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Palladium-Catalyzed Carbo-Heterofunctionalization of Alkenes for the Synthesis of Oxindoles and Spirooxindoles

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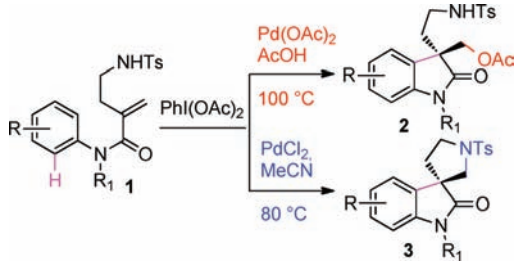
ABSTRACT



A palladium-catalyzed oxidative carbo-heterofunctionalization of aniline derivatives involving concomitant direct C−H functionalization and C−X bond formation was developed. By simply changing the reaction conditions (solvent and catalyst), either 3,3′-disubstituted oxindole or spirooxindole was accessible from the same starting material.

3,3′-Disubstituted oxindoles are ubiquitous heterocycles found in a wide range of natural products, pharmaceuticals, and agrochemicals.[1] Among many reported synthetic strategies, the transition-metal-catalyzed cyclization−functionalization of *ortho*-functionalized aniline derivatives is one of the most investigated routes.[2] More recently, metal-catalyzed C−H activation/cyclization has also been developed to get access to this family of heterocycles.[3] However, in this latter case, the oxindole was constructed by forming either one single C−C bond[4,5] or one C−N bond.[6] We report herein a palladium-catalyzed oxidative carbo-heterofunctionalization of anilide derivatives (**1**) with concomitant formation of one C−C and one C−X bond.[7] With a properly

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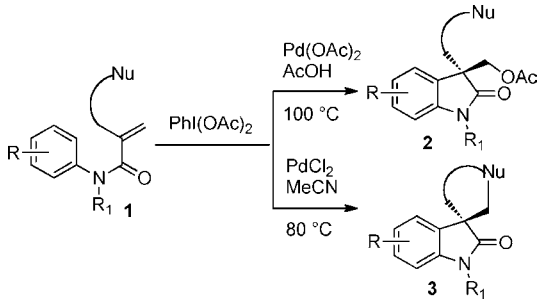
tethered nucleophile at the α-position of acrylamides, we document that either carboacetoxylation or carboamination can take place leading to 3,3′-disubstituted oxindoles (**2**) or spirooxindoles (**3**), respectively, under appropriate conditions (Scheme 1).

Scheme 1. Palladium-Catalyzed Oxidative C−C and C−N Bond-Forming Processes



Palladium-catalyzed alkene diamination,[8] aminoacetoxylation,[9] dioxygenation,[10] aminohalogenation,[11] fluoroamination,[12] oxidative amination,[13] and hetero-Heck reaction[14] have recently been developed into powerful methods for the bis-functionalization of alkenes.[15] Whereas carbonylation[16] and Heck reaction[17,18] have been combined with Wacker-type processes, carbo-heterofunctionalization of alkenes involving direct C−H functionalization of arenes remains rare.[19] The elegant carbo-heterofunctionalization of alkenes, developed by Wolfe, allowed building simultaneously one C−X and one C−C bond.[20] On the basis of this sequence, we recently developed a domino spirocyclization for the formation of spiropyrrolidinyl-oxindoles.[21] However, in these examples, aryl halides have to be used as starting materials to initiate the domino process.

