Palladium-catalyzed annulations of arynes with 2-(2-iodophenoxy)-1-substituted ethanones†

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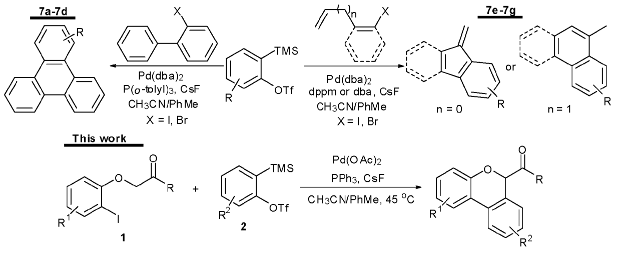
Palladium-catalyzed annulations of arynes with 2-(2-iodophenoxy)-1-substituted ethanones for the synthesis of 6*H*-benzo[*c*]chromenes are presented. This mild route allows formation of two new carbon–carbon bonds *via* an α-arylation/annulation process.

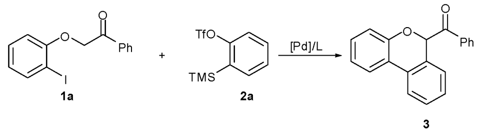
Benzo[*c*]chromenes are important structural units found in many naturally and biologically active compounds, as well as being valuable building blocks in organic synthesis.[1–4] 5*H*-Dibenzo[*c*,*g*]chromen-3-ol, for example, has been reported as an estrogen receptor.[2,3] Although diverse synthetic approaches toward benzo[*c*]chromenes have been developed,[2–4] versatile and efficient methodologies to construct these compounds with selective control of substitution patterns using readily accessible building blocks are still needed. Recently, the carboannulations of arynes have become an important methodology for constructing a multiplicity of carbocycles and heterocycles since 2-(trimethylsilyl)aryl triflates, aryne precursors, were reported by Kobayashi.[5–9] Among these carboannulations, Pd-catalyzed annulations of arynes with aryl halides displayed particular efficiency for these cycles construction. For example, four groups independently reported an interesting palladium-catalyzed approach to the annulation of an aryne with an aryl halide and an sp^2 carbon in an arene[7a–d] or an olefin,[7e–g] providing the corresponding polyaromatic compounds in good yields and high selectivities (Scheme 1). Encouraged by these results, we envision that benzo[*c*]chromene can be prepared using a similar strategy. Here, we report a novel protocol, palladium-catalyzed annulations of arynes with 2-(2-iodophenoxy)-1-arylethanones, for the synthesis of 6*H*-benzo[*c*]chromenes through α-arylation of ketones (Scheme 1).[10] To the best of our knowledge, it is the first example of direct annulations between arynes and aryl halides through the functionalization of an sp^3 carbon at the α-position of a carbonyl compound.[8g]



Scheme 1 Some routes to the annulations of arynes with halides.

As shown in Table 1, the reaction between 2-(2-iodophenoxy)-1-phenylethanone (**1a**) and 2-(trimethylsilyl)phenyl triflate (**2a**), an aryne precursor, was chosen as a model reaction to optimize the reaction conditions. Initially, three Pd catalysts were investigated (entries 1–3), and $Pd(OAc)_2$ displayed the most efficiency (entry 2). In the presence of $Pd(OAc)_2$ and CsF, the desired annulation product **3** was isolated in a 31% yield. Subsequently, a series of ligands, including PPh_3, P(*o*-tol)$_3$, PCy_3, Xantphos and dppp, were examined (entries 4–8). We found that both PPh_3 and P(*o*-tol)$_3$ could improve the reaction in terms of yields (entries 4 and 5), but the other ligands disfavored the reaction (entries 6–8). Although only 5% yield of **3** was obtained using toluene as the medium (entry 9), MeCN combined with toluene sharply enhanced the yield to 65% (entry 10). The amount of

Table 1 Screening conditions[a]



1a + **2a** → **3**

Entry	[Pd]/ligand	Solvent	*T*/°C	Isolated yield (%)
1	$PdCl_2$	MeCN	45	13
2	$Pd(OAc)_2$	MeCN	45	31
3	$Pd(dba)_2$	MeCN	45	28
4	$Pd(OAc)_2/PPh_3$	MeCN	45	55
5	$Pd(OAc)_2$/P(*o*-tol)$_3$	MeCN	45	52
6	$Pd(OAc)_2/PCy_3$	MeCN	45	Trace
7[b]	$Pd(OAc)_2$/Xantphos	MeCN	45	Trace
8	$Pd(OAc)_2$/dppp	MeCN	45	28
9	$Pd(OAc)_2/PPh_3$	PhMe	45	5
10	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	45	65
11[c]	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	45	30
12[d]	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	45	61
13[e]	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	45	35
14[f]	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	45	36
15	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	rt	16
16	$Pd(OAc)_2/PPh_3$	MeCN–PhMe	80	10

