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3-Acylindoles *via* palladium-catalyzed regioselective arylation of electron-rich olefins with indoles†

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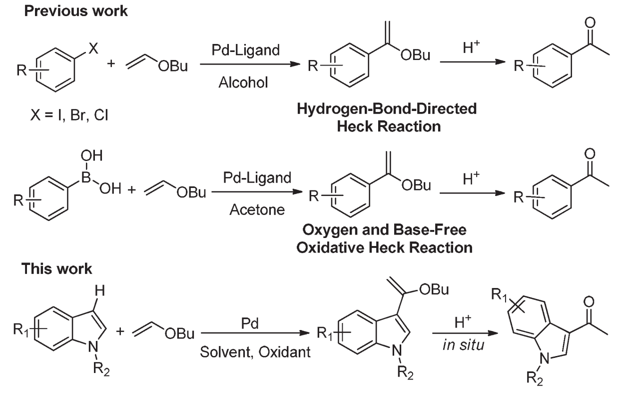
An efficient method for the preparation of 3-acylindoles has been developed, which centres on the palladium-catalyzed regioselective oxidative Heck reaction of *N*-protected indoles with electron-rich olefins.

The formation of new C–C bonds through the palladium-catalysed Heck reaction is one of the most important tools in synthetic chemistry.[1] Most Heck reactions deal with electron-deficient olefins, for which arylation or vinylation occurs at the least-substituted terminal β position of the double bond.[1] However, a regioselectivity issue exists when electron-rich olefins are employed; these olefins tend to afford a mixture of branched α and linear β regioisomers under normal Heck conditions.[2] Recently, we disclosed hydrogen-bond-directed Heck reactions which allow the α-arylation of electron-rich olefins with aryl halides to proceed in a faster, productive, and highly regioselective manner.[3] As alternative halide surrogates, arylboronic acids also showed good reactivity and regioselectivity in oxidative Heck reaction with both electron rich and deficient olefins.[4] On the other hand, transition-metal-catalyzed cross-coupling through C–H bond activation has emerged as one of the most powerful methods for the construction of C–C bonds;[5] this includes the Pd-catalyzed Heck reaction.[6,7] In continuing our research into the Heck and related reactions,[3,8] herein we report an efficient method for preparation of 3-acylindoles *via* palladium-catalyzed regioselective oxidative Heck reaction of *N*-protected indoles with electron-rich olefins (Scheme 1).

3-Acylindoles[9] have been found to exhibit various pharmaceutical activities, such as anticancer, antidiabetic, HIV-1 integrase inhibiting and antinociceptive abilities. Friedel–Crafts reaction is the traditional method for the preparation of these compounds.[10] Vilsmeier–Haack reaction,[11] coupling of 3-indolylzinc chloride with acyl chloride under Pd catalysis,[12] and the reaction of indole with *N*-(2-haloacyl)pyridinium salt[13] are the other significant approaches. Our and others' work has shown that aryl ketones can be readily synthesized by the Pd-catalyzed Heck reaction between Ar–X (X = B(OH)$_2$, Br, Cl) and vinyl ethers.[2,3] Bearing in mind the importance of 3-acylindoles, we explored the Heck reaction of indoles with vinyl ethers.

As showed in Table 1, initial result was disappointing. Using Pd(OAc)$_2$ as catalyst and Cu(OAc)$_2$ as oxidant, the reaction of *N*-methyl indole **1a** with *n*-butyl vinyl ether **2a** led to no desired product at 70 °C in DMSO for 12 h (Table 1, entry 1). It is somehow surprising that, if 4 equivalents of water were added, 3-acetyl-*N*-methyl indole **3a** could be obtained in 36% yield, under otherwise the same conditions (Table 1, entry 2). The formation of **3a** most likely proceeds *via* *N*-methylindole reacting with *n*-butyl vinyl ether to give the α-arylation product at the 3-position, which is *in situ* hydrolyzed in the reaction system under Brønsted or Lewis acid catalysis. The arylated vinyl ether intermediate (Scheme 1) was never detected, however. The preference for α-selectivity observed in this oxidative Heck reaction involving C–H bond activation is similar to that found in the arylation with ArX of electron-rich olefins.[3]



Scheme 1 Palladium-catalyzed Heck reaction with electron-rich olefins.

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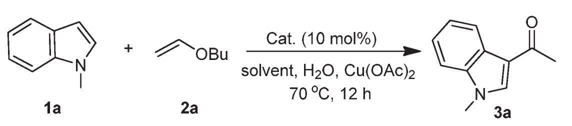
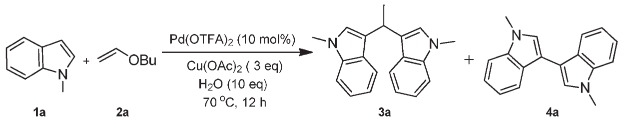
Table 1 Optimization of reaction conditions[a]



