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Palladium Catalyzed C–C and C–N Bond Formation via *ortho* C–H Activation and Decarboxylative Strategy: A Practical Approach towards *N*–Acylated Indoles

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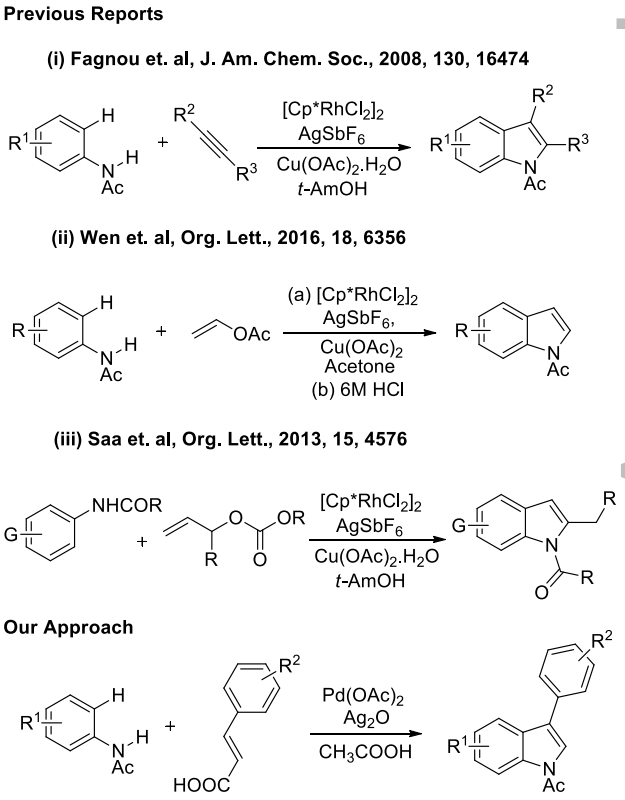
Abstract. A concerted palladium catalyzed C–H activation and decarboxylative strategy has been explored for the efficient synthesis of *N*–acylated indoles. The process allows a facile step- and atom-economic assembly of 3-arylated indole ring from inexpensive and readily available anilides and cinnamic acids as reacting partners.

Keywords: Synthetic methods; C–H Activation; Palladium; C–C/C–N bond formation; Decarboxylation

Indoles are the most widely distributed heterocyclic compounds in nature, and therefore its synthesis and functionalization has forever attracted a great deal of attention. Fisher synthesis from phenylhydrazones of aldehydes and ketones, Gassman synthesis from *N*–halo-anilines, Madelung cyclization using *N*–acyl-o-toluidines, Bischler synthesis using α-arylaminoketones and Batcho-Leimgruber synthesis involving amino-enamine intermediate are among the few prominent and extensively used methods to achieve diverse indole derivatives. *N*–Acylated indoles are particularly the cherished targets of synthetic chemists as they comprise the core nucleus of many important biologically active molecules and pharmaceuticals.[1,2] Although there exist several reports for the synthesis of indoles using *ortho* substituted anilides,[3] but those concerning *ortho* C-H activation of anilides are still scarce,[4] and the work by Fagnou, Wen and Saa deserve special attention (*cf.* Scheme1).

The C–C and C–N bond formation *via* C–H activation/ decarboxylative coupling has gained considerable current interest owing to its potential as an appreciated tool for step-economic and environmentally benign approach in organic synthesis.[5,6] Various transition metal complexes involving Ru,[7] Rh,[8] Pd,[9] Ir,[10] and Co,[11] have been effectively applied for the *ortho* C–H functionalization of anilides and other directing groups. In light of the above, we designed a one pot strategy for *ortho* vinylation of anilides using α,β-unsaturated carboxylic acids as vinyl source adopting co-existing dehydrogenative and decarboxylative cross coupling.

Carboxylic acids are commercially available in great structural diversity, easy to store and handle, and can be readily prepared by means of a large number of well-established methods, which make them valuable raw material in organic transformations.[12] Moreover, the α,β-unsaturated carboxylic acids offer exceptional regioselectivity unlike the corresponding alkenes or alkynes, thereby attracting more of the present interest towards decarboxylative cross coupling. Our group has recently explored the decarboxylative strategy for the synthesis of vinyl sulfones, 2-substituted benzothiazoles, thioamides and α,β-epoxy ketones, using easily accessible α,β-unsaturated carboxylic acids as functional surrogate.[13]



Scheme 1. Synthesis of *N*-acylated indoles

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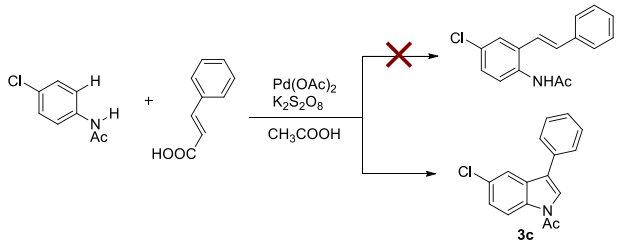
In view of the above and as a part of our ongoing research programme,[14] we wish to report an exigent protocol for the palladium catalyzed decarboxylation and chelation assisted synthesis of *N*–acylated indoles (Scheme 1).

