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Palladium-Catalyzed Carbonylative Cyclization of Aryl Alkenes/Alkenols: A New Reaction Mode for the Synthesis of Electron-Rich Chromanes

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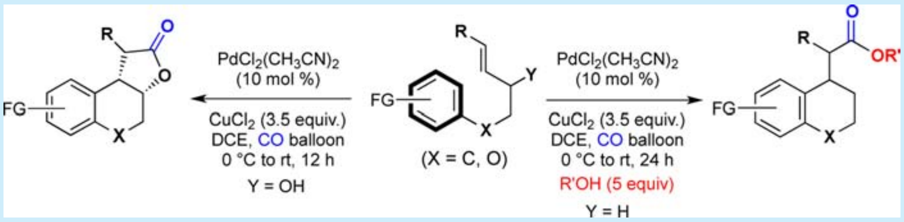
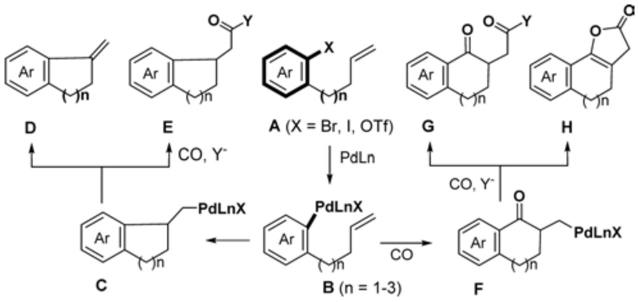
Supporting Information



ABSTRACT: The Pd(II)-catalyzed intramolecular carbonylative cyclization reaction of aryl alkenes and aryl alkenols is reported for the synthesis of structurally diverse chromanes. $PdCl_2(CH_3CN)_2$ was used as the catalyst and $CuCl_2$ as the oxidant under the balloon pressure of CO. The reaction is conducted under mild conditions, and chromane-type esters and lactones can be generated in a highly regio- and stereoselective manner.

Transition metal catalyzed carbonylation reactions are a powerful method to realize the direct fixation of carbon monoxide and produce various carbonyl compounds.[1] The palladium catalyzed Heck-type carbonylation reactions have been extensively studied by chemists in the past decades.[2] The insertion of CO into an aryl-palladium bond leads to the formation of an acylpalladium complex, and subsequent reaction of this complex with various nucleophiles is used to prepare aryl carbonyl compounds. The intramolecular version of this reaction, in which a carbon−carbon double bond is tethered to an aryl halide, has been well studied (Scheme 1).[3] However, this type of reaction usually gives multiple products, and products **D**, **E**, **G**, and **H** are frequently obtained. Furthermore, the ratio of products **D**, **E**, **G**, and **H** depends on different reaction conditions, such as the CO pressure, reaction temperature, and solvent.[3a,b]

Scheme 1. Palladium-Catalyzed Heck-Type Carbonylation Reaction of Ar−X



Hence, the direct Pd-catalyzed carbonylative cyclization of a carbon nucleophile and a carbonyl group across the C═C bond of an unactivated olefin would be an ideal way to make functionalized polycyclic aryl derivatives from simple alkenyl arenes in terms of atom and step economy. In 2004, Widenhoefer et al. reported the Pd-catalyzed carbonylative cyclization reaction of an indole-linked alkene to give polycyclic indole derivatives (Scheme 2, eq 1).[4] In this reaction, the electron-rich C3 and C2 of indole were used as carbon nucleophiles.

Chromane scaffolds are privileged structural motifs in natural products and pharmaceuticals. Examples include anthopogochromane,[5] catiguanins A,[6] and myristinin B.[7,8] We envisioned that this Pd-catalyzed carbonylative cyclization to afford an aromatic carbonyl compound would be useful (Scheme 2, eq 2). Furthermore, when **Y** in **I** is a hydroxyl group, lactone **K** could be made in one step.[9] If developed, this methodology would provide straightforward access to a variety of densely functionalized multisubstituted chromanes.[10]

