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Access to 6*H*-naphtho[2,3-*c*]chromenes by a palladium-catalyzed reaction of 2-haloaryl allene with 2-alkynylphenol†‡

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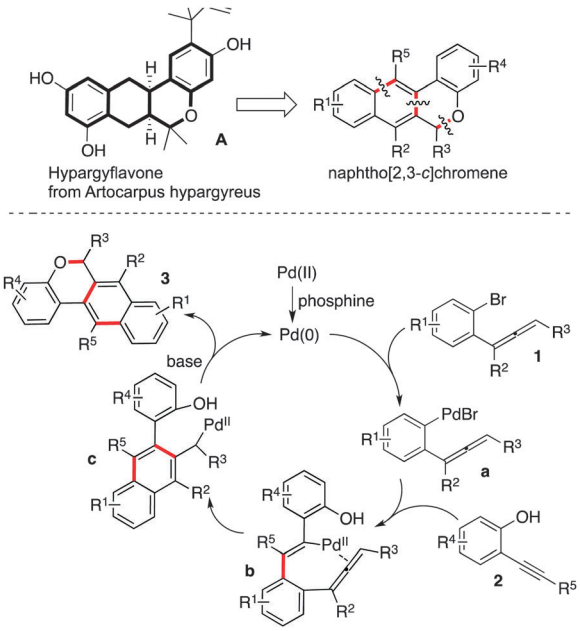
A palladium-catalyzed reaction of 2-haloaryl allene with 2-alkynylphenol is described, leading to 6*H*-naphtho[2,3-*c*]chromenes in good to excellent yields. This transformation proceeds efficiently with excellent chemoselectivity and regioselectivity.

Heterocyclic compounds[1] are always in great demand in organic synthesis, especially in medicinal chemistry, chemical biology, and the drug discovery process. Among the approaches developed for the generation of heterocycles with complexity and diversity,[2] the domino reaction[3] is an attractive pathway to efficiently synthesize natural product-like compounds with privileged skeletons. In the past decade, this strategy has been applied broadly for the formation of complex small molecules.

Recently, we have been interested in 6*H*-naphtho[2,3-*c*]chromenes and their related derivatives, which show broad and remarkable biological activities. An example is displayed in Scheme 1, which is a kind of natural product containing the core of naphtho[2,3-*c*]-chromene. Additionally, this skeleton has been widely employed as a critical structural intermediate to synthesize some natural products and pharmaceuticals in total synthesis.[4] Among the methods available for the generation of complex polycycles, double carbometallation of alkynes is a powerful and efficient strategy.[5] For instance, 5*H*-cyclopenta[*c*]quinolines were produced *via* a palladium-catalyzed reaction of 2-alkynylhalobenzene with an amine.[5e] This reaction process involved double insertion into the triple bond with the formation of four new bonds.



Scheme 1 A proposed synthetic route for the generation of naphtho-[2,3-*c*]chromenes.

However, only [6-5-6-6] or [6-5-7-6] tetracyclic skeletons could be generated through this approach. Encouraged by these results, we envisioned that the core of naphtho[2,3-*c*]chromene could also be constructed *via* a similar double carbometallation. The proposed synthetic route is illustrated in Scheme 1. We conceived that the allene substrate **1** could be taken into consideration as a building block instead of an alkyne for the formation of [6-6-6-6] tetracyclic polycycles.

Retrosynthetically, the core structure of naphtho[2,3-*c*]chromene can be traced back to 2-bromoaryl allene **1** with 2-alkynylphenol **2**. In the presence of palladium(0) generated *in situ* with a phosphine ligand,[6] an oxidative addition occurred to afford Pd(II) species **a**. After the insertion of Pd(II) species **a** into the triple bond of 2-alkynylphenol **2**, a vinyl palladium(II) **b** was afforded. The regioselectively intramolecular coordination and insertion

