Angewandte Chemie

DOI: 10.1002/anie.200605192

Domino Reactions

Palladium-Catalyzed Three-Component Synthesis of 3-(Diarylmethylene)oxindoles through a Domino Sonagashira/Carbopalladation/C−H Activation/C−C Bond-Forming Sequence**

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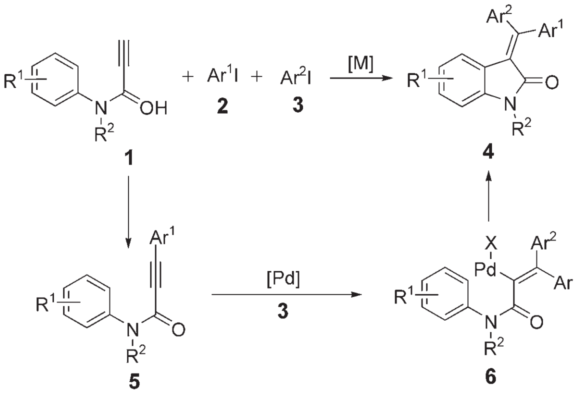
Devising novel multicomponent reactions (MCRs) that achieve the formation of multiple bonds in one operation is one of the major challenges in modern organic synthesis.[1] As such processes avoid time-consuming and costly purification processes, as well as protection–deprotection steps, they are inherently environmentally benign and atom economic.[2] Whereas some powerful MCRs such as the Passerini[3] and Ugi[4] reactions proceed in the absence of external reagents, most chemical transformations involve reactants that are not active enough to be self-assembled. Thus, the use of catalytic rather than stoichiometric amounts of external reagents to trigger the reaction is highly desirable to minimize the production of waste.[5] As a continuation of our ongoing project on the development of palladium-catalyzed domino processes[6] as well as direct C−H functionalization,[7] we report herein a palladium-catalyzed three-component synthesis of 3-(diarylmethylene)indolinones.[8–13] The underlying principle of our approach is shown in Scheme 1. The Sonogashira coupling[14] of *N*-aryl-*N*-alkyl propiolamides **1** with an aryl iodide **2** should give the phenyl propiolamide **5**, which would then react with a second aryl halide **3**, ideally in the presence of the same catalyst, to afford the target compound **4** through a sequence of intermolecular carbopalladation, C−H activation, and a C−C bond-forming process.[15,16] Whereas many palladium-catalyzed transformations have been developed and widely used in novel domino processes for the syntheses of heterocycles,[17,18] the MCR that combines mechanistically distinct reactions by a single catalyst is by far less developed owing to the specificity of each catalytic system to each individual reaction.[19] To our knowledge, the use of a single palladium catalyst to catalyze three different reactions, namely aryl alkynylation, carbopalladation, and direct C−H functionalization, has not been reported previously.[20]



Scheme 1. Proposed three-component reaction to synthesize 3-(diarylmethylene)oxindoles.

Very few examples have been reported that deal with the successful Sonogashira reaction of electron-deficient alkynes, such as propiolic esters[21] and propiolamide,[22] with aryl halides. Despite this potential pitfall, we performed a survey of reaction conditions using *N*-(4-methoxyphenyl)-*N*-methyl propiolamide (**1a**), phenyl iodide (**2a**), and 2-nitrophenyliodide (**3a**) as test substrates. In the event, stirring a solution of **1a** and **2a** in *N*,*N*-dimethylformamide (DMF) in the presence of [Pd(PPh$_3$)$_4$] (5 mol %), copper iodide (15 mol %), and Et$_3$N at 60 °C for 1 h followed by addition of **3a** and heating to 110 °C for 15 h afforded the expected oxindole **4a** in 28 % yield. Control experiments indicated that a) Sonogashira coupling between **1a** and **2a**, the presumed first step of this domino process, proceeded smoothly to furnish the phenylpropiolamide **5a** in over 90 % yield, b) copper iodide is required for the successful Sonogashira coupling between **1a** and **2a**,[23] and c) the Sonogashira coupling between **1a** and **2a** proceeded sluggishly under ligand-free conditions, although such conditions were of choice for the carbopalladation/C−H functionalization step. With these results in hand, we set out to focus on the overall reaction efficiency of this novel three-component reaction instead of optimizing the individual steps[24] by varying the palladium source, the ligand, the amount of copper, the base, and the solvent. The results are summarized in Table 1.

