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Synthesis of 6*H*-Benzo[*c*]chromenes via Palladium-Catalyzed Intramolecular Dehydrogenative Coupling of Two Aryl C−H Bonds

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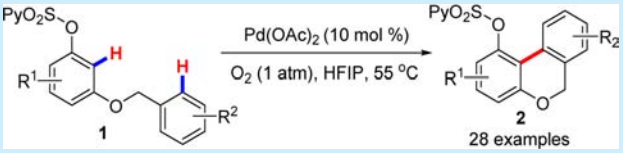
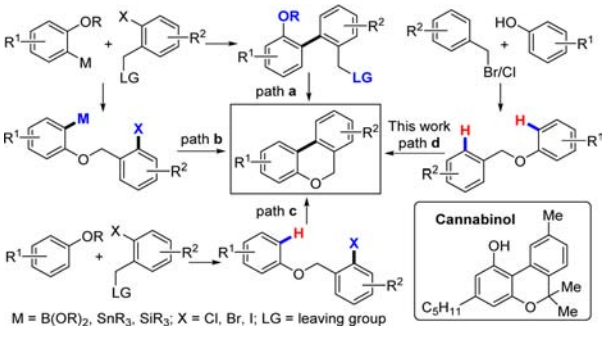
Supporting Information

ABSTRACT: The palladium-catalyzed intramolecular C−H/C−H coupling reaction of two simple arenes to generate 6*H*-benzo[*c*]chromenes has been reported for the first time. The approach features broad substrate scope and good tolerance of functional groups and uses molecular oxygen as the terminal oxidant. The high efficiency of the approach is verified by concise total synthesis of natural product cannabinol.



6*H*-Benzo[*c*]chromenes are an important class of organic compounds present in numerous natural products and bioactive molecules.[1] A typical natural product case is cannabinol, which is a family member of the cannabionoids that can interact with the G-protein coupled cellular receptors CB1 and CB2,[2] exhibiting analgesic, antiemetic, anticonvulsant, antibiotic, and psychotropic activities.[3] Considering the potential utilities of these molecules, the synthesis of 6*H*-benzo[*c*]chromenes remains of long-standing interest in organic chemistry.[4−6] In view of the structural feature of 6*H*-benzo[*c*]chromenes, the formation of the aryl−aryl bond is undoubtedly the key step. Classically, the aryl−aryl bond can be reliably achieved by cross-couplings of organometallic aryls with aryl halides (Scheme 1, paths a and b).[7] In the past decade, an attractive alternative to this approach, namely the direct arylation of nonactivated aryl C−H bonds with aryl halides (path c),[4a,5,6] has been greatly developed. The approach often undergoes a transition-metal-catalyzed coupling[5] or a homolytic aromatic substitution with aryl radicals.[6] The advantage of the transformation is obviating the need to work with organometallic reagents. Nevertheless, the simplest and ideal approach to access 6*H*-benzo[*c*]chromenes is the dehydrogenative coupling of two nonactivated aryl C−H bonds to form the key aryl−aryl bond (path d), particularly when the coupling can be performed with molecular oxygen as the terminal oxidant. But, to the best of our knowledge, there is no report in the literature on employing the ideal strategy in the construction of 6*H*-benzo[*c*]chromene. The major hindrance to the ideal strategy lies in two challenges:[7d] (i) the low reactivity of the aryl C−H bond due to its high bond strength[8] and (ii) the regioselectivity issue especially when there are several reactive sites; moreover, the dimerization is also unavoidable sometimes. Continuing our interest in the C−H bond activation, we hypothesized that, in order to accomplish the ideal approach, an appropriate direct group might be introduced into the arene substrate to control the regioselectivity, simultaneously enhancing the reactivity of the aryl C−H bond. Meanwhile an efficient catalytic system should be sought. Herein, we demonstrate this hypothesis to develop the first intramolecular two aryl C−H bonds dehydrogenative coupling to construct 6*H*-benzo[*c*]chromenes. The high efficiency of the method is verified by concise total synthesis of natural product cannabinol.

