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Palladium-catalyzed domino N-arylation/carbopalladation/C–H functionalization: three-component synthesis of 3-(diarylmethylene)oxindoles

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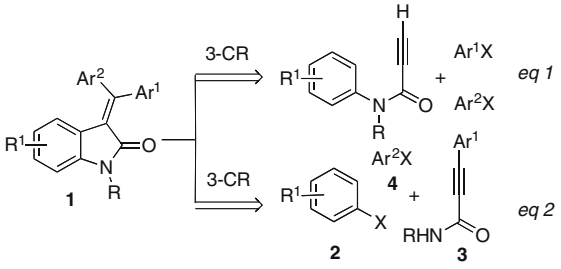
ABSTRACT

A palladium-catalyzed three-component synthesis of 3-(diarylmethylene)indolin-2-ones has been developed. A sequence of intermolecular N-arylation/intermolecular carbopalladation/C–H activation/C–C bond formation was realized in a one-pot fashion allowing the construction of one C–N bond and two C–C bonds by way of three distinct catalytic cycles.

Synthesis of oxindoles bearing a tetrasubstituted exocyclic double bond at the C-3 position has recently captured attention of synthetic chemists due to the utility of such bicyclic structure in the development of new drug leads.[1] In this regard, the metal-catalyzed domino cyclizations of 2-iodoarylpropynamides,[2] 2-alkynylaryl isocyanates,[3] and 2-alkynyl anilines[4] are notable examples.[5] We have developed a palladium-catalyzed domino carbopalladation/C–H functionalization process for the synthesis of 3-(diarylmethylene)oxindoles (**1**) from arylpropynamide and aryliodide.[6] Li, Wang, and co-workers have elegantly exploited the potential of this approach and have synthesized a variety of heteroatom-substituted oxindoles by performing the domino transformation under oxidative conditions.[7] We have subsequently devised a three-component variant using arylpropiolamide and two different aryliodides as starting materials (Scheme 1, Eq. 1).[8] As a continuation of our interest in the synthesis of oxindoles[9] and in the development of palladium-catalyzed domino sequence,[10] we report herein a novel three-component synthesis of **1** starting from readily available arylbromide (**2**), *N*-alkylpropynamide (**3**), and aryliodide (**4**) by a sequence of N-arylation/carbopalladation/C–H functionalization (Scheme 1, Eq. 2).[11]

The N-arylation of *N*-alkylpropiolamide **3** is unprecedented in the literature.[12] Indeed, two competitive reactions, N-arylation and carbopalladation, can take place when haloarene **2** and *N*-alkylpropiolamide **3** are reacted in the presence of a given palladium catalyst. Our first concern was thus to find conditions to favor the N-arylation of **3**. Under reaction conditions developed by Buchwald [$Pd(dba)_2$ (1 mol %), Xantphos (3 mol %), Cs_2CO_3 in refluxing dioxane)[13], N-arylation of **3** with 4-bromoanisidine or bromobenzene indeed furnished the expected anilide albeit in low yield (<30%). Changing the ligands (Xphos and Binap) or the bases (NaOAc and NaOtBu) failed to improve the reaction outcome. However, the reaction between **3a** (R = Me, Ar^1 = Ph) and more reactive 4-bromo nitrobenzene (**2a**) went well to afford *N*-methyl-*N*-(4-nitrophenyl)-3-phenylpropiolamide **5a** in 96% (structure not shown).

With these results in hand, the three-component reaction was examined by sequential addition of two different aryliodides. However, stirring a solution of **2a** and **3a** in dioxane in the presence of



Scheme 1. Palladium-catalyzed three-component synthesis of oxindoles.

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[$Pd_2(dba)_3$] (1 mol %), Xantphos (3 mol %), and Cs_2CO_3 at 100 °C for 15 h followed by addition of phenyl iodide in DMF[14] and heating at 110 °C for 24 h failed to afford the expected oxindole **1a**. A control experiment revealed that the domino carbopalladation/CH functionalization was completely inhibited in the presence of Xantphos. We therefore decided to undertake a survey of reaction conditions for the whole sequence, instead of optimizing the individual steps[15] by varying the palladium source, the ligand, and the base. The results are summarized in Table 1.

