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# Palladium/Copper-Catalyzed Oxidative C–H Alkenylation/N-Dealkylative Carbonylation of Tertiary Anilines**

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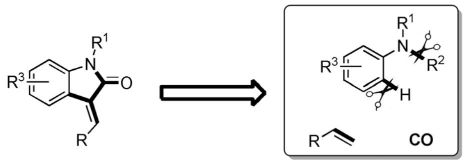
*Dedicated to Professor Xiyan Lu on the occasion of his 85th birthday*

Anilines are valuable commodity chemicals and useful synthetic building blocks for agrochemicals, active pharmaceutical ingredients, and process chemicals. Although anilines have been widely utilized in chemical synthesis, the *ortho*-selective C–H bond functionalization of anilines still remains an outstanding challenge.[1] During the past decade, Pd-catalyzed aromatic C–H functionalization to form C–C and C–X bonds has been intensively investigated.[2] However, to our best knowledge, the oxidative alkenylation of anilines through the *ortho*-selective direct C–H bond functionalization have never been achieved. On the other hand, activation of the C–N bond has become a hot topic in organic synthesis recently, in which most efforts were focused on the amination transformation.[3] As a typical example of tertiary amines, tertiary anilines have also been utilized in C–N bond cleavage transformations.[3g,i] However, the utilization of tertiary anilines as nitrogen nucleophiles with alkyl as leaving group in oxidative carbonylation has remained undeveloped. Herein, we present the first palladium/copper-catalyzed oxidative C–H alkenylation/*N*-dealkylative carbonylation of tertiary anilines towards the synthesis of 3-methyleneindolin-2-ones derivatives (Scheme 1).

3-Methyleneindolin-2-ones are recognized as a particularly useful class of compounds in medicinal chemistry that exhibit extraordinary biological and pharmaceutical properties (for example protein kinase inhibitors, phosphodiesterase inhibitors, and anti-rheumatic agents).[4] For example, Sunitinib was commercialized by Pfizer, Inc. in 2006 to treat renal cell carcinoma and gastrointestinal stromal tumors.[5] Tenidap (commercialized in 1993; Pfizer, Inc.) is an anti-inflammatory medicine for the therapy of arthritis and other ailments.[6] Moreover, 3-methyleneindolin-2-ones could be easily utilized to synthesize important indolin-2-one derivatives.[7] Consequently, considerable efforts have been made to develop efficient methods for the synthesis of oxindole derivatives. However, most of these methods involve multistep procedures under harsh reaction conditions.[8] Herein, we have developed an efficient and straightforward approach for the synthesis of 3-methyleneindolin-2-one derivatives by using commercial and simple tertiary anilines, olefins, and CO gas as the substrates.



***Scheme 1.*** Strategies towards syntheses of indolin-2-ones.

Our experiment was initiated by treating 4-methylstyrene (**2a**) with *N*,*N*-dimethylaniline (**1a**) in the presence of 1 atm CO/$O_2$ (Table 1). By optimizing various reaction parameters, the combination of a catalytic amount of [$PdCl_2(PPh_3)_2$], $Cu(OAc)_2\cdot H_2O$, dppp, and AcOH in a solvent mixture of toluene and DMF using $O_2$ as the terminal oxidant at 100 °C was found to be the best reaction conditions for this transformation (Table 1, entries 1, 13, and 14). No product was detected without the addition of $Cu(OAc)_2\cdot H_2O$ (entry 2). Removing dppp or replacing dppp with $PPh_3$ both decreased the yield dramatically (entries 3 and 11). The carbonylation reaction afforded lower yield when AcOH was removed (entry 4). The variation of the mixed solvent also led to less efficiency in terms of chemical yields (entries 5 and 10). When [$PdCl_2(PPh_3)_2$] was replaced by $Pd(OAc)_2$ or $PdCl_2$, a relatively low yield of corresponding product was obtained (entries 6 and 7). The use of a copper salt is essential for the reaction. No product was detected with $CuCl_2$ as the co-catalyst, while $Cu(OAc)_2$ showed less efficiency (entries 8 and 9). Decreasing the reaction temperature slowed the reaction, affording 46 % yield of **3a** (entry 12). With lower loading of [$PdCl_2(PPh_3)_2$], 71 % yield of **3a** was obtained by lowering the amount of $Cu(OAc)_2\cdot H_2O$, dppp, and solvent accordingly (entry 13). When the carbonylation was conducted under mixed gas outside the CO/$O_2$ explosion limits (CO/$O_2$ = 1:7), 74 % yield of desired product was obtained (entry 14).

