-catalyzed aerobic [2 + 2 + 2] cyclization reaction for the synthesis of complex aromatic carbocycles and heterocycles, which provides a highly efficient strategy to prepare poly substituted Indane, 2,3-dihydro-1*H*-isoindole, 1,3-dihydro-isobenzofuran, and 3*H*-isobenzofuran-1-one derivatives.

Recently, we have developed novel syntheses of multisubstituted arenes via palladium-catalyzed aerobic [2 + 2 + 2] cyclizations of alkenes and alkynes. A unique reaction mechanism which goes through the chloropalladation process has been proposed to explain the formation of desired products.[3] In addition, a palladium-catalyzed 1:2 linear/cyclic cross-trimerization of alkyne with alkenes has been carried out to support the proposed reaction mechanism (Scheme 1).[4] However, our efforts to detect and separate the key intermediate vinylpalladium complex **B** were not fruitful.[5] Since we envisioned that the cyclization reaction of 1,6-diynes through intermediate **B** might provide important mechanistic information about this novel chloropalladation process, we have devoted our efforts to develop a tandem cycloaddition-cyclization reaction of alkynes and alkenes. This chemistry can also provide a versatile synthesis for polysubstituted aromatic compounds with interesting properties.[6]

In order to obtain optimal reaction conditions, 1,7-diphenyl-hepta-1,6-diyne (**1a**) and ethyl acrylate (**2b**) were allowed to react in the presence of different catalysts, oxidants, and solvents as shown in Table 1. Initially, the reaction was conducted using previously reported conditions (5 mol % of $PdCl_2$, 5 atm of dioxygen in wet DMF at 80 °C for 24 h), and a 34% yield of the desired product (**3ab**) was obtained (Table 1, entry 1). When the pressure of dioxygen was decreased to 1 atm, only a 22% yield of the indan product was evident as indicated by GC−MS analysis (entry 2). To our delight, when $CuCl_2 \cdot 2H_2O$ (5 mol %) was employed as co-oxidant, this transformation afforded a 79% yield of the desired product (entry 3). Other cooxidants, such as $Cu(OAc)_2$, $CuBr_2$, Ag_2CO_3, PIDA (iodosobenzene diacetate), and BQ (1,4-benzoquinone) had also been examined in this system, but none of these reactions afforded higher yields (entries 4−8). Subsequently, $Pd(OAc)_2$ was employed in this transformation, but only 13% of the desired product was formed (entries 9 and 10). We also closely examined the effect of solvents, and it appears that NMP is the most suitable solvent for this reaction (entry 11 vs entries 12−14). For instance, when CH_3CN was employed as solvent, a side reaction involving [2 + 2 + 2] cycloaddition of alkyne and acetonitrile proceeds predominantly (entry 13).[7] Using $CuCl_2 \cdot 2H_2O$ as the sole oxidant dramatically decreased the reaction efficiency, and a 44% yield of **3ab** was obtained (entry 15). Thus, the best conditions for this novel [2 + 2 + 2] cyclization reaction are: 5 mol % $PdCl_2$, 5 mol % $CuCl_2 \cdot 2H_2O$ and 1 atm dioxygen in NMP at 90 °C for 24 h (Table 1, entry 12).[8]

With the optimal conditions in hand, we next examined the scope and limitations of this methodology. A variety of 1,6-diynes and alkenes had been employed in this transformation, and

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Scheme 1. (a) Transition-Metal-Catalyzed [2 + 2 + 2] Cycloaddition through Metalcyclopentadiene. (b) Our Aerobic Cyclizations Triggered by Chloropalladation

