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A Domino Palladium-Catalyzed C−C and C−O Bonds Formation via Dual O−H Bond Activation: Synthesis of 6, 6-Dialkyl-6*H*-benzo[*c*]chromenes

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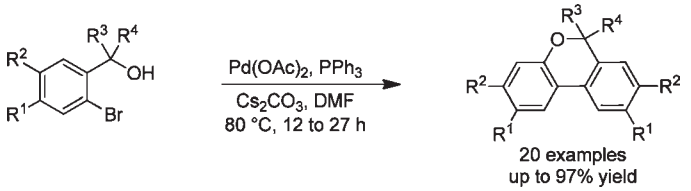
ABSTRACT



An efficient Pd-catalyzed domino reaction of α,α-dialkyl-(2-bromoaryl)methanols to 6,6-dialkyl-6*H*-benzo[*c*]chromenes is presented. Their formation can be explained via a five membered Pd(II)-cycle that efficiently involves a domino homocoupling with the second molecule, β-carbon cleavage, and finally intramolecular Buchwald−Hartwig cyclization. This domino process effectively involves breaking of five σ-bonds (2C−Br, 2O−H, and a C−C) and formation of two new σ-bonds (C−C and C−O). This mechanistic pathway is unprecedented and further illustrates the power of transition metal catalysis.

The development of efficient and sustainable synthetic methods to achieve molecular complexity in one-pot domino processes is an important and challenging task in synthetic organic chemistry.[1] In this aspect, transition-metal catalysis is a powerful tool that permits C−C and C−X (heteroatom) bond forming reactions most efficiently. A metal that in particular has been used for such transformations is palladium.[2,3] A unique method of generating C(sp)−Pd, C(sp^2)−Pd species as potential intermediates in subsequent coupling reactions is via Pd-catalyzed arylative β-carbon cleavage of tertiary alcohols.[4,5] Subsequently, Yorimitsu, Oshima, and co-workers employed a useful

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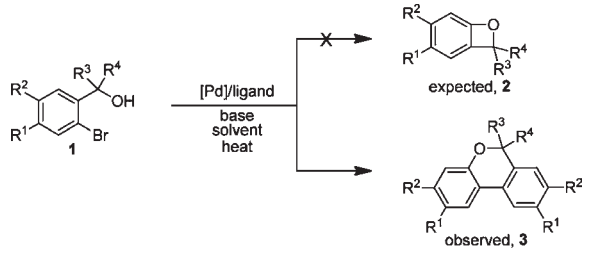
extension where σ-allyl(aryl)palladium intermediates were generated via retroallylations of homoallylic alcohols through a six-membered homoalkenyloxy(aryl)palladium transition state. The obtained arylpalladium intermediates were suitable for allylation coupling with aryl moieties.[6] Very recently, Cramer and Waibel reported a novel stereocontrolled Pd-catalyzed arylative ring-opening reaction on norbornene-derived tertiary alcohols for the synthesis of highly substituted acyl cyclohexenes, quinolines, and tetrahydroquinolines.[7]

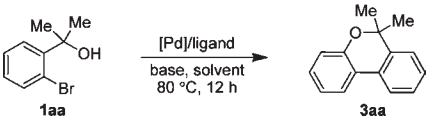
Herein, we report a novel protocol, a domino Pd-catalyzed reaction of α,α-disubstituted-(2-haloaryl)-methanols **1**,[8] for the efficient synthesis of 6,6-dialkyl-6*H*-benzo[*c*]chromenes **3**.[9] This domino process effectively involves breaking of five σ-bonds (2C−Br, 2O−H, and a C−C) and formation of two new σ-bonds (C−C and C−O). In continuation of our interest in the development of synthetic methods by Pd-catalysis,[10] we became interested in exploring a Pd-catalyzed intramolecular C−O bond formation on substrates **1**, anticipating the formation of strained four membered 8,8-dialkyl-7-oxabicyclo[4.2.0]octa-1,3,5-trienes **2** (see Scheme 1). This in fact was presumed based on previously reported results using Pd-catalyzed synthesis of strained cyclobutanes, cyclobutanones, and exocyclic cyclobutenes.[11] However, surprisingly, the only sole product

Scheme 1. Unexpected Formation of Homocoupled Biaryl Cyclic Ether **3**



isolated from performing the reaction on the parent α, α-dimethyl-(2-bromophenyl)-methanol **1aa** was the corresponding 6,6-dialkyl-6*H*-benzo[*c*]chromene **3**. Therefore, it was understood that the reaction does not permit the formation of the strained four membered cyclic ether via an intramolecular ring-closing reaction, but rather prefers the intermolecular homocoupling followed by cyclization with a second α,α-disubtituted-(2-haloaryl)-methanol molecule in a domino fashion. One should note that it is well documented that Pd-catalyzed intramolecular Buchwald−Hartwig cyclization, up to the formation of five membered carbo-cylic ethers and also to cyclic silyl ethers, is feasible.[12]