With the above optimized conditions in hand, the carbonylation of a variety of styrene derivatives with *N*,*N*-dimethylaniline were tested (Scheme 2). The products obtained are mixtures of *Z*- and *E*-isomer because of the isomerization between them.[9] In general, both electron-donating and

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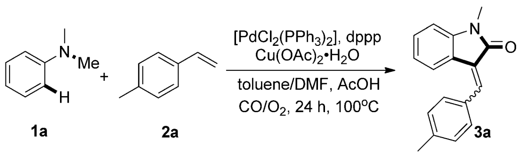
***Table 1:*** Palladium/copper-catalyzed oxidative C–H alkenylation/*N*-dealkylative carbonylation of **1a** and **2a**.[a]

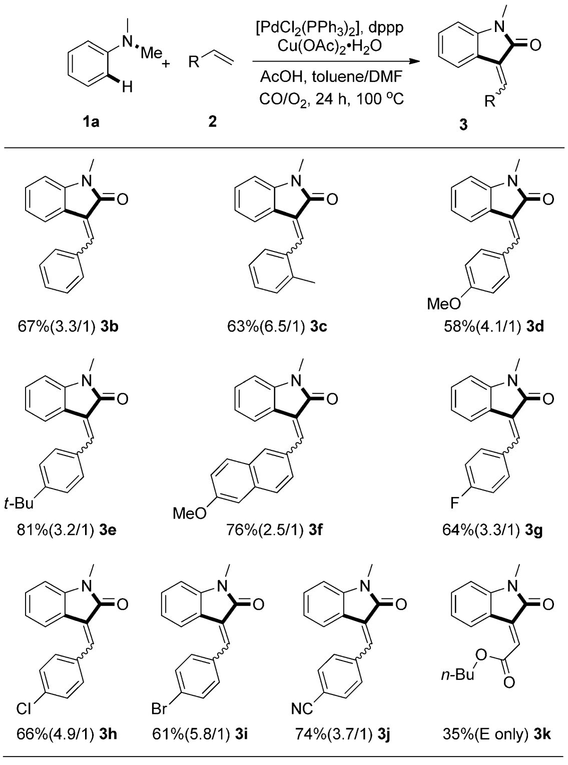


| Entry | [Pd] | [Cu] | Ligand | Solvent | Yield [%] |
|---|---|---|---|---|---|
| 1 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 74 |
| 2 | $[PdCl_2(PPh_3)_2]$ | – | dppp | Tol/DMF | 0 |
| 3 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | – | Tol/DMF | 14 |
| 4 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 28 |
| 5 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Toluene | 6 |
| 6 | $Pd(OAc)_2$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 26 |
| 7 | $PdCl_2$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 13 |
| 8 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2$ | dppp | Tol/DMF | 65 |
| 9 | $[PdCl_2(PPh_3)_2]$ | $CuCl_2$ | dppp | Tol/DMF | 0 |
| 10 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMSO | 32 |
| 11 | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | $PPh_3$ | Tol/DMF | 26 |
| 12[b] | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 46 |
| 13[c] | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 71 |
| 14[d] | $[PdCl_2(PPh_3)_2]$ | $Cu(OAc)_2{\cdot}H_2O$ | dppp | Tol/DMF | 74 (66) |