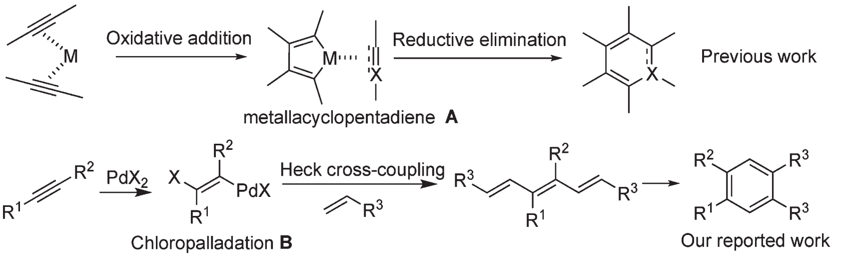
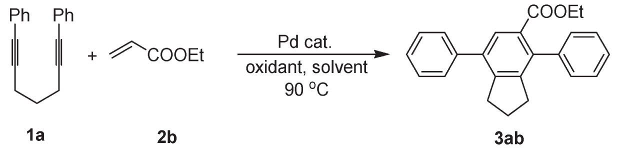


Table 1. Optimization of Reaction Conditions for the [2 + 2 + 2] Cyclization of 1a and 2b[a]



entry	Pd (5 mol %)	oxidant	solvent	yield[b] (%)
1[c]	$PdCl_2$	O_2 (5 atm)	DMF	34
2	$PdCl_2$	O_2 (1 atm)	DMF	22
3	$PdCl_2$	O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	DMF	79
4	$PdCl_2$	O_2 (1 atm)/$Cu(OAc)_2$ (5 mol %)	DMF	73
5	$PdCl_2$	O_2 (1 atm)/$CuBr_2$ (5 mol %)	DMF	trace
6	$PdCl_2$	O_2 (1 atm)/Ag_2CO_3 (5 mol %)	DMF	26
7	$PdCl_2$	O_2 (1 atm)/$PhI(OAc)_2$ (5 mol %)	DMF	trace
8	$PdCl_2$	O_2 (1 atm)/BQ (5 mol %)	DMF	14
9	$Pd(OAc)_2$	O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	DMF	13
10		O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	DMF	0
11	$PdCl_2$	O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	NMP	87
12	$PdCl_2$	O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	DMA	81
13	$PdCl_2$	O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	CH_3CN	trace[d]
14	$PdCl_2$	O_2 (1 atm)/$CuCl_2\cdot 2H_2O$ (5 mol %)	dioxane	34
15	$PdCl_2$	$CuCl_2\cdot 2H_2O$ (100 mol %)	NMP	44

[a] Reaction was carried out using **1a** (0.5 mmol), **2b** (0.6 mmol), [Pd] catalyst (5 mol %), oxidant, and 2 mL of solution in a capped tube, heating at 90 °C for 24 h. [b] Determined by GC. [c] The reaction was carried out in a 15 mL autoclave. [d] With products from the cycloaddition of **1a** and CH_3CN.

representative examples are summarized in Table 2. Alkenes bearing electron-withdrawing groups afford good to excellent yields of the substituted indan derivatives (Table 2, entries 1−5). 1,7-Diaryl-1,6-diynes bearing either electron-withdrawing or electron-donating substituents on the aryl groups afford 79−91% yields of the desired products (entries 6−12). It appears that *N*-substituted 1,6-diyne could also be employed in this reaction, and a 91% yield of 2,3-dihydro-1*H*-isoindole has been obtained after chromatography (entry 13). We have successfully extended this chemistry to the synthesis of 1,3-dihydro-isobenzofuran, and a 93% yield of the expected product was obtained (entry 14). Finally, an unsymmetrical 1,6-diyne source, 3-phenylprop-2-ynyl oct-2-ynoate (**1k**), afforded a 89% yield of two isomeric 3*H*-isobenzofuran-1-one **3kb-a** and **3kb-b** in a 8:92 ratio (entry 15). However, when 3-phenylprop-2-ynyl but-2-ynoate(**1l**) was treated with methyl acrylate (**2a**), the reaction provided a good yield of **3la** but with lower regioselectivity than **3kb**, which means the electron effect of 1,6-diynes cannot effect the reaction's selectivity obviously but the steric effect can. In summary, this novel [2 + 2 + 2] cycloaddition reaction provides a viable route to a variety of substituted five-membered aromatic compounds.