The base played an important role in the overall efficiency of this three-component reaction. Simply by switching from triethylamine to sodium acetate under otherwise identical conditions furnished the desired oxindole **4a** in 73 % yield.

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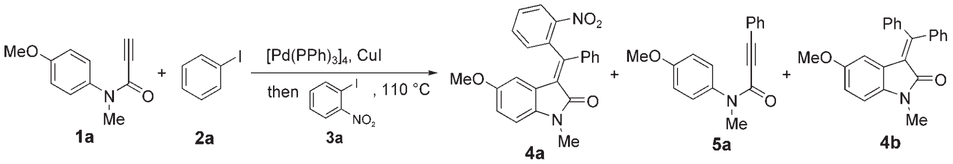
[**] Financial support from the CNRS and the Institut de Chimie des Substances Naturelles, CNRS, is gratefully acknowledged. A.P. thanks the “Ministère de l’Enseignement Supérieur et de la Recherche” for a doctoral fellowship.

Supporting information for this article, including experimental procedures, product characterization, as well as copies of ^{1}H NMR spectra of oxindoles **4a**–**4s**, is available on the WWW under http://www.angewandte.org or from the author.

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

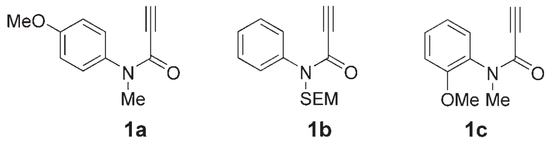


Entry	[Pd] (mol %)	CuI [mol %]	Base (equiv)	Solvent	t_1, t_2 [h]	Yield [%]		
						4a	**5a**	**4b**
1	$[Pd(PPh_3)_4]$ (5)	15	Et_3N (2)	DMF	1, 15	28	–	–
2	$[Pd(PPh_3)_4]$ (5)	15	NaOAc (2)	DMF	4, 45	73	11	3
3	$Pd(OAc)_2/PPh_3$ (5:10)	15	NaOAc (2)	DMF	4, 17	58	–	6
4	$[Pd(PPh_3)_2Cl_2]$ (5)	15	NaOAc (2)	DMF	4, 3	48	–	3
5	$[Pd(dba)]/PPh_3$ (5:10)	15	NaOAc (2)	DMF	1, 13	58	–	10
6	$[Pd(PPh_3)_4]$ (5)	15	NaOAc (2)	DMA	1, 42	53	5	8
7	$[Pd(PPh_3)_4]$ (5)	15	NaOAc (2)	DMSO	1, 42	52	46	–
8	$[Pd(PPh_3)_4]$ (5)	15	NaOAc (2)	Dioxane	17, 48	–	n.d.[b]	–
9[c]	$[Pd(PPh_3)_4]$ (10)	5	NaOAc (2)	DMF	1, 39	–	6	79
10[c]	$[Pd(PPh_3)_4]$ (5)	5	KOAc (2)	DMF	1, 24	79	13	–
11[c]	$[Pd(PPh_3)_4]$ (10)	5	K_2CO_3 (2)	DMF	1, 28	66	7	11
12[c]	$[Pd(PPh_3)_4]$ (10)	5	$NaHCO_3$ (2)	DMF	1, 39	63	6	3
13[c]	$[Pd(PPh_3)_4]$ (10)	5	K_3PO_4 (2)	DMF	1, 26	63	5	5
14[c]	$[Pd(PPh_3)_4]$ (10)	5	NaOAc (3)	DMF	1, 44	82	–	3
15[c]	$[Pd(PPh_3)_4]$ (5)	2.5	NaOAc (3)	DMF	1, 24	77	6	3