Scheme 1. Routes to 6*H*-Benzo[*c*]chromenes



We began this study by examining the phenol protecting group which had potential directing feature for the *otho*-functionalization of arenes. A set of protecting groups was tested with 10 mol % $Pd(OAc)_2$ as the catalyst and oxygen as the oxidant in dimethyl sulfoxide (DMSO) (Table 1). The reaction did not occur at all when the protecting group was Ac, $-CONMe_2$, $-CONEt_2$, or *O*-(2-pyridyl)carbonyl group, although they were excellent directing groups in many functionalization reactions of arenes (entries 1−4). These experiments indicated the low reactivity of aryl C−H bond once again. Gratifyingly, when the *O*-(2-pyridyl)sulfonyl group

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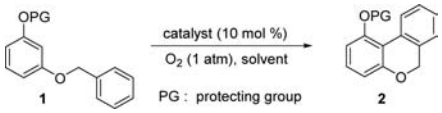
Table 1. Optimization of the Reaction Conditions[a]



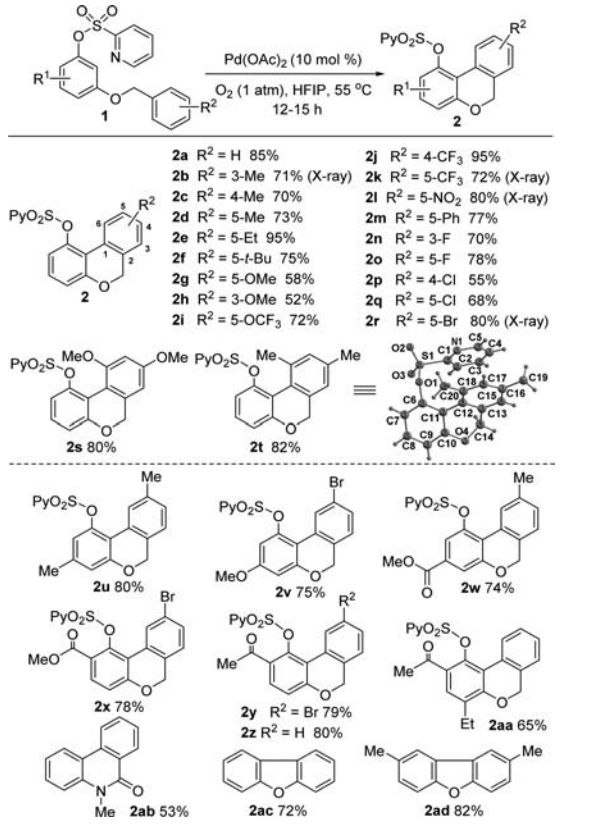
entry	cat.	PG	solvent	yield[b] (%)
1	$Pd(OAc)_2$	−Ac	DMSO	0
2	$Pd(OAc)_2$	$-CONMe_2$	DMSO	0
3	$Pd(OAc)_2$	$-CONEt_2$	DMSO	0
4	$Pd(OAc)_2$	−CO(2-Py)	DMSO	0
5	$Pd(OAc)_2$	$-SO_2$(2-Py)	DMSO	10
6[c]	$Pd(OAc)_2$	$-SO_2$(2-Py)	other solvent	trace
7	$Pd(OAc)_2$	$-SO_2$(2-Py)	HFIP	85
8	$Pd(TFA)_2$	$-SO_2$(2-Py)	HFIP	86
9[d]	$Pd(OAc)_2$	$-SO_2$(2-Py)	HFIP	52
10[e]		$-SO_2$(2-Py)	HFIP	0

[a]Reaction conditions: **1a** (1 mmol), catalyst (0.1 mmol), and O_2 (1 atm) in solvent (5 mL) for 15 h. [b]Isolated yield. [c]Other solvents: CH_2Cl_2, $ClCH_2CH_2Cl$, EtOAc, DMF, THF, *n*-hexane, toluene, xylene, anisole, acetone, CH_3CN, dioxane, Et_2O, $CHCl_3$, $HCONH_2$, CH_3NO_2, EtOH, *i*-PrOH, *t*-BuOH. [d]Using air as oxidant. [e]Without catalyst.

used as the protecting group, the desired aryl C−H/C−H coupling product was generated albeit only in 10% yield (entry 5). We considered that the reactivity of the *O*-(2-pyridyl)-sulfonyl group should attribute to its not only being good directing group but also being a great activating group to facilitate the formation of a phenyl−Pd complex through the electrophilic substitution of the *ortho* C−H bond of phenol.[9] Encouraged by the preliminary result, we then carefully investigated various parameters of the reaction including solvent, temperature, different metal catalysts, and their loadings to improve the yield of the C−H/C−H coupling reaction. It turned out that the solvent was critical for the reaction efficiency, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) combined with $Pd(OAc)_2$ at 55 °C afforded the best yield (85%) (entry 7). $Pd(TFA)_2$ was also equally effective for the reaction (entry 8). In view of the price concern, we further carried out studies with $Pd(OAc)_2$ as the catalyst. The reaction rate and the yield were obviously dropped when air was used as the oxidant instead of oxygen (entry 9). The reaction could not happen without $Pd(OAc)_2$ catalyst (entry 10).

