Oxindole synthesis by palladium-catalysed aromatic C–H alkenylation†

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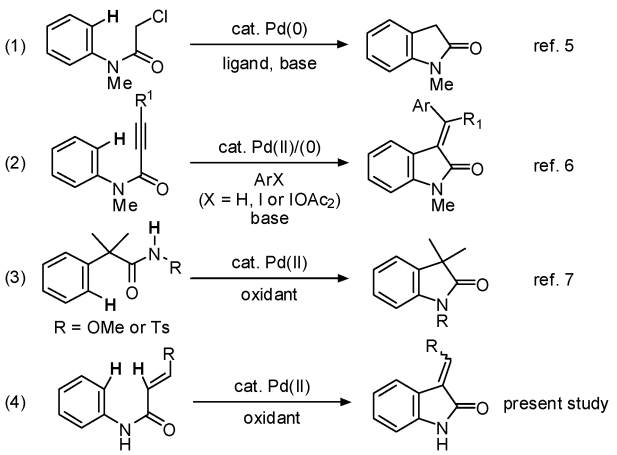
A strategy involving palladium-catalysed aromatic C–H functionalisation/intramolecular alkenylation provides a convenient and direct synthesis of 3-alkylideneoxindoles. In the presence of 5 mol% of $PdCl_2MeCN_2$ and $AgOCOCF_3$, a wide variety of *N*-cinnamoylanilines gave 3-alkylideneoxindoles in moderate to good yield.

The oxindole structure is present in a number of structually diverse natural products and pharmaceutical agents. Among them, 3-(monosubstituted methylene)oxindoles are recognized as a particularly useful class of compounds in medicinal chemistry due to their biological properties that include activities as protein kinase inhibitors,[1a,b] phosphodiesterase inhibitors[1c] and anti-rheumatic agents.[1d] Consequently, considerable efforts have been made to develop efficient methods for the synthesis of oxindoles.[2] However, most synthetic routes to the oxindole core structures require an *ortho* substituted aniline as a starting material. Recently, the development of transition metal-catalysed synthetic methodologies that directly functionalize arene C–H bonds have received considerable attention.[3] In fact, several groups have reported syntheses of oxindoles by palladium-catalysed aromatic C–H functionalisation (Scheme 1).[4] These include C–H functionalisation/C–C bond formation of α-chloroacetanilides[5] (eqn (1)) and *N*-arylpropiolamides[6] (eqn (2)) and C–H functionalisation/C–N bond formation of 2-arylpropanamides (eqn (3)).[7]

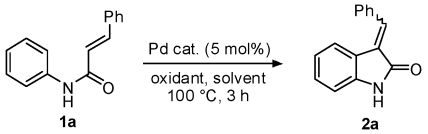


Scheme 1 The strategies for the synthesis of oxindoles by palladium-catalysed C–H functionalisation.

As a part of our ongoing effort to develop transition-metal catalysed oxidative syntheses of nitrogen heterocycles,[8] we have explored the direct synthesis of 3-alkylideneoxindole **2a** from *ortho* unsubstituted *N*-cinnamoylaniline **1a** by palladium-catalysed aromatic C–H activation and intramolecular alkenylation (eqn (4)). Previously, Stoltz and co-workers reported an elegant synthesis of annulated indoles and methoxylated benzofuranes by a palladium-catalysed oxidative intramolecular Heck/Fujiwara-Moritani reaction.[9] However, to date, the oxidative Heck cyclization approach using simple arenes has not been reported except for the stoichiometric palladium(II) mediated indene formation.[10] We report herein a facile synthesis of 3-alkylideneoxindoles by palladium-catalysed aromatic C–H functionalisation/alkenylation (Heck reaction) of unactivated arenes.

We first examined cyclization of **1a** in the presence of a palladium catalyst and oxidant. The screening of reaction conditions revealed that **2a** could be obtained in 81% yield with an *E* : *Z* ratio of 5.6 : 1 using 5 mol% of $PdCl_2MeCN_2$ as a catalyst and $AgOCOCF_3$ as an oxidant in chlorobenzene (Table 1, entry 1). The use of $Pd(OAc)_2$ as a catalyst slightly lowered the yield (entry 2). The choice of the oxidant was found to be critical for the reaction. Thus, other oxidants such as AgOAc, AgCl, Ag_2O, $Cu(OAc)_2$ and benzoquinone were not effective (entries 3–6 and 8). It is noteworthy that the use of $Cu(OCOCF_3)_2$ gave the product in moderate yield (entry 7).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield (%)	*E* : *Z*
1	$PdCl_2MeCN_2$	$AgOCOCF_3$	PhCl	81	5.6 : 1
2	$Pd(OAc)_2$	$AgOCOCF_3$	PhCl	74	5.4 : 1
3	$PdCl_2MeCN_2$	AgOAc	PhCl	0	—
4	$PdCl_2MeCN_2$	AgCl	PhCl	0	—
5	$PdCl_2MeCN_2$	Ag_2O	PhCl	0	—
6	$PdCl_2MeCN_2$	$Cu(OAc)_2$	PhCl	0	—
7	$PdCl_2MeCN_2$	$Cu(OCOCF_3)_2$	PhCl	40	N.D.[b]
8	$PdCl_2MeCN_2$	Benzoquinone	PhCl	0	—
9	$PdCl_2MeCN_2$	$AgOCOCF_3$	DME	46	N.D.[b]
10	$PdCl_2MeCN_2$	$AgOCOCF_3$	DMSO	0	—
11	$PdCl_2MeCN_2$	$AgOCOCF_3$	DMF	0	—

[a] Reaction conditions: **1a** (0.3 mmol), Pd catalyst (5 mol%) and oxidant (0.6 mmol) in solvent (0.6 ml). [b] Not determined.