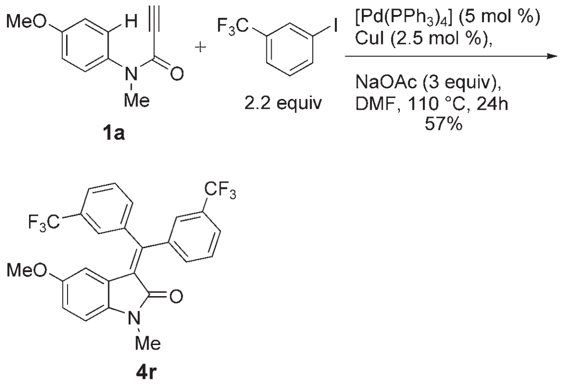
[a] All reactions were carried out under argon using **1a** (1.0 equiv), **2a** (1.0 equiv), Pd catalyst, base, and solvent (c = 0.1 M) at 60 °C for the indicated time (t_1); then, **3a** (1.1 equiv) was added and the reaction mixture was heated at 110 °C (t_2). [b] Only compound **5a** formed, but its yield was not determined (n.d.). [c] 1.1 equiv **1a** was used. dba = dibenzylideneacetone.

Other inorganic bases were examined, and NaOAc and KOAc were found to be superior to $NaHCO_3$ and K_3PO_4 (Table 1, entries 9–13), with three equivalents of NaOAc being optimal (entry 14). Among the palladium catalysts investigated (Table 1, entries 2–5), palladium tetrakis(triphenylphosphine) was found to be the most effective (entry 2). DMF proved to be a better solvent than *N*,*N*-dimethylacetamide (DMA) or dimethyl sulfoxide (DMSO), while dioxane was inefficient in promoting the second step (Table 1, entries 6–8). The presence of copper iodide is essential to the Sonogashira coupling, but it retarded the carbopalladation/C–H functionalization process. The best Pd/Cu ratio was found to be 2:1 (Table 1, entry 2 vs. 9). Overall, under optimum conditions (5 mol % $[Pd(PPh_3)_4]$, 2.5 mol % CuI, 3 equiv NaOAc, DMF, c = 0.1 M; Table 1, entry 15), the reaction of **1a**, **2a**, and **3a** provided the desired oxindole **4a** in 77 % yield. Under these conditions, the phenylpropiolamide **5a** and the symmetrically substituted oxindole **4b** were also isolated in yields of 6 % and 3 %, respectively.

To probe the scope and limitation of this new three-component reaction, a range of substituted aryl iodides and propiolamides were next examined (Scheme 2, Table 2). The outcome of this three-component reaction was found to be only weakly influenced by the electronic properties of the aryl halides, and a variety of oxindoles substituted by an electron-donating or an electron-withdrawing group were readily synthesized in good to excellent yields (Table 2, entries 1–5). Whereas *ortho*-, *meta*-, and *para*-substituted aryl iodides can be used as the second aryl iodide (Table 2, entries 1, 6, and 8), only *para*- and *meta*-substituted aryl halides were well tolerated when used as the first aryl iodide added. The chlorine atom is compatible with this reaction sequence by providing a handle for further functionalization (Table 2, entries 4 and 8). The *N*-(2-trimethylsilylethoxymethoxy)anilide **3b** participated in this three-component reaction albeit the yield was slightly decreased (Table 2, entry 8). As an *N*-SEM group is readily removed, it constituted a route to N-unsubstituted oxindoles. Note that both