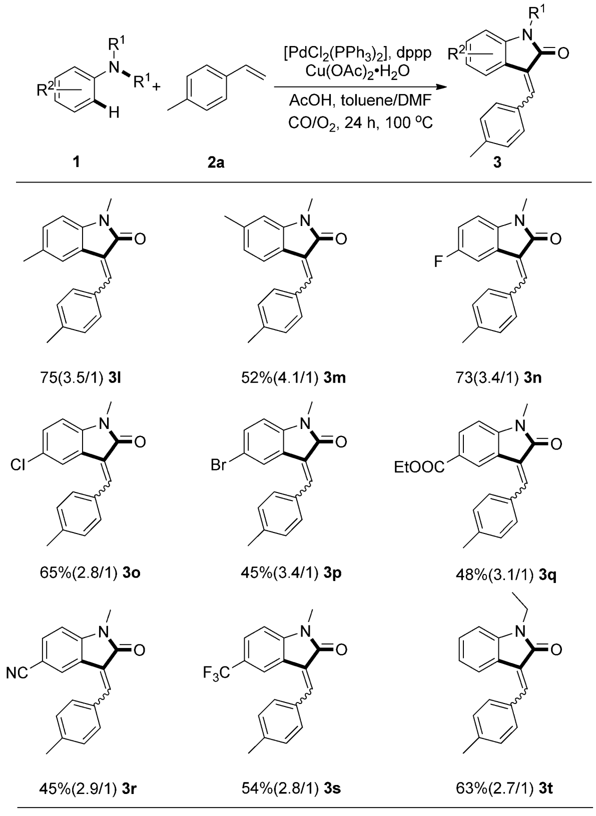
[a] The yield was determined by HPLC, calibrated using biphenyl as the internal standard. Standard reaction conditions: **2a** (0.2 mmol), **1a** (0.4 mmol), $[PdCl_2(PPh_3)_2]$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), dppp (10 mol%), AcOH (50 mol%), $CO/O_2 = 3{:}1$, toluene/DMF = 3.0:0.3 mL, 100°C, 24 h. [b] 80°C. [c] $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), dppp (5 mol%), toluene/DMF = 2.0:0.2 mL, 36 h. [d] $CO/O_2 = 1{:}7$. Yield of isolated product; $E/Z = 4.1{:}1$, which was determined by $^1H$ NMR spectroscopy.

electron-withdrawing substituents on the benzene ring of substituted styrenes were well-tolerated under the current conditions (**3b, 3d, 3e, 3f**, and **3j**). The position of substituent on benzene ring seems to have little influence on the product yield (**3c**). Styrenes substituted with the halogens F, Cl, and Br afforded the corresponding 3-methyleneindolin-2-ones in moderate to good yields (**3g, 3h**, and **3i**). To our delight, a 35% yield was obtained by employing butyl acrylate as the reactant (**3k**), in which only *E*-isomer was detected.

Furthermore, we investigated the scope of *N*,*N*-dialkylanlines, and the results are listed in Scheme 3. *N*,*N*-dimethylaniline substituted with a methyl group underwent smooth reactions with **2a**, giving the desired products in 75% and 52% yields, respectively

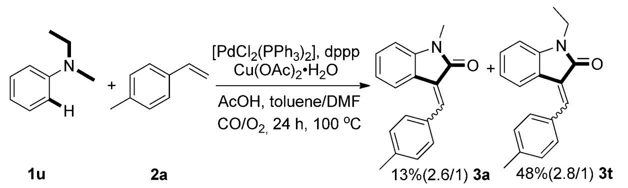


***Scheme 2.*** Palladium/copper-catalyzed oxidative C–H alkenylation/*N*-dealkylative carbonylation between various olefins **2** and **1a**. Standard reaction conditions: **2** (0.2 mmol), **1a** (0.4 mmol), $[PdCl_2(PPh_3)_2]$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), dppp (10 mol%), AcOH (50 mol%), $CO/O_2 = 1{:}7$, toluene/DMF = 3.0:0.3 mL, 100°C, 24 h. Yield of isolated product. The ratio of *E*/*Z* was determined by $^1H$ NMR spectroscopy.