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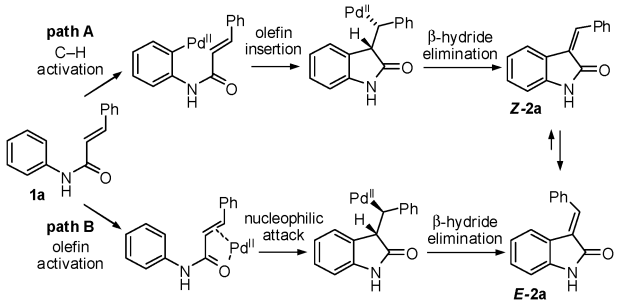
† Electronic supplementary information (ESI) available: Experimental details, compound characterization and NMR spectra. See DOI: 10.1039/b926560k



Scheme 2 Possible reaction mechanisms.

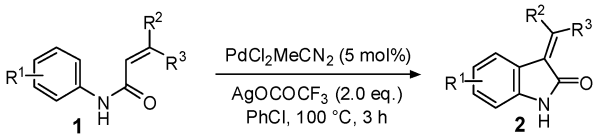
These results suggest that the counter anion of the metal oxidant plays an important role in this reaction. One explanation for this observation is that $AgOCOCF_3$ and $Cu(OCOCF_3)_2$ could generate highly electrophilic Pd species by ligand exchange, thus promoting palladium-mediated aromatic C–H activation or an olefin activation process (see Scheme 2).[11] The reaction fails completely in polar solvents such as DMSO and DMF.

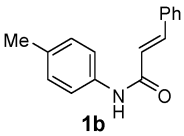
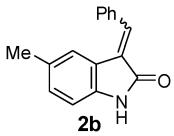
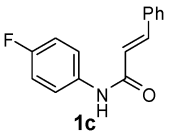
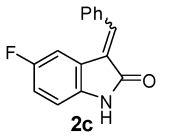
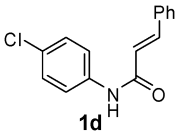
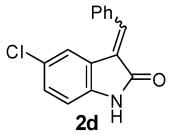
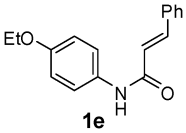
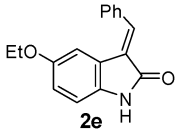
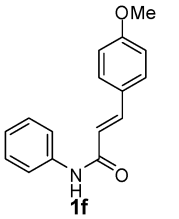
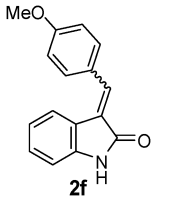
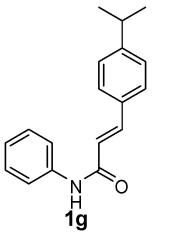
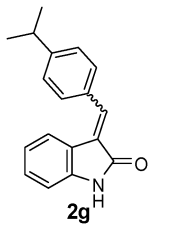
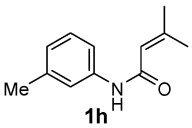
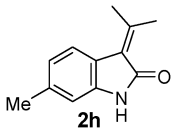
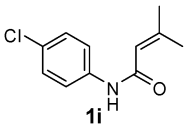
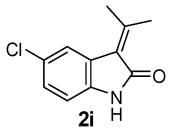
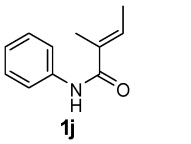
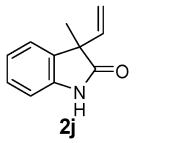
Optimized reaction conditions were then applied to other substrates as shown in Table 2. *N*-Cinnamoylanilines with alkyl, alkoxy and halogen gave oxindoles **2b–2e** in good yield (entries 1–4). In each case, the thermodynamically more stable *E*-isomer was predominantly formed. The presence of a methoxy substitution on the cinnamoyl arene had no effect on the *E*:*Z* selectivity (entry 5). The reaction of *N*-4-isopropylcinnamoylaniline **1g** gave a good yield of **2g**, known to be a potent inhibitor of tyrosine kinase[1a] (entry 6). 3-Methyl substituted anilide **1h** cyclised exclusively at the less sterically hindered 2-position to give 6-methyl substituted oxindole **2h** (entry 7). The substrate possessing the vicinal dimethyl olefin **1j** gave 3,3-disubstituted oxindole **2j** (entry 9).