Entry	Cat.	Solvent	Water[b]	Yield[c] (%)
1	$Pd(OAc)_2$	DMSO	0	0
2	$Pd(OAc)_2$	DMSO	4	36
3	$Pd(OTFA)_2$	DMSO	4	44
4	$Pd(OTFA)_2$	DMSO	0	0
5	$Pd(OTFA)_2$	DMF	4	0
6[d]	$Pd(OTFA)_2$	DMSO-DMF	4	46
7[e]	$Pd(OTFA)_2$	DMSO-DMF	4	59

[a] Reaction conditions: *N*-methyl indole (0.5 mmol), olefin (1 mmol), catalyst (10 mol%), oxidant (1.5 mmol) and solvent (4 mL) at 70 °C for 12 h. [b] Equivalent of water added to dried solvent relative to **1a**. [c] Isolated yield. [d] DMSO (2 mL) and DMF (2 mL). [e] DMSO (4 mL) and DMF (4 mL).



Scheme 2 Alkylation of indole **1a** with olefin **2a**.

To make the reaction practically useful for the preparation of 3-acylindoles, we next surveyed the reaction conditions. The change of Pd source from $Pd(OAc)_2$ to $Pd(OTFA)_2$ promoted the yield to 44% (Table 1, entry 3). Similar to the reaction catalyzed with $Pd(OAc)_2$, without water no desired product was detected with $Pd(OTFA)_2$ as catalyst under identical conditions (Table 1, entry 4). Although the reaction did not work in DMF (entry 5), a mixture of DMSO and DMF was beneficial to the conversion, particularly when the volume of solvent was increased and so the concentration of the coupling partners decreased (Table 1, entries 6–7). Subsequently, we examined in more detail the effect of water on the arylation in the mixed solvents. Fig. 1 reveals a surprising volcano relationship for the yields of **3a** *vs.* the equivalents of water added relative to **1a.** The best yield of 89% was obtained with 3 equivalents of water.[14] When 10 equivalents of water were added, an alkylation poduct[15] was obtained in a yield of 80% (**3a**) alongside 15% of 3,3-biindole[16] (**4a**, Scheme 2). This unusual effect of water may stem from its conflicting roles in the reaction (*vide infra*).

With the optimized reaction conditions in hand, we next investigated the substrate scope of the reaction. As can be seen from Table 2, the Heck reaction between a range of *N*-protected indoles **1a–o** and *n*-butyl vinyl ether **2a** proceeded smoothly to afford 3-acylindoles in good to excellent yields. In all the reactions, the Heck olefination occurred exclusively at the 3 position of the indoles, with the α carbon of **2a** participating in the C–C bond formation, affording 3-acylindoles in a highly regioselective manner. Thus, with *N*-protected indoles bearing either strongly electron-withdrawing or electron-donating substituents, such as $–NO_2$ and –OMe, the oxidative Heck reaction showed only α-selectivity. Another feature of the reaction is the tolerance of functionalities in indole derivatives, such as chloro, nitro and methoxy groups, which provides opportunity for their further chemical transformation. However, indole itself showed no reaction with **2a** under the conditions employed, with indole being recovered after the workup.

With the success in *n*-butyl vinyl ether **2a**, we then turned our attention to other electron-rich olefins. In contrast to the previous report,[3d] using the hydroxyalkyl vinyl ether **2b** led to no cyclic ketal product and the 3-acylindole **5g** was obtained in 87% yield (Table 2, entry 16). Enamides are another class of electron-rich olefins. Similarly, their oxidative Heck reaction also afforded **5g**, albeit with lower yields (Table 2, entries 17 and 18). This is again different from the reaction with aryl halides catalyzed by palladium.[3d] However, in all these cases, the reaction preceded with exclusive α-selectivity, which is the same as the reactions with aryl halides or arylboronic acids.[3]

A plausible pathway is showed in Scheme 3. It starts with coordination of the vinyl ether to Pd(II). This is consistent with the observation that upon mixing **2a** with $Pd(OTFA)_2$ in deuterated DMSO-D_6, new resonances arising from presumably-coordinated **2a** appeared in the ^1H NMR spectrum at room temperature. In contrast, no change in the ^1H NMR spectra of **1a** was seen when it was used instead, indicating that **2a** is more likely to coordinate to Pd(II) than **1a.**[7e] However, when **1a** was heated at 70 °C in the

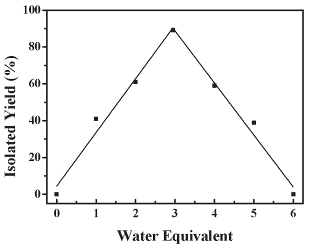
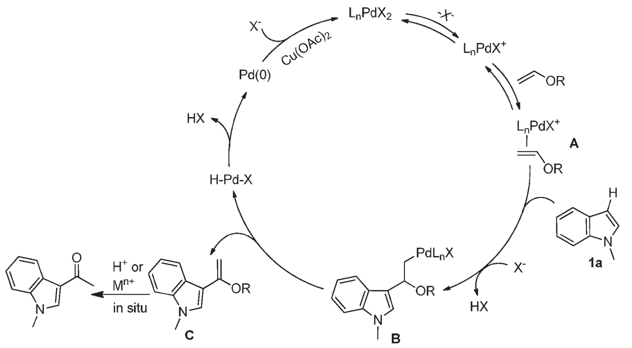
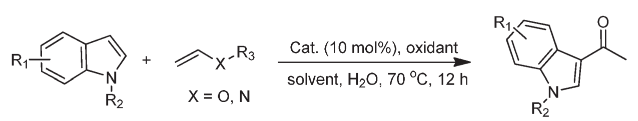


