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COMMUNICATION

Synthesis of isatins by the palladium-catalyzed intramolecular acylation of unactivated aryl C(sp^2)-H bond†

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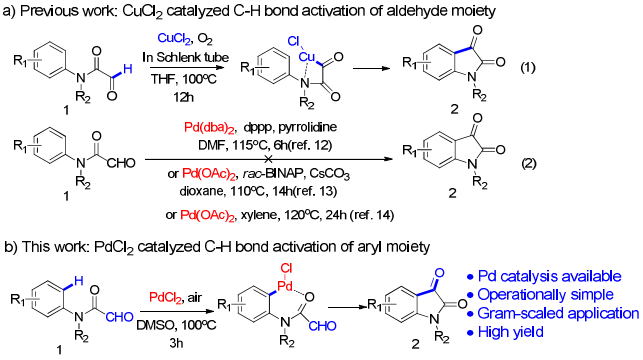
Synthesis of isatins from formyl-N-arylformamides is achieved *via* $PdCl_2$-catalyzed intramolecular acylation. This method shows the possibility of Pd-catalyzed aryl C(sp^2)-H bond activation on the synthesis of isatins, affording an array of isatins in good yields. Yet this protocol is operationally simple and atom economical.

Over the last decade, transition-metal-catalyzed C-H bond functionalization has emerged as a useful and powerful synthetic strategy, and has allowed chemist to assemble complex molecular structures efficiently. Metals such as Pd, Cu, Ni, Fe, Ru, etc. play vital roles on the transformation of unactivated C(sp^2)-H bond to C(sp^2)-C bond with the assistance of directing group.[1] In particular, the Pd-catalyzed direct C-H bond acylation protocols using aryl compounds and some simple precursors have been widely investigated,[2] such as the Pd catalyzed *ortho*-aroylation using benzyl bromides as aroyl surrogates,[2a] the decarboxylative acylation of arenes with mandelic acid derivatives *via* palladium catalyst,[2b] and the Pd-catalyzed oxidative C-H bond acylation of acetanilides employing toluene derivatives as the coupling precursors.[2c] These methods provide efficient pathway to afford arylketone motifs.

On the other hand, the isatin derivatives, which have similar structures with arylketone motifs, have received much attention, due to their biological activity and potential medical value [3] and the activities of C-3 carbonyl group as a synthetic intermediate.[4] Traditionally, Sandmeyer procedure,[5] Stollé procedure[6] and Martinet procedure[7] are used to synthesize isatin. However, these methods suffer from the harsh conditions, poor yields and limited substrate choices. This motivates the development of new synthetic methods to overcome these limitations. Inspiringly, a number of modern and efficient methods have been exploited, for example, the ylide-mediated carbonyl homologation of anthranilic acids,[8] and the I_2-mediated[9] or Cu-catalyzed[10] intramolecular cyclic amidation from *ortho*-substituted anilines. Although these reactions showed some improvements, the requirement of the *ortho*-functionalized aromatic substrates, which were not readily available, were the obvious drawbacks. In contrast to preparation of *ortho*-functionalized substrates, the direct transformation from sp^2 C-H bonds of aryl moiety to C-C bonds for the synthesis of isatin is a more appealing alternative approach.

In a recent *J. Am. Chem. Soc.* communication, Li and co-workers have reported intramolecular acylation of formyl-N-arylformamides **1** to indoline-2,3-diones **2** based on Cu-catalyzed activation of C-H bond of aldehyde[**Scheme 1a**, Eq. (1)][11]. Their work was interesting as it simplified the substrate preparation and revealed the possibility of intramolecular acylation. They suggested that the C-H bond on aldehyde can be activated by $CuCl_2$ with O_2 in Schlenk tube at 100°C. Notably, they also mentioned that some palladium complexes, including Xiao's catalytic system [$Pd(dba)_2$ and dppp in DMF at 115°C],[12] Martin's catalytic system [$Pd(OAc)_2$ and *rac*-BINAP in dioxane at 110°C][13] and Cheng's catalytic system [$Pd(OAc)_2$ in xylene at 120°C],[14] are not compatible to this reaction[**Scheme 1a**, Eq. (2)]. This, however, is in contrary with the well accepted Pd-catalyzed *ortho*-acylation of acetanilides.[2c,2h-2i] Considering formyl-N-arylformamide **1** is a acetanilide derivative, it is



Scheme 1. Synthesis of isatins using Pd catalyst

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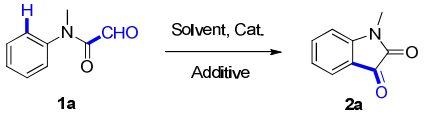
Table 1. Optimization of the reaction conditions.