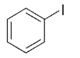
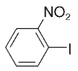
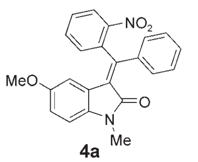
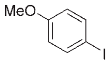
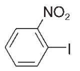
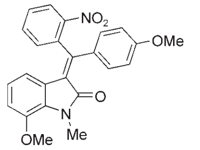
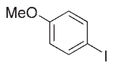
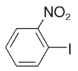
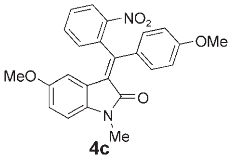
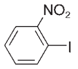
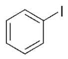
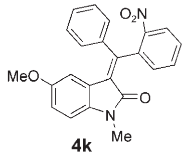
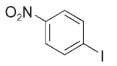
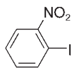
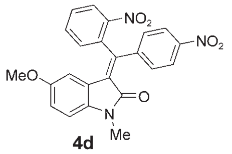
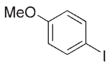
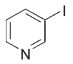
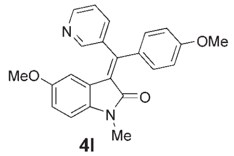
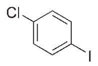
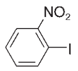
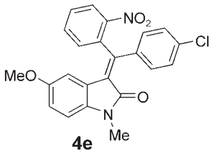
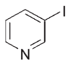
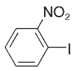
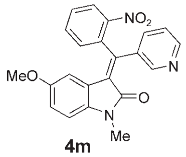
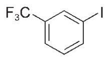
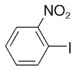
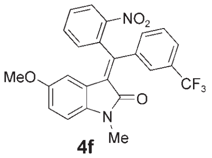
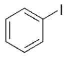
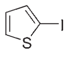
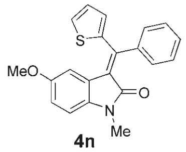
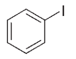
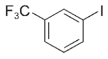
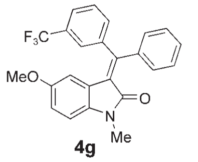
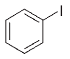
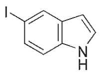
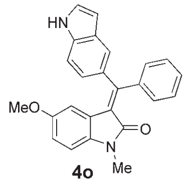
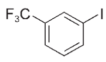
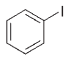
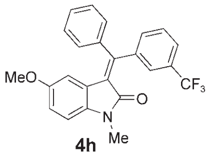
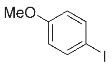
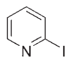
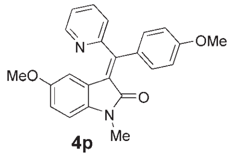
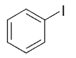
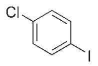
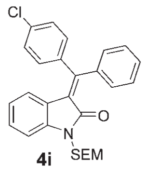
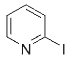
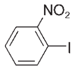
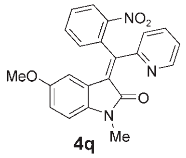


Scheme 2. Anilides **1** used in Table 2.



Scheme 3. Synthesis of symmetrically substituted 3-(diarylmethylene)oxindoles.

Table 2: Scope of the palladium-catalyzed three-component synthesis of 3-(diarylmethylene)oxindoles.[a] Structures of anilides **1** are given in Scheme 3.

Entry	**1**	Ar^1I	Ar^2I	Product	Yield [%][b]	Entry	**1**	Ar^1I	Ar^2I	Product	Yield [%][b]
1	**1a**			 **4a**	77	9	**1c**			 **4j**	67
2	**1a**			 **4c**	82	10	**1a**			 **4k**	<10
3	**1a**			 **4d**	71	11	**1a**			 **4l**	69
4	**1a**			 **4e**	76	12	**1a**			 **4m**	81
5	**1a**			 **4f**	78	13	**1a**			 **4n**	61
6	**1a**			 **4g**	66	14	**1a**			 **4o**	45
7	**1a**			 **4h**	43	15	**1a**			 **4p**	0
8	**1b**			 **4i**	59	16	**1a**			 **4q**	51

[a] General conditions: **1a** (1.1 equiv), Ar^1I (1.0 equiv), CuI (2.5 mol%), $[Pd(PPh_3)_4]$ (5 mol%), NaOAc (3 equiv), DMF ($c = 0.1$ M), 60 °C; then Ar^2I (1.1 equiv), 110 °C. [b] Yield of product isolated after flash column chromatography.

the *E*- and the *Z*-oxindole can be prepared from the same starting materials by simply changing the order of addition of the two aryl halides (Table 2, entries 6 and 7).