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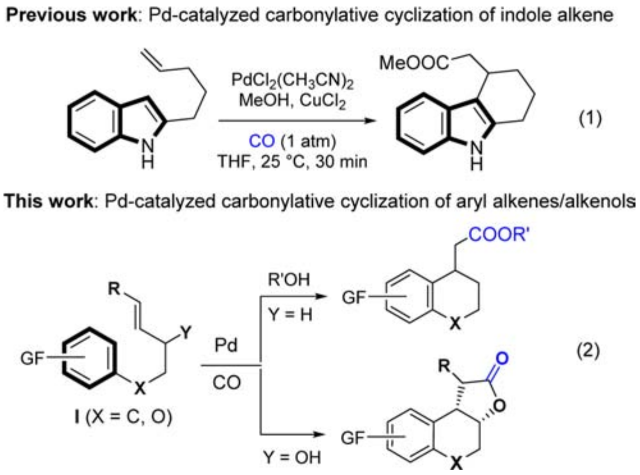
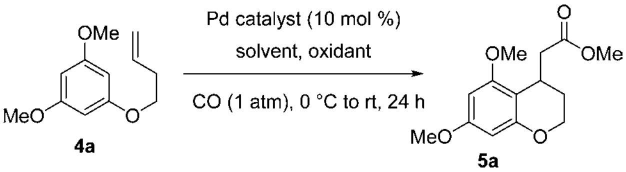
Scheme 2. Palladium-Catalyzed Carbonylative Cyclization Reactions of Ar−H



Aryl alkene **4a** was then selected as a model to explore the scope of this reaction. Initially, $PdCl_2(CH_3CN)_2$ was used as the catalyst and $CuCl_2$ as the oxidant, with a balloon of CO at room temperature in THF and MeOH;[11] no desired annulation product was observed (Table 1, entries 1 and 2). This could be because the Pd(II)-based cationic active species[12] is extenuated when exposed to oxygen-containing solvents.

Table 1. Screening of the Reaction Conditions[a]



4a

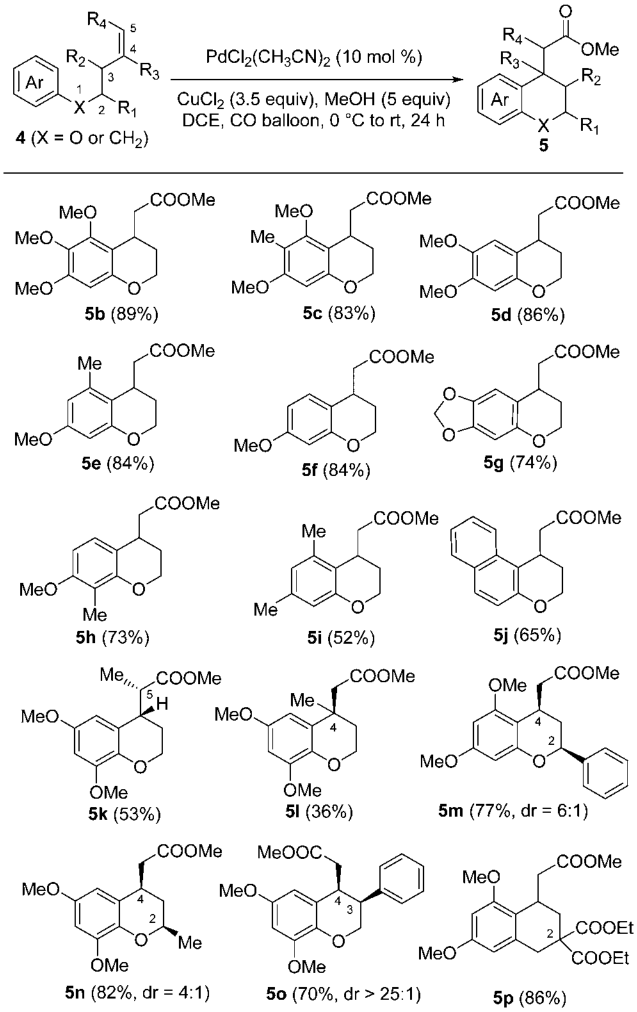
5a

entry	solvent	MeOH (equiv)	catalyst	oxidant (equiv)	yield (%)[b]
1	THF	10	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (2.5)	0
2	MeOH	–	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (2.5)	0
3	DCM	10	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (2.5)	55
4	DCE	10	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (2.5)	68
5	DCE	50	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (2.5)	40
6	DCE	5	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (2.5)	75
7	DCE	5	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (3.5)	90
8	DCE	5	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (3.5)	70[c]
9	DCE	5	$PdCl_2$	$CuCl_2$ (3.5)	82
10	DCE	5	$Pd(OAc)_2$	$CuCl_2$ (3.5)	60
11	DCE	5	$PdCl_2(CH_3CN)_2$	benzoquinone (3.5)	0
12	DCE	5	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$ (3.5)	0

[a] Reaction conditions: **4a** (0.2 mmol), palladium catalyst (10 mol %), solvent (5 mL), oxidant (0.5 or 0.7 mmol), CO (1 atm pressure), 0 °C for 2 h then rt for another 22 h. [b] Isolated yield. [c] Palladium catalyst (5 mol %).

