Heterocycle Synthesis

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From Anilines to Isatins: Oxidative Palladium-Catalyzed Double Carbonylation of C–H Bonds**

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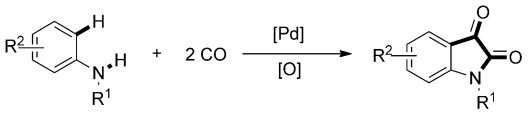
Abstract: *A novel palladium-catalyzed C–H double carbonylation introduces two adjacent carbonyl groups for the synthesis of isatins from readily available anilines. The reaction proceeds under atmospheric pressure of CO with high regioselectivity and without any additives. Density functional theory investigations indicate that the palladium-catalyzed double carbonylation catalytic cycle is plausible.*

Palladium-catalyzed carbonylation for the construction of carbonyl compounds has received considerable attention in recent years.[1] In contrast to the well-known palladium-catalyzed process of introducing one carbonyl group into organic compounds, palladium-catalyzed double carbonylation as a powerful tool for the preparation of organic compounds with two adjacent carbonyl groups, has remained largely undeveloped. In fact, palladium-catalyzed double carbonylation is limited to the use of aromatic halides or vinyl halides.[2] In comparison, the direct utilization of aromatic C–H bonds in double carbonylation would be more appealing. Thus far, no direct oxidative double carbonylation of C–H bonds for introducing two adjacent carbonyl groups in the synthesis of heterocyclic compounds has been developed.[3] Herein, we report a palladium-catalyzed double carbonylation of a C–H bond *ortho* to an amino group and it involves the use of commercially available anilines for the synthesis of isatins [Eq. (1)].

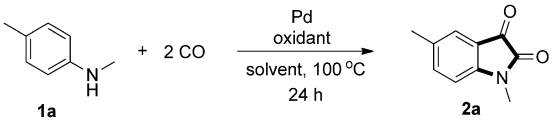


(1)

Isatin (indoline-2,3-dione) is a well-known natural product which is present in bioactive compounds, synthetic intermediates, and pharmaceuticals.[4] Many isatin derivatives exhibit a broad range of biological activities such as anticancer,[5] anticonvulsant,[6] antifungal,[7] anti-HIV,[8] and anti-inflammatory,[9] and others.[10] Although a number of methods have been established for the construction of such structures, the reported synthetic methods of isatins often require substrate pre-functionalization, multiple steps, and starting materials which are not readily available.[11] Most importantly, most of the methods are not atom economical as only a part of the reagent used for the introduction of carbonyl group is retained. Given the importance of the isatin skeleton, development of direct and economic strategies, as well as control of the regioselectivity has attracted considerable attention from synthetic chemists.

Our initial efforts focused on the double carbonylation of *N*-methyl-4-methylaniline (**1a**; Table 1). We were pleased to observe the desired product under the combined reaction

Table 1: Reaction optimization for the palladium-catalyzed double carbonylation of *N*-methyl-4-methylaniline.[a]



1a **2a**

Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	$[PdCl_2(PPh_3)_2]$	$Cu(OPiv)_2$	DMSO	54
2	$[PdCl_2(PPh_3)_2]$	$Cu(OPiv)_2$	toluene	trace
3	$[PdCl_2(PPh_3)_2]$	$Cu(OPiv)_2$	DMF	trace
4	$[PdCl_2(PPh_3)_2]$	$Cu(OPiv)_2$	DMSO/tol (1:1)	70 (70)[c]
5	$[PdCl_2(MeCN)_2]$	$Cu(OPiv)_2$	DMSO/tol (1:1)	21
6	$Pd(OAc)_2$	$Cu(OPiv)_2$	DMSO/tol (1:1)	16
7	$[PdCl_2(PPh_3)_2]$	$Cu(OPiv)_2/O_2$	DMSO/tol (1:1)	trace[d]
8	$[PdCl_2(PPh_3)_2]$	O_2	DMSO/tol (1:1)	trace
9	$[PdCl_2(PPh_3)_2]$	$Cu(OAc)_2$	DMSO/tol (1:1)	41

