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Palladium-Catalyzed Regioselective Carbonylation of C−H Bonds of *N*-Alkyl Anilines for Synthesis of Isatoic Anhydrides

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Supporting Information

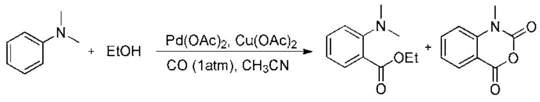
ABSTRACT: A Pd-catalyzed regioselective C−H bond carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides has been developed. The key Pd-catalyst intermediate has been isolated and characterized. This novel Pd-catalyzed carbonylation reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available *N*-alkyl anilines into a variety of substituted isatoic anhydrides under mild conditions.

Carbonylation reactions with CO have been and continue to be a very active area of research.[1] Since the pioneering work of Heck in 1974,[2] carbonylations of aryl halides and pseudohalides with CO have become one of the most common methods for the addition of a carbonyl group to organic molecules.[3] In recent decades, much progress has been made in C−H bond activation and functionalization.[4] However, C−H carbonylation has remained largely undeveloped.[5] A breakthrough in this area was made with the Pd-catalyzed carbonylation of aromatic C−H bonds by Fujiwara et al., but the reaction lacks regioselectivity and requires a large excess of the arene as solvent.[6]

Recently, transition-metal-catalyzed chelation-assisted carbonylation of C−H bonds for the synthesis of ketones, acids, amides, and esters has been developed by Murai,[7] Yu,[8] Chatani,[9] Orito,[10] Lloyd-Jones and Booker-Milburn,[11] our,[12] and other groups.[13−19] Despite these advances, there is no efficient protocol for C−H bond carbonylation to synthesize anhydrides directly.[8a] As a class of powerful building blocks in organic chemistry, the synthesis of anhydrides by C−H bond carbonylation is high desirable.

Directing groups which could assist the *ortho* electrophilic metalation of C−H bond are important in C−H bond carbonylations.[20] A small number of functional groups, such as carboxy, amide, urea, pyridin-2-ylmethylamine, and azaheterocycles, have been explored for direct C−H bond carbonylation. The search for new directing groups which are synthetically versatile is still a challenging task. We have found that synthetically versatile secondary anilines can be used for *ortho* C−H bond carbonylation. Here, we report a Pd-catalyzed *N*-alkyl amino directed carbonylation of C−H bonds for the synthesis of isatoic anhydrides.

We began our study with the Pd-catalyzed carbonylation of anilines using *N*,*N*-dimethylamino as the directing group. The carbonylation product **2′** was formed along with isatoic anhydride **2a**, in 4% and 5% yields respectively, with 72% recovery of *N*,*N*-dimethylaniline (eq 1). Importantly, the carbonylation of the C−H bond of aniline was observed in both products. Isatoic anhydrides are valuable chemicals and versatile building blocks.[21] Present methods for the synthesis of isatoic anhydrides involve cyclization of anthranilic acid by highly toxic chloroformate or triphosgene.[22] The C−H carbonylation of anilines for the synthesis of isastoic anhydrides would be an ideal and environmentally friendly approach.

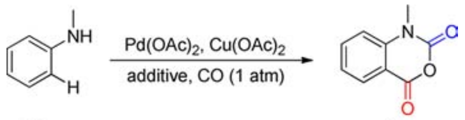


(1)

2' (4%) **2a** (5%)

Since demethylation is required for *N*,*N*-dimethylaniline,[23] we moved to *N*-methylaniline. The yield of *N*-methyl isatoic anhydride **2a** improved dramatically to 40% (Table 1 entry 1). Screening various oxidants, such as AgOAc, $CuCl_2$, BQ, and Oxone, revealed $Cu(OAc)_2$ to be the most effective for the

Table 1. Optimization of Conditions for the Pd-Catalyzed Carbonylation of *N*-Methyl Aniline[a]



1a **2a**

entry	additive	solvent	*T* (°C)	yield (%)[b]
1		MeCN	100	40
2	NaI	MeCN	100	71
3	Bu_4NI	MeCN	100	76
4	I_2	MeCN	100	60
5	KI	MeCN	100	80
6	KI	DMSO	100	68
7	KI	DMF	100	65
8	KI	toluene	100	20
9	KI	1,4-dioxane	100	37
10	KI	MeCN	60	85
11[c]	KI	MeCN	60	68

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), oxidant (2.2 equiv), MI (0.2 equiv), CO (1 atm), solvent (2 mL). [b]Isolated yield. [c]$Cu(OAc)_2$ (0.5 equiv), CO/O_2 (5:1) 1 atm.