With the optimal conditions in hand, we first examined the effect of the substituent on the right aromatic ring for the aryl C−H/C−H coupling (Scheme 2, **2b−t**). A variety of aryls with both electron-donating and electron-withdrawing groups could be engaged in this transformation, providing the desired benzochromenes in good to excellent yields. It should be noted that the substrates with electron-withdrawing groups reacted slightly faster than those with electron-donating groups. The position of the substituent on the aromatic rings had almost no effect on the reactivity (**2b−d**). A series of important functional groups, including methyl, ethyl, *tert*-butyl, methoxy, $-CF_3$,$-OCF_3$, nitro, and phenyl were compatible with this procedure (**2b−m**). Fluoro, chloro, and bromo groups were tolerated under the reaction conditions (**2n−r**). This was a synthetically interesting result because such substituents could be versatile handles for further transformations. It is worth noting that, for *meta*-substituted substrates that bear two potentially reactive sites, the reactions only occurred at the less sterically hindered position without the product of other position observed,

Scheme 2. Scope of the Two-Aryl C−H/C−H Coupling Reaction



indicating that the reaction possessed complete regioselectivity (**2c**, **2j**, **2p**). Disubstituted aryls were also suitable substrates, affording the desired products **2s** and **2t** in 80% and 82% yields, respectively. The structures of **2b**, **2k**, **2l**, **2r**, and **2t** were confirmed by single-crystal X-ray diffraction (see the Supporting Information).

Next, we investigated the substituents on the left phenol ring (Scheme 2, **2u−aa**). Again, the aryl C−H/C−H coupling reaction was not insensitive to the steric hindrance and the electronic property of the substituent groups. A series of substituent groups with various properties (methyl, ethyl, methoxy, bromo, CO_2Me, and acetyl) tolerated the reaction conditions, and the corresponding substrates all gave the desired products in good yields. These results might allow high diversity in the synthesis of functionalized 6*H*-benzo[*c*]-chromenes. Finally, other heteroatom links were checked (Scheme 2, **2ab−ad**). Under the current reaction conditions, the substrate replacing the oxygen atom with a sulfur atom did not react to provide 6*H*-benzo[*c*]thiochromene, which was likely attributed to the toxicity of sulfur to palladium catalyst. Delightedly, *N*-methyl-*N*-phenylbenzamide reacted smoothly to give 5-methylphenanthridin-6(5*H*)-one (**2ab**) in 53% yield with the same reaction conditions, and the reaction also was successfully extended to the construction of dibenzo[*b*,*d*]furans (**2ac**, **2ad**).

To gain insight into the reaction mechanism, we carried out a series of experiments. First, dimethyl maleate ester was introduced into the reaction system of **1aa** in order to trap the palladium intermediate with a Fujiwara−Moritani-type alkenylation reaction (Scheme 3, eq 1). Pleasingly, the alkenylation product (**3aa**) was obtained in 72% yield,

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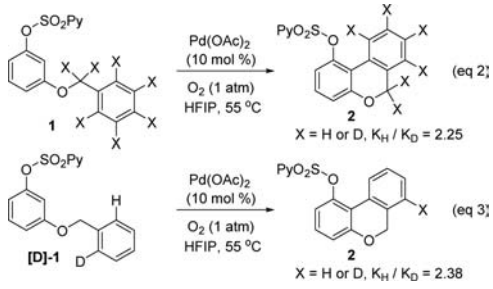
Scheme 3. Alkenylation Reaction 1aa

indicating that the palladiation of the aromatic ring first occurs likely at the *ortho*-position of the phenol. Subsequently, kinetic isotope effect (KIE) experiments were performed (Scheme 4,