We next investigated *N*-aryl or *N*-alkyl anilides as substrates (Table 3). Since the *N*-substituted substrates were found to be less reactive than NH free anilides, we slightly modified the reaction conditions (10 mol% Pd catalyst, 110 °C for 12 h). Under the modified reaction conditions, the reaction of *N*-phenylanilide **3a** gave *N*-phenyloxindole **4a** in 80% yield (entry 1). Substrate **3b** was less reactive than **3a** and product **4b** was obtained in 43% yield (entry 2). Similarly, *N*-methyl substituted anilide **3c** reacted sluggishly to give **4c** in 41% yield (entry 3). On the other hand, the conformationally restricted tetrahydroquinoline-derived substrate **3d** gave **4d** in 73% yield (entry 4). Again, the oxindoles with the thermodynamically more stable *E*-olefin were predominantly formed and the *E*:*Z* ratios were similar to those obtained from NH free anilide.

On the basis of known palladium chemistry, two possible reaction pathways can be proposed (depicted for **1a** in Scheme 2). The first pathway involves aromatic C–H palladation followed by *syn*-olefin insertion and β-hydride elimination to give *Z* as the initially formed product (path A). In the second mechanism, the reaction proceeds through olefin activation by the formation of a Pd-π-complex, nucleophilic attack of arene and β-hydride elimination to give *E* (path B). As shown by our experimental results, the reactions of disubstituted *E*-olefin substrates gave a mixture of *E* and *Z*

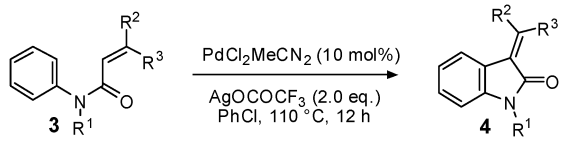
Table 2 Synthesis of 1*H*-oxindoles[a]

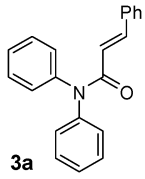
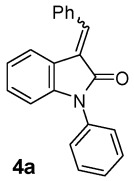
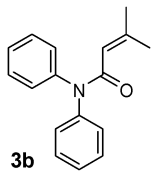
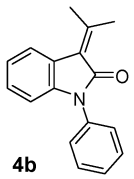
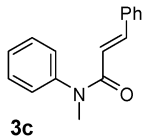
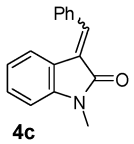
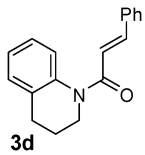
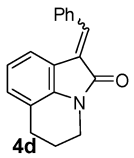


Entry	Substrate	Product	Yield (%)	*E*:*Z*
1	 **1b**	 **2b**	77	6.3:1
2	 **1c**	 **2c**	74	5.5:1
3	 **1d**	 **2d**	68	5.8:1
4	 **1e**	 **2e**	58	—[b]
5	 **1f**	 **2f**	62	5.2:1
6	 **1g**	 **2g**	70	4.9:1
7	 **1h**	 **2h**	55[c]	—
8	 **1i**	 **2i**	38[c]	—
9	 **1j**	 **2j**	28[c]	—

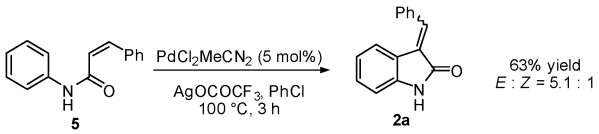
[a] Reaction conditions: **1** (0.3 mmol), Pd catalyst (5 mol%) and oxidant (0.6 mmol) in solvent (0.6 ml). [b] The *Z*-isomer couldn't be isolated in pure form. [c] 10 mol% catalyst was used at 120 °C.

Table 3 Synthesis of *N*-aryl and *N*-alkyloxindoles[a]



Entry	Substrate	Product	Yield (%)	*E*:*Z*
1	 **3a**	 **4a**	80	5.5 : 1
2	 **3b**	 **4b**	43	—
3	 **3c**	 **4c**	41	5.3 : 1
4	 **3d**	 **4d**	73	6.8 : 1

[a] Reaction conditions: **3** (0.3 mmol), Pd catalyst (10 mol%) and oxidant (0.6 mmol) in solvent (0.6 ml).



Scheme 3 Oxidative cyclization of *Z*-olefin **5**.

isomers of 3-arylidenyloxindoles in ratios of 4.9–6.8 : 1. However, the reaction of *Z*-olefin substrate **5** under identical conditions gave the product **2a** in a similar *E*:*Z* ratio (Scheme 3). These results suggest that the reaction products *E*- and *Z*-3-arylidenyloxindoles are in equilibrium under the reaction conditions.[12] This configurational ambiguity complicates interpretation of the reaction mechanism based on product stereochemistry.[13]

In summary, we have developed a direct synthesis of 3-alkylideneoxindoles based on palladium-catalyzed aromatic C–H activation/alkenylation. The reaction can be used for the synthesis of NH free, *N*-aryl and *N*-alkyl oxindoles, thus providing structurally diverse 3-alkylideneoxindoles from readily accessible starting materials.

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