[a] Reaction conditions: **1a** (0.20 mmol), catalyst (0.01 mmol), oxidant (0.40 mmol), and solvent (1.0 mL) under 1 atm CO at 100 °C for 24 h. [b] Determined by NMR spectroscopy using CH_2Br_2 as an internal standard. [c] Yield of isolated product. [d] 0.04 mmol $Cu(OPiv)_2$ was employed. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, OPiv = trimethylacetate, tol = toluene.

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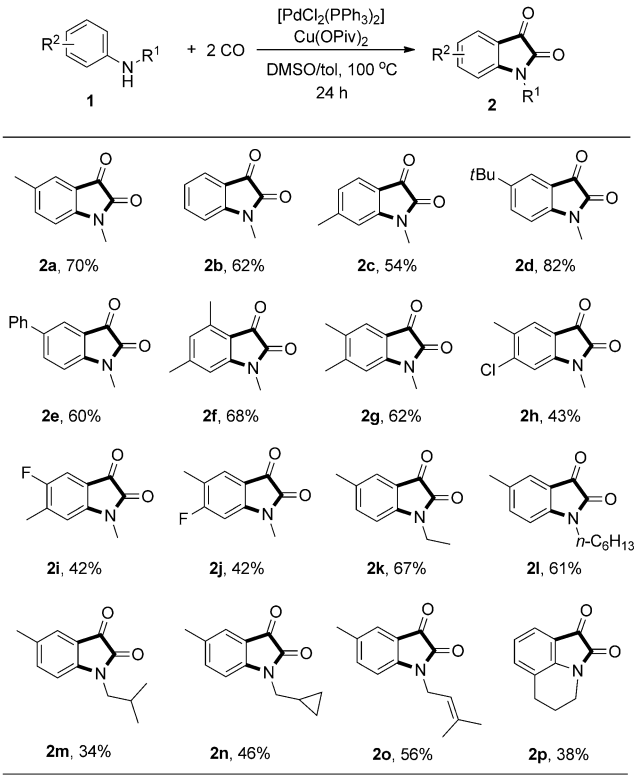
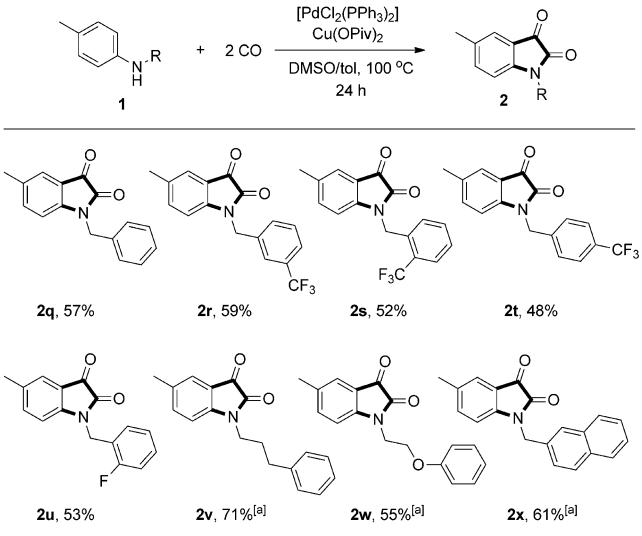
conditions of $[PdCl_2(PPh_3)_2]$ and $Cu(OPiv)_2$ in DMSO at 100 °C under 1 atm CO (entry 1). Under these reaction conditions, a 54 % yield (determined by NMR spectroscopy) of **2a** was obtained in 24 hours. Only trace amounts of product was obtained while using DMF or toluene as the solvent (entries 2 and 3). Further optimization of the reaction conditions showed that the reaction was most productive when a mixed solvent of DMSO/toluene (1:1) was used (entry 4). The use of other palladium(II) pre-catalysts, such as $[PdCl_2(MeCN)_2]$ and $Pd(OAc)_2$ resulted in much lower yields (entries 5 and 6). Only trace amounts of the desired product was detected when decreasing the loading of $Cu(OPiv)_2$ to a catalytic amount and using O_2 as the terminal oxidant (entry 7), and no product was detected when using O_2 as the sole oxidant (entry 8). This outcome may arise because anilines are easily decomposed under aerobic conditions at high temperature. It should be noted that $Cu(OAc)_2$ was less effective for this reaction compared with $Cu(OPiv)_2$ (entry 9). Actually, under the reaction conditions used in entry 9 of Table 1 the *N*-acetylation of aniline was detected through GC-MS and the acetyl group was believed to be generated from $Cu(OAc)_2$. The acylation of substrate was completely inhibited when $Cu(OPiv)_2$ was used as the oxidant. Furthermore, the solubility of $Cu(OPiv)_2$ is better compared to that of $Cu(OAc)_2$ in organic solvents, and could be considered as another promotion to the reaction.