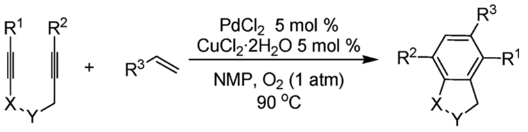
A plausible mechanism for this Pd-catalyzed [2 + 2 + 2] cycloaddition reaction is proposed in Scheme 2. Intermediate **B** was first generated by the chloropalladation of diyne **1a** with Pd(II) species. Subsequent intermolecular Heck reaction with ethyl acrylate would be expected to afford triene **C**. Vinylpalladium intermediate **D** was then generated by the oxidative addition of triene **C** to Pd(0) species, and an intramolecular Heck reaction would lead to the desired product **3ab**. Finally, dioxygen and $CuCl_2\cdot 2H_2O$ oxidize Pd(0) to Pd(II) to complete the catalytic cycle. Consequently, the formation of intermediate **C** appears to be crucial for the success of the reaction, and it could also provide insightful information with regard to understand the reaction mechanism. Indeed, vinyl chloride **C** has been isolated from the reaction solution of the controlled experiments (Scheme 3), which is consistent with the proposed reaction mechanism. Plus, further study indicated that the formation vinylchloride **C** could be promoted via increasing the amount of $CuCl_2\cdot 2H_2O$ used. Additionally, when intermediate **C** was allowed to react under standard conditions but in the absence of dioxygen, compound **3ab** was obtained in 91% yield, suggesting the involvement of intermediate **C** in the catalytic cycle.[9] However, when **C** was treated under standard conditions but without $PdCl_2$, a trace **3ab** was obtained, which suggests the transformation of **C** to **3ab** should be a Heck cross-coupling but not an electrocyclic reaction.

In summary, we have developed an aerobic and general [2 + 2 + 2] cyclization for the synthesis of polysubstituted aromatic carbocycles/heterocycles from readily available 1,6-diynes and acrylates through a tanden process. The key most absorbing point is the detection of intermediate **C** had been successfully isolated and characterized, and which is the first mechanistic evidence in [2 + 2 + 2] cyclization reactions via chloropalladation process. Plus, this methodology is highly valuable for the synthesis of substituted aromatic carbocycles/heterocycles, which had found numerous applications in theraputic reagents and optoelectronic materials.

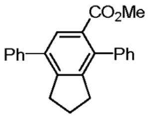
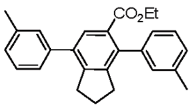
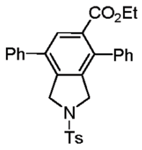
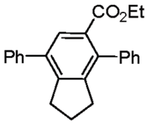
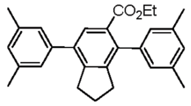
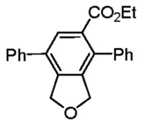
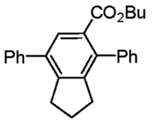
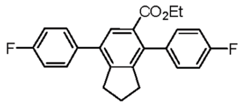
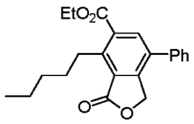
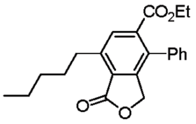
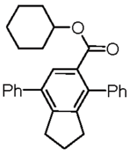
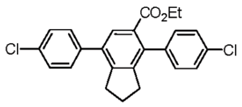
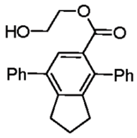
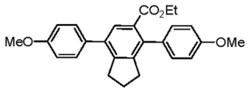
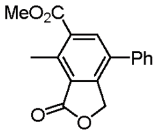
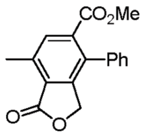
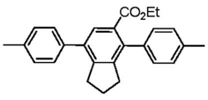
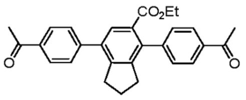
■ EXPERIMENTAL SECTION

General Procedure. To a 25 mL round-bottom flask were added $PdCl_2$ (4.4 mg, 5 mol %), $CuCl_2\cdot 2H_2O$ (4.2 mg, 5 mol %), and **1a** (122 mg, 0.5 mmol). The flask was then purged with O_2 for three times, followed

Table 2. [2 + 2 + 2] Cyclization of 1,6-Diyne and Alkene via Chloropalladation process[a,b]