Except for XPhos, other monodentate phosphines examined were ineffective as supporting ligands for the present N-arylation reaction (entries 2–5). Xphos and Binap were good for the N-arylation, but were deleterious for the subsequent steps (entries 6 and 7). Dppf was found to be effective for the whole sequence affording oxindole **1a** in moderate yield (entry 8). Using $Pd(OAc)_2$ (at higher loading) instead of $Pd_2(dba)_3$ as a pre-catalyst improved the yield of **1a** to 41% (entry 11). Among the bases investigated, Cs_2CO_3 was found to be far superior to K_3PO_4 and KO^{t}Bu as the latter bases failed to promote the N-arylation reaction under otherwise identical conditions (entries 11–13).

Knowing that Xantphos was a very efficient ligand for N-arylation, but inhibited the carbopalladation step, we next turned our attention to find conditions that can deliver the palladium catalyst active for both steps in its presence. One possibility would be to add a ligand that could modify the properties of the active catalyst after the first step.[16] This strategy would nevertheless be difficult to realize in our case since Xantphos is a bidentate ligand. Sequestering the ligand could also be an option as ligand-free catalysis is beneficial for the second step of our sequence. Copper has recently been used as a scavenger to recover (remove) phosphine ligands.[17] However, addition of CuCl to the reaction mixture after the N-arylation step failed to produce any cyclized product. Finally, we found that using an excess amount of palladium relative to ligand was an effective solution. Thus performing the reaction in the presence of 2 mol % of $Pd_2(dba)_3$ (4 mol % palladium) and 3 mol % of Xantphos, furnished compound **1a** in 26% yield (Table 1, entry 14 vs entry 1). Further improvement was observed using $Pd(OAc)_2$ (0.05 equiv) as a pre-catalyst in the presence of Xantphos (0.03 equiv) to afford **1a** in 48% yield (entry 15). It should be noted that further lowering the ligand to palladium ratio was detrimental to the reaction (entry 16).

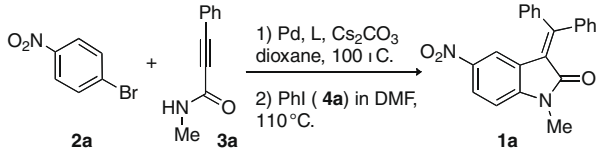
We next investigated the scope of this three-component reaction under the optimized reaction conditions [$Pd(OAc)_2$ (0.05 equiv), Xantphos (0.03 equiv), Cs_2CO_3 (3.0 equiv), **2** and **3** in dioxane at 100 °C, then a DMF solution of **4**, and heating at 110 °C]. Results are presented in Table 2. As N-arylating agent, various aryl bromides containing an electron-withdrawing group at the *para*-position were found to be active. Indeed, cyano, ketone, ester, and even aldehyde proved to be compatible with the reaction conditions (entries 1–5). On the other hand, *ortho* or *meta* bromo nitrobenzene was found to be unsuitable substrate (data not shown). With regard to the *N*-alkyl phenylpropiolamides (**3**), both *N*-methyl and *N*-benzyl (entry 6) derivatives participated in the reaction. The presence of a methoxy group in the phenyl ring of **3** was also tolerated (entries 7 and 8).[18]

A possible reaction sequence that accounts for the formation of oxindole is depicted in Scheme 2. Oxidative addition of haloarene (**2**) to Pd(0) generated the Pd(II) species (**A**) which upon transmetallation with the amide (**3**) would afford intermediate (**B**). Reductive elimination of (**B**) would afford the amide (**C**) with concurrent regeneration of Pd(0). Oxidative addition of second aryliodide to Pd(0) led to (**D**) that would in turn react with (**C**) to furnish the carbopalladation product (**E**). The C–H activation followed by reductive elimination from the palladacycle (**F**) would then afford the oxindole (**1**) and regenerate the Pd(0) species.

In contrast to our previous synthesis,[6,8] all oxindoles were produced as a mixture of *E* and *Z* isomers. This was surprising as carbopalladation of alkyne with ArPdX is known to be *syn* selective. Control experiment indicated that compound (*E*)-**1h** that was prepared independently[6] did not undergo isomerization upon standing (Scheme 3).[20] In addition, phosphine-induced isomerization by 1,4 addition-elimination sequence[19] was excluded since heating a DMF solution of (*E*)-**1h** in the presence of Xantphos for several hours did not induce isomerization. Consequently, we reasoned that both isomers were produced during the reaction. We hypothesized that an isomerization occurred after the carbopalladation step, which is believed to deliver *cis* adduct **E** (Scheme 2). When C–H activation process is fast, the stereochemical integrity of this adduct is transferred to the product as it was observed previously. However, when this step is slow as in the present case due to the presence of Xantphos, isomerization could become competitive. A plausible cis–trans isomerization mechanism is illustrated in Scheme 4. Both anionic (**7**) and cationic (**8**) palladium species have been postulated in the literature to explain the cis–trans isomerization.[21] In our case, we assumed that isomerization via cationic palladium intermediate (**8**) was more feasible as it involves a negative charge that can be stabilized by the neighboring nitro group (Scheme 4).