To explore the feasibility of our planned domino process, we first targeted the synthesis of acetoxylated oxindole **2a** from *N*-methyl-*N*-phenylmethacrylamide (**1a**). The reaction conditions were initially screened using a combination of $PhI(OAc)_2$ (2 equiv) and $Pd(OAc)_2$ (10 mol %) in different solvents.[22] As seen, nonpolar or weakly polar solvent such as dichloromethane (CH_2Cl_2), dioxane, or CH_3CN furnished at best a trace amount of the desired product **2a** (Table 1, entries 1−3). However, we were pleased to isolate the expected oxindole (**2a**) in 54% yield when the reaction was performed in pure acetic acid (entry 4). Mixtures of solvents (AcOH/dioxane, AcOH/CH_3CN, or AcOH/Ac_2O[23]) provided inferior results (data not shown). It should be mentioned that a temperature of 100 °C was necessary, as incomplete conversion was observed at 80 °C. Addition of a base (Bu_4NOAc) did not influence significantly the outcome of the reaction (entry 5). Moreover, the reaction was only marginally affected by the nature of the catalyst as various Pd(II) salts [$PdCl_2$, $Pd(TFA)_2$, or $Pd(BINAP)Cl_2$, entries 6−8]

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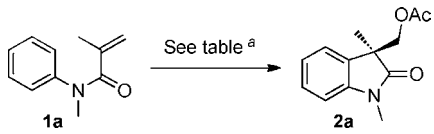
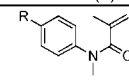
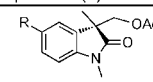
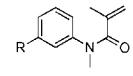
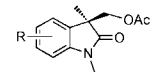
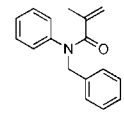
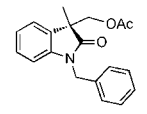
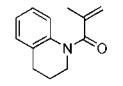
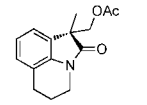
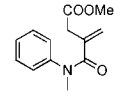
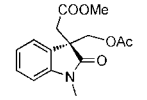
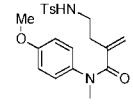
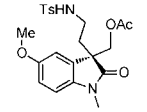
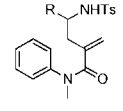
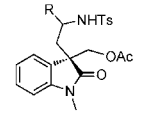
Table 1. Survey of Reaction Conditions



entry	Pd source	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	$PhI(OAc)_2$	CH_2Cl_2	trace[c]
2	$Pd(OAc)_2$	$PhI(OAc)_2$	CH_3CN	trace[c]
3	$Pd(OAc)_2$	$PhI(OAc)_2$	dioxane	trace
4	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH	54
5[d]	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH	52
6	$PdCl_2$	$PhI(OAc)_2$	AcOH	44
7	$Pd(TFA)_2$	$PhI(OAc)_2$	AcOH	42
8	$Pd(BINAP)Cl_2$	$PhI(OAc)_2$	AcOH	32
9	$Pd_2(dba)_3$	$PhI(OAc)_2$	AcOH	52
10	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH + Bipy[e]	N.R.
11	$Pd(OAc)_2$	*m*-CPBA	AcOH	trace
12	$Pd(OAc)_2$	BQ	AcOH	N.R.
13	$Pd(OAc)_2$	$Cu(OAc)_2 + O_2$	AcOH	N.R.
14	$Pd(OAc)_2$	AgOAc	AcOH	40
15	$Pd(OAc)_2$	IBX	AcOH	24
16	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	38
17	$Pd(OAc)_2$	H_2O_2	AcOH	18
18	$Pd(OAc)_2$	oxone	AcOH	51
19	$Pd(OAc)_2$	-	AcOH	N.R.
20		$PhI(OAc)_2$	AcOH	N.R.

[a] Reactions were carried out under an argon atmosphere using **1a** (1 equiv), oxidant (2 equiv), catalyst (0.1 equiv), 100 °C, 20 h. [b] Isolated yield. [c] Reaction performed in a sealed tube. [d] Bu_4NOAc (2 equiv) was added to the reaction. [e] 0.2 equiv.