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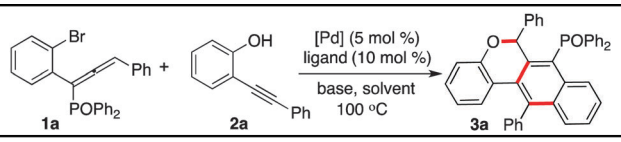
of Pd(II) into the double bond of the allene generated intermediate **c**. In the presence of a base, a C–O bond was formed with the release of Pd(0), which re-entered the catalytic cycle. Although this route seemed feasible, we had to face several competitive reaction pathways. For example, benzofuran compounds were easily produced *via* the direct cyclization of 2-alkynylphenols. Moreover, after the oxidative addition of Pd(0) with aryl bromide **1**, the *in situ* generated Pd(II) species **a** activated the triple bond of 2-alkynylphenol **2** to furnish 3-aryl substituted benzofurans.[7]

Among various allenes, those substituted by phosphine oxide which are relatively stable and easily prepared have drawn our attention. Meanwhile, a growing interest has been paid to arylphosphonates in medicinal chemistry[8] and nucleic acid chemistry[9] due to their remarkable biological activities. Additionally, it has been found that phosphonates also have extensive applications in organic synthesis.[10] Therefore, considering the easy preparation of the starting materials and the incorporation of a phosphonate fragment into the scaffold of naphtho[2,3-*c*]chromene, (1-(2-bromophenyl)-3-phenylpropa-1,2-dien-1-yl)diphenylphosphine oxide[11] was selected as a model substrate for the exploration of this transformation.

Our initial exploration focused on the reaction between phosphonated 2-bromoaryl allene **1a**[12] and 2-(phenylethynyl)-phenol **2a** in the presence of $Pd(OAc)_2$ (5 mol%) and PCy_3 (10 mol%) under reflux. Several bases were initially screened.

Table 1 Initial studies for the palladium-catalyzed reaction of 2-bromoaryl allene **1a** with 2-(phenylethynyl)phenol **2a**