The studies were indeed undertaken with an objective to achieve the *ortho* vinylation of anilides by cinnamic acids in the presence of $Pd(OAc)_2$ and $K_2S_2O_8$ in AcOH. However, the characterization data did not support the formation of the desired stilbene derivative. Rather to our utmost surprise and pleasure, we were confronted with a serendipity leading to the formation of the *N*–acylated indole **3c** (Scheme 2), whose structure was conclusively proved by the single crystal X-ray (Figure 1)[15] and was also corroborated by the spectral data.



Scheme 2.

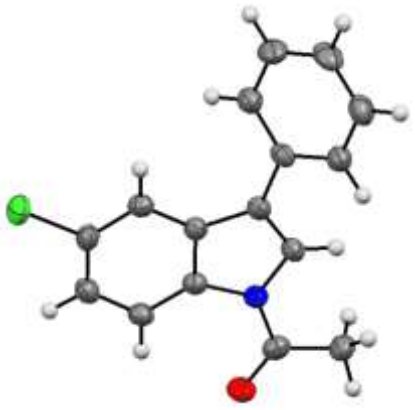
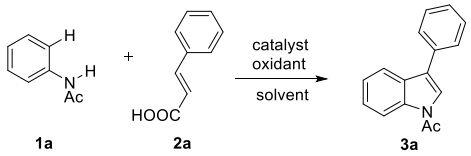


Figure 1. ORTEP diagram of **3c**.

Encouraged by this unique observation, a model reaction employing acetanilide (**1a**) and cinnamic acid (**2a**) was then screened thoroughly by varying different parameters such as catalyst, oxidant, solvent, temperature and time; and the findings are given in Table 1. The initial reaction conditions involved the use of $Pd(OAc)_2$ (10 mol%) and $K_2S_2O_8$ (1 eq.) in AcOH (1 ml) at 130 °C for 30 h (entry 1), which gave rise to the product 1-(3-phenyl-1H-indol-1-yl)ethanone (**3a**) in 38% yield. Keeping the use of $Pd(OAc)_2$ as catalyst, some other oxidants, such as $NH_4S_2O_8$, TBHP, $Cu(OAc)_2.H_2O$ and $AgNO_3$ were also tried, but they either worked poorly or did not work at all (entries 2-5). However, when silver salts like Ag_2CO_3, Ag_2O and AgOAc were used as oxidant, appreciably high product yields were observed (entries 6-8). Markedly when the reaction was carried out in the absence of the oxidant or catalyst, no product formation was observed (entries 9 & 10). Maintaining other parameters of the entry 7 intact, the effect of different solvents was then explored. The use of TFA and pivalic acid did not assist yielding **3a** in 54% and 57% respectively (entries 11 & 12), whereas the use of other solvents like DMSO, toluene and n-butanol along with solvent-free conditions remained completely futile (entries 13-16). Decreasing the reaction temperature to 120 °C reduced the product yield to 62% (entry 17), while an increase in the reaction temperature could not enhance the yield further. Other palladium catalysts like $Pd(TFA)_2$ and $PdCl_2$, when examined, could not match the efficacy of $Pd(OAc)_2$ as they afforded 57% and 42% product yields only (entries 18 & 19). An attempt to utilize copper catalysts namely $Cu(OAc)_2$ and $Cu(OTf)_2$ also remained futile (entries 20 & 21). The catalytic use of Ag_2O (0.2 and 0.5 equiv.) could not provide the product in appreciable amount. Further, the catalytic combination of Ag_2O (20 %) with a co-oxidant $K_2S_2O_8$ (1 equiv.) also gave rise to a pretty low yield (entry 22), thereby compelling the use of equivalent amount of silver salt. The catalyst concentration was also varied from 5 to 15 mole % revealing 10 mole % as the best fit. Thus, the optimum conditions comprised of $Pd(OAc)_2$ (10 mole %) as catalyst and Ag_2O (1 equiv.) as oxidant in AcOH at 130 °C (entry 7).