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv.), [Pd] (10 mol%), ligand (20 mol%), and CsF (4 equiv.) in CH_3CN–PhMe (1/1, 2 mL) for 30 h. [b] Xantphos = (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis-(diphenylphosphine). [c] $Pd(OAc)_2$ (5 mol%). [d] $Pd(OAc)_2$ (20 mol%). [e] CsF (2 equiv.). [f] KF (4 equiv.) and 18-crown-6 (4 equiv.) in THF (2 mL).

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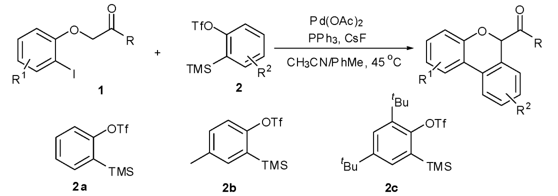
$Pd(OAc)_2$ was also tested: the yield was decreased to some extent at 5 mol% Pd (entry 11), and 20 mol% Pd gave the same results as those with 10 mol% Pd (entries 10 and 12). Among the fluoride sources examined, it turned out that 4 equiv. CsF gave the best yield (entry 10). However, either 2 equiv. CsF or 4 equiv. KF lowered the yield (entries 13 and 14). Finally, the reaction temperatures were evaluated, and the reactions were less effective at room temperature or 80 °C (entries 15 and 16).

With the optimal reaction conditions in hand, the scopes of both 2-(2-iodophenoxy)-1-arylethanones (**1**) and *ortho*-silyl aryltriflates (**2**) were investigated (Table 2). Two other *ortho*-silyl aryltriflates **2b** and **2c** were initially examined by reacting them with 2-(2-iodophenoxy)-1-phenylethanone (**1a**), $Pd(OAc)_2$, PPh_3 and CsF: the reactions were carried out smoothly in moderate yields with two regioselective isomers (entries 1 and 2).[11]

Table 2 Palladium-catalyzed annulation of 2-(2-iodophenoxy)-1-arylethanones (**1**) with arynes (**2**)[a]



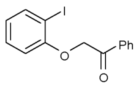
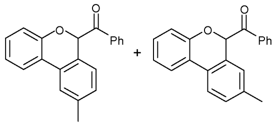
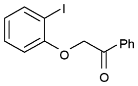
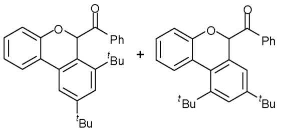
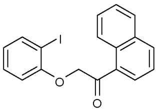
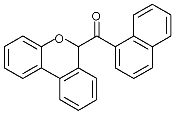
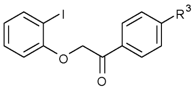
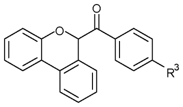
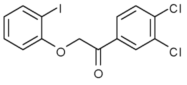
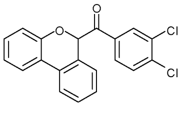
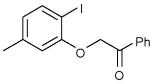
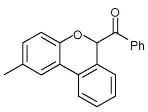
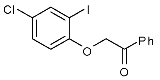
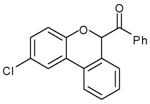
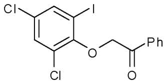
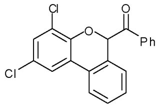
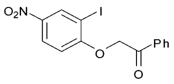
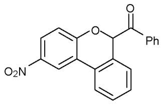
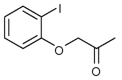
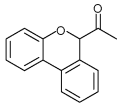
Entry	Substrate **1**	Aryne **2**	Product/isolated yield (%)
1[b]	 **1a**	**2b**	 55 (1.2:1, **4**)
2[b]	 **1a**	**2c**	 54 (1.1:1, **5**)
3	 **1b**	**2a**	 71 (**6**)
		**2a**	
4	R^3 = Me, **1c**	**2a**	R^3 = Me, 86 (**7**)
5	R^3 = MeO, **1d**	**2a**	R^3 = MeO, 41 (**8**)
6	R^3 = F, **1e**	**2a**	R^3 = F, 72 (**9**)
7	R^3 = Cl, **1f**	**2a**	R^3 = Cl, 54 (**10**)
8	 **1g**	**2a**	 84 (**11**)
9	 **1h**	**2a**	 52 (**12**)