Dichloromethane (DCM) and dichloroethane (DCE) were selected as alternative solvents and used with MeOH (10 equiv). The desired product **5a** was then obtained in 55% and 68% yield, respectively (Table 1, entries 3−4). The yield was reduced to 40% on addition of MeOH (50 equiv) (Table 1, entry 5). It was then improved to 90% yield when $PdCl_2(CH_3CN)_2$ (10 mol %) and $CuCl_2$ (3.5 equiv) were used in DCE and MeOH (5 equiv) (Table 1, entry 7). However, changing the catalyst to $PdCl_2$ and $Pd(OAc)_2$, or replacing $CuCl_2$ with $Cu(OAc)_2$ and benzoquinone, resulted in low yields (Table 1, entries 9−12).

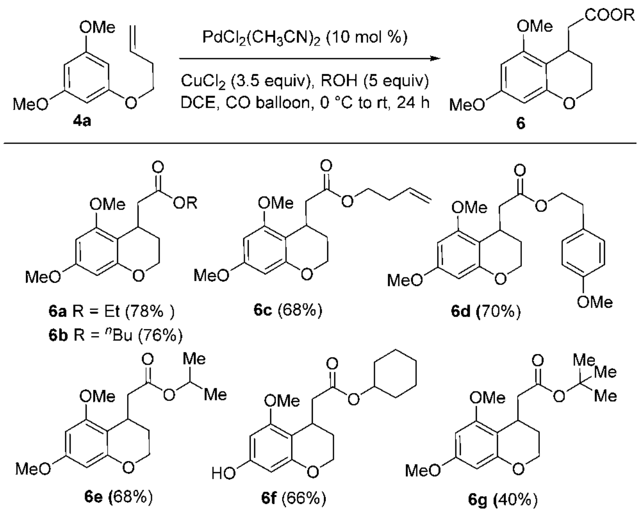
Scheme 3. Pd(II)-Catalyzed Carbonylative Cyclization of Aryl Alkenes[a]



[a] Isolated yield. For products **5i**, **5j**, **5k**, and **L**, the reaction time is 36 h.

The substrate scope was then investigated (Scheme 3). Various electron-rich aryl alkenes **4b**−**4p** were prepared and annulated under the optimized conditions. The following observations were made from the results: (1) the alkoxyl substituted electron-rich aryl alkenes **4b**−**4h** gave annulated products **5b**−**5h** in good yields, and a strong *para*-directing effect was observed; (2) aryl alkene **4i** with two methyl groups, and the naphthalene-based aryl alkene **4j** gave desired products **5i**−**5j** in moderate yields, although a longer reaction time was required; (3) substituted alkenes **4k**−**4l** with methyl groups at R_2 and R_3 were used as substrates to undergo the expected annulation; however, the yields were relatively low and a significant amount of starting material remained after 36 h; (4) substitution with methyl and phenyl groups at the C2 and C3 positions gave desired products **5m**−**5o** in good yields with a predominant *cis*-relationship at the newly generated chiral center; (5) substrate **4p** with gem-diester substitution at the C2 position gave the desired tetrahydronaphthalene product **5p** in good yield.

Scheme 4. Pd(II)-Catalyzed Carbonylative Cyclization of Aryl Alkene 4a with Alcohols[a]



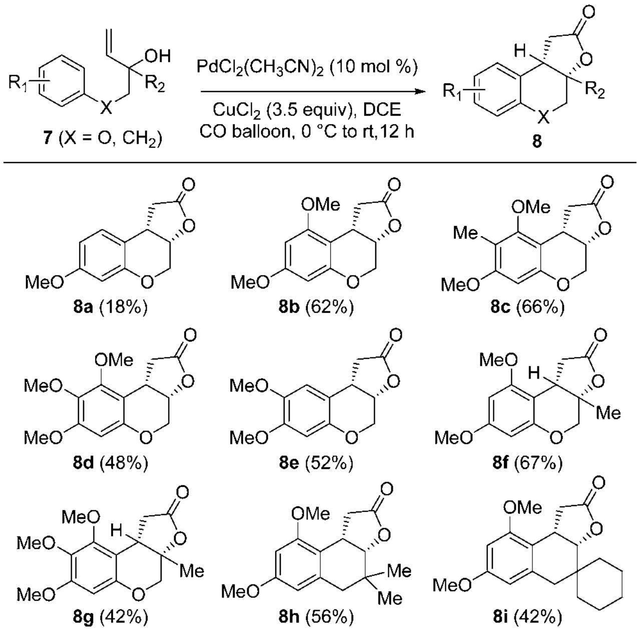
[a]Isolated yield.