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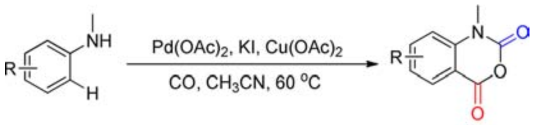
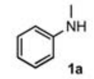
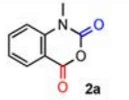
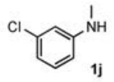
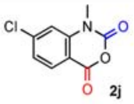
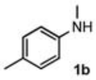
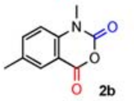
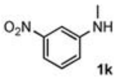
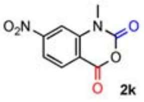
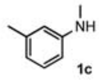
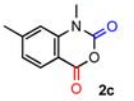
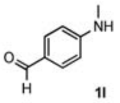
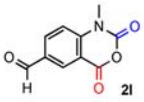
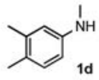
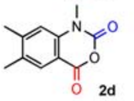
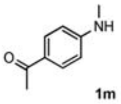
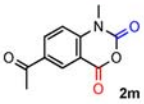
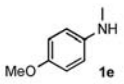
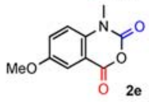
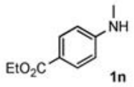
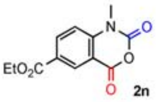
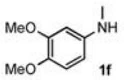
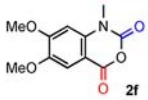
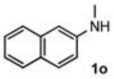
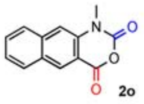
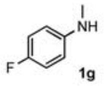
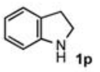
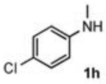
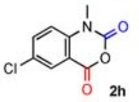
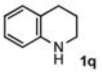
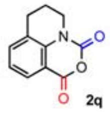
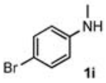
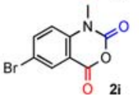
Table 2. Scope of Pd-Catalyzed Carbonylation of *N*-Methyl Anilines for the Synthesis of Isatoic Anhydrides[a]



entry	substrate	product	yield (%)[b]	entry	substrate	product	yield (%)[b]
1	 1a	 2a	85	10	 1j	 2j	76[d,e]
2	 1b	 2b	76	11	 1k	 2k	63[d,e]
3	 1c	 2c	79	12	 1l	 2l	77[d,e]
4	 1d	 2d	65[c]	13	 1m	 2m	80[d,e]
5	 1e	 2e	70[c]	14	 1n	 2n	85[d,e]
6	 1f	 2f	62[c]	15	 1o	 2o	68[d]
7	 1g	 2g	66[d,e]	16	 1p	 2p	<5
8	 1h	 2h	78[d,e]	17	 1q	 2q	75[d]
9	 1i	 2i	86[d,e]				

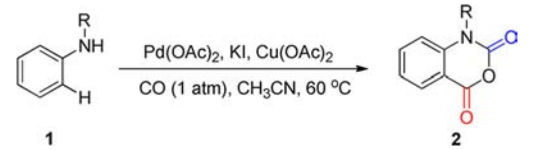
[a]Reaction conditions: aniline **1** (0.2 mmol), Pd(OAc)$_2$ (5 mol %), Cu(OAc)$_2$ (2.2 equiv), KI (0.2 equiv), CH$_3$CN (2 mL), CO (1 atm), 60 °C. [b]Isolated yields. [c]At room temperature. [d]Pivalic acid (1.0 equiv) was added. [e]CO/O$_2$ (2:1) (3 atm).

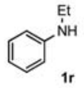
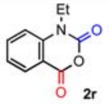
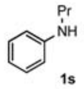
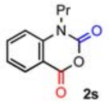
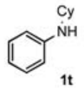
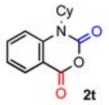
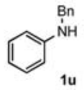
transformation (see Supporting Information (SI), Table S1). To further improve the reaction outcome, iodide compounds which have been shown to improve the efficiency of Pd-catalyzed carbonylations were also screened (Table 1, entries 2−5).[12b,24] KI was found to be the most effective and gave the desired product **2a** in 80% yield (Table 1, entry 5).[25] Other solvents such as DMSO, DMF, toluene, and 1,4-dioxane are inferior to CH$_3$CN in the reaction (Table 1, entries 6−9). Finally, the reaction temperature was also varied, and 60 °C gave the best yield (see SI Table S1). It should be noted that the isatoic anhydride **2a** could also be obtained in 68% yield using only a catalytic amount of Cu(OAc)$_2$ (50 mol %) under 1 atm of CO/O$_2$ (5:1) (Table 1, entry 11).