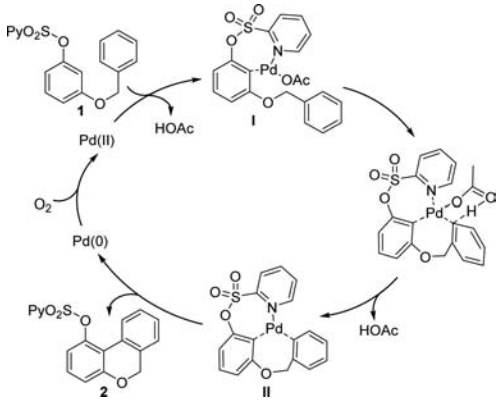
Scheme 4. Kinetic Isotope Effect



eqs 2 and 3). The KIE value of two parallel competition reactions of **1a** and [D_7]-**1a** was found to be 2.25 (Scheme 4, eq 2), and the intramolecular KIE value for the reaction of [D]-**1a** was 2.38 (Scheme 4, eq 3). These results implied an electrophilic aromatic palladation mechanism is unlikely, and the cleavage of the C−H bond on the right aromatic ring could be involved in the rate-determining step. Furthermore, radical-trapping experiments illustrated a low possibility for a free-radical pathway.[10]

On the basis of the above results and relevant publications,[11] a plausible mechanism is proposed in Scheme 5. Initially, the *O*-

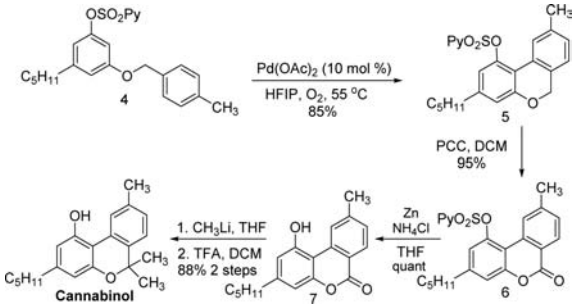
Scheme 5. Plausible Mechanism



(2-pyridyl)sulfonyl group-directed palladation forms complex **I**, which then undergoes a concerted metalation−deprotonation (CMD) step to afford intermediate **II**. Finally, reductive elimination of intermediate **II** produces the 6*H*-benzo[*c*]-chromene products along with Pd(0), which is reoxidized by O_2 to regenerate the Pd(II) species to complete the catalytic cycle.

To demonstrate the synthetic application of this methodology, we employed it as key step to synthesize natural product cannabinol. Cannabinol is always a hot molecule in medicinal chemistry due to its broad biological activities;[12] therefore, it has also received substantial interest from the synthesis community.[13] Recently, Song et al. accomplished the total synthesis of cannabinol using an intramolecular pyranone Diels−Alder cycloaddition reaction as the key step.[14] More recently, Chi et al. developed a base-mediated [4 + 2] reaction to construct the benzene ring and with it as the key step finished the total synthesis of cannabinol.[15] Our synthesis of cannabinol started from compound **4**, which could be obtained from commercially available 5-pentyl-1,3-diphenol through two steps in 78% overall yield (for details, see the Supporting Information). Then, under our optimized conditions, intramolecular two aryl C−H/C−H coupling cyclization of **4** smoothly gave the 6*H*-benzo[*c*]chromene **5** in 85% yield (Scheme 6). The oxidation of ether by PCC afforded lactone **6**

Scheme 6. Total Synthesis of Natural Product Cannabinol



in excellent yield. Removal of the 2-pyridysulfonyl group was easily achieved by reduction with zinc in NH_4Cl (aq)/THF (1:1) at room temperature in quantitative yield. Dimethylation with MeLi followed by the treatment of TFA afforded natural product cannabinol in 88% yield over two steps.

In summary, we have developed the first palladium-catalyzed intramolecular C−H/C−H coupling between two simple arenes to construct 6*H*-benzo[*c*]chromenes. The approach is featured by broad substrate scope, good tolerance of functional groups, and use of molecular oxygen as the terminal oxidant. Notably, the products are useful synthetic intermediates as clearly demonstrated by efficient total synthesis of natural product cannabinol with simple operation in 55% overall yield from commercially available materials. Further studies to expand the reaction and their applications as well as investigations of the reaction mechanism are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03763.

Experimental procedures, spectral data for all new compounds, and crystallographic data (PDF)
X-ray data for compound **2b** (CIF)
X-ray data for compound **2k** (CIF)
X-ray data for compound **2l** (CIF)
X-ray data for compound **2r** (CIF)
X-ray data for compound **2t** (CIF)

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Notes

The authors declare no competing financial interest.

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