1a 2a

Entry	Catalyst(mol%)	Additive	Solvent	Temperature(^{o}C)	Time(h)	Yield[b](%)
1	$Pd(OAc)_2$(10)	Cs_2CO_3/BINAP/air	dioxane	110	14	6
2	$Pd(dba)_2$(10)	pyrrolidine/dppp/air	DMF	115	6	11
3	$Pd(OAc)_2$(10)	air	xylene	120	24	13
4	$PdCl_2$(10)	air	xylene	120	24	61
5	$PdCl_2$(10)	air	xylene	100	3	70
6	$PdCl_2$(10)	air	dioxane	100	3	76
7	$PdCl_2$(10)	air	DMF	100	3	65
8	$PdCl_2$(10)	air	toluene	100	3	73
9	$PdCl_2$(10)	air	DMSO	100	3	92
10	$Pd(TFA)_2$ (10)	air	DMSO	100	3	90
11	$Pd(PPh_3)_4$ (10)	air	DMSO	100	3	<5
12	$PdCl_2(dppf)\bullet CH_2Cl_2$ (10)	air	DMSO	100	3	33
13	$PdCl_2(PPh_3)_2$	air	DMSO	100	3	<5
14	-	air	DMSO	100	3	-
15	$PdCl_2$(5)	air	DMSO	100	3	78
16	$PdCl_2$(20)	air	DMSO	100	3	92
17	$PdCl_2$(100)	argon	DMSO	100	3	18

[a]Reaction conditions: **1a** (0.4mmol), catalyst(as indicated), solvent(2ml) and additive(as indicated) were heated for indicated reaction time. [b]Isolated yield. BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl; TFA = Trifluoroacetate; dba = Dibenzylideneacetone; PPh_3 = Triphenylphosphine; dppf = 1,1'-Bis(diphenylphosphino)ferrocene; dppp = 1,3-bis(diphenylphosphino)propane.

possible that unactivated aryl C(sp^2)-H bond of compound **1** would be activated *via* suitable Pd catalyst and intramolecular acylation could happen, upon which isatins **2** could be obtained(Scheme 1b). So we carefully reviewed Li and co-workers' work, and repeated the experiments with conditions mentioned above. *N*-Methyl-2-oxo-*N*-phenylacetamide **1a**, which we had previously synthesized, was employed as the substrate (**Table 1**, entry 1-3).[15] Not surprisingly, all reactions suffered from poor yield (6-13%) although the reaction facilitated by $Pd(OAc)_2$ in xylene had a relatively higher yield (13%). However, replacing $Pd(OAc)_2$ by $PdCl_2$ in the later reaction, the yield of **2a** was increased to 61% (**Table 1**, entry 4). This encouraged us as it implies that there might be a possibility to further improve the reaction. By our best knowledge, no previous reports have described such intramolecular acylation of acetanilide derivatives *via* Pd-activated aryl C(sp^2)-H bond**(Scheme 1b)**, therefore, we explored more about it.

In beginning of our study, side products were detected when the reaction ran at 120^{o}C for more than 24 hours (**Table 1**, entry 4). After testing the reaction with different temperatures and different reaction time, it was found that the reaction gave a better yield at 100^{o}C after 3h (**Table 1**, entry 5). Thus, later reactions were carried out at 100^{o}C for 3h. Then we tested different solvents and found that DMSO was more effective than other solvents such as DMF, toluene and 1,4-dioxane(**Table 1**, entry 6-9). Furthermore, evaluation on other Pd compounds was carried out, and suggested that $PdCl_2$ was still the most suitable catalyst (**Table 1**, entry 10-13). It is also found that 10mol% $PdCl_2$ was necessary as neither increasing nor decreasing the catalyst loading did not give a higher yield of **2a**. No desired product was obtained without the presence of $PdCl_2$ (**Table 1**, entry 14-16). Notably air served as the essential factor because the yield of **2a** was unsatisfied when this reaction was run in argon atmosphere, even though the catalyst loading was up to 1 equiv (**Table 1**, entry 17).