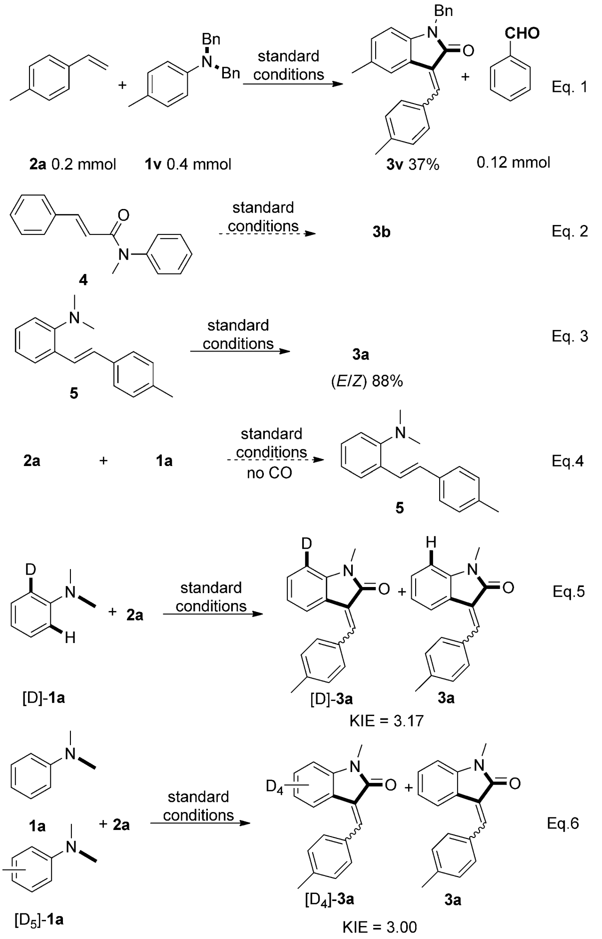
***Scheme 3.*** Palladium/copper-catalyzed oxidative C–H alkenylation/*N*-dealkylative carbonylation between various *N*,*N*-dialkylanilines **1** and **2a**. Standard reaction conditions: **2a** (0.2 mmol), **1** (0.4 mmol), $[PdCl_2(PPh_3)_2]$ (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), dppp (10 mol%), AcOH (50 mol%), $CO/O_2 = 1{:}7$, toluene/DMF = 3.0:0.3, 100°C, 24 h. Yield of isolated product. The ratio of *E*/*Z* was determined by $^1H$ NMR spectroscopy.

(**3l** and **3m**). *N*,*N*-dimethylanilines bearing halogens and electron-withdrawing substituents were also allowed to react with **2a** to afford the corresponding 3-methyleneindolin-2-ones in moderate yields (**3n**, **3o**, **3p**, **3q**, **3r**, and **3s**). When *N*,*N*-diethylaniline was employed as a substrate, the reaction also took place smoothly to furnish the desired product (**3t**). Interestingly, when *N*-ethyl-*N*-methylaniline was treated with **2a**, two types of products **3a** and **3t** were obtained in 13% and 48% yields respectively, indicating that the less sterically hindered alkyl group is much more facile for cleavage (Scheme 4).



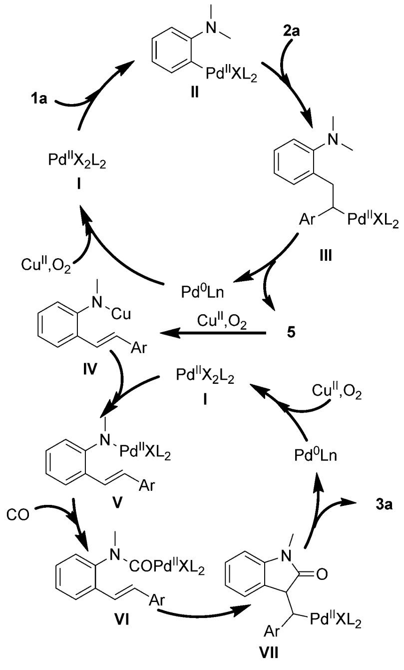
**Scheme 4.** Palladium/copper-catalyzed oxidative C—H alkenylation/*N*-dealkylative carbonylation between **2a** and **1u**.