1 **2** **3**

Entry	Products	Entry	Products	Entry	Products
1	 **3aa** 83%	7	 **3cb** 80%	13	 **3ib** 91%
2	 **3ab** 84%	8	 **3db** 87%	14	 **3jb** 93%
3	 **3ac** 71%	9	 **3eb** 80%	15[c]	 **3kb-a**  **3kb-b** **3kb** (a:b = 8:92) 89%
4	 **3ad** 90%	10	 **3fb** 79%		
5	 **3ae** 89%	11	 **3gb** 91%	16[c]	 **3la-a**  **3la-b** **3la**(a:b=26:74) 84%
6	 **3bb** 86%	12	 **3hb** 81%		

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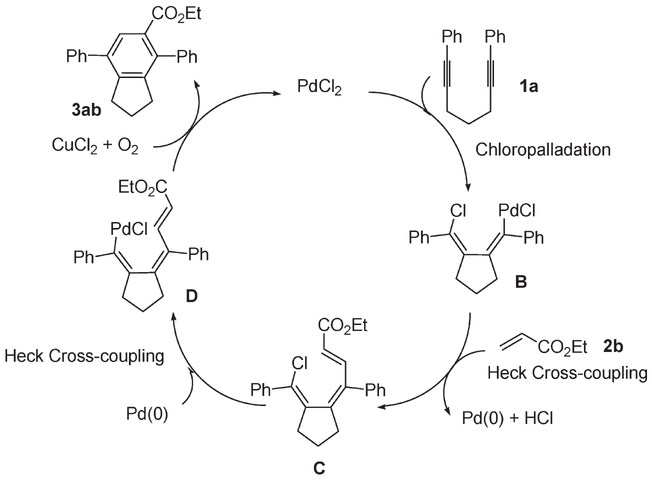
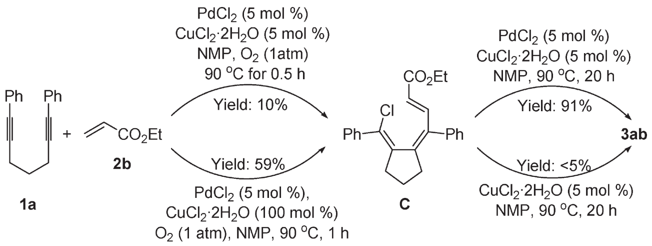
[a] Reaction conditions: 1,6-diyne (0.5 mmol), alkene (0.6 mmol), $PdCl_2$ (5 mol %), $CuCl_2 \cdot 2H_2O$ (5 mol %), and 2 mL of solution in a capped tube with 1 atm of oxygen, heating at 90 °C for 24 h. [b] Isolated yield. [c] At 75 °C for 24 h; the ratio of **a**/**b** was determined by GC−MS and ^{1}H NMR.

Scheme 2. Proposed Mechanism



Scheme 3. Controlled Experiments



by addition of **2b** (60 mg, 0.6 mmol) and NMP (2 mL). The formed mixture was gradually heated from rt to 90 °C under O_2 (1 atm keeped with a balloon) and stirred for 24 h as monitored by TLC. The solution was then cooled to rt, diluted with ether (30 mL), washed with H_2O (3×10 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by TLC on silica gel to afford a benzo-fused five-membered cycle whose structure was determined by ^{1}H NMR, ^{13}C NMR, MS, NOE. Compound **3ab**: colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1H), 7.49−7.51 (m, 2H), 7.43−7.46 (m, 2H), 7.31−7.41 (m, 4H), 7.26 (s, 2H), 4.02 (q, J = 6.6 Hz, 2H), δ 3.04 (t, J = 6 Hz, 2H), 2.76 (t, J = 6 Hz, 2H), 1.96−2.03 (m, 2H), 0.93 (t, J = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 145.7, 144.8, 140.5, 140.3, 137.6, 137.1, 129.9, 128.5, 128.4, 128.3, 127.9, 127.2, 126.8, 60.6, 33.4, 32.8, 25.6, 13.6; MS (EI, 70 eV) m/z 342 (M^+, 100), 297 (60), 269 (40), 252 (29), 149 (20). Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48. Found: C, 84.26; H, 6.40.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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