To further exploit the generality of this catalytic MCR and because of the biological relevancy of heterocycles, we investigated the possibility of incorporating heteroaryl groups into the target compounds. As is seen from Table 2 (entries 11–16), 3-iodopyridine, 5-iodoindole, and 2-iodothiophene were appropriate starting materials for this MCR. Whereas 3-iodopyridine was a suitable reactant for both the Sonogashira coupling and the carbopalladation step, leading to compound **4l** and **4m**, respectively, 2-iodopyridine could only be used as a reaction partner in the Sonogashira coupling (Ar^1I). When it was used for the carbapalladation/direct C–H functionalization sequence (Ar^1I), the expected oxindole **4p** was not formed. Most probably, the nitrogen atom of 2-pyridine is able to sequester the Pd^{II} species by forming a five-membered chelate after the carbopalladation step, thereby blocking the subsequent C–H activation process. Nevertheless, 2-thiophene was a suitable partner to furnish the oxindole **4n** in 61% yield (Table 2, entry 13). Finally, a symmetrically substituted oxindole, **4r**, was synthesized in 57% yield by simply conducting the reaction with two equivalents of 3-(trifluoromethyl)phenyl iodide (Scheme 3).

In summary, we have developed a flexible and stereocontrolled three-component synthesis of unsymmetrically substituted 3-(diarylmethylene)indolinones. The overall reaction involves a sequence of Sonogashira reaction/carbopalladation/C–H activation, and C–C bond formation and is catalyzed by a single Pd/Cu catalytic system. The ready accessibility of the starting materials and the generality of this process make it highly valuable in view of the synthetic and medicinal importance of these heterocycles.

Experimental Section

Typical procedure: Copper iodide (2.5 mol%), NaOAc (3 equiv), and $[Pd(Ph_3)_4]$ (5 mol%) were added to a degassed solution of anilide (1.1 equiv) and aryl iodide (1.0 equiv) in DMF ($c = 0.1$ M). The mixture was heated at 60°C for 1 h, and then the second aryl iodide (1.1 equiv) was introduced. After being stirred at 110°C for 28 h, the reaction mixture was quenched with saturated aqueous NaCl solution and extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4), and then concentrated. The residue was purified by flash chromatography to give the corresponding oxindole.

(3*E*)-5-methoxy-1-methyl-3-[(2-nitrophenyl)(phenyl)methylene]-1,3-dihydro-2*H*-indol-2-one (**4a**): 72 mg (77% yield); red solid; m.p. 197–200°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.19$ (dd, $J = 8.2$, 1.1 Hz, 1H), 7.77 (dt, $J = 7.5$, 1.1 Hz, 1H), 7.65 (dt, $J = 8.2$, 1.5 Hz, 1H), 7.55 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.44–7.39 (m, 2H), 7.36–7.31 (m, 3H), 6.73 (dd, $J = 8.5$, 2.4 Hz, 1H), 6.65 (d, $J = 8.5$ Hz, 1H), 5.60 (d, $J = 2.4$ Hz, 1H), 3.48 (s, 3H), 3.17 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.0$, 155.0, 149.4, 147.5, 137.6, 136.4, 136.2, 134.3, 131.3, 130.2, 129.9, 129.5, 127.6, 125.6, 125.0, 123.4, 114.1, 110.0, 108.17, 55.5, 25.9 ppm; HRMS: calcd for $C_{23}H_{18}N_2O_4Na$ $[M+Na]^+$: 409.1164; found: 409.1182.

Received: December 22, 2006

Keywords: C–H activation · domino reactions · multicomponent reactions · nitrogen heterocycles · palladium

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