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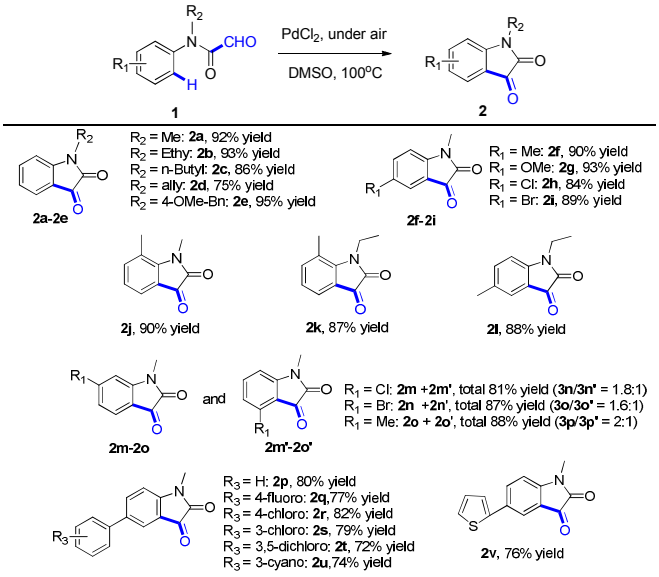
Table 2. Synthesis of indoline-2,3-diones [a,b]

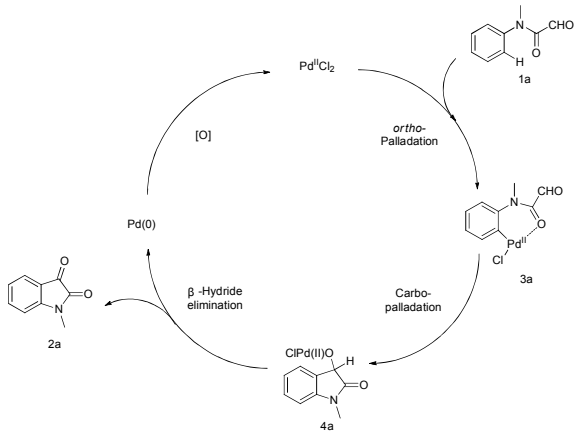


[a]Reaction conditions: **1** (0.4mmol), $PdCl_2$ (10mol%), DMSO(2ml) were heated at 100°C for 3h under air. [b]Isolated yield.

Accordingly, the reaction conditions are optimized as follows: 10mol% $PdCl_2$ under air in DMSO at 100°C for 3h.

After the reaction condition was optimized, the substrate scope of this synthetic methodology was also established and the results were shown in **Table 2**. Functional groups attached to the nitrogen atom, such as ethyl, n-butyl, allyl, gave the corresponding products in good yields (**Table 2,** Compound **2a**-**2d**). Electron-donating and electron- withdrawing groups at 4th position of aromatic ring were well tolerated during the reaction (**Table 2,** Compound **2f**-**2l**). Notably the substrates with *meta*-methyl or *meta*-halogens provided a mixture of 4-substituted and 6-substituted indoline-2,3-diones in different proportion (**Table 2,** Compound **2m**-**2o**). Other functional groups, such as cyano, substituted phenyls, and heterocycle, were compatible with the optimal condition (**Table 2,** Compound **2p**-**2v**). It was noteworthy that under the optimal condition the reaction can be easily scaled up, for example, when 6.1 mmol of **1a** (1.0 g) was used, this reaction was showed to have similar efficiency when it was under the optimal condition (88%).

According to the previous studies, [2,16] a plausible mechanism as shown in **Scheme 2** was proposed. Firstly, intermediate **3a** was formed through *ortho*-palladation of **1a**. Then a carbonpalladation reaction between the aryl-Pd(II) moiety and the formyl group would give the Pd(II) alkoxide intermediate **4a**. Subsequently, the isatin **2a** and Pd(0) could be obtained by β-Hydride elimination. The Pd(0) was then oxidized to Pd(II), hence the regeneration of the Pd(II) catalyst, which fulfil the catalytic cycle.



Scheme 2. Proposed mechanism

Conclusions

In conclusion, we have described an efficient synthesis of isatin derivatives *via* $PdCl_2$-catalyzed intramolecular acylation of formyl-N-arylformamides using air as oxidant. This atom economical method implies that such a transformation could also be facilitated by a suitable Pd catalyst, albeit some reported palladium complexes did not work.[12-14] This method offers not only good yields of the corresponding product, but also has a good tolerance with different functional groups. In addition, this protocol can be easily scaled up. Also, using air and DMSO as catalytic system makes this method operationally simple. This powerful tool that shows versatility and flexibility can be a good addition to thefield of organic synthesis and medicinal chemistry.

Acknowledgements

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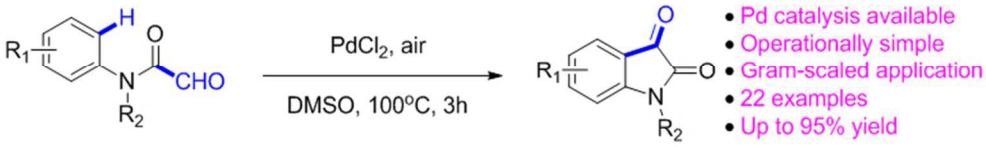

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