With the optimized reaction conditions in hand, the substrate scope was studied (Scheme 1). The isatin **2b** was obtained in 62 % yield by direct double carbonylation under the optimized reaction conditions. The sole product **2c** was produced in moderate yield by reaction at the less hindered *ortho* position of *N*-methyl-3-methyl aniline. The reaction of an *N*-methyl aniline bearing either a *tert*-butyl or phenyl group proceeded well to give the corresponding products **2d** and **2e** with high yields. 3,5-Dimethyl-substituted *N*-methyl aniline smoothly led to **2f** in 68 % yield. 3,4-Dimethyl-substituted *N*-methyl aniline was converted into the corresponding isatin in good yields (**2g**). Substituents such as chloro and fluoro were well tolerated, and the corresponding products could be isolated successfully (**2h**–**j**). Furthermore, various kinds of *N*-alkyl substituents such as ethyl, *n*-hexyl, and isobutyl were also investigated and provided the desired products in moderate to good yields (**2k**–**m**). Cyclopropyl and allyl groups were also well tolerated (**2n**,**o**). In addition, tetrahydroquinoline proceeded smoothly to give the double carbonylation product **2p** in 38 % yield.

To further demonstrate the utility of this method for organic synthesis and to confirm its efficiency in the complex molecules preparation, we explored strategies for the preparation of drug-type derivatives. *N*-Benzyl isatins can be successfully achieved under basic conditions using alkyl chlorides and bromides. Although conventional heating is used to generate *N*-benzyl products, the base lability of the isatin nucleus and use of starting materials which are not readily available would be considered a limitation of such protocols. We were pleased to find that the desired *N*-benzyl isatins could be successfully obtained with highly chemoselectivity and good yields under our reaction conditions (**2q**–**u**; Scheme 2). Not surprisingly, the expected double carbon-



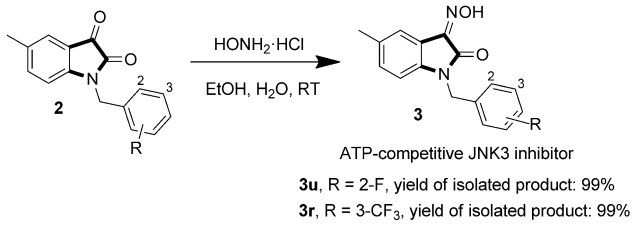
Scheme 1. Palladium-catalyzed oxidative double carbonylation of *N*-alkyl anilines for the synthesis of isatins. Reaction conditions: **1** (0.20 mmol), $[PdCl_2(PPh_3)_2]$ (0.01 mmol), $Cu(OPiv)_2$ (0.40 mmol), and DMSO/toluene (0.5 mL/0.5 mL) under 1 atm CO at 100 °C for 24 h. Yields are those of isolated and purified products.