In summary, we have developed a three-component synthesis of unsymmetrically substituted 3-(diarylmethylene)indolinones. The overall reaction involves a sequence of N-arylation reaction/carbopalladation/ C–H activation/C–C bond formation and it is catalyzed by a single Pd catalytic system. Finding a suitable palladium to ligand ratio has been determinant to the success of the present transformation.

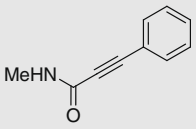
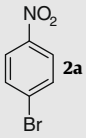
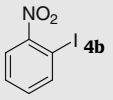
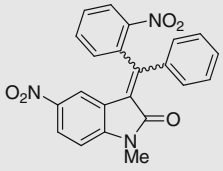
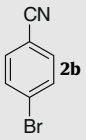
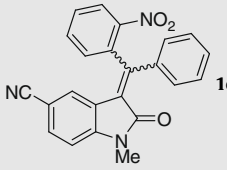
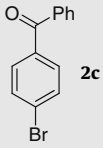
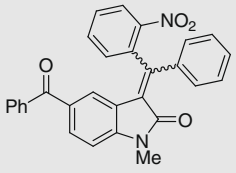
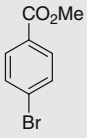
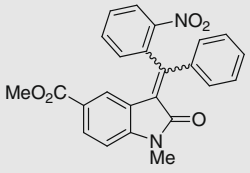
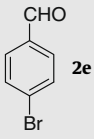
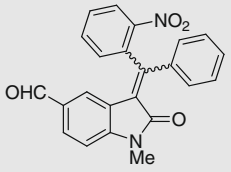
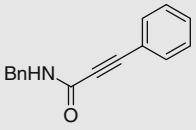
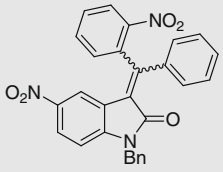
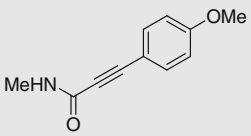
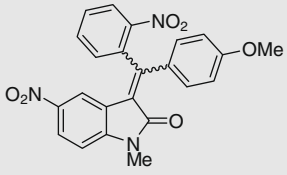
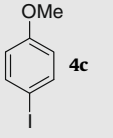
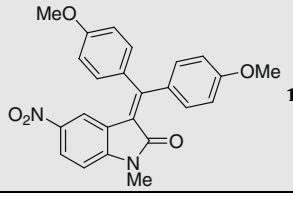
Table 1
Palladium-catalyzed three-component synthesis of oxindoles: a survey of reaction conditions[a]



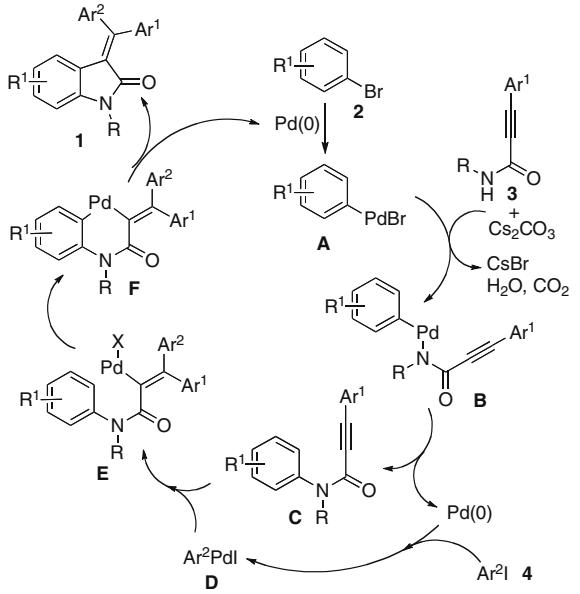
Entry	[Pd] (mol %)	Ligand (mol %)	t_1,t_2 (h)	Yield[b]
1	$Pd_2(dba)_3$ (1)	Xantphos (3)	15, 24	0%
2	$Pd_2(dba)_3$ (1)	P(Cy)$_3$ (3)	17	—[c]
3	$Pd_2(dba)_3$ (1)	HP(*t*-Bu)$_3$BF$_4$ (3)	18	—[c]
4	$Pd_2(dba)_3$ (1)	JohnPhos (3)	24	—[c]
5	$Pd_2(dba)_3$	DavePhos (3)	16	—[c]
6	$Pd_2(dba)_3$ (1)	X-Phos	17,48	0%
7	$Pd_2(dba)_3$ (1)	BINAP (3)	17, 24	0%
8	$Pd_2(dba)_3$ (1)	dppf (3)	16, 24	24%
9	$Pd_2(dba)_3$ (1)	dppe (3)	18	—[c]
10	$PdCl_2$ (5)	dppf (10)	24	—[c]
11	$Pd(OAc)_2$ (5)	dppf (10)	15, 10	41%
12[d]	$Pd(OAc)_2$ (5)	dppf (10)	24	—[c]
13[e]	$Pd(OAc)_2$ (5)	dppf (10)	24	—[c]
14	$Pd_2(dba)_3$ (2)	Xantphos (3)	15, 24	26%
15	$Pd(OAc)_2$ (5)	Xantphos (3)	6, 15	48%
16	$Pd(OAc)_2$ (5)	Xantphos (1.5)	10, 17	0%