Table 1. Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst (10 mol %)	Oxidant (1 equiv.)	Solvent	Yield[b]
1.	$Pd(OAc)_2$	$K_2S_2O_8$	CH_3COOH	38
2.	$Pd(OAc)_2$	$NH_4S_2O_8$	CH_3COOH	12
3.	$Pd(OAc)_2$	TBHP	CH_3COOH	0
4.	$Pd(OAc)_2$	$Cu(OAc)_2.H_2O$	CH_3COOH	0
5.	$Pd(OAc)_2$	$AgNO_3$	CH_3COOH	0
6.	$Pd(OAc)_2$	Ag_2CO_3	CH_3COOH	70
7.	$Pd(OAc)_2$	Ag_2O	CH_3COOH	72
8.	$Pd(OAc)_2$	AgOAc	CH_3COOH	57
9.	$Pd(OAc)_2$	-	CH_3COOH	0
10.	-	Ag_2O	CH_3COOH	0
11.	$Pd(OAc)_2$	Ag_2O	TFA	54
12.	$Pd(OAc)_2$	Ag_2O	PivOH	57
13.	$Pd(OAc)_2$	Ag_2O	DMSO	0
14.	$Pd(OAc)_2$	Ag_2O	toluene	0
15.	$Pd(OAc)_2$	Ag_2O	n-butanol	0
16.	$Pd(OAc)_2$	Ag_2O	-	0
17.	$Pd(OAc)_2$	Ag_2O	CH_3COOH	62[c]
18.	$Pd(TFA)_2$	Ag_2O	CH_3COOH	57
19.	$PdCl_2$	Ag_2O	CH_3COOH	42
20.	$Cu(OAc)_2$	Ag_2O	CH_3COOH	0
21.	$Cu(OTf)_2$	Ag_2O	CH_3COOH	0
22.	$Pd(OAc)_2$	$Ag_2O/K_2S_2O_8$	CH_3COOH	35[d]

[a]Using **1a** (2 mmol) & **2a** (1 mmol). [b]Isolated yield after column chromatography, [c] at 120 °C, [d]Ag_2O(20 mol %)/ $K_2S_2O_8$(1 eq.).

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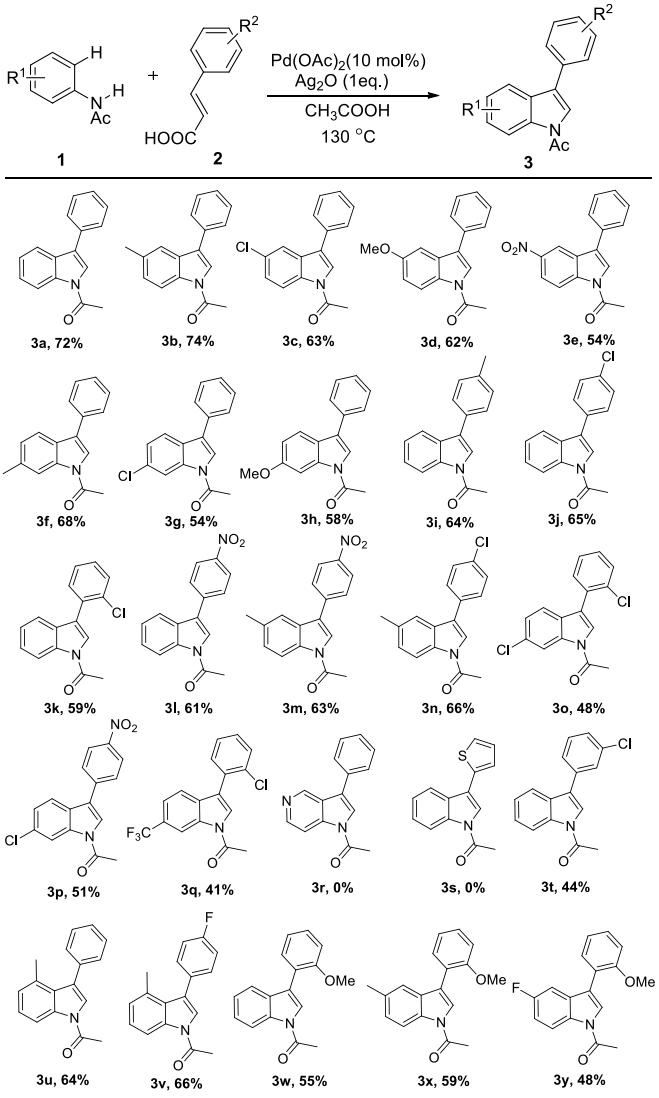
With the established conditions in hand, the scope and versatility of the reaction was examined using a variety of anilides and cinnamic acids with different substitution patterns (*ortho/meta/para*). The outcome is given in Table 2. Both the reacting partners containing different electron-donating as well as electron-withdrawing substituent participated nicely in the reaction and offered the desired products **3a-3q** in reasonably good yields. Anilides containing electron-rich substituent provided higher yields, while those with electron-deficient substituent gave lower conversions. A number of substituent like CH_3, Cl, OMe and NO_2 were well tolerated during the course of reaction. *N*-(3-(Trifluoromethyl)phenyl)acetamide also participated in the reaction to afford the product **3q**, albeit in lower yield (41%). Contrarily, cinnamic acid derivatives with electron-rich substituent gave lower yields than those with electron withdrawing groups.