Scheme 2. Palladium-catalyzed oxidative double carbonylation for the synthesis of isatins. Reaction conditions: **1** (0.20 mmol), $[PdCl_2(PPh_3)_2]$ (0.01 mmol), $Cu(OPiv)_2$ (0.40 mmol), and DMSO/toluene (0.5 mL/0.5 mL) under 1 atm CO at 100 °C for 24 h. Yields are those of isolated and purified products. [a] Pivalic acid (2.0 equiv) was added.

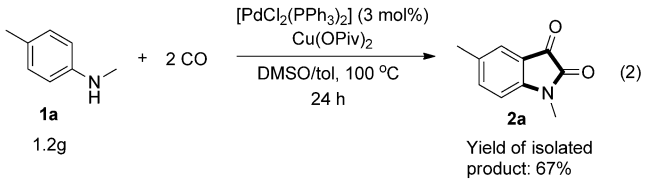
ylation products *N*-phenylpropyl, *N*-phenoxypropyl, and *N*-naphthalen-2-ylmethyl isatins (**2v–x**) were obtained smoothly in high yields.

N-Benzylated isatin oximes have gained much attention in the pharmaceutical industry because of their inhibitory effects of the mitogen-activated kinase JNK3.[12] The *N*-benzyl isatins were further transformed into the target inhibitory active *N*-benzyl isatin oximes in excellent yields (Scheme 3).[13]

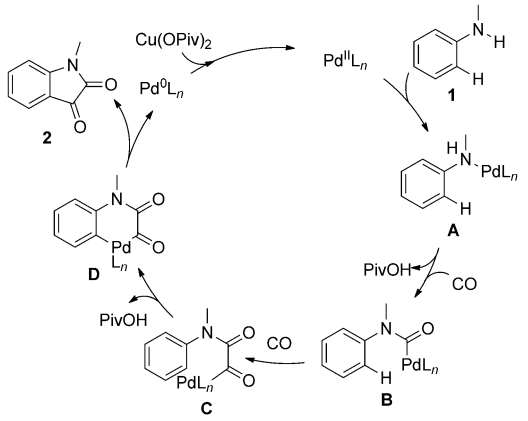


Scheme 3. Preparation of *N*-benzyl isatin oximes.

Notably, this reaction could be run on gram scale, and the desired product **2a** was obtained in 67% yield by using 3 mol% $[PdCl_2(PPh_3)_2]$ [Eq. (2)], thus demonstrating the scalability of this reaction.



A possible mechanism for this reaction has been outlined in Scheme 4. First, aryl N–H activation by the palladium complex forms the intermediate **A** from **1**. Then, coordination and insertion of CO into **A** affords the carbamoyl intermediate **B**.[14] Then **B** undergoes another CO insertion to give the intermediate **C**. The C–H activation of **C** generates a six-membered cyclic carbamoyl intermediate (**D**), which is followed by a reductive elimination reaction to give the product **2**. Finally, the Pd^0 species is reoxidized to the Pd^{II} catalyst in the presence of $Cu(OPiv)_2$. Finally, density functional theory investigations have elucidated the mechanism of the direct oxidative palladium-catalyzed C–H/N–H double carbonylation (see the Supporting Information). Density functional theory results indicate that the double carbonylation catalytic cycle in the Scheme 4 is favorable.



Scheme 4. Proposed mechanism for the palladium-catalyzed double carbonylation of a C–H bond.

In conclusion, we have developed the first direct oxidative palladium-catalyzed C–H/N–H double carbonylation which introduces adjacent carbonyl groups for the direct synthesis of isatins. This transformation offers a general process for converting readily available substrates into potentially useful compounds. Density functional theory investigations indicate that the palladium-catalyzed double carbonylation of C–H is favorable. Studies into the substrate scope and mechanism are ongoing in our laboratory and will be reported in the near future. Hopefully, these studies will inspire the development of oxidative double carbonylation for the synthesis of various heterocycles.

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