The effect of alcohols was then examined. Scheme 4 shows that the primary and secondary alcohol based nucleophiles gave the annulated products **6a**−**6f** in good yields. In the case of tertiary alcohol **6g**, the yield decreased dramatically, indicating that steric hindrance played an important role in this reaction. Interestingly, when alcohol was replaced with water, no carboxylic acid was formed, indicating the nucleophilicity of the hydroxyl group is critical.

To extend the synthetic scope of this Pd-catalyzed reaction, we intended to explore its potential application to the synthesis of the chromane lactone core.[13] Encouraged by early work on Pd-catalyzed alkoxycarbonylative cyclization reactions,[14] we hypothesized that the synthesis of chromane lactones from aryl alkenol substrates could be achieved by using our newly developed Pd-catalyzed carbonylative cyclization methodology.

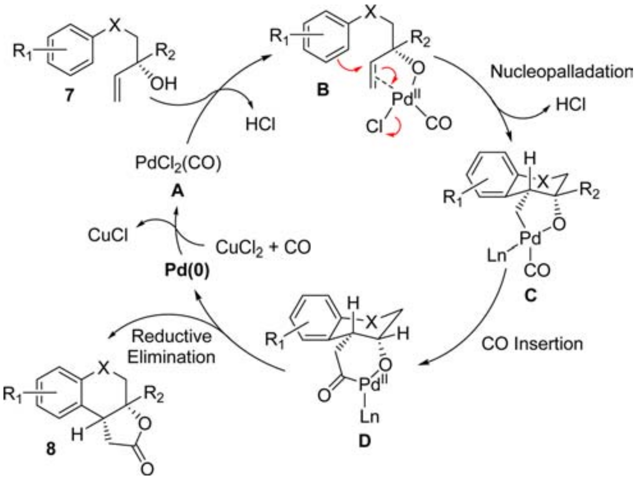
To validate this hypothesis, nine electron-rich aryl alkenols were prepared and annulated under the optimized reaction conditions (see Supporting Information for details). The results are listed in Scheme 5, and the following conclusions can be made: (1) Substrates with two or more methoxy groups on the phenyl ring gave the desired products **8b**−**8i** in reasonable yields; however, when a single methoxy group was present on the phenyl ring, only 18% annulated product **8a** was obtained, presumably because when the nucleophilicity of the aryls reduced, decomposition reactions will be prominent under the Pd(II)-catalyzed reaction conditions; (2) substrates with a tertiary allylic alcohol gave the desired lactones **8f** and **8g**; (3) the carbon-tethered substrates were converted to their corresponding lactones **8h** and **8i** in acceptable yields; (4) excellent diastereoselectivity was observed for this reaction to give *cis*-chromane lactone as a single diastereomer. The structure of **8b** was determined with X-ray analysis.[15]

Scheme 5. Pd(II)-Catalyzed Carbonylative Cyclization of Aryl Alkenols[a]



[a]Isolated yield.

Scheme 6. Proposed Mechanism for the Pd-Catalyzed Carbonylativa Cyclization of Aryl Alkenols



A plausible mechanism was proposed to account for this transformation (Scheme 6). We envisioned that the allylic alcohol in substrate **7** could react with the palladium carbonyl complex **A** to generate complex **B**,[16] which would undergo an intramolecular nucleopalladation to afford a *cis*-configured palladocyclic intermediate **C**. Following migratory insertion of CO into the alkyl-Pd bond, the resultant complex **D** would undergo reductive elimination to stereoselectively produce lactone **8** and palladium(0). The palladium(0) would then be oxidized with $CuCl_2$, and chelation with CO would occur to give palladium(II) complex **A** and complete the cycle.

In conclusion, we have developed a novel synthetic route to highly substituted and electron-rich chromanes. Unlike the previous Pd-catalyzed carbonylation of halo-aryl alkenes, our newly developed reaction mode of the Pd-catalyzed carbonylative cyclization allows for the synthesis of the structurally diverse chromanes in a highly regio- and stereoselective manner from simple aryl alkenes and aryl alkenols. Further application of this method for the total synthesis of biologically active natural products is currently underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral and other characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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