Table 1. Optimization Reaction Conditions for the Synthesis of 6,6-Dimethyl-6*H*-benzo[*c*]chromene **3aa**



1aa 3aa

entry[a]	[Pd] (5 mol %)	ligand (10 mol %)	solvent	base (2 equiv)	**3aa** (%)[b]
1	$Pd(OAc)_2$	PPh_3	DMF	K_2CO_3	42
2	$Pd(OAc)_2$	PPh_3	DMF	K_3PO_4	73
3	$Pd(OAc)_2$	PPh_3	DMF	$NaHCO_3$	0
4	$Pd(OAc)_2$	$AsPh_3$	DMF	Cs_2CO_3	51
5	$Pd(OAc)_2$	PPh_3	dioxane	Cs_2CO_3	70
6	$Pd(OAc)_2$	PPh_3	CH_3CN	Cs_2CO_3	75
7	$Pd(OAc)_2$	PPh_3	toluene	Cs_2CO_3	79
8	**$Pd(OAc)_2$**	**PPh_3**	**DMF**	**Cs_2CO_3**	**89**
9	$Pd(dppf)_2Cl_2$	PPh_3	DMF	Cs_2CO_3	60
10	$Pd(dba)_2$	PPh_3	DMF	Cs_2CO_3	62
11	$Pd(PPh_3)_2Cl_2$	PPh_3	DMF	Cs_2CO_3	66
12	$Pd(PPh_3)_4$	nil	DMF	Cs_2CO_3	69

[a] All reaction were performed on a 100 mg (0.46 mmol) scale of **1aa** in a 0.23 M concentration. [b] Isolated yields of chromatographically pure products.

The α,α-dialkyl-(2-bromophenyl)-methanols **1**, which are required for this study, could be obtained easily using a well established one-pot alkyl Grignard addition to the corresponding *o*-halobenzoates or alkyl Grignard addition, oxidation, and alkyl Grignard addition protocol to *o*-halobenzaldehydes (see Supporting Information (SI)). The Pd-catalyzed transformation of the parent α,α-dimethyl-(2-bromophenyl)-methanol **1aa** was explored under various conditions. Thus, reaction of **1aa** in presence of the catalyst $Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) and base K_2CO_3 (2 equiv) in hot DMF at 80 °C for 12 h furnished the product 6,6-dimethyl-6*H*-benzo[*c*]chromene **3aa** in 42% moderate yield (Table 1, entry 1). Interestingly, base K_3PO_4 drastically improved the product yield to 73% (Table 1, entry 2). Discouragingly, $NaHCO_3$, a weaker base, lead to complete recovery of the starting material (Table 1, entry 3). Using ligand $AsPh_3$ and base Cs_2CO_3 furnished **3aa** in moderate yield (51%, Table 1, entry 4).

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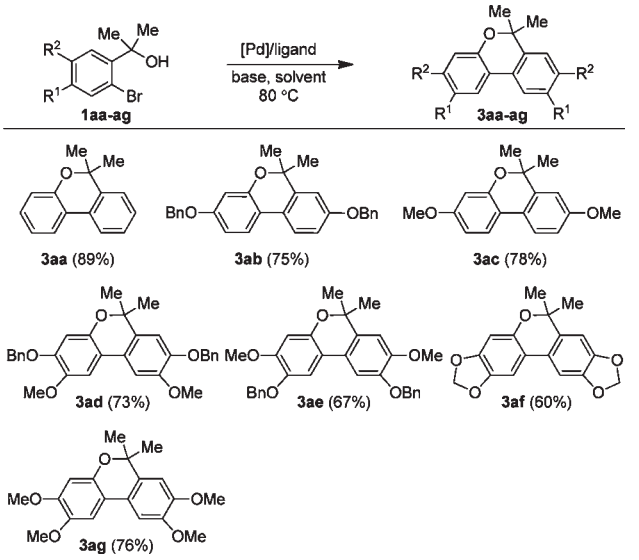
Interestingly, use of different solvents improved the yield of product (Table 1, entries 5–7). Gratifyingly, the reaction with the catalyst $Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %), in the presence of base Cs_2CO_3, in hot DMF furnished the product in excellent yield (89%, Table 1 entry 8). A change of Pd-catalyst for other than $Pd(OAc)_2$, in hot DMF and base Cs_2CO_3, showed an incremental effect in yields (Table 1, entries 9–11). Reaction with $Pd(PPh_3)_4$ (5 mol %) and Cs_2CO_3 (2 equiv) furnished the product in good yield (69%, Table 1, entry 12).