Fig. 1 The effect of added water on the acylation of **1a** (0.5 mmol) with **2a** (1 mmol) catalyzed by $Pd(OTFA)_2$ (10 mol%) in the presence of $Cu(OAc)_2$ (1.5 mmol) at 70 °C for 12 h in DMSO-DMF (1 : 1, 8 mL).

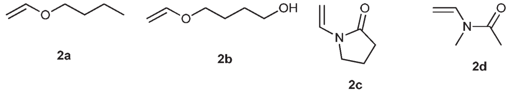


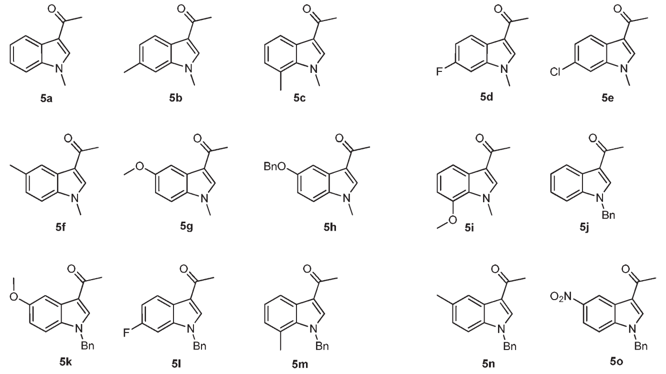
Scheme 3 Proposed reaction mechanism, where X is an anion such as acetate and L is an additional ligand such as solvent.

Table 2 Acylation of substituted indoles with electron-rich olefins[a]



Entry	Indole	Olefins	Products	Yield (%)
1	**1a**	**2a**	**5a**	89
2	**1b**	**2a**	**5b**	71
3	**1c**	**2a**	**5c**	73
4	**1d**	**2a**	**5d**	40
5	**1e**	**2a**	**5e**	65
6	**1f**	**2a**	**5f**	78
7	**1g**	**2a**	**5g**	91
8	**1h**	**2a**	**5h**	86
9	**1i**	**2a**	**5i**	75
10	**1j**	**2a**	**5j**	60
11	**1k**	**2a**	**5k**	74
12	**1l**	**2a**	**5l**	42
13	**1m**	**2a**	**5m**	61
14	**1n**	**2a**	**5n**	64[b]
15	**1o**	**2a**	**5o**	44
16	**1g**	**2b**	**5g**	87
17	**1g**	**2c**	**5g**	70
18	**1g**	**2d**	**5g**	51





[a] *N*-Methyl indole (0.5 mmol), olefin (1 mmol), catalyst (10 mol%), oxidant (1.5 mmol), H_2O (3 eq.) and solvent (8 mL) at 70 °C for 12 h. [b] NaOAc (0.05 mmol) was added.

reaction solvent in the presence of 3 equivalents of D_2O and 10% of $Pd(OTFA)_2$, H–D exchange in **1a** took place, affording 39% of deuterated indole at the 3 position. This suggests that indole may attack the Pd(II) centre under the reaction conditions. The next step involves nucleophilic attack of **1a**, *via* its 3 position, at the Pd(II)-**2a** species **A**, affording **B**. The attack may occur at the coordinated vinyl ether,[7n] although the possibility for **1a** to react directly with the Pd(II) cannot be ruled out, given the observation just mentioned. In the latter case, electronically-biased migration of the indolyl group to the α carbon of **2a** would then result in the formation of **B**. Subsequent β-hydrogen elimination at **B**, reductive elimination of HX and oxidation of the resulting Pd(0) to Pd(II) close the catalytic cycle.

Water may play a role in promoting the dissociation of the anion X from Pd(II), generating a cationic Pd(II), which is expected to be more reactive towards the vinyl ether than the neutral Pd(II).[17] The subsequent attack by **1a** at **A** is likely to benefit from the positive charge on Pd(II) as well. Consistent with this, the yield of **1a** reacting with **2a** decreased to 55% when 2 equivalents of NaCl was added (compare with entry 1, Table 2). However, in the presence of excessive water, HOAc and/or more active cationic Pd(II) may form, which catalyzes the decomposition of the vinyl ether and alkylation of **1a**,[18,19] explaining why an optimal level of water is needed for the Heck reaction.

In summary, we have developed a new method for the synthesis of 3-acylindoles with high regioselectivity and good yields. The process is based on the direct oxidative Heck reaction of *N*-substituted indoles with electron-rich olefins catalyzed by palladium. Water is found to play a key role in the reaction, with a certain amount needed to promote both the reaction rate and chemoselectivity.

Acknowledgements

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