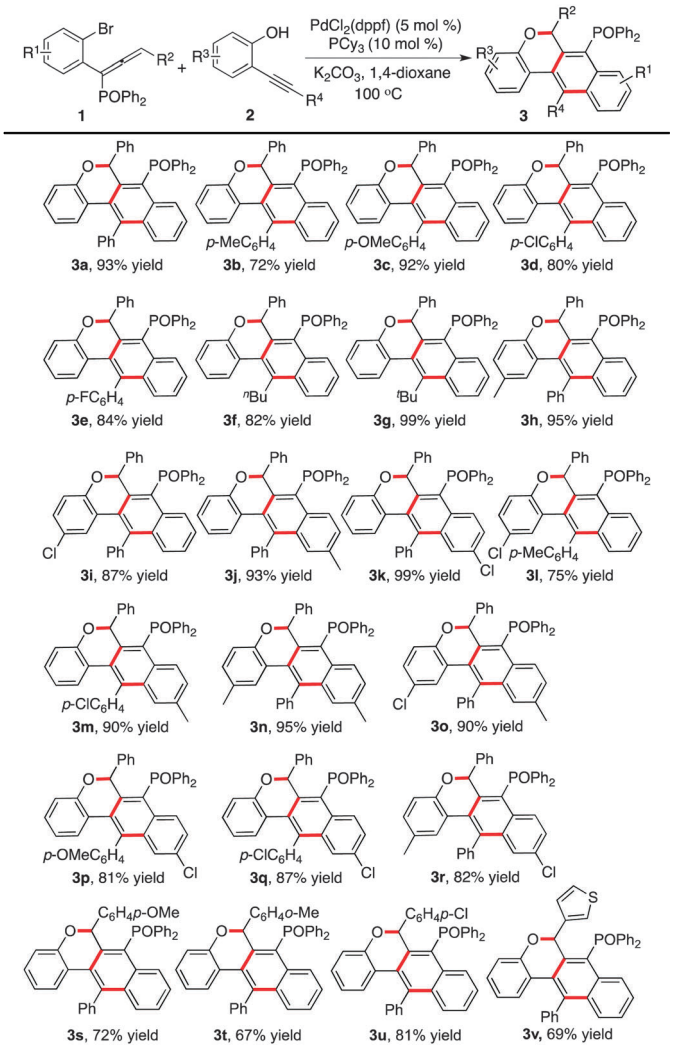


Entry	[Pd]	Ligand	Solvent	Solvent	Yield[a] (%)
1	$Pd(OAc)_2$	PCy_3	*t*-BuOK	Dioxane	nd
2	$Pd(OAc)_2$	PCy_3	KOH	Dioxane	Trace
3	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	Dioxane	16
4	$Pd(OAc)_2$	PCy_3	NaOMe	Dioxane	14
5	$Pd(OAc)_2$	PCy_3	Na_2CO_3	Dioxane	21
6	$Pd(OAc)_2$	PCy_3	K_3PO_4	Dioxane	36
7	$Pd(OAc)_2$	PCy_3	K_2CO_3	Dioxane	54
8	$Pd(OAc)_2$	DPPP	K_2CO_3	Dioxane	Trace
9	$Pd(OAc)_2$	P^tBu_3	K_2CO_3	Dioxane	Trace
10	$Pd(OAc)_2$	SPhos	K_2CO_3	Dioxane	25
11	$Pd(OAc)_2$	DPE-Phos	K_2CO_3	Dioxane	23
12	$Pd(OAc)_2$	DPPF	K_2CO_3	Dioxane	37
13	$Pd(OAc)_2$	PPh_3	K_2CO_3	Dioxane	32
14	$PdCl_2(PhCN)_2$	PCy_3	K_2CO_3	Dioxane	33
15	$PdCl_2$	PCy_3	K_2CO_3	Dioxane	47
16	$PdCl_2(PPh_3)_2$	PCy_3	K_2CO_3	Dioxane	42
17	$Pd_2(dba)_3$	PCy_3	K_2CO_3	Dioxane	65
18	$PdCl_2$(dppf)	PCy_3	K_2CO_3	Dioxane	93
19	$PdCl_2$(dppf)	PCy_3	K_2CO_3	DMSO	61
20	$PdCl_2$(dppf)	PCy_3	K_2CO_3	DMF	44
21	$PdCl_2$(dppf)	PCy_3	K_2CO_3	Toluene	61
22	$PdCl_2$(dppf)	PCy_3	K_2CO_3	Diglyme	68
23	$PdCl_2$(dppf)	PCy_3	K_2CO_3	$PhCF_3$	58
24	$PdCl_2$(dppf)	PCy_3	K_2CO_3	1-Pentanol	64
25[b]	$PdCl_2$(dppf)	PCy_3	K_2CO_3	Dioxane	62
26[c]	$PdCl_2$(dppf)	PCy_3	K_2CO_3	Dioxane	34

[a] Isolated yield based on 2-(phenylethynyl)phenol **2a**, nd = not detected. [b] The reaction was performed at 90 °C. [c] The reaction occurred at 70 °C.

The reaction did not occur when *t*-BuOK was employed as the base (Table 1, entry 1). A trace amount of product was detected using KOH as a replacement (Table 1, entry 2). The outcome improved slightly when the base was changed to Cs_2CO_3, NaOMe or Na_2CO_3 (Table 1, entries 3–5, respectively). Compared to K_3PO_4, potassium carbonate seemed to be a better choice for this transformation, giving rise to the desired product **3a** in 54% yield (Table 1, entries 6 and 7, respectively). Encouraged by this result, we then examined different ligands, but no higher yields were obtained (Table 1, entries 8–13). Further investigation showed that the conversion was sensitive to palladium sources. The reaction was more complex when $PdCl_2(PhCN)_2$, $PdCl_2$, or $PdCl_2(PPh_3)_2$ were utilized as the catalyst (Table 1, entries 14–16, respectively), while the use of Pd_2dba_3 enhanced the reaction yield to 65% (Table 1, entry 17). Finally, we identified that Pd(dppf)Cl_2 was the most efficient palladium source, affording compound **3a** in 93% yield (Table 1, entry 18). The reaction could also take place in other solvents, such as DMSO, DMF, toluene,