With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). This new carbonylation reaction displayed high functional group tolerance and proved to be a quite general methodology. Anilines with methyl, methoxyl, fluoro, and sensitive functional groups such as chloro, bromo, and formyl (aldehyde) and strong electron-withdrawing groups such as nitro, acetyl, and ester groups all gave the corresponding substituted isatoic anhydrides in good to high yields. Generally, the electron-rich substrates showed more reactivity, which is consistent with an electrophilic palladation mechanism.[8,11] Dimethyl, methoxyl, or dimethoxyl substituted anilines were converted to corresponding isatoic anhydrides in good yields at rt (Table 1, entries 4−6). When pivalic acid was used as an additive, isatoic anhydrides bearing electron-withdrawing groups were afforded in high yields under 3 atm of CO/O$_2$ (2:1) (Table 1, entries 7−14). The steric effect was observed in the transformation. *Ortho*-substituted anilines gave low yields of the corresponding isatoic anhydrides.[8b,11a] But the steric effect improves the regioselectivity of the carbonylation of *meta*-substituted anilines, in which case only less sterically hindered products were obtained (Table 2, entries 3−4, 6, 10−11). Similarly, the isatoic anhydride **2o** from the carbonylation of 2-naphthylamine **1o** was observed as the only product in 68% yield (Table 1, entry 15). Although the indoline **1p** was inert to the transformation, the carbonylation of tetrahydroquinoline **1q** proceeded smoothly to give the tricyclic isatoic anhydride in 75% yield (Table 1, entries 16−17).

Furthermore, different alkyl substituents on the anilines were also investigated (Table 3). *N*-Ethyl, propyl, or cyclohexyl

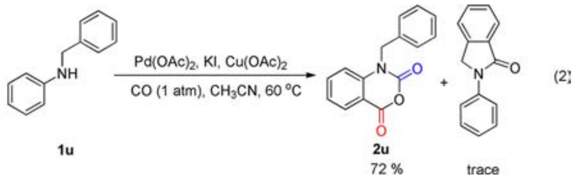
Table 3. Pd-Catalyzed Carbonylation of *N*-Alkyl Anilines[a]



entry	substrate	product	yield (%)[b]
1	 1r	 2r	84
2	 1s	 2s	63
3	 1t	 2t	51
4	 1u	 2u	72

[a]Reaction conditions: aniline **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2.2 equiv), KI (0.2 equiv), CH_3CN (2 mL), CO (1 atm), 60 °C. [b]Isolated yields.

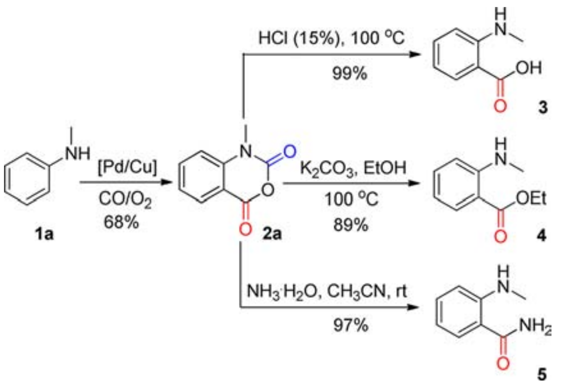
substituted anilines could be used and provided the corresponding carbonylation products in moderate to good yields (Table 3, entries 1−3). Even *N*-benzylaniline **1u** gave the isatoic anhydride **2u** as the product in 72% yield (eq 2).



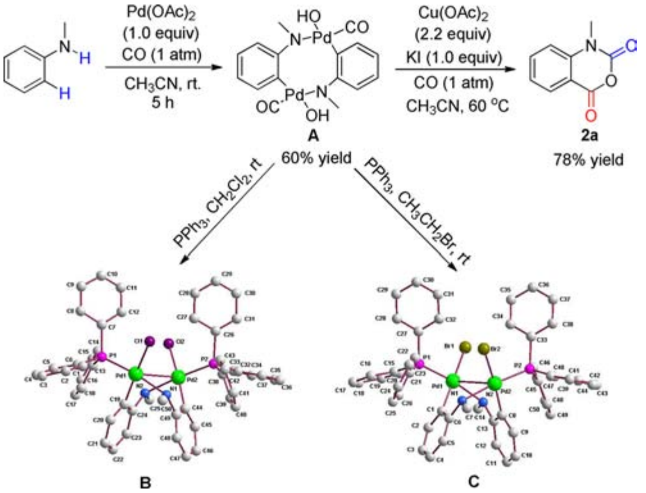
To demonstrate the synthetic utility of this reaction, the isatoic anhydride **2a** which was synthesized by catalytic amounts of $Pd(OAc)_2/Cu(OAc)_2$ under a CO/O_2 atmosphere was easily transformed into *N*-methylanthranilic acid **3**, ethyl 2-(methylamino)benzoate **4**, or 2-(methylamino)benzamide **5** in high yields (Scheme 1).