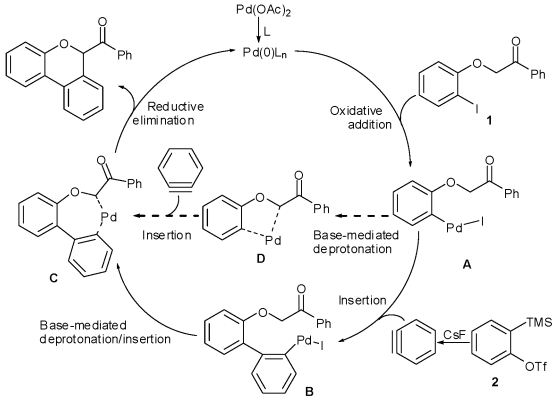
Table 2 (***continued***)

Entry	Substrate **1**	Aryne **2**	Product/isolated yield (%)
10	 **1i**	**2a**	 67 (**13**)
11	 **1j**	**2a**	 83 (**14**)
12	 **1k**	**2a**	 40 (**15**)
13	 **1l**	**2a**	 30 (**16**)

[a] Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and CsF (4 equiv.) in CH_3CN–PhMe (1/1, 2 mL) at 45 °C for 30 h. [b] The ratios of the products are determined by ^1H NMR spectra.

Subsequently, a variety of 2-(2-iodophenoxy)-1-arylethanones **1b–1l** were employed to react with aryne **2a** under the optimal conditions (entries 3–13). To our delight, naphthalen-1-ylethanone **1b** could react with aryne **2a**, $Pd(OAc)_2$, PPh_3 and CsF to afford the desired product **6** in good yield (entry 3). We were pleased to find that several functional groups, such as methyl, methoxy, fluoro, chloro and nitro groups, on the aromatic ring were tolerated well under the optimal conditions (entries 4–12). For example, substrate **1c**, bearing a methyl group on the phenylethanone moiety, was reacted with aryne **2a** efficiently in good yields (entry 4). We found that the optimal conditions were consistent with both fluoro- and chloro-substituted substrates **1e–1g** (entries 6–8). Gratifyingly, substituents, either electron-donating or electron-withdrawing groups, on the 2-iodophenoxy moiety were also uniformly tolerated (entries 9–12). Substrates **1h** and **1i** with a methyl or a chloro group performed the annulation with aryne **2a**, $Pd(OAc)_2$, PPh_3 and CsF smoothly, furnishing the corresponding products in moderate yields (entries 9 and 10). Good yield was also achieved from substrate **1j** with two chloro groups (entry 11). Substrate **1k**, having a strongly electron-withdrawing NO_2 group, lowered the yield to 40% (entry 12). We found that alkyl ketone **1l**, 1-(2-iodophenoxy)propan-2-one, displayed less activity leading to the desired product **16** in 30% yield (entry 13). Unfortunately, ethyl 2-(2-iodophenoxy)acetate (**1m**) could not undergo the reaction under the optimal conditions.

A possible mechanism is proposed as outlined in Scheme 2.[5–10,12] Oxidative addition of $Pd(0)L_n$ with 2-(2-iodophenoxy)-1-substituted ethanone **1** affords intermediate **A**.[6–8] Two pathways may take place from intermediate **A**: one pathway involves sequential insertion of intermediate **A** with an aryne and an active sp^3 carbon (the active sp^3 carbon is activated *in situ* by base-mediated deprotonation of intermediate **B**)[10]



Scheme 2 A possible mechanism.

to give intermediate **C**,[6–8] and the other pathway is base-mediated deprotonation of an sp^3 carbon[10] in intermediate **A** leading to intermediate **D**,[12] followed by insertion of an aryne to afford intermediate **C**. Reductive elimination of intermediate **C** takes place to yield the desired product and regenerate the active Pd(0) species. The present results support the former pathway in terms of the selectivity of entry 2 in Table 2.

In summary, we have developed a mild method for the synthesis of 6*H*-benzo[*c*]chromenes by palladium-catalyzed annulations of 2-(2-iodophenoxy)-1-arylethanones and 1-(2-iodophenoxy)propan-2-one with arynes. This new route allows formation of two carbon–carbon bonds in one-pot through an sp^3 carbon functionalization process. Importantly, we provide a convenient approach to the important class of 6*H*-benzo[*c*]chromenes. Work to extend the reaction and study the detailed mechanism is currently underway.

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