Table 2. Synthesis of 3,3′-Disubstituted Oxindoles by Palladium-Catalyzed Carboacetoxylation[a]

entry	substrate (**1**)	product (**2**)	yield (%)[b]
1			**2b**, R = OMe, 52
2			**2c**, R = Me, 66
3			**2d**, R = Cl, 53
4			**2e**, R = CN, 0
5			**2f**, R = 6-Me, and **2f'**, R = 4-Me, 55 (6/1)
6			**2g**, 54
7			**2h**, 38
8			**2i**, 58
9			**2j**, 53[c]
10			**2k**, R = H, 43;
11			(66[c])
12			**2l**, R = Ph, 83
			2m, R = *i*-Pr, 85

[a] General conditions: $Pd(OAc)_2$ (0.1 equiv), $PhI(OAc)_2$ (2 equiv), HOAc, 100 °C. [b] Isolated yield. [c] Reaction performed in dioxane at 80 °C.

or Pd(0) [$Pd_2(dba)_3$, entry 9] could be used in this transformation. However, a catalytic amount of bipyridine, which has been used as ligand in oxidative palladium processes,[24] completely inhibited the reaction (entry 10). We also investigated various oxidants that have been successfully employed in palladium-catalyzed oxidative transformations.[25] Whereas *m*-CPBA, benzoquinone, or $Cu(OAc)_2$ was inefficient, AgOAc, IBX, $K_2S_2O_8$, H_2O_2, or oxone allowed the formation of the desired product (entries 14−18). Nonetheless, $PhI(OAc)_2$ stood out as the oxidant of choice. Finally, control experiments ensured that both the palladium catalyst and the oxidant were required for the present process (entries 19 and 20).

With the optimum conditions [$Pd(OAc)_2$ (0.1 equiv), $PhI(OAc)_2$ (2.0 equiv), in AcOH at 100 °C] in hand, the scope of this domino process was examined (Table 2). Anilides bearing electron-donating groups at the *para*-position (OMe, Me) react smoothly to generate the expected oxindoles **2b** and **2c**. A weakly electron-withdrawing group (Cl) was also tolerated in the reaction (entry 3), but a strong electron-withdrawing group like nitrile was incompatible with the domino sequence (entry 4). When *meta*-substituted *N*-*m*-tolylmethacrylamide was employed, a 6:1 mixture of regioisomers **2f** and **2f′** was isolated in favor of the 6-substituted oxindole (55%). N-Benzylated oxindole **2g** and the tricyclic oxindole **2h** derived from tetrahydroquinoline were obtained in 54% and 38% yields (entries 6 and 7), respectively. The use of tertiary amides was nevertheless mandatory. Variation at the α-position of the acrylamide was also evaluated. The methyl ester group proved to be stable under the reaction conditions as illustrated with the synthesis of compound **2i** (58% yield, entry 8). Tosyl-protected alkylamine side chains were also compatible with the present transformation. Interestingly, when a substituent was introduced α to the tosylamine function, the domino process afforded oxindoles **2l** and **2m** in excellent yields as a single diastereoisomer (83% and 85%, respectively, entries 11 and 12).[26]

When compound **1k** was submitted to the domino cyclization in acetic acid at 100 °C, the oxindole **2k** was isolated in 43% yield along with spirooxindole **3a** in 26% yield. This interesting observation prompted us to re-evaluate the conditions to drive the reaction toward the spirocycle. After a survey of reaction conditions varying the palladium sources, the temperature, the oxidants, and the solvents, the best conditions found consisted of performing the reaction in MeCN (*c* 0.1 M) in the presence of $PdCl_2$ (0.1 equiv) and

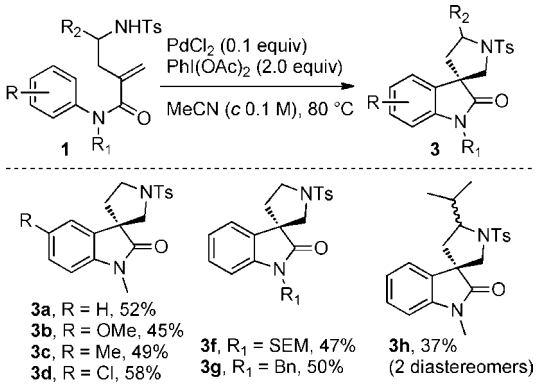
(24) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836–5837.