Scheme 2. Scope of Homocoupling Reaction on α, α-Dimethyl-(2-bromoaryl)-methanols[a]

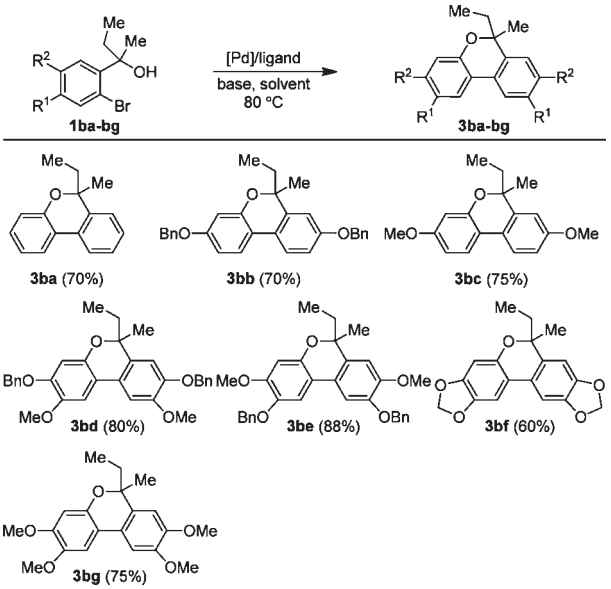


[a] Reaction conditions: **1aa**–**ag** (100 mg, 0.21 to 0.47 mmol), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), 0.14–0.23 M in DMF, at 80 °C for 12–27 h. Yields in the parentheses are isolated yields of chromatographically pure products.

In all, the conditions found in entry 8 of Table 1 turned out to be the best with regard to the yield of 6,6-dimethyl-6*H*-benzo[*c*]chromene **3aa**. Therefore, these optimized conditions were applied to the other higher substituted aromatic ring systems of α,α-dimethyl-(2-bromoaryl)-methanols **1aa**–**ag** to examine the scope and limitations of the present method. Delightfully, the reaction went smoothly even with electron-rich substituents and furnished the products **3aa**–**ag** in very good and comparable yields, as summarized in Scheme 2. The only difference from the above optimized reaction conditions was the increase in reaction time (12 to 27 h), which was found to be essential for complete consumption of the starting material, especially for higher substituted substrates.

After successful accomplishment of cyclic ethers **3aa**–**ag**, we turned our attention to checking the scope and limitations of the method by changing the alkyl substitution pattern of the tertiary alcohol domain. Thus, Pd-catalysis on α,α-ethylmethyl-(2-bromoaryl)-methanols **1ba**–**1bg** was also investigated. In general, the results were quite consistent with those observed in the case of α,α-dimethyl-(2-bromoaryl)-methanols **1aa**–**ag**, with furnished products **3ba**–**3bg** in very good yields, as depicted in Scheme 3.

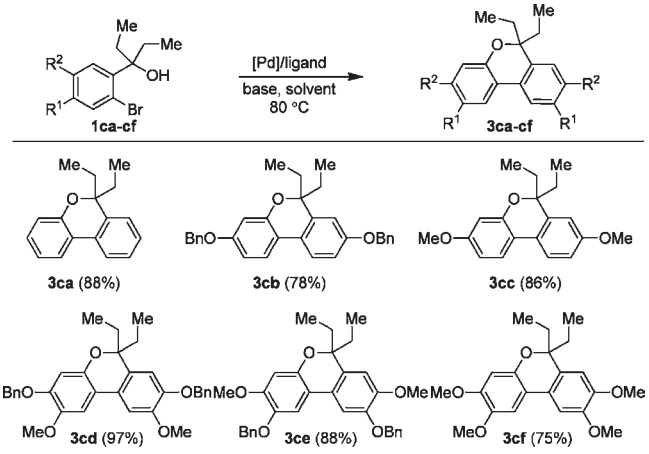
Scheme 3. Scope of Homocoupling Reaction on α, α-Ethylmethyl-(2-bromoaryl)-methanols[a]



[a] Reaction conditions: **1ba**–**bg** (100 mg, 0.20 to 0.45 mmol), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), 0.13–0.22 M in DMF, at 80 °C for 12–27 h. Yields in the parentheses are isolated yields of chromatographically pure products.

Furthermore, to study the generality of this method, Pd-catalyzed reaction on α,α-diethyl-(2-bromoaryl)-methanols **1ca**–**cf** was also explored. Gratifyingly, under optimized conditions the corresponding products **3ca**–**cf** were obtained in good yields (Scheme 4).