Table 2 Synthesis of phosphonated naphtho[2,3-*c*]chromenes by a palladium-catalyzed reaction of 2-bromoaryl allene **1** with 2-alkynylphenol **2**[a]



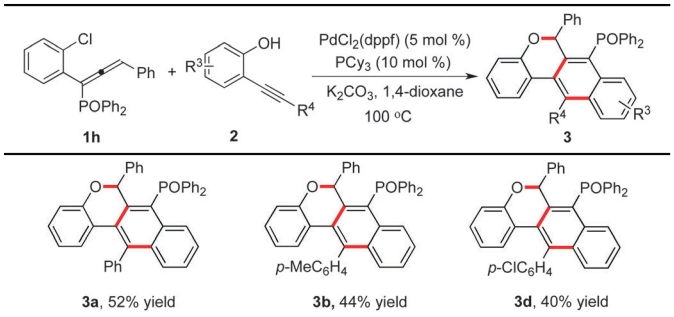
[a] Isolated yield based on 2-alkynylphenol **2**.

diglyme, trifluoromethylbenzene and 1-pentanol. However, only moderate yields were achieved (Table 1, entries 19–24, respectively). The yield was reduced when the reaction temperature was decreased (Table 1, entries 25 and 26). The structure of compound **3a** was determined by X-ray crystallography analysis (see ESI,‡ CCDC 977123).

Subsequently, exploration of the scope of this conversion was carried out under the optimized conditions: $Pd(dppf)Cl_2$ (5 mol%), PCy_3 (10 mol%), K_2CO_3 (2.0 equiv.), 1,4-dioxane, under reflux, 12–16 hours. The results are presented in Table 2. All of the reactions between the (1-(2-bromophenyl)-3-phenylpropa-1,2-dien-1-yl)diphenylphosphine oxides **1** and 2-alkynylphenols **2** proceeded well with high efficiency and excellent selectivity to generate phosphonated naphtho[2,3-*c*]chromenes. In addition, 2-alkynylphenols with alkyl groups (R^4) also had high reactivity, especially with the *tert*-butyl group, illustrating that steric hindrance was not a barrier in the transformation. No difference was observed for the reactions of 2-alkynylphenols with electron-donating groups or electron-withdrawing groups attached to the aromatic ring. Various 2-bromoaryl allenes **1** were also examined, and the corresponding phosphonated naphtho[2,3-*c*]chromenes were afforded in good to excellent yields. Meanwhile, to expand the scope of this transformation, allenes with different R^2 substituents were explored. These reactions successfully provided the corresponding products when R^2 was the electron-donating group, electron-withdrawing group, heterocycle or sterically hindered group. Furthermore, 2-chloroaryl allenes were also employed to afford the desired products, although they showed lower activity in this reaction (Table 3).

In conclusion, we have developed an efficient route for the facile assembly of diverse phosphonated naphtho[2,3-*c*]chromenes by a palladium-catalyzed reaction of 2-haloaryl allene **1** with 2-alkynylphenol **2**. In this process, complexity could be easily introduced with the formation of three new bonds. Under the reaction conditions, the phosphonated naphtho[2,3-*c*]chromenes were generated in good to excellent yields. Moreover, the transformation showed excellent chemoselectivity and regioselectivity, since competitive reaction pathways for the formation of benzofurans seem to have been inhibited completely. Further work on the applications of double carbometallation for the construction of other polycycles is ongoing in our laboratory.

Table 3 Synthesis of phosphonated naphtho[2,3-*c*]chromenes by a palladium-catalyzed reaction of 2-chloroaryl allene **1h** with 2-alkynylphenol **2**[a]



[a] Isolated yield based on 2-alkynylphenol **2**.

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