(25) The solvent could act as an acetate source, see: Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141–1144.

(26) Conversion of oxindoles **2j**−**2m** to: Jaegli, S.; Vors, J.-P.; Neuville, L.; Zhu, J. *Synlett* **2009**, 2997–2999.

$PhI(OAc)_2$ (2 equiv) at 80 °C. Under these conditions, compound **1k** was converted to spirooxindoles **3a** in 52% yield. This domino carboamination process proved to be applicable to various substrates. Spirooxindoles synthesized by this novel spirocyclization are depicted in Scheme 2. In

Scheme 2. Scope of Spirocyclization



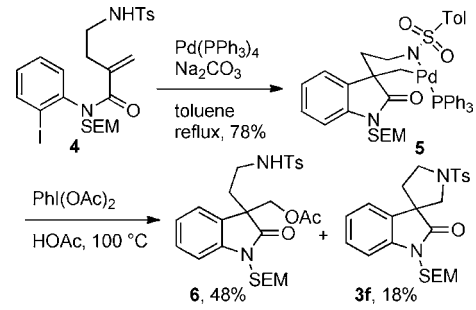
each case, the oxindole **2** was also isolated, explaining the moderate yields of spirocycles **3a**−**3h**.

We have previously synthesized a cyclopalladate (**5**) by reaction of **4** with a stoichiometric amount of $Pd(PPh_3)_4$ (Scheme 3).[21,27] When the complex **5** was submitted to the conditions described for the conversion of **1** to **2** [$PhI(OAc)_2$, HOAc, 100 °C], the acetoxylated compound **6** was obtained in 48% yield together with the spirooxindole **3f** (18% yield).[28] This control experiment indicated that complex of type **5** could well be a possible intermediate in the conversion of **1** to oxindoles **2** and/or **3**. The formation of type **5** complex can be accounted for by a sequence of amide-directed CH

(27) See also: (a) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439–1442. (b) Clique, B.; Fabritius, C.-H.; Couturier, C.; Monteiro, N.; Balme, G. *Chem. Commun.* **2003**, 272–273. (c) Burke, B. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 16820–16833. (d) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 15415–15422.

(28) Heating the complex **5** in toluene under neutral and basic (Na_2CO_3) conditions at 110 °C for a prolonged time (15 h) in the presence or in the absence of additional ligand (*tert*-butyl MePhos) led to full recovery of the complex; this was also the case when the reaction was performed in the presence of benzoquinone or $Cu(OTf)_2$, whereas complete degradation was observed when a toluene solution of **5** was stirring in the presence of $PhI(OAc)_2$ at room temperature.

Scheme 3. Transformation of a Possible Reaction Intermediate **5**



palladation followed by intramolecular Heck reaction. Alternatively, coordination of the double bond to Pd(II) followed by nucleophilic attack of the tethered arene to olefin could also be a viable manifold to account for the formation of **5**.[29] However, further detailed studies are needed to understand the exact reaction mechanism.

In summary, we have developed a novel oxidative palladium-catalyzed carbo-heterofunctionalization of alkenes involving a direct intramolecular aromatic C−H functionalization. The divergent process allowed the conversion of simple *N*-aryl acrylamides into acetoxylated 3,3′-disubstituted oxindoles or spiropyrrolidinyloxindoles depending on the proper choice of solvent (AcOH or CH_3CN) and palladium salt [$Pd(OAc)_2$ or $PdCl_2$].

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Supporting Information Available: Experimental procedures, product characterization, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101778C

(29) For Fujiwara−Moritani reaction and mechanistic divergence, see: (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579. (c) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636–5637.