[a] All reactions were carried out under argon using **2a** (1.0 equiv), **3a** (1.0 equiv), Pd catalyst, Cs_2CO_3 (3.0 equiv), and ligand in dioxane (c = 0.2 M) at 100 °C for the indicated time (t1); then a DMF solution of iodobenzene (1.5 equiv, c = 0.3 M) was added and the reaction mixture was heated at 110 °C (t2).
[b] Yield refers to chromatographically pure product.
[c] N-arylation was not observed.
[d] K_3PO_4 (3.0 equiv) was used as the base.
[e] KO*t*Bu (3.0 equiv) was used as the base.

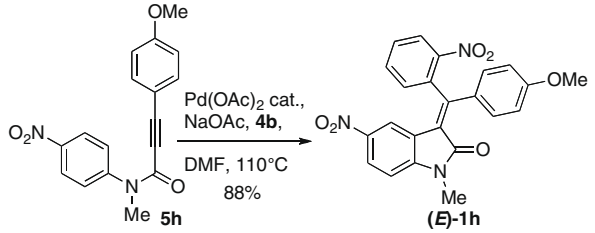
Table 2
Scope of the palladium-catalyzed three-component synthesis of 3-(diarylmethylene)oxindoles[a]

Entry	Amide	Ar[1]	Ar[2]	Product	Yield %[b]
1	 **3a**	 **2a**	 **4b**	 **1b**, *E*/*Z* = 1:3	64
2	**3a**	 **2b**	**4b**	 **1c**, *E*/*Z* = 1:3	63
3	**3a**	 **2c**	**4b**	 **1d**, *E*/*Z* = 1:1	56
4	**3a**	 **2d**	**4b**	 **1e**, *E*/*Z* = 1:2	67
5	**3a**	 **2e**	**4b**	 **1f**, *E*/*Z* = 1:4	35
6	 **3b**	**2a**	**4b**	 **1g**, *E*/*Z* = 1:4	53
7	 **3c**	**2a**	**4b**	 **1h**, *E*/*Z* = 1:3	33
8	**3c**	**2a**	 **4c**	 **1i**	32

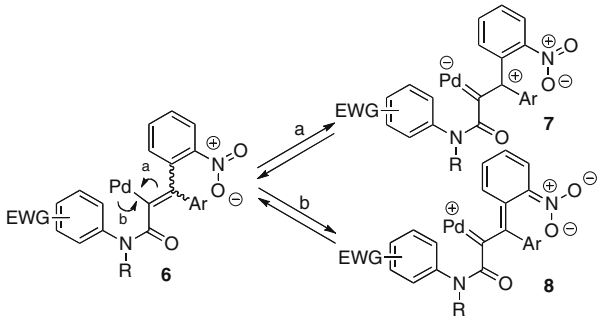
[a] General conditions: **3** (1.0 equiv), **2** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), Xantphos (3 mol %), and Cs_2CO_3 (3.0 equiv) in dioxane (*c* = 0.2 M) at 100 °C, then a solution of **4** in DMF (1.5 equiv, *c* = 0.3 M) was added and the reaction mixture was heated at 110 °C.
[b] Yield refers to chromatographically pure product.



Scheme 2. Three-component synthesis of oxindole, mechanistic rationale. Ligand associated with Pd was omitted for the sake of clarity.



Scheme 3. Synthesis of geometrically pure (*E*)-**1h**.



Scheme 4. Isomerization of carbopalladation adduct.

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