Scheme 4. Scope of Homocoupling Reaction on α,α-Diethyl-(2-bromoaryl)-methanols[a]



[a] Reaction conditions: **1ca**–**cf** (100 mg, 0.20 to 0.42 mmol), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), 0.12–0.20 M in DMF, at 80 °C for 12–27 h. Yields in the parentheses are isolated yields of chromatographically pure products.

The molecular structure of **3** was further confirmed by the single crystal X-ray diffraction analysis of **3af**[13] as shown in Figure 1 (see SI for X-ray data of **3cc** as well).

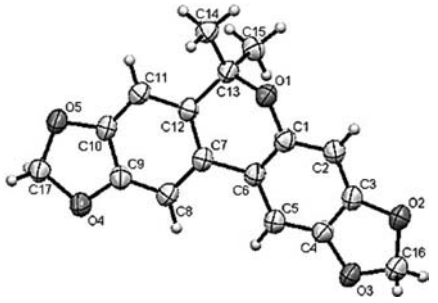


Figure 1. X-ray crystal structure of product **3af**. Thermal ellipsoids are drawn at 50% probability level.

The formation of 6,6-dialkyl-6*H*-benzo[*c*]chromene **3** can only be explained by insertion of the initially formed aryl-palladium(II) species **A** from **1aa** to the O−H bond of the tertiary alcohol, yielding a five-membered palladacycle **B** (Scheme 5). Via elimination of H−Br the reactive Pd(II) species **C** might form. The key palladacycle **C** could undergo insertion into the C−Br bond of a second molecule of **1a** leading to the Pd(IV) complex **D**. Intramolecular transfer of an aryl group leads to the Pd(II) intermediate **E**, which on spontaneous β-carbon cleavage affords Pd(II) species **F**. Finally, an intramolecular Buchwald−Hartwig cyclization of **F** with tertiary alcohol via a reductive elimination of a Pd-catalyst completes the catalytic cycle with the formation of 6,6-dialkyl-6*H*-benzo[*c*]chromene **3aa**. The reaction might be driven also by the gem-dialkyl effect to facilitate the formation of **B**.[14] Surprisingly, we could determine a practical use for the gem-dialkyl effect in these cases. This was concluded when the reaction was performed under optimized conditions on simple 2-bromoarylmethanol, which yielded benzaldehyde (not the expected cyclic ether benzochromene) in about the same time as compared with substrates with a gem-dialkyl group. Its formation can be explained via fast cleavage of five a membered Pd-cycle assisted by β-hydrogen.[15] We also performed the reaction on alkyl-(2-bromoaryl)-methanols. However, these substrates furnished an inseparable mixture of products.

(13) Crystal data for **3af**: CCDC 857035, $C_{17}H_{14}O_5$, M = 298.28, monoclinic, a = 6.4053(5) Å, b = 15.8952(13) Å, c = 13.1993(11) Å, α = 90°, β = 101.104(7)°, γ = 90°, V = 1318.71(18) Å^3, T = 150.01 (10) K, space group $P2_1/n$, Z = 4, 4977 reflections measured, 2479 unique used for calculation (R_{int} = 0.0270). The final wR_2 was 0.1804 (all data) and R_1 was 0.0577 [$I > 2\sigma(I)$].

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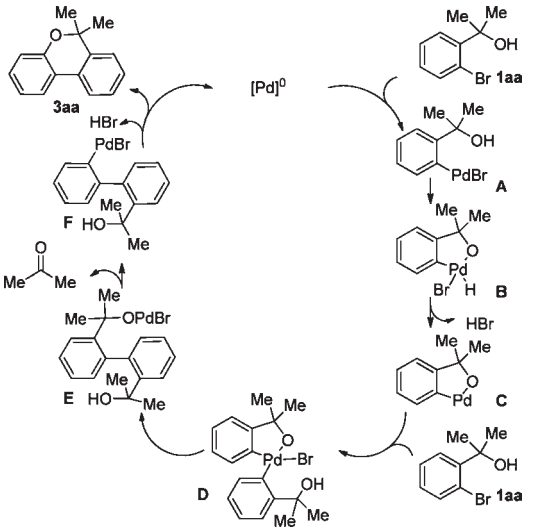
In summary, we have disclosed an efficient domino Pd-catalyzed homocoupling followed by a ring closing reaction, for the synthesis of 6,6-dialkyl-6*H*-benzo[*c*]chromene. This mechanistic pathway is unprecedented and further illustrates the power of transition metal catalysis. Further extension of this domino process to access various useful heterocyclic systems is in progress.

Scheme 5. Plausible Reaction Mechanisms for the Formation of **3aa**[a]



[a] For simplicity, phosphine ligands are omitted.

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Supporting Information Available. Experimental procedures and characterization for all new compounds, copies of NMR spectra, and CIF files for **3af** and **3cc** provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(15)