To gain some preliminary understanding of the reaction mechanism, several experiments were carried out under the standard conditions (Scheme 5). First, the reaction of *N*,*N*-dibenzyl-4-methylaniline with **2a** afforded the desired product in 37% yield as well as 0.12 mmol of benzaldehyde, which indicated that the benzyl group was converted into benzaldehyde by C—N bond cleavage (Scheme 5, Eq. 1). *N*-Methyl-*N*-phenylcinnamamide **4** was reported to undergo an intramolecular Heck reaction to form **3a**.[8e] Therefore, **4** was tested as the substrate in our reaction. To our surprise, no product was detected under the standard conditions, which rules out the intermediacy of amide **4** (Scheme 5, Eq. 2). Under the standard conditions, **5** underwent an intramolecular carbonylation smoothly to afford **3a** in 88% yield (Scheme 5, Eq. 3). Surprisingly, the reaction of **2a** and **1a** did not take place in the absence of CO (Scheme 5, Eq. 4). From the above results, we assume that **5** might probably be the reaction intermediate and that CO plays an important role in the oxidative C—H alkenylation step. Both intramolecular and intermolecular KIE experiments were carried out, affording KIE values in 3.17 and 3.00, respectively (Scheme 5, Eq. 5 and Eq. 6). Furthermore, we conducted the experiments measuring the reaction rates of **1a** and [D$_5$]-**1a** by using in situ IR spectroscopy, in which a KIE of 3.0 was observed (see the Supporting Information). All these results indicated that the C—H cleavage might be involved in the rate-determining step.



**Scheme 5.** Preliminary mechanistic studies.

Huang et al. had recently investigated the copper-catalyzed oxidative amination of benzoxazoles using tertiary amines as nitrogen group sources.[3a] They proposed that C—N bond activation was promoted by copper and oxygen. The above experimental results induced us to propose a mechanism for this novel palladium/copper-catalyzed oxidative C—H alkenylation/N-dealkylative carbonylation (Scheme 6). Taking 4-methylstyrene **2a** with *N*,*N*-dimethylaniline **1a** as an example, the electrophilic palladation of **1a** afforded the intermediate II, and the following olefin insertion and $\beta$-H elimination produced **5**. Then, **5** underwent C—N bond cleavage in the presence of copper salts and $O_2$, affording the intermediate IV,[3a,h] which further underwent transmetalation and CO insertion to form the intermediate VI. The



**Scheme 6.** Proposed mechanism.

subsequent intramolecular Heck reaction gave **3a** and released Pd$^0$, which was oxidized by $O_2$ to regenerate Pd$^{II}$.

In conclusion, we have developed the first aerobic palladium/copper-catalyzed oxidative C–H alkenylation/N-dealkylative carbonylation of tertiary anilines to form 3-methyleneindolin-2-ones derivatives. Moderate to good yields were obtained and a variety of functional groups were tolerated. This transformation provides an effective and straightforward method towards the synthesis of biologically and medicinally useful 3-methyleneindolin-2-ones from commercial and simple substrates. Preliminary mechanism studies revealed that the intermolecular selective *ortho*-alkenylation of *N*,*N*-dialkylanilines is the first and rate-determining step, and the alkyl leaving group was converted into the corresponding aldehyde. Further studies on substrate scope and mechanism are currently underway and will be reported in due course.

## Experimental Section

General procedure: [$PdCl_2(PPh_3)_2$] (14.0 mg, 10 mol%) and Cu($OAc)_2{\cdot}H_2O$ (12.0 mg, 30 mol%) were combined in an oven-dried Schlenk tube equipped with a stir-bar. In a glove box, dppp (8.2 mg, 10 mol%) was added in the tube. A balloon filled with CO and $O_2$ (the ratio is 1:7) was connected to the Schlenk tube via the side tube and purged 3 times. Then DMF (0.3 mL) and toluene (3.0 mL) were added to the tube via a syringe. Styrene (0.2 mmol), anilines (0.4 mmol), and AcOH (6 mg, 50 mol%) were then added to the tube. The Schlenk tube was heated at 100°C for 24 h and then cooled to room temperature. After the balloon gas was released carefully, the reaction was quenched by water and extracted with $CH_2Cl_2$ three times. The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated under vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel with hexane/ethyl acetate.

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