To gain insight into the mechanism of the reaction, a stoichiometric reaction of $Pd(OAc)_2$ with *N*-methylaniline was conducted under a CO atmosphere in the absence of $Cu(OAc)_2$ (Scheme 2). A palladium complex whose structure is consistent with **A** by ^{1}H NMR and mass spectrometry analysis was obtained in 60% yield.[26] This complex is poorly soluble in common organic solvents. To confirm the structure of the palladium complex **A**, it was converted to the more soluble PPh_3 coordinated palladium complexes **B** and **C**. The structures of **B** and **C** were then characterized by X-ray crystallography, thus confirming **A** is a CO coordinated palladium hydroxide dimer.[26,27] Treating the palladium dimer **A** with $Cu(OAc)_2$ (2.2 equiv) in the presence of KI (1.0 equiv) in CH_3CN under a CO atmosphere gave the isatoic anhydride **2a** in 78% yield. Therefore, the palladium dimer **A** should be a key intermediate in the reaction.

Scheme 1. Subsequent Decarboxylative Transformations

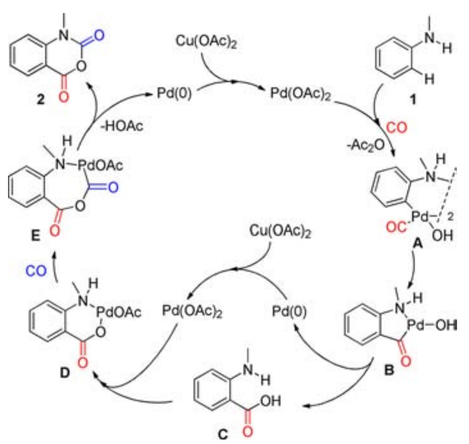


Scheme 2. Formation and Characterization of Palladium Intermediate



Therefore, a tentative mechanism for this carbonylation is proposed in Scheme 3. Electrophilic palladation of the C−H bond of *N*-methyl aniline **1** by $Pd(OAc)_2$ under a CO atmosphere forms a dimeric palladium intermediate **A**. Insertion of CO to intermediate **A** followed by a reductive elimination reaction gives *N*-methylanthranilic acid **C**[28] and Pd(0). Pd(0) was assumed to be oxidized by $Cu(OAc)_2$ to generate the $Pd(OAc)_2$ catalyst. Then, metathesis of *N*-methylanthranilic acid **C** and $Pd(OAc)_2$ produces the intermediate **D**. Coordination

Scheme 3. Tentative Mechanism of the Reaction



and insertion of CO to **D** affords intermediate **E**. Nucleophilic attack of the amino group on the acylpalladium moiety gives the isatoic anhydride **2** and Pd(0).[8d,14] Finally, Pd(0) was reoxidized by $Cu(OAc)_2$ to regenerate the $Pd(OAc)_2$ catalyst.

In summary, we have developed a novel palladium-catalyzed C−H bond carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides. The mechanism was investigated, and a key intermediate was isolated and characterized. This novel palladium-catalyzed carbonylation reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available *N*-alkyl anilines into a variety of substituted isatoic anhydrides under mild conditions. Further scope and mechanistic studies of the reaction are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures; mechanistic studies; X-ray structures of **2a**, **B**, **C**; and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) Palladacycles are usually observed in dimeric, see: (a) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (b) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. (c) Borduas, N.; Lough, A. J.; Dong, V. M. *Inorg. Chim. Acta* **2011**, *369*, 247. (d) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420 For dinuclear ruthenium catalytic intermediate, see ref 9a, b.

(27) See Supporting Information for details.

(28) *N*-Methylanthranilic acid **C** can be converted to *N*-methyl isatoic anhydride **2a** in 88% yield under the standard conditions.