Table 2. Scope and versatility of the reaction[a,b]



[a]Using **1a** (2 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2O (1 equiv) in closed vessel at 130 °C for 30 h. [b]Isolated yield after column chromatography.

Ortho substituted 2-chloro cinnamic acid afforded somewhat low product yield (**3k**, 59 %) perhaps due to steric factor. The reaction of *N*-(pyridin-4-yl)acetamide with cinnamic acid and the reaction of acetanilide with 3-(thiophen-3-yl) acrylic acid, however failed, (**3r** and **3s**). This may be ascribed to the nitrogen or sulfur atoms present in the heterocyclic moiety, which strongly coordinate with the metals leading to catalyst poisoning and thereby limiting the application of C–H activation.[16] With a view to explore the applicability of (*Z*)-cinnamic acids in the aforementioned reaction, a representative reaction of *cis*-2-methoxycinnamic acid with different anilides namely *N*-phenylacetamide, *N*-(*p*-tolyl)acetamide and *N*-(4-fluorophenyl)acetamide was carried out under the established reaction conditions leading to the formation of the products **3w-3y**. It is worthwhile to mention that the reactions using (*Z*)-cinnamic acids also proceeded well with the same regioselectivity affording 3-substituted indoles. 2-Substituted indoles were not formed at all in this reaction due to electronic factors and not due to the steric factors. The Palladium is probably inserted at the alpha position of olefin (COOH attached carbon) which exclusively leads to 3-substituted indoles exhibiting high regioselectivity.[17]

Based on the existing literature,[18-21] and isolation of product; a plausible mechanism involving palladium catalytic cycle is outlined in Figure 2. The reaction is assumed to proceed via *ortho*-palladation of the anilide **1** giving intermediates **I** and **II** in succession. The intermediate **II** then combines with the α,β-unsaturated acid **2** to form the intermediates **III** and **IV** sequentially. The intermediate **IV** finally gives rise to the product **3** via decarboxylation. The role of silver salt is presumed to be an oxidant which helps reoxidize the palladium to its catalytic form and also assists in the decarboxylation step.[22-24]

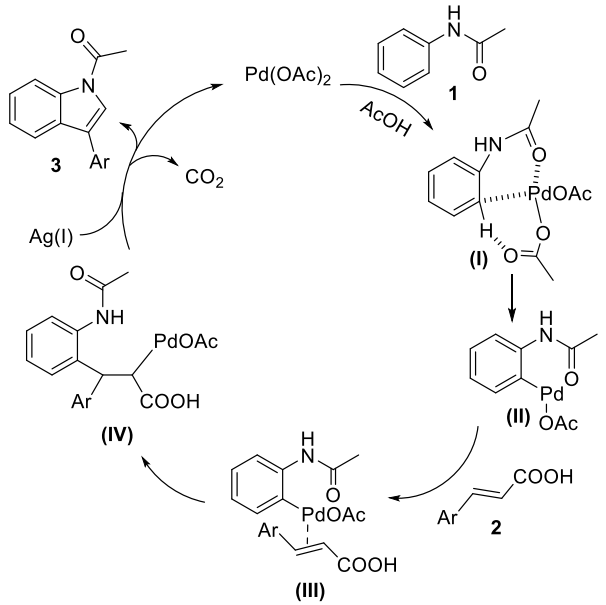


Figure 2. Plausible reaction mechanism

In summary, a practical palladium catalyzed C–H activation and decarboxylative strategy has been developed for the synthesis of biologically important *N*-acylated indoles from anilides and cinnamic acids. A reaction pathway involving palladium catalytic cycle has been proposed.

Experimental Section

Anilide **1** (2 mmol), cinnamic acid **2** (1 mmol), acetic acid (1mL), $Pd(OAc)_2$ (10 mol %) and Ag_2O (1 equiv) were placed in a sealed pressure regulation vial (15-mL) containing a Teflon coated magnetic stir bar. The reaction mixture was stirred for 30 h at 130 °C in a preheated oil bath. After completion of the reaction (monitored through TLC), the mixture was worked-up using aqueous solution of sodium bicarbonate-ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product was finally purified by silica gel column chromatography using *n*-hexane and ethyl acetate as eluent.

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[15] CCDC 1551256 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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